IOWA | Carver College of Medicine

Thursday, November 13, 2025

Atypical Hemolytic Uremic Syndrome and Thrombotic Microangiopathy

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Disclosures

- I have no relevant disclosures
- I use brand names and reference particular institutions for familiarity given their clinical utility

- Abbreviations
  - TMA = thrombotic microangiopathy
  - HUS = hemolytic uremic syndrome
  - aHUS = atypical hemolytic uremic syndrome
  - MAHA = microangiopathic hemolytic uremia

Objectives

- Understand the Pathophysiology of TMA
- Review the Differential Diagnosis of TMA
- Understand the Pathophysiology of Complement-Mediated TMA
- Review the Incidence
- Review the Diagnostic Workup
- Review Treatment Strategies

Let’s go back in time

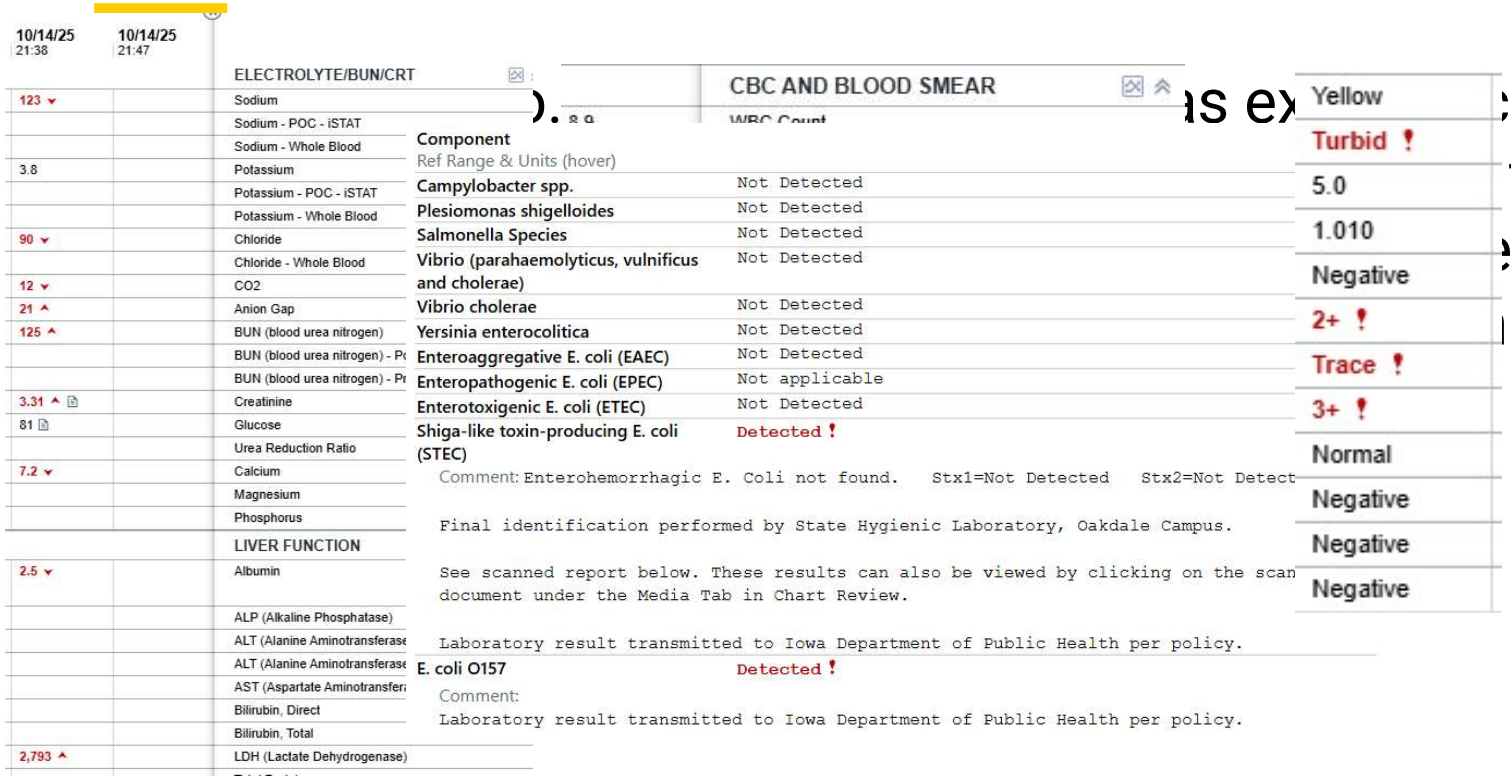
Hemolytic Uremic Syndrome

- 1955
- Gasser, Gautier, Steck, Siebanmann, and Oeschslin
- Five children, 2 months – 7 years
- “Acquired hemolytic anaemia, bizarre poikilocytoses, and renal insufficiency.”
- All died
- “Gasser’s Disease”

Hemolytic Uremic Syndrome

- Thrombocytopenia
- Hemolytic Anemia
- Renal Insufficiency (Renal Failure)
- 1977 – Shiga Toxin Producing E. Coli discovered
- 1982 – Shiga Toxin Producing E. Coli O157H:7 recognized as pathogenic
- 1983 – Shiga Toxin Producing E. Coli linked to HUS
  - Karmali

Clinical Vignette: HUS



10/14/25 21:38	10/14/25 21:47	ELECTROLYTE/BUN/CRT
123 ↓		Sodium
		Sodium - POC - iSTAT
		Sodium - Whole Blood
3.8		Potassium
