PEDIATRIC AND MATERNAL-FETAL DIVISION NEWS
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AACC Better health through laboratory medicine.

FROM THE MIND OF THE CHAIR

This time of year, my thoughts turn to changing leaves and pumpkin spice lattes, but not usually to the AACC Annual Meeting! That has changed this year, due to the rescheduling and relocation of the conference and expo to late September in Atlanta, GA.

Unfortunately, we have decided to cancel the PMF Division Mixer this year. We hope to see you at a future event where we can all eat, drink, and network with more comfort. If you are attending the meeting in person or remotely via the virtual option, please be on the lookout for the many sessions that feature pediatric and maternal-fetal content, which are highlighted in this issue.

In this issue we discuss H in The ABCs of Pediatric Laboratory Medicine, and H is for (atypical) Hemolytic Uremic Syndrome (aHUS). Excerpts from the Literature considers a recent JAMA Pediatrics systematic review on the perspectives of transgender youth in accessing health care.

Thank you to our newsletter editor, Sarah Wheeler, and her team for compiling the sessions of interest to our members. This edition also announces the winners of our poster awards and award for outstanding contribution to pediatric and maternal-fetal clinical chemistry. Congratulations to the awardees, and please make sure to view their virtual posters.

Please enjoy the annual meeting, however you choose to participate, and be on the lookout for opportunities to become involved with the Pediatric and Maternal-Fetal Division.

Take care,

Angela Ferguson, PhD
Chair, AACC PMF Division

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THE ABC'S OF PEDIATRIC LABORATORY MEDICINE:

H is for (atypical) Hemolytic Uremic Syndrome

Brooke Andrews, PhD
Clinical Chemistry Fellow
Department of Pathology & Laboratory Medicine
University of Kentucky College of Medicine

Alison Woodworth, PhD, DABCC, FAACC
Professor, Pathology & Laboratory Medicine
Director, Core Clinical Laboratory & Point of Care Testing
University of Kentucky Medical Center

Alexander J. Fenwick, MD
Assistant Professor, Pathology & Laboratory Medicine
Director, Apheresis
Associate Director, Microbiology
University of Kentucky College of Medicine

Definition & Etiologies

Hemolytic uremic syndrome (HUS) is one of the thrombotic microangiopathies that is characterized by the triad of hemolytic anemia, thrombocytopenia, and renal impairment. Over 90% of HUS cases are caused by Shiga toxin-producing *E. coli* (STEC) infection [1]; the remaining, non-STEC associated cases are categorized as "atypical HUS (aHUS)" after ruling out other possible infectious and metabolic etiologies as well as thrombotic thrombocytopenia purpura (TTP) [2,3]. Primary aHUS often results from the combination of genetic predisposition plus a triggering event such as an acute infection or pregnancy [4]. Interestingly, SARS-CoV-2 has been implicated as one such triggering event for both new-onset aHUS and relapses [5,6]. Secondary aHUS has been associated with malignancy, HIV, transplantation, drug toxicities, and autoimmune diseases, among others [3,4]. The prevalence of aHUS in the United States is estimated at 2 per million individuals and comprises approximately 5-10% of all HUS cases. An estimated 40% of aHUS cases occur in young children, generally within the first few months of life. While there appears to be no gender predilection for pediatric patients, adult women are more commonly affected than men, which may be a result of pregnancy [3,7].

Atypical HUS is either caused by dysregulation of the alternative pathway of complement or autoantibodies to Factor H, a complement-regulating protein. A simplified representation of this pathway including pathological mutations is illustrated in Figure 1. Mutated genes linked to aHUS include complement regulators: complement factor H (*CFH*), membrane cofactor protein (*MCP, CD46*), and complement factor I (*CFI*) and activators: complement factor B (*CFB*) and complement component 3 (*C3*). Other implicated mutations involve members of the coagulation pathway: thrombomodulin, diacyglycerol kinase ε (DGKE) and plasminogen [8]. Unfortunately, no mutation or autoantibody is identified in 40-50% of aHUS cases [9].

