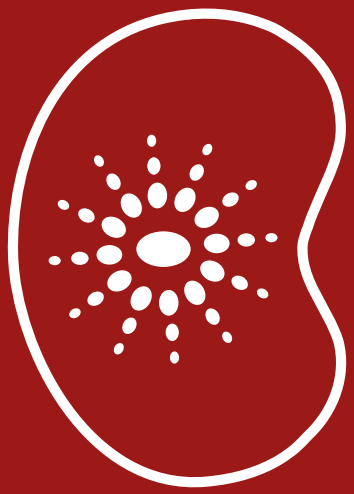
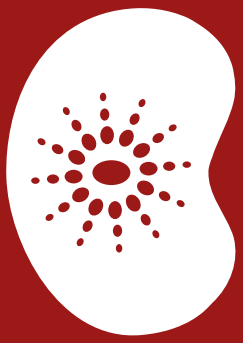
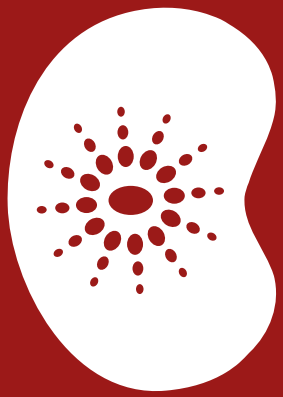
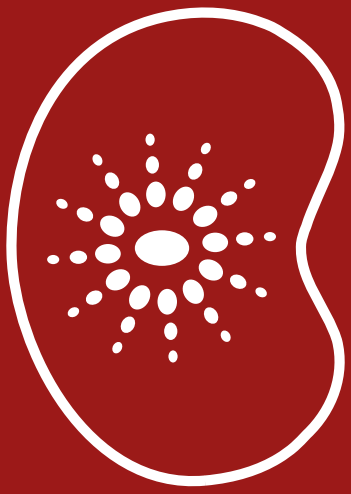
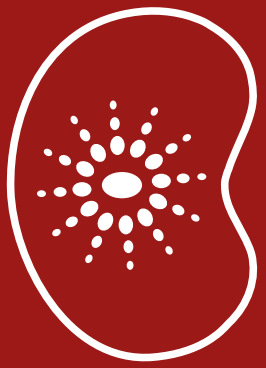
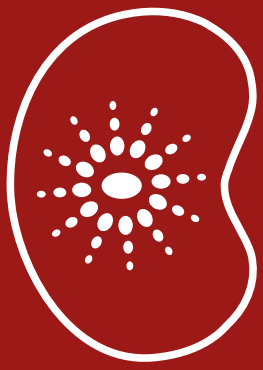
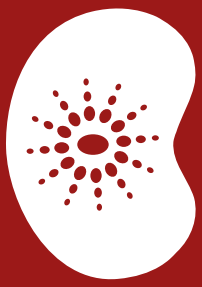
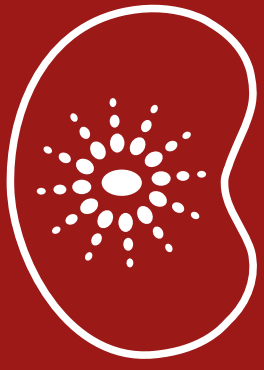
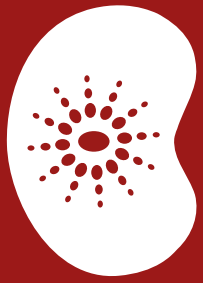
NATIONAL RENAL COMPLEMENT THERAPEUTICS CENTRE

NHS
The Newcastle upon Tyne Hospitals
NHS Foundation Trust

The Annual Report of the **National Renal Complement Therapeutics Centre** 2022/23

Newcastle University

www.atypicalhus.co.uk

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The Annual Report of the **National Renal Complement Therapeutics Centre** 2022/23

aHUS
ATYPICAL HAEMOLYTIC URAEMIC SYNDROME

NATIONAL RENAL COMPLEMENT THERAPEUTICS CENTRE

C3G
C3 Glomerulopathy

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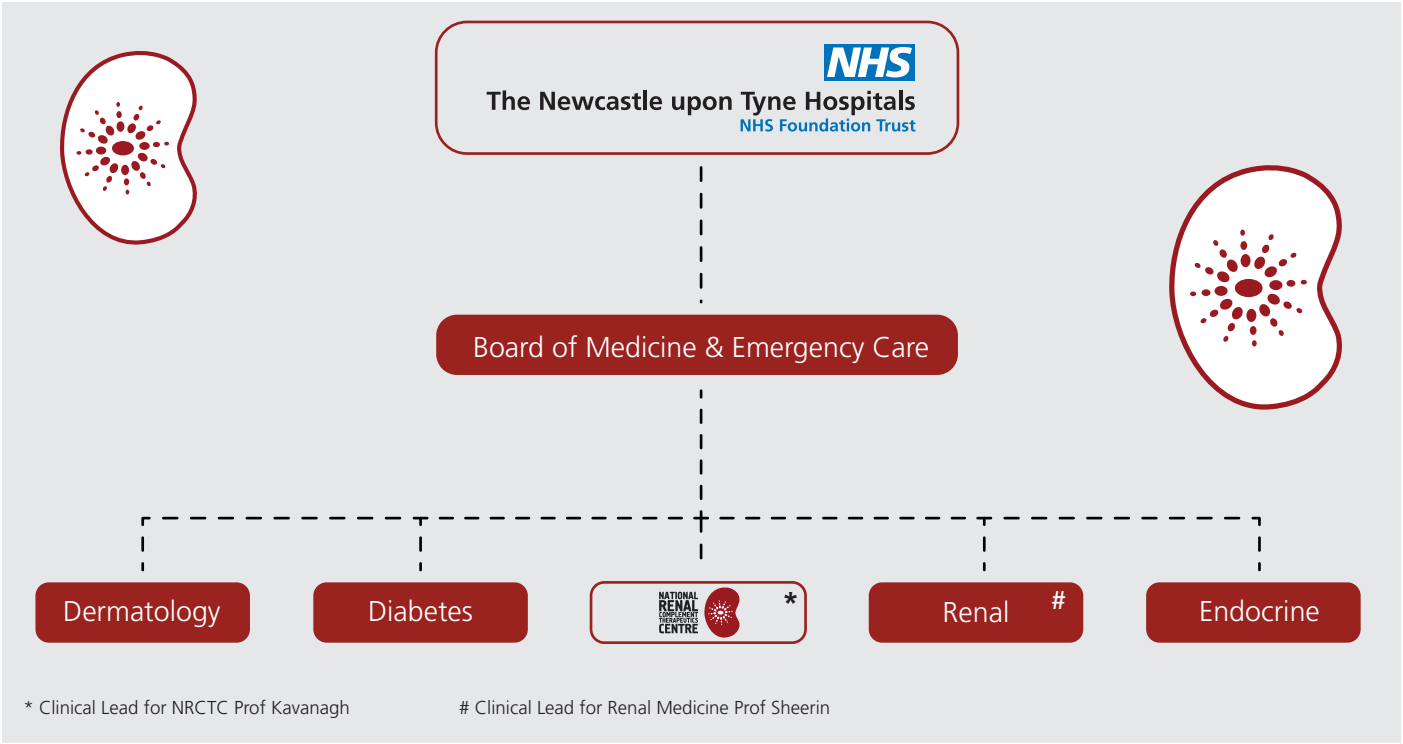
1. Service Overview

1.1 The National Service

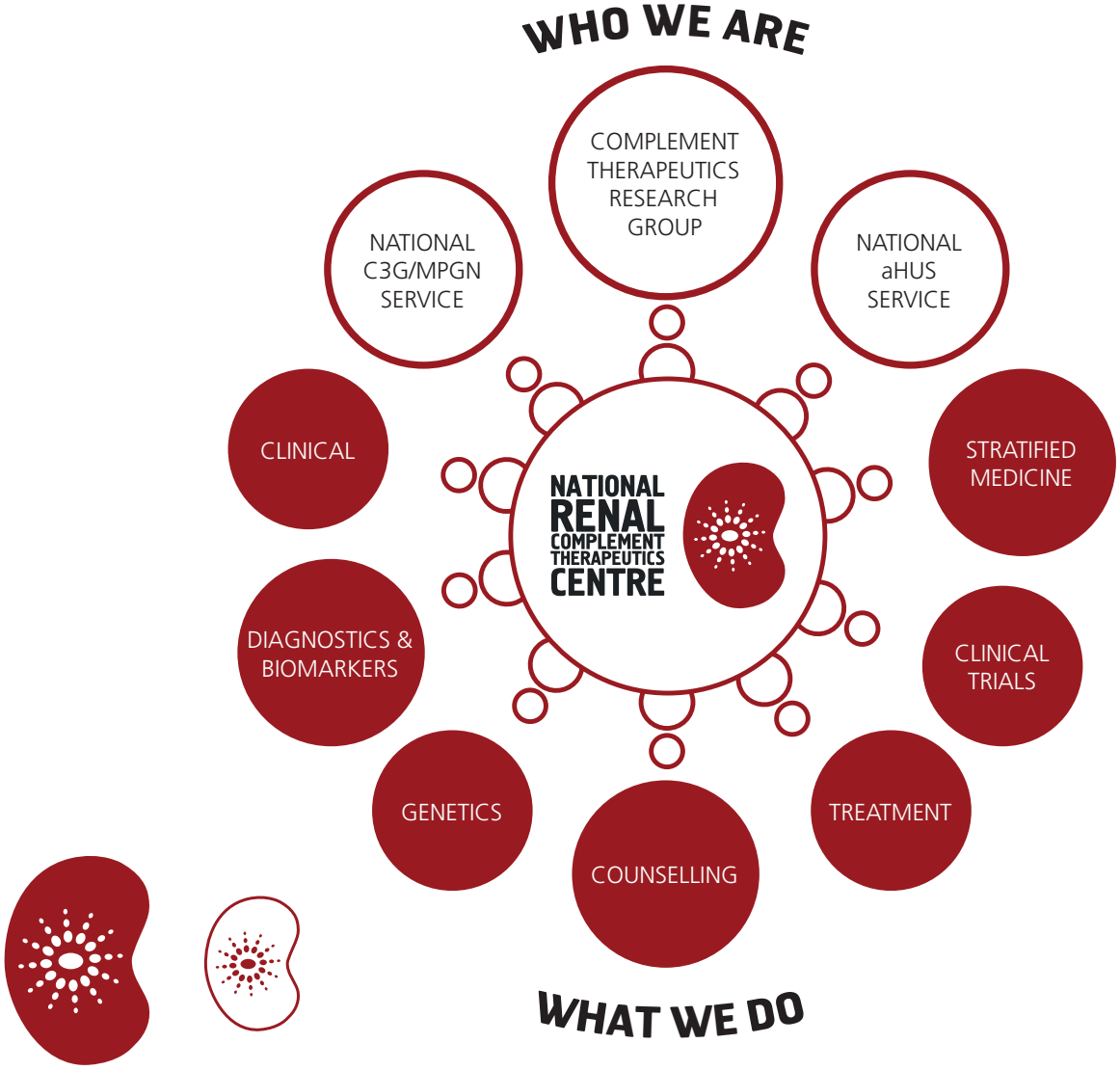
The National Renal Complement Therapeutics Centre (NRCTC) is a highly specialised multidisciplinary service focused on complement mediated kidney disease. Our expertise spans adult, paediatric and transitional nephrology; genetics, diagnostics and treatment; basic science, translational and clinical research. The National Atypical Haemolytic Uraemic Syndrome (aHUS) Service, co-ordinates the management of patients with aHUS and other thrombotic microangiopathies and was commissioned in May 2016 by NHS England. The National C3G/MPGN service manages the investigation and treatment of these diseases recurring after kidney transplantation and was added to our portfolio in February 2017.

Our service delivers a fully integrated care pathway to expedite optimal management of patients referred to us on a shared-care basis with the referring clinicians. Our core team currently comprises six consultant nephrologists (four adult and two paediatric), a clinical lecturer, three nurse specialists and an administration team. We also have seven dedicated clinical scientists and consultants working across genetics, haematology and immunology that help us deliver our cutting-edge diagnostics. The National Renal Complement Therapeutics Centre sits within the board of medicine and emergency care at the Newcastle upon Tyne Hospitals NHS Foundation Trust. Our consultants also work at the renal units at the Freeman Hospital and the Great North Children's Hospital, who are part of the Newcastle upon Tyne Hospitals NHS Trust.

Board of Medicine Organisational Structure



The NRCTC is also fully integrated with the Newcastle University Complement Therapeutics Research Group who were responsible for the discovery of the role of complement in aHUS, which ultimately led to the successful treatment of our patients with Eculizumab.



1.2 Our Vision and Values

Our vision is to be a centre of clinical excellence for patients with complement mediated renal diseases, including aHUS and C3G, at the forefront of international research. Our primary core value "achieving local excellence and global reach through compassionate and innovative healthcare, education and research." We wish to empower our patients to be knowledgeable about the care they require and receive. Our aspiration is to encourage our patients to co-design the care we deliver, enabling personalised management.

Our Vision

"To be 'the health service for Greater Newcastle' and a leading national healthcare provider."

Our Core Values

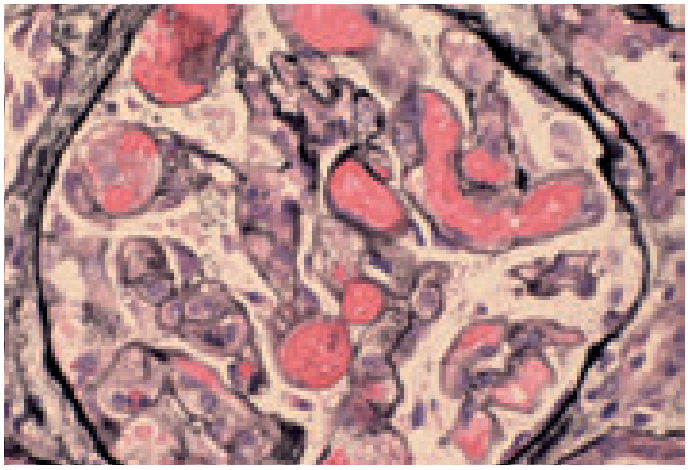
"Putting patients at the heart of everything we do"

1. **Patients come first**
2. **People and partnerships are important**
3. **Professionalism at all times**
4. **Pioneering services**
5. **Pride in what we do**

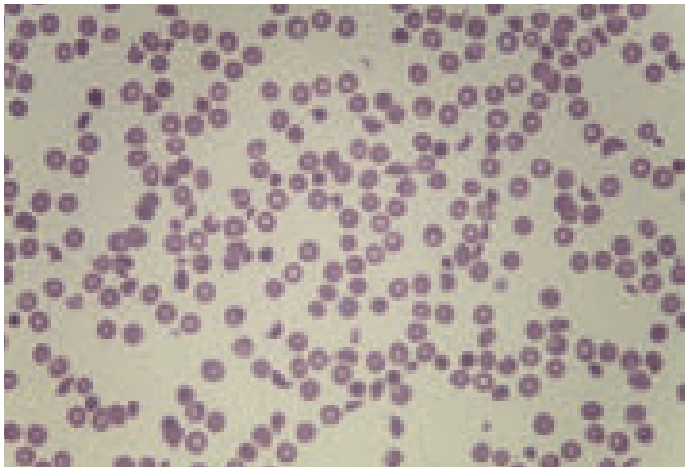
1.3 Disease Context

1.3.1 What is aHUS?

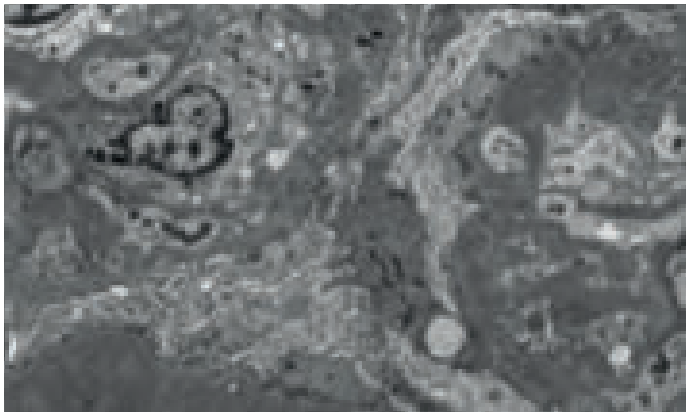
Atypical haemolytic uraemic syndrome is a rare disease with an incidence in the UK of 0.4-0.5 per million population. It presents with thrombocytopenia, microangiopathic haemolytic anaemia and acute kidney injury. Without treatment the prognosis for patients was poor with 60.5% of patients developing kidney failure or dying in the first year after presentation. There is no rapidly available test to confirm the diagnosis of complement mediated aHUS and the initial diagnosis is based on clinical, laboratory and pathological findings and the exclusion of other pathologies; in particular, infection related Shiga Toxin E.coli (STEC)-HUS and Thrombotic Thrombocytopenic Purpura (TTP). Eculizumab was licenced for the treatment of aHUS in 2011 having been shown to be effective in non-randomised, single arm open label studies. After initial review, preliminary interim funding for the use of Eculizumab to treat patients with aHUS in England was approved in 2013 whilst the National Institute for Health and Care Excellence (NICE) undertook further review. NICE published its guidance in 2015 recommending that Eculizumab was commissioned for the treatment of aHUS. However, reflecting the high cost of Eculizumab, NICE recommended that treatment of patients was co-ordinated through an expert centre. Since 2016, the National aHUS Service has been available 7 days a week 24 hours a day to provide advice on diagnosis and management from consultants experienced in the management of aHUS. We also provide rapid diagnostic testing and support for clinicians to exclude other forms of thrombotic microangiopathy (TMA).



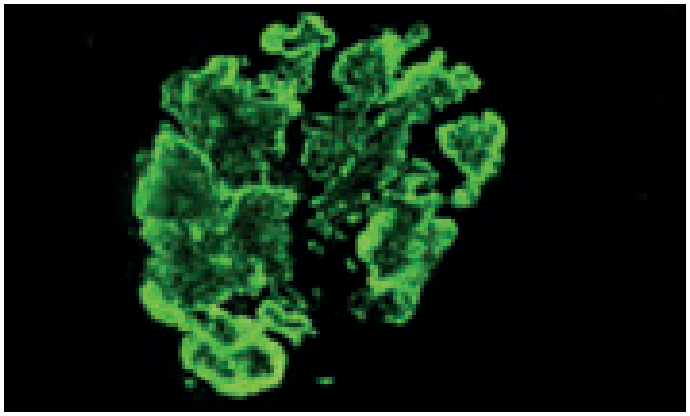
Renal biopsy showing thrombus formation in aHUS



Blood film from aHUS patient showing schistocytes



Sub-endothelial deposits in C3GN seen on electron microscopy



Strong C3 staining in C3GN

1.3.2 What is C3G?

C3 Glomerulopathy is a rare disease with an estimated incidence of 1-2 per million worldwide.

The clinical presentation is variable, ranging from an acute rapid progression of kidney injury to a more indolent presentation of chronic kidney disease. On average, patients develop kidney failure within 10 years of initial diagnosis and most patients who are subsequently transplanted develop recurrent disease, with approximately half of patients losing their kidney transplant to disease recurrence. The diagnosis of C3G is made on renal biopsy and based on the presence of dominant C3 deposition on immunofluorescence. Sub-classification of C3G into dense deposit disease and C3 glomerulonephritis is then based on the appearances on electron microscopy.

Eculizumab is not licensed for treatment of C3G but a review of the available evidence of its use in C3G led to approval for use in a Clinical Commissioning Policy (NHSE 16054/P) published in February 2017. The implementation of this policy is co-ordinated through an expert C3G panel comprising the National Renal Complement Therapeutics Centre and the Imperial C3G Service.

1.4 Our Strategy

Our service strategic objectives reflect how we wish to meet our vision, focusing on where we are now and what we want to achieve in the future.

Providing exceptional shared care today

- Advice/care will be offered in a timely manner to every person contacting the NRCTC.
- Every person requiring advice/care from the NRCTC will be provided with safe and high quality advice/care.
- Patients and their families engaging with the NRCTC will receive an excellent patient experience.

Striving to improve our service

- The NRCTC team will explore ways to improve the delivery of care and advice we offer to clinicians, patients and their families.
- Each member of the NRCTC team will be an advocate for patients and their families.

Advancing care for tomorrow

- We will enhance the reputation of the Newcastle upon Tyne Hospitals NHS Foundation Trust as the provider of a Highly Specialised Service, for the UK and the world.
- We will continue to be the world leaders in complement research with our partners, Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation Trust.

1.5 Service Development

The NRCTC strives to improve its service year on year.

This year we undertook peer review with the Quality Nursing Team from NHS England and the outcomes are summarised in section 1.5.1.

Also, Christine Maville from the NRCTC has been appointed Chair of the NHS England Quality nursing and allied health professionals Highly Specialised Programme of Care subgroup committee [described in section 1.5.2.

These specific activities and others help inform key objectives for 2023/24 for the NRCTC.

Developing Current Patient Pathways

We are continuing to innovate and evolve our aHUS appointments with patients under shared care to discuss diagnosis, current and emerging treatment options as they arise.

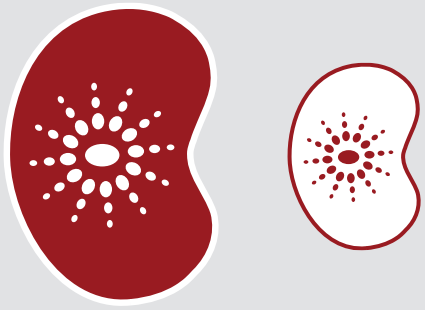
Patient engagement

We are working alongside the trust patient experience team to integrate patient feedback into our patients' consultations by linking into the trust's own friends and family test and develop "always events".

We are updating current patient packs and alert cards and developing new online resources & interactive applications.

Clinical research

We will continue to improve optimal diagnostic and treatment pathways for patients referred to us through audit and research programmes that are embedded within the NRCTC



1.5.1 Peer Review by NHS England

Aim of the review:

To inform key stakeholders of the quality of service provision for atypical haemolytic uraemic syndrome, C3 glomerulopathy and other complement mediated kidney diseases, including:

- the roles of service referral pathways and protocols
- management of patients through diagnosis, shared care arrangements, medication advice and monitoring and ongoing patient review

As part of this process, we received feedback from patients, clinicians and allied health professionals, as well as the peer review team.

