Atypical Hemolytic Uremic Syndrome

Achieving positive patient outcomes with early diagnosis and appropriate management

Dmitriy Sverdlin, RN, OCN®, and Brenda Peters-Watral, RN(NP), MN, AGD, ANP, PhD, AOCN®

BACKGROUND: Atypical hemolytic uremic syndrome (aHUS), a condition found in adult and pediatric populations, can be idiopathic or acquired as a result of major systemic changes. aHUS presents with a wide array of symptoms that can be attributed to other less dangerous conditions. Because of its complex nature and rare occurrence, it is typically diagnosed in later stages and with multiple organ involvement.

OBJECTIVES: This article provides an overview of aHUS and available interventions.

METHODS: Current aHUS literature was reviewed, and implications for nursing care were identified.

FINDINGS: Early diagnosis is crucial to achieve positive patient outcomes. The difference in pathology among the different thrombotic microangiopathies and their appropriate management must be understood. Although aHUS requires a multidisciplinary approach, nurses play a crucial role in assessing disease progression and identifying possible complications.

CLASSIFICATION AND DEFINITION
aHUS falls under the category of thrombotic microangiopathy (TMA). TMA is a disease process in which endothelial damage within capillaries and arterioles results in inflammation and activation of coagulants, leading to the formation of lesions caused by platelet-rich thrombi (Riedl et al., 2014). Although an immune response is typically an appropriate reaction to cellular damage, in this particular microenvironment, the process becomes uncontrolled. Thrombus formation at the micro level can cause more damage to the vessels, creating a cycle of inflammation and coagulation (Afshar-Kharghan, 2008). The lack of blood flow to distal tissues leads to tissue ischemia and is what engenders the various clinical manifestations of a TMA. This will continue as long as the underlying condition is left untreated.

TMAs are divided into two main categories: thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) (Cataland & Wu, 2014). The overlap of presenting symptoms and organ involvement has some literature referring to them as a combined TTP/HUS. However, the pathophysiology behind TTP differs from that of HUS in that TTP is caused by deficient serum levels of the ADAMTS13 protease (Loirat & Frémeaux-Bacchi, 2011).

KEYWORDS
thrombotic microangiopathy; atypical hemolytic uremic syndrome; thrombotic thrombocytopenic purpura; cancer

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The ADAMTS13 gene is located at chromosome 9q43—the long arm of chromosome 9 at position 43 (Kremer Hovinga & Lämmle, 2012). This gene is responsible for the production of the enzyme, which plays an important role in systemic coagulation. ADAMTS13 is involved in the cleaving of von Willebrand factor (vWF), which is released in response to endothelial damage (Riedl et al., 2014). vWF acts as a binding agent for platelets, creating a localized clot. ADAMTS13 breaks down the vWF, controlling the size of the clot itself, as well as the amount of clots in the area. In a low-level ADAMTS13 enzyme scenario, a spontaneous binding of factors and platelets occurs, causing a formation of thrombi in the vasculature and leading to tissue ischemia (Williams & Marques, 2016). Tissue ischemia not only damages organs but also recruits more inflammatory cells and cell signaling to attempt to correct this process. In an already disrupted and dysfunctional process, this activation of the immune system causes more harm than good.

**Diagnosis**

A TTP diagnosis is likely when serum ADAMTS13 enzyme levels are less than 5% (DeLoughery, 2015). In instances in which levels are within normal limits, the likelihood of TTP would essentially be ruled out, pointing toward HUS. According to Galbusera, Noris, and Remuzzi (2006), individuals with HUS (typical and atypical) have no deficiency in the enzyme. Of note, even with normal ADAMTS13 enzyme levels, patients presenting with a TTP clinical picture should be treated as if they have TTP (Williams & Marques, 2016). Although levels of the enzyme may be within range, patients should still be started on treatment immediately if they still display clinical signs of a TMA and all other pathology has been ruled out. About 10%–25% of patients do not show a deficiency in their ADAMTS13 enzyme levels (Loirat & Frémeaux-Bacchi, 2011); although a key diagnostic marker, other laboratory values and extensive patient history are important to properly manage patients with suspected TMA.

