The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Haemolytic Uraemic Syndrome and The ECUSTEC Trial

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14th October 2016

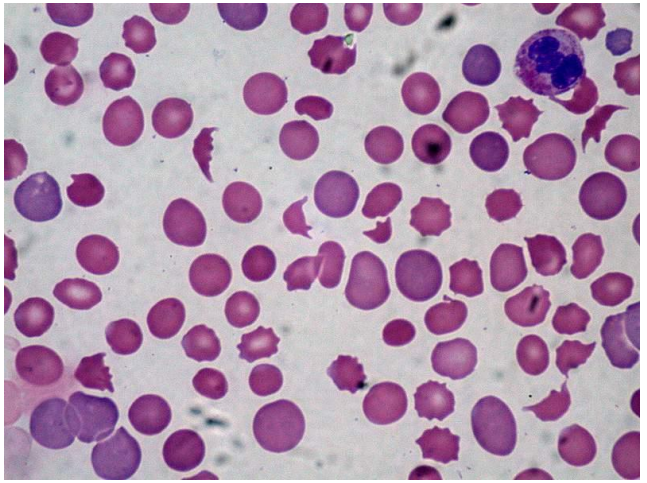
ECUSTEC

NHS National Institute for Health Research

THE great north CHILDREN'S HOSPITAL

Haemolytic Uraemic Syndrome

- Commonest cause of intrinsic acute kidney injury in children
- Classical triad
  - Microangiopathic haemolytic anaemia
  - Thrombocytopenia
  - Acute kidney injury
- 100 - 120 cases per year in UK
- 95% cases follow infection with Shiga-toxin producing E. coli (STEC)



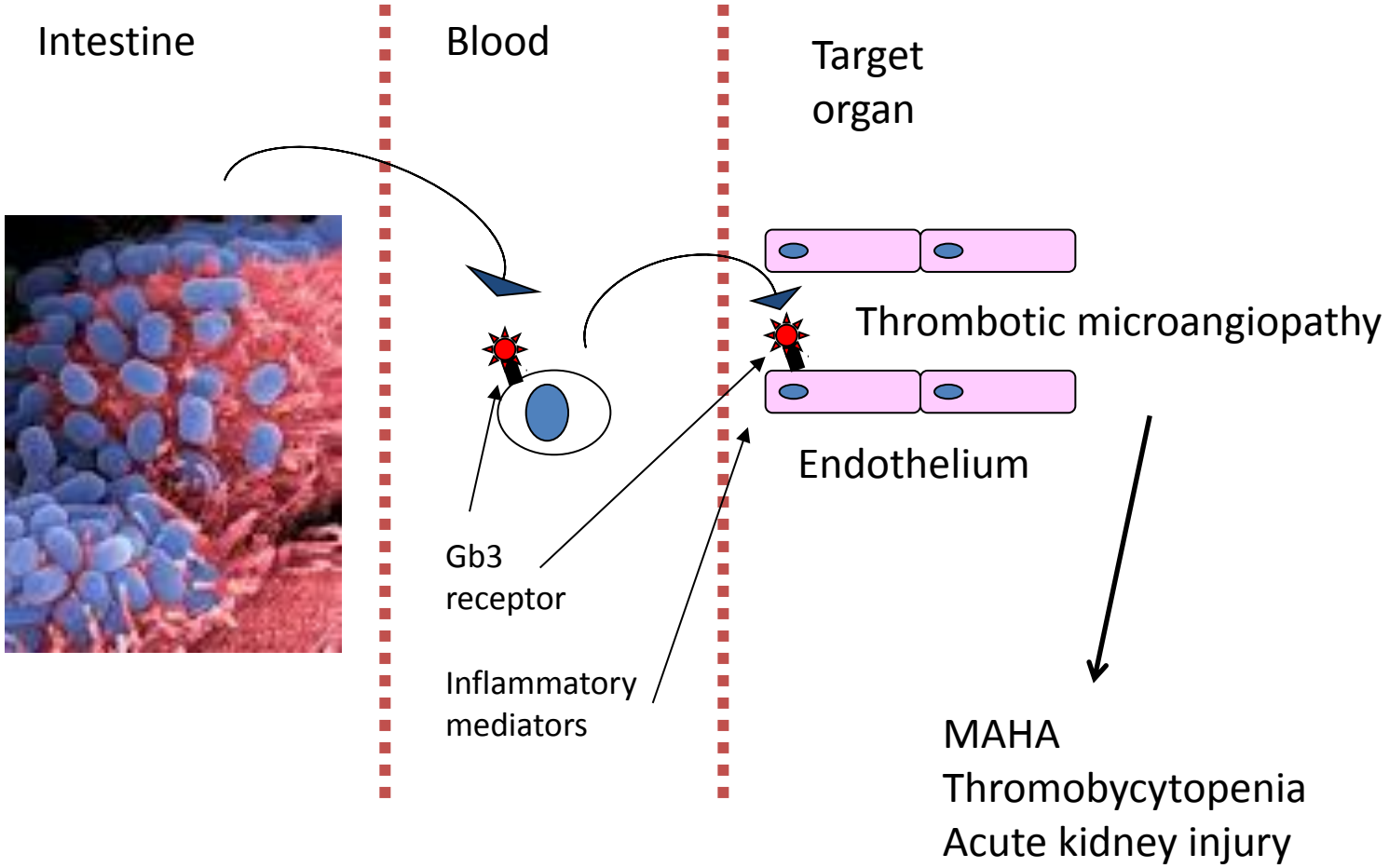
STEC infection

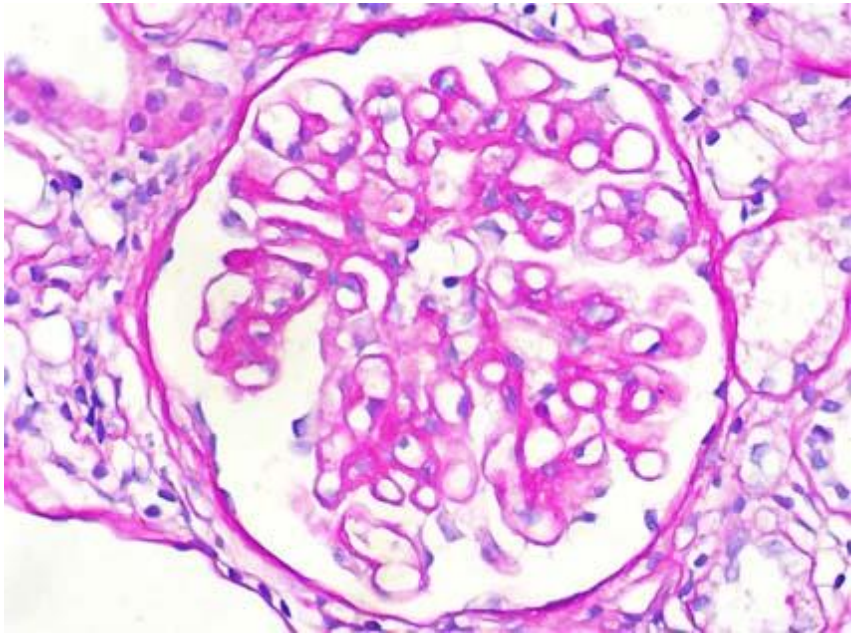
- STEC causes around 1000 cases of gastro-enteritis in England p.a.
  - Diarrhoea and vomiting, abdominal pain
  - Bloody diarrhoea (red flag symptom)
- Natural reservoir of STEC - intestines of ruminants
- Infection follows
  - Ingestion of contaminated foods/water
  - Direct or indirect contact with animals (e.g. cattle, sheep)
  - Person-to-person spread
- Commonest serotype is O157
  - Also O55, O26, O111 and others
  - Key attribute is the secretion of Shiga-toxin
- Diagnosis
  - Stool culture – specialised culture
  - Stool PCR for Shiga-toxin
  - Serology

