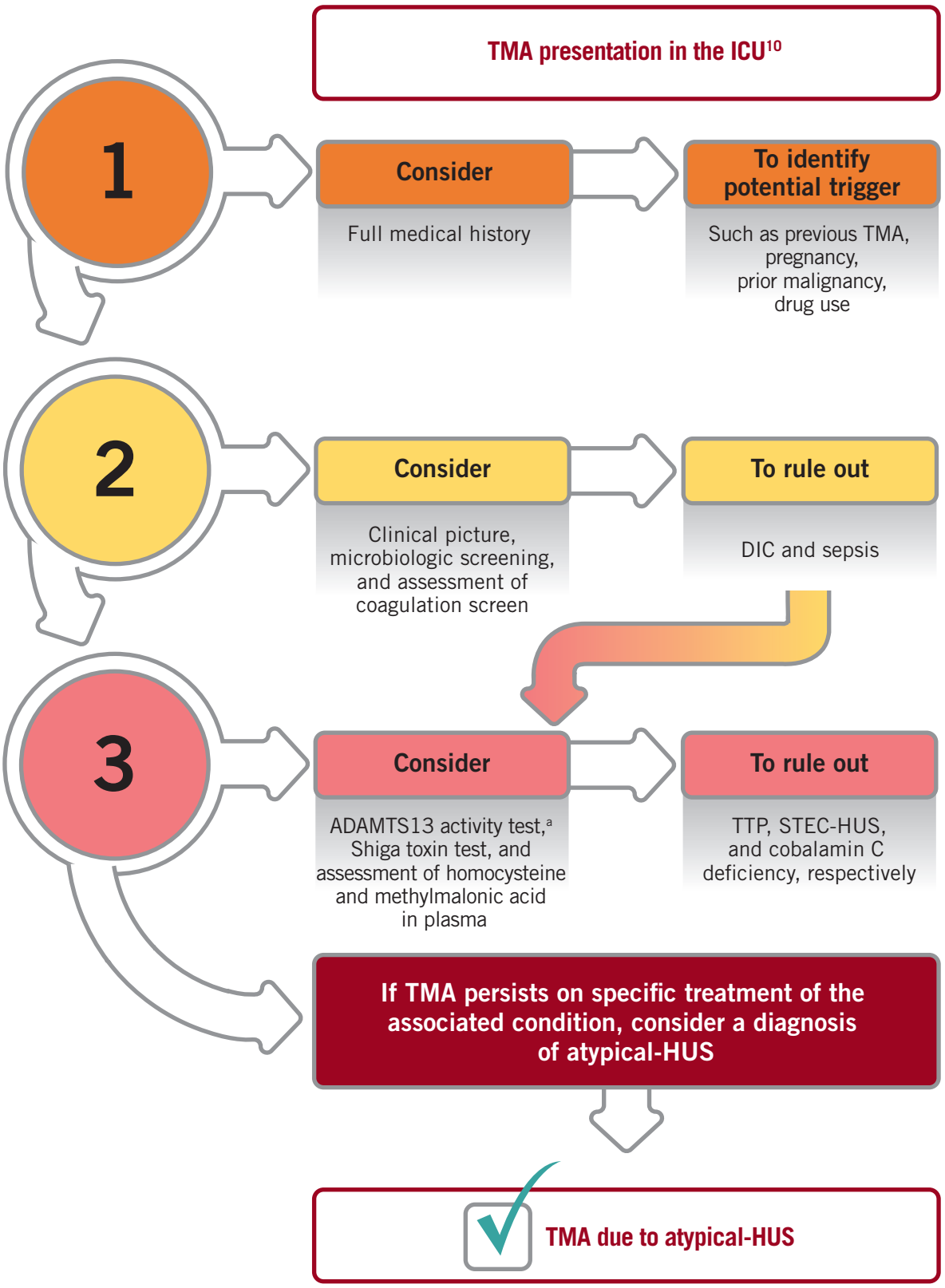
# Identifying Atypical Hemolytic Uremic Syndrome in the Intensive Care Unit Setting