Although anti-factor H autoantibodies have been observed in patients with genetic variants in *CFHR1*, autoantibodies can exist exclusive of a complement mutation. An estimated 25-50% of pediatric cases of aHUS involve autoantibodies but their presence is detected in less than 10% of adult cases. Antibody-mediated disease elicits an equally severe presentation as mutation, with 30% of cases progressing to end-stage renal

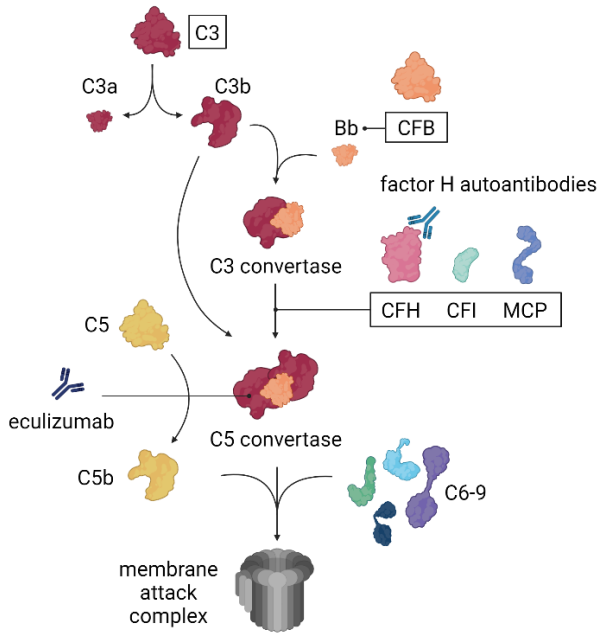

Figure 1. Simplified alternative pathway of complement. C3 hydrolyzes to C3b, which combines with Bb, a product of complement factor B (CFB) to yield C3 convertase. Addition of a second unit of C3 produces C5 convertase, which cleaves C5 into C5b, a requisite component of the membrane attack complex. Eculizumab, a monoclonal antibody therapeutic, binds to C5 convertase and inhibits C5 cleavage. Common pathogenic gene mutations in aHUS are shown at relevant stages in boxes. Complement factor H (CFH) autoantibodies also shown. Adapted from Ref 1.

disease (ESRD) and 40-60% of cases demonstrating abnormally low levels of C3 [3,8].

aHUS is a Diagnosis of Exclusion

As a subset of thrombotic microangiopathy (TMA), clinical manifestations of HUS and aHUS include anemia, thrombocytopenia, elevated LDH, decreased haptoglobin, and the presence of schistocytes in a blood smear [3,4,10]. aHUS is a diagnosis of exclusion, requiring ruling-out of toxin- or infectious HUS, metabolic (cobalamin) etiologies, and TTP. Testing for STEC-associated HUS is primarily based on molecular (i.e. polymerase chain reaction, PCR) detection of the *stx* toxin genes and STEC and/or isolation of bacteria from culture. Other potential infectious etiologies (i.e. *Streptococcus pneumoniae*, influenza virus H1N1, human immunodeficiency virus, cytomegalovirus, human herpesvirus 6, or parvovirus) can be identified via routine microbiology testing such as virus-specific blood or sputum cultures and/or PCR-based antigen detection [8,10]. Cobalamin C defect-HUS is suspected when plasma concentrations of homocysteine and methylmalonic acid are elevated with concurrently decreased plasma methionine. Confirmatory diagnosis requires sequencing of the *MMACHC* gene [3]. TTP is diagnosed based on an ADAMTS-13 activity of <10% and/or the presence of antibodies/inhibitors against ADAMTS-13, both of which can be obtained via commercial testing [10]. Rapid differentiation of TTP from aHUS is crucial because therapeutic plasmapheresis, the primary intervention for TTP, has limited value for most aHUS patients except in autoimmune-related cases [2-4].

Exclusion of metabolic or infectious causes and sufficient ADAMTS-13 activity imply complement involvement.

Treatment

Empiric treatment of a TMA must include plasma (either plasmapheresis or infusion) until TTP can be ruled-out. Although removal of mutant complement proteins is achievable via plasma exchange (American Society for Apheresis, ASFA category III indication), the utility of therapeutic plasmapheresis in aHUS is largely limited to removal of anti-factor H autoantibodies (ASFA category I indication) [3,11]. Plasma therapy is also generally more successful in conjunction with immunosuppression; the five-year risk of relapse for antibody-mediated aHUS falls from 60% to 10% when both therapies are administered [8]. Anti-FH antibody titers have the potential to guide therapy, with a normal threshold of 100-150 AU/mL [12,13].

