The Turkish Journal of Pediatrics 2024; 66: 1-16
https://doi.org/10.24953/turkjped.2023.596

Review

Management of pediatric hemolytic uremic syndrome

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ABSTRACT

Classical clinical triad of hemolytic uremic syndrome (HUS) is microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury associated with endothelial cell injury. Several situations, including infections, medications, malignancies, and transplantation can trigger endothelial damage. On the HUS spectrum, atypical hemolytic uremic syndrome (aHUS) deserves special attention in pediatric patients, as it can cause end-stage kidney disease and mortality. A dysfunction in the alternative complement pathway, either acquired or genetic, has been shown to be the main underlying cause. In the last decades, breathtaking advances have been made in understanding the pathophysiology of this rare disease, which has led to more efficient treatment. Recent studies have implicated genes in pathways beyond the alternative complement system, such as *DGKE*, *TSEN2*, and *INF2* highlighting the importance of personalized management. Eculizumab has brought about dramatic improvements in the treatment of aHUS. Beyond eculizumab, there are many alternative therapeutics in the pipeline that target the complement system. Because of the rarity of aHUS, data from multiple patient registries are very important. The present report aimed to summarize the most important aspects of diagnosing and treating aHUS based on the Turkish national registry and the literature so as to improve clinical practice.

Key words: hemolytic uremic syndrome, shiga toxin-producing *Escherichia coli*, TRACK syndrome, monoclonal complement C5 antibody.

Hemolytic uremic syndrome (HUS) is an important differential diagnosis in pediatrics as it has a significant potential for morbidity and even mortality. It is clinically characterized by microangiopathic hemolytic anemia, low platelet count and acute kidney injury.[1] Although kidney involvement takes an important place both in diagnosis and prognosis, other vital organs can also be affected.[2]

Thrombotic thrombocytopenic purpura (TTP), a major differential diagnosis among this group of disorders, is characterized by ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin motif type 1, member 13) deficiency. ADAMTS13 breaks down the large multimers of von Willebrand Factor (vWF) on endothelial cells. In TTP patients, ADAMTS13 activity is <10%. The incidence of HUS in pediatric thrombotic microangiopathy (TMA) patients is higher than that of TTP.[2]

HUS has attracted significant attention in terms of etiologic diversity, pathogenesis and management in recent years.[3] Since its first description in 1955, our understanding of its pathophysiology has vastly improved. For many years, it was investigated mainly in two categories; "diarrhea-positive" (typical) and "diarrhea-negative" (atypical) HUS; however, this classification system was abandoned in 2015 as it was considered misleading. Currently, the disease is categorized according to etiological subgroups. Nevertheless, the

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Received 10th Aug 2023, revised 5th Feb 2024, accepted 6th Feb 2024.

terms "typical" and "atypical" are still used in daily practice. Typical HUS is mainly caused by STEC (Shiga toxin-producing *Escherichia coli*) or other verotoxin-producing *E. coli* (VTEC), and is referred to as STEC-HUS. In addition, HUS can develop secondary to infections caused by *Streptococcus pneumoniae*, underlying disease (such as malignancy), some medications (such as cyclosporine, tacrolimus and quinine), bone marrow transplantation, and pregnancy. Atypical HUS (aHUS) is a rare form of HUS with an annual incidence of 0.26-1.9 per million. It may be a devastating disease if not managed properly.[4] The kidneys are usually involved and it may progress to chronic kidney disease (CKD) stage 5, requiring sustained kidney replacement therapy (KRT). Less commonly, extrarenal organs, primarily the central nervous and cardiovascular systems, lungs, gastrointestinal (GI) tract, eyes, and skeleton, can also be affected by TMA associated with aHUS, modifying the clinical presentation of the disease.[5-10]

From the pathogenetic point of view, HUS is a clinical expression of TMA characterized by platelet aggregation and thrombus formation in small vessels that lead to luminal narrowing or occlusion resulting in end-organ ischemia and infarction. Endothelial cell damage is the primary cause that initiates TMA.[1] In aHUS, the induction of endothelial cell injury is sustained, such as dysregulation of the alternative complement pathway (complement-induced HUS), mutations that cause loss of function of the lipid kinase diacyl glycerol kinase epsilon (DGKε),[9,10] or recently identified *TSEN2* mutations that disrupt tRNA biology (Table I).[11] Complement-mediated HUS, the most common type of aHUS, occurs due to dysregulation of the alternative complement system that is caused by mutations in genes encoding complement factors or autoantibodies against some of the complement components. To date, more than 120 mutations responsible for aHUS have been found in the genes encoding regulatory proteins of the complement alternative pathway (Fig. 1).[12-14]

Complement-blocking therapies have significantly improved the prognosis of aHUS and are the first line therapy for complement mediated aHUS; however, there is still no consensus regarding long-term therapeutic management in children with aHUS. Therapeutic approaches vary geographically due to differences in healthcare policies. For instance, eculizumab is still not available in underdeveloped countries because of economical constraints. As such, currently available treatment guidelines may not be applicable in all countries, which highlights the necessity of each country developing their own national treatment protocol based on consensus. The present report aimed to summarize the most important aspects of diagnosing and treating aHUS based on the Turkish national registry and the literature, so as to improve clinical practice.

Table I. Classification of hemolytic uremic syndrome (HUS).

