Hematologic manifestation in MICRo angiopathic hemolytic anemia

k.Goudarzipour

Pediatric congenital hematologic disorders research center shahid beheshti university of medical sciense

- Case
- Mechanism
- Causes and DDx(hematology oncology)
- Hematologic manifestation
- Lab data
- PBS

CASE 1

- The pt is 4 y/o female , with cc of discoloration of urine, chills and fever since one week ago.in her past Hx: bloody diarrhea since 2 weeks ago.
- Lab data:
- WBC:18000.P:70,L:30

  RBC:3.000.000

  Hb:9

  MCV:96

  MCH:34

  MCHC:35.5

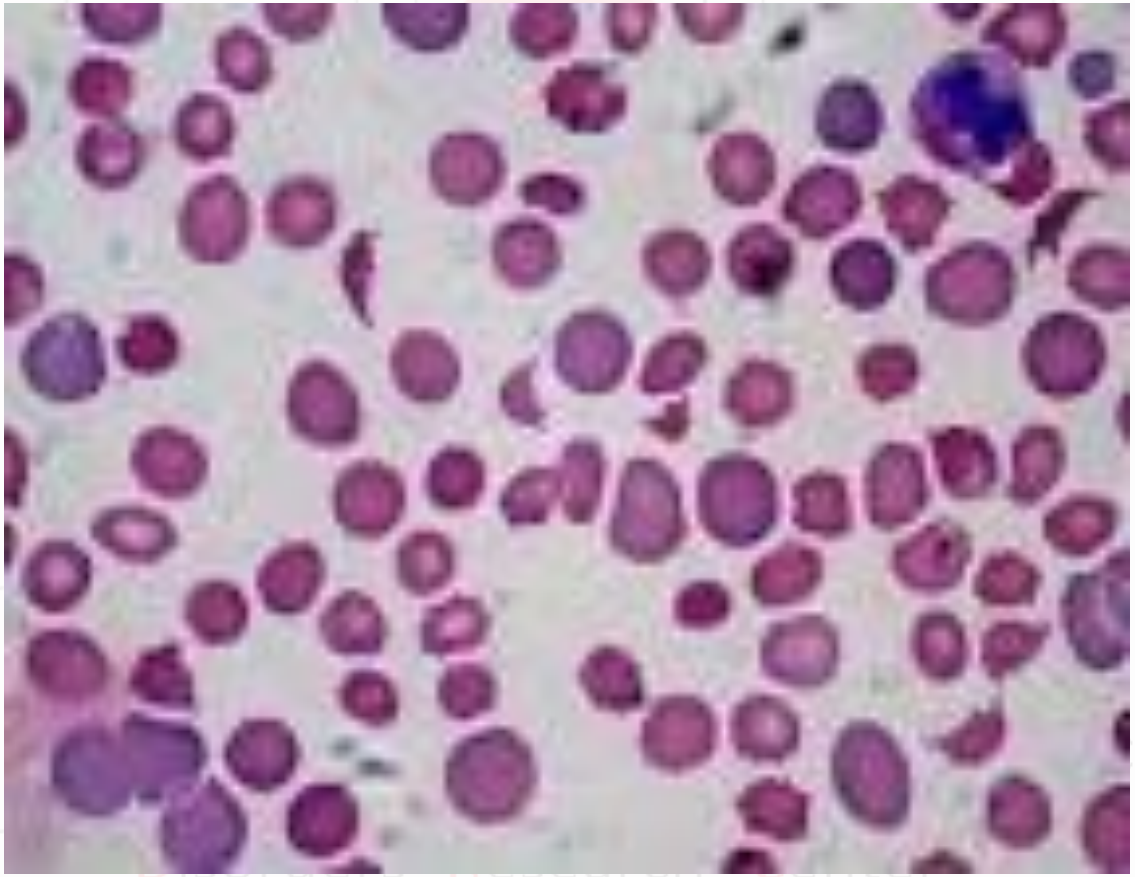
  PLT:168.000

  RDW:18

CASE 1

- Retic:12%
- Coomb,s:neg
- BUN:40
- Cr:1.6

CASE 1



CASE 2

- A 7 year-old previously healthy female, was admitted after three days abdominal pain, vomiting, headache, general malaise, one time convulsion and fever since the night prior to admission.

CASE 2

- Two weeks earlier, the patient noticed red urine and excessive gum bleeding during teeth brushing. No medications were . Physical examination revealed low grade fever of 37.8°C, blood pressure 121/54 mmHg, and regular heart rate of 89/min.

CASE 2

- There were some purpura on her legs and back, a moderate splenomegaly and mild jaundice.

CASE 2

- Laboratory tests at admission showed hemoglobin: 9.9 g/dl, white blood cells: 5.4 x109/L, platelets: 7 0.000and reticulocyte counts: 5.7%. Peripheral blood smear presenteded red blood cell fragmentation (schistocytes).

CASE 2

- Lactate dehydrogenase was 3,046 IU/L, aspartate aminotransferase 153 IU/L, gamma-glutamyl transferase 39 IU/L, alkaline phosphatase 138 IU/L, total bilirubin 6.6 mg/dl, direct bilirubin 2.5mg/dl. Blood urea nitrogen and creatinine were within normal limits.

CASE 2

- Urinalysis showed hematuria and hemoglobinuria. Coagulation screening tests were normal.

CASE 2

- Viral serology tests, including hepatitis B virus, hepatitis C virus, Epstein-Bar virus, cyto-megalo virus and parvo virus were all negative, as well as anti-nuclear antibodies, anti double-stranded DNA, anti Sm and anti RNP. C3 and C4 levels were normal. ADAM13 activity was 5%. Chest x-ray was normal, while abdominal ultra-sound showed moderate splenomegaly

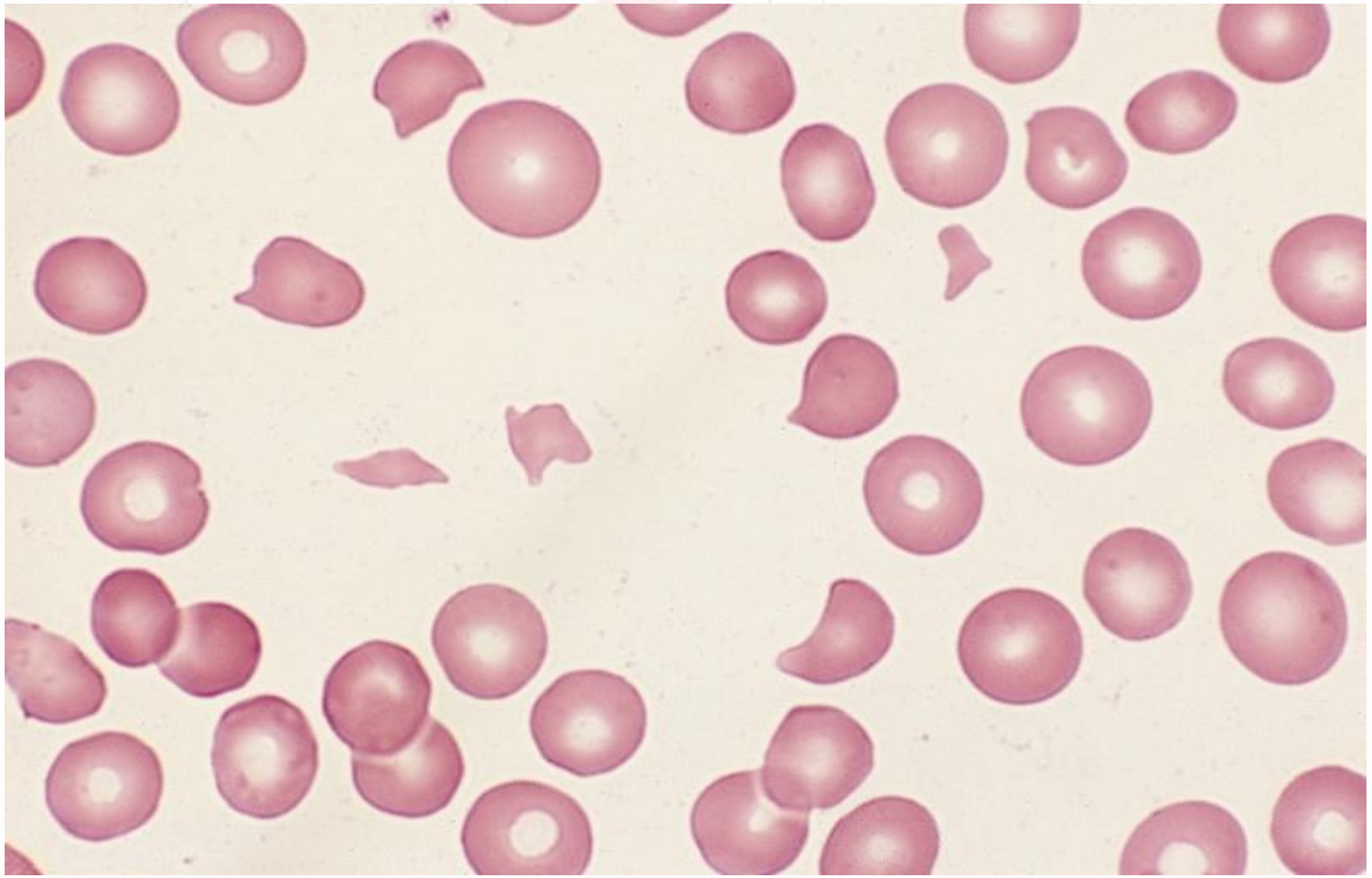
CASE 2

- A diagnosis of TTP was made, and treatment with intravenous methylprednisolone was started, but the hemoglobin continued to drop to levels of 5.9 mg/dl without significant improvement in the platelet count, which entitled red blood cell and platelet transfusions. Plasma-exchange was performed with significant improvement in platelets and hemoglobin levels.

CASE 2

- On the 8th day after admission, blood culture yielded Brucella. Brucella agglutination titer was positive .Brucella agglutination titer was 1/640 for Brucella abortus. Antibiotic treatment with doxycycline and gentamicin was commenced.

Case 2



- MAHA is a type of hemolytic anemia that occurs in numerous, but not all, conditions known as the "thrombotic microangiopathies (TMA)"
- Though diverse, TMAs are somewhat similar in that many involve endothelial injury and clotting activation in the microvasculature.
- the pathophysiology of the underlying disorder many times leads to microthrombi in capillaries and arterioles that results in end organ injury usually by ischemia

BCSLS Congress 2012
Kamloops, BC

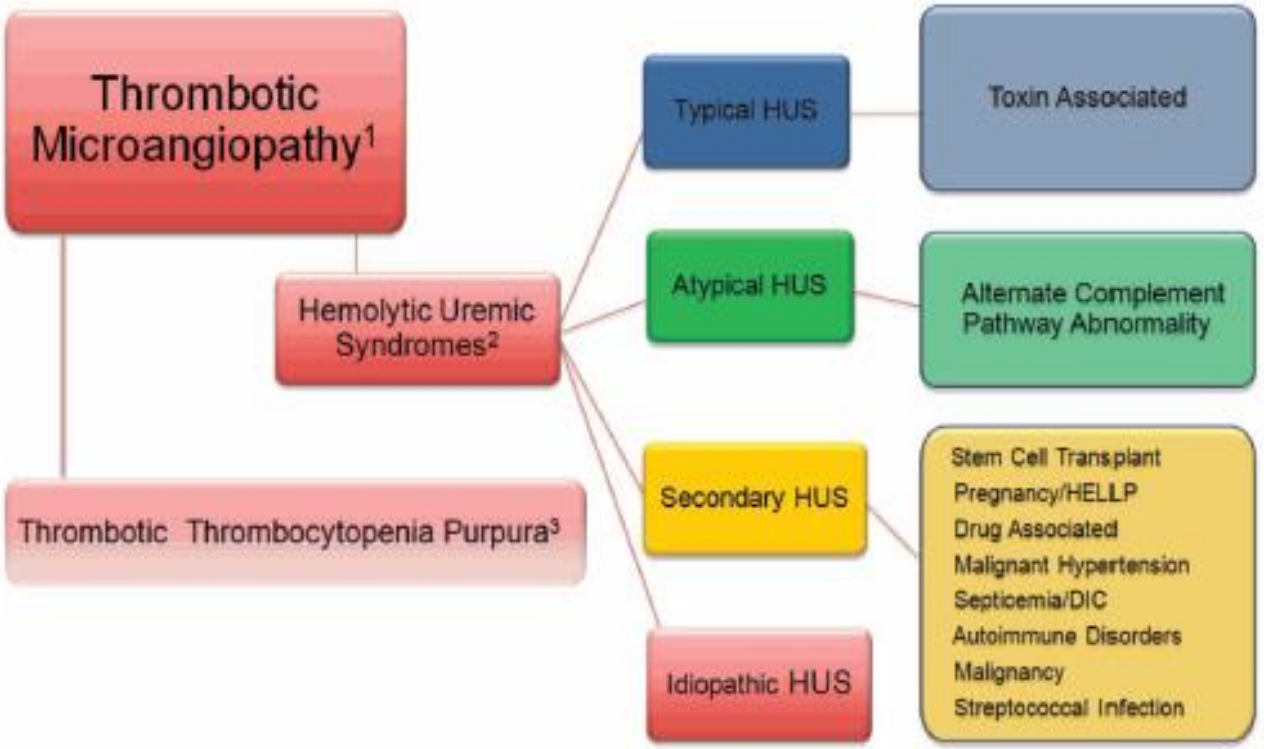
Dr. Gerry James
Royal Inland Hospital
Kamloops,BC
Interior Health

- the hemolysis that occurs in MAHA is due to physical destruction of the red blood ce in the small blood vessels as they pass by the microthrombi

- characterized by red cell fragmentation and associated with peripheral thrombocytopenia

BCSLS Congress 2012
Kamloops, BC

Dr. Gerry James
Royal Inland Hospital
Kamloops,BC
Interior Health



Atypical hemolytic uremic syndrome: what is it, how is it diagnosed, and how is it treated?