Eculizumab (Soliris, Alexion Pharmaceuticals, Inc., Boston, MA, USA), a commercially available humanized anti-C5 monoclonal antibody therapy approved by the FDA in 2011, is the primary therapy for aHUS. Antibody binding inhibits the cleavage of C5 by C5 convertase, thereby preventing formation of C5a (anaphylatoxin, pro-inflammatory) and the C5b-9 terminal complement membrane attack complex [2,3,8,13,14]. Eculizumab has been shown to be effective in aHUS cases regardless of whether a specific complement-related

genetic mutation has been identified [3,8]. A longer-acting derivative of eculizumab, ravulizumab-cwvz (Ultomiris, Alexion Pharmaceuticals, Inc., Boston, MA, USA), was recently approved (2019) for patients over one month of age. Use of ravulizumab in place of eculizumab allows for the time between doses to be extended from two to eight weeks [15].

For patients with non-antibody mediated aHUS, rapid exclusion of TTP from the differential diagnosis is critical. Multiple studies have demonstrated that early administration of eculizumab (within 24-48 hours of acute symptom onset) yields improved patient outcomes and that it is more effective than plasma therapy [2,8,16]. Given the adverse outcomes associated with delayed treatment, it is reasonable to consider administering eculizumab without an identified genetic complement defect.

Monitoring Therapy

As complement blockade therapy is both costly (>$600,000/year) and heightens the risk for infections with encapsulated bacteria (including meningococcal meningitis), there has been a recent focus on how to best monitor eculizumab treatment and/or establish the therapy duration [8,9,17-19]. Hemoglobin, platelet count, LDH, and haptoglobin do not necessarily reflect the degree of complement blockade, nor do C3 or C5 concentrations or activities. Normal plasma concentrations of C3 should also not be taken as evidence for a lack of genetic mutation [3].

Complement function is best assessed by a hemolytic assay of total complement activity, CH50. In the historical Mayer method, patient serum is incubated with sheep erythrocytes, which elicit complement-based formation of the membrane attack complex and leads to spectrophotometrically quantifiable hemolysis; a serum dilution ratio is reported at which 50% hemolysis is observed. Most modern automated methods use synthetic liposome lysis assays [20]. Due to methodological variation, it is important to be cognizant of the assay employed. During treatment with eculizumab, CH50 should fall below 10% within an hour of initial administration [3]. However, CH50 is unsuitable for patients with homozygous *CFH* deficiency because these patients have a permanently undetectable activity [8]. Checking for complement blockade during therapy is generally unnecessary unless there are clinical indications of apparent resistance to treatment or relapse. In clinical trials, trough concentrations of eculizumab $\geq$ 100 µg/mL have been associated with complete complement blockade [3].

Remission is indicated by a normal platelet count and LDH activity, the absence of hemolysis, and stable kidney function [9]. However, as there is a risk of relapse, strict patient monitoring is suggested and discontinuation of complement blockade therapy should be considered on a case-by-case basis. A minimum of 6-12 months of treatment is recommended and discontinuation is not advised for patients who received a renal transplant, those suffering recurrent relapses, or for children under 5 years of age [3]. Short-term studies on eculizumab cessation indicate higher risk of relapse in patients with identified *CFH* or *MCP* mutations, albeit in small sample populations [2,8,18,19]. Thus far, no studies have examined the risk of non-relapse sequelae (e.g. stroke, myocardial infarction) in aHUS patients after discontinuing eculizumab [9].

The Role of Genetic Testing in aHUS

During a patient's first episode of aHUS, genetic screening is appropriate after thorough exclusion of other etiologies of TMAs as different mutations have been linked to distinct prognoses and risks of relapse [2,3,8,9]. The most common genetic abnormalities identified in aHUS are described in Table 1. Less common but clinically significant mutations include *CD46*, *THBD*, *CFHR1*, and *CFHR5* [13]. If genetic testing has not yet been performed in cases of relapse or when a hereditary defect is suspected (i.e. two or more family members are affected greater than 6 months apart, excluding a common triggering infection), it may be valuable to identify any relevant mutation. Detection of a known mutation confirms a complement-dependent diagnosis. Genetic screening of the recipient is essential prior to kidney transplantation from a living related donor due to the increased risk of allograft loss. In general, the presence of a

pathogenic mutation, especially *CFH* or *MCP* is associated with a high risk of relapse [8].

Table 1. Summary of the most common genetic mutations identified in aHUS. Data are from references 9[a], 2[b], 3[c], and 8[d].

