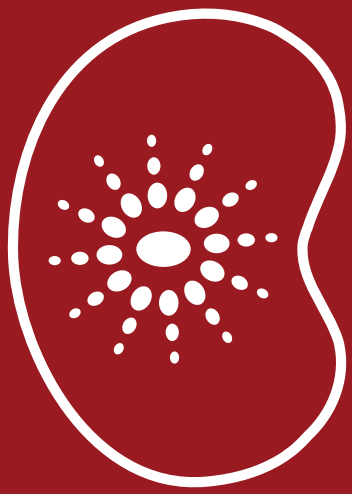
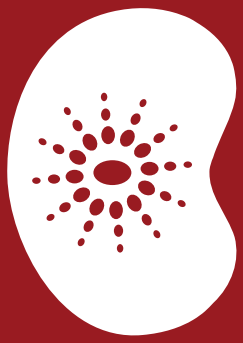
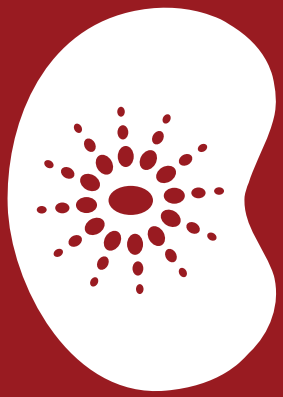
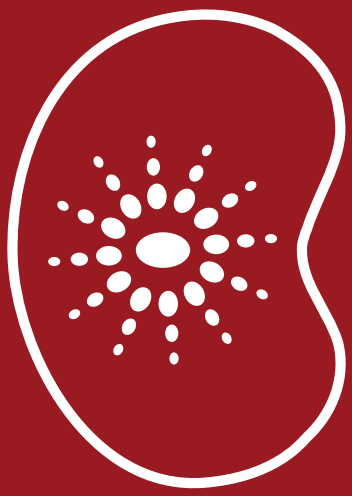
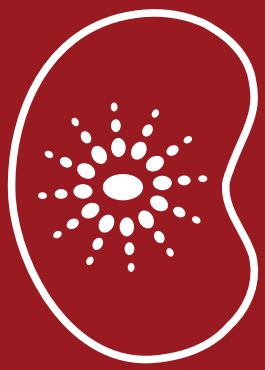
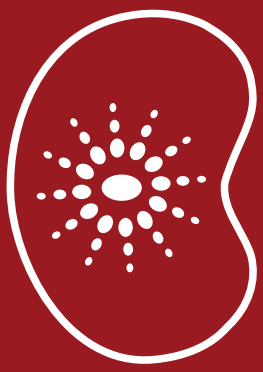
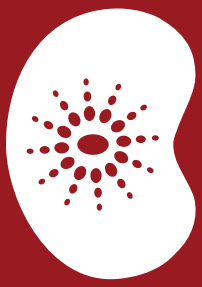
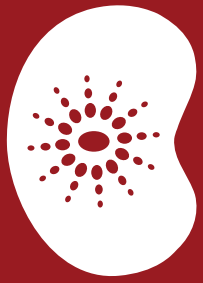
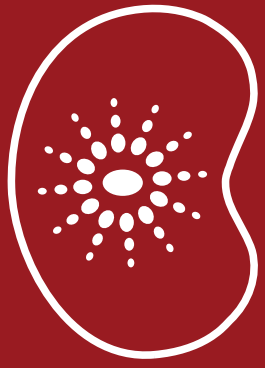
NATIONAL RENAL COMPLEMENT THERAPEUTICS CENTRE

NHS
The Newcastle upon Tyne Hospitals
NHS Foundation Trust

The Annual Report of the **National Renal Complement Therapeutics Centre** 2021/22

Newcastle University

www.atypicalhus.co.uk

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Photographs used in this report were in line with any government guidance on social distancing that was in place for COVID-19.

