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Optimization of care for patients with hereditary angioedema living in rural areas

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Review

Optimization of care for patients with hereditary angioedema living in rural areas

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Key Messages

- Approximately one-fifth of the US population lives in a rural location, where barriers to optimal health care exist, particularly for those with rare medical conditions.
- Individuals affected by hereditary angioedema (HAE) in rural areas may face increased diagnostic and treatment challenges owing to a lack of access to specialists, medication, and other health care services.
- Educational and diagnostic resources for HAE are needed for rural health care providers managing patients with HAE.
- Access to specialist health care for patients living in rural areas may be improved through telemedicine, facilitating collaborative care among specialists, and local health care teams.
- Management plans for HAE should be individualized and based on multiple factors that affect the total burden of disease rather than any rigid criteria.
- Prevention of HAE attacks may be a stronger consideration in a rural setting in which an emergency department may not be as readily accessible.

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ABSTRACT

Background: People living in rural areas of the United States experience greater health inequality than individuals residing in urban or suburban locations and encounter several barriers to obtaining optimal health care. Health disparities are compounded for patients with rare diseases such as hereditary angioedema (HAE), an

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autosomal dominant genetic disorder characterized by recurrent, severe abdominal pain and life-threatening oropharyngeal or laryngeal swelling.
Objective: To explore the challenges of managing patients with HAE in rural areas and suggest possible improvements for optimizing care.
Data Sources: PubMed was searched for articles on patient care management, treatment challenges, rural health, and HAE.
Study Selections: Relevant articles were selected and reviewed.
Results: Challenges in managing HAE in the rural setting were identified, including obtaining a diagnosis of HAE, easy access to a physician with expertise in HAE, continuity of care, availability of telemedicine services, access to approved HAE therapies, patient education, and economic barriers to treatment. Ways to improve HAE patient care in rural areas include health care provider recognition of the patient with undiagnosed HAE, development of individualized management plans, expansion of telemedicine, effective care at the local level, appropriate access to HAE medication, and increased awareness of patient support and advocacy groups.
Conclusion: For patients with HAE living in rural areas, optimal care is complicated by health disparities. Given the scarcity with which these topics have been covered in the literature to date, it is intended that this article will serve as the impetus for a range of further initiatives focused on improving access to care.

Introduction

Approximately 19% (ie, almost 60 million people) of the US population lives in a rural location.[1] The definition of rural populations varies according to the measures used. "Rural" may be defined as an area characterized by small population density or size and at a notable distance to a metropolitan or urban area.[2] Residents of rural areas in the United States experience greater health inequality than individuals residing in urban or suburban locations.[3,4] According to the Centers for Disease Control and Prevention, rural Americans are more likely to die from heart disease, stroke, cancer, unintentional injury, and chronic lower respiratory disease than urban residents.[5]

Patients in rural areas may encounter a range of challenges and health disparities, including geographic, societal, and economic barriers to obtaining optimal health care. These barriers to health care are compounded for patients living with rare diseases such as hereditary angioedema (HAE). HAE is an autosomal dominant genetic disorder with an estimated global prevalence of approximately 1 in 67,000, although, because of its rarity, estimates vary. HAE is most typically caused by a deficiency in the C1 inhibitor protein (C1INH), a serine protease that inhibits the activation of the contact and complement systems.[6] HAE owing to C1INH deficiency (HAE-C1INH) is caused by mutations in the *SERPING1* gene, which results in a lack of functional C1INH. There are 2 main types of HAE-C1INH. In HAE type 1, mutations in the affected gene result in low levels of C1INH, whereas in HAE type 2, mutations lead to the production of nonfunctioning C1INH.[7] In HAE-C1INH, the lack of C1INH leads to aberrant activation of pathways that cause overproduction of bradykinin and results in recurring attacks of bradykinin-mediated cutaneous and submucosal angioedema that can last up to 5 days.[6,8] In some individuals, an extremely rare subtype of HAE can occur with normal levels of C1INH (previously described as type 3), which has been associated with mutations in genes other than *SERPING1*.[6,8] The focus of this review will be HAE-C1INH (HAE types 1 and 2), which accounts for most HAE cases.

