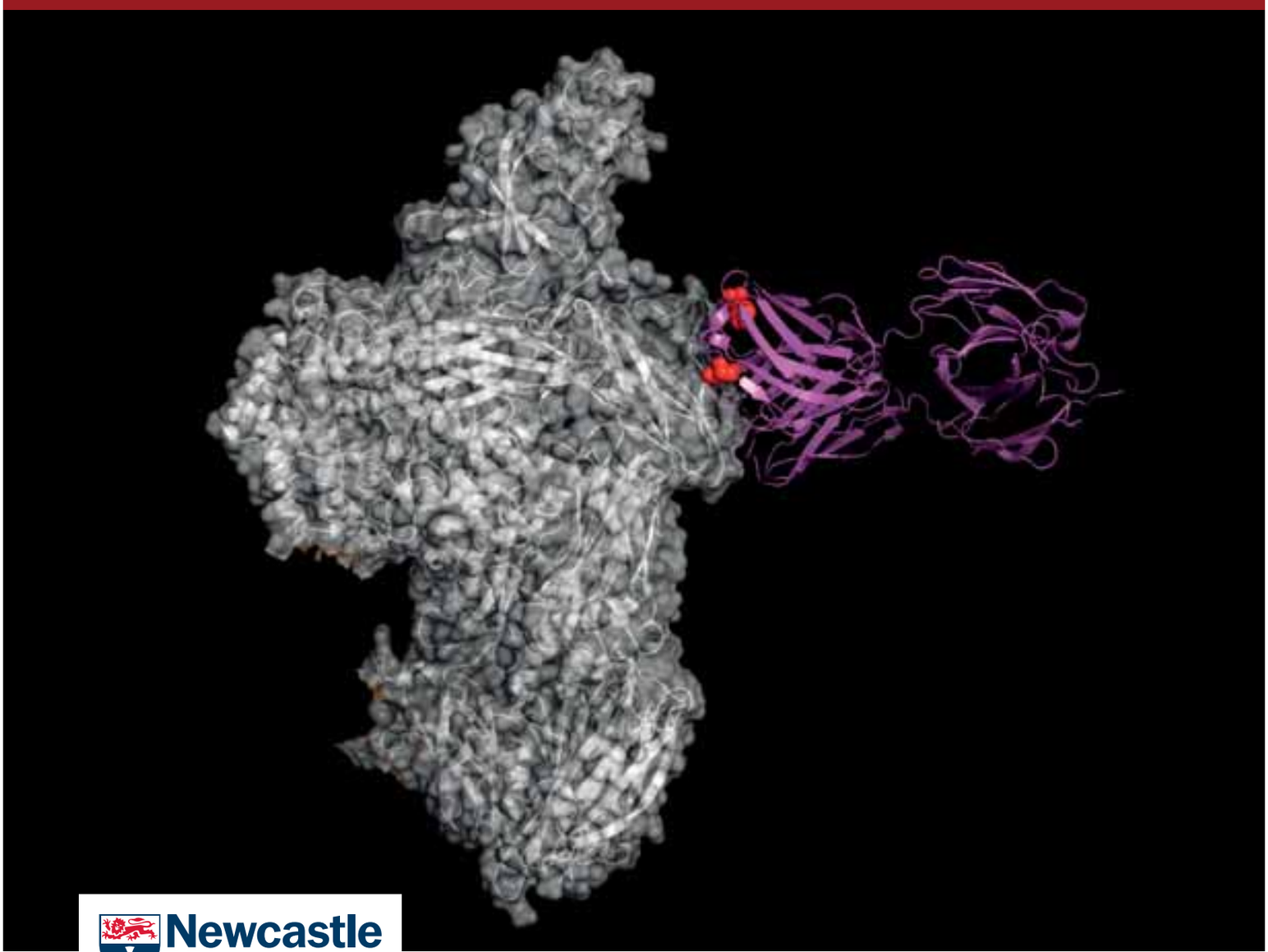
NATIONAL RENAL COMPLEMENT THERAPEUTICS CENTRE

NHS
The Newcastle upon Tyne Hospitals
NHS Foundation Trust

# The Annual Report of the **National Renal Complement Therapeutics Centre** 2020/21



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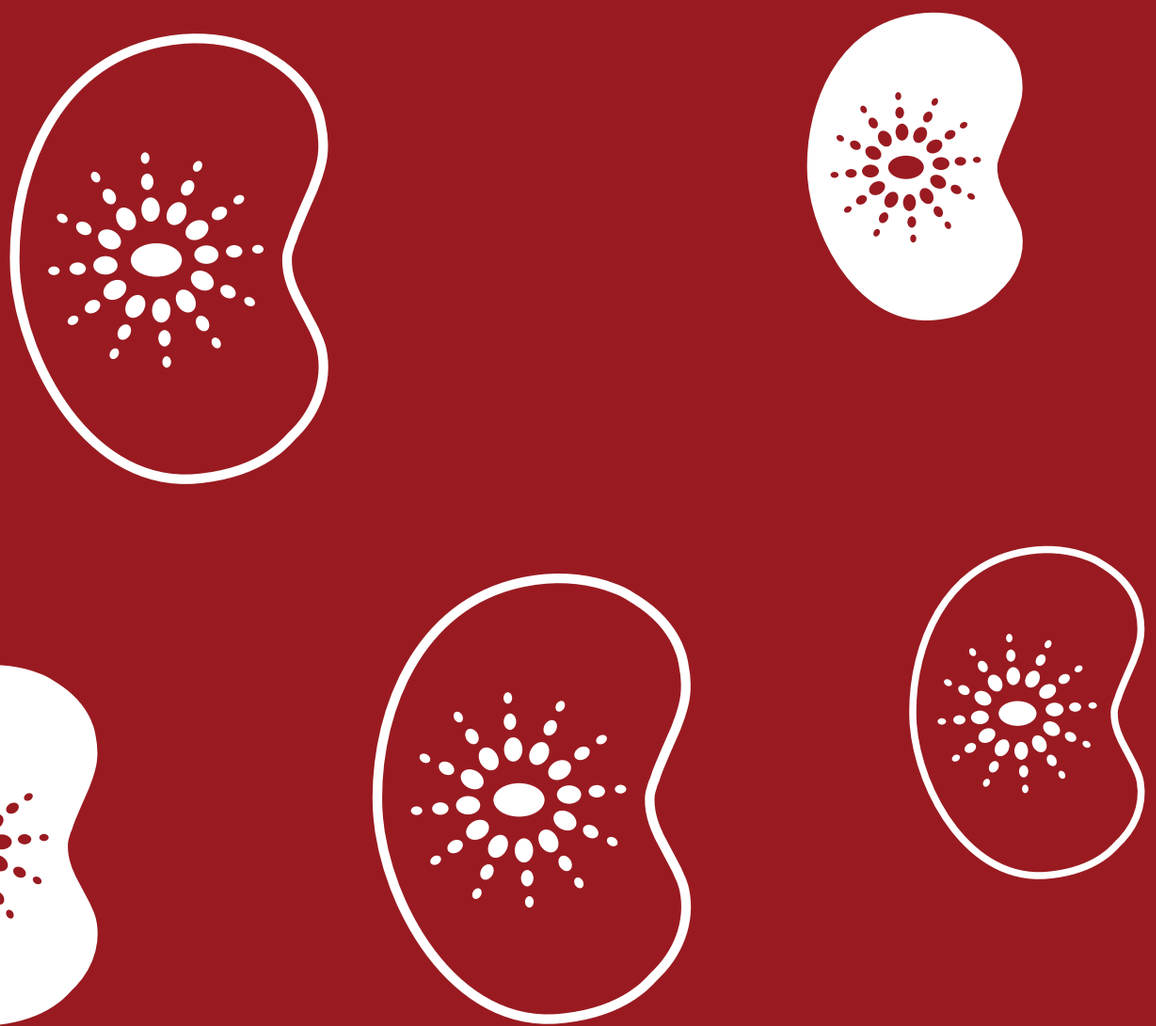


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Some photographs used in this report were taken prior to the COVID-19 pandemic. All other photographs used in this report are in line with any government guidance on social distancing that in place for COVID-19.

# The Annual Report of the **National Renal Complement Therapeutics Centre** 2020/21

aHUS
ATYPICAL HAEMOLYTIC URAEMIC SYNDROME

NATIONAL RENAL COMPLEMENT THERAPEUTICS CENTRE

C3G
C3 Glomerulopathy

# Contents

# 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; treatment and 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 five consultant nephrologists (three adult and two paediatric), three nurse specialists and an administration team who are part of the Newcastle upon Tyne Hospitals NHS Trust. We also have seven dedicated clinical scientists and two consultants working across genetics, haematology and immunology that help us deliver our cutting edge diagnostics. Our consultants also work at the renal units at the Freeman Hospital and the Great North Children's Hospital. 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 aligns with that of Newcastle upon Tyne Hospitals NHS Foundation Trust, "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 influence the care we deliver, enabling personalised management.

### Our Vision

"a centre of clinical excellence for patients with complement-mediated renal disease, including aHUS and C3G at the forefront of international research."

### Our Core Values

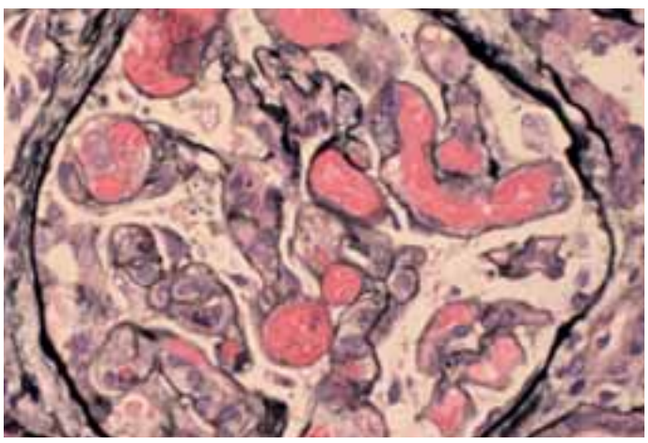
"putting patients at the heart of everything we do"

## 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 50% of patients developing kidney failure or dying in the first year after presentation.

