Αιμολυτικό Ουραιμικό Σύνδρομο

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Νεφρολογικό Τμήμα 417 ΝΙΜΤΣ
Μ.Χ.Α. «Νεφροιατρική»
Επιστημονικός Συνεργάτης ΜΗΤΕΡΑ

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Haemolytic uraemic syndrome

Syndrome comprising

acute renal failure of varying severity
microangiopathic anaemia
thrombocytopenia of varying severity

Multiple aetiologies

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Table 1 Classification of Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura and related disorders

Etiology identified	Etiology unknown
HUS infection-induced	
(1) Shiga and shiga-like toxin producing bacteria, Enterohemorrhagic *Escherichia Coli*, Shigella dysenteriae type 1	HIV infection
(2) Streptococcus pneumoniae	
HUS induced by disorders of complement regulation	Malignancy, cancer chemotherapy, ionizing radiation
(1) Genetic	
(2) Acquired	
ADAMTS13 deficiency	Calcineurin inhibitors and transplantation
(1) Genetic	
(2) Acquired	
Defective cobalamin metabolism	Pregnancy, HELLP syndrome, contraceptive pill
	Systemic lupus erythematosus, anti-phospholipid antibody syndrome
	Glomerulopathy
	Drug induced

Besbas N, Karpman D, Landau D, Loirat C, Proesmans W, Remuzzi G, Rizzoni G, Taylor CM, Van de Kar N, Zimmerhackl LB. A classification of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and related disorders. *Kidney Int* 2006; **70**: 423-431 [PMID: 16775594 DOI: 10.1038/sj.ki.5001581]

Noris M, Mescia F, Remuzzi G. STEC-HUS, atypical HUS and TTP are all diseases of complement activation. *Nat Rev Nephrol* 2012; 8: 622-633 [PMID: 22986360 DOI: 10.1038/nrneph.2012.195]

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Level 1: aetiology advanced
1.i Infection induced
(a) Shiga and shiga-like toxin-producing bacteria; enterohaemorrhagic Escherichia coli, Shigella dysenteriae type 1, Citrobacter freundii
(b) **Streptococcus pneumoniae, neuraminidase and T-antigen exposure**

Typical/diarrhoeal/ D+ HUS

1.ii Disorders of complement regulation
(a) **Genetic disorders of complement regulation**
(b) Acquired disorders of complement regulation, e.g. anti-factor H antibody
1.iii **von Willebrand proteinase, ADAMTS13, deficiency**
(a) Genetic disorders of ADAMTS13
(b) Acquired ADAMTS13 deficiency; autoimmune, drug induced

Atypical/ non-diarrhoeal/ D- HUS

1.iv Defective cobalamin metabolism
1.v Quinine induced
Level 2: aetiology unknown
2.i Human immunodeficiency virus (HIV)
2.ii Malignancy, cancer chemotherapy and ionising radiation
2.iii Calcineurin inhibitors and transplantation
2.iv Pregnancy, HELLP syndrome and oral contraceptive pill
2.v Systemic lupus erythematosus and antiphospholipid antibody syndrome
2 vi Glomerulopathy
2.vii Familial, not included in part 1
2.viii Unclassified

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What is Post-Diarrheal Hemolytic Uremic Syndrome (D+HUS) and where did it come from ?

- The syndrome includes:
  - **Acute kidney failure**
  - **Hemolytic anemia**
  - **Thrombocytopenia (low platelet count)**

- Most common cause of acute renal (kidney) failure in young children; also occurs in older children and adults

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E. coli O157 Emergence

1993

Large western states outbreak, 500 cases and 4 deaths

CDC-**MMWR**. 1993.

Association of STEC with HUS, Karmali et al.

Karmali et al. 1985. J.Infect.Dis.

Description of Shiga toxin: O'Brien, others

O'Brien and Holmes. 1987. Microbiol.Rev.

O'Brien and LaVeck. 1983. Infect.Immun.

1982

First clinical isolation, "Rare E. coli serotype"

Riley et al. 1983. NEJM

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Northern German outbreak May-July 2011

- Source: bean sprout farm in Lower Saxony
- Sprouted from batch of seeds from Egypt
- 3793 cases of diarrhoea – O104:H4
- Delay in symptoms, ingestion → diarrhoea 8 days
- 827 (22%) developed HUS, 88% in adults
- 53 deaths
- 2010 European data
  - 4000 STEC cases reported, 5.5% developed HUS
  - O157 (41%), 026 (7%), O103 (2.5%)

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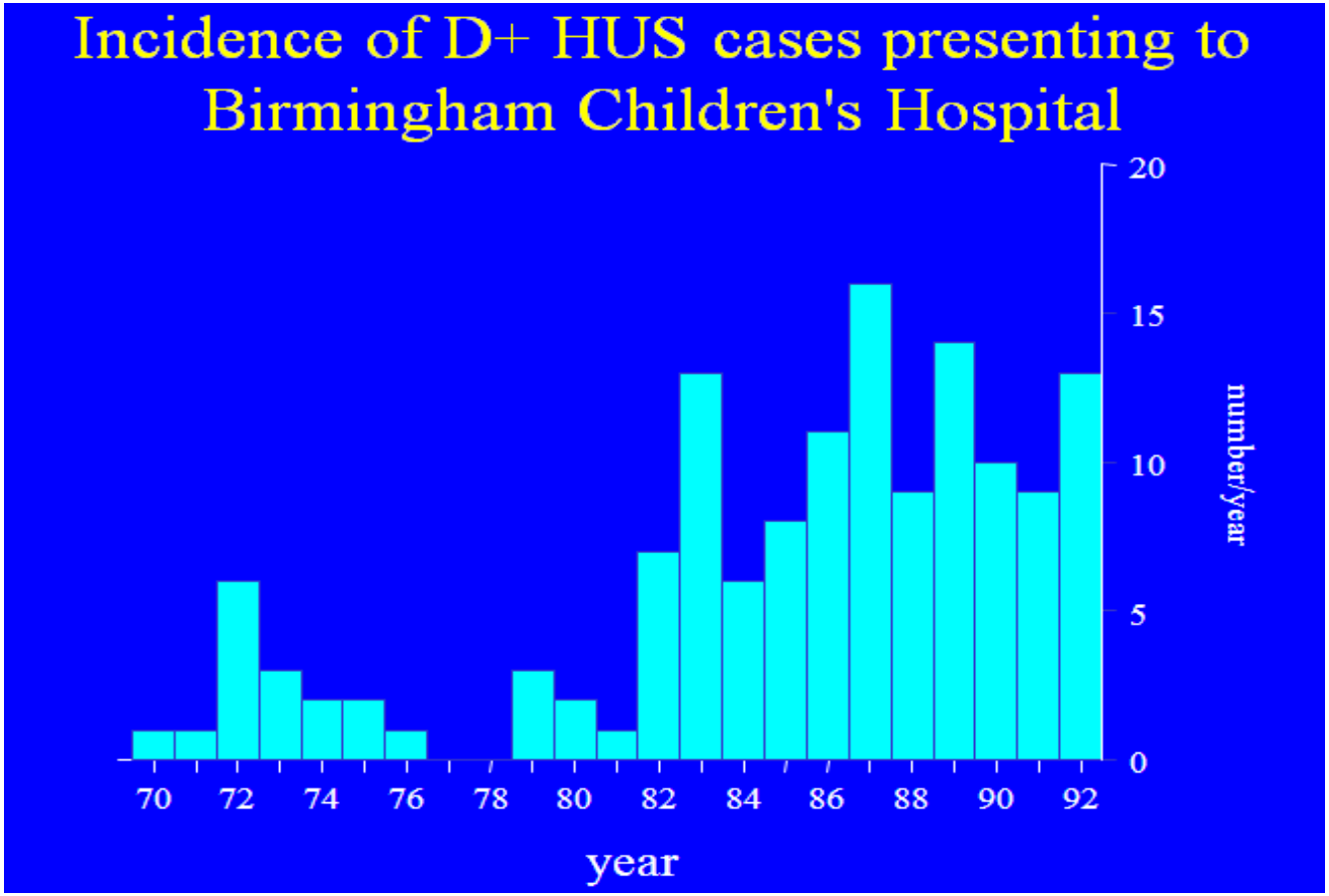
Birmingham Children's Hospital NHS
NHS Foundation Trust



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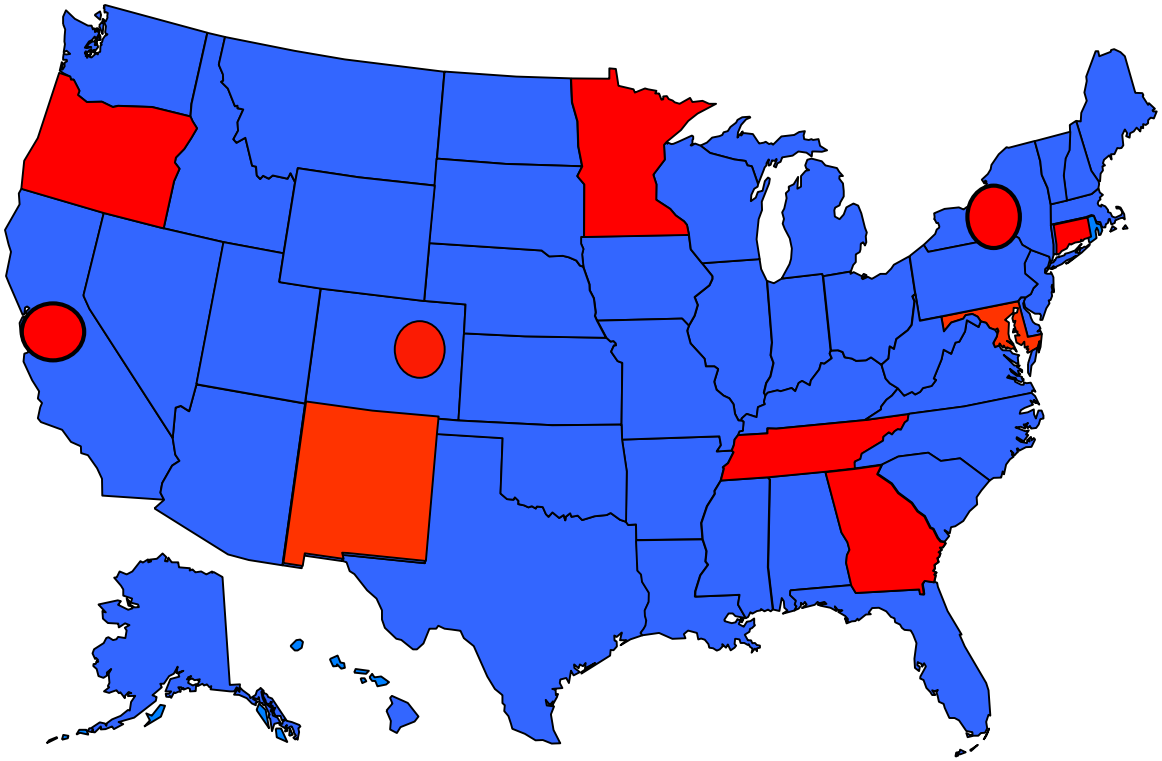
2004 FoodNet Catchment Area



Catchment population 44.1 million persons
15.2% of U.S. population

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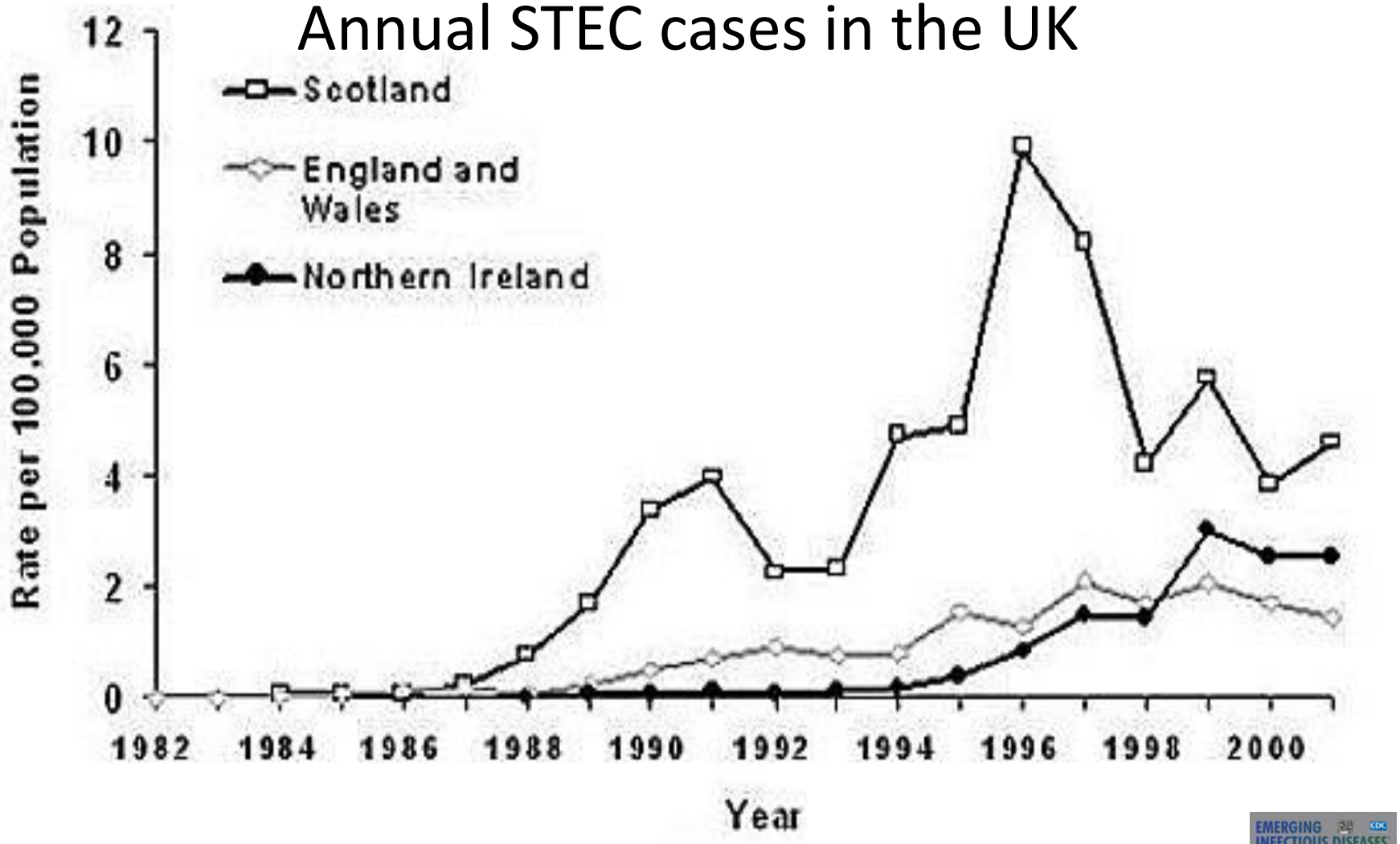
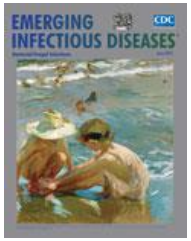
Annual STEC cases in the UK



