

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

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*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 treat-

ment of RRMS include interferon beta-1a (IFN β -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 (IFN β -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

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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 (IFN β) 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 IFN β 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}

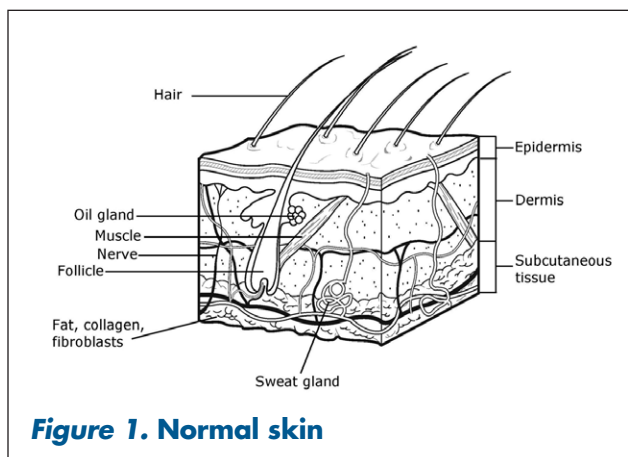


Figure 1. Normal skin

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 IFN β -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 IFN β -1b and IFN β -1a found a significant proportion of pain-free injections with IFN β -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 glatiramer acetate injections, pain, inflammation, and



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 IFN β 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 IFN β -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 ISRs using the new formulation and a smaller-gauge

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 IFN β -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 IFN β -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 IFN β 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 IFN β 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 immune reaction, mechanical injury over time, and

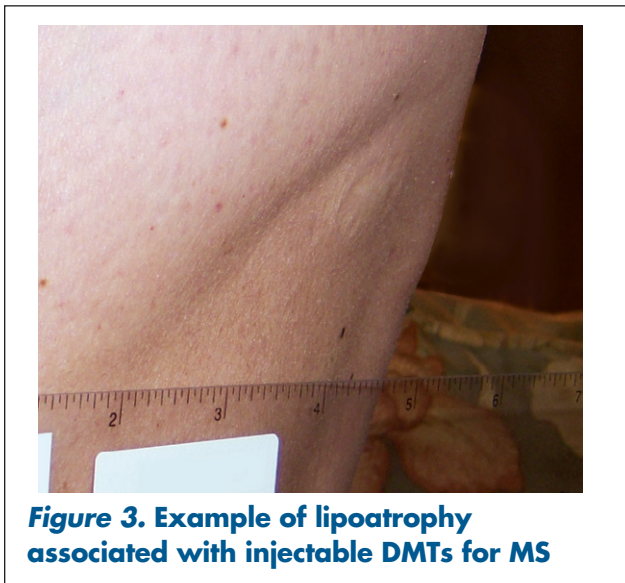


Figure 3. Example of lipoatrophy associated with injectable DMTs for MS

delayed inflammatory response.³⁰ In severe lipoatrophy, depressions may measure up to 60 cm² 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 patients³³ 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 suggestive of lobular panniculitis.³⁴ Lipoatrophy in

patients on IFN β 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 therefore efficacy.

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 palpation due to fluid) can also be used to diagnose an



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

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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 IFN β -1 α

(Courtesy of Colleen Harris, RN.)

injection-site infections, one nurse noted recurrent infection after systemic corticosteroid treatment (L McEwan, unpublished data).

Management of Injection-Site Infections

Cleansing of the injection site with alcohol is considered to be the optimal skin preparation to avoid infection.⁴⁹ Cleansing the skin with 70% alcohol for 5 seconds can reduce bacteria counts by 82% to 91%. However, diabetic patients who did not use skin preparation before insulin injection every other week for 3 to 5 months had no incidence of injection-site infection.⁴⁹ Similar results were found for patients receiving botulinum toxin type A injections without alcohol skin preparation.⁵⁰ In the use of insulin, infection is more likely to be caused by contaminated needles, syringes, and solutions than by lack of skin preparation.⁵¹

Treatment for mild or typical cases of infection should include use of an appropriate oral antimicrobial agent.⁵² Severe cases may require hospitalization and intravenous antimicrobial therapy. Although the usual course of therapy is 10 to 14 days, a 5-day course of antibiotic treatment has been shown to be as effective as a 10-day course in uncomplicated cellulitis.⁵³ In some cases, cutaneous inflammation may worsen during the first 24 hours of antimicrobial treatment because of the sudden destruction of pathogens, releasing inflammatory enzymes. Administration of adjunct corticosteroids may reduce inflammation but does not alter outcome.^{54,55} Elevation of the affected site may promote drainage of edema and inflammatory substances.

