

This HAE bibliography project was completed for the US HAEA by college student and HAE patient Chelsea L. Vincent as part of a college senior honors project. Chelsea accessed MEDLINE via the PubMed database in order to obtain a list of HAE literature using specific search criteria. The keywords "hereditary angioedema OR angioedema/genetics" were entered in the search field. The date range includes literature published through June 1, 2009, so as to include the most recent and up-to-date material.

Select Annotated Bibliography

CASE REPORTS

Adhikesavan, L. G., and T. P. Oleginski. "Hereditary Angioedema in a Family Presenting as Transient Periarthritis." J Clin Rheumatol 14.5 (2008): 289-91.

This article features a patient who was initially diagnosed with arthritis following recurrent attacks of edema surrounding her peripheral joints; she was then diagnosed with HAE which lead to subsequent diagnoses within her family. It suggests that HAE should be considered in the differential diagnosis of recurrent periarticular swelling.

Altman, A. D., et al. "Hereditary Angioedema Managed with Low-Dose Danazol and C1 Esterase Inhibitor Concentrate: A Case Report." J Obstet Gynaecol Can 28.1 (2006): 27-31.

This article features a nulliparous female patient diagnosed with HAE at 22 weeks of gestation. She was treated with danazol for prophylaxis which failed, and then exclusively was treated with C1EI at weekly intervals. The article concludes that low dose danazol was ineffective in treating this patient's HAE during pregnancy.

Berkun, Y., and M. Shalit. "Hereditary Angioedema First Apparent in the Ninth Decade During Treatment with Ace Inhibitor." Ann Allergy Asthma Immunol 87.2 (2001): 138-9.

This article features a 90 year old patient who was diagnosed with HAE eight years after her first attack during angiotensin-converting enzyme inhibitor use at age 82. It emphasizes that a family history should be taken in patients of all ages, with specific focus on HAE, before beginning treatment with ACE inhibitor.

Bernedo, N., et al. "Hereditary Angioedema and Pneumomediastinum." J Investig Allergol Clin Immunol 13.2 (2003): 137-9.

This article features an 18-year-old woman with a previous history of HAE, who was diagnosed with pneumomediastinum as a complication of an angioedema episode, after presenting with an episode of coughing and vomiting.

Binkley, K. E., and A. Davis, 3rd. "Clinical, Biochemical, and Genetic Characterization of a Novel Estrogen-Dependent Inherited Form of Angioedema." J Allergy Clin Immunol 106.3 (2000): 546-50.

This article focuses on the identification of a third type of HAE (HAE type III) which is an estrogen-dependent phenotype. It focuses on a family whose HAE appears to not have resulted from C1 inhibitor deficiency or dysfunction, but rather is due to estrogen dependency.

Bork, K., D. Gul, and G. Dewald. "Hereditary Angio-Oedema with Normal C1 Inhibitor in a Family with Affected Women and Men." Br J Dermatol 154.3 (2006): 542-5.

This article features a four generation family of patients with type III HAE, one male member of whom was mainly affected after taking ACE inhibitors. It suggests that the current type III HAE doesn't affect only females as was previously thought, or that type III HAE may reflect a completely different underlying defect all together.

Bork, K., et al. "Asphyxiation by Laryngeal Edema in Patients with Hereditary Angioedema." Mayo Clin Proc 75.4 (2000): 349-54.

This article focuses on the occurrence of fatal laryngeal edema in patients with HAE. It emphasizes the importance of familial and physician awareness of the manifestations of the disease.

Cadena Silva, M. A., M. I. Castrejon Vazquez, and V. M. Almeida Arvizu. "[Hereditary Osler Angioedema (Report of Case)]." Rev Alerg Mex 47.3 (2000): 94-5.

This article features a case of Osler's HAE, showing classic signs and symptoms of HAE starting at seven years old.

Caliskaner, Z., et al. "A Successful Pregnancy and Uncomplicated Labor with C1inh Concentrate Prophylaxis in a Patient with Hereditary Angioedema." Allergol Immunopathol (Madr) 35.3 (2007): 117-9.

This article focuses on a pregnant patient with HAE who suffered recurrent attacks during her pregnancy; however, she was able to experience an uncomplicated labor while being administered prophylactic C1-INH concentrate.

Campanile, E., et al. "Changes in Splenoportal Axis Calibre and Flow in a Patient Affected by Hereditary Angioedema." Panminerva Med 43.4 (2001): 307-10.

This article features a patient with HAE suffering from abdominal pain and ascites. The authors suggest that using ultrasound techniques may help physicians to make earlier diagnoses of HAE and avoid invasive procedures while ruling out abdominal complications.

Celikel, S., et al. "Hereditary Angioedema Associated with Heterozygous Factor V Leiden Mutation in a Patient with Purpura Fulminans." Int Arch Allergy Immunol 142.2 (2007): 175-8.

This article features a female patient with HAE and factor V Leiden mutation who experienced purpura fulminans after she started using oral contraceptives for hormone replacement therapy due to irregular menstrual cycles.

Chagas Kde, N., et al. "[Therapeutic Approach of Hereditary Angioedema]." Rev Assoc Med Bras 50.3 (2004): 314-9.

This article features 10 patients from four families and describes the different treatment chosen for each patient, along with the evolution of each treatment plan; it also includes an evaluation of the different treatments for each patient and eludes that although the disease is caused by a mutation that causes the same deficiency, it clearly manifests differently in each patient, presenting a need for individualized treatment plans.

Chaney, J. D., et al. "Hemostatic Analysis of a Patient with Hereditary Angioedema Undergoing Coronary Artery Bypass Grafting." Anesth Analg 93.6 (2001): 1480-2, table of contents.

This article features a case of HAE in a patient who underwent cardiopulmonary bypass surgery. The patient also had multiple other medical conditions which were described in the case. This report describes the impact of having HAE on hemostasis in a surgical environment.

Church, J. A. "Oxandrolone Treatment of Childhood Hereditary Angioedema." Ann Allergy Asthma Immunol 92.3 (2004): 377-8.

This article focuses on a 6-year-old-boy who experienced recurrent HAE attacks and was treated with oxandrolone – the effects the drug had on the young boy were highlighted. It implicates that using low dose oxandrolone to control HAE attacks is a necessary procedure to follow.

Cicardi, M., and L. Zingale. "How Do We Treat Patients with Hereditary Angioedema." Transfus Apher Sci 29.3 (2003): 221-7.

This article features the experiences of a single department in treating many patients with HAE. The authors present their findings regarding 441 patients whom they have treated for this disease.

Dinkel, H. P., J. Maroske, and L. Schrod. "Sonographic Appearances of the Abdominal Manifestations of Hereditary Angioedema." Pediatr Radiol 31.4 (2001): 296-8.

This article features a case of a 12-year-old girl with HAE experiencing recurrent abdominal attacks. The importance of using ultrasound and imaging technologies while diagnosing an attack of HAE are stressed, as intestinal edema is a characteristic marker for the disease.

Dirks, K., J. Deuerling, and H. Lutz. "[Sonography in Hereditary Angioedema: Typical Findings Demonstrated by the Example of 3 Cases]." Ultraschall Med 22.4 (2001): 186-90.

This article features three patients of whom had ultrasonograms performed during abdominal edema episodes of HAE to analyze the affected layers of intestine. It is suggested that an ultrasonic examination should be completed each time a patient experiences an abdominal episode in order to determine the severity of the edema, aiding in the decision of whether or not to administer C1-INH concentrate.

Dollin, M., et al. "Unilateral Lacrimal Gland Atrophy in a Patient with Hereditary Angioedema." Cornea 26.4 (2007): 505-6.

This article features the case of a 32-year-old woman with HAE who experienced dryness and irritation of her left eye. It is suggested that recurrent inflammation in the eye due to HAE may lead to lacrimal gland atrophy.

Duvvur, S., F. Khan, and K. Powell. "Hereditary Angioedema and Pregnancy." J Matern Fetal Neonatal Med 20.7 (2007): 563-5.

This article stresses the importance of awareness regarding patients with HAE and their obstetricians during their reproductive years, as HAE is potentially life threatening. It is imperative that obstetricians are aware of the potential dangers regarding their HAE patients during pregnancy.

Eckert, S., B. Eifrig, and T. Standl. "[Perioperative Treatment of a Patient with Hereditary Angioedema (Hae) in a Case of a Young Patient with Osteosynthesis from a Femoral Fracture]." Anesthesiol Intensivmed Notfallmed Schmerzther 35.12 (2000): 776-81.

This article features a case involving a juvenile male who suffered from a femoral fracture. The article discusses the difficulties involved with administering anesthesia in patients with HAE. It indicates the importance of distinguishing between HAE and allergic angioedema, as there are differences in drug treatment and therapy.

El-Hachem, C., et al. "[Hereditary Angioneurotic Edema: A Case Report in a 3-Year-Old Child]." Arch Pediatr 12.8 (2005): 1232-6.

This article features the case of a three-year-old girl experiencing facial edema who was misdiagnosed with allergic asthma, as opposed to HAE. It emphasizes the importance of correct diagnosis of HAE, especially in the case of laryngeal edema.

Ergin, H., et al. "A Case of Hereditary Angioedema with Recurrent Arthritis, Erythema Marginatum-Like Rash and Chest Pain." Turk J Pediatr 45.3 (2003): 261-4.

This article features a patient with HAE who also presented with autoimmune-like symptoms, including nondeforming polyarthritis. After treatment with the anabolic steroid danazol, laboratory tests and physical examinations of the patient returned to normal for more than five years. It is suggested that pediatricians should become familiar with this disease in order to treat patients as necessary.

Fabiani, J. E., A. Avigliano, and J. C. Dupont. "Hereditary Angioedema. Long-Term Follow-up of 88 Patients. Experience of the Argentine Allergy and Immunology Institute." Allergol Immunopathol (Madr) 28.5 (2000): 267-71.

This article features the cases of multiple HAE patients all of whom receive treatment at the same clinic. The authors describe the onset of the disease, how it manifests in, and the complications involved with each patient. The authors also include the results obtained using different therapies among the patients for both preventative and acute needs.

Farhoudi, A., et al. "Two Related Cases of Primary Complement Deficiency." Immunol Invest 32.4 (2003): 313-21.

This article features a 40-year-old woman who suffered multiple HAE episodes involving orofacial and laryngeal edema without a previous family history of the disease. It emphasizes that HAE can be a diagnosis even if a previous family background of the disease is lacking.

Farkas, H., et al. "Acute Abdominal Attack of Hereditary Angioneurotic Oedema Associated with Ultrasound Abnormalities Suggestive of Acute Hepatitis." Acta Paediatr 91.8 (2002): 971-4.

This article focuses on the case of a 14-year-old male who was admitted to the hospital for an abdominal episode caused by HANO (Hereditary angioneurotic oedema – an outdated name for the disease). It focuses on the importance of using diagnostic clues and tools, such as ultrasound, during an attack to aid in diagnosis and administration of proper treatment.

---. "[Hereditary Angioneurotic Edema in Children]." Orv Hetil 141.47 (2000): 2541-7.

This article features the summation of 21 cases of children who are all affected by HAE. The article analyzes the cases as a whole group, reporting the most common causes of episode induction, as well as the effectiveness of drug treatments. It emphasizes the

importance of lowest dose drug therapy for prophylaxis and the quality of life improvement the drug therapy can provide for pediatric patients.

