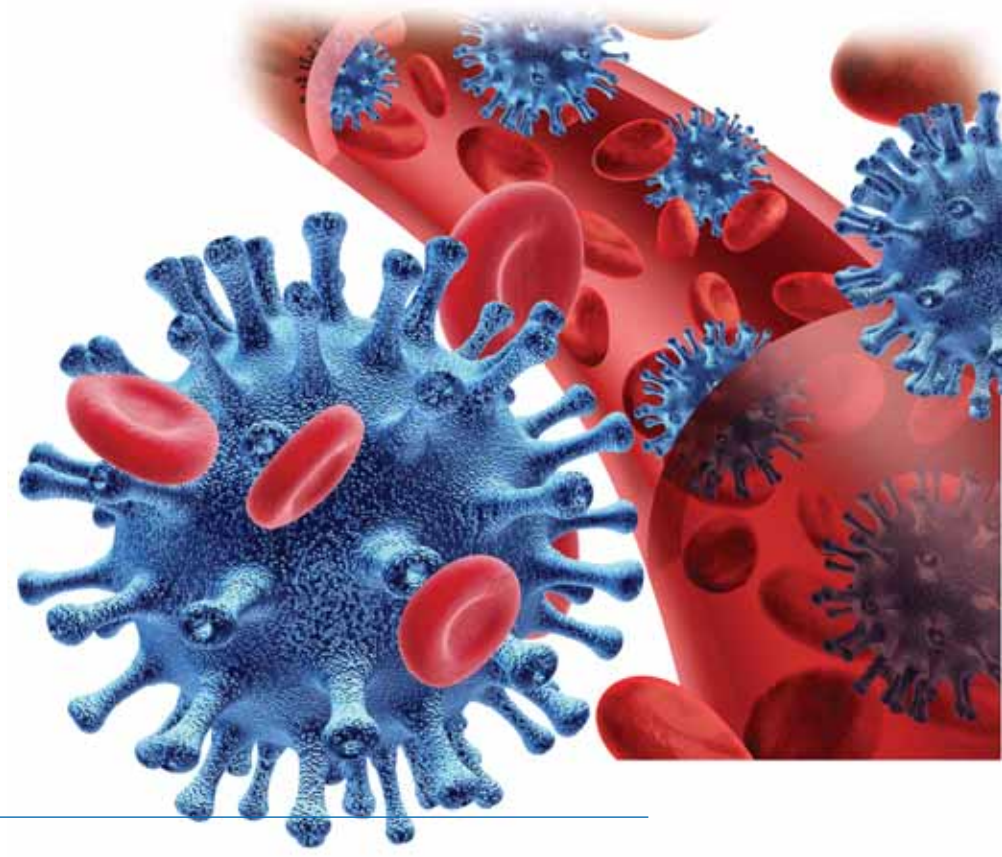
Catheter-related Bloodstream Infections



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Health care–associated infections (HAIs) are an important cause of morbidity and mortality and place a significant economic burden on the health care system.[1-3] An estimated 1.7 million HAIs (4.5 infections per 100 hospital admissions) occurred in the United States in 2002, resulting in nearly 100,000 deaths.[4]

Catheter-related bloodstream infections (CRBSIs), most of which are associated with central venous catheters (CVCs), account for 11% of all HAIs.[4-6] Agencies such as the National Healthcare Safety Network (NHSN; formerly the National Nosocomial Infections Surveillance System) of the Centers for Disease Control and Prevention (CDC) were formed in response to the growing awareness that HAIs are urgent public health and patient safety issues.[1] The recent action plan proposed by the Department of Health and Human Services identified CRBSIs as a priority area for prevention.[7]

In 2002, the National Quality Forum created and endorsed a list of Serious Reportable Events (SREs) to increase public accountability and consumer access to critical information about health care performance. These SREs soon became known as "never events." Following this lead, in 2007 the Centers for Medicare & Medicaid Services (CMS) declared it would no longer reimburse HAIs such as CRBSIs, increasing the urgency for rational and effective prevention and treatment strategies to reduce the morbidity, mortality, and costs associated with them.[8] The policy, which went into effect in late 2008, was created to help improve the care of patients by incentivizing hospitals to prevent serious hospital-associated adverse events. Beginning in January 2011, CMS mandated that hospitals report

CRBSI rates through the NSHN. This new CMS regulation makes CRBSI reporting a national requirement to receive full Medicare inpatient payments; facilities that fail to report will not receive the annual 2% Medicare payment increase.

Intravascular catheters play a central role in the care of critically and chronically ill patients; an estimated 5 million CVCs are inserted in patients each year. However, more than 250,000 central line–associated bloodstream infections (CLABSIs) also occur annually, with an estimated mortality rate of 12% to 25%.[3] A recent meta-analysis of patients in the intensive care unit (ICU) found that mortality rates were significantly higher when a CRBSI occurred (random effects model: odds ratio [OR], 1.96; 95% confidence interval [CI], 1.25-3.09).[9] Each episode significantly increases hospital length of stay, with additional health care costs ranging from $4,000 to $56,000 per episode.[6,10,11] The NHSN has published surveillance criteria for defining CRBSIs. The criteria for patients older than 1 year of age are the following: isolation of a recognized pathogen from blood culture(s), the presence of clinical signs of sepsis and/or shock (eg, fever, chills, or hypotension), a determination that the infection is not from other sources, and confirmation that the organism is not a contaminant.[1]

Intravascular devices (IVDs) include peripheral vascular catheters (venous and arterial), pulmonary artery catheters, midline catheters, peripherally inserted central catheters (PICCs), and various CVCs, including tunneled (usually long-term devices) and nontunneled catheters (percutaneously placed CVCs commonly used in ICUs).[3,5,6,12] This review covers the pathogenesis, microbiology, and treatment of CRBSIs, highlighting advances in the areas of prevention and government policy.

Table 1. Diagnosis of CRBSIs

	Diagnostic Method	Description	Criteria for Positivity	Sensitivity, %	Specificity, %
Methods not requiring CVC removal	Qualitative blood culture through device	One or more blood cultures drawn through CVC	Any growth	87	83
	Quantitative blood culture through device	Blood culture drawn through CVC, processed by pour-plate methods or a lysis-centrifugation technique	≥100 CFU/mL	77	90
	Paired quantitative blood cultures	Simultaneous cultures drawn through CVC and percutaneously	Both cultures positive with CVC culture yielding 5-fold higher or more than peripherally drawn culture	87	98
	Differential time to positivity	Simultaneous blood cultures drawn, through CVC and percutaneously, and monitored continuously	Both cultures positive with CVC positive ≥2 h earlier than peripherally drawn culture	85	81
Methods requiring CVC removal	Qualitative catheter segment culture	Segment from removed CVC is immersed in broth media and incubated for 24-72 h	Any growth	90	72
	Semiquantitative catheter segment culture	A 5-cm segment from removed CVC is rolled 4 times across a blood agar plate and incubated	≥15 CFU	85	82
	Quantitative catheter segment culture	Segment from removed CVC is flushed or sonicated with broth, serially diluted, plated on blood agar, and incubated	≥1,000 CFU	83	87

CFU, colony-forming units; **CRBSI**, catheter-related bloodstream infection; **CVC,** central venous catheter

Adapted from reference 22.

