Antimicrobial IV Dressings:
Algide AG® versus Chlorhexidine Gluconate
Approximately 250,000 central line-associated bloodstream infections are acquired each year in US hospitals with death occurring in 28,000 cases [1], [2]. The average cost to treat each patient is estimated to be $29,156 and places a $2.3 billion burden on the United States healthcare system each year [1]. Additionally, the Centers for Medicare and Medicaid have classified central line-associated blood stream infections as “never events” preventing hospitals from obtaining reimbursement for treating these infections, further amplifying the burden on the healthcare system [3]. The prevalence and designation of central line-associated bloodstream infections as “never events” highlights the importance of preventing these nosocomial infections. To combat these infections, intravenous (IV) dressings have been developed to prevent blood borne infections originating from intravenous lines.

Chlorhexidine Gluconate (CHG) impregnated dressings and silver alginate dressings represent the two primary classes of antimicrobial IV dressings. CHG is a common antiseptic used in numerous medical applications for its robust antibiotic effect on bacteria. Silver alginate dressings obtain their antibiotic properties through the release of silver ions that have been well documented for antiseptic applications since ancient times. DeRoyal has developed a novel wound dressing called Algidex AG® that incorporates maltodextrin into the silver alginate matrix. The purpose of this paper is to summarize the antibacterial mechanisms of action, to compare the potential for antibacterial resistance and to compare the safety of CHG and silver for use in humans to highlight the advantages of the Algidex AG® IV patch for patients with catheter access sites.

Mechanisms of Action for Antibacterial Properties of CHG and Algidex AG®

The mechanisms of action for the antibiotic properties of CHG, silver, and maltodextrin are important to the understand of the benefits and risks associated with each compound in preventing IV line associated infection. Chlorhexidine (CHL), discovered in 1954, is a strong antiseptic with widespread use in medicine due to its strong bacteriostatic, bactericidal, and fungicidal activity. Since CHL is insoluble in water, clinical solutions are formulated with gluconic (CHG) or acetic acid (CHA) to disinfect patient skin, medical equipment, and surfaces in medical centers. The antimicrobial properties of CHL arise from the net cationic charge of the molecules that permits binding to the negatively charged phospholipids on the bacterial cell disrupting the cell wall [4]. Once the cell wall has been ruptured, the CHL molecule crosses the cell membrane and lyses the cell body by binding to negative charges on the intracellular membrane. This action leads to apoptosis of the bacterium. This antibacterial mechanism acts rapidly causing cell death in 20 seconds [5]. Clinical studies have also shown that the CHL molecule binds to skin proteins allowing the slow release of bound CHL thus prolonging the duration of the antibacterial environment [6]; however, this interaction with human cells can lead to individuals develop sensitivities or allergies to CHL that can cause adverse reactions and affect skin integrity.

Antimicrobial IV Dressings: Algidex AG® versus Chlorhexidine Gluconate

Figure 1: Zone of inhibition tests results comparing Algidex IV dressing to CHG IV dressing*
Algidx AG® combines the antibacterial properties of silver ions and maltodextrin to create a unique multipronged attack on bacteria. Similar to CHG, silver ions bind to negative charges on the bacteria cell wall to disrupt the wall integrity allowing silver ions to diffuse across the cell membrane. Once inside the cell, the silver ion binds to intracellular structures interfering with several bacterial processes that result in cell death of the bacterium. These processes include disruption of the cell membrane, interfering with organelle function, disrupting organelle membranes, impairing cellular respiration, denaturing intracellular enzymes, RNA, and DNA, and disrupting metabolic events modulated by other ions [7], [8]. The maltodextrin incorporated into the Algidx AG® IV dressing matrix has been demonstrated to create an acidic environment that is not conducive to bacteria survival, and upsets osmotic gradients which disrupt the cell wall and cell membrane [9], [10]. These properties of maltodextrin are thought to increase the antibacterial properties of Algidx AG® IV patch that is designed to act as an anti-bacterial barrier to bacteria that commonly infect IV access points. Figure 1 demonstrates that Algidx AG® IV dressing is equivalent at inhibiting bacterial growth for MRSA and standard Staph aureus compared to a CHG impregnated IV dressing, and that Algidx AG® is superior to the CHG impregnated IV dressing at inhibiting the gram negative bacteria Pseudomon a aeruginosa as determined from standard zone of inhibition tests. A similar independent study demonstrated that the Algidx AG® IV patch exhibits similar antibiotic properties to the same CHG impregnated IV dressings and was more effective than other silver dressings compared in the study [11]. A clinical study in very low birth weight infants demonstrated that the Algidx AG® IV dressings decreased infection rates by 45.8% in patients with central lines compared to no antimicrobial dressing, an important finding considering CHG is cautioned against use in neonates due to porous fragile skin [12]. Furthermore, Algidx AG® has been shown to be safe in neonates as no adverse events were reported for Algidx AG® IV dressings in two studies involving 114 NICU patients [12], [13]. The wound healing properties of Algidx AG® dressings have recently been demonstrated through effective treatment of chronic tracheostomy ulcers in PICU patients without causing adverse skin reactions [14]. These clinical findings support the clinical effectiveness of Algidx AG® dressings and support Algidx AG® IV dressings as a viable alternative to CHG impregnated IV dressings. To fully appreciate the advantages of the Algidx AG® IV patch over CHG impregnated dressings, a review of potential bacterial resistance and safety in humans of each dressing is warranted.

