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Best Practices in Multiple Sclerosis

Infusion Reactions Versus Hypersensitivity Associated With Biologic Therapies

ABSTRACT

Infusion nurses are uniquely positioned to play a vital role in the early identification and management of infusion and hypersensitivity reactions during the administration of biologic therapies. This article reviews the current evidence regarding reactions related to the administration of monoclonal antibodies, namely, natalizumab, a humanized monoclonal antibody against the cellular adhesion molecule α 4-integrin, in patients with multiple sclerosis. In addition to differentiating between infusion and hypersensitivity reactions, the article presents general guidelines for the management of these reactions and provides case studies to better illustrate the use of appropriate interventions.

In the past 15 years, new and effective therapeutic options have become available for the treatment of multiple sclerosis (MS), with the goal of improving the lives of patients with this often debilitating disease. However, complex treatment protocols, unpredictable disease progression, and the special needs of many patients with MS present considerable challenges to successful treatment outcomes. Best practices related to complex approved and emerging therapies underscore the critical importance of appropriately evaluating and monitoring patients, providing training for infusion nurses in the identification and management of the side effects of these therapies, and fostering the nurse-patient relationship.

In addition to providing a brief overview of the diagnosis and symptoms of MS, this article discusses the special needs of patients with this condition, available

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treatment options, and potential side effects associated with MS therapies. Particular emphasis is placed on experience with the infusion of natalizumab, the first monoclonal antibody therapy approved by the US Food and Drug Administration (FDA) for the treatment of relapsing forms of MS. Criteria for differentiating between infusion and hypersensitivity reactions associated with any infusible therapy are described with particular reference to MS. In addition to management guidelines, case studies are provided to illustrate the use of appropriate strategies in such situations. Infusion nurses can play a key role in meeting the complex needs of patients undergoing infusion therapy and ensure the best possible care for their patients with MS.

MS: AN OVERVIEW OF THE DISEASE

Multiple sclerosis is an autoimmune disorder affecting the central nervous system (CNS). Although the exact etiology of the disease is unknown, the underlying pathology consists of focal inflammatory demyelination and axonal loss within the brain and spinal cord.¹⁻³ Relapses and disease progression are hallmarks of the natural history of MS, which is characterized by the ongoing destruction of myelin, subsequent axonal damage, and the formation of inflammatory lesions in the white matter of the CNS. These pathologic changes lead to the disruption of nerve transmission and loss of brain tissue (ie, brain atrophy). Even in early MS, irreversible neurologic damage can occur.⁴⁻⁶ Later-stage disease is generally associated with a greater degree of axonal loss and an accumulation of related disabilities.⁶

The symptoms of MS vary considerably among patients and reflect the heterogeneous nature of disease pathogenesis and the varied pattern of neuronal destruction within the brain and spinal cord.^{2,4} Common symptoms of MS include fatigue, weakness, visual disturbances, difficulty with walking and balance, impaired speech, bowel and bladder dysfunction, limb numbness or tingling, and various forms of pain. In addition to this wide range of physical disabilities, individuals with MS may experience cognitive impairment, manifesting as memory loss or attention problems, as well as depressive symptoms.^{2,4}

The progression of MS in an individual patient is largely unpredictable. However, 4 distinct clinical courses of the disease have been identified.^{4,6,7} A patient's disease course can be characterized as (1) relapsing–remitting, (2) secondary progressive, (3) primary progressive, or (4) progressive–relapsing MS. The majority of patients (approximately 80%) initially experience a relapsing–remitting course of MS, which is characterized by periods of remission (ie, no apparent disease progression) interspersed with clearly defined clinical relapse stages during which new or recurrent

symptoms emerge (also referred to as *exacerbations* or “flare-ups”).^{4,6,7} Prior to the emergence of disease-modifying therapies, nearly three-quarters of patients with relapsing–remitting MS eventually experienced a more progressive form of the disease known as *secondary progressive MS*, in which fewer relapses occur but function gradually worsens over time.^{4,7} Primary progressive MS is characterized by a slow and steady decline from the onset of disease. This type of disease pattern occurs in approximately 20% of patients. Progressive–relapsing MS is the rarest form of the disease and is characterized by a steady progression from diagnosis, with clear acute relapses, but without periods of remission.^{4,6,7}

DISEASE-MODIFYING MS THERAPIES

A number of disease-modifying therapies are available for the treatment of MS.^{4,8} These therapies have been shown to reduce relapses but do not necessarily improve a patient's symptoms or decrease the outlook for long-term disability. Injectable disease-modifying therapies are approved by the FDA to treat relapsing forms of MS: interferon (IFN)- β 1a, which may be given subcutaneously (SC) or intramuscularly; IFN- β 1b, which is administered via the SC route; and glatiramer acetate, which is also administered via SC injection.⁸⁻¹³ In general, these injectable disease-modifying therapies are well tolerated and have been shown to reduce relapse rates, accumulation of physical disability (IFN- β 1a only), and disease activity as measured by magnetic resonance imaging (MRI).^{2,4,8,14} All of these agents are associated with potential adverse events, however. Common treatment-related adverse events among patients treated with the β IFNs include depression and suicidal ideation; flu-like symptoms; injection-site reactions; laboratory abnormalities, including decreased peripheral blood cell counts and elevated hepatic transaminases; and menstrual irregularities.^{9,11,12,15,16} In controlled clinical trials, glatiramer acetate has been most commonly associated with injection-site reactions, vasodilation, chest pain, asthenia, infection, pain, nausea, arthralgia, and hypertonia.¹⁰ Each of these therapies has also been associated with hypersensitivity reactions, as manifested by anaphylaxis and other allergic reactions, including urticaria, rash, flushing, dyspnea, bronchospasm, tongue edema, chest pain, and palpitations.⁹⁻¹² In general, these reactions were an uncommon complication of treatment,^{9,11,12} generally transient,¹⁰ and, in the case of IFN- β 1a, not always clearly associated with the dose or duration of treatment.¹¹

Injectable disease-modifying therapies have been shown to be only partially effective and may not impact disease progression or fully suppress relapses.^{2,4} Although not formally approved by the FDA for this purpose, corticosteroids are primarily used to manage

clinically significant relapses to facilitate a more rapid recovery. A short course of intravenous (IV) methylprednisolone is typically administered and may be followed by an oral prednisone taper (per the discretion of the prescriber). Corticosteroids may also be given on a regular basis via infusion (known as pulse therapy) to modify disease activity, especially in patients whose symptoms are worsening over time. Although evidence indicates that corticosteroids reduce the duration of relapses, subsequent axonal damage, and associated short-term morbidity, the responsiveness to corticosteroid therapy may decline over time and permanent neurologic deficits may not be prevented.^{2,4,8}