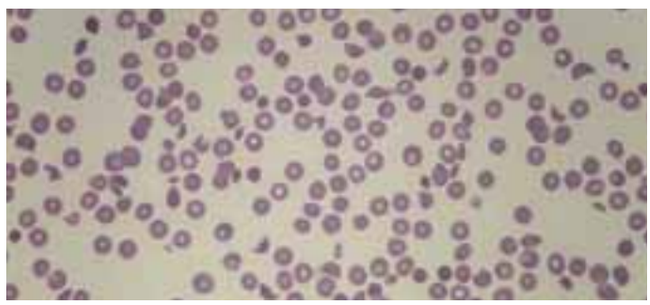
There is no rapidly available test to confirm the diagnosis of complement mediated aHUS and the initial diagnosis is based on clinical, laboratory and pathological findings and the exclusion of other pathologies; in particular, infection related Shiga Toxin (STEC)-HUS and Thrombotic Thrombocytopenic Purpura (TTP).



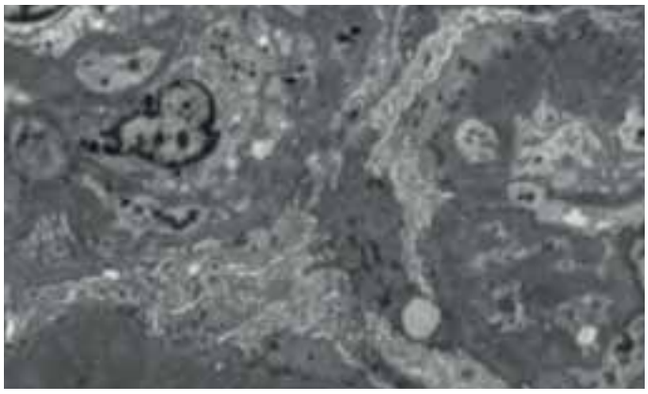
***Renal biopsy showing thrombus formation in aHUS***

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.

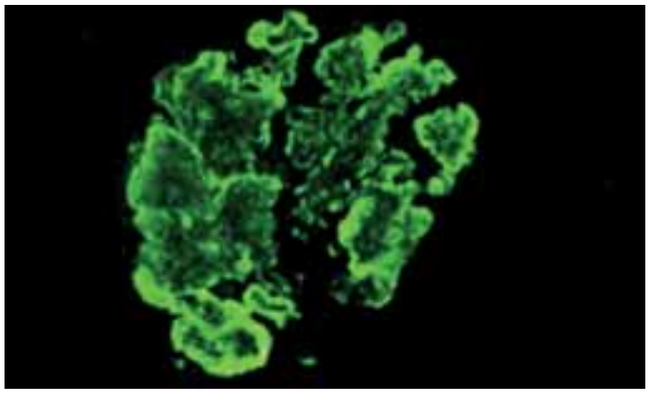
Since 2016, the National aHUS Service has been available 7 days a week 24 hours a day to provide advice on diagnosis and management from Consultants experienced in the management of aHUS. We also provide rapid diagnostic testing and support for clinicians to exclude other forms of Thrombotic Microangiopathy (TMA).



***Blood film from aHUS patient showing schistocytes***



***Sub-endothelial deposits in C3GN seen on electron microscopy***



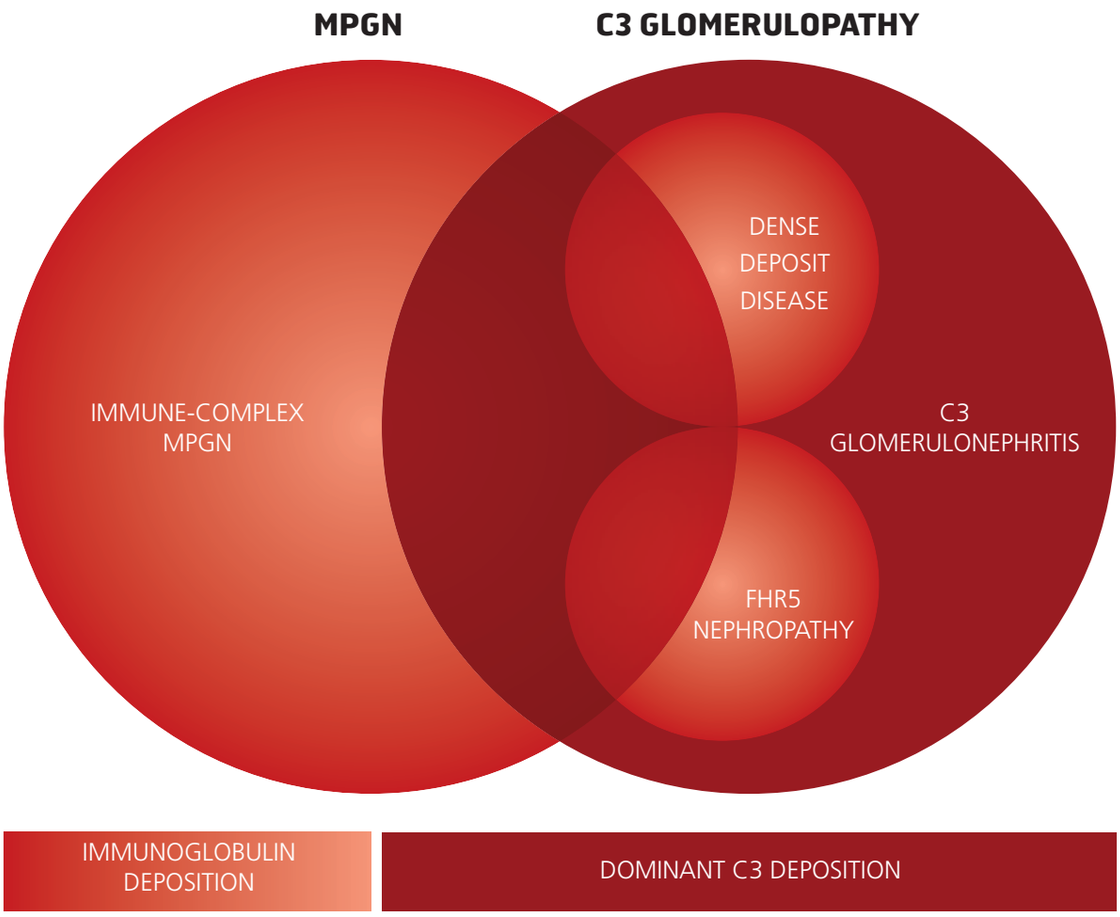
***Strong C3 staining in C3GN***

### 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 renal failure to a more indolent presentation of chronic kidney disease. On average, patients progress to endstage renal failure within 10 years 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.




***Overlap of MPGN and C3 Glomerulopathy***

## 1.4 Service Development

The NRCTC strives to improve its service year on year. Patients currently benefit from the following services provided by the NRCTC:

- Defined pathways for access to optimal diagnostics and treatments of aHUS and C3G
- Shared care between the NRCTC and an increasing number of clinical teams nationwide
- Consultations with patients and their families using remote technologies (Attend Anywhere), telephone clinics and face-to-face
- Access to disease specific information via our website and virtual live webinars
- Direct input to service development through patient engagement
- An active research programme comprising basic science and clinical studies, including clinical trials in aHUS and C3G

## 1.5 Our Strategy

Our six 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

- Each member of the NRCTC team will be exploring 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 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.

## 1.6 Patient Engagement

We now have a newly appointed specialist nursing team we continue to develop their role in the national aHUS service.

- We provide every patient and family the opportunity to feedback their experiences of being diagnosed with aHUS.
- We contact newly diagnosed patients by letter, providing an introductory pack, alert cards and wristbands.
- We offer a joint consultation with one of the aHUS Consultants at the three month mark and then continue with regular nurse-led follow-up
- All letters are copied to the GP and local managing consultant
- We offer familial screening of patients' relatives, and provide them with "at risk" cards
- We are in the process of agreeing a contract with homecare companies so that meningococcal titres can be taken by the infusion nurse within the patients home, reducing the number of healthcare interventions for patients
- We continue to publish our aHUS newsletter
- We have been responding to an increasing volume of email communication with patients
- We have produced a letter for school- aged children that we can send at the parents request to the school
- We have hosted webinars with patient Q and A

## 1.7 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 National aHUS Service each understand their roles and responsibilities in delivering that care. This was mandated in the service specification: namely to facilitate optimal patient management on a shared care basis with referring clinicians. The shared care protocol was initially rolled out to all incident patients commenced on Eculizumab in the new National aHUS Service with subsequent enrolment of the prevalent patients that were already receiving Eculizumab. This protocol is now embedded into our referral pathway.

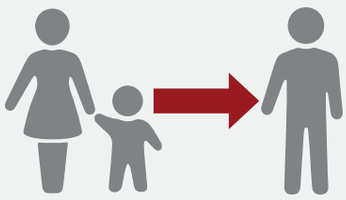
As part of this pathway, we have a system in place to ensure precious patient samples are couriered to our specialist laboratories in Newcastle (section 1.8.1) including those that require shipping on dry ice. We continue to work closely with the public health england laboratories in Colindale and Manchester (section 1.8.7 ).

Once a diagnosis has been confirmed, all patients are allocated a named consultant who are then responsible for coordinating their care and liaising with their local team. Paediatric patients will have their ongoing care coordinated by one of our paediatric nephrologists. Transition to adult services will be managed primarily by the local team but at the appropriate time their care will also be transferred to one of our adult nephrologists at the National aHUS Service. Within our trust we also have a dedicated renal young adult care coordinator and our shared care model allows us to utilise their expertise if required.

