THE CSN WELCOMES YOU TO A VIRTUAL BREAKFAST SYMPOSIUM

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BLOCK IT!

Case based approach to aHUS:
New Advances in Complement Blockade

Section 1 accredited symposium

Canadian Society of Nephrology/
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Disclosure of Potential Conflicts of Interest

Dr. Todd Fairhead	Honoraria for provision of educational speaking engagements: Alexion Pharma Membership on National Advisory Board: Alexion Pharma
Dr. Jocelyn Garland	Advisory Board and CME: Alexion Pharma
Dr. Susan Huang	Speakers but no financial grant/payment to me, donated to LHSC Foundation fund for any honorarium: Alexion Pharma and Sanofi

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Disclosure of Financial Support

This program has received:

Financial support from Alexion Inc. in the form of an unrestricted educational grant

Potential for conflict(s) of interest:

Alexion Inc. benefits from the sale of the following products that may be discussed in this program:

- ravulizumab
- eculizumab

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Learning Objectives

After this session, participants should be better able to:

- Recognize complement-related diseases
- Understand the association between MPGN and aHUS
- Select treatment(s) for complement pathway–related disease
- Discuss preliminary neurological data from patients with aHUS
- Describe an initial approach to TMA diagnosis
- Outline treatment strategies for TMA during pregnancy and post-partum
- Discuss atypical HUS therapy

Clinical Conundrums in aHUS: A case-based presentation

Dr. Jocelyn Garland

November 4th, 2020

Challenging Case

- First meeting with this patient
- Nov 5, 2019
  - 31 year old female, G2P1A0, 15 weeks pregnant
  - Problem list:
    - CKD – IgA nephropathy, July 2018 kidney biopsy
    - Baseline creatinine approx 84umol/L eGFR 78;
    - Proteinuria (uACR 200 mg/mmol),
    - Hypertension – (prescribed Candesartan - switched to labetolol when pregnancy test known).
    - No history of DM, obesity, or renal disease in family.
    - Referred for pregnancy care in CKD.

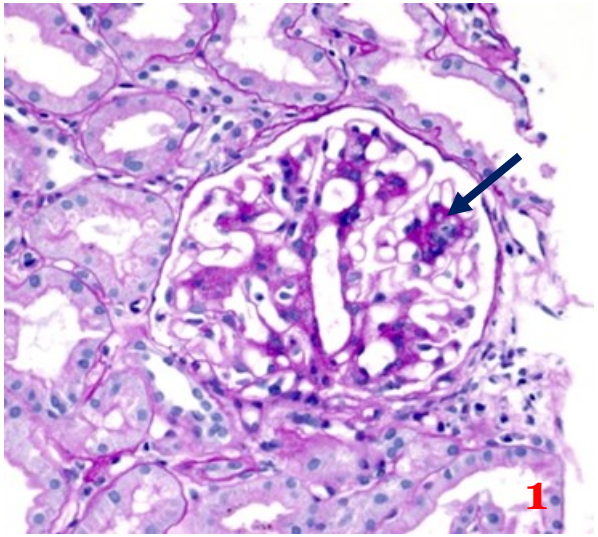
Past Obstetrical history

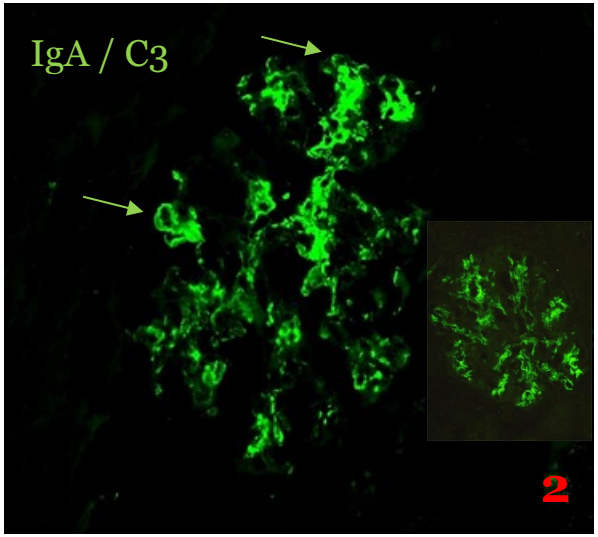
- G2 P1 A0
  - 2014 first pregnancy - Alberta
  - From first OB visit – Hypertension.
  - Proteinuria throughout pregnancy which escalated.
  - No data on renal function with 1st pregnancy.
  - Pre-eclampsia eventually diagnosed.
  - Induced at 38 weeks
  - Baby 5 pounds - no NICU required
  - Moved to Ontario

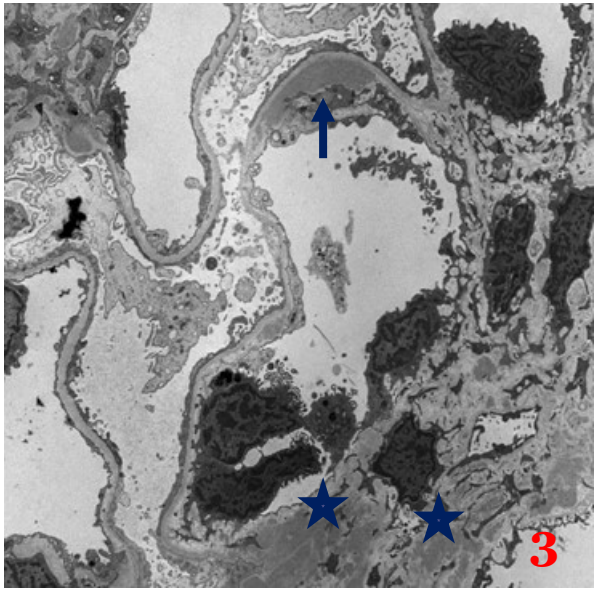
Past Nephrological history

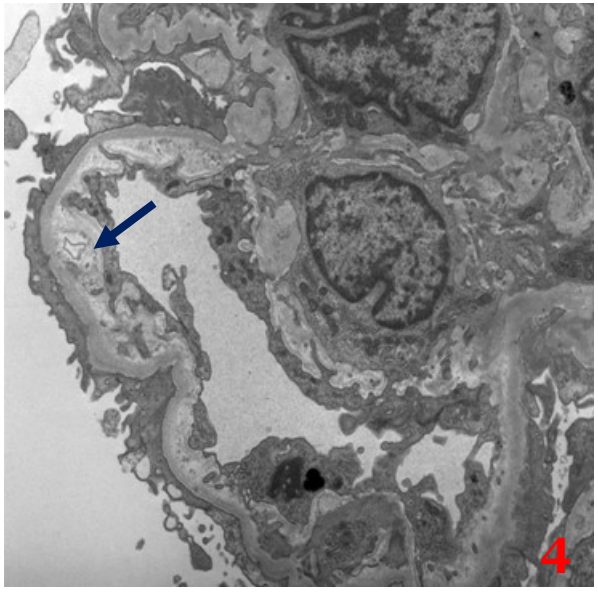
- ER visit for UTI, 2018 – High BP noted.
  - March 2018 Creatinine 84, UACR 230 24 hour urine 2.12 g per day; urine creatinine 8.6
  - U/A 5+ protein, 10+ blood.
  - June 2018 local nephrology referral
    - CTD serology done - neg.
    - C3/C4 normal.
    - BP treated with Candesartan
  - Renal ultrasound normal including kidney size
  - July 2018 Renal Biopsy - read at UHN

Renal biopsy # 1(2018 07 24)









Slides Courtesy Dr. Rohan John

Renal Biopsy Summary

- Diagnosis
  - IgA nephropathy: M1 E0 S0 T0 - C0.
- Prominent mesangial hypercellularity; no endocapillary hypercellularity (somewhat limited sample for LM)
- 5 of 31 gloms globally sclerosed with minimal interstitial fibrosis.
- IF: IgA 3+, IgG 1-2+, C3 3+, Lambda 2-3+, Kappa 2+
- EM: Numerous mesangial, and a few subendothelial deposits; Mild subendothelial expansion (away from deposits) with cellular interpositioning; TRI's present.
- COMMENT: Suggestion of incipient endocapillary hypercellularity / early MPGN pattern

Assessment

- Considerations re: previous biopsy
  - Bx most consistent with IgA nephropathy.
  - MPGN with dominant IgA (which is more like IC MPGN is a definite possibility)
    - Suggested by IF and EM (limited LM sample)
  - She had pre-eclampsia before….. Could finding of double contours without deposits (endocapillary hypercellularity) indicate possible old TMA?
  - Does she have unrecognized CTD with the sub epi- and sub- endothelial deposits/TRIs?

Some issues discussed on her first visit.

- CKD and pregnancy:
  - Consider kidney function – (pre-pregnancy GFR of 78).
  - Consider underlying disease (IgA; Previous PET).
  - Consider baseline blood pressure status (High BP)and proteinuria (high grade).
- How will these issues impact on the woman and her kidneys/underlying disease?
- How will these issues impact on fetus?
- Plan: watch BP, and follow her very closely.
- She is taking ASA, 81 mg - increased to 162 mg per day.

Risk of Adverse Pregnancy outcomes in women with CKD

Characteristic	CKD 1	CKD 2	CKD 3	CKD 4/5	P
Referral wk	15	11	8	8	<0.001
Systemic Dz %	12	36	43	40	< 0.001
HTN %	22	41	54	20	< 0.001
Proteinuria					< 0.001
<0.3 %	78	65	33	22	
> 3 grams %	2.5	7.0	-	11	
Gest. Age wk	37	35	34	32	< 0.001
Birth Wt	3000	2500	2200	1600	< 0.001
NICU %	10	27	44	70	< 0.001
CKD worse%	8	13	16	20	< 0.001
Severe outcome %	21	44	60	80	< 0.001

Severe = preterm, NICU, SGA

TOCOS study JASN 26: 2011-22;2015

What is Pre-eclampsia (PET)?