Mitoxantrone, an antineoplastic agent, is approved by the FDA for the treatment of patients with relapsing forms of MS that continue to worsen.^{17,18} Studies with this therapy have demonstrated significant reductions in relapse rates and disease activity based on MRI scans.^{2,16,17} This agent is potentially more toxic than other disease-modifying therapies, however.^{2,17,18} In clinical trials, patients treated with mitoxantrone experienced mild to moderate nausea, alopecia, urinary tract infections, and menstrual disorders more frequently than did those patients in the placebo group. Because of potential serious adverse effects, mitoxantrone must be administered slowly via IV infusion and cannot be given by other parenteral routes. Patients must be assessed for cardiac signs and symptoms before receiving treatment because of the potential for cardiac toxicity, particularly in patients who have previously received other cardiotoxic drugs (eg, anthracyclines) or in patients with preexisting cardiovascular disease.¹⁷ Mitoxantrone is contraindicated in patients with a baseline left ventricular ejection fraction of less than 50%.¹⁷ As has been observed with other chemotherapeutic agents with the same mechanism of action (eg, etoposide and anthracyclines), mitoxantrone has also been associated with an increased risk of treatment-related, secondary acute myelogenous leukemia in patients with cancer and MS.^{17,18}

BIOLOGIC THERAPIES FOR THE TREATMENT OF MS

Monoclonal antibodies represent an important new treatment option for MS, particularly for patients who continue to experience relapses while receiving other therapies.¹⁹ Although several monoclonal antibodies are being evaluated for the treatment of MS,¹⁹ natalizumab is the only such agent approved by the FDA to date and is currently licensed for the treatment of relapsing forms of MS.²⁰ A novel selective adhesion molecule inhibitor that blocks the interaction of α 4-integrin with vascular cell adhesion molecule-1, natalizumab (administered every 4 weeks intravenously) has been shown to reduce the risk of sustained

disability progression by 42% and to decrease the annual rate of relapse by 68% ($P < .001$ for both comparisons) over a 2-year period when compared with the placebo.²¹ Moreover, natalizumab has also demonstrated efficacy in patients with MS who have experienced breakthrough disease activity while on IFN- β 1a therapy. Specifically, the addition of natalizumab to IFN- β 1a therapy reduced the risk of sustained disability progression compared with treatment with IFN- β 1a alone.²² These findings suggest that natalizumab may be of greater clinical benefit in patients with relapsing disease than previously available treatments.

Although monoclonal antibodies and other biologic agents may be effective in stabilizing symptoms in patients with MS, it should also be noted that, similar to the infusion of other foreign proteins, treatment with these agents is not without risk. Thus, some patients with MS may experience adverse infusion-related reactions during or shortly after the administration of natalizumab.^{21,22} Similar reactions have been observed with monoclonal antibody therapy in other diseases (eg, infliximab in the treatment of Crohn's disease²³⁻²⁵ and rituximab in the treatment of non-Hodgkin's lymphoma²⁶ and Sjögren's syndrome²⁷).

SPECIAL CONSIDERATIONS FOR TREATING PATIENTS WITH MS

A number of patient-related issues have emerged over time regarding the administration of MS therapies, many of which can have a negative impact on adherence and the overall success of the treatment. Special considerations for treating patients with MS are summarized in Table 1. For example, it is important to consider that patients with MS may become socially isolated because of their declining physical function, thus hindering necessary support for managing and coping with their illness. Cognitive changes can also impair patients' understanding of their disease as well as their ability to clearly consider various treatment options and understand complex drug treatment procedures. They may not be able to cope with the inevitable financial burdens associated with the high costs of treatment, coupled with the reduction or loss of income that may accompany an inability to work. Finally, it is common for patients with MS to initially harbor unrealistic expectations regarding treatment outcomes. When these expectations are not met, patients may become disheartened and lack motivation to continue therapy. Among the most common reasons for decreased adherence to treatment are a perceived lack of efficacy and the onset of adverse effects often associated with disease-modifying therapies, such as injection-site reactions and flu-like symptoms.²⁸⁻³⁰ Particularly relevant to injectable therapies, many patients may find self-injection difficult, painful,

**TABLE 1**

Special Considerations for Treating Patients With Multiple Sclerosis

Patient-Related Issue	Consequence
Cognitive changes	Impaired understanding of their disease
	Impaired ability to clearly consider treatment options and understand complex treatment procedures
Declining physical function and mobility	Barrier to receiving treatment in an infusion clinic
	May require significant transfer assistance at the infusion clinic
	Social isolation and lack of support for coping with illness
	Inability to work and reduced or lost income (difficult to cope with high financial burden)
Unrealistic expectations for treatment success	Lack of motivation and decreased treatment adherence (if expectations are not met)
Bladder dysfunction	May require interventions to control urinary urgency and frequency
	May require easy accessibility to restroom facilities and minimization of time spent at the infusion clinic
	Increased risk of urinary tract infections; may delay treatment
Poor hydration, scarring of veins from overuse, increased motor tone, and other disease-related symptoms	Vascular access may be difficult to obtain

and especially inconvenient because of the nature of their illness and a lack of support. Clinical MS teams (including infusion nurses) can help to ensure patient adherence to therapy and to sustain motivation through support programs and by promoting adherence to protocols. Proactive education should guide patients toward the appropriate management of adverse events and should help to minimize discomfort associated with injections.^{29,30}

Additional considerations may be specifically relevant to therapies administered intravenously. For instance, impaired mobility and the severity of their illness may present barriers for some patients with MS to receive treatment in infusion clinics. Bladder dysfunction, which can include urinary frequency and urgency, may present a significant challenge, especially for patients receiving IV infusions over extended periods of time. Patients with MS may use medications or self-catheterization, or restrict fluid intake, to control urinary urgency and frequency. An added complication of bladder dysfunction is the increased risk of urinary tract infections because of incomplete bladder emptying. In addition, vascular access may be difficult to obtain because of poor hydration, scarring of veins from overuse, decreased neurologic function, tremors, spasticity, contractures, or decreased muscle tone. Thus, interventions such as optimal nutrition and hydration and improved vascular access may facilitate successful infusion therapy in patients with MS.