STEC (typical) HUS

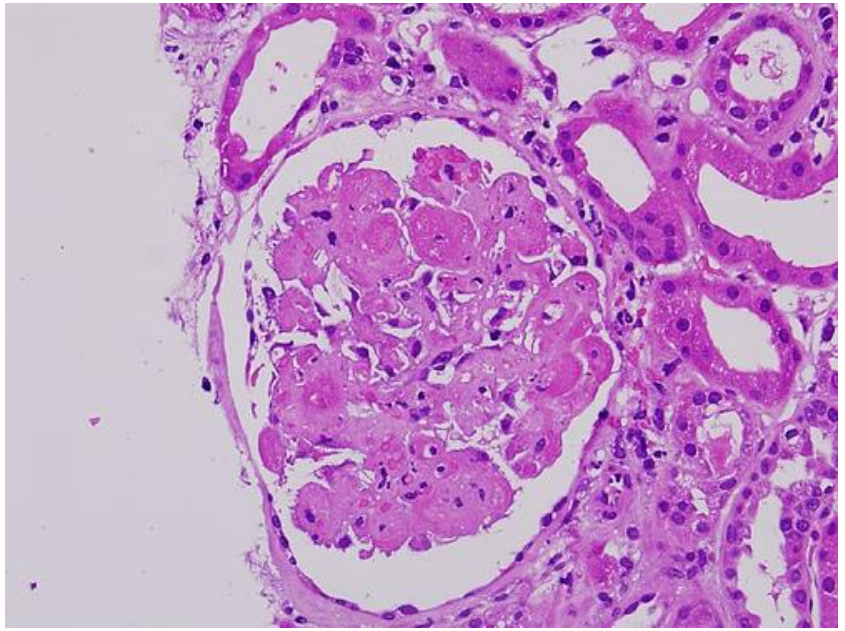
- Occurs after 10-15% of STEC infections
- 3-10 days following colitis onset
  - 50% require Renal Replacement Therapy (RRT), mean duration 10 days
  - 1-3% acute mortality
- Extra renal complications
  - 20-25% CNS involvement
  - Severe gut disease
  - Pancreatitis
- Management entirely supportive
  - Aim for euvolaemia - saline
  - RRT and blood transfusion
  - Anticipation and management of complications
- Outcome
  - 12% risk end-stage renal failure or death
  - 25% risk chronic kidney disease
- Long term follow-up advocated

STEC HUS


Intestine
Blood
Target organ
Thrombotic microangiopathy
Endothelium
Gb3 receptor
Inflammatory mediators
MAHA
Thromobycytopenia
Acute kidney injury



Normal glomerulus



Thrombotic microangiopathy

Shocking E coli pictures of toddler left in coma for five days by deadly stomach bug

12:15, 28 NOV 2014 | **UPDATED** 12:54, 28 NOV 2014 | **BY** SAM RKAINA

Freddy Osbourne, just 21 months old, was one of 10 people struck down in a serious outbreak of E coli in Dorset

Intensive Care Freddy Osborne was in a coma for five days after contracting E coli

