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HEREDITARY ANGIOEDEMA: CLINICAL CHARACTERISTICS AND CURRENT THERAPEUTIC APPROACHES

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ABSTRACT

Hereditary angioedema (HAE) is a condition characterized by recurrent edema caused by the dysfunction of bradykinin production. Advances in understanding the pathophysiology of this disease have changed the diagnostic approach, acute management and prophylaxis. Optimal treatment now combines early diagnosis, targeted therapy and patient education. This narrative review provides an overview of current evidence regarding the clinical presentation, treatment options and promising new therapies for HAE. A systematic search of the PubMed and Google Scholar databases was conducted using terms such as hereditary angioedema, therapeutics, C1 inhibitor deficiency, bradykinin and disease management. Additional relevant studies were identified by manually reviewing reference lists and citations. The basis for effective treatment is an accurate diagnosis based on clinical symptoms, family history, and laboratory test results. On-demand treatment, such as C1 esterase inhibitor (C1-INH), icatibant, and ecallantide provides rapid symptomatic control. Long-term prophylaxis with agents such as lanadelumab, berotralstat or plasma-derived C1 esterase inhibitor (pdC1-INH) significantly reduces the frequency of attacks and improves patients' quality of life. New data confirm that modern biologic therapies can maintain disease control with a favorable safety profile. Current HAE treatment strategies emphasize personalized prophylaxis, adequate intervention in acute attacks and continuous patient education. Combining modern therapies with individual patient preferences improves daily functioning, mental well-being and overall prognosis.

KEYWORDS

Hereditary Angioedema, Therapeutics, C1 Inhibitor Deficiency, Bradykinin, Disease Management

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1. Introduction

Hereditary angioedema (HAE) is a rare and potentially life-threatening genetic disorder, affecting about 1 in 50,000 people. It is typically inherited in an autosomal dominant pattern (Marco Cicardi et al., 2014; Maurer et al., 2022). However, de novo mutations responsible for the development of the disease have been described (Marco Cicardi et al., 2014; Pappalardo et al., 2000). As early as 1888, William Osler described in detail familial cases of HAE and named it "hereditary angioneurotic edema," emphasizing its hereditary nature (Osler, 2010). A landmark discovery was made in 1963 by Donaldson and Evans, who demonstrated that the disease is caused by a deficiency of C1 esterase inhibitor (C1-INH) (Donaldson & Evans, 1963). The condition results from dysregulated vascular permeability. It is characterized by recurrent episodes of localized, non-pruritic edema involving the skin, mucosal, or submucosal tissues. Overproduction of bradykinin is due to dysregulation of the kallikrein-kinin pathway, which results from deficiency or dysfunction of C1-INH. These episodes are the result of the excessive bradykinin activity, which is a vasoactive peptide that promotes vasodilation and increased endothelial permeability (B. L. Zuraw & Christiansen, 2016).

The clinical course is highly unpredictable, often having a negative impact on patients' quality of life (Caballero, 2021; Maurer et al., 2022; B. L. Zuraw & Christiansen, 2016). The pathophysiological basis of HAE lies in a deficiency or dysfunction of C1-INH, which is a critical regulator of the complement activation system. A mutation in one of the two alleles of the SERPING1 (serpin family G member) gene, which encodes the C1-INH protein, results in this defect (Germenis & Speletas, 2016). Based on the underlying defect, HAE is classified into two primary types: Type I, characterized by reduced quantitative level of C1-INH in the plasma, and Type II, marked by the presence of a dysfunctional but quantitatively normal protein (Marco Cicardi et al., 2014).

Then there is HAE with normal C1 inhibitor function (HAE-nl-C1INH), a subtype of angioedema disorder that differs from classic HAE types I and II. This variant is characterized by a normal level and activity of C1 inhibitor protein, although its clinical manifestations are like HAE-C1-INH symptoms, when patients

often experience episodes of localized, non-pruritic swellings that may involve the skin, mucosal tissues or gastrointestinal tract (Bork et al., 2020; Maurer et al., 2022). HAE-nl-C1INH is less common, and in some cases genetic mutations have been identified as the cause of the disease. These mutations include changes in genes encoding coagulation factor XII (FXII), angiopoietin-1, plasminogen, kininogen-1, myoferlin and heparan 6-O-sulfotransferase. Some of the cases, without detectable genetic abnormalities and of uncertain origin, are classified as HAE of unknown etiology (Bork et al., 2020; Maurer et al., 2022).