Feedback from patients

Satisfaction with care

- Majority of respondents felt involved in decisions regarding their care and had trust and confidence in the professionals providing their care 71% said "Yes definitely", 26% "Yes to some extent".
- When asked to identify what was positive about the care they received, respondents highlighted the care and attention of staff, the excellent communication, access to both local and national specialist services, and the ability to receive treatment within their home.
- Majority of patients felt they had been provided with enough information regarding treatment options.
- The Peer Review panel noted positive results within the patient survey when patients were asked "Do you feel involved as much as you want to be in decisions about your care and treatment?" - 66% of respondents said "Yes definitely", 31% "Yes to some extent"

Awareness and use of services

- Majority of respondents preferred new information about aHUS to be provided in the form of email newsletters from the National aHUS Service, rather than during a consultation with their local team or by phone
- The majority of patients were aware that their care is shared between their local renal team and the National aHUS Service.
- Patients found telephone and email correspondence with a member of the national service clinical team, alongside the newsletter, the most useful

Impact on Lifestyle

Majority of patients felt they could manage their condition day-to-day and were able to holiday and travel as they would like to, although the impact of managing medications was acknowledged.

Majority of patients felt they had a single point of contact for any emergency health needs, but worried about what the condition meant for their family. Respondents felt that their ability to exercise as much as they wanted had been affected as had some aspects of employment and education.

Patients would also like.	We are providing.
increasing awareness around the condition	face-to-face roadshows and the patient forum
increased opportunities to meet with other aHUS patients	
length of time to switch from Eculizumab to Ravulizumab due to perceived delays with paperwork	ongoing support with local teams when switching patients from eculizumab to ravulizumab for a smoother transition
Patients were aware of the National HUS Service roadshows, newsletters and the option to correspond by email, not all patients were aware of our website	Information about how to find out more about us will continue to be provided, ensuring all methods to find our more about us are shared.

Clinical Feedback from NHSE peer review

Overall an outstanding service - rapidly responsive, helpful, always available, sensible, clear… just brilliant

Amazing service. I have used it many many times and always get immediate and expert advice

Expert advice from International experts on complex patients

Responsive helpful rapid advice; couldn't want for more!

Clinical advice excellent and really prompt when I've made referrals

Very helpful, thorough and attentive

The aHUS Nurses have been invaluable

High quality Consultant opinion

Flawless. An example of clinical expertise at its absolute best!

Very efficient team. Always offered help and advice

Fantastic website and referral checklist

Excellent efficient clinical service allowing prompt diagnosis and access to treatment that keeps local physician integral to the care pathway and part of MDT discussion with families

Both in an acute and chronic setting, I have always found the team extremely helpful and thorough. Patients are discussed in detail and good support given to managing cases

Absolutely fantastic service - should be a blueprint for all national centres to aspire to

Clinical Feedback from NHSE peer review

Clinician and AHP Feedback:

They Said / **We Did**

There could be a referral system nationwide with more awareness campaign.

We have sent out posters about our service. Investigating the possibility of having a centralised an online referral service.

Ensuring correct samples are sent via our labs is very time-consuming

Blood forms have been revised which hopefully simplifies things for clinicians and labs

It would be helpful to have feedback on test results, as it can take some months before results are fed back

Acknowledged that some results take some months to be processed which is normal and are fed back by summary letter to referrer, but when positive results which would change patient's management occur, we feed back to managing local clinician immediately

Eculizumab can be difficult to get in an emergency for newly diagnosed patients from the drug company

aHUS Nurses worked with Alexion, the drug manufacturer of eculizumab and ravulizumab, and produced a "how to" guide on obtaining eculizumab and ravulizumab inside and outside of normal working hours. This is designed for clinicians and pharmacists and is featured on our website, but also embedded into the "authorisation of treatment email" sent to the clinician when our service agrees treatment is indicated.

It can be difficult to find things on the website and some bits are out of date.

Website has been completely overhauled, and relaunched in December 2022 with easier navigation and search facility.

In relation to pre-approved [to receive eculizumab at point of transplantation] patients, because numbers are low, it can be difficult to maintain awareness of any changes regarding aHUS specific monitoring post-transplant, and may only become aware when they notify our service patient has been transplanted, which is not ideal.

- When patients are pre-approved to receive eculizumab at point of transplant, aHUS nurses reach out to local team plus transplant centre to identify all members of the care team who will look after that patient and introduce themselves.
- aHUS Nurses have created template letters which are customised with patient-specific information and letter details explicit guidance regarding management on relation to aHUS and transplantation, with all relevant links to our website. Letters sent in hard copy form and email form to all members of the care team. If anything changes, aHUS nurses make all members of the care team aware.
- aHUS Nurses follow this group up on a 6 monthly basis, which involves seeking clinical updates from local team, and speaking to the patient.
- Patients are also issued with an abridged version of the letter detailing aHUS care, and advised to take a copy with them if called for transplant, as a backup to letter provided to all members of the care team.

NHSE Peer Review - Good practice points or achievements by the service identified as:

- Good cohesive service and team
- Strong relationships with patients
- Strong research outputs, particularly the stopping eculizumab treatment safely (SETS) study
- The service's international profile and standing
- Clarity of genetics reports
- Excellent feedback from patients, nurses, clinicians, and pharmacies with strong working relationships
- Analysis by NHS England did not identify under-represented areas

NHSE Peer Review recommendations:

They Said / **We Did**

Building relationships with the wider country and utilising tools, for example the roadshow, to integrate the entire system and bring more teams on board, and help patients to understand the shared care model.

- Regular patient roadshows (2/year)
- Local clinicians are invited to attend
- The concept of shared care is discussed with patients at his/her first consultation
  - Role of the national vs local service
  - Responsibilities of national vs local services
  - Support offered by national service
- Shared care document has been reviewed and updated following the peer review
- Referring clinicians are invited to attend the MDT discussion relating to the referral
- Referring clinicians invited to attend virtual consultations

Consider how patients are embedded into the service design. Co-design the service with the patients.

- Utilise patient panel meetings as a mechanism to ensure patients are embedded into service design or re-design by exploring different themes of the service. Have co-created a patient information leaflet.
- Plan for ongoing periodic patient and clinician questionnaires – to evaluate service users views on service which can then be used to shape and improve service in the spirit of continuous service improvement
- We have plans to embed seeking patient feedback following virtual clinic appointments as a way of obtaining ongoing feedback from patients and service users

Formalise inclusion of referring clinician within MDT discussion and clinic appointment with the patient.

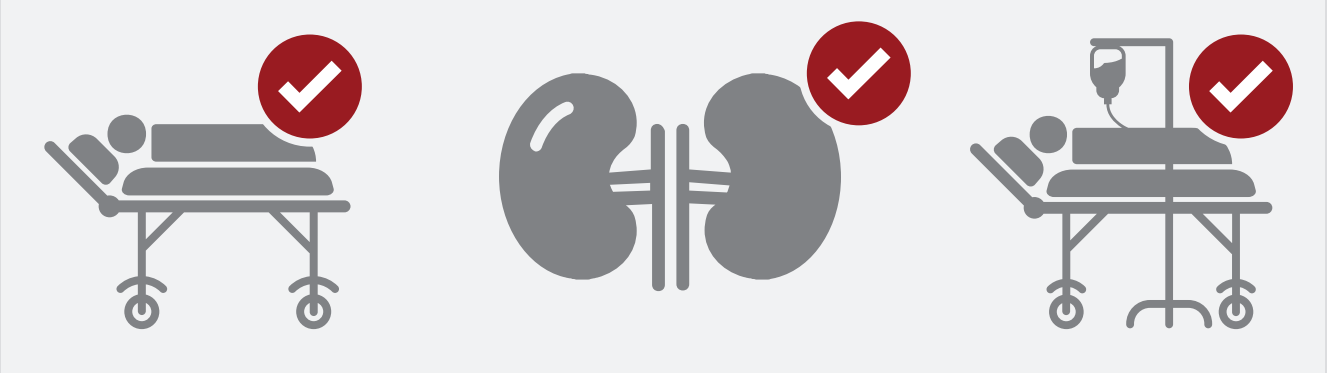
We have formalised this by adding a section on the diagnostic checklist that referring clinicians complete as part of referral to the service, that they are welcome to join our aHUS MDT if they would like to, and what they need to do if this is the case.

Clarify the process for STEC evaluation in local centre or national PHLS

- We have met with the head of the gastrointestinal laboratory at the UK Health Security Agency to discuss challenges regarding samples being sent to UKHSA for STEC testing in some patients referred to the service
- We have totally re-designed the STEC testing form with explicit guidance regarding practicalities for clinician and laboratory staff, and put this on our website

aHUS Service are already aware that accessing eculizumab at time of transplantation for pre-approved patients receiving a deceased donor transplant can be challenging, as ordering drug at short notice can be problematic. If transplanting centres hold the drug on a "just in case" basis and the patient is not transplanted before drug expires, they bear the financial cost.

To overcome this, aHUS Nurses worked closely with Alexion (drug manufacturer of eculizumab) and transplant centres with pre-approved patients. Alexion now offer a process which allows transplant centre to hold eculizumab on a named-patient basis. If drug is not used before expiry, Alexion will provide replacement stock without further charge – improves patient safety and protects NHS finances. Information about this has been disseminated via Renal Pharmacy Network, is on our website, and we have reached out to transplant clinicians and pharmacists on a bespoke basis.



Patients requiring pre-emptive eculizumab who are called up for kidney transplant now have access to eculizumab on a named-patient basis.

1.5.2 Specialised and highly specialised nurse and allied health professional forum

The aHUS nurses are working closely with the team for NHS England Quality within Specialised Commissioning to develop a network for nurses and allied health professionals working within specialised and highly specialised commissioned services. The purpose of the network will be to:

- Share best practice
- Disseminate information
- Explore workforce development
- Provide a forum which can focus on the specialised and highly specialised care provided by nursing and allied health professionals
- Arrange education and training for nursing and allied health professionals
- Collaborate to understand the challenges of specialised and highly specialised services nationwide

We see the network as an opportunity to learn from other clinicians working in similar services, with the intention that any learning can be implemented to improve the standard of care delivered by our service to patients.

The first meeting took place in September 2023 and has had over 300 expressions of interest from potential attendees. The aHUS nurses shared their expertise at this initial meeting following which, Christine Maville from the NRCTC was appointed Chair of the NHS England Quality nursing and allied health professionals Highly Specialised Programme of Care subgroup committee.

1.6 Working in Partnership and Offering Seamless Care

In order for patients with aHUS to receive excellent care, it is essential that the local clinical team and the National aHUS Service each understand their roles and responsibilities in delivering that care and that this information is communicated clearly to patients, so that they can be signposted to seek care, advice and support appropriately. This was mandated in the service specification; namely to facilitate optimal patient management on a shared care basis with referring clinicians. The shared care document is embedded into our patient flow pathway. We help patients to understand and navigate the shared care concept and process, and what it means for them and their care.

As part of this pathway, we have a robust system in place, to ensure samples are couriered to our specialist laboratories in Newcastle (section 1.7.1) including those that require shipping on dry ice.

Oversight of these specialist samples is managed by the aHUS specialist nurses. We continue to work closely with the UK Health Security Agency laboratories in Colindale and Manchester (section 1.7.7). Once a diagnosis of aHUS has been confirmed, all patients are allocated a named consultant, who work alongside the aHUS specialist nurses to coordinate the patient's care and liaise with their local team. As part of our patient flow pathway, the aHUS specialist nurses contact patients with an initial introductory letter and share some of our patient information that is part of our handheld records (separate records for children and adults), at risk cards and alert wristbands. We offer patients and their local clinical teams an initial introductory joint consultation between the named aHUS consultant and the aHUS specialist nurses.

This year the National Renal Complement Therapeutics Centre welcomed Smeeta Sinha, the National Clinical Director for Renal Medicine.

It was a great opportunity for the service to discuss our clinical practice with Professor Sinha, and share our recent developments and the continued quest to improve our patients' experience.

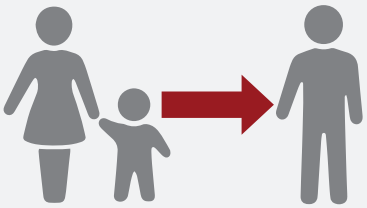
Smeeta fed back,

"The National aHUS service is a gem of UK nephrology. The team provide a fab clinical service and deliver important research like the SETS aHUS trial. They're also lovely people who have built a service around the patients. Thanks for a great day."

> ***Professor Smeeta Sinha 3rd from right and NRCTC team.***

The NRCTC provides its patients with:

Named consultant (adult or paediatric)



Access to services to help transition from paediatric to adult care

Alert cards and wristbands

1.7 Ensuring High Quality Care that Delivers Optimal Use of Eculizumab and Ravulizumab

1.7.1 Combined aHUS & C3G Lab Diagnostics

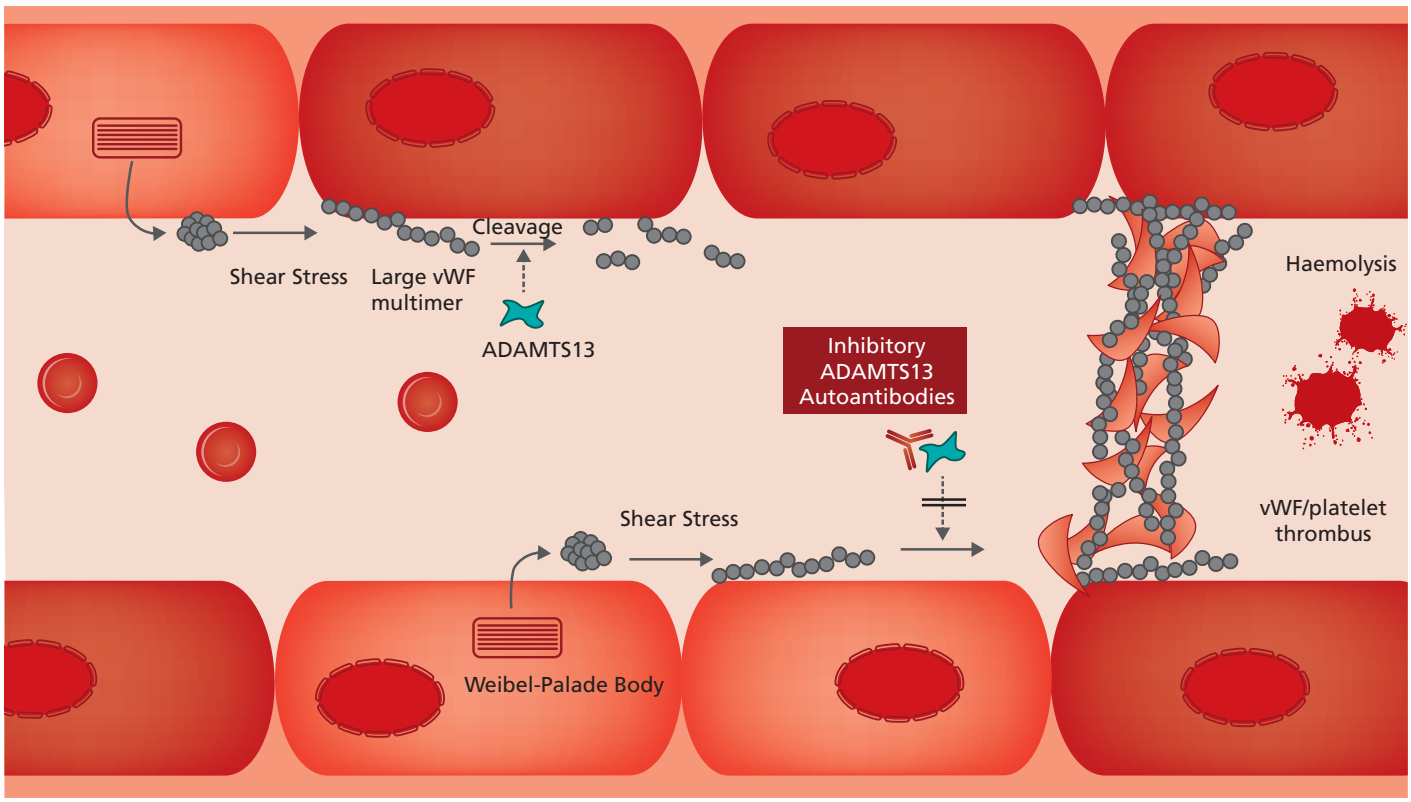
To ensure optimal personalised care for our patients, the NRCTC has developed a combined biochemical, haematological, immunological and genetic diagnostic tool kit for aHUS and C3G. This allows for the rapid diagnosis of atypical HUS, secondary thrombotic microangiopathies, C3 glomerulopathies (including dense deposit disease, C3 glomerulonephritis and factor H related 5 nephropathy) and membranoproliferative glomerulonephritis. These assays also allow for therapeutic profiling to tailor the management of these diseases.

Link to www.atypicalhus.co.uk website.

1.7.2 Measurement of ADAMTS13 Activity

Urgent measurement of ADAMTS13 is the essential initial test in the management of thrombotic microangiopathies as it determines divergent treatment strategies. A very low ADAMTS13 activity is diagnostic of thrombotic thrombocytopenic purpura (TTP). Von Willebrand Factor (vWF) is a large protein that promotes blood clotting by adhering to platelets. Under normal conditions vWF is cleaved by ADAMTS13 to regulate platelet adherence and stop excessive blood clot formation. In TTP, ADAMTS13 deficiency, either acquired (ADAMTS13 autoantibodies) or inherited (recessive mutations in ADAMTS13) results in reduced cleavage of vWF. Platelets bind to vWF forming thrombi resulting in tissue ischemia, platelet consumption, and microangiopathic haemolytic anaemia. The initial management of both TTP and aHUS is plasma exchange except in children (KDIGO 2016) until the ADAMTS13 activity is available. Eculizumab is ineffective in the management of TTP therefore only once it has been excluded can Eculizumab be commenced for aHUS.

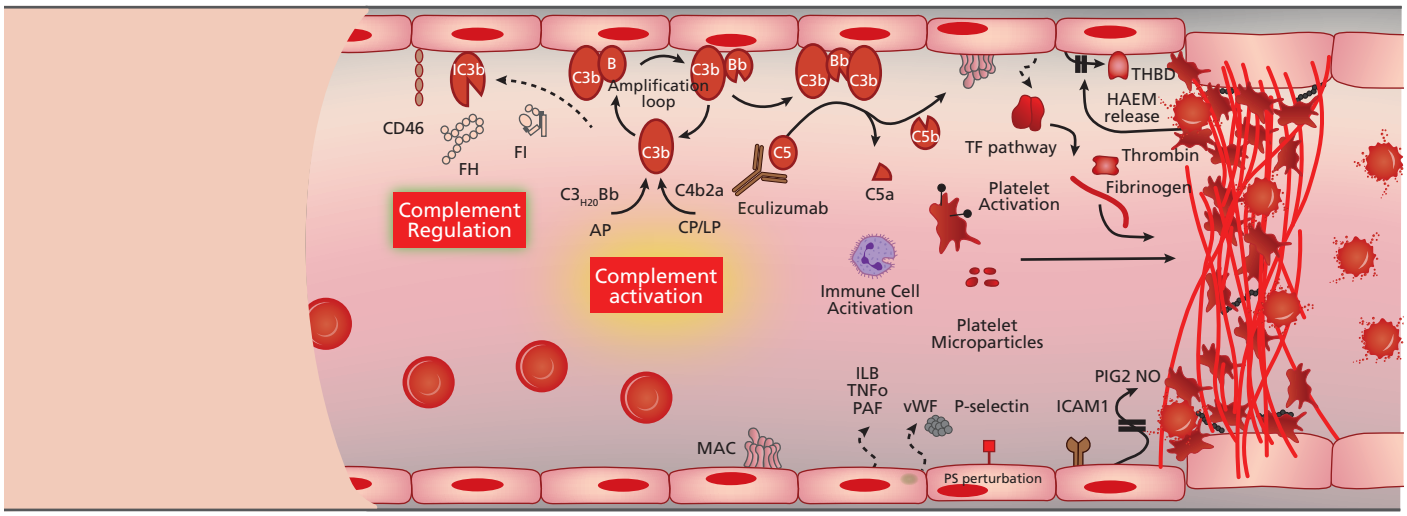
To facilitate rapid management the NRCTC have a 7 days/week, same day service for ADAMTS13 measurements at the Newcastle Haematology laboratory led by Alison Brown. Where testing cannot be carried out locally we provide this urgent analysis, including transport of specimens to the Newcastle laboratory.



Thrombus formation in TTP

1.7.3. Genetics

Since the initial description of mutations in the complement system in aHUS in Newcastle in 1998, genetic analysis has proved a key tool in the diagnosis of aHUS. The Northern Genetics Service (NGS) under Dr David Bourne has long provided complement genetic testing for atypical HUS and C3G both nationally and globally. Catherine Roberts and Lorna Wilkinson currently deliver the laboratory expertise as part of a fully integrated care pathway at the NRCTC with genetics at its core to expedite optimal personalised patient care.



Thrombus formation in patients with aHUS

Complement Genetics

Standard sequencing of the complement genes factor H, factor I, CD46, C3 and factor B is undertaken on all patients referred to the National aHUS Service. Many complement genes are found on chromosome 1 in a region called The Regulators of Complement Activation (RCA) gene cluster. This region is thought to have arisen from several large genomic duplications. The genetic architecture of this region predisposes to gene conversions and genomic rearrangements and therefore copy number variation analysis is critical to detect them.

Complement pharmacogenetics

In addition to providing definitive confirmation of complement mediated aHUS, the NGS lab also provides urgent complement pharmacogenetics analysis. A rare genetic polymorphism in the C5 gene (c.2654G>A) predicts Eculizumab non-response. The consequent amino acid alteration prevent eculizumab binding and thus complement activation is not inhibited. This analysis is immediately performed to identify patients who will not respond to eculizumab allowing plasma exchange to be rapidly resumed.

Eculizumab non response

In addition to complement mediated aHUS, there are other genetic causes of thrombotic microangiopathies that are not complement mediated: *DGKE; MMACHC; TSEN2* and *EXOSC3*.Additionally nephrotic syndrome genes and hypertension associated genes may present with a secondary TMA. Routine sequencing of the genes *DGKE* and *MMACHC* and bespoke analysis for syndromic TMAs is undertaken to avoid ineffective treatment with eculizumab and to allow other effective treatments to be instituted (e.g hydroxycobalamin in patients with MMACHC associated TMA).

