In the name of god

# Thrombotic Microangiopathy after Renal Transplantation


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# OBJECTS

1. Introduction:
    1. Definition
    2. Current classifications of TMA
2. Post Tx TMA:
    1. Introduction
    2. Classification
    3. De novo TMA: Precipitating factors
    4. Clinical manifestations
    5. Recurrent TMA
    6. Diagnosis
    7. Management

# TMA: DEFINITION

**Thrombotic microangiopathy** is a pathology that results in thrombosis in capillaries & arterioles, due to an endothelial injury.

Glomerular Disease

# Thrombotic Microangiopathy and the Kidney

*Vicky Brocklebank,[1,2] Katrina M. Wood,[3] and David Kavanagh[1,2]*

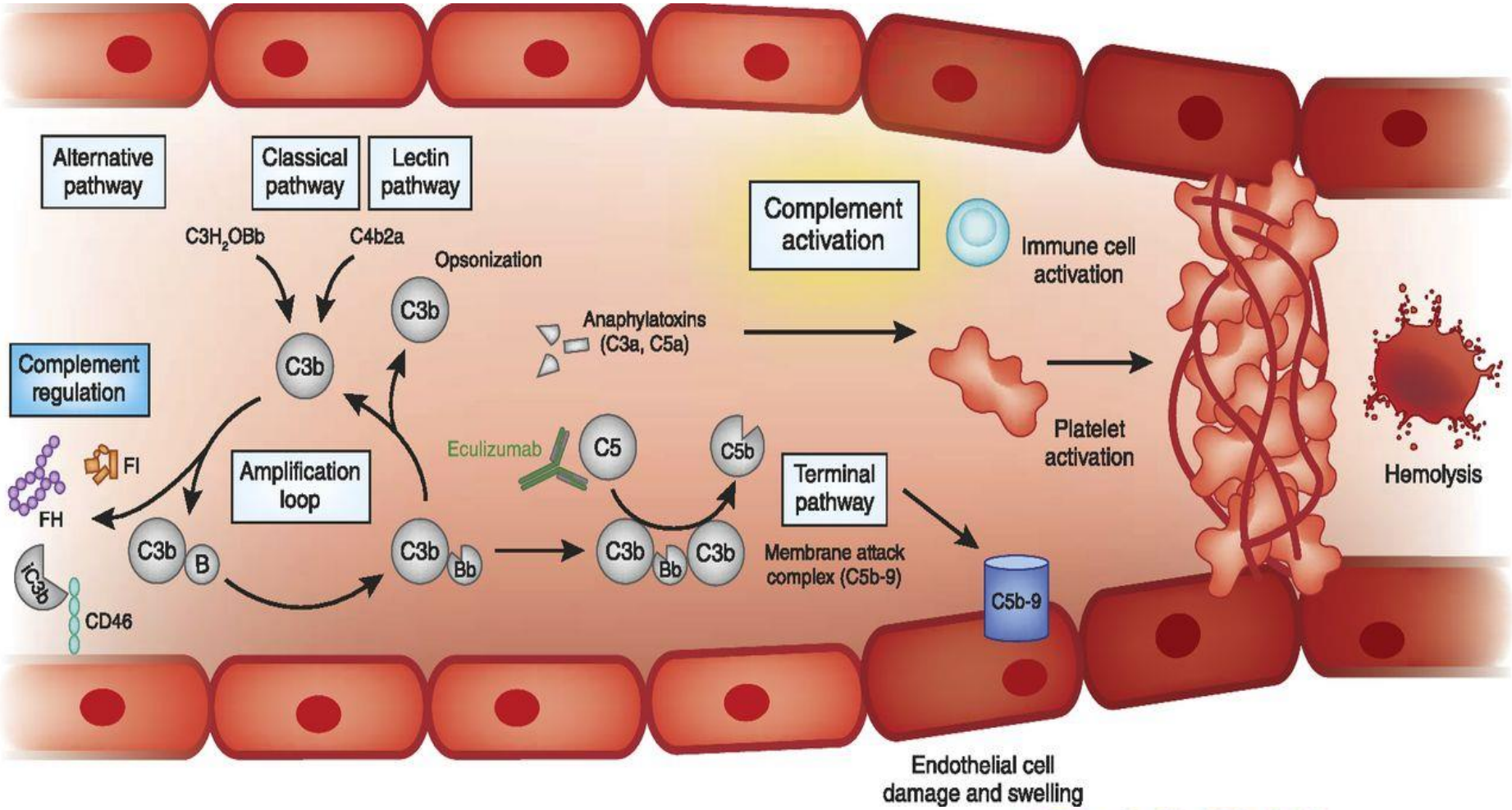
Abstract

**Thrombotic microangiopathy can manifest in a diverse range of diseases and is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and organ injury, including AKI. It can be associated with significant morbidity and mortality, but a systematic approach to investigation and prompt initiation of supportive management and, in some cases, effective specific treatment can result in good outcomes. This review considers the classification, pathology, epidemiology, characteristics, and pathogenesis of the thrombotic microangiopathies, and outlines a pragmatic approach to diagnosis and management.**

*Clin J Am Soc Nephrol* 13: 300–317, 2018 doi: https://doi.org/10.2215/CJN.00620117

[1]National Renal Complement Therapeutics Centre, Newcastle upon Tyne, Hospitals National Health Service Foundation Trust

# Unfettered complement activation ultimately results in thrombus formation, platelet consumption, vascular occlusion & mechanical hemolysis.

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# INTRODUCTION: CURRENT CLASSIFICATIONS

1. **Primary inherited TMAs** (e.g., complement mutations, ADAMTS13 mutations)
2. **Primary acquired TMAs** (factor H autoantibodies, ADAMTS13 auto- antibodies)
3. **Infection-associated TMAs**
4. **Secondary TMAs**