## A Guide To Differential Diagnosis

Identifying Atypical Hemolytic Uremic Syndrome in the Intensive Care Unit Setting

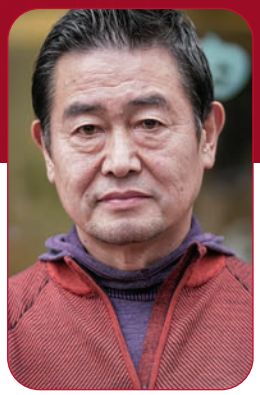
# Important Considerations for a Differential Diagnosis

**Identifying atypical-HUS as the cause of thrombotic microangiopathy (TMA) in the ICU setting is essential for an accurate and timely diagnosis and optimal management decisions**




[a]Prior to plasma exchange/plasma infusion (PE/PI) for an accurate baseline reading, though it may be conducted afterward.

# Case Study: Adult Patient in ICU[1-5]



## Patient overview

- 62-year-old Japanese male; height: 165 cm; weight: 99 kg (218 lb)
- Presented to local hospital after 1 month of mucous and bloody stool and 2 weeks of worsening abdominal pain
- Lab results showed leukocytosis, thrombocytopenia, and elevated blood urea nitrogen and serum creatinine

## Clinical presentation and management

| At presentation | ICU day 1 | ICU days 9-11 | ICU day 26 |
|---|---|---|---|
| 1 month of mucous and bloody stool and 2 weeks of worsening abdominal pain | Condition deteriorated despite treatment; patient transferred to ICU | Lower GI endoscopy showed no evidence of colitis or inflammation. Thrombocytopenia persisted. Patient experienced respiratory distress and pleural effusion | Thrombocytopenia persisted after 8 TPE sessions |
| Diagnosis: sepsis secondary to intra-abdominal infection; broad-spectrum antimicrobial therapy initiated | Diagnosis: severe bacterial enteritis | Revised diagnosis: TMA<br>Therapeutic plasma exchange (TPE) initiated, ADAMTS13 activity test ordered | Negative for STEC-HUS; normal ADAMTS13 activity, ruling out TTP<br>Final diagnosis: atypical-HUS |

## Laboratory Values

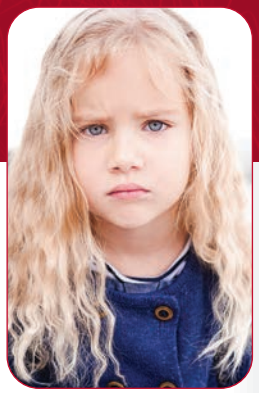
| Laboratory Tests | Normal values | ICU day 1 | ICU days 9-11 | ICU day 26 |
|---|---|---|---|---|
| White blood cell count, × $10^9$/L | 3.5-10.5 | 12 | | |
| C-reactive protein, mg/dL | 0.0-0.8 | 23.9 | | |
| Procalcitonin, ng/mL | ≤0.15 | 8.92 | | |
| Platelet count, × $10^9$/L | 150-350 | 38 | 21 | 59 |
| Prothrombin time, % | 100 | 41 | | |
| Fibrin degradation product level, µg/mL | <5 | 53.1 | | |
| LDH, IU/L | 60-100 | 392 | | |
| Aspartate transaminase, IU/L | 0-35 | 50 | | |
| Alanine transaminase, IU/L | 0-35 | 17 | | |
| Total bilirubin, mg/dL | 0.3-1.2 | 6.2 | | |
| Direct bilirubin, mg/dL | 0-0.3 | 4.6 | | |
| BUN, mg/dL | 8-20 | 92 | | |
| Serum creatinine, mg/dL | 0.7-1.3 | 2.09 | | |
| Lactic acid, mg/dL | 6-16 | 4 | | |
| **Complement measurements** | | | | |
| CH50, U/mL | 30-50 | 40.6 | | |
| C3, mg/dL | 65-135 | 85 | | |
| C4, mg/dL | 13-35 | 23 | | |
| **Differential diagnosis evaluation** | | | | |
| Anemia | Negative | Negative | | |
| Schistocytes | Negative | Negative | 0.5 | |
| *Enterococcus sp.* | Negative | Positive | | |
| *Corynebacterium striatum* | Negative | Positive | | |
| ADAMTS13 activity | >10% | | | 25.1 |
| STEC-HUS | Negative | | | Negative |