A polymorphism (red sphere) in the C5 protein (white) prevents Eculizumab (magenta) binding to C5 (protein database identification code:515k)

1.7.4 Genetic research

The NRCTC University complement genetics group under Professor Kavanagh and the Northern Genetics Service are now fully integrated to provide rapid translational benefits to patients. The use of next generation sequencing technology either locally or via 100,000 genome project (now NHS genomics) was key in discovery of novel genes that predispose to aHUS. More recent innovation has been the introduction of nanopore sequencing for analysis of known aHUS genes in the RCA cluster. This combined entity is utilising these cutting edge technologies to personalise management of our patients

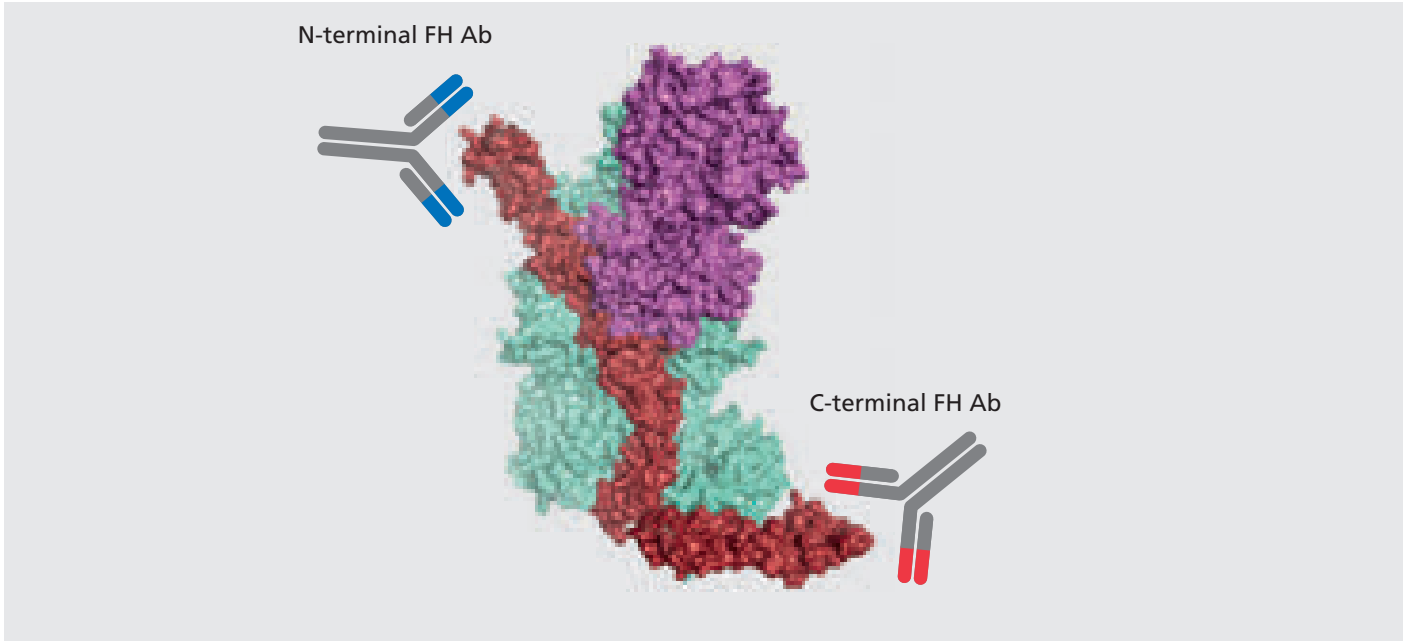
1.7.5 Complement Analysis in aHUS & C3G

Complement assays are a key part of the diagnostic toolkit, providing evidence of complement activation, validation of genetic findings and allowing therapeutic profiling. The Newcastle upon Tyne Hospitals Blood Sciences' Complement Immunology laboratory overseen by Dr Suzy Elcombe and Professor David Kavanagh's Complement Therapeutics Research Group at the NRCTC collaborate closely to develop and validate a broad range of assays. All patients referred to the service will have C3, C4, FB, sC5b9, FH, FI, complement haemolytic activity and CD46 measurements. In addition, bespoke analysis can be undertaken in the university laboratories including complement activation products (C3, C5 and FB split products) and detection of very low levels of other complement proteins. Measurement of both complement proteins and their split products accurately profiles complement activation status and improves diagnostic potential.

1.7.6 Autoimmune Complement Mediated aHUS & C3G

Professor Kevin Marchbank, head of autoimmune aHUS analytics, leads the complement autoantibody service. Autoantibodies to complement factor H are one of the commonest causes of complement mediated aHUS and are also found in C3G.

In addition to the detection of FH antibodies, an epitope mapping service is available to determine the likely functional consequences of these autoantibodies. C-terminal FH epitopes are most commonly detected in aHUS while N-terminal epitopes are usually detected in C3G. Tailored analysis of autoantibodies to other complement protein is available where appropriate. Furthermore, the autoantibody team continues to work with other reference centres around the world to unify analysis and standardise read outs from complement autoantibody tests providing increasing clarity regarding the importance of a given level of a detected autoantibody.



Epitope mapping of FH autoantibodies. *The kidney is normally protected from damage by complement activation when C3b (cyan) is degraded by the enzyme factor I (purple) and the cofactor factor H (red) (protein database identification:5O35). The location of the autoantibody binding to factor H determines the nature of the disease with C-terminal antibodies predisposing to aHUS and N-terminal autoantibodies predisposing to C3G.*

For patients with C3G, C3 nephritic factors are routinely measured and C4 and C5 nephritic factor assays are also under development in Professor Kavanagh's group. These autoantibodies are historically difficult to identify and analyse. The research group is working towards a set of simplified and streamlined assays to enable rapid and semi-automated detection of nephritic factors. Testing for anti-factor B antibodies is being introduced as routine given their diagnostic potential to differentiate post-infectious glomerulonephritis and C3G.

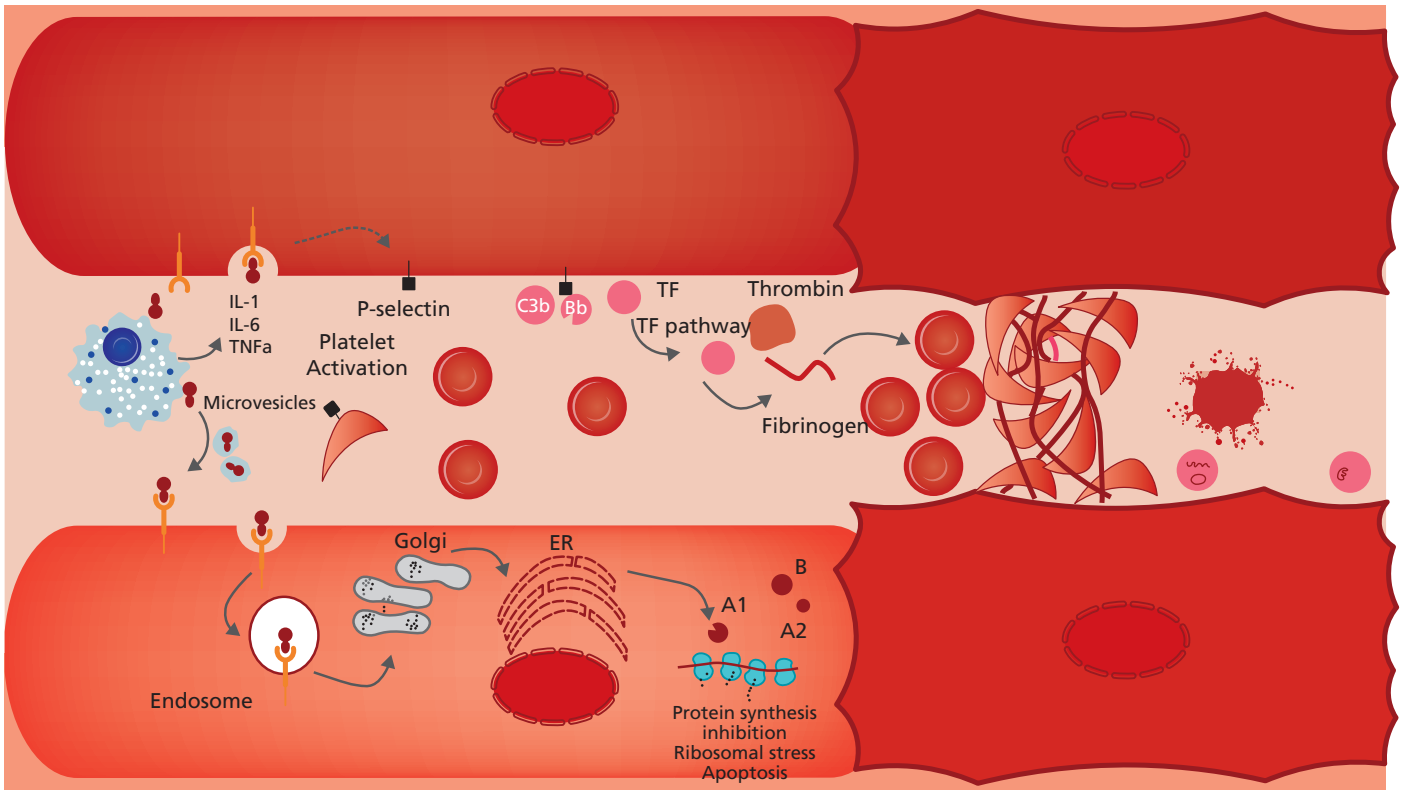
1.7.7 Microbiology Specialist Laboratories

Enterohemorrhagic E. coli testing

Shiga Toxin induced HUS is one of the main causes of acute kidney injury in young children and occurs following infection with Shiga toxin-producing enterohemorrhagic E. coli (STEC) or Shigella. These bacteria produce Shiga toxin which is transported from the gut to the kidney via leucocytes, erythrocytes and platelets.

The toxin is taken up by cells within the kidney where it inhibits protein synthesis, leading to endothelial cell death and exposure of the underlying basement membrane.

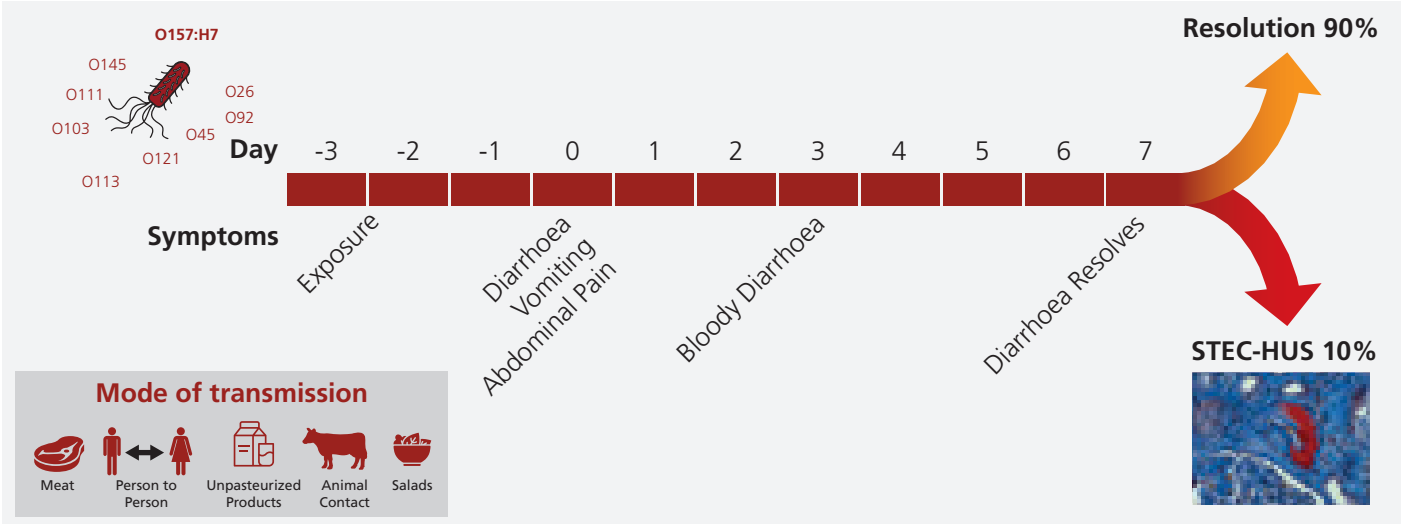
Shiga toxin is also able to enhance the release of pro inflammatory cytokines, amplifying inflammatory events. Shiga toxin can also upregulate P- selectin and cause complement activation. The consequent thrombosis results in microangiopathic haemolytic anaemia and end organ damage.



Thrombus formation in STEC HUS

Unlike in aHUS, the role of eculizumab in STEC HUS is unclear at present. While evidence shows that early use in a mouse model of STEC HUS may be of benefit, clinical trials have not demonstrated any benefit. At present, STEC HUS remains a key differential diagnosis of aHUS.

Prompt and reliable diagnosis of STEC-HUS is essential to ensure appropriate treatment. The UK Health Security Agency reference laboratory in Colindale led by Dr Claire Jenkins provides these specialised services and we have established close links to expedite the results to facilitate decision making.



Potential vectors for E.coli transmission and current prevalent serotypes. Typical timescales for diarrhoea prodrome resulting in STEC-HUS in 10% of cases

Meningococcal vaccination response

Susceptibility to infection with encapsulated organisms, particularly Neisseria infections, is the most serious side effect of eculizumab and ravulizumab treatment. Because of this meningococcal vaccination is mandatory for all patients receiving eculizumab and ravulizumab. Patients on these drugs are vaccinated against serotypes A, C, W, Y and B.

The UK Health Security Agency meningococcal reference unit in Manchester led by Professor Ray Borrow is the national centre for England and we work closely with him to develop current best practice to assess the response to vaccination to provide optimal protection against infection.

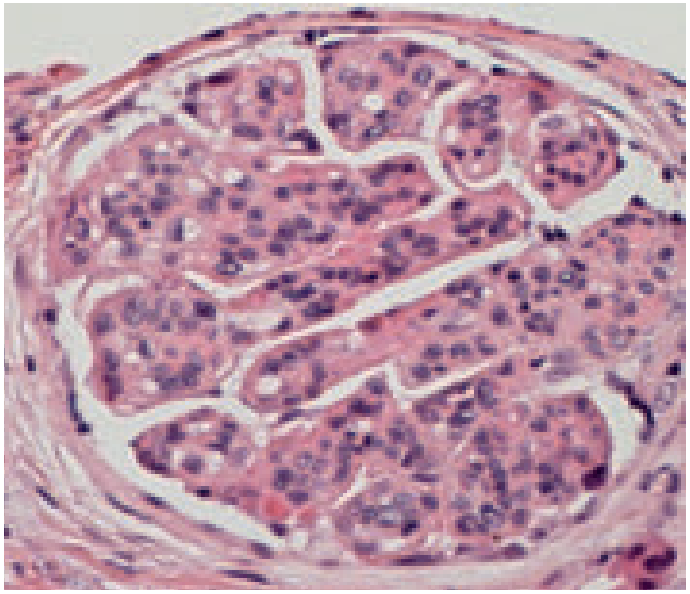
For patients on eculizumab and ravulizumab, meningococcal titres are measured around 6 weeks post-vaccination, to measure C, W and Y titres (we no longer measure A titres, because there has not been a case of this in the UK for over two decades). B titres are not measured in patients receiving eculizumab or ravulizumab due to interference of complement inhibition and the B titre assay, making results clinically uninterpretable.

For patients pre-approved to receive eculizumab at the point of kidney transplant, but not yet transplanted, so not on eculizumab, we measure C, W, Y, In these patients we are able to measure B titres as patients are not yet on eculizumab.

Meningoccal serotypes and vaccination

1.7.8 Histopathology

The NRCTC and Newcastle upon Tyne Hospitals pathologist Dr. Katrina Wood work in close collaboration with the Imperial C3G team to provide expert review of renal biopsies as part of the implementation of the policy for Eculizumab in the treatment of recurrent C3G following renal transplantation. Eligibility for treatment with Eculizumab is dependent on confirmation of the C3G as the original cause of kidney failure and its recurrence in the transplant kidney. Eligibility also requires the presence of crescentic disease and of C9 staining in the transplant graft. A protocol has been in place since the start of the policy for Eculizumab for recurrent C3G following renal transplantation, ensuring appropriate samples are sent to the histopathology department at Imperial College NHS Foundation Trust. An expert pathology opinion is provided within 5 working days of receipt of samples.



1.8 Global Reach for Optimal Patient Care

The NRCTC is recognised as one of the global hubs for complement research and care for atypical HUS patients. Members of the NRCTC team collaborate with the European Reference Network Thrombotic Microangiopathy Workgroup of ERKNet as external partners.

The NRCTC is approached regularly for clinical consultations not only across Europe but also Africa, Asia, North and South America and Oceania.

NRCTC Global Consultations

1.9 Education and Audit

Improving Clinician Knowledge

The team at the NRCTC is committed to improving clinician knowledge to enhance patient care. As part of this programme, we have delivered virtual and in person lectures to thousands of delegates across local, national and international platforms.

Edwin at the World Congress Nephrology 2023

David and our pathologist, Dr Katrina Wood, recording a symposium on diagnosis and management of C3G

The NRCTC has hosted several prominent European nephrology leaders and HUS experts visits. This year we hosted Dr. Kathleen Claes, head of the Belgian Renal Association and also Professors Nicole van de Kar and Jack Wetzels from the Dutch National aHUS Service.

Dr Kathleen Claes and NRCTC team members.

Dutch aHUS Service and NRCTC team members.

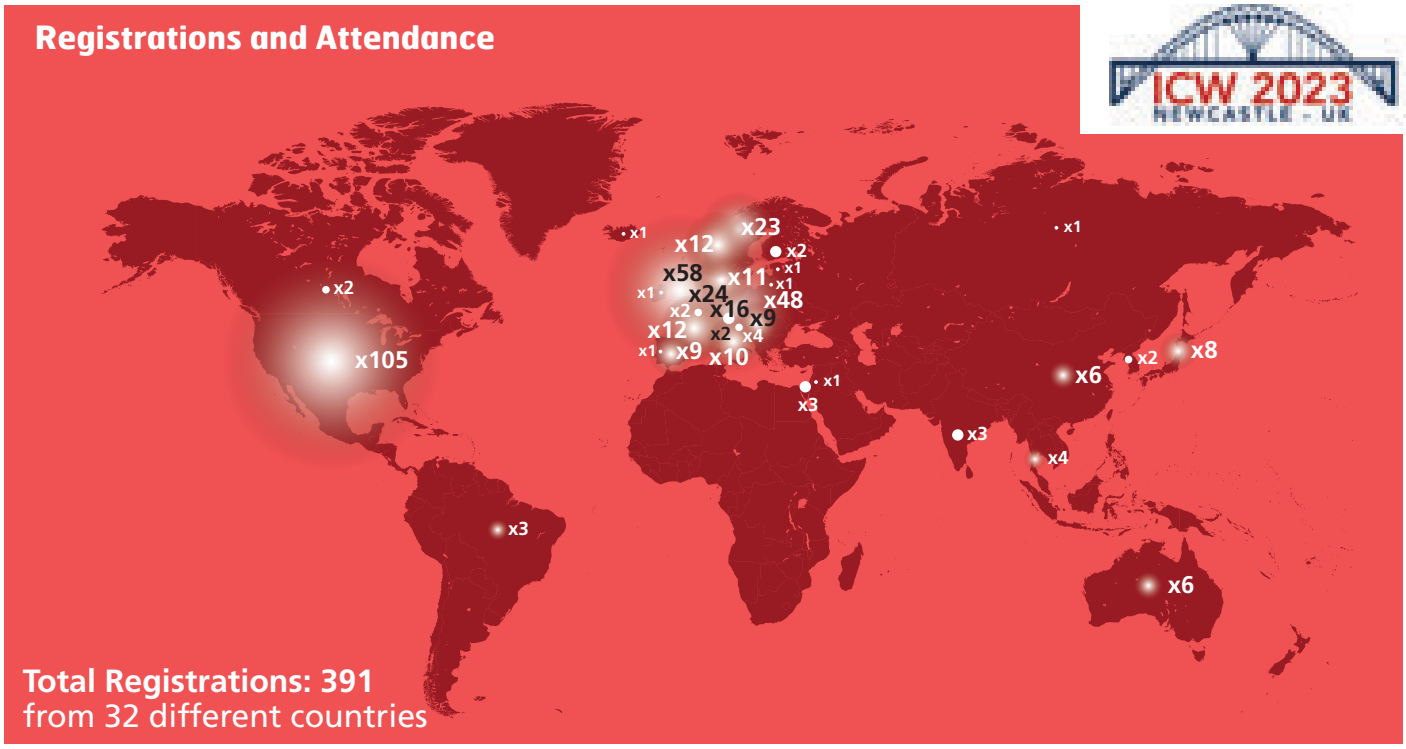
International Complement Workshop 2023

Newcastle was proud to host the International Complement Workshop in 2023 (ICW 2023), the biennial meeting of the International Complement Society (https://www.complement.org/). The NRCTC's Professor Kevin Marchbank co-chaired the local organising committee (LOC). Professor David Kavanagh (NRCTC) and Professor Neil Sheerin (NRCTC) were also LOC members along with Professor Claire Harris (Novartis, co-chair), Professor Paul Barlow (Edinburgh University), Dr. Doryen Bubeck (Imperial College London) and Dr Wioleta Zelek (Cardiff University).

That Newcastle was chosen to host the ICW 2023 owes much to the initial work of the NRCTC's Professor Tim Goodship who defined the role of complement in aHUS, which ultimately led to the successful introduction of Eculizumab into clinic practice. This work was the kernel that spawned the next generation of complement investigators currently investigating a broad range of complement mediated diseases in Newcastle. This critical mass of complement researchers made Newcastle a logical choice for the meeting.

With 400 delegates from more than 30 countries representing Healthcare, Academia and Pharma, the ICW proved a truly international forum to drive research and innovation into therapies aimed at diseases driven by the complement system.

The NRCTC was delighted to welcome the complement world to our home city of Newcastle in 2023 and we believe the collaborations fostered during this meeting will further drive complement therapeutics in the clinic.



Attendance at ICW2023 from Delegates from all over the world

Ongoing Audit and Review of Practice

The NRCTC undertakes constant audit and research to optimise practice. We continue to review our data that allows us to continually refine our diagnostic and treatment pathways that we discuss with NHS England and the PNH National Service, Leeds. Data from this process forms a key part of this report.

Nurse Education

The aHUS nursing team offer national teaching for all homecare nurses that provide care to aHUS patients and administer infusions of Eculizumab and Ravulizumab to patients across the UK within the home. The sessions cover the pathophysiology of aHUS, treatments, patient safety, escalation and red flags as well as a Q&A session. We also deliver ad-hoc sessions to shared care providers. We are committed to improving service quality and so we are in the process of meeting with other highly specialized services to learn and share practice innovations, as well as develop a network of contacts within the highly specialised services group. This has subsequently been formalised by the introduction of the Nursing and AHP Forum for those working in specialised and highly specialised services, in collaboration with NHS England as described in section 1.5.1.

