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CENTRE FOR NEPHROLOGY

ROYAL FREE

Complement, TMA and AKI

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Conflict of interest statement

Honoraria and consulting: Alexion, Otsuka

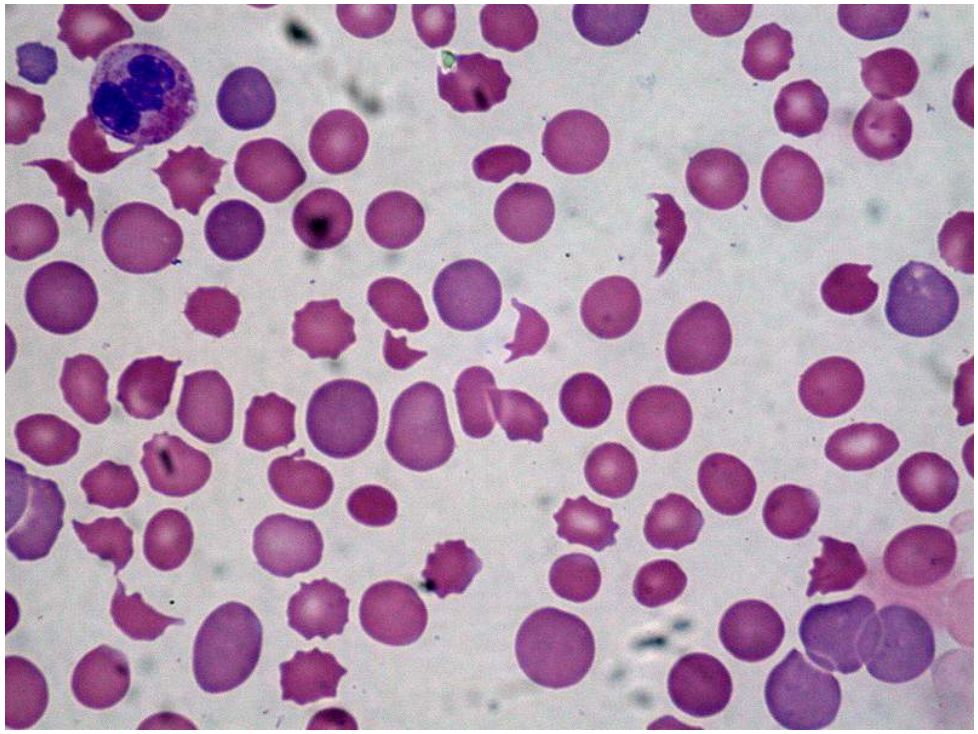
Case – presentation and history

- 28 year old Bulgarian woman, previously well
- Presented to local hospital at 3 am one Friday with abdominal pain, headache and vomiting for ~2 days
- Painless, patchy rash over the last 2 weeks associated with symptoms of a viral infection
- No diarrhoea
- No medications
- One daughter aged 6 (healthy)
- No significant family history

Examination

- Pale, tachycardic (HR 104 bpm), BP 140/90
- Apyrexial, respiratory rate 24/min, Sats 99% on air
- Very sparse and patchy purpuric rash on legs
- Euvolaemic
- Cardiovascular, respiratory, abdominal and neurological examination otherwise normal
- Urinalysis showed ++ haematuria
- Not pregnant

Labs



- Hb 8.3 g/dL
- Plt 65 x10^9/L
- LDH 1051 IU/L
  - Haptoglobin <0.2 g/L
- Blood film: microangiopathic haemolytic anaemia
- Creat 709 µmol/l
- LFTs, Ca^{2+}/PO_4^-, CK normal, CRP 29
- WBC/Coagulation normal, DAT -ve
- CXR, USS renal tract normal

Transferred to renal unit within 12h of presentation

Differential diagnosis

Differential diagnosis

- Haemolytic uraemic syndrome (HUS)
- Thrombotic thrombocytopaenic purpura (TTP)
- SLE ± antiphospholipid syndrome
- Accelerated hypertension (eg SRC) and PET
- Infection
  - HIV
  - Bacterial sepsis and DIC
  - Endocarditis
  - Leptospirosis
  - Brucellosis
  - Viral haemorrhagic fevers

  } LFTs usually deranged
- Drugs

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Management – general considerations

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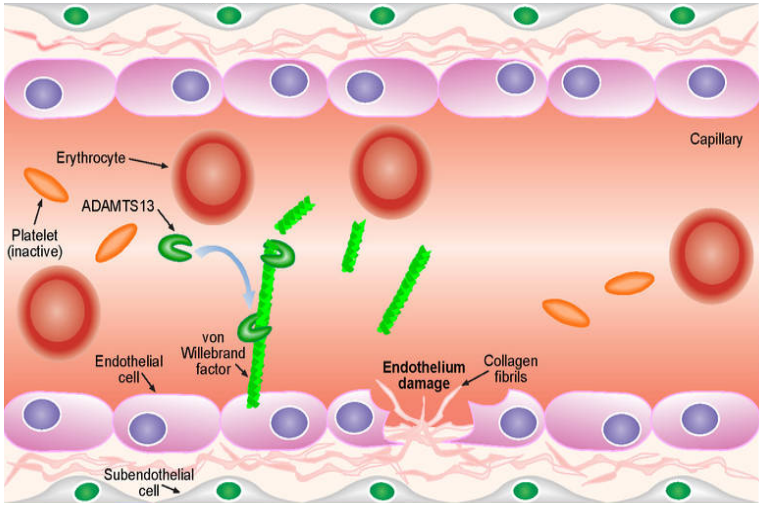
- Organ support

Management – general considerations

- Do not give platelets!!
  - Fuel to the fire
- Control BP
- Organ support
- Treat cause promptly
  - Specialised/confirmatory test results not always immediately available
  - Renal recovery often possible
  - Neurological deficits or death may occur

Pathophysiology of TMA

- Damage to endothelium of small vessels results in platelet aggregation, microthrombosis, infarction
  - Thrombotic microangiopathy
  - Abnormal blood film (MAHA) and end-organ damage
- Kidney and brain particularly susceptible
  - Heart, liver, gut, lungs also frequently affected
- Not always possible to determine cause from these clinical consequences
  - Different causes have different organ predilections
- **Treatment depends on underlying cause**



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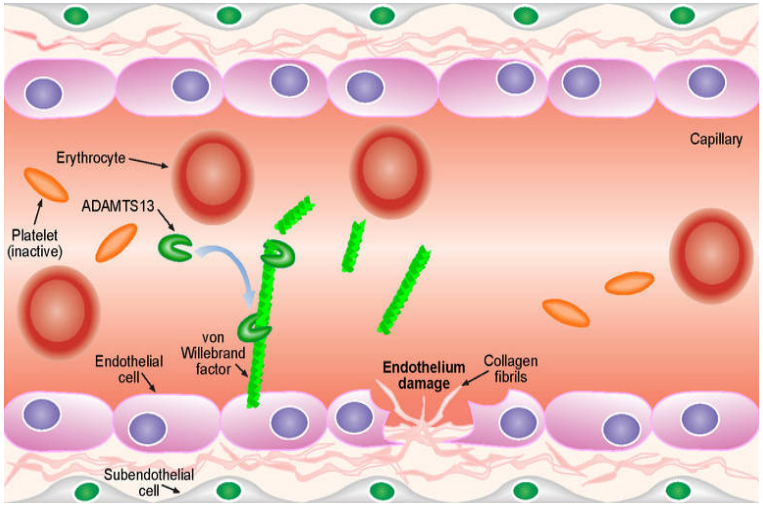
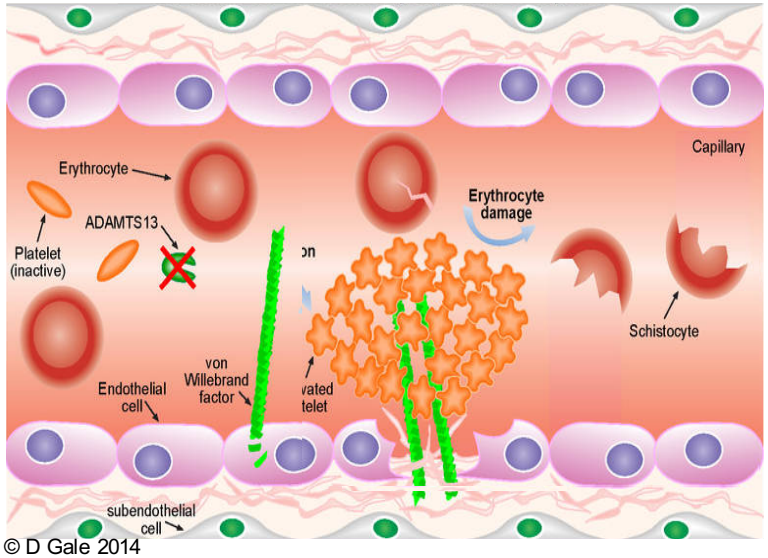
TTP



ADAMTS13 deficiency



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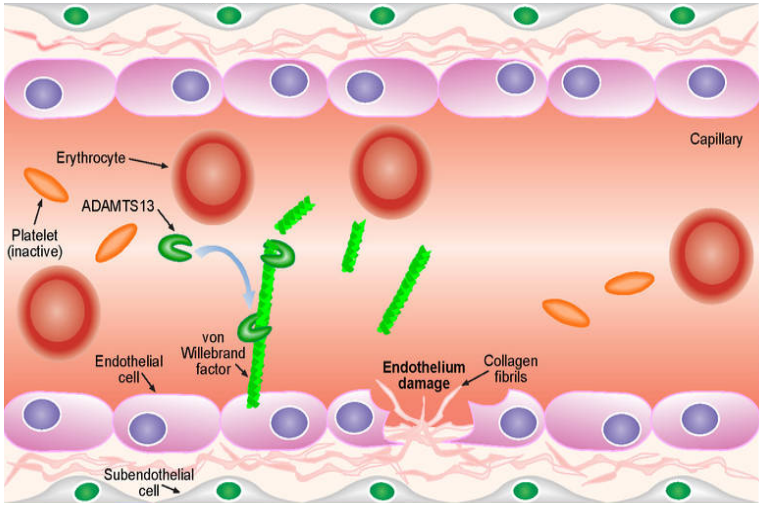

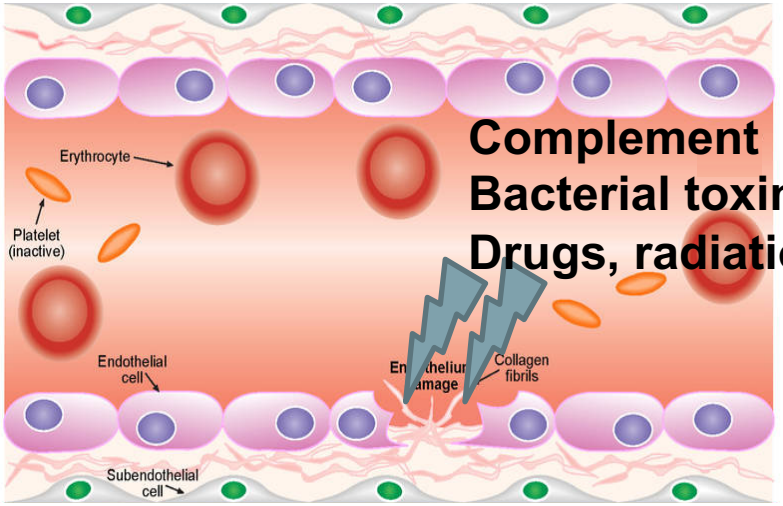

Complement
Bacterial toxins
Drugs, radiation etc

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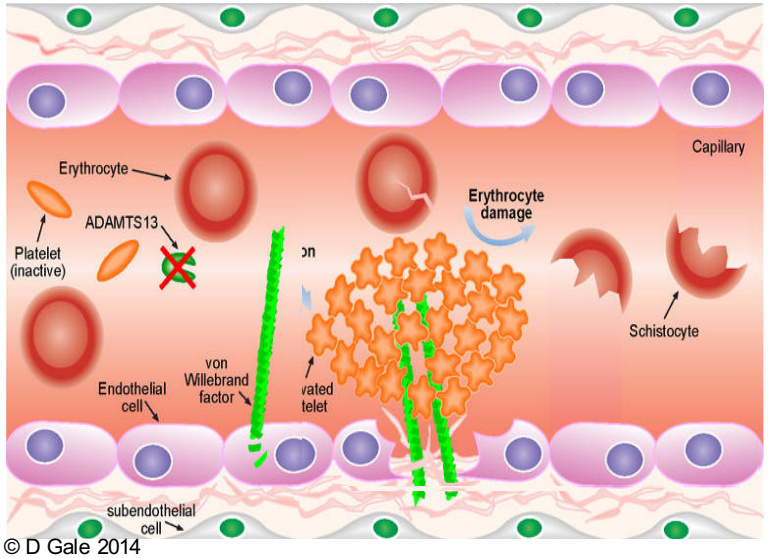

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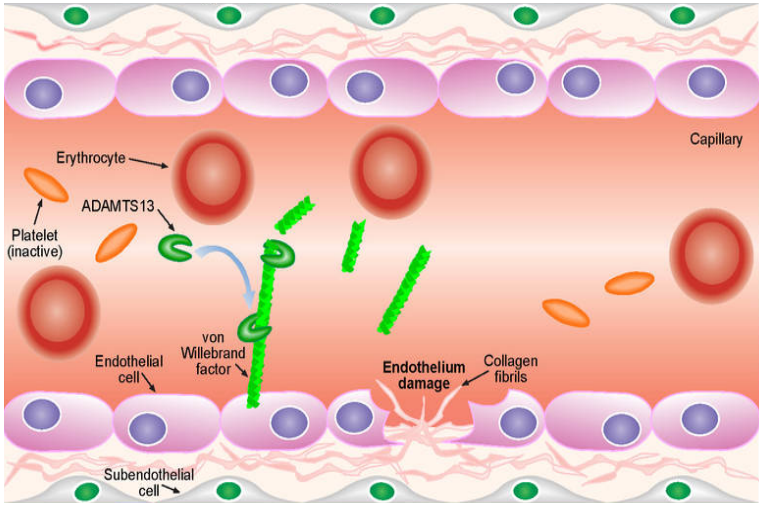