		Potassium - POC - iSTAT
		Potassium - Whole Blood
90 ↓		Chloride
		Chloride - Whole Blood
12 ↓		CO2
21 ↑		Anion Gap
125 ↑		BUN (blood urea nitrogen)
		BUN (blood urea nitrogen) - Pc
		BUN (blood urea nitrogen) - Pr
3.31 ↑		Creatinine
81		Glucose
		Urea Reduction Ratio
7.2 ↓		Calcium
		Magnesium
		Phosphorus
		LIVER FUNCTION
2.5 ↓		Albumin
		ALP (Alkaline Phosphatase)
		ALT (Alanine Aminotransferase
		ALT (Alanine Aminotransferase
		AST (Aspartate Aminotransferi
		Bilirubin, Direct
		Bilirubin, Total
2,793 ↑		LDH (Lactate Dehydrogenase)

CBC AND BLOOD SMEAR

WBC Count 8.9

Component Ref Range & Units (hover)	
Campylobacter spp.	Not Detected
Plesiomonas shigelloides	Not Detected
Salmonella Species	Not Detected
Vibrio (parahaemolyticus, vulnificus and cholerae)	Not Detected
Vibrio cholerae	Not Detected
Yersinia enterocolitica	Not Detected
Enteroaggregative E. coli (EAEC)	Not Detected
Enteropathogenic E. coli (EPEC)	Not applicable
Enterotoxigenic E. coli (ETEC)	Not Detected
Shiga-like toxin-producing E. coli (STEC)	Detected !

Comment: Enterohemorrhagic E. Coli not found. Stx1=Not Detected Stx2=Not Detect

Final identification performed by State Hygienic Laboratory, Oakdale Campus.

See scanned report below. These results can also be viewed by clicking on the scan document under the Media Tab in Chart Review.

Laboratory result transmitted to Iowa Department of Public Health per policy.

E. coli O157	Detected !

Comment:
Laboratory result transmitted to Iowa Department of Public Health per policy.