IDENTIFICATION AND MANAGEMENT OF INFUSION VERSUS HYPERSENSITIVITY REACTIONS

With the approval of natalizumab and the emergence of several promising monoclonal antibody therapies for patients with MS, it is important for infusion nurses who administer these agents to anticipate potential infusion or hypersensitivity reactions that may occur and to be knowledgeable about appropriate management strategies. In general, infusion reactions are defined as non-immune-mediated reactions that occur during or shortly after monoclonal antibody administration, whereas hypersensitivity (allergic) reactions are defined as an immune-mediated subset of reactions.³¹ Nurses should be aware of the signs and symptoms specifically associated with each of these reaction types, as well as management strategies and measures to prevent such reactions from recurring with future treatment.³²

Infusion Reactions

Infusion reactions may occur at any time following the start of the infusion, often within a few hours. Symptoms are frequently nonspecific and may include headache, dizziness, nausea, fatigue, facial flushing, sweating, and pruritus. Possible causes of infusion reactions include the drug itself, the infusion solution, infusion equipment, or

the infusion method (particularly if the drug infusion rate is too rapid). Patient anxiety may also be an important contributing factor in the development of an infusion reaction.³¹

When infusion reactions occur, they should be treated in accordance with symptom severity and the protocol of the facility. For example, vasovagal infusion reactions generally involve nausea, weakness, diaphoresis, slow pulse, and/or a moderate drop in blood pressure (BP). As shown in Table 2, suggested interventions for vasovagal reactions include placing patients in a supine position with their legs elevated above the level of the heart (ie, Trendelenburg position), temporarily discontinuing the monoclonal antibody infusion, infusing 250 mL of normal saline solution (NSS: 0.9% sodium chloride) or 5% dextrose/0.9% sodium chloride solution (D5/NSS), and carefully observing the patient.³³ After discontinuing the monoclonal antibody infusion, signs and symptoms of an infusion reaction should resolve within 10 to 15 minutes. When the patient has stabilized (ie, vital signs have returned to normal baseline values), the infusion may be restarted. When restarting the infusion, the patient should remain in the supine position or reclined. The infusion itself should resume at a slower rate (eg, 60-80 mL/h for approximately 15 minutes) and then be increased (eg, to 80-100 mL/h) for the remainder of the infusion. More frequent monitoring of the patient should be performed, including assessments of general disposition, skin moisture, and BP.

Hypersensitivity Reactions

In contrast with infusion reactions, symptoms observed in patients with hypersensitivity reactions range from localized effects (such as hives) to a more severe, generalized immune response that may lead to cardiopulmonary dysfunction and death. Hypersensitivity may result from the drug itself, the components of the infusion solution, or sensitivity to individual components of the infusion equipment (ie, latex tourniquets, packaging, rubber-stoppered vials, or injection ports). Of note, different classes of drugs tend to cause distinctly different types of hypersensitivity reactions.³¹

Hypersensitivity reactions usually occur within the first few infusions and are classified as either immediate- or delayed-type reactions. Immediate hypersensitivity reactions generally occur within minutes (or less commonly, within the first 24 hours) of infusion and depend on the release of inflammatory mediators that include histamine, leukotrienes, prostaglandins, platelet-activating factor, enzymes, and proteoglycans. Drugs can trigger the release of these mediators either directly (ie, anaphylactoid reaction) or via immunoglobulin (Ig) E-specific antibodies.³⁷ Immediate hypersensitivity reactions are often characterized by dizziness, hypotension/shock, rigors, fiery red rashes, flushing, nausea, vomiting, abdominal cramps, wheezing, chest

tightness, shortness of breath, upper airway edema, and angioedema, occurring alone or in combination.³⁸

Delayed hypersensitivity reactions are usually observed within 7 to 10 days following the infusion, with variable symptoms depending on the type of hypersensitivity reaction. For example, serum sickness is caused by the deposition of circulating immune complexes with consumption of complement and is characterized by fever; arthritis; nephritis; neuritis; edema; and an urticarial, papular, or purpuric rash.³⁷ First described following the administration of foreign sera, serum sickness has now been observed in patients treated with monoclonal antibodies.^{23,27} In classic serum sickness, symptoms develop 6 days or more after exposure to a drug (the latent period required to produce the antibody). Cutaneous and systemic vasculitides are relatively rare delayed hypersensitivity reactions that may also be a result of immune complex deposition.³⁷ Finally, delayed hypersensitivity mechanisms directed by drug-specific T cells may be the most important mechanisms involved in delayed reactions and can result in the rare and severe hypersensitivity syndrome known as Stevens-Johnson syndrome, as well as toxic epidermal necrolysis syndrome.^{37,38}

Hypersensitivity reactions that have been observed following treatment with natalizumab generally occur within 2 hours of the start of the infusion. Symptoms associated with these reactions include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, hypotension, flushing, dyspnea, and chest pain.²⁰ A small number of delayed hypersensitivity reactions following natalizumab therapy have also been reported.^{39,40}

If a hypersensitivity reaction occurs during natalizumab infusion, administration should be discontinued while maintaining vascular access for fluid support and emergency treatment. The patient should be reclined in a supine or Trendelenburg position, and the prescribing physician should be notified immediately. As the needs of the patient dictate (and consistent with physician and facility policies), proper supportive measures should be initiated (Table 2).^{31,33,34} Possible measures include administration of antihistamines (eg, diphenhydramine 25-50 mg IV), corticosteroids (eg, hydrocortisone 100 mg or methylprednisolone 20-40 mg IV), or epinephrine 1:1000 (0.2-0.5 mL SC or intramuscularly, repeated every 15 minutes for 2 doses, then every 4 hours as needed), oxygen (2-4 L via nasal catheter), vasopressors for hypotension, IV fluids as needed, and cardiopulmonary resuscitation if necessary.^{35,36} Patient vital signs should be monitored every 2 minutes until they are within normal limits and subsequently every 15 minutes for the next hour (or as required by the individual facility protocol). The physician may choose to prescribe an oral corticosteroid at a tapered dose for the patient upon discharge from the infusion facility. Subsequent treatment should be determined by the treating physician on a case-by-case basis; however, retreatment with natalizumab is not recommended.

