Best Practices in Skin Care for the Multiple Sclerosis Patient Receiving Injectable Therapies

Lynn McEwan, NP, MScN, MSCN; Janet Brown, RN, MSCN; Josée Poirier, BSc, MSCN; Janene Spring, RN, BScN, MSCN; Judith Brouillette, RN, BSc, MScN, MSCN; Kathleen Carr, RN, MSCN; Christine Guérette, RN, BSc, MBA, MSCN; Colleen Harris, MN, NP, MSCN; Donna Howard, RN, BScN, MSCN; Diane Lowden, NMSc(A), MSCN; Nicolee Richard, BScN, MSCN

Although a cure for multiple sclerosis (MS) has not yet been discovered, a number of treatment options are available to help control symptoms, slow disease progression, and improve quality of life in patients with relapsing-remitting MS (RRMS). These include disease-modifying therapies (DMTs) such as beta-interferons, glatiramer acetate, and natalizumab. Disease-modifying therapies requiring frequent, self-administered injections can be particularly troublesome for some patients, as they may result in localized skin reactions at the injection site. A variety of injection-site reactions (ISRs) have been reported, including pain and erythema, lipoatrophy, abscesses and infections, necrosis, rash, swelling, and lumps. In order to appropriately distinguish between normal and abnormal reactions and to determine when further intervention is required, nurses involved in the care of patients with MS should be knowledgeable about the potential ISRs associated with DMTs. This best practices document was developed by a panel of Canadian MS clinic nurses in order to increase recognition among nurses that MS patients are at high risk for skin-site reactions with injectable therapies, and to provide the basis for skin-care practices in these patients. It reviews the risk factors associated with adverse skin reactions in MS patients treated with injectable therapies; the current attitudes and beliefs of nurses with respect to skin care; and the optimal skin-care interventions for MS patients at risk for adverse skin reactions when treated with injectable therapies. Areas requiring further research are discussed. ***Int J MS Care.*** **2010;12:177–189.**

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by the demyelination of nerve cells.[1] The most common form of the disease is relapsing-remitting MS (RRMS), in which patients experience multiple exacerbations over time. At present, there is no cure for MS; however, a number of treatment options are available to help control symptoms, slow disease progression, and improve quality of life in patients with RRMS. These include disease-modifying therapies (DMTs), which act on the immune system and modulate the inflammatory processes involved in the disease pathology.[2] Medications used for the treatment of RRMS include interferon beta-1a (IFNβ-1a; Avonex, Biogen Idec, Mississauga, Ontario, Canada, administered intramuscularly once weekly; or Rebif, EMD Serono, Mississauga, Ontario, Canada, administered subcutaneously 3 times per week), interferon beta-1b (IFNβ-1b; Betaseron, Bayer Inc, Toronto, Ontario, Canada; or Extavia, Novartis Pharmaceuticals Canada Inc, Dorval, Quebec, Canada; administered subcutaneously every 48 hours), glatiramer acetate (GA; Copaxone, Teva Canada Innovation, Montreal, Quebec, Canada; administered subcutaneously once daily), and natalizumab (Tysabri, Biogen Idec; administered intravenously every 4 weeks). The subcutaneously administered

From the London Health Sciences Centre Multiple Sclerosis Clinic, London, Ontario, Canada (LM); MS Clinic–Eastern Health, St. John's, Newfoundland, Canada (J Brown); Clinique Sclérose en Plaques, Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada (JP); Fraser Health MS Clinic, Burnaby Hospital, Burnaby, British Columbia, Canada (JS); Jewish General Hospital, Montreal, Quebec, Canada (J Brouillette); Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (KC); Clinique Neuro Rive-Sud and Hôpital Charles LeMoyne, Greenfield Park, Quebec, Canada (CG); Multiple Sclerosis Clinic, Foothills Medical Centre, Calgary, Alberta, Canada (CH); Teva Neuroscience, Montreal, Quebec, Canada (DH, NR); and Multiple Sclerosis Program, McGill University Health Centre, Montreal Neurological Hospital, Montreal, Quebec, Canada (DL). *Correspondence:* Lynn McEwan, NP, MScN, MSCN, LHSC University Hospital, Room

drugs requiring frequent, self-administered injections can be particularly troublesome for some patients, as they may result in localized skin reactions at the injection site.

