Anti factor H associated hemolytic uremic syndrome

Arvind Bagga

Apollo Children's HOSPITALS

Pediatric Atypical HUS*

%	Bacchi* N=89	Noris* N=152	Schaefer n=387	Adults N=693
CFH	**21.3**	**25.6**	**21**	**21-32**
MCP (CD46)	13.5	9.2	14	3.8-6.4
CFI	6.7	2.6	3	5.7-10
C3	7.8	3.9	5	5.7-8.8
CFB	1	-	2	0.4-2.4
Anti-FH	**11**	**3.9**	**24** [45% 6-17 yr]	**1.9-19**
THBD	-	7.8	-	0.9
Complement	**64.7**	**53**	**43**	**43-67**
None defined	**27.4**	**47**	**57**	**33-57**
DGKε	-	-	**8**/101	

French. CJASN 2013;8:554; **Europe**. CJASN 2010;5:1844 JASN 2018; **93 genes; N=400**

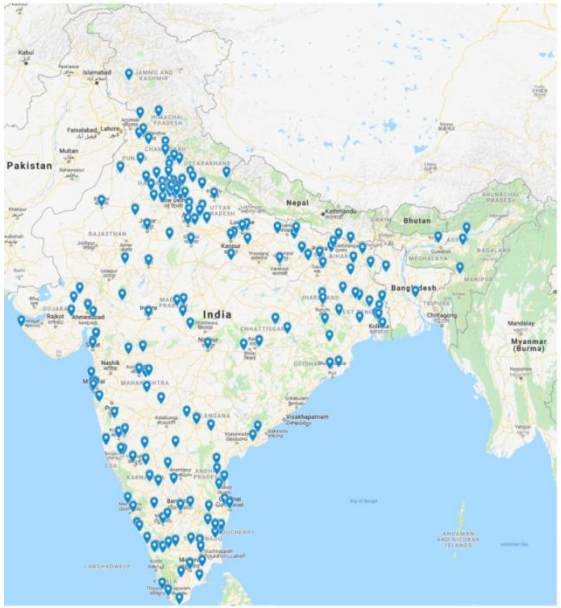
Global aHUS (n=851): 45% had mutation, antibody KI 2018;94:408

CLINICAL RESEARCH www.jasn.org

J Am Soc Nephrol 21: 2180–2187, 2010.

Clinical Features of Anti-Factor H Autoantibody–Associated Hemolytic Uremic Syndrome

Marie-Agnès Dragon-Durey,*†‡ Sidharth Kumar Sethi,§ Arvind Bagga,§ Caroline Blanc,† Jacques Blouin,* Bruno Ranchin,‖ Jean-Luc André,¶ Nobuaki Takagi,** Hae Il Cheong,†† Pankaj Hari,§ Moglie Le Quintrec,‡‡ Patrick Niaudet,§§‡ Chantal Loirat,‖‖ Wolf Herman Fridman,*†‡ and Véronique Frémeaux-Bacchi*†



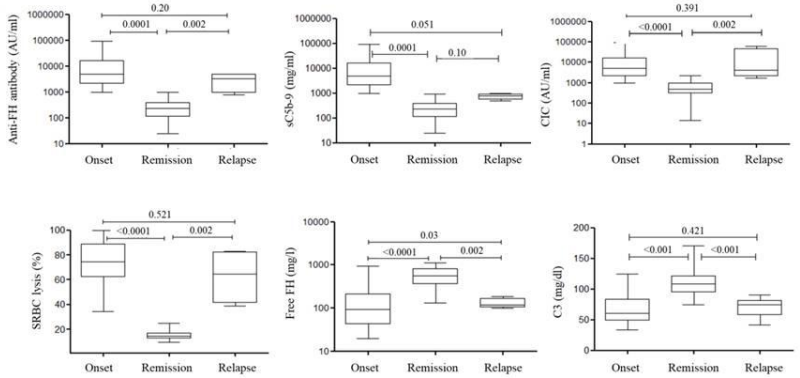
Positive threshold: 150 AU/ml (n=250)

Nation wide database, >70 centers

Anti-FH antibodies: 601/1070 (**56%**)

KI 2014

Antibody, CIC, sC5b-9, SRBC lysis, C3 & free FH levels



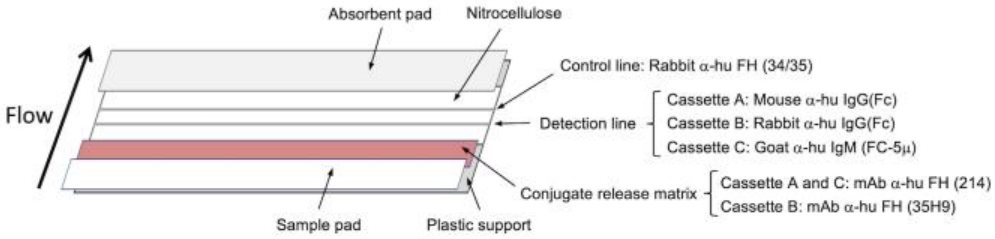
Clinical and Immunological Profile of Anti-factor H Antibody Associated Atypical Hemolytic Uremic Syndrome: A Nationwide Database

Front Immunol 2019

ELISA for detecting anti-FH antibodies by different groups

	ELISA	Dilution	Units	Plate	Coat buffer	Standard	Normal
Newcastle	Manual	1/50	OD	Thermo-Flexi	AbD Serotech pH 8.5	62.5-4000	OD <0.15
Jena	Manual	1/500	Arbitrary units, AU	NuncMaxisorp	Dulbecco PBS pH 7.4	37.5-2400	<500 AU/ml
Paris	Manual	1/50	AU	NuncMaxisorp	Dulbecco PBS pH 7.4	37.5-2400	<100 AU/ml
London	Manual	1/100	AU	NuncMaxisorp	35 mM $NaHCO_3$ 15 mM Na_2CO_3	37.5-2400	<100 AU/ml
Madrid	Manual	1/100	AU	NuncMaxisorp	Dulbecco PBS pH 7.4	37.5-2400	<100 AU/ml
Helsinki	Manual	1/20	OD	NuncMaxisorp	50 mM $NaHCO_3$ pH 8.5		?
Lund	Manual	1/50	AU	NuncMaxisorp	75 mM $NaHCO_3$ pH 9.6		100 AU/ml
New Delhi	Manual	1/50	AU	NuncMaxisorp	0.25 g $NaHCO_3$ 0.212 g Na_2CO_3	37.5-2400	<150 AU/ml
Abnova	Kit	1/100	AU	Pre-coated	Pre-coated	0-250	Calculated
Vidia	Kit	1/100	AU	Pre-coated	Pre-coated	0-250	18 AU/mL