Carla M. Nester[1,2] and Christie P. Thomas[1,2]

- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic uremic syndrome (HUS)
- Other TMA syndromes can occur with:
  - Disseminated intravascular coagulation (DIC)
  - Pregnancy
  - Cancer and chemotherapy
  - HIV infection
  - post hematopoeitic stem cell transplant
  - drugs (ie. quinine)

BCSLS Congress 2012
Kamloops, BC

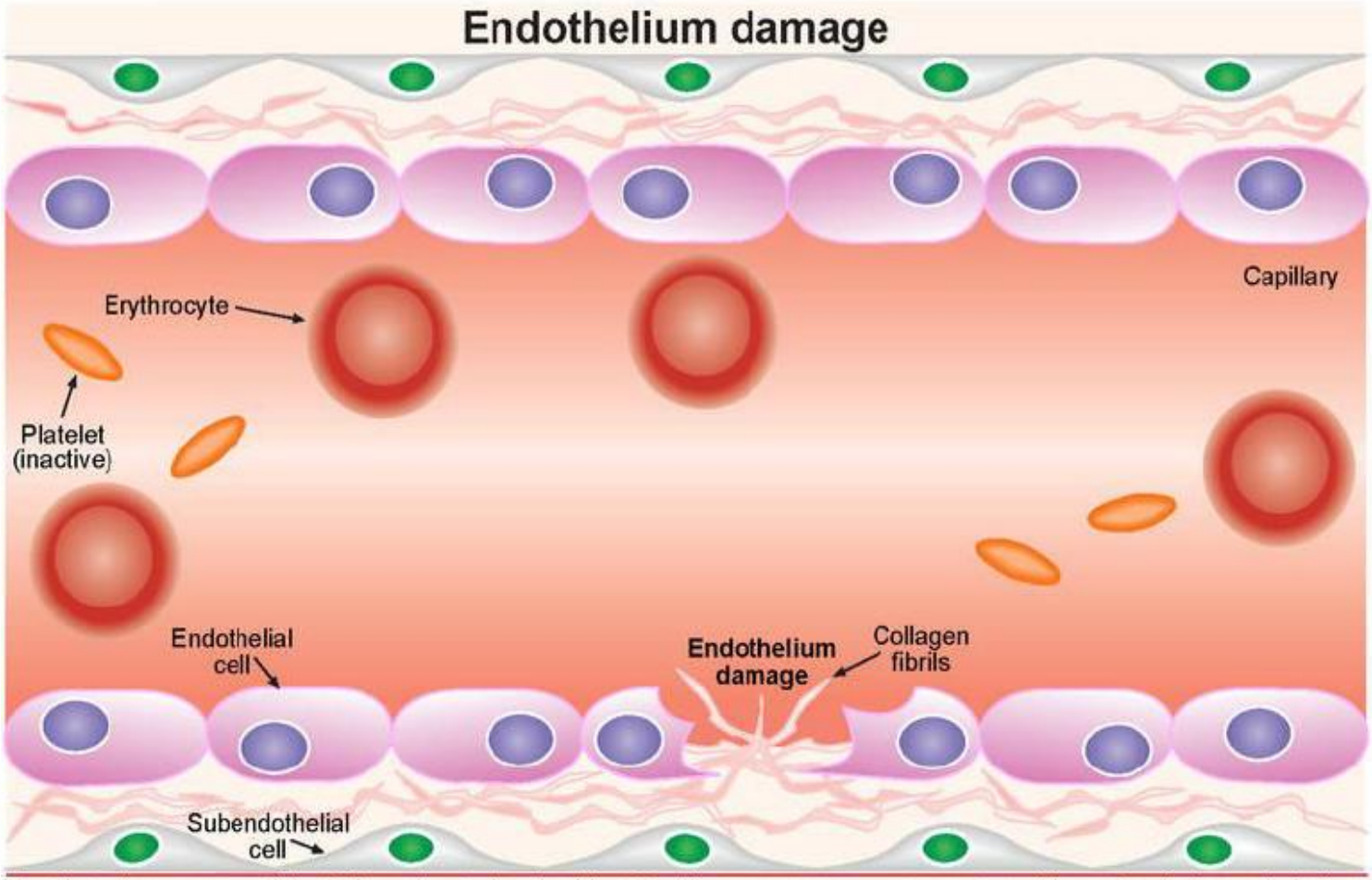
Dr. Gerry James
Royal Inland Hospital
Kamloops,BC
Interior Health

TTP Pathophysiology

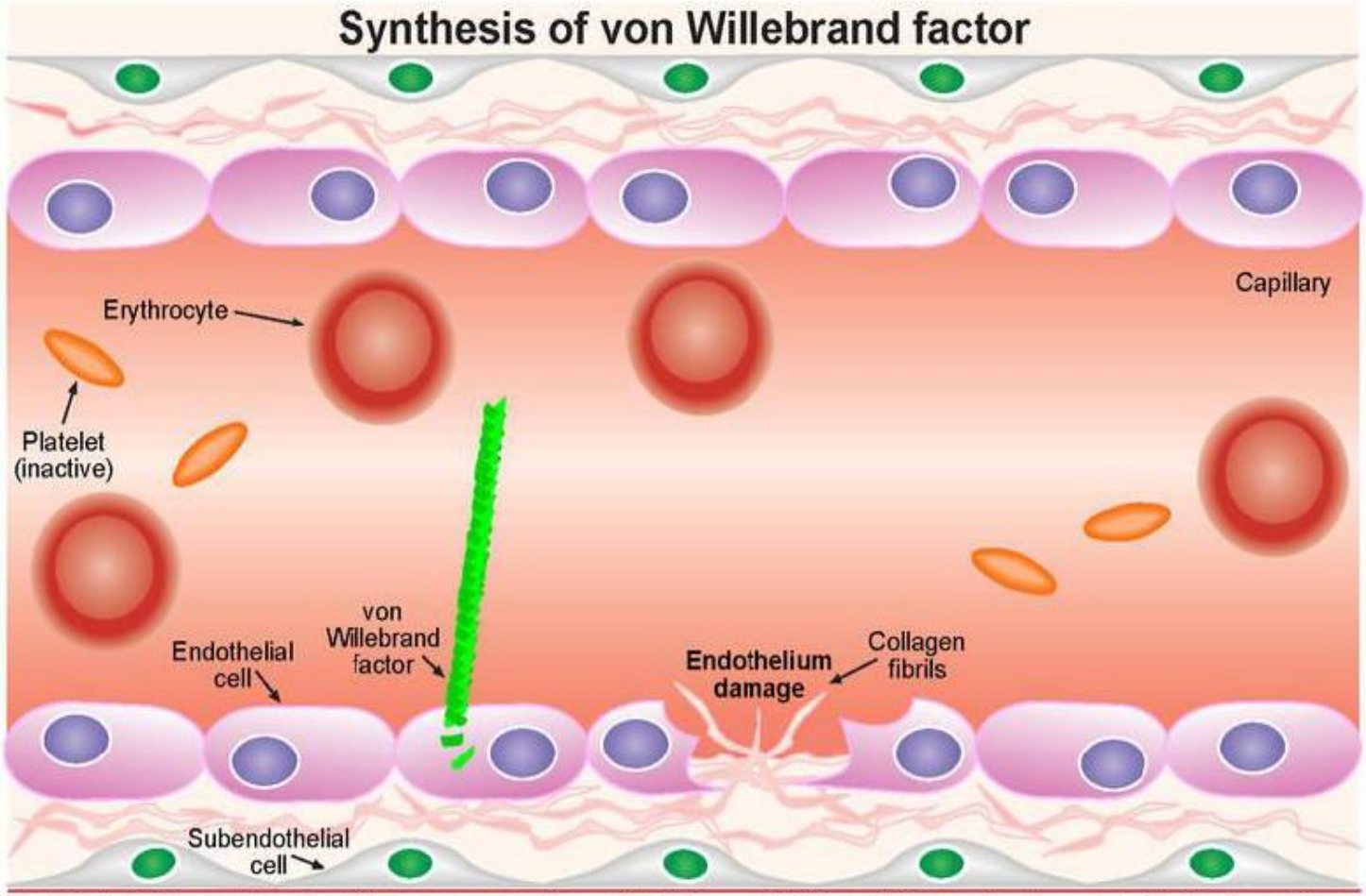
- ultimate cause is unknown
- endothelium damage (possibly from infection) and activation of clot formation may be involved as an initiation event
- vonWillebrand factor (vWF) plays a central role in the pathogenesis of TTP
  - a large multimeric protein involved in the initiation of platelet clumping
- patients with TTP lack a protease enzyme that is essential in the breakdown of ultralarge vWF multimers
- ADAMTS13 – a disintegrinlike and metalloprotease with thrombospondin type 1 motif 13

BCSLS Congress 2012
Kamloops, BC

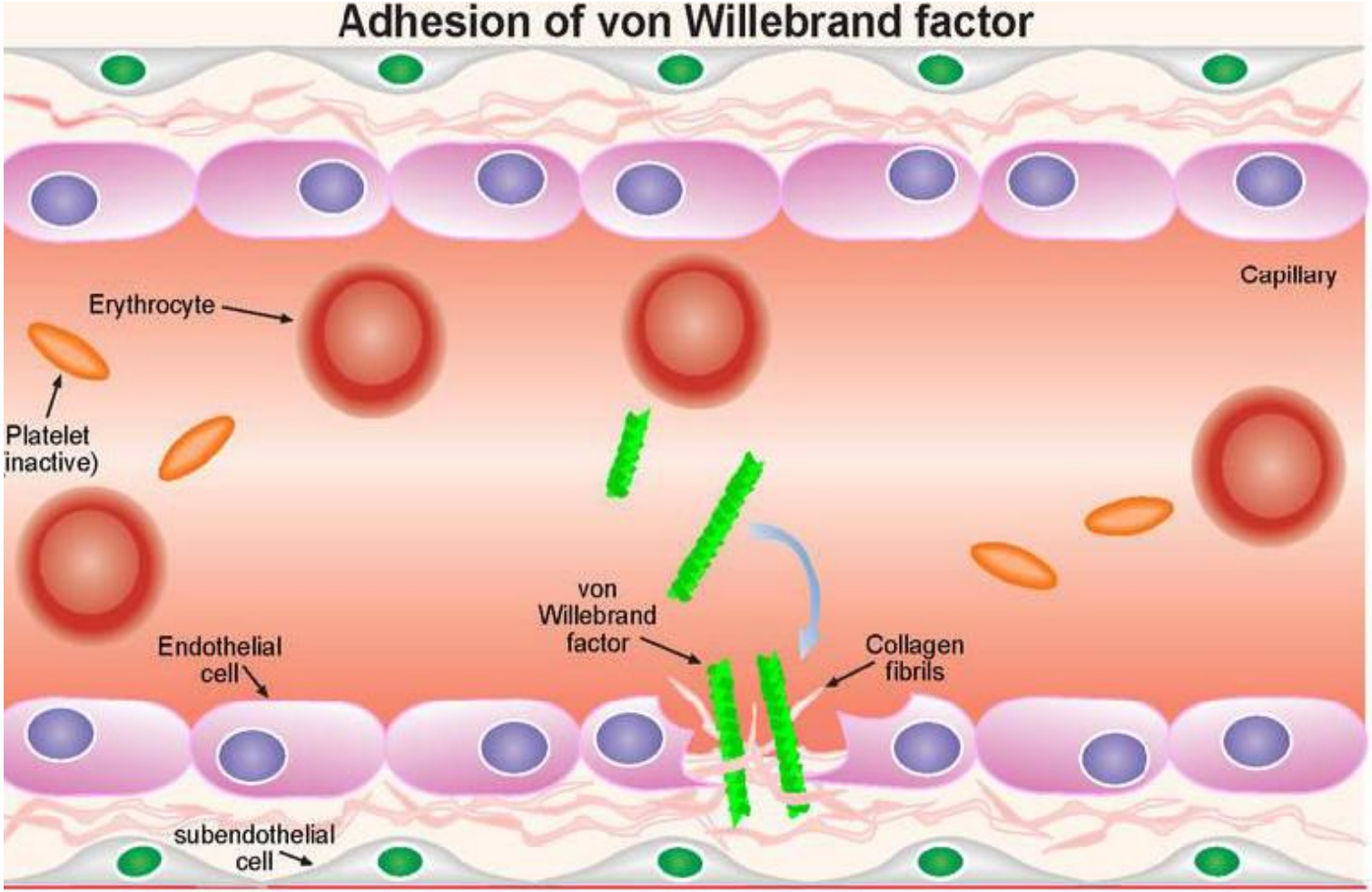
Dr. Gerry James
Royal Inland Hospital
Kamloops,BC
Interior Health