Causes of TMA

1.10 Research

1.10.1 Clinical Trials

Professor Neil Sheerin is the Chief investigator for:

Stopping Eculizumab Treatment Safely in aHUS Study (SETS aHUS):

The NICE appraisal recommended the use of eculizumab on condition that a research programme with robust methods to evaluate when withdrawing treatment or reducing the dose might occur was developed. In addition, although the product licence is for life-long eculizumab there is growing evidence that this may not be necessary and a proportion of patients may be able to withdraw safely from treatment. A National Institute for Health Research (NIHR) Health Technology Assessment award has been funding a single arm, study assessing the safety of eculizumab withdrawal in patients currently on treatment. The primary endpoint is patient safety over a two year period, with eculizumab re-introduced if a relapse occurs. There are also embedded health economic and qualitative arms of the study to understand the impact on the health economy and patients' and carers' attitudes towards treatment withdrawal.

Recruitment into the trial was suspended during the Covid-19 pandemic but has since reopened and completed recruitment. The last patient last visit is due November 2023 with reporting of the results to NIHR in early 2024. Aside from minimising treatment burden to the patient, we estimate a projected saving to the NHS of over £17 million to date.

Professor David Kavanagh is the Chief Investigator for:

APL2-C3G-204:

The APL2-C3G-204 (NOBLE) trial is a randomized, controlled study evaluating the safety and efficacy of pegcetacoplan in patients who have post-transplant recurrence of C3G or IC-MPGN Study (NOBLE) NCT04572854.

APL2-C3G-310:

The APL2-C3G-310 (VALIANT) study is a phase 3 study to assess the efficacy and safety of twice-weekly subcutaneous (SC) doses of pegcetacoplan compared to placebo in patients with C3 glomerulopathy (C3G) or immune-complex membranoproliferative glomerulonephritis (IC-MPGN) NCT05067127.

APPELHUS:

The CLNP023F12301 (APPELHUS) trial is a Phase 3 study is to determine whether iptacopan (LNP023) is efficacious and safe for the treatment of aHUS in adult patients who are treatment naive to complement inhibitor therapy. NCT04889430.

MAGICAL STUDY

The MAGICAL study is a Kidney Research UK funded study to develop a pathological classification of TMA with high inter-observer reproducibility that defines morphological and immunohistochemical features that correlate with underlying aetiology, response to complement inhibitory therapy and recovery of renal function.

Dr. Edwin Wong is the Chief Investigator for:

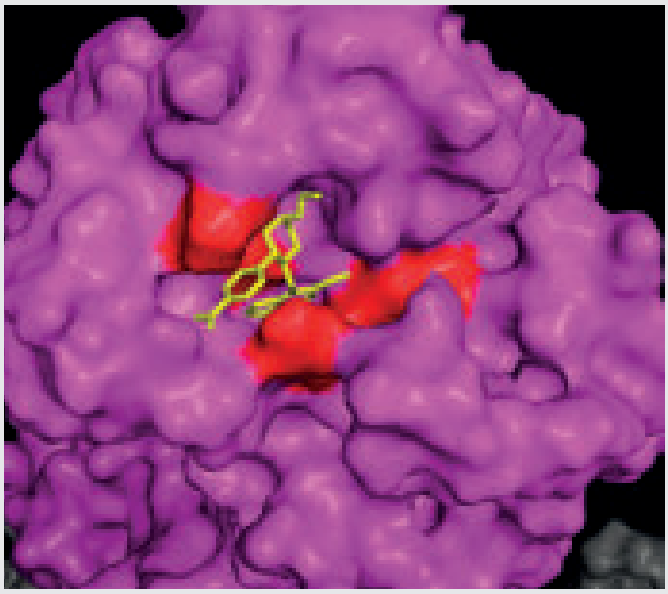
Trials of iptacopan in C3G:

The team recruited the first global patient for this open-label phase 2 study studying the safety and efficacy of iptacopan in patients with C3 glomerulopathy (NCT03832114). Patients who completed the initial 12 weeks of treatment were rolled over into an open-label extension trial (NCT03955445).

Data from this trial has now been published and showed a statistically significant 45% reduction in proteinuria amongst 16 patients with native C3G. It also showed a statistically significant reduction in C3 staining in patients with recurrent C3G in their transplant graft.

The efficacy and safety of iptacopan is currently being studies in the APPEAR-C3G trial. This is a phase 3 double-blind, randomised, placebo-controlled trial of iptacopan in patients with C3 glomerulopathy (NCT04817618) to which the team recruited patients from all around England.

Link to the publication



The small molecule Iptacopan [yellow stick] binds to catalytic residues His57 and Ser195 [red] and other key residues of the ligand binding pocket of factor B [magenta]

1.10.2 Translational Research

Newcastle University Complement Therapeutics Research Group

Professor Marchbank and Professor Kavanagh also oversee an active bench to bedside research programme within the NRCTC. Research in the group encompasses basic, translational and clinical science, ranging from deciphering of disease mechanisms using intricate in vitro assays, through animal models of disease, to drug design for clinical use and testing of therapeutics.

Thriving collaboration between the scientific and clinical teams at Newcastle enables in-depth mechanistic insight into a number of renal diseases. This is provided by probing functional consequences of disease-associated gene and protein changes as they are identified in patient populations. Mechanistic data, together with in-house biomarker profiling, provides powerful knowledge into the causes of acute and chronic kidney disease. Insight into disease provided as a consequence of genetic, functional and biomarker analyses not only streamlines personalised management of patients, by enabling stratification for clinical trials, but also guides discovery of novel and targeted drugs.

Our drug discovery portfolio is supported by numerous interactions at a national and global level. We welcome collaboration with industry in order to support drug development, whether external or within Newcastle. Our preclinical work is supported by development of novel in vivo experimental models of renal disease, such as aHUS. These models provide unparalleled opportunities to improve patient care, both by defining triggers of disease and also by exploring the most effective therapeutic avenues.

The research team includes clinical fellows, research associates and assistants and supports training of a large number of students at all levels, including undergraduate, Masters and PhD students. While renal disease is our main research focus, we study other diseases, including ocular age related macular degeneration (AMD) and haematological paroxysmal nocturnal haemoglobinuria (PNH) disorders and enjoy numerous national and international collaborations including Cardiff University, the PNH National Service (Leeds), University of Manchester, University of Bristol, University of Edinburgh, Southampton University and Washington School Of Medicine, St Louis.

1.10.3 Generation of Real World Evidence

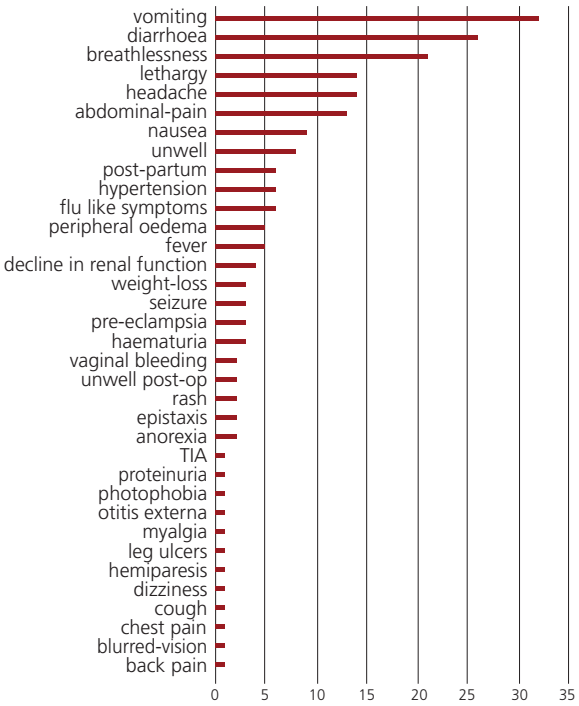
Complement-mediated aHUS in native kidneys

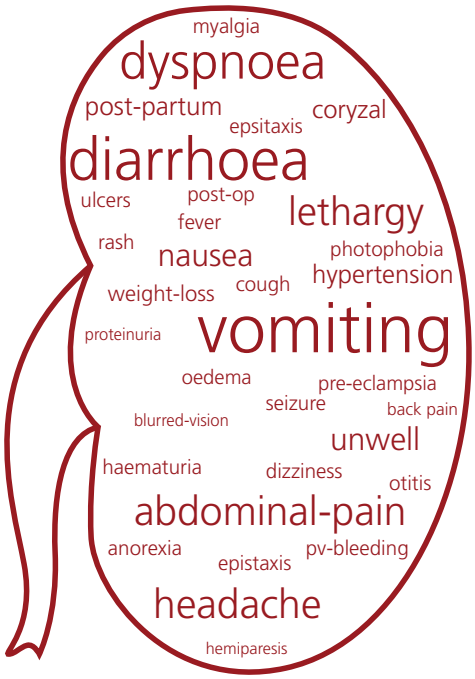
We have undertaken extensive review of almost 2000 patients with suspected aHUS referred to the NRCTC over a period of 24 years. We also have reviewed a further 86 patients with a confirmed diagnosis of aHUS in whom 118 kidney transplants were performed. We have summarised key learning below.

Symptoms of aHUS

Patients with aHUS present with a wide variety of symptoms with vomiting, diarrhoea and dyspnoea common.

As published in Brocklebank et al, Blood

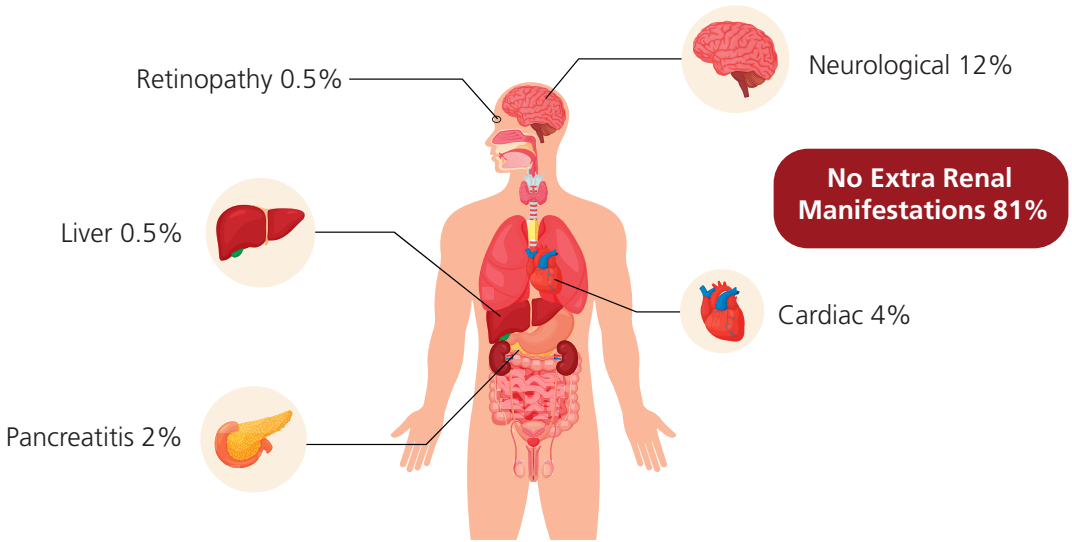




*Brocklebank et al, **Blood**. 2023 doi: 10.1182/blood.2022018833.*

Extra-renal manifestations

Extra-renal manifestations of aHUS are rare in the UK with only 19% of patients experiencing them. Neurological manifestations were the most common in 12% of cases however these were mostly mild.

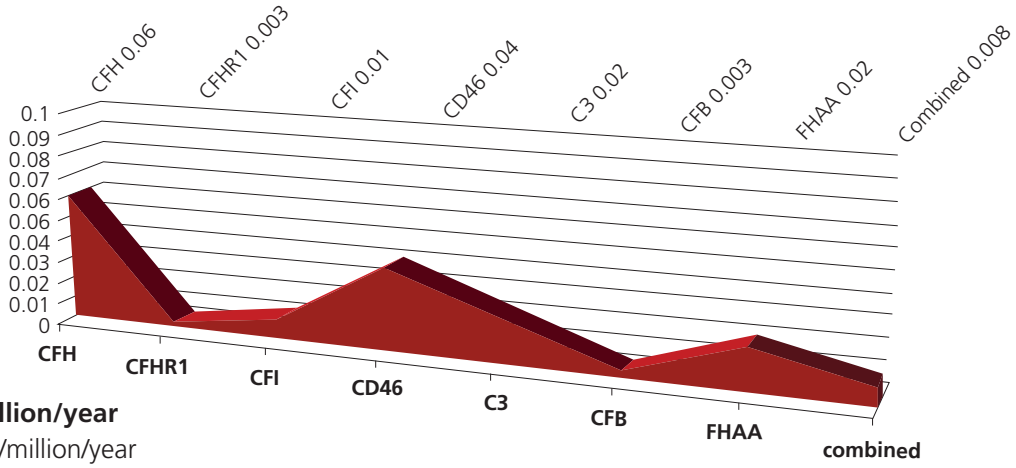


*Brocklebank et al, **Blood**. 2023 doi: 10.1182/blood.2022018833*

Incidence by mutation type

The incidence in the UK is ~0.4/million population/year. aHUS secondary to factor H mutations are the commonest followed by CD46 mutations.

Incidence (per million per year)



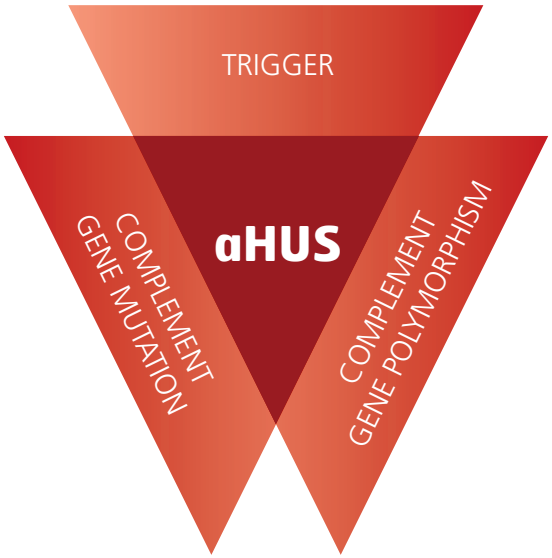
Overall incidence 0.41/million/year

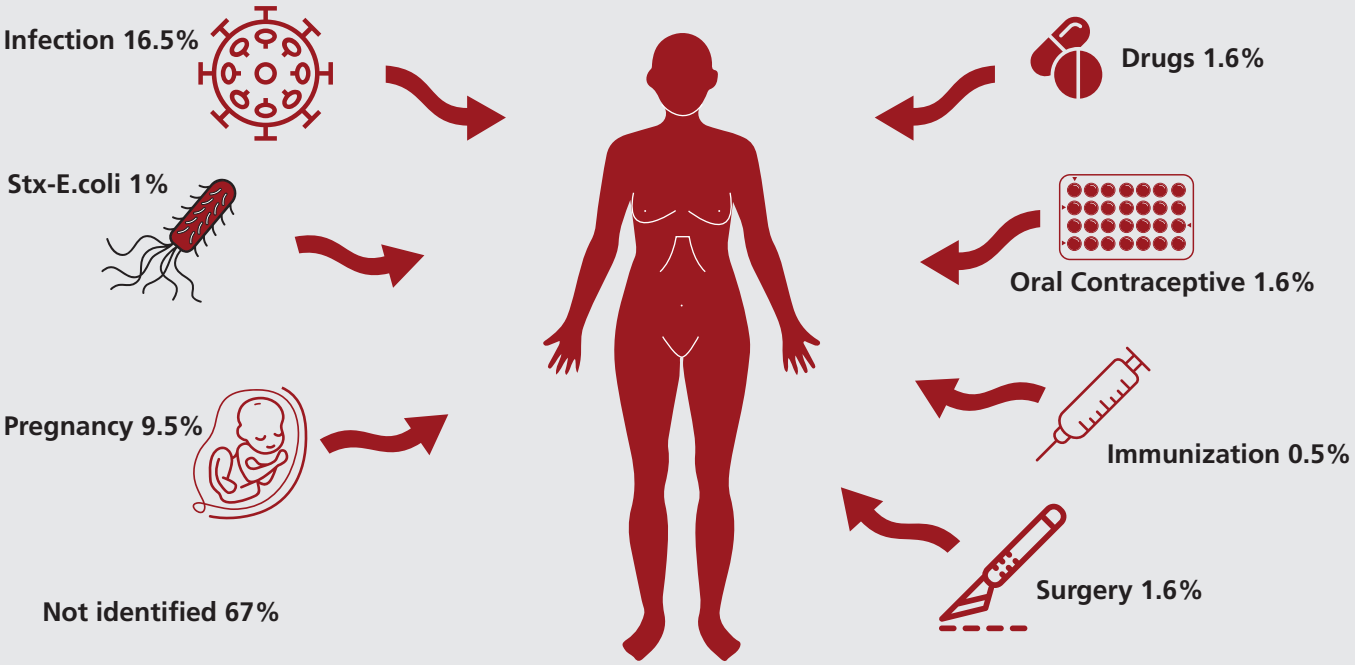
No mutation incidence 0.24/million/year

Triggers of disease

Genetic variants in aHUS are not causative but are predisposing with penetrance low. Single nucleotide polymorphisms have been shown to alter penetrance.

Most cases of complement mediated aHUS also require an environmental trigger, which is believed to initiate a complement cascade that unmasks the latent regulatory defect. In the United Kingdom we demonstrate that infections such gastroenteritis and respiratory tract infections are the most common trigger. Other common triggers include pregnancy and drugs. In the majority of cases however we could not confirm a trigger (~67%).

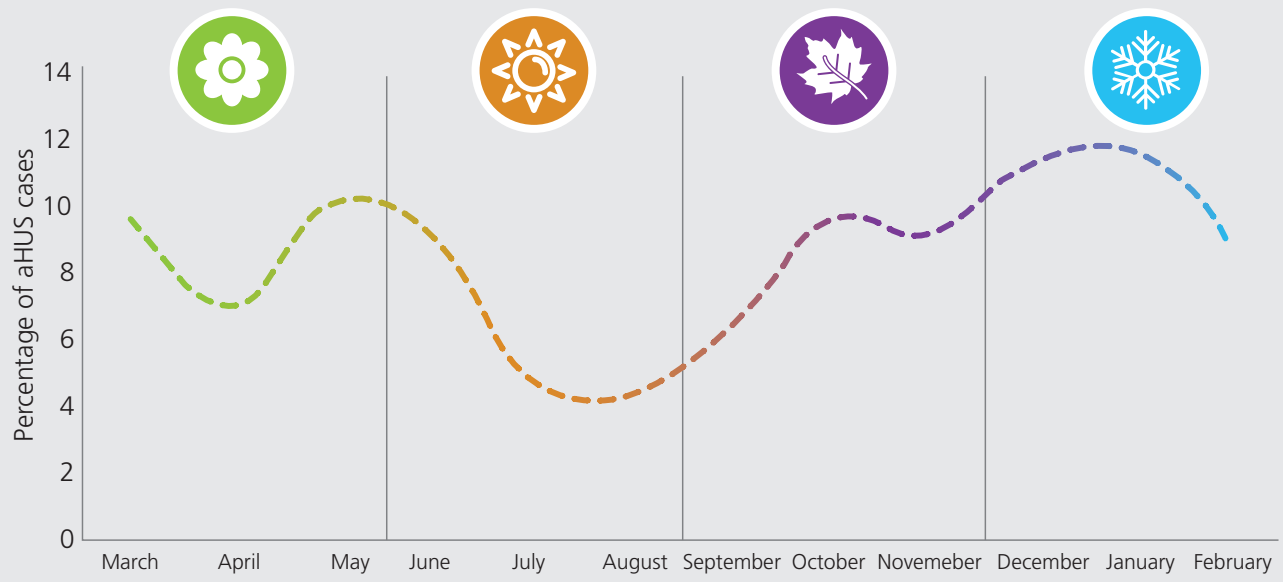




*Brocklebank et al, **Blood**. 2023 doi: 10.1182/blood.2022018833*

Seasonal incidence

Although in many cases we could not identify a trigger we demonstrate that there is a seasonal variation in aHUS presentation with higher rates in the winter months and lower rates in summer. This may suggest that seasonal viruses may represent the unconfirmed triggers of disease.

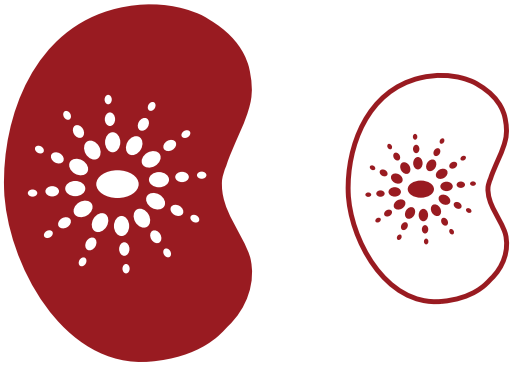


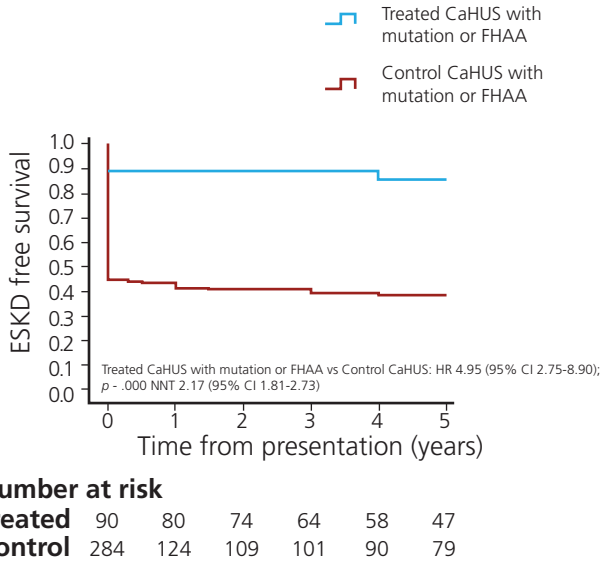
Brocklebank et al, ***Blood****. 2023 doi: 10.1182/blood.2022018833*

Eculizumab significantly improves kidney outcomes in complement mediated aHUS

The United Kingdom is unique worldwide in that all cases of aHUS are managed through a single National Centre allowing an unparalleled biorepository with >2000 cases over 30 years. As an ultra orphan disease, aHUS treatment with eculizumab had only been assessed in small, single arm studies without a control population. We set out to prove for the first time in a genotype matched control population that Eculizumab was effective in complement mediated aHUS.

