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

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Abstract

Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare hematological emergency that is characterized by microangiopathic hemolytic anemia (MHA), 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 of management of aTTP that 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. in addition, published data on early diagnosis, referral, and treatment patterns of aTTP patients in Gulf Council Countries (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 to share their views on current trends and practice 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 patients' 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 Gulf region.

Keywords: Acquired thrombotic thrombocytopenic purpura; thrombosis; Microangiopathic hemolytic anemia; Gulf region.

Introduction

Since its first description in the early 1920s in a 16-year-old female with severe thrombocytopenia and microangiopathic hemolytic anemia (MHA), thrombotic thrombocytopenic purpura (TTP) has emerged as 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 TTP develops secondarily to critical deficiency in ADAMTS13 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 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 of 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 vWF-glycoprotein 1b interaction, has demonstrated promising efficacy and well-tolerable safety profile in the management of acute episodes of aTTP.[10]

In the Middle East, including 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 GCC countries are still lacking. Therefore, the present consensus report aimed to present an overview of aTTP situation in GCC countries by bringing together a panel of experts from three GCC countries to share their views on current trends and practice regarding aTTP.

Consensus Development and Objectives

The present consensus report was developed as a 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 and its unmet needs. One meeting was planned and engaged nine consultant hematologists from six different institutions at three GCC countries: Kuwait (number of experts = 3), Oman (number of experts = 2), and United Arab Emirates (UAE; number of experts = 4). The virtual meeting was held on August 7, 2020. The panel of experts represented the current practice 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.

Epidemiology of aTTP in GCC countries

Thrombotic microangiopathies are a rare group of hematological disorders with a reported cumulative incidence rate of ten cases per million population per year.[11] aTTP is an ischemic variant of thrombotic microangiopathies that accounts for nearly 14% of thrombotic microangiopathies 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 United States, the initial incidences of TTP plus hemolytic uremic syndrome (HUS) 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 was 1.2 cases per million population per year in the UK. The incidence of aTTP episodes was shown to be 2.1 cases per million population per year in 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]

In the Gulf region, limited data are available regarding the epidemiology of aTTP. We could not identify any published reports that address the incidence and prevalence of TTP in GCC countries; however, the currently published data describe the epidemiological and clinical features of TTP patients from the Gulf region. In a 2016 study from Saudi Arabia, a total of 24 patients with TTP treated at King Fahad Medical City through the period from October 2006 to April 2015 were described. The majority of the patients were females with a mean age of 33.5 ± 13.9 years old. Nearly 90% of the patients had neurological involvements; while the classic pentad features of TTP were present in two cases only.[15] In a more recent retrospective study from Oman, a total of 38 TTP patients with a mean age of onset of 36 years old were described.

Of them, 66% of the patients were females, and nearly 59% had neurological manifestations.[16] In 2011, Al-Awadhi et al.,[17] described 41 patients with different thrombocytopenic disorders from Kuwait; of them, four patients had TTP.

Consensus Statement: The experts demonstrated that the incidence of aTTP was relatively low in Oman (one case per million population per year) and the UAE (three to six cases per million population per year); however, the experts reported that the incidence of aTTP is notably higher in Kuwait (4 cases per million population per year). 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 patient presentation. Relapse rates were very low in Oman and Kuwait; on the other hand, the relapse rates were reported to vary between 10 and 20% in Dubai hospitals. Nonetheless, there are no reliable registry data regarding the incidence of aTTP in 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; the published reports included patients from one institution or one district of the Gulf region. The panel recommended the conduction of future multicenter studies to reflect the real epidemiology of aTTP in GCC countries.