The skin, or integument, is the largest organ, providing the body with protection against ultraviolet light, injury, and infection and helping to regulate body temperature. The skin receives about 30% of the body's cardiac output of oxygenated blood and contains nerve receptors to help the body adapt to an ever-changing environment. It is made up of two main layers—the outer epidermis, which constantly regenerates by shedding dead cells and bringing new cells up from the dermis layer, and the inner dermis, a thicker layer of dense connective tissue (Figure 1). When skin is normal and healthy, the surface does not differ from surrounding skin and is smooth to the touch. When the skin barrier is broken through injection, the door is opened to harmful environmental factors.

A variety of injection-site reactions (ISRs) have been reported with the DMTs, including pain and erythema, lipoatrophy, abscesses and infections, necrosis, rash, swelling, and lumps. Subcutaneous interferon beta (IFNβ) injections result in ISRs in 85% to 92% of MS patients during the early phase of treatment, as seen in the large pivotal trials.[3] In a prospective study of 60 patients on IFNβ therapy, 24% never experienced ISRs, 57% had an occasional reaction, and 19% had a reaction with each injection.[4] Women and smokers undergoing interferon therapy are reported to be more susceptible to adverse skin reactions, although the reason for this is not clear.[5,6] Mild erythema, induration, and pain are the most common adverse events associated with subcutaneous injection of GA.[7] Among 251 patients with RRMS randomly assigned to treatment with GA or placebo for 2 years, 66% to 90% of patients given GA developed an ISR, compared with 37% to 59% of patients who received the placebo.[7,8]

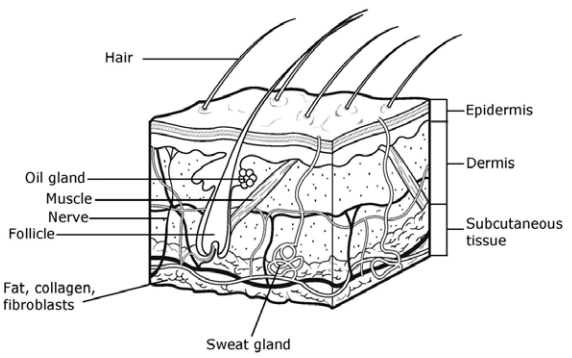

Figure 1. **Normal skin**

Although ISRs are rarely serious, they can promote negative attitudes about injection therapy and reduce adherence to therapy, particularly in the early stages of treatment. In addition to providing MS patients with appropriate instruction on the preparation and administration of injectable therapies, health-care professionals must inquire about ongoing issues, assess skin reactions, and periodically review the injection technique.

In May 2009, a panel of Canadian MS clinic nurses convened to discuss the scope of a best practices document in order to increase recognition among nurses that MS patients are at high risk for skin-site reactions with injectable therapies, and to provide the basis for skin-care practices in these patients. Subsequently, a search of the literature for clinical practice guidelines, systematic reviews, relevant research studies, and other types of evidence was conducted. Where applicable, recommendations were made and categorized according to the levels of evidence outlined in the "Summary of Recommendations." Anecdotal practices that were identified by the MS nurses through consensus but have not been studied are identified as "good practices."

This best practices document addresses the risk factors associated with adverse skin reactions in MS patients treated with injectable therapies; the current attitudes and beliefs of nurses with respect to skin care; and optimal skin-care interventions for MS patients at risk for adverse skin reactions when treated with injectable therapies. Areas requiring further research are also discussed.

ISRs Associated with DMTs for MS

Erythema and Pain

Erythema is characterized by redness of the skin due to inflammation and may involve dilated or congested capillaries (Figure 2). It may be localized or generalized and may occur suddenly or gradually. Skin color can range from bright red in patients with acute conditions to pale violet or brown in those with chronic problems. Erythema and pain are common in patients receiving injectable therapies. In a postmarketing review of 1443 adverse event reports of ISRs with subcutaneous IFNβ-1b, erythema (57%) and pain (30%) were most frequently reported and often occurred together.[6] An international cohort study of 445 patients comparing subcutaneous injection-site pain between IFNβ-1b and IFNβ-1a found a significant proportion of pain-free injections with IFNβ-1b regardless of needle size.[9] However, injection-site pain may occur with any agent and may even present 24 to 48 hours after injection. With