**TABLE 2**

Suggested Interventions for the Management of Natalizumab-Related Infusion and Hypersensitivity Reactions^{31,33-36}

Reaction Type	Suggested Interventions
<i>Infusion reactions</i>	
Mild (Grades 1-2)	
Frequently nonspecific symptoms (eg, headache, dizziness, nausea, fatigue, facial flushing, sweating, and pruritus)	Grade 1 reactions do not necessarily require infusion slowing and/or interruption, or specific intervention
	Grade 2 reactions may require infusion slowing and/or interruption while appropriate symptomatic treatment is administered
	While the infusion is temporarily suspended, reassess response to appropriate symptomatic treatment (eg, oral or IV antihistamines, nonsteroidal anti-inflammatory drugs, and IV fluids)
	Administer prophylactic treatment (eg, oral antihistamines) for the proceeding ≥ 24 h
Moderate (Grade 3)	
Similar symptoms, which are prolonged and not immediately responsive to treatment	Interrupt the infusion immediately
	Expect prolonged symptoms that are not rapidly responsive to appropriate symptomatic treatment (eg, oral or IV antihistamines, nonsteroidal anti-inflammatory drugs, and IV fluids)
	Acute care evaluation or hospitalization may be indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates); further or more intensive treatment may be indicated
Vasovagal reactions (symptoms include nausea, weakness, diaphoresis, slow pulse, and/or a moderate reduction in blood pressure)	Place the patient in a supine or Trendelenburg position
	Discontinue the infusion temporarily
	Infuse 250 mL NSS or D5/NSS and observe
	Signs and symptoms should abate within 10-15 min
	Restart the infusion when symptoms resolve and vital signs are stabilized
	Resume the infusion at a slower rate for the first 15 min
Severe (Grades 4-5)	More frequent assessments of the patient are recommended
Symptoms may be life threatening	Discontinue the infusion immediately
	Place the patient in a supine or Trendelenburg position
	Initiate emergency measures, including the following:
	Call 911
	Vasopressors (eg, epinephrine) for hypotension
	Keep vascular access; give IV fluids as needed
	Oxygen (2-4 L via nasal catheter) as needed
	Monitor patient's vital signs frequently
	Cardiopulmonary resuscitation if necessary
	When appropriate, IV atropine sulfate 0.4 mg IV may be given

(continues)

**TABLE 2 Continued**

Suggested Interventions for the Management of Natalizumab-Related Infusion and Hypersensitivity Reactions^{31,33-36}

Reaction Type	Suggested Interventions
<i>Hypersensitivity reactions</i>	
Mild (Grade 1)	
Transient flushing or rash, itching, scattered hives or erythema (no angioedema), or drug fever <38°C (<100.4°F)	Discontinue the infusion
	Place the patient in a supine or Trendelenburg position
	Administer oral or IV antihistamines
	If symptoms resolve, restart the infusion at a slower rate
	If symptoms persist or worsen, administer antihistamines and/or IV corticosteroids and discontinue the infusion
	Observe the patient and monitor vital signs frequently
Moderate (Grades 2-3)	
Rash, flushing, bronchospasm with or without urticaria, other respiratory symptoms (eg, dyspnea, hoarseness, or wheezing), drug fever >38°C (≥100.4°F), allergy-related edema or angioedema	Discontinue the infusion
	Positioning dependent on patient comfort
	Administer epinephrine as appropriate; further acute care and evaluation by a physician may be necessary
	Keep vascular access; give IV fluids as needed
	Oxygen (2-4 L via nasal catheter) as needed
	Observe the patient and monitor vital signs frequently
	Cardiopulmonary resuscitation if necessary
	Call 911
Blood pressure reduction of ≥15%, not associated with typical vasovagal symptoms	Discontinue the infusion
	Place the patient in a supine or Trendelenburg position
	Administer oral or IV antihistamines and IV corticosteroids as needed
	If symptoms persist, epinephrine may be necessary
Severe (Grades 4-5)	
Overt anaphylaxis or life-threatening symptoms	Discontinue the infusion immediately
	Positioning dependent on patient comfort
	Administer epinephrine, oral or IV antihistamines, and IV corticosteroids as needed; further acute care and evaluation by a physician may be necessary
	Keep vascular access; give IV fluids as needed
	Oxygen (2-4 L via nasal catheter) as needed
	Observe the patient and monitor vital signs frequently
	Cardiopulmonary resuscitation if necessary
	Call 911
	If acute care response is delayed, IV atropine sulfate 0.4 mg should be available and administered as necessary
	Monitor for delayed hypersensitivity reactions and manage on the basis of signs, symptoms, and severity

Abbreviations : D5/NSS, 5% dextrose/0.9% sodium chloride solution; IV, intravenous; NSS, normal saline solution.

The facility protocol for handling emergency hypersensitivity reactions should be prominently posted in the infusion center. In addition, patients should be educated about the symptoms of an immediate hypersensitivity reaction and instructed to report such symptoms to their healthcare provider promptly if they occur. Patients should also be instructed regarding the symptoms of a delayed hypersensitivity reaction and when to seek medical attention. This should include written instructions regarding the symptoms of delayed hypersensitivity, as well as whom to contact if they experience signs of such a reaction.³¹

CASE STUDIES

The following case studies have been selected to provide an overview of the range of infusion-related reactions typically observed with natalizumab treatment, as well as recommended management strategies.

Case 1

Infusion/Vasovagal Reaction

A 46-year-old female patient diagnosed with relapsing MS in 1997 began receiving monthly IV administration of natalizumab in 2007. The patient had been previously treated with IFN- β 1a for approximately 3 years prior to the initiation of natalizumab therapy. Although accustomed to needles from her prior therapy, the patient remained somewhat reticent at the time of peripheral access with subsequent infusions. In December 2007, the patient was scheduled to receive her eighth natalizumab infusion. All preinfusion procedures went smoothly and peripheral access with a 24-gauge catheter was obtained using the median cephalic vein of the right forearm. Preinfusion vital signs included a BP of 118/72 mm Hg, heart rate of 82 beats per minute (bpm), and a respiration rate of 18 breaths per minute. The patient was made comfortable and the infusion proceeded as usual. Approximately 20 to 30 minutes into the infusion, the patient complained of dizziness, nausea, and stomach discomfort; however, no skin rash or other systemic issues were noted.