Clinical Spectrum and Diagnostic Challenges

Historically, a pentad of thrombocytopenia, MHA, fever, central nervous system involvement, and renal insufficiency was considered as a classic phenotype of aTTP; nonetheless, the current guidelines discourage the use of this classic pentad to clinically identify aTTP since the aTTP pentad is present in less than 10% of the patients with aTTP.[18–20] Rarely, patients with aTTP may present with atypical clinical features at initial presentation, which are later diagnosed

as TTP. In the case of atypical TTP, patients usually present with thrombotic events before the development of MHA and thrombocytopenia, such thrombotic events include acute coronary syndrome, stroke, scotomas, other visual disturbance, and acute pancreatitis.[21]

The clinical diagnosis of aTTP is challenging due to the extensive overlap between classic features of aTTP and various clinical syndromes. The main differential diagnosis of aTTP includes other thrombotic microangiopathies, HUS, 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 current literature from GCC countries exhibited heterogeneous clinical spectrums of TTP amongst the affected patients in the region. 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

The findings of routine laboratory evaluation are not specific for TTP and are usually used for calculation of clinical scores. The typical features include evidence of hemolytic anemia, thrombocytopenia, and reticulocytosis with undetectable haptoglobin level. Besides, laboratory evaluation may reveal high lactate dehydrogenase (LDH) 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 the TTP patients, electrocardiogram changes may be detected.[24] A biopsy is rarely needed to study histological changes in 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 score incorporates seven clinical/laboratory parameters and exhibited superior diagnostic utility than the commonly used clinical assessment methods for the prediction of TTP. The PLASMIC score was further validated by many retrospective studies that demonstrated high sensitivity and specificity of the score for prediction of TTP and severe ADAMTS-13 deficiency.[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 less than 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 functional assays are commonly used for the detection of ADAMTS-13 activity: collagen-binding activity and FRETS-VWF73-based assays.[9]

4. ADAMTS-13 Autoantibodies Assays

ADAMTS-13 exerts a proteolytic activity on ultra-large Von Willebrand Factor (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[32] or immunochemical assays.[33] Although functional assays have the advantage of accurate detection of autoantibodies, their use are limited by high technical demands and being time-consuming.[9] On the other hand, immunochemical assays are simple and rapid methods that can be used in local emergency settings; however, previous reports demonstrated lower reliability and accuracy of immunochemical assays, compared to the standard functional assays.[9,33,34]

5. Genetic Testing

Congenital TTP is a very rare autosomal-recessive disorder with a prevalence rate of 0.05-0.4 per 100,000 population.[35] The diagnosis of congenital TTP is based mainly on the absence of anti-ADAMTS-13 antibody 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] The identification of 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 clinical syndromes. The assessment of ADAMTS-13 activity is usually not available in the emergency setting, 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 plasma exchange should be initiated or not in patients with acute episodes.[23]

Consensus Statement: The panel of experts highlighted that the diagnosis of aTTP is challenging in 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 stated that the test remains of limited utility as the results are often received 10 to 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 remains predominately used for the prediction of thrombotic microangiopathy among patients with clinically atypical aTTP symptoms.

On the other hand, the experts listed several diagnostic challenges. Many patients, especially those from remote areas, do not have access to tertiary, well-equipped, centers. In addition, the availability of ICU beds for hospitalization of aTTP during acute episodes is another challenge. The emergency physicians' awareness about the signs and symptoms of thrombotic microangiopathies may be limited in some centers in GCC countries, which, in return, can lead to delayed referrals and initiation of plasma exchange. However, experts from Oman stated that physician awareness about aTTP, its management, and its urgency had improved recently, particularly in the ICU or the emergency department. The panel recommended awareness campaigns for general practitioners and ICU physicians to improve early recognition of thrombotic microangiopathies.

Management of aTTP in GCC countries

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

1. Therapeutic Plasma Exchange

Blood transfusion has been the only acknowledged effective modality for the management of TTP since the 1920s.[37] Subsequently, plasma was identified as the active component that drives the clinical response to transfusion.[38] Since then, a cumulative body of evidence has supported the efficacy and tolerability of plasma exchange concerning survival and clinical outcomes of 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 due lack of large vWF substrates within its component;[43] however, the current evidence is equivocal regarding 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 plasma volume exchange is administered for the first procedures, followed by 1.0 fold patient plasma volume 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 Haemostasis (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 with suboptimal response 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 few cases of relapse and 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 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 by many retrospective studies in refractory patients, which 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 preserved for severe cases with poor response to other lines of treatment.[9]

4. Novel Therapeutics

Recurrence is a major concern in the setting of aTTP, patients with persistent ADAMTS-13 deficiency can develop life-threatening recurrence, which can occur as late as 20 years after aTTP acute 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 shorter duration 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.