Yellow
Turbid !
5.0
1.010
Negative
2+ !
Trace !
3+ !
Normal
Negative
Negative
Negative

as ex ced 4 days of
following a
e ED ill
e output for

Hemolytic Uremic Syndrome

Clinical Constellation:

- Thrombocytopenia
- Non-immune, Microangiopathic Hemolytic Anemia
- Acute Kidney Injury

Causative Agent: Shiga Toxin Producing E. Coli, O157:H7

Therapy: Supportive Care (incl. Dialysis) and Time

Clinical Vignette

10/14/25 21:38	10/14/25 21:47	
		ELECTROLYTE/BUN/CRT
123 ↓		Sodium
		Sodium - POC - iSTAT
		Sodium - Whole Blood
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21 ↑		Anion Gap
125 ↑		BUN (blood urea nitrogen)
		BUN (blood urea nitrogen) - Post Dial
		BUN (blood urea nitrogen) - Pre Dialy
3.31 ↑		Creatinine
81		Glucose
		Urea Reduction Ratio
7.2 ↓		Calcium
		Magnesium
		Phosphorus
		LIVER FUNCTION
2.5 ↓		Albumin
		ALP (Alkaline Phosphatase)
		ALT (Alanine Aminotransferase)
		ALT (Alanine Aminotransferase with P
		AST (Aspartate Aminotransferase wit
		Bilirubin, Direct
		Bilirubin, Total
2,793 ↑		LDH (Lactate Dehydrogenase)

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Enteroaggregative E. coli (EAEC)	Not Detected
Enteropathogenic E. coli (EPEC)	Not Detected
Enterotoxigenic E. coli (ETEC)	Not Detected
Shiga-like toxin-producing E. coli (STEC)	Not Detected
E. coli O157	Not Detected
Shigella/Enteroinvasive E. coli (EIEC)	Not Detected
Cryptosporidium	Not Detected
Cyclospora cayetanensis	Not Detected
Entamoeba histolytica	Not Detected
Giardia lamblia	Not Detected
Adenovirus F 40/41	Not Detected
Astrovirus	Not Detected
Norovirus	Not Detected
Rotavirus	Not Detected
Sapovirus	Not Detected

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s seen at an
irus. He was
wo days he has
as not been able
, and his urine
oms caused his
rhea.

nHg, Wt: 59 kg

Hemolytic Uremic Syndrome?

Clinical Constellation:

- Thrombocytopenia
- Non-immune, Microangiopathic Hemolytic Anemia
- Acute Kidney Injury

Causative Agent?

- ~~Shiga Toxin Producing E. Coli, O157:H7~~
- ~~Diarrhea~~

Atypical HUS (aHUS)

Thrombotic Microangiopathy (TMA)

Thrombocytopenia

Prothrombotic

Consuming platelets

Non-immune Hemolytic Anemia

Microangiopathic Hemolytic Anemia

Not bone marrow failure

DAT negative

Multiorgan Dysfunction

AKI

Neurologic Dysfunction

Veno-occlusive Disease (VOD)

Pancreatitis

Thrombotic Microangiopathy (TMA)

Renal Specific Manifestations of Thrombotic Microangiopathy (TMA)

Glomerulonephritis

Proteinuria

- Nephritic or Nephrotic range

Hematuria

- Gross or Microscopic

HTN

AKI

Oliguria

Renal Congestion/Edema/Enlargement

Biopsy

Non-specific - Proliferative

Fibrin deposition

Vascular endothelial thickening/swelling

Arteriolar Onion Skinning

Acute or Chronic findings (IFTA, Glomerulosclerosis, duplication of membranes)

Podocyte Foot Process Effacement

Thrombotic Microangiopathy (TMA)

Clinical Constellation:

- Thrombocytopenia (Plts <150 or decreasing by 50%)
- Non-immune, Microangiopathic Hemolytic Anemia (<10.5 g/dL)
  - Lactate Dehydrogenase (High)
  - Haptoglobin (low)
  - Schistocytes present
- Organ Dysfunction
- Hypertension

