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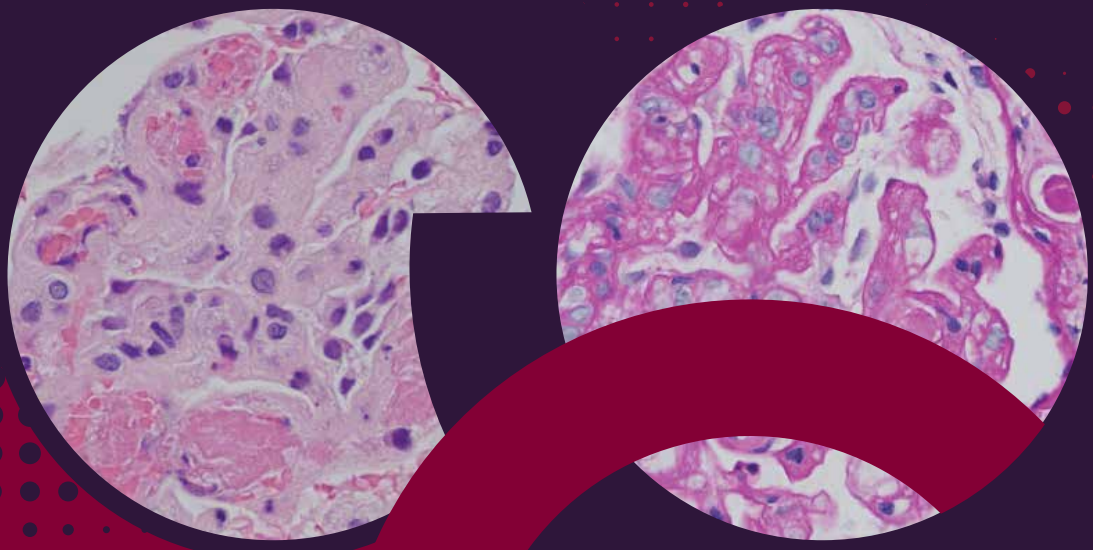
Best Practices in the Diagnosis of HSCT-TMA

IMPLICATIONS FOR CURRENT AND EMERGING TREATMENTS



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ACTIVITY DESCRIPTION

Thrombotic microangiopathy (TMA) is a devastating complication that can follow hematopoietic stem cell transplantation (HSCT). The pathogenesis is complex, but endothelial damage leading to coagulation, aberrant immune activation, and complement activation are all thought to play a role. Recent research has shed light on the natural history of HSCT-TMA and early signs and tests that could be used as predictive screening tools. The landscape of treatment for HSCT-TMA is also evolving, as are best practices in stepwise, individualized treatment. In this activity, experts discuss these advances and how they might improve outcomes for affected patients. The desired results of this activity are to increase screening, identification, and timely treatment of HSCT-TMA and to build awareness of emerging treatments.

TARGET AUDIENCE

This educational activity is intended for hematologist oncologists and onco-nephrologists.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Describe the pathogenesis and risk factors for HSCT-TMA
- Design evidence-based screening strategies for earlier detection of HSCT-TMA
- Contrast the clinical utility of current diagnostic criteria for HSCT-TMA
- Demonstrate ability to develop individualized, stepwise treatment strategies for patients with HSCT-TMA
- Interpret the clinical relevance of trial data for established and emerging therapies for HSCT-TMA

SATISFACTORY COMPLETION

Learners must pass a post test and complete an evaluation form online by going to **https://tinyurl.com/dxHSCT-TMA**. Upon passing, you will receive your certificate of completion immediately. You must score 70% or higher to receive credit for this activity, and may take the test up to 2 times. You must participate in the entire activity as partial credit is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

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Best Practices in the Diagnosis of HSCT-TMA

IMPLICATIONS FOR CURRENT AND EMERGING TREATMENTS

INTRODUCTION

Thrombotic microangiopathy (TMA) is a serious complication that ranges in severity but can be associated with significant morbidity and, in some cases, mortality following hematopoietic stem cell transplantation (HSCT). HSCT-associated TMA (HSCT-TMA or TA-TMA) is characterized by widespread endothelial cell dysfunction leading to microangiopathic hemolytic anemia, platelet activation, microthrombi within the microvasculature, and, finally, end-organ damage and loss of function.[1] HSCT-TMA was first described in the 1980s,[2,3] but a growing body of recent research has dramatically increased understanding of risk factors, pathophysiologic drivers, and potential treatment strategies. In this review, based on the proceedings of a live roundtable discussion held during the 62nd American Society of Hematology Annual Meeting & Exposition, experts in the management of adult and pediatric HSCT-TMA discuss the current evidence supporting diagnosis and treatment of HSCT-TMA, with a focus on earlier diagnosis and targeted treatment to decrease the rate of mortality.

EPIDEMIOLOGY, RISK FACTORS, AND PATHOGENESIS OF HSCT-TMA

Because HSCT-TMA is a clinical diagnosis in which multiple diagnostic criteria have been proposed, but no single one is universally adopted, the reported incidence of this condition in the literature is highly variable. It is estimated that up to 40% of HSCT recipients might develop TMA as a complication following transplantation, and the incidence is likely higher in children than in adults.[1] Among affected patients, there is a wide range of disease severity; in severe cases, mortality can be high, especially in cases associated with steroid-refractory graft-versus-host disease (GVHD).[1,4] The lack of a consensus clinical diagnostic criteria or validated risk scoring system continues to hamper the ability to study HSCT-TMA, although recent elucidation of the potential pivotal role of complement in the pathogenesis and encouraging results of complement blockade as therapy, especially in the pediatric setting, have generated renewed interest in this condition.

The incidence of HSCT-TMA appears to be higher among specific populations, including allogeneic transplantation recipients and older adults.[5,6] Increasingly recognized populations at higher risk are patients with multiple complement gene polymorphisms, females, and African Americans **(Figure 1)**.[4-6] Some well-recognized risk factors for endothelial injury—including certain conditioning regimens, posttransplant calcineurin inhibitor (CNI) use, viral infections, and acute GVHD—are also predictive of developing HSCT-TMA.[5,6] A few unifying concepts emerge when these factors are examined together, namely, endothelial injury and aberrant complement activation. Examination of risk factors in the context of patients' clinical history and treatment course suggests a "3-hit" hypothesis, wherein factors that predispose patients to either complement activation or endothelial damage compose the "first hit".[4-6] The "second hit" occurs when endothelial damaging agents are given during the course of conditioning and/or GVHD prophylaxis. Finally, a "third hit" from

infection, GVHD, or medication toxicity perpetuates existing endothelial injury, crossing a threshold for activation of the complement cascade **(Figure 1)**.[4-6]

