

HENRY'S STORY

In November 2009, Henry Masters of Medfield, Mass., died at the age of 25, possibly because the emergency room doctors and attending hematologists were unaware of how rapidly autoimmune hemolytic anemia (AIHA) can progress in teenagers and young adults. To be clear, there is scant information available to clinicians on the subject, except dry textbook explanations of general AIHA, which can progress much more slowly in pediatric and older adult patients.

Today, Jeff and Lucy Masters, Henry's parents, have made significant progress in their quest to help the medical community to recognize AIHA and standardize how to treat afflicted patients. They have started a foundation in their son's memory: The Henry Loring Masters Foundation, Inc.

"We faced our fears in a virtual information void," says Masters. "We know we can guide clinical staff toward best practices and better outcomes for AIHA patients by systematically sensitizing providers to the danger of moving slowly and to the risks of relying *only* on their institutional protocol for general AIHA or their discipline's default treatment."

Autoimmune hemolytic anemia is not well-understood, diagnosed, or treated when it presents in young adults. It occurs seldom enough in this age group that clinicians might see it only once or twice in their career. The chances are slimmer at smaller or rural medical facilities.

"AIHA can be very aggressive and therefore needs to be diagnosed quickly so that appropriate therapy can be instituted and modified, if necessary," says Masters. "Because of its potentially aggressive nature, any young adult presenting with jaundice or other signs of hemolysis, such as a dropping red blood cell count, an enlarged spleen, or dark urine, needs to be considered an AIHA patient until proven otherwise. As with other rapidly progressive conditions, such as myocardial heart attack or stroke, AIHA should be treated as a medical emergency, and the proper diagnostics and support systems should be mobilized with urgency."

In simple terms, AIHA results when the body's own immune system begins to see itself as it would a foreign invader, such as a virus or bacteria. When red blood cells are targeted by the immune system, the body's natural response is to destroy those cells, as it would any pathogen. Hemoglobin spilling out of these destroyed red blood cells is metabolized by the liver, resulting in jaundice. Even in a previously healthy person with a strong immune system, the red cell destruction can occur at such a catastrophic rate that it overwhelms the body's ability to produce more red blood cells.

Henry Masters died in 2009 during his second fight with idiopathic AIHA. No underlying cause or trigger for his hemolytic anemia was ever confirmed for his first illness in 2002. (It is believed that the H1N1 flu virus was the trigger in his second illness in 2009.)

Henry had initially presented in Boston in 2002, just before his high school graduation, arriving at Boston Children's Hospital Emergency Department with a severe case of jaundice. He was diagnosed with AIHA quickly enough, and his initial treatment course included standard-of-care measures such as steroids, and intravenous gamma globulin.

While there were some temporary responses, Henry continued to break down his own red blood cells, requiring almost twenty units of blood over his first few weeks of care. Finally, when removing his engorged spleen failed to stem the tide of massive hemolysis, Henry was treated with an experimental drug therapy called rituximab. Thankfully, Henry showed a positive and lasting response to this infusion, which is given four times over one month. After making a full recovery, Henry went on with his busy lifestyle, and the memories of his battle with AIHA began to fade into the past.

Fast forward seven years to November 2009. Henry had finished college, and after considering veterinary medicine and law school and building an impressive nonprofit resumé, he was

approaching the halfway point in a graduate program in public health policy at Dartmouth College. He had been home for the weekend with a Dartmouth classmate, and he felt the onset of a cold or flu as he headed back to school. When he awoke the next morning sick and with jaundice, he drove himself to nearby Dartmouth-Hitchcock Medical Center. Although a relapse of his hemolysis was unexpected, Henry knew his AIHA had returned.

Despite aggressive intensive care and multispecialty support, Henry died five days later, in the early hours of Saturday, November 21, 2009, at the age of 25. After his death, laboratory analysis confirmed the suspicion that he had contracted Type A Influenza/H1N1, or the so-called "swine flu." It is believed that the H1N1 attack on his immune system was vigorous enough to trigger a hyperactivated autoimmune response.

A possible complicating factor in his second illness was that he no longer had a spleen. It had been removed as part of his treatment in 2002. Another contributing factor was the fact that it was extremely difficult to match his blood for transfusion, since his 17 transfusions in 2002 had exposed him to many different blood surface antigens, making his blood profile extremely complex.

"AIHA is a race against time," says Masters. "If we get nothing else accomplished through this foundation, we need the medical community to know to start steroids right away when they see a jaundiced teenager. They don't have the luxury of waiting as long as they might with younger or older patients."

There is a standard test, Coombs blood test, to diagnose AIHA. But not all medical facilities have this technology in-house, and even those that do may not order the test quickly enough and/or may wait for test results to start steroids, etc. There is evidence to suggest that AIHA treatment should begin as soon as AIHA is suspected, before Coombs results are in. The Coombs test should be used to confirm the diagnosis rather than signal the start of treatment.

The Coombs test requires special equipment, and interpretation of results can require a degree of expertise. The test reveals whether the immune system is coating the red blood cells with the proteins that flag them for destruction.

Traditional treatment protocols are aimed at modulating and "cooling off" the immune system. As such, the mainstay of therapy remains corticosteroids, which are very effective in dampening the immune response. As with any immune-modulating therapy, results are not instantaneous, and there is a delay from the time of therapy initiation until a response is observed. Since the spleen is one of the body's primary agents for removing the targeted red blood cells, the next step in therapy often is to remove this organ. While this is curative for some, it renders the patient (especially children) more susceptible to infection with certain kinds of bacteria, and therefore lifelong immunization against these organisms is recommended.

More sophisticated and targeted means of immune modulation have emerged over the past decade, and one such agent was used for Henry in 2002 when other methods failed to slow the tide of red cell destruction. Rituximab is an antibody that targets a receptor on the surface of B-type white blood cells, rendering those particular white cells unable to target red blood cells for destruction. Of course, this B cell destruction is indiscriminate, leaving the patient at an increased susceptibility to infection for months. Once one or more of these maneuvers has stemmed the tide of hemolysis, the body can begin to compensate and slowly regenerate the pool of circulating red blood cells.

The use of these more sophisticated immune-modulating agents has yet to be studied in any systematic way as front-line therapy for AIHA. Given the relative ease and mostly benign side-effect profile for corticosteroids, and the fact that most patients respond to conservative measures, it would be difficult to argue for agents such as Rituximab as first-line therapy. Nevertheless, for some, the presentation of AIHA can be aggressive and fatal, possibly requiring a multifaceted therapy approach, including the front-line use of immunosuppressants such as Rituximab. Because of its extremely low

incidence in young adults, a large multi-arm trial studying these options would be difficult or impossible.

However, it is obvious that the timeline is key, and that rapid diagnosis and treatment can make a huge difference in outcomes. This is where The Henry Loring Masters Foundation is making a difference. THLMF has launched a campaign to alert staff in emergency rooms, regional trauma centers, college and school infirmaries, and other places where first responders may be unaware of the need for proper diagnosis and early intervention in young adults.

THLMF also is building a web presence that aggregates information for clinicians and lay persons. Over time, THLMF hopes to build a library of data and papers, presentations and case studies, or linkages to libraries of materials that offer best practice and objective information.

Equally important, THLMF hopes to form a community for families and patients who want to develop a better understanding of what they are facing.

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