Generally, sterile abscesses resolve spontaneously and do not require treatment. Use of warm compresses over the abscess may hasten drainage or reabsorption of the abscess. Treatment for septic abscesses should include incision and removal of collected material and pus. Adjunct antimicrobial therapy varies and should be based on Gram stain, culture, and symptoms. Currently, there is insufficient evidence to support abscess cavity packing or wound closure, and the former has been associated with increased pain.⁵⁶⁻⁶⁰ However, in a randomized trial comparing primary closure of superficial abscesses with conventional packing, duration of healing was significantly decreased with primary closure.⁶⁰ Clinical trials are lacking on the appropriate management of abscesses.

Proper diagnosis is the key to effective management of patients with injection-site infections. Although nurses may not be responsible for prescribing drug therapy, they should have knowledge of the signs and symptoms of cellulitis and soft-tissue abscesses and be familiar with treatment recommendations. Nurses also have a funda-

mental role in the prevention of injection-site infections by educating patients on correct injection technique and skin care.

Induration, Swelling, Lumps, Rash, and Necrosis

Although *swelling* and *induration* are sometimes used interchangeably, an induration is a localized hardening around the injection site that is usually well demarcated with palpable borders (Figure 6), while swelling is typically caused by fluid accumulation in tissue and may be soft or firm.⁶¹ Induration may appear several hours after injection and last from 24 to 72 hours, causing a feeling of warmth, itching, hypersensitivity to touch, and swelling, and forming a round or elliptical lump less than 5 cm² in size. Thirteen percent of the 1443 ISRs reported over 30 months of postmarketing surveillance of IFN β -1b were of induration.⁶ The mechanisms of injection-site inflammation in patients on interferon therapy are unknown but are thought to involve an inflammatory response to interferon influenced by the injection path and depth, with inflammation less likely to occur in areas with a higher proportion of subcutaneous fat such as the abdomen or buttocks.¹² In the phase 3 clinical trial of GA, induration affected 19% of 125 subjects treated with GA.⁷ In some cases, these reactions persisted for several days.

In some patients, erythematous patches develop around injection sites, leading to necrotic ulcers (Figure 7).⁶² Necrosis has been reported in 3% to 5% of patients on IFN β -1b therapy^{3,6}; however, necrosis is probably underreported, as many adverse event reporting systems rely on passive reporting by clinicians.⁶ Cutaneous necrosis has also been described in patients on intramuscular IFN β -1a.⁶³ One case of subcutaneous injection giving rise to persistent erythematous plaques has been reported.⁶⁴ Risk factors for necrosis include

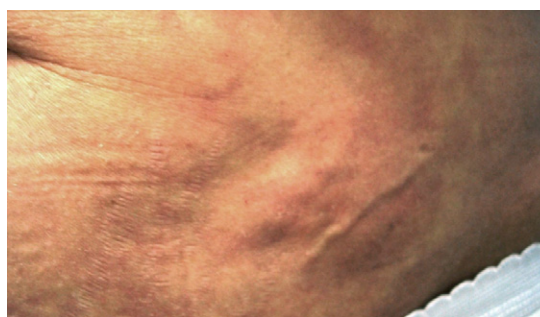


Figure 6. Induration associated with injectable DMTs for MS

(Courtesy of Stanley Hashimoto, MD, Division of Neurology, Department of Medicine, University of British Columbia.)