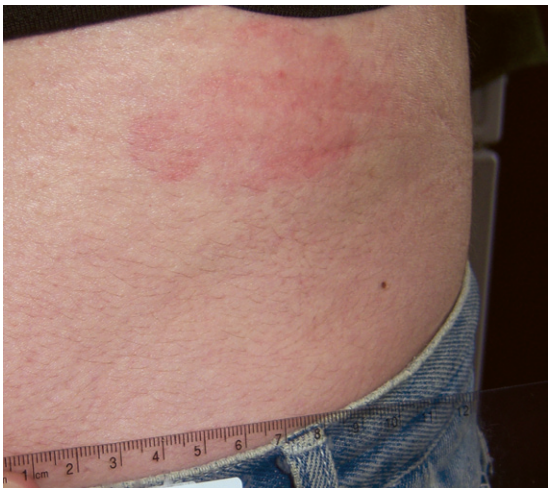

***Figure 2.* Example of erythema associated with injectable DMTs for MS**

induration have been reported to occur in 20% to 60% of patients.[10]

Erythema must be differentiated from purpura, which is caused by bleeding into the skin; application of pressure directly to the skin causes blanching of purpura but not erythema. The cause of erythema with DMTs is unclear. However, local chemokine induction is believed to be an underlying cause of inflammatory skin reactions seen in patients receiving subcutaneous IFNβ injections.[11] It has also been suggested that injection depth and injecting into sites with less subcutaneous fat (arms and thighs) are contributing factors in injection-site erythema.[12] The use of auto-injectors and ensuring that needle tips are free of medication may reduce erythema.[13]

A number of factors may contribute to injection-site pain, such as intrinsic drug properties and use of excipients in formulation, as well as other formulary properties, such as temperature, osmolarity, pH, concentration, and injection volume. Additional factors related to injection include needle size and shape, location, speed of injection and rate of drug administration, the person performing the injection, and the individual's perception of pain.[14]

Management of Erythema and Pain

Recognition of formulary components and injection techniques contributing to ISRs and pain has led to changes in drug formulations and the use of smaller-gauge needles and auto-inject devices.[9,13,15-21] A new formulation of subcutaneous IFNβ-1a without fetal bovine serum and human serum albumin showed a threefold reduction in ISRs compared with the original formulation (EVIDENCE Study),[22] and there were also fewer needle (REGARD Study).[17,23] In comparative studies of needle gauge size of 27 versus 29, the thinner needle size of 29 gauge demonstrated a significant reduction in injection-site pain for both subcutaneous IFNβ-1a and GA.[16,18] Interferon beta-1b is now available with a 30-gauge needle, but no studies to date have assessed the impact on injection-site pain or reactions. A study of patients' perceptions of using a shorter, thinner needle (1 inch/25 gauge vs. 1.25 inch/23 gauge) when injecting intramuscular IFNβ-1a found that 70% of patients identified the 1-inch/25-gauge needle as being more comfortable and causing less pre-injection anxiety.[15] Although the use of a smaller, thinner needle (29 or 30 gauge) and an auto-inject device has been shown to reduce pain and reactions,[13,15-18] for intramuscular injections the needle should be long enough to inject into the muscle rather than subcutaneous fat.[15,24]

To avoid the development of erythema and pain following injection of a DMT, the site should be examined before injection, with care taken to avoid injecting in damaged areas. The auto-injector and needle tips should be kept free of medication and the syringe held in an upright position when removing the needle cap to reduce the chances of medication adhering to the needle tip.[13] Following an injection, the nurse should observe for redness and palpate the skin by gently pressing the fingers over the injection site to feel for lumps, hardness, or thickening of the skin. As erythema is commonly diagnosed through self-examination, the importance of self-examination should be emphasized to patients and caregivers, who should be encouraged to report and discuss their findings with their health-care professional. Depending on the type of erythema, treatment includes administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids.

Injection-site pain may be reduced by applying warm compresses before injection and cold compresses after injection for up to 5 minutes.[25-27] The application of lidocaine/prilocaine cream has also been shown to reduce pain and the fear of pain after injection of IFNβ in a small cohort of patients with MS.[28]

A topical cream with cortisone such as betamethasone valerate 0.1% can reduce erythema, as can gentle massage for 15 to 30 seconds after IFNβ injection.[29]

Lipoatrophy

Lipoatrophy is a localized loss of subcutaneous adipose tissue at an injection site and appears as "dents" or depressions in the skin, which may range in size and severity (Figure 3). Although the exact mechanism leading to lipoatrophy is unknown, theories include local