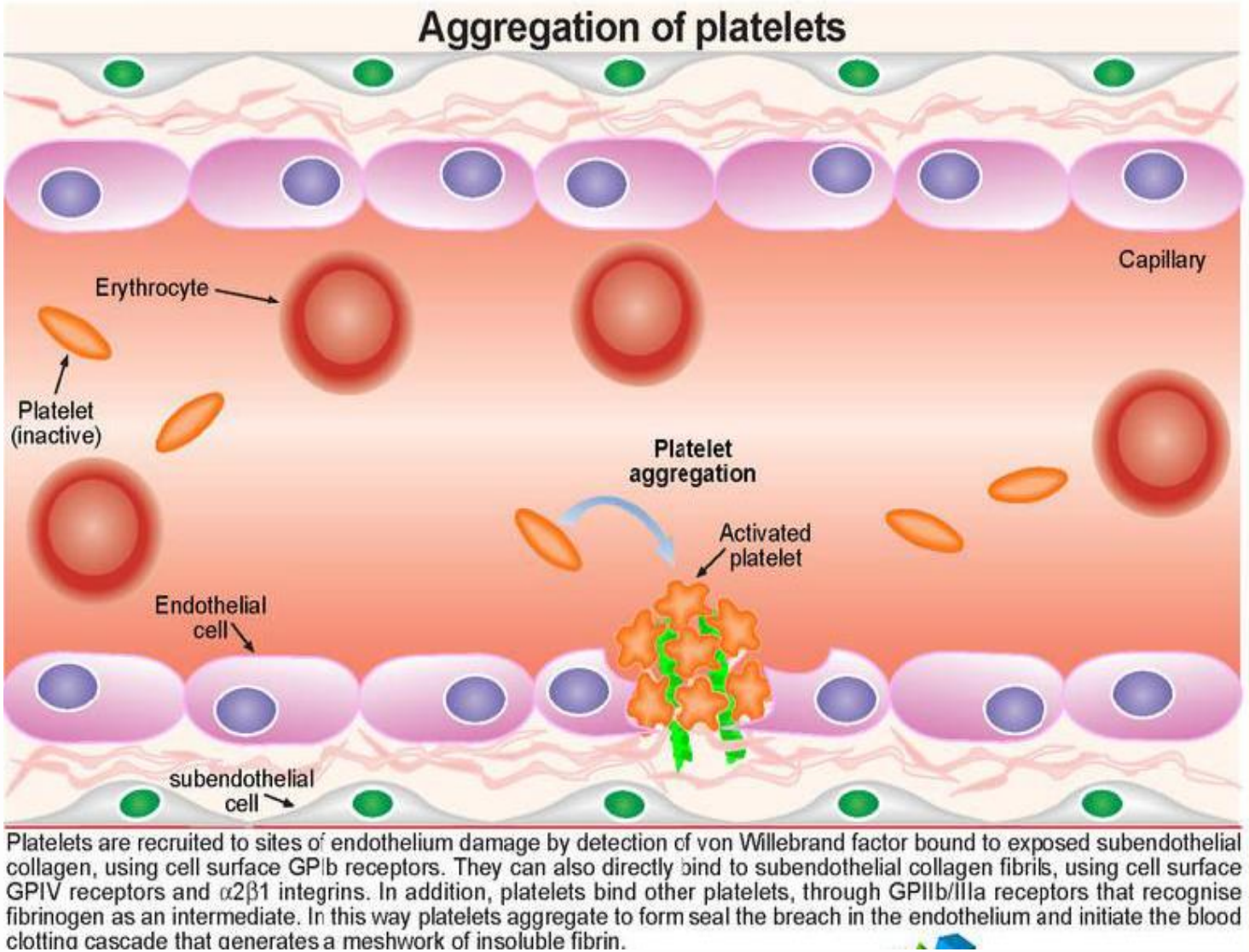
Platelets play an essential role in orchestrating the blood clotting processes necessary to seal breaches in the endothelium of blood vessels that may be caused through injury. Platelets circulate in an inactive form for a 9-10 days before removal by the spleen. Recruitment and activation of platelets at sites of endothelium damage is dependent on cellular factors, such as von Willebrand factor, produced by endothelial cells.



Endothelial cells near the site of damage respond by synthesising von Willebrand factor which is secreted in the form of large multimeric chains. Platelets express cell surface receptors, such as GP1b, that allow them to adhere to von Willebrand factor bound to subendothelial collagen fibrils.

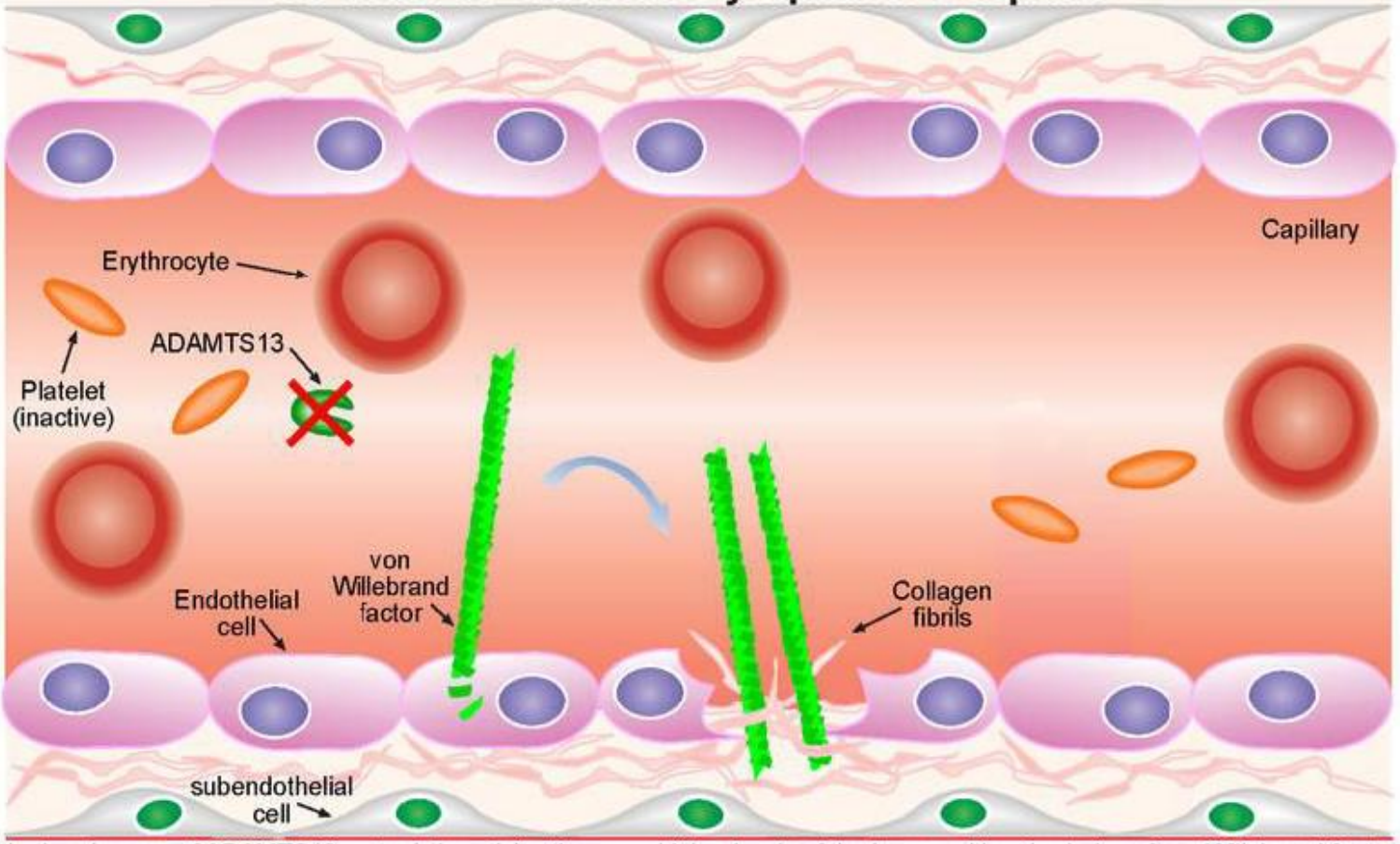


Von Willebrand factor binds to subendothelial collagen fibrils that become exposed at the site of endothelium damage.



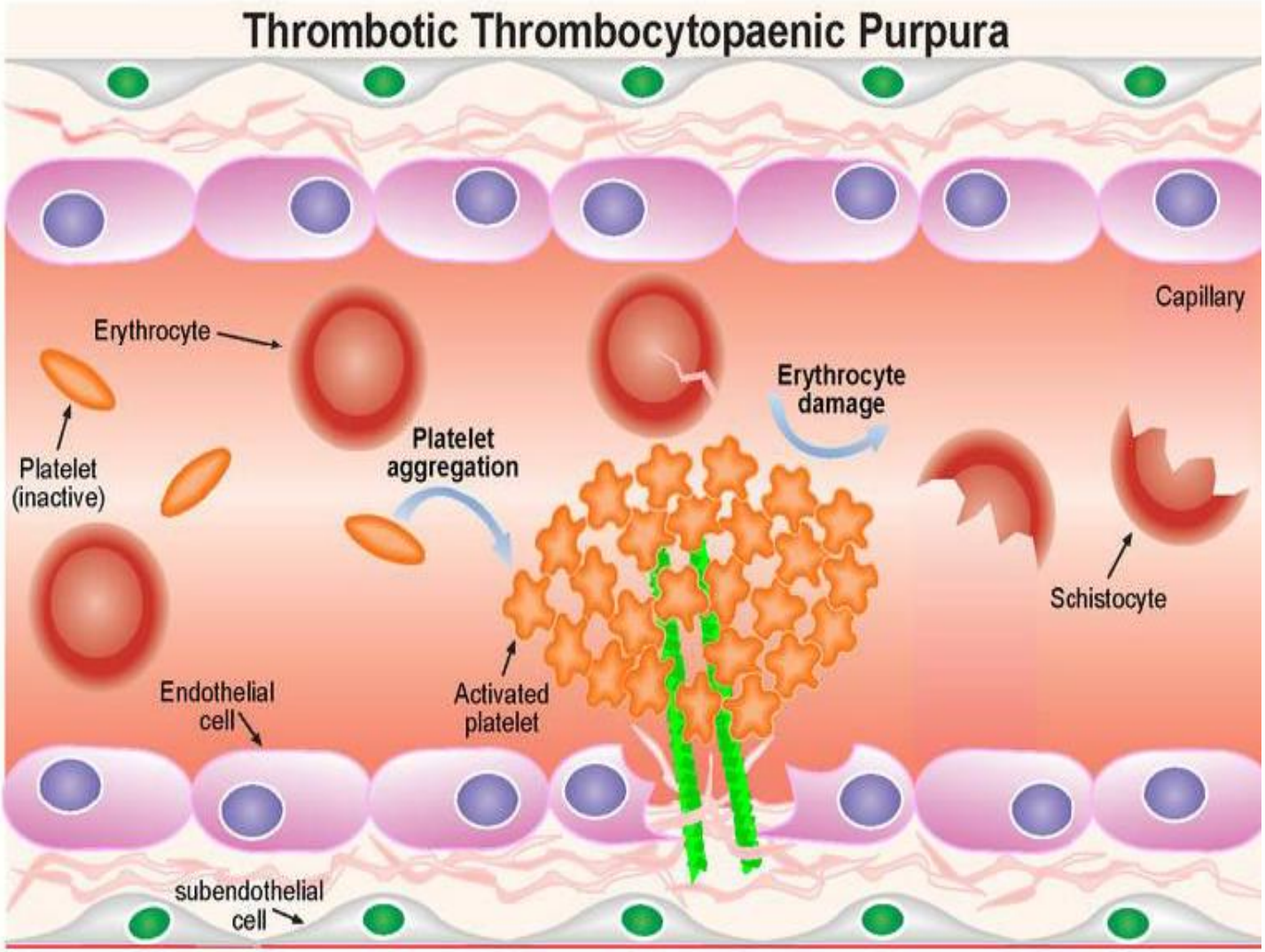
Platelets are recruited to sites of endothelium damage by detection of von Willebrand factor bound to exposed subendothelial collagen, using cell surface GPIb receptors. They can also directly bind to subendothelial collagen fibrils, using cell surface GPIV receptors and $\alpha 2\beta 1$ integrins. In addition, platelets bind other platelets, through GPIIb/IIIa receptors that recognise fibrinogen as an intermediate. In this way platelets aggregate to form seal the breach in the endothelium and initiate the blood clotting cascade that generates a meshwork of insoluble fibrin.