Emerging Infectious Diseases 2005; 11: 590-6



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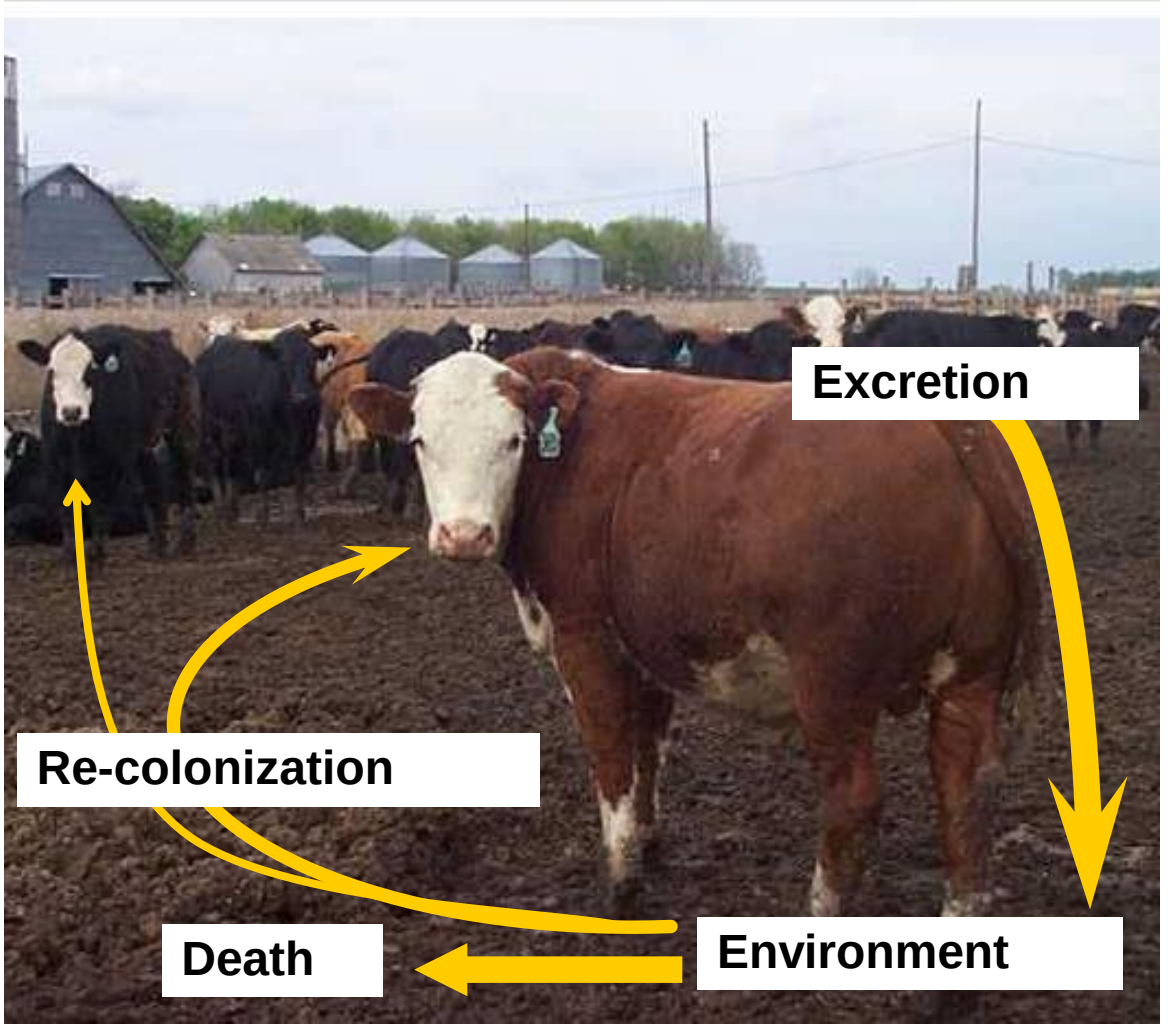
Two habitat model

Primary habitat:
large intestine, recto-anal junction?

- warm, constant
- nutrient rich
- vigorous growth

Secondary habitat:
water, soil, sediment

- cool, fluctuating
- nutrient limiting
- survival



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Direct contact transmission

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Indirect contact (environmental) transmission

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Pathogenic Cascade; from diarrhea to dialysis

- **Chain of events:**
  - ingestion of Stx producing E. coli
  - multiplication in bowel
  - absorption of Stx into circulation

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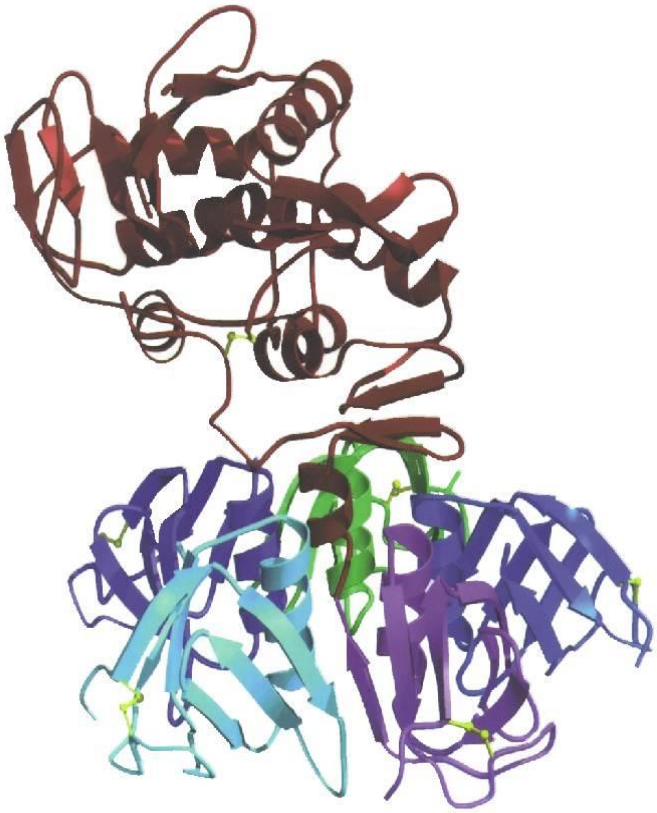
pathogenic cascade, cont.

- Chain of events, cont.:
  - attachment of Stx to receptors in kidney, and occasionally other organs
  - movement of toxin into cells
  - cell injury or death



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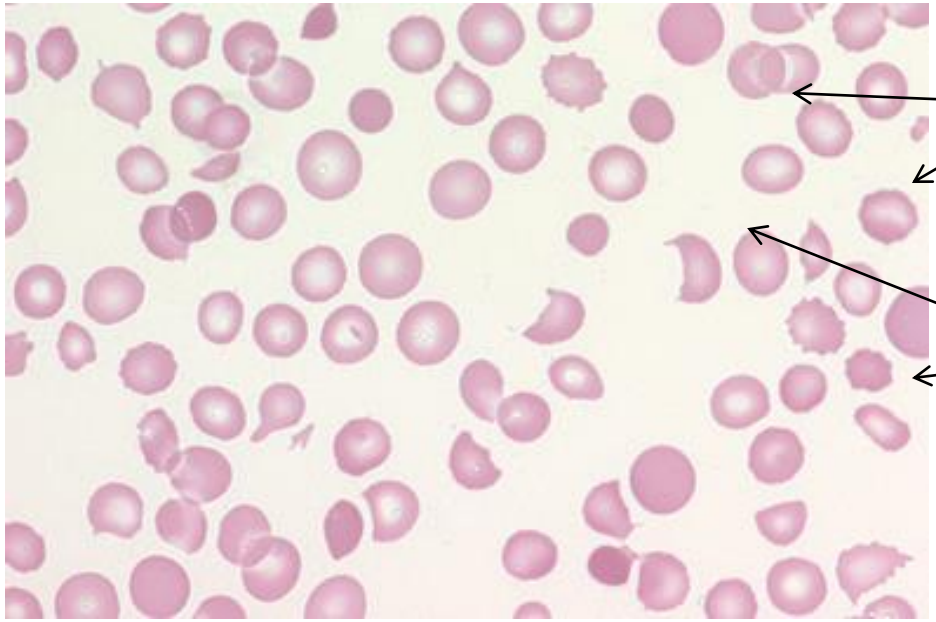
D+ HUS and EHEC

- Enterohemorrhagic *Escherichia coli* (EHEC) serotype O157:H7, EHEC colonise cattle
- Transmission – contaminated meat, milk, water, fruit, vegetables
- Exposure to EHEC → diarrhoea in ≈ 10% children
- HUS develops in ≈ 15% of children with EHEC diarrhoea
- **O157:H7 predominant serotype in the UK**
  - **O26:H11, O103:H2, O111:NM, O121:H19, O145:NM**

Diagnosis

- Diarrhoea (often bloody)
- Haematological – microangiopathic haemolytic
  - anaemia
  - thrombocytopenia



Fragmented red cells

Absence of platelets

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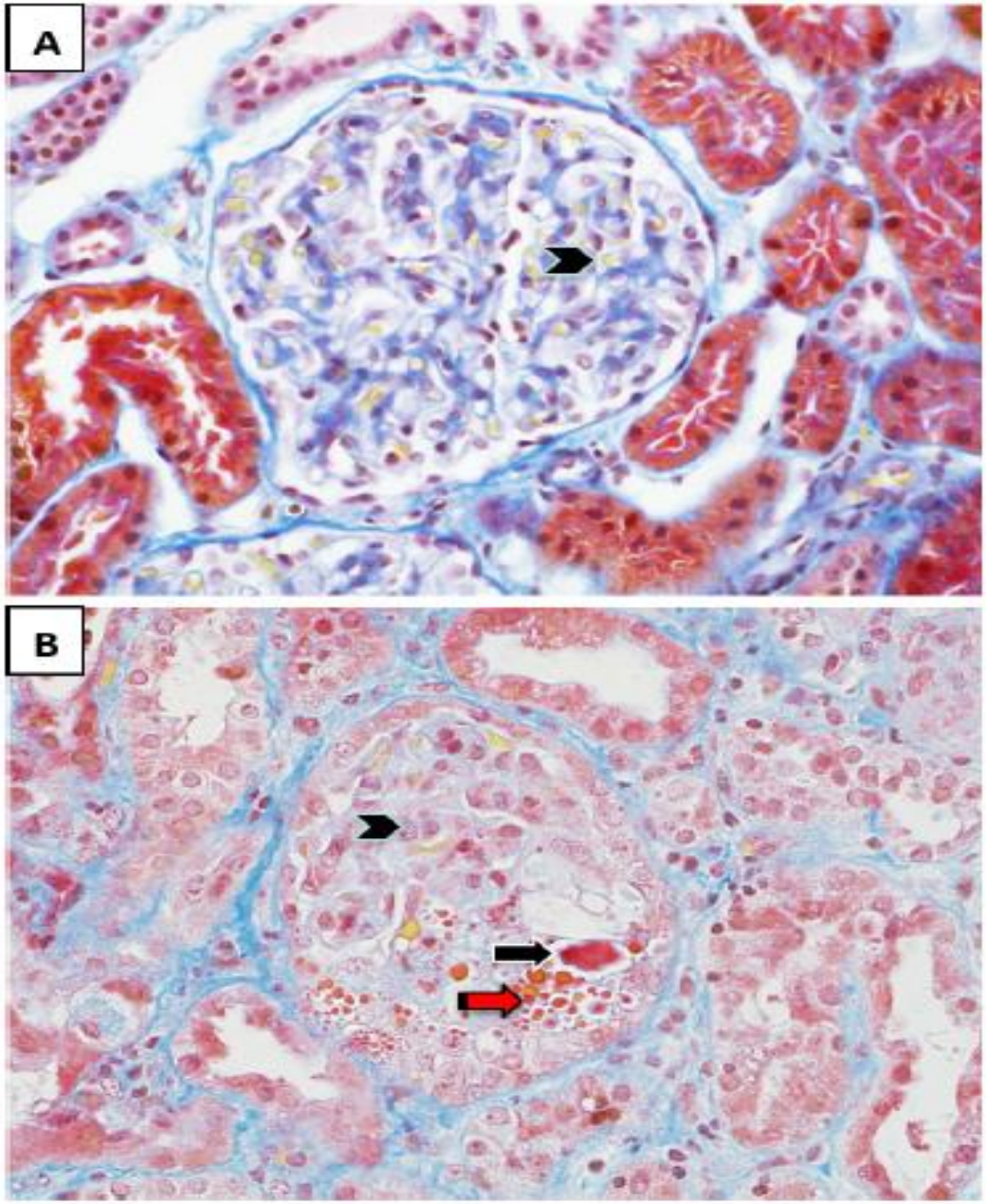
- Fibrin thrombi
- Endothelial cell swelling
- Red cell fragmentation