Gene	% of aHUS	Age of Onset (years)[d]	↓C3 (% cases)[d]	ESRD (% cases)	Relapse (within 5 years)[d]
CFH	25%[a]	<2	70%	60-80%[b]	20-40%
MCP	10%[a]	>1, generally 2 -12	0%	6-38%[b]	80%
C3	< 5%[a]	-	70%	> 60%[b]	20-40%
CFB	< 5%[a]	-	100%	70%[b]	-
CFI	5-10%[a]	<2	60%	58%[b]	20-40%
DGKE	3-8%[c]	< 1	21%	7% [d]	80%
Unidentified	40-50%[a]	-	-	27%[d]	20-40%

Summary and Clinical Considerations

Atypical HUS is a complex and life-threatening genetic and/or autoimmune condition in which dysregulation of the alternative pathway of the complement cascade leads to autonomous complement activation and TMA. Rapid diagnosis and rule out of overlapping syndromes is critical to effective treatment of patients with aHUS. Empiric plasma therapy for TMA is ineffective against complement dysregulation (i.e. aHUS) unless coupled to immunosuppression in patients with autoantibodies against Factor H. Eculizumab therapy is exclusively recommended in non-antibody-associated cases of aHUS, and treatment should be initiated well before the results of any confirmatory genetic testing would return. The resolution of symptoms with complement blockade therapy strongly suggests a complement-mediated etiology and the absence of an identified mutation neither excludes a diagnosis of aHUS nor indicates that eculizumab will be ineffective. Thus, gene sequencing currently seems to hold the most value for genetic counseling. Penetrance of aHUS with an associated mutation is approximately 50% and carrier status could be useful information for family members and future reproduction [8]. Specific mutations may predict risk for future relapse after treatment cessation, but more studies are needed to confirm this link. Long-term outcome studies are needed to carefully assess the utility of genetic testing in aHUS patients.

(References on pg. 9)

Excerpts from the Literature

Emily L Gill, Ph.D.

Clinical Chemistry Fellow
Children's Hospital of Philadelphia
University of Pennsylvania

Affirmative Healthcare for Transgender Youth

Transgender youth are at high-risk for exposure to prejudice and discrimination, which are forms of minority stress [1]. Minority stress refers to unique, added stress that results from marginalization (above and beyond general, universally-experienced stress) [1]. Minority stress has been linked to health disparities among transgender youth, including increased risk for psychiatric disorders such as anxiety, depression, and substance use disorders, among others. Transgender youth are more likely to die by suicide, compared to the general population, illustrating the severity of these disparities [2, 3]. There are also a number of unique healthcare stressors for transgender youth that must be understood by providers, including parental consent, psychiatric evaluations, and access to providers who specialize in adolescent gender dysphoria.

A recent systematic review by Chong et al., published in JAMA pediatrics and entitled "Experiences and Perspectives of Transgender Youths in Accessing Health Care," identifies themes regarding healthcare experiences of transgender youth; the negative experiences that the authors highlight can be prevented through the practice of inclusive, affirmative healthcare [4]. The authors underscore a need for breaking down barriers to affirming therapies by removing stressors. Chong et al., affiliated

with various institutions across Australia and the Netherlands, conducted a systemic review and thematic synthesis of primary qualitative studies of transgender youth (9-24 years old), following Enhancing Transparency of Reporting the Synthesis of Qualitative research (ENTREG) guidelines. Exclusion criteria removed studies in which participants did not identify as transgender, non-English language articles, and any data corresponding to non-binary individuals because the studies did not elaborate on data specific to that population. Chong et al., focus their review on qualitative studies that specifically focus on individuals whose gender identity does not align with their sex assigned at birth but who still identify within the gender binary of man and women. To ensure quality in research they also evaluated each study using Consolidated Criteria for Reporting Qualitative Research (COREQ). They also cross-checked selected references in terms of eligibility criteria and transparency of reporting criteria. The authors settled on 91 articles from 17 different countries, with a total of 884 participants.

This review identified 6 main themes within the research that both discourage and encourage transgender youth in seeking healthcare, including: 1) pervasive stigma and discrimination in healthcare, such as fear of transphobia, 2) vulnerability and uncertainty in decision-making, such as the burden of needing to educate physicians on transgender identities, 3) systemic barriers to gender-affirming therapies/surgeries, such as puberty-blockers, 4) internalized fear of consequences, such as being outed by anatomical exposure, 5) prejudice undermining efforts to seek out healthcare due to societal marginalization, and 6) feeling of affirmation and allyship. These first five themes highlight social and institutional barriers to high-quality, culturally-sensitive healthcare. These barriers exacerbate gender dysphoria and risky behaviors by encouraging transgender youth to avoid healthcare altogether. This avoidance of care may include preventative care, such as a PAP smear for a transman or a prostate exam for a transwoman when they become of age, due to the harmful impacts of prejudice and discrimination. The final theme, however, serves to facilitate access to healthcare and includes positive experiences such as an affirmed gender identity, leading to increased confidence in pursuing gender-affirming treatment(s), and finding allyship in providers. It is important to note that similar negative experiences in healthcare have also been reported by non-binary (gender non-confirming) populations [2].

