Central vascular access devices are essential tools in the delivery of chemotherapy to patients with cancer; however, they also are potential sources of infection for this immunocompromised population. A peripherally inserted central catheter (PICC) is a type of central vascular access device typically inserted into the basilic or cephalic veins of the upper arm above the antecubital fossa. In an effort to prevent and reduce central line–associated bloodstream infections (CLABSI), the Centers for Disease Control and Prevention (CDC) recommend a minimum concentration of 0.5% chlorhexidine gluconate (CHG) in an alcohol solution as the preferred topical antiseptic (prior to the insertion of central lines), for skin care during dressing changes, or when accessing implanted ports (O’Grady et al., 2011; Safer Healthcare Now!, 2009). In a meta-analysis by Chaiyakunapruk, Veenstra, Lipsky, and Saint (2002), the rate of catheter-related bloodstream infections (CRBSI) was reported to be lower (1%) in patients with catheter sites disinfected with CHG compared to a rate of 2% when povidone-iodine (polyvinylpyrrolidone iodine [PVP-I]) was used. Findings from the meta-analysis supported a reduction in CRBSI by 49% (risk ratio = 0.51, 95% confidence interval [0.27, 0.97]) when CHG versus PVP-I was used as a disinfectant for insertion site care. The current state of evidence on topical antiseptics has CHG designated as the skin antiseptic of choice since 2002 (O’Grady et al., 2011), with reported economic benefits in the prevention of CLABSI by reducing the costs associated with central line infections (Chaiyakunapruk, Veenstra, Lipsky, Sullivan, & Saint, 2003). CHG, a water-soluble, cationic biguanide, topical antiseptic with broad-spectrum antimicrobial activity, has been in use since the 1950s (Denton, 2001; Milstone, Passaretti, & Perl, 2008). The antimicrobial mechanism of action for CHG varies by concentration (0.05%–4%), formulation (i.e., aqueous or alcohol solution), and pH (optimal at 5.5–7). At low concentrations, CHG exhibits bacteriostatic properties and binds to the negatively charged cytoplasmic membrane (inner cell wall) of bacteria, causing cell membrane disruption and leakage of cell components. Bactericidal properties of CHG are observed at higher concentrations, causing congealing and denaturation of the cytoplasm and, eventually, cell death (McDonnell & Russell, 1999; Milstone et al., 2008). CHG has a broad-spectrum of antimicrobial activity and mechanism of action against a number of aerobic and anaerobic gram-positive and gram-negative bacteria, some Chlamydia trachomatis, certain fungi, and...
certain enveloped viruses (i.e., cytomegalovirus, HIV, influenza, herpes simplex virus 1 and 2, and respiratory syncytial virus). CHG is inactive against mycobacteria, bacterial spores, and some gram-negative bacteria that have cell walls impermeable to CHG (Kampf & Kramer, 2004). Contraindications to the use of CHG include previous sensitivity or allergic reaction when exposed to products that contain chlorhexidine. Those products might include preoperative antiseptic solutions, hand rub antiseptics or washes, or skin care products such as make-up.

Tincture of iodine (an iodophor) or 70% alcohol both are good alternate options for antisepsis when CHG is contraindicated (O’Grady et al., 2011). The combined antiseptic effects of CHG with alcohol are greater than either solution alone. Alcohol in concentrations of 70% has excellent gram-negative and gram-positive bactericidal coverage, and good virucidal activity against enveloped viruses (Larson, 1988). CHG binds to the stratum corneum for six hours, providing excellent sustained residual activity with minimal inactivity from exposure to organic matter, and has a cumulative effect to maximize bactericidal activity (Crosby & Mares, 2001; Larson, 1988; Stokowski, 2010). Unfortunately, the effect of repeated long-term exposure of alcohol on the integrity of central vascular access devices is unknown, leading manufacturers of certain types of polyurethane and silicone catheters to discourage the use of alcohol-based products for routine access device care and maintenance (Alyangar, Crone, Crnich, & Maki, 2002; Crnich, Halfmann, Crone, & Maki, 2005). To minimize the risk of damaging catheter integrity, many healthcare institutions have adopted a CHG aqueous (CHGA)-based solution for central line care. Although a CHG alcohol-based solution may provide broader spectrum antimicrobial coverage than CHGA, PVP-I, or PVP-I alcohol-based formulas in reducing the risk of CLABSI (Larson, 1988), no evidence exists to date to unequivocally identify the best antiseptic for the prevention of CLABSI (O’Grady et al., 2011). Consequently, whether any of the combined alcohol formulations have superior cutaneous antiseptic properties compared to CHGA or what the impact of a combined formulation is on the integrity of the skin is unknown.