Exeter fundraiser for boy with E-coli

By **Exeter Express and Echo** | Posted: March 24, 2015

Henry Marsh with his father, Philip

Adapted from Besbas Kidney Int 2006

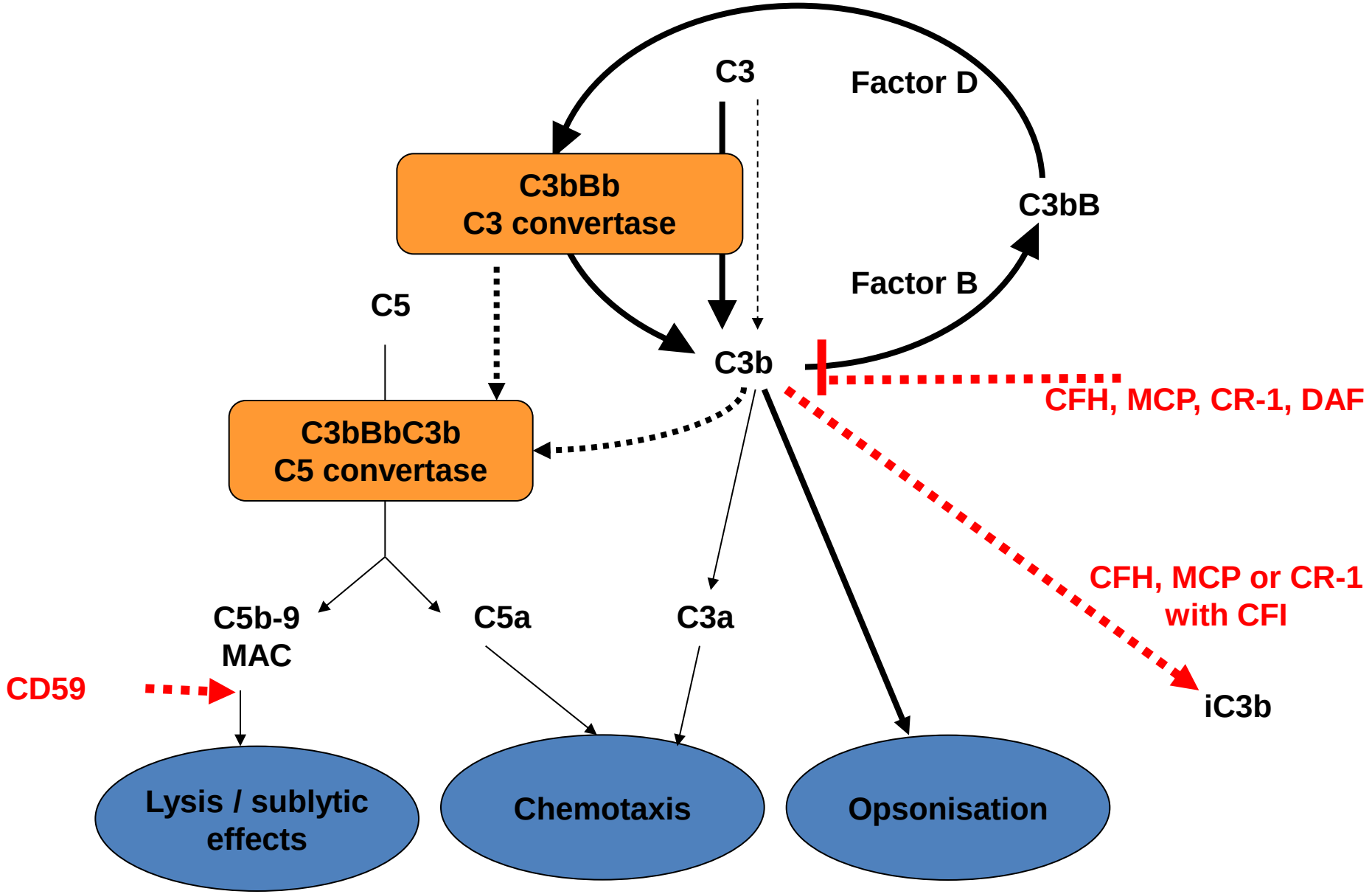
Causes of HUS

95%

5%

Infection-induced
(a) Shiga toxin-producing bacteria (STEC, Shigella)
(b) Streptococcus pneumoniae
Disorders of complement regulation
(a) Genetic
(b) Acquired
Miscellaneous
ADAMTS13 deficiency
Defective cobalamin metabolism
Quinine-induced
Malignancy, cancer chemotherapy, ionizing radiation
Calcineurin inhibitors and transplantation
SLE, anti-phospholipid antibody syndrome
HIV infection
Pregnancy, HELLP syndrome, contraceptive pill

Alternative complement pathway

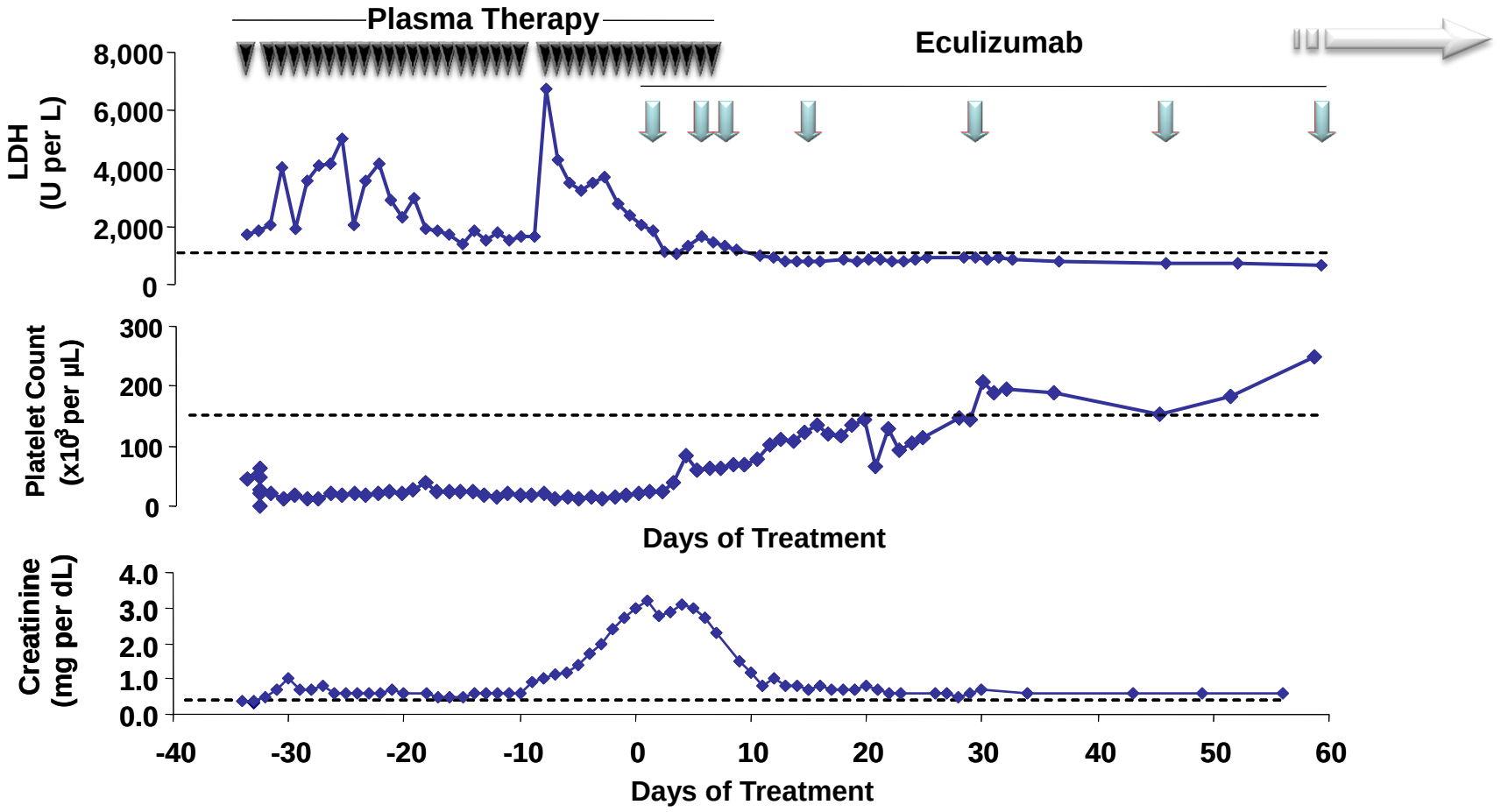


Atypical HUS – underlying abnormalities

Gene or abnormality	Frequency
Complement Factor H	20-30%
Membrane Cofactor Protein	5-15%
Complement Factor I	4-10%
Complement Factor B	1-4%
C3	2-10%
Thrombomodulin	0-3%
DGKe	3-5%
Anti-CFH antibodies	6%
Unexplained	30-40%

- Relapsing course
- Progressive
- 50% end stage renal failure or death at 5 years from diagnosis
- Traditional therapy – plasma therapy

Case report of chronic eculizumab therapy



Gruppo RA, et al. *N Engl J Med.* 2009;360(5):544-6.

Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome

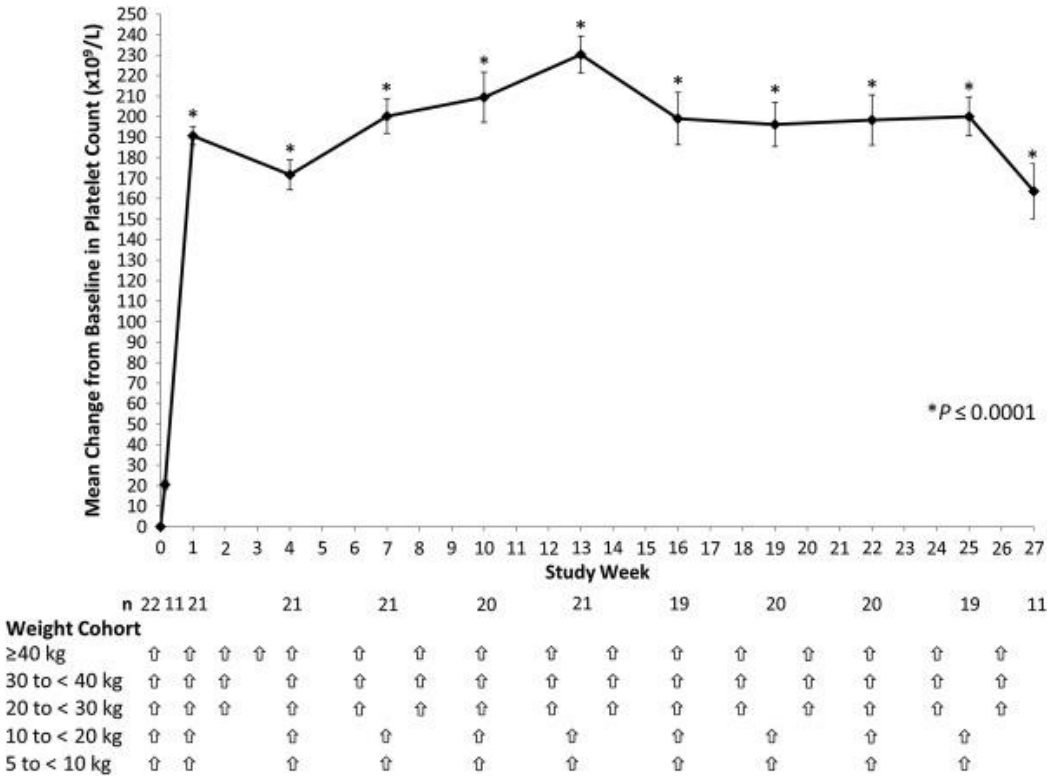


Figure 2. Improvement in platelet count over 27 weeks of eculizumab treatment. N values <5 were not included. Bars represent SEM. Arrows denote administration of eculizumab.

Larry A. Greenbaum, Marc Fila, Gianluigi Ardissino, Samhar I. Al-Akash, Jonathan Evans, Paul Henning, Kenneth V. Lieberman, Silvio Maringhini, Lars Pape, Lesley Rees, Nicole C.A.J. van de Kar, Johan Vande Walle, Masayo Ogawa, Camille L. Bedrosian, Christoph Licht

Kidney International, Volume 89, Issue 3, 2016, 701–711

http://dx.doi.org/10.1016/j.kint.2015.11.026

Eculizumab in Severe Shiga-Toxin–Associated HUS

TO THE EDITOR: The hemolytic–uremic syndrome (HUS), a thrombotic microangiopathy, most commonly occurs secondary to infection with Shiga-toxin–producing *Escherichia coli* (STEC-HUS), although rare, atypical forms are associated with abnormalities in complement-regulating proteins. The inhibition of terminal complement complex formation by the monoclonal C5 antibody eculizumab has recently been reported as a treatment for atypical HUS.[1]

We report on three 3-year-old patients with severe STEC-HUS that required hemodialysis. In Patient 1, plasma exchanges were performed because of low C3 and elevated C3d serum concentrations, which suggested complement activation. Plasma exchange was also performed in Patient 2 because of severe central nervous system involvement, a rare complication that often leads to death or permanent neurologic damage.[2] Progressive involvement of the central nervous system developed in both patients despite 5 consecutive days of plasma exchange.

Given the devastating prognosis, we administered eculizumab to these two patients, as well as to a third patient with a similar disease course, at 7-day intervals, twice in Patients 1 and 3 and four times in Patient 2. The neurologic status in all three patients improved dramatically within 24 hours after the first eculizumab infusion. let counts normalized, and lactate dehydrogenase levels decreased within 5 days in all patients (Fig. 1, and the Supplementary Appendix, available with the full text of this letter at NEJM.org).

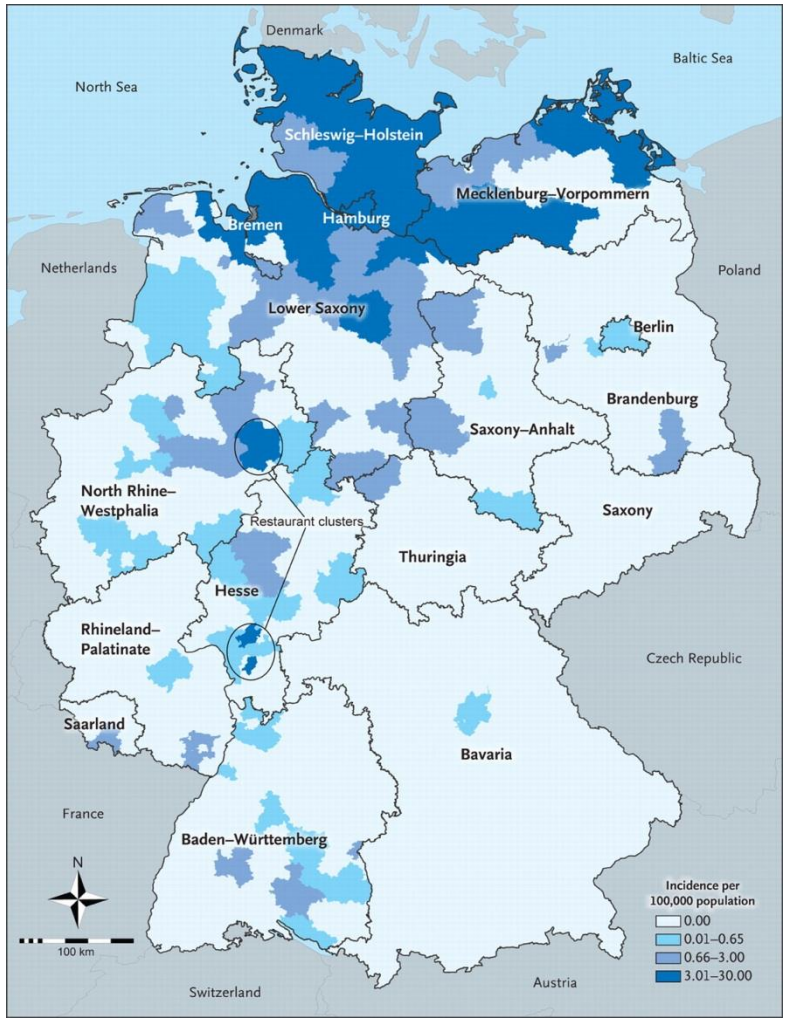
Dialysis was discontinued after 3 days in Patient 1, after 16 days in Patient 2, and after 13 days in Patient 3, and the patients were discharged with apparently normal neurologic status 9, 35, and 20 days, respectively, after the administration of the first dose of eculizumab. Renal function fully recovered, with mild residual proteinuria and hypertension in Patients 1 and 3. All patients have remained in full remission for the past 6 months. Screening for mutations in the genes encoding complement regulatory proteins (*CFH*, *CFI*, *MCP*, *C3*, *CFB*, and *THBD*) and testing for anti-CFH antibodies were negative in all patients.