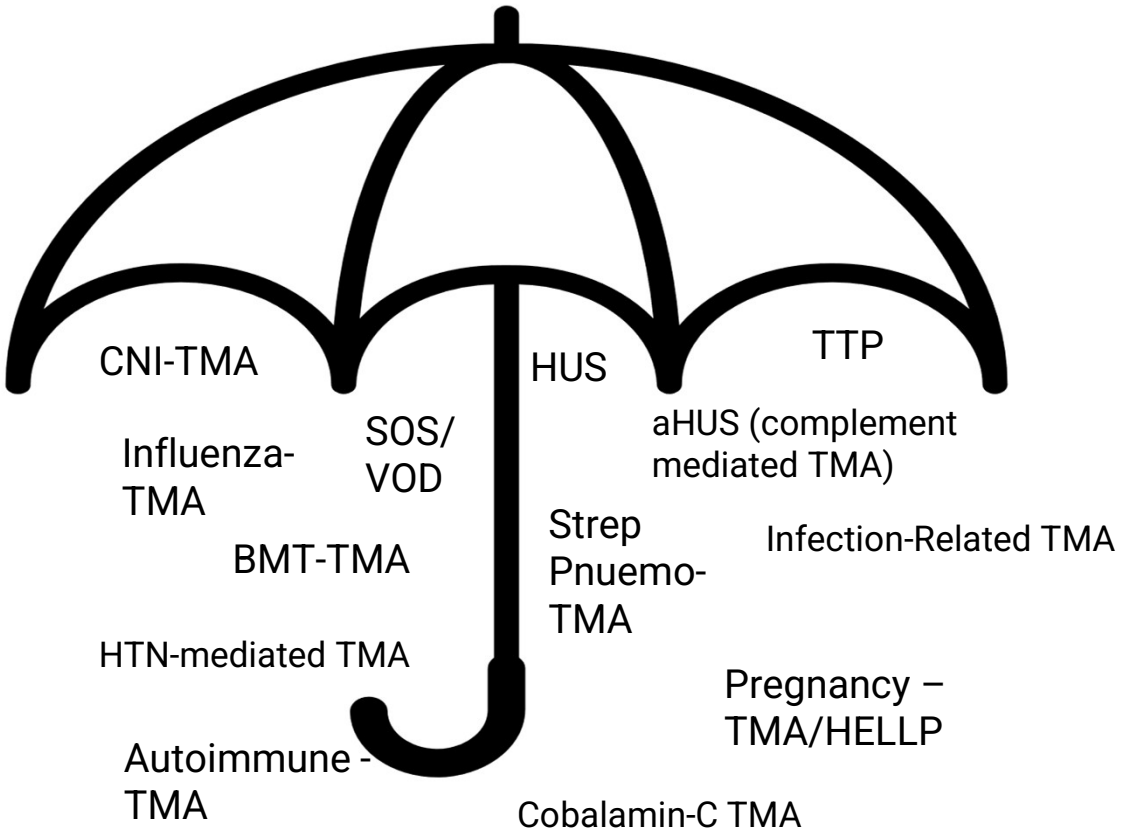
Causative Agent? LOTS

Why?

Endothelial Injury & Prothrombotic State

- Shiga-Toxin (STEC-HUS)
- Ultra-large von Willebrand factor Multimeters due to ADAMTS13 deficiency (TTP)
- Endothelial Injury from chemotherapy (BMT-TMA)
- Complement dysregulation (Complement-Mediated TMA)

Thrombotic Microangiopathy (TMA)?



Differential Diagnosis

- Broad
- Three you can’t miss:
  - Thrombotic Thrombocytopenia Purpura
  - STEC-HUS
  - Complement-Mediated TMA (aHUS)
- Others you should think about:
  - Influenza Associated-TMA
  - Streptococcal Associated-TMA
  - Bone Marrow Transplant-TMA
  - Calcineurin Inhibitor-TMA
  - Hypertension Induced-TMA

Thrombotic Thrombocytopenic Purpura

- TMA ± neurologic involvement → high morbidity and mortality
- Lack of ADAMTS13 (*a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13*) → cleaves vWF
- Ultra-large von Willebrand Fibers in circulation → Prothrombotic → TMA
- **ADAMTS13 deficiency syndrome**
  - Acquired (autoantibodies)
  - Congenital (lack of production)
- **ADAMTS13 LEVEL WILL BE SEVERELY LOW/SUPPRESSED (ie <10% of normal activity)**
- TX: **Plasmapheresis (therapeutic plasma exchange)**