2. Methodology

This paper discusses the current knowledge regarding the clinical features and available methods of treatment for HAE, with particular emphasis on studies published between 2015 and 2025. The PubMed and Google Scholar databases were systematically queried using the following keywords: hereditary angioedema, therapeutics, C1 inhibitor deficiency, bradykinin and disease management. In addition, reference lists and citations of selected articles were reviewed to identify potentially relevant studies. Articles were evaluated based on their title and abstract and then selected for full text review.

3. Clinical presentation

Clinical manifestations typically emerge during childhood or adolescence and may involve diverse anatomical regions, including the face, extremities, respiratory tract, genital region and gastrointestinal system (Marco Cicardi et al., 2014; Jacobs & Neeno, 2021; Sinnathamby et al., 2023). Symptom patterns vary among individuals, but most experience recurrent episodes of skin swelling and abdominal pain, with laryngeal edema occurring more rarely (Bork et al., 2012; Sinnathamby et al., 2023). Episodes are distinguished by their gradual onset over several hours, persistence for 2–5 days and spontaneous resolution. Following symptom onset, the condition typically persists lifelong in most affected individuals (Jacobs & Neeno, 2021; Nowicki et al., 2020). Prodromal symptoms such as erythema marginatum or nonspecific fatigue may precede attacks and are often misdiagnosed as allergic reactions (Caballero et al., 2016). Resher et al. reports that up to 82.5-95.7% of HAE patients notice prodromal symptoms in themselves and most can predict an impending attack in most cases (Reshef et al., 2013). Triggers for edema attacks include mechanical trauma, stress, infections, physical exertion and medical procedures. Additionally, in case of females, an increase in estrogen levels during puberty and pregnancy may exacerbate symptoms (Busse & Christiansen, 2020; Caballero et al., 2016; Jacobs & Neeno, 2021). The frequency and severity of attacks can also be heightened by oral contraceptives, hormone replacement therapy and ACE inhibitors (Jacobs & Neeno, 2021). A notable feature of HAE is its resistance to conventional therapies for angioedema, including antihistamines and corticosteroids (Nowicki et al., 2020).

4. Diagnostics

For patients presenting recurrent swelling of the extremities, facial or genital region, a diagnosis of HAE type I and II should be considered, especially for episodes accompanied by severe abdominal pain or laryngeal involvement (Maurer et al., 2022). In the clinical diagnostic process, medical history provides important diagnostic clues. Determining whether any family members have experienced similar symptoms is crucial, as this significantly increases the likelihood of confirming HAE. In addition, the lack of response to standard antiallergic drugs, such as antihistamines, corticosteroids or epinephrine is important (Nowicki et al., 2020).

Laboratory diagnostics for this type of edema are mainly focused on evaluating the levels and functionality of C1 inhibitor, alongside the measurement of the C4 complement component. To confirm the diagnosis, these parameters should be measured twice, with an interval of 1–3 months, using different blood samples. In patients with a clinical suspicion of HAE-C1-INH, obtaining normal values requires repeating the tests during an edema attack. In most patients, the C4 component level is decreased even during asymptomatic periods, both in HAE-1 and HAE-2 (Maurer et al., 2022; Nowicki et al., 2020). Genetic testing, including the analysis of mutations in the SERPING1 gene, is typically required in diagnostically challenging cases, such as those with a negative family history and late onset of symptoms. It is also useful for differentiating hereditary angioedema from other hereditary edema conditions with normal levels and activity of C1-INH (Maurer et al., 2022; Pedrosa et al., 2016).

5. Treatment strategy

The pharmacological management of HAE is based on three primary principles: on-demand treatment for acute attacks, short-term prophylaxis (STP), and long-term prophylaxis (LTP) (Marco Cicardi et al., 2014; Jacobs & Neeno, 2021; Maurer et al., 2022; Nowicki et al., 2020). A key element of treatment is educating patients about potential triggers and strategies to avoid them. Early recognition of prodromal symptoms is also crucial for effective treatment, as prompt intervention can significantly improve therapy outcomes (Busse & Christiansen, 2020; Caballero et al., 2016; Sinnathamby et al., 2023). Therapeutic strategies should be tailored to the individual patient's clinical profile, taking into consideration the frequency, anatomical location, and severity of attacks, as these factors may evolve over time (Nowicki et al., 2020; Sinnathamby et al., 2023).

