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Hugh McCulloch
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Recent Advances in Management and Treatment of Hereditary Angioedema

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KEY WORDS

hereditary angioedema, treatment, prophylaxis, C1 inhibitor, bradykinin

ABBREVIATIONS

HAE—hereditary angioedema
C1-INH—C1 inhibitor
SDP—solvent detergent-treated plasma
FFP—fresh-frozen plasma
TA—tranexamic acid
nfC1-INH—nanofiltered C1 inhibitor
pdC1-INH—plasma-derived C1 inhibitor
rhC1-INH—recombinant human C1 inhibitor
FDA—Food and Drug Administration

Drs Sardana and Craig developed and worked on the manuscript and meet the requirements for being authors on the basis of substantial contribution to design of the study and the manuscript, drafting of the article and revising it as necessary, and approving the final version submitted; neither author is a government employee.

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abstract

CONTEXT: Hereditary angioedema (HAE) is a rare autosomal-dominant disease characterized by recurrent self-limiting episodes of skin and mucosal edema. Morbidity and mortality are significant, and new and pending therapies are now available to reduce the risk associated with the disease.

OBJECTIVE: To update the reader on new advances in HAE to improve patient care.

METHODS: We performed a literature search of Ovid, PubMed, and Google to develop this review. Articles that are necessary for the understanding and use of the new therapeutic options for HAE were chosen, and studies of high quality were used to support the use of therapies, and in most cases, results from phase III studies were used.

RESULTS: Until recently, therapy for HAE attacks in the United States consisted of symptom relief with narcotics, hydration, and fresh-frozen plasma, which contains active C1 inhibitor. Therapy to prevent HAE attacks has been confined to androgens and, occasionally, antifibrinolytic agents; however, both drug groups have significant adverse effects. The approval of C1-inhibitor concentrate for prevention and acute therapy has improved efficacy and safety. Ecallantide has also been approved for therapy of attacks, and icatibant is expected to be approved in the next few months for attacks. Recombinant C1 inhibitor is presently in phase III studies and should be available for attacks in the near future.

CONCLUSION: In this article we review the changing therapeutic options available for patients in 2011 and beyond. *Pediatrics* 2011;128:1173–1180

The objective of this state-of-the-art review is to update the pediatric physician on recent and pending advances in the prevention and treatment of hereditary angioedema (HAE). We focus mainly on therapeutic changes that have occurred over the past 3 years and are expected to occur in the next 2 years.

OVERVIEW

HAE is characterized by self-limited tissue swelling that most often affects the skin and upper respiratory and gastrointestinal tracts. The prevalence of HAE is estimated between 1 in 10 000 and 1 in 150 000 worldwide, and the estimated population of people with HAE in the United States ranges from 6000 to 10 000 people; however, we expect that the number of patients with HAE is greater. Most data show no deviation correlated to either gender or ethnicity. There is a significant age-related difference in frequency of HAE attacks (there is an increase at the time of puberty), but quality of life is affected significantly at all ages.^{1,2}

The underlying cause of HAE is attributed to autosomal-dominant inheritance of mutations in the C1 inhibitor (C1-INH) gene (*SERPINC1*), which was mapped to chromosome 11 (11q12-q13.1). More than 200 mutations of this gene have been linked to the clinical HAE manifestations.³ The majority of the HAE cases show a familial pattern of inheritance, whereas 25% are related to spontaneous mutations.

Two types of HAE account for the majority of cases. An estimated 85% of all patients have type 1 HAE, characterized by low production of functionally active C1-INH. The majority of patients with non-type 1 HAE have type 2 HAE, characterized by normal or elevated levels of C1-INH but with functional impairment of the protein. Recently, a type 3 HAE (Mendelian Inheritance in Man No. 610618) was described. Type 3

HAE has similar clinical manifestations to the first 2 types but differs in that there are no abnormalities in C4 or C1-INH level or function. A mutation in coagulation factor XII protease (Hageman factor) with dominant inheritance is suspected to occur in some case of type 3 HAE, but causation has not been documented.⁴⁻⁷ Type 3 HAE will not be discussed further in this review.