Thrombotic Thrombocytopaenic Purpura

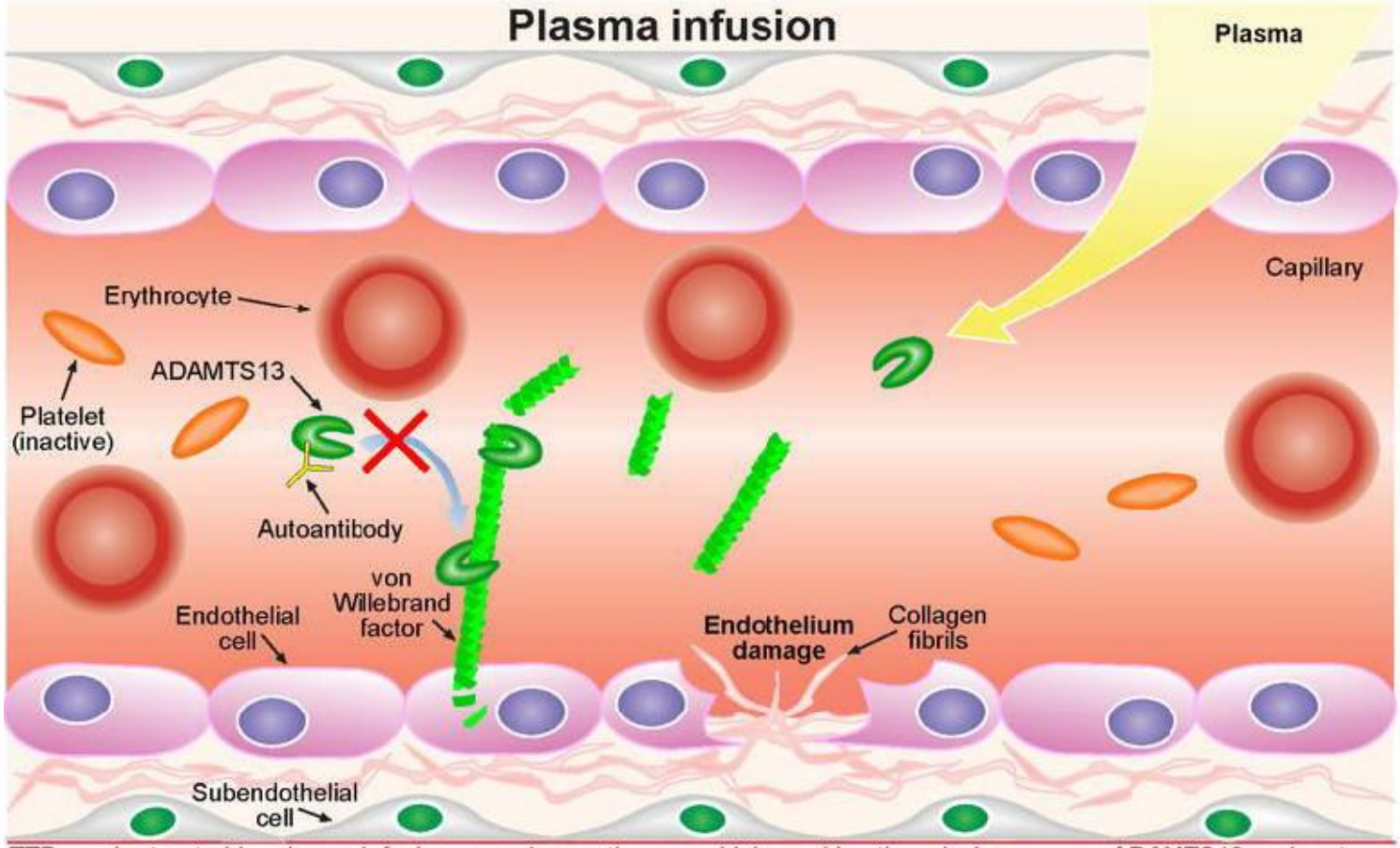


In the absence of ADAMTS13 proteolytic activity, there are higher levels of the large multimeric chains of von Willebrand factor in circulation that are able to bind to exposed subendothelial collagen fibrils and initiate recruitment of large numbers of platelets to sites of endothelium damage.

N ENGL J MED 371;7 NEJM.ORG AUGUST 14, 2014



Platelets express cell surface GPIb receptors that recognise von Willebrand factor bound to collagen fibrils exposed at th site of endothelium damage. In TTP, the large multimeric chains of von Willebrand factor recruit and activate excessive numbe of platelets, which in turn leads to platelet depletion (thrombocytopaenia). The large aggregation of platelets also impedes th passage of erythrocytes through small blood vessels and can cause the cells to shear, resulting in anaemia and organ ischaemi Fragments of erythrocytes are visible in blood smears and are known as schistocytes



TTP can be treated by plasma infusion or exchange therapy which provides the missing enzyme ADAMTS13 and restores proteolytic cleavage of the large multimeric chains of von Willebrand factor into smaller fragments. Plasma exchange therapy additionally contributes to the removal of the ADAMTS13 inhibitor, such as autoantibodies.

Coppo and Veyradier
Thrombotic Microangiopathies: Towards a Pathophysiology-Based Classification
Cardiovascular &Haematological Disorders – Drug Targets, 2009, Vol 9, No.1, pp36-50.

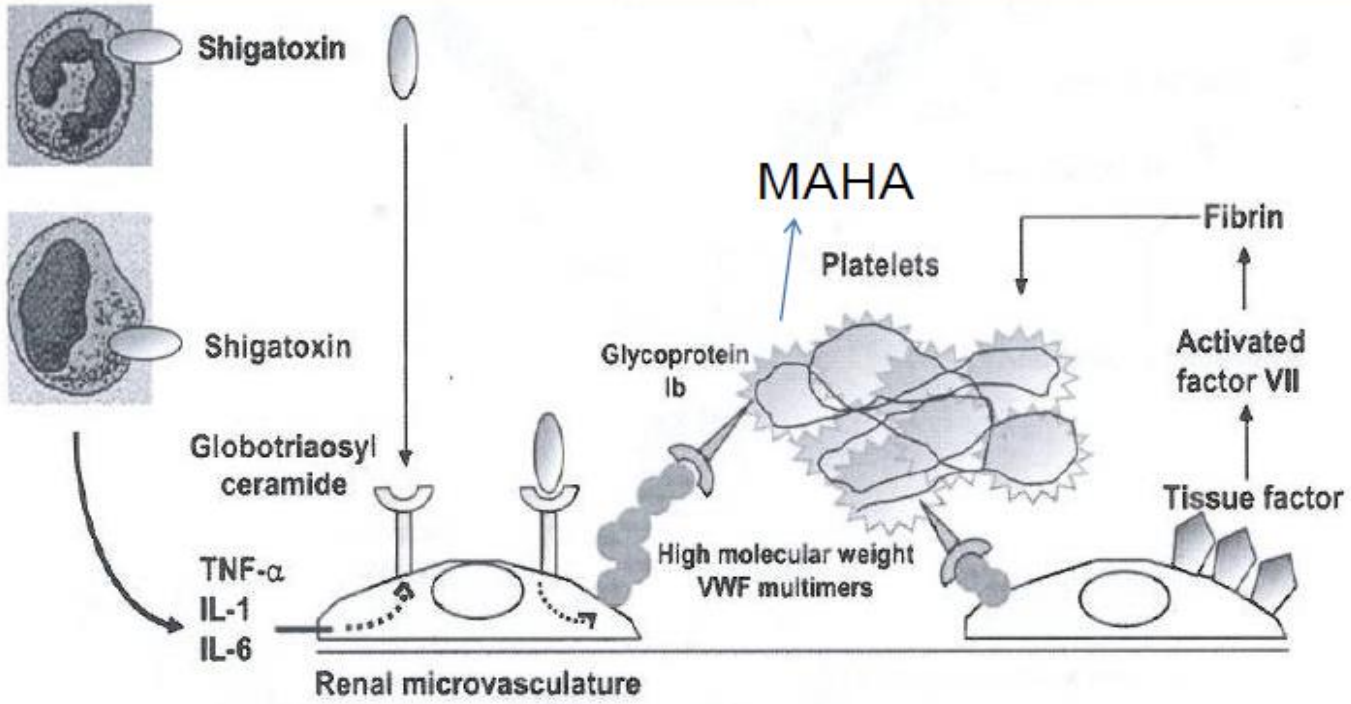


Fig. (4). Pathophysiological mechanisms leading to microthrombi formation in diarrhea-associated HUS. Shigatoxins are transported in blood flow by neutrophils, platelets and monocytes, and bind their receptors (globotriaosyl ceramide) at the surface of renal endothelial cells. IL-1, IL-6 and TNF-α up-regulate expression of shigatoxins receptors on endothelial cells surface. After internalization, they interfere with protein traduction machinery and thereby induce endothelial cell apoptosis. Damaged cells express surface high molecular weight VWF, which initiates platelet clumping through interaction with glycoprotein Ib. Shigatoxins also induce tissue factor expression on endothelial cells, leading to factor VII activation and fibrin formation. VWF: von Willebrand factor.

D- HUS Pathophysiology

- Complement proteins are part of our immune system that act in a controlled way to destroy invading microorganisms.
- Normally, these complement proteins are regulated by other proteins (ie.Factor H,I,CD46/MCP) so our own cells are not destroyed.
- If there are genetic mutations (or rarely, loss of action by an autoantibody) in these regulator proteins our own cells come under attack by excessive activation of the complement pathway.

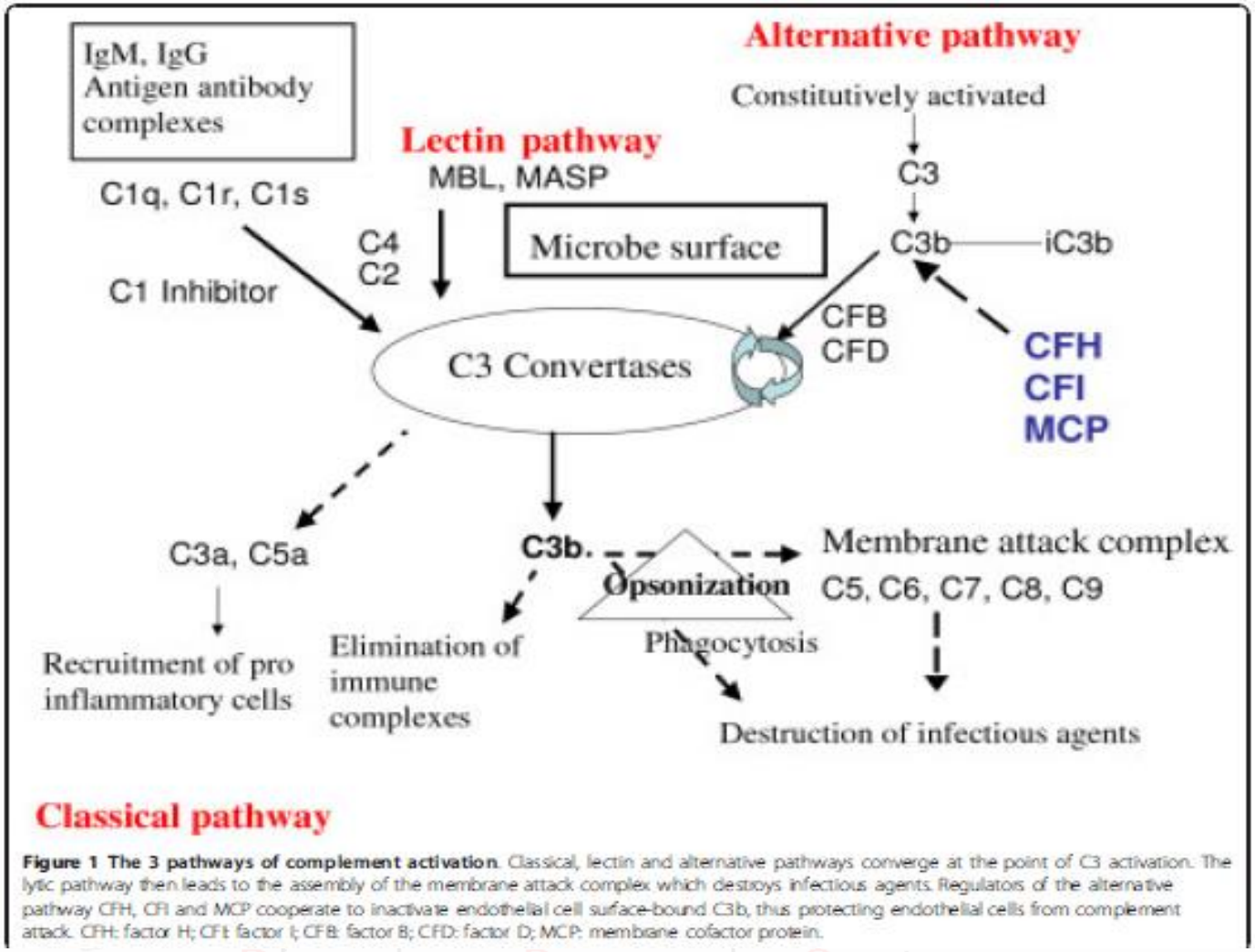


Figure 1 The 3 pathways of complement activation. Classical, lectin and alternative pathways converge at the point of C3 activation. The lytic pathway then leads to the assembly of the membrane attack complex which destroys infectious agents. Regulators of the alternative pathway CFH, CFI and MCP cooperate to inactivate endothelial cell surface-bound C3b, thus protecting endothelial cells from complement attack. CFH: factor H; CFI: factor I; CFB: factor B; CFD: factor D; MCP: membrane cofactor protein.