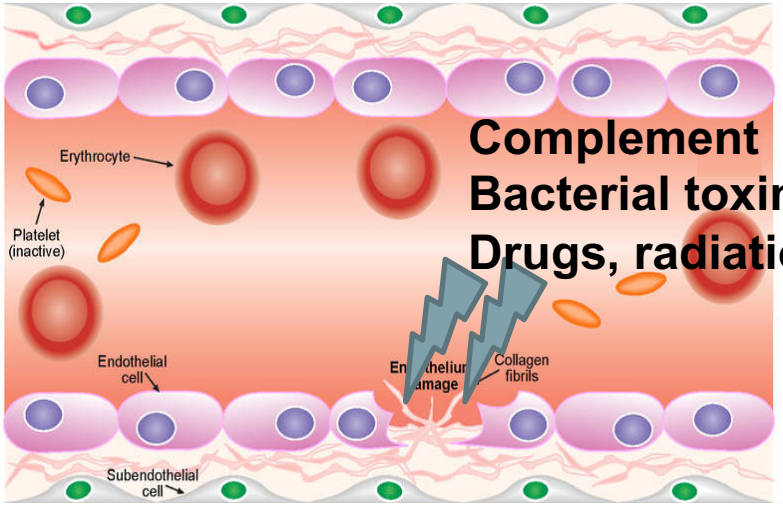

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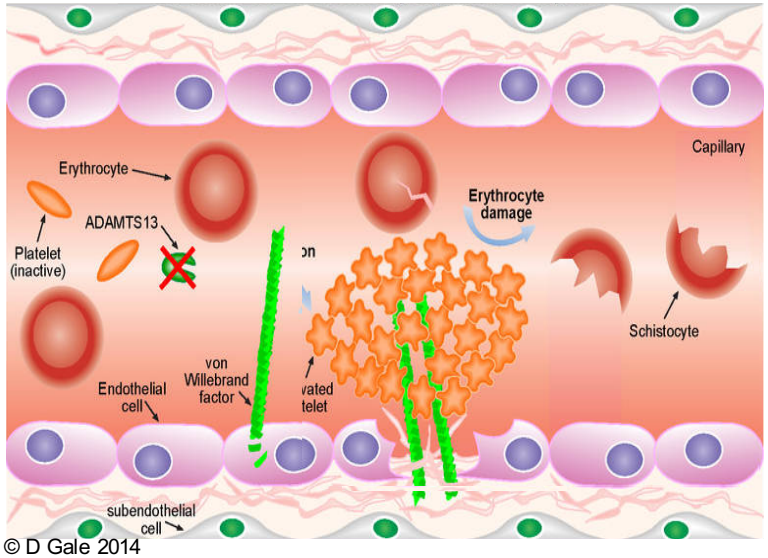
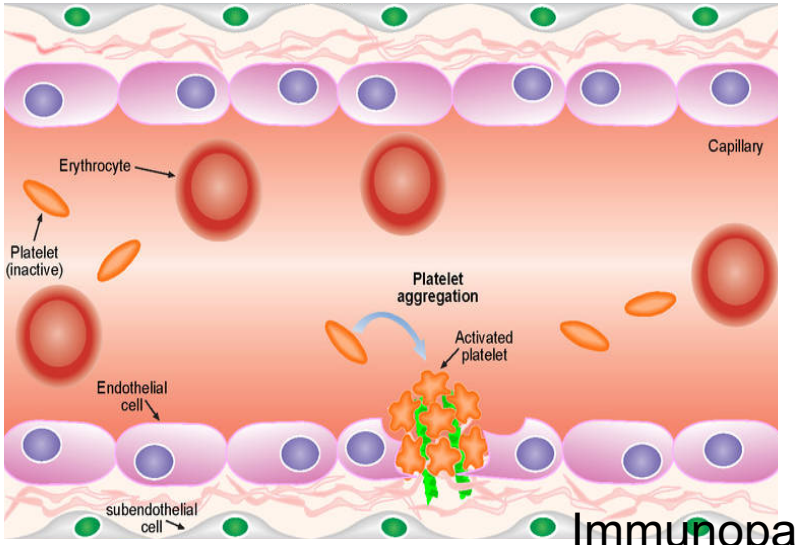
Widespread endothelial damage





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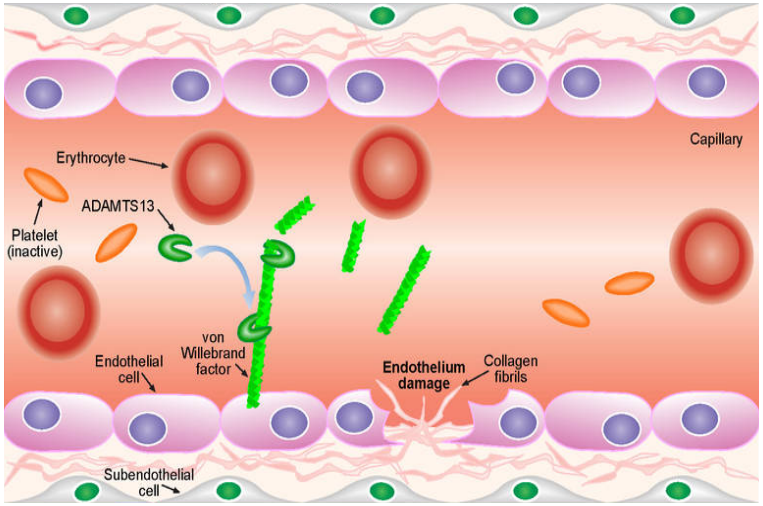

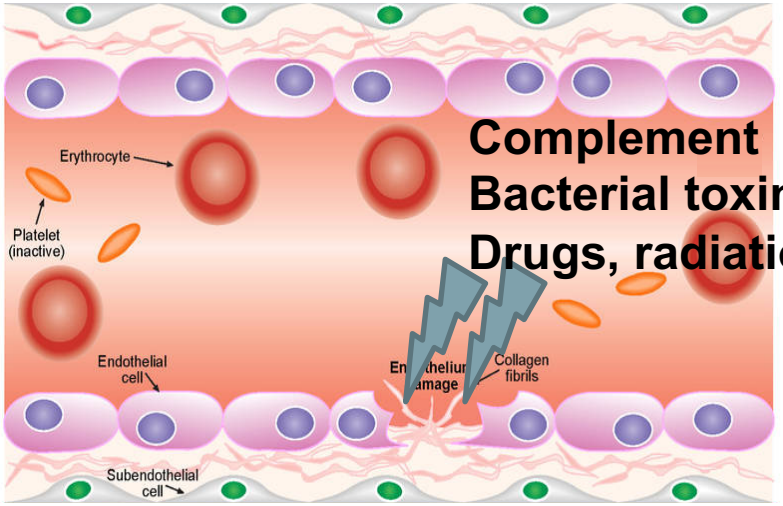

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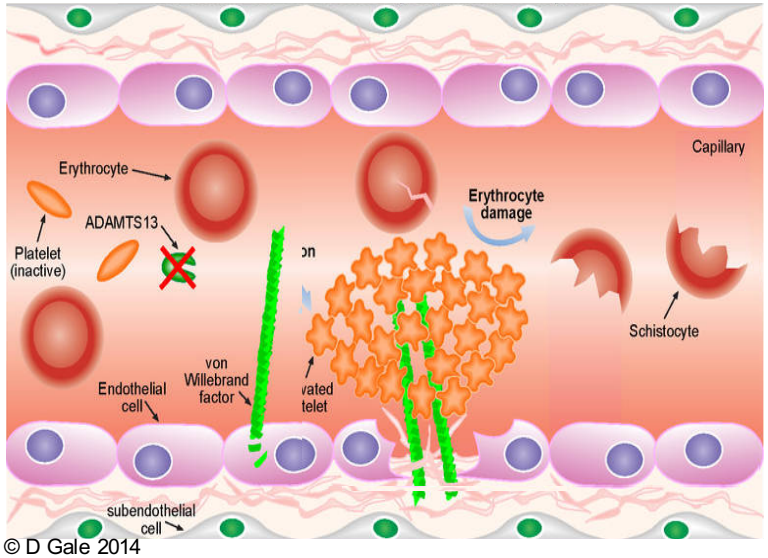

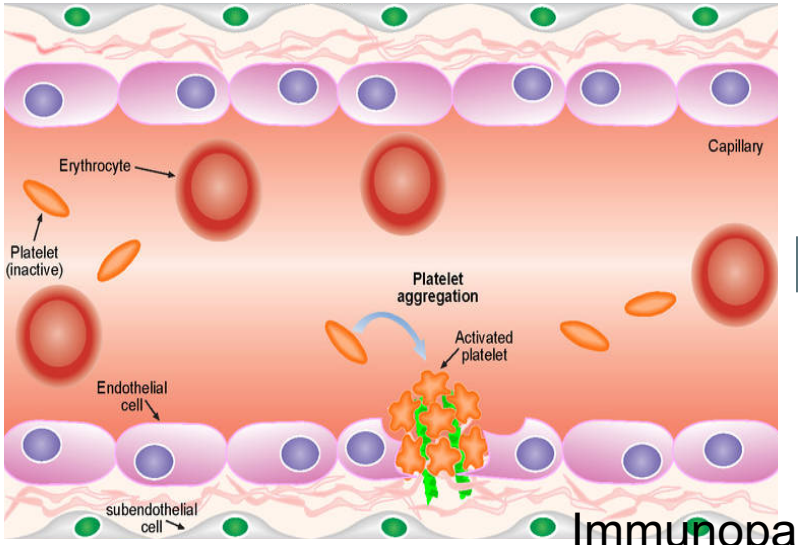

TMA and organ failure

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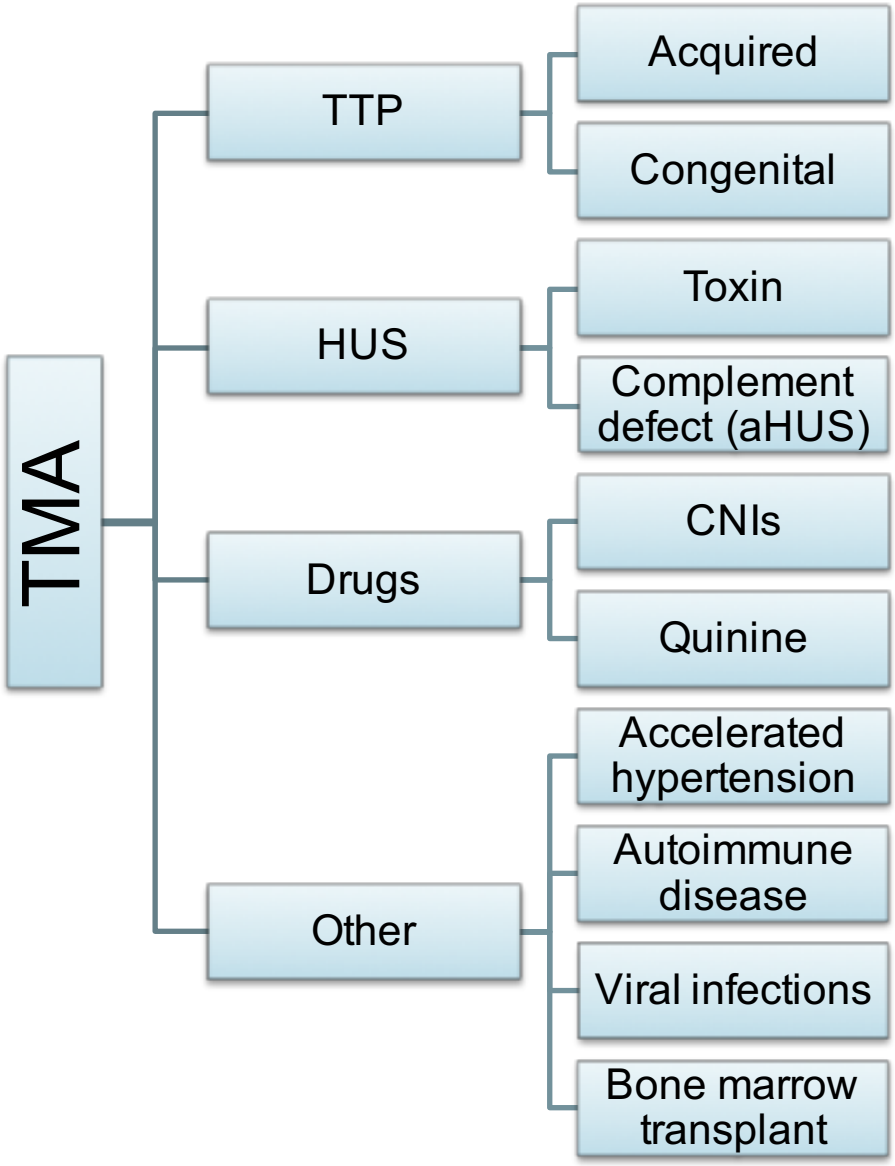
Important causes of TMA



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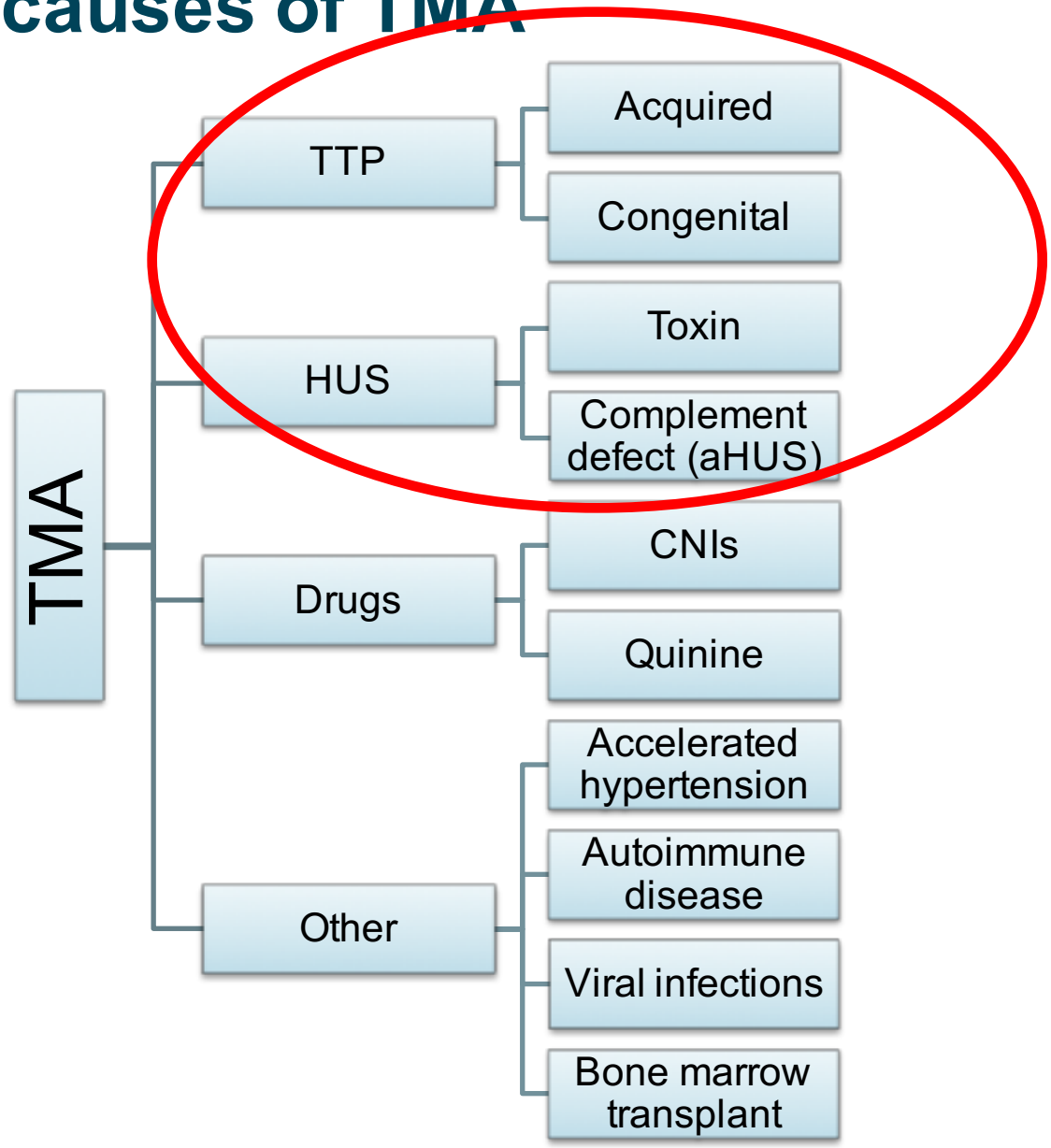

Thrombotic thrombocytopaenic purpura (TTP)

- Very rare – incidence: 6 per million per year
- Mortality >90% without treatment
- Diagnosis most strongly suggested by fluctuating neurological deficits and MAHA
  - Up to 50% have elevated troponin
  - Can present with MAHA only
- Caused by congenital or acquired deficiency of VWF cleavage protease ADAMTS13

Diagnosis proven by functional ADAMTS13 assay <5%

Treatment of acutely presenting TTP

- Plasma exchange should be initiated promptly:

  "In view of the high risk of preventable, early deaths in TTP, treatment with plasma exchange (PEX) should be initiated as soon as possible, preferably within 4-8 hours, regardless of the time of day at presentation, if a patient presents with a MAHA and thrombocytopenia in the absence of any other identifiable clinical cause (1B)."