Figure 1. Glomerular pathology in hemolytic uremic syndrome



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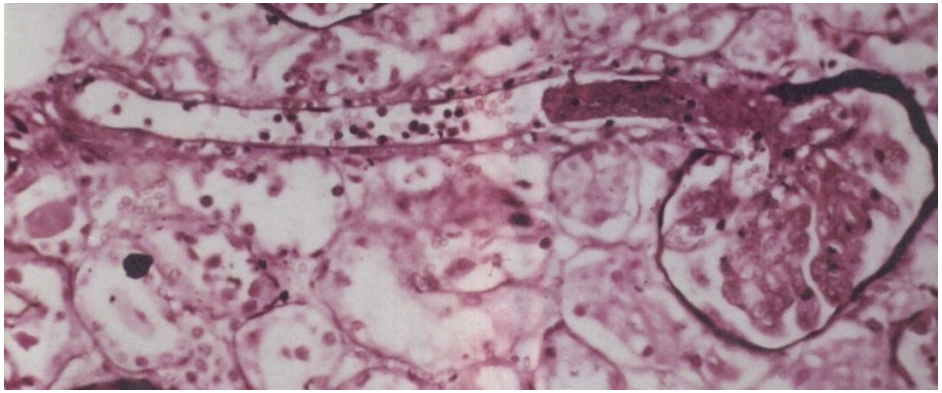
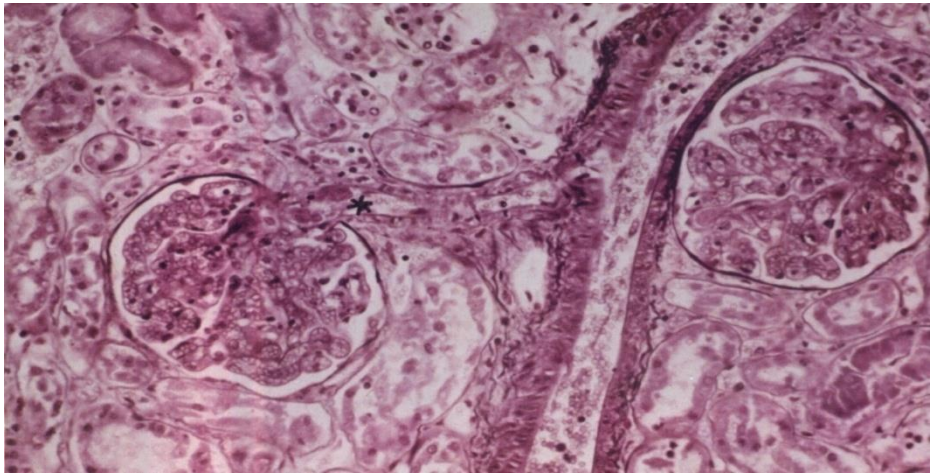
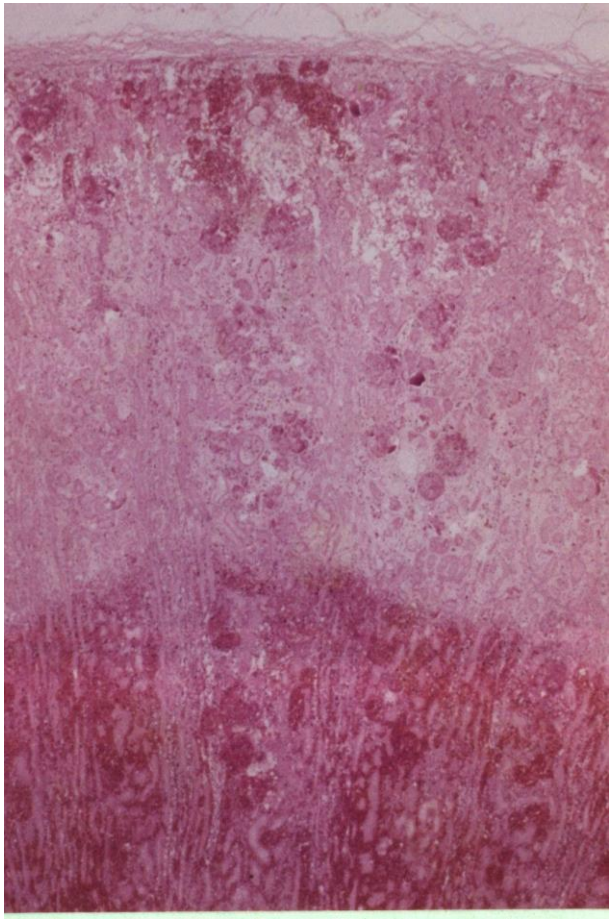
Acute Kidney Injury







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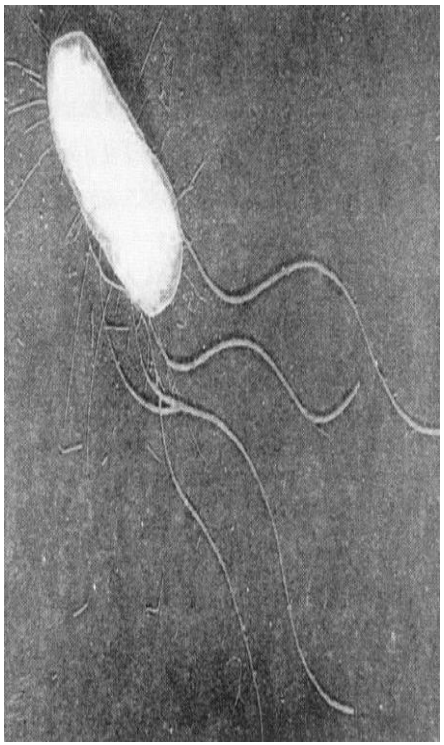
ISSN 2220-6124 (online)

REVIEW

Update on hemolytic uremic syndrome: Diagnostic and therapeutic recommendations

Maurizio Salvadori, Elisabetta Bertoni



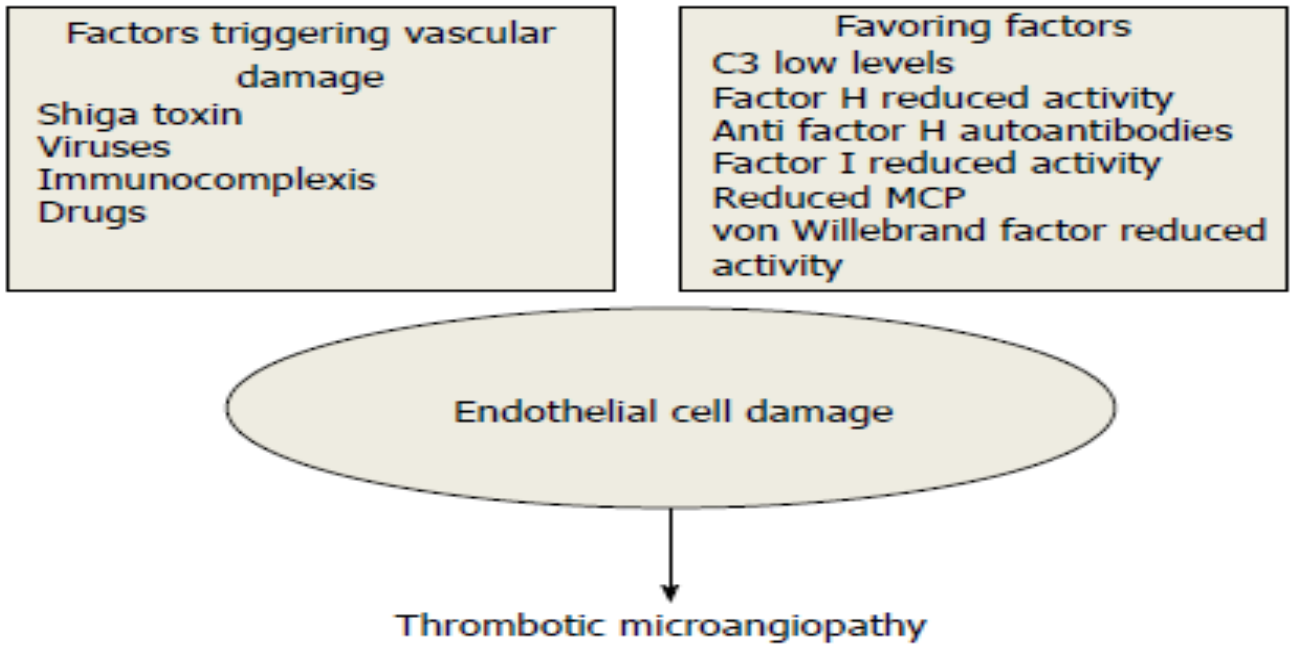


Figure 1 Pathogenetic mechanisms of thrombotic microangiopathy. MCP: Membrane cofactor protein.

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REVIEW

Update on hemolytic uremic syndrome: Diagnostic and therapeutic recommendations

Maurizio Salvadori, Elisabetta Bertoni

Table 2 Development of Shiga-toxin-associated hemolytic uremic syndrome

Pathogenetic steps	Clinical
Ingestion of *Escherichia Coli* through contaminated food or patient to patient transmission or transmission from animal to man	Colonization of the gut
Diarrhoea	Local tissue damage
Bloody diarrhoea	Systemic toxinemia
Generation of host cytokines and chemokines	Endothelia cell damage, activation of local thrombosis in kidneys and in other organs
Renal involvement→ HUS	Damage to glomerular endothelial cells, arteriolar damage, mesangial cell activation/damage, podocyte injury, tubular damage
Renal Insufficiency	Acute renal failure Chronic renal failure
	Arterial hypertension, proteinuria, hematuria

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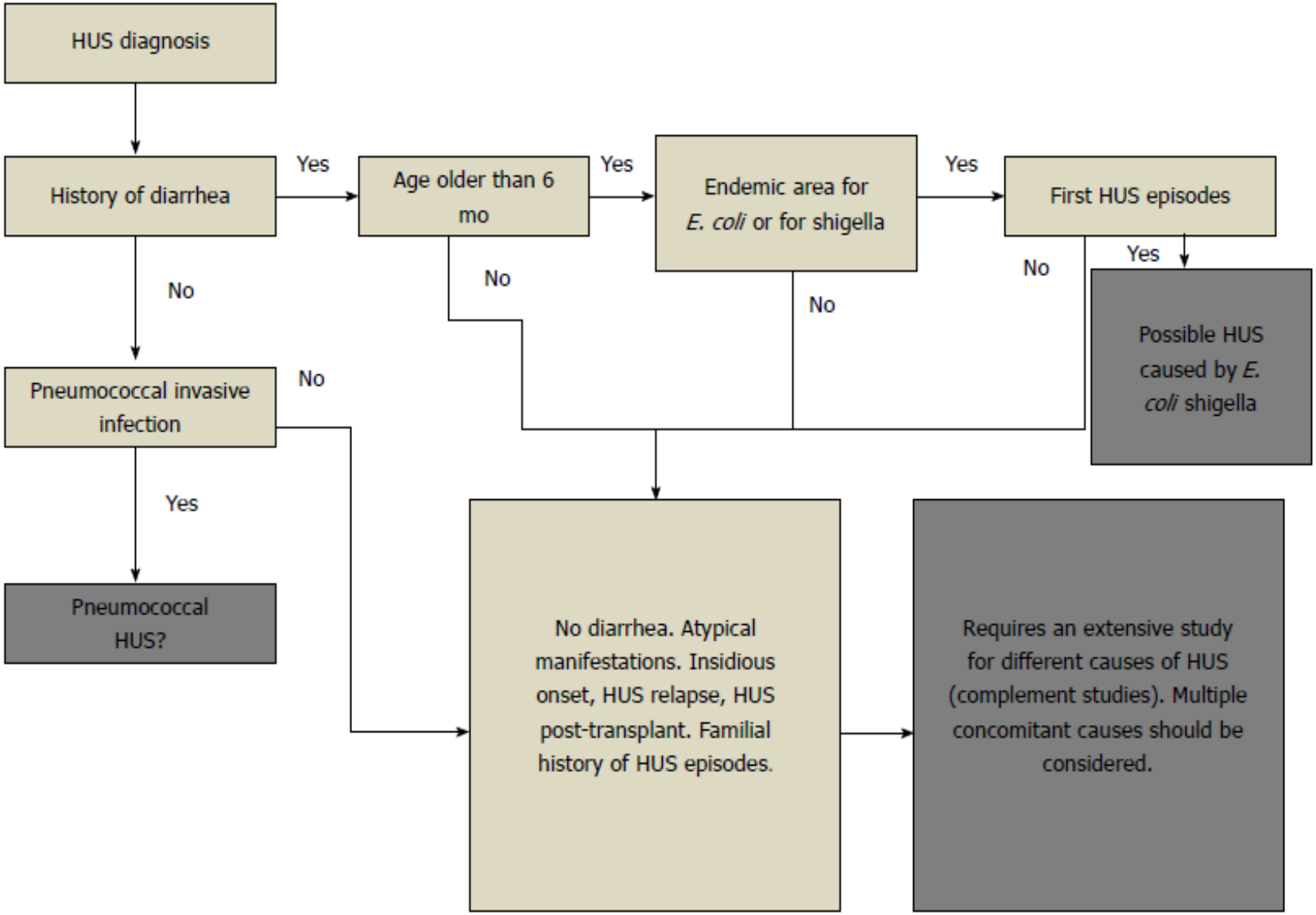

Figure 2 Diagnostic algorithm to distinguish among different Hemolytic uremic syndrome. HUS: Hemolytic uremic syndrome; *E. coli*: *Escherichia coli*.