Clinical Manifestations and Diagnosis

Since the introduction of CHG into the practice of routine central line dressing care in the early 2000s, oncology nurses have observed a skin irritation localized to the dressing area and insertion site of PICCs. The initial presentation manifests as a scalded skin appearance (burn) with papules and/or vesicles on an erythematous patchy background with possible weeping and/or edema present (see Figure 1). The rash often is preceded by a burning sensation in the area when exposed to CHGA 2% antiseptic to cleanse the skin around the PICC insertion site during dressing changes. More recently, anecdotal speculation has arisen that certain chemotherapy regimens may be associated with these skin changes. Patients with cancer receiving continuous fluorouracil or a taxane chemotherapy appear to be the most commonly affected population presenting to clinic with skin changes at their PICC site. Pruritis, scaling, and roughness were noted in some cases following the development of the initial acute skin changes.

Starting in 2002, two regimens using infusional 5-fluorouracil (5-FU) for the treatment of colorectal cancer (CRC) were introduced for use in Canada (B. Chin, personal communication, July 2011). Infusional schedules of 5-FU vary according to protocol and may typically infuse in 24 hours every two weeks for CRC regimens and may be continuous for seven days for six to seven weeks for other gastrointestinal cancer sites (BC Cancer Agency, 2011; Cancer Care Ontario, 2011). Analogous findings of irritant contact dermatitis (ICD) have been observed with the introduction of taxane-containing regimens for the adjuvant treatment of early-stage breast cancer. The timing of the introduction of protocols using 5-FU or taxanes and the corresponding skin changes at PICC sites leads to speculation by nursing staff that the combined effects of CHG on the skin and the administration of these two systemic chemotherapies may contribute to ICD.

Rietschel (2004) proposed a conceptual framework for diagnosing ICD that is in keeping with findings reported by oncology nurses. According to Rietschel (2004), ICD is the
likely diagnosis if the following major diagnostic criteria are present: (a) onset within minutes to hours following exposure (note: this may take repeated exposures but usually develops within two weeks of the most recent exposure), and (b) pain, burning, and stinging discomfort are experienced more than itching, particularly at early onset of clinical findings. Objective major criteria includes the presence of macular erythema, hyperkeratosis, or fissuring exceeding the presence of vesicles; glazed, parched, or scalded appearance; healing that usually occurs after exposure to the offending agent is ended (otherwise, this would suggest endogenous disease, such as eczema); and negative patch testing. Reitschel (2004) suggested the presence of pronounced pruritus over burning, stinging, or pain, as well as vesicular eruptions, increase the likelihood of allergic contact dermatitis (ACD). However, vesicles adjacent to patches of erythema, erosions, or bullae may suggest the presence of small differences in irritant concentration or exposure time, producing large differences in epidermal injury.

A thorough assessment and documentation of the morphologic skin changes and a careful history are essential to successfully identify the cause and treat the affected area while still maintaining PICC securement and access, preventing infections, and optimizing patient comfort. In this case, the physical findings and history are strongly suspect for a differential diagnosis of ICD secondary to repeated exposure of CHG. 2% topical antiseptic solution (Ale & Maibach, 2010; Reitschel, 2004). Definitions describing various differential diagnoses or subtypes of contact dermatitis as well as physical findings are outlined in Figure 2. Other differential diagnoses include eczema, Candidiasis cutaneous, cellulitis, impetigo, erysipelas, or drug eruptions (Hogan, 2009).