- **Pre-treatment samples for ADAMTS13 must be taken**

Plasma exchange for TTP

- Duration and number of exchanges required to induce remission is variable
- Exchange against S/D plasma (Octaplas)
  - Reduced risk of infection
- Typically 1.5x plasma volume exchanged daily
  - Until 2 days after platelet count >150x10^9/L
  - Longer for antibody-mediated disease
- Twice daily exchanges sometimes needed
- Start steroids/rituximab early unless known congenital TTP

Treatment of TTP

- Congenital TTP caused by **DEFICIENCY** of enzyme
  - Relatively low volume plasma infusion sufficient to prevent disease
  - ADAMTS13 also present in BPL 8Y (Factor VIII)
  - Logical treatment is recombinant ADAMTS13
- Acquired TTP caused by antibody **INHIBITOR** of enzyme
  - Large volume plasma exchange required acutely
  - Treatment aims to suppress antibody production
  - Steroids and rituximab are mainstay of treatment

TTP in pregnancy

- Pregnancy well documented trigger for TTP
  - Congenital and antibody mediated
- In congenital TTP, intensive monitoring and early treatment reduces foetal loss from 16/38 in those pregnant before diagnosis known to 0/15
  - Suggests that intensive monitoring and aggressive treatment is valuable

Haemolytic Uraemic Syndrome: HUS and aHUS

- HUS is characterised by the clinical triad of:
  - Anaemia
  - Thrombocytopaenia
  - Acute kidney injury
- Other organs (particularly brain and heart) also affected
- Caused by endothelial damage and secondary microthrombus formation
  - Exogenous toxin (HUS)
  - Dysregulated host complement system (aHUS)

Toxin associated HUS

- Reportedly the commonest cause of AKI in children
- Infection with Shiga-toxin producing organisms
  - *E. coli* (80-90% cases, including most epidemics)
  - *Strep. Pneumoniae* (~5% cases)
  - *Shigella dysenteriae*
  - *Campylobacter jejuni*
- Often follows prodromal bloody diarrhoeal illness or pneumonia

Other causes TMA presenting as HUS:

- Bone marrow transplant (GVHD)
- Drugs
  - Calcineurin inhibitors
  - Quinine
  - Chemotherapy: gemcitabine, mitomycin
  - Clopidogrel

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16th October 2014:

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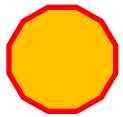
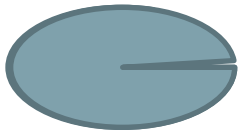
The Complement System

- The ability of serum to “complement” antibodies in the destruction of microbes was recognised by Bordet in the 19th Century
- Composed of a heat labile system of proteins in the circulation
- Crucial component of host defence
  - Highly conserved across evolution
  - Rapid, high amplitude response
  - Amplification loop requiring regulation

Complement Pathways

Bacterium





C3

Complement Pathways

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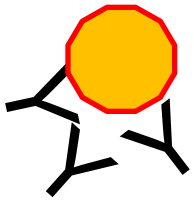
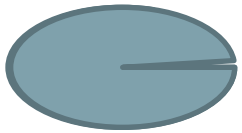


Antibody activation



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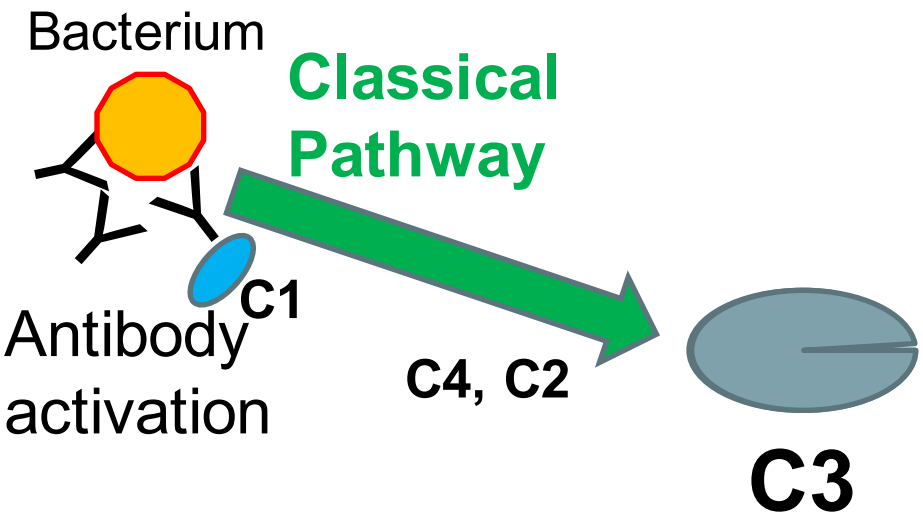

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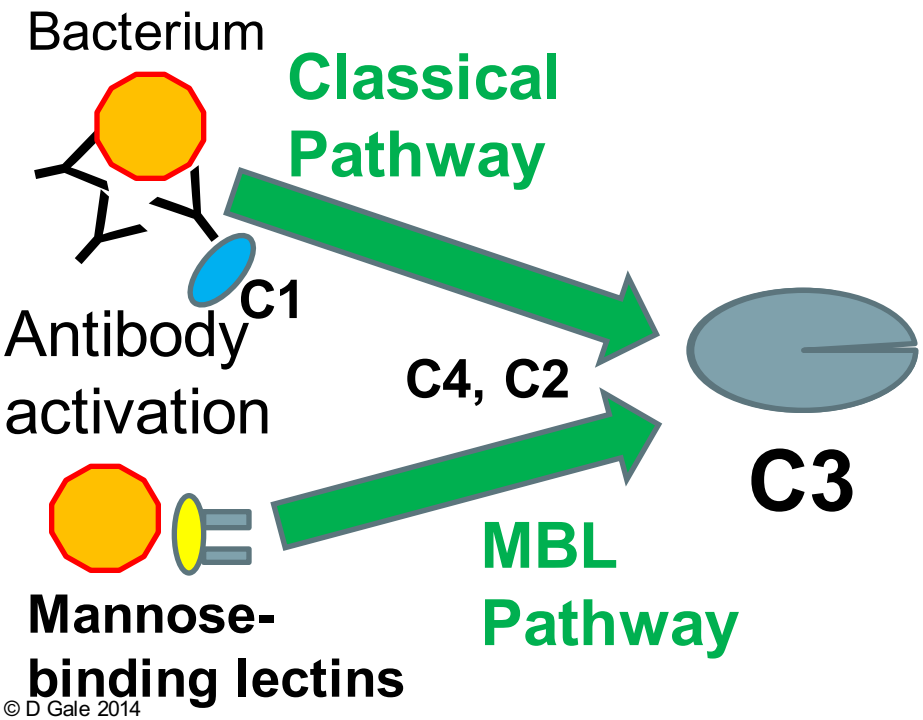

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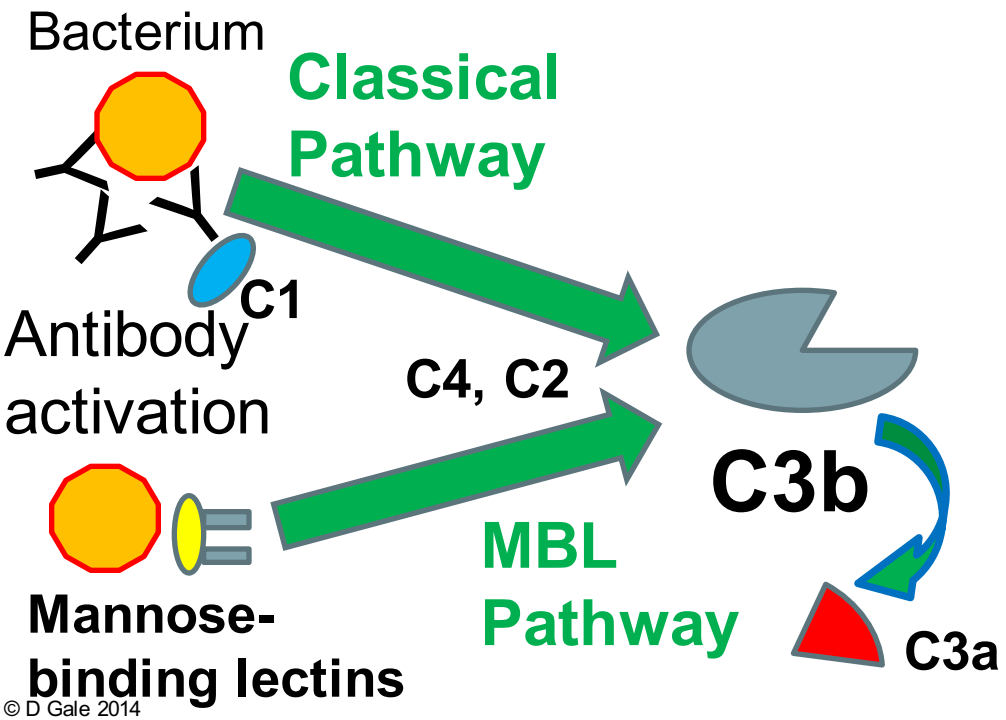

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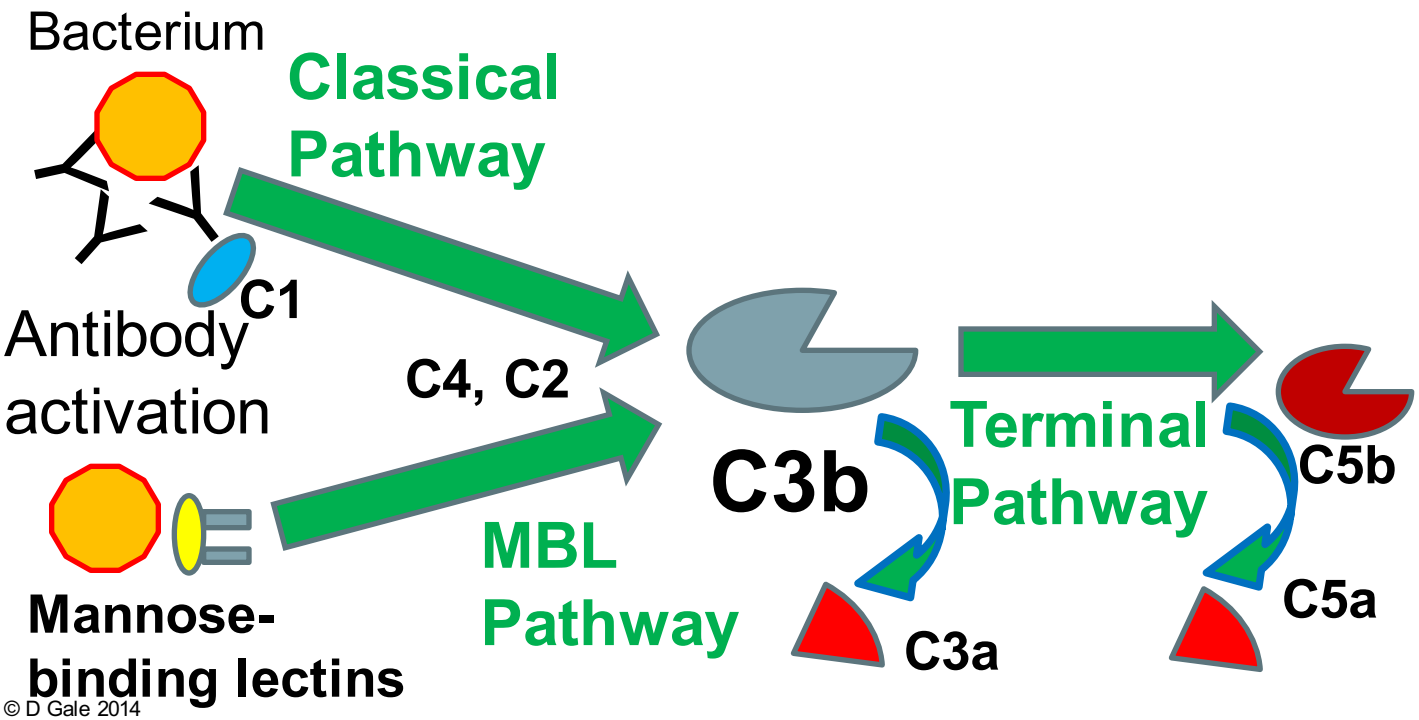

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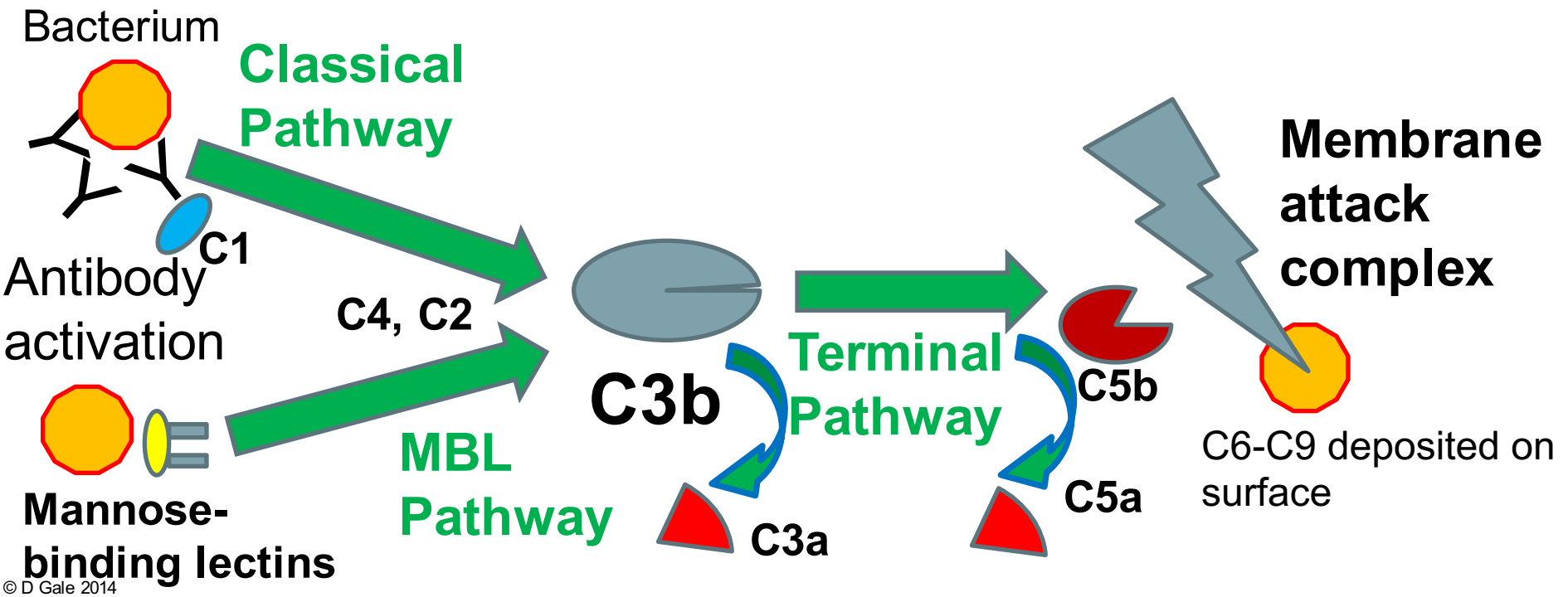