The most frequent symptoms of HAE are recurrent, severe abdominal pain and cutaneous angioedema (48% and 50% of episodes, respectively), including swelling of the face, extremities, or genitalia, all of which can cause substantial morbidity.[7] Although oropharyngeal or laryngeal swelling occurs in only 1% of HAE attacks, more than 50% of patients will experience such an episode, which may be life-threatening.[7] HAE, however, can be effectively treated and managed with a comprehensive treatment plan that includes therapies approved by the US Food and Drug Administration for prophylactic and on-demand use.

The diagnosis and treatment of patients with HAE are often complex and challenging. Based on HAE's rarity and similarity to allergic angioedema, it is often misdiagnosed, or the diagnosis is substantially delayed.[9] In the United States, 89% of patients (n = 445) reported being under the care of an allergist or immunologist, but some (27%) also saw their general practitioner, family or primary care physician, or an internist for management of their HAE.[10] Most patients were under the care of physicians who managed very few patients with HAE.

Treatments for HAE are effective and comprised of on-demand (acute) treatment and short- and long-term prophylaxis.[11] Medications approved by the US Food and Drug Administration indicated for on-demand use in HAE are ecallantide, icatibant, plasma-derived C1 inhibitor, or recombinant human C1INH.[11] Recommended first-line agents for long-term prophylaxis include C1INH and lanadelumab. Oral berotralstat is also available for prophylactic treatment of patients ages 12 years and older.[12] Androgens are second-line agents used for the prevention of HAE attacks and may be more typically used in a rural setting as they are less expensive and administered orally.[11] Notably, HAE treatment guidelines do not recommend the routine use of androgens for long-term prophylaxis of HAE. Androgens have a well-known profile of adverse events and newer targeted HAE treatments may be more effective. Successful prevention of attacks may be a stronger consideration in a rural setting, as an emergency department (ED) may not be readily accessible for patients with HAE in rural areas.

Despite the availability of effective prophylaxis and because of the unpredictable nature of the attacks and wide range of triggers, some patients in the United States still require frequent on-demand medication. Effective management of HAE, therefore, requires a multifaceted approach, and, ideally, an ongoing comprehensive treatment plan that includes access to a physician with expertise in HAE.[13] Decisions regarding the use of long-term prophylaxis should be tailored to individual patient needs and should be done in consultation with the patient (ie, shared decision-making).[11]

Limited data are available on the geography of HAE in the United States, but information from 2 surveys of patients with HAE in 2013 and 2015 suggest that approximately 22% to 23% live in areas with a population of less than 20,000, and another 25% to 29% in towns of 20,000 to 100,000 people.[9] A 2013 survey of US physicians treating patients with HAE found that 17% of practices were in areas with population sizes of less than 100,000.[14] Challenges, therefore, exist in the care of patients with HAE living in rural areas. There are concerns that patients in rural areas may not have readily accessible health care to a level appropriate for this rare disorder. The objective of this review is to explore the challenges of managing patients with HAE in rural areas and suggest possible improvements for optimizing care.

Data Sources and Study Selections

PubMed was searched for articles published in the 5 years before May 15, 2020, on patient care management, treatment challenges, and rural health. The search resulted in 580 articles, which were reviewed for relevancy. Of 580 articles, 484 articles were excluded (Fig 1). Three additional articles were identified by means of a review of the references of the articles. The 99 articles were analyzed for inclusion of rare genetic disorders or HAE; no articles specific to HAE or any rare genetic disorder were identified. However, a second, more specific search for "HAE and rural" identified 2 relevant articles. The 101 articles were analyzed for rural health disparities that would be exacerbated for a patient with HAE. Areas identified included the following: obtaining a diagnosis of HAE, easy access to a physician with expertise in HAE management, continuity of HAE care, patient education on HAE management, access to approved HAE therapies, availability of telemedicine services, and economic barriers to treatment.