## Differential Diagnosis

- A final diagnosis of atypical-HUS was made based on ruling out other potential causes of TMA (STEC-HUS, TTP)

Patient case is hypothetical.

# Case Study: Pediatric Patient in ICU[6-8]



## Patient overview

- 5-year-old Caucasian female; height: 110 cm; weight: 18 kg (40 lb)
- Presented to the department of pediatric nephrology with vomiting, petechiae on the lower extremities, yellowish sclera, systolic heart murmur, weakness, catarrhal infection, and oliguria present for 2 days
- Upper airway infection without diarrhea for 3 days
- Lab results consistent with hemolytic anemia, thrombocytopenia, acute renal failure, elevated LDH activity, proteinuria, and hematuria

## Clinical presentation and management

| | | |
|---|---|---|
| Vomiting, petechiae on the lower extremities, yellowish sclera, systolic heart murmur, weakness, catarrhal infection, and oliguria present for 2 days; upper airway infection without diarrhea for 3 days | Improvement in LDH and renal and hematologic findings | Good clinical condition |
| **At presentation** | **1 week after presentation** | **11 months after presentation** |
| Admitted to ICU<br>Diagnosis: Mycoplasma pneumonia with TMA<br>Treatment with clarithromycin therapy, fresh-frozen plasma on days 3, 4, 5, and 6, and renal replacement therapy with peritoneal dialysis on days 2, 3, 4, and 5 | Differential: negative Coombs and STEC-HUS tests, normal ADAMTS13 activity<br>Diagnosis: atypical-HUS | Genetic analysis revealed mutations in the complement pathway |

## Laboratory Values

| Laboratory Tests | Normal values | At presentation | 1 week after presentation | 11 months after presentation |
|---|---|---|---|---|
| Hemoglobin, g/dL | 11.4-14.3 | 9.7 | 11.0 | 12.7 |
| Hematocrit, % | 34-42 | 28.9 | 32.4 | 38.8 |
| White blood cells × $10^9$/L | 4.4-12.9 | 6.0 | 8.9 | 6.2 |
| Platelets × $10^9$/L | 187-445 | 15 | 332 | 310 |
| BUN, mg/dL | 7-20 | 84.01 | | 13.16 |
| Serum creatinine, mg/dL | 0.12-1.06 | 1.38 | 0.64 | 0.43 |
| LDH, U/L | 145-345 | 7669 | 1682 | 627 |
| CRP, mg/L | <1.0 | 12.4 | 9.6 | <5.0 |
| **Complement measurements** | | | | |
| CH50/mL | 48-103 | 47 | | 56 |
| C3, g/L | 0.9-1.8 | 0.87 | | 1.0 |
| C4, g/L | 0.15-0.55 | 0.10 | | 0.13 |
| **Differential diagnosis evaluation** | | | | |
| *Mycoplasma pneumoniae* IgM | Negative | Positive | | |
| Coombs test | Negative | | Negative | |
| STEC test | Negative | | Negative | |
| Influenza A | Negative | | Negative | |
| ADAMTS13 | >10% | | Normal | |

## Differential Diagnosis

- A diagnosis of atypical-HUS was made based on
  - The presence of laboratory findings consistent with atypical-HUS
  - ADAMTS13 activity level that was >10%, ruling out TTP as a cause of TMA
  - Genetic analyses indicating mutations in the complement pathway

Patient case is hypothetical.