FH immune complexes: Immunochromatography

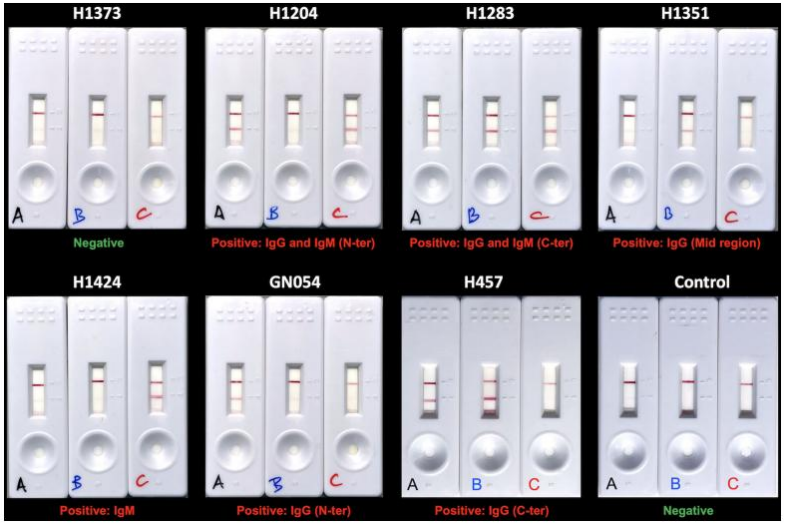


Cassette A: All FHAA(**IgG**)-FH complexes except those with FHAA to mid region

Cassette B: All FHAA(**IgG**)-FH complexes except those with FHAA to N-terminus

Cassette C: All FHAA(**IgM**)-FH complexes except those with FHAA to mid region

Detects & quantitates: IgG & IgM **immune complexes** in EDTA-plasma, serum



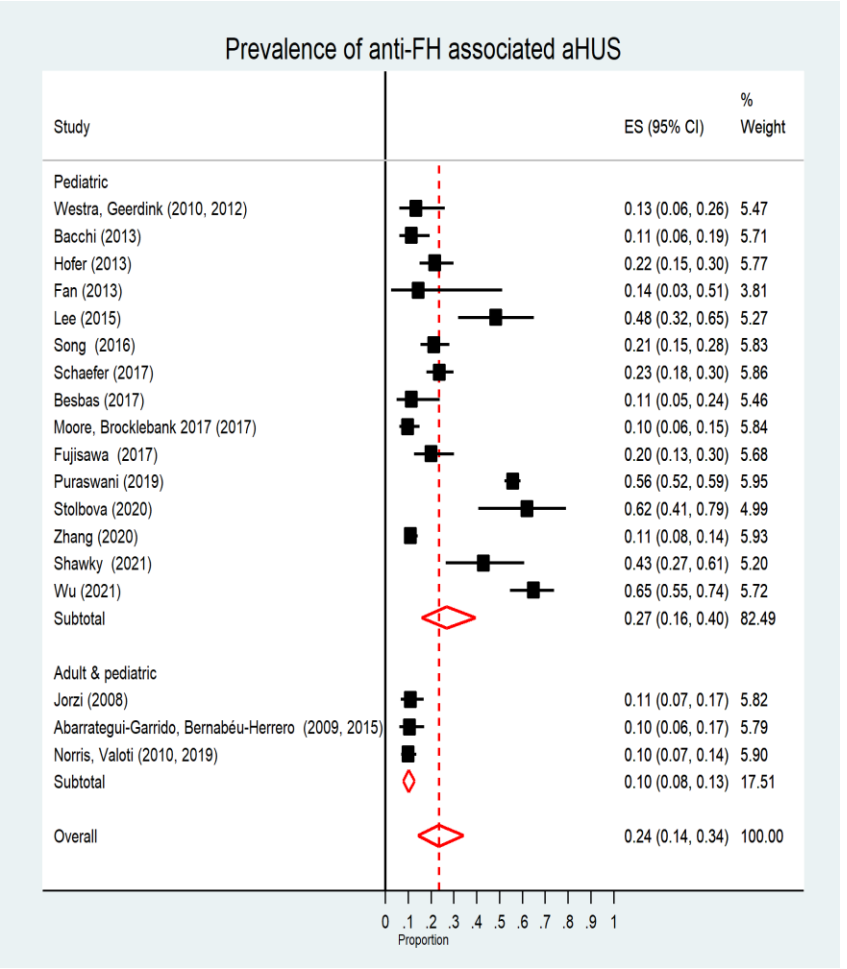
de Cordoba. Frontiers Immunol 2025

Parameter (n=17)	Estimate, %	95% CI
Sensitivity	86.7	62.1, 96.3
Specificity	100	34.2, 100
PPV	100	77.2, 100
NPV	50	15, 85
Diagnostic accuracy	88.2	65.7, 96.7

Prevalence of anti-FH HUS varies

Study	Event Size/Sample Size (presence of Anti-FH Ab)	Estimated % (95% CI)
Puraswani M et al., 2019 (11)	436/781	55.83 [0.5273, 0.05893]
Valoti E et al., 2019 (15)	30/305	9.83 [0.0000, 0.1993]
Bernabéu-Herrero et al., 2016 (21)	14/367	3.81 [0.0000, 0.1472]
Lee et al., 2015 (16)	15/51	29.41 [0.0801, 0.5081]
Fremeaux-Bacchi et al., 2011 (17)	14/214	6.54 [0.0000, 0.2034]
Hofer et al., 2013 (10)	30/116	25.86 [0.1236, 0.3936]
Noris et al., 2010 (22)	8/273	2.93 [0.0000, 0.1683]
Durey M et al., 2009 (23)	14/177	7.91 ([0.0000, 0.2291]
Moore I et al., 2009 (9)	13/142	9.15 ([0.0215, 0.1615]
Józsi M et al., 2008 (24)	16/147	10.88 [0.0000, 0.3850]
Durey M et al., 2005 (25)	3/48	6.25 [0, 0.651]
Jozsi M et al., 2007 (26)	5/51	9.80 [0, 0.453]
Gurjar et al., 2018 (27)	98/164	59.76 [0.536, 0.659]
Brocklebank et al., 2017 (18)	17/175	9.71 [0, 0.242]
Shawky et al., 2021 (2)	12/26	46.14 [0.224, 0.698]
Song et al., 2017 (20)	33/156	21.15 [0.087, 0.336]
Total Random Effects	758/3160	23.9 [0.213, 0.266]

Front Immunol 2022; Pediatr Nephrol 2022



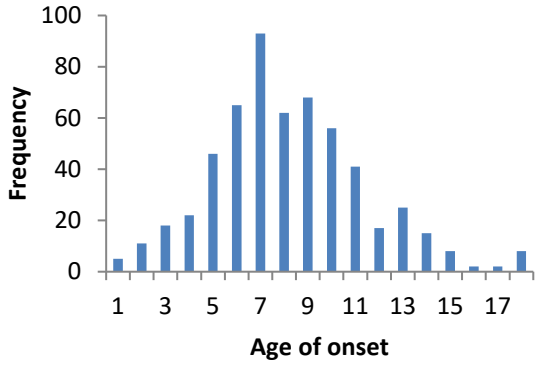
CFHR1 del (88-90%)

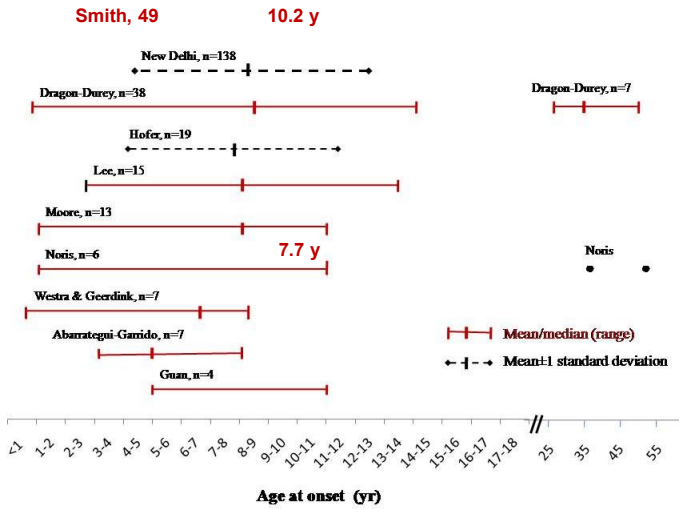
Is anti-FH associated HUS under-recognized?