Challenges for the Care of Hereditary Angioedema in Rural Areas

Barriers to Diagnosis

There are several barriers to diagnosis in patients with HAE. For example, there may be limited recognition of HAE by hospitalists and ED physicians, and HAE may not be considered in a differential diagnosis.[15] Misdiagnosis is frequent, with approximately 50% of patients (n = 185) diagnosed as having HAE type 1 or 2 reporting that they had previously been misdiagnosed, most frequently with allergic angioedema, appendicitis, or other gastrointestinal disorders.[16] Misdiagnosis frequently entails patients being diagnosed as having allergic angioedema and receiving medications that lack efficacy for bradykinin-associated angioedema, leading to ongoing morbidity and potentially to unnecessary procedures (eg, exploratory laparotomy).[17] Furthermore, with the lack of access to a board-certified allergist, patients are usually managed by a primary care provider, with approximately a quarter of patients across the United States in both rural and urban areas reporting that their general practitioner, family or primary care physician, or an internist provided HAE management (in some cases in addition to seeing an HAE specialist).[10] Laboratory testing for HAE is necessary for diagnosis, including serum C4 levels and functional and antigenic C1INH levels.[11] In addition, interpretation of laboratory test results is not always straightforward and may contribute to misdiagnosis. For example, low C4 levels are associated with HAE type 1 and 2 and this is often used to screen for the need to measure C1INH levels and function.[18,19] However, patients with HAE due to C1INH deficiency and normal C4 levels during asymptomatic periods have been reported[19–21]; thus, this laboratory finding does not definitively exclude the diagnosis of HAE. In addition, reference ranges for typically used enzyme-linked immunosorbent assay–based CINH functional assays in US commercial laboratories were found to be less sensitive in detecting C1INH deficiency compared with the reference standard chromogenic assay, which is less accessible.[22,23] Although biochemical tests are widely available, samples may have to be sent to a larger hospital or specialty laboratories for these tests to be run, delaying the turnaround time for test results. Concerns regarding sample shipping, storage, and handling may lead to a lack of confidence in some assays.[24] Similarly, access to genetic testing away from large centers may not be straightforward or covered commercially, thus, being cost-prohibitive. Because HAE can be inherited, family members of patients with an HAE diagnosis or who receive a new diagnosis of HAE merit screening for HAE as well.[25]

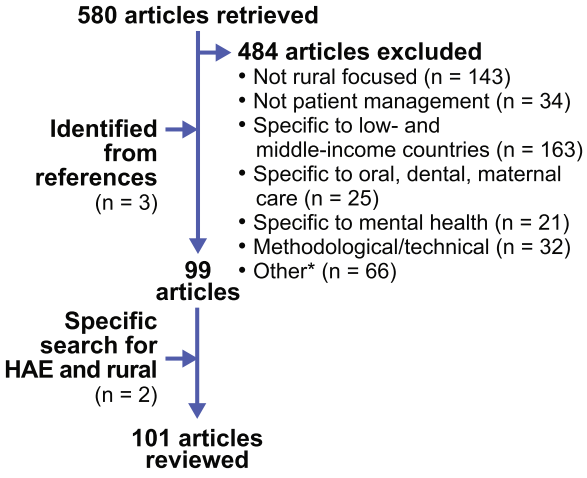

Figure 1. Literature search flow chart. The asterisk indicates that other articles included were those describing health care professional experiences/education, care of elderly/end-of-life care, engagement/recruitment of patients into clinical studies/health programs specific to acute/emergency care, cancer, HIV, physical rehabilitation, telehealth/visiting health care professionals, insurance, transfer of patient from rural to urban center, refugees, and posttransplant care. HAE, hereditary angioedema.

Access to Specialist Care

Management of rare diseases such as HAE in rural settings presents several challenges for patients, their families or caregivers, and health care practitioners. Patients with HAE need access to a physician with expertise in HAE to optimize their treatment plan, coordinate ongoing care, and provide patient and family or caregiver education. However, as in the case with general patient care in rural settings, such a level of specialist care is rarely available without travel to secondary or tertiary health care facilities in urban centers.[4,11] The difficulty and cost of travel to distant centers can be a barrier to health care for patients in rural areas.[4] Transportation and resulting time lost from work have been recognized as contributing to the burden of illnesses such as HAE.[26]

Local Health Care

Difficulties with recruitment and retention of health care providers in rural settings are well-documented (Fig 2).[3,27–29] Physician shortages throughout the United States are even more evident for specialists like allergists.[30] A combination of high turnover and high patient loads could adversely affect the continuity of care for patients with chronic conditions such as HAE, with the local physician possibly not having the time, preferring to refer them for consultation with an HAE specialist to assist in implementing a management plan for the patient at the local level. These factors may lower the quality of care, which, in the case of HAE, could increase the risk of attacks.[4] Conversely, there is some evidence that patients in rural areas may be less likely to be referred to a specialist for diagnosis or treatment of a health condition compared with those in nonrural areas.[31] Lack of timely and coordinated care and economic and geographic factors can lead to reliance on EDs for acute and long-term health care in rural communities,[4,27] in which they may also be the only provider available within a reasonable distance. According to 1 recent US physician survey, emergency care was required at least once a month by 5% of those with HAE.[32] Increased use of the ED for treatment management also leads to increased costs in a disease that is already costly to treat. Notably, the amount of work required to start a patient on the available HAE drugs is extensive. The paperwork and phone time spent by providers and staff to start on-demand or prophylactic therapy is an ongoing consideration for providers.