Fernandez Romero, D., P. Di Marco, and A. Malbran. "Acute Edema Blisters in a Hereditary Angioedema Cutaneous Attack." Allergol Immunopathol (Madr) 36.3 (2008): 182-3.

This article features a patient who experiences recurrent acute edema blisters as a result of cutaneous HAE attacks. The pathophysiology behind the blisters is explained.

Fiedler, E., et al. "[Angioedema in Hereditary Deficiency of Complement Factor 1 Esterase Inhibitor and Alpha 1-Antitrypsin]." Dtsch Med Wochenschr 130.4 (2005): 150-2.

This article features the unusual case of a 13-year-old female HAE patient who also has a hereditary alpha (1)-antitrypsin deficiency. This patient is unique, as her case is the first reported of multiple hereditary enzyme deficiency.

Foix-L'Heliass, L., et al. "Recurring Acute Abdominal Pains in an Adolescent as the Presenting Manifestations of Hereditary Angioneurotic Oedema." Acta Paediatr 94.8 (2005): 1158-61.

This article features the case of an adolescent patient who underwent an appendectomy after being hospitalized for current abdominal pains. Further investigation led to the patient being diagnosed with hereditary angioneurotic oedema. It suggests that HAE needs to be ruled out as a potential diagnosis in children with recurrent abdominal pain before proceeding with surgery, especially if abdominal edema is present.

Freeman, H. J. "Hereditary Angioneurotic Edema and Familial Crohn's Disease." Can J Gastroenterol 14.4 (2000): 337-9.

This article features a 50-year-old woman and her 29-year-old son who have both been diagnosed with Crohn's disease and HAE. The woman was diagnosed with HAE after recurrent abdominal pain, along with Crohn's disease. Due to the close linkage of the Crohn's disease, a family history was taken revealing other family members either effected with Crohn's or HAE. These case reports coupled with a previous report in Hungarian literature of a similar case suggest a close genetic linkage between HAE and familial Crohn's disease.

Garcia Cobas, C. Y., et al. "[Atypical Presentation of Hereditary Angioedema. A Report of a Case and Literature Review]." Rev Alerg Mex 53.5 (2006): 189-93.

This article features an unusual case of HAE manifested in a 27-year-old female patient who experiences recurrent episodes of edema on a daily basis. The article highlights her struggle with androgen therapy and emphasizes her need for treatment with C1 inhibitor concentrate.

Gorman, P. J. "Hereditary Angioedema and Pregnancy: A Successful Outcome Using C1 Esterase Inhibitor Concentrate." Can Fam Physician 54.3 (2008): 365-6.

This article features the report of a 21-year-old female patient who suffered from angioedema attacks for many years and saw many physicians before a definitive diagnosis of HAE was determined. Although she was using danazol on a prophylactic basis, she was still experiencing severe attacks, including oral edema. In May 2005, she presented to her physician with a positive pregnancy test, and a more intensive therapy treatment was determined. She began receiving infusions of C1-INH concentrate every other week for the duration of her pregnancy. She did continue to experience minor episode even after beginning C1-INH infusions, so the dosage was increased and she subsequently became asymptomatic. At the end of the pregnancy, her baby was delivered via cesarean section without complications. This case report demonstrates the usefulness and safety of C1-INH infusion during pregnancy.

Gugila, I., et al. "[Osler's Hereditary Angioneurotic Edema as Rare but Possible Cause of False Surgical Acute Abdomen]." Chirurgia (Bucur) 98.5 (2003): 437-41.

This article features a case of HAE in which the patient presented with clinical signs and symptoms resembling surgical acute abdomen. The focus of this article is on the importance of correct, and early diagnosis of HAE versus acute abdomen, as HAE often presents much like acute abdomen but requires a much different treatment regime.

Guilarte, M., et al. "Acquired Angioedema Associated with Hereditary Angioedema Due to C1 Inhibitor Deficiency." J Investig Allergol Clin Immunol 18.2 (2008): 126-30.

This article features a rare case of HAE which resulted in a developed case of acquired angioedema that was due to a lymphoma. The lymphoma was likely caused by a reduction in levels of C1q. The 51-year-old female patient had experienced episodes of edema since age 12 and was diagnosed with HAE at age 40, but managed her symptoms with stanazolol, until the lymphoma developed.

Hemels, M. A., et al. "[Episodes of Angioedema in Children with C1 Esterase Inhibitor Deficiency]." Ned Tijdschr Geneeskd 150.11 (2006): 631-4.

This article parallels two pediatric cases which both appear to be HAE. The 3.5-year-old female patient had a family history which resulted in her inheritance of the disease, explaining her episodes of angioedema. The 6-year-old male patient however did not have a family history of the disease, but still presented with unexplained, recurrent episodes of angioedema. The article emphasizes the need for early diagnosis of HAE to properly treat both acute episodes and for prophylaxis, especially in pediatric patients.

Hermans, C. "Successful Management with C1-Inhibitor Concentrate of Hereditary Angioedema Attacks During Two Successive Pregnancies: A Case Report." Arch Gynecol Obstet 276.3 (2007): 271-6.

This article highlights the case of a female patient experimenting with infusions of C1-INH concentrate during two different pregnancies for management of HAE. This article demonstrates that using C1-INH at home can be done successfully to manage and treat the symptoms of HAE during pregnancy; it also emphasizes that since the disease manifests differently in every patient, the treatment plan would need to be personalized for each individual patient to be successful.

Heusse, J. L., O. Claude, and L. Lantieri. "[Can One Propose Aesthetic Surgery to One Male or Female Patient with an Hereditary Angio-Oedema?]." Ann Chir Plast Esthet 53.3 (2008): 289-92.

This article features a female patient experiencing mammary hypotrophy due to prophylactic treatment with the androgen danazol and she wishes to correct the issue with breast implants. The article focuses largely on the risks and complications involved with performing surgery on patients with HAE due to the likelihood of oro-tracheal intubation triggering an episode of edema. This report provides a look into the surgical care and planning needed to accommodate those affected by HAE.

Hsieh, F. H., and A. L. Sheffer. "Episodic Swelling in a Pregnant Woman from Bangladesh: Evaluation and Management of Angioedema in Pregnancy." Allergy Asthma Proc 23.2 (2002): 157-61.

This article features a patient who developed acquired angioedema during her pregnancy. It is relevant because it discusses and explains the mechanisms involved with C1 inhibitor deficiency leading to the development of angioedema; it is also very useful as it focuses on management of a pregnant patient with angioedema.

Huang, Y. T., et al. "Hereditary Angioedema: A Family Study." Asian Pac J Allergy Immunol 23.4 (2005): 227-33.

This report features the first ever reported cases of HAE in Taiwan. A 33-year-old patient experienced painful swelling of her face and hands since the age of 27, during her first pregnancy. Further research revealed similar episodes of edema in other members of her family. Laboratory results were studied on a total of 11 members of the patient's family, including the patient. Seven members of the family were diagnosed with type I HAE based on the laboratory test findings.

Hubiche, T., et al. "[Reticular Erythema Signalling the Onset of Episodes of Hereditary Angioedema in a Child]." Ann Dermatol Venereol 132.3 (2005): 249-51.

This article features the case of a pediatric female patient who experienced recurrent episodes of reticular erythema every four to six weeks since she was an infant and abdominal pain or edema of her lower limbs following eruptions two to three times yearly. At the age of 12, she was hospitalized due to a facial edema episode associated with another eruption. Laboratory results confirmed a diagnosis of HAE. This article

strongly emphasizes the importance of recognizing eruptions of reticular erythema as an early symptom of HAE, and to use it as an aid for an earlier diagnosis in many patients.

Janardhanan, D., S. Nair, and T. S. Subramanian. "Recurrent Abdominal Pain Due to Hereditary Angioedema." Indian J Pediatr 74.1 (2007): 83-4.

This article features the case of a pediatric female patient who experienced multiple cases of abdominal pain without cutaneous manifestations. Each time she presented, her episodes were handled as acute surgical emergencies and invasive laparotomies were performed. Eventually, quantitative assays of C1-INH were evaluated and a diagnosis of HAE was reached. This article emphasizes the need for HAE to be considered in the differential diagnosis of children presenting with recurrent abdominal pain, as to avoid multiple unnecessary invasive procedures.

Joynt, G. M., V. Abdullah, and P. J. Wormald. "Hereditary Angioedema: Report of a Case." Ear Nose Throat J 80.5 (2001): 321, 24.

This article reports the case of a 24-year-old male who experienced an acute HAE attack after he discontinued use of his prophylactic medication therapy. This case demonstrates the necessity of prophylactic medication routines for most patients diagnosed with HAE, and the potential adverse affects that can be associated with the cessation of an existing routine.

Kamboj, S., et al. "Hereditary Angioedema: A Rare but Potentially Lethal Disease." J La State Med Soc 154.3 (2002): 121-4; quiz 25.

This article features the case of a patient who presented with facial edema, and discusses the processes of diagnosis and management of HAE in this particular patient. It emphasizes that HAE should be considered in the differential diagnosis of all patients who present with facial edema.

Karim, Y., H. Griffiths, and S. Deacock. "Normal Complement C4 Values Do Not Exclude Hereditary Angioedema." J Clin Pathol 57.2 (2004): 213-4.

This article features the case of a young female patient who had a family history of HAE but had the disease ruled out for her based upon primary laboratory result findings – she had consistently normal levels of C4. However, at age 10, she presented with recurrent abdominal pain over the previous three months and edema in her hands over the previous eight months. C4 levels and C1-INH levels were then measured, and although her C4 levels remained normal, her C1-INH levels were very low. This case report demonstrates the need for both C4 and C1-INH levels to be measured before excluding HAE as a diagnosis.

Kasamatsu, Y., I. Nakayama, and T. Kobayashi. "[a Case of Lung Cancer with Hereditary Angioedema Treated Effectively by Chemo-Radiotherapy with C1 Esterase Inhibitor Concentrate and Danazol]." Nihon Kokyuki Gakkai Zasshi 42.5 (2004): 435-9.

This article features the report of a 69-year-old male patient with HAE and lung cancer. The report details the effects of having both lung cancer and HAE; it also highlighted how HAE effected the treatment of his lung cancer. Due to complications, C1-INH concentrate was administered following an acute attack of edema; following his chemotherapy in order to avoid the foreseen complications, danazol therapy was implemented.

Khan, S., et al. "Secondary Systemic Lupus Erythematosus: An Analysis of 4 Cases of Uncontrolled Hereditary Angioedema." Clin Immunol 123.1 (2007): 14-7.

This article features a report of four patients with uncontrolled HAE and the correlation between serum levels of C4 and the development of lupus or lupus-like syndrome. This report is one of many which work to further develop a hypothesis that HAE and secondary SLE are linked.

Kim, S. H., et al. "A Case of Hereditary Angioedema Associated with Idiopathic Hypoparathyroidism." Korean J Intern Med 16.4 (2001): 281-3.

This article features the case of a 34-year-old male patient with HAE who developed idiopathic hypoparathyroidism. Like many other articles, this report elutes that there is likely an association between HAE and other autoimmune developments.