Table 2. Common Disorders Associated with Microangiopathic Hemolytic Anemia and Thrombocytopenia.*

Systemic infection
Systemic cancer
Severe preeclampsia, eclampsia, HELLP syndrome
Severe hypertension
Autoimmune disorders (e.g., systemic lupus erythematosus, systemic sclerosis, antiphospholipid syndrome)
Hematopoietic stem-cell or organ transplantation

N ENGL J MED 371;7 NEJM.ORG AUGUST 14, 2014

The New England Journal of Medicine
Downloaded from nejm.org on September 11, 2015. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

Table I. Characteristic spectrum of pathophysiological features seen in microangiopathic haemolytic anaemia.

Diagnosis	TTP	HUS	Pre-eclampsia/ eclampsia	HELLP	DIC
CNS symptoms/signs	+++	+/–	+/–	+/–	+/–
Renal impairment	+/–	+++	+	+	+/–
Fever	+/–	–/+	–	–	+/–
Liver impairment	+/–	+/–	+/–	+++	+/–
Hypertension	–/+	+/–	+++	+/–	–
Haemolysis	+++	++	+	++	+
Thrombocytopenia	+++	++	+/–	++	+++
Coagulopathy	–	–	+/–	+/–	+++

British Journal of Haematology, 2003, 120, 556–573

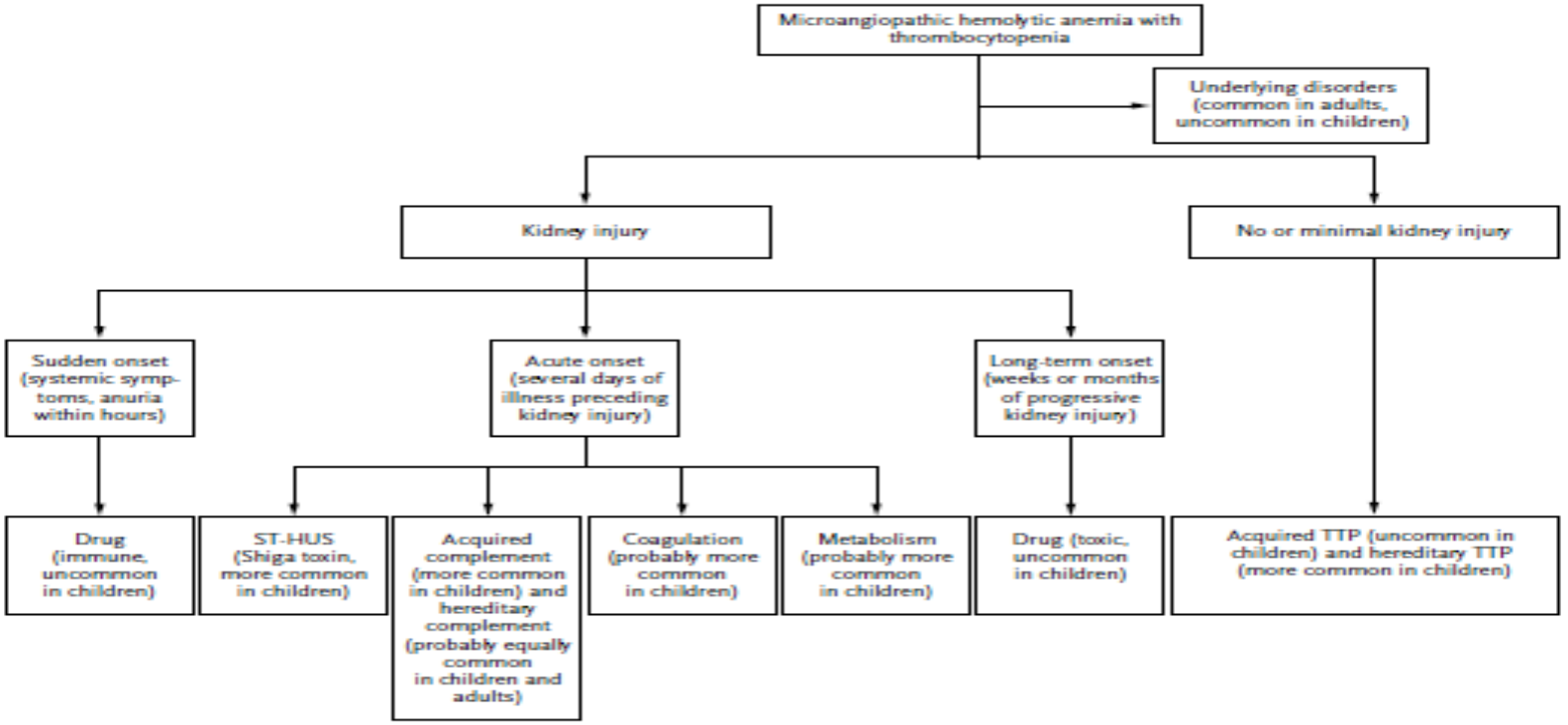
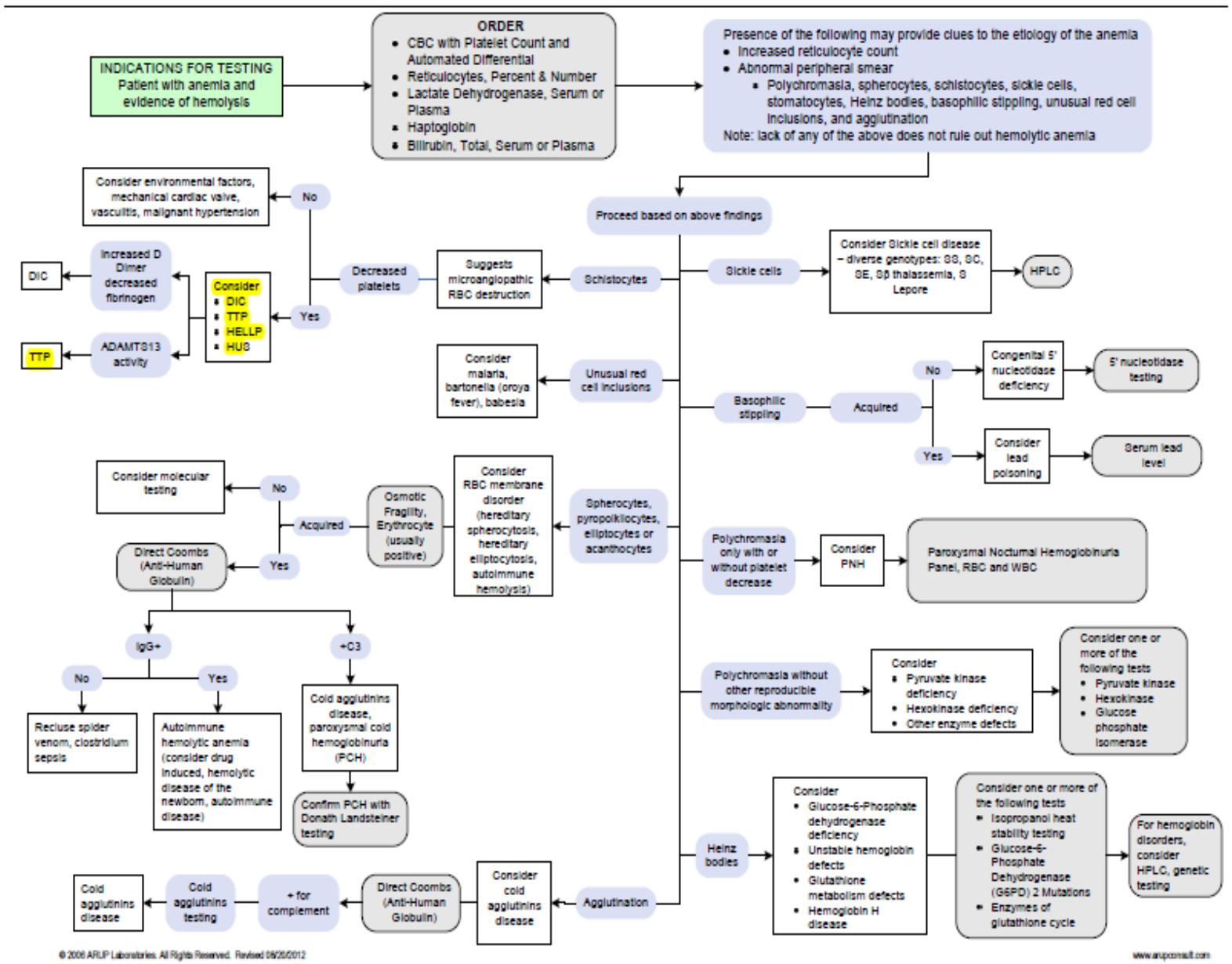


Figure 3. Algorithm for the Evaluation of Children and Adults Presenting with Microangiopathic Hemolytic Anemia and Thrombocytopenia. After the exclusion of common underlying disorders, the severity of kidney injury is a distinguishing feature. Among patients with severe acute kidney injury, the initial clinical diagnosis is related to the pace of onset of kidney injury. In this regard, complement-mediated TMA that may be acquired is not distinguished from hereditary complement-mediated TMA. Although kidney injury is characteristic of complement-mediated TMA, it may be minimal. Several conditions (e.g., pregnancy, surgery, and inflammatory disorders) may precipitate acute TMA episodes. Not included in this algorithm are patients with microangiopathic hemolytic anemia and thrombocytopenia in whom neither an underlying condition nor a primary TMA syndrome is identified. Such patients with idiopathic disease represent about 20% of all adults who present with microangiopathic hemolytic anemia and thrombocytopenia. TTP is also called ADAMTS13 deficiency–mediated TMA.



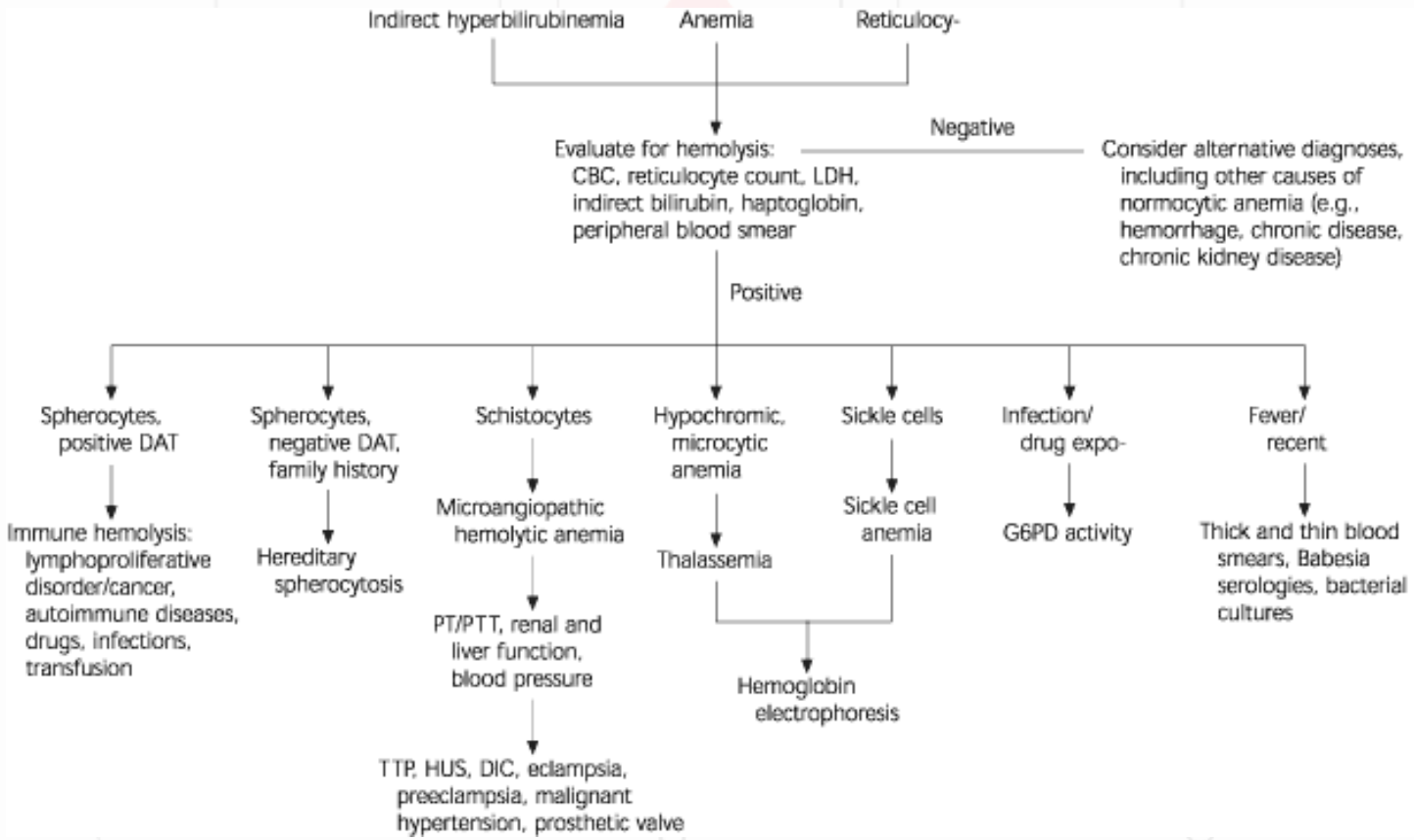


Table I. Differential diagnosis of thrombocytopenia and microangiopathic haemolytic anaemia.