Patients are also provided with alert cards and wristbands with disease specific information and contact details.

**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**

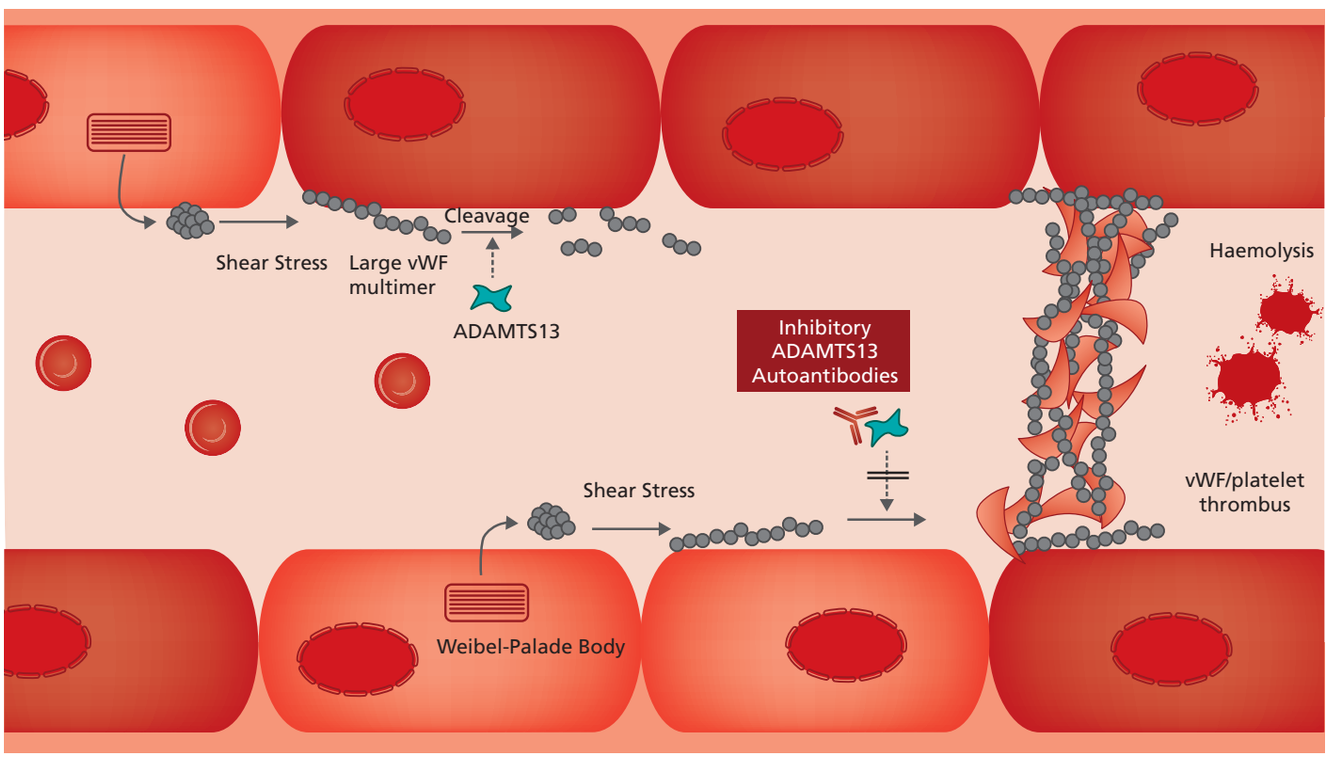
## 1.8 Ensuring High Quality Care that Delivers Optimal Use of Eculizumab

### 1.8.1 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.

### 1.8.2 Measurement of ADAMTS13 Activity

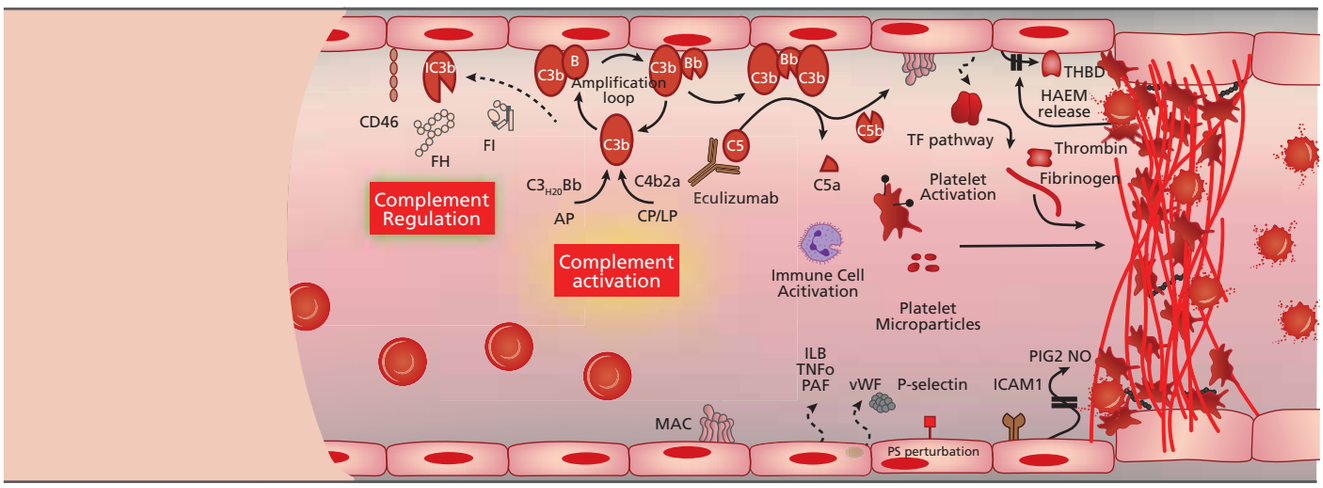
Urgent measurement of ADAMTS13 is the essential initial test in the management of thrombotic microangiopathies as it determines divergent treatment strategies. A very low ADAMTS13 activity is diagnostic of thrombotic thrombocytopenic purpura (TTP). Von Willebrand Factor (vWF) is a large protein that 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 Paul Murphy. Where testing cannot be carried out locally we provide this urgent analysis, including transport of specimens to the Newcastle laboratory.




***Thrombus formation in TTP***

### 1.8.3. 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 both atypical HUS and C3G both nationally and globally. The NRCTC provides a fully integrated care pathway 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; and INF2*. Routine sequencing of the genes *DGKE* and *MMACHC* and bespoke analysis for *INF2* 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)***

### 1.8.4 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 the 100,000 genome project allows the discovery of novel genes that predispose to aHUS. This combined entity is utilizing these cutting edge technologies to personalise management of our patients.

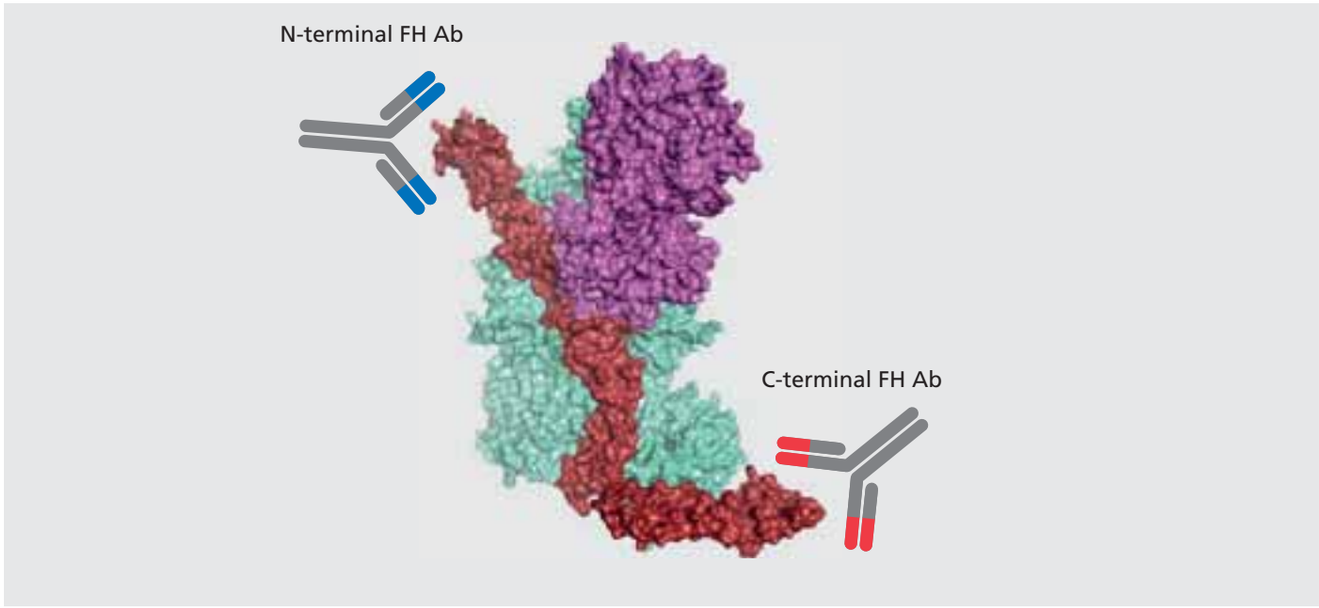
### 1.8.5 Complement Analysis in aHUS & C3G

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.