Potential bacterial resistance to CHG and Algidx AG®

Microbial resistance to antimicrobial agents has been a major concern for clinicians and scientist since the advent of antibiotics in 1937. The wide spread use of antibiotics in medicine has led to an explosion of antibiotic resistant strands of bacteria that led to superbugs immune to powerful antibiotics that thrive in and plague medical centers throughout the world. The resistance of bacteria to antibiotic agents developed from native genetic elements in bacterium that mutated and rapidly evolved to survive antibiotic exposure. In fact, several years before penicillin was introduced for clinical use, scientist identified the first antibiotic resistance enzyme, penicillinase, that neutralized penicillin before damaging and killing the targeted bacteria. Following the introduction of penicillin to the clinic, antibiotic resistance quickly spread among different species of bacteria leading to widespread resistance through transmission of genetic material via bacterial plasmids and up-regulation of self-preserving genes [15]. Scientists have realized that widespread antibacterial resistance is due to a number of contributing factors that include the inability of antibiotics to kill all individual bacteria cells, through exposure of bacteria to non-lethal levels of antibiotic molecules, and the unfortunate conglomeration of different bacterial strands that naturally occurs in medical centers transferring genetic material. These realizations motivated research that led to the development of modern artificial antiseptics like CHL to combat resistant bacteria that colonize most modern medical centers; however, scientific research is starting to indicate that bacteria are gaining resistance to these agents through similar mechanisms that foster resistance to antibacterial drugs. The specific mechanisms of bacterial resistance to CHG, silver, and maltodextrin and potential for clinical relevant resistance will be briefly discussed.

Potential bacterial resistance to chlorhexidine

Chlorhexidine is the current antiseptic of choice in the clinical community due to its rapid bactericidal mechanisms; however, this widespread use has led to the identification of several genetic markers indicating antibacterial microbes are developing resistance to CHL. Several studies and review articles have highlighted the presence of resistance mechanisms to CHL in bacteria strains obtained from clinical isolates and clinical professionals[16]–[19]. Most research on bacterial resistance to CHL has focused on identifying the presence of efflux proteins that remove multiple types of antimicrobial molecules, including CHL, from the intracellular space of bacteria [17], [18]. In total, 11 known efflux proteins have been confirmed to be transport CHL out of the bacteria causing the minimal inhibitory concentration for CHL to increase in a given strand of bacteria [17]. A review by Horner et al. cites 18 studies that have identified presence of multidrug efflux genes in bacteria isolates obtained from the clinical environment and hospital personnel. Each of these studies demonstrated a decrease in susceptibility to CHL compared to standard wild type bacteria [17]. A study from a single hospital in Taiwan demonstrated a progression of increased resistance in bacteria isolates and increased prevalence of resistance in individual strands over 15 years (1990 – 2005, every five years) [17], [19]. Wang and colleagues hypothesized that the increased resistance and increased prevalence of resistance was due to
increased usage of CHL in hospital units. This hypothesis was supported by identifying an increase in the percentage of MRSA isolates that had a minimal inhibition concentration > 4 mg/L from 1.7% to 46.7% during the 15 year duration of the study [19]. Vali et al. performed extensive research to identify the frequency of biocide genes and study the effects of CHL exposure on clinical strains of MRSA [18]. Experiments designed to simulate conditions associated with surface disinfection demonstrated that CHL was less effective on clinical strains compared to control strains not previously exposed to CHL. Additionally, minimal effects of CHL were observed on control and clinical isolates following a CHL residual test designed to simulate residuals that may be present on surfaces in the hospital. These results demonstrate that clinical isolates have acquired CHL resistance features and establish a plausible method for bacteria naïve to CHL to develop resistance. This study also identified an increased resistance to antibiotics in control strains of bacteria following the CHL residue test suggesting CHL exposure in the hospital environment may evoke increased antibacterial resistance in bacteria that survives CHL disinfection. Vali and colleagues conclude that reduced susceptibility to CHL is a serious concern and stresses the importance of continuously assessing the susceptibility of clinical MRSA to CHL exposure to evaluate the protocols designed to prevent nosocomial infections at individual medical centers [18].

The review by Horner et al. and the studies by Vali et al. and Wang et al. demonstrate that current well established resistance mechanisms are being adapted by bacteria to contend with CHL and other antiseptics; however, it was not until recently that a specific bacterial protein was identified that specifically functions to remove CHL from bacteria. Hassan et al. recently characterized a family of CHL efflux proteins originally identified in Acinetobacter baumannii clinical isolates that have been shown to survive exposure to clinically relevant CHL concentrations of at least 1%. The new class of CHL efflux proteins was identified through a whole-genome microarray that showed an unidentified protein was overexpressed following CHL exposure. The researchers transfected the gene to encode for this protein into E. coli and demonstrated that the transfected line had increased resistance to CHL compared to control E. coli confirming the role of the protein. Additional experiments utilized tryptophan fluorescence quenching to demonstrate the specificity of the protein to exclusively bind CHL by comparing fluorescence levels induced by CHL to 11 additional antimicrobial compounds [16]. While not addressed in the paper, the authors inferred in a press release that the clinical isolates used in this study originated from medical facilities in Iraq and Afghanistan that treated injured soldiers where A. baumannii was observed to develop superbug antibiotic resistance, and cite its ability to survive exposure to disinfectants like CHL as the primary reason for developing marked antibiotic resistance [20]. Clearly, these studies summarize a continuous increase in bacterial resistance to CHL and highlight the risk of widespread use of CHL in the clinic without proper controls to prevent bacteria from developing effective resistance to CHL.

