aHUS CANADA

atypical Hemolytic Uremic Syndrome

Supporting patients and families living with aHUS

WHAT YOU NEED TO KNOW

www.ahuscanada.org

What is Hemolytic Uremic Syndrome (HUS)?

Hemolytic Uremic Syndrome (HUS) is part of a group of diseases called thrombotic microangiopathy (TMA). TMA causes damage to the inner walls of the blood vessels (called endothelium) and results in the formation of blood clots (called thrombosis).

Classical or Typical HUS occurs after ingesting toxic strains of bacteria, usually types of E. coli (called shiga toxin) contained in contaminated food or water. With treatment, most people recover from this type of HUS. In some cases (and more rarely) HUS can be more severe and be caused by a variety of other triggers, including other types of bacterial or viral infections, medication and radiation.

What is atypical Hemolytic Uremic Syndrome (aHUS)?

About 5-10% of HUS cases are due to changes or genetic mutations that cause lasting and uncontrolled activity of the complement system, a part of the body's immune system. This type of HUS is called complement-mediated **atypical HUS (aHUS)** and it occurs in approximately 1 in one million births.

aHUS is an ultra-rare, life-threatening, chronic, genetic disease that can damage the body's vital organs. The disease can occur at any age and can lead to potentially devastating consequences, such as failed kidney function and the need for an organ transplant. aHUS affects children and adults almost equally.

What causes aHUS?

aHUS is a genetic disease. The human body is made up of tens of thousands of genes. Genes contain information to make proteins. Each protein is 'coded' or built to serve a specific function in the body. For example, the complement (immune) system has various types of proteins that ensure the system works properly. In times of sickness, the proteins make sure that the complement system is turned 'on' or 'up' to attack foreign invaders.

In times of wellness, the proteins make sure the system is turned 'off' or 'down' to protect the body's healthy cells. Specific gene mutation(s) (mixed-up coding) in the alternative pathway (part of the complement system) causes the proteins in that pathway to be 'broken' or 'missing,' preventing them from properly controlling the system. The pathway then remains 'turned on' at all times, causing the complement system to attack its own healthy cells, specifically the inner lining of blood vessels.

When blood vessels are damaged by this 'self-attack,' blood or platelet clots (called thrombi) form, which affects the function of the kidneys, as well as that of other vital organs, such as the brain, lungs, heart and stomach, as well as muscles and bones.

For these reasons, aHUS is described as a **systemic** (affects many organs and body systems), **chronic, complement-mediated** (immune-controlled) **TMA** (clots in blood vessels).

How does aHUS affect the vital organs?

aHUS affects multiple vital organs and tissues. 63% of aHUS patients have at least one complication outside of the kidney, including involvement of the neurological (brain), cardiovascular (heart), and gastrointestinal (stomach) systems.

Despite the potential for damage to many organs and tissues, aHUS most often targets the kidneys. The kidneys are responsible for filtering blood, keeping the materials the body needs, and removing waste through urine. When clots form in the blood vessels of the kidney, platelets and red blood cells that would otherwise circulate normally around the body are 'used up' in the clot, causing undesirable symptoms. Once formed, the clots take up space in the kidney's blood vessels, making it difficult for blood to pass by and be properly filtered. When red blood cells pass through the narrowed space, they are shattered, becoming jagged fragments called schistocytes. When blood cells cannot remain intact and be properly filtered, the kidney struggles to do its job. Wastes such as creatinine are not removed through the urine, and levels rise to dangerous levels

within the body. Over time, the kidney becomes more damaged and less able to function, causing irreversible organ damage.

For these reasons, low platelet and red blood cell counts, presence of schistocytes, and elevated blood creatinine levels are present and can be measured (by blood tests) in patients with aHUS.

What are the symptoms of aHUS?

aHUS presents with variable symptoms. The initial onset can appear to be flu-like, with lethargic behaviour, pale skin tone, and loss of appetite. Clinical symptoms of aHUS may occur in one severe episode, or continue to worsen during active episodes or 'attacks.' They most often include:

Complaints/signs of:

- nausea and vomiting
- confusion
- shortness of breath (dyspnea)
- fatigue

In some cases, severe, non-kidney related symptoms present themselves right away, and in others, symptoms do not occur until later, or not at all.

Non-kidney related symptoms and conditions can include:

- stroke
- gastrointestinal problems, including severe stomach pain
- inflamed colon
- blood vessel damage
- heart attacks
- neurological issues including seizures

Lab test results showing:

- anemia (low red blood cell count)
- thrombocytopenia (low platelet count in the blood)
- kidney (renal) symptoms, including kidney damage, kidney failure or end-stage kidney disease (i.e. damage requiring chronic dialysis, measured by creatinine and urea levels in the blood)

How is aHUS diagnosed?

Because aHUS is so rare, many doctors may have never encountered it. In addition, signs and indicators of aHUS are similar to other illnesses (like thrombotic thrombocytopenic purpura, also known as TTP, E. coli HUS and other forms of TMA) and, for these reasons, it is difficult to diagnose. Doctors and their health care team must look at many factors when making a diagnosis of aHUS, including clinical symptoms and lab findings.