1. Infection-associated HUS
- Shiga toxin-associated HUS
- *Pneumococcus*-associated HUS
2. HUS with coexisting conditions
- Malignancy
- Medications (e.g., VEGF inhibitors)
- Bone marrow transplantation
3. Atypical HUS (aHUS)
- Complement mediated aHUS
• Genetics (*CFH, CFI, CD46 (MCP), C3, CFB,* CFHRs)
• Autoimmunity (Anti-CFH antibody)
- Complement independent aHUS
• Genetics (*DGKE,* cblC, *INF2*)
• Syndromic form (TRACK syndrome)

aHUS: atypical hemolytic uremic syndrome, CblC: cobalamin C, *CFB*: complement factor B, *CFH*: complement factor H, CFHR: complement factor H related proteins, *CFI*: complement factor I, *DGKE*: diacylglycerol kinase epsilon, HUS; hemolytic uremic syndrome, *INF2*: inverted formin 2, *MCP*: membrane cofactor protein, TRACK syndrome; *TSEN2* related atypical hemolytic uremic syndrome, craniofacial malformations, kidney failure, VEGF: vascular endothelial growth factor

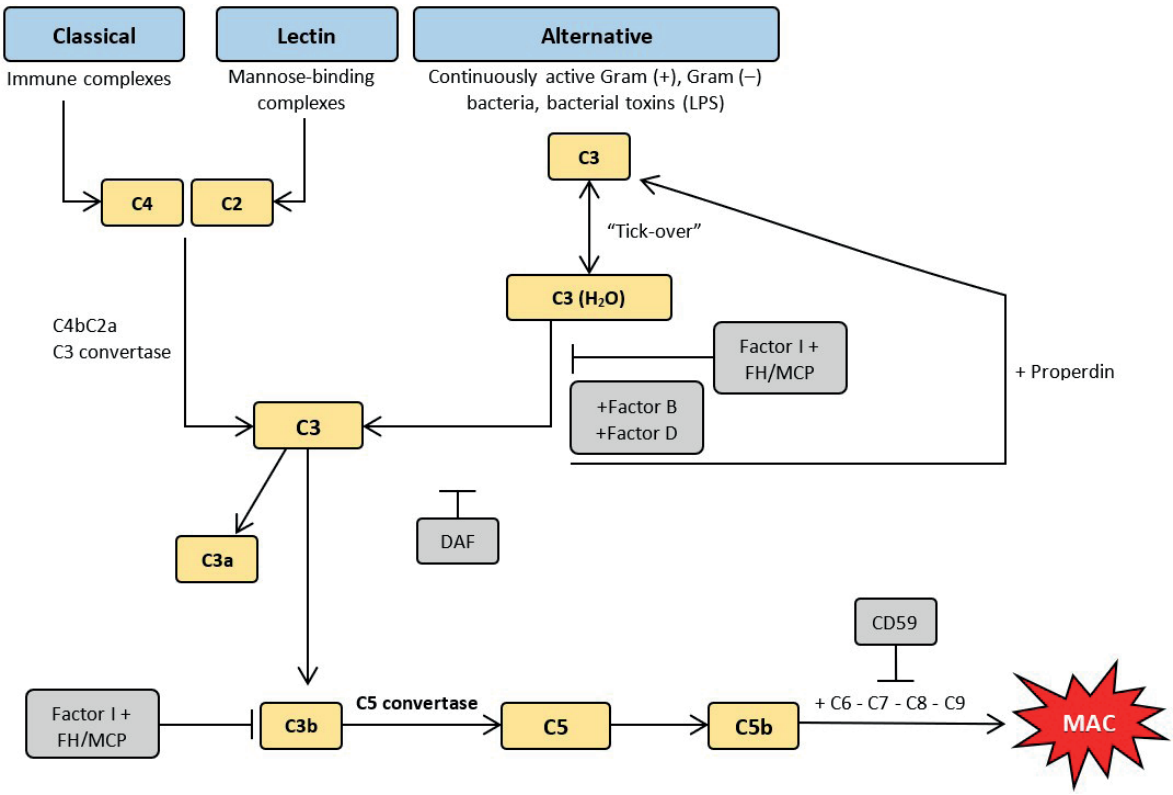


Fig. 1. The classical, lectin and alternative complement pathways and their regulatory proteins.

C: complement, DAF: decay accelerating factor, FH: factor H, LPS: lipopolysaccharide, MAC: membrane attack complex, MCP: membrane cofactor protein.

1. Classification of HUS

The current classification, which was proposed by Lemaire et al.[15] is based on etiological subgroups. STEC-HUS and pneumococcus-associated HUS (SP-HUS) are classified as infection-associated HUS. The term aHUS is generally used for cases related to the alternative pathway dysregulation or complement independent genetic abnormalities such as *DGKE*, *MMACHC* (CblC), *INF2* and *TSEN2* mutations. Coexisting conditions and/or medications with the potential to cause HUS should also be investigated (Table I). Despite all efforts, the etiology may not always be determined for a particular group of patients.

1.1. STEC-HUS

Definition and clinical characteristics

STEC-HUS occurs following acute gastroenteritis secondary to enterohemorrhagic *E. coli* or *S. dysenteriae*, and most commonly occurs in children aged 3-5 years. In patients with STEC gastroenteritis, *E. coli* O157 is usually isolated; however, infections caused by non-O157 strains of *E. coli* have increased in the last decade. The most prevalent strain in the outbreak in Germany was O104:H4.[15-17] Diarrhea typically begins 3–8 days after consuming contaminated food, direct contact with the cattle or as a result of household contact and precedes the clinical manifestation of HUS. Watery diarrhea occurs in the early stages, which may turn into bloody diarrhea. Fever, nausea, vomiting, and abdominal pain are also common symptoms. These symptoms typically appear 2-14 days following the onset of diarrhea.[18]

Diagnostic criteria

1. Microangiopathic hemolytic anemia: Hemoglobin level below the lower limit of

normal, reticulocytosis and increased lactate dehydrogenase (LDH), decreased haptoglobin level, hemolysis in red blood cells (such as schistocytes on peripheral blood smear), negative direct Coombs test (sometimes positive in SP-HUS, autoimmune diseases, or with prior transfusion of blood products).

2. Thrombocytopenia: Platelet count <150x10^9/L or >25% decrease from baseline.

3. Kidney compromise: Acute kidney injury (AKI) is defined when serum creatinine increase ≥0.3 mg/dL within 48 h or a ≥1.5-fold increase in the baseline value, which is known or presumed to have occurred within the previous 7 days[2,19,20], and oliguria/anuria.

