This review summarises highlights from a lecture by Prof. Jeffrey Laurence (New York), Understanding atypical haemolytic uraemic syndrome: Differential diagnosis of thrombotic microangiopathies, which was given at major centres in Adelaide, Melbourne, Perth, and Sydney during August 2015. This review is intended as education information for healthcare professionals and is sponsored by Alexion.

Although the thrombotic microangiopathies (TMA) appear to be a diverse set of syndromes they are united by common defining clinical and pathological features. The common clinical features are microangiopathic haemolytic anaemia, thrombocytopenia, and organ damage, while the common pathological features are vascular injury in the form of arteriolar and capillary thrombosis with characteristic endothelial and vessel wall abnormalities. The critical distinction among the major TMAs is the mechanisms underlying those clinical and pathological features, differences requiring different therapeutic interventions. Three of the primary TMAs are thrombotic thrombocytopenic purpura (TTP), atypical haemolytic uraemic syndrome (aHUS), and Shiga-like toxin-producing Escherichia coli haemolytic uraemic syndrome (STEC-HUS).

### Diagnosis and differentiation of TMA

TMA is defined by thrombocytopenia and microangiopathic haemolysis in addition to involvement of at least one organ system. The most prominent systems involved include neurological symptoms, renal impairment, and/or gastrointestinal symptoms, as indicated by the recognised algorithm for diagnosis of TMA (Figure 1). However, within that diagnostic pathway, certain features differentiate aHUS, TTP, and STEC-HUS.

In terms of laboratory results, thrombocytopenia is present in TMAs, but there is a pathophysiological distinction between TTP and aHUS. TTP is essentially a consumptive disorder of platelets, so the median platelet count in TTP is 20 x 10^9/L, compared with counts often approaching normal (150 x 10^9/L) in aHUS. Microangiopathic haemolysis also defines TMA; this is typically recognised by fragmented RBCs (i.e. schistocytes in peripheral blood smear) and an elevated lactate dehydrogenase (LDH) blood level. TMA is also defined by organ system involvement. Historically, the presence of neurological symptoms was thought to indicate TTP; however, it has since been shown that up to half of all individuals with aHUS can have CNS symptoms, including seizures, stroke, and encephalopathy.

With regard to renal disease, although the term ‘HUS’ inherently implies renal impairment, one in five individuals with an elevated lactate dehydrogenase (LDH) blood level. TMA is also defined by organ system involvement. Historically, the presence of neurological symptoms was thought to indicate TTP; however, it has since been shown that up to half of all individuals with aHUS can have CNS symptoms, including seizures, stroke, and encephalopathy.

### Abbreviations:

- eGFR = estimated glomerular filtration rate
- LDH = lactate dehydrogenase

### Figure 1. An algorithm for the diagnosis of thrombotic microangiopathy.

| Thrombocytopenia Platelet count <150 x 10^9/L or >25% decrease from baseline AND Microangiopathic haemolysis Schistocytes and/or elevated LDH and/or decreased haptoglobin and/or decreased haemoglobin |
| Neurological symptoms Confusion and/or seizures and/or other cerebral abnormalities |
| Renal impairment Elevated creatinine and/or decreased eGFR and/or elevated blood pressure and/or abnormal urinalysis |
| Gastrointestinal symptoms Diarrhoea and/or nausea and/or abdominal pain and/or gastroenteritis |

**TTP versus aHUS**

The differing pathophysiology of TTP and aHUS emphasises the need for differential treatment (Figure 2 – see page 3).