Figure 7. Necrosis associated with injectable DMTs for MS

(Courtesy of Colleen Harris, RN.)

incorrect injection techniques, insufficient needle length, cold drug, repeated use of the same injection site, and excessive exposure of recent injection sites to sunlight or ultraviolet rays.¹²

Although rash is not a common ISR, all DMTs have had isolated reports of either localized or systemic “rash-like” reactions (Figure 8). A cutaneous lesion resembling lupus erythematosus has been described in MS patients receiving IFN β injections.⁶⁵⁻⁶⁷ A more widespread erythematous, maculopapular rash occurring on the trunk and extremities following intramuscular injection of IFN β -1a has also been reported.⁶⁸ In one report, red, vascular, itchy lesions developed after injection of IFN β in the arms or abdomen but not in the thighs, and the problem resolved after the patient used the correct injection technique with a longer needle.⁶⁹ Interferon beta has also been associated with limited or diffuse systemic cutaneous sclerosis.^{62,70} There have been case reports of focal and diffuse urticaria and pruritus occurring within 30 minutes to several months after the initiation of GA, as well as a single case of urticarial vasculitis.^{71,72}

The reason for rash formation is unknown, but it has been suggested that MS patients have abnormalities of platelet activation and that IFN β may enhance platelet aggregation in these patients, causing a platelet-dependent thrombosis.⁶²

The literature contains little information on lumps, swelling, and redness associated with DMTs in MS. These symptoms alone may occur often, possibly disappearing and then reappearing.

Management of Induration, Swelling, Lumps, Rash, and Necrosis

As with other ISRs, proper injection-site rotation practices are important in preventing induration, swelling, rash, and necrosis. On scheduled visits, MS nurses should review injection preparation procedures with the patient and caregivers and inspect injection areas to identify any problems. Between visits, patients and caregivers

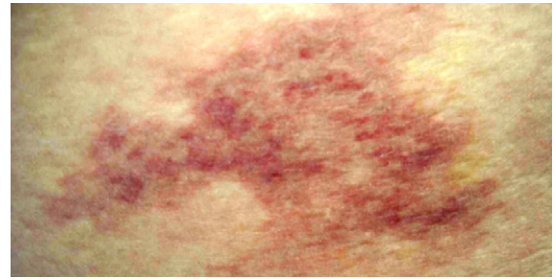


Figure 8. Example of a rash associated with injectable DMTs for MS

(Courtesy of Stanley Hashimoto, MD, Division of Neurology, Department of Medicine, University of British Columbia.)

should be advised to perform regular visual inspection and manual palpation of the skin to identify these problems.

To prevent inflammation, the area should be warmed sufficiently before injection. Warming also serves to relax the tissue, improve medication absorption, and improve circulation to allow the medication to be more easily dispersed from the area.²⁹

If indurations are present, alcohol should not be used to clean the skin because it can cause irritation; soap and water should be used instead.⁷³ The indurated site may be massaged with moisturizing cream, either immediately following injection in the case of IFN β or 24 hours after injection in the case of GA. Local application of ice has been shown to reduce inflammation due to injection, with the effect being most beneficial when performed immediately after injection.^{73,74} In cases of prolonged inflammation, local application of heat may be useful.⁷³ Antihistamines may also be effective in reducing inflammation; however, recent studies have shown no significant effect of antihistamine on ISRs associated with GA injection.^{27,75} Subcutaneous desensitization with GA has been shown to be effective in patients with focal and systemic reactions, enabling them to return to therapy without further reactions.⁷¹

Indurations, swelling, and rashes may respond to cortisone cream; however, in cases of necrosis, cortisone can delay the healing process and increase the likelihood of secondary infections. Betamethasone valerate 0.1% cream is recommended for ISRs because the level of cortisone is high enough to manage inflammation but low enough to prevent additional problems. However, betamethasone should not be used on thin, fragile areas. Hydrocortisone 1% is insufficient to manage inflammation and should not be used.²⁹

Areas of necrosis must be evaluated for signs and symptoms of infection. As incorrect injection practices are common causes of necrosis,¹² patients who develop

necrosis at a DMT injection site may require an evaluation of their cognitive ability in order to validate their understanding of proper self-injection procedures. Treatment of necrosis generally includes antibiotics or surgery, including incision and drainage, debridement, excision, and/or skin grafting.⁶

Overall Good Practices in DMT Injection for MS

Both health-care providers and patients self-administering DMTs should be aware of the potential for ISRs. Educating patients on proper injection techniques and potential side effects is very important.⁷⁶ Patients need to understand that DMTs can reduce the number of exacerbations but will not prevent them. These therapies may also slow disease progression and reduce the frequency and severity of relapses. This will help the patient have a realistic view of therapy, resulting in better patient adherence. Patients should be informed of the importance of continuous observation for skin changes and be instructed to report these to a health-care professional so that any reaction is promptly addressed.