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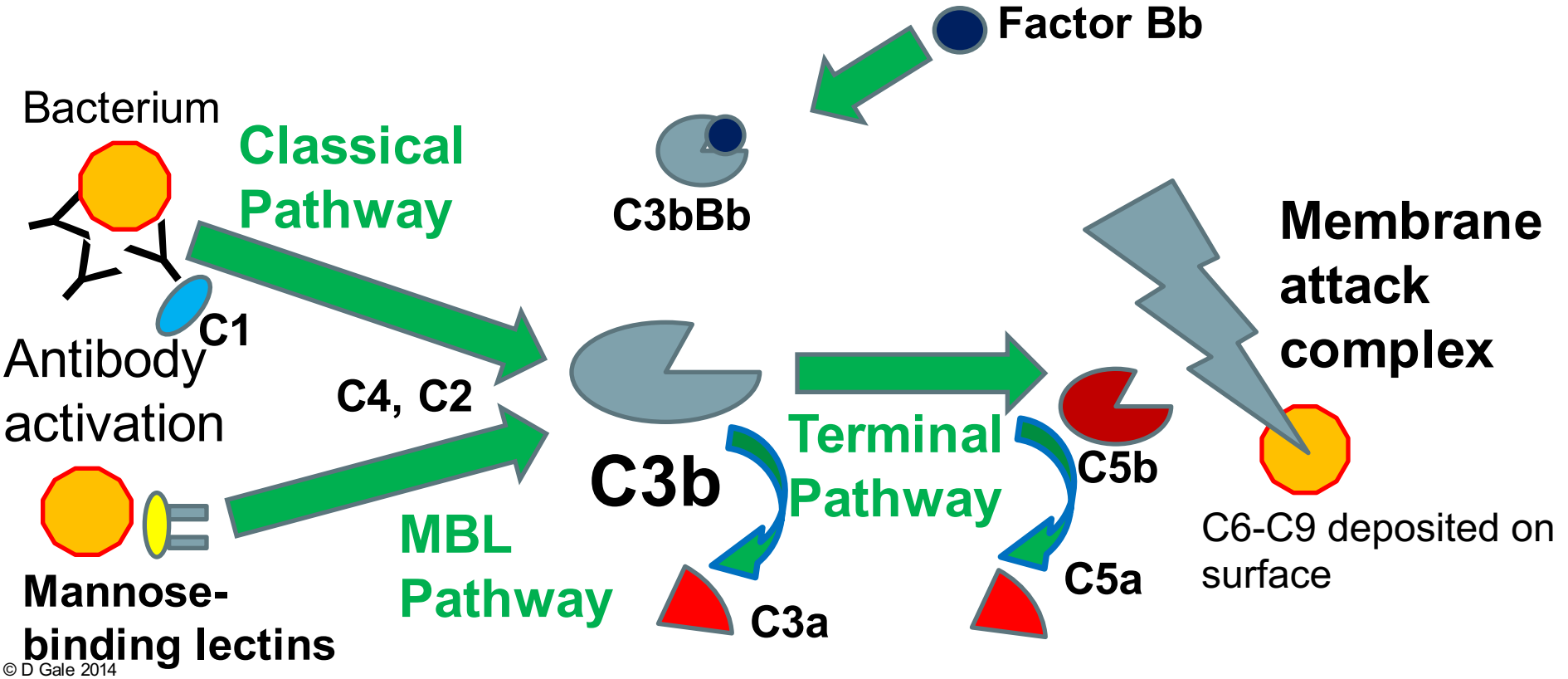

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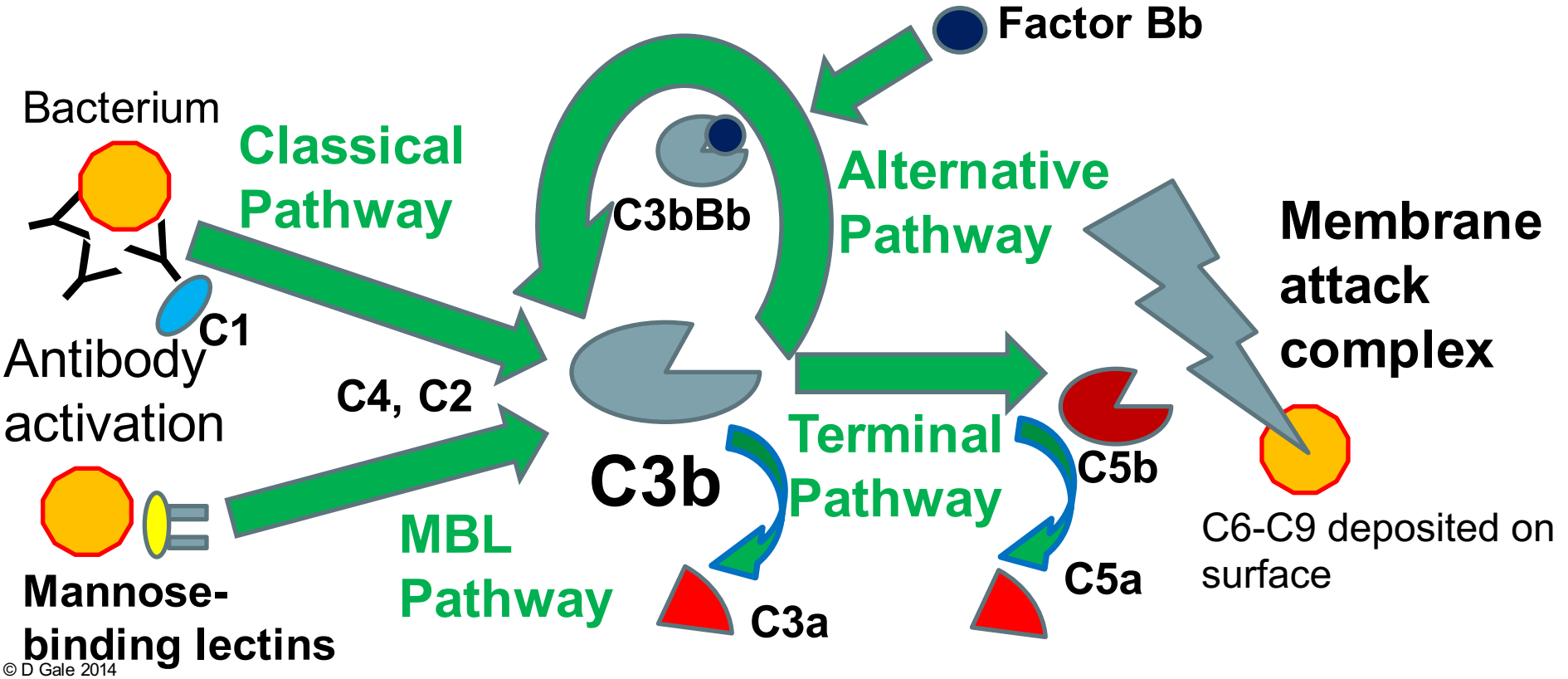

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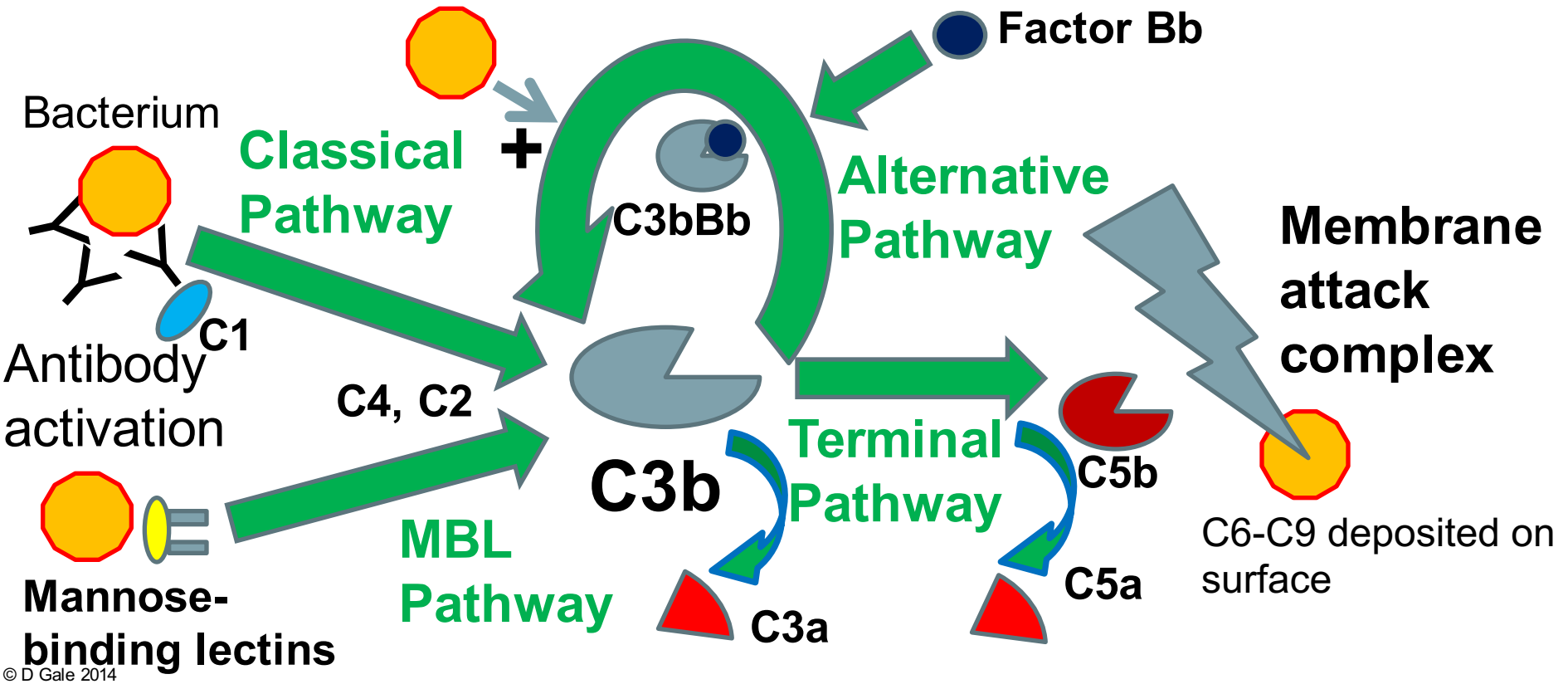

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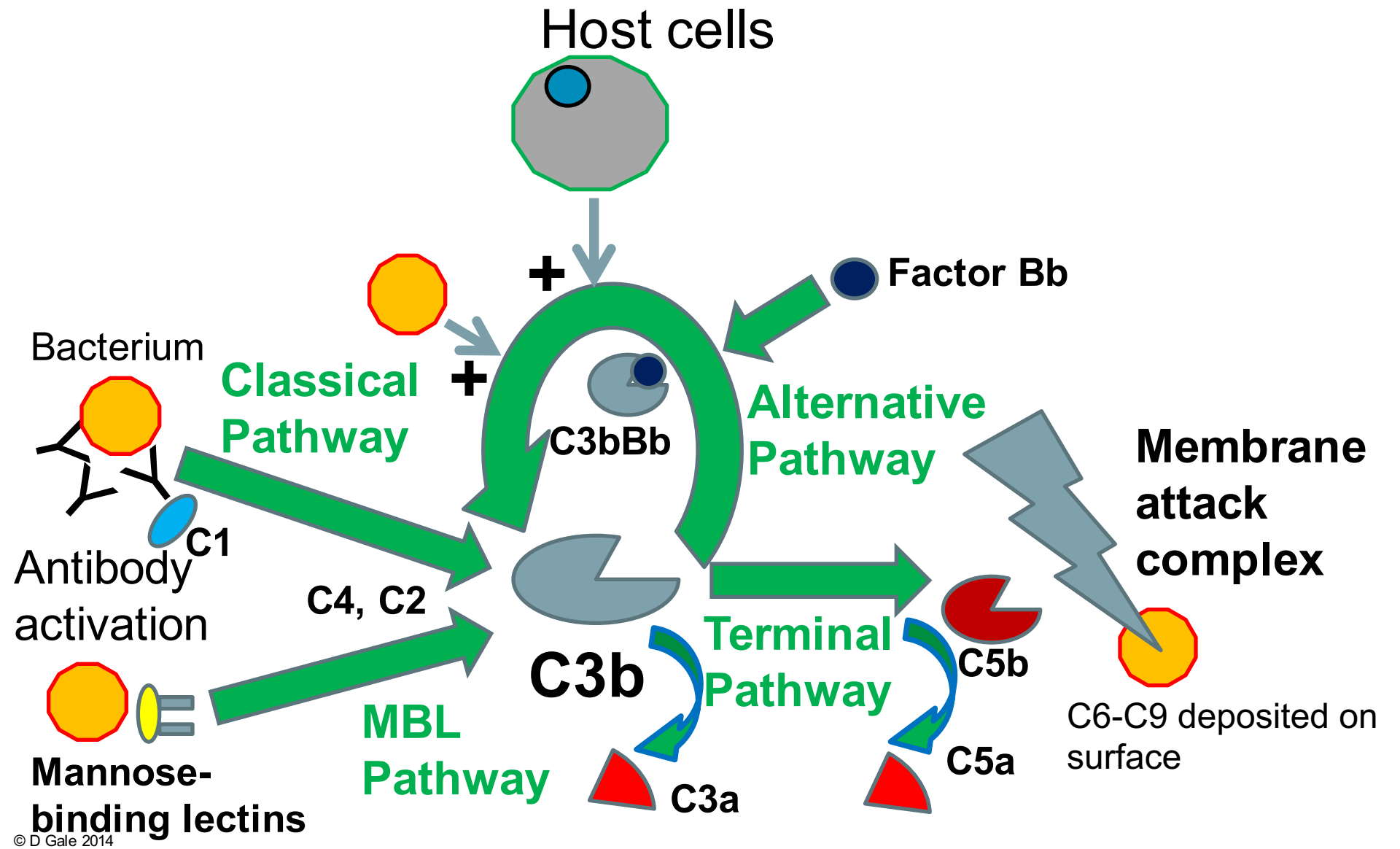

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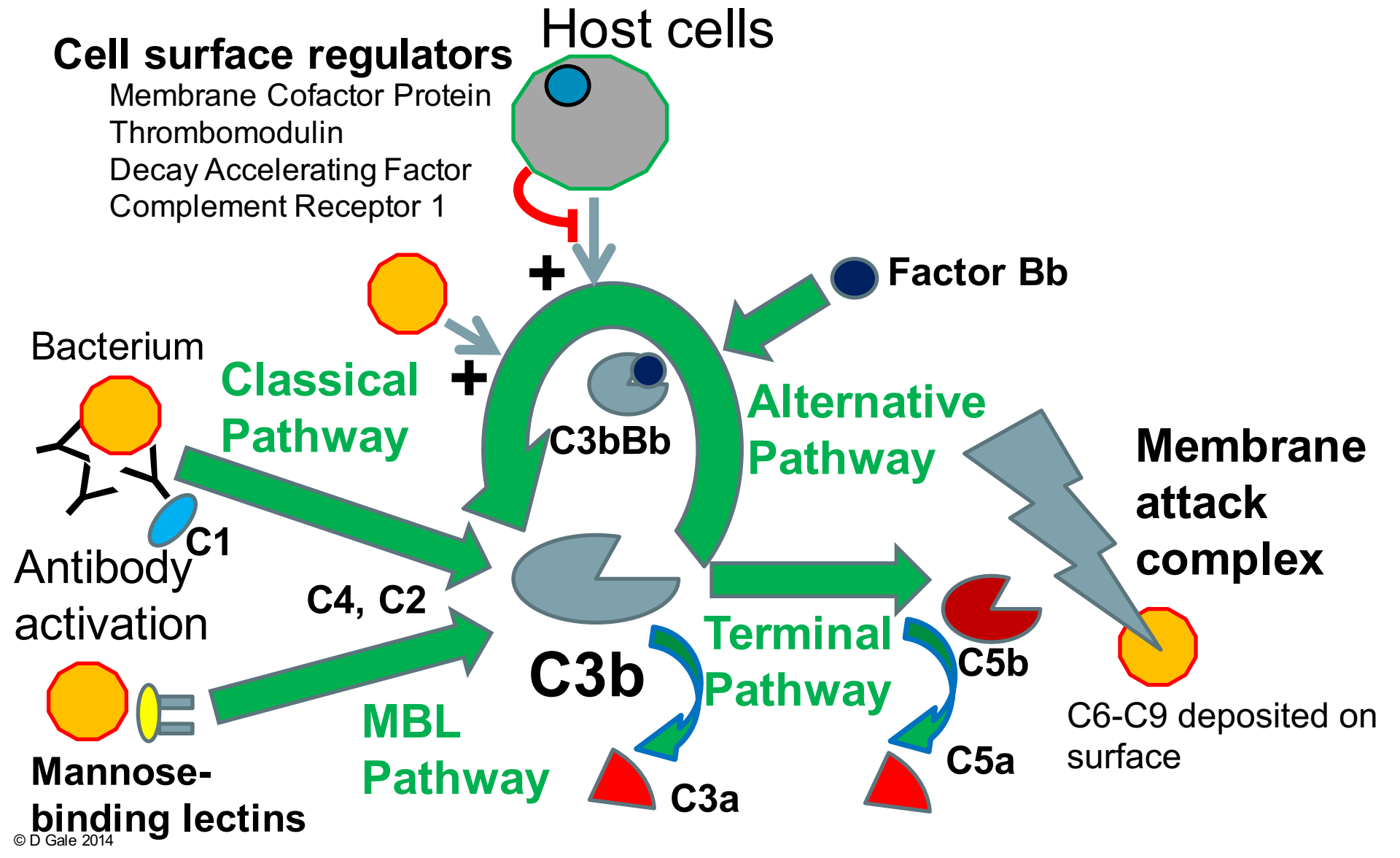