# QUESTION

- **TMA after Renal Transplantation belongs to which category of TMA?**

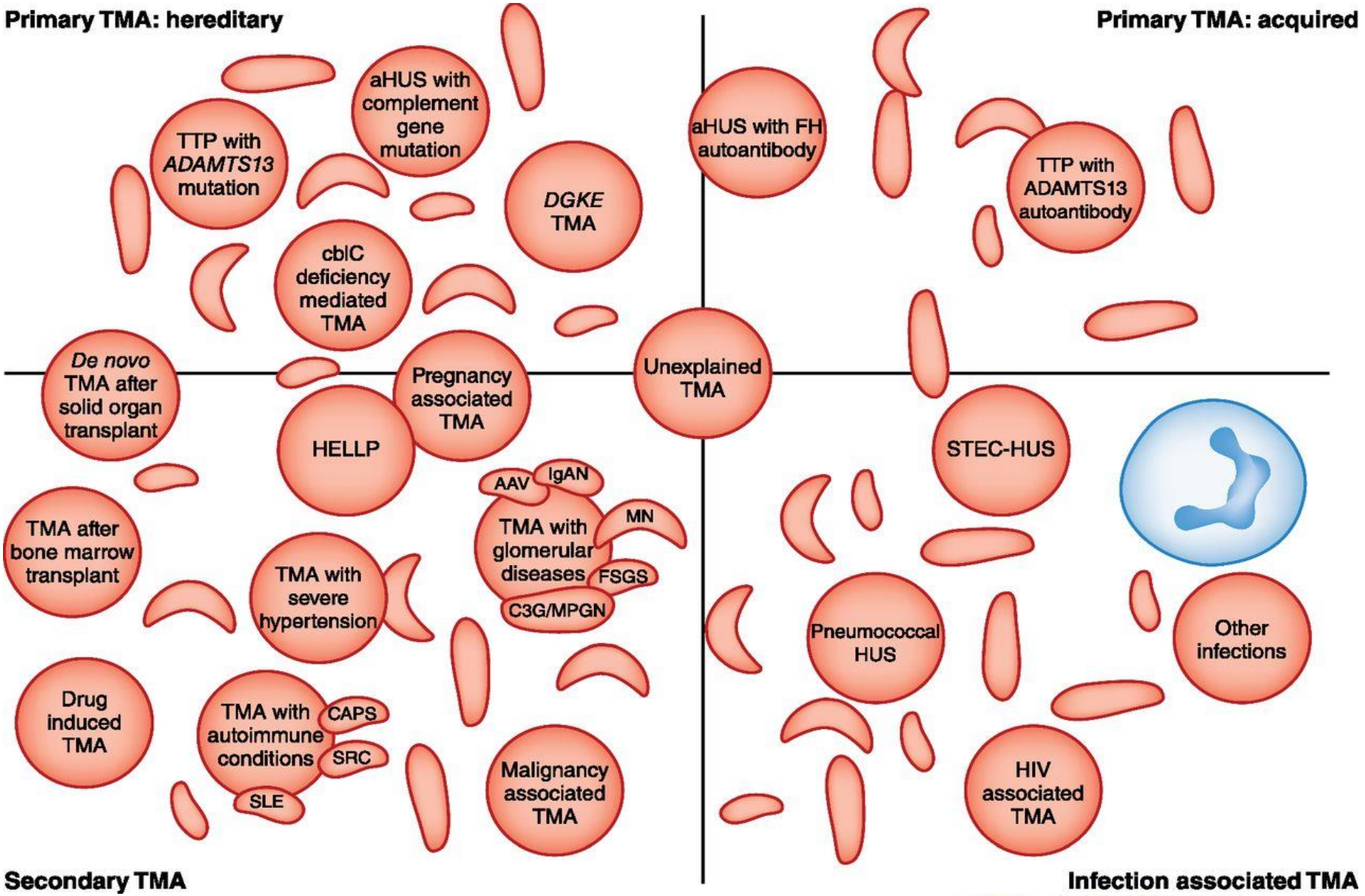
  **A. Primary hereditary**

  **B. Primary acquired**

  **C. Infection-associated**

  **D. Secondary**

# TMA classification

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# INTRODUCTION: CURRENT CLASSIFICATIONS

**It is necessary to remember that patients with an underlying complement genetic mutation often require a secondary trigger for aHUS to manifest.**

# QUESTION

- **Which one is the most sensitive marker of hemolysis?**

  **A. Low Haptoglobin level**

  **B. Elevated LDH**

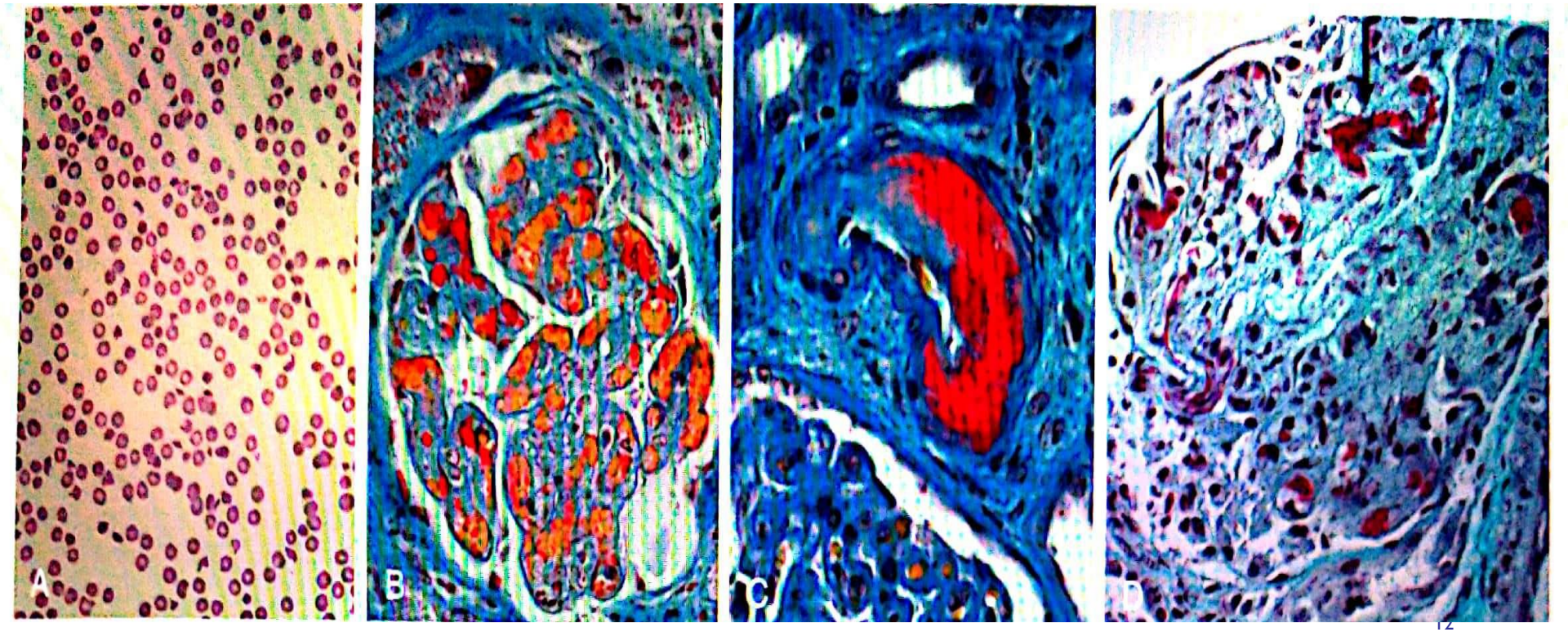
  **C. Negative direct Coombs**

  **D. Elevated Bilirubin**

# INTRODUCTION: CLINICAL & LAB FINDINGS

1. Thrombocytopenia & MAHA are defining features of TMAs
2. Elevated LDH is the most sensitive marker of hemolysis
3. Low Haptoglobin level
4. Negative direct antiglobulin test (DAT/ direct Coombs) with the exception of pneumococcal HUS
5. AKI is a common manifestation of TMAs

