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Management of hereditary angioedema in resource-constrained settings: A consensus statement from Indian subcontinent

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ABSTRACT

Hereditary angioedema (HAE) is an uncommon disorder characterized clinically by recurrent episodes of nonitchy subcutaneous and/or submucosal swellings. The estimated prevalence of HAE is ~ 1: 10,000 to 1: 50,000. There are no prevalence data from India, however, estimates suggest that there are 27,000 to 135,000 patients with HAE in India at present. The majority of these, however, remain undiagnosed.

Replacement of plasma-derived or recombinant C1-esterase inhibitor (C1-INH) protein, administered intravenously, is the treatment of choice during the management of acute episodes of angioedema (i.e., "on-demand treatment") and is also useful for short-term prophylaxis (STP) and long-term prophylaxis (LTP). This has been found to be effective and safe even in young children and during pregnancy.

Until recently, none of the first-line treatment options were available for "on-demand treatment," STP or LTP in India. As a result, physicians had to use fresh frozen plasma for both "on-demand treatment" and STP. For LTP, attenuated androgens (danazol or stanozolol) and/or tranexamic acid were commonly used. These drugs have been reported to be useful for LTP but are associated with a significant risk of adverse effects.

Intravenous pd-C1-INH, the first-line treatment option, is now available in India. However, because there is no universal health insurance, access to pd-C1-INH is a significant challenge.

HAE Society of India has developed these consensus guidelines for India and other resource-constrained settings where plasma-derived C1-INH therapy is the only available first-line treatment option for the management of HAE and diagnostic facilities are limited. These guidelines have been developed because it may not be possible for all patients to access the recommended therapy and at the recommended doses as suggested by the international guidelines. Moreover, it may not be feasible to follow the evaluation algorithm suggested by the international guidelines.

Keywords: Androgens; hereditary angioedema; on-demand therapy; plasma derived C1-estrase inhibitor; prophylaxis; tranexamic acid

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1. Introduction

Hereditary angioedema (HAE) is an uncommon disorder characterized clinically by recurrent episodes of nonitchy subcutaneous and/or submucosal swellings. The estimated prevalence of HAE is ~ 1: 10,000 to 1: 50,000. There are no prevalence data from India or other developing countries. Estimates suggest that there are 27,000 to 135,000 patients with HAE in India at present [1]. The majority of these, however, remain undiagnosed [2].

HAE is a potentially life-threatening disorder. In the past, mortality figures as high as 30% have been reported. Deficiency or dysfunction of the C1-esterase inhibitor (C1-INH) protein (caused by pathogenic variants in the *SERPING1* gene) is the most common pathogenic abnormality for HAE (seen in 90–97% of patients). Replacement of plasma-derived or recombinant C1-INH protein, administered intravenously, is the treatment of choice during the management of acute episodes of angioedema (i.e., "on-demand treatment") and is also useful for short-term prophylaxis (STP) [3, 4]. This has been found to be effective and safe even in young children and during pregnancy. Icatibant (bradykinin B2 receptor inhibitor) is the recommended alternative for "on-demand treatment" and is now emerging as a commonly used therapy. For long-term prophylaxis (LTP) also, plasma-derived (pd) C1-INH protein, administered subcutaneously, may be used. However, there are other treatment options

available for LTP especially in developed countries, including oral berotralstat (selective inhibitor of plasma kallikrein) and subcutaneous lanadelumab (human monoclonal antibody that inhibits plasma kallikrein). These may be more convenient to administer but may not necessarily be more effective than pd-C1-INH.

Until recently, none of the first-line treatment options were available for "on-demand treatment," STP or LTP in India. As a result, physicians had to use fresh frozen plasma (FFP) for both "on-demand treatment" and STP [5–7]. For LTP, attenuated androgens (danazol or stanozolol) and/or tranexamic acid were commonly used [5, 8]. These drugs have been reported to be useful for LTP but are associated with a significant risk of adverse effects, especially with attenuated androgens [8] or incomplete efficacy, especially tranexamic acid. Attenuated androgens have been suggested not to be used in children and are contraindicated during pregnancy [9, 10].