Objectives

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- Understand the Pathophysiology of aHUS and Complement-Mediated TMA
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- Review Treatment Strategies

aHUS & Complement-Mediated TMA

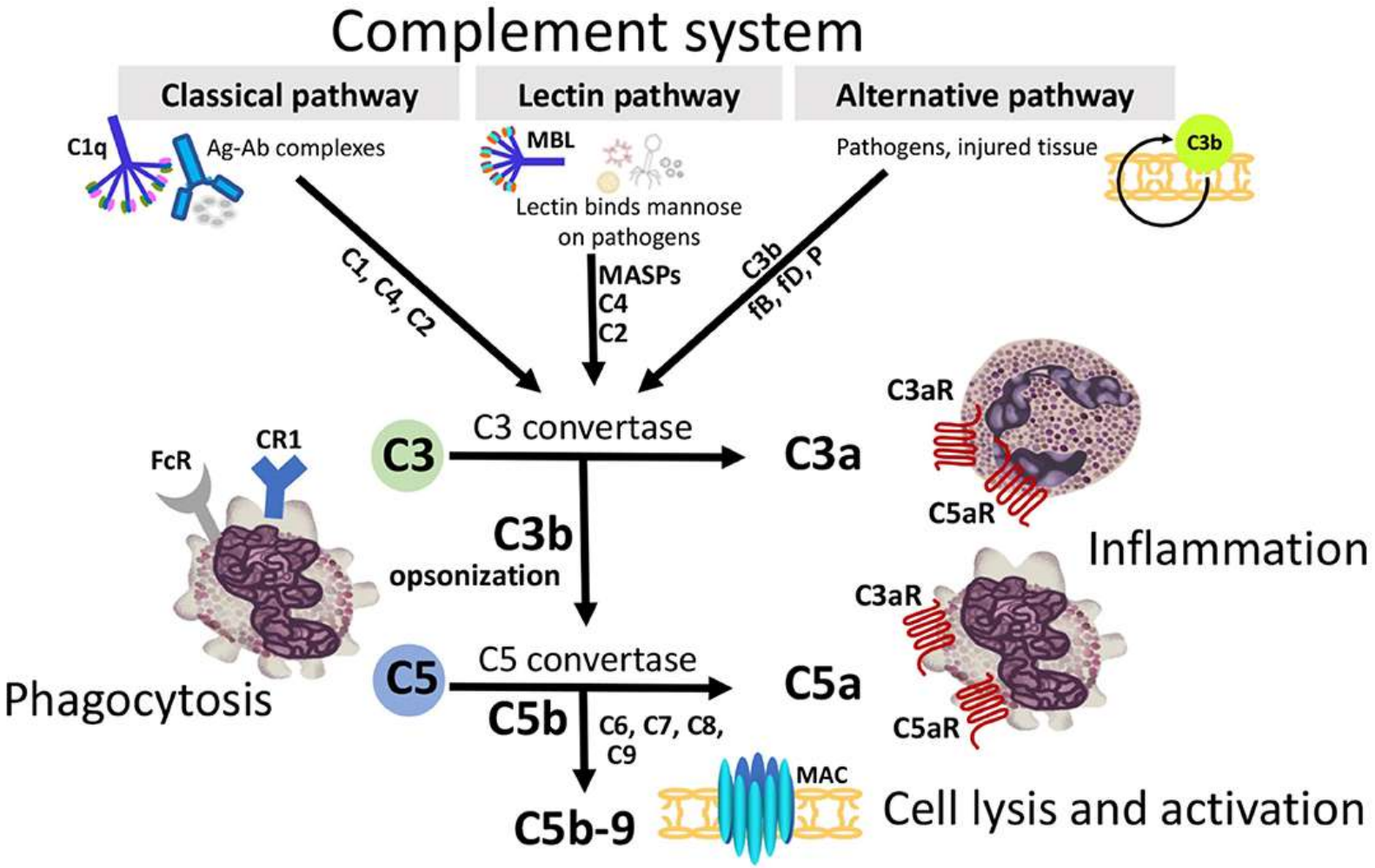
aHUS

- Rare:
  - ~2-7/1,000,000
  - ~5% of all TMA

- Young age (infancy)
- Family hx
- Hx of recurrent symptoms/attacks

aHUS

- Severe:
  - Mortality after initial event: ~5-30%
  - 1-year incidence of ESRD: ~16%
  - 5-year incidence of ESRD: ~50%
  - 5-year incidence of ESRD or Death: 77%