Almost half of all patients with HAE manifest the disease before puberty. The earliest onsets of HAE occur within the first year of life, and in 35% the disease presents between puberty and 20 years of age.^{8,9} Another 15% develop their first episode later in young-adult life, and only ~4% of patients experience their first attack after the age of 40.^{9,10}

The number of attacks also varies among patients. Evidence indicates that patients with onset of symptoms before the age of 5 have attacks more frequently than those who develop HAE after 15 years of age.⁹ In a study of 226 patients with HAE, the frequency of yearly attacks varied; 50% experienced ≤5 per year, whereas 30% had >12 attacks per year.⁸ The diagnosis of HAE is commonly delayed. The average time from the beginning of symptoms to diagnosis ranges between 13 and 21 years.^{1,11} This delay results in significant morbidity and even mortality in affected patients. The knowledge of affected family members expedites recognition of the disease.¹¹

Clinical presentation of HAE can involve any area of the skin, upper airway, or abdomen. Almost all patients with HAE experience skin swelling. The disease commonly affects extremities but can target any body part and cause temporary debilitation and disfigurement that can last for up to 1 week. Facial edema might occasionally progress to laryngeal swelling, which can be life-threatening and cause prolonged intensive respiratory care or

even death from asphyxia.¹² Laryngeal edema is most common in patients between 11 and 45 years of age.¹³ Untreated laryngeal edema usually progresses for up to 8 to 12 hours and can last for up to 4 days. Patients with laryngeal edema might require urgent ventilator support and, therefore, should be observed in well-equipped facilities such as emergency departments or ICUs.

Abdominal HAE represents a different scope of medical and social problems for patients. Abdominal attacks can last for 1 to 8 days and often keep patients on bed rest with a loss of productive time. Children with abdominal attacks might require hospitalization. During abdominal attacks patients may experience significant pain, which might be misdiagnosed as a surgical abdominal emergency. Accordingly, more than one-third of patients with HAE have had their appendix removed or carry a history of exploratory laparoscopies.⁸

ADVANCES

Treating Patients With HAE

Treatment options for HAE vary in terms of treatment for acute attacks, chronic therapy for patients with frequent attacks, and short-term prophylactic treatment before or during a known exposure to triggers such as infection, surgery, dental work, and trauma. According to the current 2010 international consensus algorithm for the diagnosis, therapy, and management of HAE, supportive therapy combined with the specific therapies discussed below is the preferred therapy for HAE attacks.¹⁴ General measures for treating attacks involve hydration, pain relief, and treating as soon as possible with plasma-derived C1-INH (pdC1-INH) or ecallantide. It is anticipated that icatibant (presently available in Europe) and recombinant human C1-INH (human protein derived from rab-

bits) (rhC1-INH) will soon be available in the United States as additional therapies for attacks. If first-line drugs are not available, solvent detergent-treated plasma (SDP) or fresh-frozen plasma (FFP) may be used as second-line agents.¹⁴

Infusion of FFP is effective for HAE attacks.^{14,15} Active C1-INH is one of the ingredients in FFP, which replenishes the protein. Reservations about the use of FFP include greater risk of blood-borne pathogens when compared with SDP or C1-INH concentrate and anecdotal reports of worsening of angioedema after administration of FFP or SDP secondary to the kinin substrate contained in the products.¹⁵ Nonetheless, data support that SDP/FFP is effective and tolerated in the majority of patients but should be used only when C1-INH or ecallantide is not available.¹⁵

For patients with frequent episodes of angioedema or severe HAE, preventive measures with attenuated androgens, antifibrinolytic agents, or C1-INH are recommended. Danazol is the most common androgen used worldwide. Three other androgens, methyltestosterone, stanozolol, and oxandrolone, are used as alternatives.^{16–21} Oxandrolone is the preferred androgen for the pediatric population, but it is still relatively contraindicated.^{19,20} Stanozolol is no longer available in the United States unless it is specifically compounded. The exact mechanism of action of androgens is still debated. Blood levels of C1-INH increase with chronic use of androgens; however, many suspect that effects on the generation of factor 12 might also result in benefit. Because of the wide range of potential adverse effects (weight gain, hypertension, dyslipidemia, acne, virilization, menstrual irregularities, decreased libido, hepatic necrosis, premature closure of growth plates, and hepatic neoplasms), patients treated

with attenuated androgens should be monitored closely.^{20,21} The major concern in children is early closure of the epiphyseal plate leading to decrease in growth and virilization. Because of these adverse effects, the use of androgens is often delayed until after puberty or when full height has been achieved; an exception is short-term use before procedures, in which case these risks are minimized and preferred over the use of FFP.^{19–22}

