The Role of Antimicrobial Transparent Film Dressings in the Prevention of Catheter-Related Bloodstream Infections

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Background

Intravenous (IV) catheters, comprised of a wide variety of designs and inserted in diverse body sites, have been used in the medical profession for decades to administer such life-sustaining formulations such as fluids, medications, and blood products, as well as for hemodynamic monitoring. It is estimated that there are 8.5 million central venous catheters (CVC), 10 million peripherally inserted central catheters (PICCs), 4 million midline catheters, and 350 million peripheral intravenous (PIV) devices sold each year in the United States alone.[1,2] The wide usage of these devices accounts for millions of insertion, maintenance, and access procedures, thereby increasing the risk for infection complications.

However, estimating the number of nation-wide infections associated with all IV devices is difficult due to the lack of available surveillance data. There is currently no federal or state requirement for hospitals, skilled nursing facilities, or other healthcare entities, to report all Catheter-Related Bloodstream Infections (CRBSIs) occurring in patients in these settings. Central Line-Associated Bloodstream Infections (CLABSIs), infections that are in essence a subset of CRBSI, are currently the only national reporting requirement related to an IV device, with data relayed by hospitals using defined surveillance criteria to the Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN).[3]

The findings on the prevalence and impact of CLABSI alone is concerning. The most recent estimate published by the CDC[4] is based on a single study published in 2003, which indicates that at that time as many as 248,000 hospitalized patients per year in the United States developed a CLABSI. It is also known that CLABSIs are often associated with significant and serious impacts on patient morbidity and increases the overall mortality rate by 15%-25%.[5] There can also be a considerable economic impact for healthcare facilities. Estimates are that this type of infection has an annual attributable cost between $0.67 and $2.68 billion dollars.[4] Moreover, there currently are federal regulations that specify no hospital reimbursement for these types of infection.[6] Intensive care patients developing these infections have been reported to have an increased length of stay ranging from 9.6 to 14.3 days.[7]

In response to findings of significantly high infection rates in hospitals associated with the CLABSI metric, quality and regulatory organizations issued evidence-based interventions or "bundles" (including appropriate hand hygiene, maximal sterile barriers used during insertion, chlorhexidine skin antisepsis, prompt removal of unnecessary catheters).[8] As a result, infection rates among patients with CVCs have decreased by 28% over the last five years.[12, 13]

Despite this success, there remains today an unknown and a likely significant number of infections occurring not only in patients with CVCs but with other IV catheters. This white paper attempts to provide relevant information emphasizing the need to establish the prevention of Hospital-Onset Bacteremia (HOB), an evolving and broad prevention concept that addresses all IV catheters[14] and that may be advanced with use of evolutionary antimicrobial dressings.

Skin: The main source of CRBSIs

Skin is the largest organ of the human body and is continuously inhabited by microorganisms, some beneficial and others potentially pathogenic. Bacteria, fungi, and even viruses are masked within a complexity of millions of spaces found along skin folds, invaginations, and specialized niches such as sweat glands and hair follicles of the epidermis and dermis layers.[15] The skin acts as a protective barrier against foreign organisms, incorporating diverse physical and immunological mechanisms for this purpose.[16] When skin is bypassed, as occurs when a medical device is inserted into a blood vessel, there begins a process that may under specific circumstances, lead to systemic infection.