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HEMOLYTIC UREMIC SYNDROME, ATYPICAL

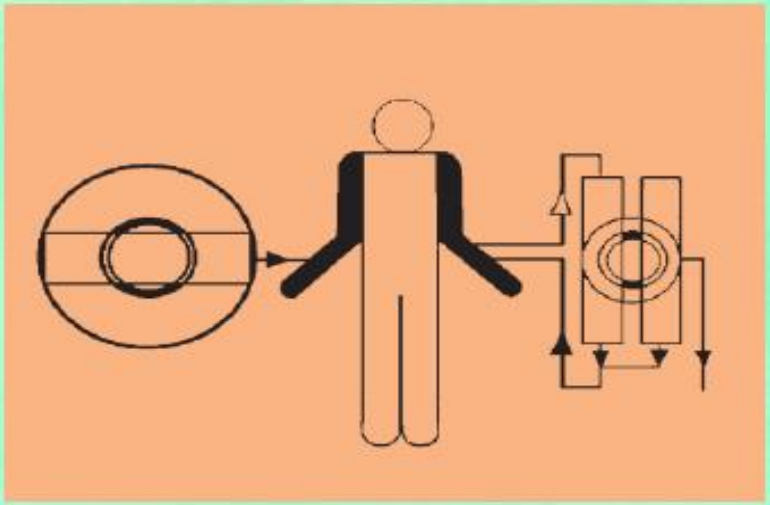
Incidence: 3.3/1,000,000/yr (<18 yo); 7/1,000,000/yr (children in European community)

Condition	Procedure	Recommendation	Category
Complement factor gene mutations	TPE	Grade 2C	II
Factor H autoantibodies	TPE	Grade 2C	I
MCP mutations	TPE	Grade 1C	IV

# of reported patients*: >300

	RCT	CT	CS	CR
Complement factor gene mutations	0	0	4(23)	21(26)
Factor H autoantibody	0	0	2(6)	2(2)

MCP = membrane cofactor protein



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Atypical Hemolytic Uremic Syndrome

- 5-10% of HUS cases
- Incidence of 3-7 per million per year
- Noninfection-related
- Poorer prognosis and outcome
  - 2/3 die, require dialysis, or have permanent kidney injury during the first year
- Sporadic or familial
- About two-thirds are associated with genetic or acquired disorders of regulatory components of the complement system

Atypical HUS: Classification

Table 1. **Classification of Atypical Hemolytic–Uremic Syndrome.***

Form of Disease	Complement Abnormalities
Familial	Mutations in *CFH*, 40–45%; in *CFI*, 5–10%; in *C3*, 8–10%; in *MCP*, 7–15%; in *THBD*, 9%; and in *CFB*, 1–2%.
Sporadic	
Idiopathic	Mutations in *CFH*, 15–20%; in *CFI*, 3–6%; in *C3*, 4–6%; in *MCP*, 6–10%; in *THBD*, 2%; and in *CFB*, 2 cases; anti-CFH antibodies: 6–10%
Pregnancy-associated	Mutations in *CFH*, 20%; in *CFI*, 15%
HELLP syndrome	Mutations in *CFH*, 10%; in *CFI*, 20%; and in *MCP*, 10%
Drugs	Rare *CFH* mutations (mostly unknown)
Organ transplantation	Mutations in *CFH*, 15%; in *CFI*, 16%
Human immunodeficiency virus infection	Unknown†
Cancer	Unknown†

* HELLP denotes hemolytic anemia, elevated liver enzymes, and low platelet count.
† There are no published data on the frequency of complement gene mutations or anti-CFH autoantibodies in patients with this condition.

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Pregnancy associated

- 8-18%
- Pregnancy associated TMA may be related to ADAMTS13 deficiency, complement dysregulation or unknown mechanisms. ADAMTS13-deficiency-related TMA occurs mainly during the second and third trimester of pregnancy.
- HELLP syndrome is considered a TMA-like disorder based on several similarities between HELLP and HUS/TTP. *Interestingly, some forms of HELLP syndrome share a common genetic risk factor of complement dysregulation with aHUS*
- The question of whether HELLP syndrome is a TMA is relevant because if the link between HELLP syndrome and complement dysregulation is confirmed, complement inhibition may represent a treatment for severe HELLP syndrome.

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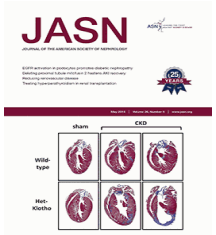
Pregnancy associated

- TMA may also occur in the post-partum period.
- It is associated with alternative C3 convertase dysregulation.
- In a recent review of 21 cases of pregnancy-related aHUS from the French aHUS registry, 80% of patients had abnormal complement dysregulation.

Fakhouri F, Roumenina L, Provot F, Sallée M, Caillard S, *Couzi L, Essig M, Ribes D, Dragon-Durey MA, Bridoux F, Rondeau E, Frémeaux-Bacchi V. Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. J Am Soc Nephrol 2010;* ***21: 859-867***



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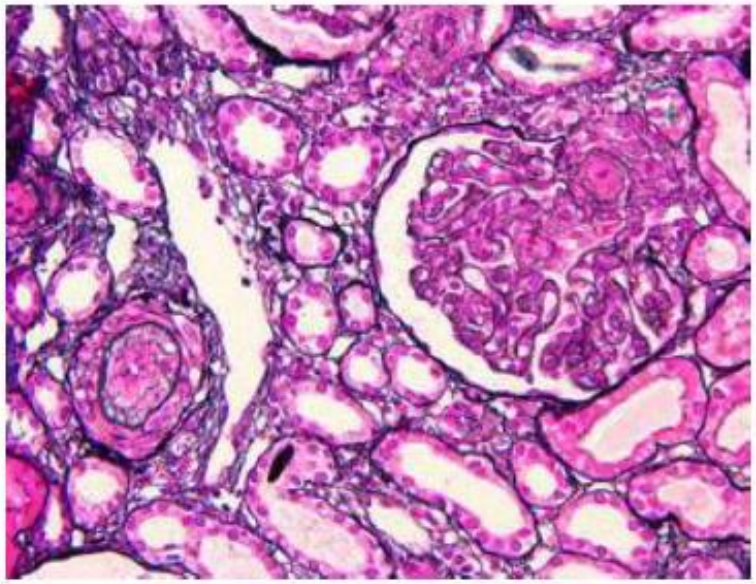
Pathogenesis of aHUS



- PAS section showing obliterated arteriolae, mesangial infiltration, narrowing of the capillary lumina

- Endothelial injury
- Formulation of platelet-fibrin hyaline micro-thrombi
- Occlusion of arterioles and capillaries
- NEW INSIGHTS:
  - Caused by uncontrolled activation of the alternative complement system

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Main Complement Regulators Involved in the Alternative Complement Pathway

Table 1 | Main complement regulators involved in the alternative pathway and their function

Complement regulator name	Abbreviation/ alternative names	Function
Factor I	CFI	Plasma serine protease that cleaves C3b, producing inactive iC3b, in the presence of soluble cofactors and/or membrane-bound complement regulators
Factor H	CFH	Plasma molecule that recognizes C3b and cell surfaces through the C-terminus, whereas the N-terminus region mediates cofactor activity for CFI; CFH also directly accelerates the decay of C3-convertase C3b/Bb
Membrane cofactor protein	MCP/CD46	Integral transmembrane protein that binds C3b and C4b and serves as a cofactor for CFI
Thrombomodulin	THBD	Transmembrane protein; in addition to its well-established anticoagulant function, it is involved in the generation of thrombin-activatable fibrinolysis inhibitor, a plasma carboxypeptidase B that cleaves C3a and C5a; thrombomodulin binds to C3b, accelerating its inactivation by CFI in the presence of CFH
Decay accelerating factor	DAF/CD55	Phosphatidylinositol-anchored glycoprotein that prevents the assembly of the C3b/Bb complex or accelerates its decay
Protectin	CD59	Phosphatidylinositol-anchored glycoprotein that binds C5b/C6/C7/C8, preventing C9 from binding and polymerizing

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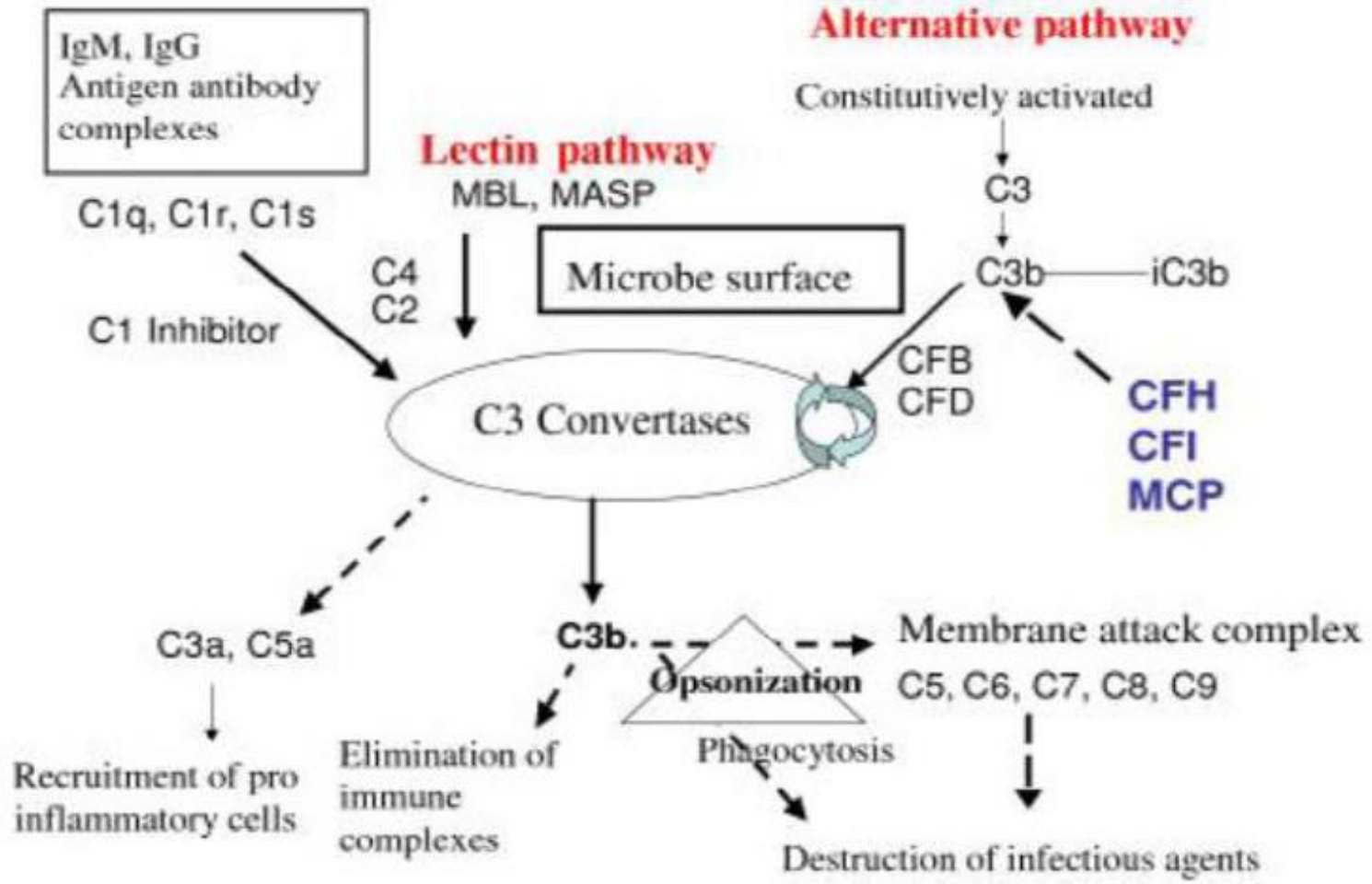
Complement Activity and aHUS