Lab findings:
Whether at initial onset or during recurring episodes, patients with aHUS usually experience symptoms because of some sort of major event that occurs elsewhere in the body. During an attack of aHUS, there are tell-tale signs that are more obvious, which can be detected from the following lab findings:

- Platelets: decreased levels (may fall below 150×10^9/L, when normal levels should be $150\text{-}400 \times 10^9$/L)
- Hemoglobin: decreased levels (may fall to 60-70 g/L, when normal levels should be 120-153 g/L)
- Haptoglobin: decreased levels
- Lactate Dehydrogenase (LDH): elevated levels
- Creatinine: elevated levels (indicative of declining kidney function)
- BUN (blood urea nitrogen): elevated levels (indicative of declining kidney function)

ADAMTS13 test:
ADAMTS13 is a type of protein that occurs naturally in the body and works against another protein that produces clots. ADAMTS13 and this partner protein work together to both make and break up clots. In some cases, clots are good for the body – for example, when you cut yourself and need a clot to stop the bleeding. In TTP, ADAMTS13 levels are very low and, in aHUS, levels are normal. Therefore, the ADAMTS13 test is helpful in ruling out a diagnosis of TTP.

Genetic testing:
Approximately half of aHUS patients have a known mutation(s) in genes that control the complement system, based on current research evidence. Researchers are working to identify additional genes. Identifying a genetic mutation(s) is not usually required to diagnose aHUS and start treatment, but can be helpful with ongoing disease management decisions, such as eligibility for a kidney transplant. In addition to genetic testing, doctors can also test for the presence of proteins called autoantibodies, which have the same effect on the activity of the complement system as a mutation. Genetic testing may take up to 3 months to complete.

What will happen once I am diagnosed with aHUS? Is there a cure?

aHUS is a chronic (life-long) disease for which there is no cure. Until recently, the standard approach to aHUS treatment was a supportive and reactive strategy to treat symptoms, but not the underlying disease. In general, these therapeutic options are effective at treating symptoms, but do not offer significant protection against disease 'relapses.' In addition, these therapies add various burdens on the patient, including the required frequency of treatment and a substantial impact on quality of life.

In 2013, Soliris (eculizumab) was approved in Canada as a new, superior treatment option for children and adults diagnosed with aHUS, and is fast becoming the new standard of care. Unfortunately, Soliris is not currently funded by provincial and territorial governments (with the exception of Quebec, which provides funding on a case-by-case basis) and, therefore, is not accessible as a first-line treatment option for aHUS unless covered under private health insurance.

Once a conclusive diagnosis (often defined by a failure to respond to plasma therapy) is made and the patient's symptoms are assessed, a comprehensive treatment plan can be developed to address both the symptoms and the cause of the disease.

How will a diagnosis of aHUS affect me today?

If you've just been diagnosed with aHUS, depending on the severity of your disease, you can expect to be hospitalized for anywhere from a few days to several weeks, until your blood levels have been stabilized. This can be a very frightening and confusing time for a patient and their family.

As aHUS is a life-long disease, the symptoms and management of your condition could have a serious impact on your health and overall quality of life. Treatment of the underlying disease with Soliris offers many advantages.

If you have been prescribed a different therapy for aHUS and are having trouble accessing Soliris because it isn't funded by your private insurance plan or your provincial drug program, please contact aHUS Canada at **info@ahuscanada.org**.

I was originally diagnosed with TTP, and later with aHUS. Do I have both diseases?

aHUS and TTP are both members of the TMA group of diseases and present with similar symptoms; however, the diseases differ in the underlying cause. While TTP results from a deficiency in a type of protein called ADAMTS13, aHUS is not associated with this deficiency, rather with genetic or acquired disorders of the complement system. Until recently, it was thought that a patient could only have one or the other – TTP or aHUS. However, there could be an overlap between the two diseases. Tests can confirm whether a patient's diagnosis is aHUS or TTP, or both.

What type of doctor will care for me?

Depending on the location and age of the patient, as well as the stage of the disease, a nephrologist (a doctor specializing in kidney function) and/or a hematologist (a doctor specializing in blood disorders) will be involved in the care of an

aHUS patient. They will treat aHUS patients with some supportive therapies that help with initial and severe symptoms. After a diagnosis of aHUS, your doctors will likely recommend treatment with Soliris. However, Soliris is not currently publicly funded by any province or territory (except Quebec, which provides funding on a case-by-case basis), and is only accessible through private health insurance plans which cover it.

Ideally, you should be assigned a nephrologist and a hematologist, and both doctors should communicate with each other so they are aligned on your treatment plan. This is an important element for which you should advocate for yourself. A nephrologist may be more involved in a patient's care where kidney damage has occurred.