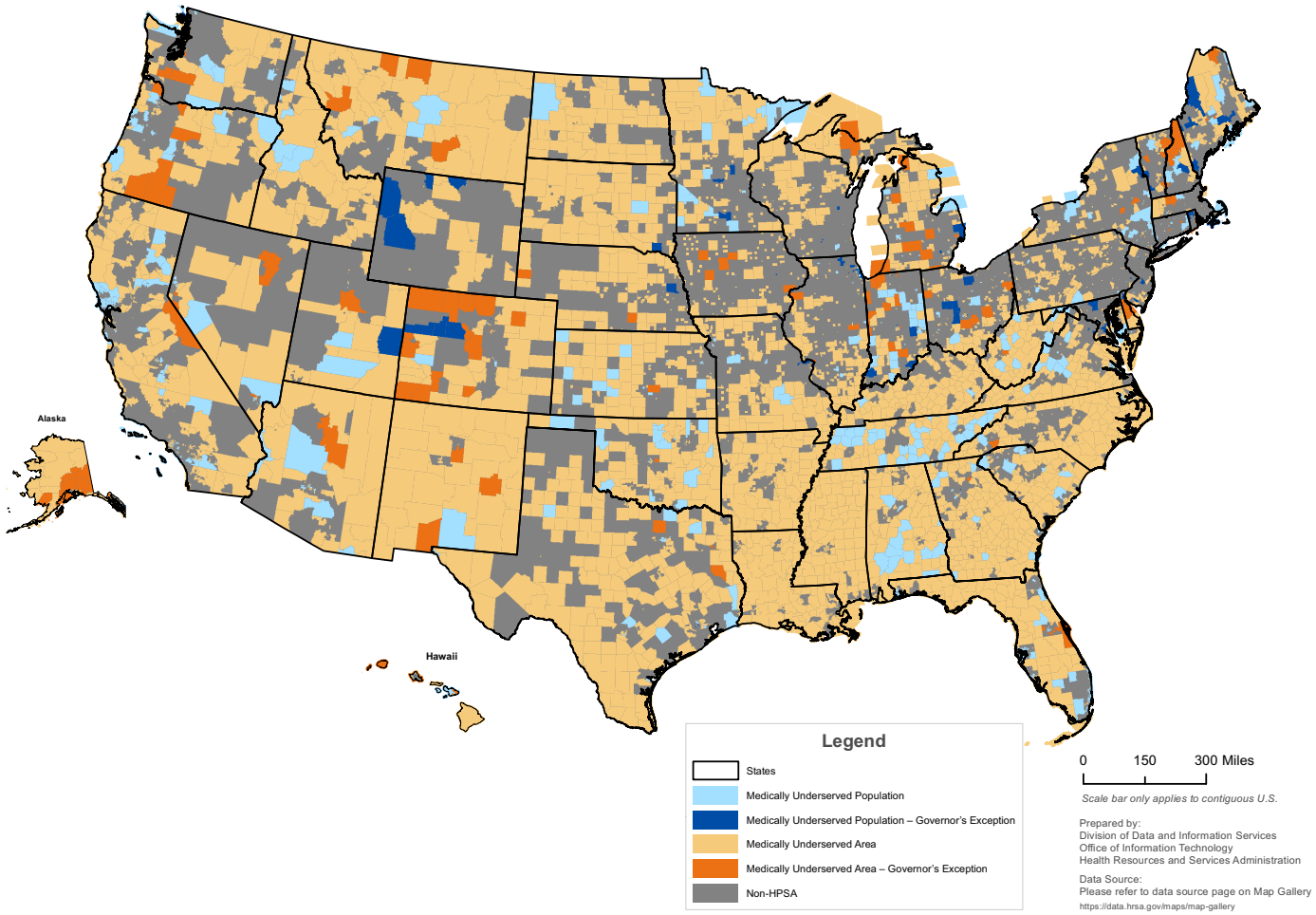

Figure 2. The United States medically underserved areas. Data as of September 15, 2021. Adapted from https://data.hrsa.gov/ExportedMaps/MapGallery/MUA.pdf. HPSA, Health Professional Shortage Area.