Kozowicz, M., et al. "[Hereditary Angioedema in a 16-Year-Old Girl]." Wiad Lek 59.11-12 (2006): 869-72.

This article features the report of a 16-year-old girl who was admitted to the hospital during an episode of massive facial edema. She experienced recurrent edematous episodes despite a course of prophylactic treatment. This report includes an explanation of not only the therapeutic problems the patient encountered, but also the issues involved with providing her with a proper diagnosis.

Liekenbrocker, T., et al. "[Hereditary C1 Esterase Inhibitor Deficiency Type I. Divergence of Clinical Symptoms and Laboratory Chemical Findings]." Hautarzt 52.5 (2001): 434-8.

This article features two different cases of HAE that are paralleled in order to provide a picture into the different clinical courses that HAE can take in different individuals. For both patients, two females aged 35 and 29, laboratory analyses showed a deficiency of C1-INH, but both patients had different histories of recurrent episodes of edema. Based on this observation, the authors emphasize that there is not a correlation between the clinical presentation of a patient and his/her laboratory results.

Lim, Y. C., et al. "Hereditary Angioneurotic Edema of the Larynx." Acta Otolaryngol 125.11 (2005): 1240-3.

This article features the case of a 37-year-old female patient who experienced an attack of laryngeal edema. The patient was diagnosed early and thus received the proper treatment and survived the laryngeal episode, which unfortunately is often a high cause of death in many HAE patients. The case in this article is a perfect example for the necessity of an early diagnosis of HAE, especially in the case of laryngeal edema.

Maeda, S., et al. "Management of Oral Surgery in Patients with Hereditary or Acquired Angioedemas: Review and Case Report." Oral Surg Oral Med Oral Pathol Oral Radiol Endod 96.5 (2003): 540-3.

This article features a case of oral surgery management for a patient with HAE. The patient underwent a tooth extraction and was administered C1-INH concentrate effectively for prevention of edema during and after the procedure. Multiple other cases were also reviewed throughout this article in which similar cases were discussed. All of the cases reported led to the conclusion that the type of angioedema present in the patient needs to be evaluated before proceeding with a prophylactic treatment option preceding any major surgeries.

Majoni, S. W., and S. R. Smith. "Membranous Nephropathy in a Patient with Hereditary Angioedema: A Case Report." J Med Case Reports 2 (2008): 328.

This article features the presentation of the first reported case of membranous nephropathy associated with HAE. The affected 43-year-old male patient presented with acute intestinal edema among other symptoms, many of which indicated a severe nephritic syndrome; if left untreated, the symptoms would likely result in renal failure. This case is unique as the HAE created a great challenge for treatment of the membranous nephropathy in this patient.

Matesic, D., et al. "Acute Pancreatitis Due to Hereditary Angioedema." Ann Allergy Asthma Immunol 97.5 (2006): 611-4.

This article features the report of a patient who experienced HAE-associated acute pancreatitis. This article emphasizes the necessity for clinicians to suspect acute pancreatitis when caring for a patient experiencing intestinal edema due to HAE; it also emphasizes the need to properly treat HAE in a prophylactic manner in order to avoid more serious complications, such as acute pancreatitis.

McGlinchey, P. G., and D. R. McCluskey. "Hereditary Angioedema Precipitated by Estrogen Replacement Therapy in a Menopausal Woman." Am J Med Sci 320.3 (2000): 212-3.

This article presents the first reported case of a patient experiencing symptoms of HAE after beginning estrogen replacement therapy to manage her symptoms of menopause. This case is very unusual in many aspects including a late presentation of HAE and attacks proceeding doses of estrogen replacement.

Mitrovic, S., et al. "[Hereditary Angioedema in Organs of the Head and Neck as an Indication for Emergency Tracheotomy]." Med Pregl 54.1-2 (2001): 81-4.

This article features the report of a patient who was hospitalized for edema of the neck and lower lip. Soon after hospitalization his situation worsened, as massive edema of the larynx developed; intravenous steroid therapy, calcium and adrenaline did not improve his respiration, and eventually emergency tracheotomy was necessary to keep the patient alive. Laboratory results and family history lead to the diagnosis of HAE. This article emphasizes the definite need for HAE to be considered in the differential diagnosis when a patient presents with laryngeal edema, as the situation can quickly become fatal.

Monnier, N., et al. "Characterisation of a New C1 Inhibitor Mutant in a Patient with Hepatocellular Carcinoma." Mol Immunol 43.14 (2006): 2161-8.

This article features the report of the first developed case of hepatocarcinoma associated with HAE. It was originally hypothesized in the article that the development of hepatocarcinoma was due to a 13-year long prophylactic exposure to the androgen danazol. Using molecular detection techniques, it was then determined amidst the article that an accumulation of mutated C1-INH protein in conjunction with danazol exposure was, in fact, not the cause of the hepatocarcinoma that the patient developed.

Montalto, M., et al. "Gastrointestinal Involvement in a Case of Hereditary Angioedema: Could the Early Weaning Have Had a Role?" Am J Med Sci 334.3 (2007): 231-3.

This article features a case of type II HAE in a young adult male patient. The patient experienced recurrent episodes of abdominal edema, sometimes with ascites. The authors theorize that since the patient experienced an early weaning, his abdomen – specifically the gastrointestinal tract – may have been left as a vulnerable area for the HAE to continually affect this patient.

Moon, M. G., et al. "A Tracheostomy Obturator for a Patient with Hereditary Angioneurotic Edema." J Prosthet Dent 91.5 (2004): 494-8.

This article features a patient with HAE who has a need for a permanent tracheostoma, and details the technique involved with creating a custom tracheostomy obturator for this patient. Since the patient has HAE, the impression technique and creation of the custom tracheostoma valve retainer required special steps and careful prophylactic procedures.

Nalbanski, B., et al. "[the Rare Case of Successful Pregnancy and Delivery in Patient with Hereditary Angioedema]." Akush Ginekol (Sofia) 41.5 (2002): 39-42.

This article features the case of a patient with HAE who had a successful pregnancy, which resulted in the successful delivery of a newborn. This article discusses the complication of HAE involved with pregnancy and the management of treatment which can often be difficult since a fetus is involved and most of the usual treatments can be harsh to a growing fetus.

Nathani, F., H. Sullivan, and D. Churchill. "Pregnancy and C1 Esterase Inhibitor Deficiency: A Successful Outcome." Arch Gynecol Obstet 274.6 (2006): 381-4.

This article presents the case of a 34-year-old patient who was previously diagnosed with HAE, but was able to experience a well managed pregnancy. There were extensive plans drawn out and put in place (clearly documented) for treatment throughout her pregnancy. C1-INH concentrate was administered aggressively in an effort to keep the patient episode free during her pregnancy, which was relatively successful; the C1-INH concentrate therapy allowed the patient to experience a successful vaginal delivery of her child as well.

Neri, S., D. Ierna, and L. Sfogliano. "Unusual Manifestations of Hereditary Angioedema." Eur J Emerg Med 7.2 (2000): 111-2.

This article features the case of a 35-year-old male who presented with acute abdomen and parasellar edema, resulting in emergency situations. This case was considered unusual since the patient has type II HAE, characterized by the presence of non functional C1-INH. This emphasizes the need for early diagnosis of HAE, and the need for classifying which subtype is manifested in the patient as well.

Nzeako, U. C., E. Frigas, and W. J. Tremaine. "Hereditary Angioedema as a Cause of Transient Abdominal Pain." J Clin Gastroenterol 34.1 (2002): 57-61.

This article features the report of a young adult experiencing abdominal pain as a result of type II HAE. The article suggests that HAE should be included in possible diagnoses in young adults who present with recurrent abdominal pain, especially once common causes of the pain have been excluded from possible diagnoses.

O'Bier, A., A. E. Muniz, and R. L. Foster. "Hereditary Angioedema Presenting as Epiglottitis." Pediatr Emerg Care 21.1 (2005): 27-30.

This article features a pediatric case of HAE in which the patient presented with edema of the epiglottis, which required intubation to keep an open airway. The article highlights the important treatment steps that should be taken to manage similar situations; first an open airway must be established to allow for adequate oxygenation, and then administration of C1-INH concentrate should occur if it is available. The article also explains that usage of common treatments for airway edema tends to be ineffective at reducing laryngeal edema for patients with HAE.

Ohsawa, I., et al. "Worsening Fluid Retention in a Patient with Hereditary Angioedema and End-Stage Renal Disease." Intern Med 43.8 (2004): 708-12.

This article features an unusual case in which a 60-year-old woman diagnosed with HAE then developed nephritic syndrome with end-stage renal disease approximately two and a half years later. In the time that she started to develop end-stage renal disease, she

experienced a few episodes of edema which resulted in fluid retention. The authors theorized that the patient's renal insufficiencies were largely responsible for her attacks of HAE.

Palazzi, C., et al. "Non-Rheumatoid Erosive Arthritis Associated with Type I Hereditary Angioedema." Clin Rheumatol 24.6 (2005): 632-3.

This article features the report of an association between HAE and non-rheumatoid erosive oligoarthritis affecting the hips and wrists for the first time. HAE has been reported in association with many autoimmune diseases, and this case adds to the repertoire.

Pecsi, S. A., et al. "Management of Hereditary Angioedema During Off-Pump Coronary Arterial Surgery." Ann Thorac Surg 85.3 (2008): 1079-81.

This article features the case of a 62-year-old man with HAE who developed coronary artery disease. The HAE created complications, and required very extensive preparations, along with cooperation among many teams of medical professionals in order to properly provide successful treatment to this individual.

Pekdemir, M., et al. "Effective Treatment of Hereditary Angioedema with Fresh Frozen Plasma in an Emergency Department." J Emerg Med 33.2 (2007): 137-9.

This report focuses on the successful use of fresh frozen plasma as an alternative treatment method for HAE in three patients. Often times, C1-INH concentrate is not available for a method of treatment, so finding alternatives that work just as effectively is an absolute necessity for the safety of HAE patients.

Porebski, G., et al. "[Recombinant Human C1-Inhibitor Is Effective in the Treatment of Acute Attacks of Hereditary Angioedema--Case Report]." Przegl Lek 62.5 (2005): 317-20.

This article features a report of effective development and use of recombinant human C1-INH for treatment of HAE. Two patients in Poland with severe HAE were administered the recombinant drug and were safely and effectively treated. The need for recombinant C1-INH is great, as the only source previously for C1-INH was donated human plasma, causing a restriction of the availability and carried risks as well.

Pritzker, H. A., T. L. Levin, and G. Weinberg. "Recurrent Colocolic Intussusception in a Child with Hereditary Angioneurotic Edema: Reduction by Air Enema." J Pediatr Surg 39.7 (2004): 1144-6.

This article features the case of a pediatric HAE patient who experienced recurrent bouts of colocolic intussusceptions. Fortunately, each bout was successfully reduced by using an air enema. This article goes to prove that HAE manifests itself differently in each patient, and may or may not be symptomatic.

Rice, S., et al. "Emergency Management of Upper Airway Angio-Oedema after Routine Dental Extraction in a Patient with C1 Esterase Deficiency." Br J Oral Maxillofac Surg 46.5 (2008): 394-6.