TTP, in almost all cases, is an acquired disease involving an autoantibody against the von Willebrand factor-cleaving protease, ADAMTS13. The role of ADAMTS13 is to turn off the clotting process and formation of platelet microthrombi in response to microvascular endothelial cell injury after the microvessel has been repaired. The presence of an autoantibody that inactivates ADAMTS13 results in the uncontrolled clotting process that is TTP. A vascular biopsy will show the presence of ‘platelet white’ clots, immunohistochemical staining will test for von Willebrand factor, ultra-high molecular weight complexes tethered to platelets, and there will be no evidence of inflammation. Treatment of TTP requires plasma exchange or infusion (PE/PI) because fresh frozen plasma contains high levels of ADAMTS13. PE/PI may also help to reduce autoantibody levels and remove some of the ultra-high molecular weight von Willebrand factor complexes. Even though aHUS may look clinically identical to TTP, albeit with one exception (lung involvement), its pathophysiology is very different. When the microvascular endothelium is injured, thrombin is generated and the thrombin exposes a normally unavailable site on complement factor 5 (C5) leaving it susceptible to cleavage by C5-convertase. This leads to the production of C5a (anaphylatoxin) and C5b-9 (lytic membrane attack complex). In addition, if the endothelial cell injury is associated with a condition that activates the alternative complement pathway, such as infection, autoimmune disease, pregnancy, and surgery, it is necessary to shut this process off. Otherwise, this can lead to the uncontrolled production of C5a and C5b-9 resulting in inflammation, haemolysis, and endothelial cell damage as well as a prothrombotic state that is associated with a clotting disorder. Individual susceptibility to be unable to control this pathway is not due to an acquired autoantibody but to a congenital genetic defect that is present from birth. Damage occurs when the alternative pathway is super-activated. Vascular biopsy will predominantly show the presence of “thrombi” clots, immunohistochemical staining will test for C5b-9, and there will be evidence of inflammation.

In aHUS, as with TTP treatment involves PE/PI, at least initially until the TMA is diagnosed as aHUS, since fresh frozen plasma contains some complement-controlling proteins. However, this is only a temporary measure. PE/PI may normalise platelet counts, haemoglobin and haptoglobin levels, and dramatically reduces LDH levels. PE/PI has no effect on the underlying pathophysiology of aHUS though and hence has no effect on the morbidity and mortality of the patient. Appropriate ongoing anti-complement therapy is therefore required.
Different TMAs have different aetiologies and it may be possible to identify the underlying complement-amplifying condition. The main complement-amplifying conditions are: infection, particularly diarrhoeal-type infections, autoimmune disorders, such as systemic lupus erythematosus (SLE) and scleroderma, malignant hypertension, and pregnancy. Certain drugs can also activate the complement pathway. In approximately one-third of cases it may not be possible to immediately identify the complement-amplifying condition but that does not exclude the possibility that the underlying cause of TMA is aHUS. In addition, TTP, as a thrombin-generating condition, has the potential to activate the alternative complement pathway. In approximately one-third of cases it may not be possible to immediately identify the complement-amplifying condition but that does not exclude the possibility that the underlying cause of TMA is aHUS. In addition, TTP, as a thrombin-generating condition, has the potential to activate the alternative complement pathway and cause aHUS in a congenitally-susceptible person, as can STEC infection, which is a diarrhoeal infection.

### aHUS is driven by uncontrolled activation of complement

There are multiple ways to activate the complement pathway. When the alternative complement pathway (which is in a continual state of low-level ‘tick over’ so that it is ready to deal with invading pathogens) is super-activated and a heterozygous mutation exists in just one of the complement regulatory proteins (the two main proteins being soluble complement factor H (CFH) and l) the combination is sufficient to precipitate the inability to control the pathway. The end result is inflammation induced by C5a and haemolysis and endothelial injury induced by C50-9.

aHUS is a chronic disease with life-threatening consequences and patient morbidity and mortality are not altered by PE/PI. On first clinical manifestation, 33-40% of aHUS patients progress to end-stage renal disease (ESRD) or death no matter how many PE/PI treatments are performed.

Genetic defects lead to chronic uncontrolled activation of the complement system

#### Treatment goal: Inhibit ongoing complement activation

PE/PI fails to inhibit complement activity that drives pathophysiology in aHUS

#### Treatment goal: Suppress inhibitor autoantibody; replace ADAMTS13

PE/PI replenishes ADAMTS13 and decreases autoantibodies

### Understanding aHUS in the differential diagnosis of TMA

The differential diagnosis of TMAs, with emphasis on aHUS and how these differences underscore the need for differential treatment. Note that apheresis procedures themselves may stimulate complement activity via granulocyte aggregation.