Indian aHUS database: 2010-2023

N=1070	**Anti-FH HUS** 601, **56.2%**	**Other HUS** 469, **43.8%**	*P*
Boys, %	416 (69.5)	292 (62.3)	0.014
Age, yr	**7.5 (5.7-9.7)**	**4.1 (1.2-9.6)**	<0.0001
Days to presentation	7 (3-17)	5 (2-9)	<0.0001
Oliguria, %	80.6	88.9	<0.0001
Seizures, %	28.6	21.2	0.017
Hemoglobin, g/dl	5.2 (4.4-6.0)	6 (5-6.9)	<0.0001
Platelets, 1000/mm^3	52 (31-80)	56 (27-95)	0.48
Reticulocytes, %	7 (4-12)	3.3 (1.5-5.6)	<0.0001
LDH, IU/l	2636 (1480-4211)	2010 (1070-3420)	<0.0001
Hematuria, %	53.2	32.8	<0.0001
Creatinine, mg/dl	5 (3.3-7.3)	4.9 (2.8-7.5)	0.13
C3, mg/dl	**68 (50-86)**	**80 (57-101)**	<0.0001

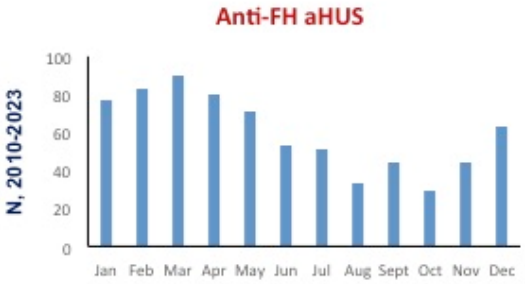
Clinical features similar





	Dragon-Durey 2010; N=45	Hofer 2013; N=19	India 2017 N=386	Lee 2015 N=15	Brocklebank 2017 N=17
GI	84% pain, vomit diarrhea 53%	87% pain, vomit diarrhea 13%	7.5% diarrhea	14%	53% pain, vomit diarrhea 47%
Infections	9% varicella, URI STEC, norovirus	42% URI	54% fever	14% URI	24% fever
Dialysis	57%	74%	86%	67%	47%
CNS	23.5%	11%	29%	7%	24%
Pancreatitis	23%	58%	34%	7%	12%
Hepatitis	50%				6%
Cardiac	8%			33%	

Infectious triggers in HUS



No. of organisms	Anti-FH negative, n=48/61 (78.69)	Anti-FH positive, n=69/74 (93.24)
Single pathogen	8 (16.67)	10 (14.45)
Adenovirus	1 (2.08)	1 (1.45)
Coronavirus OC46	1 (2.08)	0 (0)
Coronavirus NL63	2 (4.17)	1 (1.45)
Rhinovirus	1 (2.08)	0 (0)
Influenza A H1 (2009 strain)	1 (2.08)	1 (1.45)
Respiratory syncytial virus	2 (4.17)	4 (5.80)
Chlamydia pneumoniae	0 (0)	3 (4.35)
Multiple pathogens	8 (16.67)	9 (13.07)
Rhinovirus	8 (16.67)	9 (13.07)
Enterovirus	8 (16.67)	9 (13.07)
Adenovirus	1 (2.08)	1 (1.45)
Respiratory syncytial virus	1 (2.08)	1 (1.45)
Parainfluenza type 3	1 (2.08)	1 (1.45)

N=135; ICMR

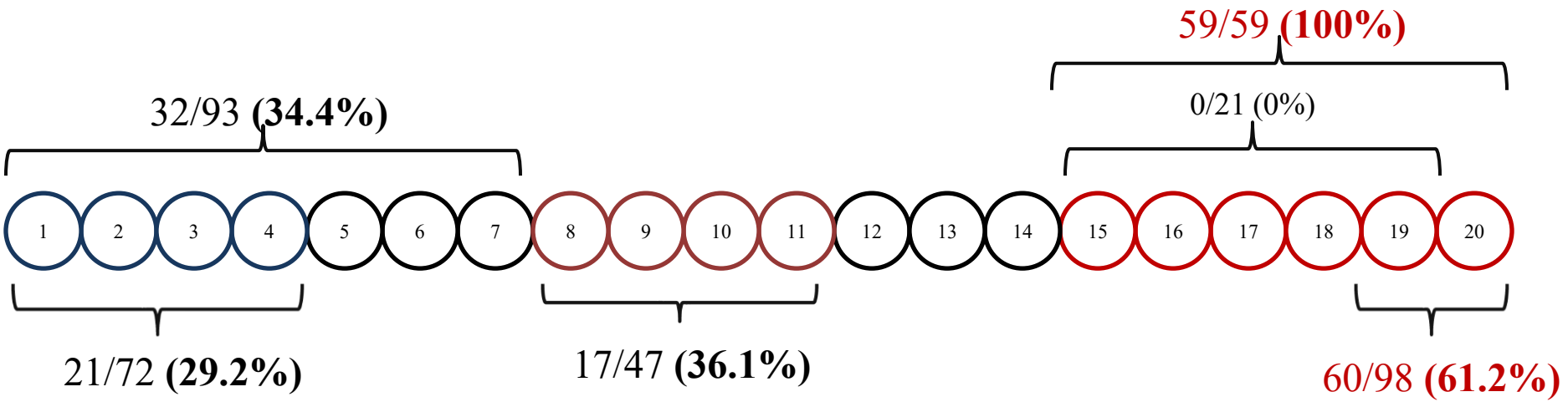
No. of organisms	Anti-FH negative, n=48/61 (78.69)	Anti-FH positive, n=69/74 (93.24)
Single pathogen	17 (28.81)	11 (17.19)
Rotavirus	5 (10.42)	0 (0)
Sapovirus	2 (4.17)	0 (0)
Enteroaggregative *Escherichia coli*	5 (10.42)	4 (5.80)
Enterotoxigenic *Escherichia coli*	1 (2.08)	0 (0)
Clostridium difficile A/B	1 (2.08)	0 (0)
Giardia lamblii	0 (0)	5 (7.25)
Cryptosporidium sp.	3 (6.25)	2 (2.90)
Multiple pathogens	4 (6.78)	8 (12.5)
Norovirus G1/G2	4 (6.78)	2 (2.90)
Enteroaggregative *Escherichia coli*	2 (4.17)	3 (4.35)
Enterotoxigenic *Escherichia coli*	1 (2.08)	0 (0)
Enteropathogenic *Escherichia coli*	0 (0)	2 (2.90)
Shiga toxin producing *Escherichia coli*	2 (4.17)	0 (0)
Salmonella sp.	2 (4.17)	1 (1.45)
Campylobacter sp.	0 (0)	2 (2.90)
Vibrio sp.	3 (6.25)	1 (1.45)