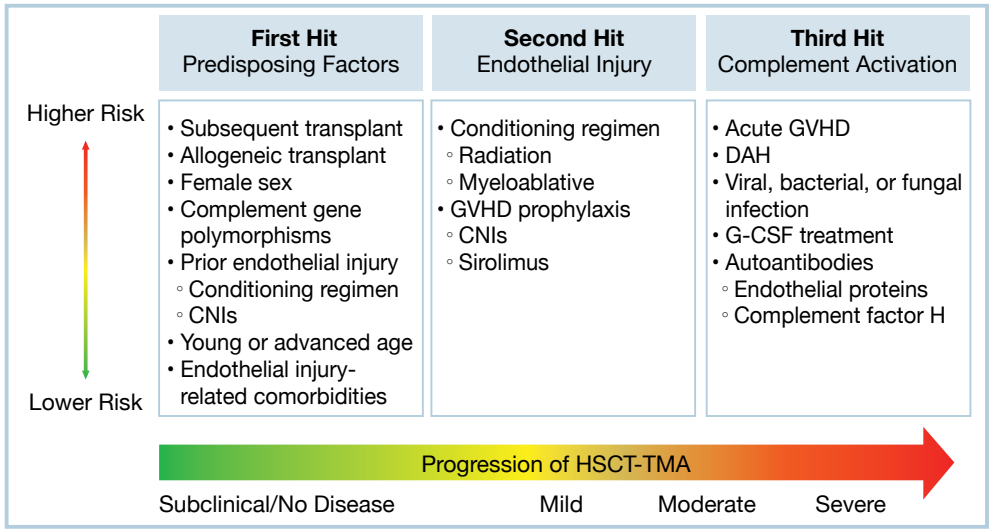

Figure 1. Risk factors and "3-hit hypothesis" for HSCT-TMA[4-6]

Abbreviations: CNI, calcineurin inhibitor; DAH, diffuse alveolar hemorrhage; G-CSF, granulocyte-colony stimulating factor; GVHD, graft-versus-host disease; HSCT-TMA, hematopoietic stem cell transplantation–associated thrombotic microangiopathy.

The pathogenesis of HSCT-TMA is complex and incompletely understood, although there is consensus that injury to the microvascular endothelium is central, with complement activation being the primary mediator in most cases. The pathogenesis of HSCT-TMA ties together several pathways involved in coagulation and immunity, culminating in complement activation.[5,6] Endothelial cell activation by conditioning agents or other medications leads to a procoagulant state, with thrombus formation and recruitment of immune cells. Reductions in nitric oxide and prostacyclin result in loss of suppression of the coagulation cascade, whereas decreased vascular endothelial growth factor levels promote release of angiotensin-2 and vascular destabilization. Expression of adhesion molecules (including E-selectin, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1) promotes recruitment of immune cells, which then produce inflammatory cytokines, autoantibodies, and alloantibodies that perpetuate the immune response and activate the alternative and classical complement pathways. Interleukin-8 released from damaged endothelial cells causes neutrophils to produce neutrophil extracellular traps, which in turn activate the alternative complement pathway. Damaged endothelial cells also express damage-associated molecular patterns on their surface, which are recognized by lectins, and in turn by mannan-binding lectin–associated serine proteases (MASPs).[7,8] Activated MASP-2 cleaves C4 as part of the lectin complement pathway, whereas activated MASP-1 is capable of activating C2 or C3, contributing to activation of the classical and alternative complement pathways, respectively.[7,8] MASP-2 also has factor Xa-like activity, activating thrombin in vitro, and activated MASPs participate in thrombotic reactions in vitro and in vivo.[9,10] Finally, the complement pathways converge, activating C5b-9 and the membrane attack complex.[5] This leads to direct endothelial cell lysis, microthrombi formation, and resulting tissue and organ ischemia. **Figure 2** outlines this process.[5,6]

DIAGNOSTIC CHALLENGES IN HSCT-TMA

Histologic examination of biopsied kidney tissue remains the gold standard in HSCT-TMA diagnosis.[5] Renal biopsies, however, are seldom performed in patients with suspected HSCT-TMA because of the high risk of bleeding in the setting of severe thrombocytopenia. Therefore, this invasive procedure is often deferred until there is significant renal dysfunction (eg, rising serum creatinine and falling glomerular filtration rate) if there is diagnostic uncertainty. Some have suggested a more aggressive diagnostic approach with early biopsy if TMA is suspected, but this has not been widely adopted at present. Although renal impairment is common, TMA is a systemic disease, and other organs can be compromised. For example, TMA can also affect the brain, resulting in seizures, strokes, and altered mental status. The severe hypertension (along with CNIs) associated with TMA could also trigger posterior reversible encephalopathy syndrome, but it is often unrecognized or not appreciated and very difficult to diagnose. TMA of the lungs can lead to respiratory failure and pulmonary hypertension. Intestinal TMA, often seen in the context of intestinal GVHD, presents with abdominal pain, lower gastrointestinal bleeding, and diarrhea. Once end-organ damage has occurred, survival rates decline, although there is variation in the degree of damage and reversibility. Survivors are often left with lingering organ dysfunction, and many require long-term hemodialysis.[11,12] Several groups have endeavored to establish diagnostic clinical criteria that are sensitive enough to detect true HSCT-TMA while the prognosis remains favorable, yet specific enough to differentiate symptoms and clinical signs from other related disorders **(Table 1)**.[5,13-17]

In 2014, Jodele and colleagues suggested that according to a large prospective study of pediatric HSCT recipients (N = 100), older diagnostic criteria are not met until many patients have had symptoms of TMA for several weeks, most notably hypertension and proteinuria **(Figure 3A)**.[1] Importantly, schistocytes were required for diagnosis, per older diagnostic criteria, but represented a relatively late event in the course of TMA for the population studied. Patients in this study met established diagnostic criteria for TMA at a median of 32 days (interquartile range, 17-43) posttransplantation, with 92% diagnosed by day 100. TMA significantly increased the risk of mortality among participants **(Figure 3B)**.[1] Factors associated with death in this cohort included proteinuria ≥ 30 mg/dL and elevated soluble C5b-9 (sC5b-9) **(Figure 3C)**.[1]

On the basis of these observations, a proposed screening, diagnostic, and treatment algorithm was developed. Diagnostic criteria were similar to those outlined by Uderzo and colleagues, also in 2014 **(Table 1)**,[1,14] but in 2018, Jodele and colleagues suggested that *ANY 4* of the criteria outlined previously could be considered suggestive of a diagnosis of TMA.[17] Using these criteria, TMA can be diagnosed without the documentation of schistocytes on a peripheral blood smear, a change from previous criteria. The clinical use of the various diagnostic criteria is discussed subsequently.