Definition

- Hypertension > 140/90
- > 20 weeks gestation
- Proteinuria > 300 mg /24 hours or organ dysfunction
- Previously normotensive woman

- If new onset HTN without proteinuria, after 20 weeks, PET diagnosed if low platelets, increased liver transaminases, increased creatinine, pulmonary edema, cerbral or visual symptoms.

Pre-eclampsia prophylaxis for High RISK recommended

- Renal Disease**
- Past history of PET**
- History of HTN**, or Diabetes
- Family history PET
- Multiple gestation
- Pre-pregnancy elevated BMI
- Maternal age < 20 > 40

SOGC recommends ASA 81 mg at < 16 weeks for high risk. For CKD, start ASA as soon as conception known until 34-36 wks. Calcium supplementation for those with inadequate intake

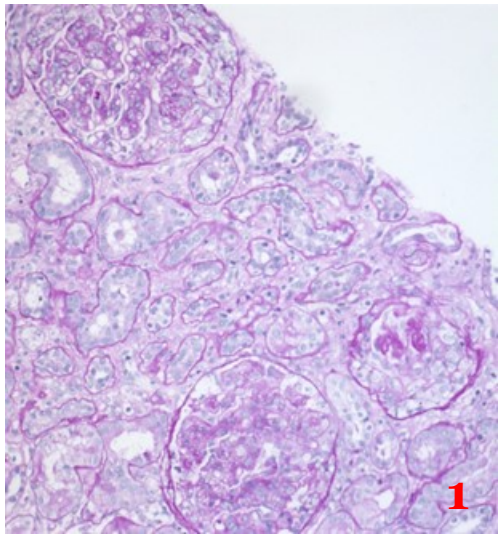
Pregnancy course

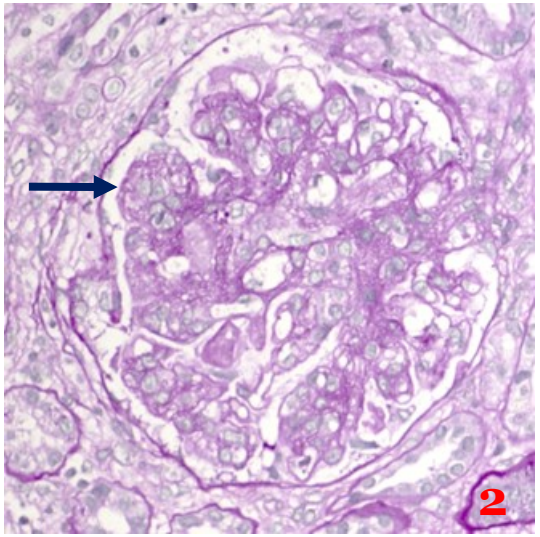
- 1 month later - 20 weeks GA.
- ALPA checked - neg. CH50 normal. Hapto normal.
- Jan 13 2020 - 25 weeks. H/A, Creatinine starts to rise - 125. BP high. Labetolol increased.
- Uterine artery Doppler done – high RI's bilaterally.
- Jan 31 - 28 weeks Severe BP, Headache, vision changes UACR 641 LFT normal. Pre-eclampsia.
- C section Feb 2, 28 weeks, live male 965 grams
- Feb 07 - Creatinine 140-150.
- She is discharged home February 7. Baby in NICU.

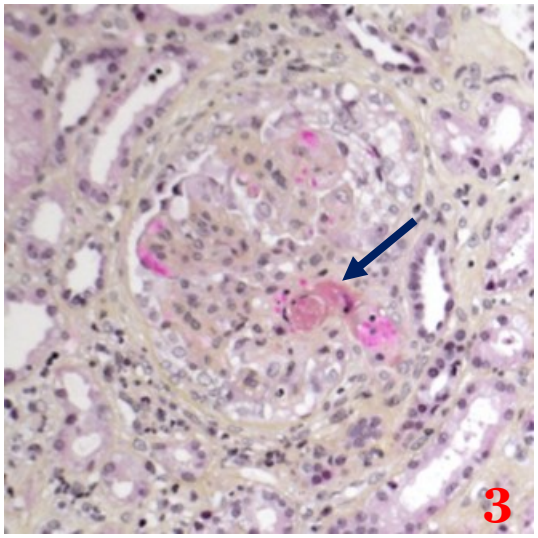
GN clinic follow-up

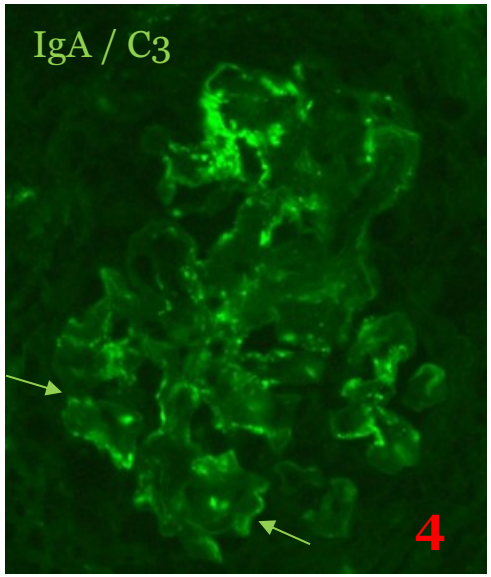
- February 25, 2020 - 3 weeks post partum
- BP is good 120/80
- very edematous.
- Hb 78, platelets 169.
- Hapto - undetectable. LDH 339, Creatinine 265.
- Ordered: ADAMTS13, complement genetics, C3, C4, CH50, C5b-9 and CFH auto antibody
- Arrange kidney biopsy for AKI/TMA

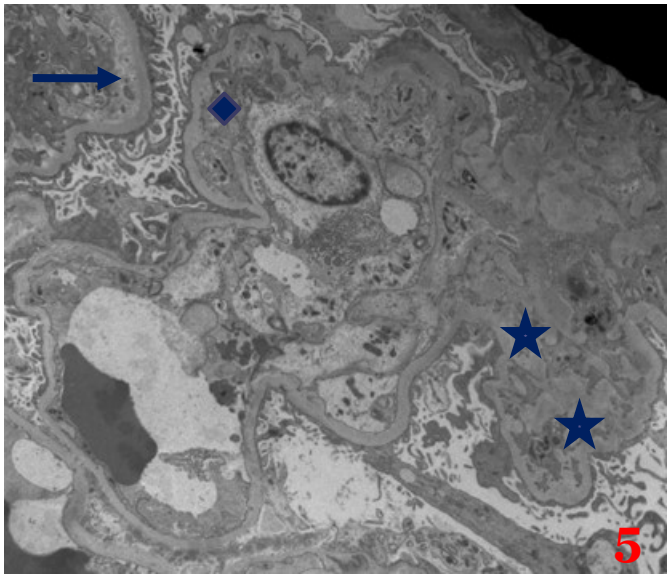
Renal biopsy # 2 (2020 02 28)

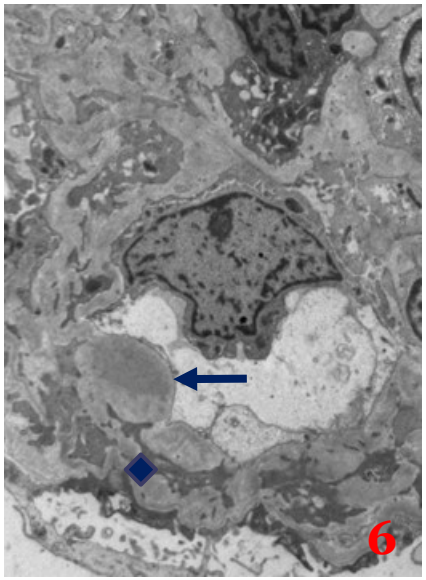












Slides Courtesy Dr. Rohan John

Renal Biopsy Summary

- Diagnosis:
  - Acute Thrombotic microangiopathy
  - IgA nephropathy with MPGN pattern
    - (M1 E1 S1 T0 – C1).
- 7 of 62 gloms globally sclerosed with mild interstitial fibrosis.
- 8 gloms with cellular / fibrocellular crescents
- IF: IgA 3+, IgM 1+, C3 3+, Lambda 2-3+, Kappa 2-3+
- EM: Many mesangial, and a few subendothelial deposits; Mild subendothelial expansion (away from deposits) with cellular interpositioning
- COMMENT: TMA superimposed on IgAN; MPGN pattern possibly a combination of TMA and IgAN

What TMA syndrome does she have?