Patient Education

Patient education is an essential part of HAE management, including education regarding managing on-demand self-administered treatment and on early recognition and self-treatment of attacks.[11,13] As in other health conditions, living in a rural location away from treatment centers, local shortages of health care providers, disrupted continuity of care, and inadequate online access to resources[33] are potential barriers to effective and ongoing patient education in HAE. In addition, patients are increasingly turning to social media for health information and may obtain information that is low quality or not accurate.[34]

On-Demand and Prophylactic Medication

A barrier that patients with HAE in rural areas may face is maintaining an adequate supply of on-demand medication. Medications for HAE require a temperature-controlled chain of delivery that can be broken by logistical issues and delivery delays.[35] In-hospital or ED access to medications is also a concern because hospitals and EDs may not keep ready supplies of medications for on-demand treatment of HAE or perioperative prophylaxis.[36] In addition, health care providers may not be aware of how or when the medications should be used.[37]

Availability of Telemedicine Services

Telemedicine is widely used in the United States, especially during the coronavirus disease 2019 (COVID-19) pandemic, and can be as effective as face-to-face consultations for some chronic conditions. Telemedicine can also be cost-effective or cost-saving and is acceptable to patients.[38] In remote and rural areas, it has been used to improve access to services for patients and health care providers across a range of specialties and subspecialties.[37] In HAE, for example, a telemedicine service operated by trained clinicians has been found to be helpful in reducing hospital admissions for severe HAE attacks.[39] Lack of access to adequate technology for delivery of telemedicine services such as broadband services or smartphones is a barrier for patients in rural settings.[4,33]

Health Economic Disparities

Economics plays an important role in health care disparities and are often amplified in a rural setting. Patients in rural areas are more likely to lack health insurance than those in nonrural areas.[40] In the southern and western regions of the United States, rural areas have a greater proportion of Medicaid enrollees than urban areas, which influences reimbursement rates.[3,28] In some states,[27] there is a risk that payments may not be sufficient to cover the cost of physician visits, placing a financial burden on physicians and services.[4] The costs of medications for HAE are high.[41] As a result, patients with HAE may be subject to considerable coinsurance or copayment rates, preauthorizations, access-only through specialty pharmacies, and limits on supply,[41] which could present the rural patient with additional challenges.[29] In addition, patients and providers may not be

aware of patient assistance programs run by charitable or advocacy groups.

Strategies for Improvement

The Patient With Undiagnosed Hereditary Angioedema in a Rural Setting

Improved HAE awareness and the approach to diagnosis among health care providers are needed in rural and nonrural settings.[16] A number of signs and symptoms should raise a suspicion of HAE, including recurrent angioedema without urticaria lasting 2 to 5 days, slow onset to peak swelling (taking several hours to reach maximal severity), abdominal pain, and no improvement of symptoms with antihistamines, corticosteroids, or epinephrine.[11,36] Diagnostic algorithms can provide useful guidance to the physician suspicious of HAE.[42] In a rural setting, laboratory testing (as outlined previously) that can provide results quickly may not be readily available. The ED physician may have to rely on previous knowledge of the clinical presentation of HAE, response to treatment, and medical and family histories. Blood samples taken at the time of an attack can, however, be useful for follow-up and for planning future care.[36] Rapid and more reliable testing methods for HAE are needed. Testing for functional C1INH using a dried blood spot assay, for example, was found to be straightforward, affordable, and not limited by logistical considerations. Dried blood spot testing may, therefore, be especially suitable for future reliable screening in rural areas.[43]

Individualized Management Plans for the Diagnosed Rural Patient With Hereditary Angioedema

Individualized and regularly reviewed management plans developed with a specialist improve patients' quality of life (QoL) and are recommended for all patients with HAE, regardless of setting.[11,13] Patients with HAE and their providers should review any recent attacks, discuss the patient's general physical and mental health, and prepare or review the plan of action in case of an attack. As part of these plans, there should be ready access to on-demand medication, long-term prophylaxis if considered appropriate, and short-term prophylaxis when indicated.[11] Education for the patient and their caregivers should be provided on prevention of attacks and how to administer treatments. Patients should be encouraged to keep a diary of symptoms and attacks. Despite the benefits of self-administration for patients, some patients may still be unable or unwilling to self-administer, a situation that could perhaps be rectified by better access to education and improved guidance on self-administration procedures. For the time being, as more HAE treatment options become available, physicians and patients will need to balance the value of using highly efficacious treatments against the route of administration.