Confirmation of STEC

The collection of material for Shiga toxin testing is very important. The probability of obtaining a positive shiga toxin test via polymerase chain reaction (PCR) or stool culture diminishes 10 days after the diarrhea. Accordingly, 90% of patients have a negative stool culture result after 15 days.[21] Immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies against *E.coli* lipopolysaccharides increase in the acute phase of the disease and high levels of IgG antibodies persist in later stages of the disease when fecal specimens fail to demonstrate Shiga toxin.[2,22]

Clinical characteristics

In STEC-HUS, the kidney presentation may be different from patient to patient, ranging from severe AKI with anuria to only proteinuria, hematuria, or both. In rare cases, ischemia can lead to cortical necrosis as a pathological finding.[1] Ardissino et al.[23] reported that only 41% of patients met the 3 criteria for the standard diagnosis of HUS; therefore, a high degree of suspicion is necessary for appropriate management of patients. Multisystem involvement can occur; the most frequently involved system is the central nervous system (CNS). Findings suggesting CNS involvement include disorientation, altered mental state, convulsions and stroke. GI involvement can also be observed in some patients. In this case, intestinal ischemia, necrosis, or thrombosis, perforation, pseudomembranous colitis, rectal prolapse, elevated transaminases or hyperbilirubinemia may occur.[24] An outbreak of HUS was reported in 2013 that included 70 patients with a median age of 5.7 years; the rate of CNS complications and mortality was 21.4% and 4.2%, respectively.[25]

Management

The management of STEC-HUS is supportive. The constitution of circulatory volume is very crucial. Ake et al.[26] reported that patients with non-oliguric kidney failure had more intravenous fluid and sodium before HUS development compared to the patients with oligo-anuric HUS. Subsequent studies and meta analyses also highlight the importance of early fluid infusion, which decreases the requirement for dialysis, duration of hospitalization, and even mortality[27,28]; therefore, when HUS is associated with diarrhea, every normotensive patient with a normal cardiac silhouette on chest X-ray and no signs of fluid overload should be evaluated for early fluid infusion.[29] Intravenous furosemide can be considered in children with hypervolemia and oligo-anuria. Blood pressure should be kept within normal limits for age, sex and height; for this purpose appropriate antihypertensive medication can also be indicated. Angiotensin converting enzyme (ACE) inhibitors are generally avoided as these drugs can cause further impairment of kidney functions and severe hyperkalemia. In patients with electrolyte and/or acid-base abnormalities, or volume overload unresponsive to diuretics, KRT should be administered. The type of KRT chosen should be based on clinician experience and healthcare center infrastructure. Electrolyte and acid-base abnormalities should be corrected. For ongoing hemolysis, erythrocyte transfusion may be required.[18] A transfusion is usually necessary if the hemoglobin level is below 7 g/dL or below 7.5 g/dL with a decline of more than 2 g/dL from the level of the previous

day.[30] Because of the risks of hyperkalemia and hypervolemia, it is recommended that a decision for blood transfusion be made in consultation with the nephrologist. Routine thrombocyte infusion is not recommended unless there is active bleeding, but may be given before catheter insertion for KRT. These patients are usually in a catabolic state and therefore adequate nutritional support is also critical.[30]

For patients with CNS involvement, plasma-based therapies are employed as salvage therapies.[30,31] The benefits of plasma infusion (PI) and plasma exchange (PE) on the course of the disease are not widely accepted. Recovery after PE has been demonstrated in some studies and case reports[32], but extensive research has not been done to demonstrate the effectiveness of plasma-based therapy.[33,34] Eculizumab was administered to STEC-HUS patients with CNS involvement in the 2011 German epidemic; however, detailed analyses did not show a clear benefit.[17] Similarly, Ağbaş et al.[35] reported 21 STEC-HUS; no difference in kidney prognosis was found between patients treated with and without eculizumab. Thus, complement-blocking therapies can be considered transiently during the acute phase in selected STEC-HUS patients in whom supportive treatments fail and severe disease is present. Therefore, despite clear evidence of the therapeutic utility of eculizumab in patients with aHUS, further studies are warranted for its use in patients with STEC-HUS.[30]

1.2. S. pneumoniae-associated HUS (SP-HUS)

Invasive pneumococcal disease has become less common since the introduction of the conjugated pneumococcus vaccine; however, SP-HUS incidence has not decreased. It is estimated that invasive pneumococcal infection causes roughly 0.4% to 0.6% of HUS cases.[1,36] It typically occurs following pneumonia (especially when complicated by empyema) and meningitis. Preformed IgM antibodies against Thomsen-Friedenreich cryptantigen (T-antigen) react with red blood cells (RBCs), platelets, and endothelial cells, all of which result in the development of HUS. The onset of SP-HUS typically occurs 3–13 days (often within 7-9 days) following the start of pneumococcal illness. In comparison to individuals with STEC-HUS, children with SP-HUS are younger, typically have more severe kidney and/or hematological disease, therefore need an increased duration of hospitalization.[37,38] There is no specific laboratory test for SP-HUS nor are there validated diagnostic criteria. Furthermore, it may have some overlapping features with disseminated intravascular coagulation (DIC). Therefore, Scobell et al.[39] suggested modified criteria for SP-HUS with 3 categories. According to these criteria, evidence for HUS or invasive *S. pneumoniae* infection (in any biological fluid that should be sterile) or positive sputum culture in association with pneumonia and no clinical and laboratory evidence of DIC have been considered definite. Probable cases have been defined as having evidence for HUS or invasive *S. pneumoniae* infection in any biological fluid that should be sterile or positive sputum culture in association with pneumonia (in the presence of pneumonia) with presence of evidence of DIC and of T-activation via positive Coombs test or peanut lectin assay. Possible cases have been defined as those with evidence for HUS, toxic appearance with pneumonia, meningitis or evidence of other invasive infection without identification of a specific organism, positive Coombs test or peanut lectin assay with or without evidence of DIC.