Antifibrinolytic agents may be used when androgens are contraindicated (prepuberty, pregnancy, lactation, hepatitis) or poorly tolerated and when other treatments have failed. However, antifibrinolytic agents are generally less effective than androgens.^{14,19} Antifibrinolytic agents are often recommended as a drug of choice for children with severe HAE; however, off-label use of C1-INH is an alternative (its main limitation is cost). The therapeutic effect of antifibrinolytic agents is thought to be a result of deactivation of plasminogen and subsequent decreased consumption of C1-INH. In general, the adverse effects of antifibrinolytic agents include hypotension, cardiac arrhythmias, rhabdomyolysis, and generation of thrombi and associated risk of emboli. ϵ -Aminocaproic acid, although used for treatment of HAE in the past, has been replaced with tranexamic acid (TA) because of its fewer adverse effects and better tolerability; however, TA is rarely used in the United States.¹⁴ TA dosage is not standardized, and close monitoring (creatinine kinase levels, urinalysis, liver and renal function, ophthalmology examination) for adverse events is required.¹⁹

Plasma-Derived C1-INH

C1-INH concentrate derived from human plasma has been used for the treatment of acute HAE for >3 decades in Europe.^{16,23–29} Sanquin (Leiden, Neth-

erlands) produces C1-INH concentrate in Europe under the trade name Ceter, and in the United States it is referred to as Cinryze (nC1-INH) (ViroPharma, Exton, PA). nC1-INH is a nanofiltered, pasteurized C1-INH concentrate for intravenous use. It has been approved by the US Food and Drug Administration (FDA) for adolescent and adult prophylaxis at a dose of 1000 U every 3 to 4 days; however, it has not been approved for treatment of acute attacks.²⁸

The phase III study of nC1-INH performed for FDA approval demonstrated that it is effective as a prophylactic agent to reduce the number of attacks. The number of attacks was significantly reduced, but not eliminated, at a dose of 1000 U given every 3 to 4 days by intravenous infusion. The approximate reduction in attacks was 50%; however, the attacks that did occur in most cases were less severe and shorter in duration. Adverse events recorded during the phase III study were minimal, and there were no recorded episodes of anaphylaxis or seroconversion to HIV, hepatitis A, B, or C, or parvovirus.²⁸ These data led to FDA approval for nC1-INH for prophylactic therapy at 1000 U twice per week; however, nC1-INH was not approved for the treatment of HAE attacks.

A more recently approved C1-INH concentrate, Berinert (pdC1-INH) (CSL Behring, King of Prussia, PA), has been approved for use in acute attacks of HAE in the United States.²⁵ It is a pasteurized lyophilized human pdC1-INH concentrate. A phase III study of pdC1-INH compared the efficacy of 2 doses of the drug (10 and 20 U/kg) to that of placebo in 125 patients with HAE with abdominal or facial angioedema attacks. Compared with those who received placebo, subjects who received 20 U/kg of pdC1-INH had significant reduction in median time to onset of relief of symptoms of HAE attacks (0.5 vs

1.5 hours; $P = .0025$).²⁵ The number of adverse events noted during the phase III studies were greater in those who received placebo compared with those who received the 2 different doses of pdC1-INH, and the adverse effects seemed to represent symptoms of the HAE attack. Secondary to these data, pdC1-INH has been approved for therapy of acute attacks; however, it has not been FDA-approved for prophylactic therapy. The approval is for acute treatment of attacks of HAE at 20 U/kg given as an intravenous infusion.

Recombinant Human C1-INHs

Rhucin (Pharming Technologies BV, Leiden, Netherlands) is an rhC1-INH protein produced from the milk of transgenic rabbits.^{30–32} rhC1-INH is presently under review by the FDA for treatment of acute attacks of HAE. Except for differences in glycosylation, which results in a shorter half-life, rhC1-INH is very similar to native human C1-INH.^{31–33} rhC1-INH has been well tolerated without significant adverse events during phase III studies. Previous allergic reaction to rabbits is a contraindication for therapy; during phase I studies, a person with rabbit allergy had anaphylaxis. An allergic reaction caused by the unique glycosylation is possible but has not yet been described. Otherwise, the adverse-effect profile is similar to that of other C1-INHs and placebo but without the concern of blood-borne pathogens. Because of its short half-life, rhC1-INH is unlikely to be effective for prophylaxis. The accelerated clearance of rhC1-INH compared with pdC1-INH, along with higher C1-INH levels after infusion, make it a promising addition to the therapeutic line of drugs for attacks of HAE. In June 2010, Rhucin received a positive review from the European Medicines Agency Committee for the treatment of acute angioedema in patients with HAE, but Pharming is repeating their phase III study as re-

quested by the FDA in the United States. The anticipated dose will be 50 or 100 U/kg by intravenous infusion as needed for an attack.