Studies of this nature that both highlight and integrate important research from the social sciences are of great importance for minority visibility in healthcare. Chong et al., present a strong case for focusing on inclusive, affirming care by first acknowledging the barriers faced by minority populations, followed by making a conscious decision to educate ourselves on how we can achieve equity in healthcare for all. Support and affirmation of gender identity are key protective factors for transgender youth that have been linked to improved health and well-being outcomes [2, 4]. Thus, it is essential that healthcare providers support transgender youth and affirm their identities through a culturally-sensitive lens, improving their healthcare experiences and empowering them to seek care, including gender-affirming treatment(s).

Increasing provider education and improving accessibility to specialized services for transgender youth should be a priority, breaking down barriers to healthcare for all. Nonetheless, healthcare has a long way to go to ensure equity and inclusion for all populations, especially underserved, at-risk groups such as transgender youth. It is essential that we learn from studies like the one by Chong et al., and that strategies are put in place to improve quality of care, and, ultimately, health outcomes.

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2021 AACC ANNUAL SCIENTIFIC MEETING & CLINICAL LAB EXPO: PMF Sessions of Interest and Meeting Highlights

September 26-30, 2021

Sunday September 26th

Opening Plenary:

Regina Barzilay, PhD
11001 Artificial Intelligence in the Clinic: Strengths, Weaknesses, and Opportunities

Monday September 27th

Roundtables:

42130 and 52230 Cell Free DNA in Prenatal Care Setting: Current Practices and Future Developments

Plenary:

Margaret Liu, MD, DSchc, MDhc, FISV
12001 COVID-19: Vaccines and the Tango of Viral Evolution and Host Immune Responses

Scientific Sessions:

32106 Conventional and Modern Approaches To Assessing Pediatric Growth Hormone Deficiency

32221 Case Studies in the Use of Emerging Technologies in Pediatric Laboratory Medicine

Tuesday September 28th

Roundtables:

43101 and 53201 Biochemical Genetics 101: Laboratory Testing for Inborn Errors of Metabolism - A Case-Based Discussion

43110 and 53210 Harmonizing Pediatric and Adult Lipid Reporting: The Canadian Society of Clinical Chemists (CSCC) Harmonized Reference Interval (hRI) Working Group

43111 and 53211 Hemoglobinopathies and Thalassemias: Techniques and Interpretation

Plenary:

Bonnie Ramsey, MD and Caley Mauch

13001 The Remarkable Journey from Bench to Bedside: Changing Lives of Individuals with Cystic Fibrosis

Scientific Sessions:

33104 The Right Tools for the Job: The Diagnosis, Treatment, and Complications of Hemoglobinopathies

Wednesday September 29th

Plenary:

Holden Thorp, PhD
14001 Curating and Documenting Research During Chaos: Lessons from COVID-19 and Beyond

Scientific Sessions:

34110 What's New in Newborn Screening?

34226 Congenital and Acquired Bleeding Disorders: Properly Interpreting Coagulation Assays for Accurate Coagulopathy Diagnosis

34230 The Role of the Clinical Laboratory in the Diagnosis, Management, and Understanding of MIS-C: An Update

Thursday September 30th

Plenary:

Wilbur Lam, MD, PhD
15001 Clinical Translation of Engineered Microsystems: From COVID-19 to Hematology and Hemostasis

Scientific Sessions:

35103 Laboratories Ally with Clinicians in Mitigating the Burden of Heart Disease from Childhood

PMF Division Awardees

Please help us congratulate the winners of this year's PMF Division Awards on the Artery!

Best Abstract by a Student or Young Investigator:

Jessica Miller PhD
Clinical Chemistry Fellow
University of Toronto
Title: Beyond 25(OH)D: Using the Vitamin D Metabolite Ratio to Assess Vitamin D Status

Best Abstract:

Tatiana Yuzyuk, PhD
ARUP Laboratories and University of Utah School of Medicine
Title: Abnormal lipoprotein particle profiles in children and adolescents with Cystic Fibrosis: the effects of modulator therapy

Outstanding Contributions to Pediatric Maternal-Fetal Laboratory Medicine:

Michael L. Astion, MD, PhD
Medical Director
Department of Laboratories
Seattle Childrens Hospital
Clinical Professor of Laboratory Medicine
University of Washington

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