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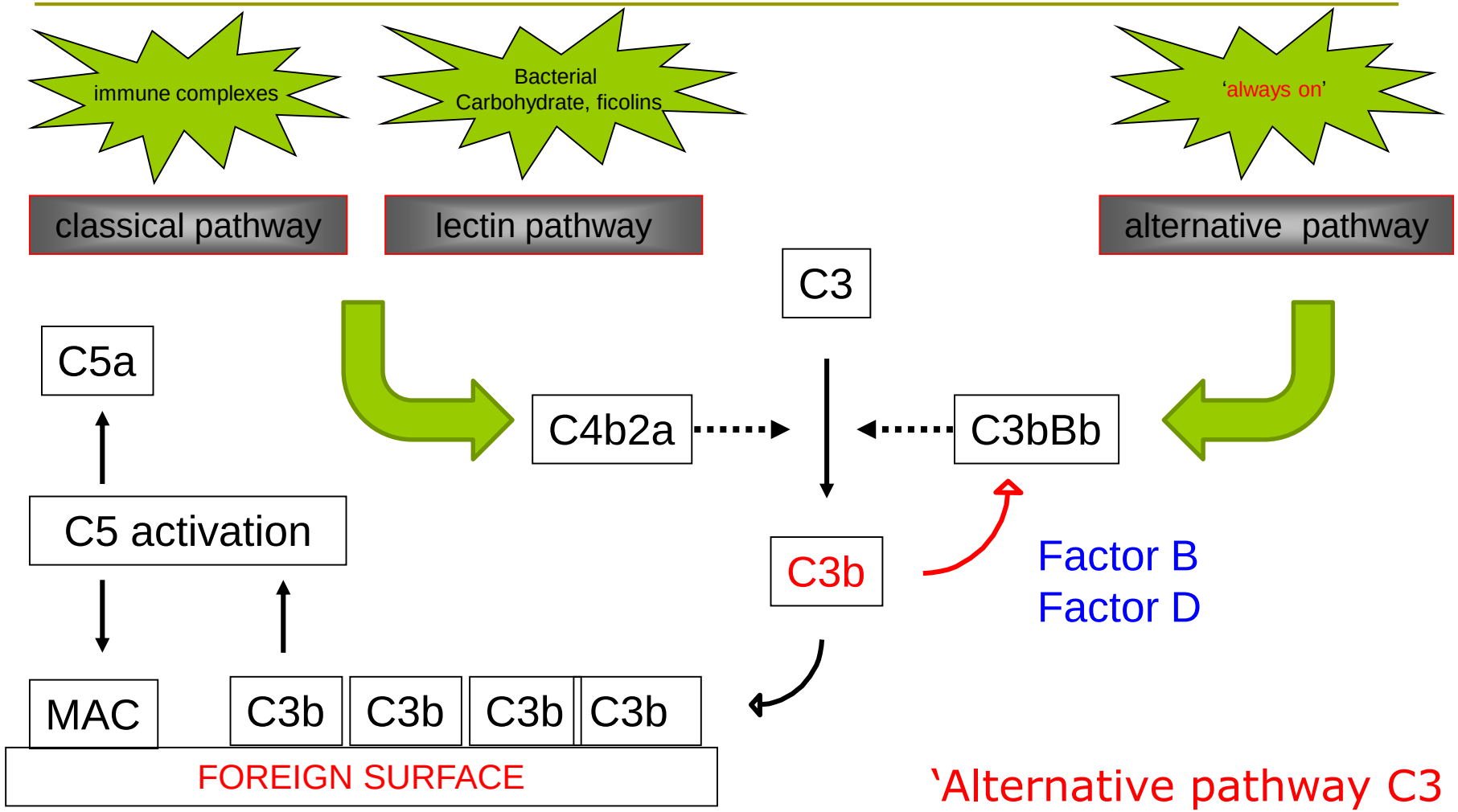
Complement activation



'Alternative pathway C3 amplification loop'

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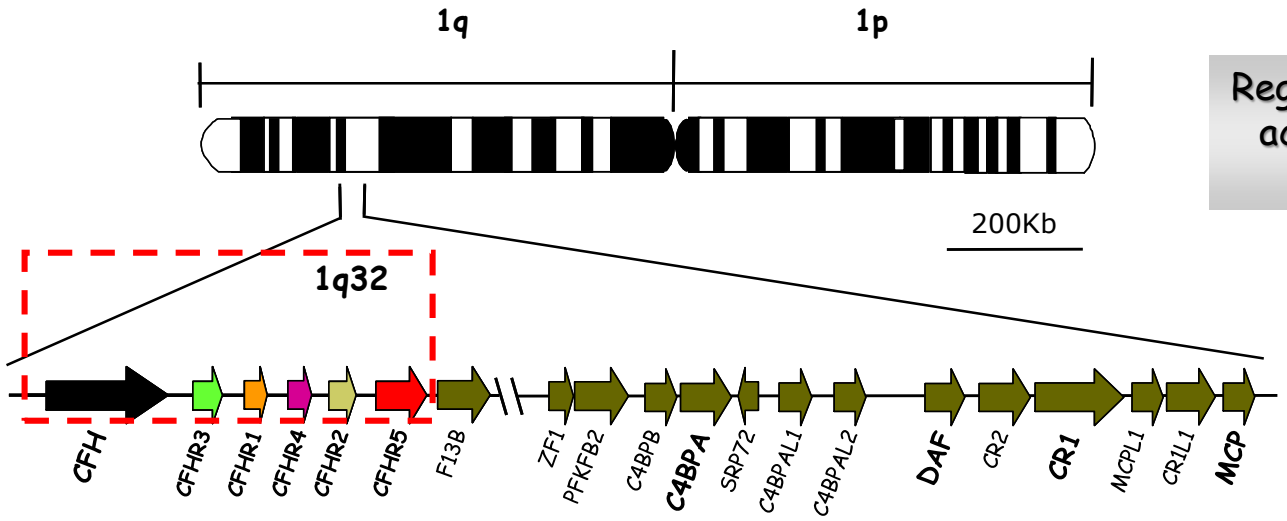
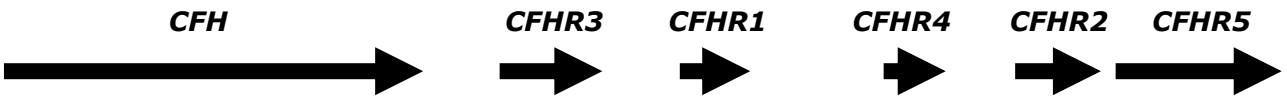
The factor H family



Regulators of complement activation gene cluster (RCA)



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F1000Prime REPORTS

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Management of hemolytic uremic syndrome

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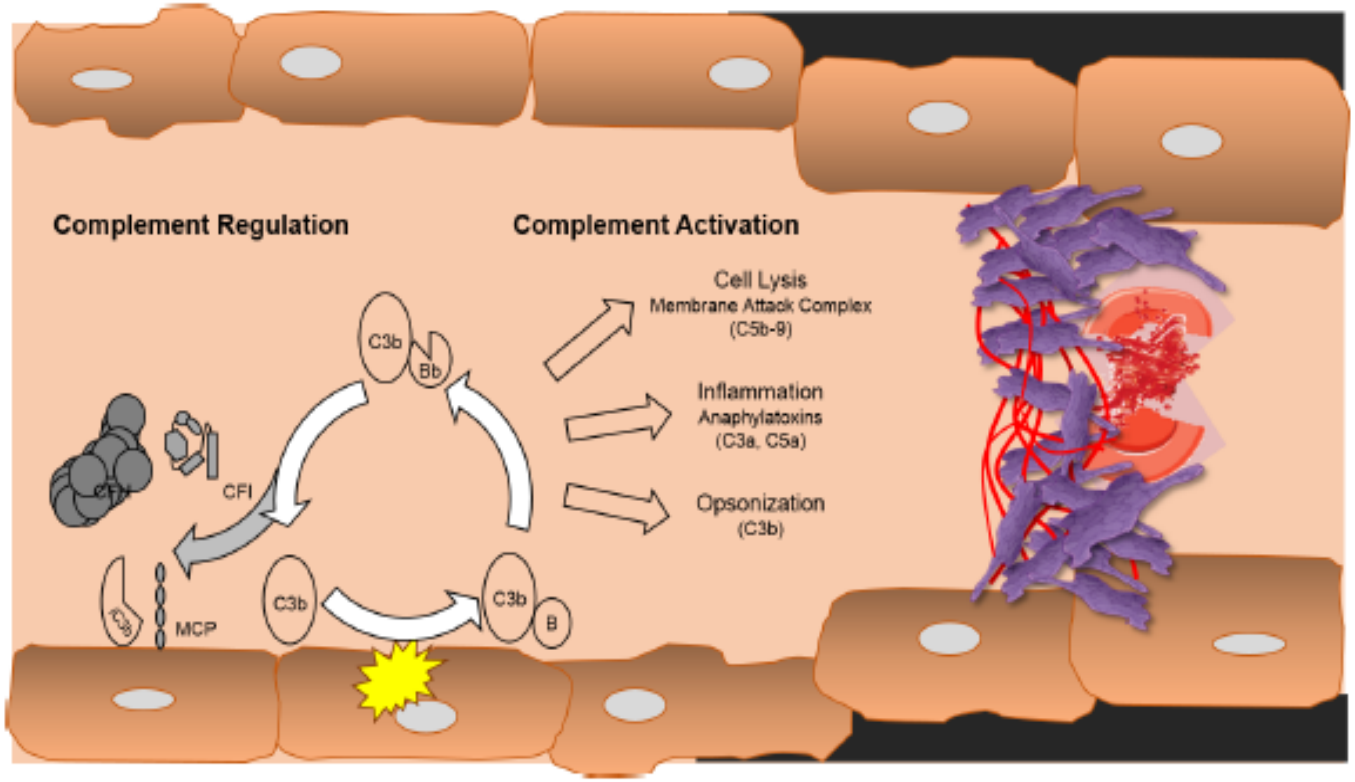
Figure 3. Complement activation in atypical hemolytic uremic syndrome



The complement system, through the alternative pathway, is in a state of continuous low-level activation with generation of a fluid phase C3 convertase ($C3H_2OBb$). This generates the fragment of C3, C3b, which can bind to cell membranes, which leads to cell-bound C3 convertase. If unchecked, this process leads to rapid amplification of complement activation and generation of the effector proteins of the system: C5b-9, C3a, C5a, and more C3b. To prevent this, there are cell surface (or membrane co-factor protein [MCP]) and fluid phase—complement factor H and complement factor I (CFI)—inhibitors of complement activation. Failure to adequately control activation leads to endothelial injury, with thrombus formation, red cell fragmentation, and platelet consumption.

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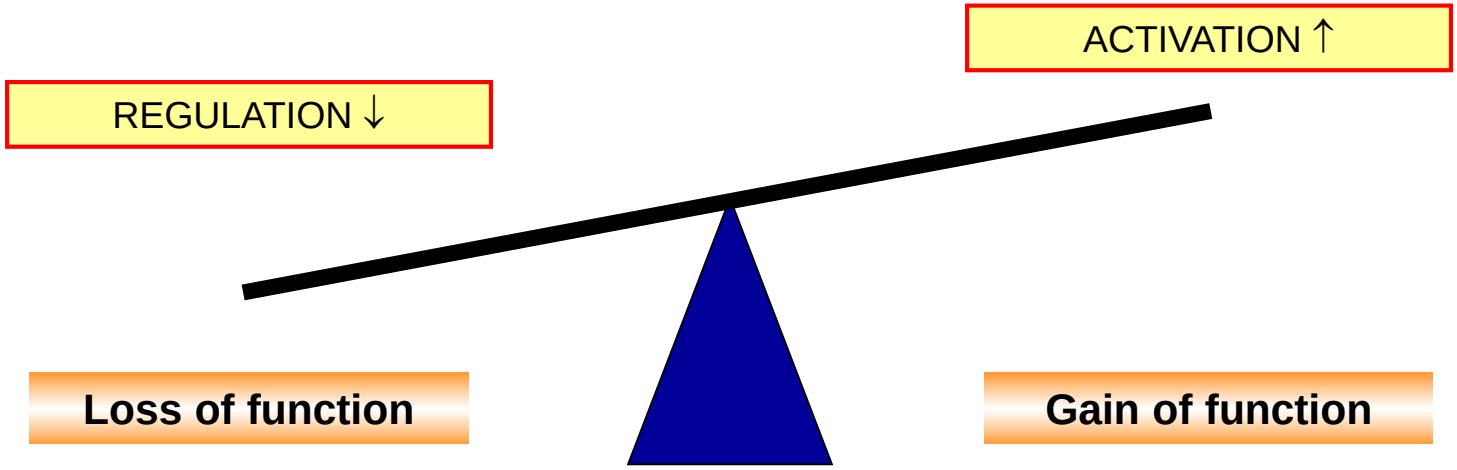
Atypical Haemolytic uraemic syndrome

- Impaired surface regulation



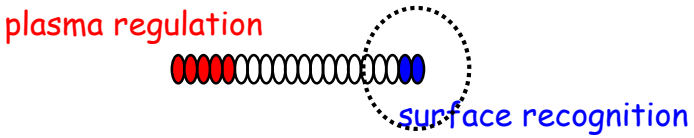


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Table 3 Gene mutation rate of different complement factors according r-hemolytic uremic syndrome registries data

Abnormality	Gene locus	Atypical HUS rate
Factor H	*CFH* (RCA:1q32)	11%-29%
Membrane co-factor protein	*MCP* (RCA)	3%-17%
Factor I	*CFI* (4q25)	2%-17%
C3	C3 (19p13)	2%-17%
Factor B	*CFB* (6p21)	0%-5%
Thrombomodulin	*THBD* (20p11)	0%-5%
Anti factor H autoantibodies		4%-13%

HUS: Hemolytic uremic syndrome.

Table 4 Main clinical characteristics of patients with atypical hemolytic uremic syndrome according complement abnormality

Gene	Atypical HUS incidence	Risk of death or renal failure within 1 yr	Risk of relapse	Relapse after transplantation	Plasma-therapy indication
CFH	20%-30%	50%-70%	50%	75%-90%	Yes
CFI	4%-10%	50%	10%-30%	45%-80%	Yes
MCP	5%-15%	0%-6%	70%-90%	< 20%	???
C3	2%-10%	60%	50%	40%-70%	Yes
CFB	1%-4%	50%	100%	100%	Yes
THBD	3%-5%	50%	30%	1%	Yes
Anti-CFH Ab	6%	30%-40%	40%-60%	Yes	Yes

HUS: Hemolytic uremic syndrome

Laboratory Diagnosis of aHUS

- Conventional complement tests: C3, C4, CH50, AH50
  - Abnormal in 30%
  - Not specific for aHUS
- Plasma CFH and CFI protein concentrations
  - Decreased in 30% of patients with CFH or CFI mutations
- Mutation analysis (CFH, MCP, CFI, CFB, C3, THBD)
  - Abnormal in 40% (sporadic) - 70% (familial)
- CFH antibody
  - 5% - 10%

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Thrombotic thrombocytopenic purpura

- TTP is an uncommon thrombotic microangiopathy that is primarily observed in adults, often with central-nervous system involvement, a high relapse rate and with a mortality rate of 15%-20% also in patients treated by plasma exchange.

- Due to its potentially similar clinical presentation,a differential diagnosis of HUS D+ and aHUS should be considered.

- TTP is associated with acquired (or less commonly genetic) ADAMTS13 deficiency.