# Checklist to confirm TMA

Clinical recognition of thrombotic microangiopathy (TMA) requires documentation of **microangiopathic hemolysis** (confirmed by any one of the following labs: fragmented red blood cells or schistocytes on peripheral blood smear, low haptoglobin levels, elevated lactate dehydrogenase (LDH), decline in baseline hemoglobin), **thrombocytopenia**, and clinical involvement of **at least 1 organ system**, the most common sites being the central nervous system, kidneys, and gastrointestinal tract.[9] Triggers are conditions that can activate complement and may unmask atypical-HUS. It is imperative to treat the trigger, but if the signs and symptoms of TMA do not resolve, consider a diagnosis of unmasked atypical-HUS.[9]

## Microangiopathic hemolysis (evidence of any 1 of the below)

Mark test result in column below each date

| DATE OF TEST | | | | |
|---|---|---|---|---|
| **Schistocytes** (present) | | | | |
| **LDH** (elevated) | | | | |
| **Haptoglobin** (low) | | | | |
| **Hemoglobin** (low) | | | | |

## Thrombocytopenia

Mark test result in column below each date

| DATE OF TEST | | | | |
|---|---|---|---|---|
| **Platelet count** (<150,000/mm$^3$ or >25% decrease from baseline) | | | | |

## Organ involvement (≥1 organ system, check which apply)

| | | |
|---|---|---|
| ☐ **CNS** (Confusion, seizures, stroke) | ☐ **GI** (Diarrhea, nausea, vomiting abdominal pain) | ☐ **CV** (MI, hypertension, arterial stenosis) |
| ☐ **Renal** (Decreased eGFR, elevated creatinine, abnormal urinalysis) | ☐ **Pulmonary** (Dyspnea, pulmonary hemorrhage or edema) | ☐ **Visual** (Blurred vision, retinal vessel or ocular hemorrhage) |

## Triggers (can "unmask" atypical-HUS, may or may not be present) (check which apply)

| | | |
|---|---|---|
| ☐ **Infection** | ☐ **Pregnancy/post-partum** (HELLP, pre-eclampsia) | ☐ **Transplant** (solid organ, HSCT) |
| ☐ **Malignant hypertension** | ☐ **Autoimmune disease** | |

## If a TMA is confirmed, it is important to order an ADAMTS13 activity test and determine the cause:

☐ **ADAMTS13 activity test ordered**

- Take a thorough medical history[10]
- Order tests to rule out TTP, STEC-HUS, DIC[9,10]
  - Note that if baseline platelet values are >30 x 10$^9$/L or if serum creatinine is >1.7 to 2.3 mg/dL, a diagnosis of TTP is almost eliminated[9]
- Involve specialists in determining diagnosis such as hematologists or nephrologists[11]

# Differential Diagnosis of Atypical-HUS[9,10,12,13]

**Thrombocytopenia**
**Platelet count <150 × $10^9$/L or >25% decrease from baseline**

**AND**

**Microangiopathic hemolysis**
**Schistocytes and/or**
**Elevated LDH and/or**
**Decreased haptoglobin and/or**
**Decreased hemoglobin**

**Plus 1 or more of the following**

## Common Signs and Symptoms

### Neurological symptoms
**Confusion** and/or
**Seizures** and/or
**Stroke** and/or
**Other cerebral abnormalities**

### Renal impairment
**Elevated creatinine level** and/or
**Decreased eGFR** and/or
**Elevated blood pressure** and/or
**Abnormal urinalysis results**

### GI symptoms
**Diarrhea ± blood** and/or
**Nausea/vomiting** and/or
**Abdominal pain** and/or
**Gastroenteritis/pancreatitis**