The clinical relevance of the documented bacterial CHL resistance in clinical isolates is heavily debated in the medical community. The primary reason for this debate is limited documentation of catheter associated blood infections that resulted from CHL resistant gram positive bacteria commonly implicated in nosocomial acquired infections; however, there are numerous reports of nosocomial catheter-associated bloodstream infections resulting from CHL contaminated with gram negative bacteria. The most commonly cited bacteria associated with contaminated CHL solutions that cause catheter related bloodstream infections is Burkholderia cepacia (formerly Pseudomonas cepacia) [21]–[24]. In each of these epidemic reports, the outbreak was determined to be caused by bacteria present in purified water used to dilute high concentration CHL solutions to concentrations that ranged between 0.5% to 2.5% that were used to disinfect catheter access sites. Rose et al. showed that the MIC and MBC for CHL to inhibit B. cepacia was greater than 100 mg/L demonstrating significant resistance of this bacteria to CHL [25]. The four epidemic reports combined with Rose et al. demonstrates that CHL is not an effective antiseptic against all bacteria species.

Archomobacter xylosoxidans have also been shown to cause catheter related bloodstream infection through contamination of CHL. The first report on an outbreak of catheter-related bacteremia due to A. xylosoxidans contamination of CHL occurred in a hemodialysis unit where the disinfectant was used to clean vascular access point. In this case, the bacteria were localized to an atomizer used to spray CHL on the skin before placement and during maintenance of dialysis catheters. Testing of the ionized water used to dilute the CHL from 5 to 2.5% were negative for bacterial growth indicating that the bacteria had colonized directly into the atomizer that contained the CHL [26]. This report represented the second study to implicate contaminated CHL in a delivery vessel and the first to implicate A. xylosoxidans in causing bloodstream infections [26], [27]. An outbreak of A. xylosoxidans infection was also described in a neonatal care unit that was attributed to CHL used to disinfect skin. In this report, 52 patients were determined to be colonized with CHL resistant bacteria and 8 developed an infection. Five of the eight had positive blood culture samples and the other three had positive cerebral spinal fluid cultures. All infections resolved with appropriate antibiotic treatment and no deaths were attributed to the infection. The bacteria was found to be colonized in all vessels containing the antiseptic and on one faucet in the unit leading the authors to hypothesize that the contamination of CHL occurred when staff washed the exterior of the CHL vessels [28]. This report highlights the importance of a multitier approach to infection control. The report indicates that CHL was heavily used in the NICU but not in other areas of the hospital which was offered as a reason why the infection epidemic was contained in the NICU.
Silver is the primary antimicrobial component of the Algidex AG® IV patch. Silver has been employed as an antimicrobial agent to combat infection. Potential bacterial resistance to silver has not adopted additional antimicrobial strategies to combat infection. Bacterial resistance to CHL will continue to increase with heavy application of CHL in the clinic, especially if medical centers do not adopt additional antimicrobial strategies to combat infection. Alarmingly, the majority of these studies reporting on CHL resistance have been published in the last 10 years and corresponds with the increased adoption of CHL for clinical use. The history that describes the development of bacterial resistance to CHL is disconcerting and is similar to the development of antibacterial resistance that has become widespread. At the discovery of CHL, there was no known resistance to the molecule; however, 61 years later, scientists are discovering that bacteria are slowly developing resistance to CHL through similar mechanisms that gave rise to the antibacterial resistant superbugs. The study found that the most common infection type was bloodstream infections.

The study was conducted on all patients with S. aureus infections from 2001 to 2011 to determine trends associated with infection and disease type. Additionally, all isolates obtained during this period were analyzed for the presence of qacA/B genes that encode for efflux channels associated with CHL removal. The study found that the qacA/B gene was initially found to be present in 7.6% of 156 isolates tested at qacA/B emergence in 2007; however, by the end of the study in 2011, 22.2% of the isolates had obtained the qacA/B gene. The authors indicate that the percent increase in qacA/B positive isolates significantly increased each year, and found that the increase in CHL resistance was correlated with increased infection in patients that received hematopoietic stem cell transplant (HSCT) or had acute myelogenous leukemia (AML). Additionally, isolates that obtained the qacA/B gene were found to gain resistance to ciprofloxacin commonly used to treat infections in the unit. Interestingly, the qacA/B gene was not detected until two years after the unit adopted CHL as the antiseptic of choice for disinfecting the skin prior to placement of a central venous line or peripheral arterial catheter. Although qacA/B prevalence occurred only after the introduction of CHL to the unit, overall infections from S. aureus did decrease during the study suggesting CHL had a positive impact; however, the authors note that increased resistance to CHL is concerning and state that the full clinical significance is not understood. A major concern raised by the authors was the increase in proportion of infections in AML and HSCT patients, the patients with the highest exposure to CHL[29]. While heavy CHL usage in these patients could not be directly implicated, this study is the first to provide statistically relevant evidence that supports CHL resistance as a causality of S. aureus blood stream infections.