Autoimmune haemolysis/Evans syndrome
Disseminated intravascular coagulation
Pregnancy-associated e.g. HELLP (haemolysis, elevated liver enzymes and low platelets), eclampsia, haemolytic uraemic syndrome
Drugs eg quinine, simvastatin, interferon, Calcineurin inhibitors
Malignant hypertension
Infections, typically viral (cytomegalovirus, adenovirus, herpes simplex virus) or severe bacterial (meningococcus, pneumococcus), fungal
Autoimmune disease (lupus nephritis, acute scleroderma)
Vasculitis
Haemolytic uraemic syndrome (diarrhoea positive/negative)
Malignancy
Catastrophic antiphospholipid syndrome

Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies

Marie Scully,[1] Beverley J. Hunt,[2] Sylvia Benjamin,[3] Ri Liesner,[4] Peter Rose,[5] Flora Peyvandi,[6] Betty Cheung,[7] Samuel J. Machin[8] and on behalf of British Committee for Standards in Haematology

Table V. Differential Diagnosis of haemolytic uraemic syndrome.

Infection (diarrhoea-positive)	Shiga & *verocytoxin* (Shiga-like toxin)-producing bacteria
Disorders of complement regulation (diarrhoea-negative)	Genetic disorders of complement regulation e.g. Factor H, I, MCP (CD46), factor B (*CFB*), C3 (C3), thrombomodulin
	Acquired disorders of complement regulation e.g. anti-FH antibody
Other causes of secondary HUS	*Streptococcus pneumoniae*
	HIV
	Malignancy
	Defective cobalamin metabolism
	Drugs e.g. quinine, some chemotherapy e.g. gemcitabine, bleomycin)
	Pregnancy
	Other autoimmune diseases e.g. SLE, APLS

HUS, haemolytic uraemic syndrome; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus; APLS, antiphospholipid syndrome.

Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies

Marie Scully,[1] Beverley J. Hunt,[2] Sylvia Benjamin,[3] Ri Liesner,[4] Peter Rose,[5] Flora Peyvandi,[6] Betty Cheung,[7] Samuel J. Machin[8] and on behalf of British Committee for Standards in Haematology

Table II. Presenting clinical features and signs in acute TTP.

Thrombocytopenia	Epistaxis, bruising, petechiae, gingival bleeding, haematuria, menorrhagia, gastrointestinal bleeding, retinal haemorrhage and haemoptysis
Central neurological – often flitting and variable 70–80%	Confusion, headache, paresis, aphasia, dysarthria, visual problems, encephalopathy, coma (10%)
Fever (>37·5°C)	
Non-specific symptoms	Pallor, jaundice, fatigue, arthralgia or myalgia
Jaundice	Resulting from microangiopathic haemolytic anaemia
Renal Impairment	Proteinuria, microhaematuria
Cardiac	Chest pain, heart failure, hypotension
Gastro-intestinal tract	Abdominal pain

Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies

Marie Scully,[1] Beverley J. Hunt,[2] Sylvia Benjamin,[3] Ri Liesner,[4] Peter Rose,[5] Flora Peyvandi,[6] Betty Cheung,[7] Samuel J. Machin[8] and on behalf of British Committee for Standards in Haematology

Table III. Recommended diagnostic laboratory investigations at presentation of TTP.

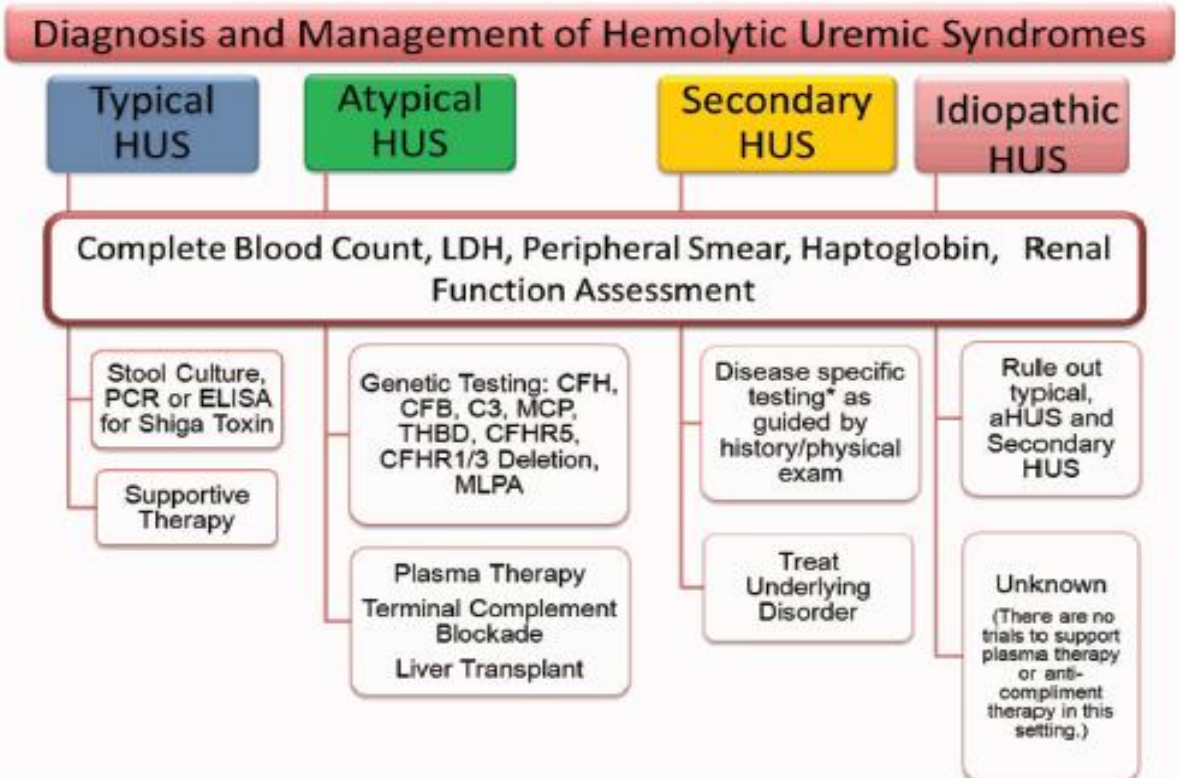
Full blood count and blood film
Reticulocyte count
Clotting screen including fibrinogen and D-dimers
Urea and electrolytes
Liver function tests
Lactate dehydrogenase
Urinalysis
Direct antiglobulin test

Table III. Testing and expected results for patients with a suspected diagnosis of TTP. Blood samples should be sent for investigation before first PEX.

For diagnosis	
Full blood count and blood film	Anaemia, thrombocytopenia, fragments on film
Reticulocyte count	Raised
Haptoglobin	Reduced
Clotting screen including fibrinogen	Normal
Urea and electrolytes	Renal impairment
Troponin T/Troponin I	For cardiac involvement
Liver function tests	Usually normal
Calcium	May reduce with PEX
Lactate dehydrogenase	Raised due to haemolysis
Urinalysis	For protein
Direct antiglobulin test	Negative
Blood group and antibody screen	To allow provision of blood products
Hepatitis A/B/C and human immunodeficiency virus testing	Pre-blood products and to exclude an underlying viral precipitant
Pregnancy test (in women of child-bearing age)	
ADAMTS 13 assay (activity/ antigen and inhibitor/antibody in specialized laboratory)	Do not wait for result before starting treatment in suspected TTP
Electrocardiogram/Echocardiogram	To document/monitor cardiac damage
CT/MRI brain	To determine neurological involvement*
For possible underlying cause	
Thyroid function tests	To exclude Graves Disease
Auto-antibody screen (ANA/RF/ LA/ACLA), including lupus anticoagulant	Exclude associated autoimmune disease
Stool culture	For pathogenic *Escherichia coli* (if diarrhoea)
CT Chest/abdomen/pelvis (if indicated) ± tumour markers	To look for underlying malignancy

Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies

Marie Scully,[1] Beverley J. Hunt,[2] Sylvia Benjamin,[3] Ri Liesner,[4] Peter Rose,[5] Flora Peyvandi,[6] Betty Cheung,[7] Samuel J. Machin[8] and on behalf of British Committee for Standards in Haematology



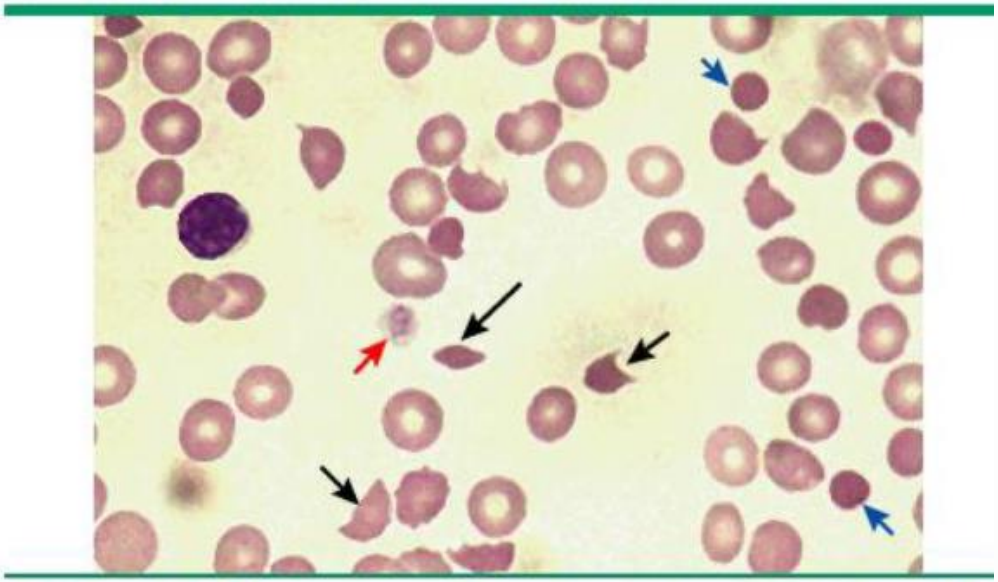
Atypical hemolytic uremic syndrome: what is it, how is it diagnosed, and how is it treated?

Carla M. Nester[1,2] and Christie P. Thomas[1,2]