We demonstrated a highly statistically significant improvement in 5 year end stage kidney disease survival in patients with complement mutations or autoantibodies treated with Eculizumab compared to those who presented before its availability. Only 14.5% of patients treated with Eculizumab reached end stage kidney failed or died compared to 60.5% in the pre-Eculizumab era (p = .000; number needed to treat [NNT], 2.17)



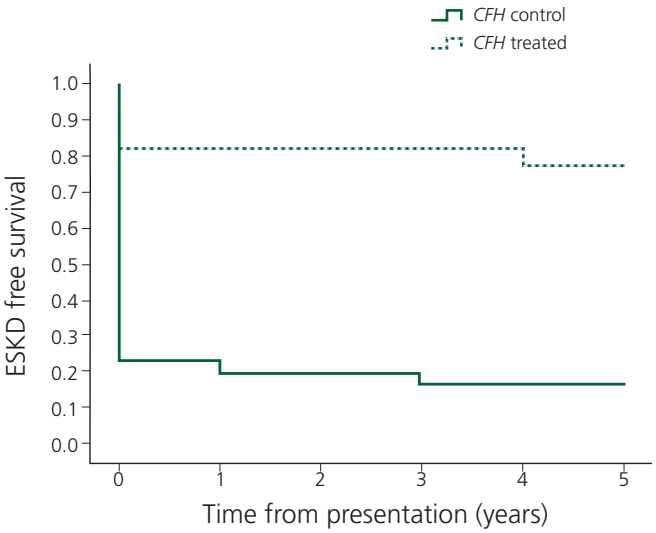


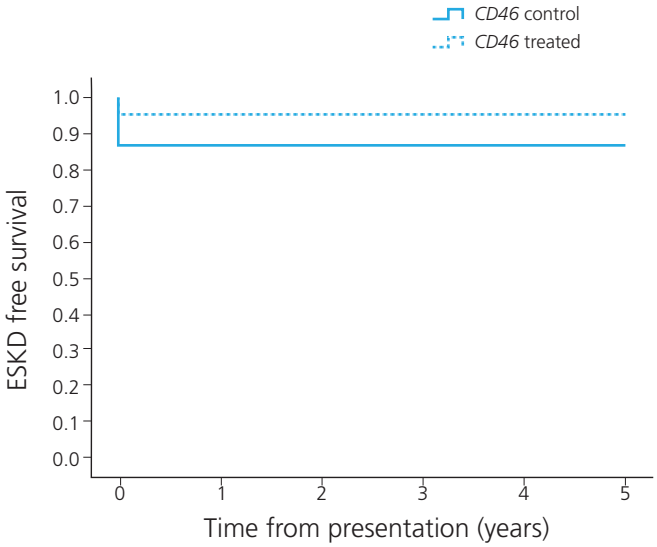
Number at risk

Treated	90	80	74	64	58	47
Control	284	124	109	101	90	79

The response to Eculizumab varied according to the underlying mutation or autoantibody.

The response to Eculizumab varied by genotype. For those patients with a *CFH* mutation, Eculizumab improved outcome over standard of care (p = .000; NNT, 1.64). For those with a *CD46* mutation, the outcome following Eculizumab treatment was not improved (p = 0.274) although this reflect the good outcome historically). There was also a statistical improvement in those with *CFI* and *C3* mutations.





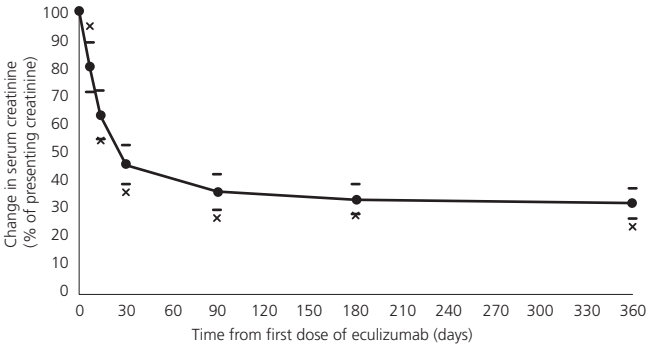
Clinical response time to Eculizumab

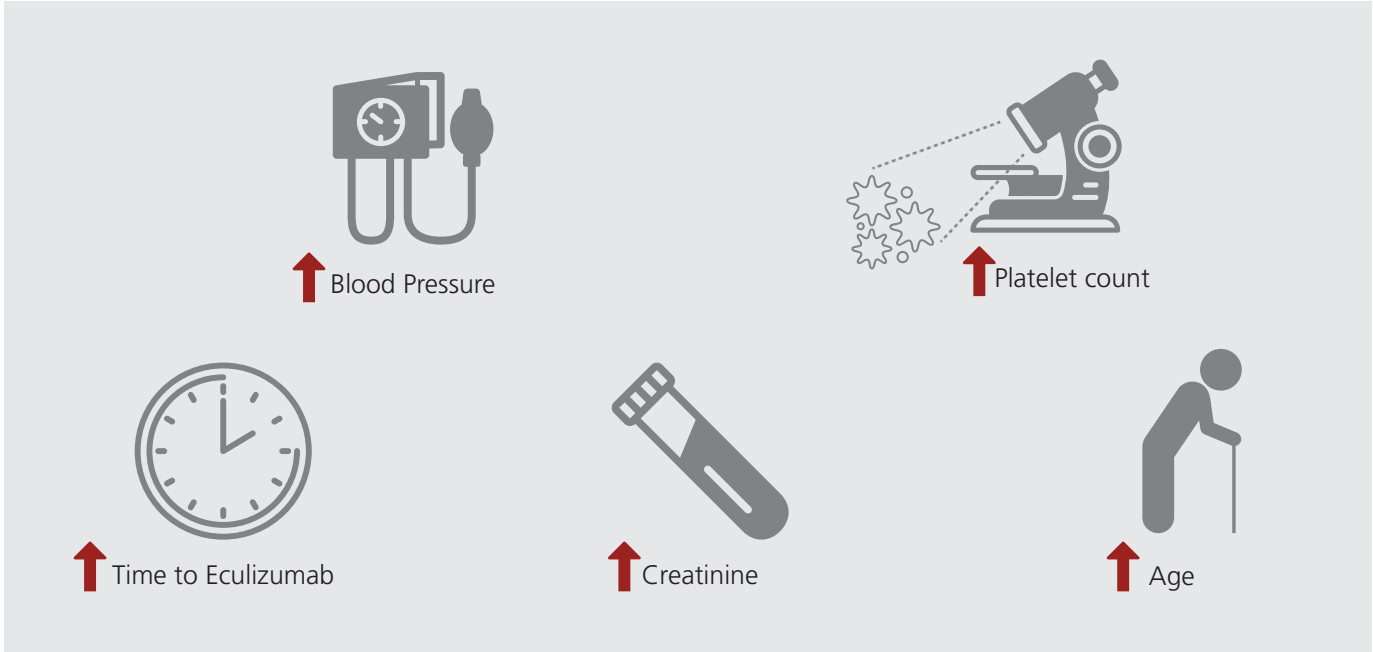
The response to Eculizumab therapy in complement mediated aHUS is very quick with most kidney recovery within the first 30 days. The median time to platelet normalisation was only 4 days.

Predictors of Outcome

To assess predictors of response, multivariate analysis was undertaken. Higher platelet count, higher blood pressure, older age at presentation, higher creatinine and longer time to Eculizumab treatment were associated with worse renal outcome.

Improvement in kidney function following Eculizumab administration

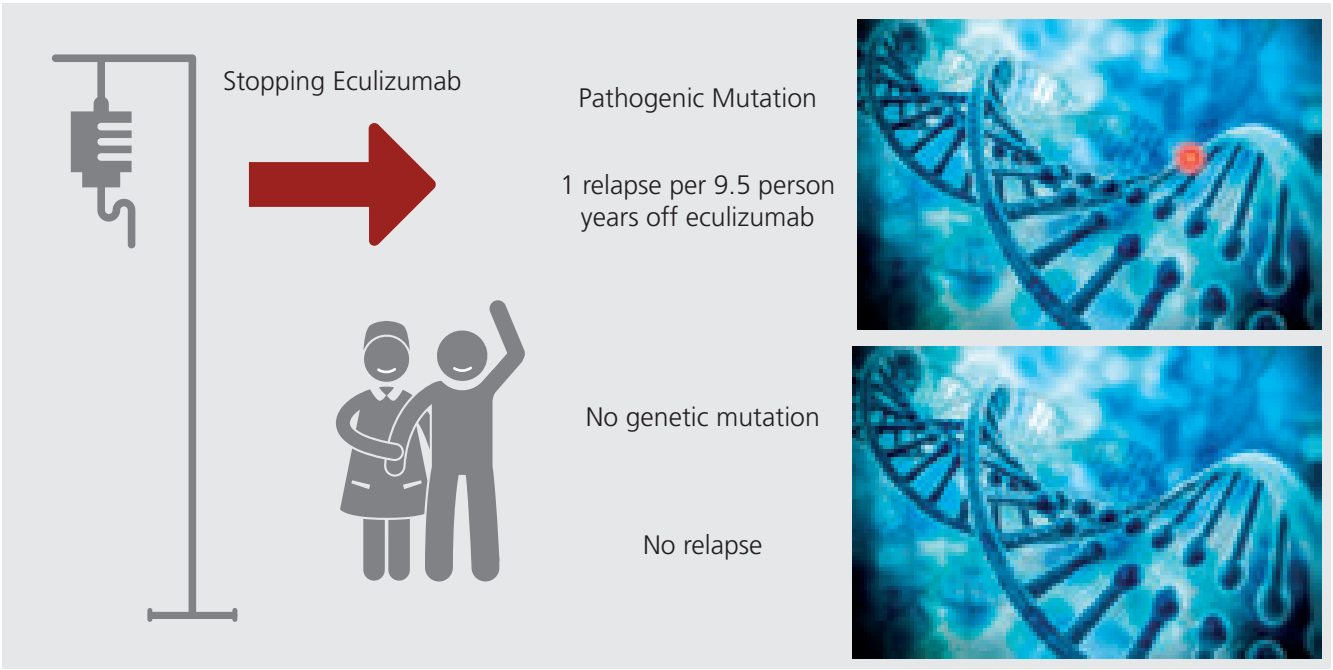




Predictors of poor outcome following Eculizumab treatment for aHUS

Time limited treatment of aHUS with Eculizumab

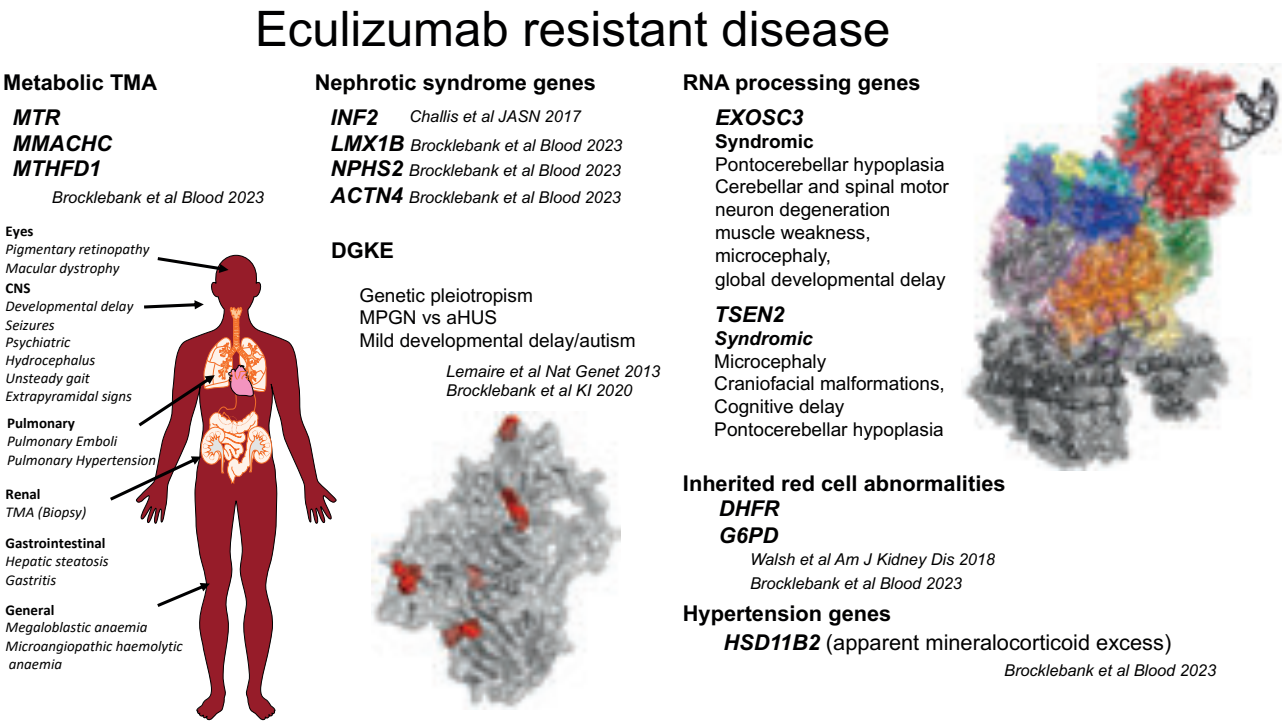
In those individuals with complement mediated aHUS who responded to treatment, 49 patients wished to stop Eculizumab or had to stop due to a clinical reason. In those patients where no complement mutation or FH autoantibody was found, there were no relapses. In those individuals with a pathogenic complement mutation or Factor H autoantibody the relapse rate was 1 per 9.5 person years without eculizumab. In those individuals Eculizumab was reintroduced and everybody recovered with no patient requiring dialysis.



Eculizumab non response

The increasing use of next generation DNA sequencing in the NHS has resulted in the discovery of several novel genetic causes of aHUS that do not respond to Eculizumab. *EXOSC3* and *TSEN2* have recently been discovered to cause a syndromic aHUS suggesting a previously unrecognised role for disorders in RNA processing in the pathogenesis of aHUS. These cases were eculizumab resistant. Hypertension genes *HSB11B2* have been demonstrated to present with a TMA on renal biopsy. Many nephrotic syndrome genes including *INF2*, *LMX1B*, *NPHS2* and *ACTN4* have been demonstrated to present with an aHUS phenotype. TMAs have previously been associated with nephrotic syndrome and is thought to be a secondary phenomenon. Disorders of cobalamin metabolism (*MMACHC* and *MTR*) and *DGK*E are also known to cause a complement independent aHUS.

Eculizumab non response in aHUS

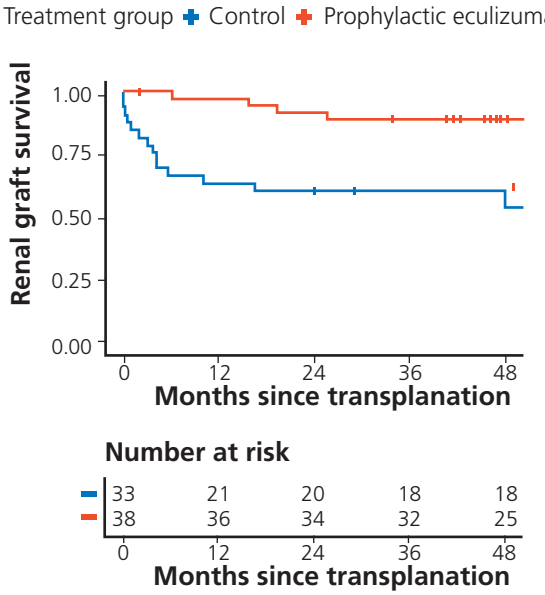


Complement-mediated aHUS in transplanted kidneys

We recently published our data on kidney transplant outcomes in patients with aHUS to assess the impact of prophylactic eculizumab on transplant survival. 71 kidney transplants in 70 recipients with medium or high risk of aHUS recurrence transplanted since 2002 were included. In those that received prophylactic eculizumab, death-censored graft survival 1 year post-transplant was 97% compared to 64% in those who did not receive eculizumab. The dramatic improvement in graft survival seen with prophylactic eculizumab treatment has made transplantation a viable therapeutic option in those with medium or high risk of aHUS recurrence [Shown in figure right].

Additionally, we explored the impact of complement defects on graft outcomes by reviewing 80 kidney transplants in patients with aHUS not treated with eculizumab. These transplants took place between 1978 and 2016. Our results conform with previous findings showing high levels of graft loss in those with *CFH* pathological variants and good graft survival in those with *CD46* pathological variants. We also demonstrate 42% graft loss within one year of transplantation in those with variants of uncertain significance, suggesting some of these variants may be functionally important. Our data supports the stratification approach advised by KDIGO to assess the risk of posttransplant aHUS recurrence.

Renal graft survival with and without prophylactic eculizumab treatment (adapted from original article)



As Published in Glover at al, Transplantation 2023

1.11 Meet the team

DR SALLY JOHNSON

Sally Johnson is a paediatric nephrologist at the Great North Children's Hospital, which provides tertiary renal services to children in the North East and North Cumbria. She undertook her undergraduate and postgraduate training in the West Midlands, including a PhD studying atypical HUS. She is the lead clinician for paediatric aHUS at the NRCTC. She leads translational research into complement-mediated renal disease. She was Chief Investigator of The National Study of MembranoProliferative GlomeruloNephritis and C3 Glomerulopathy and of the ECUSTEC trial, a randomised controlled trial of Eculizumab in STEC- HUS.

She was Research Secretary for the British Association for Paediatric Nephrology from 2019 to 2022 and is co-chair of the BAPN Clinical Studies Group. She is a trustee of the Northern Counties Kidney Research Fund (NCKRF) and a member of the Kidney Research UK (KRUK) grants committee since 2020. In her spare time she enjoys running, fundraising for both NCKRF and KRUK.

PROFESSOR DAVID KAVANAGH

David Kavanagh is the Professor of Complement Therapeutics at the National Renal Complement Therapeutics Centre (NRCTC). He graduated in Medicine and Immunology from the University of Glasgow in 1998 and obtained his PhD from Newcastle University in 2006. He subsequently undertook a Postdoctoral Fellowship at Washington University School of Medicine, St. Louis and a Kidney Research UK Fellowship at the University of Edinburgh. For his work defining the role of complement in aHUS, he was awarded the Renal Association's Young Investigator award. David moved to Newcastle to start his own lab in 2008 with a Wellcome Trust Fellowship to continue his work on complement mediated renal diseases. In addition, David is chief investigator on several clinical trials of novel complement therapeutics in C3G and aHUS.

More recently David has also focused on the genetics of the complement system in the eye. David was academic founder of Gyroscope Therapeutics which is using gene therapy to treat Age Related Macular Degeneration, the commonest cause of blindness in the developed world. This therapy is based on his finding of the causative role of complement factor I haploinsufficiency in disease pathogenesis. Gyroscope therapeutics was recently acquired by Novartis following initial clinical trials.

1.11 Meet the team continued

PROFESSOR NEIL SHEERIN

Neil Sheerin is the Professor of Nephrology at Newcastle University, a Consultant Nephrologist and Head of Service at the Freeman Hospital, Newcastle upon Tyne and the lead for transplantation in the National atypical HUS service which is part of the National Renal Complement Therapeutics Centre.

Neil qualified at Guy's Hospital and after a period working in Leicester he returned to London to undertake a PhD in complement biology and complete his clinical training. From 1999 he was the Wingate lecturer at Guy's Hospital before obtaining a Wellcome Trust intermediate fellowship in 2002. He moved to Newcastle in 2007 to take up his current role where he leads a research group focused on the role of the complement system in kidney disease and renal transplantation. He has funding from NIHR, MRC, Welcome Trust and Kidney Research UK. His clinical interests include complement mediated renal diseases, progressive chronic kidney disease and kidney transplantation.

DR MICHAL MALINA

Michal Malina is a paediatric nephrologist in the NRCTC and at the Great North Children's Hospital in Newcastle. He received his M.D. in 2007 at Second Faculty of Medicine Charles University Prague. He followed his training with combined clinical and academic programme at University Hospital Motol (Prague) and obtained PhD in Human Physiology in 2012, defending a thesis on genetics of nephrotic syndrome and atypical HUS. He performed research and clinical fellowship at Heidelberg University Hospital in Germany and research scholarship in Cordeliers Research Centre in Paris, funded by French Embassy research award. The focus of the research was on complement C3 molecule and its link to atypical HUS. He is a recipient of 2014 Czech Young Paediatrician Research Award.

After returning to Prague, he worked as a paediatric nephrology consultant and established and lead a research laboratory funded by EU grant dedicated to understanding of molecular background or rare disease in children. Before moving to England, he was a National Coordinator of International aHUS Registry for Czechia and participated in ERKNet European Reference Network initiative in a workgroup for HUS.

Michal has moved to Newcastle in 2018 attracted by the prospect of practising the whole breath of paediatric nephrology and combining it with specialised aHUS clinical and research opportunities. In addition to his clinical commitments, he currently serves as a PI for Newcastle in a study of stopping eculizumab safely (SETS) and a study looking into perioperative fluids in kidney transplant in children (PLUTO).

DR EMMA MONTGOMERY

Emma Montgomery is a Consultant Nephrologist at the National Renal Complement Therapeutics Centre and Renal Services at the Freeman Hospital. She graduated (MBBS) from Newcastle University in 2007 before completing her higher specialist medical training in the North-East in both renal medicine and general internal medicine. She has additional postgraduate qualifications in solid organ transplantation and genomic medicine.

At the National Renal Complement Therapeutics Centre, her interests focus on post transplant TMAs. Her clinical nephrology interests include renal transplantation, advanced chronic kidney disease management and nephro-oncology. She is a Honorary Clinical Senior Lecturer at Newcastle University and renal lead for clinical undergraduate education program. Dr Montgomery has an interest in improving service delivery and care via quality improvement projects on patient equality and access to health care.

DR EDWIN WONG

Edwin Wong is a Consultant Nephrologist at the National Renal Complement Therapeutics Centre and Renal Services. He graduated from University of St. Andrews and University of Manchester in medicine. He subsequently undertook his Medical Research Council Clinical Research Training Fellow at Newcastle University from 2013 until 2016 during which time he obtained his PhD. For his work studying complement abnormalities in MPGN and C3G, he won the Renal Association's Young Investigators Award in 2017.

He is the lead clinician at the NRCTC for C3 glomerulopathy and is chair of the MPGN, DDD and C3G rare disease group. He is chief investigator on several trials of novel complement therapeutics in C3G and IgA nephropathy. He is also the speciality group lead for renal medicine for the North East and North Cumbria Clinical Research Network.

1.11 Meet the team continued

DR PATRICK WALSH

Dr Patrick Walsh is the paediatric clinical lecturer at the National Renal Complement Therapeutics Centre. Dr Walsh graduated in Medicine and Genetics from University of Leicester in 2013. He previously was on the Academic Foundation Programme at the University of Bristol and worked as an Honorary Research Collaborator at the Institute of Child Health & Great Ormond Street. He moved to Newcastle in 2015 to take up an Academic Clinical Fellow post at the NRCTC. He obtained his PhD from the University of Newcastle in 2023 on the genetics of Eculizumab resistant atypical haemolytic uraemic syndrome.

aHUS Nurse Specialists

GEMMA ALLEN

Gemma Allen trained as an adult nurse in London. She has spent the majority of her nursing career working as a Senior Sister in Intensive Care at The Royal Marsden Hospital, London, where she also worked as a Practice Development Sister. Gemma completed a Diploma in Tropical Nursing at The London School of Hygiene and Tropical Medicine in 2013 and has worked oversees improving access to healthcare for rural communities. She has lectured in intensive care nursing at Kings College, London and St Georges University of London. She has most recently completed her Masters Degree in intensive care healthcare practice.