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aHUS
ATYPICAL HAEMOLYTIC URAEMIC SYNDROME

NATIONAL RENAL COMPLEMENT THERAPEUTICS CENTRE

C3G
C3 Glomerulopathy

Contents

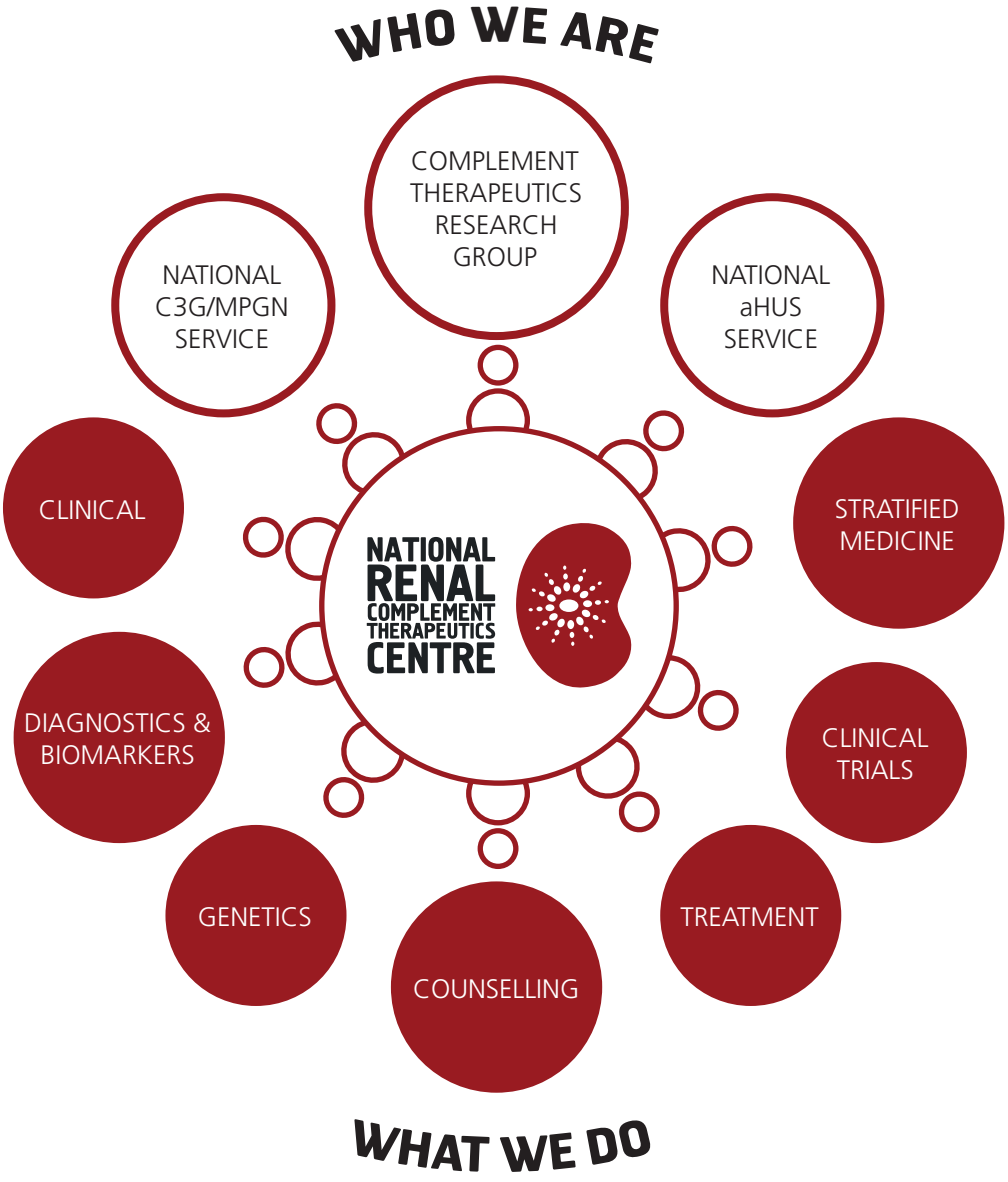
1. Service Overview

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

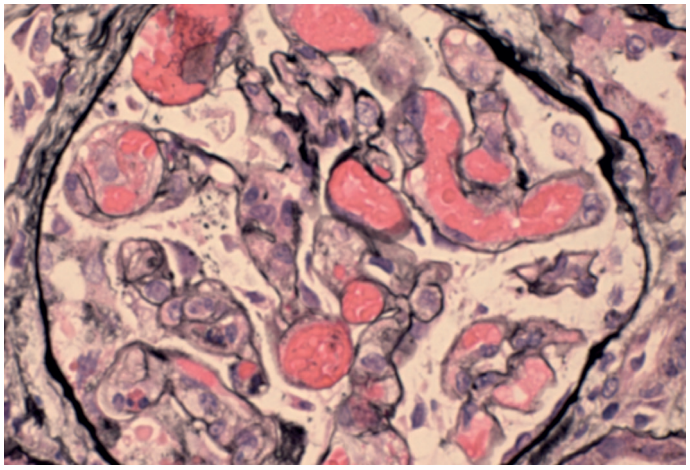
"putting patients at the heart of everything we do"

1.3 Disease Context

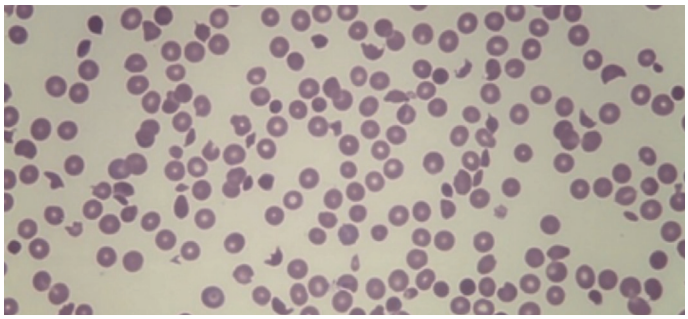
1.3.1 What is aHUS?

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).

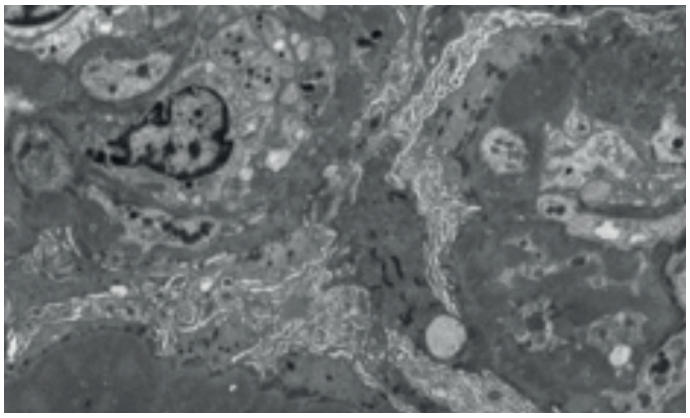
Eculizumab was licenced for the treatment of aHUS in 2011 having been shown to be effective in non-randomised, single arm open label studies. After initial review, preliminary interim funding for the use of Eculizumab to treat patients with aHUS in England was approved in 2013 whilst the National Institute 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).



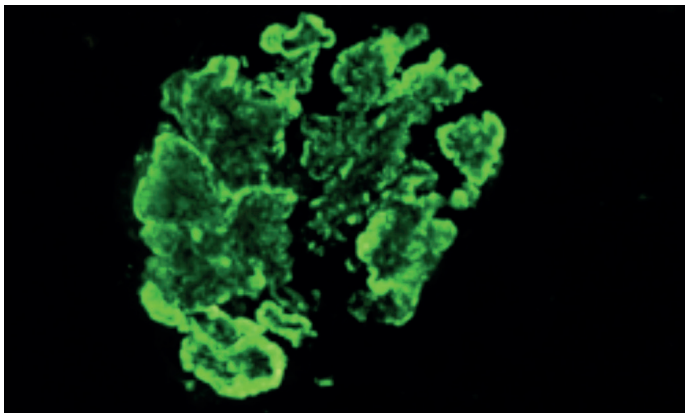
Renal biopsy showing thrombus formation in aHUS



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 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.

