REVIEW ARTICLE

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# The Challenges in Diagnosis and Management of Acquired Thrombotic Thrombocytopenic Purpura: Consensus Report from Three Gulf Countries

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**ABSTRACT**

Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare hematological emergency characterized by microangiopathic hemolytic anemia, thrombocytopenia, fever, and multiorgan failure due to autoimmune-mediated deficiency in ADAMTS-13 activity. Currently, plasma exchange, with or without steroids, is the frontline option for the management of aTTP. The treatment should be started promptly once the disorder is clinically suspected. Besides, immunomodulators were studied in patients with aTTP to achieve stable remission and reduce the risk of relapse in patients with suboptimal response to plasma exchange; however, clinical trials showed equivocal results. Published data on early diagnosis, referral, and treatment patterns of aTTP patients in the member nations of the Arabian Gulf Cooperation Council (GCC) are still lacking. Therefore, the present consensus report aimed to present an overview of aTTP situation in GCC by bringing together a panel of experts from three GCC nations, to share their views on current trends and practices regarding aTTP. The experts discussed challenges including the lack of reliable data regarding the incidence of aTTP in GCC and delayed results of ADAMTS-13 activity testing. Limited patient access to tertiary centers and low level of awareness about the aTTP clinical spectrum among general practitioners are other challenges. The experts agreed that there is a need for national and regional consensus regarding the diagnosis and treatment of aTTP in the Gulf region.

Thrombotic thrombocytopenic purpura (TTP) was first described in early 1920s in an adolescent female with severe thrombocytopenia and microangiopathic hemolytic anemia (MHA). TTP is now understood to be a life-threatening hematological disorder with a relatively high mortality rate.[1] The disorder is characterized by an acute attack of widespread thrombosis of terminal arterioles and capillaries, in combination with MHA, fever, thrombocytopenia, and eventually, organ failure.[2]

While the exact pathogenic mechanisms underlying the development of TTP have not been fully elucidated yet, previous experiments demonstrated that it develops secondarily to critical deficiency in ADAMTS-13 activity.[3] The vast majority of TTP cases occur due to the presence of acquired autoantibodies that inhibit the cleavage activity of ADAMTS-13, leading to acquired TTP (aTTP).[1] Despite its rarity, aTTP represents a challenging situation for the treating hematologist, with reported mortality rates of 10%–20% in patients receiving aggressive treatment, and a nearly 90% mortality rate in untreated cases.[4–7]

Currently, plasma exchange with or without steroids, is the frontline option for the management of aTTP that should be started promptly once the disorder is clinically suspected.[8] Besides, immunomodulators, such as rituximab and vincristine, were studied in patients with aTTP to achieve stable remission and reduce the risk of relapse in patients with suboptimal response to plasma exchange; however, clinical trials showed equivocal results.[9] Recently, caplacizumab, an inhibitor of von Willebrand factor (VWF)-glycoprotein 1b

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interaction, has demonstrated promising efficacy and well-tolerable safety profile in the management of acute episodes of aTTP.[10]

In the Middle East, including the Gulf Cooperation Council (GCC) countries, limited data are available regarding the epidemiology and clinical presentation of aTTP. In addition, published data on early diagnosis, referral, and treatment patterns of aTTP patients in the GCC countries are still lacking. Therefore, the present consensus report aimed to present an overview of aTTP situation in the GCC countries by bringing together a panel of experts from three GCC countries to share their views on current trends and practices regarding aTTP.

## *Evidence-based discussion and consensus*

The present consensus report was developed as part of the GCC experts' efforts to explore the epidemiology of aTTP in the GCC countries, as well as local challenges in aTTP awareness and diagnosis among hematologists and non-hematologists. Moreover, it aimed to explore the current local aTTP management practices and its unmet needs.