**Prevalence and Incidence**

Contact dermatitis is a highly prevalent skin disorder with irritants representing the underlying etiology in 80% of cases; only 20% of cases are the result of an allergen (Reitschel, 2004). ICD is found to be more common in patients age 50 and older (because of slowed epidermal cell regeneration) and in women who are employed in occupations with frequent hand washing, such as nursing and hairdressing. Hands are the most common site affected by ICD, followed by the inner forearm and eyelids. A history of endogenous skin reactions, such as eczema, also may influence the development of cutaneous reactions (Hogan, 2009; Reitschel, 2004). A wide variety of chemical and physical agents are responsible for prompting ICD, including frequent exposure to friction (e.g., repeated exposure of antiseptic scrubbing with dressing changes), water, soaps and detergents, and dry air (Reitschel, 2004). In addition, various formulations of CHG have been associated with contact dermatitis (Kampf & Kramer, 2004; Larson et al., 2006; Lasthein Anderson & Brandrup, 1985; Osmundsen, 1982; Reynolds & Harman, 1990), although limited evidence exists to support the incidence of ICD at central line sites as an adverse event caused by the use of this antiseptic solution. In a meta-analysis by Chaiyakunapruk et al. (2002), eight randomized controlled trials compare the effectiveness of CHG to 10% PVP-I skin antiseptic in the prevention of CLASBI. Of these eight studies, only one study (Maki, Ringer, & Alvarado, 1991) reported observed skin changes from the antiseptics used at the insertion sites. The insertion sites of the central lines treated with CHG were almost twice as likely (45%) as the 10% PVP-I treated sites (28%) to have erythema develop (p < 0.001) (Maki et al., 1991). Maki et al. (1991) reported this as a skin hypersensitivity reaction that may contribute to unnecessary removal of the central line because of suspicions of the erythema at the site representing infection. Ho and Litton (2006) conducted a meta-analysis evaluating the efficacy of CHG-impregnated dressings in preventing vascular and epidural catheter colonization and infection, reporting a 5.6% incidence of cutaneous reactions at the dressing site in neonates (Ho & Litton, 2006). To date, the incidence of cutaneous reactions related to topical antiseptic solutions may be under reported and underestimated. Additional research is needed to assess the incidence and prevalence of skin irritations from topical antiseptics.

**Pathophysiology**

The outermost layer of the skin (the stratum corneum barrier) is composed of 9–50 layers of keratin discs (corneocytes) surrounded by a thin layer of ceramides, cholesterol, and free fatty acids produced by the epidermal cells (keratinocytes) (Wickett & Visscher, 2006). The combined work of the keratin discs and epidermal cells serves to provide a protective seal preventing water loss and act as a barrier for normal skin defense. The introduction of an irritant results in alteration of the skin barrier (breaking down of the lipid barrier), epidermal cellular changes (atrophy of corneocytes), and cytokine activation. When the skin barrier is disrupted, irritants are able to make contact with the epidermal cells activating the release of proinflammatory cytokines that signal vascular and immune responses. The end result is vasodilation, increased vascular permeability, and an inflammatory response that produces symptoms of skin irritation such as redness, swelling, heat, and vesicle formation (Ale & Maibach, 2010; Kownatzki, 2003; Wickett & Visscher, 2006).
Irritants produce ICD and have the potential to elicit an immunogenic delayed hypersensitivity reaction by producing antigen-specific memory T cells associated with an ACD response (Ale & Maibach, 2010). Ale and Maibach (2010) emphasized that the early recognition and treatment of ICD may prevent the development of ACD.

Possible Contributing Factors

Regeneration of the stratum corneum is a continuous process; two to three weeks are needed for keratinocytes to mature and migrate to the surface, where they die and become keratin disks (corneocytes). The corneocytes are then gradually worn away with one layer sloughed off and replaced each day (Kownatzki, 2003; Wickett & Visscher, 2006). The process of normal epidermal growth and regeneration varies by age with those age 20 and younger able to renew epidermal cells every 14 days, and those age 50 and older renewing epidermal cells every 37 days. In the presence of advancing age, the lipid barrier and ceramides are altered, allowing for increased exposure and penetration to irritants and the slowing of the process of cell regeneration (Seyfarth, Schliemann, Antonove, & Elsner, 2011). Seyfarth et al. (2011) acknowledged that age plays a factor in the delay of the epidermal barrier regeneration following irritation, and contributes to ICD. In addition to age, a number of factors may coexist and may work in unison to increase the risk of ICD. According to Kartano and Maibach (2006), the tandem or sequential application of various physical and chemical irritants may produce a skin response that is different from repeated exposure to a single agent. Increased temperature, airflow, friction, and chemical agents may work synergistically or have an additive effect on the skin to produce ICD (Kartano & Maibach, 2006). A number of these factors coexist in patients with cancer receiving chemotherapy treatment through a PICC.