If you are a patient at a smaller medical centre, ask if they are consulting an aHUS expert, or what their source of treatment information is. A list of doctors who treat aHUS across Canada is available on the aHUS Canada website at **www.ahuscanada.org**.

What supportive therapies are available to address the symptoms of aHUS?

Blood transfusions:
Blood transfusions are almost always the first line of symptom management. aHUS patients are typically admitted to the hospital with anemia, a condition in which the body does not have enough healthy red blood cells. A patient may receive packed red blood cells, whole blood, and/or platelets in order to stabilize their symptoms. These products help to return the blood to a more normal level for a brief time, but do not treat the disease.

Plasma therapies:
Almost all patients who present with a TMA and no clear diagnosis receive plasma therapy, which is life-saving for the majority of patients who are later determined to have TTP or a TMA associated with another disease. A minority of patients will suffer from an E. coli-related HUS or aHUS.

Approximately 50% of aHUS patients initially respond to plasma therapy. Plasma therapies are the most traditional way to treat patients with aHUS but do not treat the underlying disease, especially over the long term.

There are two types of plasma therapy:

- Plasma infusion occurs when plasma (the liquid part of the blood) from healthy donors is transfused into an aHUS patient.
- In plasmapheresis, blood is drawn from the patient and the damaged plasma (missing or defective proteins of the complement system) is removed from the blood and replaced with donor plasma. A single plasmapheresis treatment can take one to three hours to complete, with a single plasma infusion taking from 30 minutes to several hours.

Plasma therapies are usually performed daily until the patient's symptoms, platelet count and LDH normalize.

As it is a human blood product, plasma therapy may cause mild to severe allergic reactions in some patients, which may require the addition of anti-allergy medication, use of solvent/detergent-treated plasma or withdrawal of treatment altogether. Currently, all patients who present with a TMA with no clear diagnosis will be provided with plasma therapy. There are no randomized control trials on the role of plasma therapy in aHUS.

Clinical studies have shown that plasma therapies are associated with an immediate clinical response in nearly half of patients; however, even in those who initially respond, almost half will deteriorate over time. Plasma exchange/infusion does not treat the underlying disease, is not a cure, and symptoms may return over time.

Dialysis:
aHUS can cause a patient's kidneys to permanently or temporarily stop functioning. If the patient's kidneys cannot perform properly, dialysis can be

used as an interim replacement for kidneys. Dialysis uses a special machine to remove waste and excess water from the blood, providing an artificial replacement for lost kidney function. Though it is necessary to sustain life, dialysis is an invasive treatment that can produce a variety of additional symptoms and complications.

Kidney transplants are not a viable option for the vast majority of patients with aHUS. Without a treatment or cure that puts the disease in remission so that the new kidney(s) won't be damaged, the majority of kidney transplants will fail.

Are there any medications available that treat aHUS?

Recently, Soliris (eculizumab) was approved in Canada as the first and only pharmaceutical treatment option that treats aHUS, instead of just its symptoms. Whereas, in plasma therapy, missing or defective proteins of the complement system are replaced by donor blood, Soliris targets and blocks key areas of the complement system itself to stop it from running on high and attacking healthy blood cells.

Clinical trials using Soliris in adolescent and adult patients with aHUS have shown to be highly effective and safe (when appropriate protection against certain infections was applied) in controlling aHUS and improving reported quality of life of patients. Unlike plasma therapies, this new treatment option has the potential to change the course of the disease, to repair and restore kidney function in some patients and, for the first time, offers a real opportunity for transplant in those aHUS patients on chronic dialysis.

Internationally, experts recommend that treatment with Soliris should be started immediately upon a confirmed diagnosis (usually achieved after exclusion of other TMAs) of aHUS in children and adult patients. Experts also advise that treatment with Soliris should begin immediately in patients with kidney damage or failure, whether they are on dialysis or have had a kidney transplant.

It is important to be aware of all available treatment options and discuss specific management plans with your nephrologist and/or hematologist.

If aHUS is a genetic disease, should I have my family tested?

When a genetic diagnosis of aHUS is confirmed (a mutation is found), there is the potential that blood-related family members could be carriers of the disease, whether or not they are presenting with symptoms. While it is not necessary that family members get tested, genetic testing can be helpful in disease management of the patient (especially in treatment management and cases of kidney transplant), as well as awareness and education for family members.

Genetic testing is a personal decision that patients and their family members can choose to discuss with their doctor or a genetic counselor. Speaking with a professional can help if you are questioning the need, benefits and risks of genetic testing for you and your family members.

This brochure is meant for informational purposes only. If you or someone you know has aHUS, or think they might, it is important to speak to a healthcare professional about reaching a diagnosis, managing symptoms and accessing treatment.

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ABOUT aHUS CANADA

aHUS Canada was formed in November 2012 to support Canadian patients and families living with aHUS. In addition to establishing a Canadian aHUS community, the group is committed to building public awareness and understanding of aHUS and advocating for the best possible care and treatment for patients. For more information, please visit **www.ahuscanada.org** or contact us at **info@ahuscanada.org**.

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