In the cases reported here, spontaneous recovery seemed unlikely, given the rapidly progressive course of the disease. The rapid clinical response to eculizumab in all three children supports the concept that Shiga toxin may activate complement directly,[3] providing a rationale for therapeutic complement blockade in STEC-HUS with severe complications. Complement hyperactivation was recently demonstrated in STEC-HUS,[4] and a mutation in the complement-regulating gene *MCP* was reported in a fatal case of STEC-HUS.[5] The dramatic resolution of symptoms after

Lapeyraque
NEJM 2011

German outbreak May-July 2011

- 3816 STEC cases
- 845 (22%) developed HUS
- 54 deaths
- 88% of those with HUS were adults, mostly women
- Causative serotype E coli O104:H4
  - Combination of characteristics from EAEC and EHEC



Frank NEJM 2011; Wadl Euro Surveill. 2011

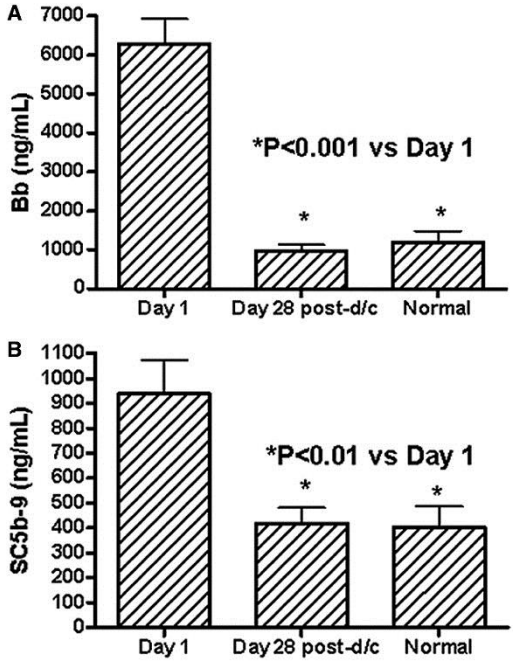
German outbreak data

- Ad hoc use of eculizumab
- Compassionate use
- Often combined with plasma exchange
- Outcome data difficult to interpret
- Industry sponsored trial
  - 198 patients
  - 7 doses (£84,000)
  - Data presented to ASN 2012, no publication
- Off-label use increasing globally

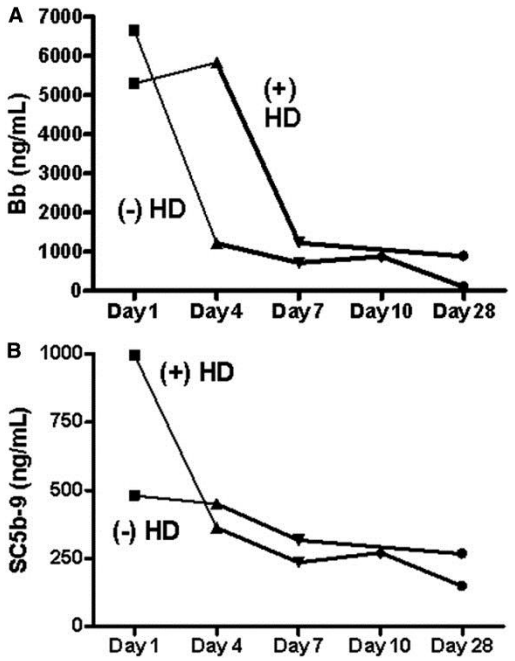
Kielstein NDT 2012
Menne BMJ 2012

Complement in STEC HUS

- Low plasma C3 levels in acute STEC-HUS are associated with leucocytosis and severe disease
- Levels of C3a, Bb and sC5b-9 are transiently elevated in children with STEC-HUS



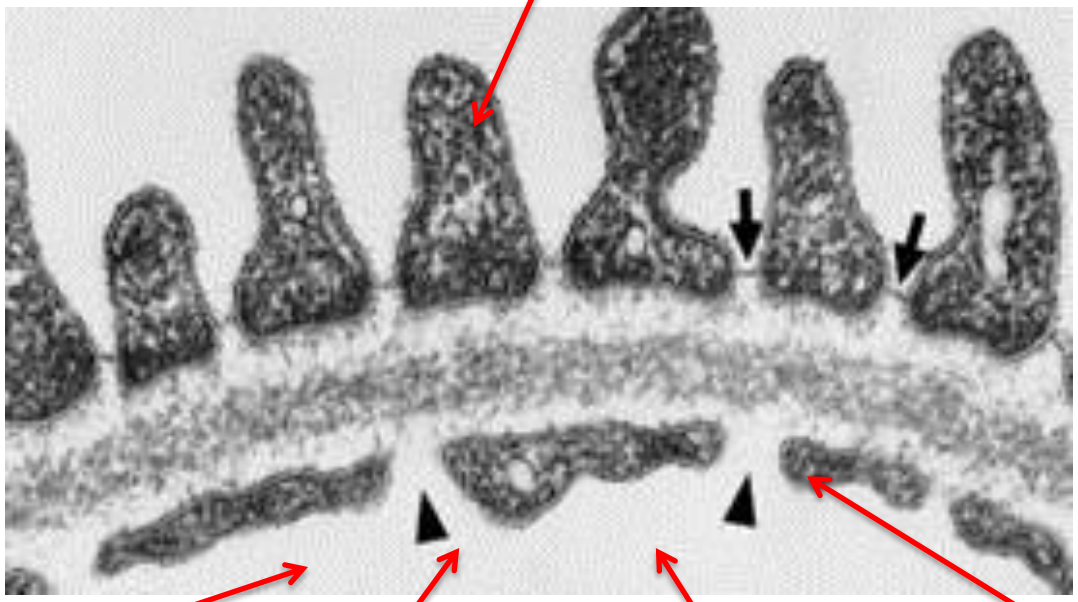
mean plasma concentration of Bb (A) and SC5b-9 (B) in patients with D+HUS



plasma concentration of Bb (A) and SC5b-9 (B) over the course of the D+HUS episode

Robson 1992 Thurman 2009 Stahl 2011 Morigi 2001

Shiga toxin reduces podocyte VEGF which in turn reduces endothelial complement regulator expression



Podocyte

GBM

Endothelium

Stx interacts with CFH in fluid phase

Stx activates complement on endothelium via ACP (P-selectin binds C3)

Activated complement components are detected on platelet-leucocyte complexes

Complement mediates proliferative response to vascular injury (C3a/C5a)

Orth J Immunol 2009, Sakuma Art Thromb Vasc Biol 2010, Mason J Biol Chem 2004
Eremina NEJM 2008, Keir Ped Nephrol 2014, Morigi J Immunol 2011

ECUSTEC

A randomised, double-blind placebo controlled trial of ECUlizumab in STEC Haemolytic Uraemic Syndrome