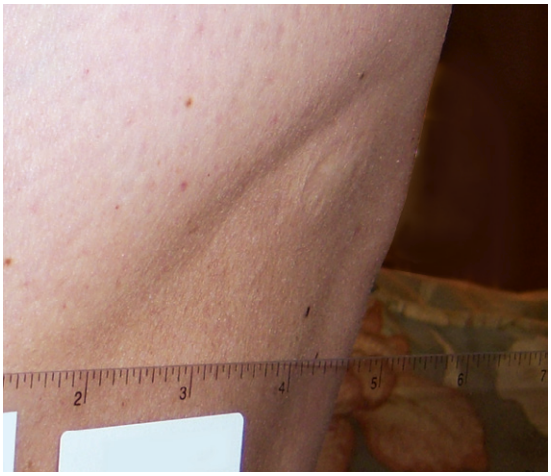

***Figure 3.* Example of lipoatrophy associated with injectable DMTs for MS**

delayed inflammatory response.[30] In severe lipoatrophy, depressions may measure up to 60 cm^2 and be 1 to 2 cm deep, with normal-appearing overlying skin. Mild lipoatrophy may be difficult to detect, and patients are sometimes unaware of the condition unless identified by a family member or a health-care professional.

Lipoatrophy can occur with prolonged injection therapy and has been observed with injection of GA and interferon as well as corticosteroids, insulin, vasopressin, growth hormone, dextran, diphtheria/tetanus vaccine, and antihistamines.[31] Among MS patients, lipoatrophy occurs more frequently in those taking GA than in those on interferon therapy.[32] The reported incidence of lipoatrophy among patients on GA has varied from 15% in an Italian study of 27 patients[33] to 64% in a US study of 14 patients.[34] A retrospective Canadian study identified lipoatrophy in 34 of 76 (45%) MS patients, all of whom were female; in some, the condition appeared within 28 ± 14 months of therapy.[30] Lipoatrophy was defined as severe in 5 patients, moderate in 9 patients, and mild in 20 patients; however, severity of lipoatrophy may be subjective and difficult to define. Interferon beta injections can also cause lipoatrophy, as found in 46% of patients in a study of 12 cases of panniculitis.[35] Although longer treatment times are more strongly associated with development of lipoatrophy, a small number of cases occur within months of injection.

Initial reports on the pathology of lipoatrophy described it as a noninflammatory condition, but subcutaneous localized panniculitis at the injection site has been described.[10,36] More recent reports have noted as much as a 40% T-cell subcutaneous infiltration, more patients on IFNβ often shows features of pancreatic panniculitis.[35]

Lipoatrophy is more common in females, occurring predominantly on the anterolateral surface of the arms and thighs.[33] It occurs more commonly in both men and women who are prone to cellulite formation. Uncertainty exists about whether lipoatrophy is permanent and how to treat it. The condition can be disfiguring and may adversely affect quality of life, including social functioning, emotional functioning, and mental health.[30]

Management of Lipoatrophy

As interventions to reduce the appearance of lipoatrophy are limited, preventive measures should be reinforced regularly with MS patients undergoing treatment with an injectable DMT. MS nurses should regularly review current injection preparation and site rotation procedures with MS patients and their care partners to ensure that they understand the rationale for injecting into healthy tissue—to avoid lipoatrophy and to ensure adequate absorption of medication. When therapy is initiated, and at regular follow-up intervals, the MS nurse should ensure that patients are able to recognize lipoatrophy through visual inspection and manual palpation. Patients and caregivers should be advised to report the appearance of lipoatrophy. Patients should be advised to rotate their injection sites regularly and to avoid injecting in or near an area of lipoatrophy.[37-40] At scheduled follow-up visits, the MS nurse should inspect injection areas to identify any areas of pitting.

If lipoatrophy occurs, the MS nurse should assess the injection and rotation practices and reinforce appropriate procedures, including the setup and appropriate depth selection of the auto-injector and preparation of the prefilled syringe. A ring left on the surface of the skin following the use of the auto-injector or syringe is an indication of excessive pressure being applied to the skin.

Attempts to correct lipoatrophy through autologous fat transplantation or the use of commercial cosmetic fillers have achieved some benefits but are not commonly used in MS patients.[41,42] Successful use of local injection of dexamethasone in insulin-related lipoatrophy has been reported, but no studies of this treatment have been conducted in MS patients.[43]

Potential areas of exploration in the management of lipoatrophy include blocking the localized inflammatory reaction and thereby reducing the damage to the subcutaneous tissue, as well as the possibility that damaged subcutaneous tissue may decrease absorption and