This article features the case of a 28-year-old female patient who experienced orofacial edema and drooling shortly after experiencing a dental extraction. The original diagnosis for the edema was a spreading dental infection, but upon further investigation including facial review and family history, HAE was diagnosed. As soon as HAE became the diagnosis, the patient received C1-INH concentrate and was able to make a complete recovery. This article emphasizes the importance of an early diagnosis of HAE, especially before undergoing any surgical procedures which may result in edema.

Ricketti, A. J., et al. "Hereditary Angioedema Presenting in Late Middle Age after Angiotensin-Converting Enzyme Inhibitor Treatment." Ann Allergy Asthma Immunol 98.4 (2007): 397-401.

This article features the unique presentation of HAE in an older male patient. The patient first presented with life threatening edema at age 52, and it was determined that the symptoms were triggered by the administration of ACE inhibitors. This article clearly states that physicians must be reminded that administration of ACE inhibitors, especially in the older population, could lead to the diagnosis of a previously asymptomatic HAE.

Roberts, A., M. Shah, and I. L. Chapple. "C-1 Esterase Inhibitor Dysfunction Localised to the Periodontal Tissues: Clues to the Role of Stress in the Pathogenesis of Chronic Periodontitis?" J Clin Periodontol 30.3 (2003): 271-7.

This article features a very unusual case of HAE in a 24-year-old female patient. The patient had been undergoing surgical reduction of her gingival tissues for 21 years for what was thought to be a very aggressive form of periodontitis. However, after 21 years of reduction surgery, serological techniques were finally utilized and a diagnosis of HAE was made. This article reports the first known case of HAE that is localized only to the gingiva.

Sadeghi, N., et al. "Hereditary Angio-Edema Involving the Gastrointestinal Tract: Ct Findings." Eur Radiol 11.1 (2001): 99-101.

This article features a case involving a young adult male patient who experienced recurrent abdominal pain for multiple years. After a CT scan was performed during one of the abdominal episodes, HAE became the differential diagnosis; a definite diagnosis was then made after measuring the level of serum C1-INH.

Sanchez, A., et al. "[Hereditary Angioedema Causing Colocolic Intussusception]." Arch Pediatr 15.3 (2008): 271-4.

This article features the case of a 15-year-old female patient who experienced intestinal intussusception due to HAE. The authors discuss possible treatments for pediatric patients with HAE who experience digestive crisis as a complication of the disease.

Sanchez-Morillas, L., et al. "[Hereditary Angioedema of Delayed Onset]." An Med Interna 21.2 (2004): 84-6.

This article features the report of a 56-year-old male who recently started to experience episodes of edema in multiple locations. Laboratory tests were completed and results showed low levels of C4 and C1-INH, which lead to the diagnosis of HAE.

Sanhueza, P. I. "Contraception in Hereditary Angioedema." Fertil Steril 90.5 (2008): 2015 e21-2.

This article features a report of a female patient, who after beginning the use of oral contraception, experienced episodes of edema every month or two and was eventually diagnosed with type I HAE. It was decided that the oral contraceptive method needed to be suspended and a transdermal hormonal contraceptive method was put into place. After 26 months, the patient is still symptom free; this case provides great evidence that using transdermal hormonal contraceptives can likely be an alternative for other HAE patients.

Sekijima, Y., et al. "A Novel Rna Splice Site Mutation in the C1 Inhibitor Gene of a Patient with Type I Hereditary Angioedema." Intern Med 43.3 (2004): 253-5.

This article presents the case of a patient who has type I HAE and presented with recurrent episodes of skin edema and abdominal pain. Laboratory tests were performed and decreased levels of C1-INH and C4 were both identified. Molecular techniques were also employed and a point mutation at nucleotide 8722 was discovered; it is suggested that the point mutation may result in unstable mRNA and thus be the cause of HAE in this patient.

---. "Massive Mesenteric Edema in a Patient with Type I Hereditary Angioedema." Mod Rheumatol 15.5 (2005): 361-3.

This article features a patient who presented with edema of the skin and abdominal pain. Abdominal CT was performed which showed edema of the mesentery and thickened walls of the duodenum and transverse colon. The article stressed the importance of differentiating abdominal pain associated with HAE from abdominal pain that qualifies as a surgical emergency.

Serrano, C., et al. "Oestrogen-Dependent Hereditary Angio-Oedema with Normal C1 Inhibitor: Description of Six New Cases and Review of Pathogenic Mechanisms and Treatment." Allergy 63.6 (2008): 735-41.

This article serves to report on type III HAE – estrogen-dependent HAE – which is not caused by alterations in C1-INH quantity or function. The cases of six women with type III HAE are presented and paralleled in order to find commonalities and report differences among them.

Seth, A. K., et al. "Hereditary Angioedema with Recurrent Abdominal Pain." Indian J Gastroenterol 21.2 (2002): 82-3.

This article features a family of patients who presented with recurrent episodes of edema and abdominal pain. The patients were positively diagnosed with HAE after quantitative C1 assays were performed. One patient in the family was successfully treated with danazol.

Socket, M., C. Boyle, and M. Burke. "Angio-Oedema in Dentistry: Management of Two Cases Using C1 Esterase Inhibitor." Dent Update 32.6 (2005): 350-2, 54.

This article features the management of two cases – one HAE and one acquired angioedema. The cases are paralleled in order to demonstrate the use of C1-INH in a prophylactic manner. It is emphasized that proper history must be given by the patient regarding his/her angioedema so that the correct treatment can be administered, and in a timely fashion.

Steinbach, O., R. Schweder, and B. Freitag. "[C1-Esterase Inhibitor in Ace Inhibitor-Induced Severe Angioedema of the Tongue]." Anaesthesiol Reanim 26.5 (2001): 133-7.

This article features a case of severe developed angioedema after long-term use/treatment of an ACE-inhibitor. It is stressed that HAE can present very differently in each patient, and treatment should depend upon the pathogenesis as it presents. In this case, the only successful treatment was C1-INH concentrate.

Steiss, J. O., et al. "[Hereditary Deficiency of C1-Esterase Inhibitor Presenting with Recurrent Abdominal Pain]." Klin Padiatr 214.1 (2002): 20-1.

This article features the case of a 17-year-old female patient who experienced recurrent abdominal pain and edema of her hands. It is stressed that diagnosis of HAE in patients presenting with edema of the face, trunk or extremities should not be missed; in undiagnosed cases, up to 30% fatality has been documented, and further indicates the need for prompt diagnosis.

Sugiyama, E., et al. "Hereditary Angioedema with a De Novo Mutation of Exon 8 in the C1 Inhibitor Gene Showing Recurrent Edema of the Hands around the Peripheral Joints: Importance for the Differential Diagnosis of Joint Swelling." Arthritis Rheum 44.4 (2001): 974-7.

This article features the case of a female patient who experienced episodes of edema for three years before being diagnosed with HAE. The patient presented with edema around

her peripheral joints, and was suspected to have rheumatoid arthritis. Laboratory test results indicated that the patient had HAE, however there wasn't an established family history of episodes of edema, so further laboratory investigations were performed and gene analysis occurred. It is suggested that HAE should be considered in the differential diagnosis in patients experiencing joint edema.

Tricker, N. D., K. M. Malone, and M. M. Ellis. "Hereditary Angioedema: A Case Report and Literature Review." Gen Dent 50.6 (2002): 540-3.

This article serves to present the complex difficulties associated with diagnosing and treating episodes of edema due to HAE. It emphasizes that HAE should be included in the differential diagnosis when presented with a case that includes episodes of edema and/or abdominal pain, since it is unfortunately often missed or overlooked.

Vacca, V. M., Jr. "Hereditary Angioedema: A Case Study." J Neurosci Nurs 39.5 (2007): 311-5.

This article focuses on explaining the many symptoms associated with HAE, how a patient with HAE might present to a physician's office or emergency room, and the different phases of treatment for the disease. This article is meant to inform nurses of what to expect and how to treat a patient with HAE should the occasion arise.

van der Klooster, J. M., et al. "[Recurrent Attacks of Angioedema Ascribed to the Use of Estrogen Preparations and a Pregnancy (Hereditary Angioedema Type 3)]." Ned Tijdschr Geneesk 146.34 (2002): 1599-602.

This article features a case of the rare type III HAE. A female patient experienced the common symptoms of HAE from ages 17 to 21 while using estrogens, and ceased after she stopped taking the medication. During her first pregnancy, her symptoms of HAE returned. This article highlights the signs and symptoms associated with the recently discovered type III HAE versus the classic types I and II.

Wakisaka, M., et al. "Computed Tomography of the Gastrointestinal Manifestation of Hereditary Angioedema." Radiat Med 26.10 (2008): 618-21.

This article features the case of a patient who experienced abdominal edema in association with HAE. CT scan was performed and revealed edema throughout the gastrointestinal tract. The article emphasizes the importance of considering HAE in the differential diagnosis when CT scan findings are similar to the one in this case report.

Webb, M. D., S. Hakimeh, and L. K. Holly. "Management of Children with Hereditary Angioedema: A Report of Two Cases." Pediatr Dent 22.2 (2000): 141-3.

This article presents the clinical signs and symptoms, classifications, physical manifestations, and treatment methods for patients with HAE. The article emphasizes the importance of knowing these important features of the disease when dentists are treating

patients with HAE and highlighted the importance of taking extremely careful precautions during treatment.

Wei, S. C., K. Fitzgerald, and D. D. Maglinte. "Ct Findings in Small Bowel Angioedema: A Cause of Acute Abdominal Pain." Emerg Radiol 13.5 (2007): 281-3.

This article features the report of a patient who presented with abdominal pain due to HAE. The importance of including HAE in the differential diagnosis of patients who present with acute abdominal pain is emphasized.

Wen, D. C., et al. "Hereditary Angioedema: A Taiwanese Family with a Novel Gene Mutation." Asian Pac J Allergy Immunol 25.2-3 (2007): 163-7.

This article features a unique case report involving 15 living members of the same family. Blood of each family member was analyzed for levels of the complement components C3, C4 and C1-INH; the SERPING1 gene, which codes for C1-INH, was also sequenced for each individual. Six of the family members were found to have the same genetic mutation of the SERPING1 gene which had been previously reported to account for HAE within the family; the same six individuals had decreased serum levels of C4 and C1-INH, which is also characteristic of HAE.

Yano, C., A. Ota, and H. Nakagawa. "A Case of Angioedema Associated with Decreased C1 Inhibitor Activity." Allergol Int 56.3 (2007): 309-11.

This article features the report of a 31-year-old female patient who was referred to the clinic of the authors due to the previous difficulty other doctors were having with completing a diagnosis. At the age of 20, the patient started experiencing edema of her extremities, but then her symptoms spontaneously resolved. Multiple immunologic assays were employed in an effort to reach a diagnosis, including levels of complement factors and tests to rule out SLE. Based upon laboratory results and previous clinical manifestations, a diagnosis of HAE was finally reached.

Yilmaz, M., et al. "Hereditary Angioedema: Case Report of a Family." Turk J Pediatr 42.3 (2000): 230-3.

This article features the case reports of 11 patients from within the same family, all who have HAE. Each individual case was compared to the others, and commonalities were reported. Most often, patients experienced episodes of edema in the extremities, and others experienced some of the other common clinical symptoms of HAE including crippling abdominal pain, laryngeal edema requiring tracheotomy, and facial edema. Serum levels of complement proteins were measured and reported. The article emphasized the importance of an early diagnosis of HAE so that proper treatment can be administered to each patient.