Comparison of TMA syndromes in Pregnancy

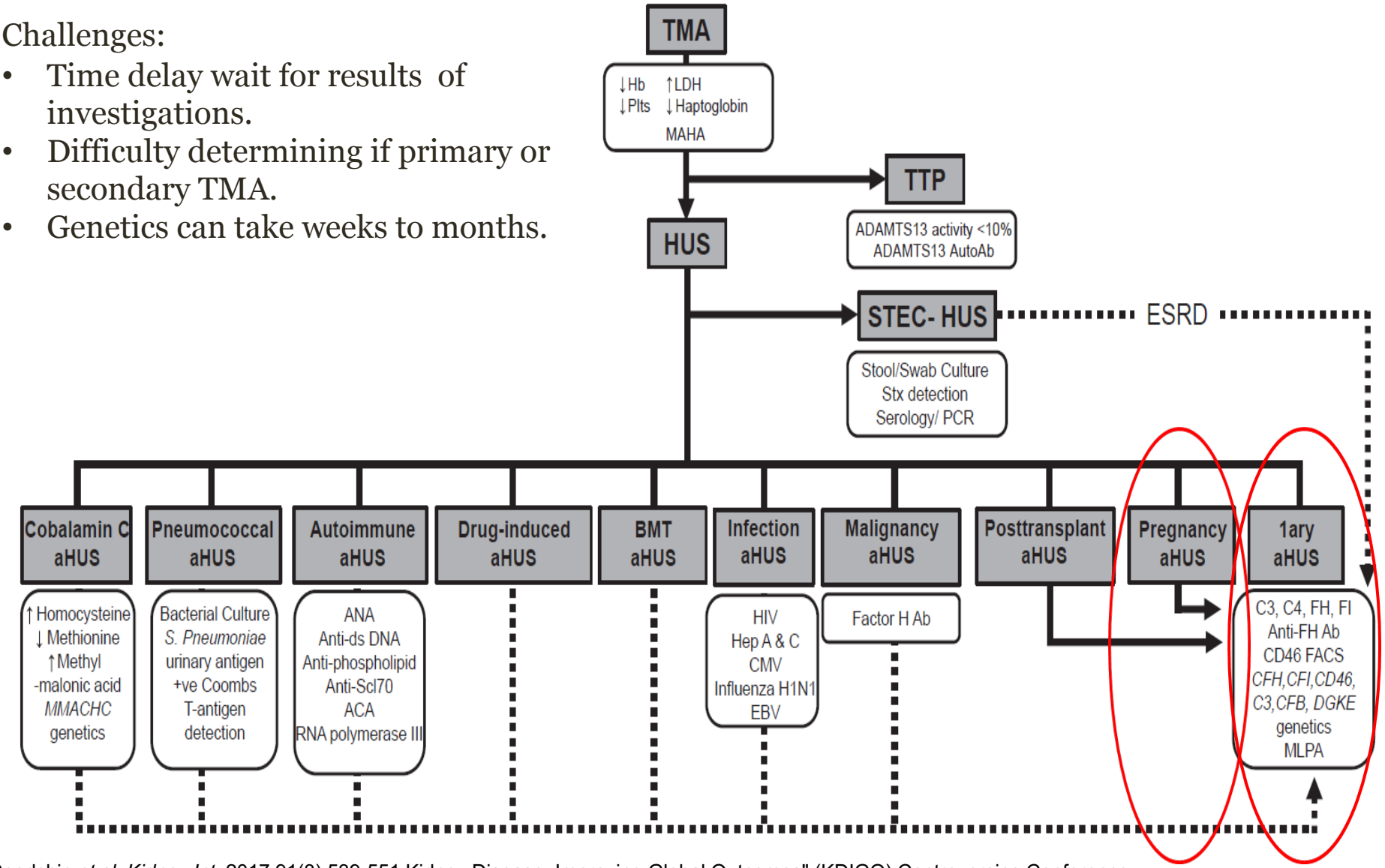
Feature	PET/HELLP	TTP	a-HUS
Incidence	1000	1	unknown
Timing	After 20 weeks, more common near term/post-partum	During pregnancy but most common near term/post-partum	? Most common near term/post-partum
Blood pressure	By definition > 160/110	Normal	High
Neuro	Yes including severe	Severe in 30%	Can occur.
MAHA/platelet	Moderate	Severe	Moderate
Kidney injury	Mild	Mild	More severe
Liver ALT/AST	May be markedly increased	Mild	? Can occur

Adapted from: Syndromes of thrombotic microangiopathy associated with pregnancy. George J.N. et al *Hematology Am Soc Hematol Educ Program* (2015) 2015 (1): 644–648.

Approach to TMA

Challenges:

- Time delay wait for results of investigations.
- Difficulty determining if primary or secondary TMA.
- Genetics can take weeks to months.



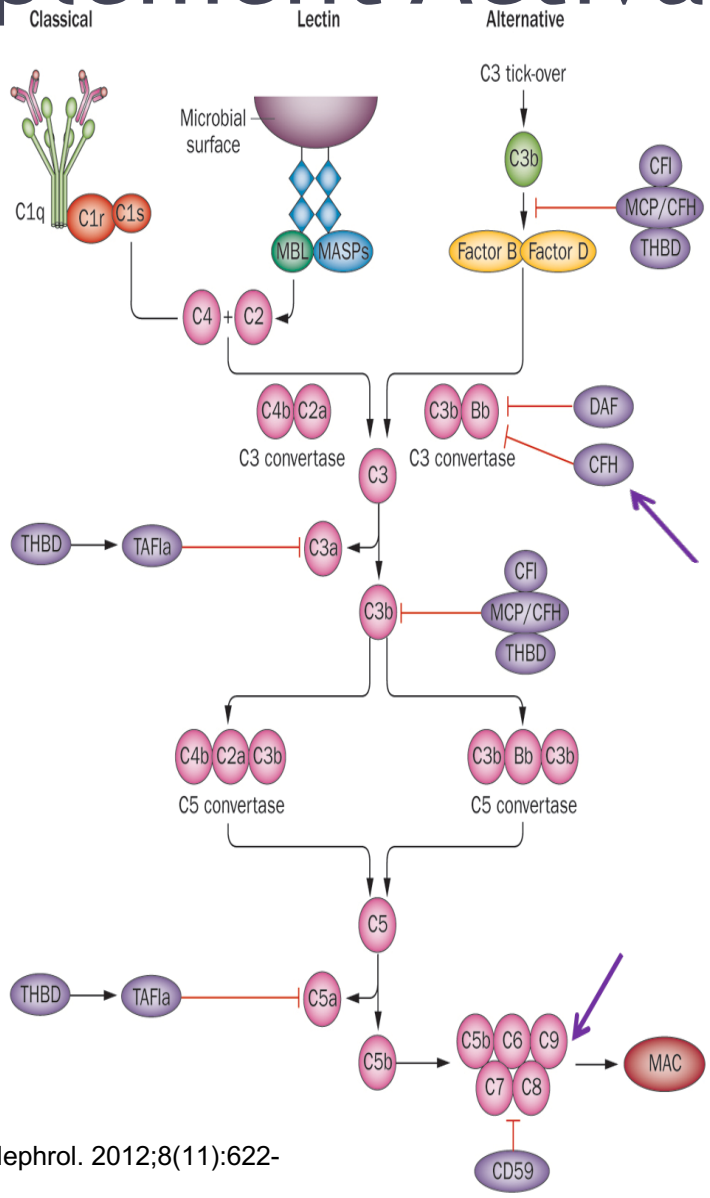
Goodship *et al. Kidney Int*. 2017;91(3):539-551 Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

Her clinical status is getting worse.

- Feb 28 creatinine up to 288.
  - ADAMTS 13 - neg.
  - LDH 356; platelet 127; Hb 97

- Since this is not TTP, and liver Transaminases normal, we cannot exclude aHUS and consider prescribing Eculizumab
- We also prescribe prednisone for the documented IgA Nephropathy/? IC GN.
- March 10 - C5b-9 normal, but low titre detectable CFH autoantibody detected.

Complement Activation



1. Complement factor H autoantibody
2. C5b-9 level
3. C5b-9 deposition on endothelial cells or similar

Noris M, et al. Nat Rev Nephrol. 2012;8(11):622-633.

Complement biomarker testing - International Registry of HUS/TTP patients with or without aHUS mutations

- Overall: reduced C3 in only 56% of patients in acute phase and 47% in remission.
- About half of aHUS patients had normal plasma C5a and sC5b-9 levels.

Complement parameters	Disease phase	Overall[b]	Mutations or anti-CFH Ab	No mutations
Reduced **C3 serum** levels (83–180 mg/dL)[a]	Acute Remission	10 (18) 15 (32)	5 (9) 11 (25)	5 (9) 4 (7)
Increased C5a plasma levels (1.9–13.1 ng/mL)[a]	Acute Remission	9 (19) 21 (36)	3 (10) 15 (27)	6 (9) 6 (9)
Increased **SC5b-9** plasma levels (127–400 ng/mL)[a]	Acute Remission	10 (19) 23 (36)	4 (10) 20 (27)	6 (9) 3 (9)

[a]Limits of normal ranges; [b] numbers outside brackets refer to the number of patients with reduced C3 or increased C5a or C5b-9 levels, and numbers in brackets refer to the number of patients for whom data were available

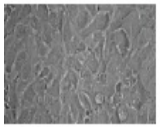
Noris M. Blood. 2014;124:1715–1726.

CLINICAL COURSE POST ECULIZUMAB

2020	CH50	Hb	GFR	Cr	LDH	Hapto	AST	UACR	24 hr urine
Feb	N	71	19	288	339	<0.3	N	641	6.14
March	14	85	25	218	496	0.48	N		5.48
April	<14	118	26	203	208	<0.3	N	226	
May	<10	120	28	190		0.95	N	100	1.79
August	<10	112	35	165		1.02	N	70	
October 2020	N/A	113	35	164	175	N/A	N/A		0.74

- Steroids - did not seem to be of any clinical benefit. Tapered.
- First dose Ecu – Feb 28th, 2020
- Took 2 months to suppress CH50
- At 6 mos (end July, 2020), renal function improved (still low eGFR)
- Still highly proteinuric, but better than her baseline proteinuria.
- We applied for 6 more months Ecu

SERUM FROM aHUS PATIENTS IN ACUTE PHASE CAUSES THE FORMATION OF C5b-9 ON RESTING AND ACTIVATED HUMAN MICROVASCULAR ENDOTHELIAL CELLS (HMEC)



HMEC
-1

Resting
10 min

Control or aHUS serum

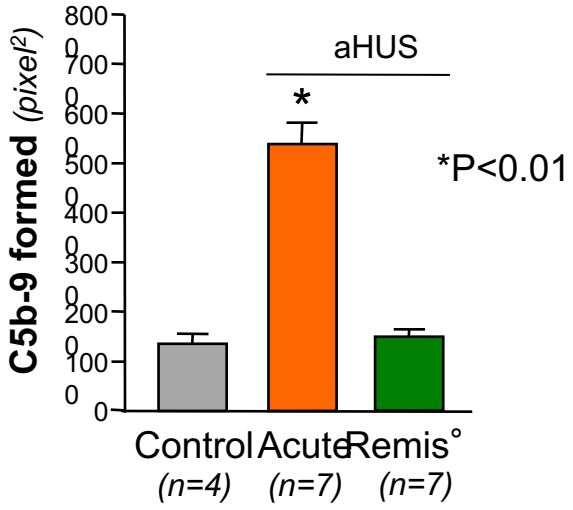
Static incubation
4 hours

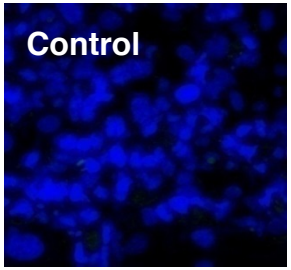
anti-C5b-9 Ab staining
Confocal microscopy

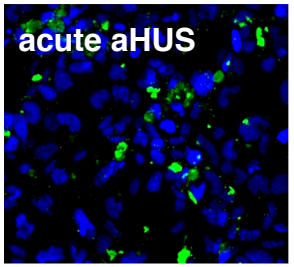
C5b-9 deposition

In <u>active aHUS</u> (ongoing TMA) aHUS patients have increased C5b-9 deposition even on non-activated endothelial cells.