# THE PATHOLOGIC FEATURES OF TMA

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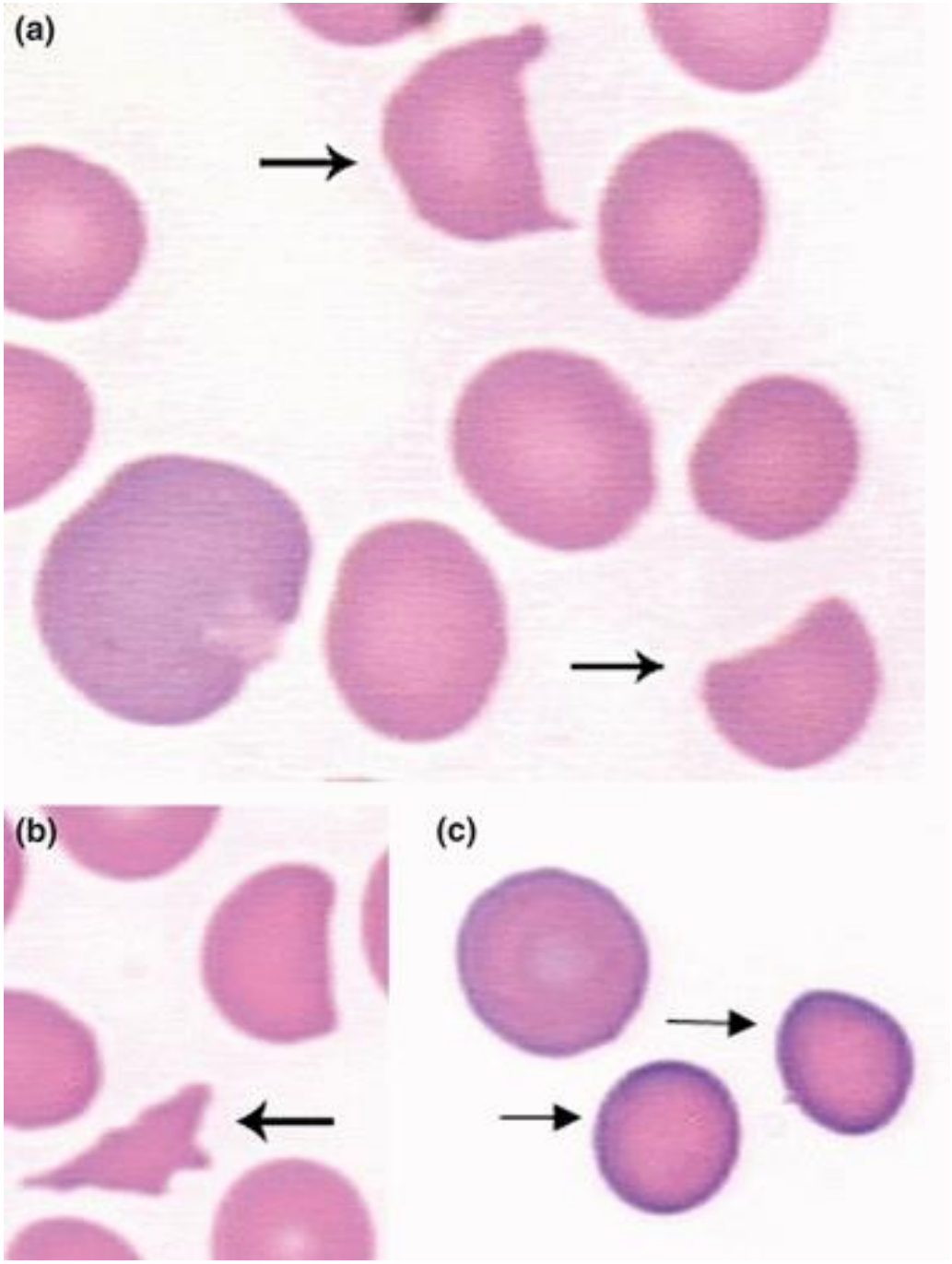



# Schistocytes

# QUESTION

- **What percentage of schistocytes is a strong cytomorphological indicator for the diagnosis of TMA in adults?**

  **A.** above 1%

  **B.** above 2%

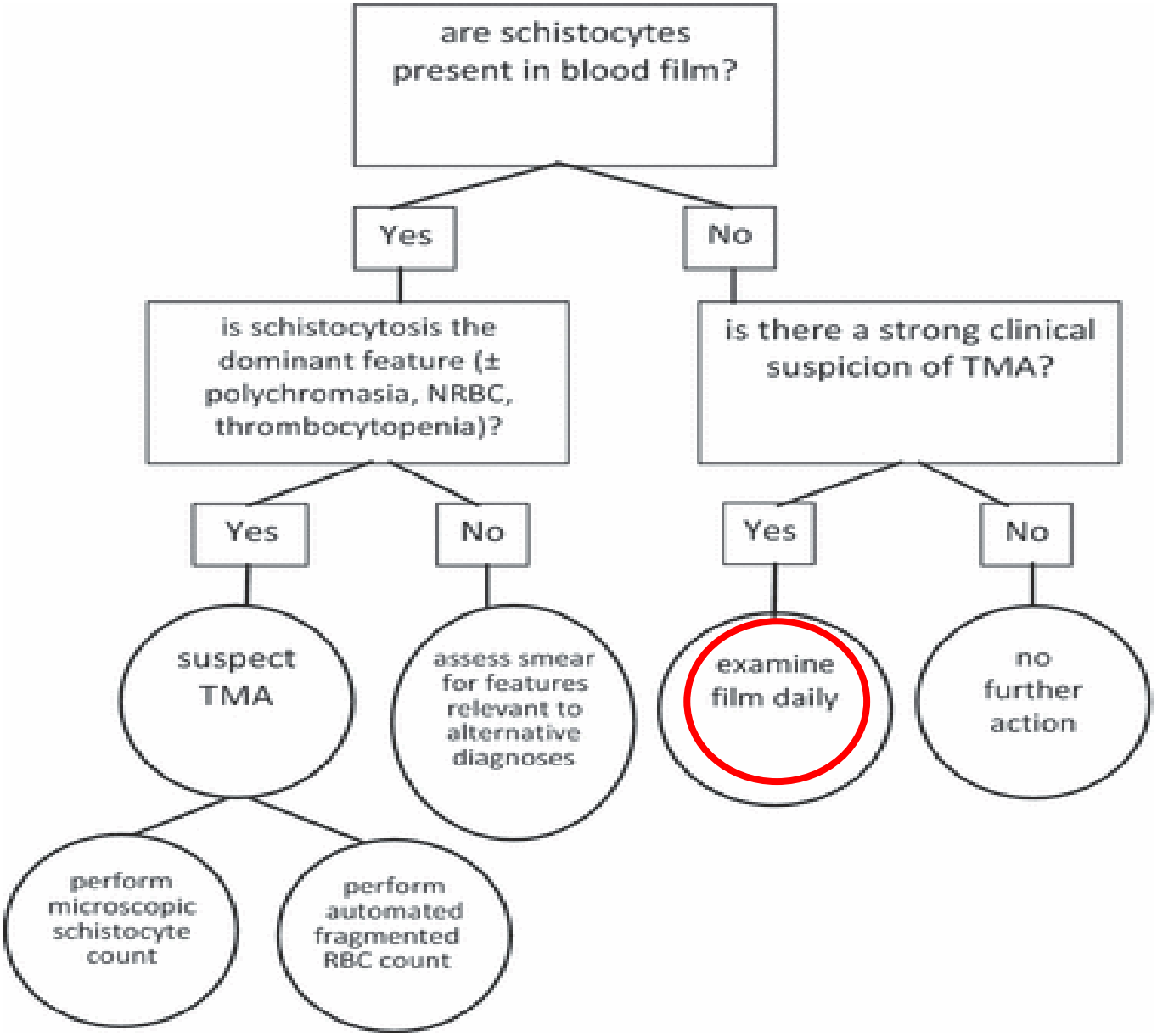
  **C.** 2.5%

  **D.** 5%



International Journal of Laboratory Hematology, Volume: 34, Issue: 2, Pages: 107-116, First published: 15 November 2011