Clostridium difficile A/B	1 (2.08)	2 (2.90)
Giardia lamblii	0 (0)	5 (7.25)
Cryptosporidium sp.	0 (0)	3 (4.35)

Gastrointestinal pathogens in anti-FH antibody positive and negative Hemolytic Uremic Syndrome

Pediatric Research (2018) 84:118–124;

Antibodies (IgG3) bind multiple epitopes

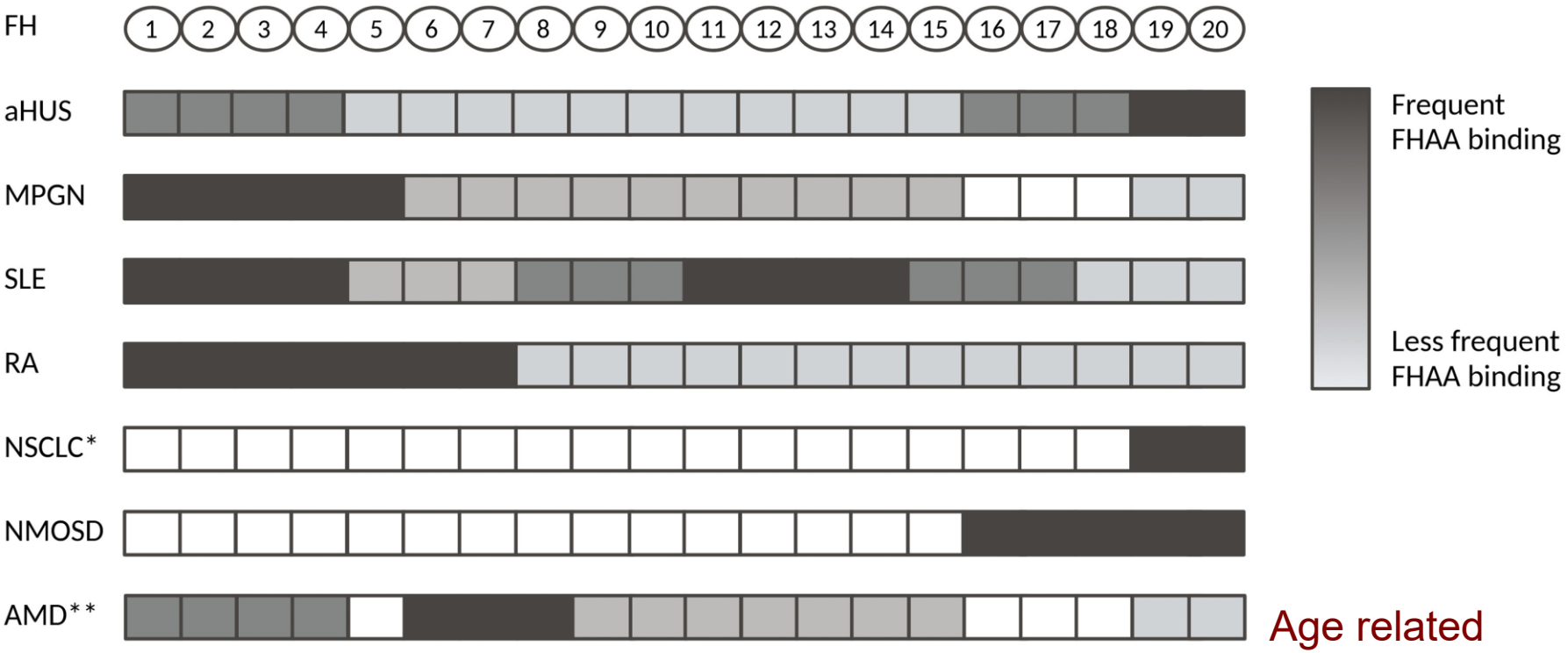


Author	SCR 1-4	SCR 1-7	SCR 8-11	SCR 15-19	SCR 15-20	SCR 19-20
Blanc	13/14	17/18	5/18		18/18	8/17
Bhattacharjee		5/10			10/10	10/10
Moore	1/12					7/12
Jozsi		0/16	4/16	0/16	16/16	16/16
Jozsi		0/5	1/5	0/5	5/5	5/5
Strobel	0/2				2/2	2/2
Guo **China-TMA**	4/36	6/36				12/36*
Puraswani **AIIMS**	**3/8**	**4/8**	**7/8**		**8/8**	

Front Immunol June 2019

*No epitope in 50%
Pediatr Nephrol (2019) 34:269

FH domains targeted by anti-FH antibodies



Age related

MN Antibody binding sites are not yet specified

APS Antibody binding sites are not yet specified

MIS-C Antibody binding sites are not yet specified

PE** Antibody binding sites are not yet specified

Immunology Letters Aug 2025

Variants in complement genes are uncommon in patients with anti-factor H (FH) autoantibody associated atypical hemolytic uremic syndrome (aHUS)

Nationwide cohort

Patients < 18 years old with anti-FH aHUS

- 77 consecutive patients
- 21 relapsing course
- 9 ESKD and/or death

Median anti-FH titers 5670 (IQR 2177-13,545) AU/ml

Genetic testing

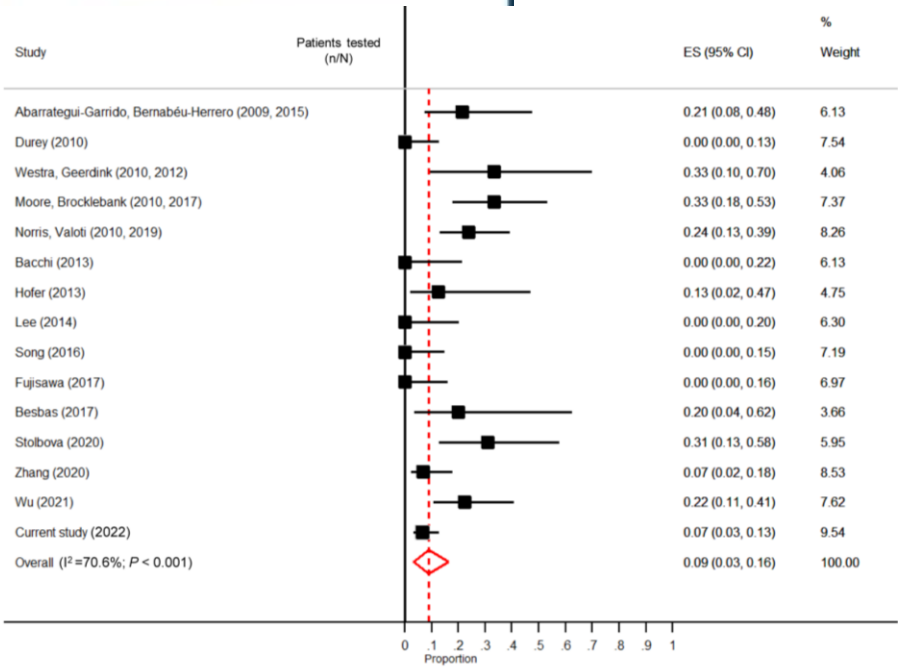
Targeted sequencing (27 gene panel)