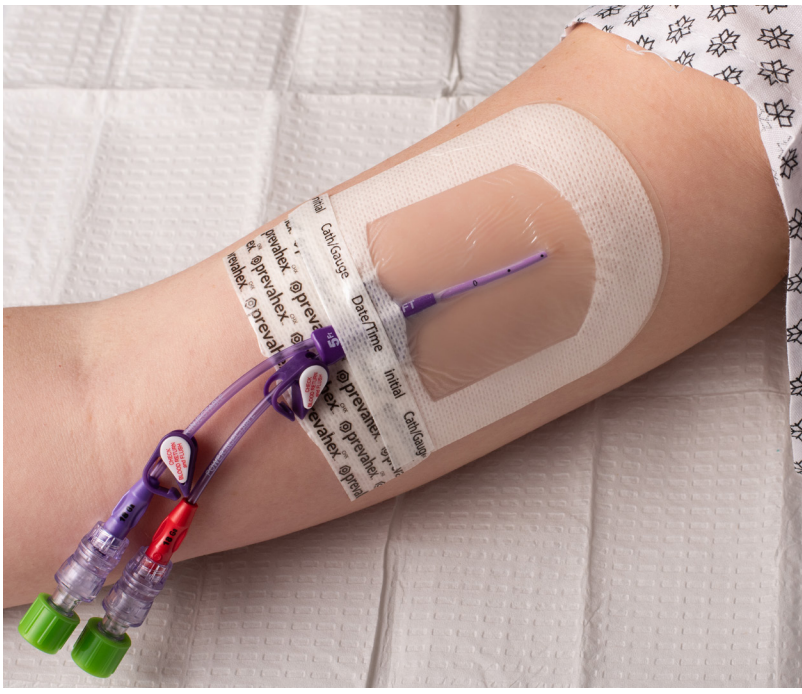
Mechanism of CRBSI Development

The most common mechanism by which CRBSIs occur is via an extraluminal route, resulting from translocation of bacteria from the patient's skin flora, as transient bacteria, via the hands of caregivers, or because of breaks in techniques during maintenance. This problem is compounded by rapid bacterial re-colonization that occurs within hours of application of a skin antiseptic at the time of catheter insertion. Microorganisms proceed to migrate from the catheter insertion point onto the catheter surface. Colonies of bacteria invariably form biofilms on the surfaces of medical devices and pose a significant infection threat. Biofilms form despite the host immune response. Moreover, the organisms within are well-known to be resistant to antimicrobial therapy due to the masking effect of a fibrinous matrix composed of proteins, platelets, and other organic materials. Research has shown that biofilms may develop within three days of catheter insertion and increase in size and numbers particularly in short-term catheters (inserted for ≤14 days).[17, 18] Detaching cell aggregates or individual cells originating from the mature biofilm has been demonstrated to be the source of a variety of infections including CRBSI. An intervention that enhances antisepsis at the catheter insertion area would therefore appear to be an important prevention strategy.

Chlorhexidine effectiveness

Chlorhexidine has been researched since the 1950s[19] and has become widely included in medical products used in procedures conducted in health care settings for prevention of bacterial proliferation on the human body.[20] Chlorhexidine is a broad-spectrum antiseptic effective against gram-positive and gram-negative bacteria, aerobic and anaerobic bacteria, and fungi.[21] Furthermore, the use of chlorhexidine on skin can prevent the transmission of organisms frequently associated with CRBSI, such as methicillin-sensitive (MSSA) and methicillin-resistant Staphylococcus aureus (MRSA).[22] The mechanism of chlorhexidine action on bacterial organisms is well understood. Chlorhexidine is a cationic surfactant and works by causing severe disruption to the osmotic equilibrium of the permeation barrier on the negatively charged cell membrane of the pathogenic organism. Leakage of potassium and other elements results in cellular destruction.

As a result of extensive research, chlorhexidine has been used in a wide variety of medical applications: as hand hygiene and surgical scrub solutions, as a part of pre-operative and bathing protocols for



skin decolonization, used as an oral antiseptic intended for reduction of respiratory infection, as a skin antiseptic during IV catheter insertion, and introduced in recent years as an additive on the surface of IV dressings as a means to curtail the growth and subsequent introduction of microorganisms into the bloodstream.

Antiseptic dressing studies

Protecting the skin is a critical factor in preventing infections originating at IV puncture sites. A key prevention initiative is to properly dress the catheter insertion site. Ullman and colleagues described the principles of a central venous access device (CVAD) dressing to prevent associated complications as "... providing a barrier to microbial colonization and contamination.... [while] providing these functions using coating, adhesion, antimicrobial properties, absorbency, moisture vapor transmission...and maintaining visibility of the insertion site".[23] It is important to note that skin is never completely sterilized even after the application of an antiseptic prior to catheter insertion.[24] The shielding action of site dressings is only effective when the surrounding environment does not allow organisms to proliferate. Human body temperature, environmental humidity, and sweating are contributors to microbial growth under IV dressings. The next step in the evolution of dressing design attempted to address the problem of moisture accumulation. In the 1990s, manufacturers developed occlusive polyurethane dressings that provided semi-permeability to oxygen and water. The transparent nature of these materials, which allowed for easier visual site assessment by the clinician, became an important feature in quality medical care leading to wide adoption across patient settings. Despite this advancement, polyurethane dressings were reported to be associated with higher occurrences of CRBSI.[25] The short efficacy periods of skin antiseptics combined with creation of environments under polyurethane dressings that allowed for rapid organism growth are likely contributors to increased rates of infection.