Microbiology

Antimicrobial resistance, now considered a global crisis, continues to loom large, and the organisms that cause CRBSIs are no exception. In the past 2 decades, the proportion of CRBSIs caused by antimicrobial-resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant gram-negative bacilli, and fluconazole-resistant *Candida* species, has been increasing at an alarming rate.[3,13-15] Overall, the organisms most frequently responsible for nosocomial CLABSIs are coagulase-negative staphylococci (CoNS) (31%), *S. aureus* (20%), enterococci (9%), *Escherichia coli* (6%), *Klebsiella* species (5%), and *Candida* species (9%). A large prospective surveillance study using data from SCOPE (Surveillance and Control of Pathogens of Epidemiological Importance) that included 24,179 cases of CRBSIs from a 7-year period at 49 hospitals found that the rates of MRSA isolates increased from 22% in 1995 to 57% in 2001 ($P<0.001$). Rates of ceftazidime-resistant *Pseudomonas aeruginosa* isolates increased from 12% in 1995 to 29% in 2001 ($P<0.001$), and 60% of isolates contained vancomycin-resistant *Enterococcus faecium*.[15]

Pathogenesis

The pathogenesis of CRBSIs can be attributed to 2 primary causes: bacterial colonization of the device and contamination of the fluid being administered.[16] Contaminated infusate leads to the majority of epidemic IVD-related BSIs, but it is rare.[16,17] Colonization of the device may be either extraluminal (from surrounding skin or hematogenous seeding of the catheter tip) or intraluminal (caused by an organism adhering to the device followed by the creation of a biofilm, a process responsible for persistent infections and hematogenous spread).[3,16,17] In short-term devices, the extraluminal route is more frequent, whereas the intraluminal

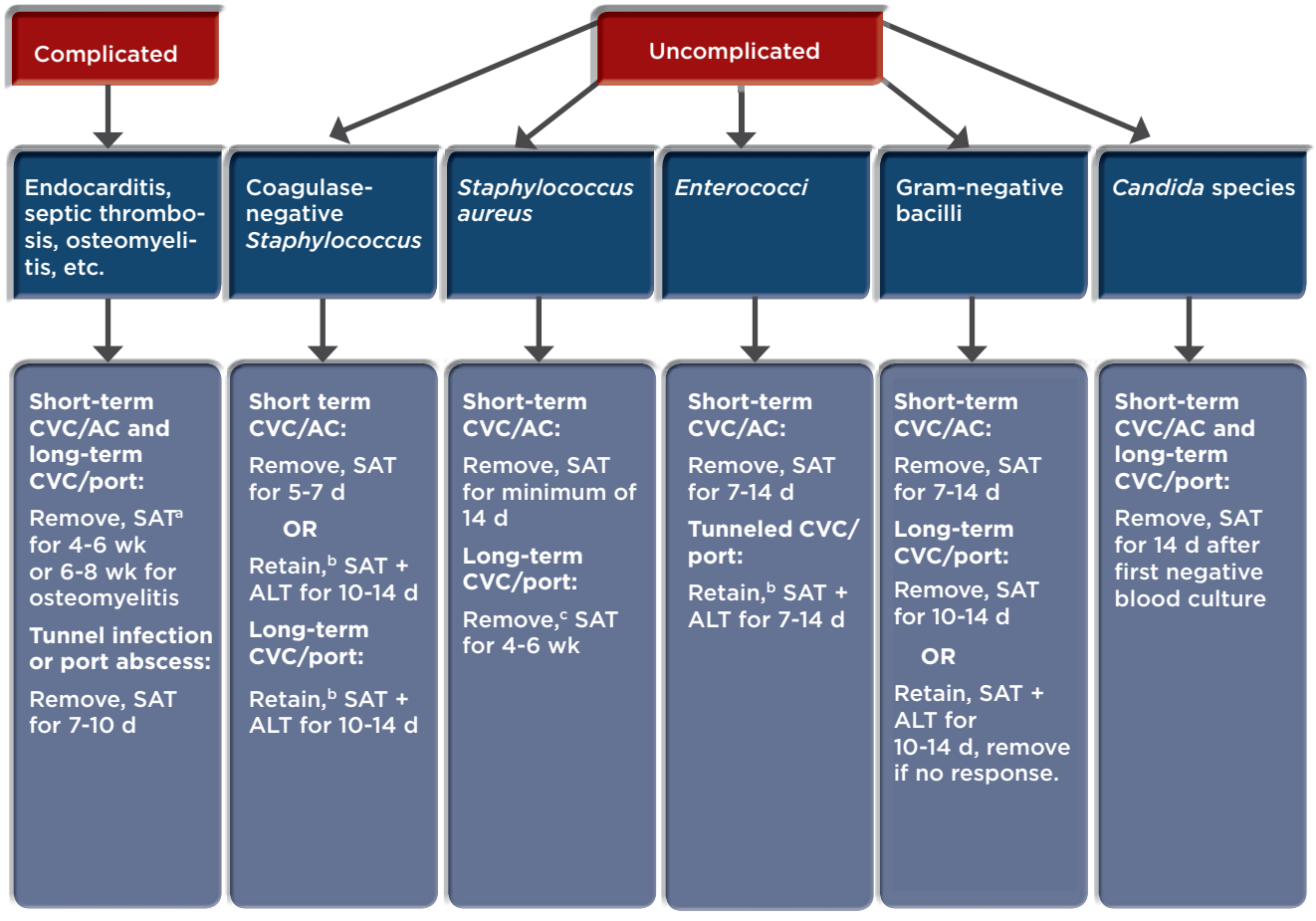

Figure. Management of CRBSIs.

AC, arterial catheter; **ALT,** antibiotic lock therapy; **CRBSIs,** catheter-related bloodstream infections; **CVC,** central venous catheter; **SAT,** systemic antimicrobial therapy

[a] Choose most appropriate systemic antimicrobial therapy based on current published guidelines.

[b] Remove retained catheter if there is clinical worsening, relapsing, or persisting infection.

[c] Current guidelines recommend considering catheter salvage therapy; however, outcomes may be poor.