Accordingly, on 7 August 2020 a virtual meeting was conducted involving nine consultant hematologists from six different institutions in three GCC countries: three experts from Kuwait, two from Oman, and four from the UAE. They shared and discussed the prevailing protocols and practices in different healthcare sectors across the GCC countries. The consensus statement in each aspect was reached by the agreement of all attendants. In case of any disagreement on any of the listed statements, a second round of discussion was held to modify the statement and reach a consensus. The following is a summary of the information shared in the meeting, followed by the final consensus.

## *Epidemiology of aTTP*

Thrombotic microangiopathies (TMAs) are rare group of hematological disorders with a reported cumulative incidence rate of 10 cases per million population per year.[11] aTTP is an ischemic variant of TMAs that accounts for nearly 14% of TMAs in adults.[12] According to previous epidemiological figures, the global incidence of aTTP is roughly three cases per million population per year and the global prevalence is 10 cases per million population per year.[1] In the US, the initial incidences of TTP plus hemolytic uremic syndrome were reported to be 3.7 and 3.8 cases per million population annually, according to data from death certificates[13] and health insurance claims,[14] respectively. In another report from Canada, the age-standardized incidence rate of TTP was reported to be 3.8 cases per million population per year.[14]

In Europe, similar numbers were reported regarding the incidence and prevalence of aTTP. A recently published national registry from France demonstrated that the annual prevalence of TTP was 13 cases per million population.[11] According to Miller et al,[14] report the incidence of TTP in the UK was 1.2 cases per million population per year. The incidence of aTTP episodes was 2.1 cases per million population per year as per a systematic review that covered eight centers from Germany.[7] Concerning epidemiological characteristics of affected patients, aTTP mainly affects women in their third to fifth decades; while pediatric aTTP accounts for nearly 10% of the total cases.[1]

We could not identify any published report that addressed the incidence and prevalence of TTP in the GCC countries. However, a few studies describe the epidemiological and clinical features of TTP patients from the Gulf region. A 2016 study from Saudi Arabia described 24 TTP patients who were treated at King Fahad Medical City from October 2006 to April 2015. Their mean age was 33.5±13.9 years, and most were female. Nearly 90% of the cases had neurological involvements, though the classic pentad features of TTP were present in only two.[15] A more recent retrospective study from Oman described 38 TTP patients with a mean age of onset of 36 years. Two-thirds (66%) were female and nearly 59% had neurological manifestations.[16] In 2011, Al-Awadhi et al,[17] identified four TTP cases among 41 patients with different thrombocytopenic disorders from Kuwait.

## Consensus statement

The experts demonstrated that aTTP was prevalent at the rate of one per million population per year in Oman, three to six in UAE, and four in Kuwait. In all GCC countries, very few cases of overall mortality, exacerbation, or relapses were reported; except for Oman, where higher mortality rates were observed due to late presentations. Relapse rates were very low in Oman and Kuwait and higher (10%–20%) in Dubai hospitals. Nonetheless, there are no reliable registry data regarding the incidence of aTTP in

the GCC countries. While the epidemiological characteristics of the aTTP patients in the Gulf region appear to be similar to other parts of the world, the experts raised concerns about the generalizability of the published retrospective studies, which were restricted to patients from one institution or one district of the Gulf region. The panel recommended conducting future multicenter studies to assess the real epidemiology of aTTP in the GCC countries.

## *Clinical spectrum and diagnostic challenges*

Historically, a pentad comprising thrombocytopenia, MHA, fever, central nervous system involvement, and renal insufficiency was considered as a classic phenotype of aTTP. However, this pentad being present in < 10% of aTTP patients, the current guidelines discourage its use to clinically identify aTTP.[18–20] In rare cases atypical clinical features at initial presentation may be later diagnosed as TTP. Atypical TTP patients usually present with thrombotic events—such as acute coronary syndrome, stroke, scotomas or other visual disturbances, and acute pancreatitis—before they develop MHA and thrombocytopenia.[21]

