

# Hereditary Angioedema: Moving Therapy into the Home and to Self-Care

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Hereditary angioedema (HAE) is a condition that results in recurrent and often unpredictable attacks of angioedema, which is associated with significant morbidity and can be fatal. The majority of literature related to management of HAE has focused on the adult patient. There is limited information on treatment and management strategies for the pediatric HAE population. Comprehensive care has been repeatedly recommended in international guidelines for the optimal management of HAE. Home therapy is a critical pillar of such a comprehensive care plan. Hemophilia is similar to HAE in that it is a serious rare blood disorder for which comprehensive care is considered essential. There is a paucity of literature on home therapy as it relates to the pediatric HAE patient population. This review outlines the rationale for home therapy in the management of pediatric HAE by drawing on the experience in pediatric hemophilia and placing it in the specific context of HAE management principles.

## Introduction

**H**EREDITARY ANGIOEDEMA (HAE) is an autosomal dominant condition characterized by recurrent unpredictable attacks of angioedema affecting the face, extremities, upper airway, genitals, and gastrointestinal mucosa that typically start during childhood.<sup>1</sup> HAE attacks are painful, potentially life-threatening, and associated with significant impairment in patient functioning and quality of life.<sup>2</sup> The general approach to pharmacologic management involves enabling on-demand therapy for the treatment of acute angioedema attacks in all HAE patients, and long-term prophylactic therapy for selected patients with frequent or severe attacks and for those whom the disease has a significant impact on their quality of life. Acute treatment may be provided in a hospital or other medical setting, or in the home environment. Hospital-based treatment of acute attacks often requires emergency room visits, absences from school or work, and delay in access to therapy. "Home therapy" in the pediatric patient involves parent or patient administration of HAE treatment, given in the home or other locations outside of a medical environment.<sup>3,4</sup> Home therapy has been demonstrated to be effective and well tolerated in adult patients with HAE,<sup>5-8</sup> and consensus guidelines recommend consideration of home therapy for all HAE patients,<sup>3,9-12</sup> though at this point there is limited evidence for the use of home therapy in pediatric HAE. Home therapy has been used for many years in pediatric hemophilia patients, which serves as a relevant comparator and model of care. This review will discuss the available literature on

home therapy for pediatric HAE and examine the rationale, potential benefits, and limitations of home therapy in the pediatric HAE population.

## Rationale for Home Therapy for Pediatric HAE

Traditional physician administration of on-demand therapy requires the child and family to travel to the local hospital emergency room or other healthcare facility to receive pdC1INH at the onset of an acute attack. Healthcare providers may be unfamiliar with this rare condition, and patients may not be urgently triaged, leading to delay in treatment and increased time away from school or work. Under-recognition, travel, and waiting time all contribute to a delay in appropriate therapy for acute attacks, resulting in increased duration and morbidity of attacks.<sup>3,4</sup> Evidence from observational studies demonstrates that prompt treatment with HAE-specific therapy at the onset of an attack reduces the duration and severity of HAE attacks.<sup>13</sup> Home therapy has the ability to reduce these barriers by enabling fast and efficient access to HAE-specific therapy at the onset of an acute attack.

There are several products licensed by the Food and Drug Administration (FDA) for the treatment of acute attacks, but the route of administration and the indicated ages vary between products. Plasma-derived C1INH (pdC1INH, Berinert<sup>®</sup>; CSL Behring) is approved for use in adults and children older than 12 years of age and is administered intravenously. Plasma kallikrein inhibitor ecallantide (Kalbitor<sup>®</sup>; Dyax Corp) is licensed for acute therapy in patients

12 years of age or older and is administered as a subcutaneous injection. However, Kalbitor should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Recombinant human C1INH (Ruconest<sup>®</sup>; Pharming) is licensed for use in adult and adolescent patients and is administered as an intravenous infusion. Bradykinin receptor antagonist icatibant (Firazyr<sup>®</sup>; Shire) is licensed for use in patients aged 18 years of age and older and is administered subcutaneously.<sup>11</sup>

Plasma-derived C1INH is one of the therapeutic options for long-term prophylaxis. For children requiring pdC1INH for prophylaxis, home therapy eliminates the need to travel to the hospital or other healthcare facility multiple times each week for infusions. Cinryze<sup>®</sup> (Shire) is a pdC1INH licensed by the FDA for routine prophylaxis against angioedema attacks in adolescent and adult patients.