Expanding the Role of Telemedicine in Rural Areas

Timely access to specialist care is another barrier in rural areas. This barrier could be partially addressed by increasing broadband access and continued use of telemedicine for treatment management and patient follow-up and support. However, the need for physicians providing the telemedicine consultations to be licensed in each state where they provide telemedicine services, the reimbursement policies regarding telemedicine visits, and the implementation of other regulations can be barriers to its continuity.[44] As a consequence of COVID-19, most US state medical boards have modified or waived requirements for medical licensure to make it easier for physicians to see patients across state lines by using telemedicine. At the federal level, the Centers for Medicare and Medicaid Services have presently waived the Medicare requirement that a clinician be licensed in the state where the patient is located.

In rural areas that lack the necessary high-speed internet infrastructure, telemedicine visits may need to be conducted by telephone call rather than a video call. However, before the COVID-19 crisis, which, in the United States, began in early 2020, telemedicine by means of the telephone call was specifically excluded as a covered service by the Centers for Medicare and Medicaid Services. As a result of the COVID-19 crisis, Medicare, Medicaid, and many private insurance providers have allowed reimbursement for expanded telemedicine services, and, as a result, telephone-only and video visits at the time of this review have reimbursement parity. Because the expanded reimbursement for telemedicine observed during the COVID-19 crisis is unlikely to continue indefinitely, permanent change to the reimbursement policies surrounding telemedicine will require the US Congress to act. Ideally, telemedicine reimbursement that includes, at the least, coverage of video visits will remain in place beyond the immediate crisis.[45] Expanded coverage of telemedicine would enable patients to have better access to their health care provider and to attend routine appointments without the need to travel long distances. Congressional action on telemedicine best practices and benefits in chronic diseases could help fortify the evidence supporting the continuation of expanded telemedicine access for patients living with HAE in rural areas.

Care of Hereditary Angioedema at the Local Level from the Primary Care Provider

With the lack of specialists with expertise in HAE, medical care of patients with HAE in rural areas is often provided by primary care providers who require resources to improve the understanding of HAE therapeutics. The primary care provider can reinforce the treatment management plan ideally developed in collaboration with an HAE specialist, help the patient identify potential triggers of attacks, and work with the patient on their plan of action in case of an HAE attack.[11] In addition, local health care providers can administer validated questionnaires (eg, Angioedema QoL or Angioedema Control Test) to monitor the patient's QoL and guide individualized treatment plan discussions.[46,47] The local health care provider is vital to the holistic care of their patient by continuing to manage and treat any other acute and chronic medical conditions patients may have, and their HAE.

Care of Hereditary Angioedema at the Local Level from the Emergency Department

If a patient with HAE requires ED treatment, they often need to advocate for themselves. In some rural hospitals, electronic medical records with alerts under the patient's name can help the ED physician quickly treat the patient with diagnosed HAE using HAE-specific therapies. The patient's electronic medical records can also include references to treatment algorithms and contact information for specialists. Another potential solution is the use of a prepopulated electronic plan developed by the HAE expert (Fig 3), which can be held on file at the patient's local ED[13] and be used in the event of a laryngeal attack (in which a patient cannot advocate for themselves), reduce ED wait times, aid the administration of appropriate treatments, and improve treatment plan adherence for patients with HAE in the ED. In addition, the patient should carry a copy of their HAE treatment plan and contact information for the physician who manages their HAE. As mentioned previously, in-hospital or ED access to HAE medications is a serious concern because the local hospital or ED may not keep supplies of medications for on-demand treatment of HAE attacks or perioperative prophylaxis.[36] In addition, health care providers may not be aware of how or when medications should be used.[37] These are all surmountable challenges for rural patients with HAE treated at hospitals without an HAE specialist.

Sample Letter
RE: (NAME) (DOB)

To Whom It May Concern,
(NAME) carries the diagnosis of **C1 esterase inhibitor deficiency, also known as hereditary angioedema (HAE)** and is under my medical care to treat this condition.

This genetic condition is characterized by sporadic episodes of cutaneous, intestinal, and/or laryngeal angioedema. These episodes may cause severe pain, nausea, vomiting, and airway compromise, including fatal asphyxia.