The clinical diagnosis of aTTP is challenging due to the extensive overlap between its classic features and various clinical syndromes. The main differential diagnosis of aTTP includes other TMAs, hemolytic uremic syndrome, other causes of thrombocytopenia and hemolytic anemia, Evans syndrome, and autoimmune diseases with ischemic features.[22] Correct identification of aTTP is critical as many of the above-mentioned conditions do not respond to plasma exchange and other treatment modalities are usually required.[22,23] The available literature from GCC countries exhibited a heterogeneous spectrum of clinical manifestations of TTP among the affected patients. Reports from Saudi Arabia demonstrated that 42% had renal manifestations and 21% had cardiac manifestations.[15] In Oman, 59% of TTP patients were reported to have neurological involvement.[16]

## *Diagnostic algorithm*

### 1. Laboratory evaluation

Though routine laboratory evaluations do not yield results specific for TTP, they are usually used for the calculation of clinical scores. Typical features include evidence of hemolytic anemia, thrombocytopenia, and reticulocytosis with undetectable haptoglobin level. Laboratory evaluation may also reveal high lactate dehydrogenase and cardiac troponin levels.[24,25] The presence of schistocytes on the blood smear is a hallmark of MHA. The coagulation profile of the TTP patients is usually normal and Coombs' test is negative in aTTP. Renal examination may reveal proteinuria, hematuria, and to a lesser extent, elevated serum creatinine and urea levels.[9] In up to 10% of TTP patients, electrocardiogram changes may be detected.[24] Rarely, a biopsy may be needed to study histological changes in the affected organs.[26]

### 2. Clinical scores

Several clinical scores have been validated for the prediction of TTP and severe ADAMTS-13 deficiency. Bendapudi et al,[27] developed the PLASMIC score in 2017 that utilizes a combination of clinical and laboratory parameters to predict severe ADAMTS-13 deficiency. The PLASMIC score incorporates seven clinical/laboratory parameters and has exhibited superior diagnostic utility to predict TTP than the commonly used clinical assessment methods. Further, the PLASMIC score's high sensitivity and specificity in predicting TTP and severe ADAMTS-13 deficiency have been validated by several retrospective studies.[28,29]

### 3. Assessment of ADAMTS-13 activity

The assessment of ADAMTS-13 activity is the reference test for the diagnosis of TTP. A plasma ADAMTS-13 activity level of < 10% is commonly used by many centers as a cutoff value for the diagnosis of TTP in patients with no identifiable cause of MHA.[1] Many assays are currently available for assessment of ADAMTS-13 activity, which are mainly based on measuring the quantity of degraded VWF substrate in the plasma or serum of the affected patients.[30] Two commonly used functional assays are collagen-binding activity and fluorescence resonance energy transfer assay using a truncated, VWF synthetic 73-amino-acid peptide-based assays.[9]

### 4. ADAMTS-13 autoantibodies assays

ADAMTS-13 exerts a proteolytic activity on ultra-large VWF limiting its adhesion to platelets;[31] hence, a significant decline in ADAMTS-13 activity can lead to excessive accumulation of ultra-large VWF, platelets activation and aggregation, microthrombi, and eventually the cardinal pathogenic features of TTP.[9] Serum anti-ADAMTS-13 antibodies

can be detected in patients with severe ADAMTS-13 deficiency using either functional or immunochemical assays.[32,33] Although functional assays have the advantage of accurate detection of autoantibodies, their practical utility is limited by high technical demands and is time-consuming.[9] On the other hand, immunochemical assays, despite their demonstrably lower reliability and accuracy, are simple and rapid and thus useful in local emergency settings.[9,33,34]

#### 5. Genetic testing

Congenital TTP is a very rare autosomal-recessive disorder with a prevalence rate of 0.5–4 per million population.[35] The diagnosis of congenital TTP is based mainly on the absence of anti-ADAMTS-13 antibodies in patients with severe ADAMTS-13 deficiency.[31] Recently, molecular analysis was introduced to confirm the diagnosis of congenital TTP, identify the disease genotype, and screen sibling and first-degree relatives.[8] Knowing the disease phenotype may have clinical implications as previous experiments demonstrated a significant association between mutation location and the degree of disease severity.[36]