Abbreviations: PE/PI = plasma exchange/plasma infusion; vWF = von Willebrand factor.

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The differential diagnosis of TMAs, with emphasis on aHUS, is depicted in Figure 3 (see page 3). In terms of diagnosing aHUS, the primary signs and symptoms are reduced platelet count, evidence of microangiopathic haemolysis, and evidence of organ impairment (e.g. serum creatinine level greater than the upper limit of normal). Then the differentiation of aHUS from other TMAs requires ADAMTS13 activity to be >5%, which excludes severe ADAMTS13 deficiency (i.e. congenital or acquired TTP), and the absence of a positive STEC test, which excludes STEC as sole cause of TMA.

Once a diagnosis of TMA has been made and aHUS has been differentiated from TTP on the basis of ADAMTS13 and differentiated from STEC-HUS on the basis of a negative STEC test, there is little point conducting a complement gene analysis as a genetic mutation cannot be identified in 30% to 50% of aHUS patients. Hence, their measurement is not necessary for diagnosis of aHUS and does not have any prognostic significance. The identification of specific genetic mutations potentially has implications for long-term patient outcomes and may be important in genetic counselling of family members.

As to the value of measuring levels of complement protein and soluble complement regulatory factor, serum levels of complement proteins C3 and C4 may not be altered, and CFH levels are normal in about 50% of patients with aHUS who have a mutation in CFH. Hence, their measurement is not necessary for diagnosis of aHUS and does not have any prognostic significance. The difficulty in diagnosing aHUS lies in its clinical presentation being similar to that of other systemic TMAs and in its rarity (aHUS and TTP and have an incidence of approximately 2 per million in the general population), which leads to a lack of clinical suspicion. Furthermore, associated complement-amplifying conditions, such as malignant hypertension, can confound the diagnosis of aHUS.

### Figure 2. Differences in the pathophysiology of TTP and aHUS and how these differences underscore the need for differential treatment. Note that apheresis procedures themselves may stimulate complement activity via granulocyte aggregation.

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Any of the TMAs causing clotting disease in the microvasculature can affect any organ system, including extra-renal manifestations such as cardiovascular, gastrointestinal, and CNS disorders, as well as visual changes. However, the lung is never involved in TTP. Although some TTP patients will experience pulmonary symptoms, including dyspnoea, pulmonary haemorrhage, and pulmonary oedema due to back-flow issues caused by the cardiovascular and renal complications of TTP, biopsy of the lung will not show any microangiopathy. In contrast, the lung is involved about 30% of the time in aHUS.

### Figure 3. Differential Diagnosis of Thrombotic Microangiopathies

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It is also important to explore patient and family medical history in detail as doing so may reveal evidence of previously undiagnosed aHUS. The following patient or family medical history events are flags for aHUS as they are unusual in patients with TTP but not in those with aHUS:

- History of previous TMA.
- Unexplained renal failure.
- Malignant/severe hypertension.
- Unexplained stroke or myocardial infarction.
- Pre-eclampsia with renal involvement that persisted after pregnancy.

### Diagnosing aHUS in patients with complement-amplifying conditions

Complement-amplifying conditions present a situation in which aHUS can be unmasked in patients experiencing TMA who may otherwise go undiagnosed. Diarrhoea/gastroenteritis (24%), upper respiratory tract infection (18%), malignant hypertension (8%), and pregnancy (7%) are common complement-amplifying conditions at first clinical manifestation of aHUS, which have been demonstrated in two-thirds of patients. In a retrospective analysis of female patients with aHUS, 21% presented with TMA during pregnancy or post-partum; despite PE/PT treatments 81% of these women required haemodialysis and 62% progressed to ESRD within one month of first TMA manifestation. Additionally, aHUS is a known cause of TMA in patients with SLE; hence, aHUS should be considered as a diagnosis in all patients presenting with SLE and TMA.