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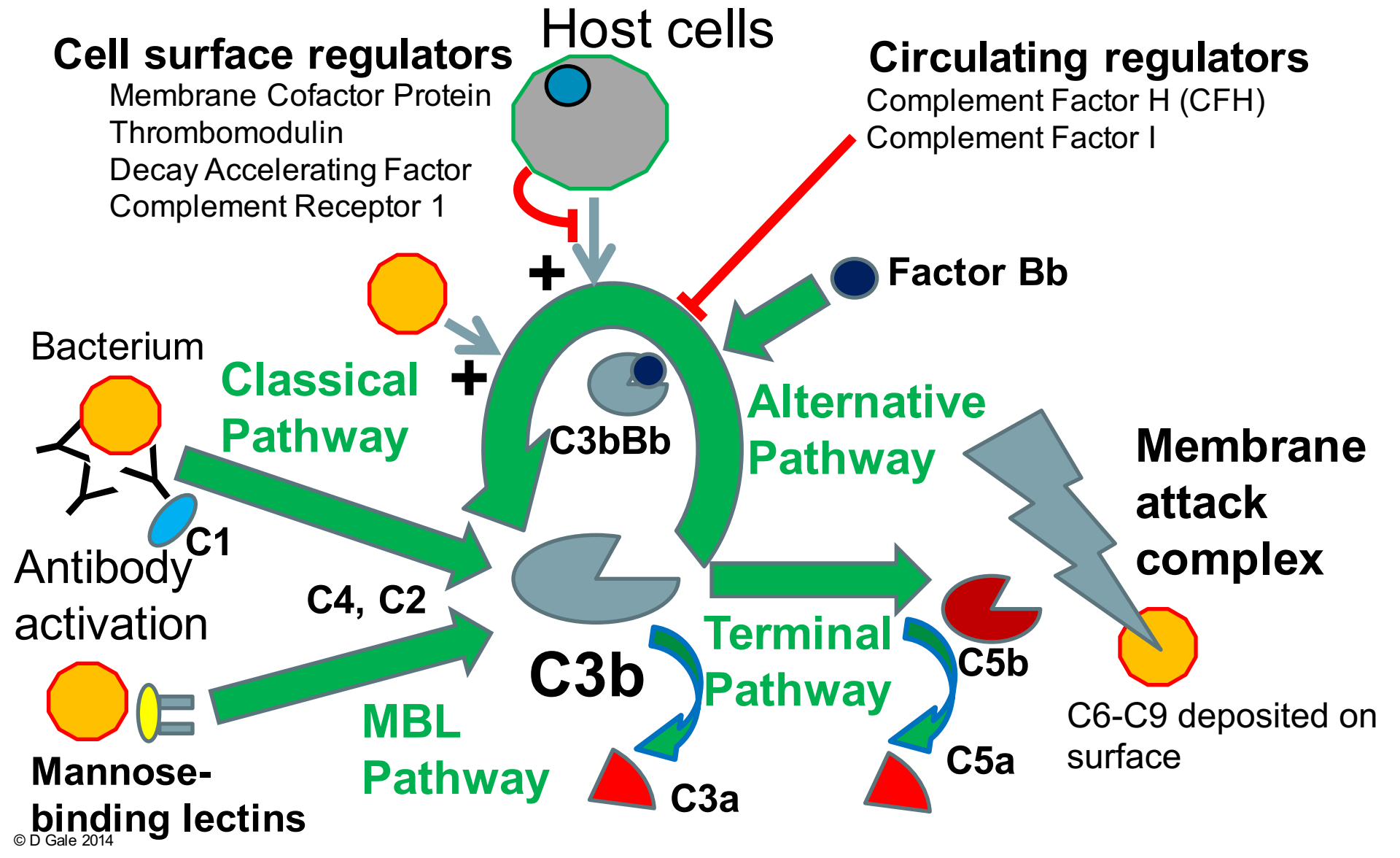

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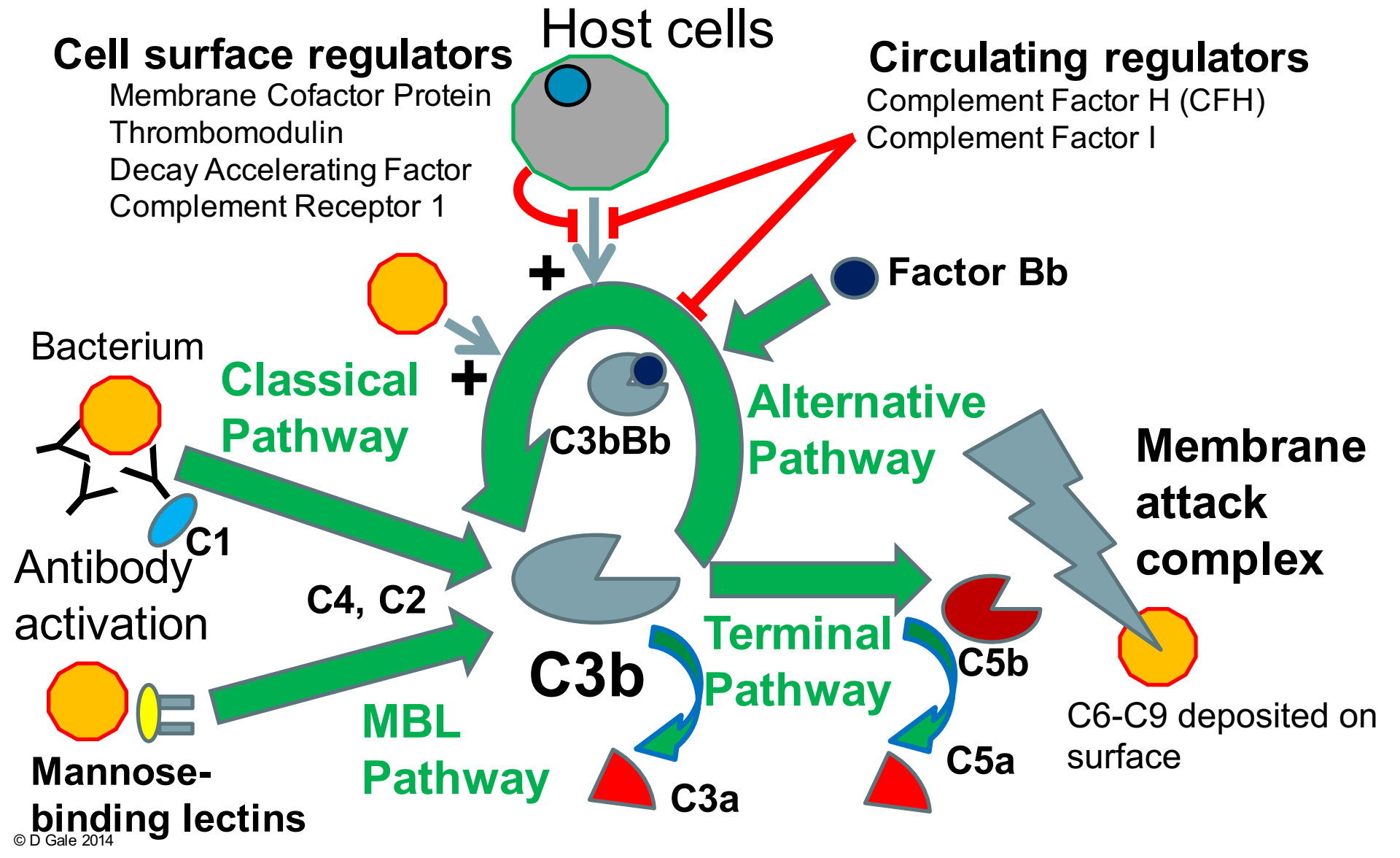

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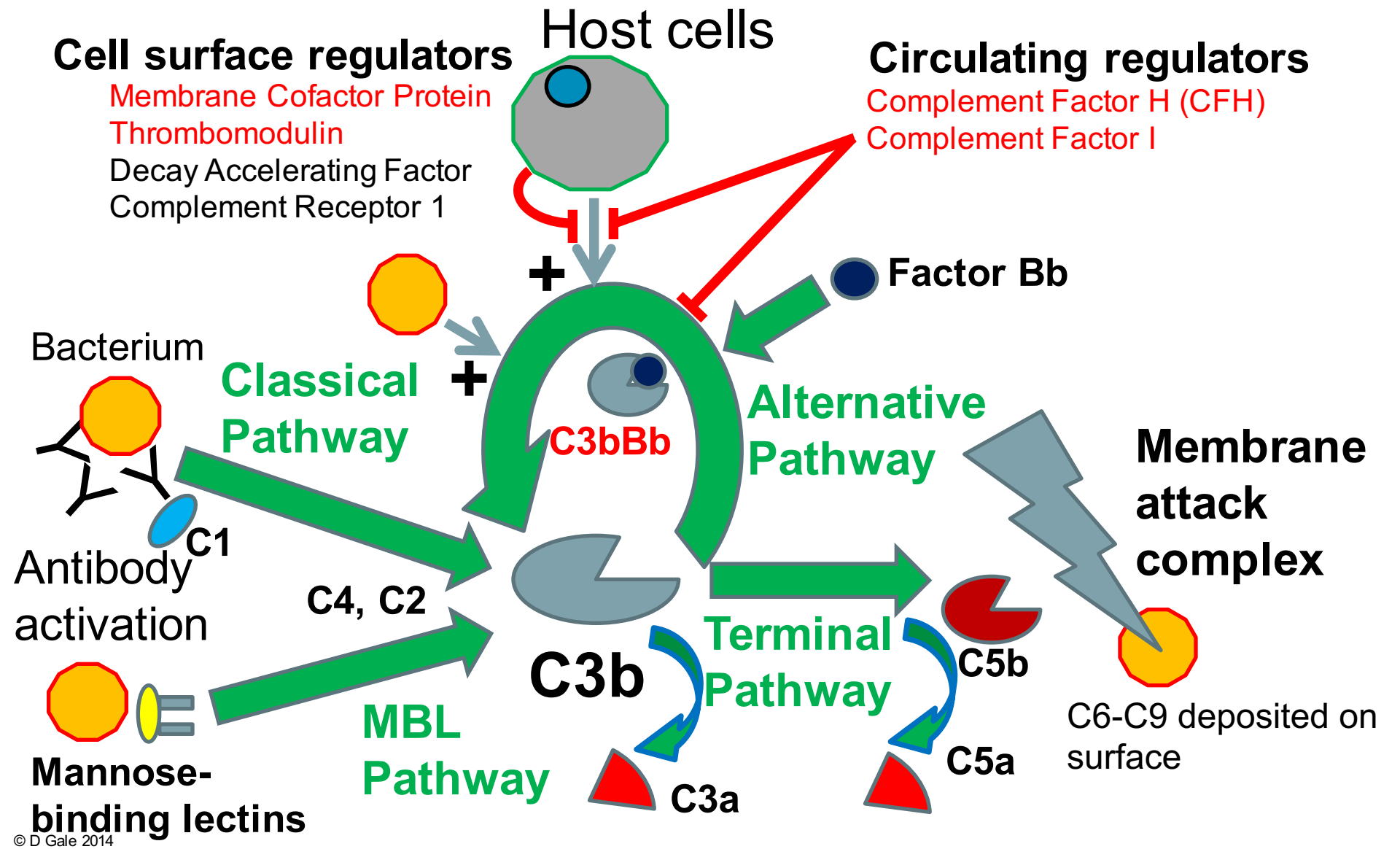
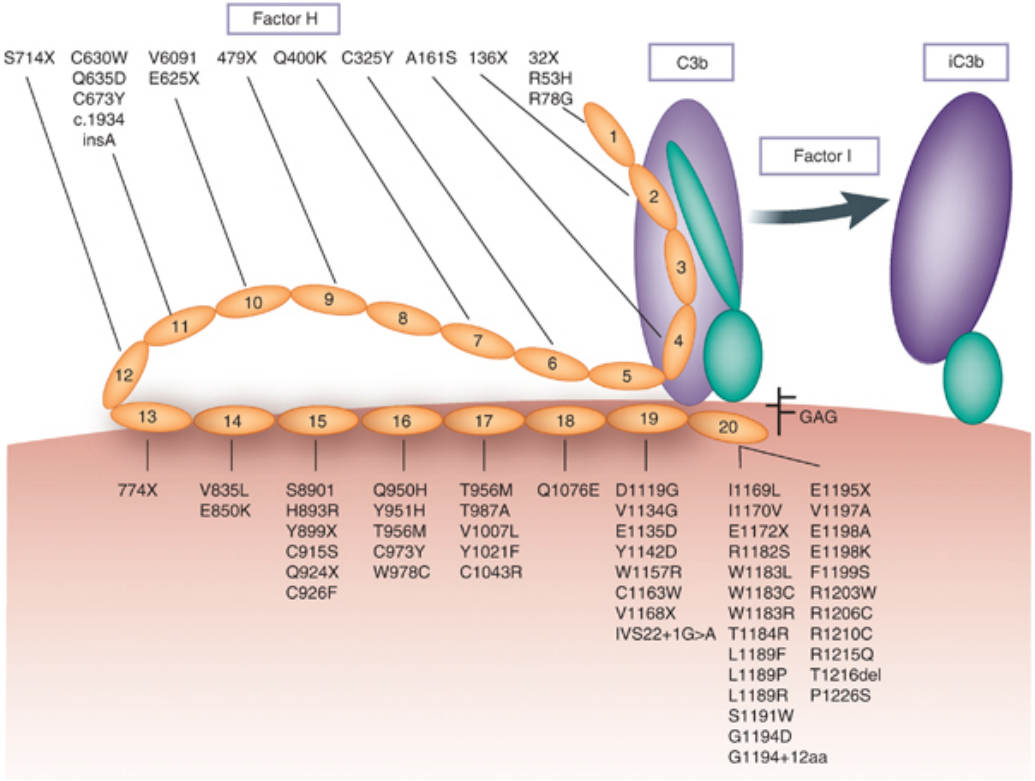


Complement components in the circulation

- Circulating complement proteins all synthesised in the liver
- C3 one of the most abundant plasma proteins
  - Normal level ~1200 µg/mL (~6 g in the circulation)
- C4 also abundant (~600 µg/mL)
  - Serum depletion of C3 and C4 indicates significant complement activation
- Other complement components far less abundant
  - All < 100 µg/mL

Complement defect found in ~75% patients

- 75% aHUS associated with CFH mutations
- Mutations usually in SCRs 19/20 that bind host endothelium



Kavanagh and Anderson, *Kidney International* 2012

- MCP, CFI, Thrombomodulin, C3 and factor B mutations (15-20%)
- Acquired antibodies against CFH (5-10%)

When does aHUS present?