Panel Discussion

Dr Ho: In 2005, my colleagues and I in the Toxicity Committee of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) convened to create consensus criteria for TMA for

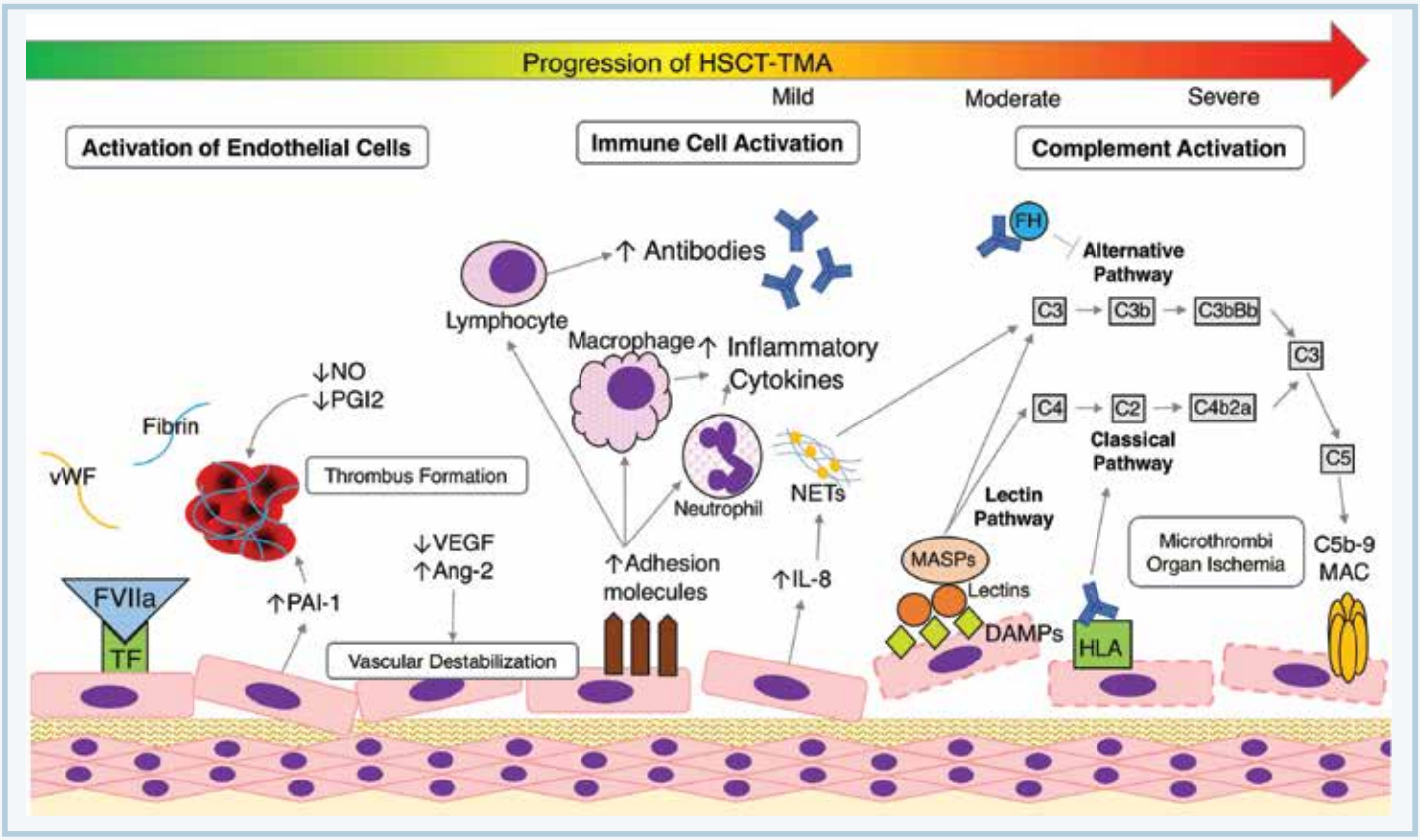

Figure 2. Pathogenesis of HSCT-TMA[5,6]

Abbreviations: Ang-2, angiopoietin-2; DAMP, damage-associated molecular pattern; FH, factor H; FVIIa, factor VIIa; HLA, human leukocyte antigen; HSCT-TMA, hematopoietic stem cell transplantation–associated thrombotic microangiopathy; IL-8, interleukin-8; MAC, membrane attack complex; MASP, mannan-binding lectin–associated serine protease; NET, neutrophil extracellular trap; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; PGI2, prostacyclin; TF, tissue factor; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor.

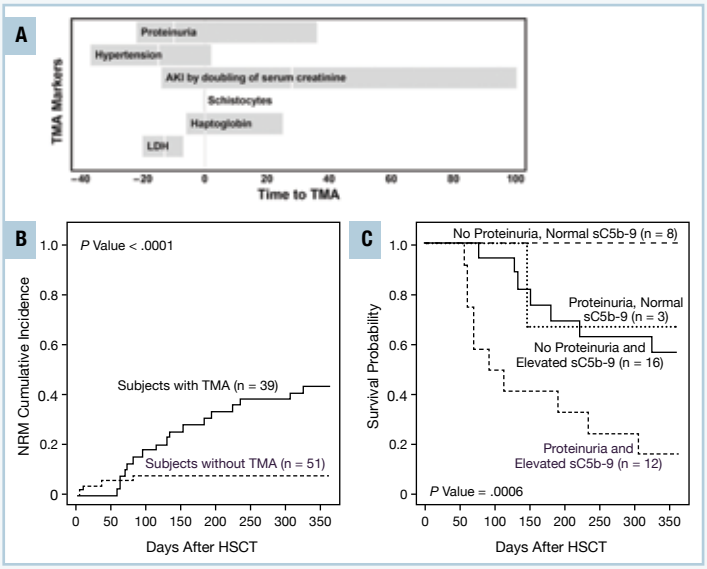

Figure 3. Clinical observations among a cohort of pediatric HSCT recipients.[1]
(A) Time course of the appearance of clinical signs and laboratory markers associated with HSCT-TMA. (B) Nonrelapse mortality among participants with and without diagnosed HSCT-TMA. (C) Survival among participants who had proteinuria, elevated sC5b-9, both, or neither.