Adapted from reference 19.

route is more common in long-term devices (≥10 days) or short-term devices left in longer than 4 to 7 days.[16,18]

Diagnosis

The clinical diagnosis of CRBSIs is difficult because both the sensitivity for clinical signs of inflammation at the catheter site and the specificity for signs of systemic infection are low.[19,20] Blood culture specimens from the catheter should be drawn from all available lumens to avoid missed infections. In a recent retrospective analysis of CRBSIs at a single institution, 27.2% would have been missed if only one lumen of the double-lumen catheter had been sampled.[21]

A number of techniques for the diagnosis of CRBSIs have been studied, including catheter-sparing and non–catheter-sparing methods (Table 1, page 85). A recent meta-analysis found that paired quantitative blood cultures were the most accurate diagnostic test, followed by quantitative blood cultures through the CVC and quantitative or semiquantitative catheter segment cultures.[22]

Paired quantitative blood cultures are labor intensive and cost almost twice as much as standard blood cultures. The widespread availability of radiometric blood culture systems (eg, BACTEC, Becton Dickinson)—in which blood cultures are continuously monitored for microbial growth (approximately every 20 minutes)—has led to their use in detecting CRBSIs.[23] The differential time to positivity (the detection of positivity in a culture of blood drawn from an IVD 2 hours or more before the detection of positivity in a culture of blood drawn simultaneously from a peripheral site) was an accurate predictor for CRBSIs in studies of short- and long-term devices.[12,23-25] Newer diagnostic techniques, including acridine orange leucocyte cytospin and endoluminal brush, are currently being investigated and have shown promise.[12,26-30]

Management

The management of CRBSIs relies on 2 major clinical decisions: 1) the appropriate and timely administration of systemic antimicrobial treatment (SAT) and 2) catheter removal or catheter salvage treatment. SAT should be selected based on the suspected or proven presence of causative agents in accordance with published guidelines and resources.[19] The decision to remove the catheter is based on the type of catheter being used and the organism in question. This decision becomes more complex when specific patient characteristics are considered, such as the type of device required (tunneled or implanted) and the ease of venous access. Guidelines from the Infectious Diseases Society of America (IDSA) recommend the removal of nontunneled catheters in all complicated infections (eg, thrombosis, endocarditis, osteomyelitis) and in all infections caused by *S. aureus*, gram-negative bacilli, *Enterococcus* species, and *Candida* species. The catheter may be retained with CoNS if systemic antibiotics are given in conjunction with antibiotic lock therapy (ALT).[19] In CRBSIs associated with tunneled or implantable devices, the catheters also require removal for any complicated infections (eg, thrombosis, endocarditis, osteomyelitis), tunnel or pocket infections and port abscesses, and all infections caused by *S. aureus* and *Candida* species.

According to the recent guidelines, catheter salvage regimens—including the use of ALT—may be attempted when necessary for infections caused by organisms other than *S. aureus*, fungi, *P. aeruginosa*, *Bacillus* species, *Micrococcus* species, propionibacteria, and mycobacteria.[19] Although device-sparing regimens with longer treatment durations and using antibiotic lock solutions have been attempted for uncomplicated *S. aureus*, gram-negative bacilli, and even fungal pathogens, the data supporting its efficacy are scant—we do not recommend catheter salvage for *S. aureus* and other virulent organisms.[12,19,31-42]

The duration of therapy varies based on the organism and whether or not the device has been removed. Systemic therapy for CoNS infections ranges from 5 to 7 days when the catheter is removed and from 10 to 14 days when it is retained in conjunction with ALT. With catheter removal and uncomplicated infections, the duration of systemic therapy for CRBSIs caused by *S. aureus* is greater than 14 days, 7 to 14 days for gram-negative bacilli infections, and 14 days from the first negative blood culture for *Candida* infections (Figure).[12,19]

Transesophageal echocardiography (TEE) should be performed in all patients with a CRBSI caused by *S. aureus* because of the propensity of this organism to cause endocarditis. Rosen et al determined that screening all patients who had a clinically uncomplicated CRBSI caused by *S. aureus* with TEE was a cost-effective way to determine duration of therapy—as short as 2 weeks if the TEE result was negative.[43]

Catheter Salvage Strategies

When the need to retain an existing long-term catheter in a patient with a CRBSI is significant, salvage can be attempted by using ALT as an adjunct to systemic therapy.[12,19,44] Approximately 2 mL of solution is infused into the lumen of the catheter and remains there for a certain amount of time per day during the course of treatment.[12,44] Solutions consist of the appropriately selected antibiotic combined with heparin (if compatible). In the lock, antibiotic concentrations range from 100 to 1,000 times the usual systemic concentrations. This increased concentration has a greater likelihood for killing organisms embedded in biofilm.[44] Current guidelines recommend that antibiotic lock solution be used for 10 to 14 days in conjunction with SAT.[19] Vancomycin, cefazolin, and ticarcillin-clavulanic acid (Timentin, GlaxoSmithKline)—all in combination with heparin—have excellent stability when used in ALTs, retaining 90% of their activity after 10 days of dwell time in the presence of susceptible organisms.[45]

CRBSIs caused by *Candida* species necessitate prompt removal of the catheter; however, this may not

Table 2. Recommendations for the Prevention of CRBSIs

	Recommendation	Rating[a]
Education	• Educate all relevant health care personnel regarding indications for IV catheter use, proper procedures for insertion and maintenance, and infection control measures	IA
Surveillance	• Conduct institutional surveillance for rates of CRBSIs, monitor trends, identify lapses in infection control practices • Express ICU data as number of CRBSIs per 1,000 catheter-days	IA IB
Antisepsis	• Maximal sterile barrier precautions during catheter insertion: cap, mask, sterile gown, sterile gloves, and large sterile full body drape • Hand hygiene: Wash hands with antiseptic-containing soap and water or waterless alcohol-based product before insertion or any manipulation of any IV catheter • Maintain aseptic technique with insertion of IV catheters • Sterile gloves required for arterial, central, and midline catheters, changed during guidewire exchange before handling new sterile catheter • Cutaneous antisepsis: Use 2% chlorhexidine before insertion and during dressing changes (if contraindicated, an iodophor or 70% alcohol are alternatives)	IB IB IB IA IA
Insertion	• When possible, use subclavian site when using a nontunneled CVC • Use jugular or femoral vein site for hemodialysis and pheresis catheters • Insertion and maintenance of IV catheters only by designated, trained personnel with known competence • Use ultrasound guidance when available • Use sterile gauze or sterile, transparent semipermeable dressing • Do not give prophylactic antibiotics to prevent catheter colonization or BSI	IB IA IA IB IA IB
Maintenance	• Dressings: Replace on short-term CVCs every 2 d for gauze and every 7 d for transparent, no more than weekly for tunneled or implanted CVC sites until site is healed • Monitor site visually or by palpation through intact dressing on regular basis and remove dressing for full exam if tender, fever without obvious source, or other manifestations suggesting local infection or BSI • Do not routinely culture catheter tips • Do not use topical antibiotic ointments or creams (except dialysis catheters) • Antimicrobial/antiseptic catheters: Use in adults if catheter is expected to remain >5 d if institutional CRBSI rates are above benchmarks despite comprehensive prevention strategies • Remove IV catheters as soon as no longer necessary • Do not routinely replace CVCs, PICCs, HD catheters, or pulmonary artery catheters to prevent CRBSIs • Replace administration sets no more frequently than 96 h but at least every 7 d, unless infection or unless infusing blood, blood products, or lipid emulsions	IB IB IA IB IA IA IB IA
Novel strategies not addressed in current guidelines	• Antibiotic lock solutions for use in patients with history of multiple CRBSIs • Use chlorhexidine-impregnated sponge dressing for short-term CVCs in patients over 2 mo of age if CRBSI rate is higher than institutional goal despite other standard measures • A sutureless catheter securement device for PICCs • Use a 2% chlorhexidine daily bath to reduce CRBSIs • Needleless devices: chlorhexidine preferred for cleaning access ports • Use "bundle" strategies to improve compliance with evidence-based guidelines for reducing CRBSIs	II IB II II IA IB