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Pathophysiology

- ADAMTS13 is a disintegrin and metalloprotease that cleaves vWF.
- vWF is central in hemostasis, because it induces platelets aggregation and thrombus formation on the damaged endothelium.
- ADAMTS13 then degrades vWF into progressively smaller circulating products.
- The deficit is more commonly acquired and caused by anti-ADAMTS13 antibodies. Severe ADAMTS13 deficiency is required to cause TTP and is variably defined as < 5% or < 10% of normal protease activity.

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Management of hemolytic uremic syndrome

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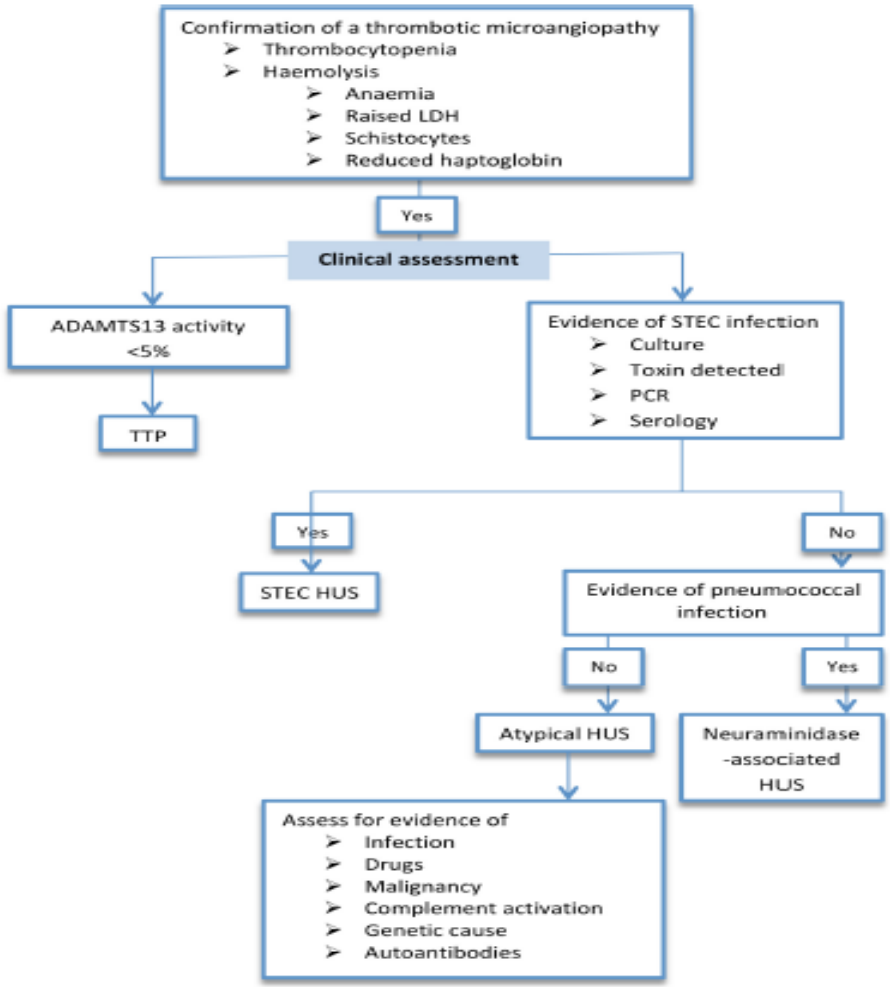
The electronic version of this article is the complete one and can be found at: http://f1000.com/prime/reports/m/6/119

Figure 2. Algorithm for the diagnosis of the main types of thrombotic microangiopathy



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Management

- Conservative
  - Monitor fluid balance, sodium, potassium, H^+,BP
  - Furosemide may be useful early
  - Sodium, protein restriction; high calorie intake
  - Transfuse with caution
  - Avoid antibiotics/anti-motility agents/NSAID
- Transfer to regional centre
  - Oliguria +
    - Fluid overload, need for transfusion, high K
  - Anuria
  - Complications of D+ HUS

Prognosis and follow-up

- BCH (n=250) 56% required acute dialysis
- Prognostic markers
  - Neutrophils >20 at presentation
  - Dialysis > 2weeks
- Mortality
  - 5% (BPSU 1985-88)
  - 1.8% (BPSU 1997-2001)
- Long term: HBP, reduced GFR, proteinuria
  - Variable in studies, probably 20-30%
  - BCH n=201 19% poor outcome at 5,10,or 15 yrs

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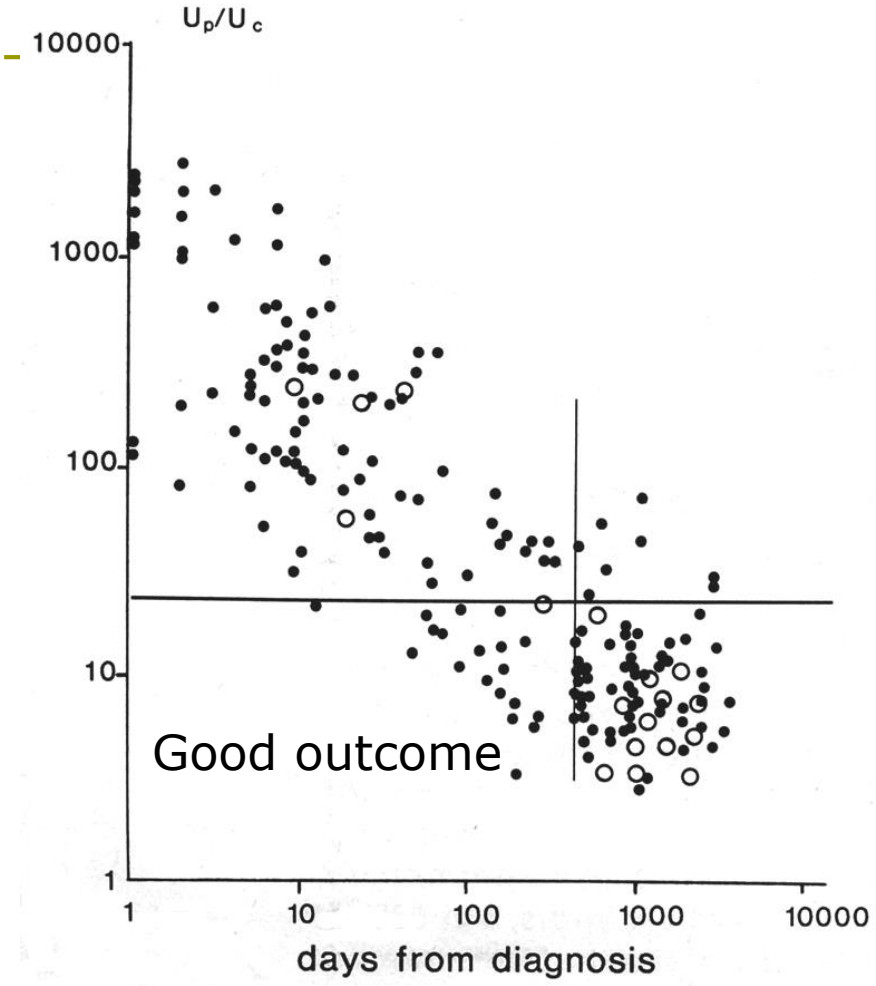
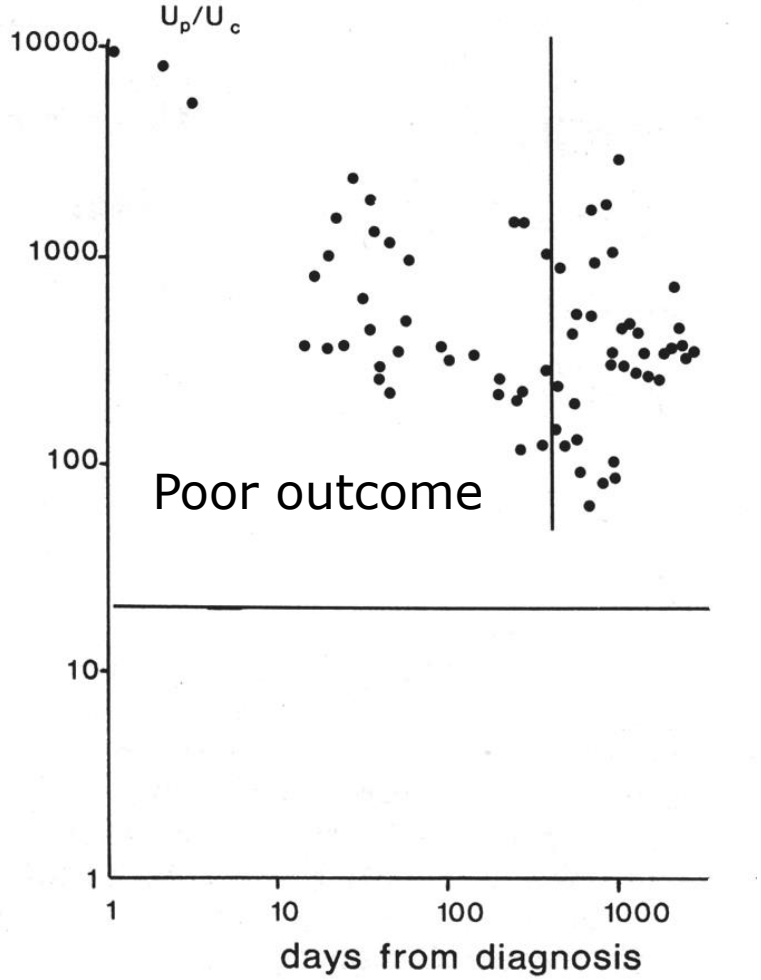
Proteinuria at 1 year and outcome





J Pediatr 1991; 118:191-4

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- Follow-up
  - Frequently until Hb and creatinine normal
  - BP, PCr and EMU protein at 1 year after illness
  - BP, EMU protein, formal GFR, renal USS at 5 years and every 5 years until post pubertal
  - BP, EMU protein by GP at intervals once discharged
- Lifestyle advice
  - Avoid overweight, high sodium intake
  - Avoid smoking
  - Girls need renal function/proteinuria monitoring during pregnancy

Recommedations

- Immunosuppresion: steroids-rituximab
- Renal transplantation:

  relapse

  living donor

  plasma therapy

Combined liver-kidney transplantation should be undertaken in patients with aHUS due to CFH or CFI mutation.

Plasma therapy before and during surgery may improve outcomes.

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Role of TPE in atypical HUS

- Therapeutic plasma exchange has been first-line treatment for all aHUS
- Can remove auto-antibody or mutated circulating complement regulators while replacing absent or defective complement regulators
- No prospective trials
- More recently, Eculizumab used in plasma-resistant atypical HUS

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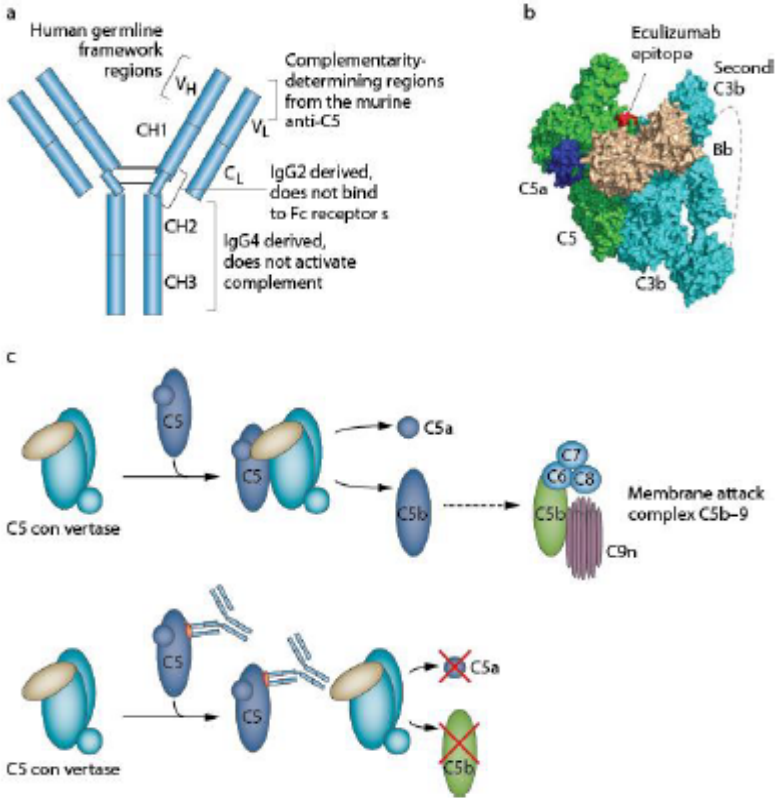
Use of Eculizumab for atypical hemolytic uremic syndrome

(Nat Rev Nephrol 2012)



- Humanized monoclonal antibody that functions as a complement inhibitor by blocking cleavage of C5 into C5a and C5b and decreasing formation of membrane attack complex

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Clinical Trials of Eculizumab for aHUS

	C08-002	C08-003	C09-001
Design	Prospective	Prospective	Retrospective
Patient age (median, y)	Adolescent-adult (28)	Adolescent-adult (28)	Children-Adult
Number	17	20	30 (19, <18 y)
Genetic mutations	76%	70%	53%
Months from Dx, median (range)	10 (0.26 – 236)	48 (0.66 – 286)	-
Entry status	Active TMA	Maintenance PE/PI	-
Duration, median (range) in mo.	PE/PI ≥4x/week	10 (2.4 – 47)	-
Dosage[1]	900 mg qW x4, 1,200 mg at W5 & q2W		-
Duration, median (range) in wk.	38 (2-64)	40 (26-52)	28 (1-70)
PE/PI or new dialysis	0 (0 – 0.31)	0	0
eGFR ↑, median (range), mL/min/1.73 m^2	+20 (-1, 98)	+5 (-1, 20)	≥15: 47%
Event free survival[2]	15 (88%)	16 (80%)	-
Normal platelet count & LDH	13 (76%)	18 (90%)	17 (89%)