Abbreviations: AKI, acute kidney injury; HSCT, hematopoietic stem cell transplantation; LDH, lactate dehydrogenase; NRM, nonrelapse mortality; TMA, thrombotic microangiopathy.

the reporting of toxicity in BMT CTN studies.[15] In this approach, the committee reviewed available literature and decided on a consensus TMA definition that includes the presence of at least 2 schistocytes per high-power field in a peripheral blood smear, elevated lactate dehydrogenase (LDH), and presence of renal and/or neurologic dysfunction in the absence of a positive Coombs test and in the absence of any abnormal coagulation tests (prothrombin time and partial thromboplastin time) to suggest disseminated intravascular coagulation. Thrombocytopenia was not included in the BMT CTN definition because the Committee felt that thrombocytopenia is universal in the early posttransplantation and pre-engraftment period. This BMT CTN definition was again intended to guide the reporting of TMA as an adverse event in BMT CTN clinical trials, so the TMA had to manifest with some sign of renal or neurologic dysfunction. At the time, this definition was well accepted, but many thought it was too restrictive because it required the presence of organ dysfunction. In other words, the BMT CTN TMA criteria were too specific and lacked the sensitivity needed to capture mild TMA cases or TMA cases earlier in their course.

Dr Dvorak: Another challenge in developing consensus diagnostic criteria is the relative reproducibility of individual metrics. For example, LDH measured in San Francisco is probably the same as LDH measured in Boston and in New York, but schistocytes are very much in the eye of the beholder, and some laboratories are less likely to call a schistocyte on a peripheral blood smear. For this reason, newer criteria, such as that proposed by Jodele and colleagues, in which only 4 of 7 criteria are needed, might be better.[17] There can also be some

Table 1. Various Proposed Diagnostic Criteria for HSCT-TMA

Parameters	Overall TMA[13]	BMT CTN Toxicity Committee[13,15]	International Working Group[13,16]	Cho et al[13] (Probable: No Renal/ Neurologic Involvement; Definite: Renal/ Neurologic Involvement)	Uderzo et al[14]	Jodele et al[5,17] (> 4 Present Strongly Suggest TMA)
Normal coagulation assays (PT, aPTT)	Yes	Yes	Yes	Yes		
Schistocytosis	≥ 2/HPF	≥ 2/HPF	≥ 4% (8/HPF)	≥ 2/HPF	≥ 1%-2%/HPF on ≥ 2 consecutive smears	Present
Increase in serum LDH	Yes	Yes	Yes	Yes	Yes	Yes
Concurrent renal and/or neurologic dysfunction without other explanations		Yes*		Yes		
Negative Coombs test	Yes	Yes		Yes	Yes	
Thrombocytopenia†	Yes		Yes	Yes	Yes	Yes‡
Decrease in hemoglobin concentration	Yes		Yes	Yes	Yes	Yes‡
Decrease in serum haptoglobin	Yes		Yes	Yes		
TA-TMA Index (ratio between LDH/platelets:1000) ≥ 20					Yes	
Proteinuria > 30 mg/dL					Yes§	Yes
Unexplained hypertension resistant to ≥ 2 treatments					Yes§	Yes‖
Serum soluble C5b-9 above normal range					Yes§	Yes
Specificity ←						→ Sensitivity

Abbreviations: aPTT, activated partial thromboplastin time; BMT CTN, Blood and Marrow Transplant Clinical Trials Network; HPF, high-power field; HSCT, hematopoietic stem cell transplantation; LDH, lactate dehydrogenase; PT, prothrombin time; TA, transplant associated; TMA, thrombotic microangiopathy.

* Doubling of serum creatinine from baseline (baseline = creatinine before hydration and conditioning) or 50% decrease in creatinine clearance from pre–hematopoietic stem cell transplantation baseline

† De novo, prolonged, or progressive thrombocytopenia (platelet count < 50 × 10^9/L or ≥ 50% reduction from previous counts)

‡ Or increased need for transfusion

§ Parameters sufficient for a diagnosis of "high-risk TA-TMA" (based on pediatric studies)

‖ > 99% for age

important differences between adults and children. For example, children typically do not have baseline hypertension, and a child who needs 3 antihypertensive agents probably has very severe hypertension. I use the following rule of thumb in children: 1 antihypertensive agent is reasonable if on a CNI or corticosteroid, and a second agent is reasonable if on both, but anything above that should count as hypertension.

Dr Perales: Underdiagnosis remains a problem. In a recent preliminary analysis of a large number of transplants at our center, we found that the more criteria you add, the fewer cases of TMA you identify. Interestingly, treatment with eculizumab was given in cases in which patients did not meet the current criteria and not given in cases in which the criteria were met, indicating prevalent variation in practice and uncertainty about the optimal time for intervention. This highlights the need for diagnostic criteria that relate to current treatment options as well as guidelines regarding thresholds for treatment using available agents.

Dr Alyea: Another important challenge is to determine the optimal timing of diagnostic tests. For example, haptoglobin might not be decreased early, but falls over time. Early assessment may be misleading, but retesting may improve diagnostic accuracy.

Dr Ho: Another limitation of screening and diagnostic tests is the availability and turnaround time. For example, ruling out thrombotic thrombocytopenia purpura using ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) is difficult because that test usually does not come back in a timely fashion, and I would not advise withholding intervention for TMA while the ADAMTS13 test result is pending. Soluble C5b-9 is likely the most specific marker of TMA, but the sC5b-9 test is not easy to send, and there is a long turnaround time in many institutions.

Dr Dvorak: At our center, we identified 3 criteria that are highly predictive of developing TMA and should raise a clinician's suspicion[6]:

1. Hypertension (> 95% for age, sex, and height)
2. New or refractory thrombocytopenia
3. Elevated LDH (> upper limit of normal for age)

Patients that meet these criteria are followed more closely, with regular screening for haptoglobin and sC5b-9.

The panel further agreed that risk assessment should be incorporated into any screening algorithm for HSCT-TMA, although the lack of a validated, quantitative TMA risk score represents an important future direction for the field.[6] Overall, the algorithm proposed by Jodele and colleagues was viewed as the most clinically useful, with a few modifications to decrease the burden of screening all patients and taking into consideration the practicality of different diagnostic evaluations **(Figure 4)**.[17]

