KDIGO aHUS & C3G
Physician Reference Guide

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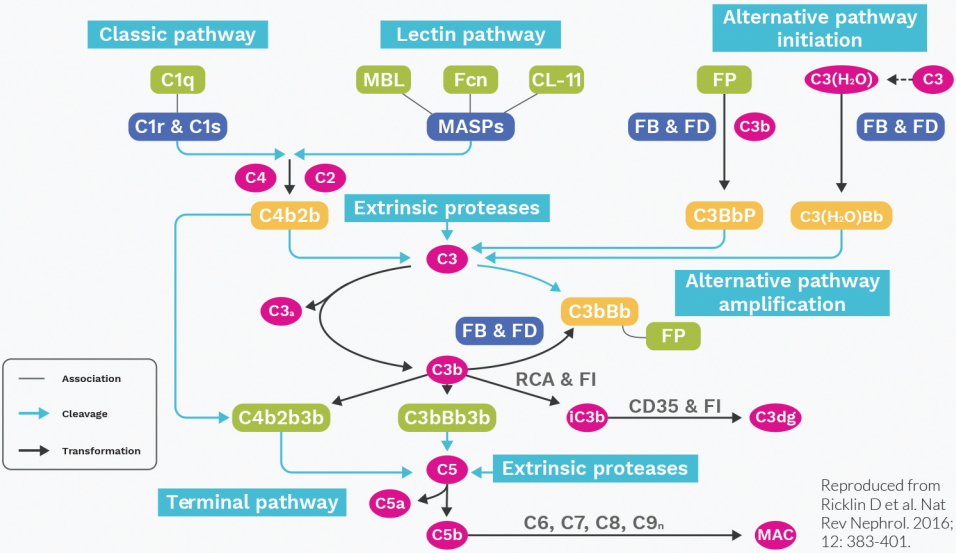
The Complement Pathways



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Atypical Hemolytic Uremic Syndrome (aHUS)

- Ultra-rare disease characterized by acute kidney injury, thrombocytopenia, and microangiopathic hemolytic anemia.
- At least 50% of aHUS patients have an underlying inherited and/or acquired complement abnormality.
- Eculizumab, a humanized mAb against C5, makes it possible to control aHUS and prevent development of ESKD.

C3 Glomerulopathy (C3G)

- C3G constitutes a group of kidney diseases driven by uncontrolled activation of the complement cascade that leads to C3 deposition within the glomerulus.
- The dysregulation of C3 convertase is driven by genetic and/or acquired defects.

RENAL PATHOLOGY

MORPHOLOGICAL FEATURES IN MICROANGIOPATHY

	ACTIVE LESIONS	CHRONIC LESIONS
GLOMERULI	• Thrombi • Endothelial swelling or denudation • Fragmented red blood cells • Subendothelial flocculent material by EM • Mesangiolysis • Microaneurysms	• Double contours of peripheral capillary walls by LM, with variable mesangial interposition • New subendothelial basement membrane by EM • Widening of the subendothelial zone by EM
ARTERIOLES	• Thrombi • Endothelial swelling or denudation • Intramural fibrin • Fragmented red blood cells • Intimal swelling • Myocyte necrosis	• Hyaline deposits
ARTERIES	• Thrombi • Myxoid intimal swelling • Intramural fibrin • Fragmented red blood cells	• Fibrous intimal thickening with concentric lamination (onion skin)