The presence of a PICC line dictates a standard of care that requires a weekly dressing maintenance schedule which introduces both mechanical and chemical insults to the skin. First, weekly chemical exposure occurs to CHGA 2% topical antiseptic solution, which is applied with friction to penetrate the epidermal layer of the skin to reduce bacterial load (Crosby & Mares, 2001). CHG is known to cause contact dermatitis and allergic sensitization (Ale & Maibach, 2010; Andersen & Brandrup, 1985). Second, application of an occlusive transparent cover dressing increases transepidermal water loss, damaging the protective barrier and enhancing penetration of the stratum corneum to CHG. In addition, the removal of the dressing may cause microtrauma to epidermal cells and the occlusive nature of the dressing may increase skin temperature, accelerating the cutaneous effects of an irritant (Kartano & Maibach, 2006). Finally, the average age of patients receiving systemic chemotherapy is typically 50 years or older. Systemic exposure of infusional fluorouracil or taxane chemotherapies are known to cause delayed cell division, and a delay in the regeneration or reparation of damaged epidermal cells (Heidary, Naik, & Burgin, 2008) combined with normal physiologic changes of slowed epidermal cell regeneration in patients age 50 and older (Farage, Miller, & Maibach, 2010; Seyfarth et al., 2011) may significantly contribute to delayed healing of traumatized skin.

Taxanes (paclitaxel) and antimetabolites (5-FU and capecitabine) are known to cause cutaneous reactions and may interfere or delay the regeneration of new keratinocytes (BC Cancer Agency, 2011; Heidary et al., 2008). Fluorouracil enters cells and interferes with the replication of rapidly dividing cells (including cancer cells) by preventing the conversion of folic acid to folinic acid, a building block for new DNA. Chemotherapy drugs that affect cells only when they are dividing are called cell-cycle specific (S-phase). Taxanes are spindle inhibitors preventing cell division, thereby interfering with the normal process of new epidermal cell formation. Chemotherapy is most effective at killing rapidly dividing cells and does not differentiate between cancerous cells and normal cells. Cutaneous skin reactions are a common side effect of antimetabolites and taxane chemotherapy. Atrophy of the epidermis takes place as a result of a decline in production of new corneocytes (Heidary et al., 2008). All of these factors combined may increase the penetration of irritants through the epidermis, accelerating damage, and triggering cytokine release and an inflammatory response of ICD.

Intervention and Treatment

A detailed physical examination of the affected area and a thorough history will help to define a differential diagnosis (Ale & Maibach, 2010; Reitschel, 2004). Current guidelines for the management of contact dermatitis recommend avoidance, protection, and substitution as the primary management methods (Bourke, Coulson, & English, 2009). Goals of treatment include the elimination of contact with irritant(s), the improvement of symptoms, and support for the healing process without complications. Practice at Royal Victoria Regional Health Centre (RVRHC) involves prompt withdrawal of the most likely offending agents (i.e., CHG and occlusive semipermeable dressing) followed by the substitution of a less irritating topical antiseptic, 10% PVP-I swabstick (10% PVP-I solution equivalent to 1% available iodine, nonmedicinal ingredients of purified water, and sodium hydroxide). That substitution is in keeping with CDC recommended alternative topical antiseptic cleansing solutions (O’Grady et al., 2011). Finally, protocol at RVRHC includes the application of a self-adhesive, soft, silicone-faced polyurethane foam island dressing with border (hypoallergenic without adhesive to absorb moisture). The skin irritation dramatically improves within 48 hours of the withdrawal of CHG and the transparent semipermeable dressing. When healed, the transparent semipermeable dressing is reintroduced with no recurrence in most cases.

The CDC has recommended the use of sterile gauze or a sterile transparent semipermeable dressing to cover central line sites (O’Grady et al., 2011); however, in the presence of

Preprinted Order Form

The Royal Victoria Regional Hospital Centre in Barrie, Ontario, Canada, has developed a preprinted order form for peripherally inserted central catheter site irritant contact dermatitis. To obtain a copy of the form, contact author Lia Kutzscher at kutzscherl@rvh.on.ca.
ICD, wound and skin care principles must be considered to promote healing (Haas & Moore-Higgs, 2010). A low-allergy adhesive (silicone-faced) polyurethane foam dressing has a number of advantages over gauze dressing for promoting healing of irritated skin, such as: (a) the absorption of exudate, (b) an outer cover that is breathable (which promotes the evaporation and escape of excess moisture), (c) an outer cover that provides protection from exposure to water and bacteria, (d) a nonadherent wound contact layer, and (e) required changing every seven days (Ashton et al., 2008). Gauze dressings require changing every 24–48 hours (O’Grady et al., 2011) and may potentially aggregate or delay the healing process by allowing irritated skin to dry and adhere to the gauze with the risk of further skin damage from the use of adhesive tapes to secure gauze.