Hemolytic syndromes are defined as typical (of infectious origin) or atypical (noninfectious origin). *Escherichia coli* (E. coli) 0157:H7 is the bacteria most commonly associated with typical HUS, caused by the Shiga toxin that this particular strain of bacteria produces (Williams & Marques, 2016). The incubation period is about 10 days from the point of infection, and the release of bacterial toxins results in intestinal wall damage, triggering the TMA process (Picard et al., 2015). Damage to the intestinal wall also results in gastrointestinal symptoms. These patients usually present with profuse, bloody diarrhea, which is a tell-tale symptom of typical HUS. Some literature refers to typical HUS as diarrhea-positive HUS (Kavanagh et al., 2006). However, not all patients with typical HUS will present with diarrhea. *Streptococcus pneumoniae* infections present without diarrhea but also have been known to cause aHUS (Salvadori & Bertoni, 2013). Much like with TTP, the whole clinical presentation must be assessed.

“Given the broad range of symptoms, accurate identification of aHUS could prevent serious or fatal outcomes.”

Whereas the typical form has a true root cause, aHUS is a complex, multifaceted condition. aHUS is the result of the activation of platelets and proteins involved with coagulation, which becomes uncontrolled because of changes to the complement system (Cataland & Wu, 2014). The complement system consists of three pathways responsible for mounting an immune response to a pathogen. Patients with aHUS have a dysregulation of their alternative pathway related to changes to their complement proteins (Loirat & Frémeaux-Bacchi, 2011). aHUS can be acquired or idiopathic in nature, with lesions primarily found in the kidneys (Noris, Bresin, Mele & Remuzzi, 2016). aHUS damages the renal endothelium by exposing its membranes, thereby allowing for deposits of red blood cells and thrombi (Kavanagh et al., 2006).

**Genetic Sequencing**

Genetic sequencing of complement proteins, or factors, should be assessed alongside with ADAMTS13 enzyme levels. Complement factor H (CFH) is typically the focus of genetic testing. CFH is the most common genetic variant associated with aHUS (Riedl et al., 2014). This glycoprotein not only controls the homeostasis of the complement system but also plays an important role in complement-mediated cellular damage (Ferreira, Pangburn, & Cortés, 2010). An important function of CFH is to activate and regulate membrane attack complexes (MACs) that are responsible for cell apoptosis of bacteria. Mutations in CFH may disrupt the ability to recognize self, which could explain why MAC attacks host cells in aHUS (Ferreira et al., 2010). MAC C5b-9, the particular membrane attack complex that is formed at the end of this cascade, becomes uncontrollable and has actually become the focus of treatment for aHUS (Palma & Langman, 2016).

These MACs are found throughout the microvasculature. A study by Magro et al. (2015) found evidence of MAC C5b-9 deposits in skin using punch biopsy. This is evidence of how far-reaching aHUS can be, despite generally originating in the renal system. Whereas ADAMTS13 levels, complement studies, and stool samples for Shiga toxins are all appropriate measures,
they lack specificity and sensitivity for aHUS (Farah, Hildebrand, Huang, Dammas, & Clark, 2014). Therefore, a vast number of tests are ordered for patients with suspected TMA. A skin punch biopsy may be valuable in aHUS diagnosis, but it may be useful only for patients with certain mutations, like the CFH mutation.

Several other mutations have been identified in aHUS. These include CD46, CFI, C3, CPB, THBD, and DGKE (Noris et al., 2016). Combinations of mutations potentially can be active at one time. Mutations in CFH, CFI, and MVP may account for more than half of aHUS cases (Kavanagh et al., 2006). Complement studies are important for accurate diagnosis, because variation in serum ADAMTS13 enzyme levels can be superimposed atop complement mutations. According to Feng et al. (2013), about 80% of their 29-patient cohort had at least one mutation in the gene responsible for ADAMTS13 production. The nurse’s role is to ensure that proper collection of blood and stool samples is done for the appropriate treatment to be initiated as early in the disease process as possible.