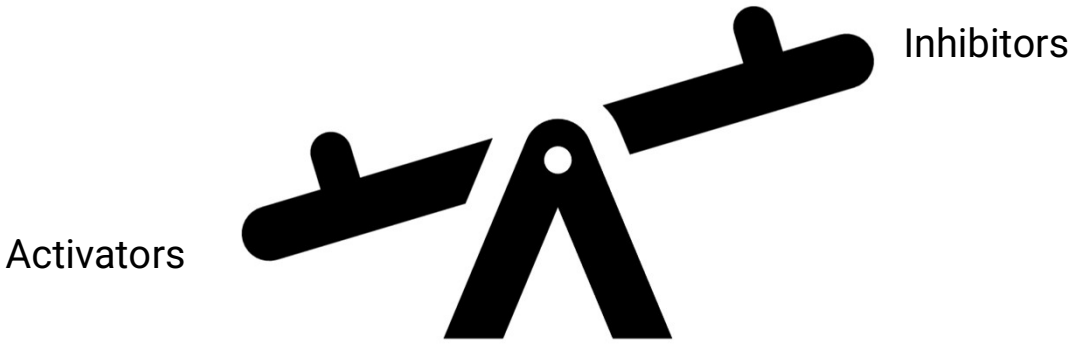

Complement system
Classical pathway
Lectin pathway
Alternative pathway
C1q
Ag-Ab complexes
MBL
Lectin binds mannose on pathogens
Pathogens, injured tissue
C3b
C1, C4, C2
MASPs
C4
C2
C3b
fB, fD, P
C3
C3 convertase
C3a
C3aR
C5aR
FcR
CR1
C3b
opsonization
Inflammation
Phagocytosis
C5
C5 convertase
C5a
C5b
C6, C7, C8, C9
C5b-9
MAC
Cell lysis and activation

Natural Defense

- Infections:
  - Encapsulated Bacteria
  - Fungi
- *Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenza B, Escherichia Coli, Klebsiella pneumonia*
- Specialized proteins designed for:
  - Initiation
  - Amplification
  - Termination

Complement System

Complement System



aHUS

- Significant proportion related to a complement dysregulation
  - Alternative pathway
- Autoantibodies
  - Factor H auto-abs (factor H inhibitor)
  - Factor B auto-abs (stabilizer of alternative complement system)
- Genetic Abnormalities
  - 40-60% carry some identified gene abnormality
  - Loss of function inhibitors: Factors H, I, and MCP
  - Gain of function in activators: C3, Factor B
- Genetics AND Autoantibodies:
  - CFHR1-5 homozygous deletions associated with generation of Factor B auto-abs

Complement-Mediated TMA

- Abnormality results in overactivation of the complement system
  - Genetic
  - Acquired
- Cascading into the soluble terminal complement MAC (C5b-9)
- Inflammation and cell death
- Triggered by routine infections or insults
  - Cold
  - Surgery

Complement-Mediated TMA

- Rule out TTP → ADAMTS13 level
- Consider stool panel, influenza screen, and streptococcal infection
- Send complement studies:
  - Additional Testing for inhibitors, activating factors, alternative pathway, fluid-phase activity, autoantibodies, C3, C4, CH50, SC5b-9
- Send complement genetic testing
  - Cincinnati Children's Thrombotic Microangiopathy
  - University of Iowa MORL

Complement-Mediated TMA Treatment

- C5 inhibitors
  - Eculizumab (soliris)
  - Ravulizumab (ultimiris)
- Prevent formation of MAC (C5b-9)
- Reduce cell lysis
- MAC important for antibacterial protection
  - Encapsulated bacteria (streptococcus, Hemophilus Influenza B, meningococcus)
  - Fungal infections