Nonavailability of the first-line treatment options in India was the first among many challenges for patients suffering with HAE in India as also for the physicians involved in the care of these patients. Intravenous pd-C1-INH, the first-line treatment option, is now available in India. However, because there is no universal health insurance in India, access to these drugs is another significant challenge for patients and physicians.

International guidelines for the management of HAE recommend that all attacks of HAE should be considered for "on-demand treatment" [3]. Hereditary Angioedema Society of India (HAESI) was established in February 2021 with the aim to promote knowledge of HAE in the country and to provide a better quality of life for patients with HAE. HAESI has developed these consensus guidelines for India and other resource-constrained settings because it may not be possible for all patients to access the recommended therapy and at the recommended doses as suggested by the international guidelines. Moreover, the diagnostic facilities are often limited in most developing countries. It may not be feasible to follow the evaluation algorithm suggested by the international guidelines [1, 2]. A consensus statement approach was used instead of the usual structured Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach because of the paucity of evidence from randomized controlled trials/systematic reviews with substantial participation from resource-constrained settings and the lack of evidence with the use of attenuated androgens and antifibrinolytics, making it unfeasible to rate the certainty of the evidence and strength of a recommendation.

2. Suggested diagnostic evaluation for HAE and family screening in resource-constrained settings

Patients with HAE present with non-pruritic, non-urticarial, and non-inflammatory episodic subcutaneous and/or submucosal angioedema. It is important to clinically differentiate HAE from mast cell mediator-mediated angioedema.

The international guidelines for the diagnosis of HAE recommend assessment of C4 levels, C1-INH levels, and C1-INH function in all patients suspected to have HAE [3]. However, in a resource-constrained setting, it may not be possible to carry out these 3 tests in all patients. Assessment of C1-INH levels and C1-INH function is available in tertiary care referral hospitals only. Moreover, these tests are not reliable if carried out on a transported sample wherein the delay has been more than 12 hours and the adequate temperature has not been maintained during transport [11].

The present guidelines provide a simplified approach for the diagnosis of HAE in a resource-constrained setting (Fig. 1). These guidelines have been formulated keeping in mind the fact that more than 99% of patients with HAE in India and in many countries in Asia Pacific region remain undiagnosed at present [2].

C4 is a low-cost, easily available, and sensitive test for the diagnosis of HAE [12]. C4 levels are low in ~80% of patients [13]. However, if C4 alone is used as a screening test, it may miss the diagnosis of HAE in approximately 20%. The sensitivity of the C4 test may increase if this test has been carried out during an episode of angioedema [3]. C4 levels, if normal, should therefore be repeated during an episode of angioedema if clinical suspicion is high. A few studies, carried out long ago, have also shown that if C4 is normal, it nearly rules out a diagnosis of HAE [14, 15]. However, more recent data have shown contrary results.

There is variation in the results of C1-INH levels when performed using different techniques. It has been suggested to use nephelometry to test for C1-INH levels.

Although a genetic test is not mandatory in all patients with HAE, it may be helpful for prenatal diagnosis; for diagnosis in young children especially younger than 1 year and during pregnancy as complement studies may not be reliable during the first year of life and during pregnancy [3]; and also, for family screening. In many developing countries including India, doing a targeted Sanger sequencing for family screening is cost-effective as compared with doing the C4, C1-INH levels, and C1-INH function. Moreover, the genetic test can easily be carried out even on a transported and stored sample. Hence, it may be recommended to do the genetic test in all patients whenever possible.

Family screening including parents, siblings, grandparents, and grandchildren must be carried out as soon as the diagnosis is established for the index case [3]. As has been reported in several studies, this helps in preventing mortality and also improves the quality of life of these patients [12]. In our own experience (unpublished data), the risk of death is very high in undiagnosed patients. As has been discussed previously, if the genetic diagnosis of the index case is established, targeted Sanger sequencing is a cost-effective way of doing the family screening.

3. Availability of first-line treatment options for HAE in India

Intravenous formulations of pd-C1-INH therapy are now available in India. One of these is being manufactured within the country and one FDA-approved brand is also available. In addition, another FDA-approved brand of intravenous pd-C1-INH is likely to be available very soon. This has been remarkable progress in the field of HAE in India and is likely to significantly improve the outcome of patients.

The HAESI and patient support groups in India are constantly trying to provide access to other first-line treatment options such as icatibant (bradykinin B2 inhibitor). However, to the best of our knowledge, there is no proposal for any other first-line treatment options to be marketed in India in the immediate future.