The following are practical considerations in the diagnosis of aHUS in the setting of complement-amplifying conditions:

- Document the presence of the management of TMA.
- Establish that the patient has been adequately treated for the associated complement-amplifying condition.
- Recognise the kinetics of response to the management of TMA manifestations (thrombocytopenia, elevated LDH, haemolysis, etc.) typically seen in the patient, or comparable patients, with a given therapy.
  - If the patient has not had adequate time for a response, what should a complete response look like once adequate time has passed.
  - If the patient has had adequate therapy, have the signs and symptoms of TMA resolved.
- If the response was minimal or transient, consider aHUS.

### Case study 1: a TMA occurring in the setting of pregnancy and infection

A 24-year-old female who was 16 weeks pregnant presented to her obstetrician with a 2-day history of fever, marked fatigue, and diffuse abdominal pain. Her BP was 90/60 mmHg, but historically had been low normal. Fluids were administered. The following day her obstetrician could not detect a foetal heartbeat and the woman was referred to a hospital emergency department. Her temperature was 40.3°C and her BP was stable (94/58 mmHg). She had focal right upper quadrant abdominal pain/tenderness, new vaginal bleeding, respiratory distress, and bibasilar pulmonary opacities on chest x-ray. Fluids were given and antibiotics were initiated. Within 6 hours she became hypotensive and was intubated and pressor drugs were administered.

Laboratory tests revealed an international normalised ratio (INR) of 3.0; plasma prothrombin time (PTT) of 55 seconds; platelet count of 50 x 10^9/L to 60 x 10^9/L; serum creatinine of 2.0 mg/dL, which rose to 4.0 mg/dL by hospital day 2/3; LDH of 5000 IU/L; aspartate aminotransferase (AST) of 1600 IU/L and alanine aminotransferase (ALT) of 3000 IU/L; bilirubin (direct) of 10 mg/dL, which rose to 16 mg/dL by hospital day 4; and haptoglobin of <45 mg/dL. Endoscopy showed pus exuding from her gall bladder and blood culture grew Klebsiella spp. and Escherichia spp. Bronchoscopy revealed no evidence of infection, nor was there evidence of pulmonary oedema.

The primary diagnosis was sepsis and disseminated intravascular coagulation (DIC). Within 1.5 days of commencing antibiotic therapy, her INR and PTT had normalised and her temperature also returned to normal. However, her LDH level remained elevated and schistocytes were present on peripheral blood smear. Because her creatinine was still 4.0 mg/dL, and her platelet count was still only 60 x 10^9/L she was transferred to the hospital’s renal service where the nephrologist made a secondary diagnosis of HELLP syndrome (haemolysis, elevated liver enzymes, and low platelet count) versus eclampsia versus TTP. The patient was started on PE as well as continuous veno-venous haemofiltration (CVVH). Her platelet count and haptoglobin level normalised, and there was a dramatic reduction in her LDH level.

Two and a half days later, HELLP was discounted on the basis that it would be unlikely to occur at 16 weeks pregnancy and eclampsia was excluded on the basis of her low BP throughout the pregnancy, being protein-negative until this episode, and being hyporeflexive. TTP was therefore considered a valid diagnosis by the patient’s primary physician, despite ADAMTS13 study results (on blood drawn on day 3) available on day 7 showing ADAMTS13 activity of 28% and ADAMTS13 inhibitor (the presence of which is characteristic of TTP) not being detected. The CVVH was continued and haemodialysis was commenced on day 8.
Although there was marked improvement in her haematological parameters, the woman’s renal failure worsened, with her creatinine level reaching 7.0 mg/dL on day 10, and her LDH level was still not normal after several PE treatments. She also remained profoundly fatigued. On this basis, aHUS was suspected. Random skin biopsy was performed and immunohistochemical staining demonstrated terminal complement component deposition (in the form of C5b-9) in the microvasculature. A diagnosis of aHUS was therefore made. PE and haemodialysis were stopped and anti-C5 therapy with eculizumab was initiated. By the third dose of eculizumab the patient’s LDH and creatinine levels had normalised. Her fatigue also resolved and her unexplained pulmonary opacities had disappeared.