(NAME) is currently prescribed (drug/dose/route) as prophylaxis. For treatment of acute attacks, (NAME) uses (drug/dose/route), which is U.S. Food and Drug Administration approved to treat HAE. A second dose of medication may be necessary in the event of a partial response or recurring angioedema symptoms. **In the event of any laryngeal symptoms, administer HAE medication immediately.**

In addition to this medication, management of acute attacks may include supportive care, including airway monitoring, analgesic and antiemetic medications, and intravenous fluids as appropriate.
Efficacy of epinephrine, steroids, and antihistamines is doubtful when treating HAE, a bradykinin-mediated form of angioedema.

It is medically necessary that the patient carry the listed HAE medications and related treatment supplies while traveling. In addition (NAME) has been instructed to bring their rescue medication to the emergency facility in the event they are needed.

If there are any questions, please contact (Care team 24-hour contact info)

Sincerely,

Letters for planned procedures should also include plans for preprocedure prophylaxis and extended monitoring, sample below.

Procedure and Date:
Before the procedure, (NAME) should receive prophylactic (drug/dose/route) and have additional doses of prophylactic medication available in the event of a hospital stay longer than 3–4 days.

In the event of postoperative swelling, (NAME) is to have access to U.S. Food and Drug Administration approved on-demand treatment, as above. If (NAME) is to have endotracheal anesthesia, it is recommended to have rescue medication immediately available and that the patient be monitored for a minimum of 24 hours after surgery.

Figure 3. Sample letter for use when patients visit the emergency department and other hospital visits. Used with permission from Paige et al.[13]

Access to Medication

It is imperative that access to effective HAE medications is improved for patients.[41] Assistance programs funded or administered by various sources can reduce the out-of-pocket costs to patients. Depending on their insurance coverage, patients may need to meet a prespecified baseline attack rate to qualify for coverage of HAE prophylactic medications,[48-50] face having their medications denied by insurance during reauthorization,[48,50] or face insurance limitations on the number of rescue medications that they are allowed to have filled at one time.[51] Current Hereditary Angioedema Association Medical Advisory Board guidelines recommend that prescriptions for long-term prophylaxis not be based on rigid criteria and should be individualized to the patient's needs with the goal of normalizing QoL.[11] The practice parameters from the Joint Task Force on Practice Parameters similarly note that treatment should be individualized on the basis of the patient's situation, and include access to acute care among the considerations when deciding to use long-term prophylaxis.[52] For patients with HAE in rural areas with more limited access to emergency or urgent care than their urban-dwelling counterparts, and where care may not be available as quickly, a lower threshold for prescribing long-term prophylaxis is appropriate. There is a need to increase understanding among payers that HAE attacks can be life-threatening, and that patients living in rural communities have longer distances to travel for emergency treatment, putting them at potentially greater risk of fatal attacks than patients in urban areas. Physicians managing HAE should encourage payers to include distance to emergency or hospital care as an important factor to be considered when approving long-term prophylaxis medications for patients.

Patient Support and Advocacy

Various organizations in the United States are working toward improving health services in rural areas generally or more specifically focusing on HAE and rare diseases.[53-57] These organizations work with patients and physicians and play an important role in patient advocacy and peer-to-peer support, promote disease awareness, and encourage collaborative care in rural health, rare diseases, or HAE, and support research. For example, the US Hereditary Angioedema Association is developing a patient health-related QoL assessment tool,[58] an HAE rapid triage tool,[59] and an ED Toolkit for health care providers.[60] Ultimately, these organizations help bridge the gap between assessing patient needs and providing potential solutions.

Conclusion

Patients with HAE continue to face challenges in accessing optimal care. For patients living in rural areas, many of these challenges are

amplified by disparities in access to quality health care. Given the scarcity with which these topics have been covered in the literature to date, it is hoped that this article will serve as the impetus for further initiatives focused on improving access to care. These include: (1) improving access to health care for patients living in rural areas through telemedicine and access to adequate broadband internet services; (2) ensuring that patients have support and management plans that are tailored to their individual situation; (3) raising awareness of HAE and its management among rural health care providers; (4) aiding diagnosis through enhanced recognition and more convenient tests; and (5) advocating for greater access to medications for HAE prophylaxis and treatment. This review focused on HAE types 1 and 2; however, future consideration should also be given to patients with normal levels of C1INH, which carries additional challenges owing to its rarity, difficulty in diagnosis, and prevalence primarily in women.

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