A number of techniques related to drug preparation, site preparation, and injection mechanics have been found to minimize skin reactions and are summarized in Table 1.^{5,27,30,37-40,77,78} Appropriate preparation of the injection site as well as injection technique can help to minimize ISRs. Poor technique can result in ISRs and, ultimately, failure of therapy. Patients who use frequent subcutaneous injections have more problems than those who inject intramuscularly only once a week.⁷⁹ However, any break in the skin barrier can lead to complications, such as infection, bruising, edema, and possibly necrosis.

Summary of Recommendations

Levels of evidence were established by the Canadian Task Force on the Periodic Health Examination to identify supportive evidence found in the literature on which to base their recommendations. For this article, recommendations made by the group were based on modified criteria used by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.²

Grading of Studies Based on Design and Implementation

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:

- a) Primary outcome(s) is/are clearly defined.
- b) Exclusion/inclusion criteria are clearly defined.

Table 1. Injection techniques to minimize injection-site reactions associated with disease-modifying therapies (DMTs) for multiple sclerosis (MS)

- Warm DMTs to room temperature before injection.
- Wash hands before injecting DMTs.
- Clean the skin thoroughly before DMT injection. Repeated use of alcohol swabs may irritate the skin. Soap and water is a good substitute, and injecting immediately after a bath or shower can help minimize preparation of the injection site. Alcohol swabs are recommended for patients who are hospitalized or traveling. If using an alcohol swab, the area should be allowed to dry for 60 seconds before injection.
- While gentle massage after injection may reduce the risk of erythema, vigorous rubbing of the site before or after injection should be avoided.
- Avoid exposing the injected skin to the sun.
- Pain relievers (eg, ibuprofen) may be taken 1 hour before injection of interferon beta.
- Air bubbles should not be removed from the prefilled syringe.
- Inject and remove the needle at a 90° angle, making sure not to drag the needle away from the skin.
- To avoid or minimize lipoatrophy, patients and care providers should be instructed to
 - Keep a journal of injection sites and area of injection.
 - Note any unusual injection reactions and their potential contribution to lipoatrophy.
 - Self-evaluate injection preparation and techniques and review with an MS health professional at follow-up visits.
 - Rotate injection sites and avoid injecting near sites where the skin has hardened or thickened or near an injection site that shows denting or pitting.
- Remove the cap immediately before injection to avoid needle contamination.
- Never reuse a needle if titrating medication or if using reduced dose from a prefilled syringe.
- Avoid injecting the inner arms or inner thighs, or any area where clothing may irritate the injection site (eg, the waist-line).
- Apply ice or a cold compress after injecting to reduce swelling. If swelling persists for longer than 1 day, apply warmth to the site. If swelling persists, consult a physician to rule out possible infection.
- Topical creams such as diphenhydramine cream, hydrocortisone cream, witch hazel, and moisturizing body lotions and creams may offer relief of rash.

Note: Data were derived from References 5, 27, 30, 37-40, 76, and 77.

- c) Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
- d) Relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets criteria a through d above, OR a ran-

domized controlled trial in a representative population that lacks one of the criteria.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

Key Assessments

- Note the patient's age, sex, skin coloring, and propensity toward cellulite formation (Class IV).
- Conduct a comprehensive assessment at each clinic visit (Class IV):
 - Assess changes in health status or medications.
 - Assess changes in psychological health or health behaviors.
 - Visually examine and palpate the skin, noting signs of damaged skin (redness, swelling, tenderness, lumps, denting, hardness, and thickening of the skin).
- Describe in detail the appearance of any ISRs at each visit (Class IV):
 - Anatomical location
 - Skin color
 - Size (circumference and depth) or any change in size
 - Feel of skin (hard, soft, warm, mass fixed or mobile)
 - Pain with or without palpation
- If there are signs and symptoms of injection-site infection, assess for systemic infection (Class IV).
 - Obtain vital signs (temperature, heart rate, and blood pressure).
 - Collect laboratory values of complete blood count and erythrocyte sedimentation rate and/or C-reactive protein.
 - Palpate lymph nodes.
- Assess for psychosocial and physical factors that may affect the individual's ability to initiate and sustain injectable DMT (Class IV).