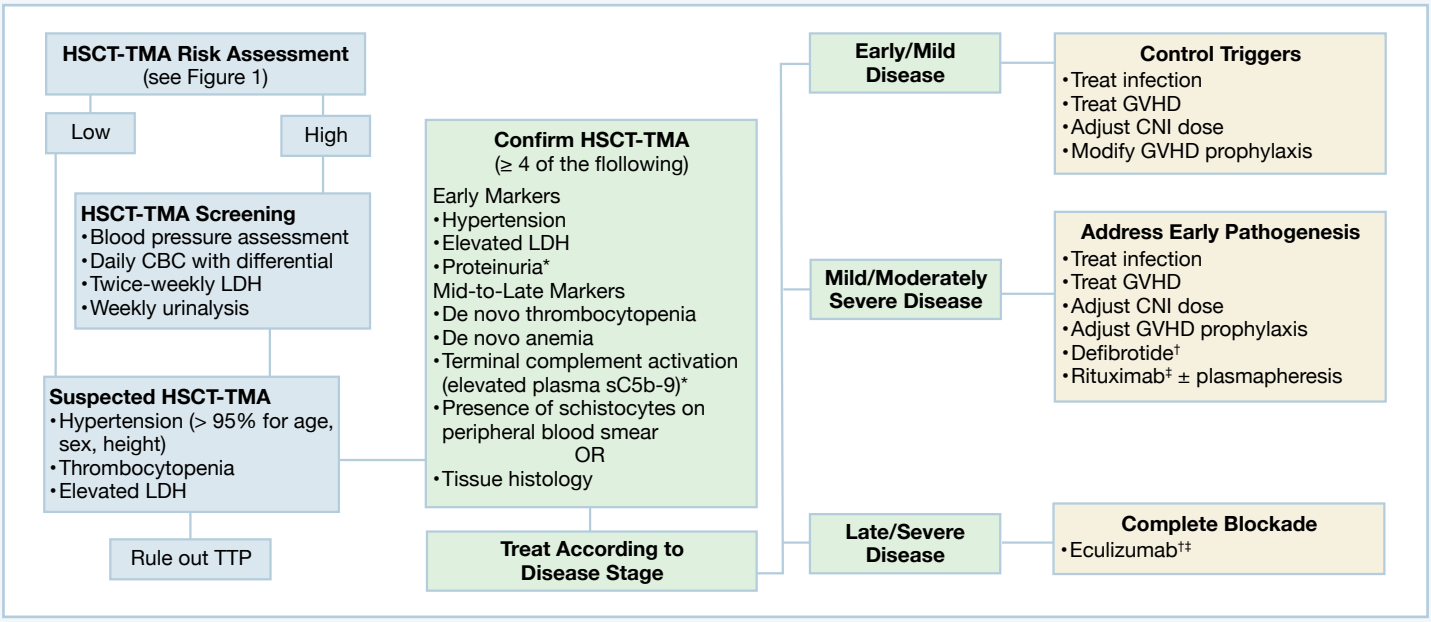

Figure 4. Modified screening, diagnostic, and treatment algorithm for HSCT-TMA[17]

Abbreviations: CBC, complete blood count; CNI, calcineurin inhibitor; GVHD, graft-versus-host disease; HSCT-TMA, hematopoietic stem cell transplantation–associated thrombotic microangiopathy; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenia purpura.

* High-risk markers that indicate a poor prognosis

† Investigational therapy

‡ Off-label use for HSCT-TMA

There are several unmet needs in the diagnosis and treatment of HSCT-TMA, including:
- A validated risk assessment tool and scoring algorithm
- Sensitive and specific screening markers
- Consensus diagnostic criteria
- More targeted, effective, and safe therapies
- Further understanding of the interplay of steroid-refractory GVHD and HSCT-TMA

TREATMENT OF HSCT-TMA

Many different treatments have been used to treat HSCT-TMA, with varying rates of success **(Table 2)**.[18-49] Although there is currently no US Food and Drug Administration (FDA)-approved treatment for HSCT-TMA, several different agents are in clinical trials, including eculizumab, narsoplimab, and nomacopan. With the understanding that HSCT-TMA has a progressive course that might be reversible with early intervention, it is intuitive to target treatments toward removing the triggers of TMA (eg, GVHD, CNI, and infections), interrupting the mechanisms causing endothelial injury (eg, complement), and/or protecting the endothelial surface and inhibiting platelet activation/thrombosis.

In its earliest stages, HSCT-TMA manifests as endothelial damage with accompanying elevated LDH, hypertension, and/or proteinuria **(Figure 3A)**.[1] During this early stage, withdrawal or adjustment of offending agents, including CNIs, or adjustment of GVHD prophylaxis might be successful. These strategies should be applied with caution, however, because GVHD itself is a risk factor for TMA.[5,6]

Defibrotide is a polydisperse oligonucleotide with aptameric activity. It functions as an antithrombotic, anti-ischemic, profibrinolytic, antiadhesive, and antiapoptotic agent.[50-53] Through these activities, including inhibition of plasminogen activator inhibitor-1,[53] it is thought that defibrotide might prevent the earliest stages of HSCT-TMA pathogenesis. It is currently FDA approved to treat hepatic sinusoidal obstruction syndrome (also known as veno-occlusive disease) in children and adults with renal or pulmonary dysfunction following HSCT.[21] Some small studies have been conducted in patients with HSCT-TMA.[18-20] An ongoing, single-center clinical trial is investigating the feasibility of administration of defibrotide during conditioning to possibly prevent development of HSCT-TMA.[22]

As TMA progresses, immune cell recruitment leads to an inflammatory cascade, which can include antibody production directed at host tissues, donor cells, or sometimes factor H, an inhibitor of the alternative complement pathway **(Figure 2)**.[5,6] Several different treatments that inhibit the cells or cytokines mediating this process have been reported to treat HSCT-TMA **(Table 2)**.[23,24,28-38] Plasmapheresis removes inhibitors or antibodies that potentiate HSCT-TMA, but has a highly variable response rate and might be more effective when used early in the disease course.[23,24] Treatment of HSCT-TMA with several other immunomodulators has been reported in small studies.[28,30-34,36-38]

The final stages of HSCT-TMA involve activation of the complement cascade. Eculizumab has been used to treat HSCT-TMA through its activity on C5, although it is not approved for this indication.[43] The success of this approach ranges from 50% to 67%, but the long-term morbidity and mortality among treated patients is poor.[40-42,54] These data have led experts in the field to suggest that earlier intervention is needed, with consideration of additional therapeutic targets that manifest earlier in the disease course.[54] Another limitation of eculizumab therapy is the Risk Evaluation and Mitigation Strategies requirement for meningococcal vaccination prior to use, which is not feasible/effective in the early post-HSCT population.[43,55] Appropriate antimicrobial prophylaxis for bacterial meningitis has the potential to counteract this limitation.[55] A similar, but longer-acting C5 inhibitor, ravulizumab-cwvz, is anticipated to be in phase 3 trials starting in 2020.[56]

Table 2. Current and Investigational Management Strategies for HSCT-TMA

Strategy	Mechanism	Response Rate, %	Adverse Effects	Ongoing Clinical Trials
Defibrotide*[18-21]	Antifibrinolytic, antithrombotic	50-65	Hemorrhage, hypotension, diarrhea, vomiting, nausea, epistaxis	NCT03384693[22] (for prevention of HSCT-TMA)
Plasmapheresis[23,24]	Removal of inhibitors and/or antibodies	27-80	Bleeding, infection, hypotension, urticaria, thrombosis[25-27]	
Daclizumab†‡[28]	Anti–IL-2	69	Infection, rash, autoimmune reactions[29]	
Rituximab†[30-34]	Anti-CD20	66-80	Infections, cardiac events, infusion reactions, renal toxicity[35]	
Vincristine†[36-38]	Immunomodulator	67-85	Leukopenia, neuritic pain, constipation, hair loss[39]	
Eculizumab*†[40-42]	C5 inhibitor	50-67	Meningococcal infection, other infections, headache, gastrointestinal disturbances[43]	NCT03518203[44]
Narsoplimab*[45,46]	Anti-MASP-2	56-68	Nausea, vomiting, diarrhea, hypokalemia, neutropenia, and fever[45]	NCT02222545[47]
Nomacopan*[48]	Anti-C5, anti–leukotriene B4		Yes	Phase 3 beginning soon[49] (severe disease)

Abbreviations: HSCT-TMA, hematopoietic stem cell transplantation–associated thrombotic microangiopathy; IL-2, interleukin-2; MASP-2, mannan-binding lectin serine protease 2.