CHRISTINE MAVILLE

Christine Maville trained in Newcastle as a children's nurse and qualified in 1996. Her background is: Staff Nurse on a children's surgical ward (1996-2004); Specialist Community Public Health Nurse (Health Visitor) (2004-2009), Children and Young People's Specialist Nurse (Inflammatory Bowel Disease) (2009-2020), and started working as a specialist nurse in the National aHUS Service in August 2020. Christine has extensive experience of managing and coordinating the care of patients who have a chronic illness and is particularly interested in service improvement and quality improvement.

Christine put her significant specialist nursing experience to good use in helping to drive forward substantial changes to the nursing service offered at the NRCTC. In addition, she and her colleagues have introduced the centralised monitoring process for patients on C5 inhibition therapy (and those pre-approved to receive C5 inhibition at the point of transplantation) to ensure all these patients' meningococcal monitoring is performed as per protocol, and acted upon if boosters are clinically indicated. Christine works across all different disciplines and agencies to ensure patients with aHUS receive the care they need to manage their condition.

CLAIRE TURNBULL

Claire qualified as a paediatric nurse in 2018 (BSc (Hons) Nursing Studies/Registered Nurse Child) and spent the beginning of her career as a staff nurse on the paediatric surgical ward within the Great North Children's Hospital, Newcastle. Having worked closely with a variety of Nurse Specialists on the surgical ward Claire was inspired to develop her career in a specialist area and joined the NRCTC in April 2021 as a Clinical Nurse Specialist.

Claire has a specific interest in shaping the NRCTC nursing service to meet the current and future needs of patients with aHUS. To help drive this growth she brings experience of developing services to improve service user outcomes from her previous role within the charitable sector, this knowledge is being utilised within the nursing team to help identify changes to improve the patient experience.

Claire and her nursing colleagues are focused on not only providing high quality specialist clinical support for patients with aHUS but also working in partnership with all stakeholders to ensure the NRCTC nursing service meets the wider needs of all their patients.

2. Service Activity

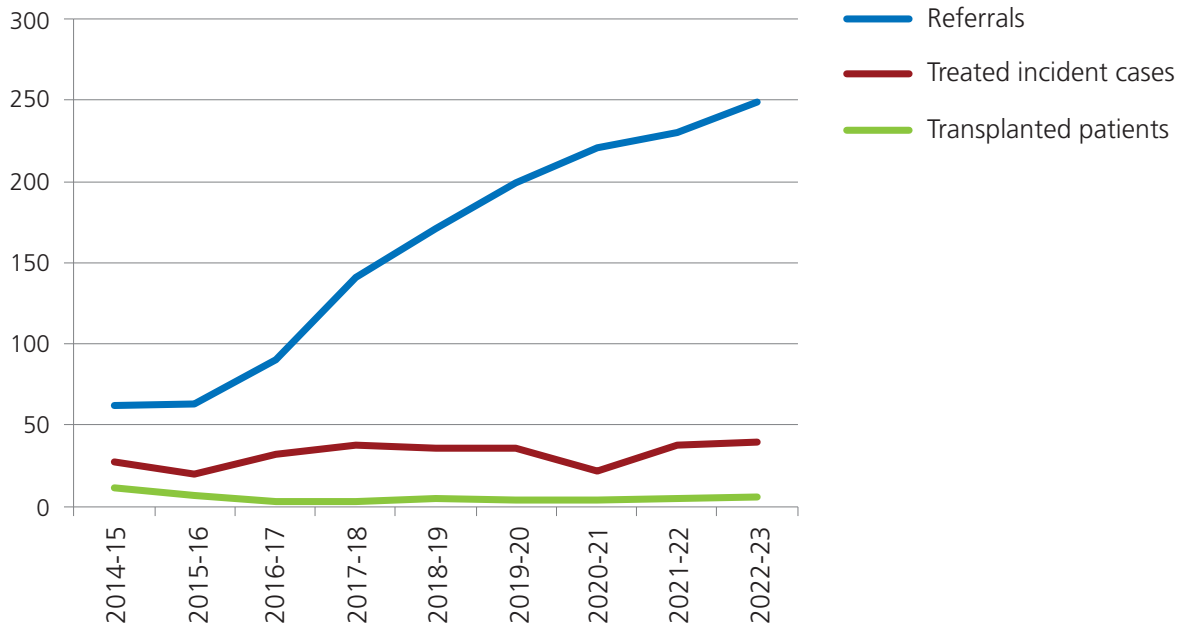
This report refers to the activity of the National aHUS Service and the National C3G service. The reporting period described is from April 1st 2022 until March 31st 2023.

Referrals from Hospitals across England & Scotland

2.1 aHUS service activity

Increasing annual activity

Referrals to the National aHUS Service continue to increase. The annual referral numbers to the service in each of the last 9 complete financial years are summarised below. The number of new patients initially treated with eculizumab and number of patients receiving eculizumab pre-emptively at time of transplantation is shown.



National aHUS Service annual activity. *Line chart shows number of patients referred to the National aHUS Service; the number of incident aHUS patients recommended for Eculizumab treatment; and the number of prevalent aHUS patients receiving pre-emptive Eculizumab at time of transplantation in each of the last 9 complete financial years.*

Referrals during the 2022-2023 reporting period

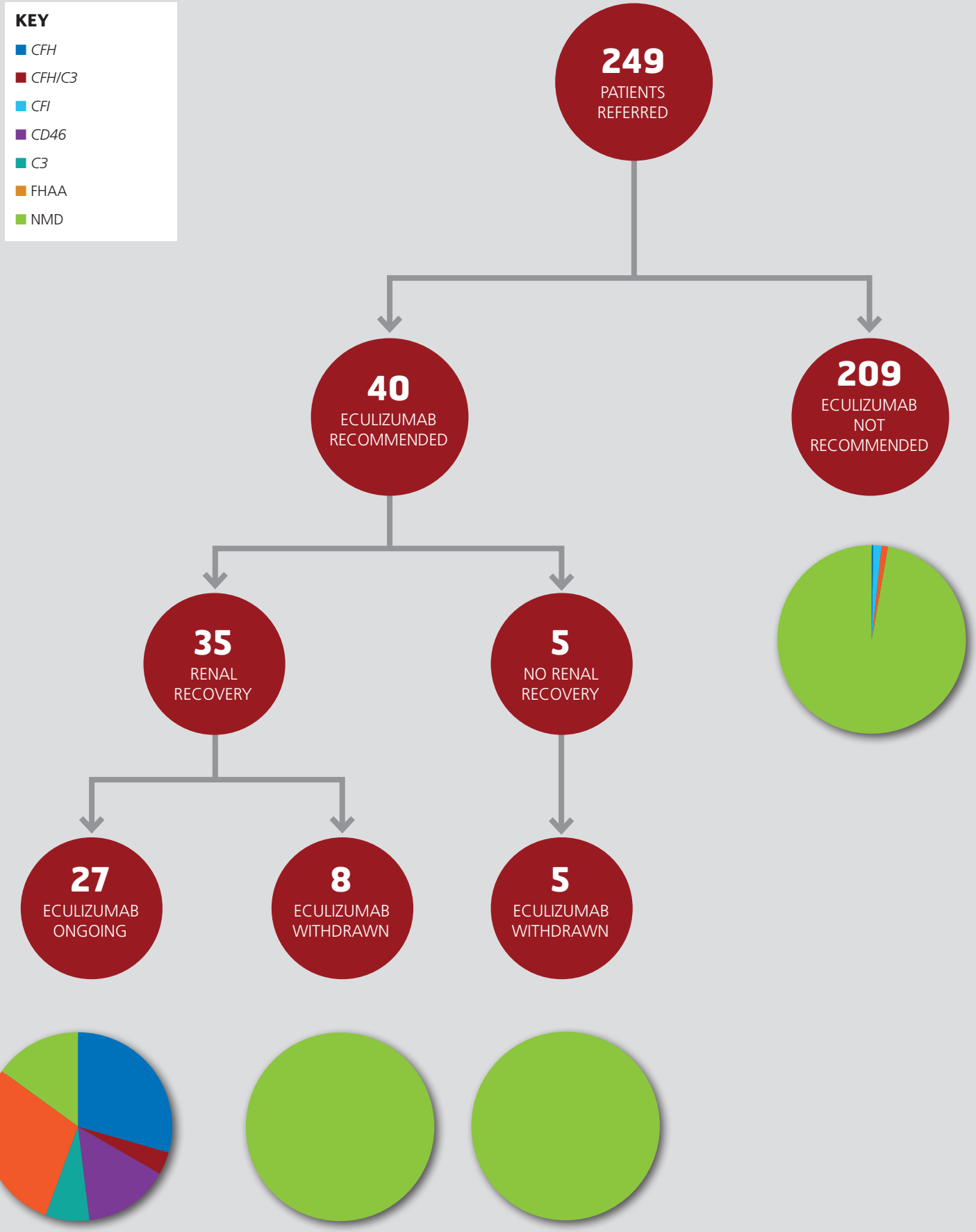
In the 2022/23 reporting period, the National aHUS Service received 249 referrals for new patients for consideration of a diagnosis of aHUS. During the same reporting period, Eculizumab was initially recommended in a total of 40 patients.

We have reported outcomes correct as of 30th June 2023. Of the patients treated with eculizumab during this period, 27 patients improved and remained on Eculizumab. Of these, 85.2% had a pathogenic mutation or acquired complement abnormality on Eculizumab. In a further 8 patients who also showed improvement, a decision to stop eculizumab was subsequently made following review taking into consideration the clinical presentation and results of the full TMA screen including complement testing. Five patients showed no significant improvement in renal function. In all of these patients, ongoing eculizumab was not recommended.

A diagnosis of aHUS was considered in a further 209 patients that were referred to the National aHUS Service. Based on the available clinical information, eculizumab was not recommended by the National aHUS service. Patients were not recommended treatment on the basis that they did not have aHUS, or if the clinical presentation indicated that there would be no clinical benefit. Reasons for this include likely or confirmed alternative diagnosis and/or clinical improvement, or futility of treatment based upon evidence of advanced / irreversible renal disease.

In 6 patients (2.9%) presenting at end stage renal failure we were able to confirm a diagnosis of aHUS. In each case the risk of aHUS recurrence at time of transplantation was assessed and the pre-emptive eculizumab authorised.

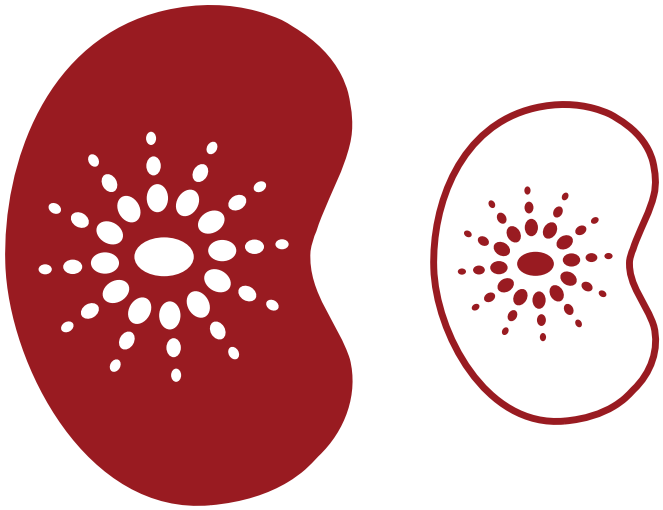
National aHUS Service activity from April 2022 until March 2023.
Eculizumab was recommended in 40 patients. The proportion of patients with a mutation in each of the genes (CFH, CFI, CD46, C3) for each treatment arm is shown. [FHAA=Autoantibodies to factor H, NMD=no mutation detected].



2.2 C3G service activity

A total of 62 patients were referred to the NRCTC for diagnostics and discussion of treatment options for suspected C3G. Patients with C3G in native kidneys were offered clinical trials if there were suitable. Furthermore, a referral pathway has been in place for consideration of eculizumab in patients with recurrent C3G since February 2017. Treatment with eculizumab can only be recommended following review by an expert C3G panel comprising the NRCTC and Imperial C3G service as part of the clinical commissioning policy [NHS England 16054/P].

Patients with recurrence of C3G were offered clinical trials or access to eculizumab depending on their clinical presentation. Since the policy was put in place, 7 patients have been treated with eculizumab in the period until March 2023.



2.3 Scotland

Since 2021-22, we have a service level agreement to provide diagnostic testing and management advice for patients referred from Scotland with a suspected diagnosis of AHUS and C3 glomerulopathy. Eculizumab may be commenced following discussions with the national aHUS service and treatment costs incurred by referring centres re-imbursed through NHS Scotland.

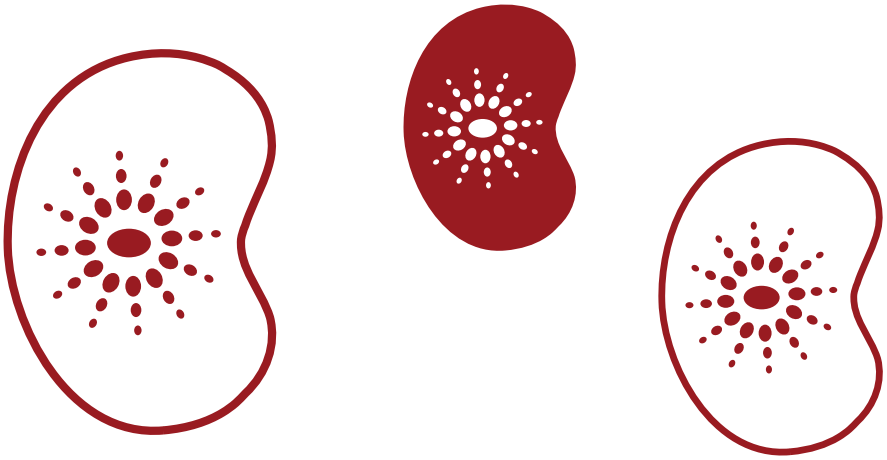
In the reporting period 2022-23, the first full year of this agreement, 49 patients were referred with a suspicion of aHUS and 10 patients were referred with a suspicion of C3G.

3. Performance Analysis

The service measures its performance across the NHS outcomes framework domains and quality indicators, detailed below.

Quality Requirement	Threshold	Method of Measurement	Consequence of Breach
Domain 1: Preventing people dying prematurely			
Zero avoidable deaths in patients with a diagnosis of complement mediated aHUS (as per current diagnostic criteria)	Zero deaths	To be notified to the commissioners including HSS national team within 24 hours	To be addressed in annual service audit meeting
Domain 2: Enhancing the quality of life of people with long-term conditions			
All patients with aHUS who are eligible for renal transplant will be listed for transplant	100% of patients on transplant waiting list	Annual audit	To be addressed in annual service audit meeting
Publish an annual report from the aHUS registry	Report published to agreed timetable	Report received by NHS England	To be addressed in annual audit meeting
Domain 3: Helping people to recover from episodes of ill-health or following injury			
To provide advice to provider centres within 24 hours of request on treatment	90%	Annual audit report	To be addressed in annual service audit meeting
Written protocols agreed with units	100%	Annual audit report	To be addressed in annual audit meeting
Domain 4: Ensuring that people have a positive experience of care			
Achieve 90% data completeness of the aHUS register to which referring units are mandated to supply data	90%	Annual audit report	To be addressed in annual service audit meeting

National aHUS Service - Quality Indicators



3.1 Domain 1: Preventing people dying prematurely

Zero avoidable deaths in patients with a diagnosis of complement-mediated aHUS

No patient died of aHUS in England in 2022/2023

As of 31st March 2023 there were 177 patients receiving either eculizumab or ravulizumab under the shared care agreement of the National aHUS Service.

When the National aHUS Service is notified of the death of a patient previously referred to us, a case review is performed to determine whether aHUS was active at the time and therefore contributed to the death.

We concluded that patients who died had appropriate management of their illness and that their deaths could not be attributed to a diagnosis of complement-mediated aHUS or its treatment.

Infection Prevention in patients receiving Eculizumab and Ravulizumab

- Eculizumab and ravulizumab treatment increases susceptibility to meningococcal infection by 550-fold. We have a series of measures that are aimed at reducing risk of meningococcal disease to minimise harm that may result as a result of eculizumab use.

Strategies to reduce risk of meningococcal sepsis:

Initial meningococcal vaccination

We recommend that patients receiving eculizumab or ravulizumab, or those activated on the transplant list who have been pre-approved to receive eculizumab at the point of renal transplantation:

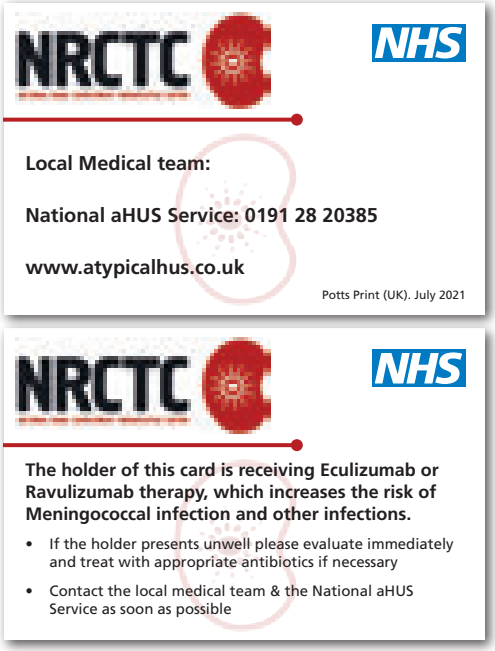
- are vaccinated against serogroups ACWY and B – we follow up all patients to ensure they are vaccinated appropriately and liaise with local teams throughout. We communicate the need for further vaccination when needed via local teams or primary care. [performance metrics relating to this are summarised in domain 4, page 45].
- are started on long-term antibiotic prophylaxis for the duration of either eculizumab or ravulizumab therapy and for a specified period after stopping either of these therapies.

Guidelines regarding reducing risk of contracting meningitis

In 2022, we updated our meningitis prevention guidelines for both adult and paediatric patients, which is published on our website.

Counselling regarding meningitis risk

- We counsel patients regarding the risk of meningitis and give information on the early symptoms of meningococcal disease and stress the need for immediate medical review if infection is suspected, to help patients identify "red flags."
- We provide "at risk" [of meningococcal infection] cards to all patients on treatment that they can present to any healthcare professional treating them, alerting to the fact they are at increased risk of contracting meningitis.
- We provide teaching to nurses administering either eculizumab or ravulizumab, particularly those who work in the homecare sector, so we can alert them to the risk of meningitis and provide them with information on escalation and how and when to seek advice.



Patient-held alert card - meningococcal risk

Meningococcal titre monitoring

We recommend annual titre measurement for meningococcal serotypes C, W and Y. The rationale for this is to identify patients whose titres are considered to be below the protective range and offer meningitis booster vaccinations. We hope that by offering a booster, immunity may be enhanced to help reduce the patient's risk of contracting meningitis on eculizumab or ravulizumab.

Since 2021 we have adopted a centralised approach to meningococcal titre monitoring for patients on eculizumab and ravulizumab, building on our previous processes where local teams were expected to arrange blood tests following our meningococcal titre recommendations.

- Our centralised approach has streamlined the process and at the consultation stage involved all of the relevant stakeholders. Patients have told us that this has reduced the number of healthcare interventions they require by obtaining blood samples during infusion appointments.
- Once bloods have been taken, samples are sent to Manchester UKHSA Meningococcal Reference Laboratory for testing
- Results are sent to the NRCTC for interpretation
- The aHUS Specialist Nurses formally feedback all results (and any recommendations for boosters) to both the patient, local clinician and GP
- If boosters are indicated, we liaise with the patient, local team and primary care, and follow up to ensure vaccines have been given.
- We then re-measure titres 6 weeks post-booster to measure response. All results are fed back to the local clinical teams

"this has reduced the number of healthcare interventions"

5 yearly meningococcal B strain boosters (Bexsero)

We cannot measure B serotype meningococcal titres whilst on eculizumab and ravulizumab, as the drug interferes with the assay, meaning that results cannot be interpreted with any accuracy. For this reason, we do not routinely measure B strains for those on eculizumab and ravulizumab.

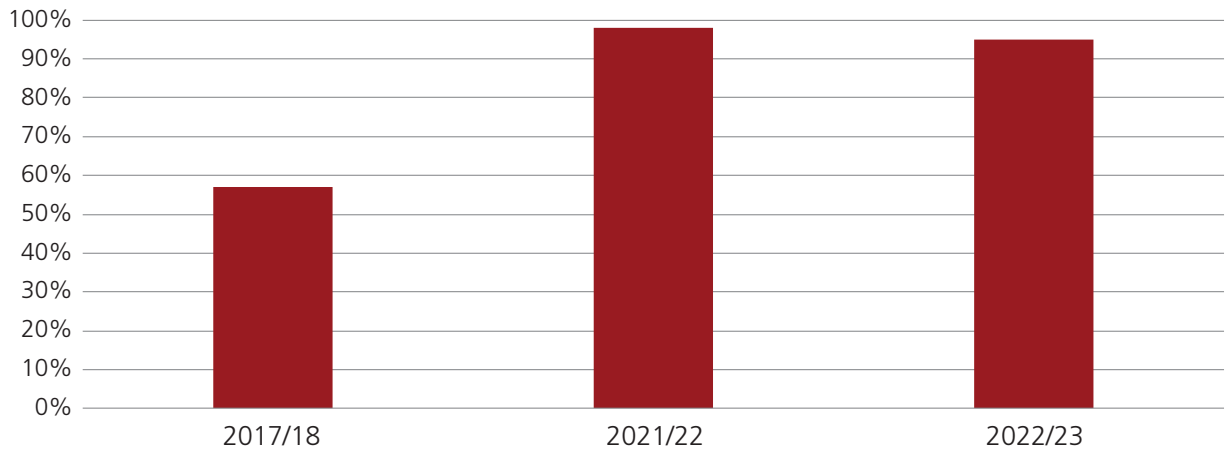
There is little evidence regarding how often patients on eculizumab and ravulizumab should be given B strain boosters. We work alongside Professor Ray Borrow at the UKHSA Manchester Meningococcal Reference Laboratory.