Risk Factors

Determining the true epidemiology of aHUS is difficult. However, according to Noris et al. (2010), the condition was found to be more common in children (aged 18 years or younger) in their study of a 273-patient cohort. The authors explained that at least 70% of their patients had a triggering event. This is an important characteristic in distinguishing TMA conditions. In addition, it shows the importance of genetic predisposition to complement mutation in the pathophysiology of aHUS. Even in the presence of multiple genetic mutations, the condition is generally not activated until a trigger activates the alternative complement pathway (Salvadori & Bertoni, 2013). Triggers can include infections, drugs, transplantation, pregnancy, and malignancies (Noris et al., 2016).

Cancer, cancer therapy, and even hematopoietic stem cell transplantation (HSCT), which can be a treatment option for hematologic malignancies, all have been associated with aHUS (Farah et al., 2014). aHUS has an incidence of as much as 15% and 0.25% in patients after allogeneic and autologous transplantations, respectively (Nadir & Brenner, 2012). As a whole, the HSCT process exposes patients to a wide array of factors that could activate aHUS. Chemotherapy, radiation, graft-versus-host disease, and calcineurin inhibitors (e.g., tacrolimus) all have been identified as risk factors (Jodele et al., 2013) (see Figure 1). Other risk factors for aHUS in patients undergoing HSCT include older age and female gender (Chapin et al., 2014).

Solid tumor malignancies have been associated with TMA. In a cross-sectional analysis of 20 patients from the TMA Registry of the French Reference Center by Oberic et al. (2009), advanced cancer with metastasis was associated with the presence of TMA. The patients were already diagnosed or were diagnosed at the same time as TMA diagnosis with having lung, breast, colon, or gastric malignancies. This is consistent with findings of aHUS presence in breast, colon, and small-cell lung carcinomas, as well as gastric adenocarcinomas (Rafiq, Tariq, Abbas, & Shenoy, 2015).

Presentation

Clinical Manifestations

TMA presents with two key clinical manifestations: thrombocytopenia and microangiopathy hemolytic anemia (Williams & Marques, 2016). Renal dysfunction is typically the most common and earliest symptom of aHUS. Together, these are known as the classic triad of HUS (Farah et al., 2014). Laboratory findings would show a platelet count less than 150 k/dl, anemia (hemoglobin less than 10 gm/dl), and elevated blood urea nitrogen and creatinine (Noris et al., 2016). Progressed disease may present like renal failure and severe hypertension from volume overload, with some patients requiring dialysis.

Nester and Thomas (2012) described several broad symptoms of aHUS: pallor, poor feeding, vomiting, fatigue, and drowsiness in pediatric and adult patients. The mild nature of these symptoms could mean a delay in treatment until more serious complications become obvious. All organ systems could potentially be involved in patients with aHUS. Thrombus formation and inflammation in any organ system could cause fatal complications. Neurologic, respiratory, and even cardiac involvement are also possible (Salvadori & Bertoni, 2013). However, TTP is known to have more neurologic involvement and slightly less renal involvement than HUS (Palma & Langman, 2016). This could be helpful in differentiating the two, although these vague, varied symptoms are more of an example of how difficult TMA can be to diagnose. Given the broad range of symptoms and presentations (see Figure 2), accurately identifying and differentiating the TMA could prevent serious or fatal outcomes.

In patients with cancer, the presenting symptoms of TMA may overlap with the underlying cancer diagnosis or cancer treatment. Lechner and Obermeier (2012) discuss cancer-related microangiopathy hemolytic anemia as a paraneoplastic syndrome of advanced cancer. In other words, rather than a primary TMA caused by an infection or a dysregulation of the complement system, it is a secondary TMA caused by metastatic cancer. They go on to explain that these patients do better with
Interventions

Patients with aHUS generally have poor outcomes. First-time diagnosis of aHUS has a 10%–15% mortality rate, with as much as 60% of patients requiring dialysis for end-stage renal disease (Noris et al., 2010). This can be a consequence of late detection or late diagnosis of the condition. Depending on the severity and underlying mutations, treatment options could include plasma exchange therapy, a monoclonal antibody called eculizumab (Soliris®), dialysis, or even organ transplantation.