The next step in the evolution of IV dressings was the development of products with antiseptic-impregnated coatings utilizing the chlorhexidine antimicrobial to protect the catheter site from bacterial proliferation. Dressings containing CHG are the most common on the market today. Two principal types of CHG-impregnated products have been extensively used, a polyurethane foam disc placed over the insertion site and an occlusive dressing, designed with a coating or with an antiseptic containing gel component on the dressing surface.

Is there evidence that dressing products containing CHG are effective in reducing the incidences of catheter colonization and CRBSI? Recently published meta-analyses and reviews have closely examined this fundamental question.[26-29] The authors of these articles reviewed 20 randomized controlled trials (RCTs) and 2 quasi-experimental (before/after) studies published between 1998 and 2018. Safdar and colleagues analyzed 9 trials enrolling 6067 patients with a total of 11,214 catheters.[26] The study characteristics were varied, including insertor specialty, skin antiseptic, type of CVAD, insertion site, dressing changes, and of particular importance, the authors used various definitions for catheter colonization and CRBSI. Most studies in the analysis used a CHG-impregnated disc, with one study using an integrated CHG dressing. Overall, the studies indicated that 6.5% of catheters were colonized in the groups using CHG-impregnated dressings while 13.2% of catheters were colonized in the control groups. Six of nine trials favored the CHG-impregnated dressing for reducing CRBSI, demonstrating a 1.2% rate versus 2.3% in the comparator groups. In patients with malignancy and in adult intensive-care unit (ICU) patients the authors found a statistically significant benefit in using antiseptic-impregnated products. Several limitations are noted: none of the studies were double blinded, increasing risk of bias; only two studies performed molecular identification of isolated organisms to establish concordance between blood, catheter tip, and hub isolates; the studies had varied populations, settings, catheter types, reasons for use, as well as differences in accepted practices for prevention of CRBSI.

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The second meta-analysis published in 2019, assessed 13 RCTS that included 7,555 patients and 11,931 catheters.[27] Studies included in the review differed in populations, settings, skin antiseptic used, site control, and importantly, the definitions used for CRBSI and catheter colonization. The incidence of CRBSI in the RCTs was reported to be 1.3% in the chlorhexidine group and 2.5% in the control group. Five of the 13 studies indicated a significant reduction in the incidence of CRBSI. In addition, sub-group analysis showed that use of a CHG dressing significantly decreased rates of CRBSI in both ICU and non-ICU patients. Seven RCTs reported a catheter colonization rate of 5.5% in the CHG dressing group and 11.8% in the control group. Several limitations should be noted. Products used in the studies differed, six using a CHG sponge and seven used a CHG dressing, with differing CHG concentrations. Rates differentiating use of a CHG sponge vs. a CHG dressing were not reported. In addition, populations were not separated in this analysis, perhaps influencing heterogenicity.

Wei and colleagues' 2019 meta-analysis included 12 RCTs and concluded a significant reduction in CRBSI and catheter colonization, however these findings were limited to those studies with sample sizes >200. (28) The rate of CRBSI was reported as 15.2% in the CHG group and 26.3% in the control group. As with the other reviews, the studies were determined to vary in study populations, settings, and definitions of infection and colonization. Frequency of dressing changes was not considered due to the data limitations.

The most recently published meta-analysis addressing the effect of CHG dressings on the prevention of bloodstream infection included additional studies, totaling 20 RCTs.[29] This analysis is the most comprehensive of the four reviews presented here. Overall, the CRBSI rate was reduced by 33% (CRBSI rates: 2.0% in the CHG group and 3.2% in the control group). CRBSI rates were significantly reduced regardless of the type of dressing used, CHG-impregnated disc or dressing; in high-quality studies conducted among ICU patients; for short-term CVADs; and in studies where the frequency of dressing change was similar in both groups. The findings did not support CHG dressing use among neonatal or pediatric populations. The authors suggest that CHG dressings be used on patients with short-term catheters based on the understanding that during the period of use, bacteria causing infection to originate from skin colonization of the insertion site. Studies in this analysis were reported to include inadequate statistical power, the preventive practices used during insertion, and the variety of skin antiseptics. The authors suggest that CHG dressings may be preferred to CHG discs based on ease of application and ability to provide visualization of the insertion site.