NIHR Efficacy and Mechanism Evaluation funded 2015

The ECUSTEC team

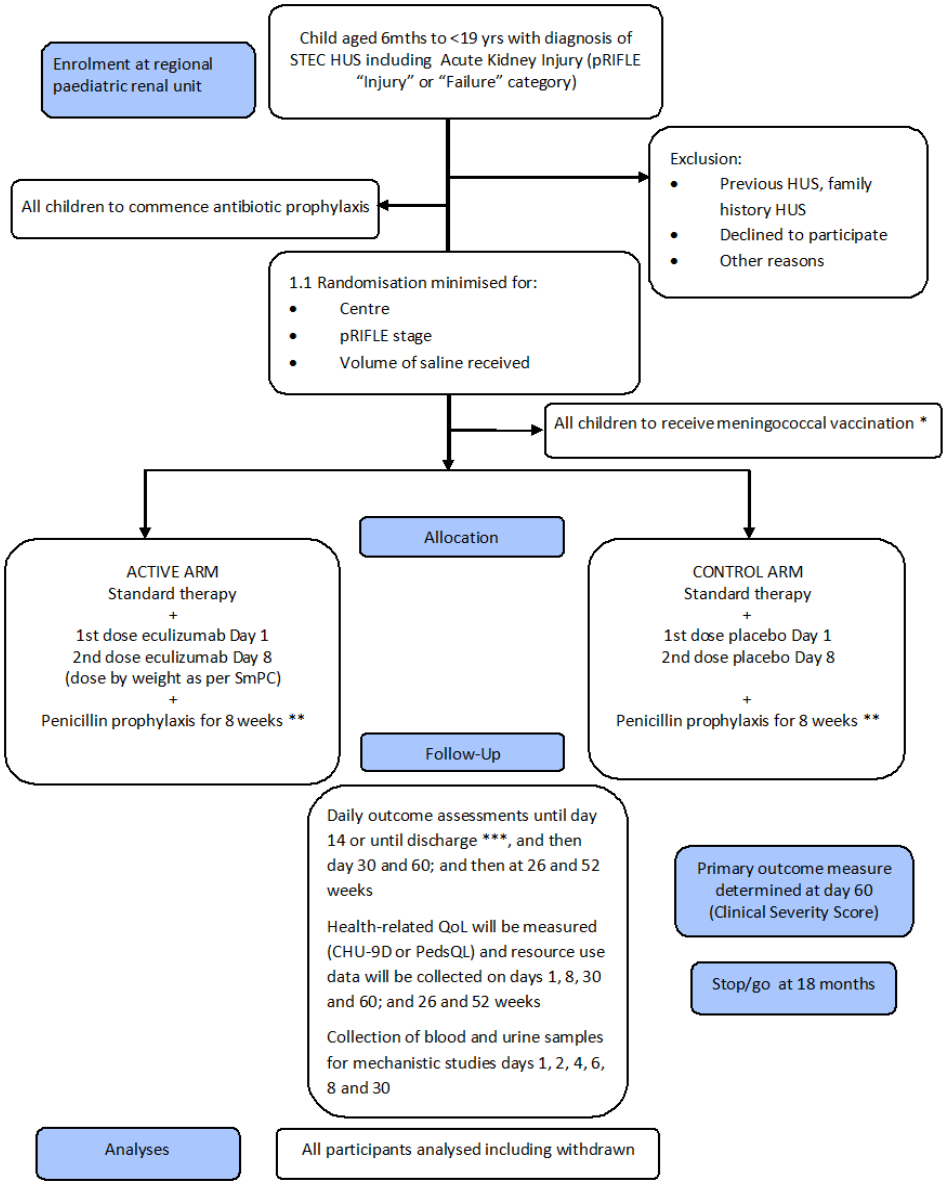
Co-applicant	Role	Institution
Sally Johnson	Consultant Paediatric Nephrologist	Newcastle
Nick Webb	Consultant Paediatric Nephrologist	Manchester
Moin Saleem	Consultant Paediatric Nephrologist	Bristol
Rodney Gilbert	Consultant Paediatric Nephrologist	Southampton
Aoife Waters	Consultant Paediatric Nephrologist	GOSH
Natalie Ives	Senior Statistician	Birmingham Clinical Trials Unit
Elizabeth Brettell	Renal Trials Manager	Birmingham Clinical Trials Unit
Hugh McCloud	Health Economist	Birmingham Clinical Trials Unit
Munir Ahmed	General Paediatrician (SPIN)	Worcestershire
Steve Nash	Co-founder	HUSH (E coli support group)
Claire Jenkins*	Head of Gastrointestinal Reference Laboratory	Public Health England

* collaborator

Research objectives

- In children aged 6 months to <19 years inclusive, we intend:
  - To determine whether the severity of STEC HUS is less in those given Ecu compared with those given placebo
  - To assess the safety of Ecu in STEC HUS
  - To determine whether the incidence of CKD following STEC HUS is less in those receiving Ecu compared with those receiving placebo
  - To evaluate the cost-effectiveness of administration of Ecu in STEC HUS from the perspective of the NHS

Trial overview



*Meningococcal B vaccine (Bexsero™) and conjugate meningococcal ACYW vaccine (Nimenrix or Menveo) will be given to all ECUSTEC trial participants (unless Bexsero™ already received as part of UK immunisation programme). Child <12 months Menveo; =12 months Menveo or Nimentrix. If platelet count $<50x10^9$/l defer vaccination until platelet $>50x10^9$/l

** erythromycin if penicillin allergic

*** assessment at day 21 and 30 if in-patient

134
participants

Inclusion criteria

- Age 6 months to <19 years
- Weight ≥5kg
- Diagnosis of HUS
  - Micro-angiopathic haemolytic anaemia (indicated by fragmented red cells on blood film **OR** plasma lactate dehydrogenase above local centre reference range)
  - **AND**
  - Thrombocytopenia (platelets <150x10^9/l)
  - **AND**
  - Acute Kidney Injury (AKI): "injury" or "failure" category of pRIFLE criteria[27] (Table 1) despite correction of hypovolaemia
- **EITHER**
  - Reported diarrhoea within 14 days prior to diagnosis of HUS (defined according to World Health Organisation as "the passage of three or more loose or liquid stools per day - or more frequent passage than is normal for the individual")
  - **OR**
  - Stool culture or shiga toxin polymerase chain reaction (PCR) or STEC serology result indicating STEC in the patient or household contact within 14 days prior to diagnosis of HUS
- Patient intended to be able to receive trial drug within 36 hours of arrival at renal unit, or within 24 hours of eligibility if already at renal unit
- Sexually active male or female patients must agree to be practicing an effective, reliable and medically approved contraceptive regimen for 6 months after enrolment.
- Written informed consent obtained from the participant's parents/guardians and written assent obtained from participant (where age appropriate). Participants aged 16 years and above will provide their own written consent.

Patient Identification Centre (PIC)