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 Working in Partnership and Offering Seamless Care

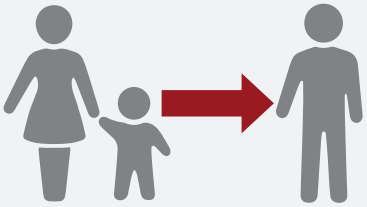
In order for patients with aHUS to receive excellent care, it is essential that the local clinical team and the National aHUS Service each understand their roles and responsibilities in delivering that care and that this information is communicated clearly to patients, so that they can be signposted 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. It was revised and updated this year to reflect changes in our clinical practice, including the introduction of Ravulizumab which has now been incorporated into our shared care protocol.

As part of this pathway, we have a robust system in place, to ensure precious 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 has been confirmed, all patients are allocated a named consultant, who work alongside the aHUS specialist nurses to coordinate their 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 an initial introductory joint consultation between the named aHUS consultant and the aHUS specialist nurses, this may be alongside the local managing clinician.

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

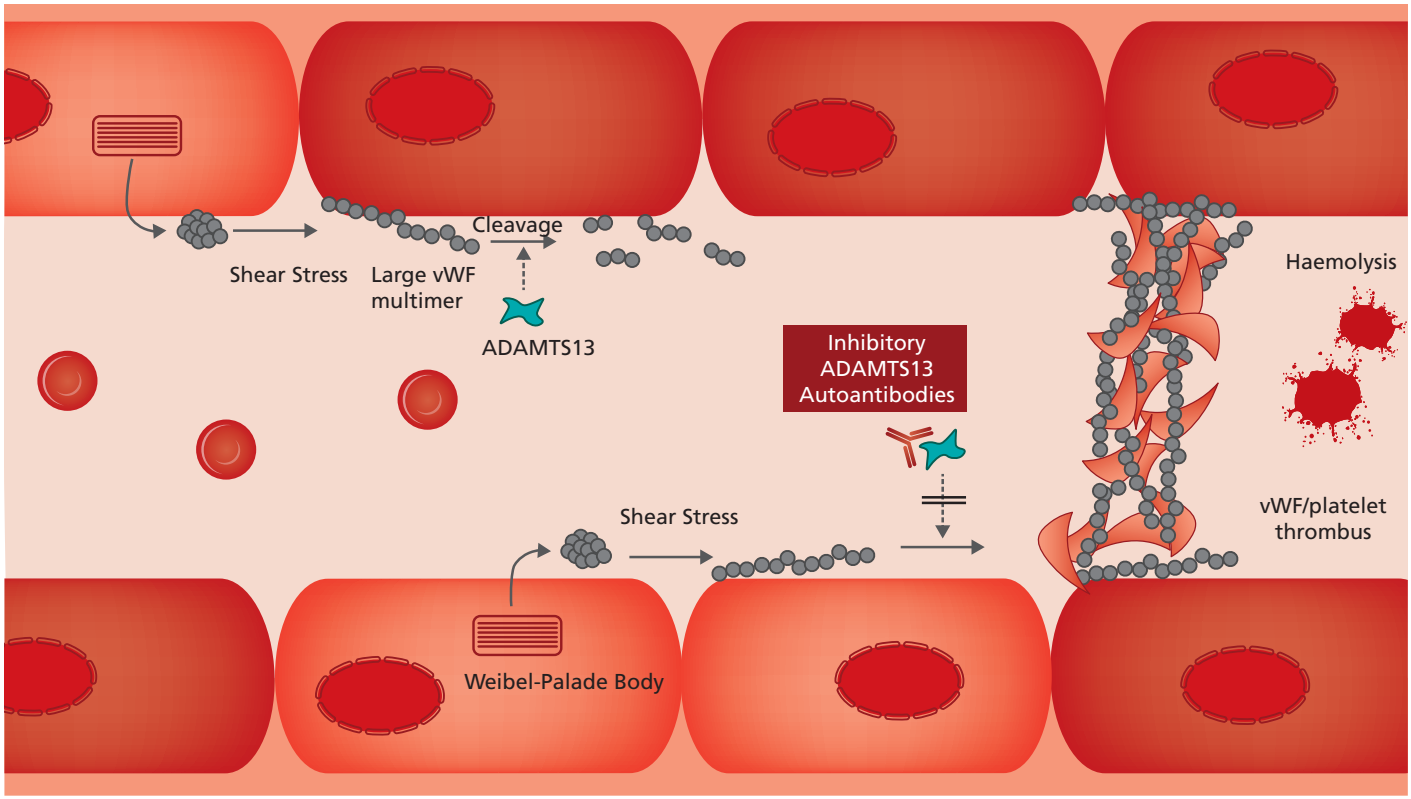
1.7 Ensuring High Quality Care that Delivers Optimal Use of Eculizumab