In remission, C5b-9 deposition is similar to controls, at rest.





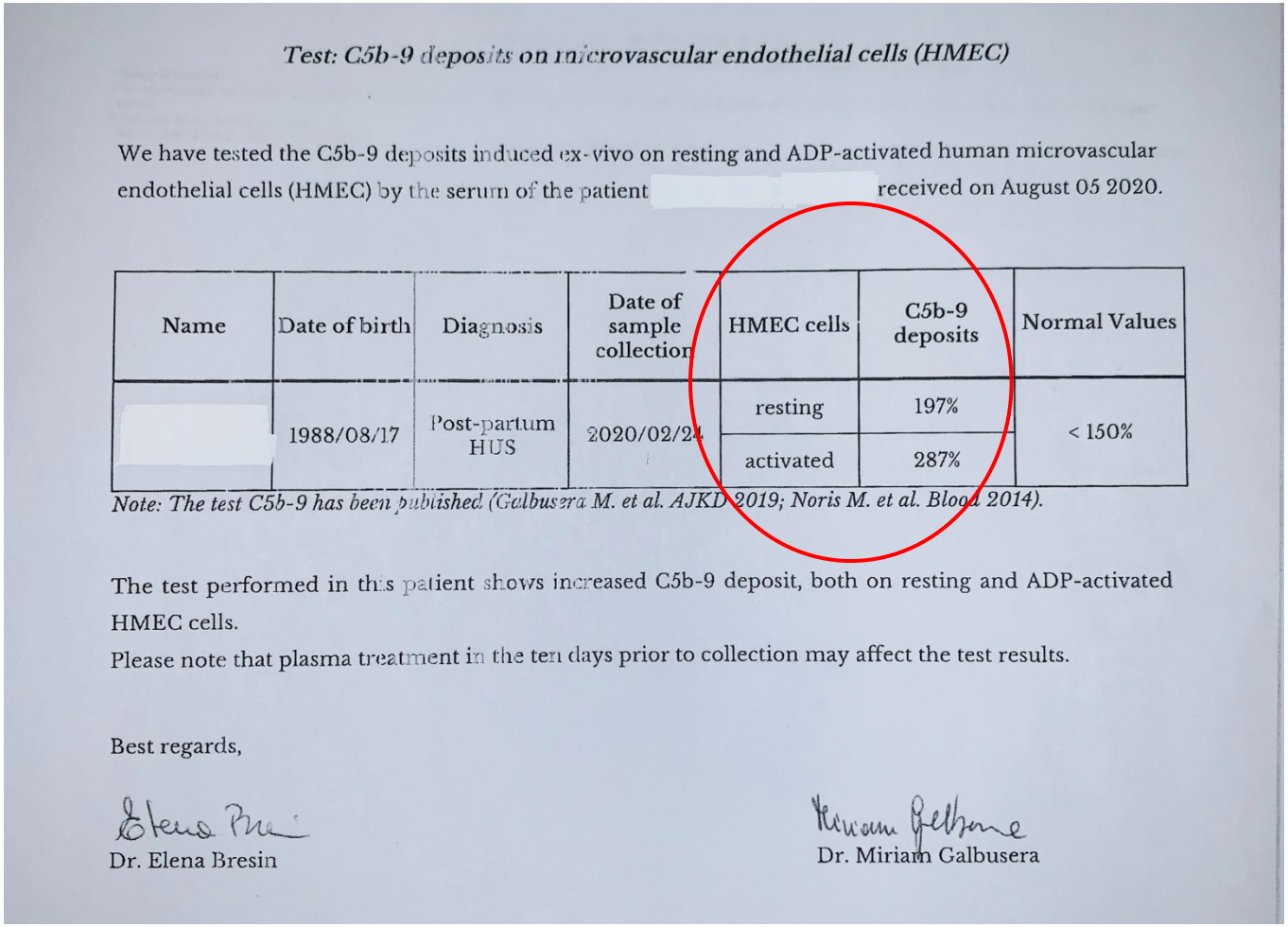


°no Eculizumab

Serum from all aHUS patients studied during the acute phase, but not serum taken in remission caused more C5b-9 deposition on resting HMEC-1 than control serum

Noris M, et al. Blood. 2014;124(11):1715-1726.

C5b-9 deposition on endothelial cells PRE-eculizumab treatment



Test: C5b-9 deposits on microvascular endothelial cells (HMEC)

We have tested the C5b-9 deposits induced ex-vivo on resting and ADP-activated human microvascular endothelial cells (HMEC) by the serum of the patient [redacted] received on August 05 2020.

Name	Date of birth	Diagnosis	Date of sample collection	HMEC cells	C5b-9 deposits	Normal Values
[redacted]	1988/08/17	Post-partum HUS	2020/02/24	resting	197%	< 150%
				activated	287%	

Note: The test C5b-9 has been published (Galbusera M. et al. AJKD 2019; Noris M. et al. Blood 2014).

The test performed in this patient shows increased C5b-9 deposit, both on resting and ADP-activated HMEC cells.

Please note that plasma treatment in the ten days prior to collection may affect the test results.

Best regards,

Dr. Elena Bresin

Dr. Miriam Galbusera

Final summary.

- Diagnosis: IgA nephropathy complicated by post partum aHUS.
- Investigations demonstrated evidence of complement mediated TMA.
- She remains on Eculizumab .
- Genetics are negative (LHSC)
- Re: CFH autoantibody - Rituximab in this scenario?
  - How significant is the low level titre of CFH autoantibody?
- She has done very well and continues to improve with Eculizumab treatment.

Discussion Period

aHUS – Case Presentation

Nov 2020

Presented by:
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Objectives

Familiar with complement-related diseases

Understand the association between MPGN and aHUS

Treatment option(s) for complement pathway related disease

Discussion on some preliminary neurological data on aHUS patients

Case

35 y.o. female with PMHx:

- Deafness secondary to viral illness in childhood
- RFR: Anasarca
- She initially presented with nephrotic syndrome. She had severe HTN (200/110 mmHg). She had an episode of seizure and severe HTN, and was admitted to ICU
- Nephrology was consulted for AKI with Cr 320 umol/L
- She was on no medications (no oral contraceptives)

Case

WBC (10^9/L)	Hgb (g/L)	Plt (10^9/L)	INR	Schistocytes	
12	102	209	1	Neg	

Na (mmol/L)	K (mmol/L)	HCO3 (mmol/L)	Urea (mmol/L)	Creat. (mmol/L)	Ca (mmol/L)
140	3.9	22	24	333	2.07

Alb (g/L)	Mg (mmol/L)	RF	LA/APLA	Urinalysis	ACR (mg/mmol)
35	0.85	Neg	Neg	+ blood	186 (1.4g)

C3 (g/L)	C4 (g/L)	Hep B/C	ANA	Cryo	ANCA
0.13 (0.66-1.68)	0.04 (0.1-0.4)	Neg	Neg	Neg	Neg

CT Head – Neg;
MRI Head - ? PRES;
EEG – Negative for status epilepticus

Case

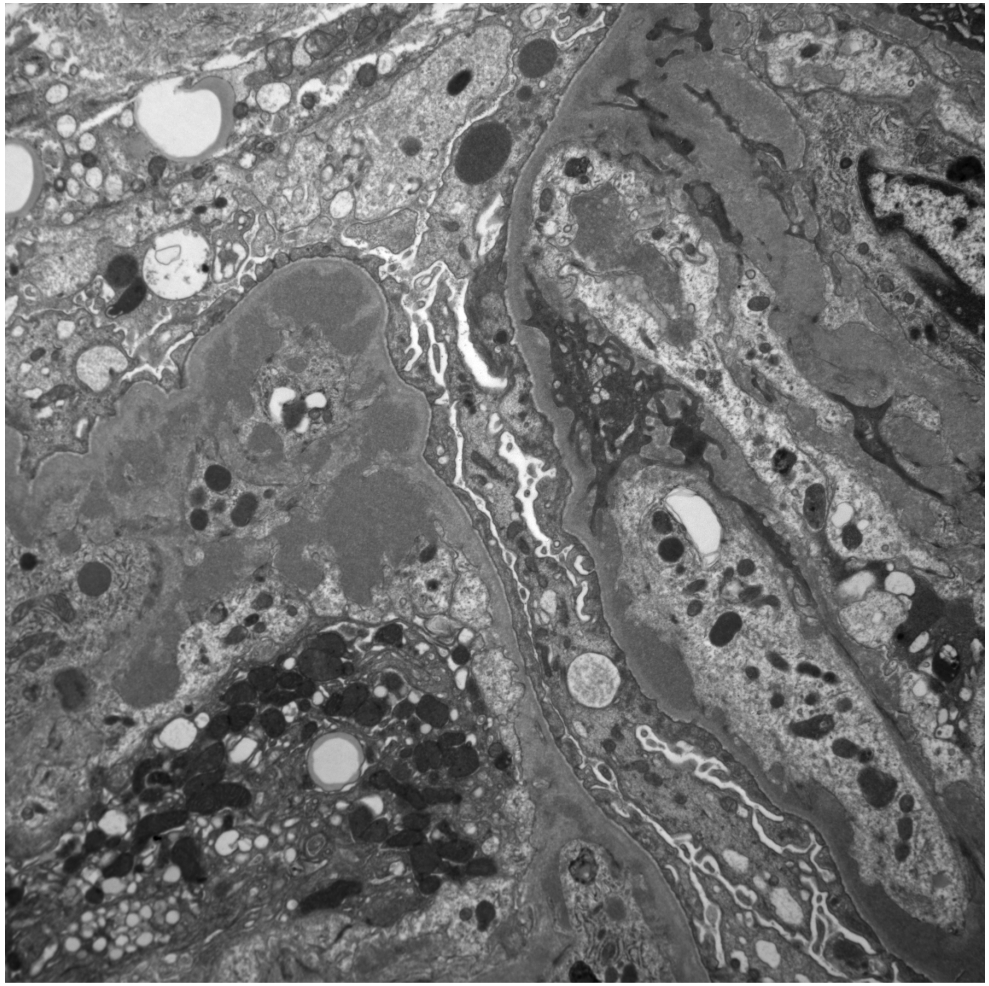
Anti-Streptolysin O antibody was positive

Preliminary Renal Biopsy showed all glomeruli had increased cellularity and abundant neutrophils but no crescent

Discharge home with tapering steroid + anti-hypertensive

New Meds are: Amlodipine, Labetalol, $CaCO_3$, Ranitidine, Vitamin D, Prednisone

Case - Biopsy



MPGN /ICGN

LM: Increase cellularity. No crescent. No focal sclerosis. No interstitial fibrosis or tubular atrophy. One possible fibrin thrombus

IF: IgG and C3 deposition in capillary loop.