- aHUS is an episodic disease
- Can present at any age – usually in childhood or early adulthood
- Presentation often follows trigger
  - Infection (commonly URTI but *can be diarrhoeal illness*)
  - Pregnancy or oral contraceptive pill use
  - Surgery
- Frequently no trigger identified

Treatment options (pre-2011)

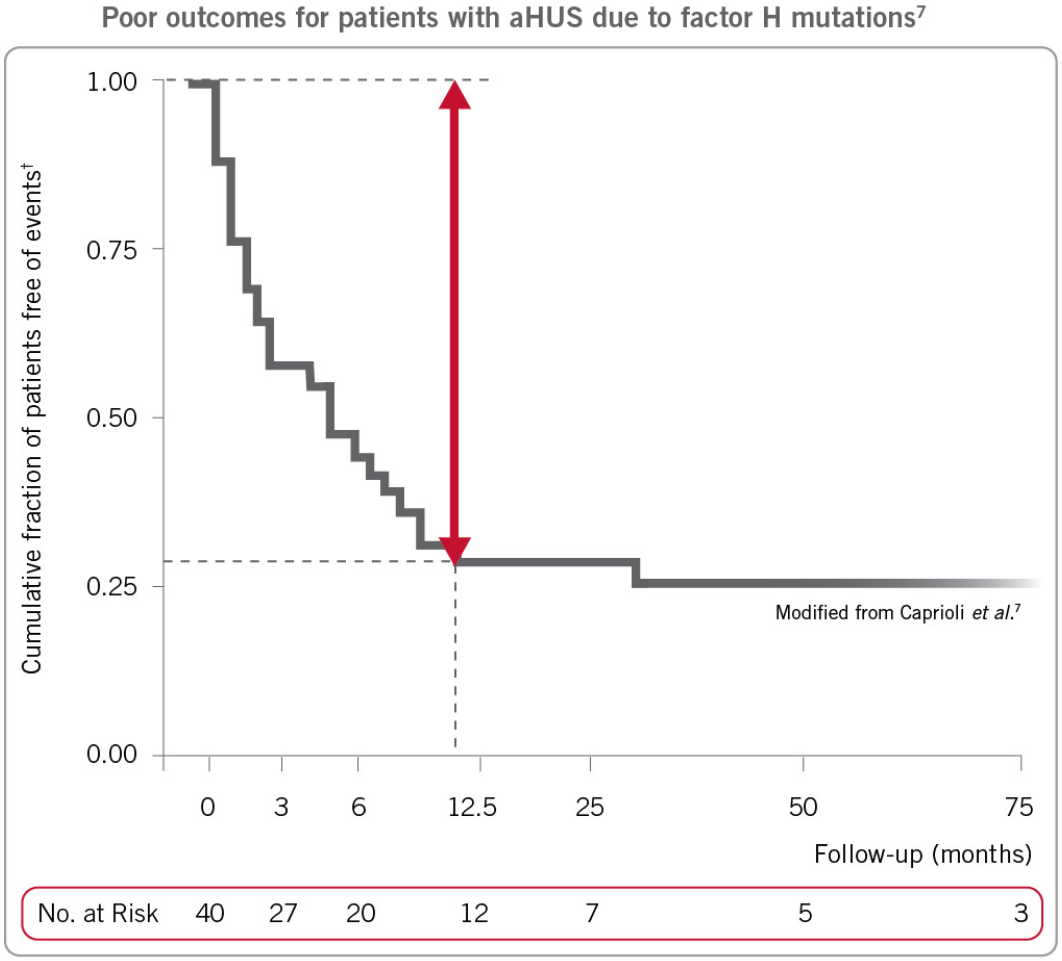
- Plasma exchange with FFP to replace deficient complement regulator and remove cytokines
  + immunosuppression or B cell depletion where anti-CFH antibodies identified
- Kidney transplantation
  – Especially where causative *MCP* mutation identified
- Liver or liver/kidney transplantation
  – Where circulating abnormality of complement regulator identified or previous graft lost
  – Mortality: 10%

Plasma exchange in aHUS

- Rationale is to remove and replace deficient/defective complement component
  - Replaces mutant CFH with pooled donor CFH
  - Also removes cytokines, exotoxin, autoantibodies and products of gain-of-function mutations (mutant C3 or factor B)
  - More effective than plasma infusion (case series)
- Advice is to commence as soon as possible
  - Do not await confirmatory molecular studies

Plasma exchange in aHUS - evidence

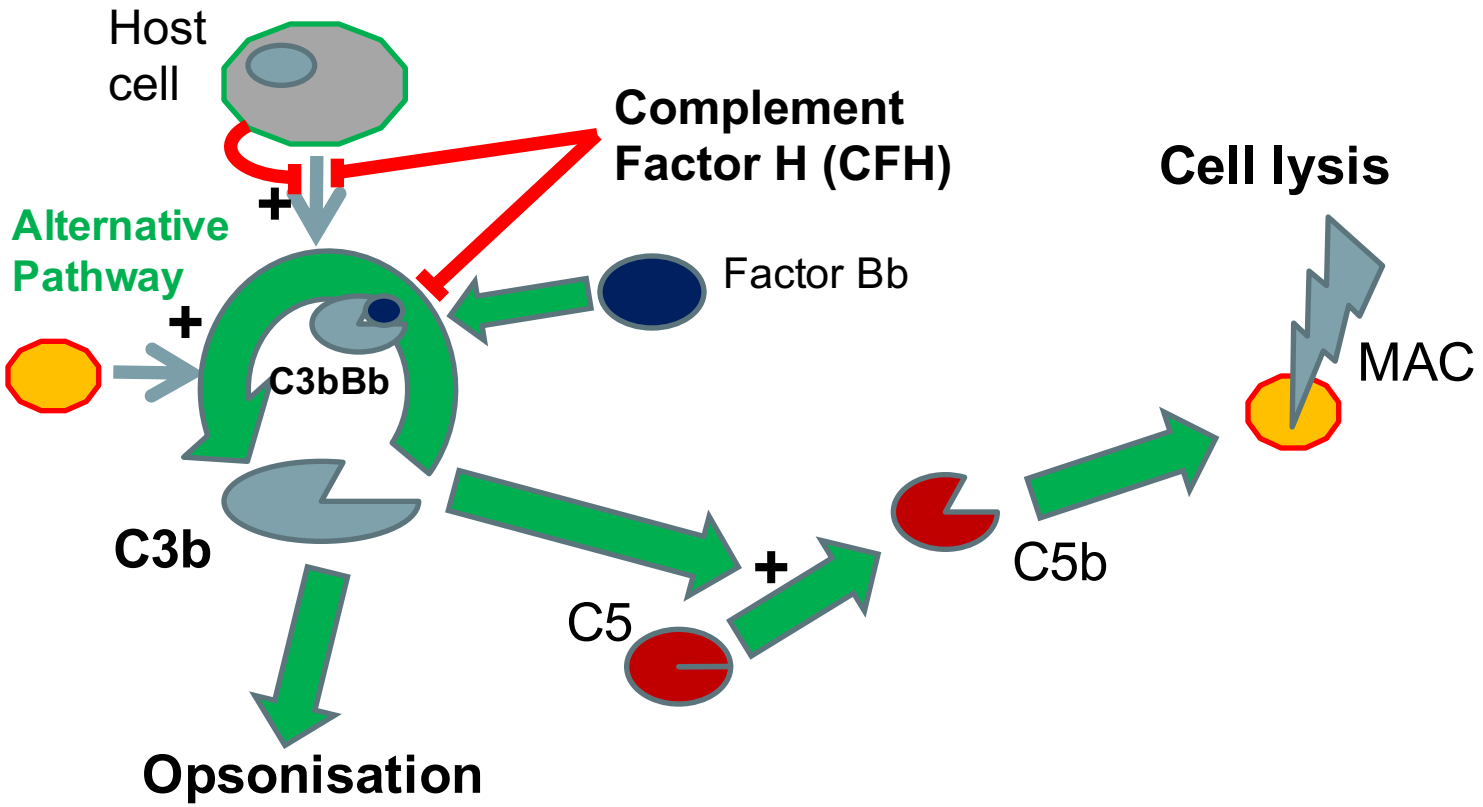
- No randomised controlled trials
- Prognosis without PEx is very poor indeed
- Prognosis even with PEx remains poor



Liver transplant in aHUS

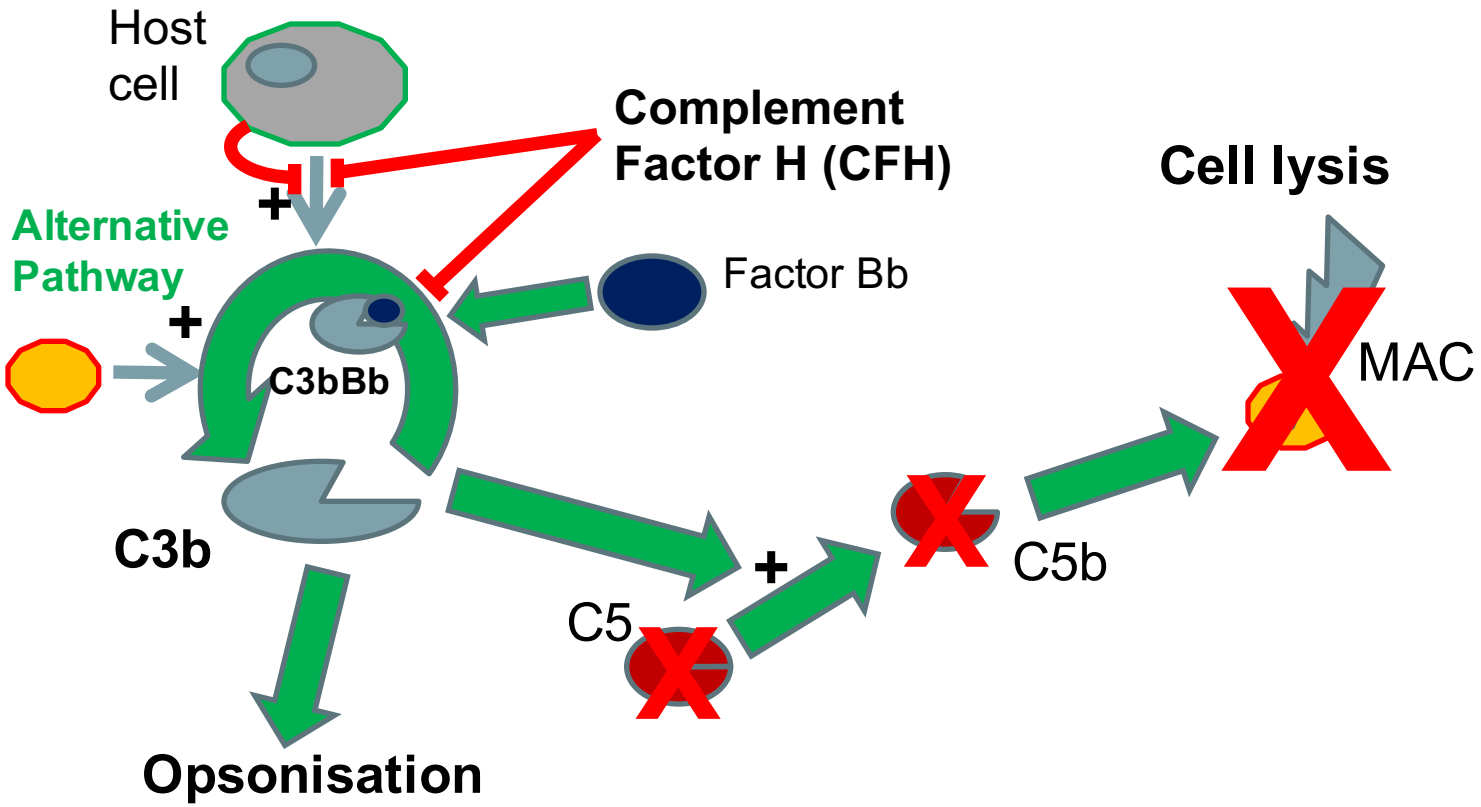
- Potentially curative but high risk (>10% mortality)
- Particular risk is aHUS flare triggered by operation
  - Intensified plasma therapy and anticoagulation recommended
- Effectiveness in presence of gain-of-function C3 or Factor B mutations unknown
  - Extra-hepatic production of mutant allele occurs
- Not indicated in anti-CFH antibody or MCP-related disease

C5 and endothelial destruction



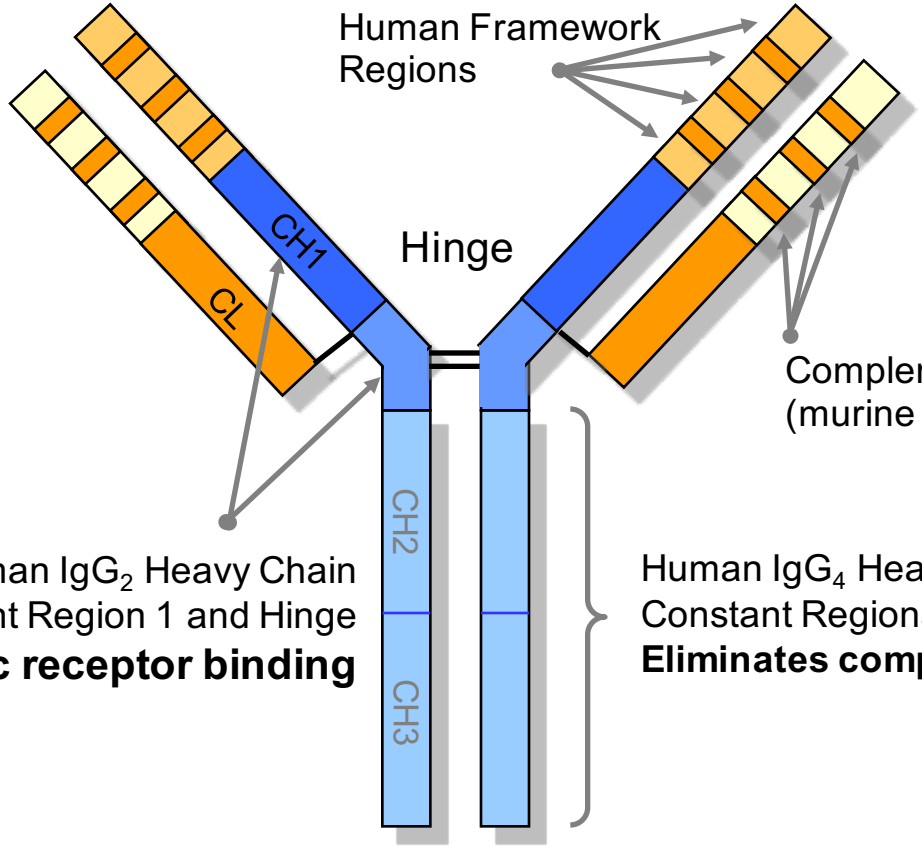
- C5 depletion a rational target to prevent organ damage in aHUS
- C5 circulates at <100 µg/mL

C5 and endothelial destruction



- C5 depletion a rational target to prevent organ damage in aHUS
- C5 circulates at <100 µg/mL

Eculizumab: Humanized anti-C5 monoclonal antibody



Complementarity Determining Regions (murine origin)