Yu, T. C., et al. "Paternal Mosaicism and Hereditary Angioedema in a Taiwanese Family." Ann Allergy Asthma Immunol 99.4 (2007): 375-9.

This article features the case report of a Taiwanese family diagnosed with type I HAE with paternal mosaicism. The article served to detail the clinical manifestations and presentations of HAE, laboratory and molecular genetics study results for this family, keeping the paternal mosaicism in mind. The authors were able to conclude that the paternal mosaicism could provide a possible explanation for apparent HAE in the children of parents who have normal levels of C1-INH.

Zhi, Y. X., H. Y. Zhang, and S. Z. Huang. "[Identification of a Novel Mutation of C1 Inhibitor Gene in a Chinese Family with Hereditary Angioedema]." Zhongguo Yi Xue Ke Xue Yuan Xue Bao 25.6 (2003): 664-6.

This article features the report of a Chinese family with HAE. The authors sought to identify the mutation in the C1-INH gene which was the cause of HAE in the family, using molecular techniques such as PCR and direct sequencing. The authors were able to successfully identify a single mutation in five members of the family, and could confidently report the results as control patients were used for correlation.

Zingale, L. C., et al. "Successful Resolution of Bowel Obstruction in a Patient with Hereditary Angioedema." Eur J Gastroenterol Hepatol 20.6 (2008): 583-7.

This article features a unique method of treatment used in a 65-year-old female HAE patient who experienced severe abdominal pain, cramping and nausea. DX-88, a recombinant protein that is a potent and selective inhibitor of plasma kallikrein, has been used successfully to treat acute attacks of HAE. The patient in this case report received an intravenous dose of DX-88 while experiencing an acute abdominal attack; 30 minutes after administration of DX-88, the abdominal pain and nausea ceased. This article demonstrates that DX-88 should be considered in the treatment methods of acute attacks of HAE.

CLINICAL RESEARCH

"C1 Esterase Inhibitor: New Preparation. A Major Advance in Emergency Treatment of Hereditary Angioneurotic Oedema." Prescrire Int 10.53 (2001): 67-70.

This article presents multiple studies that were conducted which served to evaluate the efficacy of C1-INH concentrate in treating HAE both acutely and on a prophylactic basis. A double-blind trial was conducted to evaluate the effectiveness of administering C1-INH concentrate to individuals experiencing acute attacks. The study showed that in the 36 patients who participate, 69% experienced symptom relief in less than half an hour post infusion, compared to 2% when a placebo was used. A crossover trial was also conducted in which six patients participated, receiving infusions of C1-INH concentrate on a prophylactic basis once every three days. Again, the C1-INH proved to be much more successful at reducing the occurrence of attacks versus the placebo.

Agostoni, A., and M. Cugno. "[the Kinin System: Biological Mechanisms and Clinical Implications]." Recenti Prog Med 92.12 (2001): 764-73.

This article focuses on explaining the biology and effects of the kinin system. In many clinical situations, including HAE, the kinin system is activated and involved in inflammatory reactions. As stated in this report, the study of the kinin system has been limited due to difficulties with administering dosages, until a recent change was made making specific and sensitive methods of dosage available for research.

Beinrohr, L., et al. "C1 Inhibitor Serpin Domain Structure Reveals the Likely Mechanism of Heparin Potentiation and Conformational Disease." J Biol Chem 282.29 (2007): 21100-9.

This article presents a study of the structure of C1 inhibitor. The authors were able to report finding the "first crystal structure of the serpin domain of human C1 inhibitor." They found that this structure is an explanation for the naturally occurring mutations in C1 inhibitor that lead to functional deficiencies. In this study the authors were able to explain previous studies of mutagenesis by showing how polyanions can change the activity of C1 inhibitor. This study and results obtained can hopefully be put to further use by those creating therapeutic C1 inhibitor treatments for patients with HAE.

Bentsianov, B. L., et al. "The Role of Fiberoptic Nasopharyngoscopy in the Management of the Acute Airway in Angioneurotic Edema." Laryngoscope 110.12 (2000): 2016-9.

This article presents a study which evaluated the usefulness of fiberoptic examination for patients experiencing acute edema of the upper aerodigestive tract. The study looked at a variety of patients, via charts, who had experienced "angioneurotic edema of the upper digestive tract" and evaluated each patient case based on severity of the edema and whether or not a fiberoptic examination had been performed; if a fiberoptic exam had been performed, what information had been gathered was also included in the case evaluations. It was determined that fiberoptic examinations are a very valuable tool in

assessing the airways of patients experiencing edema. It was suggested that although presenting symptoms often indicate edema of the upper aerodigestive tract, a diagnosis should be confirmed utilizing fiberoptic examination techniques, if possible.

Birjmohun, R. S., et al. "Effects of Short-Term and Long-Term Danazol Treatment on Lipoproteins, Coagulation, and Progression of Atherosclerosis: Two Clinical Trials in Healthy Volunteers and Patients with Hereditary Angioedema." Clin Ther 30.12 (2008): 2314-23.

The authors of this literature evaluated the effects of danazol treatment, both short-term and long-term, on proatherogenic intermediated end points. Short-term effects were evaluated on healthy male volunteers over a period of four weeks, whereas long-term effects were evaluated on patients with HAE who had been treated with danazol for greater than or equal to two years. The effects of danazol on lipoproteins, coagulation, and carotid intima-media thickness were evaluated. The authors found that short-term treatment with danazol in healthy males caused a decrease in both apolipoprotein A-1 and HDL-C; coagulation was not affected. In long-term treatment with danazol, lipoproteins were unaffected, and it appeared that carotid intima-media thickness was not affected; there was however, increased coagulation activation compared to controls found in patients receiving long-term treatment.

Blanch, A., et al. "First Case of Homozygous C1 Inhibitor Deficiency." J Allergy Clin Immunol 118.6 (2006): 1330-5.

The authors of this article sought to characterize the complement profile of a patient, and his family, who have HAE caused by a homozygous mutation in the C1NH gene. To complete the complement profile, biochemical tests were performed to evaluate the levels and activation statuses of the complement components. After completion of the complement profiles, seven other members of the patient's family were diagnosed with HAE, one of which had a homozygous mutation like the patient, the other six had heterozygous mutations. It was concluded that the mutations affected the coding region of C1NH, and this is the first reported case of a homozygous mutation. The homozygous mutation in the coding region resulted in a unique activation of the classical complement pathway that is different than what has been previously observed in patients with heterozygous mutations resulting in HAE. The authors suggest that since the patients with homozygous mutation lack a wild-type allele, attenuated androgen treatment may not be affective since the androgens serve to increase the C1NH gene transcription levels.

Blasko, B., et al. "Relationship between Copy Number of Genes (C4a, C4b) Encoding the Fourth Component of Complement and the Clinical Course of Hereditary Angioedema (Hae)." Mol Immunol 44.10 (2007): 2667-74.

The authors of this article studied the number of copy genes for C4A and C4B that influence the serum concentrations of C4 and the clinical course of HAE. To do this, the authors used DNA samples from 95 HAE patients to determine the copy number of C4A

and C4B genes. They found that there was a positive correlation between dosage of C4A and C4B and serum C4 concentrations, as was expected. There was an unexpected finding correlating copy number of C4B genes and a milder disease course in patients. The findings indicate that higher copy numbers of the C4B gene may lead to a less severe clinical course of HAE.

Bork, K., and S. E. Barnstedt. "Treatment of 193 Episodes of Laryngeal Edema with C1 Inhibitor Concentrate in Patients with Hereditary Angioedema." Arch Intern Med 161.5 (2001): 714-8.

The authors of this research sought to evaluate the efficacy of C1-INH concentrate in treating patients experiencing acute airway edema due to HAE. 95 patients with HAE were screened for laryngeal edema and efficacy was evaluated based upon the time of injection of C1-INH concentrate to the start of symptom resolution; duration of episodes was compared between patients who received treatment and those who did not. 193 episodes of laryngeal edema, occurring in 18 patients, were treated with injections of C1-INH concentrate and proved to be effective in all. The mean total duration of laryngeal edema episodes for patients who received treatment was 14 to 24.6 hours, whereas those patients who did not receive treatment experienced edema for 74.6 to 127 hours. It was concluded that injected C1-INH concentrate is very effective in reducing laryngeal edema and is a very rapid treatment method.

Bork, K., A. Bygum, and J. Hardt. "Benefits and Risks of Danazol in Hereditary Angioedema: A Long-Term Survey of 118 Patients." Ann Allergy Asthma Immunol 100.2 (2008): 153-61.

The authors of this research sought to analyze the risks and benefits associated with long-term treatment of HAE with danazol. Using questionnaires, information from 118 German and Danish patients with HAE who had been treated with danazol from two months to 30 years, was gathered. With each acute attack reported by the patients, the frequency, severity and duration were reported for both before and during treatment. It was found that 111 of the 118 patients were successfully treated using danazol. Overall, the frequency and severity of acute attacks was reduced drastically while using danazol. Unfortunately, multiple adverse side effects were noted in many of the patients (93 out of 118), which eventually resulted in 30 patients stopping treatment, and points toward the need for close monitoring of patient status by physicians.

Bork, K., B. Fischer, and G. Dewald. "Recurrent Episodes of Skin Angioedema and Severe Attacks of Abdominal Pain Induced by Oral Contraceptives or Hormone Replacement Therapy." Am J Med 114.4 (2003): 294-8.

The authors of this study investigated the potential interactions between use of oral contraceptives and hormone replacement therapy among the various types of recurrent angioedema. Using a large group of women with recurrent angioedema (516 participants), 228 were found to have used oral contraceptives or hormone replacement therapy. Of those 228 women, 39 had type III HAE and 32 had type I HAE. While using

oral contraceptives or hormone replacement it was found that 20 women with type I HAE, 24 with type III HAE, and 2 with idiopathic angioedema experienced attacks. Of the 46 who experienced attacks, 26 either experienced angioedema symptoms for the first time, or for those with pre-existing HAE, the attacks became much more severe. The authors conclude that oral contraceptives or hormone replacement therapy can either trigger or worsen symptoms of HAE.

Bork, K., et al. "Treatment of Acute Edema Attacks in Hereditary Angioedema with a Bradykinin Receptor-2 Antagonist (Icatibant)." J Allergy Clin Immunol 119.6 (2007): 1497-503.

The authors of this research sought to determine if Icatibant (the selective bradykinin receptor-2 antagonist) is effective in treatment for acute attacks of HAE. In this study, 15 patients experiencing a total of 20 attacks received Icatibant treatment. The severities of the attacks were measured using a visual analog scale. To determine the effectiveness of the Icatibant, plasma bradykinin levels were measured before and four hours post intravenous administration of Icatibant. It was found that compared to previously untreated attacks, Icatibant treatment reduced the mean time to onset of symptom relief by 97%; so, it was concluded that Icatibant is effective in treating acute attacks of edema in HAE patients.

---. "Hereditary Angioedema with Normal C1 Inhibitor: Clinical Symptoms and Course." Am J Med 120.11 (2007): 987-92.