#### 6. Diagnostic challenges

Hematologists usually face several diagnostic challenges when TTP patients present for the first time. Although the clinical diagnosis of aTTP is challenging due to the extensive overlap between its classic features and various other clinical syndromes. The assessment of ADAMTS-13 activity is usually not available in emergency settings owing to technical difficulties and time-consuming procedures.[9,22] Thus, clinical guidelines recommend the initiation of plasma exchange based on clinical suspicion without waiting for the results of the ADAMTS-13 investigation. However, ADAMTS-13 investigation remains crucial to confirm TTP diagnosis.[22] Also, the presence of severe ADAMTS-13 deficiency is not sufficient to decide whether or not plasma exchange should be initiated in patients with acute episodes.[23]

#### Consensus statement

The panel of experts highlighted that the diagnosis of aTTP is currently challenging in the GCC countries. ADAMTS-13 test is unavailable in most institutions and is usually outsourced, except for the Tawam Alain hospital in UAE. However, the experts agreed that the test remains of limited utility as the results are often received 10–14 days after the presentation. As such, the experts reported their reliance on the clinical presentation and surrogate laboratory parameters for the diagnosis and treatment of patients. They also agreed that the PLASMIC score is predominately used for the prediction of thrombotic microangiopathy among patients with clinically atypical aTTP symptoms.

The experts listed several diagnostic challenges for aTTP. Many patients, especially those from remote areas, do not have access to tertiary, well-equipped centers. Another challenge is the availability of intensive care unit (ICU) beds to admit emergency aTTP patients having acute episodes. The emergency physicians' awareness about the signs and symptoms of TMAs may be limited in some GCC medical facilities, leading to delayed referrals and late initiation of plasma exchange. However, experts from Oman stated that physician awareness about aTTP, its management, and its urgency had improved recently, particularly at the emergency departments and ICUs. The panel recommended awareness campaigns for general practitioners and ICU physicians to improve their skills for early recognition of TMAs.

### *Management of aTTP in the GCC countries*

As previously mentioned, early identification and prompt management represent the cornerstone for a favorable prognosis of patients' TTP. Such patients are typically managed in ICU for continuous monitoring and evaluation.

#### 1. Therapeutic plasma exchange

Since the 1920s, blood transfusion was the only modality acknowledged effective for the management of TTP.[37] Subsequently, plasma was identified as the active blood component that drives the clinical response to transfusion.[38] Since then, a cumulative body of evidence has supported the tolerability and efficacy of plasma exchange in TTP patients.[39–41] Various plasma preparations are available for exchange with relatively similar efficacy.[42] Some centers prefer cryosupernatant plasma with its theoretical superiority over other preparations, being free of large VWF substrates.[43] However, the current evidence equivocally endorses the superiority of cryosupernatant plasma.[44] Plasma

exchange is applied daily until clinical recovery is achieved. The clinical recovery is usually defined as recovery of platelet count to the normal levels, resolution of hemolysis, and recovery of any ischemic organ manifestations.[3] Usually, 1.5-fold patient plasma volume exchange is administered during the first procedures, and 1.0-fold thereafter.[9]

### 2. Steroids

Many centers recommend the use of high-dose methylprednisolone as an adjuvant to plasma exchange owing to the autoimmune nature of aTTP.[45] Although the currently published evidence supporting the use of steroids is of low quality, the last release of the International Society on Thrombosis and Hemostasis (ISTH) guideline recommends the combination of corticosteroids and plasma exchange for the management of acute episodes of aTTP.[46]