If the meta-analyses indicated that salt-based chlorhexidine dressings were largely effective in reducing CRBSI rates, then why pursue further improvements? The answer lays in the findings stemming from new research that may fundamentally lead to the next level in the evolution of CRBSI prevention.

Chlorhexidine formulations and the next evolution in antiseptic dressings

It is important to note that not all formulations of chlorhexidine are the same. During early research on pure chlorhexidine (also known as free base chlorhexidine), researchers identified the preparation as having poor solubility characteristics due to its molecular structure which includes a diverse combination of both hydrophilic and hydrophobic functional groups, thus limiting its role as an antiseptic in health care products. In response, industrial scientists adopted an approach of chemically modifying chlorhexidine molecules with a weak acid leading to the development of a variety of chlorhexidine salt formulations including chlorhexidine digluconate (CHG) and chlorhexidine diacetate (CHA), compounds which improved antiseptic solubility. While several of these salts were found to exhibit significantly improved solubility, this salt formulation strategy came at the expense of reduced chemical availability for reaction due to ionic binding and steric restriction of the

chlorhexidine molecule itself. Currently available chlorhexidine-based IV dressings are manufactured in varying concentrations and configurations using salt-based technology that was initially developed six decades ago.[30] The studies reviewed in this white paper used these types of products as the intervention for each trial.

If the meta-analyses indicated that salt-based chlorhexidine dressings were largely effective in reducing CRBSI rates, then why pursue further improvements? The answer lays in the findings stemming from new research that may fundamentally lead to the next level in the evolution of CRBSI prevention. A recent study published in the Journal of Wound Care examines the in vitro antimicrobial effects of a chlorhexidine (CHA) and silver salt-based antimicrobial dressing against a novel free-base chlorhexidine (CHX) dressing. The methodology of the study takes into account a key factor: the researchers inoculated samples of both dressing types with microorganisms that are most often implicated as causative pathogens in CRBSI events, namely Candida species, *Enterococcus* species, *Enterobacteriaceae*, and *Staphylococcus epidermidis*, as well as sensitive and resistant strains of *Staphylococcus aureus.*[31] After inoculation with each test organism, assessment was conducted to determine the $\log_{10}$ reduction of the pathogens at days 1, 3 and 7. The time frames were chosen to reflect recommendations from the CDC's clinical practice guidelines for maintenance of IV catheters.[32] A minimum of three inoculated sample dressings of each type, including non-antimicrobial controls, were used at each experimental time point. Microorganisms were extracted from each sample dressing, plated, and inoculated on growth media, and counted using standard microbiologic methods. A benchmark of 4.0 $\log_{10}$ reduction was used to define substantial antimicrobial dressing efficacy.

The first significant finding of this study indicates that the CHX dressing demonstrated a superior in vitro antimicrobial effect at 67% of the experimental time points than the CHA dressing, with at least equivalent efficacy at all other testing time points. The antimicrobial effect of the CHX dressing was also determined to be more rapid than the CHA dressing particularly at the 1-day time point. The CHX dressing achieved a >5.0 $\log_{10}$ reduction at the 7-day period against eleven of the twelve test organisms, whereas the CHA dressing demonstrated such reduction in only seven test organisms. This finding suggests that a dressing using CHX technology may provide enhanced protection against microorganism over-growth over the recommended 7-day *in vivo* life span of IV dressings. This is supported by the finding that the CHX dressing demonstrated significant $\log_{10}$ reductions versus the CHA dressing across most time points among organisms noted to be frequent pathogens associated with CRBSI, namely Methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus faecium*, and Candida species.