# ICSH recommendations for identification, diagnostic value, & quantitation of schistocytes




International Journal of Laboratory Hematology, Volume: 34, Issue: 2, Pages: 107-116, First published: 15 November 2011

# INTRODUCTION: CLINICAL & LAB FINDINGS

Once routine hematological & biochemical diagnostics have confirmed a TMA, investigations are aimed at determining the underlying etiology & excluding other differentia

# DRUGS WITH EVIDENCE SUPPORTING A CAUSAL ASSOCIATION WITH TMA

| Immune-Mediated TMA | Direct Drug-Induced Toxicity | Other |
|---|---|---|
| Quinine: Drug-dependent antibodies | • Immunosuppressive agents, e.g., CNIs, Sirolimus,<br>• IFN-a, IFN-b<br>• VEGF inhibitors, e g., bevacizumab, sunitinib<br>• Chemotherapeutic agents, e.g., gemcitabine, mitomycin<br>• Recreational drugs, e.g., cocaine | Ticlopidine: ADAMTS13 autoantibody |

**It is crucial that a full evaluation is undertaken even if drug-mediated TMA is suspected, including an urgent ADAMTS13 assay**



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REVIEW

# Thrombotic microangiopathy after renal transplantation: Current insights in *de novo* and recurrent disease

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# POST TX TMA: INTRODUCTION

- TMA is one of the most devastating sequela of KTx.
- The incidence:
  - 5.6 cases/1000 KTRs/year with a 50% mortality rate 3 years after diagnosis
  - De novo TMA is mentioned to be as high as 1.5 -14%



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# POST TX TMA: CLASSIFICATION

1. **De novo TMA**, developed for the first time without any evidence of the disease before Tx
2. **Recurrent TMA**, native kidneys failed as a result of TMA & it came back in renal Tx

- De novo TMA is more common & its prognosis is poorer than recurrent TMA



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# DE NOVO TMA: PRECIPITATING FACTORS

1. AMR
2. Immunosuppressive-associated TMA: CNI or mTORi, single or combined
3. Other medications: e.g., anti-VGFI
4. Viral infection: e.g., HCV, CMV, BK & parvovirus
5. Genetic abnormalities in the complement cascade
6. Phenotypical shift of C3 glomerulopathy , to an aHUS post Tx
7. Missed diagnosis of TMA in the native kidney as a cause of ESRD (i.e., recurrent TMA)

# CNI-INDUCED TMA

- **Underlying mechanisms:**
  1. Loss of the normal balance between the vasodilator peptides & the vasoconstrictor peptides, results in arteriolar vasoconstriction, renal ischemia & establishment of endothelial injury
  2. CNI-induced platelet activation, pro-coagulant & anti-fibrinolytic activity have been shown to be involved in TMA evolution, particularly so, with an injured endothelium due to AMR, ischemia-reperfusion injury or any other etiology
  3. Microparticle production from endothelial cells, a known effect of CyA that can result in activation of the AP, a well-known mechanism that is implicated in TMA evolution



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# CNI-INDUCED TMA

- **Oppose** the role of CNI:
  1. > 95% of KTRs utilizing CNI, & only a small percentage can develop TMA, which suggests the presence of another underlying predisposing factor (s)
  2. CNI withdrawal in de novo TMA does not always guarantee a favorable graft outcome
  3. A USRDS based study demonstrates a significantly higher incidence of TMA in the group of KTR that was not under CNI maintenance therapy (11.9/1000/year), as compared to those on CNI maintenance (5.0/1000/year)



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# MTORI-ASSOCIATED TMA

1. mTORi has antiangiogenic properties, & can decrease renal expression of VEGF with death of the endothelial progenitor cells.
2. The VEGF inhibition has been recently proven to be associated with reduced renal levels of CFH. Patients with underlying CFH genetic mutations are more susceptible to develop de novo TMA, particularly with mTORi exposure
3. Repair of endothelial injury could be hampered by mTORi use
4. The procoagulant & the antifibrinolytic activity of mTORi might play additional roles in de novo TMA development



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# AMR-ASSOCIATED DE NOVO TMA

- The role of AMR in the development of post-transplant TMA is commonly reported & well-recognized.
- Endothelial cells are a well-known target of allo-immune response.



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# OTHER CAUSES

- Several less common etiologies:
  - Viral infection, e.g., CMV, BKV, Parvovirus, chronic HCV (with or without anti-cardiolipin seropositivity)
  - Antiviral medications, e.g., ribavirin & interferon
  - Disseminated histoplasmosis
  - Ischemia-reperfusion injury



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# QUESTION

- **When do you most often encounter the post TX TMA ?**

  **A. First month**

  **B. First 1-3 months**

  **C. First 3-6 months**

  **D. First year**

# CLINICAL MANIFESTATIONS: TIMING

- At any time in the post TX course
- Mostly encountered in the first 3-6 mo post TX.
  - Probably when the CNI immunosuppressive trough levels are relatively higher



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# CLINICAL MANIFESTATIONS: SALIENT FEAYURES

- TMA manifestations are quite variable:
  - **Limited** form confined to the kidney
    - Localized (limited) TMA is usually presented later in TMA course
    - When a KTR has significant renal dysfunction & the biopsy does not show any acute rejection, one must suspect two possibilities:

      (1) TMA or (2) RAS



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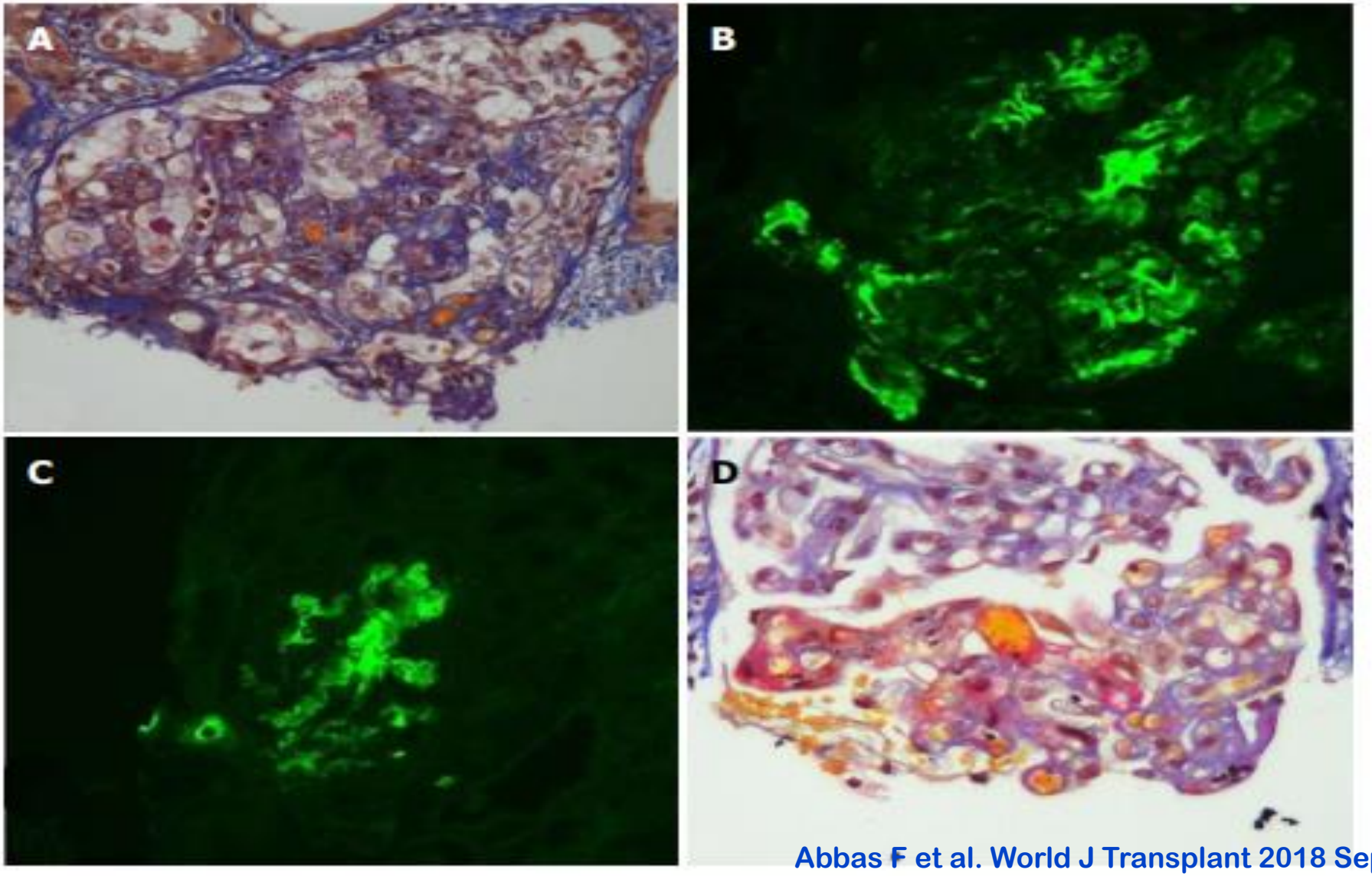
# Acute & chronic TMA & CNIs-associated arteriolopathy with severe acute ischemic tubular lesions

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# CLINICAL MANIFESTATIONS: SALIENT FEAYURES

- **TMA manifestations are quite variable:**
  - **Systemic variant.**
    - **It consists of the classic triad of:**
      1. **Thrombocytopenia**
      2. **MAHA**
      3. **AKI**
    - **Features of MAHA include:**
      - **Raised LDH, drop in HB & decreased haptoglobin with schistocytes on peripheral blood smear.**



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# DIAGNOSIS

- **TMA has been established:**
  - **Etiology of the native kidney ESRD???**
    - **In aHUS patients who do not show systemic manifestations, the diagnosis could be obscure.**
    - **In the absence of renal biopsy, many cases can be misdiagnosed as hypertensive nephrosclerosis.**
  - **Prompt testing for genetic mutations**



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# MORPHOLOGICAL FEATURES IN MICROANGIOPATHY

| Active lesions |
| --- |
| **Glomeruli:** Thrombi-Endothelial swelling or denudation - Fragmented RBCs - Subendothelial flocculent material.<br>EM: Mesangiolysis - Microaneurysms<br>**Arterioles:** Thrombi - Endothelial swelling or denudation- Intramural fibrin - Fragmented RBCs - Intimal swelling - Myocyte necrosis<br>**Arteries:** Thrombi - Myxoid intimal swelling - Intramural fibrin - Fragmented RBCs |

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# MORPHOLOGICAL FEATURES IN MICROANGIOPATHY

| Active lesions | Chronic lesions |
|---|---|
| **Glomeruli:** Thrombi-Endothelial swelling or denudation - Fragmented RBCs - Subendothelial flocculent material.<br>EM: Mesangiolysis - Microaneurysms<br>**Arterioles:** Thrombi - Endothelial swelling or denudation- Intramural fibrin - Fragmented RBCs - Intimal swelling - Myocyte necrosis<br>**Arteries:** Thrombi - Myxoid intimal swelling - Intramural fibrin - Fragmented RBCs | **Glomeruli:** Double contours of peripheral capillary walls, with variable mesangial interposition – EM: New subendothelial BM- Widening of the subendothelial zone<br>**Arterioles:** Hyaline deposits<br>**Arteries:** Fibrous intimal thickening with concentric lamination (onion skin) |



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# RECURRENT TMA AFTER RENAL TX

- Etiology:
  - aHUS
  - TTP
  - Autoimmune diseases: e.g., scleroderma & SLE, with or without APS.



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# PATHOPHYSIOLOGY OF TMA RECURRENCE

- The AP is constitutively active & is, therefore, fine-tuned.
- The regulatory components exist either in the serum or attached onto cell membranes.
- CFH is the main inhibitor of the AP.
- CFH can act as a co-factor to CFI.
- Regulatory components on cell surfaces, or "membrane regulators" include the following: (1) MCP/CD46; (2) CR1/CD35; (3) Decay accelerating factor (DAF/CD55); and (4) Protectin (CD59), which prohibits MAC formation



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# PATHOPHYSIOLOGY OF TMA RECURRENCE

- Any disturbance involving any of this protective shield will ultimately lead to complement activation with subsequent endothelial cell derangement.
- It is increasingly recognized that complement dysregulation is the fundamental etiology involved in TMA evolution.
- Both genetic aberrations as well as autoantibodies can be involved in this process.
- Usually, there is (are) an inciting environmental trigger factor(s).