### 1.8.6 Autoimmune Complement Mediated aHUS & C3G

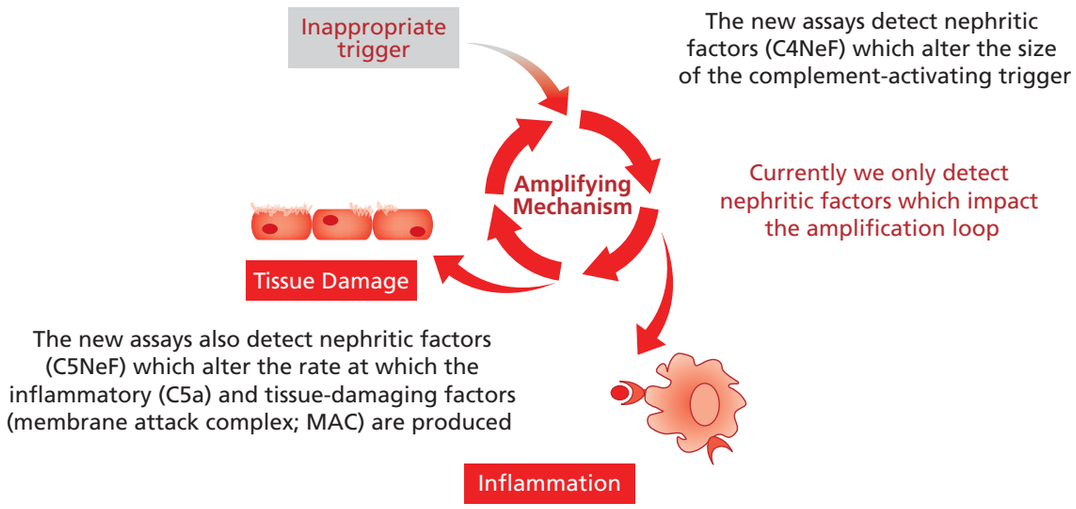
Dr Kevin Marchbank, head of autoimmune aHUS analytics, leads the complement autoantibody service. Autoantibodies to complement factor H are one of the commonest causes of complement mediated aHUS and are also found in C3G.

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.

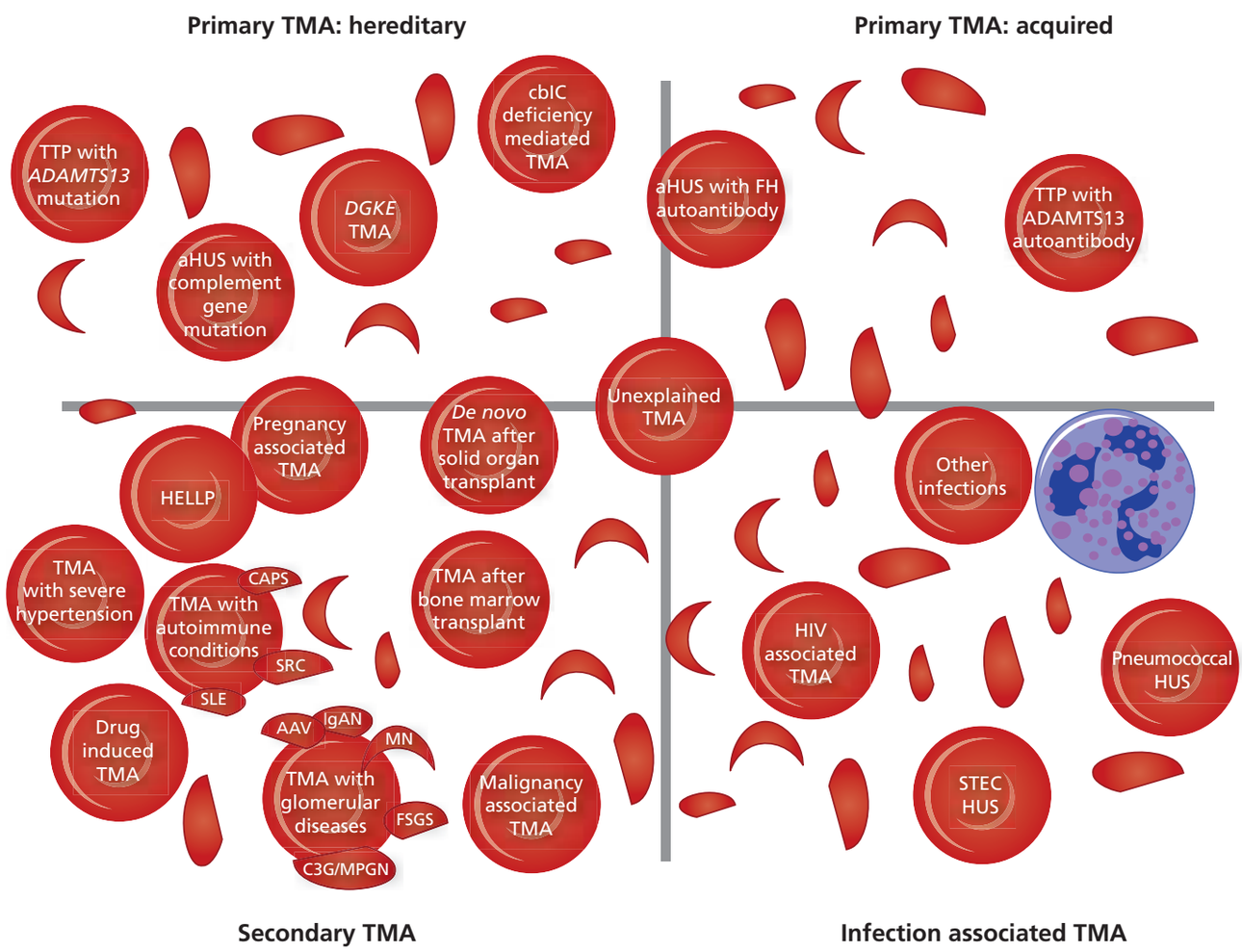



***Epitope mapping of FH autoantibodies.*** *The kidney is normally protected from damage by complement activation when C3b (cyan) is degraded by the enzyme factor I (purple) and the cofactor factor H (red) (protein database identification:5O35). The location of the autoantibody binding to factor H determines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

In C3G, C3 Nephritic factors are routinely measured and C4 and C5 Nephritic factor assays are also under development in David 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.




***Identifying nephritic factors in C3G***



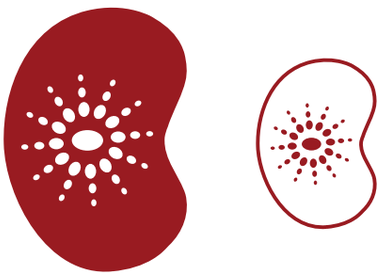

***Causes of TMA***

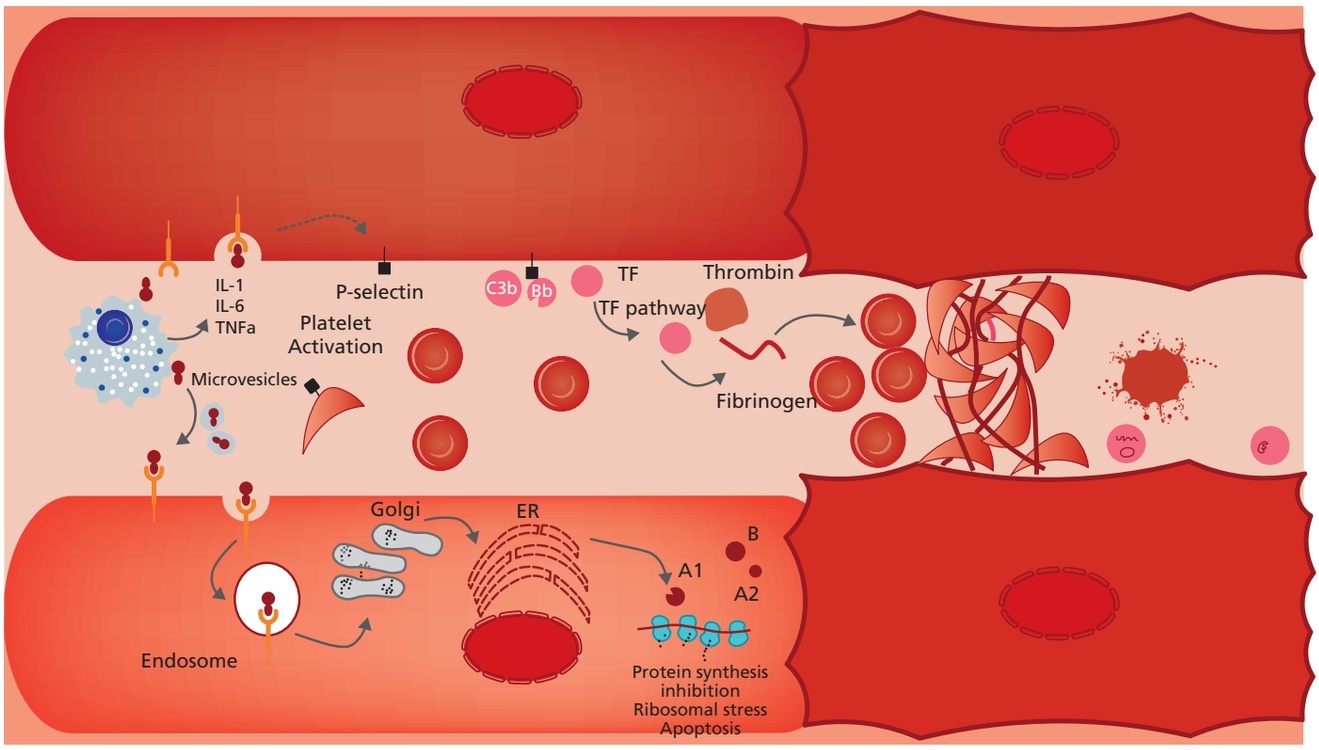
## 1.8.7 Microbiology Specialist Laboratories

### 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 cytkines, amplifying inflammatory events. Shiga toxin can also upregulate P- section and cause complement activation. The consequent thrombosis results in microangiopathic haemolytic anaemia and end organ damage.