Contact System Modulators

Other treatment options work as kinin-pathway modulators. Ecallantide (DX-88) (Kalbitor [Dyax Corp, Cambridge, MA]) is a 60-amino acid recombinant protein that acts as a potent reversible inhibitor of plasma kallikrein.^{34–39} Ecallantide has a rapid on-rate ($k_{on} = 2 \times 10^6 \text{ m}^{-1}\text{seconds}^{-1}$) and a slow off-rate ($k_{off} = 2 \times 10^{-5} \text{ seconds}^{-1}$) that results in high-affinity binding and inhibition of kallikrein. Once activity of kallikrein is suppressed, the cleavage of high-molecular-weight kininogen to bradykinin does not readily occur, which stops production of bradykinin and the edema progression in acute HAE attacks.

Two separate phase III studies of ecallantide have been performed. The first trial, EDEMA3, included 72 patients; the primary end point measured was the treatment outcome score (TOS) at 4 hours. The TOS represents a patient-reported measure of response to therapy using a categorical scale from 100 (improvement) to -100 (worsening). Patients who received ecallantide reported a mean TOS of 49.5 ± 59.4 compared with 18.5 ± 67.8 for those who received placebo. The improvement was maintained over 24 hours.^{39,40}

The second trial, EDEMA4, included 96 patients; the primary end point was mean symptom complex severity at 4 hours. Patients who received ecallantide reported a mean decrease-of-symptom score at 4 hours of 0.81 compared with a decrease of 0.37 in those in the placebo-treated groups. Because of the short half-life of ecallantide (2 hours), it is best used for acute attacks and probably will have a minimal role as a prophylactic agent. In clinical trials, the incidence of adverse

events in patients treated with ecallantide was similar to that in patients treated with placebo, and ecallantide was generally well tolerated with the exception of headache and anaphylaxis. The main adverse event is the possibility of anaphylaxis, which might occur in up to 3% of patients treated with subcutaneous ecallantide. FDA-mandated informed consent, health care provider administration, and tracking of anaphylaxis were requested by the FDA, and self-treatment at home was strongly discouraged.⁴¹

Another kinin modulator investigated for HAE is icatibant (Firazyr [Shire, Hampshire, Ireland]), a synthetic decapeptide that is a specific and selective competitive antagonist of the bradykinin B_2 receptor (BK2R). Structurally, icatibant is similar to bradykinin and binds to BK2R with high affinity.⁴² Safety and tolerability of icatibant were studied in multicenter phase I, II, and III trials that evaluated both intravenous and subcutaneous preparations. It is interesting to note that peak concentration time (0.5 hour) and half-life (1.2–1.5 hours) for icatibant were similar regardless of the route of administration.^{43–48} In a proof-of-concept phase II pilot study, 20 acute abdominal and peripheral attacks in 15 patients were treated with icatibant. Rapid relief of symptoms was observed after drug administration, and results were similar in the intravenously ($n = 12$) and subcutaneously ($n = 8$) treated groups. The median time to patient-reported first symptom improvement was <4 hours, whereas symptoms of untreated attacks started resolving in ~ 34 hours.⁴⁹

These data led to "For Angioedema Subcutaneous Treatment" (FAST-1 and FAST-2) phase III trials of subcutaneous application of icatibant for treatment of acute HAE attacks. FAST-1 was a double-blinded, placebo-controlled study with icatibant or placebo per-

formed in the United States. The treatment with icatibant significantly shortened the onset time of symptom relief (0.8 vs 16.9 hours in the treated and placebo groups, respectively; $P < .001$). However, the trial failed to show a statistical difference in median time to significant symptom relief (2.5 vs 4.6 hours in the treated and placebo groups, respectively; $P = .142$). The latter required Shire to repeat its phase III study of icatibant in the United States, which was completed just recently.⁴⁹

The FAST-2 trial was more successful. Seventy-four patients with acute HAE attacks from 11 European countries and Israel were randomly assigned to receive icatibant or its comparator (TA). Significant improvement was demonstrated in patients treated with icatibant. The time to onset of symptom relief was 0.8 vs 7.9 hours ($P < .001$), and the median time to significant symptom improvement was 2.0 vs 12.0 hours. On the basis of the results from these trials, the European Commission granted marketing authorization for icatibant for treatment of acute HAE attacks within the European Union.⁴⁹