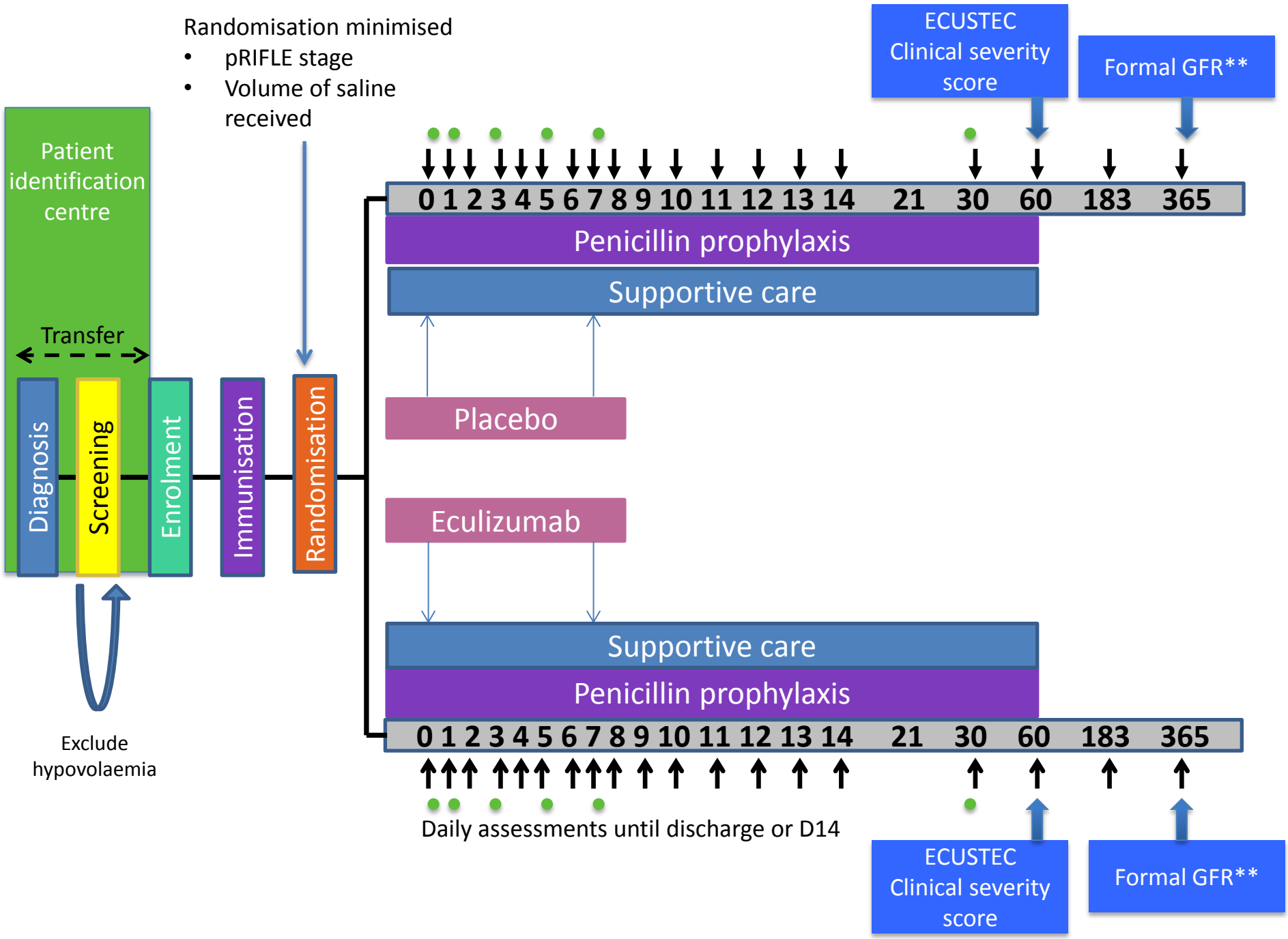
- NHS site
- Can identify and refer potential patients to another site for consideration of entry into clinical trial
- Simple set-up
- Can give patient information
- Activity is acknowledged

Sequence

- District general hospital (may or may not be a PIC)
  - STEC HUS is suspected (all inclusion criteria do not need to be met)
  - Clinical stabilisation
  - Contact the regional paediatric nephrologist on-call
- Renal unit
  - If diagnosis highly likely to be STEC HUS, will try to accept the referral and arrange transfer
  - If child does not require transfer for clinical purposes, the paediatric nephrologist will explain that transfer will be accepted earlier than usual so that participation in the trial can be offered and explain that there will be no obligation to enter the trial
- Information regarding ECUSTEC will be offered pre-transfer if the referring hospital is a PIC

After arrival at renal unit

- Clinical stabilisation and hypovolaemia correction
- Information about study given
- Creatinine repeated
- If remains eligible, seek informed consent
- Randomisation
- Completion of baseline assessments
- Meningococcal prophylaxis/vaccination
- Administration of study drug within 36 hours of arrival
  - Blinded pharmacy staff
  - Eculizumab or saline
  - Second dose 7 days later


Randomisation minimised
• pRIFLE stage
• Volume of saline received
ECUSTEC Clinical severity score
Formal GFR**
Patient identification centre
Transfer
Diagnosis
Screening
Enrolment
Immunisation
Randomisation
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 21 30 60 183 365
Penicillin prophylaxis
Supportive care
Placebo
Eculizumab
Supportive care
Penicillin prophylaxis
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 21 30 60 183 365
Exclude hypovolaemia
Daily assessments until discharge or D14
ECUSTEC Clinical severity score
Formal GFR**

Renal	Lowest eGFR >50	1
	Lowest eGFR 25-49, no oligoanuria*	2
	Lowest eGFR < 25, no oligoanuria*	3
	Oligoanuria* but no dialysis required	4
	Dialysis <48 hours	5
	Dialysis 2 days	6
	Dialysis 3 days	7
	Dialysis 4 days	8
	Dialysis 5 days	9
	Dialysis 6 days	10
	Dialysis 7 days	11
	Dialysis 8 days	12
	Dialysis 9 days	13
	Dialysis 10 days	14
	Dialysis 11 days	15
	Dialysis 12 to 13 days	16
	Dialysis 14 to 17 days	17
	Dialysis 18 to 20 days	18
	Dialysis 21 to 27 days	19
	Dialysis 28 to 34 days	20
	Dialysis 35 to 41 days	21
	Dialysis 42 to 48 days	22
	Dialysis 49 to 55 days	23
	Dialysis >55 days	24
CNS	No obvious CNS involvement	0
	Altered consciousness (Agitation, irritability, hallucinations, confusion, excessive drowsiness)	2
	Single seizure	4
	Two or more seizures 24 hrs apart**	6
	Transient focal neurological defect (>24 hrs*** but <1 week)	7
	Persistent focal neurological defect (present at day 60 and persistent for more than 1 week)	10
	Persistent global (≥ 2 brain functions - vision/hearing/cognitive/motor/sensory/memory) neurological defect at day 60	15
Pancreas	No clinical or biochemical evidence pancreatitis	0
	Raised amylase and/or lipase without clinical symptoms/signs	2
	Hyperglycaemia without insulin requirement	6
	Pancreatitis with sequelae (laparotomy, TPN, insulin required)	8
	Chronic sequelae of pancreatitis at day 60 (TPN, insulin, other)	10
Gastro-intestinal	No abdominal surgery required (except related to peritoneal dialysis catheter)	0
	Laparoscopy/laparotomy required for abdominal symptoms	5
	Intestinal perforation AND/OR bowel resection required	8
	Stoma formation	10
Cardiac	No cardiac involvement (normal CVS examination - except hypertension/volume overload)	0
	Cardiac failure confirmed by ECHO (impaired systolic ventricular function or chamber enlargement or valve regurgitation)	4
	Cardiac failure confirmed by ECHO with dilated cardiomyopathy	6
	Myocardial infarction (on standard ECG +/- troponin +/- ECHO evidence)	10