Eculizumab (Soliris)

- Humanized C5 monoclonal antibody
  - 2007
  - **2011**
- Prevents cleavage of C5 into C5a, C5b
  - No MAC formation
  - C5a inflammatory chemokine
- IV infusion
  - $
  - Loading dose weekly
- Maintenance dose Every 2 weeks*

Eculizumab

- Therapeutic Monitoring:
- Drug Level: Goal ≥100 μg/mL
- CH50: ≤12.5
- SMAC: ≤244 ng/mL

- Normalization of: plts, hgb, organ dysfunction

Ravulizumab (Ultomiris)

- Humanized C5 monoclonal antibody
  - 2018/2019
- Prevents cleavage of C5 into C5a, C5b
  - No MAC formation
  - C5a inflammatory chemokine
- IV infusion
  - $
- Loading dose
- Every 8 weeks

Ravulizumab

- Therapeutic Monitoring:
- Drug Level: not commercially available yet
- CH50: ≤12.5
- SMAC: ≤244 ng/mL

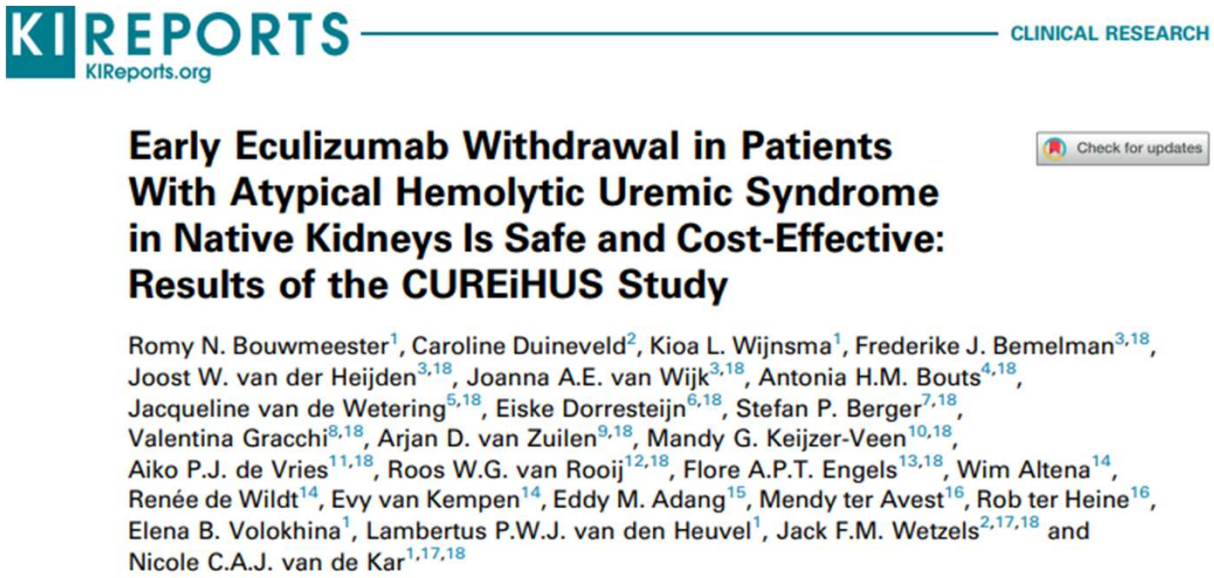
- Normalization of: plts, hgb, organ dysfunction

Terminal Complement Blockade

- Prevention of MAC (C5b-9)
- Vital for host defense against encapsulated organism
  - Immunizations
    - Meningococcus (Menveo, Menactra, Menquadfi)
    - Meningococcus B (Bexsero, Trumenba)
    - Streptococcus (PCV-13 or PCV-20)
    - Hemophilus Influenza B (PedvaxHIB, ActHIB, Hiberix)
  - Antimicrobial PPX
    - Amoxicillin
    - PCN VK

