

Hereditary Angioedema

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I AM DELIGHTED to be the guest editor for this special issue dedicated to hereditary angioedema (HAE). This disease state has grown significantly over the last decade, especially in the United States. Changes have come three decades too late for many with HAE. The exception is for those who reside in Western Europe, who have had therapy available for more than three decades. Nonetheless, there are still many patients in need. Most of the developing world is still without therapeutic choices. Even in the developed world, there are cohorts of patients who do not have access to medications. Unfortunately, children regularly fall into these cohorts and often are not able to access therapies that are effective, specific, and safe.

I would like to thank Mary Ann Liebert, Inc., publishers for their support and assistance in bringing this important topic to the attention of its readership. It is my hope that this condensed, comprehensive set of review articles can be used to support and guide the care of children with HAE.

In this special issue, I requested Dr. Marco Cicardi and his group to present the state of the art in pathophysiology. He and his colleagues, Drs. Sonia Caccia and Chiara Suffritti, have been successful in this endeavor. They highlight the multiple pathways that C1-inhibitor is instrumental in controlling from overstimulation. With deficiency of C1-inhibitor and the lack of inhibition of the contact system the end product is excessive bradykinin production leading to generation of cGMP, nitric oxide, and prostacyclin. This causes endothelial cells to contract and the tight junction to be compromised, leading to an overabundance of fluid entering the interstitial space and causing the angioedema we see in HAE. Dr. Cicardi et al. do a great review of the details of the mechanisms behind HAE.

I asked Dr. Michael Frank to discuss the management of HAE in the pediatric patient. He with his colleague, Dr. Eveline Wu, developed an outstanding evidence-based review on management and therapy of HAE in the 18 and under age group. They focused on present-day therapies and summarized what we know thus far about these therapies.

My colleague, Dr. Shana Kalaria, and I have focused on treatments in contrast to management. We wanted it to be a practical approach to treating the pediatric patient with emphasis on how to use these therapies in patients that may be 10% the weight of an adult. For this reason, extrapolation was often necessary, since evidenced-based research in those younger than 12 years of age is lacking. This was not

meant to be a meta-analysis but instead a practical approach on how we treat our children at Pennsylvania State University based on the information that is available.

In what appears to be an already-crowded space, many new therapies are in preclinical to Phase III studies. I expect that how we approach therapy now will evolve significantly over the next decade or even the next 5 years. With this in mind, I asked Dr. Andrew MacGinnitie to foresee the future and review the medications that are under research and how they may affect the care we provide in the future.

Presently, we are all trying to move patients to self-treatment. The most obvious reasons are cost, early therapy, which is important for rapid resolution, and independence. The Canadians, in my impression, have led us onto this pathway using the model on how they treat hemophilia patients and applying these techniques to the treatment of HAE. Drs. Stephen Betschel and Amanda Jagdis present these available data to support why self-care is important and also how to implement home and most importantly self-care for our patients with HAE.

We have come a long way in North America over the last 5–7 years, but evident from this collection of reviews is that we still have a way to go, especially for children with this disorder. Recently, I had the opportunity to do grand rounds with a mother, about 40 years of age, and we discussed her mom and daughter, both of whom have HAE. Her mom was incapacitated by her HAE. The woman I interviewed had a very limited quality of life until about 5 years ago, but now with therapy she has an international job and travels extensively. Her daughter also has attacks but is being treated very early, so really she has no idea what the disease is truly about. Fortunately, her daughter developed symptoms during mid-adolescence, and for this reason had access to medications approved by the FDA for her age group. What would have happened if she developed severe symptoms earlier in life? She may have suffered significantly for years.

We need to encourage companies to seek pediatric approval for their treatments even for the very young. We need to emphasize to insurers that there is a need, although not for all patients, for therapy very early in life. We need oral or subcutaneous therapy for prophylaxis, and we need therapies that can be dosed by weight, with the assumption that the same dose used for an adult who weighs 300 pounds will not be safe in a 2-year-old child. Ensuring the availability of

safe and effective therapies for our youth with HAE should be a major effort for physicians that treat HAE, our professional organizations, the U.S. Food and Drug Administration, and the patient associations, especially the HAE-A.

I hope you enjoy the reviews contained in this special issue. We have progressed significantly but still have much to achieve, and I hope this series stimulates the interest of our colleagues about this disease that has potential mortality and very significant morbidity even in the early years of life.

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