BSI, bloodstream infection; **CRBSIs,** catheter-related bloodstream infections; **CVC,** central venous catheter; **HD,** hemodialysis; **ICU,** intensive care unit; **IV,** intravenous; **PICC,** peripherally inserted central catheter

[a] CDC categories of evidence: IA, strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies; IB, strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies and a strong theoretical rationale; II, suggested for implementation and supported by suggestive clinical or epidemiologic studies or a theoretical rationale.[2]

Adapted from references 2 and 3.

always be immediately possible. A solution of ethylenediamine tetraacetic acid (EDTA) with amphotericin B lipid complex showed promise during an in vitro model of a *Candida* biofilm formation, but more research is urgently needed.[46] We do not recommend catheter salvage in the setting of *S. aureus* CRBSIs because of the high risk for metastatic infection and the slim likelihood of cure without removal of the catheter.

Prevention

The Healthcare Infection Control Practices Advisory Committee (HICPAC) of the CDC has published extensive guidelines for the prevention of CRBSIs, with a recent update released in 2011 (Table 2).[2,3] They emphasize the following: 1) educating and training all health care personnel who insert and maintain catheters; 2) using maximal sterile barrier precautions during CVC insertion; 3) using a greater than 0.5% chlorhexidine skin preparation with alcohol for antisepsis; 4) avoiding routine replacement of CVCs as a strategy to prevent infection; and 5) using antiseptic/antibiotic impregnated short-term CVCs and chlorhexidine-impregnated sponge dressings if the rate of infection is not decreasing despite adherence to prior strategies. The guidelines also emphasize performance improvements by implementing bundle strategies and documenting and reporting the compliance rates for all components of the bundle as benchmarks for quality assurance and performance improvement.[2] Novel strategies for the prevention of CRBSIs are summarized in Table 3 (page 90).[2,47-54]

Highlighted below are important topics for the prevention of CRBSIs. The recommendations are rated based on the strength of evidence supporting them as follows: IA, strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies; IB, strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies and a strong theoretical rationale; IC, required by state or federal regulations, rules, or standards; and II, suggested for implementation and supported by suggestive clinical, or epidemiologic studies or a theoretical rationale.[3]

Cutaneous Antisepsis

Historically, iodophors, such as 10% povidone-iodine, have been the most widely used skin antisepsis agents in the United States.[5,55,56] However, recent studies demonstrate that a 2% chlorhexidine preparation is the superior agent for preventing CRBSIs. A meta-analysis of 4,143 catheters found that chlorhexidine preparations reduced the risk for CRBSIs by 49% (95% CI, 0.28-0.88) compared with povidone iodine.[47] Also, an economic decision analysis based on available evidence suggested that the use of chlorhexidine rather than povidone iodine for CVCs would result in a 1.6% decrease in the incidence of CRBSIs, a 0.23% decrease in the incidence of mortalities, and cost savings of $113 per catheter used.[57] Currently, the CDC recommends a 2% chlorhexidine preparation as the first choice agent for cutaneous antisepsis (rating IA).[2]

Topical Antimicrobials

The HICPAC/CDC guidelines specifically recommend against the use of topical antibiotic ointments or creams at the catheter insertion site (except in the case of hemodialysis catheters) to avoid promotion of fungal infections and antimicrobial resistance (rating IA).[2,3] The guidelines also discourage the administration of intranasal antimicrobials before insertion or during the use of a catheter as a means to prevent colonization or CRBSIs (rating IA).[3] A meta-analysis of mupirocin prophylaxis to prevent *S. aureus* infections in patients undergoing dialysis showed a 63% reduction (95% CI, 50%-73%) in the rate of overall *S. aureus* infections.[52] The study population included both hemodialysis and peritoneal dialysis patients. Of the 10 studies, 6 used intranasal mupirocin 2 to 3 times per day for 5 to 14 days with various maintenance schedules, and 4 used mupirocin applied to the catheter exit site. Among patients undergoing hemodialysis, *S. aureus* bacteremia was reduced by 78% (relative risk [RR], 0.22; 95% CI, 0.11-0.42). However, the differences in site, frequency, and duration of mupirocin treatment in these studies and the resulting clinical heterogeneity make it difficult to draw robust conclusions. A randomized, double-blind, placebo-controlled trial evaluating mupirocin prophylaxis for nosocomial *S. aureus* infections in nonsurgical patients found that routine cultures for *S. aureus* nasal carriage at admission and subsequent intranasal mupirocin use did not prevent nosocomial *S. aureus* infections.[58] Additionally, reports of emerging mupirocin resistance are becoming commonplace.[59-64] Routine use of topical or intranasal mupirocin for prophylaxis against CRBSIs is not recommended.

The limitations of mupirocin suggest that other topical approaches for the prevention of CRBSIs should be studied. One such agent is honey. The antibacterial properties of some types of honey have made this a promising agent to study. The effect of 3-times-weekly Medihoney (commercially available; pooled antibacterial honey including *Leptospermum* species honey; Medihoney Pty Ltd, Brisbane, Australia) on infection rates in 101 patients receiving hemodialysis via tunneled, cuffed CVCs was compared with topical mupirocin in a randmozied controlled trial (RCT). The investigators found similar catheter-associated bacteremia rates in the 2 arms (0.97 vs 0.85 episodes per 1,000 catheter-days, respectively; $P>0.05$).[65] Although the preliminary results are promising, a larger trial powered to show equivalence or superiority is needed to establish the utility of Medihoney for the prevention of CRBSIs in patients receiving hemodialysis through tunneled, cuffed catheters.