The management also includes supportive care and pneumococcal infection treatment. Given the fact that blood products may contain antibodies against T-antigen, packed RBCs should be washed with dextran. Fresh frozen plasma infusions should be avoided due to the same fact. Complement-blocking medications may also be used in severe cases.[38]

1.3. aHUS

aHUS poses significant difficulties in the management and follow-up of pediatric nephrology patients, as well as in terms of prognosis. About 70% of pediatric patients

with aHUS experience their first episode before the age of 2 years, and 25% before the age of 6 months. The frequency does not differ between males and females. In general, aHUS comprises 5-10% of all childhood HUS cases.[7] An analysis of the Turkish National Registry System (NRS) showed that 36% of the patients had disease onset at <2 years of age. In total, 72% of the patients received KRT. After a median duration of 23 months CKD stage 5 developed in 1/53 patient. Hypertension and proteinuria persisted during the follow-up period in 44% and 37% of the patients, respectively.[40] On the other hand, in the Global aHUS Registry, 42.8% of the pediatric patients had disease onset <2 years of age.[41]

Gain-of-function mutations in complement 3 (C3), complement factor B (CFB), neutralizing antibody against CFH (anti-CFH antibodies), as well as loss-of-function mutations in the genes encoding regulatory proteins (complement factor H [CFH], complement factor I [CFI], membrane cofactor protein [MCP, CD46], and thrombomodulin) cause the alternative pathway to become overactive.[42] These genetic abnormalities lead to uncontrolled C5b-9 membrane attack complex (MAC) production on endothelial cells causing endothelial damage. It has been reported that, mutations in the genes encoding alternative pathway proteins are present in 60-70% of aHUS cases.[43] CFH mutations have been reported to be the most frequent and to be associated with the worst prognosis; however, genetic causes can differ by ethnicity.[42,43] As such, the *CD46* (*MCP*) mutation was found to be most prevalent in the Turkish pediatric aHUS population, based on data from the national aHUS registry.[44] It should be emphasized that mutation analysis is not necessary for an aHUS diagnosis; however, mutation analysis can help determine the prognosis, risk of recurrence, and duration of complement-blocking therapies. As such, it is recommended to perform genetic analysis at any time during the course of the disease.

Among patients, >50% (susceptible individuals) have a history of infection (i.e. acute gastroenteritis or upper respiratory tract infection) that over-activates the alternative complement pathway. Based on the Turkish NRS, CNS involvement is the most frequent extrarenal system involvement (27.2%), followed by cardiovascular and respiratory involvement. In other series, CNS involvement was observed in 8-48% of the cases.[45] Additionally, compared to the patients without CNS involvement, patients with CNS involvement have a higher mortality rate and a lower estimated glomerular filtration rate (eGFR).[8] Distended abdomen, bloody diarrhea, and intestinal perforation suggest GI involvement.[44] The differential diagnosis is summarized in Fig. 2.

Management

The management of aHUS is classified into two categories: namely supportive and specific treatment. Principles for supportive treatment are the same as those given above for STEC-HUS. Plasma-based therapies were the mainstay of management for many years; however, the risk of hypervolemia in oliguric patients is the primary concern associated with PE and PI. PE was administered at 60-75 mL/kg and PI was administered at 10-20 mL/kg for the treatment of aHUS. However, the effectiveness of plasma based treatments in aHUS patients has not been sufficiently supported by the existing literature data.[46,47] One study reported that plasma-based therapy caused hematological remission in 78% of pediatric patients and 53% of adult patients; however, within 3 years of follow-up, 50% of pediatric patients and 66% of adult patients developed CKD stage 5 or died.[12]

Recently, we assessed the prognosis in aHUS patients who had PE (n=3) and PI (n=4) from the Turkish NRS. In this cohort, 71.4% of the patients (n=5) had complete hematological remission and an eGFR >90 mL/min/1.73m^2.[48] Khandelwal et al.[49] evaluated the efficacy and safety of 109 aHUS patients who received PE. Anti-CFH antibody was found to be an etiologic factor in 74 (67.9%) patients. Heterozygous mutations in *CFH* (n=4), *CFI* (n=3), and both *CFB* and *CFI* (n=1) were identified in the remaining