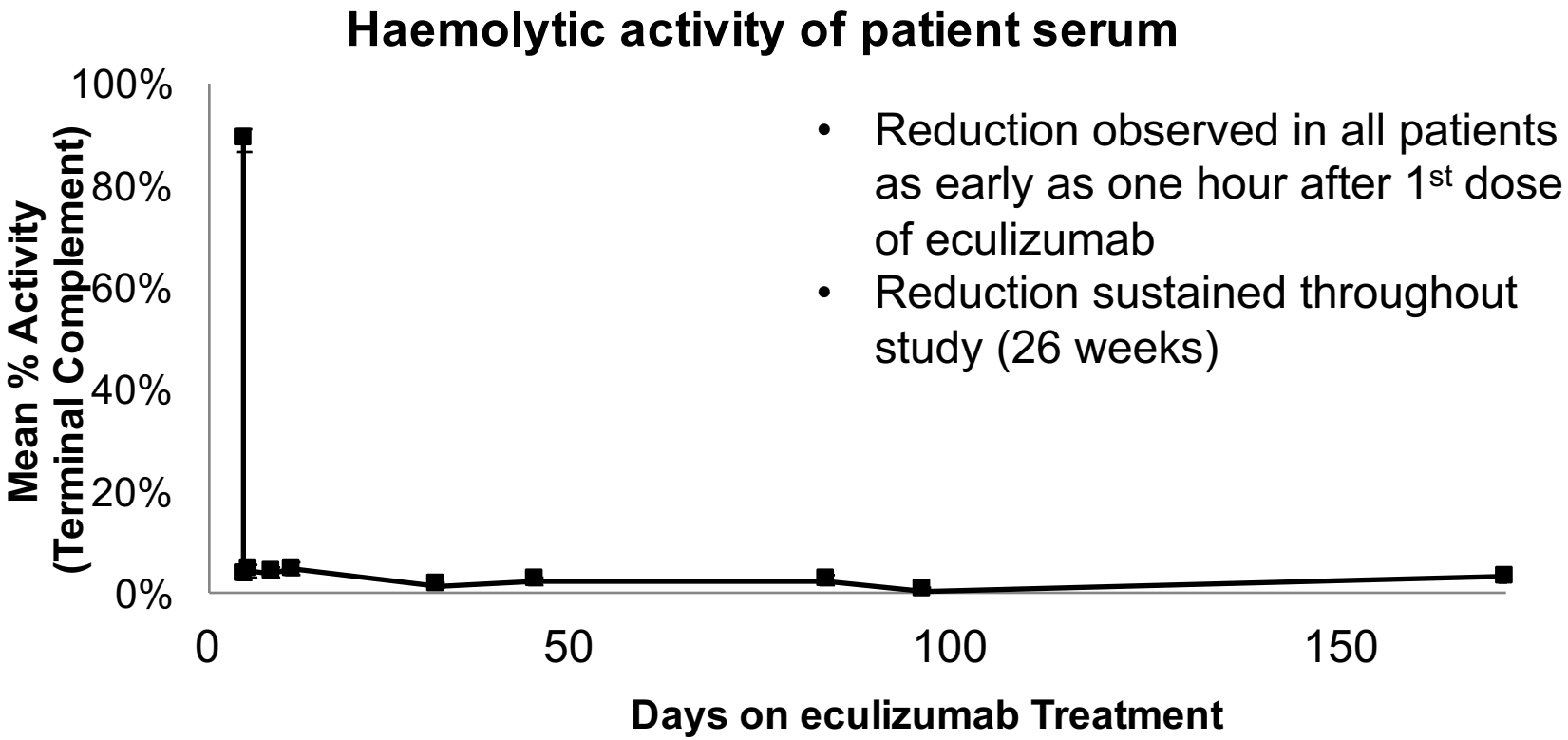
Human IgG_2 Heavy Chain Constant Region 1 and Hinge
Eliminates Fc receptor binding

Human IgG_4 Heavy Chain Constant Regions 2 and 3
Eliminates complement activation

Rother R et al. *Nat Biotech*. 2007;25:1256-1264.

Produced by US biotech firm Alexion under trade name Soliris

Pharmacology of eculizumab



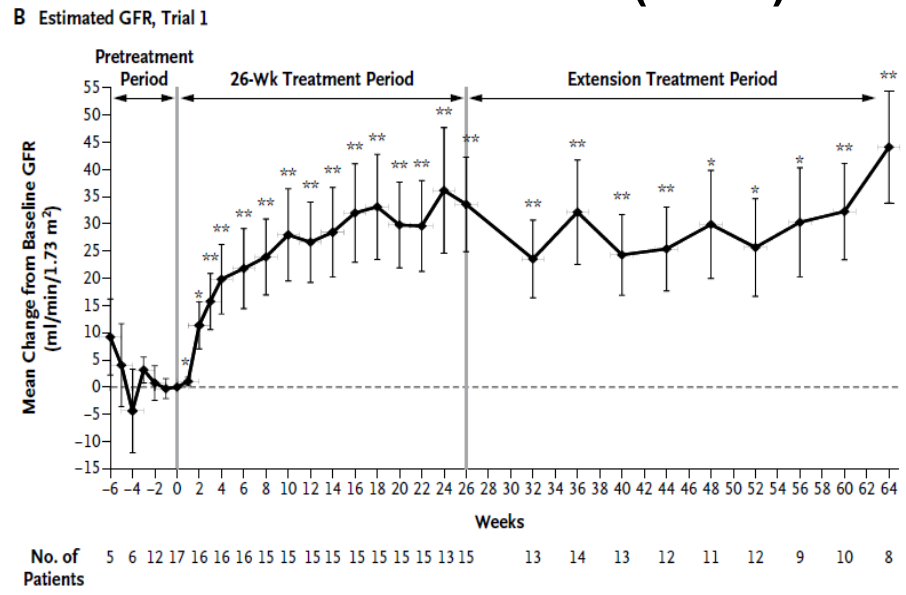
Licht C, *et al.* Poster TH-P0366. Presented at 2011 Annual ASN Congress

Very effective in depleting C5 and blocking terminal pathway activation in patients

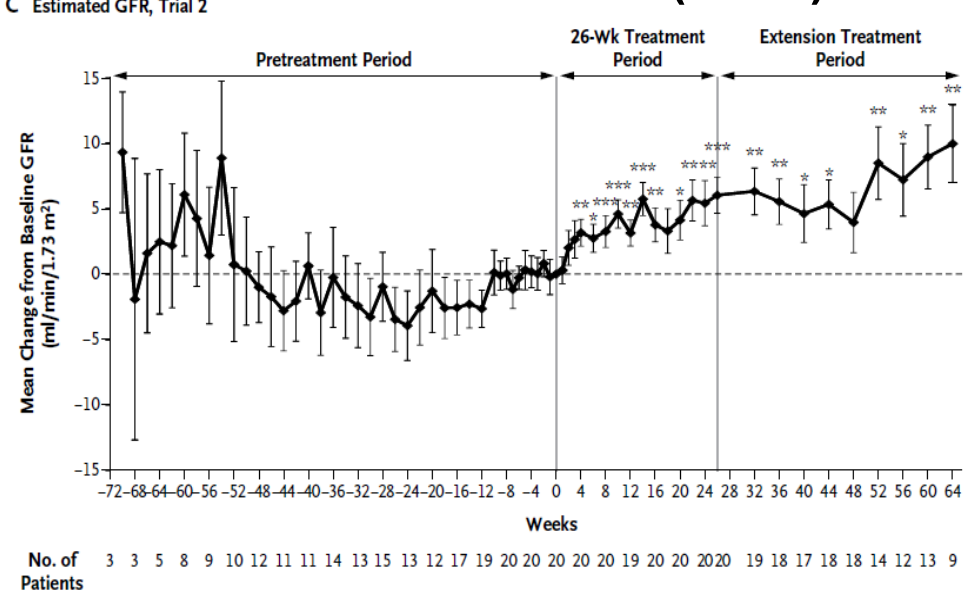
Efficacy of eculizumab in patients >12 years

- Open-label treatment associated with
  - Significant reduction in TMA (>80% event-free)
  - Significant and sustained improvement in eGFR

Progressive TMA despite PEx treatment (n=17)



Patients controlled on maintenance PEx (n=20)



Legendre et al NEJM 2013

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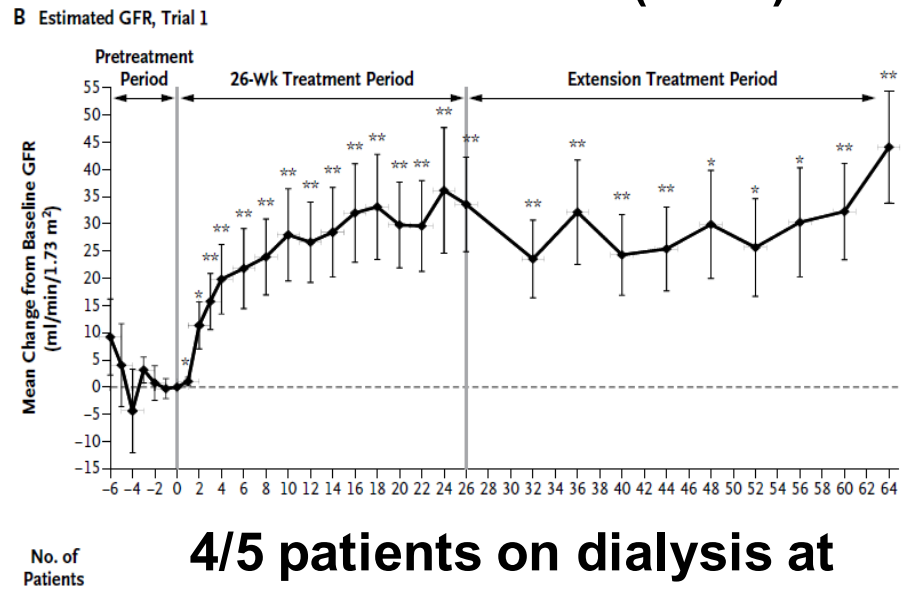

4/5 patients on dialysis at initiation of therapy came off

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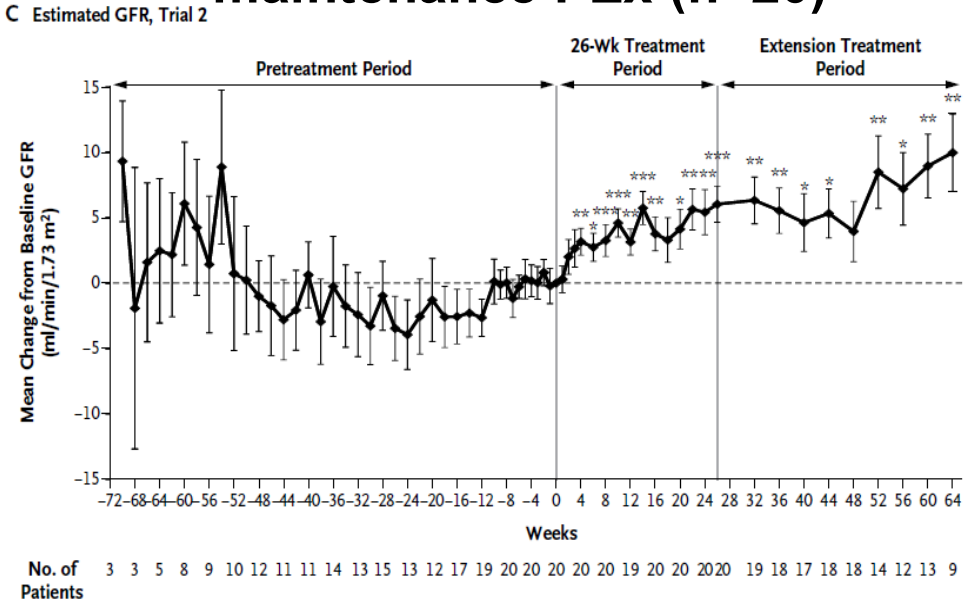

Legendre et al NEJM 2013

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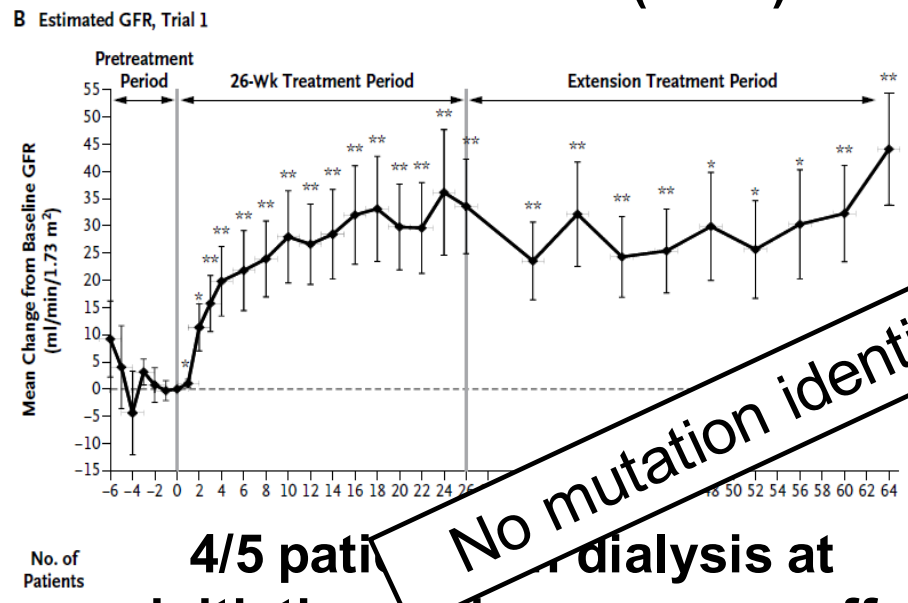

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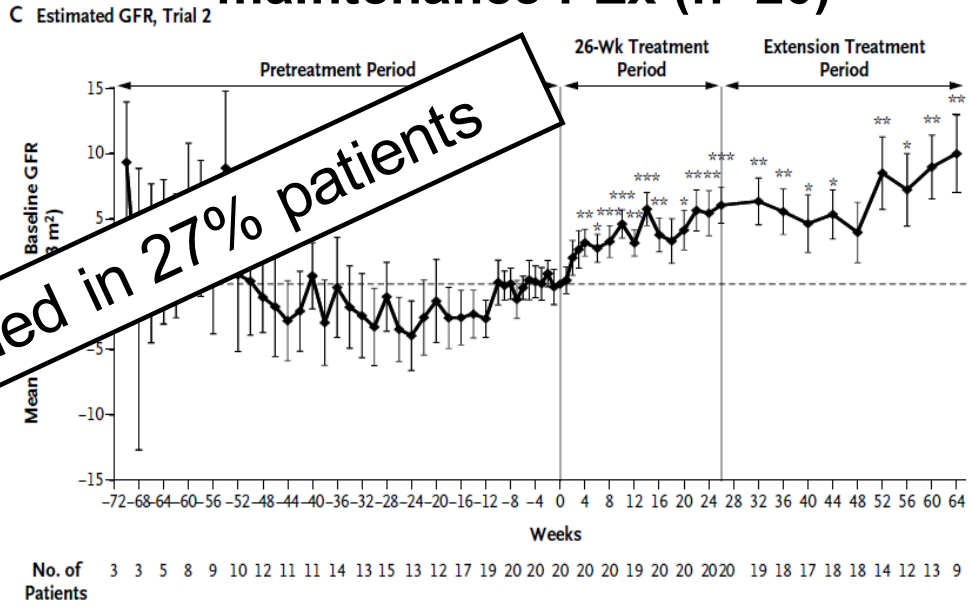
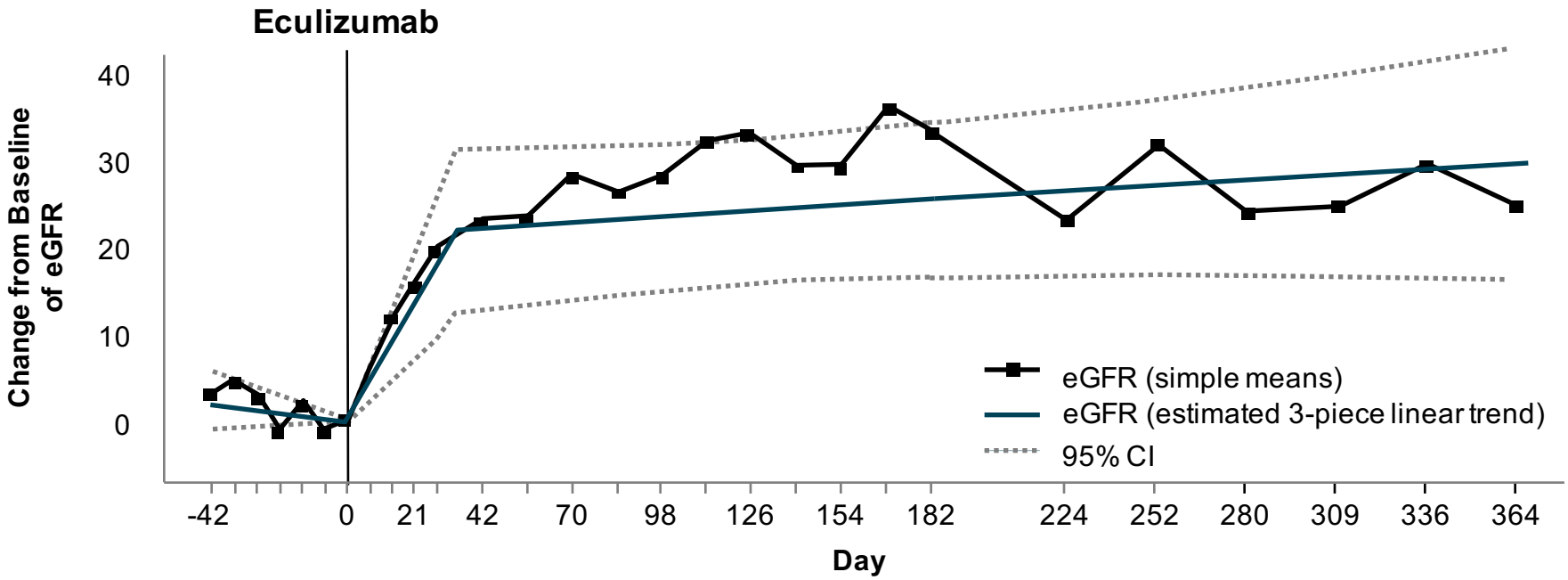


No mutation identified in 27% patients

Legendre et al NEJM 2013

Eculizumab and chronic renal impairment



Greenbaum L, *et al.* Presented at 2011 Annual ASN Congress. Poster TH-PO367

Adverse effects

- Terminal complement pathway especially important in response to encapsulated bacteria
- Eculizumab increases risk of meningococcal infection
  - Vaccination and prophylactic antibiotics from start of treatment
  - <18 year olds also vaccinated against *H. influenzae* and pneumococcus
- Neutralizing antibodies not reported

Eculizumab in clinical practice

- Appropriate first line treatment for acute aHUS
  - Molecular diagnosis not needed to justify therapy
  - Where the diagnosis clear-cut aim is to treat with eculizumab immediately (ie instead of PEx and within 6h)
- Allows patients who have lost a graft due to recurrent aHUS to receive a kidney transplant (with prophylactic cover)
- May obviate the need for liver-kidney transplants
- What are the barriers?