Maximal Barrier Precautions

Maximal barrier precautions, including cap, sterile gown, mask, large sterile drape, and sterile gloves,

Table 3. Novel Strategies for the Prevention of CRBSIs

Strategy	Study	Design	Technology	Outcome
Antimicrobial lock solution	Safdar et al, 2006[51]	Meta-analysis	Vancomycin-containing locks vs heparin	50% risk reduction (RR, 0.49; 95% CI, 0.26-0.95)
	Yahav et al, 2008[54]	Systematic review and meta-analysis	Various antibiotics[a] Antibiotic plus antiseptic[b] Antiseptic[c]	**Antibiotic solutions:** RR, 0.44; 95% CI, 0.38-0.5 **Non-antibiotic antiseptic solutions + other prevention methods[d]:** RR, 0.25; 95% CI, 0.13-0.5 **Non-antibiotic antiseptic solutions alone:** RR, 0.9; 95% CI, 0.48-1.69
	Sanders et al, 2008[84]	Double-blind randomized trial	Ethanol-containing locks vs heparin	OR, 0.18; 95% CI, 0.05-0.65
Antimicrobial catheters	Veenstra et al, 1999[53]	Meta-analysis	Antiseptic-impregnated CVCs[e]	OR, 0.56; 95% CI, 0.37-0.84
	Ramritu et al, 2008[50]	Systematic review	Antibiotic-impregnated CVCs[f]	RR, 0.39; 95% CI, 0.17-0.92
	Crnich et al, 2002[5]	Meta-analysis	Silver-impregnated CVCs	RR, 0.40; 95% CI, 0.24-0.68
	Ramritu et al, 2008[50]	Systematic review	Antibiotic vs first-generation antiseptic-impregnated CVCs	RR, 0.12; 95% CI, 0.02-0.67[g]
	Hockenhull et al, 2009[81]	Systematic review	Anti-infective CVCs (all types)	OR, 0.49; 95% CI, 0.37-0.64[h]
Chlorhexidine dressings	Ho et al, 2006[48]	Meta-analysis	Chlorhexidine-impregnated dressing vs placebo or povidone-iodine dressing	**Catheter or exit-site colonization:** 14.3% vs 27.2%; OR, 0.4; 95% CI, 0.26-0.61 **CRBSIs:** 2.2% vs 3.8%; OR, 0.58; 95% CI, 0.29-1.14; *P*=0.11
	Timsit et al, 2009[80]	Randomized controlled trial	Chlorhexidine-impregnated dressing vs standard dressing	0.4 vs 1.3 CRBSIs per 1,000 catheter days; HR, 0.024; 95% CI, 0.09-0.65; *P*=0.005
Cutaneous antisepsis	Chaiyakunapruk et al, 2002[47]	Meta-analysis	Chlorhexidine vs povidone-iodine	RR, 0.49; 95% CI, 0.28-0.88[i]
Mupirocin prophylaxis	Tacconelli et al, 2003[52]	Meta-analysis	Mupirocin prophylaxis in dialysis patients[j]	Decrease in *S. aureus* bacteremia in hemodialysis patients by 78%; RR, 0.22; 95% CI, 0.11-0.42
Chlorhexidine bathing	Silva et al, 2010[90]	Meta-analysis	Daily chlorhexidine bathing (impregnated cloths or solution) compared with soap and water baths	Decrease in risk for bloodstream infection (RR, 0.32; 95% CI, 0.22-0.46; *P*<0.0001, fixed-effects; I^2=17%)

CI, confidence interval; **CVC,** central venous catheter; **HR,** hazard ratio; **OR,** odds ratio; **RR,** relative risk
[a] Gentamicin; gentamicin + citrate; gentamicin + vancomycin; gentamicin + cefazolin; cefotaxime. [b] Minocycline with ethylenediamine tetraacetic acid. [c] Citrate; citrate with taurolidine. [d] Nasal mupirocin and exit-site iodine dressing. [e] Chlorhexidine-silver sulfadiazine. [f] Minocycline and rifampin. [g] Reduced risk with antibiotic catheters. [h] Reduced risk with anti-infective catheters: all types combined, see text for subgroup analysis. [i] Reduced risk with chlorhexidine. [j] Six studies used intranasal mupirocin 2 to 3 times daily for 5 to 14 days with various maintenance schedules; 4 studies used mupirocin applied to catheter exit site.

significantly reduce the rate of CRBSIs when used during catheter insertion.[3,66] In a study comparing maximal barrier precautions with control precautions (eg, sterile gloves and small drape), the rate of CRBSIs was 6.3 times higher in the control group (*P*=0.06).[66] The HICPAC/CDC guidelines recommend that maximal barrier precautions be used for all CVC insertions (rating IB).[2,3]

Insertion Site

According to the HICPAC/CDC guidelines, the preferred insertion site of nontunneled CVCs for adult patients is the subclavian vein (rating 1B).[2,3] The femoral site is associated with higher rates of catheter colonization as well as increased risk for deep vein thrombosis.[3,67-70] In an RCT comparing the femoral and subclavian sites, use of the femoral site was associated with a higher overall rate of infectious complications (19.8% vs 4.5%, respectively; *P*<0.001).[70] The internal jugular site has been associated with higher rates of CRBSIs than the femoral and subclavian sites in several studies.[3,69,71] However, a recent RCT comparing the jugular and femoral sites found no difference in the rate of CRBSIs between the 2 sites (2.3 vs 1.5 per 1,000 catheter-days, respectively; *P*=0.42).[72] A prospective, observational study comparing the subclavian, internal jugular, and femoral insertion sites found colonization lowest at the subclavian site but found no difference in rates of infection between sites.[73]

Using real-time ultrasound guidance for catheter insertion decreases associated mechanical complications and infection.[2,74] In a randomized study comparing real-time ultrasound guidance with the landmark technique for catheter placement in the internal jugular vein, the latter resulted in significantly fewer complications, including fewer CRBSIs (*P*<0.001).[74] A meta-analysis revealed that the use of ultrasound for insertion at the internal jugular and subclavian vein sites decreased failure (RR, 0.32; 95% CI, 0.18-0.55), complications during catheter placement (RR, 0.22; 95% CI, 0.10-0.45), and the need for multiple placement attempts (RR, 0.60; 95% CI, 0.45-0.79) in comparison with the landmark technique.[75]

Although no RCT to date has compared the 3 insertion sites, based on available data, we recommend the subclavian site as the preferred site for CVC insertion along with the use of real-time ultrasound to minimize mechanical complications.