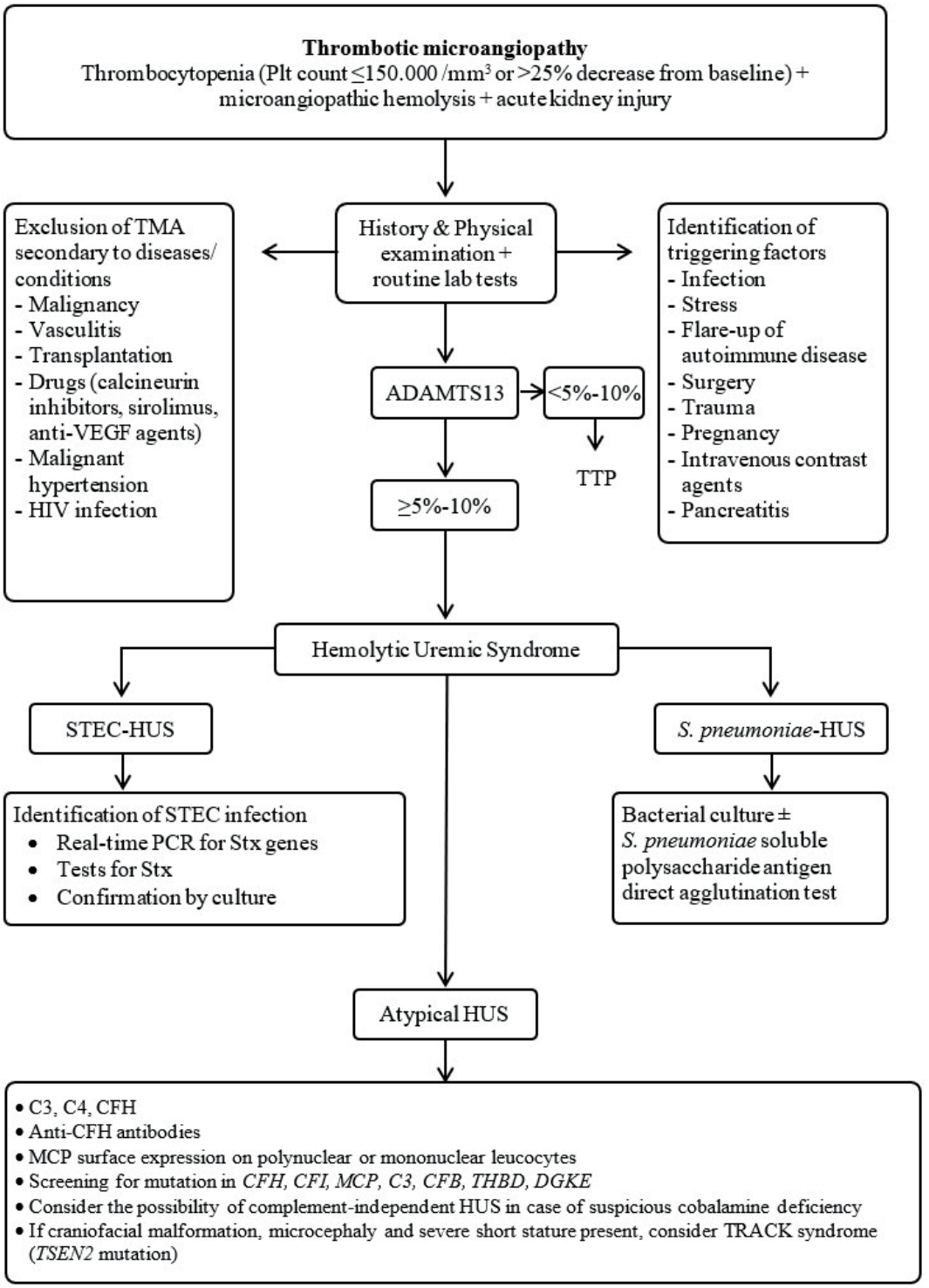


Fig. 2. Diagnostic algorithm and differential diagnosis for pediatric patients with TMA.

ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin motif type 1, member 13, C3: complement 3, C4: complement 4, CFB: complement factor B, *CFH*: complement factor H, *CFI*: complement factor I, *DGKE*: diaclyglycerol kinase epsilon, HIV: human immunodeficiency virus, HUS: hemolytic uremic syndrome, *MCP*: membrane cofactor protein, PCR: polymerase chain reaction, STEC: Shiga toxin producing *Escherichia coli*, Stx: Shiga-toxin, *THBD*: thrombomodulin, TMA: thrombotic microangiopathy, TRACK syndrome: *TSEN2* related atypical hemolytic uremic syndrome, craniofacial malformations, kidney failure, TTP: thrombotic thrombocytopenic purpura, VEGF: vascular endothelial growth factor

35 patients without anti-CFH antibodies. PE with immunosuppression (n=74), PE alone (n=19) and PE followed by PI (n=16) were applied during management. In addition, 92 (84.4%) patients underwent concomitant hemodialysis. Hematological remission was achieved in 73 (98.6%) patients with anti-CFH associated disease, whereas hematological remission occurred in 32 (91.4%) patients without anti-CFH associated disease. Dialysis independence by 1-month was achieved in 77.1% of the patients. Caprioli et al.[50] evaluated the genetics and clinical characteristics of HUS and concluded that remission was achieved in 67% of plasma-treated episodes in patients with a *CFH* mutation. Based on these results, we can conclude that plasma-based therapies might still be considered in selected patients, particularly in countries in which complement-blocking therapies are not readily available or the costs are not covered by health insurance.[48] Nonetheless, it should be kept in mind that catheter-related complications may occur in up to 31% of cases.[51]

Since 2009, the use of complement-blocking therapies (primarily eculizumab) has substantially changed the prognosis of children with aHUS. Eculizumab is a recombinant, humanized, monoclonal IgG type complement 5 (C5) antibody that blocks the cleavage of C5 into fragments and, thereby, the formation of MAC (Fig. 1). The half-life of eculizumab is 11 ± 3 days; therefore, maintenance treatment is administered every two weeks.[7] When treating aHUS, complement-blocking therapies should be the first-line treatment and should be initiated within the first 24 hours of diagnosis. If none of these therapeutics are available, PE using fresh-frozen plasma (FFP) may be an option. If PE is not available, PI should be the treatment of choice until complement-blocking therapy becomes available.[48] The results of genetic tests are not necessary for initiating complement-blocking therapies.

Monitoring the efficacy of eculizumab is another important issue in aHUS patients. Complement hemolytic activity can be monitored using the CH50 test, and the results should be <10% in aHUS patients receiving eculizumab. Measurement of the trough eculizumab level is another method for drug monitoring, but it is not available in most countries. When available, its target range (C_{min}) is recommended to be kept at >100 μg/mL.[52] In cases resistant to eculizumab despite administration at a therapeutic level, variants in the C5 binding site, increased elimination of eculizumab in urine, and the presence of other genetic causes, such as *DGKE* mutations, should be investigated.[43]

Given the fact that the risk of meningococcal disease significantly increases with eculizumab, patients should be vaccinated with A, C, W, and Y meningococcal conjugate vaccine as well as the B meningococcal vaccine before starting eculizumab therapy. In some countries, long-term antibiotic prophylaxis is recommended for aHUS patients for as long as they receive eculizumab treatment. If eculizumab treatment is initiated <2 weeks after vaccination due to urgent patient management, patients should receive antibiotic prophylaxis until 2 weeks after vaccination.[52]

The duration of eculizumab treatment in dialyzed patients is another important consideration. There are anecdotal case reports that describe the effect of eculizumab in patients under prolonged dialysis (>3 months). In these reports, the duration of dialysis before initiation of eculizumab varied between 3 and 6 months. After the initiation of eculizumab, the time to dialysis discontinuation was between 1 and 6 months.[53] Based on these findings, we recommend the maintenance of eculizumab in those patients without any mutation in alternative complement pathway genes for at least 3-6 months before concluding there is no benefit.