This case study illustrates the following factors in the management of aHUS:

1. It is a rare disease; if aHUS is not suspected it is not going to be found.
2. The clinical presentation of aHUS, including non-specific signs and symptoms, is similar to many diseases and conditions characterised by TMA (except for the lung, which appears to be frequently involved in aHUS).
3. Co-existing conditions, in this case pregnancy and infection, may mask aHUS.
4. It is almost impossible to make a diagnosis of TTP or aHUS in the setting of DIC – the DIC must first be cured.
5. Plasma intervention prior to ADAMTS13 blood draw artificially raises ADAMTS13 activity, i.e. PE should be stopped before ADAMTS13 blood draw. However, as most of these inhibitors are IgGs and of high titre, it is highly unlikely that -3 PE could have raised the patient’s ADAMTS13 from the TTP range (<5%) to 28%.
6. It should also be recalled that the “normal range” for ADAMTS13 activity of 67-120% is for a healthy adult without systemic microvessel injury. Such injury, regardless of cause, releases von Willebrand factor, which binds to ADAMTS13 in plasma and may reduce levels of this enzyme to <67%, but not to <5% (unless TTP is involved).
7. Non-renal tissue biopsy (e.g. lip, skin, rectum) is preferred to renal tissue biopsy in confirming a clinical diagnosis of aHUS since C5b-9 deposition occurs in normal renal mesangium, vessel walls, basement membrane, and Bowman’s capsule.
8. aHUS is often diagnosed late when there is already organ damage – it is not yet known how late a patient can be diagnosed before they can be rescued. Hence, diagnosis should be made as early as possible and therapy started without delay.
9. Historically there has been limited interest in differentiating aHUS from TTP because, until recently, no specific treatment for aHUS existed.
10. Anti-C5 therapy with eculizumab offers a therapeutic option in the treatment of aHUS associated with pregnancy and infection.

Case study 2: a TMA occurring 5.5 months post-allogeneic stem cell transplantation

A 33-year-old man with a history of a Janus kinase 2 (JAK2)-negative myelo-proliferative disease (MPD) since his late teens had recently progressed to myelofibrosis complicated by aHUS. He had undergone an allogeneic bone marrow transplant (BSCT) with full chimerism 13 months earlier. He engrafted quickly (day 15 after transplantation) and his splenomegaly decreased. He developed pruritic rash and laboratory results showed a platelet count of 20 x 10^9/L; haemoglobin of 7.6 g/dL; indirect bilirubin of 8.7 mg/dL; LDH of 439 IU/L; haptoglobin of <15 mg/dL; for the first time, schistocytes were recognised on aWBC count of 20 x 10^9/L. On day 172, he had lower body pruritic rash and laboratory results showed a platelet count of 9 x 10^9/L; LDH of 1663 IU/L; indirect bilirubin of 17 mg/dL; haptoglobin of 10 mg/dL; haemoglobin of 7.0 g/dL; LDH of 439 IU/L; transferrin saturation of 6%, total protein of 6.5 g/dL; and total bilirubin of 1.0 mg/dL. The patient’s LDH and creatinine levels had normalised. Her fatigue also resolved and her unexplained pulmonary opacities had disappeared.

This case study emphasises the following factors in the management of aHUS:

1. aHUS is a chronic and life-threatening disease that arises from genetic abnormalities that block control of the alternative complement system.
2. aHUS is a systemic TMA that affects multiple organs and tissues.
3. The clinical presentation of aHUS can resemble other systemic TMAs, but the underlying complement-based disease pathophysiology is different and warrants different management approaches.
4. PE/PF does not affect the underlying complement dysfunction that causes aHUS and does not alter morbidity and mortality in these patients.
5. aHUS should be a clinical diagnosis, which relies on recognition of signs and symptoms of TMA, evaluation of ADAMTS13 activity and results of Shiga toxin testing as appropriate.
6. Extensive microvascular deposition of C5b-9 supports the diagnosis of either aHUS or a subset of TTP patients with concomitant complement dysregulation. But such biopsy is not required for the diagnosis of aHUS in the vast majority of instances, nor has the sensitivity of this test for aHUS been established using large TMA patient cohorts.

References


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