Complement-Mediated TMA Treatment Duration

- Depends
- Life-Long ($)



KI REPORTS
KIReports.org
CLINICAL RESEARCH

Early Eculizumab Withdrawal in Patients With Atypical Hemolytic Uremic Syndrome in Native Kidneys Is Safe and Cost-Effective: Results of the CUREiHUS Study

Romy N. Bouwmeester[1], Caroline Duineveld[2], Kioa L. Wijnsma[1], Frederike J. Bemelman[3,18], Joost W. van der Heijden[3,18], Joanna A.E. van Wijk[3,18], Antonia H.M. Bouts[4,18], Jacqueline van de Wetering[5,18], Eiske Dorresteijn[6,18], Stefan P. Berger[7,18], Valentina Gracchi[8,18], Arjan D. van Zuilen[9,18], Mandy G. Keijzer-Veen[10,18], Aiko P.J. de Vries[11,18], Roos W.G. van Rooij[12,18], Flore A.P.T. Engels[13,18], Wim Altena[14], Renée de Wildt[14], Evy van Kempen[14], Eddy M. Adang[15], Mendy ter Avest[16], Rob ter Heine[16], Elena B. Volokhina[1], Lambertus P.W.J. van den Heuvel[1], Jack F.M. Wetzels[2,17,18] and Nicole C.A.J. van de Kar[1,17,18]

Complement-Mediated TMA Treatment Duration

- Depends
- Life-Long ($)

- Trial off:
  - Stabilization of general condition
  - Good patient education and access to healthcare system
  - Frequent monitoring of blood pressure, urine samples, and labs
  - Ability to resume therapy rapidly

Complement-Mediated TMA Recurrence

- Absolutely
- Routine triggers warrant evaluation
- Post-Transplant
  - >50%
  - <1 year (hours-days)
  - 80-90% premature graft loss
- PPX Eculizumab in renal transplantation

Practical Considerations

TMA workup

Clinical Constellation:

- Thrombocytopenia (Plts <150 or decreasing by 50%)
- Non-immune, Microangiopathic Hemolytic Anemia (<10.5 g/dL)
  - Lactate Dehydrogenase (High)
  - Haptoglobin (low)
  - Schistocytes present
- Organ Dysfunction
- Hypertension

- Rule out TTP → ADAMTS13 level
- Consider stool panel, influenza screen, streptococcal infection, and drug-induced
- Send complement studies: C3, C4, CH50, SC5b-9 +/- additional testing
- Send complement genetic testing

TMA therapeutic decisions

- TTP: Plasma exchange +/- immunosuppression (if auto-ab)
- STEC-HUS: supportive care
- Complement-Mediated TMA
  - **Terminal complement blockade:**
    - Eculizumab (Soliris)
    - Ravulizumab (Ultomiris)
  - Immunizations
    - Meningococcus (Menveo, Menactra, Menquadfi)
    - Meningococcus B (Bexsero, Trumenba)
    - Streptococcus (PCV-13 or PCV-20)
    - Hemophilus Influenza B (PedvaxHIB, ActHIB, Hiberix)
  - Antimicrobial PPX
    - Amoxicillin
    - PCN VK

Fluid and Nutrition in TMA

- Renal Function/Urine Output
  - Anuria, Oliguria, or good urine output
  - Renal function can be normal or stage III-AKI
  - Early fluid/sodium resuscitation in STEC-HUS improves renal outcomes
- Hemolysis → hyperkalemia
- Hyperphosphatemia
- Hyperglycemia → pancreatic injury

Complement-Mediated TMA surveillance

- CH50: <12.5 U/mL
- Eculizumab level: >100 μg/mL
- Soluble Terminal Complement (SC5b-9): <244 ng/mL (<0.24 mg/L)*

Objectives

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Sources

- Bagga et al. Pediatric Nephrology. Eight Edition. Volume 1. Ch 23: “Thrombotic Thrombocytopenic Purpura, Atypical Hemolytic Uremic Syndrome, and Spectrum of Thrombotic Microangiopathy”
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Questions?

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Thank you

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