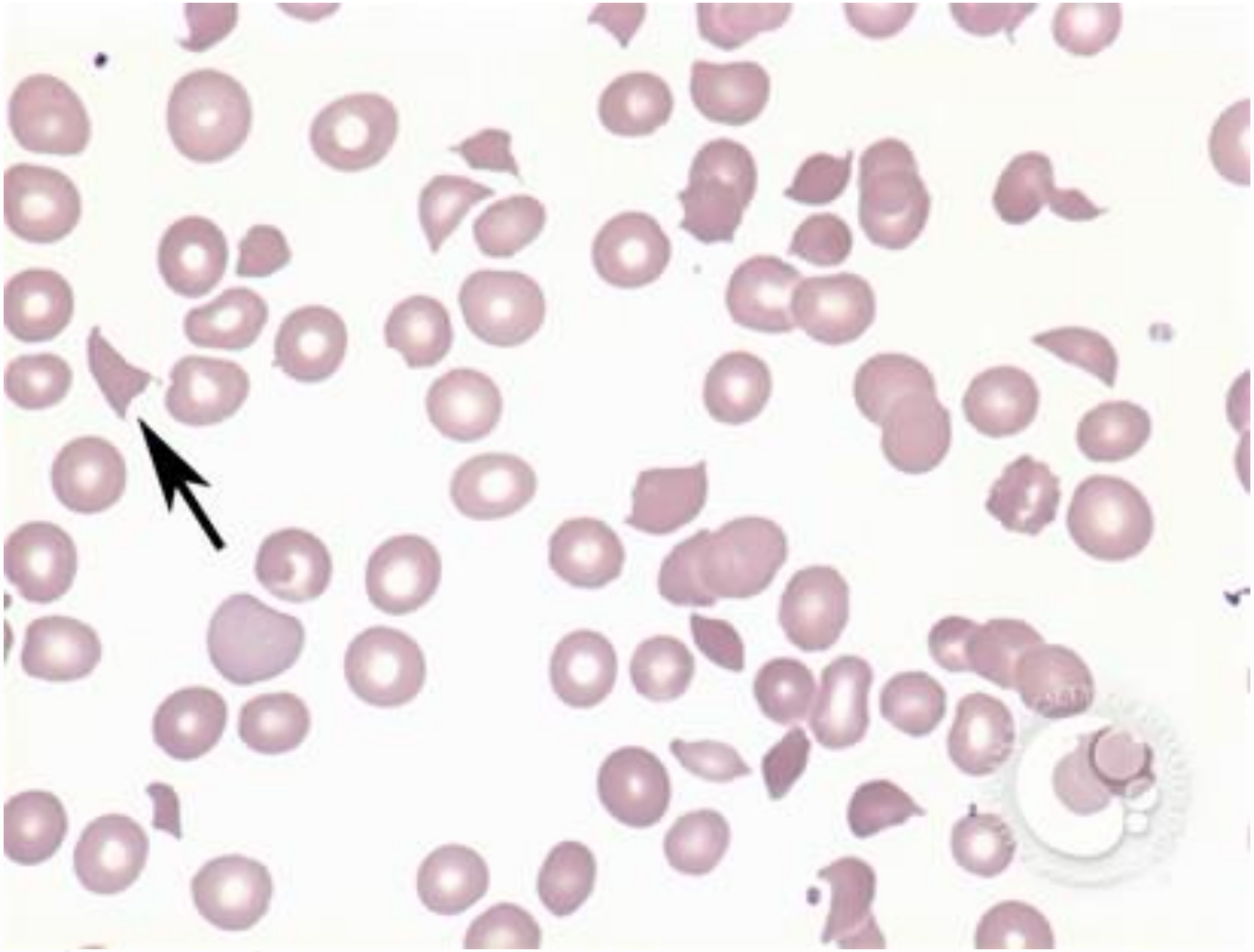
BCSLS Congress 2012
Kamloops, BC

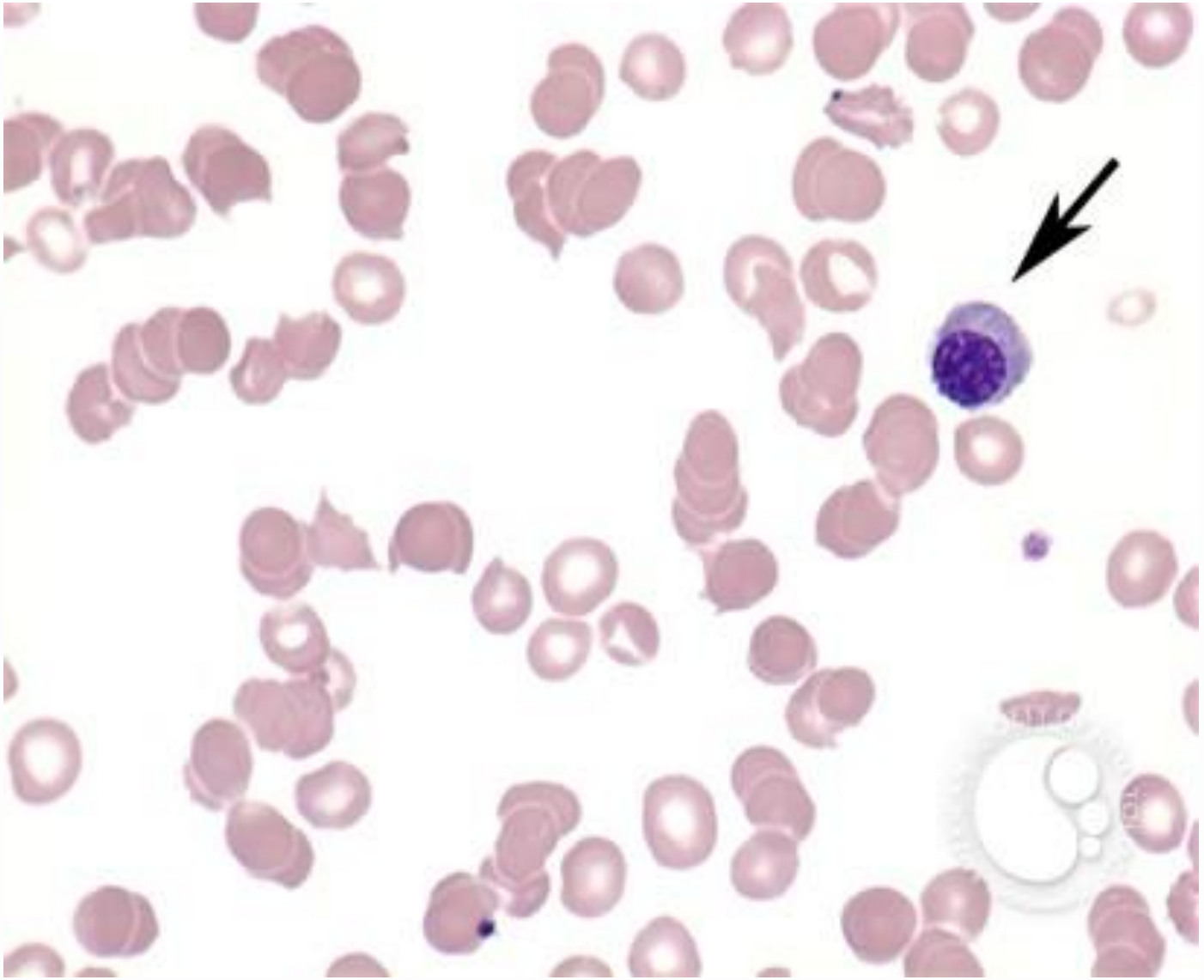
Dr. Gerry James
Royal Inland Hospital
Kamloops,BC
Interior Health

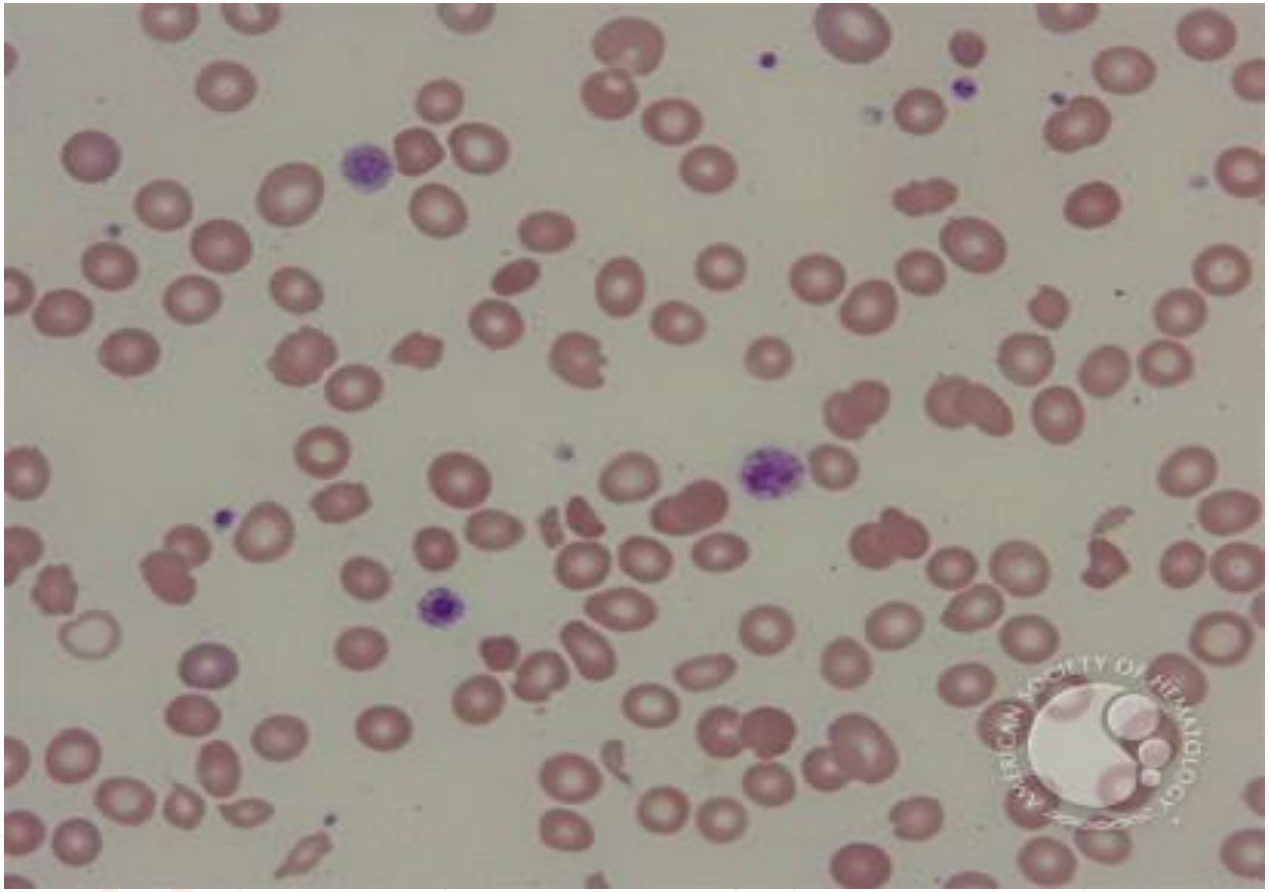
Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes

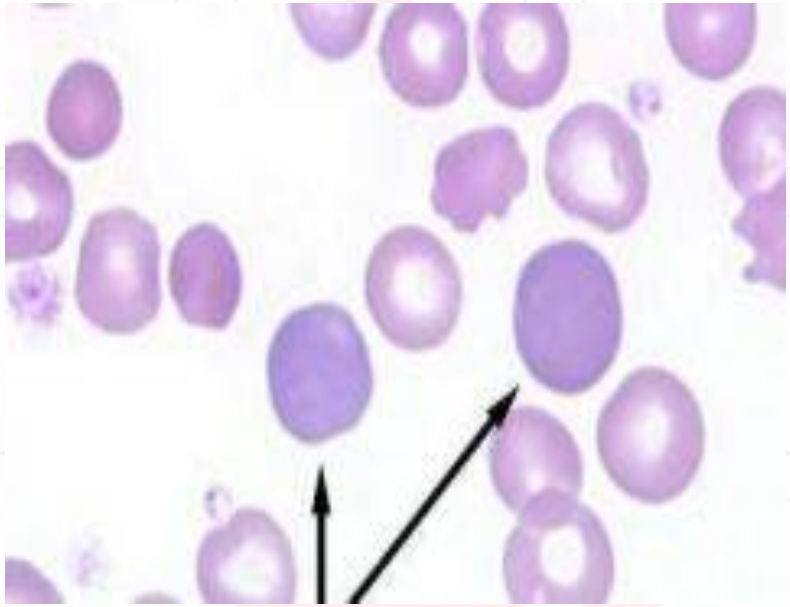


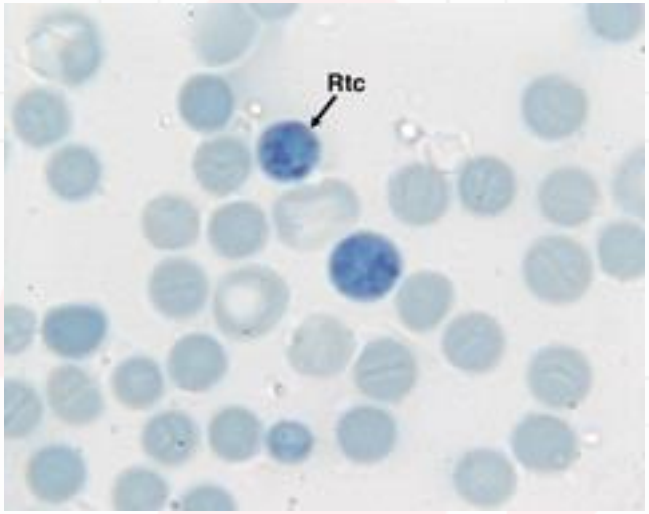
Peripheral blood smear from a patient with a microangiopathic hemolytic anemia with marked red cell fragmentation. The smear shows multiple helmet cells (small black arrows), other fragmented red cells (large black arrow); microspherocytes are also seen (blue arrows). The platelet number is reduced; the large platelet in the center (red arrow) suggests that the thrombocytopenia is due to enhanced destruction.
Courtesy of Carola von Kapff, SH (ASCP).