- Dizziness, nausea, and stomach discomfort can be symptoms of an acute infusion reaction. In this case, should the infusion be stopped, despite the lack of an apparent skin rash or other effects indicative of an infusion reaction?
- If the healthcare provider chooses to stop the infusion and the patient's symptoms subsequently resolve, should the event be considered an infusion reaction?
- What other reasons could contribute to the onset of these symptoms (ie, dizziness, nausea, and stomach discomfort)? For instance, does the patient have an empty stomach, or did she recently have the flu?

When patients experience any symptoms during an infusion, even in the absence of an apparent skin rash, it is imperative for healthcare providers to consider the possibility of an acute infusion reaction. The prudent decision is to stop the infusion temporarily and reassess the patient's symptoms. Even if symptoms such as dizziness, nausea, and stomach discomfort resolve after discontinuation of the infusion, the onset of these symptoms can still be considered an infusion reaction. However, conducting a simple assessment prior to the initiation of therapy can aid healthcare providers in determining whether there may be other underlying causes of symptoms that occur during or after the infusion (eg, empty stomach, flu).

In this case, the infusion was stopped, and vital signs were assessed. The patient was afebrile and had a BP of 112/64 mm Hg, a heart rate of 90 bpm, and a respiration rate of 22 breaths per minute. The nursing staff decided to infuse NSS for several minutes before restarting the natalizumab infusion. New tubing was used to administer the NSS. Moments after initiating the NSS infusion, the patient began to experience similar symptoms of dizziness, nausea, and stomach discomfort. The infusion was again interrupted and the patient's symptoms were resolved within minutes.

The infusion of NSS led to the onset of similar symptoms (ie, dizziness, nausea, and stomach discomfort) as were observed with the infusion of natalizumab. Is it likely that these symptoms are related to anxiety or a vasovagal reaction and that this is not an infusion reaction specific to natalizumab?

After consideration that this constellation of symptoms was potentially related to a vasovagal reaction precipitated by the location of the peripheral catheter, the initial IV site was discontinued and a new vascular access site was selected. Following reaccess in the patient's left arm, the infusion was restarted with NSS followed by natalizumab, without further incident. Vital signs were within the normal range. The patient completed a 1-hour observation period without sequelae and was discharged. Subsequent monthly infusions of natalizumab were administered without the occurrence of adverse events.

In this case, a change in the location of the peripheral access allowed resumption of the infusion without sequelae. Consideration of peripheral access location is important if there is a possibility that the patient is experiencing anxiety or a vasovagal reaction.

The vasovagal-like response observed in this case is characteristic of vasovagal syncope that can occur in other settings, including carotid sinus hypersensitivity, phlebotomy, and blood-injury phobia. Although the underlying mechanism has not been clearly defined, the occurrence of vasovagal syncope during blood-injury phobia suggests a CNS-related mechanism.⁴¹

Case 2

Delayed Hypersensitivity Reaction

A 53-year-old female patient was diagnosed with MS in August 2007, following the onset of related symptoms in 2006. At this time, the patient used a rollator walker for assistance in ambulation because of weakness in her legs and often used a wheelchair to help conserve energy. She received her first treatment with natalizumab in October 2007 and her second treatment in November 2007.

Before initiating the second natalizumab infusion, the patient's vital signs were considered normal, with a BP of 126/90 mm Hg and heart rate of 85 bpm. A 22-gauge angiocatheter was used to start an IV line and 100 mL of NSS was infused. Subsequently, IV natalizumab 300 mg was administered in 100 mL NSS over 1 hour, followed by a 1-hour postinfusion observation period per protocol. The infusion and observation periods were completed without complications. The patient's postinfusion BP was 125/82 mm Hg, and her heart rate was 92 bpm.

Two days after the second natalizumab infusion, the patient developed a rash on her arms, chest, and back that was described as red, bumpy, and scabbed. The patient also reported itching and burning.

Is the described rash indicative of a hypersensitivity reaction? Is the rash considered an allergic reaction?

How common are delayed hypersensitivity reactions posttreatment with natalizumab?

Is it appropriate to discontinue treatment if a patient reports clinical benefit?

In this case, the patient treated the rash with diphenhydramine cream and oral diphenhydramine 50 mg. When the patient returned for her next infusion in December 2007, she was denied treatment because the prescriber determined that the rash was a delayed hypersensitivity reaction, despite her perception that the natalizumab treatment was making her legs stronger.

Allergic reactions often present as hives, rigors, or the appearance of a red rash on the back, neck, or any part of the body and typically occur shortly after the administration of an infusible drug and peak with the second infusion.⁴⁰ The observed reaction occurred 2 days after the patient received natalizumab (rather than within minutes or a few hours); however, the allergic response that the patient experienced was indicative of a type I, IgE-mediated hypersensitivity reaction. Delayed hypersensitivity reactions associated with natalizumab typically occur within 7 to 10 days postinfusion, and the symptoms of these reactions differ depending on the type of reaction.³¹ In a recent study, 4 of 40 patients with relapsing–remitting MS experienced a delayed hypersensitivity reaction following treatment with natalizumab.⁴⁰ Because hypersensitivity reactions can involve many organ systems, or lead to a systemic response (eg, anaphylaxis), the signs, symptoms,

and timing of the reactions can vary considerably.^{40,42} As with any infusible therapy, it is critical for healthcare providers to clearly understand the symptoms associated with any potential hypersensitivity reactions related to the infusion of natalizumab. Patients should be educated about these symptoms and the potential for a delayed reaction and instructed as to when it is appropriate to seek medical attention.³¹ Importantly, proactive education can help to manage unrealistic expectations regarding patients' perceived clinical benefits and emphasize that the risk of potential serious adverse effects must be carefully considered before resuming therapy.

Case 3

Immediate Hypersensitivity/Anaphylactic Reaction

A 23-year-old female patient with a history of lower extremity weakness since the age of 18 was diagnosed with MS following a brain MRI in December 2003. The patient was initially treated with IFN- β 1a and pulse IV steroids but continued to experience symptoms of altered sensations with enhancing lesions on subsequent MRI scans. She received an initial IV infusion of natalizumab in February 2005 without incident. When natalizumab was unavailable, treatment with IFN- β 1a and steroids was reinitiated; however, the patient continued to experience progressive disease activity based on MRI scans. In February 2007, the patient received a second IV infusion of natalizumab 300 mg in 100 mL NSS. The only reported complaint was slight nausea that occurred approximately 15 minutes after the start of the infusion and resolved with antiemetic treatment (ondansetron 4 mg by IV push).