A recent survey carried out across the Asia Pacific region by the Asia Pacific Association of Allergy, Asthma, and Clinical Immunology demonstrated that countries or regions that had their own guidelines for the management of HAE were significantly more likely to have registered on-demand treatment as compared with those who did not have these guidelines [2].

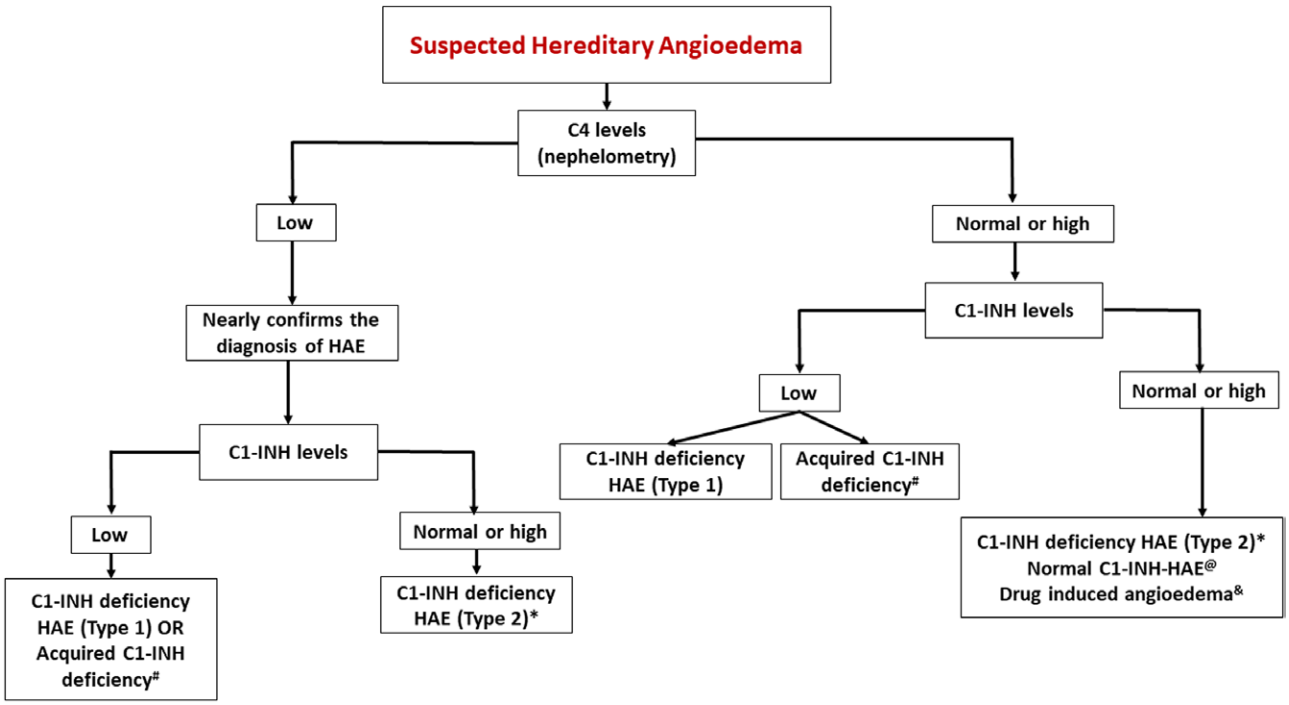

Figure 1. A simplified evaluation algorithm for patients with suspected HAE in resource-constrained settings. (Please note that C4 is approximately 80% sensitive and may be normal in up to 20% of patients with confirmed diagnosis of type 1 and 2 HAE. The sensitivity of C4 may increase when performed during an episode of angioedema. A normal C4 and low C1-INH should always raise suspicion of a sample handling error and repeat testing is advised.). *Needs functional C1-INH assay testing using enzyme-linked immunosorbent assay (ELISA) for confirmation of the diagnosis. Genetic testing for the index case is mandatory for establishing a diagnosis of normal C1-INH-HAE (either whole exome sequencing or targeted next-generation sequencing). #Seen in association with autoimmune diseases (such as Systemic lupus erythematosus) and lymphoproliferative disorders. When the onset of angioedema is after 4th decade of life and there is no family history, acquired angioedema caused by lymphoproliferative disorders must be considered. In patients with acquired angioedema caused by autoimmune diseases, clinical manifestations of autoimmune diseases are usually evident. C1q may be low in acquired angioedema and may help differentiate it from hereditary angioedema. &Commonly seen with the use of angiotensin convertase enzyme (ACE) inhibitor. C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema.