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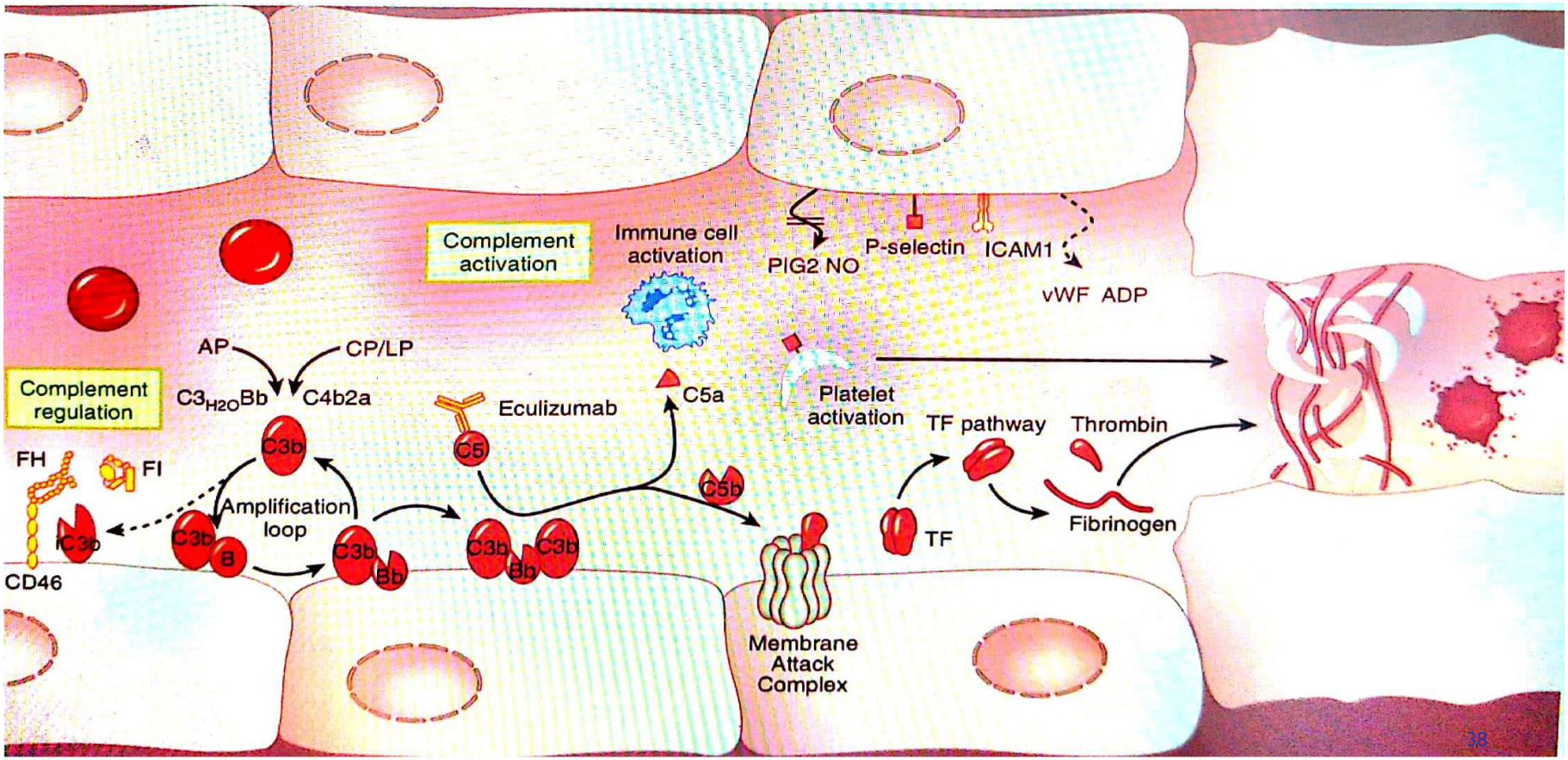
# PATHOPHYSIOLOGY OF TMA RECURRENCE






Brenner 2020

# COMPLETE COMPLEMENT EVALUATION BEFORE RTX LISTING IS RECOMMENDED IF TMA RESULTS IN ESRD

- Delay Tx until at least 6 mo starting dialysis as late renal recovery with eculizumab treatment has been reported.
- Living related kidney donation:
  - if a genetic or acquired cause is identified in the recipient & is not present in the intended donor.
- Liver Tx
  - in patients with liver derived complement pr abnormalities, in particular for KTRs with uncontrolled disease activity despite eculizumab therapy.



Goodship TH. Conclusions from a KDIGO controversies conference. KI. 2017

# COMPLETE COMPLEMENT EVALUATION BEFORE RTX LISTING IS RECOMMENDED IF TMA RESULTS IN ESRD

- The minimum set of genes that should be screened in aHUS & C3G includes:
  - CFH, CD46, CFI, C3, CFB, THBD, CFHR1, CFHR5, & DGKE.
  - This analysis should also include genotyping for the risk haplotypes CFH-H3 & MCPggaac.
  - Genetic analyses must include suitable technologies



Goodship TH. Conclusions from a KDIGO controversies conference. KI. 2017

# APPROACH TO KTX WHEN TMA RESULTS IN ESTABLISHED RENAL DISEASE

| Risk Stratification | Inclusion Criteria | Management Strategy |
|---|---|---|
| High (50-100%) | • Pathogenic complement mutations<br>• Previous early recurrence | Prophylaxis with eculizumab (KDIGO global panel suggest PE & liver Tx may also be considered) |

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| Moderate | • No complement mutation, or variant of unknown significance<br>• Isolated CFI mutation<br>• Detectable anti-factor H antibody | |

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# APPROACH TO KTX WHEN TMA RESULTS IN ESTABLISHED RENAL DISEASE

| Risk Stratification | Inclusion Criteria | Management Strategy |
|---|---|---|
| High (50-100%) | • Pathogenic complement mutations<br>• Previous early recurrence | Prophylaxis with eculizumab (KDIGO global panel suggest PE & liver Tx may also be considered) |
| Moderate | • No complement mutation, or variant of unknown significance<br>• Isolated CFI mutation<br>• Detectable anti-factor H antibody | |
| Low (<10%) | • Isolated CD46 mutation<br>• Previously positive but now consistently negative anti-factor H antibody | No prophylaxis |



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# EXTRARENAL MANIFESTATION

- 20% of aHUS patients can express extrarenal manifestations:
  - Neurologic involvement, including seizures & altered consciousness
  - Pancreatitis
  - Cardiac involvement/MI
  - GI involvement (including diarrhea, vomiting, abdominal pain)
  - Cerebral artery thrombosis/stenosis
  - Extracerebral artery stenosis
  - Digital gangrene/skin
  - Ocular involvement
  - Hepatitis
  - Pulmonary involvement



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# THERAPY OF POST-TX TMA


# TREATMENT OF DE NOVO TMA

- Should be **individualized**.
- The following approaches have been suggested:
  1. **Immunosuppressive medication management**: switching from one CNI member to another or to an mTORi
  2. **PE/IVIG** therapy
  3. **Belatacept**
  4. Complement inhibition: **Eculizumab**:

     (1) AMR-associated TMA (2) Patients who became PE-dependent; & (3) Refractory hemolysis persists despite maximum doses of PE therapy



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# TREATMENT OF RECURRENT TMA

- The minimal list of genetic screening should include:
  - CFH, CFI, CFHR, CFB, MCP & C3



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# Prevention of aHUS

1. Complement activity incited by an injury to endothelium, e.g., ischemia-reperfusion injury, viral infection & immunosuppressive medications, should be avoided
2. Certain relations have been reported between CNI use & aHUS recurrence
3. PE + Rituximab proved to be efficacious as anti-CFH-antibodies
4. Eculizumab