[1]Adult dosage
[2]Event free survival (events: platelet count decrease >25%, PE/PI, new dialysis)

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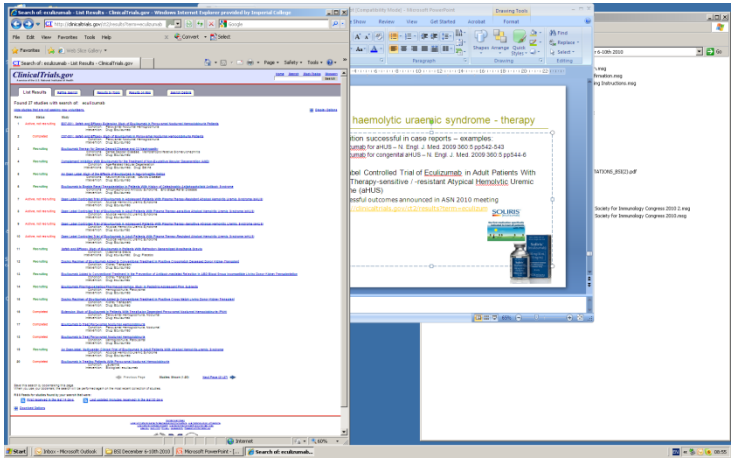
Greenbaum LA et al, Licht C et al, JASN 2011;22:197A

Atypical haemolytic uraemic syndrome - therapy

- C5 inhibition successful in case reports – examples:
  - Eculizumab for aHUS – N. Engl. J. Med. 2009 360:5 pp542-543
  - Eculizumab for congenital aHUS – N. Engl. J. Med. 2009 360:5 pp544-6

- Open Label Controlled Trial of Eculizumab in Adult Patients With Plasma Therapy-sensitive / -resistant Atypical Hemolytic Uremic Syndrome (aHUS)
  - Successful outcomes announced in ASN 2010 meeting
  - http://clinicaltrials.gov/ct2/results?term=eculizumab



New therapies

- Several complement inhibitors are in phase-I or phase-IItrials. Several of these drugs attack C5, but, in contrast to eculizumab, they are small molecules that are less immunogenic and have a potential for oral absorption.

- Some new compounds have C3 as a target. Such compounds could be more effective, but they may also be less safe, having the potential to cause more infections and autoimmune disease.

- A further possibility is the replacement of endogenous complement regulators with plasma-purified or recombinant CFH.

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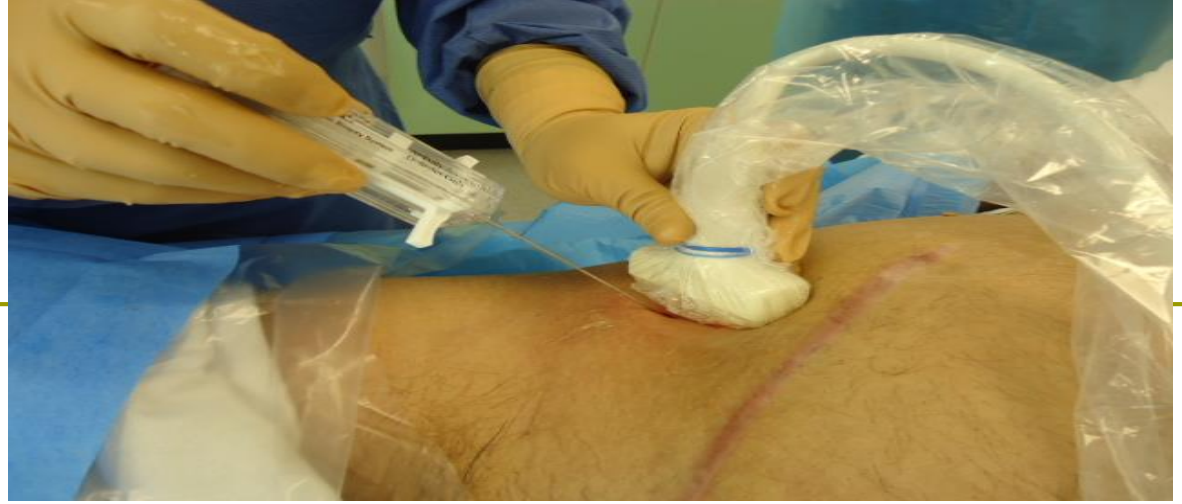
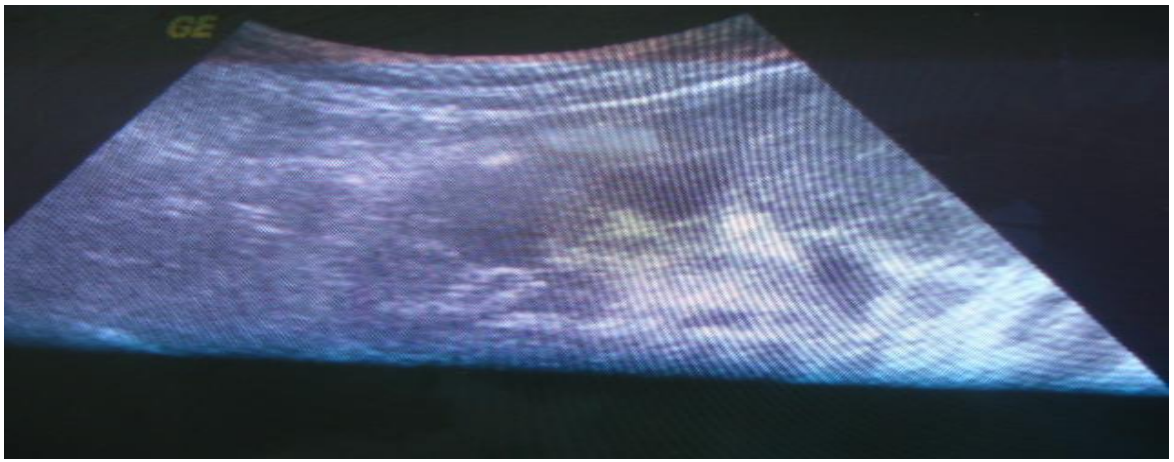
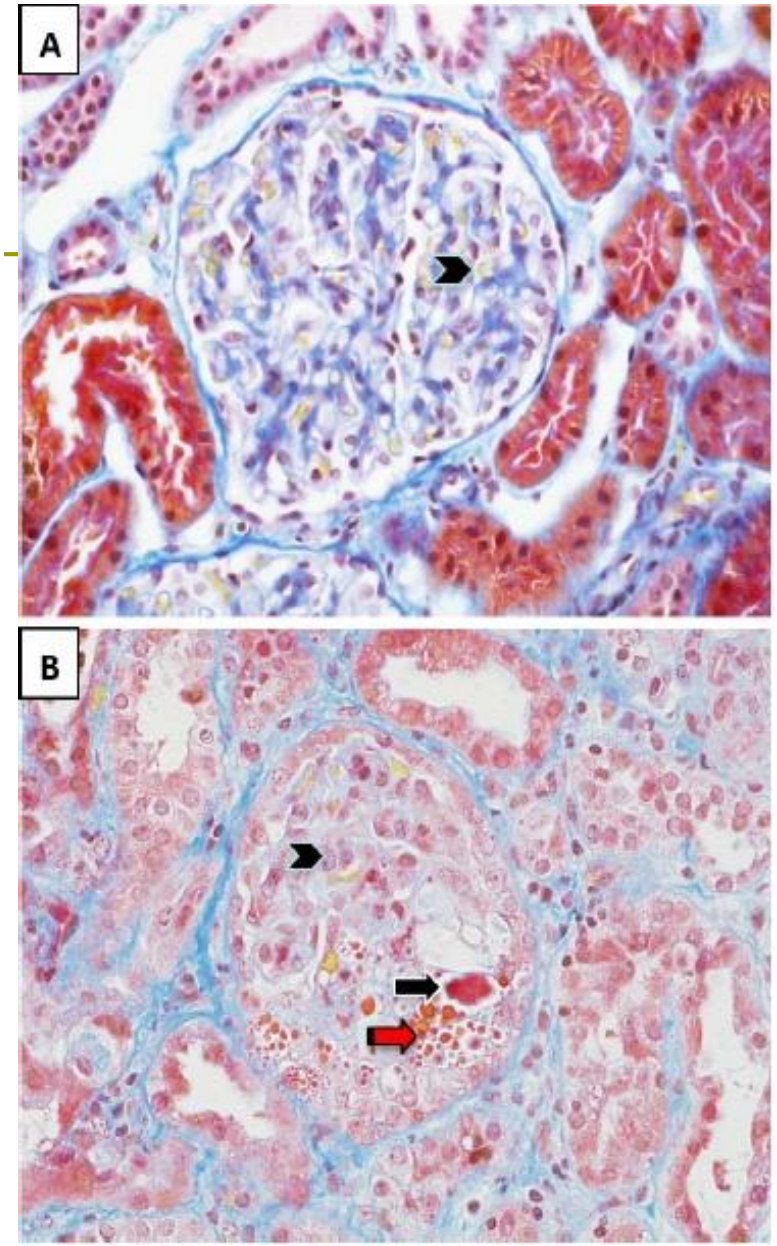




Calcineurin inhibitors and transplantation

Take Home Message

Core tip: Hemolytic uremic syndrome (HUS) is a rare disease, knowledge of which is rapidly increasing. The disease takes several forms, but recent data suggest that the physiopathologic basis in the vast majority of such diseases is complement dysregulation. New therapies are available, including a monoclonal antibody that blocks the C5 cascade. Such therapies lead to a substantial improvement in the outcome, which previously was often poor. HUS often occurs secondary to other diseases. In such cases, diagnosis may be difficult due to the overlapping of two diseases. Complement dysregulation has been found also in secondary HUS.



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Pregnancy associated

- 8-18%
- Pregnancy associated TMA may be related to ADAMTS13 deficiency, complement dysregulation or unknown mechanisms. ADAMTS13-deficiency-related TMA occurs mainly during the second and third trimester of pregnancy.
- HELLP syndrome is considered a TMA-like disorder based on several similarities between HELLP and HUS/TTP. *Interestingly, some forms of HELLP syndrome share a common genetic risk factor of complement dysregulation with aHUS*
- The question of whether HELLP syndrome is a TMA is relevant because if the link between HELLP syndrome and complement dysregulation is confirmed, complement inhibition may represent a treatment for severe HELLP syndrome.

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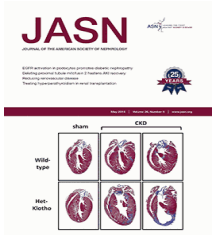
Pregnancy associated

- TMA may also occur in the post-partum period.
- It is associated with alternative C3 convertase dysregulation.
- In a recent review of 21 cases of pregnancy-related aHUS from the French aHUS registry, 80% of patients had abnormal complement dysregulation.

Fakhouri F, Roumenina L, Provot F, Sallée M, Caillard S, *Couzi L, Essig M, Ribes D, Dragon-Durey MA, Bridoux F, Rondeau E, Frémeaux-Bacchi V. Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. J Am Soc Nephrol 2010;* ***21: 859-867***



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How did these otherwise harmless E. coli become such killers?

- DNA from a Stx producing bacterium (Shigella dysenteriae type 1) transferred by bacteriophage to E. coli

- This provided E. coli with genes to produce Shiga toxin (Stx), one of the most potent toxins known to man

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Complement and tissue injury

Renal
Lupus nephritis, membranoproliferative glomerulonephritis, membranous nephritis, immunoglobulin A nephropathy, goodpasture syndrome, post-streptococcal glomerulonephritis and atypical haemolytic uraemic syndrome

Rheumatological
Systemic lupus erythematosus, lupus arthritis, rheumatoid arthritis, Sjögren's syndrome, Behçet's syndrome and systemic sclerosis

Neurological
Alzheimer's disease, multiple sclerosis, myasthenia gravis, Guillain-Barré syndrome, cerebral lupus and stroke

Infectious
Sepsis, viral infections, bacterial infections and fungal infections

Vascular
Myocardial infarction and atherosclerosis

Pulmonary
Adult respiratory distress syndrome, chronic obstructive pulmonary disease and cystic fibrosis

Haematological
Haemolytic anaemia, paroxysmal cold haemoglobinuria and paroxysmal nocturnal haemoglobinuria

Allergic
Anaphylactic shock, allergy and asthma

Dermatological
Vasculitis, pemphigus, bullous pemphigoid, phototoxic reactions and psoriasis

Other
Inflammatory bowel disease, thyroiditis, cryoglobulinaemia, foetal loss, organ graft rejection and age-related macular degeneration