Plasma Exchange Therapy

Generally, plasma exchange therapy is first-line treatment for aHUS (Cataland & Wu, 2014). Use of plasma exchange therapy dates back to a landmark paper by Bell, Braine, Ness, and Kickler (1991) that demonstrated successful treatment in 91% of their patients with TTP/HUS (sample size of 108 patients). However, this is not consistent with patients who are diagnosed with aHUS. Plasma exchange works by removing the large vWF and other dysfunctional serum components that are seen with TTP (Williams & Marques, 2016). In aHUS, the underlying mechanism is different. Plasma exchange does not correct the complement pathway mutation. This process potentially can filter out components of the blood that may be responsible for the complement dysfunction, showing a false clinical improvement. Contrarily, it may also be mutation-specific. A study by Noris et al. (2010) suggested about a 50% overall remission with plasma therapy in familial and sporadic aHUS. The success of remission differs among patients, which may be based on their complement mutations (Salvadori & Bertoni, 2013). From a management standpoint, plasma exchange should be given to any patient presenting with a suspected TMA (Rafiq et al., 2015). This can be initiated with supportive therapy, such as transfusion of blood products and fluid management, while additional laboratory results are pending. Patients who have undergone HSCT seem to respond poorly to plasma exchange therapy (Vesely et al., 2003). Similarly, aHUS with suspected primary malignancy or malignant hypertension does not respond to plasma exchange therapy (Farah et al., 2015).

Eculizumab

Eculizumab has been successful in the management of aHUS. In one of the largest adult trials with eculizumab, 73% achieved TMA remission, and 88% and 98% of patients achieved hematologic and platelet regulation, respectively (Fakhouri et al., 2013). According to Greenbaum et al. (2016), complete TMA remission was achieved in 64% of 22 pediatric patients. Eculizumab is a monoclonal antibody that competes and binds to C5, preventing it from being cleaved, thereby inhibiting the production of MAC C5b-9 (Riedl et al., 2014). Preventing the binding of C5 not only controls the complement pathway but also prevents the aggregation of MAC C5b-9. This brings the systemic inflammation under control and allows for stabilization of the patient’s condition without the need for plasma therapy or other interventions.
control, providing a rather quick response with symptom resolution. The European Medicines Agency and U.S. Food and Drug Administration approved the drug in 2011 after several successful trials (Riedl et al., 2014).

Organ Transplantation
Another less accepted and less effective treatment for aHUS is organ transplantation. Kidney transplantation in patients with aHUS typically has poor outcomes and introduces complications of its own. Fifty percent of patients undergoing aHUS kidney transplantation will experience disease relapse and graft loss (Westra, Wetzels, Volokhina, van den Heuvel, & van de Kar, 2012). Transplantation also often involves rejection prophylaxis with calcineurin inhibitor, which is a drug associated with triggering aHUS. Patients are also relatively hemodynamically unstable during aHUS episodes; weighing the benefits with respect to the risks of such a procedure is important. With existing data showing the effectiveness of eculizumab, renal transplantation may be obsolete.

Nursing Considerations
The nurse’s role is vital to successful outcomes in patients with aHUS. Nurses must deliver care and manage therapies with evidence-based practice. Therapies come with risks, and nurses are responsible for monitoring safety and effectiveness to ensure successful patient outcomes. For example, plasma exchange therapy can lead to additional complications in patients who are experiencing volume overload and severe hypertension (Westra et al., 2012). Nurses should advocate for the transition from plasma exchange to a monoclonal antibody based on their assessment. Nurses should be aware of changes in laboratory values, such as complete blood counts and tests of renal function and coagulation.