The risk of infection, high cost, and the burden of repeated infusions all contribute to the possibility of eculizumab discontinuation. On the other hand, the risk of relapse and subsequent kidney damage are arguments for not discontinuing eculizumab. Fakhouri et al.[54]

prospectively studied the effects of eculizumab discontinuation in 55 pediatric and adult aHUS patients, of whom 28 (51%) had rare variants in complement genes, most in *MCP*. During follow-up, 13 patients (23%) developed aHUS relapse, and multivariable analysis showed that female gender and the presence of a rare variant in a complement gene were linked with an increased risk of aHUS recurrence. Recently, we investigated eculizumab discontinuation in our patients from the Turkish NRS. Eculizumab treatment was discontinued in 18 (30.7%) out of 63 patients. Four patients (22.2%) experienced a recurrence; eculizumab was initiated immediately and complete remission was achieved.[55] Based on the above findings, we recommend that eculizumab discontinuation be considered during the remission period in patients without complement gene mutations, a history of relapse, or a family history of HUS, with close clinical and laboratory monitoring. In patients with *CD46* mutation, eculizumab discontinuation can be considered after 3 months of usage. The management principles for pediatric patients with TMA are shown in Fig. 3. Eculizumab has changed the poor destiny of aHUS. However, it requires intravenous infusions every two-three weeks. Therefore, a longer-acting C5 antibody, ravulizumab, was developed with the re-engineering of eculizumab. It requires infusions every 4-8 weeks. Its efficacy was shown both in eculizumab treated and eculizumab-naïve pediatric aHUS patients and has been approved in many countries.[56-58]

Research for specific treatment of aHUS is not confined to eculizumab and ravulizumab. There are many therapeutics in the pipeline that have the potential to be used in clinical practice (Table II).[59]

1.3.1. Anti-CFH antibody-associated HUS

Dragon-Durey et al.[60] studied aHUS patients that were treated with PE only and reported CKD in 39% and CKD stage 5 in 27% of the patients. Other cohorts that were treated with early PE and additional immunosuppressive drugs had a much more favorable prognosis.[61] Sinha et al.[62] evaluated the predictors of anti-CFH antibody-associated HUS. They concluded that antibody titer ≥8000 AU/ml, low C3 and time to PE≥17 days were independent predictors of adverse outcome on long term prognosis. They also studied the effects of PE combined with induction immunosuppression, which significantly decreased the risk of severe CKD and mortality, in comparison with PE alone. Mycophenolate mofetil (MMF) can also be used for maintenance treatment. Eculizumab is also effective for acute treatment, although its effect on lowering the CFH antibody has not been ascertained.[43] In light of existing literature data, we recommend PE, steroids, and such immunosuppressives as MMF and/or eculizumab for treatment. Additionally, we also recommend serial measurement of the anti-CFH antibody level on days 7-14, day 28 and every 3-6 months. Elevated titre (>1,500 AU/ml) during the first 12–24 months suggests an increased risk of relapse.[63]

1.3.2. Complement independent hemolytic uremic syndrome

The pathophysiological mechanisms of HUS are not restricted to the alternative complement system. Recent years have witnessed the definition of many complement independent mechanisms. Cobalamin C (CblC) defect-associated HUS is one of them. CblC defect is one of the most common inborn errors of metabolism and may present with HUS. CblC defect is most commonly seen in infants and neonates, and manifests as failure to thrive, hypotonia, seizures and microcephaly, delayed development, and hypertension. Prompt diagnosis and treatment with hydroxocobalamin may allow hematological and kidney recovery.[1]

Another complement independent HUS is caused by bi-allelic recessive mutations in *DGKE* (diaclyglycerol kinase epsilon). This gene was first identified in glomerular microangiopathy mimicking membranoproliferative glomerulonephritis