5.1 Treatment on demand

Exogenous administration of a C1 esterase inhibitor (C1-INH) is the basis of treatment for acute HAE attacks, effectively replacing C1-INH protein deficiency or dysfunction in patients with HAE types I and II (Marco Cicardi et al., 2014; T. J. Craig et al., 2011; Timothy J. Craig et al., 2009; Maurer et al., 2022; B. Zuraw et al., 2010). This therapy works by raising plasma C1-INH levels, which regulates the cascade mechanisms involved in bradykinin production during an attack.

A randomized, double-blind, placebo-controlled phase III study evaluated the efficacy and safety of recombinant human C1 inhibitor (rhC1INH) in the treatment of acute attacks of angioedema in patients with hereditary angioedema types I and II. rhC1INH at doses of 50 and 100 U/kg significantly reduced the time to symptom resolution during acute HAE attacks compared with placebo, with a median of 66 minutes in the 100 U/kg group compared with 495 minutes in the control group. Treatment failure occurred in 59% of patients receiving placebo, but only in 10% and 0% of patients receiving 100 U/kg and 50 U/kg rhC1INH, respectively. The therapy was well tolerated, no immune reactions were detected and adverse effects were mild (B. Zuraw et al., 2010).

The efficacy of C1-INH treatment is documented in clinical trials such as IMPACT-1 and IMPACT-2 (T. J. Craig et al., 2011; Timothy J. Craig et al., 2009). The IMPACT-1 study is a randomized, double-blind, placebo-controlled clinical trial that demonstrated the high efficacy of plasma-derived C1-INH concentrate (pdC1-INH) in the treatment of acute attacks of HAE types I and II. Administration of the drug at a dose of 20 U/kg significantly reduced the time to symptom resolution, the median was 30 minutes compared to 90 minutes in the placebo group ($p = 0.0025$). The safety profile was favorable, with no serious adverse events reported. Furthermore, the need for emergency treatment was significantly less frequent in patients receiving C1-INH than in the placebo group, it affected only 11% of patients compared to 31% in the control group. The results of the study had a significant impact on the establishment of standards for the emergency treatment of HAE (T. J. Craig et al., 2011). The results of the IMPACT-2 study confirm that pdC1-INH is both effective and safe for the long-term management of HAE attacks across different body locations. Over two years of observation, most attacks resolved quickly, with symptom relief occurring within the first hour in nearly all patients. A single 20 U/kg dose was usually enough, minimizing the need for repeat dosing. Importantly, no significant safety concerns emerged, including no development of inhibitory antibodies, which reinforces the treatment's safety profile. Adverse events were reported in 43.9% of participants during the that study, yet the majority were mild to moderate, with headaches being the one most noted (T. J. Craig et al., 2011).

Icatibant, a selective bradykinin B2 receptor antagonist is an established drug in effective on-demand treatment for acute HAE attacks in both adults and children over two years old (Henriette Farkas, 2016; Henriette Farkas & Kőhalmi, 2018; Maurer et al., 2022). Blocking the B2 receptor inhibits the action of bradykinin, which is responsible for vasodilation and increased vascular permeability, while not affecting its production or metabolism. In addition, it results in faster symptom relief and shorter attack duration, which has a real impact on patient safety and quality of their lives (Henriette Farkas, 2016; Maurer et al., 2013, 2022). The FAST-1 and FAST-2 trials evaluated the efficacy and safety of icatibant in the treatment of acute attacks of HAE. In FAST-1 icatibant was compared with placebo, however, no statistical significance was observed for the primary endpoint, the drug demonstrated a clinically meaningful reduction in time to symptom resolution. In the FAST-2 study, which compared icatibant with tranexamic acid, the results were more conclusive. Patients treated with icatibant experienced symptom relief much faster (median 2 hours compared with 12 hours). A single subcutaneous injection of 30 mg was proved effective (M Cicardi et al., 2010). The treatment had a favorable safety profile, and the most common adverse events were mild, such as transient injection site reactions (M Cicardi et al., 2010; Maurer et al., 2022).