Potential bacterial resistance to silver

Silver is the primary antimicrobial component of the Algidex AG® IV patch. Silver has been employed as an antimicrobial agent in infection control since ancient times as a method to disinfect water and to treat infections [30]. As with any biocide, bacteria exposed to silver can develop resistance mechanisms against future exposure due to selective pressure placed on the bacteria population through similar mechanisms discussed for CHL. The increased use of silver in the medical environment has raised concerns of bacteria developing a resistance to silver. Similarly to CHL, a number of studies have identified strands of bacteria that have developed a resistance to silver [31]–[36]; however, other studies have demonstrated that bacterial silver resistance is rare and transmission of genetic information for resistant mechanism is difficult [30], [37]–[41]. There are two known primary mechanisms through which bacteria can gain resistance to silver, active efflux and non-active periplasmic proteins. Active efflux proteins are encoded by qac genes similar to the qacA/B gene associated with increased resistance to CHL, and have been documented in several studies [36], [41], [42]. The active efflux protein is embedded in the cell wall of the bacteria and functions to remove silver before it can cross the cell membrane. Efflux proteins actively transport silver ions out of the cell either through an energy dependent ATPase mechanism or a chemiosmotic cation/proton antiporter [42]. Non-active periplasmic proteins are mediated by genes found in bacterial plasmids and functions by binding ionic silver rendering it inactive [36], [41], [42]. The only confirmed plasmid to contain genes that encode proteins that bind silver is pMG101 [36]. Plasmid pMG101 was originally isolated from bacteria that caused an outbreak of antibiotic/silver resistant Salmonella typhimurium and contains nine genes in three transcription units specific to silver resistance [31], [36]. A separate study has shown that the pMG 101 plasmid can be transferred to E. coli in laboratory conditions, increasing bacterial resistance to silver via periplasmic proteins [43]. Besides the studies summarized here, the exact mechanisms responsible for bacterial silver resistance are unknown and require additional research before the full scope of bacterial resistance to silver is fully understood.

Bacterial resistance to silver has been reported sporadically since the advent of silver nitrate products applied to burns in the 1970's. Despite these isolated reports of silver resistant bacteria; there is little clinical evidence that support emerging clinically relevant bacterial silver resistance that is similar to the resistance seen for antibiotics and the emerging resistance to other antiseptics like CHL. Recent studies aimed at identifying silver resistant genes in clinical isolates have demonstrated the rarity of silver resistant genes in antibiotic resistant bacteria [37], [39]. Percival et al. screened 112 bacterial isolates obtained from diabetic foot ulcers in one clinic for silver resistance genes. The study found that only two isolates of Enterobacter cloacae
contained silver resistant genes, but noted this bacteria species is rarely implicated in wound infections. Furthermore, application of a silver-containing dressing to the isolated E. cloacae exhibiting silver resistance genes killed all strains following 48 hours of exposure. All other isolates, including known wound pathogens (24 isolates of S. aureus and 9 isolates of P. aeruginosa), did not contain genes that encode for silver resistance [37]. Loh et al. investigated the prevalence of silver resistant genes in MRSA (n=33) and methicillin-resistant coagulase-negative staphylococci (MR-CNS, n=8) isolates obtained from nasal and wound sources in both humans and animals. Only three isolates in the study were found to contain a silver resistance gene and all three isolates were found to be susceptible to clinically relevant levels of silver exposure [39]. Both of these studies demonstrate that the prevalence of silver resistance genes is low and that the presence of silver resistant genes does not necessarily translate to protection from silver when the resistant bacteria is exposed to therapeutic levels of silver ions.

The use of silver in modern medicine has steadily increased since the original application of silver nitrates in burns. Silver is used to control and prevent infection in a variety of applications that includes burns, chronic wounds, and acute wounds (i.e. surgical incision and IV sites). Resistance to silver has been studied since the 1970’s; however, reported cases of silver resistance are rare and there is little evidence indicating an emerging bacterial resistance to silver as has been seen with CHL [38], [41]. As with any antiseptic, the increased use of silver in the clinic will increase exposure of antibacterial resistant bacteria to silver raising the potential for significant silver resistance to develop. Clinical researchers should continue to monitor the prevalence of silver resistant genes and bacteria; however, the risk of clinical bacteria isolates developing a clinically relevant resistance is minimal. The low potential for bacterial resistance to silver is best illustrated by comparing the history of silver to the history of modern antiseptics and antibiotics. Bacteria have been exposed to sub-clinical levels of silver ions for over 4 billion years and applied at clinically relevant levels for “modern” medical purposes for over 200 years without bacteria developing clinically relevant silver resistance [30], [41]. Scientists speculate that the primary reason why bacteria have not developed an effective resistance against silver is due to the multiple mechanisms through which silver damages and kills individual bacteria compared to the single killing mechanism of antibiotics and antiseptics associated with bacterial resistance developed within the 70 years of clinical use [8].

Potential bacterial resistance to maltodextrin

Maltodextrin is a high molecular weight polysaccharide. Application of polysaccharide (i.e. sugar) in wound healing dates back to ancient times, and sugar was first documented as a method for treating ulcers in 1714 [44]. Simple granulated sugar [45], honey [46], and high molecular weight polysaccharides (i.e. maltodextrin) [47] have all been utilized in wound care and have been characterized to have excellent antimicrobial activity due to high glucose content. The antimicrobial properties from high glucose content arise from the acidic environment and high osmotic gradients that disrupts normal bacterial function [9], [10], [48]. To date, no bacterial resistance to sugar mediated wound care products has been documented. Two recent studies have demonstrated that bacteria resistance could not be evoked following stepwise exposure to honey in S. aureus, P. aeruginosa, E. Coli, and S. epidermidis strands [49], [50]. The acidic environment and osmotic gradients established by the high glucose content of the honey was cited as the primary reasons why the tested bacteria did not develop resistance mechanisms to the honey. The failure of these experiments to create resistance in bacteria strains known to rapidly develop antibiotic resistance demonstrates the low likelihood of bacteria developing a resistance to glucose based antimicrobial agents. The unique addition of maltodextrin into DeRoyal’s silver alginate wound dressing gives AlgideX AG® an advantage over traditional silver alginates as the beneficial antimicrobial actions of silver and polysaccharides are combined for synergistic antimicrobial activity, and minimizes the potential for bacteria to develop resistance to AlgideX AG® wound dressing when applied in the clinic.