The authors of this literature sought to study in detail a new subtype of HAE that has been recently described. The new subtype of HAE is characterized by recurrent episodes of edema in multiple organs in patients with normal C1-INH (mostly women). It was found that most of the patients with HAE and normal C1-INH experienced classic HAE symptoms – skin edema, tongue edema, severe abdominal attacks, laryngeal edema and uvular edema. The authors found that the onset of the new subtype of HAE in adulthood was much more common than in classic HAE. The authors also concluded that the new subtype of HAE has a set of very characteristic manifestations and there are many differences in clinical symptoms and disease course between the new HAE and the classic HAE.

---. "Clinical Studies of Sudden Upper Airway Obstruction in Patients with Hereditary Angioedema Due to C1 Esterase Inhibitor Deficiency." Arch Intern Med 163.10 (2003): 1229-35.

The authors of this study sought to identify a common age at which laryngeal edema first occurs in HAE patients. They report the age at which laryngeal first occurs, the time between symptom onset and full development of edema, and the effectiveness of treatment and prophylaxis for the patients involved in this study. Using medical histories and reports from physicians, information for 61 patients who experienced 596 total laryngeal edema episodes were analyzed. The mean age for which laryngeal edema first occurred was 26.2, with nearly 80% of the laryngeal episodes occurring between ages 11 and 45.

More than half of the episodes cleared spontaneously, and the rest were treated with C1-INH concentrate. Based on the findings, the authors concluded that laryngeal edema can occur at any age, and does not seem to onset at any particular age.

- . "Hereditary Angioedema: New Findings Concerning Symptoms, Affected Organs, and Course." Am J Med 119.3 (2006): 267-74.

The authors of this study aimed to identify patterns of temporal and spatial swelling by evaluating hereditary angioedema long-term. Information was gathered using standard questionnaires answered by 221 patients with C1 inhibitor deficiency. Skin swellings were by far the most often experienced type of edema (97.4%). On a per patient basis, it was found that the disease course varied quite widely; however, it was determined that women overall experienced a more severe disease course than men. The researchers were able to make a determination that the swelling experienced is specific for HAE and should allow for a prompt diagnosis based upon the symptoms experienced by the patients.

- . "Treatment with C1 Inhibitor Concentrate in Abdominal Pain Attacks of Patients with Hereditary Angioedema." Transfusion 45.11 (2005): 1774-84.

This article features a retrospective study that was completed using clinical case reports of 75 HAE patients who experienced a total of 22,278 abdominal attacks, 75% of which were untreated. The results obtained clearly indicate that treatment with C1-INH concentrate shortened the duration of the attacks and drastically lessened the pain experienced by the patients, but did not halt the attacks completely – the patients still experienced some symptoms, but at a much more tolerable level. Based on the results, the authors were able to conclude that C1-INH concentrate is a very effective treatment method for HAE patients experiencing abdominal attacks of edema.

- Bork, K., and N. Ressel. "Sudden Upper Airway Obstruction in Patients with Hereditary Angioedema." Transfus Apher Sci 29.3 (2003): 235-8.

This article reports a study completed which describes patients' experience with laryngeal edema. Information was gathered regarding age at which laryngeal edema was first experienced, time between onset and full development of edema, and how effective treatment (and prophylaxis) was in 123 patients with HAE. Approximately half of the patients experienced a total of 596 laryngeal edema episodes, starting at the mean age of 26.2. More than half of the episodes resolved spontaneously, while approximately a third of the episodes were successfully treated using C1-INH concentrate. The researchers concluded that laryngeal edema can be experienced at any age, without a definitive age of onset; no matter what age the edema is experienced, observation of the patient, and often immediate action, are essential for survival of a patient experiencing laryngeal edema.

- Bork, K., et al. "Symptoms, Course, and Complications of Abdominal Attacks in Hereditary Angioedema Due to C1 Inhibitor Deficiency." Am J Gastroenterol 101.3 (2006): 619-27.

This article features an observational study completed that examined the disease course associated with 153 patients with HAE experiencing abdominal attacks; symptoms, frequency of attack and complications were all included in the analysis for each patient. The intensity of the attacks were rated on a scale of mild, moderate and severe; severe attacks outnumbered mild and moderate nearly five to one, with a mean maximal pain score of 8.4 on a scale of one to ten. A model outlining the characteristics of an abdominal attack was created which includes phases of the attack over a four day period with a pain rating along the y-axis. The results obtained in this study add to the knowledge regarding HAE attack characteristics – symptoms, course of attack – and could be useful in early recognition of an oncoming abdominal episode.

Bork, K., P. Staubach, and J. Hardt. "Treatment of Skin Swellings with C1-Inhibitor Concentrate in Patients with Hereditary Angio-Oedema." Allergy 63.6 (2008): 751-7.

This study compared skin-swelling attacks in patients with HAE; attacks that were treated with C1-INH concentrate were compared to attacks that were not treated for the same set of patients. Information regarding the attacks was gathered using standardized questionnaires; 2,104 treated skin-swelling attacks experienced by 47 patients were compared to 9,046 untreated skin-swelling attacks experienced by the same 47 patients. The data clearly shows the efficacy of treatment with C1-INH concentrate; relief of symptoms was 1/30th to 1/50th of the time it took for an untreated case to experience symptom relief, and total duration was decreased by half. The authors conclude that C1-INH is an extremely effective and safe treatment method for patients with HAE experiencing episodes of edema.

Bouillet, L., et al. "Disease Expression in Women with Hereditary Angioedema." Am J Obstet Gynecol 199.5 (2008): 484 e1-4.

This article features a retrospective study completed as part of the PREHEAT project launched in the European Union. Using questionnaires, information from 150 postpubertal women from eight countries, all with HAE, was collected, aiming to gather enough information to allow for further understanding of the disease, and subsequent treatment methods to improve the quality of life for patients with HAE. It was found that puberty, pregnancy, and oral contraceptive use all increased the severity of the disease for the majority of the patients (a large number did not experience a change, however); of the patients who had experienced menopause at the time of the questionnaires, menopause had no effect for 55% of the women. Based on all of the analyses completed, the authors concluded that physiologic hormonal changes do affect the course of HAE in affected women and physicians should take this into consideration when managing treatment.

Cichon, S., et al. "Increased Activity of Coagulation Factor Xii (Hageman Factor) Causes Hereditary Angioedema Type Iii." Am J Hum Genet 79.6 (2006): 1098-104.

This article features a study that investigates the F12 gene mutation (p.Thr328Lys) that are a proposed possible cause of type III HAE, which has only been reported to affect females. F12 is the gene that encodes for human coagulation factor XII. The researchers compared FXII activity and plasma levels in both patients who have the mutation and healthy patients. The data obtained suggests that the mutation is a gain-of-function mutation which causes a vast increase in FXII activity, but not plasma levels. They also found that F12 transcription is positively influenced by estrogens, which would explain why to date, only females are reportedly affected by this particular mutation. This research is a strong step toward understanding the underlying molecular causes of type III HAE.

Coppola, L., et al. "C1 Inhibitor Infusion Modifies Platelet Activity in Hereditary Angioedema Patients." Arch Pathol Lab Med 126.7 (2002): 842-5.

The focus of this research was to evaluate the effects of in vivo C1-INH concentrate infusion on platelet responsiveness and coagulation system activity in patients with HAE. It was stipulated that since platelets express C1-INH on their surface naturally during granule secretion, there might be a modification to the platelets and/or platelet function in C1-INH deficient HAE patients. Platelet activity and plasma levels of C1-INH were assessed pre- and post-infusion of C1-INH concentrate in six patients with previously diagnosed HAE. The results showed that post C1-INH concentrate infusion there was a rapid increase in circulating plasma levels of C1-INH, which slowly returned back to pre-infusion levels over the course of four to seven days. Results also showed that post-infusion of C1-INH concentrate, there was a decrease in platelet aggregation. From this data, the researchers were able to conclude that C1-INH does in fact play a role in platelet activity and that a deficiency of C1-INH, like that seen in patients with HAE, increases platelet aggregation.

Drouet, C., et al. "Metallopeptidase Activities in Hereditary Angioedema: Effect of Androgen Prophylaxis on Plasma Aminopeptidase P." J Allergy Clin Immunol 121.2 (2008): 429-33.

The purpose of this research was to test the hypothesis that androgen prophylaxis, for such conditions as HAE, could enhance plasma APP (aminopeptidase P – important for catabolism of kinins in human plasma) activity. Androgen prophylaxis can only provide a limited protection against episodes of edema because it has a limited reversion of C1-INH defects. After investigating patients for plasma metallopeptidase activities responsible for kinin catabolism, the researchers found that prophylaxis with androgens caused a significant increase in APP activity, but not other metallopeptidase activities. The authors concluded that not only does APP cause an increase in circulating C1-INH levels, it also could contribute to more effective control of the kinin accumulation which is considered responsible for the symptoms associated with angioedema.

Farkas, H., et al. "Ultrasonography in the Diagnosis and Monitoring of Ascites in Acute Abdominal Attacks of Hereditary Angioneurotic Oedema." Eur J Gastroenterol Hepatol 13.10 (2001): 1225-30.

This article features a study completed in order to evaluate the usefulness of serial abdominal ultrasound examinations completed on patients who present with ascites. 70 patients with HAE were documented for nearly 10 years. 22 acute episodes occurred within the patient population that were severe enough to warrant admission to the hospital during the study; ultrasound readings performed on the patients revealed thickening of the intestinal wall in 80% of the cases, alongside free peritoneal fluid in all cases. Subsequent ultrasound readings were performed at 24 and 48 hours after receiving necessary treatment. The researchers conclude that ascites seen in ultrasound should be an aid in the diagnosis of acute HAE attacks; and HAE should be considered as a possible diagnosis for a patient presenting with recurrent unexplained abdominal pain.

Gompels, M. M., et al. "A Multicentre Evaluation of the Diagnostic Efficiency of Serological Investigations for C1 Inhibitor Deficiency." J Clin Pathol 55.2 (2002): 145-7.

The research featured in this article was completed in an attempt to determine the diagnostic efficiency of assays that are routinely utilized in the diagnosis and evaluation of HAE. Analyses of 1,144 samples (over a span of four years) were performed, measuring levels of C4 and C1 inhibitor. It was noted that this is the first data indicating sensitivity, specificity and predictive values of the assays most frequently used to screen for C1-INH deficiency. Results showed that all patients with untreated C1-INH deficiency also had a low C4 value. Based on their findings, the authors concluded that all patients considered to have C1-INH deficiency should be tested for both functional C1-INH and levels of C4; if C4 values are normal then C1-INH tests need not be completed, whereas if both C1-INH and C4 values are low, then subsequent confirmatory samples should be analyzed to confirm a diagnosis of C1-INH deficiency.

Huang, S. W. "Results of an on-Line Survey of Patients with Hereditary Angioedema." Allergy Asthma Proc 25.2 (2004): 127-31.

This article contains the results obtained from an online survey that was conducted, completed by 63 patients with HAE, in order to analyze the current status of the disease management. Many statistical results were gathered, including type of HAE, the mean and median age of onset of symptoms, age at diagnosis, and the most common symptoms/manifestations. The overall consensus obtained was that the majority of the patients were unhappy with the current management of the disease.