In March 2007, the patient was refused natalizumab treatment because of a slight fever and was scheduled to return for the next infusion approximately 1 week later. At this time, the infusion nurse also learned that the patient had gone to the hospital, complaining of joint aches and a headache 1 week after receiving infusion therapy with natalizumab in February. The patient returned for the rescheduled natalizumab infusion. Baseline vital signs were a temperature of 97.4°F, heart rate of 88 bpm, and BP of 108/60 mm Hg. Within 3 minutes of the start of infusion, the patient complained of shortness of breath with erythema of the face, chest, and arms. The natalizumab infusion was stopped immediately.

Is this case typical of an immediate hypersensitivity reaction?

What is the chance of anaphylaxis? What is the danger of continuing the infusion?

In this case, the patient's symptoms of shortness of breath and rash occurred within minutes of the start of the infusion and indicated an immediate hypersensitivity reaction. As with any infusion where a hypersensitivity

or allergic reaction is suspected, there is a chance of anaphylaxis. Because patient safety is the primary concern, the infusion should not be continued.

The patient was placed in the Trendelenburg position, but she complained of having more difficulty in breathing. Within 10 minutes, the patient received 0.3 mL epinephrine 1:1000 given SC, and NSS was infused wide open. The patient's vital signs following administration of epinephrine included a BP of 110/66 mm Hg and an apical heart rate of 152 bpm. Within 15 minutes, the patient's BP was 138/60 mm Hg and apical heart rate was 128 bpm. Over the next 5 minutes, the patient continued to experience shortness of breath, and diphenhydramine 25 mg and methylprednisolone 125 mg were administered by IV push. The patient was transported to the hospital via emergency medical services. At the time of transfer, the patient's BP was 140/80 mm Hg and heart rate was 96 bpm.

What is the emergency plan for serious infusion reactions in your healthcare setting? Is the emergency plan shared with the infusion staff and appropriate training implemented?

Although antibody blood test results were negative for antinatalizumab antibodies, the patient and her physician decided to discontinue natalizumab treatment. In April 2007, the patient was seen in a follow-up appointment and reported no setbacks in disease status since her reaction to natalizumab.

Because antibody tests were negative for antinatalizumab antibodies, is it safe for the patient to continue treatment in the future?

The presence of antinatalizumab antibodies has been associated with reduced clinical efficacy and persistent infusion-related reactions.⁴³ Hypersensitivity reactions are more common among patients who develop these antibodies. Although the patient in this case was tested and did not have antinatalizumab antibodies, she experienced a serious hypersensitivity reaction. It is not recommended that patients be retreated with natalizumab following a hypersensitivity reaction.²⁰

Late in April 2007, brain MRI scans revealed several new enhancing lesions, as well as increased size and progression of the existing lesions. Treatment options were discussed with the decision to administer IV methylprednisolone for 5 consecutive days, once every 4 months. Of note, the patient is planning pregnancy. Natalizumab is considered a pregnancy category C agent; no well-controlled clinical studies have been conducted to date in pregnant women.²⁰

NURSING IMPLICATIONS

Monoclonal antibody infusions should be administered by a registered nurse who is skilled and competent in

administering biologic therapies. Although nurses do not necessarily need to be certified infusion nurses, they should be well versed in all aspects of managing infusion therapy and its potential complications, including recognition of the usual/most common signs of hypersensitivity reactions. At least 2 healthcare providers experienced in managing infusion-related reactions should be on hand during the infusion. For the administration of any IV drug, it is essential that the drug therapy is properly prepared and the patient is treated according to the protocol. In addition, it is critical for the infusion clinic staff to have a clear understanding of patient needs and to be prepared to accommodate these needs prior to treatment. The following guidelines and recommendations are intended to assist in this preparation.

Telephone Assessment

It is recommended that a telephone snapshot assessment of patients with MS be conducted by the infusion clinic staff to help determine patient care needs and facilitate the ease of drug administration when therapy is first initiated. A short assessment tool, including questions designed to determine ambulation, elimination, cognition, and caregiver requirements, can be used before a patient's first visit to assist the clinic in determining staffing and situational needs prior to the first day of treatment. There are a variety of tools available that may be adapted for use in designing a telephone assessment. Alternatively, implementing an assessment of its own design, based on the practice setting, may best serve an individual clinic's needs.

Needs assessment and quick functionality questions that are simple and easily understood can aid in ensuring the continuity and adequate provision of care in the daily operations of the infusion clinic. Some of the questions may include the following:

"Do you need assistance to walk?"

"Would you require help to or in the restroom?"

"Have you been ill recently?"

"Will someone be assisting you?"

In conjunction with other questions, these questions can provide a snapshot of the patient's functionality and the impact it may have on provision of his or her own care or that of others in the infusion clinic.

In particular, the telephone assessment should be used to determine a patient's ambulation status (eg, use of a cane, walker, or wheelchair), which can impact the seating location of a patient upon entrance into the infusion area, their proximity to handicapped-accessible restroom facilities, and the level of assistance required from the infusion clinic staff. For example, those patients with urinary urgency and frequency may require multiple uses of the restroom, which necessitates a convenient location for seating and the minimization of the time actually spent in

**TABLE 3**

Preinfusion Checklist for Nurses Administering Natalizumab

Check vital signs (including temperature, respiratory rate, heart rate, and blood pressure) before beginning the infusion (baseline data are needed).
Know your patient: conduct a preinfusion interview.
Ensure that the patient is hydrated and has eaten recently.
Ask the patient about current health status and concomitant medications, including infections, fevers, recent immunizations, cancer chemotherapy, or other immunosuppressive treatments.
In particular, inquire about any cardiovascular events, pulmonary health/asthma, diabetes/endocrine dysfunction, and history of cancer.
Ask questions regarding allergies and inquire about any family history of allergies, including food allergies, types of allergic responses, and premedication requirements.
Assure compliance with the Tysabri TOUCH [®] Prescribing Program related to drug administration. ²⁰
Review infusion instructions for natalizumab to ensure that appropriate premedication protocols, rate of infusion, and monitoring guidelines are followed.
Natalizumab is administered at a dose of 300 mg, diluted in 100 mL of 0.9% NSS, and infused over approximately 1 h, once every 4 weeks.
Know the infusion center emergency protocol (ie, recognize the typical signs and symptoms of a reaction and know how to manage these symptoms) and ensure that emergency supplies are available. In the case of patients receiving their second infusion, reaction medications should be prepared and readily available in case of hypersensitivity.
<i>Abbreviation: NSS, normal saline solution.</i>

the clinic. Some patients may also require significant transfer assistance, consequently decreasing the time nursing staff are able to assist other patients. Of note, any additional staff members who may assist in the transfer of

patients should be properly trained in transfer techniques to avoid injury to patients and/or staff. Assessment questions regarding recent infection status, particularly urinary tract infections that can translate to worsening of MS