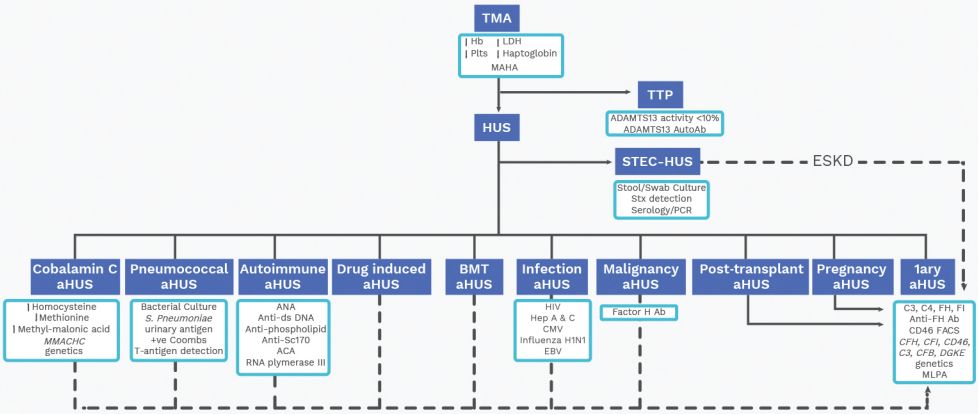
MORPHOLOGICAL FEATURES OF C3G

LM	*Active Lesions* • Mesangial expansion with or without hypercellularity • Endocapillary hypercellularity including monocytes and/or neutrophils • Capillary wall thickening with double contours (the combination of capillary wall thickening and mesangial increase is referred to as a membranoproliferative pattern) • Necrosis • Cellular/fibrocellular crescents *Chronic Lesions* • Segmental or global glomerulosclerosis • Fibrous crescents
IF	• Typically dominant C3 staining
EM	• DDD: Dense osmiophilic mesangial and intramembranous electron dense deposits • C3GN: Amorphous mesangial with or without capillary wall deposits including subendothelial, intramembranous and subepithelial electron dense deposits • Sub-epithelial 'humps' may be seen in both DDD and C3GN

CLINICAL PHENOTYPE & ASSESSMENT

	aHUS	C3G
OVERVIEW	• Current classifications of aHUS reflect an increased understanding of disease mechanisms, including the impact of genetic background and etiologic triggers. • Triggers include autoimmune conditions, transplants, pregnancy, infections, drugs, and metabolic conditions. • Although the time course and persistence of an aHUS episode is not well understood, many patients appear to be at life-long risk for recurrent acute presentation. • Disease penetrance for an acute episode of aHUS is age-related and, by age 70, may be as high as 64%.	• In the majority of patients with C3G, the disease follows a chronic, indolent course with persistent alternative pathway activation, resulting in a 10-year renal survival of approximately 50%. • However, cases of C3G presenting as a rapidly progressive glomerulonephritis are well recognized.
EXTRARENAL MANIFESTATIONS	• Digital gangrene, skin • Cerebral artery thrombosis/stenosis • Extracerebral artery stenosis • Cardiac involvement/myocardial infarction • Ocular involvement • Neurologic involvement • Pancreatic, gastrointestinal involvement • Pulmonary involvement • Intestinal involvement	• Acquired partial lipodystrophy (APL) • Retinal drusen
LABORATORY ANALYSIS	• Measure ADAMTS13 activity to diagnose or exclude thrombotic thrombocytopenic purpura (TTP) • Investigate for STEC-HUS • Measure serum/plasma complement levels	• Measure serum/plasma complement levels and test complement activity; a thorough analysis of complement is required to adequately define the type and degree of complement deregulation

DIAGNOSTIC FLOWCHART FOR THROMBOTIC MICROANGIOPATHY (TMA)



GENETIC & ACQUIRED DRIVERS OF DISEASE

UNDERSTANDING GENETIC VARIANTS

- Genetic variants should be classified as "benign," "likely benign," "variant of uncertain significance," "likely pathogenic," or "pathogenic," following international guidelines.
- In aHUS, pathogenic variants specifically impair the capacity to protect host endothelial cells and platelets from complement damage/activation.
- C3G appears mechanistically more complex than aHUS. There is limited information about genotype/phenotype correlations to distinguish different C3G subtypes, inform prognosis, and/or recommend treatment.

GENETIC TESTING

- At minimum, screen for: *CFH*, *CD46*, *CFI*, *C3*, *CFB*, *THBD*, *CFHR1*, *CFHR5*, and *DGKE*.
- Include the risk haplotypes *CFH-CFHR3* and *MCPggaac*.
- Include technologies to detect copy-number variation, hybrid genes, and other complex genomic rearrangements in the *CFH/CFHRs* genomic region.
- Genetic analysis is essential in living-related kidney donor transplantation.

aHUS

- Genetic testing is recommended for patients in whom discontinuation of eculizumab is being considered.

C3G

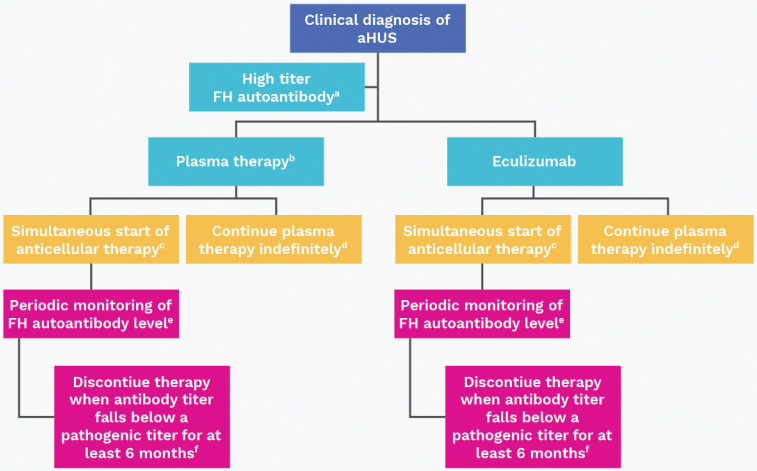
- The benefit of performing genetic analysis in C3G is currently unclear since our understanding of the genetics of C3G is not yet comparable to that of aHUS.