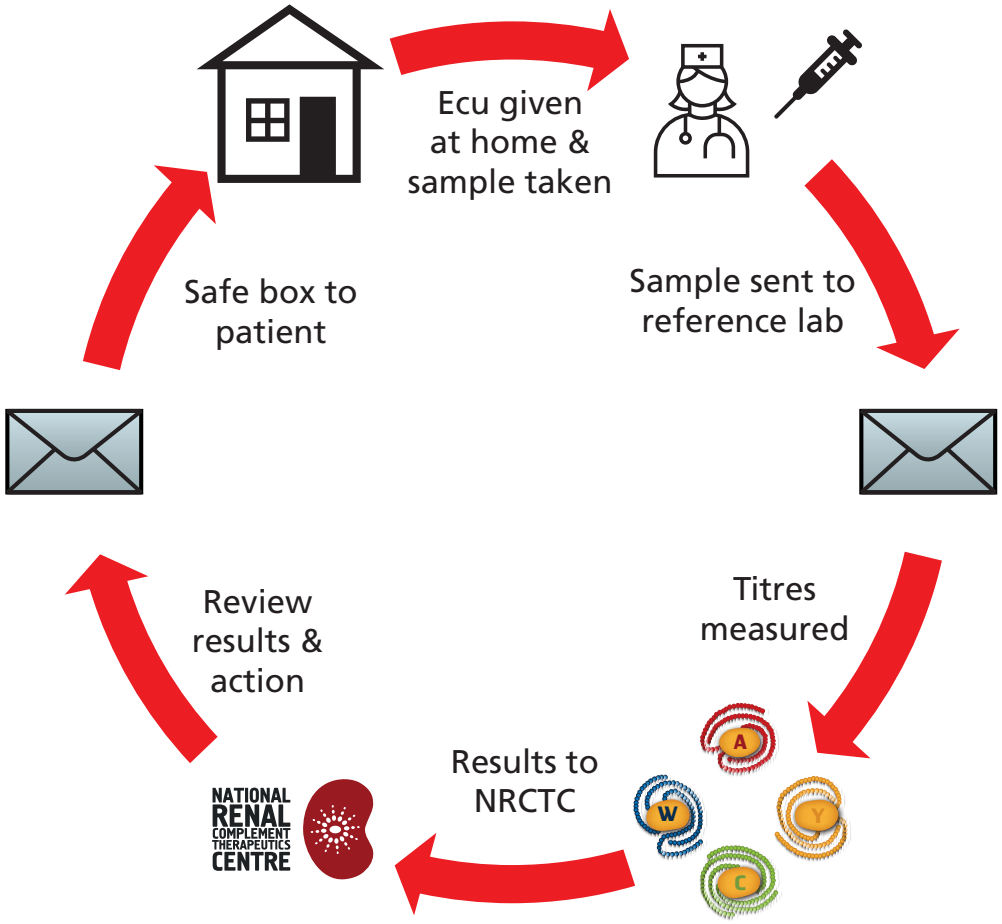
It is our practice to recommend B strain boosters are offered every 5 years.

For patients identified as being due a B-strain booster, we:

- Ensure they have not received Bexsero in the past 5 years (involves cross checking hospital and primary care systems)
- Liaise with local teams to ensure they are happy for us to request this via primary care
- Write to patients and GP recommending Bexsero booster is given
- Follow up all those we recommended is given a booster to check it was administered
- Maintain a record of any vaccines given in NRCTC records

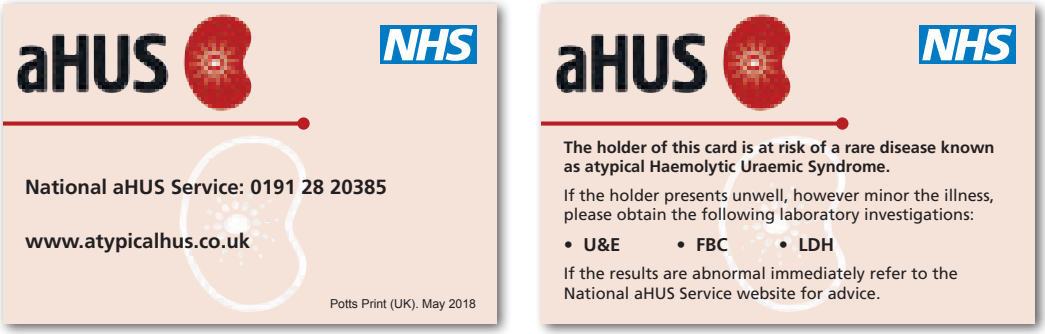
Completeness of annual meningococcal titre monitoring maintained since introduction of the centralised approach to monitoring in 2021





Familial risk of aHUS

We continue to offer counselling and genetic testing to all relatives of aHUS patients who carry a genetic mutation to identify those who are at risk of developing the disease in the future. We are able to do this through blood tests or using buccal swabs. Early recognition of the disease is important in preventing the morbidity and mortality associated with aHUS. At risk family members are provided with a medical alert card, stating that are at risk of developing aHUS and indicating where information can be found on our website.



Patient-held alert card at- risk of developing aHUS

Summary of our previous implementation in this domain

- Regular morbidity and mortality meetings and case review to ensure high quality of care
- Emphasising the importance of meningococcal prevention
- Regular prompting of referring clinicians to ensure steps are taken towards vaccination and prophylactic antibiotics use, with appropriate monitoring as soon as eculizumab is recommended
- Providing access to up-to-date monitoring guidance on our National aHUS Service website
- Highlighting risks of meningococcal infection to patients in clinics, patient roadshows, webinars and newsletters
- Providing advice to relatives at-risk of aHUS and offering genetic screening

3.2 Domain 2: Enhancing the quality of life of people with long term conditions

All patients with aHUS who are eligible for renal transplant will be listed for transplant

All patients referred to the NRCTC who are eligible for renal transplantation are considered for pre-emptive eculizumab at the time of renal transplantation.

All patients with aHUS who are being considered for renal transplantation should be referred to the National aHUS Service for consideration of preemptive Eculizumab. Guidance about this is documented within our transplantation protocol.

Patients with aHUS who require a kidney transplant undergo extensive genetic and autoimmune testing to characterise their risk of recurrent aHUS. We are able to personalise treatment and recommend pre-emptive use of eculizumab at time of transplant to prevent recurrence in patients who are at significant risk of their disease recurring following transplantation.

Six patients received a renal transplant under Eculizumab cover between 1st April 2022 and 31st March 2023. Patients approved for pre-emptive Eculizumab are reviewed at regular meetings. As of 31st March 2023, there were 29 patients pre-approved for Eculizumab to enable listing for renal transplantation.

Summary of our previous implementation in this domain

- Proactive discussions about patients referred to the NRCTC about risk of aHUS following renal transplantation
- Regular review of patients recommended for pre-emptive eculizumab

3.3 Domain 3: Helping people to recover from episodes of ill-health or following injury

To provide advice to referring centres within 24 hours of request of treatment

All referrals to the National aHUS Service were answered within 24 hours

We provide a 7 days a week consultant led on call service. The referral process has been shared nationwide in newsletters and at national meetings to the medical community. The service website was launched in 2017. Instructions as to how to make an emergency referral to request treatment is summarised – specifically to call the on-call consultant via the hospital switchboard. The emergency referral pages and access to forms were specifically updated in 2022 following consultation with referring clinicians who use our service. Automatic replies and voicemail on the aHUS service email address and office phones prompt any referring clinician to call the on-call aHUS consultant if they need to make an emergency referral to access treatment.

Written protocols agreed with units

Shared-care Protocols were implemented in 2017 and are forwarded to clinicians at the outset of treatment as part of the referral pathway. We received shared care protocols for 90% of treated patients in the period from April 2022 to March 2023.

Summary of our previous implementation in this domain

- Ensuring clear and up-to-date instructions for referral are outlined on the NRCTC website
- Collaborative effort with NHS England and referring centres to ensure 100% engagement with shared care model
- Highlighting and sending shared-care protocols early on in the referral pathway

3.4 Domain 4: Ensuring that people have a positive experience of care

Achieve 90% data completeness of the aHUS register to which referring units are mandated to supply data

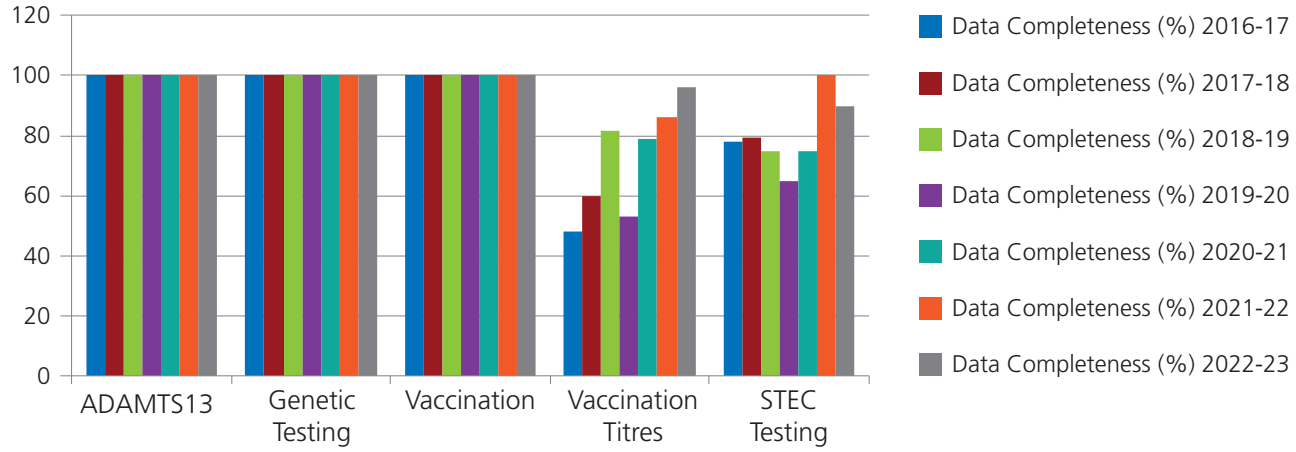
97.2% data completeness in 5 audited domains

Our key aims within this domain are to ensure that an accurate diagnosis of aHUS is made and to protect patients from treatment-related harm. We use a diagnostic checklist to ensure key data is collected from clinicians from the point of referral. We follow up with referring clinicians throughout the referral and treatment period to help achieve data completeness.

There are five categories of data we measure the standard of data completeness against for those patients approve for treatment:

- ADAMTS13 testing
- Genetic testing
- Vaccination against Meningococcal Infection
- Initial vaccination titres
- Shiga Toxin *E. Coli* (STEC) testing

The results of the data collected from patients requiring ADAMTS13 testing, genetic testing, vaccination, monitoring of vaccination response and STEC testing and are shown below. Compliance overall across the five categories was 97.2%.



Data completeness of the aHUS register. *Performance has been measured against 5 categories of data and compared with the previous reporting periods for all patients treated with eculizumab. Data for all domains was 90% or more.*

ADAMTS13 Testing

TTP was reliably excluded in all patients prior to commencing eculizumab.

Genetic Testing

All patients receiving Eculizumab had samples sent to the NRCTC for genetic testing.

Meningococcal Prevention (Vaccination and Vaccination Titres)

All patients who commenced treatment received meningococcal vaccination (ACWY and BEXSERO).

Our specialist nurses follow up with individual clinicians and highlight the importance of vaccination titres in patients who remain on treatment with eculizumab when initial vaccination titres are due.

We have direct links with the UK Health Security Agency Meningococcal Reference Unit in Manchester so that results can be collated centrally for review, in order to advise local clinicians of any further action that is required.

We highlight to clinicians of patients for whom we have shared care the need to obtain titres from the initial point of treatment. Samples for testing are then collected no earlier than 6 weeks from treatment as recommended by the Meningococcal Reference Unit. We received results for initial titres in 96.2% of patients who were under shared care with the NRCTC. Taking into account only patients who have remained on either eculizumab or ravulizumab, we have initial titres for all patients. We also have a separate programme to monitor meningococcal titres in patients receiving longer term courses of eculizumab - this programme differs in that bottles for collection of blood samples are sent directly to patients who are receiving their infusions of eculizumab (or ravulizumab) at home).

STEC Testing

Investigations to detect STEC can help ensure patients with STEC-HUS (self-resolving condition) are not subjected to potentially life-long eculizumab treatment.

We work in close collaboration with local clinical teams and their laboratories to continually improve our processes in relation to obtaining samples for STEC testing.

We met with Dr Claire Jenkins at the UKHSA Colindale Gastrointestinal Reference Laboratory to understand where improvements could be made. As a result of this meeting, we changed the guidance that we provide to referring clinicians. The guidance was revised to include very explicit information for staff collecting samples, and for local labs receiving samples, in relation to sending samples to UKHSA Colindale. This guidance was user-tested with ward nurses, junior doctors, consultants (adult and paediatric) and laboratory staff to seeks views on clarity and reduce scope for confusion. Iterative changes were made based on user feedback to produce the updated guidance. The guidance now forms part of the UKHSA STEC testing form.

We now embed communication about how to get robust STEC testing to local clinical teams to explain directly the importance of getting a result for STEC testing and provide clear instructions on how to ensure that a timely result is obtained.

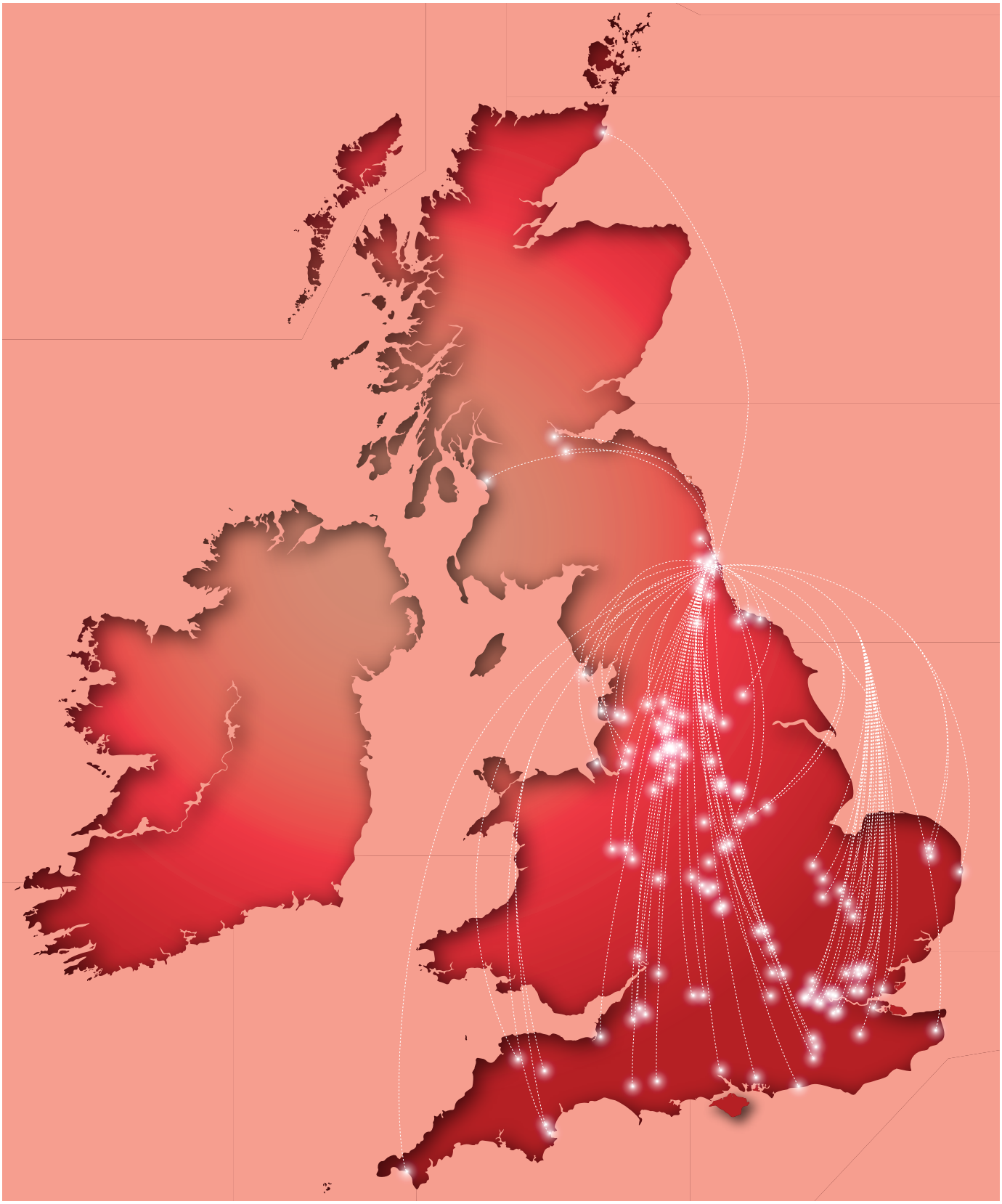
We also contact the UK Health Security Agency Gastrointestinal Reference Unit to help expedite reporting of any results that they receive. We were able to obtain samples for STEC testing in 90% of patients in whom testing was indicated.

Summary of our previous implementation in this domain

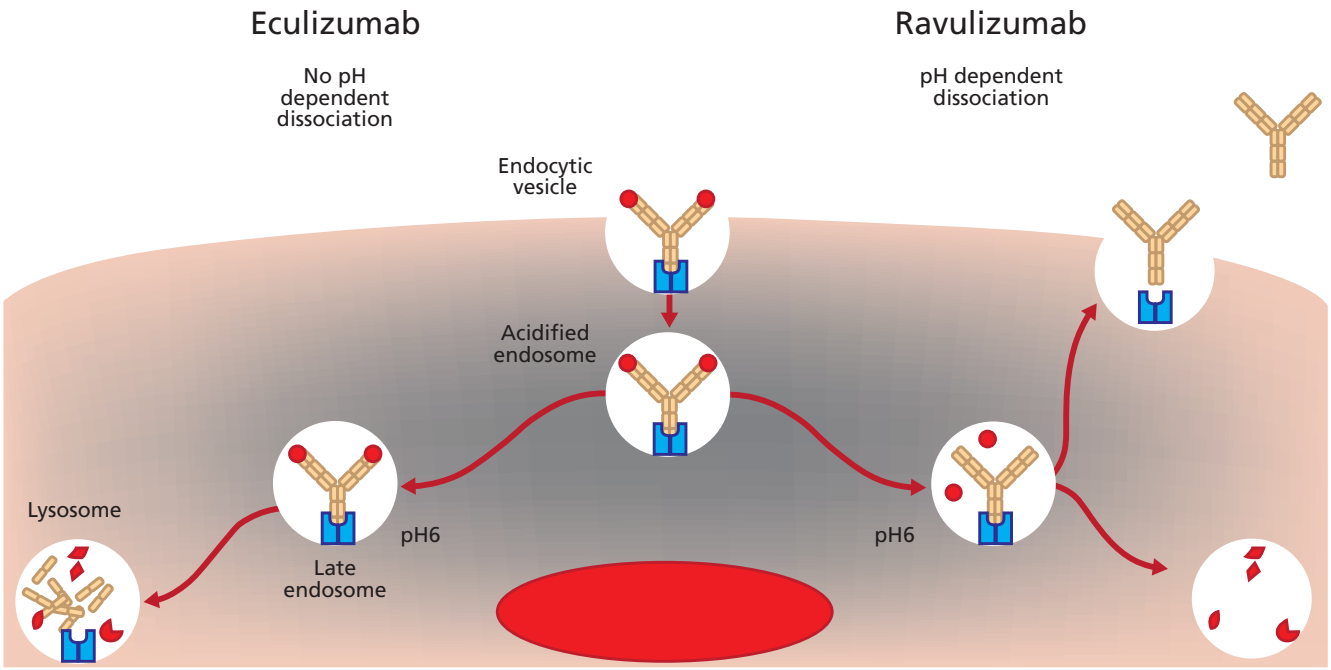
- Engagement with experts in the field (Professor Ray Borrow [National Meningococcal reference laboratory] and Dr. Claire Jenkins [National Gastrointestinal Bacterial Reference Unit] to ensure up-to-date recommendations are used in our referral pathway.
- NRCTC links directly with UK Health Security Agency laboratories and referring teams to ensure streamlined approach to requesting testing to monitor vaccination response and to detect STEC.
- Ongoing shared care between NRCTC and local team to confirm diagnosis and optimal treatment plan

Outpatients Clinics

Outpatient Clinics were commenced in 2017; each patient is offered a minimum one hour multi-professional clinic appointment which may be increased to accommodate other family members. During the period 2022-23, we have continued our specialist clinic services and offer telephone and video calls (using Attend Anywhere) and face-to-face appointments depending on the preferences of the patient. During consultations, patients are provided with a personalised description of their disease and the opportunity to ask specific questions they may have. Our patients are also informed about research, including clinical trials which may benefit them. We also discuss risk of disease in family members and ensure all have access to genetic predictive testing. We also utilised outpatient attendances to discuss possible switch from eculizumab to ravulizumab in 2021 and currently discuss both treatment options routinely with patients. The aHUS Specialist Nurses also routinely follow up patients in clinics, who were diagnosed and on treatment with eculizumab or ravulizumab from August 2020.



Patient Consultations



Amino acid change between eculizumab and ravulizumab results in increased half-life of ~52 days for ravulizumab compared with ~11 days for eculizumab.

Patients switching from eculizumab to ravulizumab

NHS England agreed to fund the use of ravulizumab in aHUS patients from September 2021.

Patient consultations

The NRCTC wrote to all existing patients who were receiving eculizumab in September 2021 who were eligible to switch therapies, inviting them to have an individualised consultation with their named NRCTC consultant, to discuss ravulizumab: how it works; effectiveness; and ultimately whether it was the right option for them to switch therapies.

- All patients and their clinical teams were invited for a consultation about a possible switch to ravulizumab

The Ravulizumab switch process

We then worked with the key stakeholders (drug company, homecare providers, pharmacists and local clinicians), to develop a pathway for the process of switching patients from eculizumab to ravulizumab. As part of this process, we identified specific challenges to overcome and ultimately developed a series of documents to support local teams in making the switch.

For each patient wishing to switch from eculizumab to ravulizumab, we are providing an individualised patient letter detailing step-by-step processes for the managing clinician and pharmacist as to how to switch a patient's therapy – a generic guide was also added to our website.