Protection from other irritants or possible sensitizers such as, but not limited to, lanolin, topical antibiotics, or vitamin E-based creams or adhesive also is important (Ale & Maibach, 2010; Bourke et al., 2009). In the presence of a known or suspected adhesive allergy, the transparent semipermeable adhesive (silicone-faced) polyurethane foam dressing has a nonadherent wound contact layer, (d) an outer cover that is breathable (which promotes the evaporation and escape of excess moisture), (e) an outer cover that provides protection from exposure to water and bacteria, (d) a nonadherent wound contact layer, and (e) required changing every seven days (Ashton et al., 2008). Gauze dressings require changing every 24–48 hours (O’Grady et al., 2011) and may potentially aggregate or delay the healing process by allowing irritated skin to dry and adhere to the gauze with the risk of further skin damage from the use of adhesive tapes to secure gauze.

Implications for Practice

- A number of factors may contribute to the development of irritant contact dermatitis (ICD) at peripherally inserted central catheter (PICC) insertion sites, necessitating an in-depth history and assessment of the morphology, pattern, and site of the skin lesions.
- Burning, stinging, or itching at the PICC site when applying chlorhexidine gluconate antiseptic cleanser may be an early sign of ICD before a visible rash even appears. The proactive elimination of the suspected offending agent often resolves the skin irritation.
- Early recognition and management of ICD, while adhering to best practices in central line and skin care, can improve the patient care experience and prevent complications related to central lines.
In the absence of a recurrence, the skin irritation is likely ICD as a result of eliminating the offending causative agent, CHG. If the skin irritation continues, Bourke et al. (2009) and Ale and Maibach (2010) recommended patch testing to determine the source of the allergen; consideration of a referral to a dermatologist may be necessary. An evidence-based approach to ICD treatment can be found in Figure 3. In RVRHC’s clinical oncology practice, the rapid resolution of a rash after eliminating CHG has led to the hypothesis that the rash may be the result of an interaction between CHG and 5-FU or taxane chemotherapy, leading to increased sensitivity of the skin. Recent advances in cancer treatment now include the addition of epidermal growth factor receptor inhibitors and tyrosine kinase inhibitors that are known to have cutaneous toxicities (Heidary et al., 2008). These known side effects may serve to complicate this theory and the management of PICC site ICD in patients who may be receiving those forms of therapy.

Nursing Implications and Future Research

Damage and destruction of the first line of skin defense may be caused by a combination of repeated exposures of chemical or physical irritants, and a delayed response in skin cell regeneration could lead to the development of ICD at PICC insertion sites. In the process of writing this article, a literature review was performed by the author and yielded one study that suggested CHG topical antiseptic may contribute to ICD (Maki et al., 1991) and has raised the question of, in patients receiving chemotherapy, what factors contribute to the incidence of ICD at PICC sites? The development and implementation of a preprinted order set, as well as specific documentation of signs and symptoms of ICD on an electronic medical record, will provide an opportunity to monitor the incidence and compare the rate of occurrence in patients receiving chemotherapy. That will provide preliminary data for the development for future descriptive correlational studies to explore and detect factors contributing to ICD that would, subsequently, lead to the identification of patients with cancer who are at high risk of ICD at PICC sites. Clinical interventional research could then be initiated to evaluate the best practice for prevention of ICD while maintaining best antiseptic practice.

The impact on quality of life from skin irritation and the associated expense of increased central line care and maintenance caused by skin irritation is significant. Transpermeable membrane dressings are one-third of the cost of silicone-faced polyurethane foam dressings (about $1.50 versus $4.52, respectively), with costs collectively escalating with the increased frequency of dressing changes and nursing visits. Similarly, the morbidity and mortality risks associated with CLABSI also are a concern. Ideally, new standards for PICC site care could be established to prevent this problem in practice. Identification of susceptible high-risk patients would ensure employment of the best antiseptic alternatives to prevent ICD while maintaining best practices in the prevention of CLABSI. That also would ensure economic benefits in today’s cost-conscious environment.

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