As STEC-HUS is the commonest differential diagnosis of aHUS, rapid diagnosis is essential for timely appropriate treatment. The Public Health England 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.






***Thrombus formation in STEC HUS***

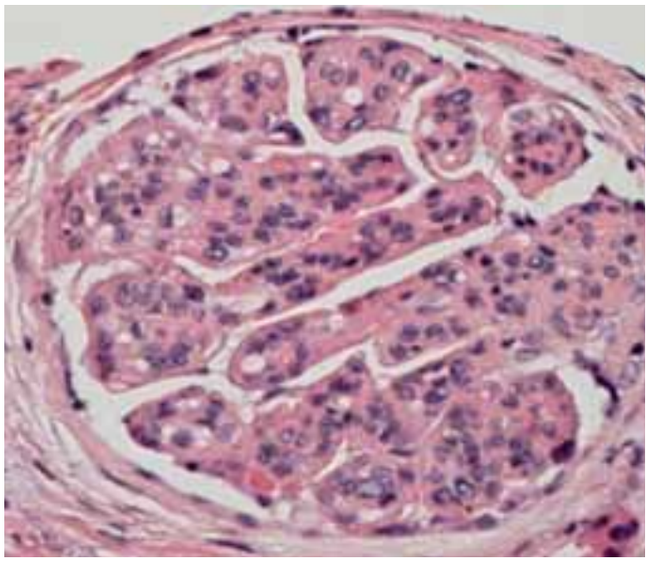
### Meningococcal vaccination response

Susceptibility to infection with encapsulated organisms, particularly Neisseria infections, is the most serious side effect of Eculizumab treatment. Because of this meningococcal vaccination is mandatory for all patients receiving Eculizumab. The Public Health England meningococcal reference unit in Manchester led by Prof Ray Borrow is the national centre for England and we work closely with him to assess the response to vaccination to provide optimal protection against infection.


***Meningoccal serotypes and vaccination***

### 1.8.8 Histopathology

The NRCTC 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 treatment of recurrent C3G following renal transplantation.. Eligiblity 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.



## 1.9 Global Reach for Optimal Patient Care

***NRCTC Global Consultations***

#### European Reference Network on Rare Kidney Disease (ERKNet)

ERKNet is the European Reference Network for rare kidney diseases. It is a consortium of 38 expert paediatric and adult nephrology centres across the European Union providing healthcare to more than 40,000 patients with rare disorders of the kidney. The NRCTC was proud to be designated a reference centre for TMA for ERKNet. This role came to an end on 1st January 2021 due to Brexit. NRCTC continues with its global reach out with ERKnet with consultations not only across Europe but also Asia, Africa and North and South America.

## 1.10 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 presentations to thousands of delegates across local, national and international platforms. This is continued despite the impact of COVID-19 with many of these opportunities now moving to a virtual forum.

The NRCTC continues to hosted specialist staff from other units to share experiences of managing these rare diseases of the kidney and developing key links to further develop our practice. Again, due to COVID-19, these have been held virtually.

### 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 specialist nursing team provides training for nurses from all over England that administer treatment to patients within their own home. This training covers the disease process, treatment options and patient safety. The nursing team have developed closer links with the nurses from around the country that provide care to patients in their own homes. The team respond to regular requests for advice.

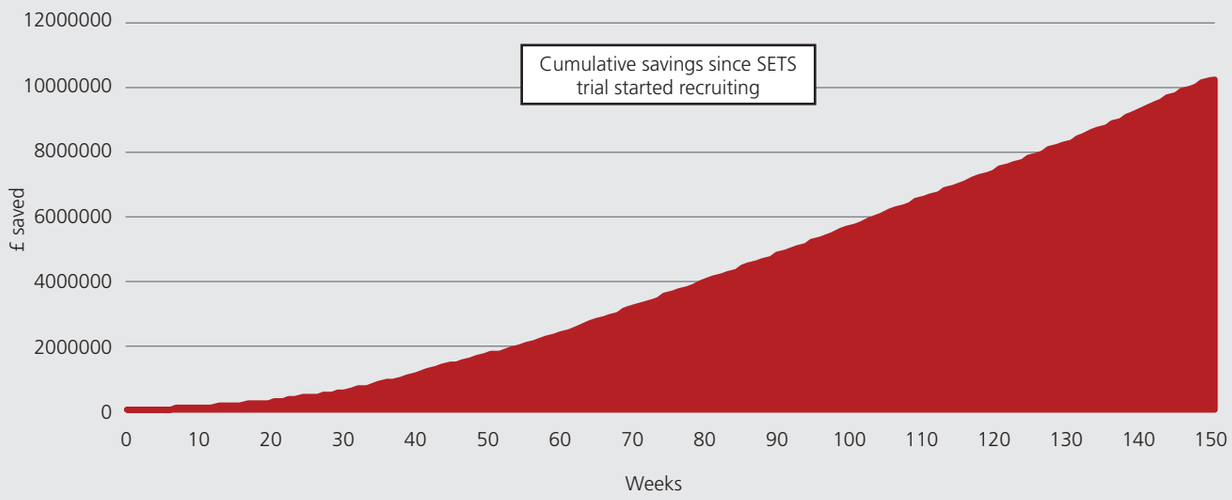
## 1.11 Research

***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 is funding a single arm, Bayesian study Eculizumab withdrawal in 30 patients currently on treatment. The primary endpoint is patient outcome over a two year period; and not relapse which we accept will occur but predict that relapse can be effectively treated with reintroduction of Eculizumab. The protocol will test the effectiveness of self-monitoring to detect relapse. There are also embedded health economic and qualitative arms of the study.

Recruitment into the trial was suspended during the Covid-19 pandemic but the trial did reopen and target recruitment has almost been reached. Aside from minimising treatment burden to the patient, we estimate a saving to the NHS of over £10 million to date.




***Cost saving benefit to the NHS to date of the SETS trial of over £10 million***

**Phase 3 Study of Ravulizumab in TMA Associated with a Trigger:**

This is a commercially sponsored trial to assess the effectiveness of complement inhibition in patients with secondary thrombotic microangiopathies. It is a double blind randomized trial of ravulizumab vs placebo which is being run internationally and in approximately 12 sites in the UK. Recruitment is starting in 2021.

***Professor David Kavanagh is the Chief Investigator for:***

**CL011_168 Trial:**

The CL011_168 Trial is a, Double Blind Placebo controlled Phase 2 Study Randomised, Placebo Controlled Study

Evaluating the safety and efficacy of Avacopan (CCX168) in patients with C3 Glomerulopathy (ACCOLADE).

NCT03301467

**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-MPGNStudy (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) on the basis of a reduction in proteinuria NCT05067127.

**APPELHUS:**

The CLNP023F12301 (APPELHUS) 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.

***Dr. Edwin Wong is the Chief Investigator in the UK for:***

**Trials of iptacopan in C3G:**

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

The team are now recruiting into the phase 3 – APPEAR study, a double-blind, randomised, placebo-controlled trial of iptacopan in patients with C3 glomerulopathy (NCT04817618).

***Dr. Sally Johnson is the Chief Investigator for:***

**ECUlizumab in Shiga-Toxin producing Escherichia Coli Haemolytic Uraemic Syndrome (ECUSTEC):**

ECUSTEC was a randomised, double-blind, placebo-controlled trial which aimed to determine whether eculizumab reduces the severity of STEC-HUS in children. The trial recruited 36 patients with STEC-HUS. Unfortunately, NIHR funding for the trial was stopped in 2020 following the COVID-19 pandemic. The data analysis will be completed during 2021 and the trial team hope that this will provide important information about the role of eculizumab in STEC-HUS.

**ALXN1210-aHUS-312 - A phase 3, open-label, multicentre study of ALXN1210 in children and adolescents with atypical haemolytic uraemic syndrome:**

This trial studied whether ALXN1210, also known as ravulizumab, a long-acting version of eculizumab, is safe and effective in children and adolescents with aHUS. Recruitment and follow-up arte now complete. Early results have been published, demonstrating the safety and efficacy of ravulizumab in children and adolescents switching from eculizumab treatment. Further publications are expected in the coming year.

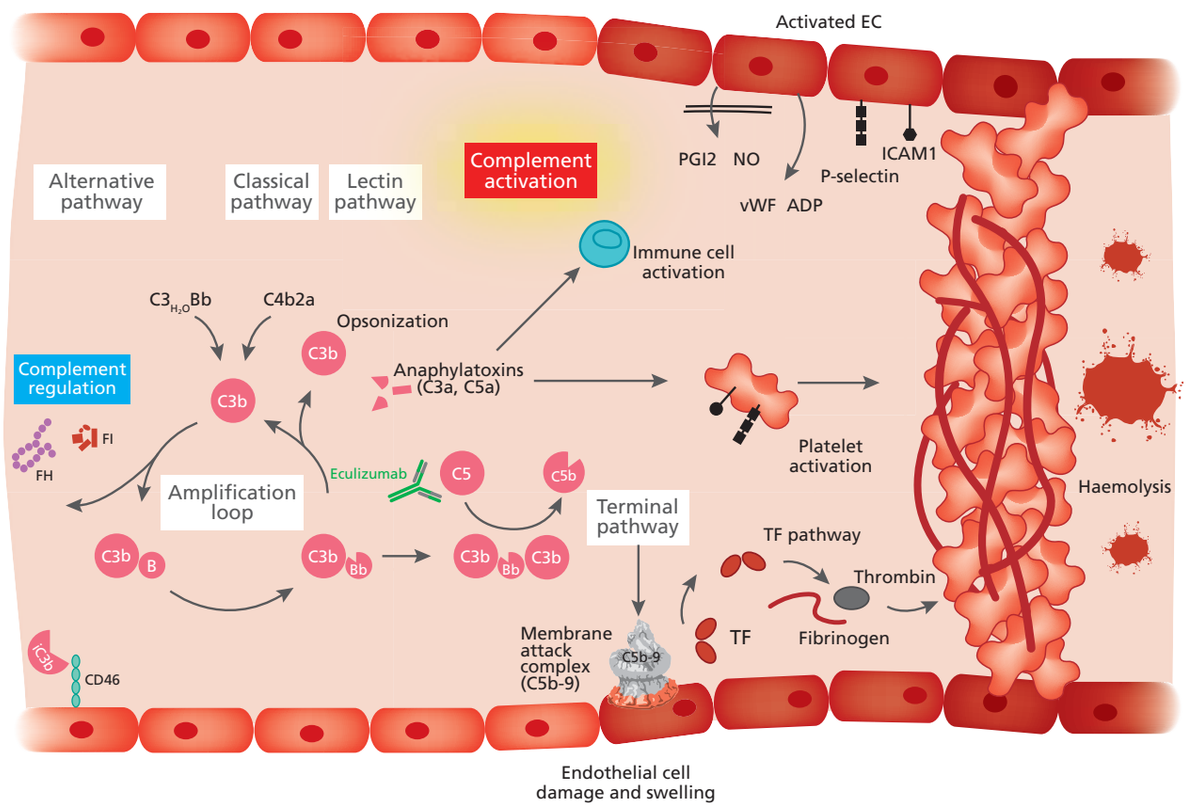
## Translational Research at the Newcastle University Complement Therapeutics Research Group