This letter includes:

- Specific details of meningococcal titre dates and meningococcal vaccines that have been previously administered, to aid local teams in completing the certificate of vaccination needed to switch therapies
- An infographic guide detailing the switch process, including recommendations for monitoring following the-switch to ravulizumab
- A certificate of vaccination required by Alexion, partially completed, with patient's known identification code with Alexion, to aid local team when submitting paperwork at their end
- Blood form needed for specialist complement blood testing in Newcastle, at 18 weeks post-switch
- A dosing and administration guide, produced by the drug company
- Relevant homecare documentation for the new therapy

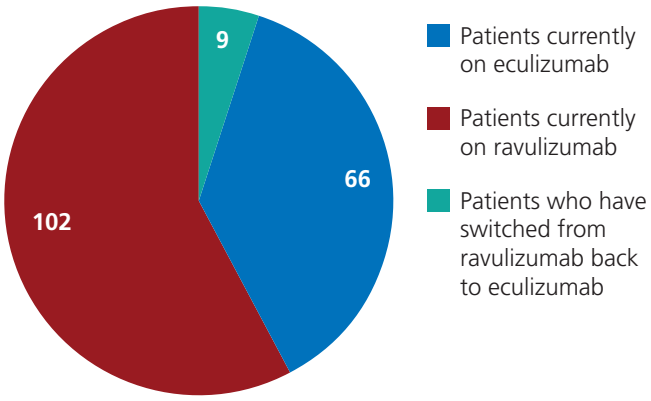
The letter and switch pack documents are then sent to both the local managing clinician and named renal pharmacist. We also follow up on all patients who have decided to switch, linking in with local clinicians and pharmacists to confirm date of switch.

After patients have switched, we arrange for specialist complement bloods (that are due at 18 weeks following switch) and continue to support local teams providing advice for any problems that arise during the switch process. We also continue to consult with patients and their clinicians and follow up to ensure patients remain well on ravulizumab.

Patients have the option to switch back to eculizumab.

The NRCTC has also discussed the option of treatment with ravulizumab with all patients who have commenced eculizumab following referral to our service since September 2021. These discussions are embedded into the routine follow-up consultations we have with our patients on treatment.

As of 31st March 2023, of the 177 patients currently receiving complement inhibition therapy, 102 are on ravulizumab and 75 are on eculizumab (of which 9 have switched back from ravulizumab. Reasons for switching back include planning for pregnancy and the onset of fatigue.



Patients receiving either eculizumab or ravulizumab as of 31st March 2023.

Nurse-led monitoring

The aHUS Nurse Specialists at the NRCTC support the monitoring of patients with aHUS in relation to meningococcal titres [described in section 3.4], Factor H autoantibody titre measurement and complement blockade.

Factor H autoantibodies

For patients in whom we have detected anti-factor H autoantibodies (a known cause of aHUS), we have implemented a centralised approach to monitoring levels in this group of patients, and co-ordinate this for patients across the country.

In most cases, these blood tests are now taken alongside patients' infusions of eculizumab or ravulizumab in an approach that mirrors the process we implemented for meningococcal titre measurements.

This has improved our adherence to six monthly monitoring which is significant for patients in whom anti-factor H antibodies are the sole cause of their aHUS, as persistently undetectable levels of antibodies may have treatment implications which we can then discuss with them and their local team during clinic consultations.

Complement blockade

When a patient is commenced on treatment with eculizumab and on a stable regime, it is important to confirm that the patient's complement system is adequately blocked on their current dose and interval of eculizumab. If the patient's complement system is not adequately blocked, this may lead to risk of aHUS relapse.

For this reason, the aHUS specialist nurses ensure that any patients commenced on eculizumab have specialist complement blockade blood tests done at appropriate intervals including during pregnancy. The nurses interpret and feedback results to both the local managing clinician and named consultant at the NRCTC. If results do not suggest complete blockade of the complement system, this prompts a discussion and review with the managing NRCTC consultant to determine further action is required.

4. Achievement of Performance Targets

The results compiled in this report are for a complete financial year and encompass the activity of the National aHUS Service from the 1st April 2022 to 31st March 2023. The performance targets are summarised below.

Quality Requirement	Threshold	Percentage achieved
Domain 1: Preventing people dying prematurely		
Zero avoidable deaths in patients with a diagnosis of complement mediated aHUS (as per current diagnostic criteria)	Zero avoidable deaths	Zero avoidable deaths
Domain 2: Enhancing the quality of life of people with long- term conditions		
All patients with aHUS who are eligible for renal transplant will be listed for transplant	100% of patients on transplant waiting list	100%
Domain 3: Helping people to recover from episodes of ill- health or following injury		
To provide advice to provider centres within 24 hours of request on treatment	90%	100%
Written protocols agreed with units	100%	90%
Domain 4: Ensuring that people have a positive experience of care		
Achieve 90% data completeness of the of the aHUS register to which referring units are mandated to supply data	90%	97.2%

National aHUS Service – Performance during reporting period from 1st April 2022 until 31st March 2023.
Performance targets for all domains were met.

5. Patient and public engagement

5.1 Patient panel

In September 2022 we welcomed a new group of volunteers to our patient panel. We had 11 volunteers that made up the panel – a mix of both patients, carers and parents. The first meeting ran virtually on 8th September 2022 and subsequently we have run 3 further remote meetings.

What is the aHUS patient panel?

- A group of volunteers made up of patients/ parents/carers
- Informal open forum for sharing thoughts and opinions on all things aHUS
- Opportunity to influence our service and resources, and steer change

What happened in the meetings?

The meetings have given an opportunity for panel members to share elements of their personal aHUS journey and also consider as a group:

- the types of information they had access to and if they found it helpful during the diagnosis period
- how and when information was communicated to patients and families at the point of diagnosis and throughout their treatment
- what are the information gaps / what resources would have helped to support patients and families more effectively?
- what we, as a national service, could do to help improve their aHUS journey

The patient panel has resulted in a number of changes to the service we offer patients, these are summarised below.

Patients Said

Patient roadshows are a great opportunity for peer support. They provide a platform for this to occur organically and should be utilised more to facilitate peer support amongst patients and families.

We Did

For roadshows from 2024 we will offer a specific allocated session which will give patients/ parents the opportunity to have peer interaction.

Nationwide reach of patient panel

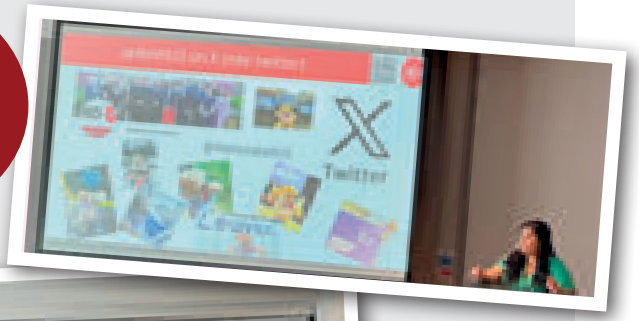
5.2 Patient Roadshows

This year we hosted one-day roadshows, held in person in London and York for patients with aHUS and their families. At each roadshow, we delivered talks around key aspects of aHUS diagnosis and its management. There was opportunity for patients and their families to meet one another and discuss their experiences. We also held a two-day roadshow in Bath, for aHUS patients and C3G patients on separate days.

Roadshows map

Highlights from aHUS roadshows:

Thank you for all you do, you are all amazing



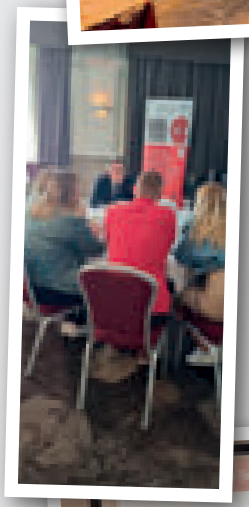
Interaction with other people

Meeting the team in Newcastle and other patients

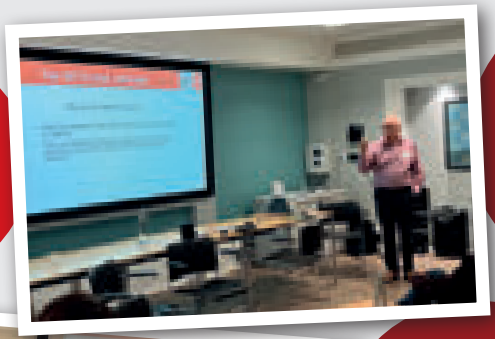
Realising that the support team are there if you really need them

Meeting others living with aHUS

Will continue repeated attendances, always worth it



Info about research and future treatments



Having been to a few now they are such a valuable source of information. Thank you!

Time to discuss issues face to face has been invaluable.

Highlights from C3G roadshow:

Being able to directly ask questions to specialists.

The information about the trials and results

This is my second [C3G roadshow] and it was very helpful and informative.

Good to see the new advances in drug trials.

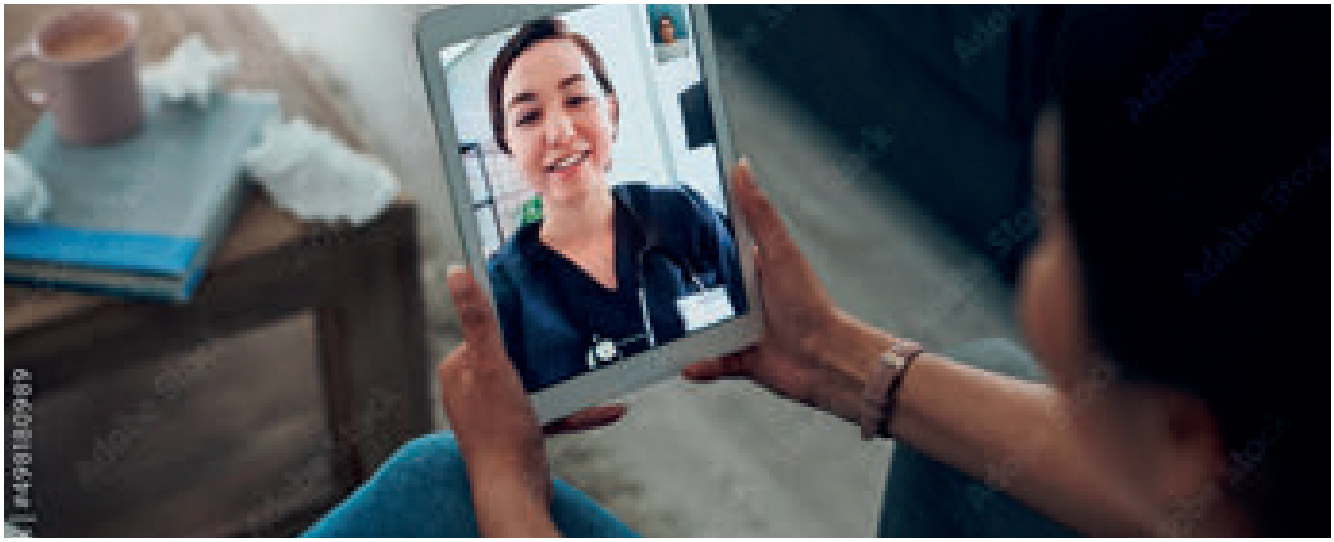
Some unanswered questions that we had, have now been answered.

It has covered everything that we would have wanted.

5.3 Nurse-led clinics

Nurse clinics allow a holistic assessment of the patient and family and results in broad discussions about their condition, results, and treatment, as well as the wider implications of their condition on their life. The nurses then summarise these discussions in a letter to the local managing clinician as well as the patient and GP. This details a plan of care in relation to aHUS.

We are currently working alongside our service manager and the Trust patient engagement team to progress how we can evaluate the effectiveness of these clinics, to ensure patient and parent feedback is embedded into the clinics. This feedback ensures the patient voice is heard, and hopefully clinics can be evaluated to see if they meet the needs of our patients, parents and carers.



5.4 Charity Nominations

We work alongside charities to try and enhance the life opportunities for our patients. This year we have been very pleased that some of our charity nominations have been successful, and our patients have the opportunity to experience some of the opportunities that these charities offer.

Willow Foundation

The Willow Foundation helps seriously ill young adults (aged 16 – 40) with life limiting or rare conditions to make fun memories.

Janette

The Willow Foundation organised a holiday for Janette and her family to Centre Parcs. She told us that they had a fantastic time and the boys got to jet ski for the first time. This was an opportunity that the family had previously missed out on, as Janette was unwell. We are very appreciative that the Willow Foundation could enable Janette and her family to enjoy this opportunity.

Dreamflight

Dreamflight is a UK charity that takes children with a serious illness or disability on their holiday of a lifetime to Orlando. We have been very lucky with previous years nominations and we are thrilled that this year we have also been successful with two nominations.

5.5 Nursing Awards

Newcastle Hospitals Celebrating Excellence Awards

This year we have been recognised for our work in a number of award nominations.

The Newcastle Hospitals Celebrating Excellence Awards are an opportunity to acknowledge individuals and team's exceptional work. The aHUS Specialist Nurses were nominated in the Quality Improvement and Patient Safety category in recognition of the work they have implemented in ensuring aHUS patients awaiting kidney transplant have access to eculizumab in a timely and co-ordinated manner at the point of transplantation.

Nursing Times Awards

The aHUS specialist nurses won in The Nursing Times Awards in the Patient Safety Improvement Category.

The 'Patient Safety Improvement' category sought nominations of initiatives which could show how they have addressed factors known to place patients at risk with clear demonstrations of improvements in patient safety.

This much coveted award recognises our initiative 'A Collaborative model of meningococcal vaccination response monitoring for patients receiving complement inhibition', which seeks to enhance effective monitoring to help prevent potentially life-threatening infections caused by a known side effect of eculizumab and ravulizumab.

The intention of the initiative – designed, led, implemented, and audited by the aHUS nurses – was to improve the percentage of patients undergoing an annual blood test to measure protection against meningitis.

We established new collaborative pathways whereby a blood sample for titres could be taken alongside the patient's infusion at home which has significantly increased uptake (from 57% to 97%) and consequently improved patient safety by reducing their risk of contracting meningococcal infection.

The Nursing Times Awards judges said "the Newcastle atypical haemolytic uraemic syndrome (aHUS) service clearly described how current approaches to effective monitoring did not work for this rare disease in a complex health landscape.

"The team recognised a gap in local management and put in place a new national collaborative pathway involving patients, multiagency partners including health, home care providers, independent sector, and pharma to reduce risk which has significantly improved patient safety."

HSJ AWARDS 2023

Finally, we have been shortlisted for **Acute Sector innovation of the Year** at the 2023 Health Service Journal Awards. This award is not seeking reinventions of the wheel: it is in recognition of teams who are doing something genuinely new, while building on the good practice already out there.

The National Renal Complement Therapeutic Centre is unique worldwide, delivering centralised care to all patients with the ultra rare diseases aHUS and C3G locally through a shared-care model. Our patients receive the C5 inhibitor, Eculizumab which leads to a >600x risk of meningococcal sepsis with mitigation through vaccination and antibiotic prophylaxis. With a geographically disparate patient group, the NRCTC team identified a deficiency of local monitoring, potentially placing patients at risk. Working collaboratively with stakeholders including patients,

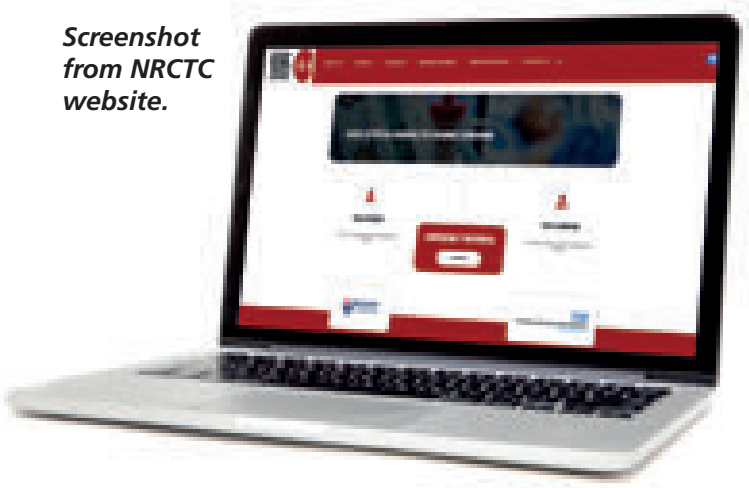
local clinicians, homecare companies and Alexion, new service level agreements across all trusts were negotiated and implemented – resulting in an innovative system to increase monitoring of meningococcal titres and revaccination. Virtual NRCTC clinics with patients provide additional reinforcement of antibiotic prophylaxis.

5.6 Online NRCTC

One of our key remits is to provide high quality advice to patients and clinicians about aHUS and C3G. Our website (http://www.atypicalhus.co.uk/) provides a hub of information and advice for patients and clinicians. For our patients, previous news and events can be viewed, as well as content and videos to explain about aHUS and STEC-HUS.

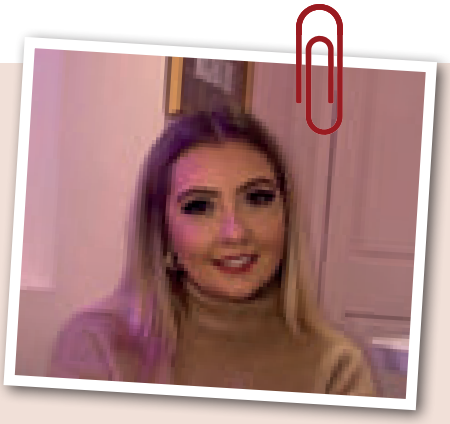
The website was updated in 2023 following engagement with patient and clinician partners.

For clinicians, the website continues to serve as a portal to access our full range of services as well as providing an up-to-date summary of complement mediated renal disease and their treatments. An emergency referrals page highlights the 24-hour 7 day a week consultant led on call service. It provides a repository for clinicians to download diagnostic checklists, diagnostic referral forms for adults and children, including meningococcal and STEC request forms and guidance, as well as our shared care protocol.



Screenshot from NRCTC website.

5.7 Patient Story



Chloe's story

Chloe Pratt thought her chances of ever living a normal life, let alone starting a family, had been dashed when she was diagnosed with aHUS last year.

The HR assistant's diagnosis came out of the blue as she was the first in her family to have presented with the disease after becoming seriously ill and being admitted to intensive care.

Within days of being diagnosed, she was given eculizumab and is doing so well on the treatment that she has regained hope for a future she once feared might be out of reach.

Had Chloe not been given the treatment she would have been on permanent dialysis, and this makes it less likely to become pregnant as well as more likely to have complications.

Chloe, 25, of Darlington, said: "I'd never heard of aHUS, so it was quite overwhelming to be told that I had a life-threatening illness and would need eculizumab.

"I was extremely tired, and I was just not feeling myself, but it wasn't until my eyes went yellow that I went to seek medical advice, leading to my shock diagnosis.

"Since I have been taking eculizumab I feel much better, and I am getting back to myself again. I can't imagine not being on this treatment, it has prevented kidney failure and it has saved my life."

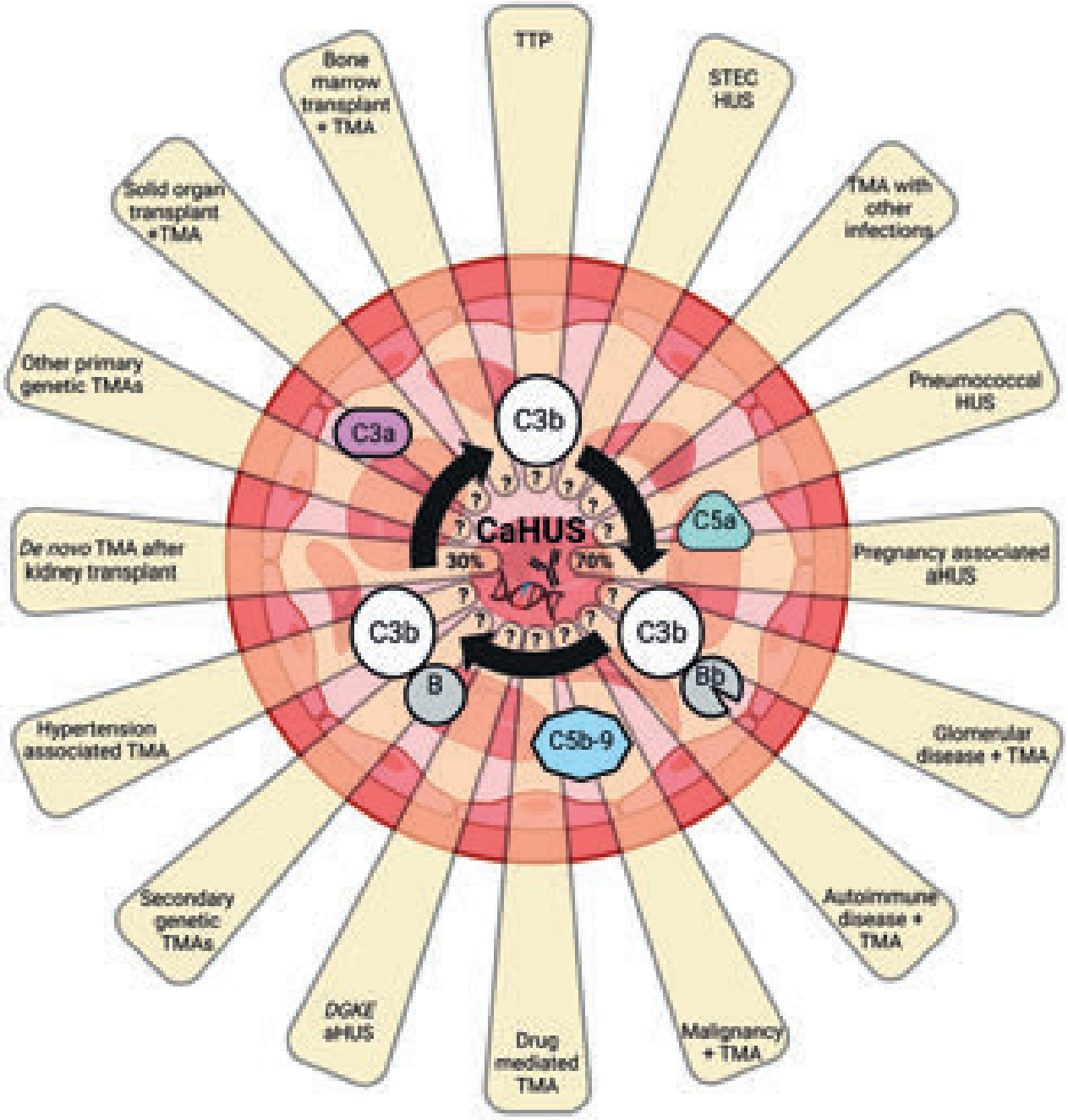
Reflecting on her future, Chloe added: "I'm now really excited about the prospect of living a normal life and even hope one day to be able to start a family.

"After my diagnosis, I feared that this dream would not be possible, but thanks to eculizumab, I see a brighter path ahead."

At least nine different genes have been identified to be associated with aHUS. Several members of Chloe's family were genetically tested for the condition and do have the affected genes, putting them at risk of developing the disease in the future.

Chloe said: "It's fantastic that the research into aHUS and eculizumab has been led in Newcastle and I feel very lucky that I have been able to benefit from this."

6. Complement Research at the NRCTC



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