3.1. Use of pd-C1-INH therapy for on-demand treatment

On-demand therapy has been recommended to be used for all attacks of HAE. However, it is mandatory for attacks that affect or may affect the upper airway [3]. A dose of 20 IU/kg of pd-C1-INH results in a shorter time to onset of relief (i.e., 0.5 hours) compared with lower doses. The onset of relief has been reported to be shorter for abdominal attacks as compared with facial attacks and even shorter for more severe and debilitating attacks. The median time to complete the resolution of attacks with 20 IU/kg dose of C1-INH therapy has been reported to be approximately 4.9 hours. A single dose is sufficient to treat an acute attack in 99% of cases [16]. Additional doses (up to 60 IU/kg per attack) may be considered in patients with a worsening attack or if there is no onset of relief after 1 hour [17].

Earlier initiation of therapy results in better resolution of symptoms and a shorter duration of the total attack [18]. It has been recommended that C1-INH be administered within 6 hours after onset [19]. Timely treatment of the attack may even result in the requirement of lesser doses (500 IU) for mild attacks. However, this depends on patient education as well as drug availability at home [18]. Administration of timely on-demand therapy is possible only if patients or caregivers have been trained to self-administer the drug or provided with 1 to 2 vials of pd-C1-INH for emergency administration at the nearest hospital in case of an attack.

The mean interval between the use of C1-INH and the onset of resolution of the laryngeal attack has been reported to be 42 minutes. Difficulty breathing and fear of asphyxiation are the first to be resolved [20]. Patients must be made aware to recognize the symptoms of upper airway obstruction such as dysphagia, lump in throat sensation, and voice change as the window of opportunity for emergency treatment of laryngeal edema lies between the start of attack and its maximum development (approximately 8 hours). It is mandatory that C1-INH be administered during this critical time period [21].

Although many patients report a prodrome before the onset of an attack, initiation of treatment during prodrome may potentially lead to over usage of the on-demand therapy and there is insufficient evidence to support the use of on-demand treatment during prodrome [22].

Our recommendations for the acute attacks of angioedema in patients with HAE are given in Table 1.

Even though our recommendations do not support the use of FFP for on-demand therapy, in settings where pd-C1-INH or icatibant is not available or accessible, FFP is still the best possible option for an acute attack of angioedema, especially the life-threatening episodes. In a few observational studies, FFP has been shown to effectively terminate the attacks of angioedema [1, 5–7]. FFP contains 1 IU of C1-INH per ml, and the recommended dose of FFP during an acute episode of angioedema is 20 ml/kg body weight.

However, there are several challenges with the use of FFP in patients with HAE. Most often, because of a lack of awareness among emergency physicians, there are delays in the

Table 1.

Consensus recommendation 1

For acute attacks of angioedema in patients with HAE:
a. Treatment of each patient needs to be individualized.
b. Intravenous pd-C1-INH should preferably be used for all acute attacks.
c. Intravenous pd-C1-INH must be used for all acute attacks that involve the larynx and tongue and for all abdominal attacks (Abdominal attacks of HAE are characterized by intense pain often associated with vomiting, diarrhea, bloating, and abdominal distension. It is important to differentiate an acute attack of angioedema affecting the abdomen from other causes of pain such as gastritis.).
d. Intravenous pd-C1-INH must be used as soon as possible, preferably within 1 hour of symptom onset and preferably through self-administration at home.
e. One should avoid using FFP for on-demand treatment of HAE unless there is no mechanism to arrange pd-C1-INH therapy.
f. Recommended dose of intravenous pd-C1-INH is 10 to 20 IU/kg for an acute attack (adult dose is 1000 IU, ie, 2 vials of 500 IU each). However, because some adult patients may respond to even a single vial of 500 IU (when given early in the disease course), it may be advisable to use a smaller dose of 500 IU, especially when pd-C1-INH is being self-administered at home. The dose may be repeated in 2 to 3 hours if there is no adequate response.
g. For an acute episode affecting the larynx, it is strongly recommended to use 20 IU/kg or 1000 IU (in adults).
h. On-demand treatment during a prodrome is not recommended.
Important note:
C1-INH has a wide therapeutic index and treatment doses may be rounded up to the nearest vial—even in young children. One should not discard any amount of C1-INH injection. A dose of more than 20 U/kg may safely be used when treating small children.