Dr 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.




***Thrombus formation in patients with aHUS***

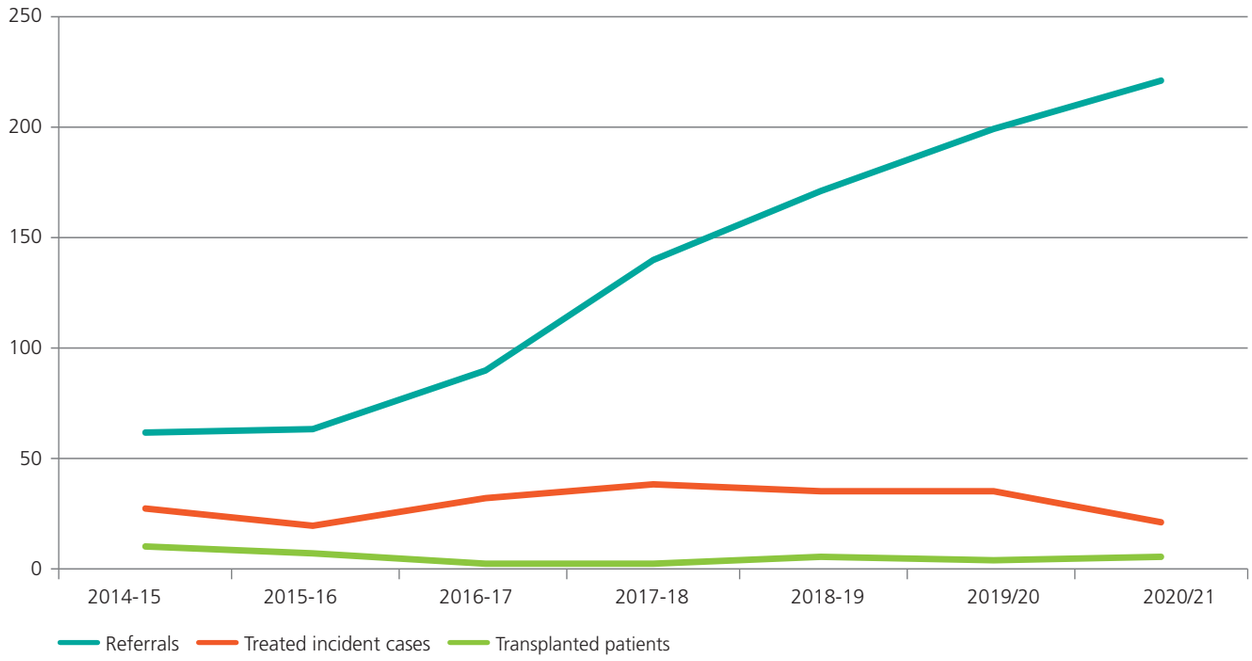
# 2. Service Activity

This report refers to the activity of the National aHUS Service and the National C3G service. The reporting period of this report is from April 1st 2020 until March 31st 2021.

## 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 7 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 patients recommended for treatment of incident cases of aHUS with Eculizumab and the number of prevalent aHUS patients receiving pre-emptive Eculizumab at time of transplantation in each of the last 7 complete financial years.*

### Referrals during the 2020-2021 reporting period

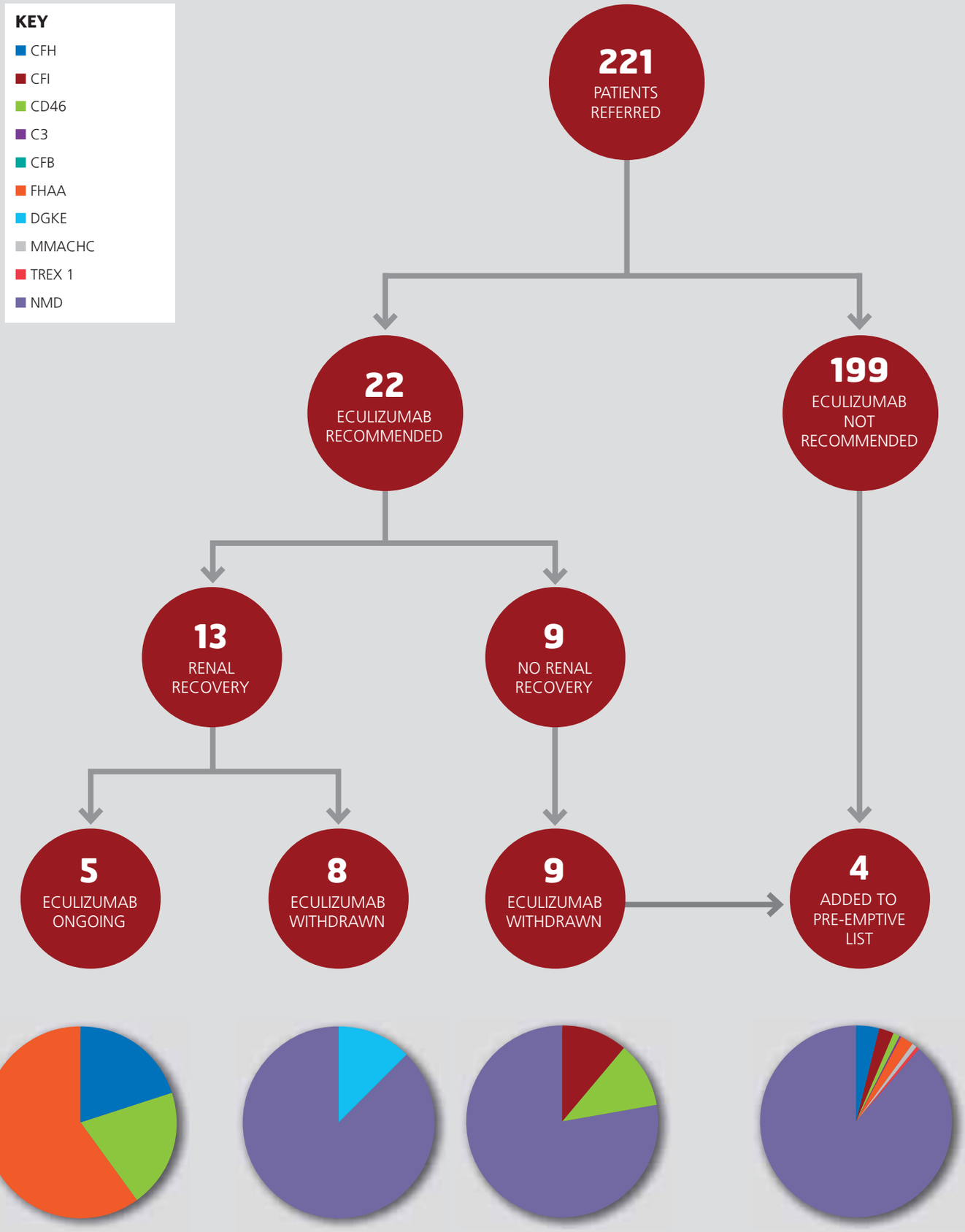
In the 2020/21 reporting period, the National aHUS Service has received 221 referrals for new patients for consideration of a diagnosis of aHUS. During the same reporting period, Eculizumab was initially recommended in a total of 22 patients.

We have reported outcomes correct as of 30th June 2021. Of the patients treated with eculizumab during this period, 5 patients improved and remained on Eculizumab. Of these, 100% had a pathogenic mutation or acquired complement abnormality. In a further 8 patients who also showed improvement, the diagnosis of aHUS was reviewed following the availability of additional clinical data. In 7 cases, an alternative diagnosis was made and eculizumab treatment was therefore withdrawn. In a further case, treatment was withdrawn as part of a clinical trial. No pathogenic mutation or acquired complement abnormality were identified amongst patients in this group.

Nine patients showed no significant improvement in renal function. In all of these patients, ongoing ecuilzumab was not recommended. A small number of patients were subsequently found to have a complement abnormality associating with aHUS. Failure to respond to treatment with eculizumab was related to other non-aHUS related contributing factors.

A diagnosis of aHUS was considered in a further 199 patients that were referred to the National aHUS Service. Based on the available clinical information, eculizumab was not recommended by the National aHUS service on the basis that there would be likely to be little or no clinical benefit. Reasons for this include likely or confirmed alternative diagnosis and/or clinically improving, or likely futility of treatment based upon evidence of advanced / irreversible renal disease. We subsequently identified an acquired or genetic complement abnormality in twenty patients (10.1%) from this group. This process of screening for complement abnormalities identifies patients who might benefit with eculizumab in the future, such as with pre-emptive treatment at time of transplantation.