Safety of CHG impregnated and AlgideX AG® IV Dressings

Safety of CHG impregnated dressings

Chlorhexidine is generally considered safe by the clinical community and is the antiseptic of choice due to the prolonged antibacterial action from CHL binding to human cells; however, in some instances, CHL interaction with cells can lead individuals to develop sensitivities or allergies that can cause serious adverse events. Studies have estimated the incidence of allergies or sensitization to CHL range between 0.5 to 13.1% [51]; however, these rates increase for patients that are very sick, immunocompromised, have venous insufficiency, or have received chronic or repetitive treatment with CHL products [4], [51]–[53]. In addition to patients, healthcare workers that are continuously exposed to CHL have been shown to be at an increased risk for developing an occupational allergy to CHL [54], [55]. Allergic reactions to CHL are typically manifested as contact dermatitis; however, case reports also indicate that CHL can cause immediate urticaria, immediate anaphylactic shock, or anaphylactic shock after repeated exposure.
Initial manifestation of CHL sensitization is typically seen as contact dermatitis characterized by local inflammation and reddening of the skin accompanied by burning and itching sensations. Contact dermatitis onset can be delayed up to 24 to 48 hours and can take 14 to 28 days to resolve [56]. Since CHL is an underappreciated allergen in the medical community, contact dermatitis induced by CHL is often misdiagnosed inadvertently increasing the risk that a patient will experience a more severe allergic reaction in future exposures to CHL [53]. In rare cases, patients may experience immediate urticarial and/or anaphylaxis shock [4]. Urticaria, commonly referred to as hives, is characterized by red, itchy, raised areas of skin that vary in size and can appear anywhere on the body following exposure to CHL or other allergens. Urticaria can resolve within hours of allergen removal or last for several days or weeks [58]. Anaphylactic reactions represent a serious whole body allergic reaction that is characterized by a rapid onset of symptoms. Symptoms of anaphylaxis include urticarial, flushing, and itchiness of the skin, soft tissue swelling, shortness of breath, nausea, and arrhythmia. Anaphylactic shock is life threatening if symptoms are not treated immediately. While anaphylaxis can develop acutely due to CHL exposure, most cases of anaphylactic shock occur after repeated CHL exposure and following an associated mild allergic reaction that went undiagnosed [51]–[53]. Repetitive exposure to CHL is clearly a concern in the medical community as CHL usage continues to increase in the clinic. Clinical researchers now recommend allergic testing for CHL allergies prior to hospitalization in an effort to prevent severe anaphylactic reactions [4], [51]–[53].

Despite the documented increase incidence of CHL allergic reactions, the usage of CHL continues to increase in the clinic and multiple companies have developed CHL impregnated devices in an attempt to prevent nosocomial infections, including the CHG impregnated IV dressings Biopatch® and Tegaderm® CHG. These dressings are designed to continuously expose the IV site to CHG to prevent nosocomial catheter related infections for up to seven days. Both dressings are secured with an occlusive dressing as is standard for IV dressings. Safety and efficacy studies that compared each CHG dressing to a standard non-antimicrobial dressing revealed contact dermatitis occurred in 1.49% (Biopatch®) and 2.3%(Tegaderm® CHG) of dressing changes [57], [58]; however the rates of contact dermatitis are likely greater than these figures as the authors indicate that “contact dermatitis usually occurred for a single catheter per patient” indicating patient contact dermatitis prevalence is likely greater. Clinical studies have reported that CHG IV dressings can cause pressure necrosis, scarring or severe sponge-associated contact dermatitis at a rate of 5.6% in pediatric patients and up to 15% in neonates [52], [59]–[61]. These complications and associated complication rates indicate that CHG IV dressings may not be ideal for use in pediatric patients. In all cases reporting adverse skin events related to the CHG IV dressing, very critically ill patients were identified to have an increased risk of developing skin lesions associated with the CHG dressing [52], [57]–[61]. With prevalence of CHL sensitization estimated to be as high as 13.1% in adults, more research is needed to fully understand the risks of CHL sensitization or allergy and to further investigate the safety of CHG impregnated IV dressings [51].