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COST: £300,000 per year

aHUSUK campaign: 30,000 signatures

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Sun+

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HEALTH chiefs are refusing to fund a miracle drug keeping a girl of two alive.

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Parents beg for 'miracle' kidney drug to keep their two-year-old daughter alive

- **Indie Smith responded to trial drug Soliris within two days of treatment**
- **But the trial is due to end and so treatment will be ceased**
- **No plans for the NHS to fund the new drug for the rare illness**
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By MARTIN DELGADO

PUBLISHED: 22:00, 23 March 2013 | **UPDATED:** 00:09, 24 March 2013

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Patient with deadly kidney disease hails wonder drug that could halt disease which killed seven family members

By LAUREN PAXMAN

UPDATED: 15:36, 10 January 2012

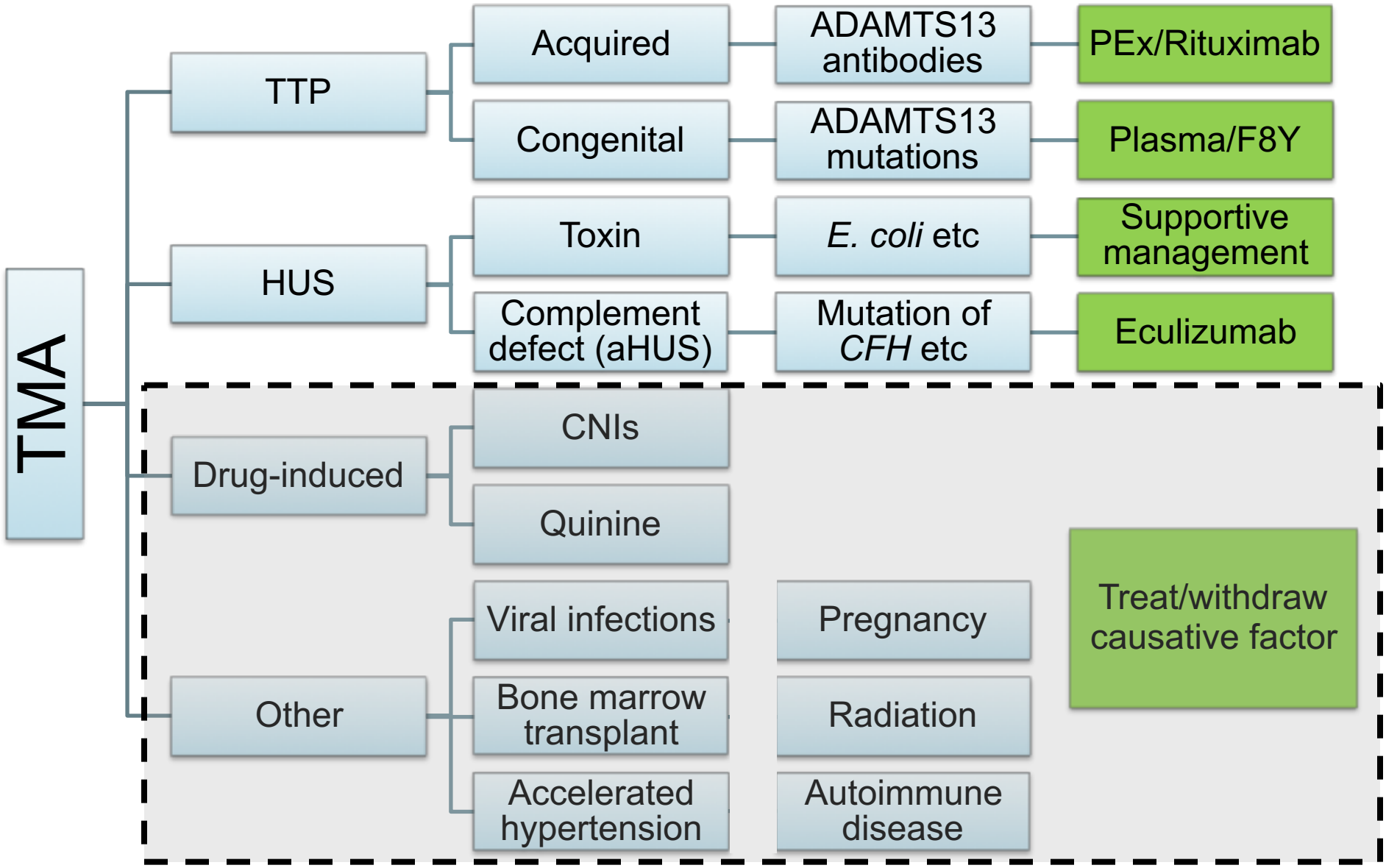
Funding for eculizumab

- In May 2013 NHS England agreed to fund eculizumab for patients in order to prevent life- or kidney- threatening TMA due to aHUS

"it is a principle to not let anybody with aHUS go into irreversible renal failure"

- Not indicated for drug- or toxin-associated HUS or other TMAs such as TTP

Approach to TMA



Take home messages

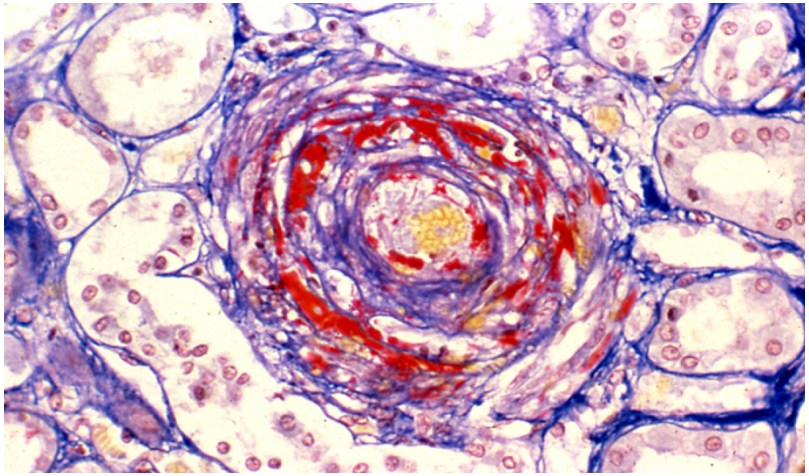
- Do not give platelets
- TTP diagnosed by reduced ADAMTS13 activity
- No rapid diagnostic test for aHUS
  - Complement regulator mutations identified in ~75%
- Treat promptly
  - Recovery of renal function possible even after many months, provided TMA is controlled
  - Significant risk of recurrent TMA in transplant, depending on cause
- Eculizumab is an effective but expensive therapy for aHUS
  - Funding is available

Further investigations

- Urgent ADAMTS13 level: 40% of normal
  - Results available 9h after presentation
- HIV test –ve
- Transthoracic echocardiogram normal
- Autoimmune screen negative
  - Negative ANA, ANCA, ACL, ENA
- Complement C3 68 mg/dl (70-165)
- Complement C4 29 mg/dl (16-54)
- Stool culture/STEC PCR –ve
- Dialysis dependent

Results back after weekend

Renal pathology in TMA



- Intimal cell swelling/hyperplasia
- Fibrinoid necrosis/thrombosis

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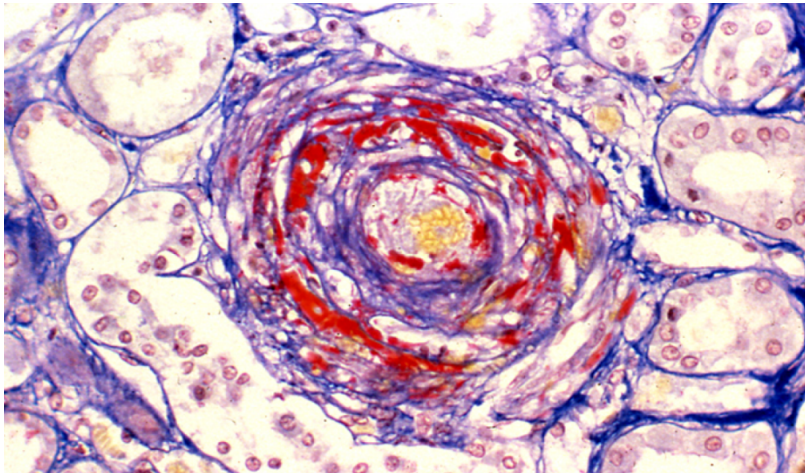

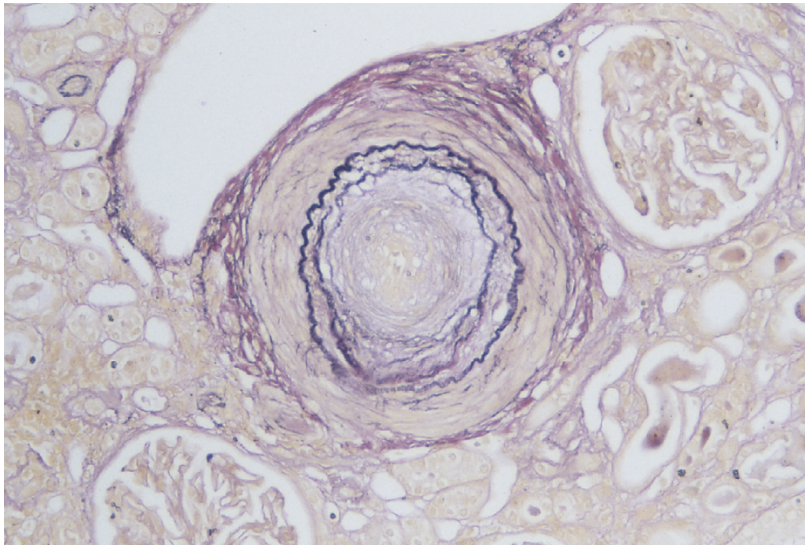

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- Myointimal proliferation
  - Onion skinning
- Duplicated basement membrane

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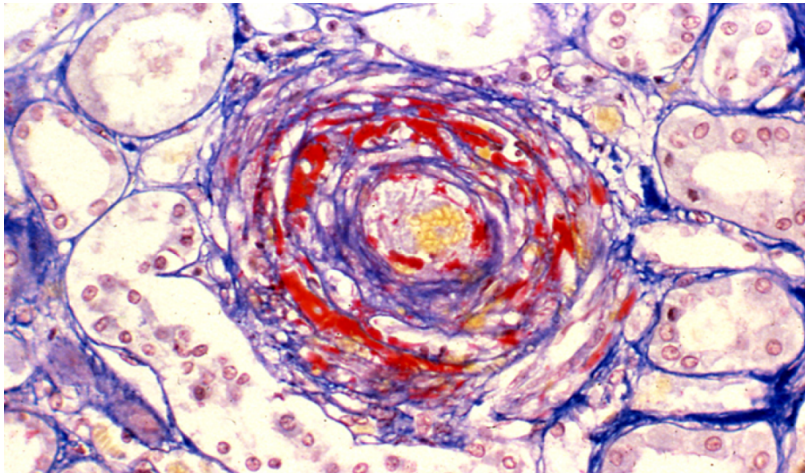

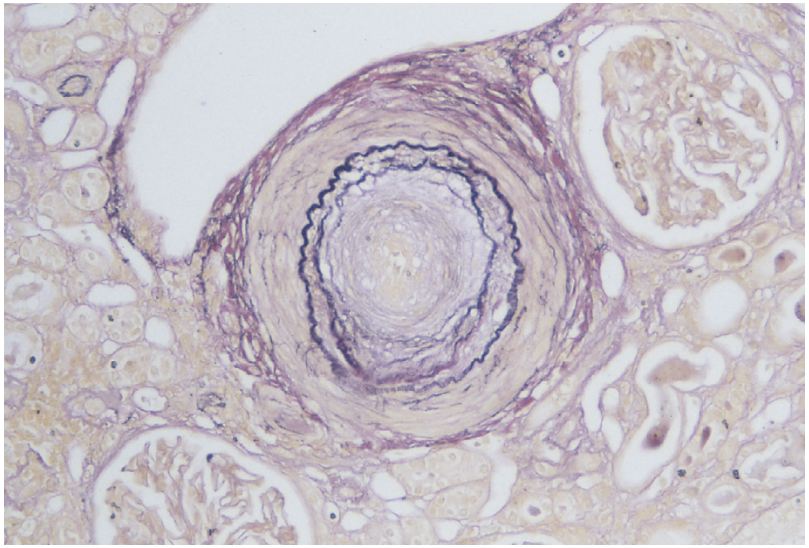

- Intimal cell swelling/hyperplasia
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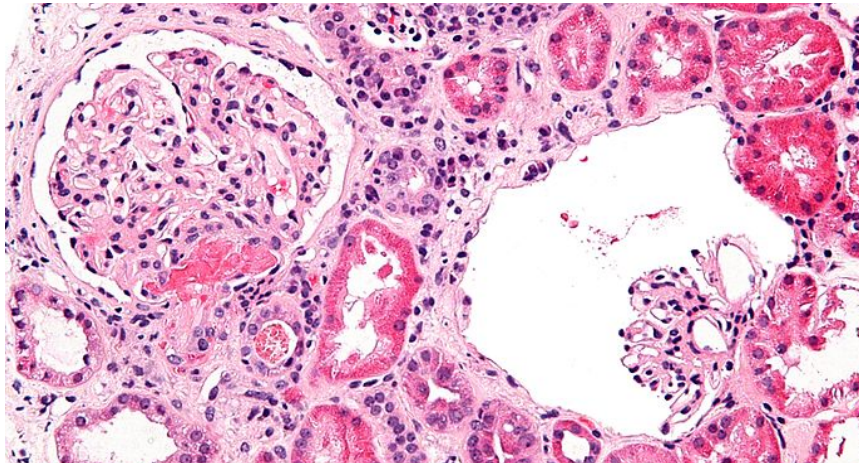
  - Onion skinning
- Duplicated basement membrane
- Bloodless/shrunken glomeruli



Electron microscopy

- Amorphous material (fibrin) interposed between endothelial cells and GBM