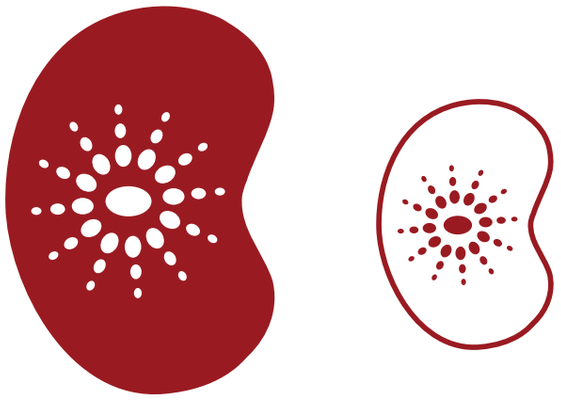
***National aHUS Service activity from April 2020 until March 2021.***
*Eculizumab was recommended in 22 patients. All patients receiving Eculizumab were screened for complement genetic mutations. The proportion of patients with a mutation in each of the genes for each treatment arm is shown FHAA = FH autoantibody NMD=no mutation detected].*



## 2.2 C3G service activity

A referral pathway has been in place for consideration of eculizumab in patients wit recurrent C3G since February 2017. The initial point of contact is the NRCTC via email: **C3.glomerulopathy@nhs.net**. Treatment with eculizumab can only be recommended following review by an expert C3G panel comprising the NRCTC and Imperial C3G service.

Since the clinical commissioning policy for Eculizumab in recurrent C3G was introduced, 6 patients have been treated in the period until March 2021.

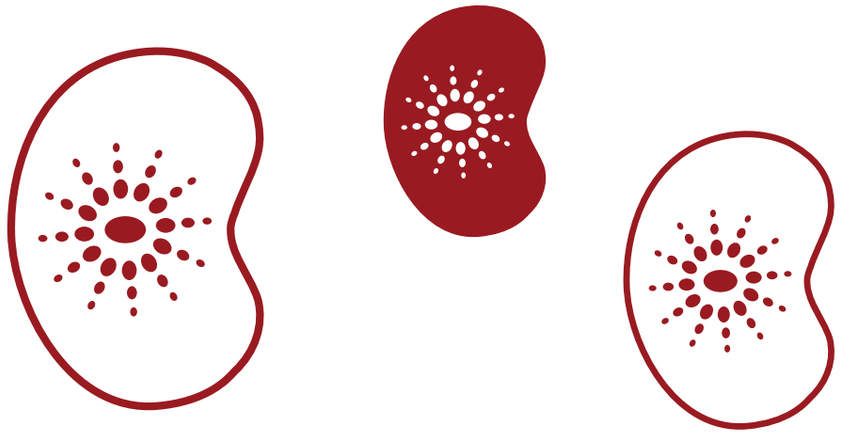


# 3. Performance Analysis

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 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 2020/2021**

As of 31st March 2021 there were 127 patients receiving Eculizumab 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

We also recognise that there is a risk of morbidity and mortality due to the risk of infection in patients receiving Eculizumab. All clinicians are informed about the risk of meningococcal infection when their patients are approved for treatment and our recommendations are summarised in regular correspondence with referring clinicians as part of the shared care we have. Information is also available on our website.

Meningococcal vaccination is required for all patients receiving Eculizumab treatment and long term antibiotic prophylaxis is recommended. One of the continuing challenges has been obtaining meningococcal antibody titres post vaccination to monitor the primary vaccination response (see domain 3). We also monitor vaccination response annually and are able to use the results of these tests to guide us regarding recommendations to offer further vaccination against ACYW serotypes. We also recommend further vaccination against serotype B at 5 years as B-titres cannot be measured whilst patients are receiving treatment with eculizumab.

Medical alert cards have been sent to patients receiving treatment to ensure they receive appropriate care when seeking medical treatment. The cards also contain the service website and contact details. The risk is also highlighted when we see patients in our clinics or at our aHUS roadshows.


***Patient-held alert card - meningococcal risk***

### Familial risk of aHUS

We continue to offer 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 pre-emptive 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.

Five patients received a renal transplant under Eculizumab cover between 1st April 2020 and 31st March 2021. Patients approved for pre-emptive Eculizumab are reviewed at regular meetings. As of 31st March 2021, there were 26 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 and has an emergency referral page to ensure the referring team have all the essential information required for making a referral and how to contact the on call clinician.

We responded to all referring units and provide advice within 24 hours of initial contact with the National aHUS Service.

***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 90.1% of treated patients in the period from April 2020 to March 2021.

**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***

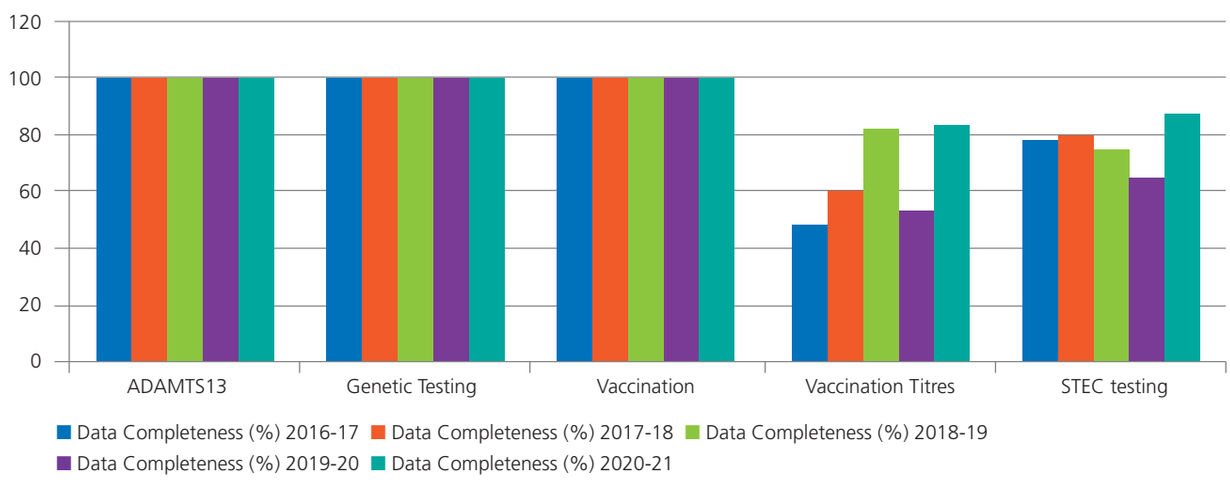
**94% data completeness in 5 audited domains**

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 94.2%.




***Data completeness of the aHUS register.*** *Performance has been measured against 5 categories of data and compared with the previous reporting period on all patients treated . Data for genetic testing, vaccination and ADAMTS13 was above the 90% quality standard. Vaccination titres and STEC testing are routinely requested and compliance has improved though still less than 90%.*


### ADAMTS13 Testing

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

### Genetic Testing

All patients receiving Eculizumab had testing to determine ensure they were not eculizumab non-responders. Additionally, all patients referred to the service were offered genetic testing to help make a genetic diagnosis.

### 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 Public Health England (PHE) Meningococcal Reference Unit in Manchester so that results can be collated centrally in order to advise local clinicians of any further action that is required.

We start the process to obtain titres in all patients from the initial point of treatment and collect no earlier than 6-8 weeks from treatment as recommended by the Meningococcal Reference Unit. We were able to measure initial titres in 83.3% of patients who remained on treatment beyond the timepoint that titres could be recommended.

### 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 have been liaising with local clinical teams and their laboratories to understand the problems we have had in the past with obtaining samples for STEC testing. We advise local teams on the potential hurdles to getting a suitable sample from the patient to the lab in a timely manner. We were able to obtain samples for STEC in 87.5% 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 Public Health England 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 appointment which may be increased to accommodate other family members. During the period 2020-21, we have continued our specialist clinic services during the COVID pandemic by offering telephone and video calls (using Attend Anywhere) in addition to traditional face-to-face appointments where possible. 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.

***Patient Consultations***

# 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 2020 to 31st March 2021. 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% | 90.1% |
| **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% | 94.2% |

***National aHUS Service – Performance during reporting period from 1st April 2020 until 31st March 2021.***
*Performance targets for all domains were met.*

# 5. Improving the Patient Experience

## 5.1 Impact of COVID-19

This reporting period has coincided with the emergence of the SARS-COV2 virus and the disease COVID-19. During these 12 months, we have had understandable concern from patients and their carers regarding the potential impact of this disease on aHUS and the ongoing use of eculizumab.

This resulted in enquiries from patients and clinicians about the management of aHUS.

We were able to reassure patients and their carers with the latest advice, including our recommendation to continue with regular eculizumab as per the usual dosing schedules and to receive vaccinations against COVID-19 in line with government guidance. The advice was summarised on our website.

## 5.2 Patient information

### Patient Roadshows

We have held roadshows in Durham, Manchester, Bristol, London and Birmingham since their inception in March 2018. Each has been met with growing popularity as well as a growing range of topics that have included pregnancy, meningococcal risk and the 'SETS' eculizumab withdrawal trial. Feedback from the roadshows has been positive, with patients and their families enjoyed talking to the team in an informal setting, listening to the team deliver presentations about their disease and meeting other patients.

Due to COVID-19, our planned meeting in Autumn 2020 was converted to a webinar format. We were able to host delegates online from all across England and discussed a range of topics including What is aHUS and COVID-19 and aHUS.

Our last webinar was in November 2021 and we hope to hold further roadshows again in the future.