* Under investigation for treatment of HSCT-TMA

† Off-label use for HSCT-TMA

‡ Daclizumab for the treatment of relapsing multiple sclerosis has been withdrawn from the market

Narsoplimab is a mannan-binding lectin serine protease 2 (MASP-2) inhibitor being investigated for treatment of HSCT-TMA. MASP-2 plays a role in early initiation of the complement cascade via the lectin pathway.[57] The exact role in the pathogenesis of HSCT-TMA is still not defined, but preliminary research presented at the 62nd American Society of Hematology Annual Meeting & Exposition suggests that HSCT induces an increase in MASP-2 plasma level following transplantation.[57] Additional research is needed to further clarify the dynamics of MASP-2 during TMA.

In a 3-stage phase 2 clinical trial, patients with HSCT-TMA treated with narsoplimab (n = 19) were compared with historical controls (n = 67).[46] Narsoplimab-treated patients demonstrated significantly improved survival vs controls (347 vs 21 days; $P < .0001$) **(Figure 5)**, and significantly improved platelet count, LDH, and haptoglobin compared with baseline.[45,46] The primary efficacy end point of the trial, complete response as defined by FDA-agreed criteria, was met in 56% of patients receiving at least 1 dose of narsoplimab and in 68% of patients who received protocol-specified dosing for at least 4 weeks.[45]

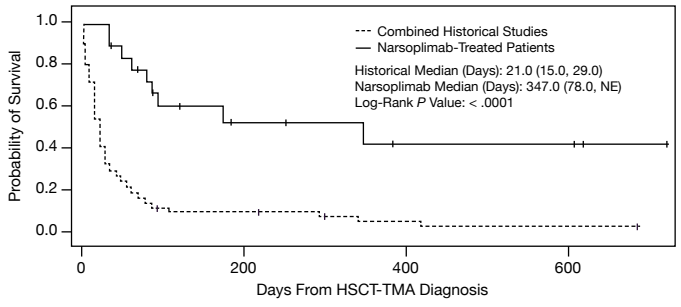

Figure 5. Kaplan-Meier survival curve comparing patients treated with narsoplimab with historical controls[46]

Abbreviations: HSCT-TMA, hematopoietic stem cell transplantation–associated thrombotic microangiopathy; NE, not estimable.

Nomacopan is also under investigation for treatment of HSCT-TMA. In a proof-of-principle case report, a patient with HSCT-TMA and a C5 polymorphism conferring resistance to eculizumab was treated with nomacopan, albeit with only modest improvement possibly due to limited drug availability.[48] A phase 3 trial in patients with severe HSCT-TMA is being planned.[49]

Panel Discussion: Where will emerging treatments for HSCT-TMA fit into the current treatment algorithm if they are approved?

Dr Alyea: Early diagnosis is critical for agents to have an opportunity to prevent end-organ damage. Clinical trials will determine if newer agents that inhibit the complement cascade may be used as the first-line intervention if other precipitating agents have been eliminated and if no resolution is noted.

Dr Dvorak: Once multiple treatments that target parts of the HSCT-TMA pathophysiologic pathway are commercially available, clinicians may be in a quandary about which one to use. Comparing response rates reported in single-agent publications will be fraught with patient-selection bias, and head-to-head trials are relatively unlikely to occur in the near future. Theoretically, agents that work on parts of the pathway earlier in the process may be superior to those that work later in the pathway. Hypothetically, agents that target different parts of the pathway may be combinable (although that can be cost prohibitive, and the safety of such an approach would need to be tested). Finally, if there is no conclusive evidence that one agent is superior to the others, cost can play an important role in agent selection.

Dr Ho: The algorithm for treatment that incorporates new emerging therapies remains to be determined, but it will likely be based on a balance of efficacy, safety/ease of administration, and cost. Ideally, TMA should be treated early in the disease course, before end-organ damage is apparent. According to studies in children, presence of proteinuria and elevated sC5b-9 denote worse prognosis, and intervention with a drug that targets the complement pathway appears reasonable.[1] In patients in whom infection and/or GVHD is a trigger for the TMA, treatment to address the underlying infection/GVHD is also important. It should be noted that the endothelial damage in TMA is probably not exclusively driven by complement activation, and future investigations might consider combining complement blockade with other treatment modalities, such as defibrotide, to further protect the endothelium.

Case 1: Clinical Course of Suspected HSCT-TMA
From the Files of Miguel-Angel Perales, MD

A 55-year-old male with Hodgkin lymphoma relapsed after autologous stem cell transplantation, and was admitted for allogeneic HSCT from a matched unrelated donor after reduced intensity conditioning with fludarabine and melphalan. GVHD prophylaxis was initiated with tacrolimus, sirolimus, and mini-methotrexate. As noted in **Table 3**, both LDH and creatinine levels started to rise early after transplantation. Of note, the levels of tacrolimus and sirolimus were monitored closely and were never supratherapeutic. On posttransplantation day 3, the patient's sirolimus level was 10 ng/mL and tacrolimus level was 9 ng/mL. The rise in creatinine level was initially attributed to a combination of tacrolimus and fluid losses secondary to significant diarrhea. The patient engrafted at day 14.

On day 16, a doubling of the LDH level and ongoing rise of creatinine level were noted, along with hypertension. TMA was suspected, and sirolimus was withheld. Of note, no schistocytes were seen on the smear at that time. On day 19, the patient demonstrated clinical deterioration, with tachypnea and hypoxia; and flexible sigmoidoscopy with biopsy showed grade 4 gastrointestinal GVHD. High-dose methylprednisolone sodium succinate was started. He was transferred to the intensive care unit the following day with worsening pulmonary function but without pulmonary hypertension. By day 21, in the face of continued clinical deterioration, the patient was started on eculizumab. He received 4 weekly doses, and was then switched to every-other-week maintenance dosing. He did not receive immunizations because they were unlikely to have any effect. He was, however, treated with aggressive antimicrobial prophylaxis.