EM: subendothelial and mesangial deposits.

Case

She was doing well for 2-3 weeks. Cr down to 190

Then she started to feel unwell: mainly with symptoms of fatigue (4 weeks later)

Case – 2 months later

WBC (10^9/L)	Hgb (g/L)	Plt (10^9/L)	LDH (IU/L)	Schistocytes	Hapto. (mg/dL)
14	61	88	1167	Mild	<0.07

Na (mmol/L)	K (mmol/L)	HCO3 (mmol/L)	Urea (mmol/L)	Creat. (mmol/L)	Ca (mmol/L)
136	4.6	22	15	303 (190)	1.94

Alb (g/L)	Mg (mmol/L)	C3 (mg/dL)	C4 (mg/dL)	CH50	ACR (mg/mmol)
33	0.85	Normal 0.66	Normal 0.13	<10	383

ADAMTS13 Activity >71%

Case – 2 months later

WBC (10^9/L)	Hgb (g/L)	Plt (10^9/L)	LDH (IU/L)	Schistocytes	INR
9.6	66	34	800	Mild	1.0

Na (mmol/L)	K (mmol/L)	HCO3 (mmol/L)	Urea (mmol/L)	Creat. (mmol/L)	Ca (mmol/L)
147	3.4	38	14	335	2.44

She was started Plasma Exchange with no responses to 13 Exchanges. She started on eculizumab

WBC (10^9/L)	Hgb (g/L)	Plt (10^9/L)	LDH (IU/L)	Schistocytes	INR
9.7	71	75	516	-	1.0

Na (mmol/L)	K (mmol/L)	HCO3 (mmol/L)	Urea (mmol/L)	Creat. (mmol/L)	Ca (mmol/L)
142	4	23	22	404	2.3

Question 1

Which of the following tests are required prior to the initiation of Eculizumab for aHUS management?

A. Shiga toxin if hx of diarrhea

B. ADAMTS13

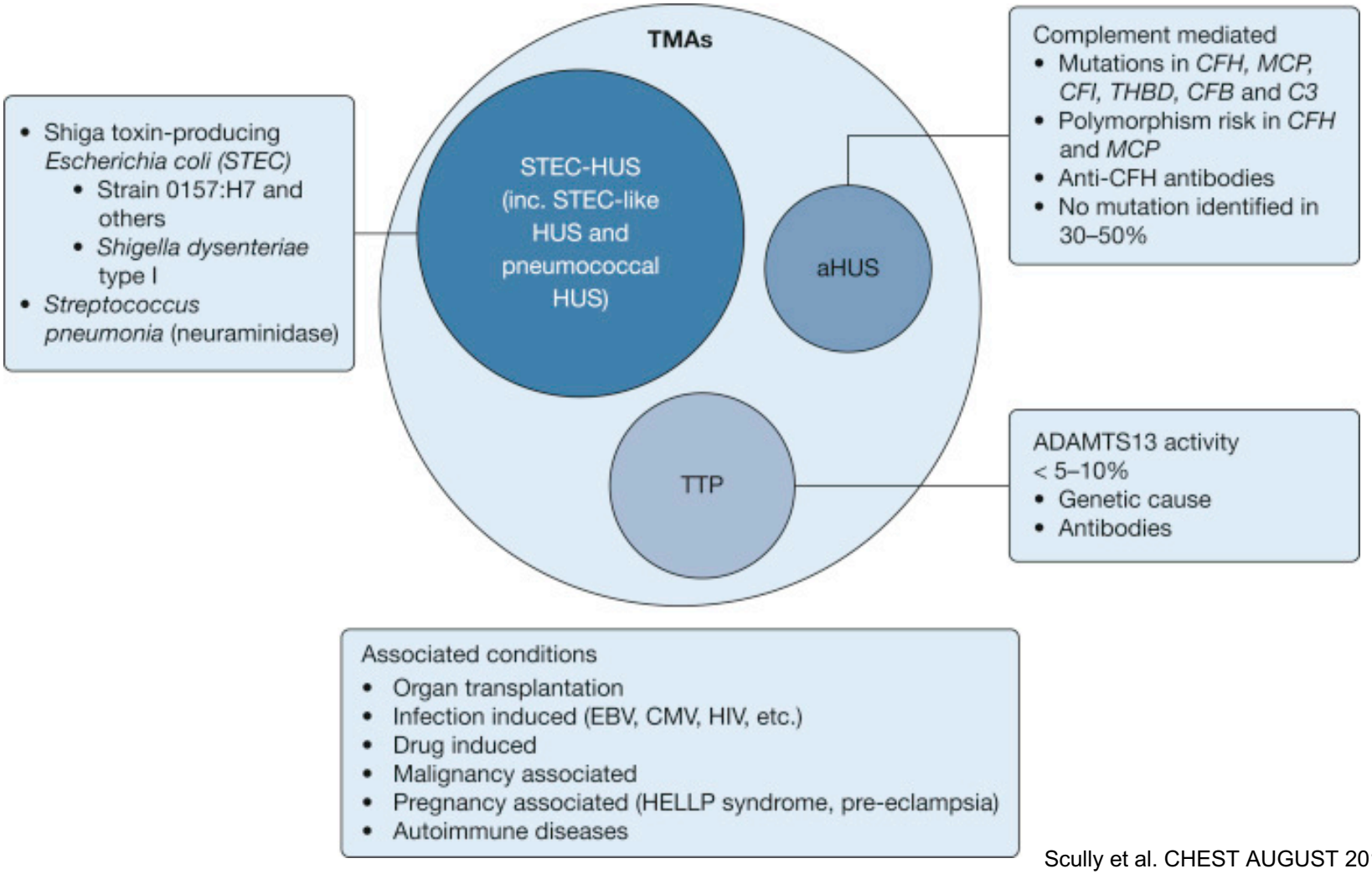
C. Genetic testing

D. A and B

E. A, B and C

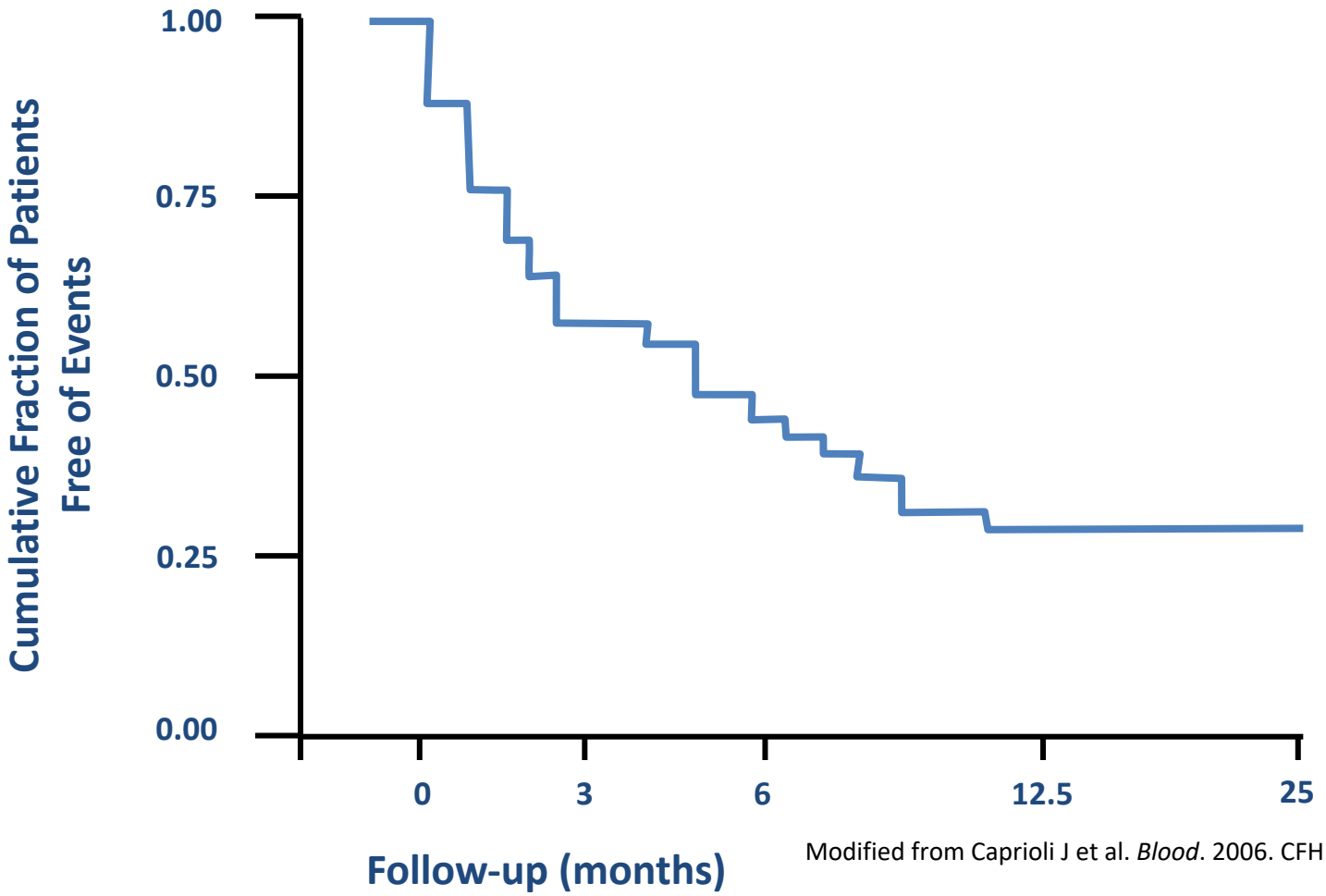
Shiga toxin	Stool: culture; Shiga toxin Serum (EDTA): anti-lipopolysaccharides antibodies, Shiga toxin PCR
Infection	Streptococcus, influenza, HIV
Complement levels	Serum (EDTA): C3, C4, CH50, C5b-9, AP50 (C3d, Bb, sMAC)
Connective Tissue Diseases	ANA, anti-dsDNA, ANCA, C3NeF
ADAMTS13	Serum (Citrate): ADAMTS13 activity Serum (Citrate): Anti-ADAMTS13 antibodies
CFH antibodies	Serum: Anti-FH, anti FB (nephritic factors)
Genetic Testing	EDTA: CFH, CFI, MCP, C3, CFB, thombomodulin, DGKE, CFHR1-5
Plasma cell disorder	Serum free light chain, SPEP/UPEP