**TABLE 4**

Checklist of Suggested Procedures for Patient Monitoring During an Infusion³¹

Ask patients how they are feeling; observe patients.
Check the intravenous infusion site for redness, warmth, pain, swelling, or leakage.
Ask patients whether they are experiencing itching or discomfort.
Skin reactions, such as hives, may indicate a hypersensitivity reaction.
If it is suspected that the patient may be experiencing a hypersensitivity reaction (eg, the patient is experiencing urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, or chest/back pain), respond calmly and follow the recommended procedures:
Discontinue the infusion.
Position the patient in the supine or Trendelenburg position (depending on patient comfort).
Maintain intravenous access in case fluid support or emergency treatment is needed.
Provide oxygen support as needed.
Check vital signs and notify the physician.
Follow the emergency protocol established by the facility for the management of hypersensitivity reactions.

symptoms (eg, spasticity, cognitive variability, and other symptoms), may prove vital in determining infusion nursing staff requirements for the day of treatment.

Preinfusion Checklist

Prior to infusion, the healthcare provider should review the patient's medical records. The records should be updated with any new information related to concomitant disease conditions, new medications, allergies, or any other changes in the patient's health status. These changes include pregnancy or breast-feeding, elevated body temperature, untreated infections, vaccinations within the preceding 2 weeks, abnormal vital signs, and skin rashes. The prescriber should be notified prior to the start of the infusion if any of these characteristics are present.

Because of the rare occurrence of progressive multifocal leukoencephalopathy in patients treated with natalizumab, the guidelines for the Tysabri TOUCH® Prescribing Program for pharmacovigilance should be followed.⁴⁴ Thus, patients should be asked questions relating to potential changes or worsening in neurologic status, such as changes in cognition, eyesight, balance, or strength. Any potential signs of progressive multifocal leukoencephalopathy warrant immediate evaluation by the physician, and natalizumab treatment should not be given until the prescribing physician has cleared the patient for treatment. At this time, the details of the infusion procedure (eg, infusion equipment used, site of the infusion, rate of the infusion, infusion start and end times, and the patient's response during the infusion) should be recorded on the patient's chart. A suggested preinfusion checklist for nurses administering natalizumab is presented in Table 3. The necessary medications for treating infusion-related reactions should be available prior to the initiation of the natalizumab infusion.

Patient Monitoring During the Infusion

In addition to monitoring a patient's vital signs and the infusion site, communication with the patient during the infusion plays a key role in ensuring the safety and success of treatment. Some patients may be so anxious for the treatment to work for them that they may not be forthcoming about any discomfort they are experiencing during the infusion. Significant cognitive and/or speech impairment may also prevent some patients from conveying their discomfort. Thus, it is especially important to observe patients for visual clues that may indicate distress (eg, the patient's eyes are turning red; he or she is sitting up or forward in the infusion chair, possibly due to nausea, difficulty breathing, or a feeling of an oncoming bowel movement). In addition, vascular access sites should be checked for signs of fluid infiltration or phlebitis. Although natalizumab is not toxic to the skin

and has not been shown to be a vascular or skin irritant, any infiltration should be treated according to the established guidelines.³² Suggested procedures³¹ for patient monitoring during the infusion are outlined in Table 4.

Postinfusion Follow-up

Patients should be monitored for 1 hour following the infusion to avoid any potential complications associated with treatment, including problems with vascular access, infusion reactions, or hypersensitivity.

SUMMARY

Multiple sclerosis is a complex disease associated with various physical, emotional, and cognitive impairments. Many unique, disease-specific challenges must be considered when providing care to patients with MS who are undergoing infusion therapy, particularly those patients who require recurrent visits for ongoing treatment. Consideration of accessibility and other environmental adaptations is recommended to facilitate the safety and comfort of these patients.

Nurses play a vital role in the early identification of infusion and hypersensitivity reactions and the proactive education of their patients. Because a rapid response and appropriate management of hypersensitivity reactions is crucial for optimal patient outcomes, infusion nurses should be familiar with the signs and symptoms of the typical infusion reactions seen with monoclonal antibody infusion, as well as the symptoms of more severe hypersensitivity reactions. By monitoring patients throughout treatment and responding promptly with appropriate management strategies, infusion nurses can have a significant and positive impact on treatment adherence and clinical outcomes in patients with MS.

REFERENCES

1. Lassmann H, Bruck W, Lucchinetti CF. The immunopathology of multiple sclerosis: an overview. *Brain Pathol.* 2007;17(2):210-218.
2. Compston A, Coles A. Multiple sclerosis. *Lancet.* 2002;359(9313):1221-1231.
3. Behan PO, Chaudhuri A, Roep BO. The pathogenesis of multiple sclerosis revisited. *J R Coll Physicians Edinb.* 2002;32:244-265.
4. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med.* 2000;343(13):938-952.
5. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S, Bo L. Axonal transection in the lesions of multiple sclerosis. *N Engl J Med.* 1998;338(5):278-285.
6. Vollmer T. The natural history of relapses in multiple sclerosis. *J Neurol Sci.* 2007;256(suppl 1):S5-S13.
7. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. *Neurology.* 1996;46(4):907-911.

8. Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002;58(2):169-178.
9. AVONEX® (Interferon beta-1a) IM Injection [package insert]. Cambridge, MA: BIOGEN IDEC Inc; 2006.
10. COPAXONE® (glatiramer acetate injection) [package insert]. Kansas City, MO: TEVA Neuroscience, Inc.; 2007.
11. Rebif® (interferon beta-1a) SC injection [package insert]. Rockland, MA: EMD Serono, Inc.; 2008.
12. BETASERON® (Interferon beta-1b) for SC injection [package insert]. Montville, NJ: Bayer HealthCare Pharmaceuticals Inc; 2008.
13. EXTAVIA (Interferon beta-1b) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2009.
14. Baumhackl U. The search for a balance between short and long-term treatment outcomes in multiple sclerosis. *J Neurol*. 2008; 255(suppl 1):75-83.
15. Ebers GC, Hommes O, Hughes RAC, et al. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. *Lancet*. 1998;352(9139):1498-1504.
16. Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Engl J Med*. 2000; 343(13):898-904.
17. NOVANTRONE® (mitoxantrone) for injection concentrate [package insert]. Rockland, MA: EMD Serono, Inc.; 2007.
18. Morrissey SP, Le Page E, Edan G. Mitoxantrone in the treatment of multiple sclerosis. *Int MS J*. 2005;12(3):74-87.
19. Rose JW, Foley J, Carlson N. Monoclonal antibody treatments for multiple sclerosis. *Curr Neurol Neurosci Rep*. 2008;8(5):419-426.
20. TYSABRI® (natalizumab) injection for intravenous use [package insert]. South San Francisco, CA: Elan Pharmaceuticals, Inc; 2008.
21. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006;354(9):899-910.
22. Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med*. 2006;354(9):911-923.
23. Gamarra RM, McGraw SD, Drelichman VS, Maas LC. Serum sickness-like reactions in patients receiving intravenous infliximab. *J Emerg Med*. 2006;30(1):41-44.
24. Kugathasan S, Levy MB, Saeian K, et al. Infliximab retreatment in adults and children with Crohn's disease: risk factors for the development of delayed severe systemic reaction. *Am J Gastroenterol*. 2002;97(6):1408-1414.
25. Colombel JF, Loftus EV Jr, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology*. 2004;126(1):19-31.
26. RITUXAN® (rituximab) injection for intravenous use [package insert]. South San Francisco, CA: Genentech, Inc.; 2008.
27. Schutgens RE. Rituximab-induced serum sickness. *Br J Haematol*. 2006;135(2):147.
28. Mohr DC, Goodkin DE, Likosky W, et al. Therapeutic expectations of patients with multiple sclerosis upon initiating interferon beta-1b: relationship to adherence to treatment. *Mult Scler*. 1996; 2(5):222-226.
29. Girouard N, Theoret G. Management strategies for improving the tolerability of interferons in the treatment of multiple sclerosis. *Can J Neurosci Nurs*. 2008;30(4):18-25.
30. Ross AP. Tolerability, adherence, and patient outcomes. *Neurology*. 2008;71(24)(suppl 3):S21-S23.
31. O'Leary S, Beavin J, Bishop C, Capolino L, Greinel E, Hudson E. Practical guidelines for administering natalizumab: a nursing perspective. *Int J MS Care*. 2007;9:1-8.
32. Infusion Nurses Society. *Policies and Procedures for Infusion Nursing*. 3rd ed. Norwood, MA: Infusion Nurses Society; 2006.
33. Waters W, Brawner J, Winter T. *MS Center of Atlanta Adverse Event Protocol*. 2007.
34. Lenz H-J. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist*. 2007;12(5):601-609.
35. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of anaphylaxis. *J Allergy Clin Immunol*. 1998;101(6, pt 2):S465-S528.
36. Update on the emergency medical treatment of anaphylactic reactions for first medical responders and for community nurses. *Resuscitation*. 2001;48(3):241-243.
37. Roujeau J-C, Stern RS, Wintroub BU. Cutaneous drug reactions. In: Fauci AS, Braunwald E, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine*. 17th ed. New York: McGraw Hill Medical; 2008:343-349.
38. Volcheck GW. Clinical evaluation and management of drug hypersensitivity. *Immunol Allergy Clin North Am*. 2004;24(3):357-371, v.
39. Krumbholz M, Pellkofer H, Gold R, Hoffmann LA, Hohlfield R, Kumpfel T. Delayed allergic reaction to natalizumab associated with early formation of neutralizing antibodies. *Arch Neurol*. 2007;64(9):1331-1333.
40. Hellwig K, Schimrigk S, Fischer M, et al. Allergic and nonallergic delayed infusion reactions during natalizumab therapy. *Arch Neurol*. 2008;65(5):656-658.
41. Bloomfield DM. Strategy for the management of vasovagal syncope. *Drugs Aging*. 2002;19(3):179-202.
42. Gobel BH. Hypersensitivity reactions to biological drugs. *Semin Oncol Nurs*. 2007;23(3):191-200.
43. Calabresi PA, Giovannoni G, Confavreux C, et al. The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL. *Neurology*. 2007;69(14):1391-1403.
44. Biogen Idec. The TYSABRI TOUCH® prescribing program. http://www.tysabri.com/tysbProject/tysb.portal/_baseurl/twoColLayout/SCSRepository/en_US/tysb/home/touch-prescribing/index.xml. Accessed November 3, 2008.



APPENDIX

Additional Resources for Infusion Nurses

- Infusion Nurses Society
315 Norwood Park South
Norwood, MA 02062
Phone: 781-440-9408
Fax: 781-440-9409
Web site: <http://www.ins1.org>
- Association for Vascular Access
5526 W. 13400 South
Suite 229
Herriman, UT 84096
Phone: 1-877-924-AVA1
Web site: <http://www.avainfo.org>
- Multiple Sclerosis Foundation
6350 North Andrews Ave
Fort Lauderdale, FL 33309
Phone: 888-673-6287
Fax: 954-351-0630
Web site: <http://www.msfacts.org>
- Multiple Sclerosis Association of America
706 Haddonfield Rd
Cherry Hill, NJ 08002
Phone: 800-532-7667
Fax: 856-661-9797
Web site: <http://www.msaa.com>
- Consortium of Multiple Sclerosis Centers
359 Main St, Suite A
Hackensack, NJ 07601
Phone: 201-837-9241
Web site: <http://www.mscares.org>
- American Nurses Association
8515 Georgia Ave
Suite 400
Silver Spring, MD 20910
Phone: 800-274-4262
Fax: 301-628-5001
Web site: <http://www.nursingworld.org>
- International Organization of Multiple Sclerosis Nurses (IOMSN)
359 Main St, Suite A
Hackensack, NJ 07601
Phone: 201-487-1050
Fax: 201-678-2291
Web site: <http://www.iomsn.org>
- National Multiple Sclerosis Society
733 Third Ave
New York, NY 10017
Phone: 800-344-4867
Web site: <http://www.nationalmssociety.org>
- Multiple Sclerosis Trust
Spirella Bldg
Bridge Rd
Letchworth Garden City
Hertfordshire SG6 4ET
United Kingdom
Phone: 01462-476700
Fax: 01462-476710
Web site: <http://www.mstrust.org.uk>