Primary outcome measure: ECUSTEC Clinical Severity Score

80% power to detect a
5 point reduction in CSS

Pilot data:
Mean score 13.16
SD score 9.66

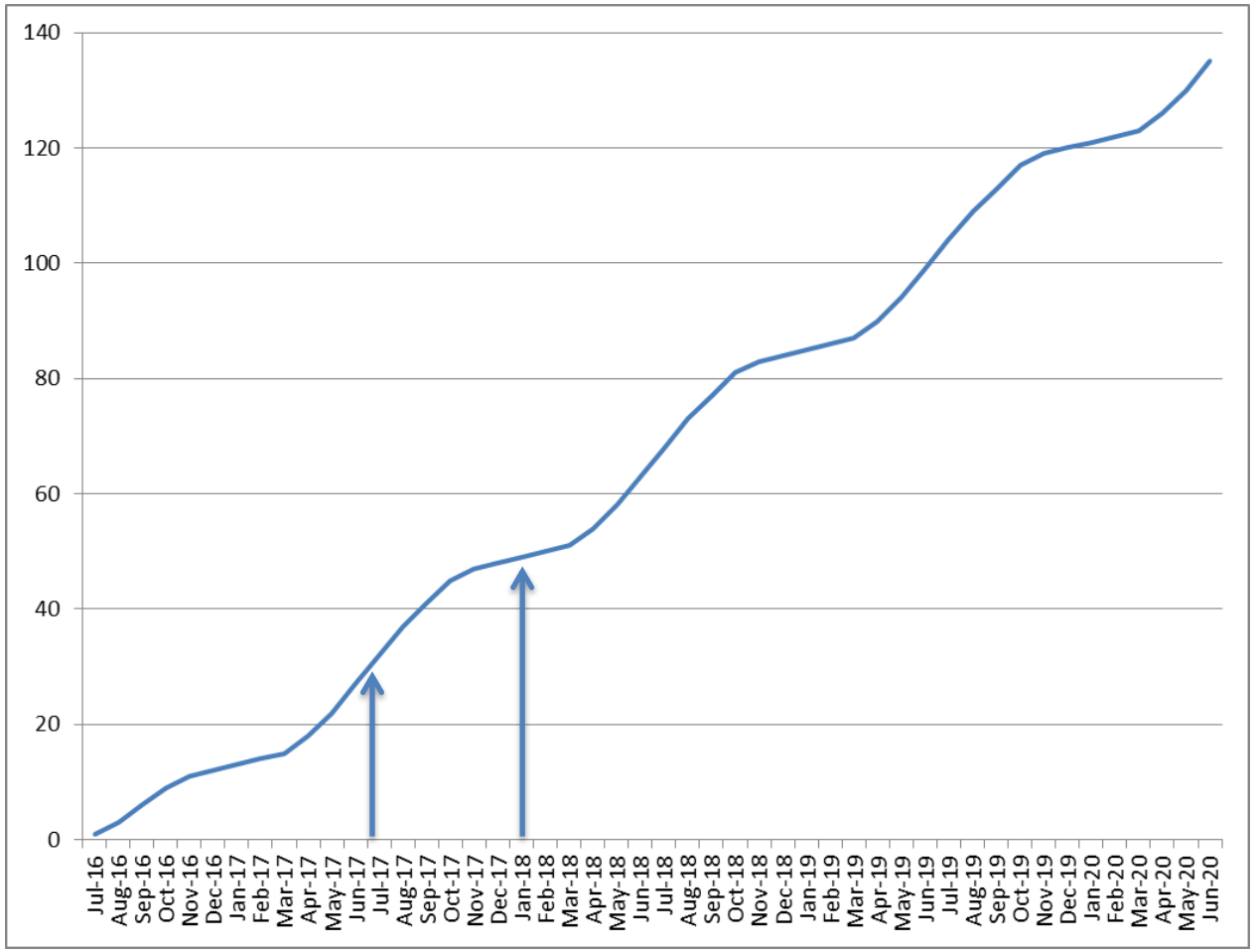
Secondary outcome measures

- Survival
- Duration of thrombocytopenia (number of days until platelet count >150x10^9/l)
- Duration of haemolysis (number of days until LDH within normal reference range)
- Number of packed red blood cell transfusions required and volume (ml/kg)
- Markers of inflammation (number of days until normal white cell count and CRP)
- CKD at 1 year - a composite endpoint of the presence of
  - Hypertension
    - Average of 3 readings by manual method using centiles for age/sex/height
    - Above 95th centile for age/sex/height
  - Albuminuria
    - Early morning urine albumin-creatinine ratio >2.5mg/mmol
  - eGFR<90ml/min/1.73m^2 at 1 year
- Persistent neurological defect at 60 days

Additional outcomes

- Safety
- Mechanistic studies
- Health economic evaluation
  - Cost-effectiveness of eculizumab vs. placebo will be measured
    - cost per ECUSTEC CSS point
    - cost per QALY
- Health-related QoL
  - CHU9D (>5y) and PEDsQL (<5y)

Recruitment projections



ECULISHU

- Inclusion criteria
  - eGFR <75
- Exclusion criteria
  - STEC-HUS patient with severe multiorgan involvement at diagnosis:
    - Neurological involvement (seizures, coma, focal deficit) with signs of microangiopathy on cerebral Magnetic Resonance Imaging.
    - Cardiac involvement (cardiac failure, ischemic myocarditis, conduction or rhythm troubles)
    - Digestive involvement (severe pancreatitis defined by lipasemia>500UI/L, severe hepatitis defined by transaminase >x10ULN and/or prothrombin time<60%, hemorrhagic colitis, bowel perforation, rectal prolapsus)
- If develops severe disease in placebo arm
  - Eculizumab

Challenges

- Patient identification
  - Your help is vital!
  - Majority of cases discussed with regional nephrology unit
  - Nominated Patient Identification Centres (e.barsoum@bham.ac.uk)
  - Please let your colleagues know!
- Transfer
  - Earlier than usual if possible
- Rapid enrolment after transfer
  - PIC can give information prior to transfer
  - Patient and carer involvement in production of patient information and pathways
- Rapid administration of study drug
  - Will require site-specific solutions

Exclusion criteria

- Family history of aHUS
- Previous episode of HUS
- Known pre-existing eGFR <90ml/min/1.73m2
- Known or suspected pneumococcal infection
- Patient taking a drug known to be associated with HUS, e.g. calcineurin inhibitors, chemotherapy, quinine, oral contraceptive pill
- Pregnancy
- Refusal of consent, including consent for meningococcal vaccination
- Currently participating in another CTIMP

Standardised non-trial management Neurological features

- Pilot data (5 centres) - 14/100 developed CNS features
- PEx in 8/14 – dependent on centre and not clinical features
- Agreement to avoid PEx in trial participants
- Agreement to avoid eculizumab in control arm

NO PLASMA EXCHANGE (8)	PLASMA EXCHANGE (6)	
Presentation	**Presentation**	**No of PEX**
1 Seizure, focal neurology <24 hrs*	Tonic Seizure- diffuse slow EEG	?
Hallucinations	Seizure- over 3 days	3
3x seizure- 2 vacant and 1 focal	Slurred Speech <24 hours	5
1x Tonic Clonic seizure	1x Tonic Clonic seizure	6
Generalised weakness Rt>Lt. >24hrs	Confusion, hemiparesis <24hrs	6
Encephalopathy then Seizures	1x Tonic Clonic seizure	3
Encephalopathy <24hours		
Tonic clonic seizure**		

pRIFLE criteria

- Schwartz 2009 (k=41.3)
- Height required
- Creatinine “real world”

	eGFR (Schwartz)		Urine output
Risk	≤ 75	OR	< 0.5 ml/kg/hr for 8 hrs
Injury	≤ 50		< 0.5 ml/kg/hr for 16 hours
Failure	≤ 35		< 0.3 ml/kg/hr for 24 hours or anuria for 12 hours
Loss	Need for Renal Replacement Therapy for > 4 weeks		
End-Stage	Need for Renal Replacement Therapy for > 3 months		