Kalmar, L., et al. "Mutation Screening of the C1 Inhibitor Gene among Hungarian Patients with Hereditary Angioedema." Hum Mutat 22.6 (2003): 498.

The aim of the research completed that is described in this article was to determine the disease-causing mutations in the C1-INH gene among Hungarian HAE patients. 26 of the estimated 40 to 50 families in Hungary with HAE participated in this study. Southern-blotting followed by real time PCR based gene dosage analysis were used to detect large deletions/insertions into the C1-INH gene. Direct sequencing of the entire coding region

and splicing sites of the C1-INH gene were used in the absence of large structural changes. Multiple different mutations were found in the 23 families with type I HAE, and the same mutation was found in the three families with type II HAE. The results obtained show that there are clearly multiple mutations responsible for HAE, potentially making diagnosis (if genotyping were employed) even more difficult.

Levi, M., et al. "Self-Administration of C1-Inhibitor Concentrate in Patients with Hereditary or Acquired Angioedema Caused by C1-Inhibitor Deficiency." J Allergy Clin Immunol 117.4 (2006): 904-8.

This article features a study completed that sought to investigate the feasibility, efficacy, and safety of on-demand and prophylactic self-administration of C1-INH concentrate in patients with frequently recurring attacks of HAE. 43 patients were trained to self-administer C1-INH concentrate when needed (some on-demand, some prophylactic). Results obtained found that all patients were capable of administering the concentrate to themselves, with minimal technical error rates. The on-demand group of patients experienced an extremely shortened period of time between onset of symptoms and relief of those symptoms; the prophylactic group had a very drastic decrease in rate of attacks per month. The researchers were able to conclude that self-administration of C1-INH concentrate is both feasible and safe for patients, and also provides a much more rapid treatment for severe attacks of HAE.

Roche, O., et al. "Hereditary Angioedema Due to C1 Inhibitor Deficiency: Patient Registry and Approach to the Prevalence in Spain." Ann Allergy Asthma Immunol 94.4 (2005): 498-503.

The purpose of the research outlined in this article is to study the prevalence of HAE in Spain, and examine the current state of diagnosis and treatment. Information was gathered from physicians who had treated patients with HAE, and from patients themselves. C1-INH levels and function were measured for diagnostic purposes and many families also underwent genetic evaluations. The results that were obtained are similar to those found with patients in the United States – 13.7% of patients were asymptomatic, but most patients had experienced symptoms and were managing the disease with long-term prophylactic androgen therapy. The authors concluded that although the prevalence of HAE in Spain is lower than it is globally, since the disease is rare there is the likelihood that some patients are misdiagnosed and the prevalence could actually be higher than is reported.

Schneider, L., et al. "Critical Role of Kallikrein in Hereditary Angioedema Pathogenesis: A Clinical Trial of Ecallantide, a Novel Kallikrein Inhibitor." J Allergy Clin Immunol 120.2 (2007): 416-22.

The research reported in this article was completed in order to determine the safety and efficacy of treatment with ecallantide (a recombinant protein thought to inhibit kallikrein) in patients with HAE. A double-blind placebo-controlled ascending-dose study was completed that assessed the efficacy and tolerability of ecallantide in patients who

experienced acute attacks due to HAE. For each dosage level, ten patients were assigned to the dose and two were assigned a placebo. Based on the results obtained, the researchers concluded that ecallantide, as a specific inhibitor of plasma kallikren, significantly improved HAE symptoms versus the placebo, and the results obtained during this research strongly support the previously theorized role of bradykinin in the pathophysiology of HAE.

Sloane, D. E., C. W. Lee, and A. L. Sheffer. "Hereditary Angioedema: Safety of Long-Term Stanazolol Therapy." J Allergy Clin Immunol 120.3 (2007): 654-8.

This article features a study completed in order to assess the frequencies of various side effects of long term use (20 to 40 years) of the attenuated androgen, stanozolol, among a population of patients with HAE. Using questionnaires completed by patients, information was gathered regarding experienced side effects due to stanozolol usage; additional information was obtained by physical examination and chemical tests measuring liver function, serum lipid levels and PSA values. Results showed that although some patients did experience drug-related side effects, none of the patients had to cease usage of the drug, as lowering the dosage proved effective. The most common side effects included hirsutism, weight gain, menstrual irregularities, acne, and mood changes. Based on the obtained data, the researchers concluded that stanozolol is in fact a safe and effective treatment method for long-term management of HAE.

Szegedi, R., et al. "Long-Term Danazol Prophylaxis Does Not Lead to Increased Carotid Intima-Media Thickness in Hereditary Angioedema Patients." Atherosclerosis 198.1 (2008): 184-91.

This article revisits a previous study completed by the researchers and looks at the effects of the previously identified decreased HDL and increased LDL levels in patients with HAE who use danazol for long-term prophylactic management. It was previously thought that the altered levels of lipid metabolism could lead to accelerated early atherosclerosis, so the team set out to investigate the impact of danazol treatment on the risk of atherosclerosis in HAE patients. The prevalence of vascular disease and carotid intima-media thickness in 32 patients undergoing long-term danazol treatment were determined and compared to 25 HAE patients not using danazol treatment and 20 healthy individuals. Using the results obtained, the authors were able to conclude that thickening of the carotid intima-media (an objective marker of atherosclerosis) was not observed in HAE patients using danazol therapy, and hypothesized that functional deficiency of C1-INH may actually provide protection against atherosclerosis in those patients.

Szeplaki, G., et al. "Adverse Effects of Danazol Prophylaxis on the Lipid Profiles of Patients with Hereditary Angioedema." J Allergy Clin Immunol 115.4 (2005): 864-9.

The goal of the study performed in this article was to investigate the potential adverse side effects caused by long term prophylactic use of danazol on serum lipid profile and the increased risk of atherosclerosis in HAE patients. Levels of serum lipids were measured and compared between HAE patients on danazol treatment and two control

groups. Results revealed that serum concentrations of HDL and apolipoprotein A-I were significantly lower for patients using danazol than the control groups; serum concentrations of LDL and apolipoprotein B-100 were higher for the danazol-treated patients than the control groups. Based on the results, the researchers concluded that long-term use of danazol in HAE patients is associated with an increased risk for early atherosclerosis and recommend that HDL and LDL levels be monitored at regular intervals.

van Doorn, M. B., et al. "A Phase I Study of Recombinant Human C1 Inhibitor in Asymptomatic Patients with Hereditary Angioedema." J Allergy Clin Immunol 116.4 (2005): 876-83.

The authors of this article sought to evaluate the effects and safety of recombinant human C1-INH (obtained from transgenic rabbit milk) in asymptomatic HAE patients. Intravenous doses of the recombinant human C1-INH (rhC1INH) were administered to the asymptomatic patients in differing doses on two separate occasions. After administration of the doses, plasma level of functional C1-INH in the patients was measured and analyzed. It was found that infusing rhC1INH at a dose of 100 U/kg was the most effective at increasing the plasma levels. The authors concluded that the safety profile and biological activity exhibited by this experiment warrants further clinical studies to assess the efficacy of rhC1INH in treating symptomatic HAE patients during attacks.

Visy, B., et al. "Sex Hormones in Hereditary Angioneurotic Oedema." Clin Endocrinol (Oxf) 60.4 (2004): 508-15.

This article features a study completed in order to determine if any relationship between the serum levels of sex hormones and prevalence of HAE attacks in HAE patients exists; sex hormone fluctuation at the start of adolescence and the perimenopausal period (primarily) along with pregnancy and oral contraceptive use all precipitate attacks of edema in HAE patients. Serum levels of LH, FSH, progesterone, estradiol, testosterone, PRL, and SHBG were measured in 78 patients with HAE. Information regarding medical histories for the patients was obtained using standardized questionnaires completed by each patient. The results that were obtained allowed the authors to conclude that progesterone and SHBG levels should be monitored in patients with HAE as they can be used in the prediction of attacks.

Weiler, J. M., et al. "Does Heparin Prophylaxis Prevent Exacerbations of Hereditary Angioedema?" J Allergy Clin Immunol 109.6 (2002): 995-1000.

The purpose of this study was to determine the safety and efficacy of inhaled and subcutaneous heparin in the prevention of HAE attacks versus that of a placebo used in a control group. A double-blind, double-dummy, saline placebo-controlled, randomized, 3-way crossover study with 11 visits was performed to obtain the best results possible. Using the results obtained during the study, the researchers were able to conclude that injected and inhaled heparin failed to attenuate average flare intensity compared to the

placebo, however after patients received injected heparin, there was a significant decrease in average flare intensity compared to that of inhaled heparin. Unfortunately, there were no differences in any of the other groups of efficacy parameters, so it was determined that commercial heparin was ineffective in preventing attacks of HAE.

NEWEST TREATMENT/FDA APPROVALS

Bygum, A., K. E. Andersen, and C. S. Mikkelsen. "Self-Administration of Intravenous C1-Inhibitor Therapy for Hereditary Angioedema and Associated Quality of Life Benefits." Eur J Dermatol 19.2 (2009): 147-51.

This article features a study completed that assessed the impact of self-administered home therapy with intravenous C1-INH concentrate on quality of life in patients with HAE, versus having to travel to an emergency area for treatment. Nine patients who fell into the category of experiencing frequent or severe debilitating HAE attacks were offered C1-INH self-administration therapy. The Dermatology Life Quality Index (DLQI) was used to assess the quality of life for the seven patients who decided to participate in this study; assessments occurred at a baseline and then three to 48 months after starting home therapy. There were drastic drops in the DLQI scores after starting the home therapy with C1-INH concentrate, and no serious side effects were noted. It was concluded that self-administration improved the quality of life for the seven patients who used this therapy regimen.

Cocchio, C., and N. Marzella. "Cinryze, a Human Plasma-Derived C1 Esterase Inhibitor for Prophylaxis of Hereditary Angioedema." PT 34.6 (2009): 293-328.

In October 2008, a new drug was approved by the FDA to be used for acute treatment and prevention of attacks in patients with HAE. In this article, the authors describe the new drug which is a human plasma-derived C1 esterase inhibitor called Cinryze and is distributed by Lev Pharmaceuticals. Cinryze is indicated for use as a prophylactic medication for attacks caused by HAE, and can also be used as a treatment for acute attacks, by providing exogenous C1-INH to the affected patient. Extensive clinical trials were conducted, using volunteer patients as the test subjects, to prove the efficacy of the drug before it was FDA approved. With the development of this new drug, many HAE patients may now be able to live a much more normal lifestyle that was once inhibited by the severe manifestations of HAE.

Kreuz, W., et al. "C1-Inhibitor Concentrate for Individual Replacement Therapy in Patients with Severe Hereditary Angioedema Refractory to Danazol Prophylaxis." Transfusion 49.9 (2009): 1987-95.

This article reports a study that investigated the efficacy, safety and quality of life associated with C1-INH concentrate for replacement therapy in patients who previously were on long-term prophylactic treatment of HAE with danazol and were not responding to the treatment. 22 patients with severe HAE who were not responding to danazol treatment participated in this study. For the patients who received C1-INH concentrate regularly, the number of attacks per year declined significantly compared to previous danazol prophylaxis, and the laryngeal edema episodes that were previously experienced ceased all together. Quality of life in all participants increased drastically once C1-INH concentrate was administered regularly. The authors concluded that for patients with severe HAE that do not respond to danazol therapy anymore, or for those who experience

severe side effects, can eliminate the incidence of laryngeal edema and reduce the incidence of acute attacks by beginning treatment with C1-INH concentrate and eliminating danazol.