CRITICAL ASSESSMENT

HAE is a serious, chronic disease that requires a highly specialized approach to treatment. The clinical presentation ranges from self-limiting skin edema to debilitating abdominal and life-threatening laryngeal edema. It can manifest in all ages but most commonly presents within the first decade of life. Some patients experience early signs of an evolving attack referred to as prodromal symptoms, but even then, severity and location of the attack can be unpredictable.⁵⁰

Traditional treatment of histamine-induced edema, typically seen in allergic and idiopathic angioedema, with epinephrine, corticosteroids, and antihistamines is still frequently used for

the treatment of HAE in the United States despite data demonstrating ineffectiveness of these medications.³⁸ FFP is often used for treatment of HAE attacks and short-term prophylaxis; however, the use of FFP^{15,22} should be reserved for when C1-INH or ecallantide are not available for acute attacks or when C1-INH is not available for preprocedural therapy.

Oral TA is used for treatment of attacks of HAE in Europe but is not very effective. It is also used for prophylaxis; however, it has a lower efficacy and more adverse effects than androgens or C1-INH. Because of possible teratogenic effect of TA in animals, this drug is rarely used in the United States.⁴⁸ Another antifibrinolytic agent, ϵ -aminocaproic acid, has previously been studied and used for prevention of HAE attacks. It has a poor adverse-effect profile and, thus, its use has been virtually abandoned in the United States and Europe.

Prophylactic prevention of recurrent HAE attacks in the United States is predominantly achieved by the use of danazol. Tolerability of androgens is poor at large-to-moderate doses, but at low doses patients often have control of their HAE with few adverse events.⁴⁷ The lowest effective dose should be used to suppress HAE attacks. Therapy should be adjusted solely on the basis of clinical response and not on serial assessment of C4 or other laboratory tests. Most HAE experts recommend that blood pressure, liver-function studies, and lipid panels be monitored initially and every 6 months and liver ultrasound every 12 months.^{14,20}

Of the available new treatment modalities for chronic prophylactic therapy, C1-INH concentrates represent an alternative treatment for prevention of HAE attacks. The FDA approved chronic prophylactic use of nC1-INH on the basis of limited data, and it will be important that physicians monitor adverse

events carefully. Thus far, it seems that the chronic use of C1-INH is safe and effective. Multiple screening steps, virus-inactivation techniques, and a virus-removal step decrease the risk of potential viral transmission.⁴⁸ Dosing should be twice per week on the basis of half-life of C1-INH. Rescue doses of C1-INH might be necessary, because breakthrough attacks occur in most patients despite replacement therapy. The main limiting factor for the use of C1-INH is cost; thus, its use should be considered carefully.¹⁴ Vaccination against hepatitis A and B and serologies to these viruses as well as to hepatitis C, hepatitis E, HIV, human T-lymphotropic virus, and parvovirus should be done before initiation of C1-INH.^{14,28}

For short-term prophylaxis before dental, surgical, or other procedures, human-derived C1-INH used off-label is indicated because of the longer half-life than ecallantide, icatibant, or rhC1-INH and it entails less risk than FFP. Also effective and much less expensive is the use of 200 mg of oral danazol three times daily for 7 days before a procedure and 2 days after the procedure. pdC1-INH and nC1-INH are off-label alternatives to androgens, especially when androgens are contraindicated or poorly tolerated.

The route of administration will likely be a factor in future marketing directions for HAE drugs. pdC1-INH and nC1-INH are currently recommended for intravenous use only and, hence, will be used predominantly in hospital settings or infused by health care services at home. Presently, the HAE Association and many experts in the field are advocating for patient self-treatment of attacks at home. The symptoms of attacks treated within the first 6 hours are relieved faster with less absenteeism and morbidity than when treatment is initiated later, so home therapy has advantages.^{27,50}

Compared with human-derived C1-INHs, rhC1-INH is unique in its absence

TABLE 1 Comparing Medications Approved or Soon to Be Approved in the United States for HAE