ACQUIRED DRIVERS OF DISEASE IN aHUS & C3G: SCREENING RECOMMENDATIONS

Acquired factor	aHUS	C3G
C3 nephritic factors	No	Yes
C5 nephritic factors	No	Yes
Anti-factor H autoantibodies	Yes	Yes
Monoclonal gammopathy	Yes	Yes

TREATMENT STRATEGIES: aHUS

TREATMENT OF COMPLEMENT FACTOR H AUTOANTIBODY-MEDIATED aHUS



[a] Abnormal titer depends on the testing laboratory.

[b] The decision to use plasma therapy versus eculizumab will be based on patient age and local resource availability.

[c] Cyclophosphamide, rituximab, or mycophenolate mofetil.

[d] The decision to continue anticomplement therapy indefinitely is not informed by data.

[e] The interval may be monthly or quarterly and is based on local resources.

[f] This recommendation is based on limited retrospective case reviews.

ECULIZUMAB DOSING IN aHUS BASED ON DOSING GOAL

TRIAL DOSE

Desire to continue dosing according trial dose schedule

Children 5 kg to <10 kg
Induction: 300 mg weekly for 1 dose; Maintenance: 300 mg at week 2, then 300 mg every 3 weeks

Children 10 kg to <20 kg
Induction: 600 mg weekly for 1 dose; Maintenance: 300 mg at week 2, then 300 mg every 2 weeks

Children 20 kg to <30 kg
Induction: 600 mg weekly for 2 doses; Maintenance: 600 mg at week 3, then 600 mg every 2 weeks

Children 30 kg to <40 kg
Induction: 600 mg weekly for 2 doses; Maintenance: 900 mg at week 3, then 900 mg every 2 weeks

Children and adults ≥40 kg
Induction: 900 mg weekly for 4 doses; Maintenance: 1200 mg at week 5, then 1200 mg every 2 weeks

Supplemental dosing for patients receiving plasmapheresis or plasma exchange

If most recent dose was 300 mg, administer 300 mg within 60 minutes after each plasmapheresis or plasma exchange

If most recent dose was ≥600 mg, administer 600 mg within 60 minutes after each plasmapheresis or plasma exchange

Supplemental dosing for patients receiving fresh frozen plasma infusion

If most recent dose was ≥300 mg, administer 300 mg within 60 minutes prior to each infusion of fresh frozen plasma

MINIMAL DOSE

Desire to continue dosing with the minimal dose required to achieve a pre-identified level of complement blockade[a]

Dose reduction or interval extension

Goal CH50 <10% (recommended)

Goal AH50 <10% (recommended)

Goal eculizumab trough >100 µg/ml

DISCONTINUATION

Desire to discontinue complement blockade

No consensus exists regarding tapering of dose

a. Additional monitoring may be required during intercurrent events (e.g., infection, surgery, vaccination) to detect unblocked complement activity.

TREATMENT STRATEGIES: C3G

RECOMMENDED TREATMENT APPROACH FOR C3G[a]

ALL PATIENTS

- Optimal blood pressure control (suggested blood pressure below the 90% in children and ≤120/80 mm Hg in adults
  - Priority agents include angiotensin converting enzyme inhibitors and angiotensin receptor blockers
- Optimal nutrition for both normal growth in children and healthy weight in adults
- Lipid control

MODERATE DISEASE

Description

- Urine protein over 500 mg/24 h despite supportive therapy

or

- Moderate inflammation on renal biopsy

or

- Recent increase in serum creatinine suggesting risk for progressive disease

Recommendation

- Prednisone - short course (2-3 months) for anti-inflammatory effect
- Mycophenolate mofetil

SEVERE DISEASE

Description

- Urine protein over 2000 mg/24 h despite immunosuppression and supportive therapy

or

- Severe inflammation represented by marked endo- or extracapillary proliferation with or without crescent formation despite immunosuppression and supportive therapy

or

- Increased serum creatinine suggesting risk for progressive disease at onset despite immunosuppression and supportive therapy

Recommendation

- Limited success of anti-cellular immune suppressants and methylprednisolone pulse dosing in rapidly progressive disease
- Data are insufficient to recommend eculizumab as a first-line agent for the treatment of rapidly progressive disease

[a]Based on a single, small prospective trial, case reports, and expert opinion.