The neurotoxicity of CHL represents another safety concern in application of CHG impregnated dressings for protecting neuraxial anesthesia access catheters from infection. A study in 1955 demonstrated that CHG caused meningeal adhesions and neural cell death when the chemical was injected into the cerebral spinal fluid of monkeys [62], and a separate study in 1984 confirmed the neurotoxicity of CHL through direct injection of the chemical in the anterior chamber of the eye causing marked and dose-dependent degeneration of adrenergic nerves in rodents [63]. These studies prompted the US Physician’s Desk Reference Manual to warn that “CHG is for external use only. Keep out of eyes and ears and avoid contact with meninges”, and led to many manufacturers to contraindicate the application of CHL products for spinal procedures including neuraxial anesthesia [64]; however, despite these warning, clinicians have used CHL products off label for antisepsis to prevent bacterial infection in neuraxial procedures. While studies have shown CHG antisepsis have a low complication rate in these procedures [65], there are at least three confirmed cases of CHG evoked adhesive arachnoiditis and six additional potential cases with similar symptom progressions [66], [67]. The first case that received wide publicity occurred in 2001. A woman received epidural anesthesia to prevent pain during an elective caesarean section. The patient debilitated rapidly progressing to a paraplegic with limited use of her arms in the following weeks. In 2007, a judge awarded civil damages due to “a measurable quantity of CHL (defined as 0.1 mL)” contaminating the anesthesia [68]. In 2012, a medical expert that testified in the original case and disagreed with the judgment released an editorial, admitting he was wrong in claiming CHL was not responsible for the adhesive arachnoiditis during the litigation. His opinion changed due to a similar case in a patient where a known quantity (8 mL) of CHG was injected in the subdural space. In both cases, the deterioration of the patient was very similar including the time course of presenting symptoms, rapid neurological deterioration, need for ventricular shunting to treat hydrocephalous, and progressing to paraplegia with upper limb involvement. The similarities between the two cases forced Bogod to change his opinion; however, he notes the amount injected in the 2001 case was significantly less and likely only a residual amount [66]. Killeen et al. reported on an additional case that occurred in 2011 and compiled a list of six additional cases with similar deterioration noted in patient without a confirmed cause of adhesive arachnoiditis. In this case, the authors report that the applied CHL was allowed to air dry for three minutes according to standard operating procedures before the epidural procedure was performed, and that there was no indication of CHL pooling prior to inserting the epidural catheter. While no direct evidence of CHL contamination was obtained, the authors concluded through a process of elimination that CHL contamination was the likely cause of the neurologic complications suffered by the patient [67]. Killeen et al also suggested the additional identified cases were also caused by CHL contamination due to similarities between the present case and the prior cases with confirmed CHL exposure described by Bogod [66], [67].
Despite documented evidence that CHL can cause neurologic complications, most anesthesiologist discount these cases due to the belief that trace amounts of CHL cannot cause adhesive arachnoiditis or other neurologic complications. A recent study investigated the effects of diluted CHL on plated neurons and Schwann cells to determine the potency of trace CHL. The researchers applied serial dilutions of 2% CHG and 10% povidone-iodine to investigate cytotoxicity of these antiseptics on human neuronal and rat Schwann cells. The investigation found that CHL was cytotoxic for neurons and Schwann cells at all concentrations tested including a 200x dilution that is well below concentration used in the clinic [69]. This finding provides supporting evidence that trace amounts of CHL cause cell death of neurons as well as the myelin producing Schwann cells giving credence to the conclusion that trace CHL could have caused the debilitating adhesive arachnoiditis in the documented cases.

Absorption of CHG through the skin into the bloodstream is the major reason why the CDC recommends against using the chemical on infants less than 2 months of age. The implications of the absorption into the bloodstream are not well understood; however, the neurotoxicity of CHL chemicals is a major concern. Chapman et al. recently reported CHG in the blood stream in 10 of 20 preterm infants that ranged between 1.6 and 206 ng/ml following cleansing of skin with CHG prior to placement of a PICC line. Seven of these infants experienced their highest concentration of CHG 2 to 3 days after exposure to CHG suggesting that the binding of CHG to skin cells can lead to further absorption in infants [70]. Milstone et al recently tested these concentrations of CHG on cerebellar granule neurons and found that these trace amounts of CHG causes inhibition of L1 cell adhesion molecule preventing proper development of the neurons. Such effects of CHG in vivo could potentially have devastating developmental consequences in neonates and more research is needed to understand if CHG can cross the blood brain barrier to damage neural tissue [71]. These studies demonstrate that CHL concentrations significantly below clinical concentrations can cause substantial damage to neurological tissue. Further research is needed to fully understand the potential risks of neurological damage associated with CHL in at risk populations.

Safety of the Algidx AG® IV dressing

Silver, in the ionic form, is an emerging antimicrobial material that is receiving increased interest from the medical community to fight infection. As previously discussed, ionic silver prevents infection through a multltier approach that disrupts the cell wall and membrane, interferes with organelle function, impairs cellular respiration, denatures intracellular enzymes, RNA, and DNA, and disrupts metabolic events modulated by other ions [7], [8]. These multiple mechanisms of ionic silver decrease the likelihood that bacteria will develop a resistance to silver treatment. In addition to silver, the DeRoyal® Algidx AG® IV patch includes maltodextrin which has been shown to have antibacterial and wound healing properties [10], [47]. Together, ionic silver and maltodextrin create an optimal antimicrobial environment that is effective at preventing infection. The safety of the Algidx AG® IV patch in humans will be briefly discussed.

Silver is generally considered non-toxic unless silver is absorbed in great amounts (2000 ng/ml). At 2000 ng/ml, Argyria, a syndrome characterized by deposition of silver in tissue leading to graying of skin, and can cause growth retardation, disturbed hemopoiesis, and cardiac, hepatic, and renal dysfunction. No clinical symptoms have been reported in adults with moderately elevated concentrations of silver (<1000 ng/ml) [72]; however, toxicity may occur below these levels in infants as indicated by one case report where the infant was reported to have a silver concentration of 323 ng/ml [73]. In terms of Algidx AG® IV patches, patients are not expected to absorb silver in amounts that exceed safe clinical values. In the study by Khattak et al., the highest reported silver absorption value in 25 patients was 103 ng/ml, three times below the silver serum reported in the case report; however, the reported average silver serum silver was 7.6±20.93 ng/ml for all infants and 22.5±40.4 ng/ml for infants below 750 g (n=6)[12]. Estimated daily exposure to silver in these patients was between 62 and 124 μg/day which is approximately 100 times less than the parenteral dosages required to cause toxicity in animals and enteral dosages reported to cause toxicity in humans [12]. If the CDC assumption of 20% dermal absorption is correct, then potential silver exposure from an Algidx AG® IV patch is almost 1000 times less than doses expected to cause silver toxicity [74]. These estimates by Khattak and colleagues are supported by the fact that no infant included in the study experienced an adverse event related to silver despite being more susceptible to absorbing silver than older patients [12]. Absorption of silver from an Algidx AG® IV patch significantly decreases for the patient population at age 2 years, as skin is more permeable during the first two years of life, increasing the safety factor of the Algidx AG® IV patch with patient age [75].