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A second important outcome reported in this study regards chlorhexidine content. Speculation would indicate that provision of a higher quantity of chlorhexidine would translate to a higher level of microbial kill. Manufacturer information indicates that the CHX polymer film has a chlorhexidine concentration of 0.27mg/cm^2, while the CHA adhesive film contains 0.42mg/cm^2 chlorhexidine salt which corresponds to a 36% greater chlorhexidine mole content. Why in this study would a lower chlorhexidine concentration product achieve higher antimicrobial activity? The answer, in part is attributed to the fact that chlorhexidine molecules within the adhesive in the conventional CHA dressing are ionically bound to acetate anions in a reversible, equilibrium reaction which thus limits the available concentration of chemically unhindered chlorhexidine molecules at any given time. Furthermore, the CHA dressing also included 0.5% wt/wt silver salts as well as a cationic triarylmethane dye which are both capable of forming chemical complexes that may moderate the release chlorhexidine and therefore effect the overall antimicrobial performance. In contrast, the adhesive in the CHX dressing does not contain any

of these additional chemical components present in the CHA dressing. For these reasons, the proportion of unbound and chemically available antimicrobial chlorhexidine molecules is generally expected to be significantly higher in a CHX-based dressing than in a CHA-based dressing of similar design. A reduced total chlorhexidine content may be of benefit when considering the existence of patient events involving skin sensitivity or rare allergic reactions when exposed to chlorhexidine formulations.[33]

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Expanding the Protection of Intravenous Catheter Insertion Sites

2021 will mark 20 years since the inception of the Institute for Healthcare Improvement's (IHI) program to reduce CRBSI in ICU patients with CVCs. Although later expanded to include patients on non-ICU wards, the initiative did not include catheters other than CVCs. The scientific literature, however, provides extensive information on blood stream infections (BSIs) associated with many other types of IV catheters that are currently standard medical devices used in a wide variety of healthcare settings. One of the multimodal strategies of infection prevention programs recommends the use of an integrated approach of healthcare systems, applying change where broad issues are identified as being inadequate.[34] Assessment of processes and practices related to IV insertion and maintenance indicates the need for implementation of a national and comprehensive strategy called HOB,[35] which includes expansion of infection surveillance that focuses on capturing all IV catheters in all settings and institutes a standard of care that comprises scientifically supported interventions and novel technologies, forming the next level in the evolution of BSI prevention.

The evidence for instituting HOB is extensive. In a comprehensive review of forty-nine studies examining BSI occurring with the use of arterial catheters, O'Horo and colleagues identified 222 cases in 30,841 devices and occurred at a rate similar to what has been reported for infections associated with short-term CVCs (1.6 infections/1000 catheter days).[36] In one large observational study of nearly 500 patients receiving hemodialysis, the cumulative risk of CRBSI exceeded 50% within 6 months of initial treatment.[37] In examining clinical outcomes among a large number of dialysis center patients, researchers reported that hospitalization occurred in 67% of those patients with S. aureus CRBSI, 34% with S. epidermidis, and 40% of those with gram negative bacteria.[38] The Making Dialysis Safer for Patients Coalition, a quality group in partnership with the CDC,[39] has published a list of interventions which assist in forming a basic prevention program prior to introducing newly researched components.

Peripherally inserted central catheters, alternative IV devices also used for administration of life-saving medications, have been associated with rates of BSI equal to those of other CVCs, including those placed in jugular vein sites in ICU patients. In a landmark analysis of 200 published studies examining the rates of CRBSI, the authors reported a pooled PICC-associated BSI rate of 2.4%.[40] The authors conclude the article with an insightful statement which provides impetus to the need to establish HOB programs: "Since almost all the national effort and progress to date to reduce the risk of IV device-related Infection have focused on short-term noncuffed CVCs used in Intensive care units, Infection control programs must now strive to consistently apply essential control measures and preventive technologies with all types of IV devices".

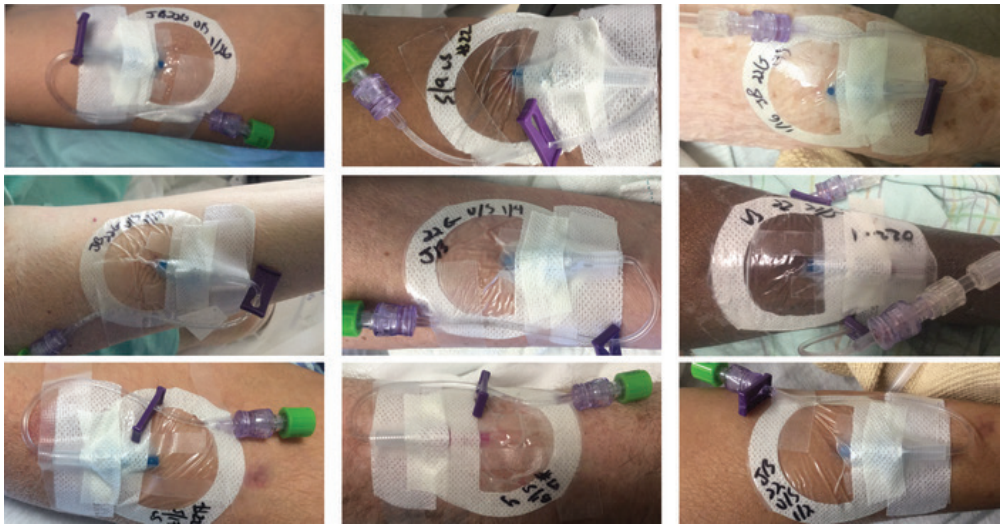
Midlines have gained popularity in clinical practice, often used as an alternate device for CVCs. Medical records of patients receiving midlines in 12 hospitals were reviewed. The reported rates of major complications were reported as 2.2% for occlusion, 1.4% for upper-extremity DVT, and 0.3% for BSI and, importantly, were often associated with the removal of the device.[40]