Pathologies in which complement is activated

Disorders of complement

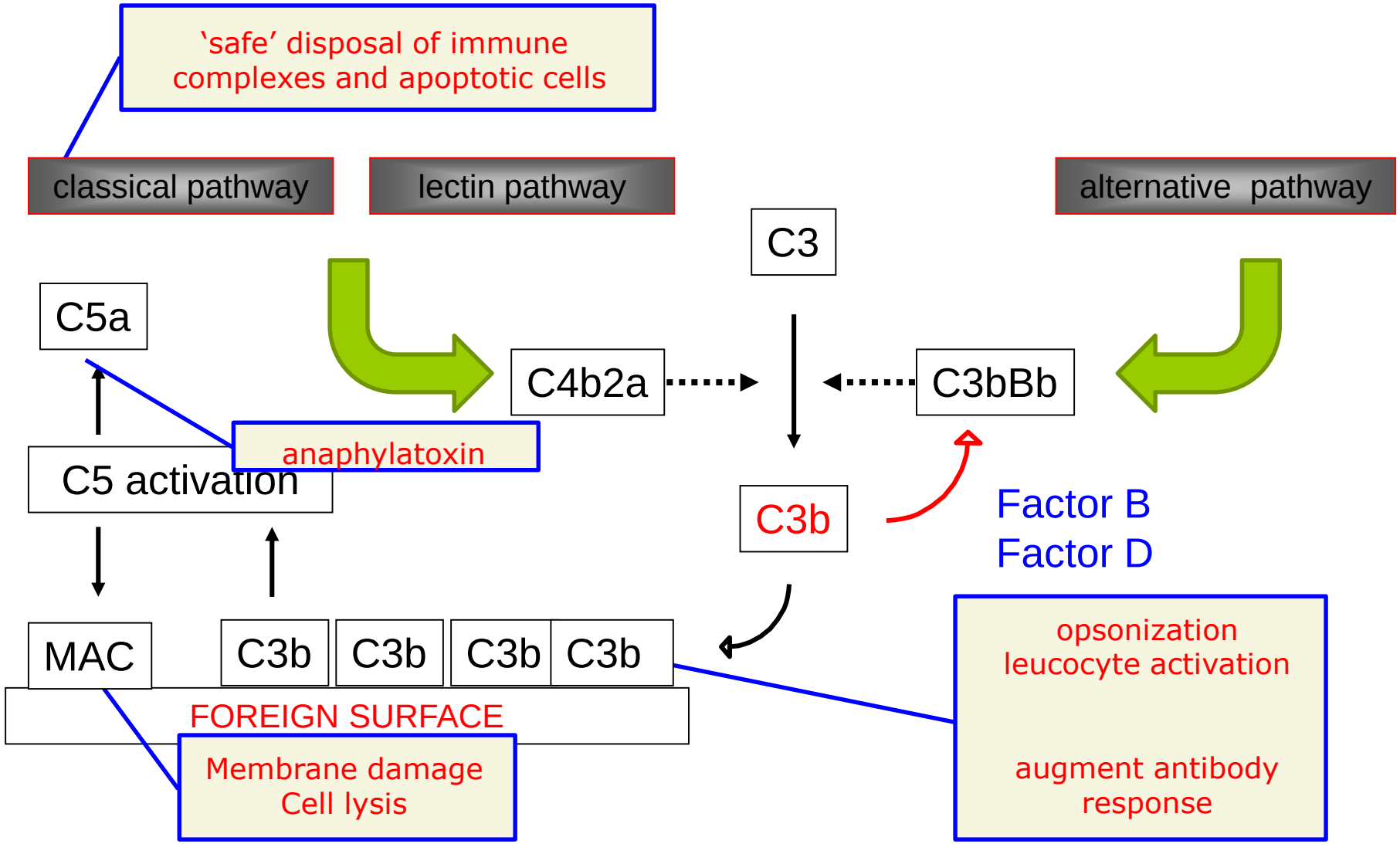
Activation protein deficiency → ‘too little’ complement

Tell us what might happen if we therapeutically inhibit complement

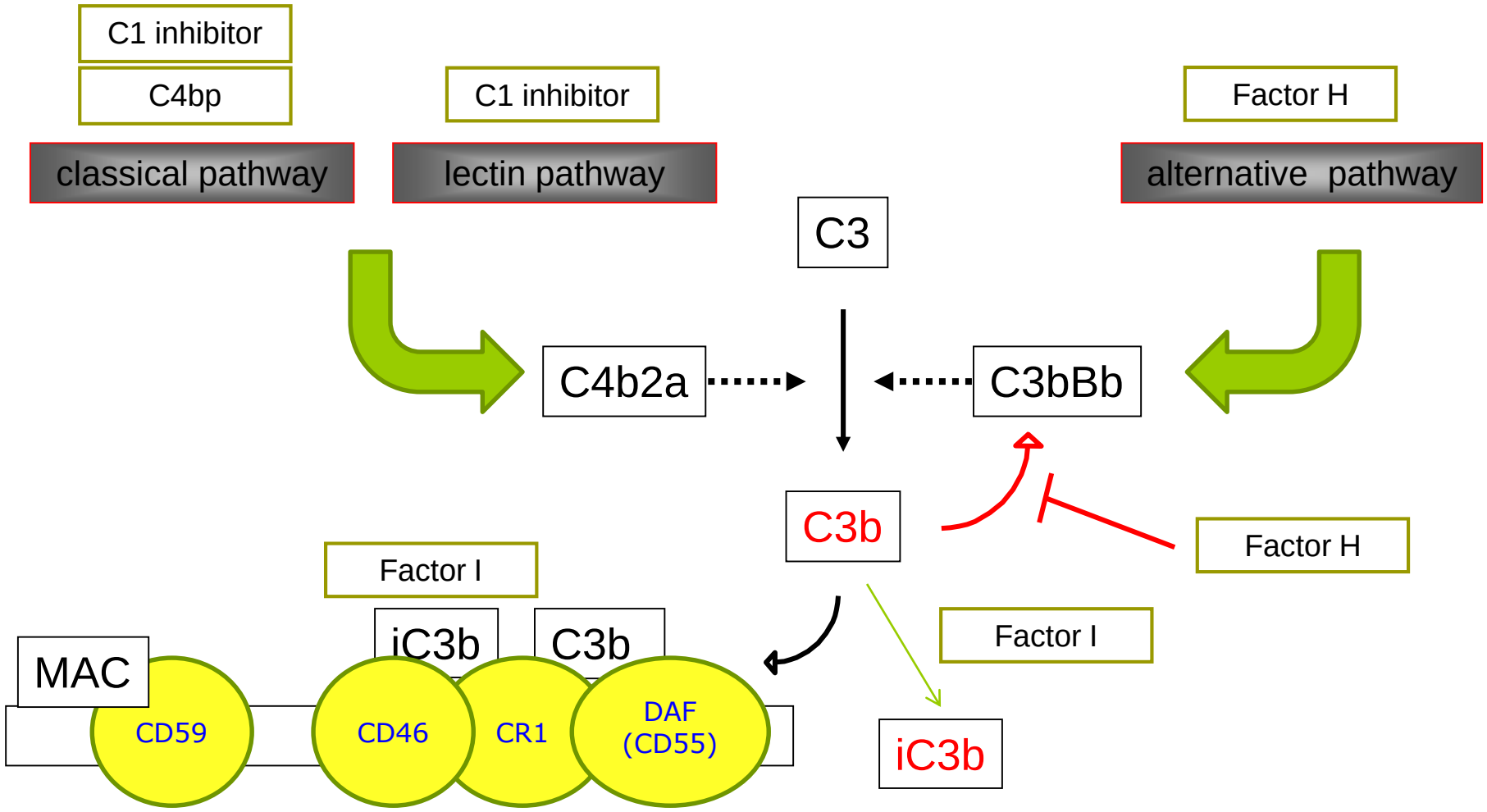
Regulatory protein deficiency → ‘too much’ complement’

Provide diseases in which complement inhibiting therapies ought to be effective

Complement function



Complement regulation

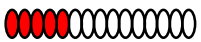


DAF – decay-accelerating factor

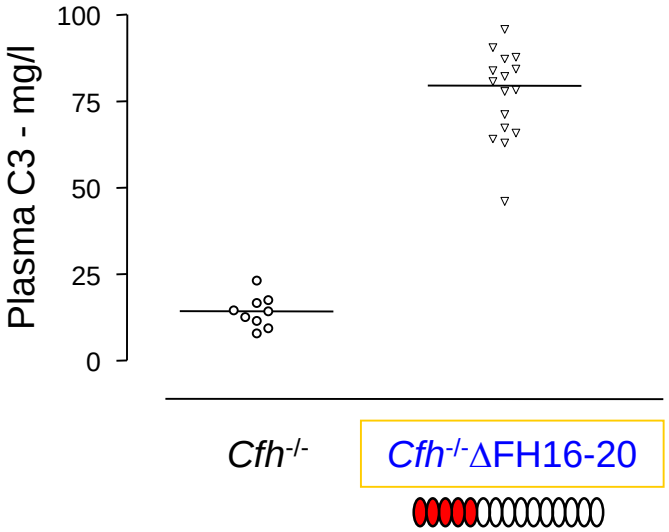
Murine model of factor H-associated atypical haemolytic uraemic syndrome

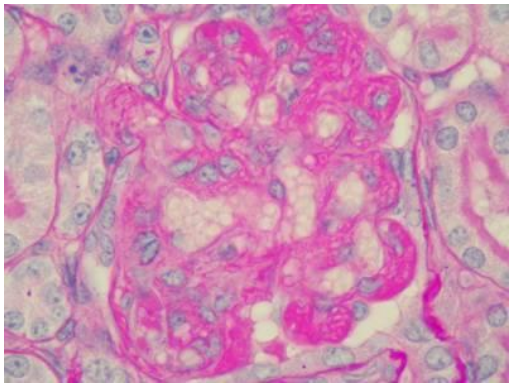
- Gene-targeted factor H-deficient mice transgenically expressing a mutant mouse factor H protein (FHΔ16-20)

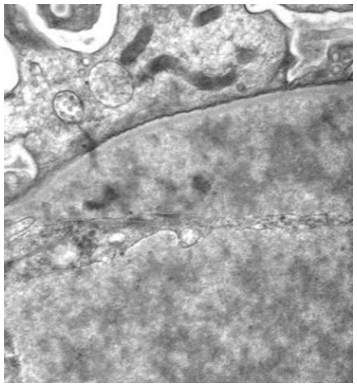
wild-type mouse CFH



Mutated mouse FHΔ16-20







Renal histology in *Cfh*$^{-/-}$.FHΔ16-20

The Development of Atypical Hemolytic Uremic Syndrome Depends on Complement C5

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J Am Soc Nephrol 22: 137–145, 2011

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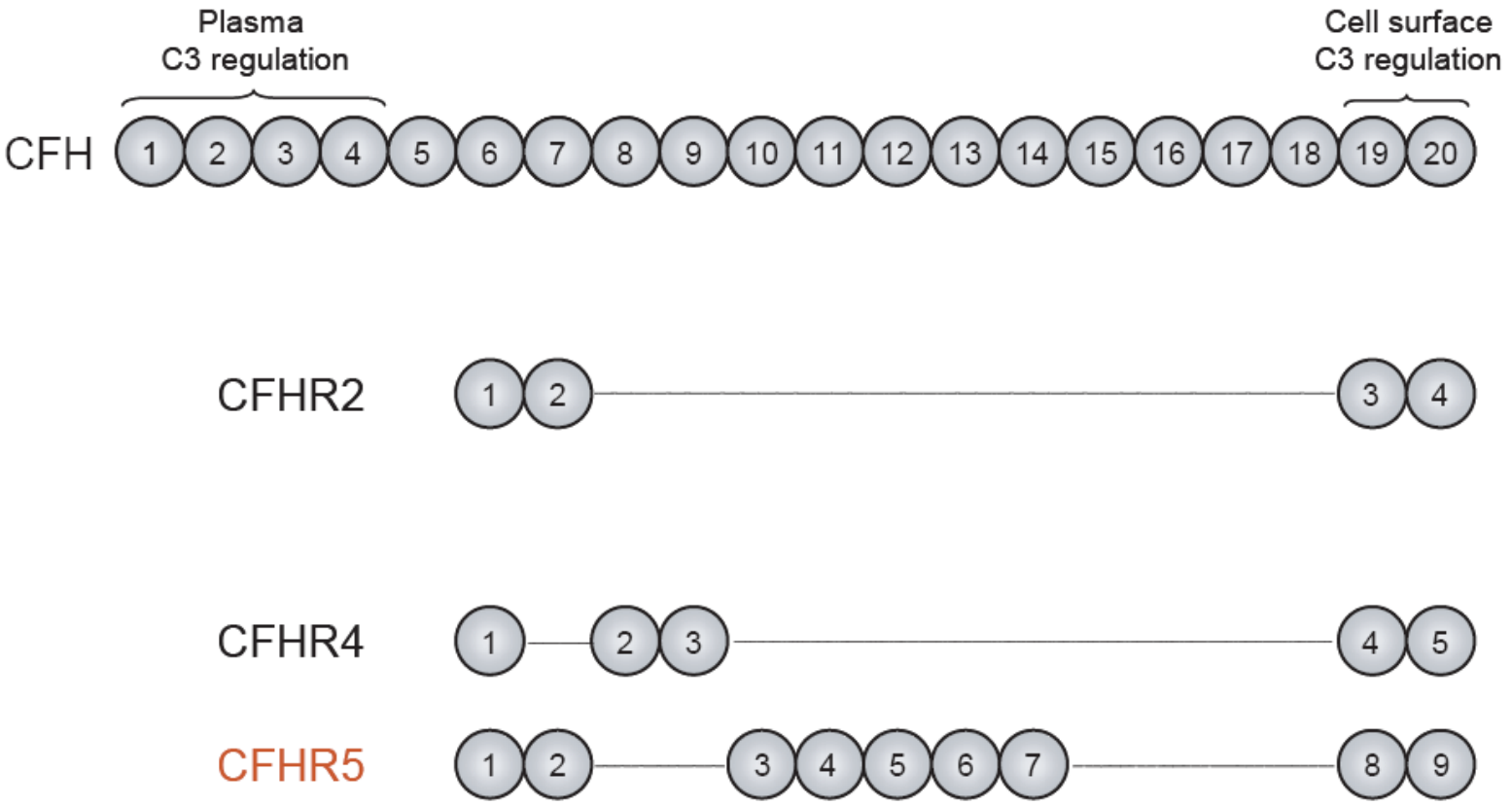
The factor H family



Deletion homozygotes:
Hageman et al, Ann. Medicine 2006

African American	16%
European Americans	4.7%

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