Multiplex-ligation dependent probe amplification for *CFH-CFHR5* copy number variation

Results

Variants in 6.5% (95% CI 3.1-13.2%); one pathogenic variant
CFI c.148G>C, p.Pro50Ala

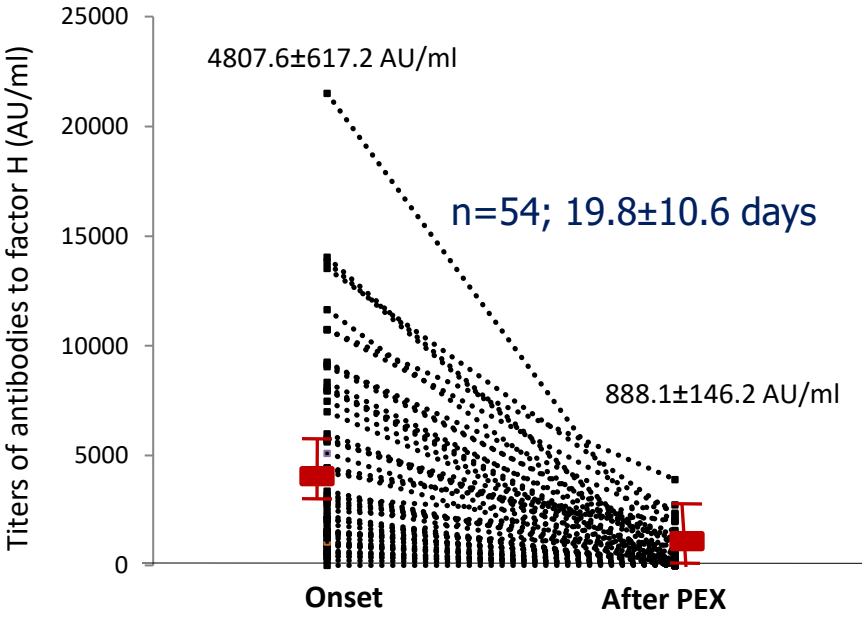
Homozygous *CFHR1* deletion in 91.6% vs. 9.8%
in 184 healthy controls