After a complicated clinical course, the patient eventually improved and was able to be discharged home 43 days after his transplantation on appropriate antibiotic prophylaxis. He was then followed in the outpatient setting, and was clinically improving, albeit with ongoing decreased blood cell counts and a need for intermittent factor support. Immunosuppressive drugs (steroids and mycophenolate mofetil) were being tapered during this time. He was readmitted on day 102 posttransplantation with a clinical picture consistent with neutropenic sepsis. Blood cultures were positive for methicillin-resistant *Staphylococcus aureus,* and he died shortly thereafter.

Table 3. Clinical and Laboratory Findings for the Patient in Case 1

Day	LDH Level, U/L	Creatinine Level, mg/dL	Other Laboratory Tests	Intervention
4	258	1.1		
6	308	1.3		
9	305	1.2		
11	411	1.4		
13	550	1.4		
16	1251	1.6		Sirolimus stopped, MMF started
18	1376	2.0		
19	1655	2.2		Methylprednisolone sodium succinate 2 mg/kg for acute GVHD
20	2220	2.5		Stopped tacrolimus, ICU transfer
21	2320	2.9	Rare schistocytes	Eculizumab
22	2722	2.8		
23	2839	2.8		
24	3084	2.9		
25	2801	3.1		
27	4523	3.8		
28	4271	4.0		Eculizumab
29	3721	3.9		
30	3427	3.8		
31	3383	4.0		
35				Eculizumab
40	2188	3.4		
42				Eculizumab
43				Hospital discharge
49	883	3.4		Eculizumab
59	429	3.2		
74	359	3.3		
102				Neutropenic sepsis

Abbreviations: GVHD, graft-versus-host disease; ICU, intensive care unit; LDH, lactate dehydrogenase; MMF, mycophenolate mofetil.

Commentary

Dr Alyea: This case provides an example of how HSCT-TMA can evolve over time and that all laboratory parameters may not be present at the outset, such as the lack of schistocytes. The development of HSCT-TMA resulted in the need to change immune suppression, which probably contributed to further complications related to the development of GVHD. This highlights the need for improved agents to prevent or treat HSCT-TMA.

Dr Ho: This patient was at increased risk for TMA because of the concurrent use of tacrolimus and sirolimus. Although sirolimus has not been implicated as a trigger for TMA in itself, its use together with a CNI (tacrolimus or cyclosporine) increases the odds of TMA approximately 1.5-fold.[4,58] As such, awareness of the possibility of TMA in these patients is paramount. This patient had TMA that appeared concurrently with onset of diarrhea at the time of engraftment, and was treated for intestinal GVHD. With his concurrent respiratory and gastrointestinal issues, one should also consider the possibility of TMA in his intestine and lungs. Finally, it should be noted that TMA that occurs in the context of severe acute GVHD is associated with very poor survival,[59] with infection being a common cause of death, as was observed in this case.

Dr Dvorak: This case highlights the difficulty of teasing out the "chicken vs the egg" aspect of HSCT-TMA and GVHD. Did the HSCT-TMA start first, and did stopping sirolimus contribute to the subsequent development of grade 4 GVHD? Or did the gut GVHD developing at a subclinical level and the alloreactivity contribute to the endothelial injury that clinically manifested as HSCT-TMA? Because of this interplay, for patients early post-HSCT with suspected HSCT-TMA, we have typically swapped steroids for either CNIs or sirolimus rather than just stopping them. The other thing to point out is that grade 4 GVHD is associated with a high risk for sepsis and transplant-related mortality independent of treatment with eculizumab, so it is difficult to determine the exact contribution of complement blockade on this patient's subsequent death.

Case 1 Take-Home Points

- The combination of tacrolimus and sirolimus has been associated with a risk of TMA, but evidence of TMA developed in this patient very early on, in the absence of toxic levels of either drug. Furthermore, the process continued even after discontinuation of both drugs.

- The clinical picture can often be complicated by other posttransplantation complications, such as acute GVHD and infections
- Although the patient improved with targeted therapy with eculizumab, he eventually died because of an infectious complication

Case 2: Atypical Presentation of HSCT-TMA

From the Files of Vincent T. Ho, MD, and Edwin P. Alyea, MD

A 74-year-old female underwent a mismatched, unrelated donor, reduced intensity conditioning, allogeneic stem cell transplantation. Her course was relatively uncomplicated early on, except for infections with vancomycin-resistant enterococcus, candidiasis, and *Clostridium difficile,* all of which resolved with treatment. Tacrolimus was stopped at approximately 6 months posttransplantation, and the patient did well until she developed cryptogenic-organizing pneumonia, necessitating steroid treatment. She responded well, but developed hypertension and was admitted with unexplained weight gain. On admission, her clinical findings were as follows:

- Sudden elevation in creatinine from 1.2 to 1.9 mg/dL
- New thrombocytopenia with hemolysis and diarrhea
- Serum LDH: 755 U/L (upper limit of normal, 225 U/L)
- Liver function tests: Normal; bilirubin, 0.4 mg/dL
- Uric acid: 8.1 mg/dL
- Complete blood count: White blood cell count, 16,000; hemoglobin, 10.4 g/dL; hematocrit 31%; platelet count, 48,000
  - Differential normal, no blasts
  - Complete blood count 2 weeks earlier: White blood cell count, 16,000; hematocrit 37%; platelet count, 133,000
- Smear: 1+ schistocytes, nucleated red blood cells; reticulocytes 6.5%
- Haptoglobin: < 5 mg/dL
- Coombs test (direct antiglobulin test): Negative
- PT-INR/PTT/Fibrinogen (Prothrombin time international normalized ratio/Partial thromboplastin time/Fibrinogen): Normal
- Urinalysis: 2+ blood (6 red blood cells), 1+ protein

On the basis of these findings, HSCT-TMA was diagnosed, although it should be noted that this was an atypical presentation. A renal biopsy confirmed TMA. This case is still ongoing.

Commentary

Dr Alyea: An important point about this case is that the clinical picture described previously took 10 weeks to develop from the time of transplantation, speaking to the chronicity and insidious nature of this disease in some patients.

Dr Ho: This is an interesting, atypical case. I am curious as to what could have been the trigger. This patient had not been on a CNI, so could it have been one of the infections the patient had early on?

Dr Perales: How will you treat this patient's TMA? Eculizumab?

Dr Ho: Interestingly, the renal biopsy was negative for complement deposition on the endothelium, so it is possible that treatment with eculizumab might not be effective. Given that information, how would you treat this patient?