Ecallantide is a plasma kallikrein inhibitor also used to treat acute episodes of HAE in patients over 12 years old. The drug is administered at a dose of 30 mg subcutaneously. Because of the risk of anaphylaxis, reported as a potential side effect, it is recommended that administration take place in a medical institution where monitoring and immediate response to hypersensitivity is possible (Maurer et al., 2022). The EDEMA4 study demonstrated that ecallantide, a subcutaneously administered plasma kallikrein inhibitor, provides significant clinical benefits in the treatment of acute attacks of HAE. A single 30 mg dose resulted in a statistically significant reduction in the severity of symptoms within four hours compared to placebo, with clinical improvement evident as early as two hours after administration. The treatment was well tolerated, with no serious adverse events related to the drug observed, the most reported adverse events were mild injection site reactions (Banta et al., 2011; R. J. Levy et al., 2010).

5.2 Short-term prophylaxis

Short-term prophylaxis (STP) is used to minimize the risk of an attack in high-risk situations such as surgery, dental medical procedures involving mechanical impact on the upper respiratory tract. Since stress is one of the factors provoking the appearance of angioedema, prophylactic treatment can also be applied before important life events or during periods of special emotional significance with increased stress (H. Farkas et al., 2012; Magerl et al., 2017; Maurer et al., 2022). In clinical practice, intravenous pdC1-INH remains the main option for short-term prophylaxis. Available data indicates that administration of pdC1-INH at a dose of 1000 units or 20 U/kg up to six hours before a planned surgical procedure can significantly reduce the risk of perioperative HAE attacks (Marco Cicardi et al., 2014; Maurer et al., 2022; Nowicki et al., 2020). Fresh frozen plasma (FFP) remains an alternative option for short-term prophylaxis when pdC1-INH is unavailable, but its use is limited due to potential risks, including a greater risk of blood transmitted diseases and the development of hypersensitivity to a foreign antigen (Busse et al., 2021; H. Farkas et al., 2012; Magerl et al., 2017). In all cases of presurgical prophylaxis attacks can occur, therefore, patients should be monitored and have access to emergency treatment. (Busse et al., 2021). In the past, attenuated androgens such as danazol, among others, were used as prophylaxis before surgery, but due to numerous side effects from long-term use, their use is being discontinued. A similar situation applies to tranexamic acid, currently not included in STP treatment guidelines (Maurer et al., 2022).

5.3 Long-term prophylaxis

Long-term prophylaxis (LTP) in the treatment of HAE focuses on reducing the frequency, duration and intensity of disease attacks. Management should focus on achieving full control of disease symptoms, which will improve patients' quality of life (Maurer et al., 2022). Maurer et al. emphasizes that long-term prophylaxis should aim to completely control HAE, going beyond reducing the number of attacks and allowing patients to return to normal daily functioning. Importantly, with modern, targeted treatments, achieving this level of disease control is becoming achievable and should be an integral part of individualized care plans (Maurer et al., 2021). Furthermore, effective long-term prophylaxis, whether with subcutaneous C1-INH or lanadelumab, can significantly reduce the frequency of HAE attacks and result in a marked, measurable improvement in patients' daily functioning and mental well-being. These results highlight that novel preventive treatment is more than just controlling symptoms, it can improve quality of life by restoring stability to people with HAE (Lumry, Weller, et al., 2021; Lumry, Zuraw, et al., 2021; Zarnowski et al., 2021). However, according to current guidelines, even with long-term prophylaxis, patients remain at risk of airway edema and other attacks, so they should always have immediate access to on-demand treatment, like intravenous C1-INH, ecalantide, or icatibant (Maurer et al., 2022).