Hemophilia is another genetic condition that manifests in childhood and requires frequent administration of intravenous blood products similar to HAE. In hemophilia, home therapy programs for intravenous factor replacement have been widely established for decades.<sup>14</sup> Comprehensive multidisciplinary care programs provide medical, nursing, and allied health support with home infusion teaching coordinated by a nursing specialist.<sup>14</sup> The implementation of home therapy had a major impact on quality of life for children with hemophilia.<sup>14</sup> Children experienced reduced pain, hospitalization, and school absences, and were observed to have improved integration with peers and participation in physical activity.<sup>14</sup> The experience in home therapy for hemophilia also suggests that children benefit from the opportunity to take an active role in their care, with transition to self-administration of factor replacement in the teenage years or as appropriate.<sup>3,14</sup>

### Evidence for Home Therapy in Pediatric HAE

Home therapy in HAE has been demonstrated to be effective and well tolerated in adults, allowing early treatment of attacks and improved quality of life.<sup>5-8</sup> The feasibility of this approach in pediatric patients is less well established. There is a single retrospective observational study examining the efficacy and safety of home therapy in 20 pediatric HAE patients.<sup>15</sup> The patients ranged in age from 7–17 years (median age 14) and were transitioned to home therapy from physician-administered therapy. Six patients self-administered treatments, and the remainder were treated by parents. Home therapy appeared to be effective, safe, and well tolerated. A reduction in laryngeal attacks and hospitalized days was observed. On home therapy, the average time from onset to treatment of attacks was reduced from 67.5 to 15 minutes, and the average time to initial symptom relief was reduced from 60 to 40 minutes. All attacks, including laryngeal attacks, were successfully treated, and no side effects were reported. Interestingly, there was an overall increase in the frequency of on-demand therapy, which, given the median age of the group, was hypothesized to relate to increased disease activity during puberty. Quality of life was not formally assessed.<sup>15</sup>

While multiple international consensus documents and guidelines recommend that all patients be considered for training to self-administer HAE therapy,<sup>3,9-12</sup> the implementation of home therapy varies by center and health-

care organization. The Frankfurt HAE center has reported that 26 of 274 (24%) of their pediatric patients are receiving home therapy.<sup>16</sup> In the United Kingdom, a survey study of pediatric centers and patients found that 10 of 16 centers could provide home therapy training to children and families, yet only 2 of 101 (2%) patients received pdC1INH therapy at home.<sup>17</sup> A descriptive analysis of database information from the United States reported that the 75% of children younger than 12 years of age were able to receive home therapy with pdC1INH after the implementation of a home therapy training program, and one child was able to self-administer home therapy.<sup>18</sup>

### Patient Selection for Home Therapy

There is little evidence to help guide the appropriate selection of children and families for home therapy. Existing guidelines from the World Allergy Association and HAE international home therapy consensus document recommend home therapy for children who have frequent or disruptive attacks, when a responsible adult is available and willing to be trained to administer the infusion.<sup>3,11</sup> In the aforementioned observational study of pediatric home therapy, most children had more than one severe attack per month.<sup>15</sup> In addition, the patient or parent had to be capable of recognizing signs of impending attack and be willing and able to administer the treatment, including establishing venous access.<sup>15</sup> Parents were required to monitor pdC1INH stock to ensure an adequate supply, and to call the clinic for advice prior to infusions.<sup>15</sup>

### Limitations to Home Therapy for Pediatric HAE

The experience with HAE home therapy in the adult population indicates that pdC1INH appears to be effective and well tolerated by most patients.<sup>5-8</sup> However, the experience in pediatric home therapy is extremely limited, and some experts have proposed that acute care would be best provided by medical professionals, with home therapy serving as an emergency contingency plan in the case that no expert help is available.<sup>1</sup> Parents or patients who undertake home therapy are essentially accepting a partial transfer in responsibility of care from their physician, and they must understand and consent to this.<sup>3</sup> In certain cases, home therapy does not eliminate the need for an emergency room visit. For example, emergency medical attention is still required for all laryngeal attacks, even after home therapy, to monitor upper airway patency, and for severe abdominal attacks to evaluate for other causes of acute abdominal symptoms.<sup>1</sup> Home therapy does not replace clinical follow-up by an HAE expert, and regular reassessment of infusion technique and clinical status are important.<sup>3</sup> In particular, adjustments need to be made regularly in growing children as their weight-based dose of pdC1INH increases, and during puberty, when disease activity often increases.<sup>3</sup> From a medico-legal perspective, pdC1INH is a blood product, and patients must ensure that instructions for documentation, storage, and preparation are followed precisely.<sup>3</sup> The requirement for intravenous administration of pdC1INH may be a barrier to patients who have difficult venous access. There are no licensed subcutaneous HAE-specific therapies available for home administration in pediatric patients. Ecallantide is licensed in the United States

for use in children older than 12 years of age, but must be administered by a healthcare professional, prohibiting home therapy. The lack of a subcutaneous HAE-specific therapy for home administration remains an unmet need in the pediatric HAE population. Lastly, implementation of a pediatric home therapy program requires personnel and infrastructure, and geographic and population disparities may impair access to specialized care and training in home therapy.

### Conclusion

Home therapy for HAE provides immediate access to HAE-specific therapy for treatment of acute angioedema attacks, which can reduce the morbidity and duration of HAE attacks. Evidence from adult HAE and pediatric hemophilia has demonstrated that home therapy can be an effective approach to care, with significant impact on patient quality of life, though it does not replace the need for regular follow-up by an HAE expert. Emerging evidence supports the safety and efficacy of home therapy in pediatric HAE, and larger randomized trials are awaited.

### Author Disclosure Statement

No competing financial interests exist.

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Received for publication October 5, 2014; accepted after revision November 16, 2014.