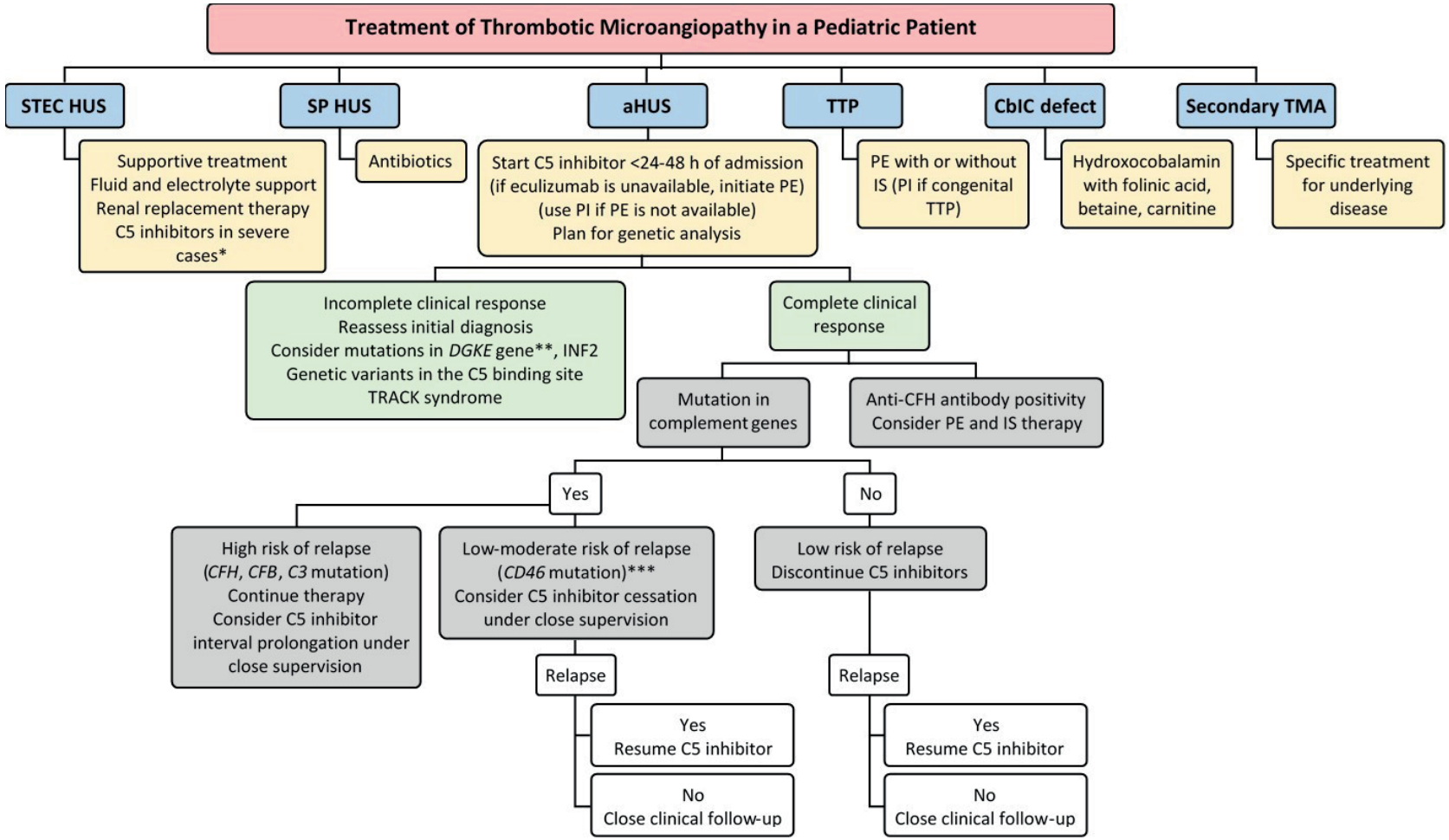


Fig. 3. Management principles for pediatric patients with different types of TMA.

*Although considered controversial, C5 inhibitors may be beneficial in cases that do not respond to supportive treatment in STEC HUS.
**If there is a *DGKE* mutation the benefit of C5 inhibitor therapy is uncertain.
***C5 inhibitor therapy can be withdrawn after 3-6 months if the clinical situation allows.
aHUS: atypical hemolytic uremic syndrome, C3: complement 3, C5: complement 5, CblC: cobalamin C, *CD46*: cluster of differentiation 46 (MCP: membrane cofactor protein), *CFB*: complement factor B, *CFH*: complement factor H, *DGKE*: diaclyglycerol kinase epsilon, HUS: hemolytic uremic syndrome, IS: immunosuppressive, PE: plasma exchange, PI: plasma infusion, PE: plasma exchange, SP HUS: *Streptococcus pneumoniae* associated HUS, STEC: Shiga toxin producing *Escherichia coli*, TMA: thrombotic microangiopathy, TRACK syndrome: *TSEN2* related atypical hemolytic uremic syndrome, craniofacial malformations, kidney failure, TTP: thrombotic thrombocytopenic purpura

Table II. Current aHUS drugs and those under development.

Therapeutics	Name of the drug	Drug class	Mechanism of action
Current therapeutics	Eculizumab	Monoclonal antibody, terminal complement inhibitor	Binds to C5 and prevents cleavage to C5a and C5b
	Ravulizumab		Prevents cleavage of C5 to C5a and C5b
	Nomacopan	C5aR1 antagonist	Inhibits C3a, C4a, and C5a protein function
	Avacopan	Recombinant protein derived from a tick C5 inhibitor	An oral antagonist of C5a receptors. Inhibits C5 and leukotriene B4
	Cemdisiran	Short sequences of interfering RNA	Matches mRNA for the C5 protein, with N-acetylgalactosamine
Biosimilars	ABP 959	Biosimilar to eculizumab	Binds to C5 and prevents cleavage to C5a and C5b
	Elizaria	Biosimilar to eculizumab	
Therapeutics under development	ALXN1720	Anti-C5 antibody	Binds to C5 protein and blocks its activation
	Avdoralimab	Anti-C5aR1 antibody	Blocks T-cell and natural killer cell activity via C5aR1suppression
	Crovalimab	Binds to a C5 epitope	Binds to C5b and prevents formation of the MAC complex. Crovalimab is a long-acting C5 inhibitor that could be administered subcutaneously.
	IFX-1	Targets C5a protein directly	Binds to C5a
	MAC Inhibitor HMR59	Promotes CD59 production	Enhances synthesis of CD59, which blocks C5b-9 formation
	Pozelimab	C5 antibody	Decreases hemolysis and the C5 level
	Tesidolumab	C5 monoclonal IgG1 antibody	Binds to C5, preventing its cleavage
	Zilucoplan	Binds to the C5b protein and the C5b part of C5	Inhibits C5b binding to C5 by binding to its C5 domain

aHUS: atypical hemolytic uremic syndrome, C3: complement 3, C4: complement 4, C5: complement 5, C5aR1: complement 5a receptor 1, IgG1: immunoglobulin 1, MAC: membrane attack complex, mRNA: messenger RNA

and was associated with aHUS thereafter.[9,10] The most important characteristics of *DGKE*-associated aHUS are significant proteinuria in addition to the classic triad of HUS and usually early onset of disease (i.e. less than 1 year of age).[9,52] INF2, a ubiquitously-expressed formin protein, regulates the actin cytoskeleton and related cell functions including secretory pathway by accelerating its polymerization and depolymerization. Challis et al.[64] identified a family in which proposita presented with aHUS unresponsive to eculizumab and her mother experienced TMA after kidney transplantation. Both patients had posttransplant Charcot-Marie-Tooth disease. Analyzing the Newcastle aHUS cohort, another family with a mutation of *INF2* was identified in which kidney transplantation has been associated with post-transplant TMA.[64]