FFP, fresh frozen plasma; HAE, hereditary angioedema; pd-C1-INH, plasma-derived C1-esterase inhibitor.

Table 2.

Consensus recommendation 2

For short-term prophylaxis in patients with HAE
1. Intravenous pd-C1-INH should be the drug of choice. Attenuated androgens, tranexamic acid, and FFP have less evidence to support their use and should not be considered the first line for STP.
2. The recommended dose of intravenous pd-C1-INH is 10 to 20 IU/kg for children and 1000 IU for adults. A lower dose that is, 500 IU may also work for STP.
3. Intravenous pd-C1-INH should be used soon before the surgery. Subsequent doses may be decided on a case-to-case basis.
4. There must be a backup of intravenous pd-C1-INH during all procedures even for minor surgeries or RCT, as there is a risk of developing an episode of angioedema even with these minor procedures.
5. STP must be used for dental procedures such as tooth extraction and endotracheal intubation, endoscopy, or bronchoscopy.
6. Attenuated androgens may be used during a few high-risk situations such as during menstruation or during travel to avoid an episode, especially for those who report specific triggers for their episodes.

FFP, fresh frozen plasma; HAE, hereditary angioedema; pd-C1-INH, plasma-derived C1-esterase inhibitor; RCT, root canal treatment; STP, short-term prophylaxis.

administration of FFP during a life-threatening episode. There are concerns with the transmission of viral infections such as hepatitis B, hepatitis C, and HIV; the risk of volume overload; transfusion reactions, and a theoretical risk of aggravation of an acute episode.

3.2. Use of pd-C1-INH therapy for short-term prophylaxis

Short-term prophylaxis, also known as situational prophylaxis, is administered to reduce the chances of developing angioedema following a procedure or an intervention that is associated with a high risk of precipitating an acute attack [11].

Major surgeries, dental procedures such as tooth extraction and endotracheal intubation, endoscopy, or bronchoscopy have been reported to be associated with an increased risk of precipitating an angioedema episode [23, 24]. Surgical procedures that cause injury to the mucous membrane of the upper respiratory and gastrointestinal tract are particularly prone to precipitating an acute episode including laryngeal edema [25].

Approximately 33% of patients may have an acute attack without STP after tooth extraction. Most attacks develop within 48 hours and the majority of them (around 2/3rd) develop within 24 hours [24, 26, 27]. Short-term prophylaxis has been recommended before tooth extraction in all patients with HAE [26, 28]. However, for minimal trauma procedures such as dental root canal treatment, the use of STP may be avoided. Nevertheless, on-demand treatment with pd-C1-INH should be available after these procedures. It is very unusual for clinical angioedema to become evident in the first 4 hours after any angioedema-provoking event.

Intravenous pd-C1-INH has been recommended as the first-line agent for STP by the World Allergy Organization and European Academy of Allergy and Clinical Immunology guidelines [11]. Studies have reported a decrease in the incidence of angioedema episodes with preprocedural intravenous use of pd-C1-INH [24, 29–32]. Significant graded dose-response has been observed for preprocedural intravenous use of pd-C1-INH [24]. However, the angioedema may develop despite the use of pre-procedural pd-C1-INH prophylaxis and may warrant post-procedural monitoring and repeat use of pd-C1-INH [24]. If a physician decides to use preprocedural prophylaxis, the time interval between the procedure and preprocedural prophylaxis should be the minimum possible. The recommended dose is 1000 units for adults or 20 IU/kg for children [11, 28, 29, 33]. There is some observational evidence for the efficacy of lower doses that is, 500 U in prophylaxis [24] albeit with an apparently lower efficacy.

Our recommendations for STP in patients with HAE are given in Table 2.