Plasma-derived C1-INH is used as a prophylactic drug that can significantly reduce HAE symptoms and reduce the need for rescue therapy. It remains the first-line option for long-term prophylaxis in HAE and remains a safe and reliable strategy for long-term prophylaxis in patients with HAE in all age groups, including children and adolescents (D. Levy et al., 2020; Maurer et al., 2022). The COMPACT study demonstrated that subcutaneous administration of a pdC1-INH twice weekly significantly reduced the number of attacks in patients with HAE types I and II. The reduction in the number of attacks was statistically significant for both studied doses 40 IU/kg and 60 IU/kg and amounted to an average of -2.42 and -3.51 attacks per month, respectively, compared to placebo ($p < 0.001$) (H. Longhurst et al., 2017). For some patients continuing the open-label extension study for more than 2 years to confirm long-term benefits and safety, sustained subcutaneous C1-INH administration maintained a very low attack rate and allowed the majority to remain attack-free for a long time. This extended follow-up demonstrated that regular prophylaxis self-administered

by patients remains well tolerated and effective over time, with the most adverse events being mild and related to injection sites, confirming that regular self-administration is generally well tolerated over time (T. Craig et al., 2019). An indirect comparison conducted in Bernstein et al. showed that subcutaneous administration of C1-INH at a dose of 60 IU/kg twice a week significantly reduced the monthly incidence of HAE attacks more than intravenous administration of C1-INH at a dose of 1000 U twice a week (mean reduction of 84% compared with 51%, $p < 0.001$). This suggests that subcutaneous administration may provide a more consistent prophylactic effect and may also help to overcome the practical difficulties associated with intravenous infusions (Bernstein et al., 2019).

Berotralstat is an orally used plasma kallikrein inhibitor approved for the prevention of HAE attacks in adults and children over 12 years old. It works by blocking the activity of this enzyme to prevent excessive bradykinin production. It provides a convenient alternative due to its oral form of administration (Lee, 2021). Berotralstat administered once daily at a dose of 150 mg, significantly reduced the average number of HAE attacks compared to placebo from 2.35 to 1.31 attacks per month, representing a reduction of approximately 44% over 24 weeks. The most common side effects include transient gastrointestinal complaints, which usually resolve during treatment (B. Zuraw et al., 2021). The extended APeX-2 study aimed to evaluate the long-term safety and efficacy of the oral plasma kallikrein inhibitor berotralstat in the prevention of HAE attacks, the results showed that daily use of the drug kept the incidence of attacks low and was generally well tolerated over a long period of time (Henriette Farkas et al., 2021).

Lanadelumab is a human monoclonal antibody that selectively blocks the activity of plasma kallikrein, a key enzyme in the process of generation of bradykinin. Thus, it inhibits the pathogenetic pathway responsible for the development of HAE attacks. It is administered subcutaneously and works by blocking plasma kallikrein (Banerji et al., 2018; Buttgereit et al., 2021). In the HELP study a randomized, double-blind, placebo-controlled trial, patients with type I or II HAE received lanadelumab subcutaneously every 2 or 4 weeks at different doses (150 mg or 300 mg). After 26 weeks, the mean number of attacks in the lanadelumab groups was significantly lower (0.26–0.53 attacks/month) compared to the placebo group (1.97 attacks/month), and the most common adverse events were mild with the most frequent including injection site reactions and headaches (Banerji et al., 2018). The recommended dose is 300 mg every 2 weeks administered subcutaneously, but it is possible to extend the interval to 4 weeks after clinical remission is achieved (Buttgereit et al., 2021). The drug is effective in reducing the number of attacks and is well tolerated, with the possibility of prolonging dosing intervals once symptom stabilization is achieved (Banerji et al., 2018; Buttgereit et al., 2021). Moreover, lanadelumab significantly improves patients' quality of life (Lumry, Weller, et al., 2021).

In summary, the available data indicate that pdC1-INH, lanadelumab, and berotralstat are effective drugs for the prevention of HAE and therefore represent a reasonable first-line choice for long-term HAE prophylaxis. The final choice should be the result of careful discussion and tailored to the patient's needs and treatment goals (Maurer et al., 2022).

6. Novel therapies

New therapeutic strategies are gradually expanding the range of treatment options for HAE by introducing innovative agents that target specific points in the bradykinin pathway. These developments promise better symptom control and greater convenience for patients who require long-term treatment.