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# ECULIZUMAB

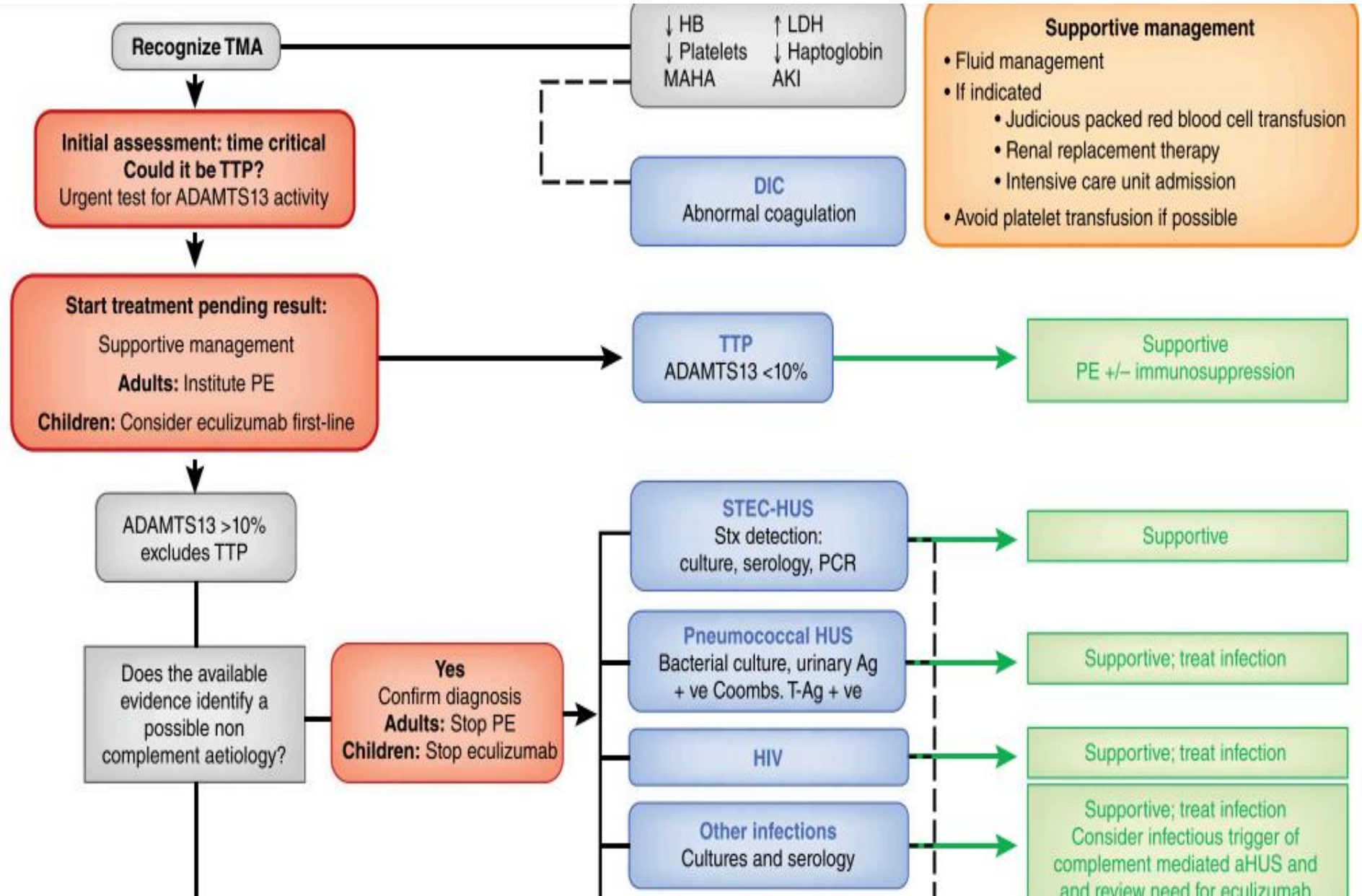
- Humanized monoclonal IgG antibody that binds to complement Pr C5.
- FDA approval for:
  - aHUS
  - PNH
  - Generalized Myasthenia Gravis


- In 2010 Alexion priced Soliris as the most expensive drug in the world, at approximately US $409,500 a year in the US (2010), & $500,000 a year in Canada (2014).

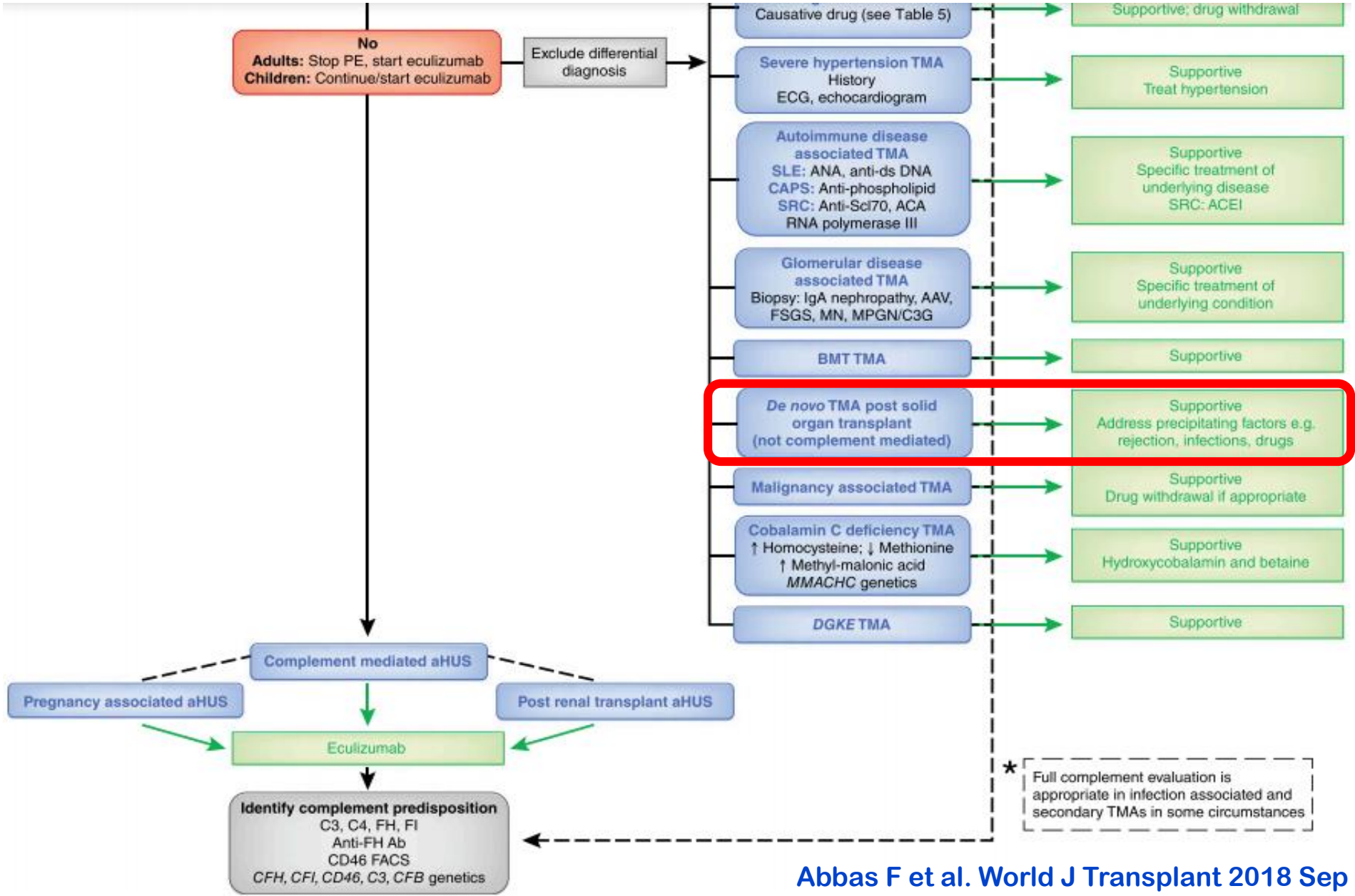
# SUMMARY

- The impact of TMA, either de novo or recurrent, on allograft longevity is underestimated.
- The spectrum of the culprit genes implicated in the evolution of TMA is currently expanding.
- Despite the landmark breakthrough of immense efficacy of complement blockade therapy, the outlook of this devastating syndrome remains poor if the diagnosis is delayed.
- In contrast, the recurrent TMA is much more optimistic if there is timely intervention by complement blockade before permanent damage sets in.