3.3. Use of pd-C1-INH therapy for long-term prophylaxis

Long-term prophylaxis is recommended for patients who have more frequent episodes of angioedema. There are no definite guidelines for who should be initiated on LTP. However, a patient who has more than 1 attack per month or who has

Table 3.

Consensus recommendation 3

For long-term prophylaxis in patients with HAE
1. Attenuated androgens or tranexamic acid or a combination of the 2 would remain the mainstay of treatment for LTP in India.
2. Intravenous pd-C1-INH may be used in special situations where other drugs such as attenuated androgens are contraindicated, and the patient continues to have frequent episodes of angioedema (eg, during breastfeeding and pregnancy). The dose recommended is 1000 IU twice weekly. The frequency of administration may be modified on a case-to-case basis to ensure the prevention of attacks.
3. Intravenous pd-C1-INH may be used for LTP in children and adolescents if they continue to have very frequent episodes of angioedema despite the use of attenuated androgens, tranexamic acid, or a combination of the 2. The dose recommended is 20 IU/kg twice weekly. The frequency of administration may be modified on a case-to-case basis to ensure the prevention of attacks.
4. Tranexamic acid is especially effective as LTP in patients with acquired C1-INH deficiency and should be recommended as first-line treatment.
Dose of attenuated androgens for long-term prophylaxis:
Stanozolol: 0.5 mg alternate days to 4 mg/day (8 mg/day may be used for a short period).
Danazol: 100 mg alternate days to 600 mg per day (avoid doses above 200 mg daily, except for short-term use).
Dose of tranexamic acid for long-term prophylaxis:
30 to 50 mg/kg/day in 2 to 3 divided doses, maximum dose of 3 g/day
Other general recommendations for patients with HAE:
1. Do not use angiotensin convertase enzyme inhibitors and estrogens.
2. Avoid triggers (please note that triggers are patient-specific, and this advice needs to be individualized). It may not be possible to avoid all triggers for all patients especially if avoiding those activities are significantly impacting the quality of life of patients. Stress is an important trigger for most patients and must be minimized.
3. To participate in patient support groups (https://haei.org and https://haeindia.haei.org/) and be involved in various activities such as workshops and patient awareness programs organized by these groups.

HAE, hereditary angioedema; LTP, long-term prophylaxis; pd-C1-INH, plasma-derived C1-esterase inhibitor.

life-threatening laryngeal attacks should consider LTP [34, 35]. Sub-cutaneous pd-C1-INH therapy is recommended for LTP [32, 36]. Subcutaneous pd-C1-INH is usually administered twice weekly at a dose of 60 U/kg of body weight [37]. This dose has been shown to be effective for the prevention of acute episodes of HAE [38, 39].

Subcutaneous pd-C1-INH is not available in India and intravenous pd-C1-INH is less effective for LTP. Moreover, the doses required for intravenous pd-C1-INH may be more frequent than twice-weekly doses. Hence, at present, if a patient needs LTP, attenuated androgens or tranexamic acid, or a combination of the 2 may be used.

Acquired C1-INH deficiency angioedema is a rare bradykinin-mediated disorder characterized by late onset of disease (usually after 40 years) and no family history. This entity is usually seen in association with lymphoproliferative disorders and autoimmune diseases. It has been observed that tranexamic acid (as compared to attenuated androgens) is very effective for LTP in patients with acquired C1-INH and should be recommended as a first-line treatment [40–42].

Our recommendations for LTP and other general recommendations in patients with HAE are given in Table 3.

4. Conclusions

In conclusion, this document provides a consensus statement on the diagnosis and treatment of HAE in resource-constrained settings where intravenous plasma-derived C1-INH concentrate is the only available treatment and access to treatment is still a challenge.

Author contribution

AKJ: Conceptualization, writing of the initial manuscript, critical revision and final approval, review of literature
AS, RA: writing of the initial manuscript, critical revision, review of literature
KV, AB, DS, AR, MSK, BS, RS, LG, DDK, RJ, TUS, JO: Editing of the manuscript and review of literature
HL, RP, SS: Conceptualization,writing of the initial manuscript, Editing of the manuscript, critical revision, and review of literature
SD: Conceptualization, critical revision and final approval, review of literature

Conflicts of interests

The authors have no financial conflicts of interest.

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