Recently, a team led by the 2nd author of the present manuscript has identified a new complement independent, syndromic form of aHUS (*TSEN2* Related Atypical hemolytic uremic syndrome, Craniofacial malformations, Kidney Failure; TRACK syndrome) that arises from pre-tRNA splicing defect.[11] In this syndrome, an intronic mutation that disrupts normal splicing of *TSEN2* (tRNA splicing endonuclease 2) has been associated with aHUS and distinct craniofacial abnormalities including microcephaly, adenohypophysial hypoplasia and associated growth retardation,

cone-shaped and sparse teeth, deeply set eyes, and long philtrum in 6 children.[11] As expected, none of the patients responded to eculizumab treatment. Three patients died at the time of writing the original article. One patient is 11 years old now and is still being followed up with peritoneal dialysis (PD). Another patient was transplanted from a deceased donor when she was 11 years old. She received a short period of eculizumab treatment during the post-transplantation period, which was stopped after a genetic diagnosis and post-transplant aHUS was not observed. She is now 14 years old with normal graft functions (serum creatinine 0.33 mg/dL). Another patient was also transplanted when he was 7 years old. He experienced a biopsy proven acute T cell mediated rejection at post-transplant 9th month and BKV associated nephropathy without evidence of TMA. Modification of the immunosuppressive regimen resulted in rapid improvement of graft functions. He never experienced a post-transplant aHUS. He is 12.5 years old now with a normal functioning graft (serum creatinine of 0.32 mg/dl). During the identification of underlying genetic abnormalities in these children, whole exome sequencing (WES) method was applied to all individuals in the index family. A stringent filtering strategy ended up with the identification of an intronic variant, that is very close to the splice site. Subsequent studies confirmed that this intronic variant disrupted normal splicing, with the presence of 3 different transcripts: (i) the retention of a normally spliced transcript, (ii) transcript in which exon 10 and correspondingly many evolutionary conserved aminoacids are skipped, and (iii) transcript that contains two extra amino acids. Accordingly, bulk RNA sequencing also showed five abnormal tRNAs confirming impaired TSEN2 enzymatic function in all affected individuals that are absent in healthy individuals. This finding also supported the hypothesis that the tRNA inventory necessary for normal life has been changed in the cells.

Future directions

In the last twenty-year period, there have been many breathtaking advances in the treatment of aHUS. Among them, eculizumab has revolutionized the management of patients but put new questions on the table. Eculizumab discontinuation is possible in selected patients. Patients in remission may have normal laboratory values in terms of TMA, however, the extent of disease activity on the kidneys is still unknown. Certain needs are reliable biomarkers that predict early relapses and that are useful in monitoring disease activity. Besides eculizumab, there are also other C5 antibodies and biosimilars for the treatment of aHUS. The safety and efficacy of these molecules in pediatric aHUS patients will be important research subjects in the future. In addition, more individualized treatment options, such as CFH administration in those patients with CFH deficiency instead of blocking the complement system, are expected. The definition of genetic abnormalities which are unrelated to the alternative complement pathway (like DGKE, cblC, etc) will also lead to the development of personalized treatment options for this group of patients. As more genetic abnormalities are identified, more insight into TMA pathogenesis will become possible.

Conclusion

In conclusion, HUS still stands for a challenging clinical condition despite recent developments leading to a better understanding of the patho-mechanisms of the disease that result in more effective therapeutic approaches. Nevertheless, these can explain a fraction of patients, which strongly suggests that many yet unidentified mechanisms may still be present.

Acknowledgement

The authors acknowledge the enrolling clinicians, data coordinators at individual enrolling centers including (with alphabetical

order of the surnames); Harika Alpay (Marmara University, Faculty of Medicine), Özlem Aydoğ (19 Mayıs University, Faculty of Medicine), Elif Bahat (Karadeniz Technical University, Faculty of Medicine), Esra Baskın (Ankara Baskent University Faculty of Medicine), Aysun Karabay Bayazıt (Cukurova University, Faculty of Medicine), Nur Canpolat (İstanbul University, Cerrahpaşa Faculty of Medicine), Nilgün Çakar (Ankara University, Faculty of Medicine), Evrim Kargın Çakıcı (Dr. Sami Ulus Gynecology Obstetrics and Child Health and Diseases Training and Research Hospital), Ali Delibaş (Mersin University, Faculty of Medicine), İsmail Dursun (Erciyes University, Faculty of Medicine), Mukaddes Kalyoncu (Karadeniz Technical University, Faculty of Medicine), Aslı Kavaz (Osmangazi University, Faculty of Medicine), Beltinge Demircioğlu Kılıç (Gaziantep University, Faculty of Medicine), Sare Gülfem Özlü (Ankara City Hospital), Alper Soylu (Dokuz Eylül University, Faculty of Medicine), Rezan Topaloğlu (Hacettepe University, Faculty of Medicine), Fatoş Yalçınkaya (Ankara University, Faculty of Medicine), Alev Yılmaz (İstanbul University, İstanbul Faculty of Medicine), Selçuk Yüksel (Pamukkale University, Faculty of Medicine).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: BG, FÖ, OS; data collection: BG, KF, ZBÖ, FÖ; analysis and interpretation of results: BG, KF, ZBÖ, FÖ, OS; draft manuscript preparation: BG, FÖ; All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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