Prevention of ISRs

- Avoid injecting in areas of damaged skin (redness, swelling, tenderness, lumps, denting, tattoo, etc) (Class IV).
- Use of a thinner needle (29 or 30 gauge) and an auto-inject device may reduce pain and reactions (Class III).
- Where appropriate, use a shorter and thinner needle for intramuscular injections. However, the needle should be long enough to inject into the muscle rather than subcutaneous fat (Class IV).

- Auto-injectors and needle tips should be free of medication. Hold the syringe in an upright position when removing the needle cap to reduce the chances of medication adhering to the needle tip (Class III).
- Patients should be advised to rotate injection sites. Do not inject in an area injected during the past week (Class IV).
- Patients should be provided with information to support their understanding of the treatment plan and outcomes (Class IV).
- Advise patients that the use of alcohol for skin cleansing is considered the optimal practice for injection preparation but is not necessary to prevent injection-site infection. Soap and water is a suitable alternative (Class III).
- Before injection, warm the area to relax the tissue, improve medication absorption, prevent inflammation, and improve circulation so that medication can be more easily dispersed from the area (Class IV).
- Review current injection preparation procedures and site rotation with patient and care partner to ensure that they understand the rationale for injecting into healthy tissue and to ensure adequate medication absorption. This should be discussed at initiation of a DMT and reinforced on a regular basis (Class IV).
- Advise the patient and care partner to perform a visual inspection and manual palpation of the skin to identify the presence of induration, swelling, lumps, rash, and necrosis. This should be discussed at initiation of a DMT and reinforced on a regular basis (Class IV).

Treatment Interventions

Pain and Erythema

- Injection-site pain may be reduced by applying warm compresses before injection and cold compresses after injection for up to 5 minutes (Class III).
- Application of lidocaine/prilocaine cream may reduce pain and the fear of pain following injection (Class III).
- Use of topical cream with cortisone such as beta-methasone valerate 0.1% can reduce erythema (Class IV).
- Gentle massage for 15 to 30 seconds after injection of IFN β can reduce erythema. In the case of GA, the skin should not be massaged until 24 hours after injection (Class IV).

Lipoatrophy

- Explore current injection preparation procedures with the patient and care partner (eg, time syringe

out of refrigerator, auto-injector setup, and pre-filled syringe preparation). A ring left on the skin surface following the use of the auto-injector or syringe is an indication of excessive pressure being applied to the skin (Class IV).

- Ensure an appropriate injection depth of the auto-injector and that the needle remains in the subcutaneous tissue for the appropriate amount of time (Class IV).
- Advise the patient to avoid injections in or near the area of lipoatrophy (Class IV).
- Re-educate patients and care partners on appropriate area and site rotation. Have them successfully demonstrate site rotation and develop a schedule for rotation to all areas identified as suitable for GA and IFN β injections (Class IV).
- In cases of severe lipoatrophy, a physician should be consulted for consideration of potential treatments or further evaluation (Class IV).
- Injection of poly-L-lactic acid (Sculptra, Sanofi-Aventis, Montreal, Canada) may reduce the signs of lipoatrophy (Class IV).
- Injection of fat in the lipoatrophy site may reduce the signs of lipoatrophy (Class IV).

Infection

- Patients should be referred to an appropriate practitioner for antimicrobial therapy and/or drainage or surgical management (Class IV).
- Patients should be educated about the importance of completing a full course of any prescribed antimicrobial therapy and of the potential for temporary worsening of inflammation during the first 24 hours of antimicrobial therapy (Class IV).
- Incision and drainage is the recommended treatment for abscess. Antimicrobial therapy may not be required unless there are signs of systemic infection (Class IV).
- In cases of cellulitis, elevation of the affected site may promote drainage of edema and inflammatory substances (Class IV).

Induration, Swelling, Lumps, Rash, and Necrosis

- If indurations are present, alcohol should not be used to clean the skin, as it can be irritating; soap and water should be used instead (Class IV).
- For induration associated with GA, massage the indurated site with moisturizing cream 24 hours after injection. For induration associated with IFN β , massage the indurated site with moisturizing cream immediately after injection (Class IV).
- To decrease inflammation, apply an ice pack to the area for 5 minutes (not direct contact). The

effect is most beneficial when performed during the postinjection period (Class IV).