Silver allergic reaction exists; however, they are very rare in a clinical setting. Delayed contact hypersensitivity most often occurs in people exposed to silver on a daily basis due to occupation. Clinically, silver allergy is most likely to develop in burn patients treated with silver products. These patients develop a silver allergy due to prolonged silver exposure and increased absorption of silver through damaged skin [76]. The risks of patients developing an allergy to silver in the Algidx AG® IV patch are considered to be very low. Maltodextrin is considered generally non allergenic since the molecule is constructed from glucose units linked together by glycosidic bonds. The only allergic concern associated with maltodextrin is residual gluten proteins sometimes present following manufacturing of maltodextrin. A report released by the European food safety authority found that maltodextrins may contain low levels of proteins and peptides capable of causing an allergic reaction; however the levels
of protein needed to cause an allergic reaction is not known and concluded that residual proteins in maltodextrin are likely not sufficient to cause a severe allergic reaction in susceptible individuals [77]. These observations for silver and maltodextrin clearly support the safety of the Algidex AG® IV patch for use in humans.

**FDA MAUDE Database CHG IV Patches versus Algidex AG® IV Patch**

The clinical literature reports a wide range of adverse event prevalence associated with CHG impregnated IV dressings. Large clinical evaluations by a French group reported a low adverse event rates of 1.49% for Biopatch® and 2.3% for Tegaderm® CHG for individual dressing changes, but did not report the adverse event rates on per patient basis [57], [58]. Other studies have reported chlorhexidine sensitivities in the general population as high as 13.1% in adults [51] and 15% in neonates [52]. Most of the adverse events associated with CHG impregnated IV dressings are likely considered minor and typically are only reported in a clinical journal when the adverse event had a profound impact on a patient's care. One of the best qualitative measures to assess a device's safety in the clinic is the MAUDE database that reports malfunctions and adverse events attributed to the device while utilized in a patient's care. The MAUDE database was queried to identify the number of records reporting adverse events for the Biopatch®, Tegaderm® CHG, and Algidex AG® IV patch to better understand prevalence of adverse events for these antimicrobial IV dressings.

A MAUDE database search for the term “Biopatch” returned 183 records dating back to 1994; however, one hundred eighty of these records were reported after January 2000 [78]. The MAUDE records were categorized as adverse skin reactions, infection, device malfunction, anaphylaxis reaction, unknown events, and events not related to the Biopatch® dressing. Adverse skin reactions were reported in 122 records or 67% of all records. In most records reporting a skin reaction, patients often experienced redness of the skin and itching sensations at the dressing location indicating sensitivity to the dressing material. A large cohort of patients experienced skin breakdown under the Biopatch® leading to ulcer formation commonly associated with grade 2 or 3 burns. At least 28 of the patients that developed full thickness ulcers where CHL products were used to prep the skin for catheter placement. One of these reports described a case of toxic epidermal necrolysis that led to eventual death of a patient that had a serious adverse reaction attributed to the CHG in the Biopatch®. In 36 reports (20%), the Biopatch® was implicated in causing an infection in the treated patient. In one case, the end user reported a 40% increase in infection rate following a trial of the Biopatch®. Additionally, 22% of these cases were reported for patients undergoing dialysis. There are 19 reports of device malfunction; however 12 of these reports were attributed to the Biopatch® adversely affecting the patient's care. In most of the 12 cases, the Biopatch® was implicated in sticking to catheter causing the catheter to be removed from the patient. Additionally, the Biopatch® dressing was implicated in three cases of anaphylaxis shock following treatment of CHL sensitive patients with multiple CHL products. The Biopatch® was used in 16 or 9% (2 unknown, 14 not related) events that did not directly implicate the dressing in causing the reported adverse event [78].

The search term “Tegaderm® CHG” was used to identify adverse events in the MAUDE database that were attributed to the Tegaderm® CHG IV dressing [79]. One hundred twenty five records were returned that dated back to 2008, and were categorized as adverse skin reactions, infection, device malfunction, and events not related to the Tegaderm® CHG IV dressing. Adverse skin reactions were reported in 118 of the 125 records (94%). The majority of adverse skin reactions reported the formation of full thickness ulcers caused by the Tegaderm® CHG dressing. A small number of the reports described minor skin reactions similar to contact dermatitis. In 17 of the reports, a CHL based antiseptic was used to clean the skin before placing the catheter implicating repeated exposure to CHL in the observed skin reaction. Infection attributed to the Tegaderm® CHG dressing was reported in 17 cases (14%). There were only two reports of device malfunction, but in each case, the patient was adversely affected through the removal of the catheter stuck to the Tegaderm® dressing. The Tegaderm® CHG IV dressing was mentioned in three reports reporting on failure of a second device (catheter) that was covered by the dressing. In these cases, the Tegaderm® CHG dressing was not implicated in the reported adverse event [79].

The MAUDE database was queried with the search term “Algidex” and returned only one record; however the record did not report on an adverse event that directly involved the Algidex AG® IV dressing [80]. The returned record reported on the infiltration of five catheters into the body involving four patients. An Algidex AG® IV patch was used to dress the catheter insertion points, but the adverse event report did not implicate the dressing. The Algidex AG® IV patch was approved for use by the FDA in 2004 and in ten years of use, no adverse events reported to MAUDE database have been attributed to the Algidex AG® IV patch demonstrating the exemplary safety record of the product [80].