***Roadshows map***

## Newsletters

We continue to provide information about our service in our newsletters. These are sent out to patients that have been referred to us and are shared on social media. They are also available to download on our website.

## Patient Pathway

As part of the pathway for patients with aHUS, our specialist nurses are usually the first members of the team to engage directly with patients referred to the NRCTC. They make the initial introductions to patients usually by letter or telephone call before sharing some of the NRCTC patient information that is part of our handheld records (separate record for children and adults), at-risk cards and alert wristbands.


***Regular newsletters are sent to patients known to the NRCTC and are available to download directly from our website***


***Screenshot from the website of the National Renal Complement Therapeutics Centre*** *depicting our videos that showcase aHUS and STEC-HUS disease mechanisms and treatment. The website also provides information for patients and their clinicians and also the referral pathway for Eculizumab [www.atypicalhus.co.uk].*

## 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 professional hub of information and advice for patients and clinicians. For our patients, all of our previous news and events can be viewed, as well as videos to explain about aHUS and STEC-HUS. We also have a presence on social media on Twitter (**@NationalaHUS** and **@NationalC3G**). and hope to support patients via a Facebook group in the near future.

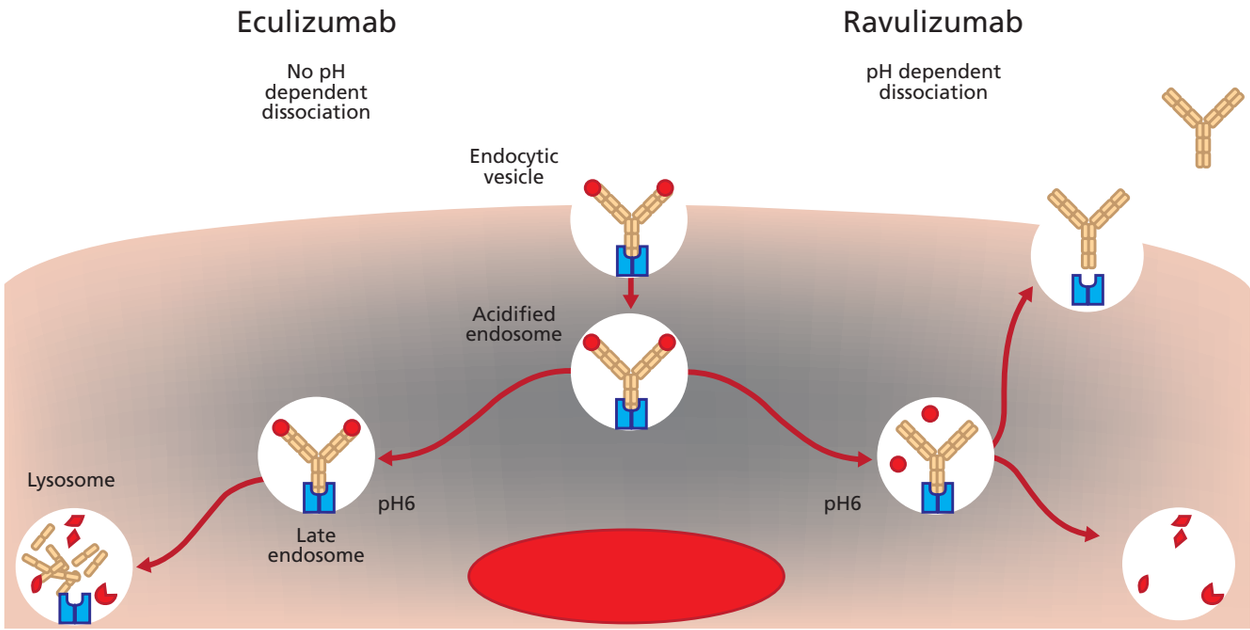
For clinicians the website continues to serve as a portal to access our full range of services as well as providing an up to date summary of complement mediated renal diseases and their treatments. An emergency referrals page **(http://www.atypicalhus.co.uk/emergency-referrals/)** highlights a 24 hour 7 day a week consultant led on call service. It provides a repository for clinicians to download diagnostic checklists, combined laboratory investigation forms including meningococcal and STEC request forms, as well as our shared care protocol.

## 5.3 Ravulizumab

In 2021, NICE approved the use of ravulizumab for patients with aHUS.

### 5.3.1 What is Ravulizumab?

Ravulizumab is a new long acting monoclonal antibody targeting C5. Ravulizumab was engineered from Eculizumab and targets the same epitope in C5. A histidine switch was performed in the complementarity-determining regions of eculizumab to preserve binding to C5 in serum but to allow dissociation of C5 from ravulizumab in the acidified endosome. Additionally amino acid alterations to the Fc region of eculizumab resulted in increased efficiency of neonatal Fc receptor- mediated recycling. This resulted in Ravulizumab having an increased half-life of ~52 days compared to ~11 days with Eculizumab. This resulted in up to an 8 week dosing interval with Ravulizumab versus 2 weekly with Eculizumab.




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

There have now been 2 clinical trials on Ravulizumab in aHUS in adults and children. Although a direct comparison of Eculizumab and Ravulizumab has not been performed, the data suggests Ravulizumab has similar efficacy and safety profile to Eculizumab.

### 5.3.2 Rollout of Ravulizumab

Since the announcement that ravulizumab would be available, the National aHUS service have worked with NHS England to ensure patients have access to it and to ensure patients currently receiving eculizumab are fully informed about the new drug. All patients on eculizumab are being offered appointments to update on this new treatment option.

# 6. NRCTC Key Recommendations

Subsequent to the review of our activity in 2020/21 and acknowledging the ongoing impact of the COVID-19 pandemic, the NRCTC have outlined key objectives for 2021/22 in the following domains:

## Clinical service

We will increase our use of remote technologies to deliver our clinical service, with a focus on specialist nurse-led patient consultations and offering eligible patients a switch of treatment from eculizumab to ravulizumab.

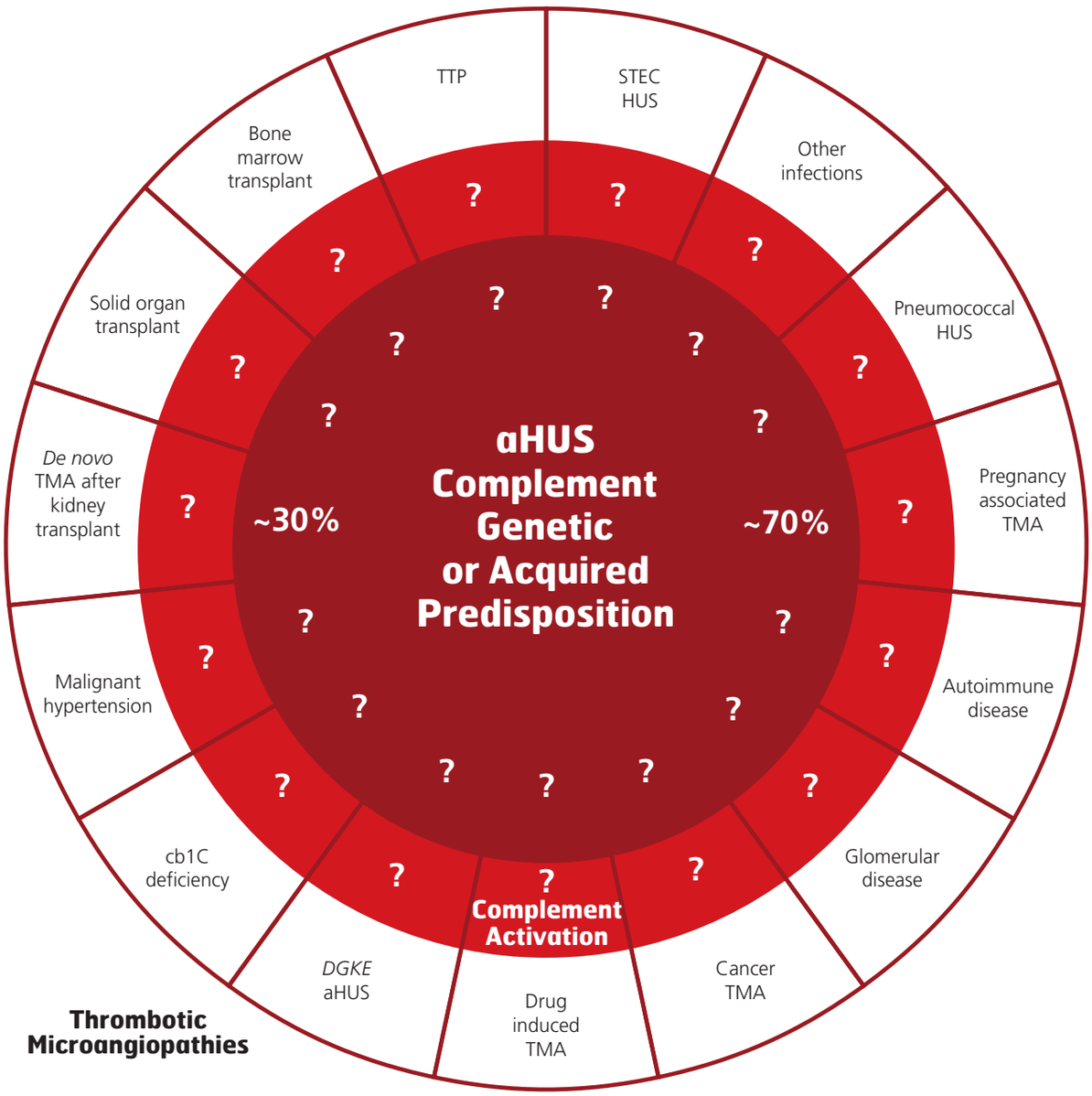
## Patient engagement

We will use remote technologies to reach a wider range of patients and ensure that their needs remain at the centre of our service.

## 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.

# 7. Complement Research at the NRCTC





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