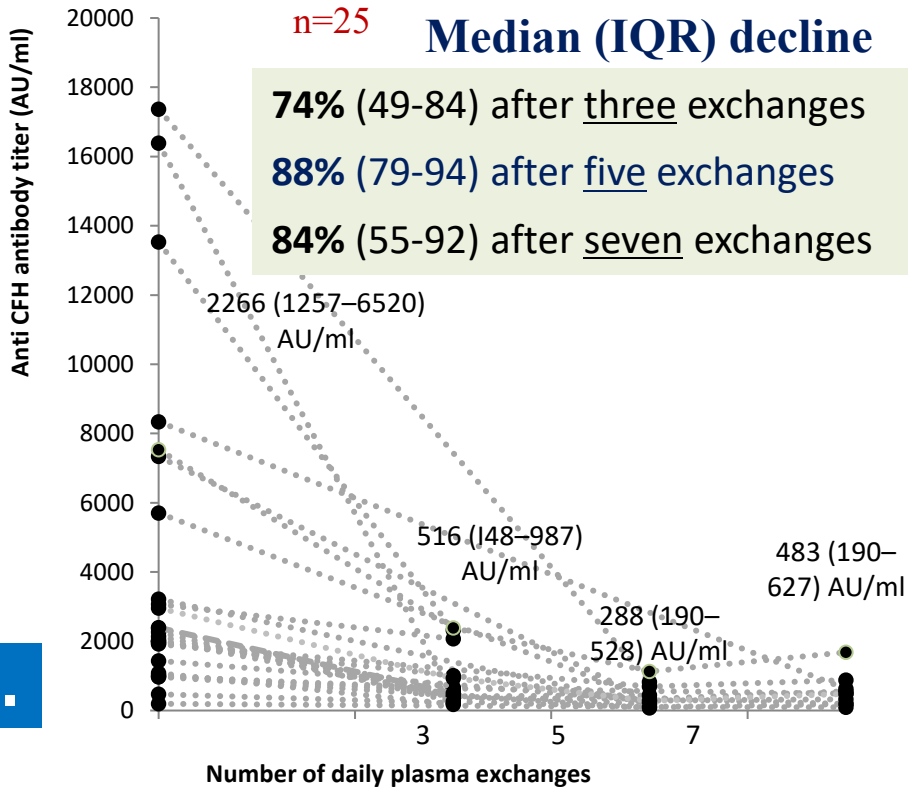


Pediatr Nephrol 2023; 38:2659

Plasma exchanges reduce antibody levels

IgG chiefly extracellular; 5-7 exchanges → 80-88% reduction



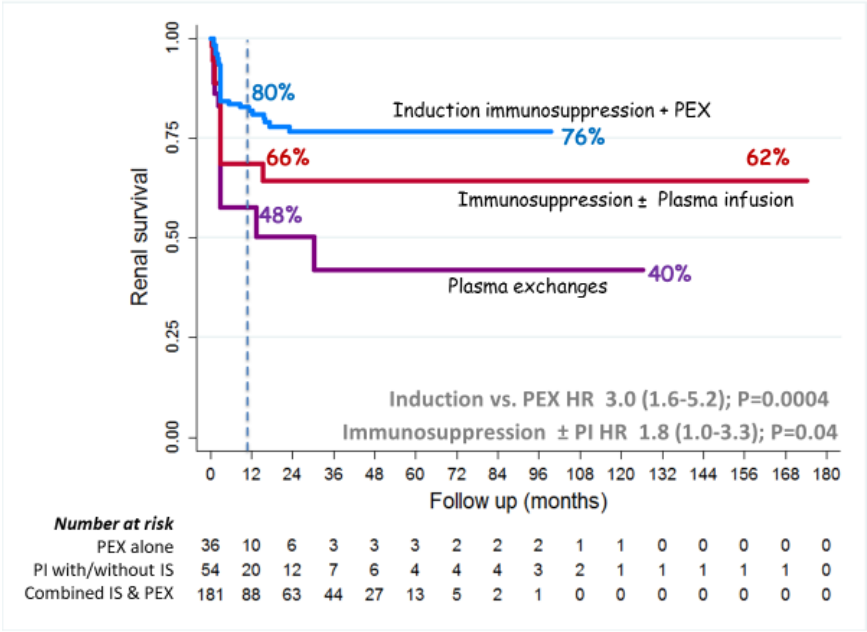


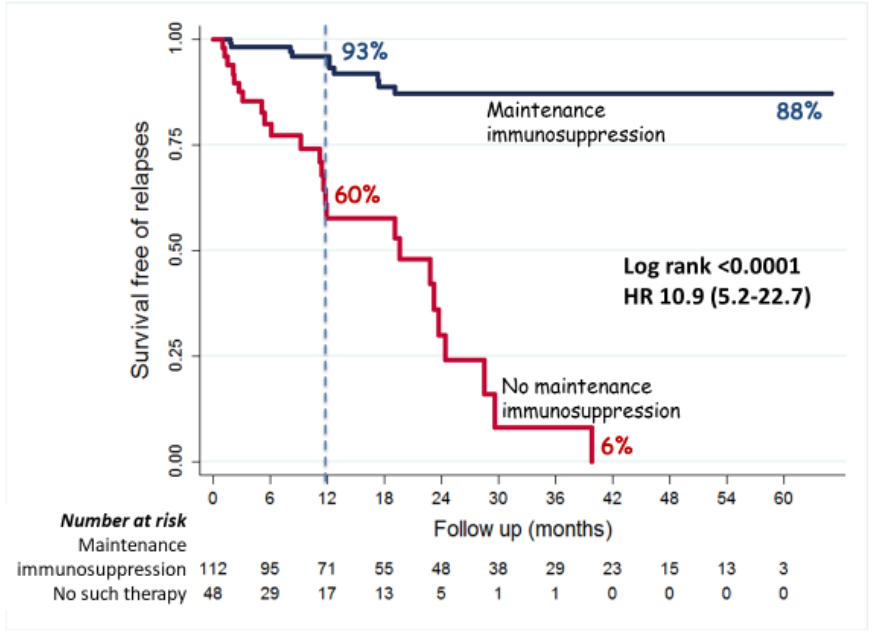
Additional IVIG does not help....

Kidney Int 2014;85:1151-60

Pediatr Nephrol 2015;30:451-7

PEX + immunosuppression improve outcomes





Adverse outcome: 20% *vs.* 52% @ 1-yr with combined therapy vs. PEX

Relapse free: 88% *vs.* 6% with or without maintenance therapy

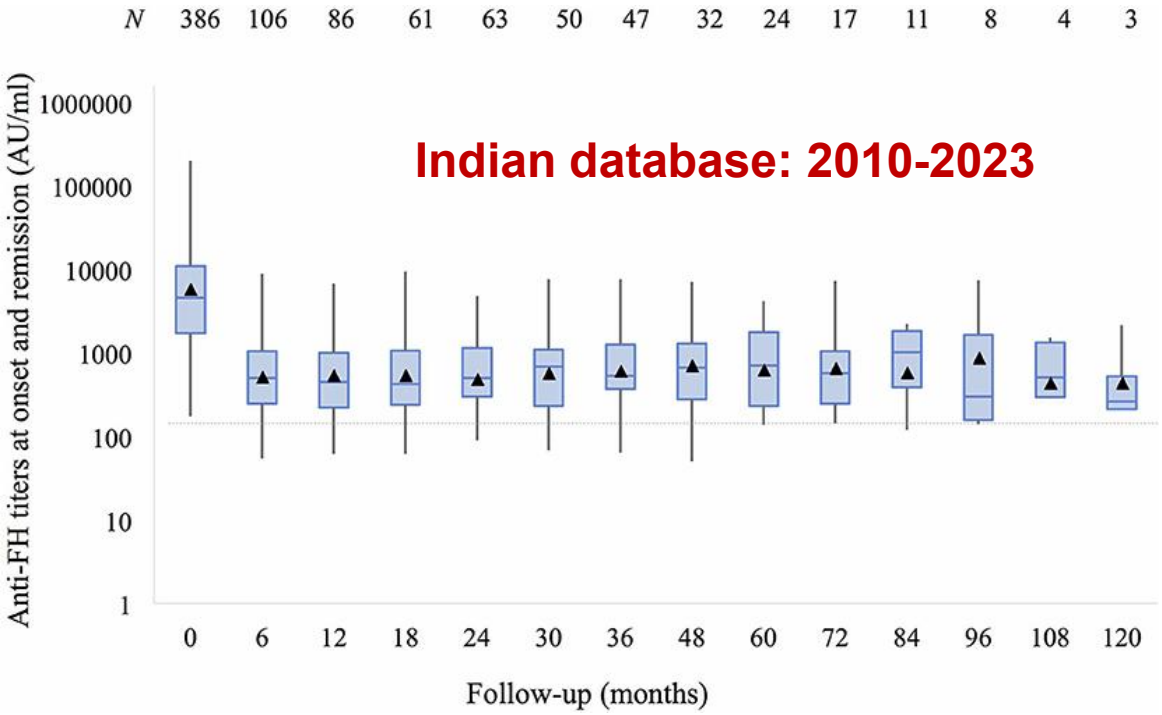
Kidney Int 2014;85:1151-60
Pediatr Nephrol 2015;30:451-7
Front Immunol 2019

Adverse outcome: Number needed to treat 2.6

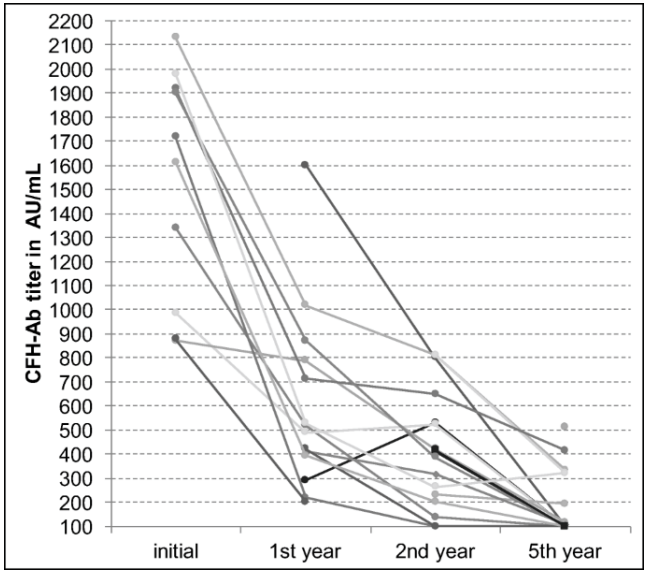
Relapse: Number needed to treat 4.5

Abbreviated PEX : Feasible & effective

Anti-FH titers decline, but stay relatively high….



Indian database: 2010-2023



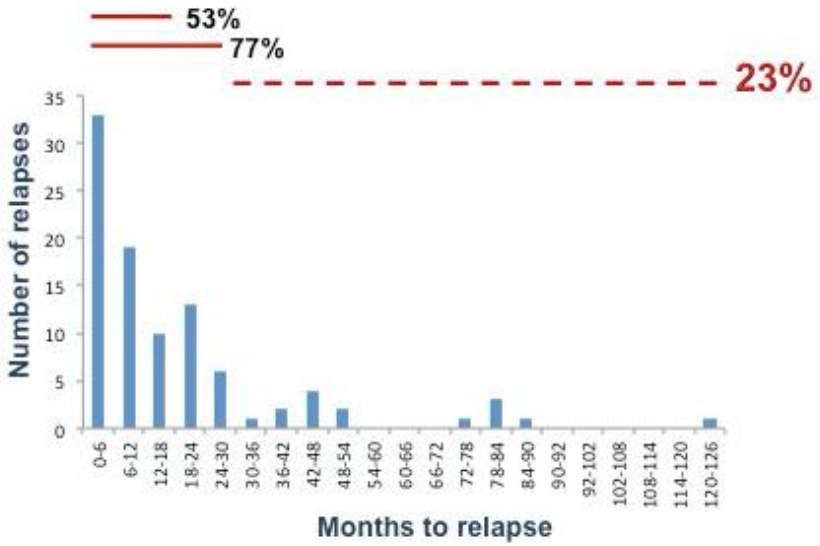
N=19 @ 5-yr, 55% patients had Ab titers <100 AU/ml