Patients with malignancies, particularly those with a confirmed or suspected TMA, are at risk for bleeding. This is important if patients present with neurologic involvement. A properly conducted neurologic assessment can mean the difference between progression of disease and new complications, such as intracranial bleeding related to platelet dysfunction. Monitoring hemoglobin can prove beneficial to patients as well. Changes in hemoglobin could mean that lysis is occurring, which puts the patient at risk for more complications. Transfusion of blood products should be initiated when indicated.

Nurses must also assess for changes in kidney function and monitor urine output. Oliguria or anuria may indicate that kidney function is decreasing, which may also imply disease progression. Resolution in kidney dysfunction may indicate that treatment is successful. Changes in kidney function may also cause hypertension. Considering fluid and electrolyte balance is also important. Patients with aHUS may need temporary dialysis for acute episodes of kidney failure. The National Kidney Foundation (2015) suggests the initiation of dialysis at a glomerular filtration rate of less than 30 ml per minute. Improvement of kidney function would not only act as a means of assessing treatment success but also as a means of reevaluating the need for hemodialysis. Management of blood pressure with angiotensin-converting-enzyme inhibitors may be useful in controlling blood pressure and reducing renal disease progression (Noris et al., 2016).

Nurses are responsible for monitoring the efficacy of treatment. Any changes in patient condition may indicate improvement or a need for further intervention. Nurses, using the laboratory data and physical assessment, should encourage the addition of medications for symptom management and the use of eculizumab. If a patient is to receive eculizumab, nurses should be aware of the importance of the meningococcal vaccination. Neisseria meningitis infection is associated with terminal complement pathway, which the drug ultimately inhibits, thereby putting patients at higher risk for infection (Westra et al., 2012). Two weeks prior to initial therapy, patients should be vaccinated to prevent complications, but in situations in which treatment must be immediate, patients must be placed on prophylactic antibiotic therapy for two weeks after vaccination (Cataland & Wu, 2014).

Nurses also play an important role in providing education to patients and their families. Primarily, this lies in understanding the pathophysiology of the condition, as well as the risk factors. Providing education on what signs and symptoms to be aware of could be lead to life-saving decisions. In cases of familial aHUS, nurses should explain the importance of genetic testing, although no true screening method exists. Patients and family members may have different types of mutations or combinations of mutations that are risk-associated and symptom-free. aHUS follows an incomplete penetrance, which accounts for differences in presentation and progression (Salvadori & Berton, 2013). This means that inherited traits may manifest differently in different individuals.

Lastly, nurses should provide appropriate comfort measures to patients and their families. Understanding the importance of transfusion of blood products and the use of medications could mean great improvements in quality of life. This sometimes becomes secondary in the light of a potentially fatal diagnosis but could play an important role in positive patient outcomes. Appropriate clinical assessment skills are necessary for this as well.

Conclusion
aHUS is a potentially fatal disease that poses a challenge to healthcare providers. It can be masked by comorbidities that superimpose symptoms, making its early detection and medical
management just as complex as the factors responsible for its incidence. Efficient and effective nursing care requires appropriate knowledge, skills, and attitude about the disease process and its complications when managing a patient with aHUS.

Nurses working with this specific population of patients will be required to advocate for their patients to promote the best patient outcomes. This means applying an evidence-based approach. Because nursing care is predominately done at the bedside, all changes, however minute, could mean life or death. Nurses, particularly when caring for a patient with aHUS, play a vital role in ensuring that the outcome is a positive one.

Dmitry Sverdlin, RN, OCN®, is a clinical nurse at Memorial Sloan Kettering Cancer Center in New York, NY; and Brenda Peters-Watral, RN(NP), MN, AGD, ANP, PhD, AOCN®, is a nurse practitioner at the Health Sciences Centre in Winnipeg, Manitoba, Canada. Sverdlin can be reached at dsverdlin@me.com, with copy to CJONEditor@ons.org. (Submitted February 2016. Accepted December 27, 2016.)

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