TRANSPLANT CONSIDERATIONS

aHUS

Recurrence Risk	Treatment Regimen
High risk (50-100%) • Previous early recurrence • Pathogenic mutation[a] • Gain-of-function mutation	Prophylactic eculizumab[b,c] Note: Start on the day of transplantation due to potential for severe recurrence and limited recovery function in renal grafts compared with native kidneys
Moderate risk • No mutation identified • Isolated *CFI* mutations • Complement gene mutation of unknown significance • Persistent low titer FH autoantibody	Prophylactic eculizumab or plasma exchange[d]
Low risk (<10%) • Isolated *MCP* mutations • Persistently negative FH autoantibodies	No prophylaxis

C3G

Recurrence Risk	Treatment Regimen
Timing	• Avoid transplantation during acute period of renal loss • Avoid transplantation during acute inflammation • No data exists to support whether specific complement abnormalities (e.g. high titer C3Nef, low C3 or high soluble C5b-9) predict increased risk for relapse
Donor selection	• No specific recommendation can be made on donor choice • When considering living donors, high risk of recurrence should be weighed against presumed risk of waiting on cadaveric donor list
Risk reduction	• Histological recurrence of C3G is as high as 90% • Limited data suggests that rapid progression to ESKD in the native kidneys increases the risk for recurrence • There are no known strategies to reduce the recurrence risk of C3G • Clinical recurrence should drive the decision to treat • In the absence of a clinical trial, the use of anti-complement therapy is based solely on a small open-label trial and positive case reports; the impact of publication bias is unknown • C3G associated with monoclonal gammopathy has a high rate of recurrence

a. Requires complete screening of all genes implicated in aHUS.

b. Prophylactic regimens are based on local center protocols; no trial data exist to support superiority of 1 protocol over another.

c. Liver transplantation can be considered for kidney transplant recipients with liver-derived complement protein abnormalities, uncontrolled disease activity despite eculizumab therapy, or financial considerations regarding cost of long-term eculizumab therapy.

d. The decision to perform or not to perform prophylactic plasma exchange or complement inhibition is left to the discretion of the clinician.

KEY MESSAGES

- ✔ **Complement plays a primary role in the pathogenesis of both aHUS and C3G, which are both ultra-rare diseases.**
  - **aHUS—acute kidney injury, thrombocytopenia, and microangiopathic hemolytic anemia.**
  - **C3G—group of kidney diseases driven by uncontrolled activation of the complement cascade, leading to C3 deposition within the glomerulus.**
- ✔ **Both aHUS and C3G are associated with extrarenal manifestations.**
- ✔ **Serum or plasma levels of complement proteins should be measured in all patients with primary aHUS and C3G.**
- ✔ **Genetic drivers of aHUS can be identified through screening; the genetics of C3G are not as well-defined.**
- ✔ **Genetic analysis is essential in living-related kidney donor transplantation.**
- ✔ **All patients with a clinical diagnosis of primary aHUS are eligible for treatment with eculizumab; however, treatment duration is controversial.**
- ✔ **If access to eculizumab is unavailable, plasma exchange therapy can be used to treat aHUS.**
- ✔ **Limited evidence supports the use of MMF in C3G, but more research is required.**

ABBREVIATIONS

1ary: primary
Ab: antibody
ACA: anticentromere antibody
aHUS: atypical hemolytic uremic syndrome
ANA: antinuclear antibody
anti-Scl-70: anti-topoisomerase I antibody
BMT: bone marrow transplant
C3G: C3 glomerulopathy
C3GN: C3 glomerulonephritis
CFI: complement factor I gene
CL-11: collectin 11
CMV: cytomegalovirus
DDD: dense deposit disease
DGKE: diacylglycerol kinase ε
EBV: Epstein-Barr virus
EM: electron microscopy
ESKD: end-stage kidney disease
FACS: flow cytometry
FB: protease factor B
Fcn: ficolins
FD: Complement factor D
FH: complement factor H protein
FP: properdin
Hb: hemoglobin
Hep: hepatitis
HUS: hemolytic uremic syndrome
IF: immunofluorescence
LDH: lactate dehydrogenase
LM: light microscopy
MAC: membrane-attack complex
MAHA: microangiopathic hemolytic anemia
MASP: MBL-associated serine proteases
MBL: mannose-binding lectin
MCP: membrane cofactor protein gene
MLPA: multiplex ligation-dependent probe amplification
MMF: mycophenolate mofetil
PCR: polymerase chain reaction
Plts: platelets
RCA: regulators of complement activation
STEC-HUS: Shiga toxin *E. coli* HUS
Stx: Shiga toxin
TMA: thrombotic microangiopathy
TTP: thrombotic thrombocytopenic purpura

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