Among the most underreported infections are those associated with the use of PIV catheters. Despite the vast numbers of PIV inserted as well as its extensive

application in all healthcare settings, BSIs associated with this device are not part of any mandatory reporting surveillance system in the United States.[2] PIV usage is far greater than that of CVCs and therefore accounts for an absolute infection rate that approaches the rate for CVCs.[42] One recent study of BSIs caused by S. aureus indicated that 20.4% of all the non-CLABSI events were related to the use of a PIV alone.[43] It becomes increasingly important to ensure that IV dressings endure and are effective until the completion of therapy given revisions in the INS Standards that recommend dressing replacement from 48-72 hours to when clinically indicated.[44] Evidence is emerging that novel CHX dressings provide a significant advancement in CRBSI prevention. In the United States, peripheral IV (PIV) catheter failure rates average 53%, or, better stated, 1 of every 2 catheter insertions fail to make it to end of treatment.[45, 46] Infiltrations, extravasations, occlusions, dislodgement, or phlebitis cause most failures.[45] In the May/June 2019 publication of the Journal of Infusion Nursing, Dr. Helm provides an update to his peer reviewed article published in 2015. He claims that "...Phlebitis is largely a misnomer — one that has significantly helped decrease progress in eliminating the general problem of SPC failure. Redness, warmth, pain, and even drainage at an insertion site are not the signs and symptoms of an inflamed vein well below the skin surface, but rather a localized catheter skin insertion-site infection."[47]

A recent Six Sigma designed study conducted with a goal of achieving 1 PIV catheter per patient, compared complication outcomes using a standard IV dressing versus a CHX dressing used as a critical component in the bundle in the intervention strategy. Assessment of each PIV was conducted during initial placement and during daily rounds with symptoms and complications documented into a cloud-based computer app. In the standard dressing group, the authors reported a complication rate of 40%, with the CHX dressing group exhibiting only a 11% complication rate. Moreover, in the 11% of those who had complications, 0% cited the CHX dressing as a site symptomatic issue vs. 61% cited the standard dressing as a site symptomatic issue. This implies that the dressing played a huge role in preventing infection at the PIVC site due to its immediate and prolonged suppression of bacterial growth. In addition, 89% of catheters in the CHX intervention group achieved end of therapy time frames vs. 15% for catheters in the standard group.[48]

PIV5R Group 2: Standard Work, EVB-Best Practice



This table, pulled from the study "Reaching one peripheral intravenous catheter (PIVC) per patient visit with lean multimodal strategy: the PIV5Rights bundle." showcases the dressing that helped to reduce complications that could have contributed to PIVC failure.

Advanced CHG Dressings in the Evolution of CRBSI Prevention

With the advent of new and emerging polymer materials and manufacturing techniques, it has recently become possible for industrial chemists and engineers to develop medical device materials which utilize the full, antimicrobial power of chlorhexidine free base. The next generation of IV dressings may significantly contribute to a new standard in the evolution of CRBSI prevention by providing edge-to-edge broad-spectrum antimicrobial effectiveness over the recommended lifespan of all IV dressings, and without the need for salt formulations of the antimicrobial moiety. The emerging technology of CHX IV dressings provides these new advantages while utilizing chlorhexidine at lower overall concentrations, as well as allowing for insertion site visualization using transparent film material. ■

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