Drug Classification	Acute Treatment	Short-term Prophylaxis	Long-term Prophylaxis	Advantages	Disadvantages
FFP/SDP	X	X		Inexpensive, widely available	Viral potential, may worsen attack
Androgens		X	X	Easy to take, oral, inexpensive	Liver toxicity, vascular disease, other adverse events
TA	X		X	Oral	Multiple toxicities, limited effectiveness
ϵ -Aminocaproic acid			X	Oral	Multiple dosing, multiple toxicities
Ecallantide (kinin modulator)	X			Subcutaneous	Short half-life, risk of anaphylaxis
Icatibant (kinin modulator)	X			Subcutaneous, room-temperature-stable	Local pain and burning at injection site, short half-life
Beriner or Ceter (pdC1-INH)	X	X (off-label use)	X (Off-label use)	Replaces deficient protein, long half-life, use for >30 y	Viral transmission possible, intravenous only, expensive
Cinryze (plasma C1-INH)	X (off-label use)	X (off-label use)	X	Replaces deficient protein, long half-life	Viral transmission possible, intravenous only, breakthrough attacks occur, very expensive
rhC1-INH	X	X (Off-label use)		No viral risk	Short half-life, potential for allergic reaction

X indicates that the medication is effective.

of risk of human blood-borne pathogen transmission. As noted previously, the use of rhC1-INH is contraindicated in patients allergic to rabbits because of trace rabbit protein in the product. The adverse-effect profile is otherwise benign. Therapy with rhC1-INH will probably be limited to acute treatment because of the short half-life of the medication. It might be effective for use in short-term prophylaxis as well, but the approval and indications are still pending in the United States. It is anticipated to be used as an alternative for those who are unable or unwilling to receive blood products.

Bradykinin modulators have provided new innovative treatments with the underlying understanding that bradykinin is the primary component in the swelling of HAE. If approved for self-administration, icatibant might become a preferred drug for self-treatment of

acute attacks, because it is administered subcutaneously and is stable at room temperature. The dose is typically 30 mg for adults; the results of pediatric testing are pending. Ecallantide, which is also a subcutaneous formulation, has been approved for the treatment of acute HAE attacks and is effective. The limiting factors for use of ecallantide is the FDA mandate that requires it to be administered in a medical facility and that it needs to be refrigerated. A postapproval survey of ecallantide's safety might lead to self-treatment approval, but a black-box warning in the package insert is a deterrent to self-medication at this time.

CONCLUSIONS

In general, all the newly approved medications for HAE are well tolerated (Table 1). Because of favorable safety pro-

files, these new therapies will likely replace FFP and antifibrinolytic agents. Subcutaneous infusion of C1-INH is being studied for prophylactic therapy. We hope that regular subcutaneous injection of C1-INH will lead to a steady-state plasma level of C1-INH and provide for long-lasting prophylaxis without the need for intravenous therapy. Coagulation factor XII is a likely therapeutic target in the future, because inhibiting factor XII will inhibit bradykinin generation.⁴⁸ Oral medication is presently being investigated and will add significantly to ease of therapy and adherence, but oral therapy for HAE is in early development and years away from the US market. A continued international effort to promote investigational drug studies for rare diseases, including HAE, should be encouraged.

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BUNNY SLOPES: Several ski resorts in Vermont opened this weekend. Around here, this is usually eagerly anticipated and big news. The last of the ski swaps and ski sales are taking place and people are getting ready for the season to begin. This year, as in the past few years, my wife and I will not have to worry too much about getting the kids to the mountain. They all have appropriate and properly fitted equipment. Years ago, however, the story was quite different. We would pack the minivan with spare mittens, helmets, foot and hand warmers, snacks, and just about anything that might make the day more enjoyable. Still, it was hit or miss. One year, my wife and I didn't get a single chance to ski together because one of our children developed cold hands and feet the first day of skiing and refused to ski again. One of us had to stay in the lodge with him while the others enjoyed their time on the slopes. According to an article in The Wall Street Journal (*Life & Culture*: October 12, 2011), ski resorts have realized how important beginner and novice skiers are to the success of a family ski vacation. To ensure that the newest skiers have a successful outing, they have redesigned not only the activities but even the slopes themselves. For example, T-bars and rope tows are being phased out. New skiers can ride to the top of the bunny slope on a conveyer belt or on special lifts that use magnets to literally stick the kids to the seat. New ski jerseys have handles built into them so picking up fallen skiers is much easier. Bunny slopes are now often immediately adjacent to the lodge and have been groomed so that gravity will take the skiers straight down the hill and not to one side. Many toddler ski programs include play rooms equipped with TV, DVDs and hot chocolate for the frequent breaks. There are several good reasons to provide new skiers with a great experience. Since the population that skis is aging and young riders, those less than 18-years-old, only make up 30% of current skiers, the number of lessons for first time skiers continues to fall. Ski resorts hope that by making skiing pleasant for the young skiers, both parents and children alike will want to return. While this sounds great, I still advise parents to invest in warm mittens and boots for their youngest skiers.

Noted by WVR, MD