## Other Signs and Symptoms

### CV symptoms
**MI** and/or
**Hypertension** and/or
**Arterial stenosis** and/or
**Peripheral gangrene**

### Pulmonary symptoms
**Dyspnea** and/or
**Pulmonary hemorrhage** and/or
**Pulmonary edema**

### Visual symptoms
**Pain and blurred vision** and/or
**Retinal vessel occlusion** and/or
**Ocular hemorrhage**

**Evaluate ADAMTS13 activity[a] and Shiga toxin/EHEC test[b]**

**While ADAMTS13 results are awaited, a platelet count >30 × $10^9$/L and/or sCr >1.7 to 2.3 mg/dL almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)**

| ≤5%[c] ADAMTS13 activity | >5% ADAMTS13 activity | Shiga toxin/EHEC positive |
|---|---|---|
| TTP | Atypical-HUS | STEC-HUS |

## TMA can also manifest in the presence of clinical conditions such as the following

- Pregnancy-postpartum
- Malignant/severe hypertension
- Solid organ transplantation
- Autoimmune disease (eg, SLE, scleroderma)
- Hematopoietic stem cell transplantation

[a]Ideally draw ADAMTS13 activity test prior to initiating plasma exchange/plasma infusion (PE/PI). [b]Shiga toxin/EHEC test is warranted with history/presence of GI symptoms. [c]Range found in published literature is <5%-10%.

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; HUS, hemolytic uremic syndrome; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EHEC, enterohemorrhagic *Escherichia coli*; GI, gastrointestinal; MI, myocardial infarction; sCr, serum creatinine; STEC-HUS, Shiga toxin–producing *Escherichia coli*-hemolytic uremic syndrome; SLE, systemic lupus erythematosus; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

# Differential Diagnosis: Identifying Atypical-HUS in the ICU Setting

- Thrombotic microangiopathy (TMA) is a serious medical condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ injury[10]
- The critical nature of acute TMA means that a high proportion of patients may be admitted to the ICU at presentation[10]
  - According to a meta-analysis, physicians in the ICU see an average of three patients with TMA per year, many of whom are not diagnosed at the time of admission[10]
- Due to the severity of the progression of atypical-HUS and other TMAs, a suspected diagnosis should be treated as a medical emergency[10]
  - Appropriate laboratory tests should be ordered immediately to rule out causes of TMA including DIC, STEC-HUS, and TTP[10]
    - To rule out TTP, an ADAMTS13 activity level (not antibody) test should be ordered[9]
  - Although plasma exchange is not an effective long-term management strategy for atypical-HUS, it may be necessary to implement while laboratory results are being determined and a diagnosis is being confirmed[9,10]
    - It is critical to recognize that a patient may have a complete or near-complete remission on plasma exchange alone, yet go on to develop ESRD or die[9]
    - According to the American Society for Apheresis, plasma exchange in atypical-HUS receives a weak recommendation, with low-quality or very low-quality evidence[14]
- In lieu of ADAMTS13 results, a platelet count >30 × $10^9$/L and/or serum creatinine >1.7 to 2.3 mg/dL almost eliminates a diagnosis of TTP[9]

**Multiple studies on a total of 806 patients with TMA have demonstrated that baseline values of serum creatinine and platelets at clinical presentation can rapidly and efficiently distinguish between sufficient and severely deficient ADAMTS13 activity[15-20,a]**

**Serum creatinine level and platelet count show statistical significance in predicting ADAMTS13 activity[a]**

| | Association with severe ADAMTS13 deficiency: *P* value | |
|---|---|---|
| **Authors** | **Serum creatinine level** | **Platelet count** |
| Bentley 2010 (N=110)[15] | *P*=0.0207 | *P*=0.0034 |
| Cataland 2012 (N=54)[16] | *P*<0.0001 | *P*<0.0001 |
| Coppo 2010 (N=214)[17] | *P*<0.0001 | *P*<0.0001 |
| Kremer Hovinga 2010 (N=261)[18] | *P*<0.001 | *P*<0.001 |
| Shah 2013 (N=60)[19] | *P*=0.0003 | *P*=0.0001 |
| George 2010 (N=107)[20] | *P*<0.001 | *P*<0.001 |

ADAMTS13 deficiency defined as ADAMTS13 activity: <5% (mild deficiency =5%-20%) (Coppo 2010), <10% (Cataland 2012, Kremer Hovinga 2010, George 2010), <15% (Bentley 2010); ≤10% (Shah 2013). ADAMTS13 assays generally have a sensitivity of 5%-10%. "Severely deficient" ADAMTS13 activity is typically defined as <5%.