MAUDE database searches for the Biopatch®, Tegaderm® CHG, and Algidex AG® IV dressings revealed significant qualitative trends that can be used to assess the safety of CHG impregnated IV dressings compared to the Algidex AG® IV dressing. Over 100 reported serious adverse events exist for both the Biopatch® and Tegaderm® CHG IV dressings with the majority of these events involving injury to the skin. Within each dataset, most patients suffered an adverse skin injury following continuous exposure to CHG over a significant period of time (typically greater than seven days) and received multiple CHG dressings
before symptoms of the injury developed. In some cases, CHG antiseptic skin cleanser was used to disinfect the skin before placing the catheter and the CHG impregnated dressing around or over IV. This action increased the patient’s exposure to the CHG and likely contributed to the adverse event. In most of the patients with skin injuries, the patients were very ill, had compromised or fragile skin, were receiving chemotherapy or dialysis, suffered organ failure, were immunocompromised or had a surgery that utilized multiple CHG impregnated devices. These categories of susceptible patients match patient types cited in the literature as susceptible to CHG reactions; however, most patients that are admitted for continuous or critical care fit within one or more of these categories at some point during their hospitalization. Blood stream infections were identified as adverse events for both CHG impregnated dressings supporting the findings in the literature that suggests CHL is not effective against all strands of bacteria. In most of these cases, the infection was preceded by skin ulceration or breakdown caused by overexposure to CHG creating an ideal environment for bacteria proliferation. Interestingly, only 3 of the 183 adverse events associated with the Biopatch® were reported from 1994 until 2000. This six year period most likely represents inconsistent reporting of adverse events to the MAUDE database; however this period could also be representative of increased incidence of CHL sensitization referenced in the literature. If the former, then approximately 77 cases (12 per year) were likely not reported during this time frame for the Biopatch®. In total, 305 reports involved one of the two leading CHG impregnated IV dressings compared to 1 the unrelated report involving the Algixex AG® IV dressing. This profound difference in number of MAUDE reports for CHG impregnated dressings compared to the reports for the Algixex AG® IV dressing qualitatively supports superior safety of the Algixex AG® IV dressing compared to CHG IV dressings.
This review highlighted the strengths and closely examined the weaknesses of both CHL and ionic silver as antiseptic agents for the prevention of central-line associated bloodstream infections. Chlorhexidine is a proven antiseptic that has seen a rapid increase in clinical utilization due to the emergence of antibacterial resistant bacteria strands. The mechanism of action for CHL kills most bacteria within 20 seconds and exerts a prolonged effect; however, there are emerging safety concerns due to a documented increase in bacterial resistance and increased prevalence of CHL sensitivities and allergies that is attributed to overreliance and indiscriminate use of CHL in medical clinics worldwide. Adverse skin reactions are the most commonly cited complication associated with CHL and is consistently attributed to repeated and continuous exposure to CHL from impregnated medical devices. These concerns surrounding CHL clinical usage have led researchers to investigate new antiseptic techniques and agents to help maintain safe and clean clinical environments, especially in maintaining clean environments surrounding catheters placed in the body.

Ionic silver as an antiseptic has seen a reemergence in modern medicine due to its effective multifaceted antimicrobial mechanism of action and safety in humans. Silver allergies are documented to be very rare often requiring large amounts of silver absorption before humans develop a silver sensitivity. Additionally, silver wound dressings have not caused serious ulceration of skin as has been documented for CHG impregnated dressings. While bacterial mechanisms to resist silver antisepsis exists, research has shown that these mechanisms are rare, not easily transferrable, and do not necessarily provide effective resistance against silver ions. Potential for bacteria to develop effective resistance to silver is considered to be minimal as no significant resistance mechanism has developed despite bacterial exposure to silver for over 4 million years and over a thousand year history of human antiseptic use. The innovation of adding maltodextrin into the silver matrix of the Algidex AG® IV dressing creates a synergistic antimicrobial medical device combining the antibacterial properties of a polysaccharide and silver. Maltodextrin is considered safe and generally non-allergenic. Like silver, the bacterial resistance to maltodextrin is unlikely as the antibacterial properties of polysaccharides have been maintained since ancient times.

Both chlorhexidine and silver products like the Algidex AG® IV patch have a place in clinical antisepsis protocols; however, the benefits and risks must be considered. In the clinic, the goal is to prevent nosocomial infection without endangering the patient to other risks. The widespread usage of CHL products threatens to increase CHL bacteria resistance similarly to the documented rapid rise of bacterial resistance to antibiotics. Medical clinics should adopt a multifaceted antisepsis protocol that includes more than one antiseptic to effectively fight bacteria with antibiotic resistance. Additionally, there is a growing trend of patients developing sensitivity or allergies to CHL from prolonged or repetitive exposure to the chemical. Reducing exposure of patients to CHL should be a priority in medical centers that exclusively use CHL for antisepsis. The Algidex AG® IV patch represents one method to significantly reduce patient exposure to CHL in medical facilities that use CHG impregnated dressings to manage inserted catheters. The safety record of the Algidex AG® IV dressing compared to CHG impregnated IV dressings is outstanding as indicated by clinical reports and records in the MAUDE database. The Algidex AG® IV dressing has been shown to have similar efficacy CHG dressings at inhibiting bacteria growth and combined with a superior safety record make it the ideal antimicrobial barrier dressing for inclusion in CLABSI prevention bundles designed to reduce the risk of nosocomial catheter related bloodstream infections in the clinic.
References