TMA



Scully et al. CHEST AUGUST 2017

Outcome in aHUS



Modified from Caprioli J et al. *Blood*. 2006. CFH mutation depicted.

1. Sullivan M et al. *Nephrol Dial Transplant*. 2010;25:2028-2032. 2. Caprioli J et al. *Blood*. 2006;108:1267-1272. 3. Noris M et al. *CJASN*. 2010;10:1844-1859.
4. Noris M et al. *N Engl J Med*. 2009;361:1676-1687.

Question 2

In patients with aHUS who has started eculizumab treatment, which of the following parameter recover the quickest?

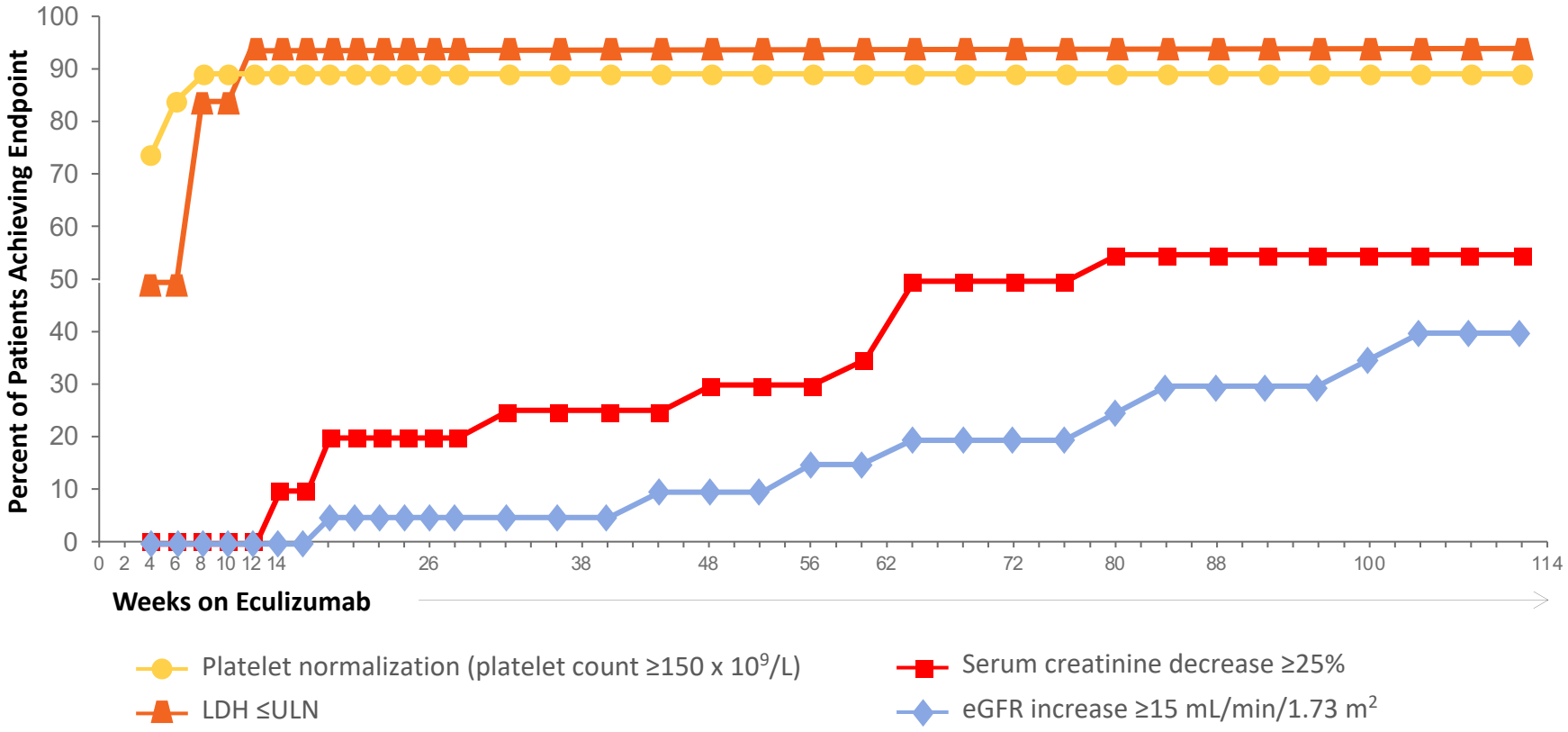
A. Platelet count

B. Renal function (serum Cr decreases by 25%)

C. LHD

Time Dependent Improvement Of Renal Function With Eculizumab

After 1 Year, continued suppression of complement mediated damage and TMA allows recovery of renal function



Licht C et al. Presented at the 54th American Society of Hematology Annual Meeting and Exposition, December 7–10, 2013, New Orleans, Louisiana.

Case – 4 years later

Na (mmol/L)	K (mmol/L)	HCO3 (mmol/L)	Urea (mmol/L)	Creat. (mmol/L)	Ca (mmol/L)
136	4.2	24	6	90	-

A variant of CFH with unknown significance (c.3325T (p. Cys1109Ser)

She continues to be on eculizumab

Question 3

Which of the following disease is primarily caused by complement dysregulation?

A. MPGN secondary to C3 GN

B. aHUS

C. MPGN secondary to Dense Deposit Disease

D. All of above

Discussion

Studies showed the association between aHUS and CFH mutation

The associations between CFH mutation and MPGN were demonstrated in animal models (Norwegian Yorkshire Pig) and a clinical case (Licht et al)

Goodship THJ. Factor H genotype – phenotype correlations: lessons from aHUS, MPGN II and AMD. KI 2006: 70, 12.

Discussion

Prior 2012, there were17 cases of aHUS associated with MPGN.

Of 248 GN patients, 6 developed aHUS (15 months): 1 FSGS, 3 MPGN, 1 HSP, and 1 ANCA vasculitis. 2 of the MPGN patients showed showed complement mutation (CFH and MCP genes).

Manenti L et al. AHUS with underlying GN: a case series and a review of literature. NDT 2013; 28: 2246

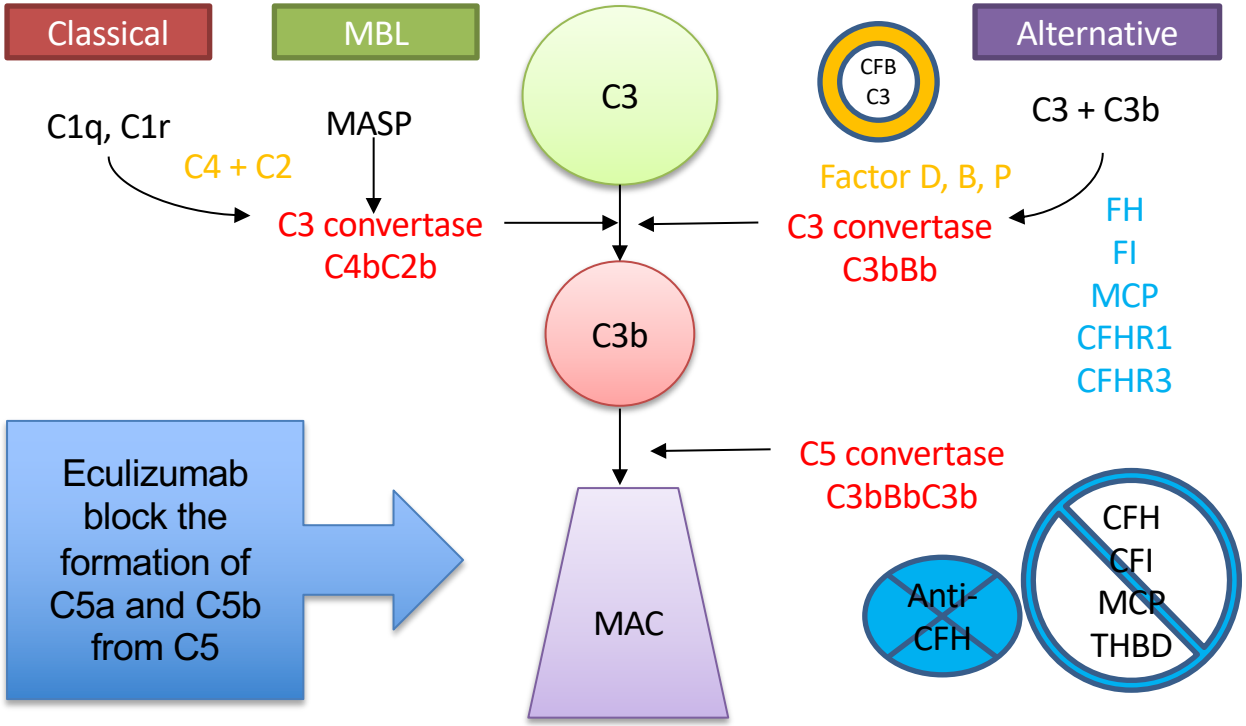
Discussion

A study examined 91 patients with aHUS, MPGN and C3GN.