Dr Dvorak: I would still start eculizumab because there is not a CNI to be removed, and she is already on steroids. Therefore, eculizumab is the only other option outside of a trial.

Case 2 Take-Home Points

- Not all TMA cases occur within the first 100 days of transplantation, and there are patients who will develop TMA months to even years after HSCT when they are no longer on a CNI
- It is important for clinicians to remain vigilant for TMA at all times, especially when there is new or worsening hypertension, an elevated LDH level, thrombocytopenia, proteinuria, or signs of renal dysfunction

Case 3: Probable Antibody-Mediated HSCT-TMA

From the Files of Christopher C. Dvorak, MD

A 12-year-old Hispanic female with severe aplastic anemia diagnosed 19 months prior was treated by her hematologist with horse antithymocyte globulin/cyclosporine. She had a partial response, but also several infections and elevated creatinine levels. Her blood cell counts fell again, and she was transferred to our care. She underwent sibling-matched bone marrow transplantation. Her conditioning regimen consisted of fludarabine, cyclophosphamide, and alemtuzumab. Tacrolimus and methotrexate were used as prophylaxis for GVHD.
She engrafted promptly, but had a number of infections with adenovirus and BK virus. **Table 4** shows her laboratory and clinical findings on posttransplantation day 50.

Table 4. Clinical and Laboratory Findings for the Patient in Case 3 at Posttransplant Day 50

Parameter	Normal Values	At HSCT-TMA Presentation (50 Days Post-HSCT)
Blood pressure, mm Hg	< 120/< 80	**160/105**
Platelet count, × 10^9/L	> 150	**28**
LDH, U/L	< 234	**287**
Urine protein-to-creatinine ratio	< 0.2	**1.48**
Fibrin d-dimers, ng/mL	< 500	**783**
Haptoglobin, mg/dL	36-195	**< 7**
Hemoglobin, g/dL	11.2-13.5	**7.2**
Creatinine, mg/dL	< 1.06	**1.35**
Schistocytes	None	None
Soluble C5b-9, ng/mL	< 244	96
Direct antibody test (Coombs)	*Negative*	*Negative*
ADAMTS13 activity, %	*> 10*	*128*
Stool test for Shiga toxin-producing Escherichia coli	*Negative*	*Negative*

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; HSCT, hematopoietic stem cell transplantation; LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy.

Commentary

Dr Dvorak: I think one important clue in this case was that her complement was actually low, although she met the Jodele criteria for HSCT-TMA.[17] Mutation analysis was normal and known antibodies were negative, but she experienced a large jump in B cell count over a month's time. She did not respond to stopping tacrolimus or starting steroids and eculizumab, and she went on to develop renal failure requiring dialysis. Eventually, we realized that her sC5b-9 level had never been elevated, so we switched gears and started her on rituximab and plasmapheresis, to which she responded robustly.

Dr Perales: This case is an important one to discuss because it illustrates that not all cases are typical and that antibody-mediated TMA should be a consideration.

Dr Ho: There are clinicians who will attempt treatment of all cases of TMA with eculizumab. This case clearly illustrates that a more individualized approach is warranted, and suggests that not all cases of HSCT-TMA are necessarily mediated by high complement activity. The question of whether sC5b-9 elevation will be a predictor of response to eculizumab remains to be answered.

Dr Alyea: This is an example in which a high index of suspicion led to early intervention. The team assessed response and was nimble in choosing a therapeutic strategy.

Case 3 Take-Home Points

- HSCT-TMA is a complex disease and probably involves more than 1 pathophysiologic pathway
- Many cases of HSCT-TMA respond to complement blockade. When patients are not responding, alternative treatment modalities should be considered.
- Plasmapheresis is less commonly used for patients with HSCT-TMA, but can still play a role in select patients, especially those without clear evidence of complement activation

CONCLUSION

In summary, recent research has begun to clarify the pathogenesis of HSCT-TMA, suggesting that the disease begins well before organ dysfunction is obvious. Diagnosis can be improved through more thorough risk assessment and through consideration of diagnostic criteria that maximize sensitivity without sacrificing specificity. Treatment should consider the severity of disease and be individualized according to laboratory and clinical findings. Defibrotide, eculizumab, narsoplimab, and nomacopan are all being investigated to prevent or treat HSCT-TMA, and their optimal use will be informed by clinical trial data if they are FDA approved.

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See detailed instructions under Satisfactory Completion on page 2.

1. Which patient-specific factor is thought to contribute to the risk of developing HSCT-TMA?
   a. Male sex
   b. Autologous transplantation
   c. Complement gene polymorphism
   d. Being transplant naïve

2. In the pathogenesis of HSCT-TMA, which event is believed to occur first?
   a. Complement activation
   b. Activation of endothelial cells
   c. Immune cell recruitment
   d. Antibody formation

3. MASP-2 is thought to participate in the pathogenesis of HSCT-TMA by:
   a. Activating lymphocytes to produce autoantibodies
   b. Recognizing endothelial damage and activating complement
   c. Upregulating plasminogen activator inhibitor-1 to produce a procoagulant state
   d. Activating neutrophils to release neutrophil extracellular traps

4. Assessing for _____ would provide the most value as a SCREENING tool, with high sensitivity for HSCT-TMA.
   a. Proteinuria and hypertension
   b. LDH, thrombocytopenia, and schistocytes
   c. sC5b-9 and proteinuria
   d. Hypertension, thrombocytopenia, and LDH

5. Assessing for _____ would provide the most value as a DIAGNOSTIC tool, with high specificity for HSCT-TMA.
   a. Proteinuria and neurologic dysfunction
   b. LDH, thrombocytopenia, and schistocytes
   c. sC5b-9 and proteinuria
   d. Hypertension, thrombocytopenia, and LDH

6. A pediatric patient who received an HSCT for aplastic anemia develops elevated blood pressure following initiation of a CNI that cannot be controlled with 2 antihypertensive agents. What would be the next best step in the management of this patient?
   a. Add a third antihypertensive agent
   b. Order a complete blood count test with differential and urinalysis
   c. Obtain a kidney biopsy
   d. Order an sC5b-9 assay

7. Which agent is currently in a clinical trial investigating the potential to PREVENT development of HSCT-TMA?
   a. Defibrotide
   b. Eculizumab
   c. Narsoplimab
   d. Rituximab

8. A patient presenting with elevated sC5b-9 and proteinuria would likely benefit most from _____.
   a. Eculizumab
   b. Cessation of CNIs
   c. Rituximab and plasmapheresis
   d. Defibrotide

9. Which investigational agent for HSCT-TMA works at the earliest point in the complement cascade?
   a. Eculizumab
   b. Narsoplimab
   c. Nomacopan
   d. Ravulizumab-cwvz