REVIEW ARTICLES

Agostoni, A., et al. "Hereditary and Acquired Angioedema: Problems and Progress: Proceedings of the Third C1 Esterase Inhibitor Deficiency Workshop and Beyond." J Allergy Clin Immunol 114.3 Suppl (2004): S51-131.

Agostoni et al. provide a fantastic resource with this article which was included as a supplement to The Journal of Allergy and Clinical Immunology in 2004. This source goes into very extensive detail about many aspects of HAE, including the different subtypes, triggers that cause attacks, clinical manifestations and diagnosis, genetic investigations, laboratory tests, treatment options and consequences, and a detailed history of the disease. This literature is a very thorough and complete resource.

Bernstein, I. L. "Hereditary Angioedema: A Current State-of-the-Art Review, Ii: Historical Perspective of Non-Histamine-Induced Angioedema." Ann Allergy Asthma Immunol 100.1 Suppl 2 (2008): S2-6.

In this article, Bernstein set out to review the evolution of the understanding of HAE starting with the first historical reference up to the present day. To obtain this information, MEDLINE and PubMed were searched using selected key terms that would ensure the highest return of applicable articles. Based upon the articles selected, Bernstein concluded that the progress that has been made thus far in understanding the pathogenesis and treatment of HAE is a great example of teamwork between clinicians and researchers.

Bernstein, J. A. "Hereditary Angioedema: A Current State-of-the-Art Review, Viii: Current Status of Emerging Therapies." Ann Allergy Asthma Immunol 100.1 Suppl 2 (2008): S41-6.

This review provides an overview of the status of current and emerging therapies for HAE in the United States. Multiple treatments were studied, including Berinert P, Cinryze, and Rhucin; summary statements from each pharmaceutical company were obtained and analyzed. From the findings, Bernstein concluded that with the current drug development taking place, the future for treatment of HAE in the United States looks promising.

Bowen, B., et al. "A Review of the Reported Defects in the Human C1 Esterase Inhibitor Gene Producing Hereditary Angioedema Including Four New Mutations." Clin Immunol 98.2 (2001): 157-63.

This review was completed in order to review the previously reported mutations found in patients with HAE after DNA sequencing was performed on the C1-INH gene. This review contains a list of 97 distinguished mutations in the C1-INH gene that cause HAE.

Boyle, R. J., M. Nikpour, and M. L. Tang. "Hereditary Angio-Oedema in Children: A Management Guideline." Pediatr Allergy Immunol 16.4 (2005): 288-94.

In this article, Boyle et al. review the current treatment options that are available for children and adolescents with HAE, including C1-INH concentrate, fresh frozen plasma and androgens. After reviewing the treatment options, they propose a management guideline for pediatric and adolescent HAE patients.

Cicardi, M., et al. "Established and New Treatments for Hereditary Angioedema: An Update." Mol Immunol 44.16 (2007): 3858-61.

This review article provides an update on clinical trials that were performed using four different products – plasma derived C1-INH, Dx-88, the receptor antagonist Icatibant, and recombinant C1-INH – that are all being tested for the efficacy in treating symptoms and acute attacks of HAE.

De Serres, J., A. Groner, and J. Lindner. "Safety and Efficacy of Pasteurized C1 Inhibitor Concentrate (Berinert P) in Hereditary Angioedema: A Review. Jean.De.Serres@Aventis.Com." Transfus Apher Sci 29.3 (2003): 247-54.

This article provides a review of literature concerning the safety and efficacy of the C1-INH concentrate, Berinert P (used in Canada). The most common results found were that since 1985, the drug has been effective, with a few adverse events. The authors were able to find many observational studies that show evidence of efficacy and safety of Berinert P.

Farkas, H., et al. "Management of Hereditary Angioedema in Pediatric Patients." Pediatrics 120.3 (2007): e713-22.

This review written by Farkas, et al. includes many features of HAE that are pertinent in affected patients. Clinical manifestations and laboratory diagnosis are discussed, as are prophylactic and acute treatment options, specifically for pediatric HAE patients. Also included in this article is a very detailed flow chart depicting a suggested management plan for HAE in pediatric patients.

Frank, M. M. "Hereditary Angioedema: The Clinical Syndrome and Its Management in the United States." Immunol Allergy Clin North Am 26.4 (2006): 653-68.

This review was completed in order to evaluate the evolution of therapy and drug management of HAE in the United States. This review discusses the pathophysiology of the disease, chronic and short term treatment, and provides a helpful overview of HAE clinically.

Frigas, E., and U. C. Nzeako. "Angioedema. Pathogenesis, Differential Diagnosis, and Treatment." Clin Rev Allergy Immunol 23.2 (2002): 217-31.

This article includes a comprehensive overview of angioedema, including the pathogenesis of the disease, treatment, common clinical presentations (including graphics) and differentiation between the multiple subtypes of angioedema. Great detail regarding the multiple treatment options are included in this review, which can be useful to both patients and physicians.

Kaplan, A. P., and M. W. Greaves. "Angioedema." J Am Acad Dermatol 53.3 (2005): 373-88; quiz 89-92.

This review was written to serve as a learning activity used to help others learn about HEA in great depth. Included in the review are history of the disease, epidemiology, the different subtypes of angioedema, how to complete a differential diagnosis, the pathophysiology of the disease, and treatment options. Included in the article is a learning objective which clearly states that this article is meant to be used as a learning activity which should aid the reader in classifying, identifying causes, formulating differential diagnoses, and developing a pathophysiology-based treatment plan for patients with angioedema.

Krishnamurthy, A., S. M. Naguwa, and M. E. Gershwin. "Pediatric Angioedema." Clin Rev Allergy Immunol 34.2 (2008): 250-9.

This article was written in order to overview HAE manifestations in pediatric patients. The authors state that although HAE discussion in association with pediatric patients is discussed often in literature, there is a missing portion which would discuss the manifestations and causes of angioedema among pediatric patients. The authors suggest that the various causes of angioedema and potential mechanisms should be cause for further research and diagnostic testing.

Longhurst, H. "Rhucin, a Recombinant C1 Inhibitor for the Treatment of Hereditary Angioedema and Cerebral Ischemia." Curr Opin Investig Drugs 9.3 (2008): 310-23.

This article discusses a new drug being developed by Pharming NV and Esteve that is in phase III clinical trials in North America (at the time of publication). Rhucin, a recombinant human C1 esterase inhibitor, was developed to treat HAE in both a prophylactic manner and for acute attacks.

Longhurst, H. J. "Emergency Treatment of Acute Attacks in Hereditary Angioedema Due to C1 Inhibitor Deficiency: What Is the Evidence?" Int J Clin Pract 59.5 (2005): 594-9.

The authors of this article reviewed three treatment options for emergency treatment of HAE – fresh frozen plasma, solvent/detergent-treated plasma, and C1-INH concentrate. After reviewing all three methods based on efficacy, composition/concentration, viral safety, risk of hypervolemia, allergic potential, time to intervention and speed of action, drug cost, therapy cost, availability and whether or not the drug was indicated for the treatment of acute HAE attacks, the authors conclude that although all three of the

treatment options reviewed are theoretically effective as emergency treatments for HAE, C1-INH is the preferred treatment option.

Longhurst, H. J., S. Carr, and K. Khair. "C1-Inhibitor Concentrate Home Therapy for Hereditary Angioedema: A Viable, Effective Treatment Option." Clin Exp Immunol 147.1 (2007): 11-7.

This article was written in order to review the current use of home therapy programs which allow HAE patients to administer injections of C1-INH concentrate to themselves at home, as opposed to the previous practice of going to the hospital for injections during attacks. The authors provide both advantages and disadvantages to the home therapy programs and review the current available literature.

Prematta, M., et al. "Fresh Frozen Plasma for the Treatment of Hereditary Angioedema." Ann Allergy Asthma Immunol 98.4 (2007): 383-8.

This review was completed in order to determine if fresh frozen plasma (FFP) can exacerbate symptoms of HAE or precipitate an attack when being used as a treatment method. Patient records obtained from physicians and medical literature using keyword searches in PubMed and OVID were researched for information. The authors found that thus far, there is no proof that FFP has exacerbated symptoms of HAE or precipitated an acute attack, and actually found many instances where there was proof that FFP has been used as a successful prophylactic treatment method.

Reshef, A., I. Leibovich, and A. Goren. "Hereditary Angioedema: New Hopes for an Orphan Disease." Isr Med Assoc J 10.12 (2008): 850-5.

The authors of this review summarize their experience with the new medications that are available for treating HAE. Icatibant, ecallantide, Berinert-P and Rhucin were all studied and reviewed. The authors conclude that the preliminary results of their studies are encouraging and will hopefully bring hope back into the lives of their patients that are dealing with the drawbacks of HAE.

Complete List of Literature

Case Reports

Adhikesavan, L. G., and T. P. Olenginski. "Hereditary Angioedema in a Family Presenting as Transient Periarthritis." J Clin Rheumatol 14.5 (2008): 289-91.

Altman, A. D., et al. "Hereditary Angioedema Managed with Low-Dose Danazol and C1 Esterase Inhibitor Concentrate: A Case Report." J Obstet Gynaecol Can 28.1 (2006): 27-31.

Amar, L., et al. "Hereditary Angio-Oedema: Effective Treatment with the Progestogen-Only Pill in a Young Woman." Br J Dermatol 151.3 (2004): 713-4.

Ashrafian, H. "Hereditary Angioedema in a Martial Arts Family." Clin J Sport Med 15.4 (2005): 277-8.

Aziz, S. R., and P. Tin. "Spontaneous Angioedema of Oral Cavity after Dental Impressions." N Y State Dent J 68.2 (2002): 42-5.

Azofra, J., and M. Lopez-Trascasa. "C4 Deficiency in Chronic Angioedema." Allergy 56.11 (2001): 1106-7.

Baraza, W., J. P. Garner, and S. N. Amin. "Hereditary Angioedema-a Forgotten Cause of the 'Medical' Acute Abdomen." Int J Colorectal Dis 22.11 (2007): 1415-6.

Bell, C. G., et al. "First Molecular Confirmation of an Australian Case of Type Iii Hereditary Angioedema." Pathology 40.1 (2008): 82-3.

Berkun, Y., and M. Shalit. "Hereditary Angioedema First Apparent in the Ninth Decade During Treatment with Ace Inhibitor." Ann Allergy Asthma Immunol 87.2 (2001): 138-9.

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- Bork, K., et al. "Asphyxiation by Laryngeal Edema in Patients with Hereditary Angioedema." Mayo Clin Proc 75.4 (2000): 349-54.
- Bouillet, L., et al. "A Case of Hereditary Angio-Oedema Type Iii Presenting with C1-Inhibitor Cleavage and a Missense Mutation in the F12 Gene." Br J Dermatol 156.5 (2007): 1063-5.
- Cace, N., et al. "Cardiopulmonary Bypass in a Child with Hereditary Angioedema." Pediatr Int 47.2 (2005): 214-6.
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