The VANGUARD phase 3 study evaluated garadacimab, the fully human monoclonal antibody of the IgG4 class targeting activated factor XIIa, as prophylaxis in patients with HAE. Due to its mechanism of action, the drug effectively inhibits bradykinin formation, thereby reducing the frequency and severity of HAE attacks. The study showed that garadacimab at a dose of 200 mg every four weeks reduced the mean number of attacks by nearly 87% compared to placebo. Importantly, 62% of patients experienced no attacks throughout the period of 6 months. The treatment was well tolerated, with mostly mild adverse events and no signs of increased risk of thrombosis or bleeding. Moreover, patients reported a marked improvement in quality of life that persisted throughout the study (Timothy J. Craig et al., 2023). The results were also confirmed in extended observation, demonstrating substantial efficacy and safety profile (Reshef et al., 2025).

OASIS-HAE is a randomized, double-blind, phase 3 study evaluating donidalorsen, a novel antisense oligonucleotide that reduce the activity of plasma prekallikrein, helping to reduce the number of HAE attacks. In the study, 90 patients with HAE were assigned to receive donidalorsen 80 mg subcutaneously every 4 weeks or every 8 weeks or placebo. Donidalorsen administered every 4 weeks reduced the mean number of attacks by 81% compared to placebo ($P<0.001$). Moreover, the median reduction in the number of attacks in the group receiving the drug every 4 weeks was 90%, in the group receiving the drug every 8 weeks 83%, and in the

placebo group only 16%. Moreover, patients treated every 4 weeks showed a significant improvement in quality of life. The results confirm that donidalorsen is effective in reducing the frequency of HAE attacks and has potential for use in long-term prevention (Riedl et al., 2024). Long-term extension confirmed that donidalorsen maintained its efficacy for 88 weeks, with a median reduction in attack frequency of 97% compared to baseline. Flexible dosing allowed some patients to continue treatment with 80 mg every 8 weeks while maintaining good disease control, therefore supporting individualized prevention strategies (Petersen et al., 2024).

Sebetralstat (KVD900) is an oral kallikrein inhibitor that selectively inhibits plasma kallikrein activity, preventing activation of the contact system, resulting in a reduction in the severity of angioedema attacks. The drug shows a rapid onset of action, achieving almost complete inhibition of kallikrein activity within 20-30 minutes, and this effect persists for 6-8 hours, making it could be useful for on-demand use to disrupt a HAE attack (Moore, 2024).

Gene therapies based on in vivo gene editing appear promising. CRISPR-Cas9 Gene Editing is a drug based on permanent correction of a genetic defect in HAE with the potential to provide a causal therapy for HAE in the future (H. J. Longhurst et al., 2024).

7. Monitoring and education

The care for patients with HAE, including children and adolescents, is expected to focus on a patient education, structured plan of action, access to registered and on-demand therapies, as well as transparent training in self-administration of drugs. This management has a crucial role in minimizing the risk of serious attacks and emergency interventions (Maurer et al., 2022; Nowicki et al., 2020; Porębski et al., 2018). Ensuring patients, families and healthcare providers with practical information on early symptom recognition and safe medication administration builds patient safety and daily confidence (Porębski et al., 2018). If possible, patients should minimize exposure to known triggers, manage stress level and stay aware of prodromal signs to act before symptoms escalate (Caballero et al., 2016; H. Farkas et al., 2012; Reshef et al., 2013). An individualized short-term prevention plan is recommended prior to surgical or dental procedures (Busse et al., 2021). Continuous follow-up in specialized centers and active patient education strengthen disease control and enable early response to changing conditions. In addition, a detailed family history documenting all cases of disease among close relatives remains a key element of monitoring and provides the basis for genetic counseling and patient education. The comprehensive therapeutic approach should prepare patients and their families to deal with attacks, providing them with a sense of safety, reducing unnecessary hospitalizations and improving their daily quality of life (Maurer et al., 2022; Nowicki et al., 2020; Porębski et al., 2018).

8. Conclusions

Currently, the treatment and management of hereditary angioedema demonstrate the significant progress in understanding the pathogenesis of the disease, its clinical course and personalization of care. Treatment is not limited to controlling attacks but focuses equally on effective long-term prevention and practical patient education. Modern biological therapies allow most patients to control their symptoms with minimal side effects, while structured patient education and consistent clinical monitoring establish trust and increase patients' sense of safety in everyday functioning. The combination of established treatment strategies and shared decision-making process ensure that clinical goals are aligned with patients' value, resulting in stability of disease course, a lower risk of unexpected exacerbations and a measurable improvement in overall quality of life.

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