Injection-Site Infections

Injection-site infections can include cellulitis (Figure 4) and soft-tissue abscesses (Figure 5). Cellulitis is diffuse inflammation that involves the region from the stratum corneum to the subcutaneous fat. It occurs where the skin barrier has previously been broken through cuts, blisters, cracks in the skin, or insect bites, or by injecting drugs, either subcutaneous or intramuscular. Conditions such as diabetes, obesity, or others that affect circulation can also increase the risk of cellulitis. The patient may present with a spreading area of redness, superficial cutaneous edema, warmth, and pain around the injection site,[44] and the skin may have the appearance of orange peel (peau d'orange) (Figure 4). This may or may not be accompanied by systemic manifestations of fever, tachycardia, and leukocytosis. Cellulitis is often caused by streptococcal or staphylococcal bacteria, which are a part of the normal skin flora and do not cause infection unless the skin is broken. It can occur within 1 to several days after skin trauma. Cellulitis is usually a clinical diagnosis, and local skin cultures may not identify causative bacteria.

An abscess is a collection of liquid or pus in the subcutaneous fat, fascia, or muscle and may be sterile or septic (Figure 5). A mass under the skin with redness, warmth, pain, swelling, and fluctuance is suggestive of an abscess. Sterile abscesses are caused by irritants such as drugs or foreign bodies (eg, splinter), whereas septic abscesses are caused by bacteria.[45] When a medication is injected and not absorbed, it can cause irritation to the surrounding tissue, forming a sterile abscess with no infection. Over time, the sterile abscess may form a hard mass or lump. An abscess usually spreads beneath the skin rather than extending to the surface of the skin, thus encapsulating the collection of liquid or pus. This encapsulation may prevent spread to other sites but also prevents immune cells from attacking the bacteria. Localized signs of inflammation, erythema, pain, swelling, or warmth on touch are signs of both sterile and septic abscesses but are usually more severe with an infectious etiology. Septic abscesses may be accompanied by fever and/or regional lymphadenopathy, while sterile abscesses are not.[45]

An infectious etiology of an abscess can be determined by needle aspiration or surgical drainage of material from the mass, with laboratory confirmation of microbiological organisms through Gram stain or culture. If a sample of material cannot be obtained, imaging techniques such as ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) or clinical evidence of fluctuance (wavelike motion on

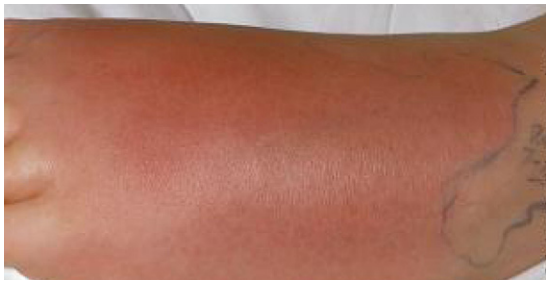

***Figure 4.* Appearance of cellulitis (ie, orange peel or peau d'orange)**

abscess, but not to differentiate between sterile and septic etiologies.[45]

The literature contains little information on the prevalence of skin and soft-tissue infections associated with MS injectable therapies. However, premarketing controlled drug trials have demonstrated a low incidence of injection-site infections in patients on drug therapy, with a reported incidence of injection-site abscess of approximately 1% to 2.5%.[37,46] A recent survey of MS nurse experts from 15 MS centers in North America also found a low incidence of injection-site infections—0% to 4.5% for cellulitis (mean, 1.01%) and 0% to 3.0% for abscess (mean, 0.37%). There were no reports of injection-site infections in the pediatric population (L McEwan, unpublished data).

Predisposing factors for injection-site skin infections and abscesses identified in other populations undergoing treatment with injectable therapies have included multidose vials, reuse of needles, poor hygiene, obesity, and immunodeficiency.[47,48] However, no such factors in MS patients have been clearly identified. Suggested factors include poor injection technique, inadequate skin cleansing, excessively shallow injections, and repeated use of the same injection site.[5] In a survey of MS nurses on

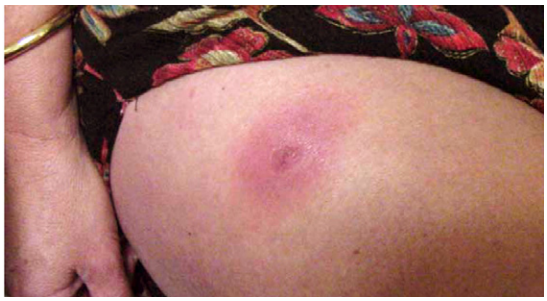

***Figure 5.* Example of an abscess developing 4 weeks after injection of IFNβ-1a**

(Courtesy of Colleen Harris, RN.)

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