The guidelines recommended that corticosteroids and rituximab should be continued after the discontinuation of caplacizumab to reduce the risk of exacerbations.[46]

5. Therapeutics Challenges and outcomes of aTTP in GCC countries

Several challenges can exist during the management of aTTP. Plasma exchange, the frontline option for aTTP patients, carries the risks of numerous complications.[23] The high rate 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 ADAMTS13 results challenged the use of plasma exchange prophylaxis as well.[46] Limited data are available concerning treatment protocols and outcomes of aTTP patients from GCC countries. In Iqbal et al.,[15] report, 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. The complete remission was achieved in 87.5% of the patients and the mortality rate was 16.7% after a median follow-up duration of 2 months.[15] In the retrospective study from Oman, all patients received daily plasma exchange and adjuvant corticosteroids, while 19 cases needed additional rituximab and ten cases needed cyclosporin. The authors reported a survival rate of 97% and a relapse rate of 17% following a mean duration of ten years.[16]

Consensus Statement: The experts stated that the ISTH 2020 recommendations are already applied in regular practice in Kuwait, UAE, and Oman. Concerning aTTP management protocol, the experts from the three countries agreed that aTTP treatment is initiated before receiving the results of the ADAMTS-13 assay due to the significant delay in the assay results. The exports reported that aTTP treatment mainly consisted of plasma exchange and corticosteroids, with rituximab sometimes added as the first-line immunomodulator. On the other hand, the experts stated that long-term immunosuppressive therapy is not used, except in cases

with underlying etiology for TTP (e.g. SLE). Patients with recurrent aTTP are usually treated with the 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 GCC countries was reported to be relatively low. It was also agreed that the unavailability of timely ADAMTS13 results challenged the use of prophylaxis.

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

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. However, they recognized the use of caplacizumab as a first-line agent which can lead to a reduction in aTTP relapse rates, mortality, and complications; and could prove to be cost-effective on the long term. Moreover, they acknowledged that caplacizumab could help in reducing the risk of long-term complications of aTTP; such as suicide, depression, and renal problems.

Discussion and Conclusion

The GCC is a council of six countries in the Middle East and North Africa (MENA) region that share many cultural and regional similarities. The majority of GCC countries are considered as high-income states, which witnessed dramatic advances in their healthcare and research sectors over the past few decades.[59] In the Gulf region, limited data are available regarding the

epidemiology, management, and unmet needs of aTTP. Thus, the present consensus aimed to bring insights from experts in the GCC countries regarding the epidemiology of aTTP, as well as local challenges in aTTP diagnosis and current local aTTP management.

To date, there are no reliable data regarding the incidence of aTTP in 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; the published reports included patients from one institution or one district of the Gulf region. The experts recommended the conduction of future multicenter studies to reflect the real epidemiology of aTTP in GCC countries.

Although ADAMTS-13 activity measurement is an essential diagnostic tool in the setting of TTP, many healthcare facilities in the Gulf region do not have access to immediate ADAMT-13 assays and many samples are sent abroad for testing. Thus, the average time for TTP diagnosis and referral from the first presentation may be prolonged with the high possibility of ischemic complications and death. Finally, the panel members recommended the development of educational and quality improvement programs to improve physicians' knowledge and awareness about TTP.

The experts also agreed that there is a need for national and regional consensus regarding the diagnosis and prompt treatment of aTTP in 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 disease in which experts get together and hence move forward in all topics related to diagnosis and management of these diseases.

Conflict of Interest

The meeting was supported by Sanofi Genzyme. The recommendations in the consensus report represent the opinions of the authors.

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