[a]Additional clinical parameters that may predict ADAMTS13 activity include indirect bilirubin,[15] reticulocytes,[15,17] estimated glomerular filtration rate,[17] antinuclear antibodies,[17] acute renal failure,[18,20] neurological features,[19] and undetectable haptoglobin.[19]

- Atypical-HUS is a disease caused by dysregulation of the alternative pathway of the complement system, leading to excessive complement activation and TMA[13,21]
  - Atypical-HUS may be triggered by conditions that activate complement such as organ transplantation, infections, malignancy, pregnancy, autoimmune disorders[9]
  - Persistence of TMA despite treatment of associated conditions may suggest atypical-HUS[10]

**Atypical-HUS is a serious disease caused by dysregulation of the alternative pathway of the complement system, leading to excessive complement activation and TMA[13,21]**

**Given the critical nature of acute TMA, many patients may be admitted to the ICU at presentation[10]**

**If TMA is suspected, consider consulting a multidisciplinary team of specialists in the diagnostic process.[11] Follow the pathway to reach a diagnosis[9]**

**It is important to diagnose atypical-HUS promptly in patients admitted to the ICU in order to reduce the risk of irreversible organ damage or death[10]**

## References


1. Omura T, et al. *Medicine*. 2016;95:27(e4104).
2. Mayo Clinic. Complete blood count. Available at: https://www.mayoclinic.org/tests-procedures/complete-blood-count/about/pac-20384919.
3. American College of Physicians. Laboratory values. Available at: https://annualmeeting.acponline.org/sites/default/files/shared/documents/for-meeting-attendees/normal-lab-values.pdf.
4. Prager D. *Ann Intern Med*. 1970;72(2):287.
5. Lab Corp. Fibrinogen Degradation Products (FDP), Plasma. Available at: https://www.labcorp.com/tests/115402/fibrinogen-degradation-products-fdp-plasma.
6. Miklaszewska M, et al. *Przegl Lek*. 2016;73:862-864.
7. Mayo Clinic. Pediatric test reference values. Available at: https://www.mayocliniclabs.com/test-info/pediatric/refvalues/reference.php.
8. Andropoulos DB. Pediatric normal laboratory values. In *Gregory's Pediatric Anesthesia*, Fifth Edition. Edited by George A. Gregory, Dean B. Andropoulos. © 2012 Blackwell Publishing Ltd. Published 2012 by Blackwell Publishing Ltd.
9. Laurence J, et al. *Clin Adv Hematol Oncol*. 2016;14:2-15.
10. Azoulay E, et al. *Chest*. 2017;152:424-434.
11. Rivera MGU, et al. *PLoS One*. 2018;13:e0206558.
12. Goodship THJ, et al. *Kidney Int*. 2017;91:539-551.
13. Asif A, et al. *J Nephrol*. 2017;30:347-362.
14. Padmanabhan A, et al. *J Clin Apher*. 2019;171:171-354.
15. Bentley MJ, et al. *Transfusion*. 2010;50(8):1654-1664.
16. Cataland SR, et al. *Br J Haematol*. 2012;157(4):501-503.
17. Coppo P, et al. *PLoS One*. 2010;5(4):e10208.
18. Kremer Hovinga JA, et al. *Blood*. 2010;115(8):1500-1511.
19. Shah N, et al. *Br J Haematol*. 2013;163(4):514-519.
20. George JN. *Blood*. 2010;116(20):4060-4069.
21. Jamme M, et al. *PLoS One*. 2017;12:e0177894.


**FPO**

**business card**



ALEXION