Simulation-based Training

A recent observational study at an urban teaching hospital evaluated the impact of a simulation-based educational intervention on the rates of CRBSIs in the medical ICU.[76] Ninety-two second- and third-year internal medicine and emergency medicine residents completed the education program, which included a pretest, an instructional video on proper CVC insertion techniques, ultrasound training, hands-on practice with the simulator device, and a post-test with a minimum score requirement. There were 3.2 infections per 1,000 catheter-days in the 16 months prior to the intervention in the hospital's medical ICU. There were 4.86 infections per 1,000 catheter-days in the hospital's surgical ICU during this preintervention period. The rate of CRBSIs in the medical ICU during the 16-month intervention period, when all second- and third-year residents had completed the training, decreased to 0.5 per 1,000 catheter-days. The rate in the surgical ICU, where no rotating residents completed the simulation training, remained stable at 5.26 per 1,000 catheter-days during the same 16-month time period.[76] The cost savings attributed to simulation training recently were evaluated using data from both the year before and the year after training.[77] The annual net savings from the simulation-based training, after accounting for the cost of the program, was more than $700,000 (2008 dollars), which translated into a 7 to 1 rate of return on investment for the training program (based on the training cost of $112,000). The use of simulation-based training exemplifies cutting-edge methods for the successful education of health care personnel regarding proper CVC insertion, which fulfills an important recommendation of the recently updated HICPAC/CDC guidelines.[2]

Chlorhexidine-Impregnated Dressings

The placement of a chlorhexidine-impregnated sponge dressing (BioPatch, Ethicon, Inc.) over the CVC insertion site has been shown to decrease CRBSIs in several randomized trials.[5,78-80] A large, open RCT compared chlorhexidine dressings with standard sterile dressings in 601 chemotherapy patients (9,731 total catheter-days). The study found a significant reduction in CRBSIs in the intervention group (6.35%; 19 of 300) compared with the control group (11.3%; 34 of 301; *P*=0.016; RR, 0.54; 95% CI, 0.31-0.94).[79] Similarly, an RCT conducted in the ICU found that the use of chlorhexidine-impregnated dressings led to significantly fewer CRBSIs than the use of standard sterile dressings (hazard ratio, 0.024; 95% CI, 0.09-0.65; *P*=0.005).[80]

The recent HICPAC/CDC guidelines for the prevention of CRBSIs recommend the use of chlorhexidine-impregnated sponge dressings with short-term CVCs in patients older than 2 months when institutional rates of CRBSIs are higher than the institutional goal, despite the consistent use of now-standard prevention measures (using well-trained personnel, chlorhexidine skin antisepsis, and maximal barrier precautions; rating 1B).[2]

Antimicrobial-Impregnated Catheters

The HICPAC/CDC guidelines recommend the use of antimicrobial-coated catheters if the device is expected to remain in place longer than 5 days if, despite use of a comprehensive CRBSI reduction strategy, the rate of infections is not decreasing (rating IA).[2,3] However, the majority of the studies have focused on the use of antimicrobial-coated CVCs used as short-term devices; few data are available on their use as long-term devices.[18,50] Several types of antimicrobial-impregnated catheters

are available: catheters coated either externally (first generation) or externally and internally (second generation) with chlorhexidine and sulfadiazine silver (CH-SS), catheters coated with minocycline or rifampin, and silver-impregnated catheters.[12] Silver-coated catheters include silver-, platinum-, and carbon-coated catheters and silver ion/alloy catheters.[5]

A meta-analysis of externally CH-SS–coated catheters found that they decreased the incidence of both catheter colonization (OR, 0.44; 95% CI, 0.36-0.54) and CRBSIs (OR, 0.56; 95% CI, 0.37-0.84) compared with uncoated catheters.[53] A recent meta-analysis found a reduced risk for CRBSIs when first-generation CH-SS–coated catheters (RR, 0.66; 95% CI, 0.47-0.93) were compared with uncoated catheters, but no significant risk reduction among patients in the ICU (RR, 0.77; 95% CI, 0.53-1.13).[50] The second-generation CH-SS–coated catheters significantly reduced CRBSIs in ICU patients (RR, 0.70; 95% CI, 0.30-1.62). Minocycline- and rifampicin-coated catheters were significantly more effective than chlorhexidine gluconate/silver sulfadiazine (CHG/SSD) catheters (RR, 0.12; 95% CI, 0.02-0.67).[50]

The most recent meta-analysis of 27 trials evaluating anti-infective catheters found a significant reduction in CRBSIs with their use when all types were analyzed (OR, 0.49; 95% CI, 0.37-0.64).[81] Subgroup analysis based on catheter type revealed reductions in CRBSIs for nearly all types compared with standard catheters: CH-SS–impregnated (5 trials; OR, 0.51; 95% CI, 0.26-1.0), silver-impregnated (6 trials; OR, 0.55; 95% CI, 0.33-0.92), minocycline-rifampin (5 trials; OR, 0.26; 95% CI, 0.15-0.47), miconazole-rifampin (1 trial; OR, 0.12; 95% CI, 0-6.07), benzalkonium chloride–impregnated (1 trial; OR, 1; 95% CI, 0.06-16.45), and CH-SS–coated (9 trials; OR, 0.62; 95% CI, 0.4-0.98).[81]

The choice of which catheter to use is governed by many factors, including efficacy, cost, cost-effectiveness, and risk for promoting drug resistance. A 2008 analysis found an estimated cost savings of approximately $227 for every anti-infective catheter inserted.[82] Antibiotic resistance is a particular concern with antibiotic-impregnated catheters, although trials assessing the efficacy of minocycline-rifampin–coated catheters found no evidence of the emergence of drug resistance.[50]

Antibiotic Lock Solutions

The major mechanism for CRBSIs in patients with long-term devices is intraluminal colonization. For this reason, antibiotic lock solutions have been considered as a logical step to prevent colonization of the intraluminal surfaces of long-term devices and thereby reduce the rate of CRBSIs. A small amount of the antibiotic solution is instilled into the lumen of the catheter and allowed to remain for a specific amount of time, after which it is either flushed or removed. A meta-analysis of 7 randomized trials (primarily involving cancer patients) demonstrated a significantly reduced risk for CRBSIs (RR, 0.49; 95% CI, 0.26-0.95) when vancomycin-containing lock solutions were used.[51] A recent systematic review and meta-analysis of patients undergoing hemodialysis included data on several lock solutions: various antibiotic combinations, minocycline with EDTA, and nonantibiotic antiseptic solutions including citrate and citrate with taurolidine. All lock solutions included in this meta-analysis showed benefit for the prevention of CRBSIs.[54] Ethanol also has been shown to be safe and effective as an antibiotic lock solution.[49,83,84] A recently published prospective, double-blind, randomized trial comparing ethanol with heparinized saline in immunosuppressed hematology patients showed a 4-fold decrease in the number of CRBSIs in the ethanol group compared with controls (OR, 0.18; 95% CI, 0.05-0.65).[84] Although a number of new antibiotics have shown promise as lock solutions during in vitro studies, more research on their efficacy is needed.[85] In general, antiseptic lock solutions are preferred over antibiotic lock solutions because of their greater spectrum of activity and smaller risk for promoting antibiotic resistance.

The HICPAC/CDC guidelines include a recommendation for the use of antibiotic/antiseptic lock solutions in patients with long-term catheters who have had multiple CRBSIs despite good aseptic technique (rating II).[2] The use of antibiotic lock solutions is also recommended for the prevention of CRBSIs in long-term devices for patients with episodes of CRBSIs and a high risk for recurrence, such as those on hemodialysis.