- Local application of heat (15 minutes of warm compresses on the injection site, three times daily) may be used to reduce inflammation in cases of prolonged inflammation (Class IV).
- Betamethasone valerate 0.1% is recommended for inflammation, as the level of cortisone is high enough to manage inflammation but low enough to prevent additional adverse effects (Class IV).
- Cortisone cream is not recommended in the presence of necrosis (Class IV).
- Hydrocortisone 1% is insufficient to manage inflammation and should not be used (Class IV).
- Subcutaneous desensitization with GA may be used in patients with focal and systemic allergic reactions following assessment with an allergy specialist (Class IV).

Summary of Good Practices

Nursing Practice Recommendations

- Nurses should assess the psychosocial and physical factors that may affect the individual's ability to initiate and sustain injectable DMT.
- Nurses should have knowledge of the factors that may increase the patient's risk of developing ISRs.
- Nurses should have the knowledge and skill to provide and/or reinforce patient education on proper injection techniques, including
 - Site selection and rotation
 - Preparation of medication for injection
 - Cleansing of injection site
 - Administration of injection
- Nurses should visually inspect and palpate all areas of injection at each clinic visit, regardless of whether the patient reports any ISRs.
- Nurses should have the knowledge and skill to identify and diagnose ISRs.
- Nurses should document assessment of findings with detailed description of ISRs at each clinic visit.
- Nurses should have knowledge of the management of ISRs and when to refer care to other health-care specialists.

Patient Recommendations

- Patients should be educated on healthy skin practices of good hygiene, moisturizing, UV protection, balanced diet, adequate hydration, and smoking cessation.
- Patients should be encouraged to perform self-examinations and be provided with information on the signs and symptoms of ISRs. Patients

should be advised to contact their health practitioner for further assessment as soon as possible if any abnormal ISR is identified (infection or necrosis).

- Patients should be educated on how to reduce and manage ISRs such as erythema, pain, lipoatrophy, and lumps.
- Patients should be advised to report any difficulty with self-injections. Those who experience lipoatrophy, injection-site infection, or necrosis should have their injection technique reassessed by the MS nurse.

Conclusion

Although limited and somewhat outdated clinical trials have evaluated the effects of injectable therapies on the skin of patients with MS, the incidence and severity of reactions appear to be declining as a result of changes in practice and product design. However, more current and collaborative data collection on skin reactions of patients on DMTs is needed to determine whether perceived reductions in the incidence and severity of ISRs are real and, if so, which interventions have led to these reductions. This would require better, standardized methods of assessing ISRs to improve the ability of MS nurses to recognize and report consistently on ISRs.

Future studies should be conducted to determine the factors that contribute to skin reactions in order to facilitate identification of patients who are at increased risk of developing adverse skin reactions. Patient factors may include level and type of disability such as sensory, visual, motor, and cognitive impairment; age (pediatric vs. adult); and body fat percentage. Medication factors may include dosage and volume (eg, the effect of splitting doses to reduce medication volume), the use of manual injectors versus auto-injectors, and alternative injection techniques. Future studies should assess the role of

adverse skin reactions in the patient's decision-making process and in patient adherence to injectable therapies.

The recent introduction of oral therapies will bring a paradigm shift in the treatment of MS. Will patients' treatment decisions be influenced by the ease of using an oral therapy and the fear of injection pain, or will other factors influence treatment decisions, such as adverse events and long-term safety data? Will the emergence of new therapies and decreased funding to clinics affect the ability of health-care providers to perform consistent and routine skin assessment? Many Canadians with MS live in remote areas and are unable to make frequent, regular visits to a clinic because of financial, physical, and geographic constraints. Potential changes to health-care funding may result in further limitations to specialty MS service and care. Future studies should address these issues. □

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PracticePoints

- Disease-modifying therapies (DMTs) for MS can result in a variety of localized skin reactions at the injection site.
- Nurses involved in the care of patients with MS should be knowledgeable about the potential injection-site reactions associated with DMTs in order to appropriately distinguish between normal and abnormal reactions and determine when further intervention is required.
- MS patients should be educated on healthy skin practices and be taught to identify the signs and symptoms of injection-site reactions.

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