They identified three missense variations located within the CFH gene cluster: rs55807605, rs61737525 and rs57960694.

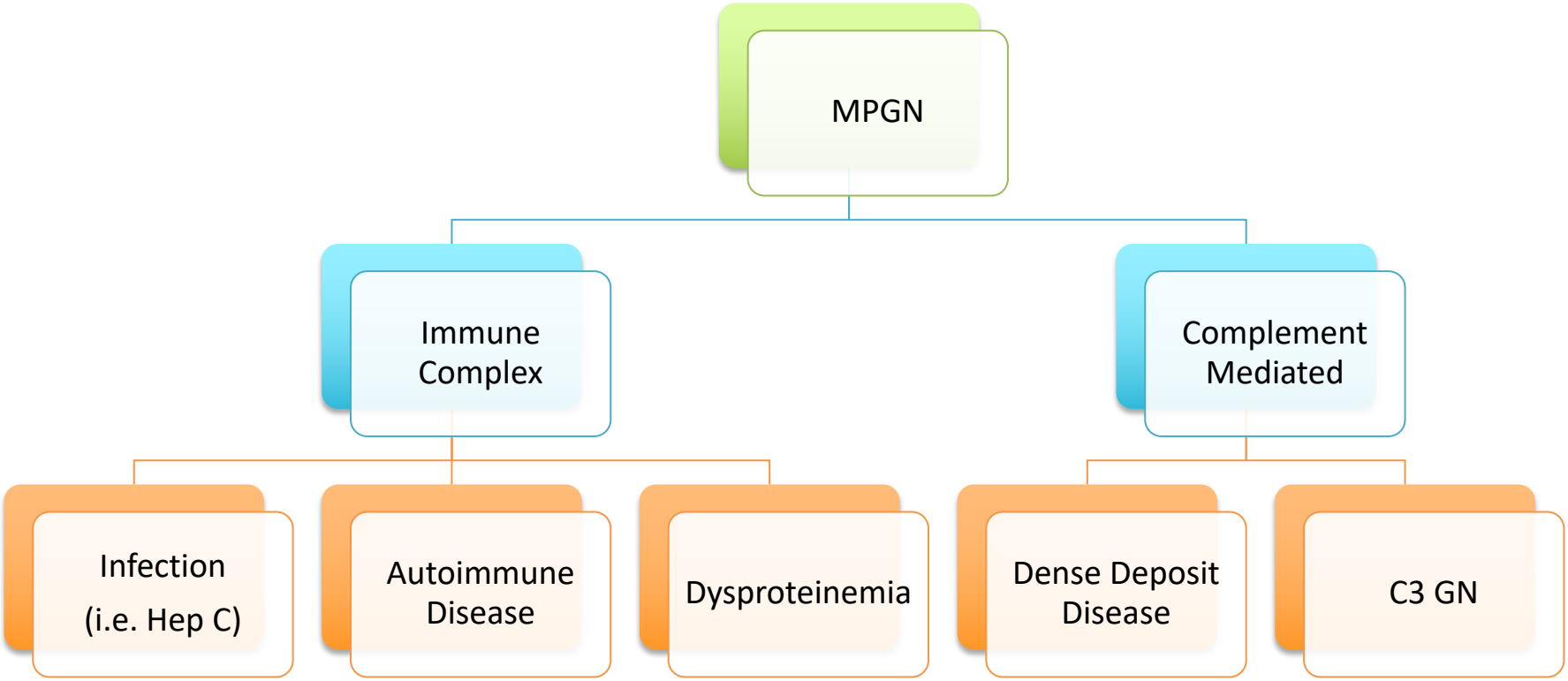
Ding Y, et al. A haplotype in CFH family genes confers high risk of rare glomerular nephropathies. Sci Rep. 2017 Jul 20;7(1):6004.

Discussion



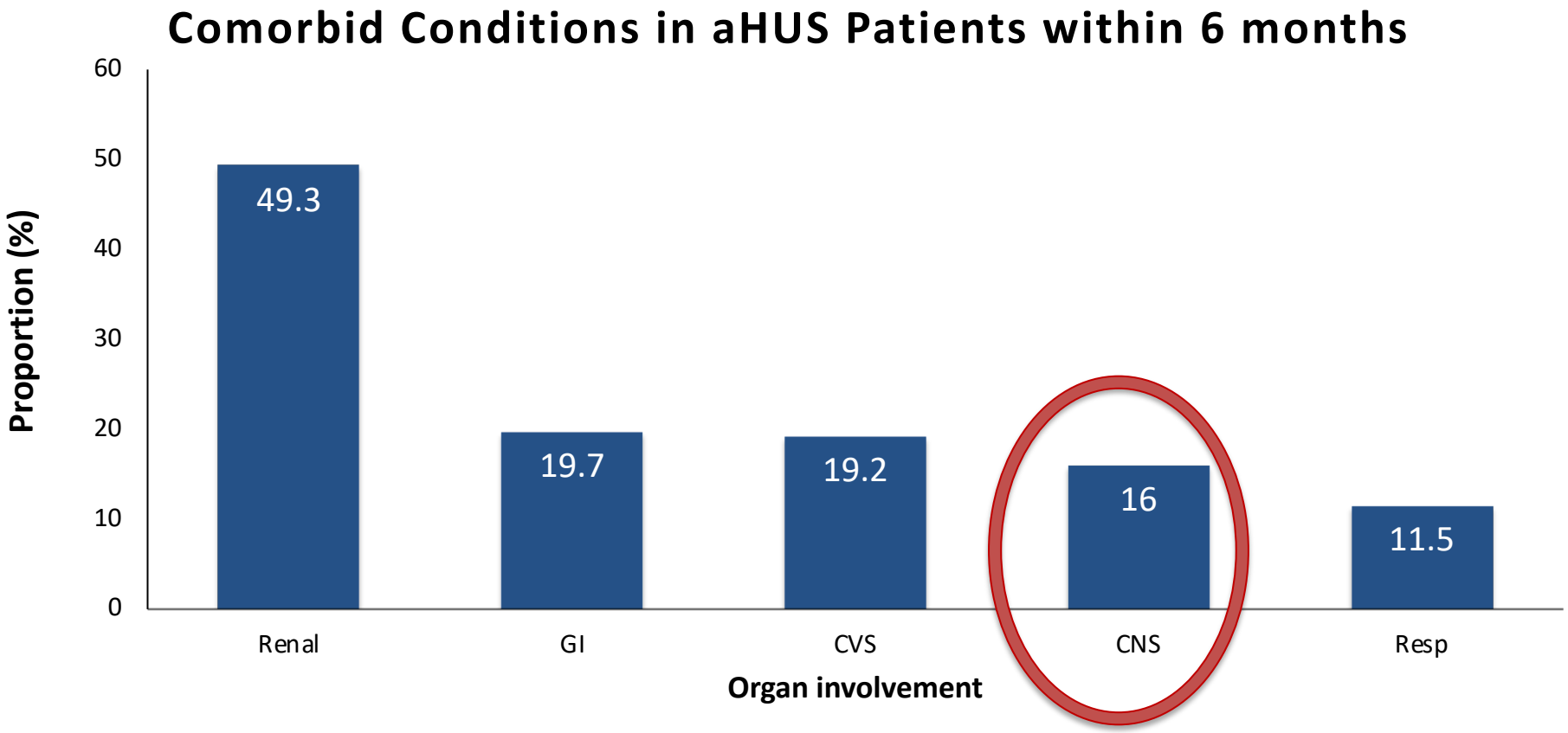
Content based on unpublished observations and/or clinician experience.

Discussion - MPGN



Sethi et al. Membranoproliferative Glomerulonephritis – A New Look at an Old Entity. NEJM 2012; 366:1119

Discussion - aHUS



Licht C et al. Charateristics of 681 Patients with aHUS in the Global aHUS registry. ASN 2015