Innsbruck. Pediatr Nephrol 2021; 36: 917–25

Relapses within 6-24 months of onset ~20%

	N
AIIMS	**83/443 (18.7%)**
Dragon-Durey	13/30 (43.3%)
Moore	3/13
Noris	3/7
Geerdink	3/6
Guan	0/4
Sana	1/4
Hofer	14/19 (74%)

Time to relapse 11.3 (3-22.6) months

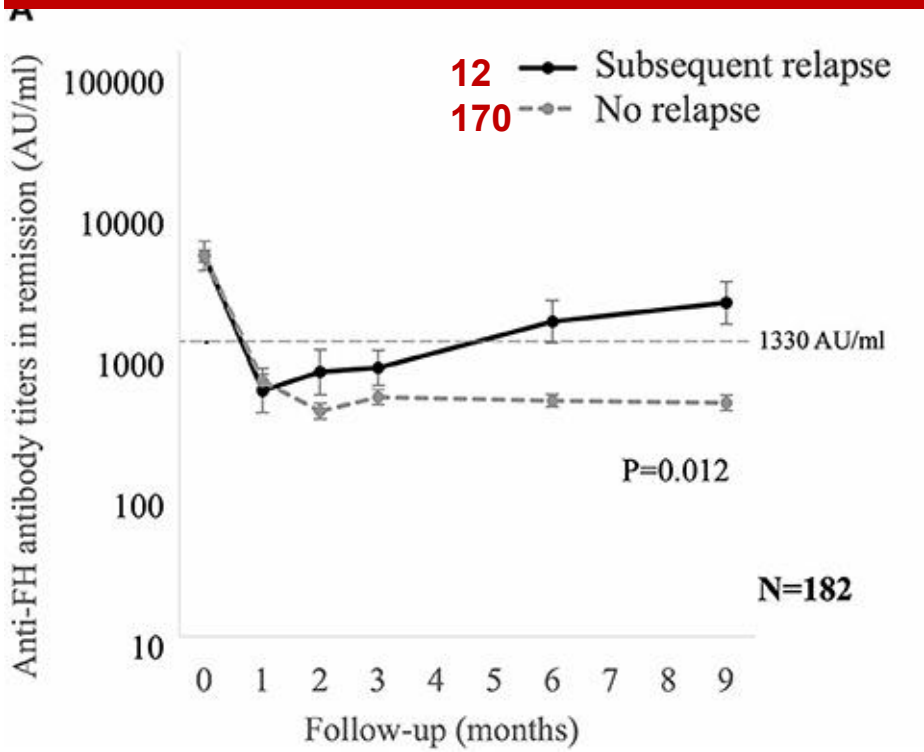


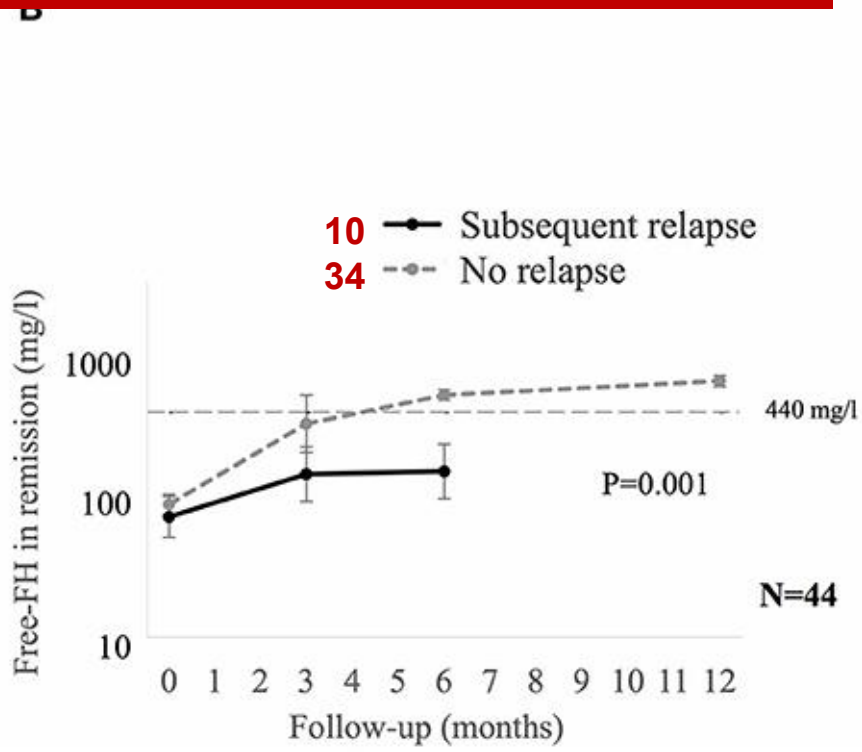
N=356

	HR	95% CI	*P*
Additional variation	4.9	1.47, 16.6	0.01
PEX + immunosuppression	0.3	0.09, 0.75	0.01