Chlorhexidine bathing has been proposed and evaluated as a strategy for reducing rates of CRBSIs.[86-89] Bleasdale and colleagues compared daily chlorhexidine bathing (n=391; 2,210 patient-days) with soap and water bathing (n=445; 2,119 patient-days) among patients in 2 medical ICUs in a 2-arm crossover trial.[86] There was a significant reduction in the risk for CRBSIs associated with the use of chlorhexidine bathing compared with the control group (4.1 vs 10.4 infections per 1,000 patient-days; incidence difference, 6.3; 95% CI, 1.2-11.0). A recent meta-analysis of RCTs and quasi-experimental studies evaluating chlorhexidine bathing versus a control bathing method (soap and water) demonstrated a significant reduction in the risk for CRBSIs with chlorhexidine bathing (pooled RR, 0.32; 95% CI, 0.22-0.46; $P<0.0001$, $I^2=17\%$).[90] However, a separate retrospective analysis evaluating the effect of switching from soap and water bathing to daily chlorhexidine cleansing in a surgical ICU found no difference in the rates of CRBSIs when the different periods were compared.[91] The HICPAC/CDC guidelines recommend daily chlorhexidine bathing as a strategy for reducing the rates of CRBSIs (rating II); however, the conflicting results of recent studies warrant further research in this area.[2]

Coated Luer-activated Devices

In addition to the previously described protection measures, the role of needleless connectors warrants attention. Needleless connectors were developed in response to demands for the improved safety of health

care workers (to prevent needlestick injuries) and are integral components of infusion systems across North America. Although needleless connectors, when properly used, clearly reduce the risk for needlestick injuries during access of an IVD or injection port,[92-95] reports published over the past decade have raised concerns about their potential to increase the risk for iatrogenic BSIs.[96-101] Most of these studies have been retrospective and uncontrolled; suboptimal manipulation of the device, rather than the device itself, may have been responsible for the increased incidence of CRBSIs in some settings. Typically, health care personnel disinfect the connector with 70% (v/v) isopropyl alcohol before IV administration. Although needleless connectors appeared to reduce contamination compared with standard caps,[102] a recent study by Menyhay et al found that conventional methods of disinfection may not prevent microbial entry if the luer-activated device (LAD) is heavily contaminated, which may account for the increased risk for CRBSIs observed in some reports.[103]

The HICPAC/CDC guidelines made no recommendation for or against LADs, given the lack of RCTs on this device. However, chlorhexidine may be the preferred agent for cleaning the ports of needleless devices.[2] A recent study evaluated the effect of switching to chlorhexidine for this purpose in a pre-post intervention design on a pediatric hemopoietic stem cell transplant ward.[104] In this study, switching from 70% isopropyl alcohol alone to 2% chlorhexidine in 70% isopropyl alcohol for catheter connector antisepsis was associated with a reduction in the rates of CRBSIs from 12 to 3 per 1,000 catheter-days *(P*=0.004).

Novel technologies have been developed to address the association of these devices with increased rates of CRBSIs. The V-Link with VitalShield (Baxter Healthcare), which recently received FDA approval, is LAD protected, with an interior and exterior antimicrobial coating (silver). Recent in vitro studies compared the V-link with VitalShield with control devices. The studies demonstrated that the antimicrobial coating is more than 99.99% effective in killing the most common organisms responsible for CRBSIs. It also prevented downstream spread and intra-device biofilm formation when *Enterobacter cloacae* was inoculated and allowed to dry on the septal membrane, followed by the infusion of Lactated Ringer's running solution at 0.5 mL per minute for 72 hours through the connected device.[105]

Another promising device, the Saralex-CL (Menyhay Healthcare Systems), is an antimicrobial-barrier cap that threads onto the end of a needleless LAD system. A recent prospective, in vitro study compared standard disinfection techniques for common LADs using 70% isopropyl alcohol with the Saralex-CL.[106] The Saralex-CL, which uses a solution of 0.25 mL of 2% chlorhexidine gluconate in 70% isopropyl alcohol to bathe the connector septum, was effective in preventing transmission of pathogens across the membranes of precontaminated LADs compared with standard techniques (positive control = 100% transmission, standard technique = 20 of 30; 67% transmission; Saralex-CL = 1 of 60; 1.6% transmission; *P*<0.001). Data on the clinical efficacy of antimicrobial-coated LADs and antimicrobial-barrier caps are awaited.

Catheter Securement

Sutureless securement devices avoid disruption around the catheter entry site and may decrease the degree of bacterial colonization.[107] Catheter stabilization also helps decrease the risk for phlebitis and catheter migration/dislodgement while diminishing the risk for needlestick injury to the health care provider.[2]

Device securement options include sutures, tape, and catheter-specific devices such as the StatLock (Venetec International, Inc., a subsidiary of CR Bard). Sutures may be uncomfortable for the patient, pose a risk for needlestick injury to the provider, and foster inflammation at the catheter insertion site, increasing the risk for infection. StatLock, a sutureless catheter securement device, reduces catheter-related complications, including CRBSIs.[107-109] A randomized trial comparing sutures with StatLock for PICC securement found significantly fewer CRBSIs in the StatLock group than in the suture group (2 vs 10, respectively; *P*=0.032).[107] The HICPAC/CDC guidelines recommend the use of a securement device for all intravascular catheters (rating II).[2]

Intensive Insulin Therapy

The appropriate level of glycemic control for critically ill patients is controversial. A large RCT of 1,548 critically ill patients in a surgical ICU compared intensive insulin therapy (maintenance of blood glucose level between 80 and 110 mg/dL) with conventional insulin therapy (insulin given only for blood glucose levels >215 mg/dL and maintenance of levels between 180 and 200 mg/dL).[110] The study found that intensive treatment reduced overall mortality rates (8% with conventional treatment vs 4.6% with intensive treatment; *P*<0.04); the greatest mortality reduction was observed in patients with multi-organ failure caused by a septic focus. A similar study in medical ICU patients found no reduction in mortality or difference in rates of bacteremia using intensive therapy.[111]

A meta-analysis that included 29 RCTs and 8,432 patients found no difference in hospital mortality rates with tight glucose control (21.6% vs 23.3%; RR, 0.93; 95% CI, 0.85-1.03), and the results did not change when patients were stratified by ICU type: surgical, medical, or medical-surgical. However, tight glucose control was associated with a reduced risk for septicemia (10.9% vs 13.4%; RR, 0.76; 95% CI, 0.59-0.97).[112]

In the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) study, a large RCT of 6,104 adult ICU patients, intensive glycemic control (goal, 81-108 mg/dL) caused increased mortality compared with conventional control (goal, ≤180 mg/dL; OR, 1.14; 95% CI, 1.02-1.28; *P*=0.02).[113] The study population included more medical

than surgical ICU patients (intensive group: 36.9% surgical, 63.1% medical; conventional group: 37.2% surgical, 62.8% medical). Severe hypoglycemia (≤40 mg/dL) was significantly more common in the intensive control group (6.8% vs 0.5%; $P<0.001$).[113]