Neurocognitive

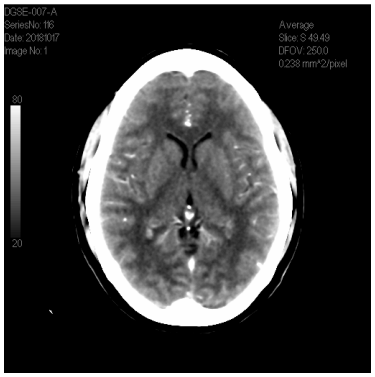
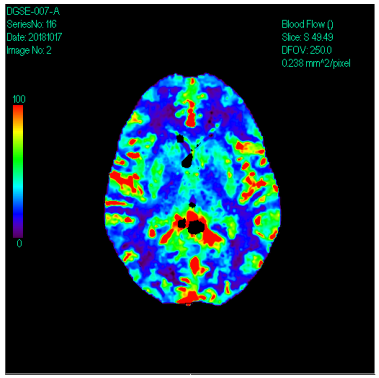
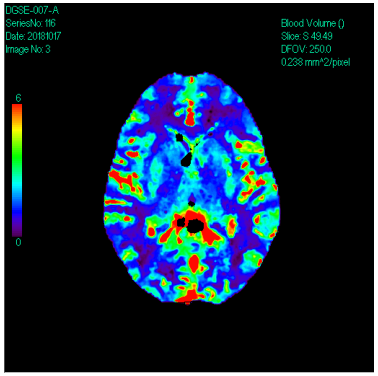
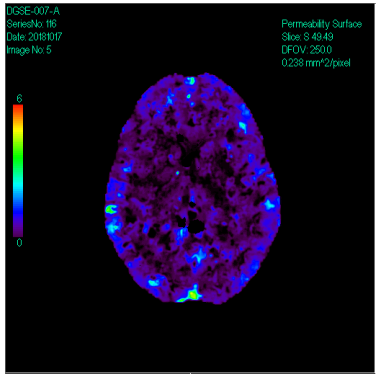
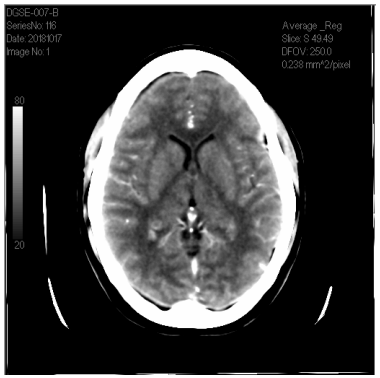
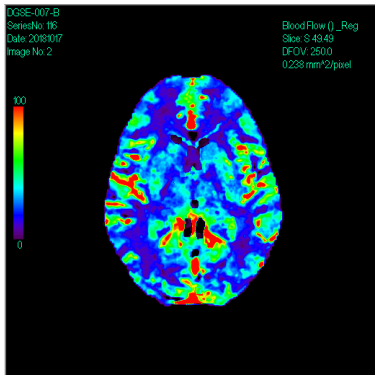
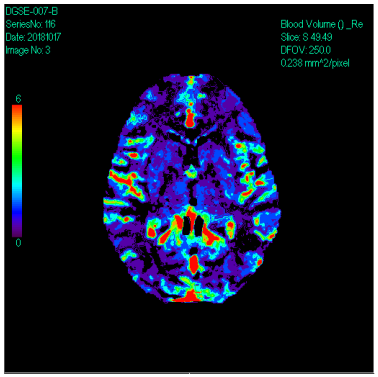
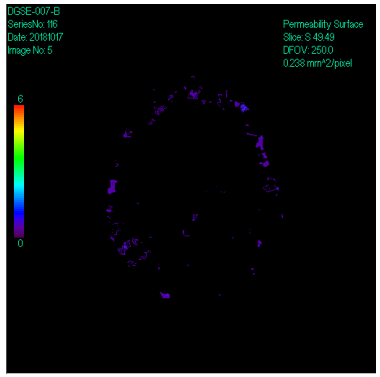
- We recently have recruited 4 newly diagnosed aHUS patients from LHSC.

- We used Montgomery-Åsberg Depression Rating Scale
  - ¼ reported moderate depression
  - ¼ reported mild depression

- Using CBS neurocognitive Test
  - ¼ patient has significantly lower neurocognitive score compare to age-matched healthy population

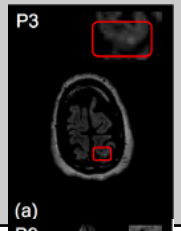
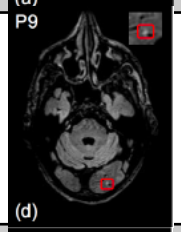
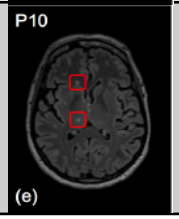
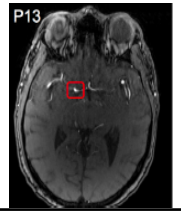
Huang et al. Unpublished Data

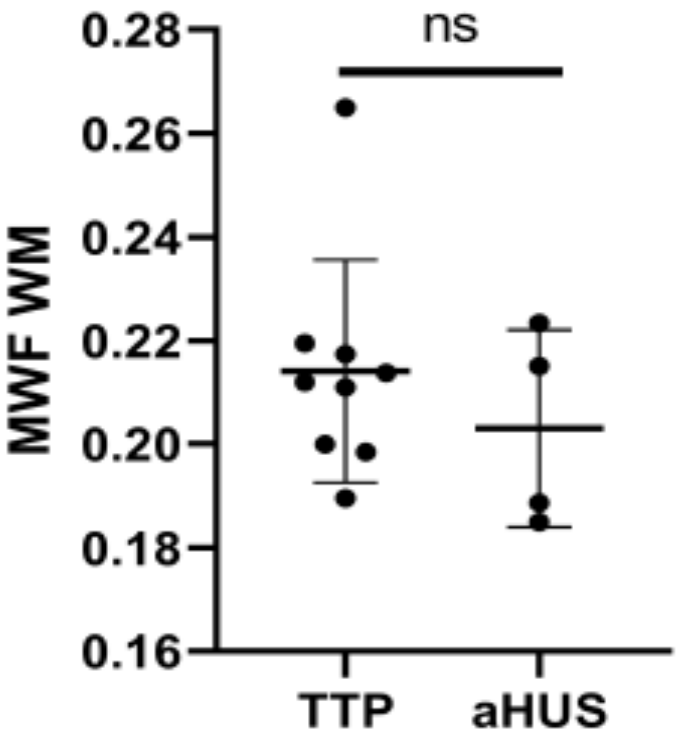
CT perfusion scan

ROUTINE CT	Blood Flow	Blood Volume	Blood Brain Barrier
			
			

Huang et al. Unpublished Data

MRI Images

Age	Sex	MRI Images	MRI findings
20	F		5 hyperintense spots
73	M		25-30 hyperintense spots Atrophy
43	F		5 hyperintense spots 2 infarct spots
47	M		30-40 hyperintense spots Atrophy



(b) MWF white matter by diagnosis

Huang et al. Unpublished Data

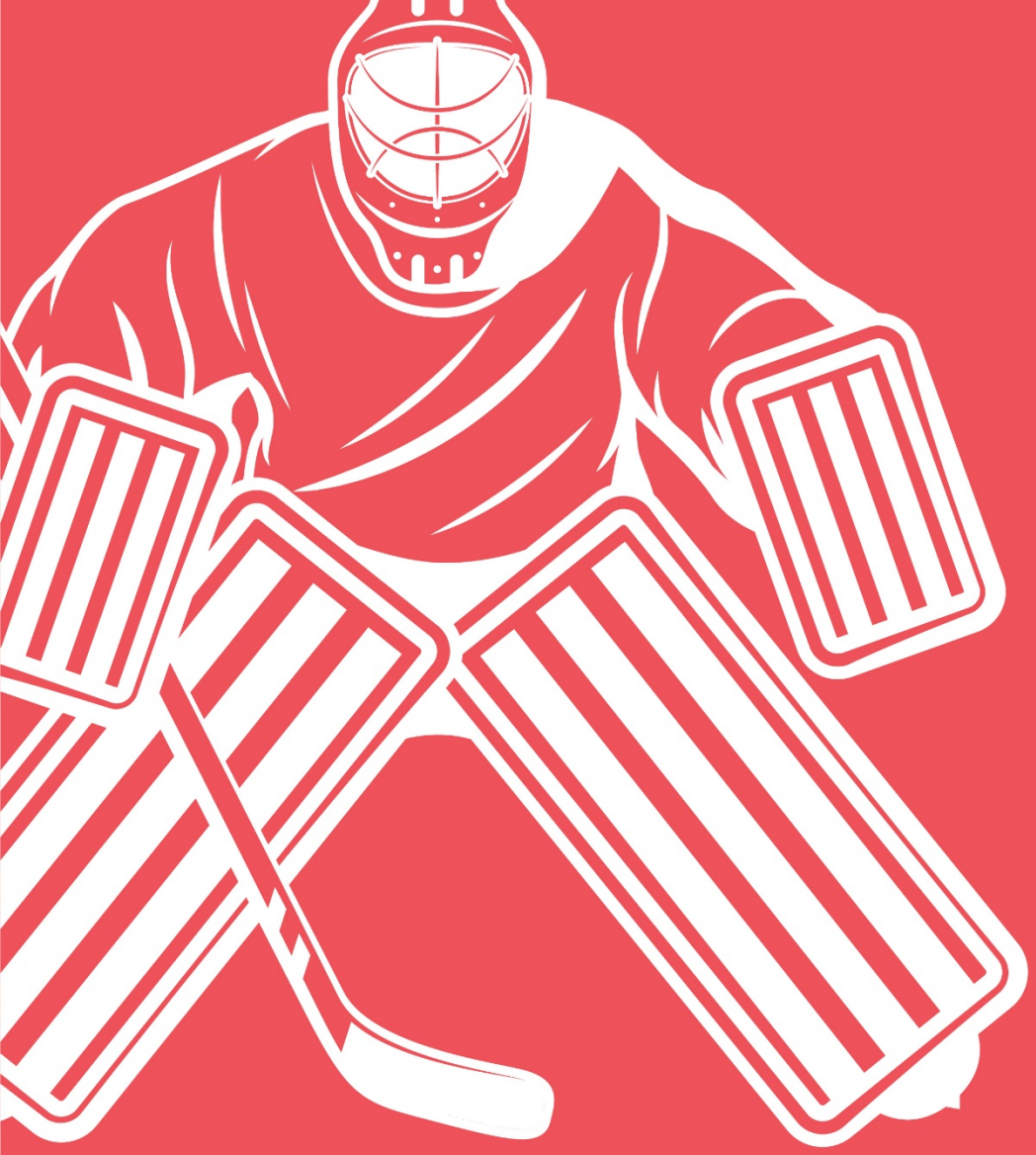
THANK YOU

MPGN can be caused by complement system dysregulation.

Complement dysregulation can lead to MPGN manifestation and/or aHUS

Humanized anti-C5 monoclonal antibody therapy (eculizumab) is the first line therapy to treat aHUS

shuang45@uwo.ca



Questions & Discussion

Thank you

Please remember to take a moment to complete the electronic evaluation

Canadian Society of Nephrology/
Société canadienne de néphrologie
CSN/SCN