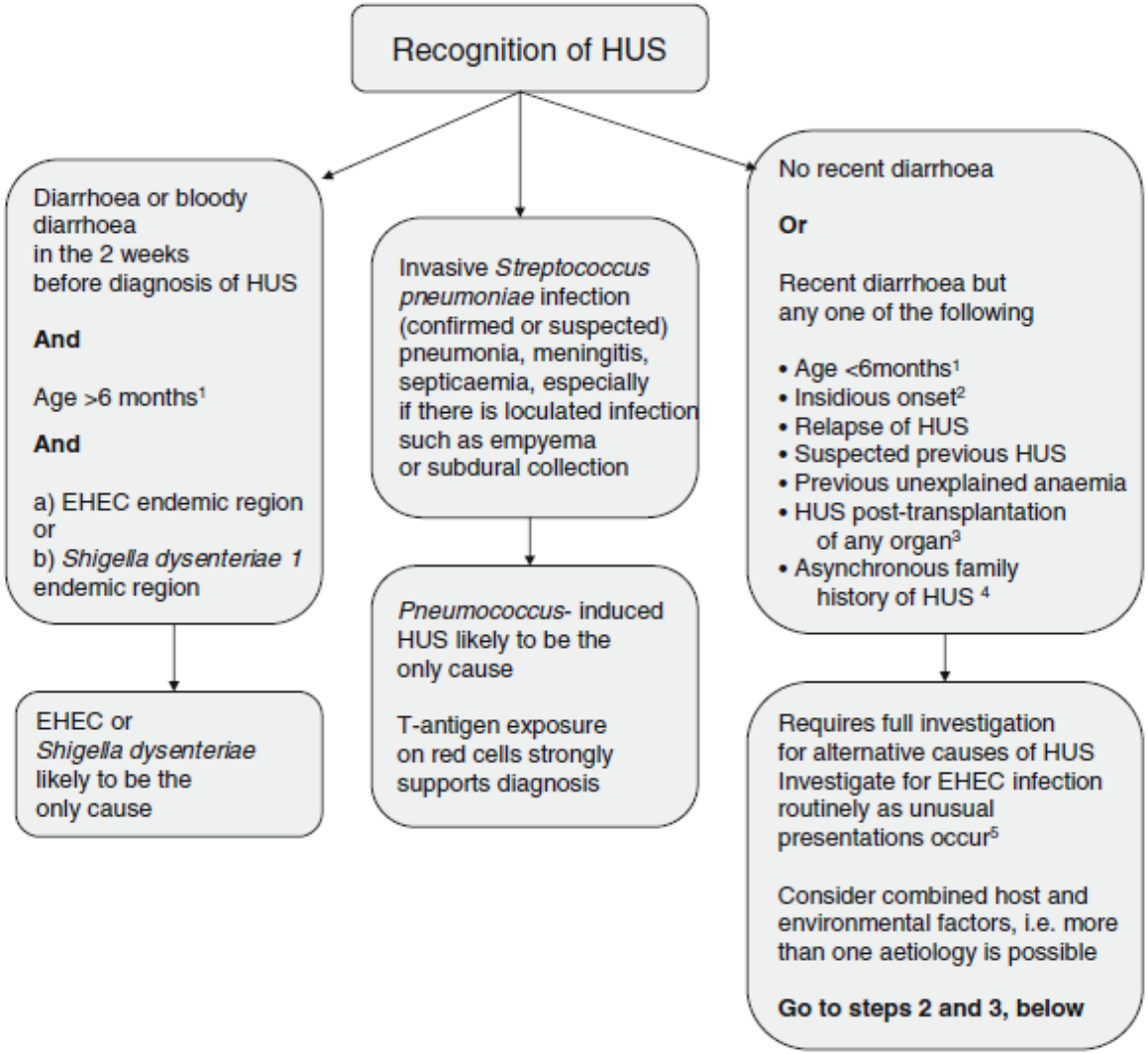




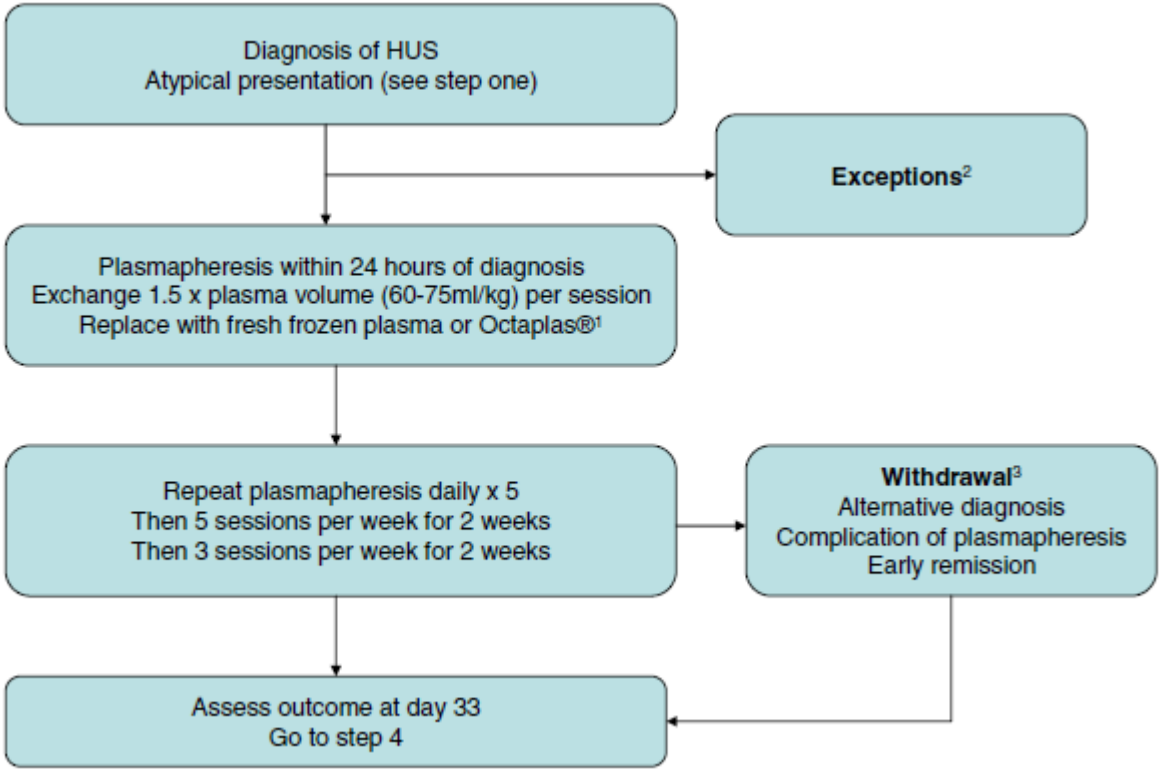




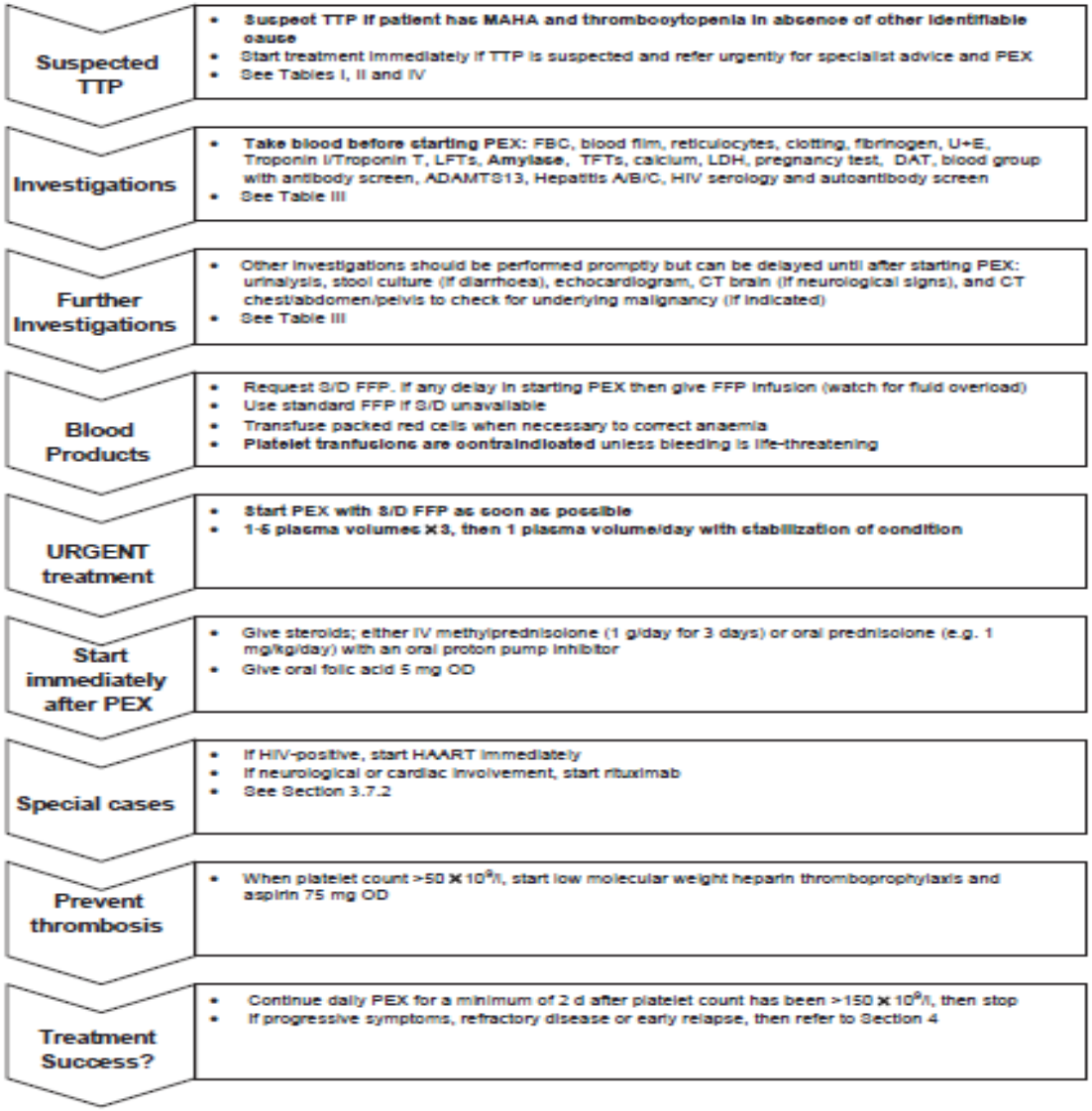




Pediatr Nephrol (2009) 24:687–696
DOI 10.1007/s00467-008-0964-1

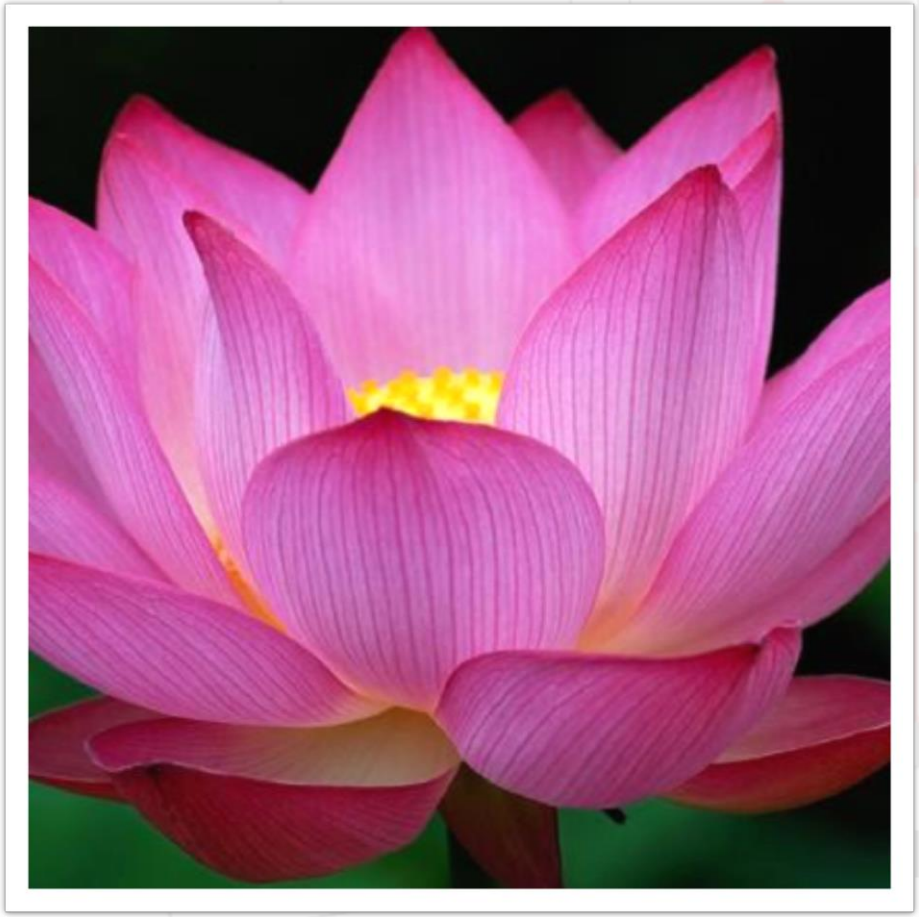


Pediatr Nephrol (2009) 24:687–696
DOI 10.1007/s00467-008-0964-1



Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies

Marie Scully,[1] Beverley J. Hunt,[2] Sylvia Benjamin,[3] Ri Liesner,[4] Peter Rose,[5] Flora Peyvandi,[6] Betty Cheung,[7] Samuel J. Machin[8] and on behalf of British Committee for Standards in Haematology



Thank you!