### 3. Immunomodulators

Immunomodulators can be offered to patients who respond suboptimally to daily plasma exchange. Previous retrospective studies demonstrated that rituximab, a monoclonal antibody against CD20, exhibited a high remission rate in refractory cases to plasma exchange.[47,48] These findings were further supported by subsequent prospective studies, in which rituximab was administrated for two to three weeks at a dose of 375 mg/m$^2$.[49,50] In the abovementioned studies, rituximab was associated with a minimum risk of relapse and demonstrated a well-tolerable safety profile.[9] The 2020 ISTH guideline recommends the addition of rituximab to the standard regimen. However, the low level of evidence supporting the addition of rituximab and the fact that many aTTP patients did not develop relapses on the standard regimen, the ISTH panel stated that the addition of rituximab in local settings should be guided by cost-effectiveness analysis and the presence of comorbid autoimmune disease.[46] In patients with relapses, the ISTH guideline recommends the addition of corticosteroid and rituximab to plasma exchange; however, special attention should be given to possible adverse events from repeated use of high-dose corticosteroids.[46]

Vincristine was studied in many retrospective studies in refractory patients, and achieved acceptable remission rates.[51] Previous reports exhibited high efficacy of cyclosporine A in patients with suboptimal response to plasma exchange.[52] Thus, the use of vincristine and cyclosporine A should be reserved for severe cases that respond poorly response to other lines of treatment.[9]

### 4. Novel Therapeutics

Recurrence is a major concern in aTTP, as patients with persistent ADAMTS-13 deficiency can develop life-threatening recurrence, which can occur as late as 20 years after an acute aTTP episode.[5,53] Recent studies have investigated the efficacy and clinical utility of several novel drugs for the management of refractory TTP. Therapeutics that target platelet adhesion to ultra-large VWF, such as N-acetylcysteine, represent promising agents for patients with TTP.[54] The use of recombinant ADAMTS-13 has emerged as another potential agent in the therapeutic arsenal against TTP, which acts by overriding autoantibodies and restoring normal ADAMTS-13 activity.[55] A previous case report reported a notable efficacy of bortezomib in a patient with refractory TTP.[56] Nonetheless, the clinical application of these agents is still limited by the lack of late-stage clinical trials confirming the efficacy and tolerability of these novel therapeutics.

Caplacizumab is a humanized, bivalent, nanobody that inhibits the interaction between the A1 domain of VWF and 1b receptor of the platelet.[57] Recently, caplacizumab demonstrated promising efficacy and a well-tolerable safety profile in the management of acute episodes of aTTP.[10] In the initial phase II trial, the addition of subcutaneous caplacizumab (10 mg daily) to the standard plasma exchange led to a shorter delay until clinical response and lower incidences of exacerbations, refractory disease, and major thromboembolic events, when compared to plasma exchange alone.[9] Such findings led to the conduction of phase 3 HERCULES trial where the treatment with caplacizumab was associated with faster normalization of the platelet count; a lower incidence of a composite of TTP-related death, recurrence of TTP, or a thromboembolic event during the treatment period; and a lower rate of recurrence of TTP during the trial than placebo.[58] Thus, the 2020 ISTH guideline recommends the use of caplacizumab in patients with acute episodes and patients experiencing relapses; under the supervision of an experienced hematologist. These guidelines recommended that corticosteroids and rituximab should be continued after the discontinuation of caplacizumab to reduce the risk of exacerbation.[46]

### 5. Therapeutics challenges and outcomes of aTTP in the GCC countries

Several challenges can manifest during the management of aTTP. Plasma exchange, the frontline option for aTTP patients, can trigger numerous complications.[23] The high rates of relapse and long-term sequelae are other therapeutic challenges that mandate close monitoring and long-term follow-up of the affected patients. The unavailability of timely ADAMTS-13 results challenged the use of plasma exchange prophylaxis as well.[46] Limited data are available concerning treatment protocols and outcomes of aTTP patients from the GCC countries. In Iqbal et al report,[15] the treatment protocol consisted mainly of daily plasma exchange and adjuvant corticosteroids, while nearly half of the patients received rituximab due to the development of refractory disease. Complete remission was achieved in 87.5% of the patients and the mortality rate was 16.7% after a median follow-up duration of two months.[15] In the retrospective study from Oman, all patients received daily plasma exchange and adjuvant corticosteroids, while 19 cases needed additional rituximab and 10 cases needed cyclosporin. The authors reported a survival rate of 97% and a relapse rate of 17% following a mean duration of 10 years.[16]