6-months: High anti-FH & low free FH predict relapse

Anti-FH ≥1,330: Sensitivity 75%, specificity 81%; AUC 0.86

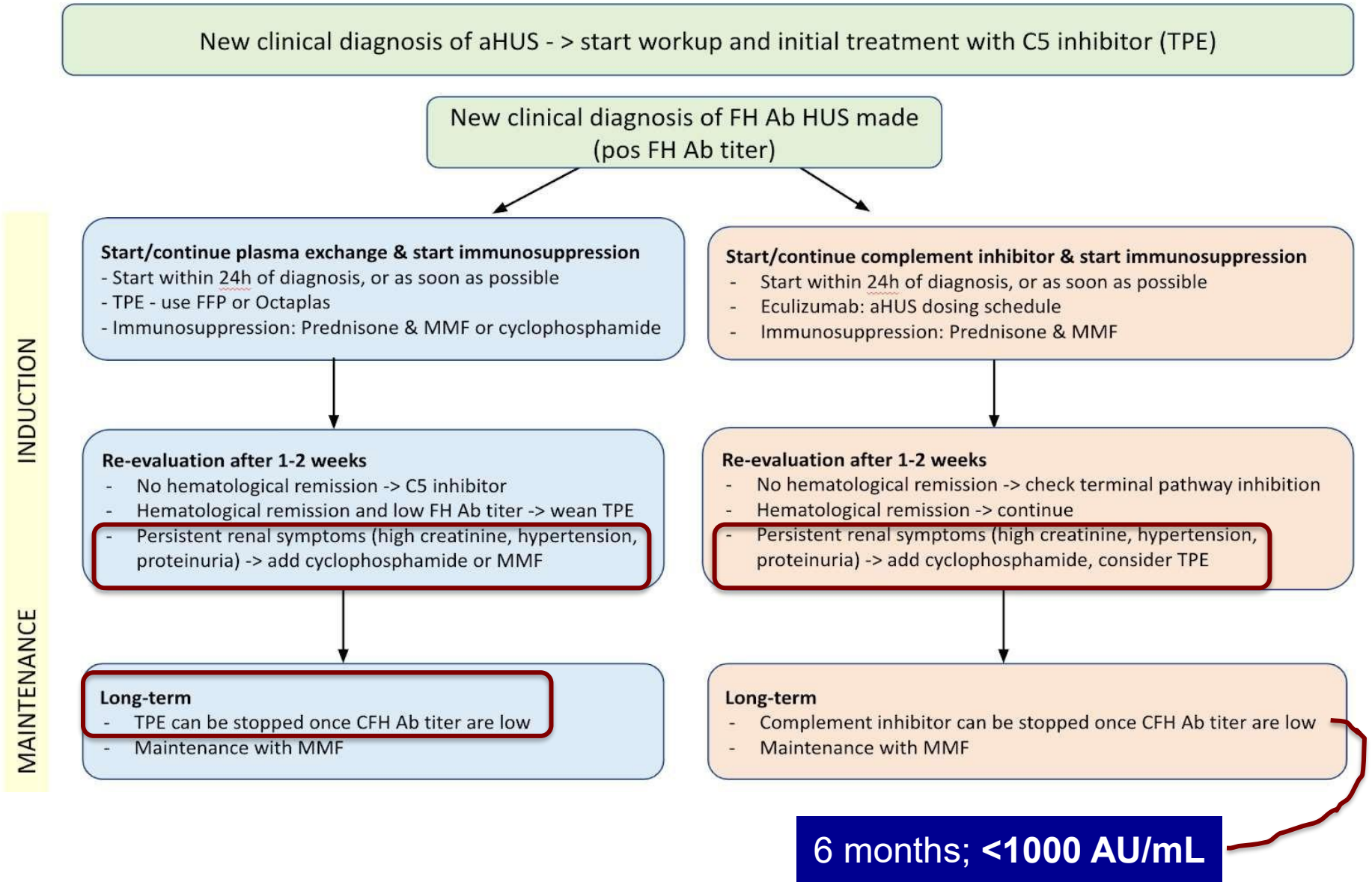




Free FH ≤440 mg/l: Sensitivity 70%, specificity 100%; AUC 0.91

Combined: Sensitivity 75%, NPV 91%; AUC 0.91; HR 6.3 (1.7, 24)

Managing anti-FH HUS : IPNA



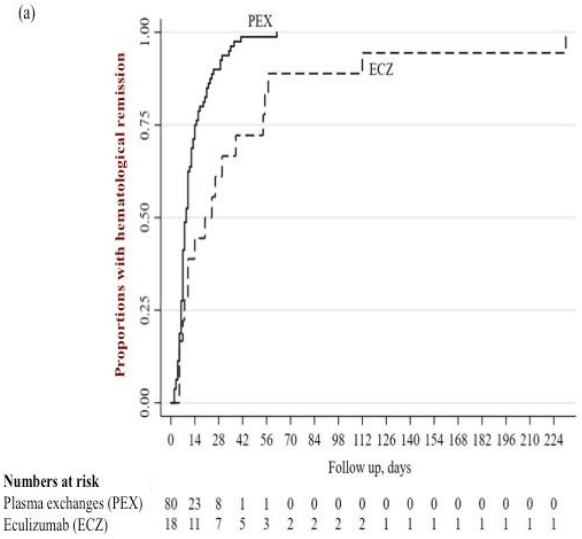
Anti-FH aHUS: Short-term outcomes of PEX *vs.* ECZ

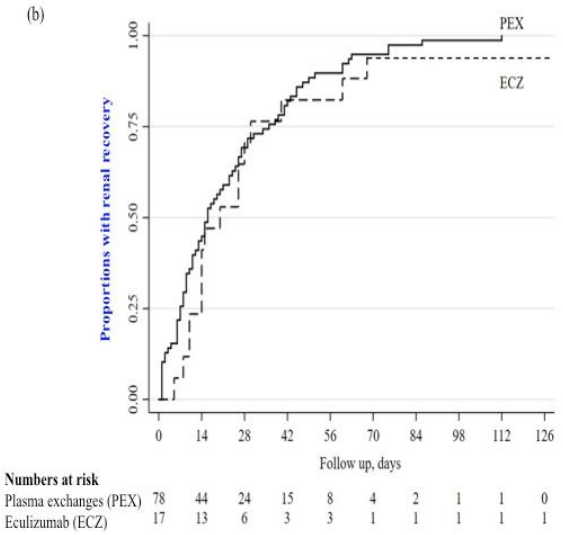
PROSPERO ID: CRD420251033150

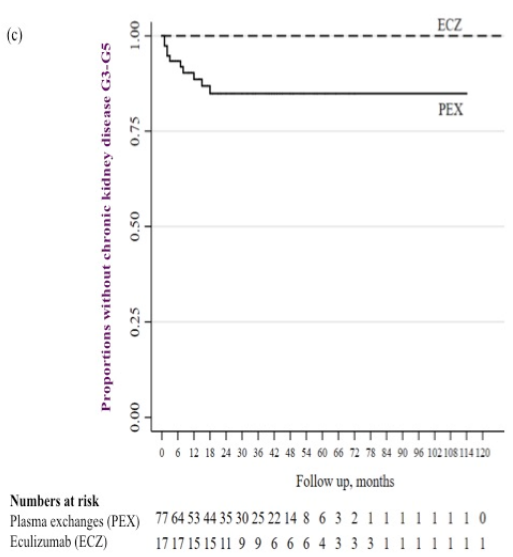
14 studies; n=99

PEX: Satisfactory initial choice for LMIC

	PEX (n=81)	Eculizumab (n=18)	HR; *P*
Time to hematological remission, days	9 (6, 14)	20 (8, 54)	**0.40 (0.2,0.7)**
Time to renal recovery, days	16 (7, 36)	20 (14, 30)	**0.78 (0.5,1.3)**
Proportion in hematological remission @ 28 d	73 (90.1%)	11 (61.1%)	***0.002***
Proportion with renal recovery @ 28 d	56 (70%)	12 (66.7%)	*0.78*
eGFR @ follow up	95.8 (77,116)	99.1 (91,107)	*0.32*
Anti FH titer, AU/L	454 (183, 977)	222 (90,1000)	*0.38*
Proportion with death	**5 (6.3)**	**0**	*0.28*







Anti-FH antibody HUS

Hemolytic uremic syndrome in a developing country:
Consensus guidelines

Recommend PEX & immunosuppressive therapy

Pediatr Nephrol 2019

Suggest daily PEX till hematological remission; taper

Frequent monitoring of titers first 12-24 months

IPNA 2026

Screen for anti-FH antibodies in all aHUS

C5 inhibition: Preferred therapy

Levels @ 1 month; q 3-6 months x 24 months; *relapses*

Genetic studies for complement variants

Allograft recurrence low (determined by antibody titers)

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Christian Medical College, Vellore
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Fortis Hospital, New Delhi
JIPMER, Puducherry

Max Action Balaji Hospital, New Delhi
Mehta Children's Hospital, Chennai
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