A meta-analysis of 26 trials including 13,567 patients—with data from the NICE-SUGAR trial—found no reduction in mortality using intensive insulin therapy for critically ill patients (pooled RR of death with intensive vs conventional therapy, 0.93; 95% CI, 0.83-1.04).[114] However, when analyzed separately, surgical ICU patients did have a benefit, whereas patients in nonsurgical ICUs did not (RR, 0.63; 95% CI, 0.44-0.91).[114]

A recent meta-analysis of 20 RCTs evaluated the effect of intensive insulin therapy on the incidence of infections in medical and surgical ICU patients. The analysis revealed an overall reduction in the incidence of infections among all pooled studies (RR, 0.80; 95% CI, 0.71-0.90; $P=0.0002$; $I^2=53.5\%$).[115] Subgroup analysis revealed significantly fewer infections in surgical ICU patients in the intensive insulin therapy group compared with standard therapy (11 studies; pooled RR, 0.66; 95% CI, 0.57-0.76; $P<0.001$). However, no difference in infection rates among medical ICU patients was observed.

Pending the results of ongoing and future research, the use of intensive glycemic control for surgical ICU patients to reduce the risk for HAIs, particularly CRBSIs, is recommended. However, avoiding severe hypoglycemia is crucial, and a glycemic target that can be safely achieved should be used.

Multifaceted Approach Using a Checklist

A multifaceted approach must be used to effectively reduce the risk for CRBSIs. The Institute for Healthcare Improvement (IHI) developed the concept of "bundles" to aid risk reduction. According to the IHI, a bundle is a structured way of improving the processes of care and patient outcomes using a checklist of 3 to 5 practices that, when performed collectively and reliably, have led to improved patient outcomes.[116] The IHI-recommended evidence-based bundle for CVC care includes the following: 1) hand hygiene; 2) maximal barrier precautions upon insertion; 3) chlorhexidine skin antisepsis; 4) optimal catheter site selection, with the subclavian vein as the preferred site for nontunneled catheters; and 5) daily review of line necessity with prompt removal of unnecessary lines.[116] A large multicenter study by Pronovost et al that used evidence-based interventions nearly identical to the IHI CVC bundle for 18 months found a significant reduction in CRBSIs from baseline. The incidence rate of CRBSIs at 0 to 3 months was 0.62 (95% CI, 0.47-0.81) and 0.34 at 16 to 18 months (95% CI, 0.23-0.5).[117] These numbers represented up to a 66% reduction in the rates of CRBSIs, a reduction that also was maintained 18 months after the intervention period. The intervention was incorporated into standard practice at the individual centers, as described in a recent follow-up publication.[118]

Bhutta et al undertook a prospective quasi-experimental study in a children's hospital, which included the stepwise introduction of interventions over a 5-year period.[119] The interventions included maximal barrier precautions, a transition to antibiotic-impregnated CVCs, annual hand-washing campaigns, and the use of chlorhexidine in lieu of povidone-iodine. Significant reductions in CRBSI rates occurred over the intervention period. These were sustained over the 3-year follow-up. Annual rates decreased from 9.7 per 1,000 catheter-days in 1997 to 3 per 1,000 days in 2005 (RR reduction, 0.75; 95% CI, 0.35-1.26). The investigators agreed that multifaceted interventions of this nature reduce the rates of CRBSIs but require a multidisciplinary team and institutional support.

The recent implementation of a multifaceted approach in a pediatric cardiac ICU, which included CVC insertion and maintenance bundles, chlorhexidine-impregnated dressings, nurse and physician education, and the addition of a unit-based infection control nurse, resulted in a reduction in the rates of CRBSIs from 7.8 to 2.3 infections per 1,000 catheter-days in less than 2 years.[120]

The HICPAC/CDC guidelines recommend that multifaceted performance improvement strategies be "bundled" to enhance compliance with evidence-based best practices (rating IB).[2]

"Getting to Zero": The CRBSI Mandate

The concept of "Getting to Zero" was first applied by the IHI for ventilator-associated pneumonia. Since then, the concept has been used for other HAIs, including CRBSIs. In the effort to "get to zero," the CMS recently partnered with the NHSN and listed CRBSIs as a "never event." This partnership creates greater transparency, builds accountability within the health care system, and promotes support for infection control programs and professionals.[121] Certainly, by making CRBSI rates available, the public has the opportunity to make informed decisions regarding health care. However, there are both concerns and controversy surrounding the concept of "getting to zero" and the CRBSI mandate.

Infection control experts have shared concerns that "getting to zero" is an oversimplification of the complexity of HAIs and does not convey the important message that although the majority of HAIs are preventable, some are not.[122] A commentary by Victoria Fraser, MD, Washington University School of Medicine in St. Louis, MO, pointed out that this slogan is controversial because it seems scientifically unrealistic. Moreover, patients and the general public may misinterpret the message to mean that any HAI is the result of an error or a suboptimal process.[123]

The concern regarding the CRBSI mandate stems mainly from the CDC's definition of a CRBSI itself. The definition is highly sensitive but poorly specific. The high sensitivity allows it to capture all cases of CRBSIs, but the low specificity causes it to suffer from the inclusion of infections that may not be CRBSIs. In a thoughtful

commentary by Sexton et al,[124] this limitation of the surveillance definition is highlighted by specific examples where it seemed that the assignation of cases as CRBSIs was done by default (ie, simply because of the absence of proof for a secondary source of infection). The low specificity also greatly undermines the reliability of the publicly reported data on CRBSI rates. The authors then emphasize the need to change and validate the existing definition. They propose the inclusion of an "indeterminate source" category for some CRBSIs, which is "more epidemiologically and clinically useful than data derived from current definitions, which are inconsistent with common clinical practice."[124]

Similarly, in a recent retrospective cohort study involving 4 medical institutions, Lin et al[125] assessed whether or not surveillance data are consistent across institutions, contending that public reporting and inter-hospital comparisons of infection rates are only valid if the surveillance methods are uniform. The authors compared a computer algorithm reference standard for CRBSI rates with reported rates from the institution's infection preventionists. The expected rate varied significantly by medical center, suggesting that there is indeed local variation among medical centers. This then raises doubt as to the validity of comparing published rates of CRBSIs among various institutions.[125]

The "getting to zero" initiative has many advantages. It has spurred dialogue about CRBSI prevention, propelled institutions to devote more resources to CRBSI prevention, and increased awareness of these severe infections. However, the campaign to publicly report CRBSIs should incorporate a uniform application of standardized definitions in institutions and a greater emphasis on process measures known to reduce the overall incidence of CRBSI.

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Drs. Abad *and* ***Safdar*** *reported no relevant conflicts of interest.*