#### Consensus statement

The experts stated that the ISTH-2020 recommendations are already applied in regular practice in Kuwait, the UAE, and Oman. Concerning aTTP management protocol, all the experts agreed that aTTP treatment is being initiated in all three countries before receiving the results of the ADAMTS-13 assay. They also reported that aTTP treatment mainly consisted of plasma exchange and corticosteroids, with rituximab sometimes added as the first line immunomodulator; however, long-term immunosuppressive therapy is not used except in cases with underlying etiology for TTP (e.g., systemic lupus erythematosus). Patients with recurrent aTTP are usually treated with the same initial administered therapy in combination with rituximab. It was noted that mycophenolate mofetil could be considered for the long-term use of infrequently relapsing patients. The use of prophylactic treatment for aTTP patients remained debatable as the risk of relapse in the GCC countries was reported to be relatively low. It was also agreed that the unavailability of timely ADAMTS-13 results challenged the use of prophylaxis.

Concerning patients' access to aTTP treatment, experts from the UAE stated that the active treatment and follow-up of any patient with life-threatening conditions, irrespective of nationality, were warranted and fully covered by the state or supported by local charities. In Kuwait, the same standard of care is provided to all patients; however, only a few non-Kuwaiti patients are eligible for free treatments for certain conditions such as rituximab. In Oman, non-national patients with life-threatening conditions are treated immediately and fully by the healthcare system, albeit without coverage of cost.

The experts agreed that in GCC countries, many practical challenges are present due to the low number of aTTP patients and the significant delay in obtaining ADAMTS-13 results. They recognized the use of caplacizumab as a first-line agent to reduce aTTP relapse rates, mortality, and complications. They also acknowledged that caplacizumab could help in reducing the risk of long-term complications of aTTP, such as suicide, depression, and renal problems, rendering this line of treatment cost-effective in the long term.

## Conclusion

The GCC is a council of six countries in the Middle East and North Africa region that share many cultural and regional similarities. Over the past few decades, all members of the GCC have grown into high-income states with commensurate advances in their healthcare and health research sectors.[59] Despite advanced facilities, information remains scarce regarding the epidemiology, management, and unmet needs of aTTP in the region. The present consensus aimed to bring insights from experts in the GCC countries regarding the epidemiology of aTTP, as well as to meet the local challenges in the diagnosis and management of this condition.

To date, there are no reliable data regarding the incidence of aTTP in GCC countries. A few isolated retrospective studies are available albeit limited to patients from one institution or one district of the Gulf region. These seem to suggest that the epidemiological characteristics of the aTTP patients in the Gulf region might be similar to other parts of the world. However, experts in the current discussion

raised concerns about the generalizability of these studies and recommended future multicenter studies that bring out the real epidemiology of aTTP in GCC countries.

Although ADAMTS-13 activity measurement is essential to accurately diagnose TTP, most healthcare facilities in the region do not have ready access to ADAMT-13 assay equipment. Consequently, many samples are sent abroad for testing. Thus, the time taken from first presentation and referral to diagnosis of TTP may stretch to weeks, leading to a high possibility of ischemic complications and death. As early identification and prompt management are required for a favorable prognosis of patients' TTP, the experts agreed that aTTP treatment should start without waiting for the results of the ADAMTS-13 assay. It was also reported that this is already being practiced in all three countries. Finally, the panel members recommended the development of educational and quality improvement programs to improve physicians' knowledge and awareness about TTP.

The experts acknowledged the need for national and regional consensus regarding the diagnosis and prompt treatment of aTTP in the Gulf region. The consensus should be comprehensive and involve all specialties and key players that deal with aTTP in order to share their ideas and suggestions. The consensus meeting can be conducted in the form of a national TTP day. Another interesting idea was to develop a national day for rare diseases where experts from different specialties get together and share information on their prevalence, diagnosis, and management.

*Disclosure*

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