# INVESTIGATION & MANAGEMENT OF TMA



# INVESTIGATION & MANAGEMENT OF TMA

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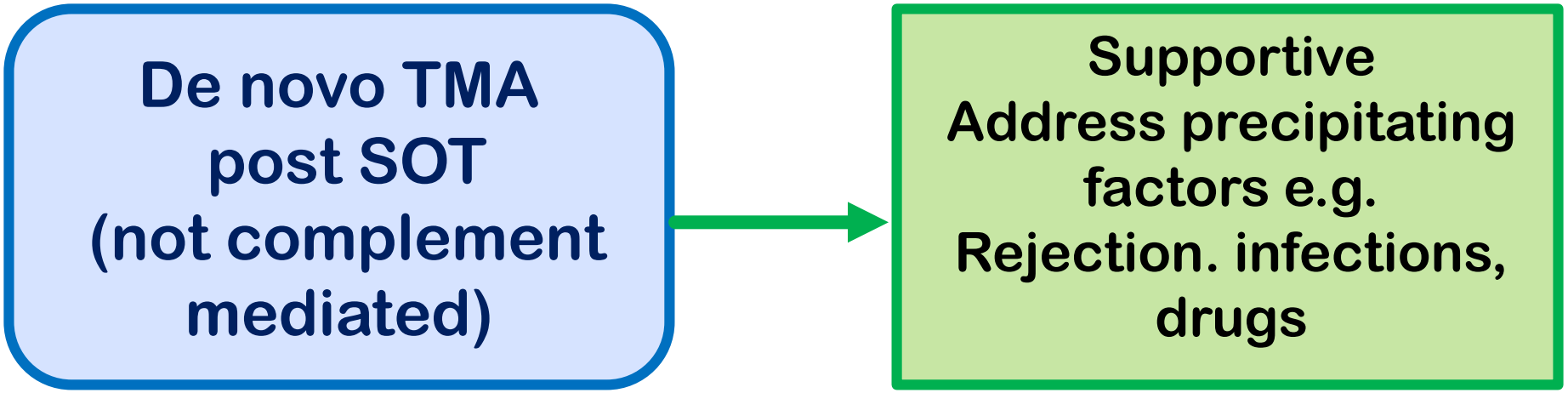
# MANAGEMENT OF POST SOT TMA



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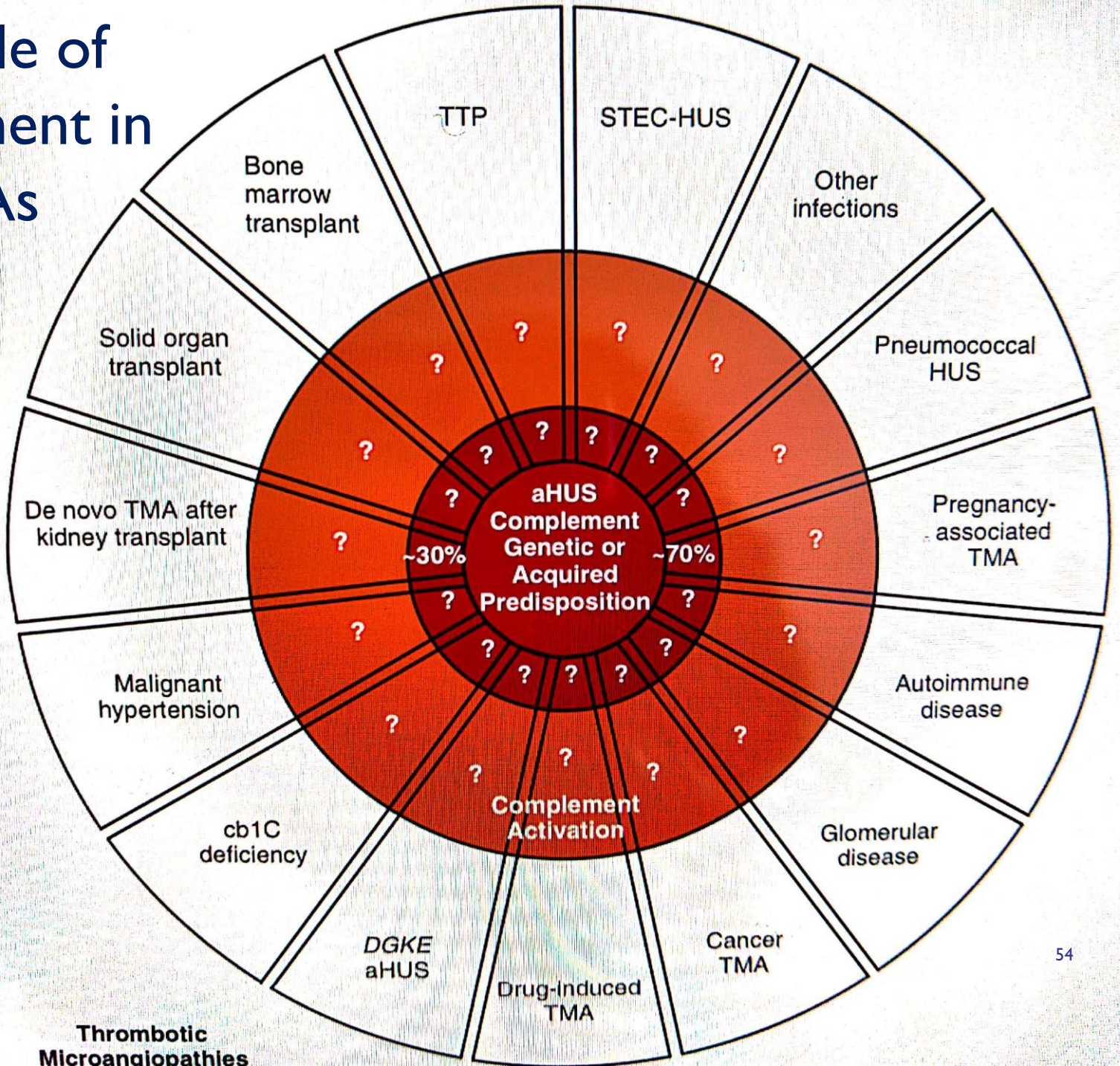
# The role of complement in TMAs



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