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.

1.7.2 Measurement of ADAMTS13 Activity

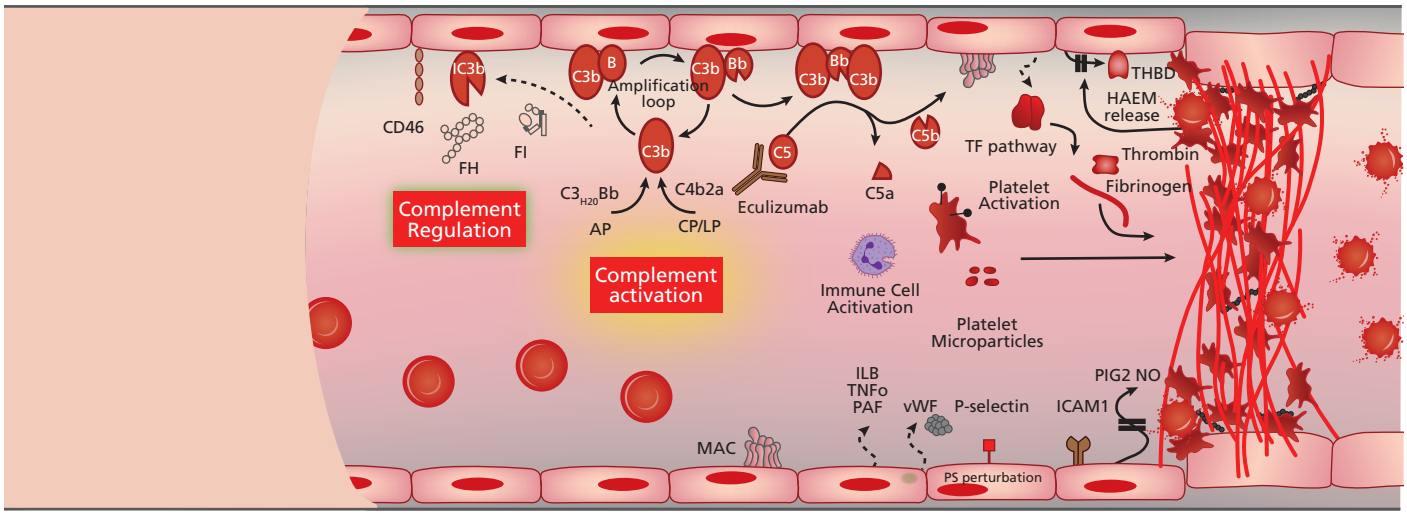
Urgent measurement of ADAMTS13 is the essential initial test in the management of thrombotic microangiopathies as it determines divergent treatment strategies. A very low ADAMTS13 activity is diagnostic of thrombotic thrombocytopenic purpura (TTP). Von Willebrand Factor (vWF) is a large protein that 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 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

1.7.3. 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 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

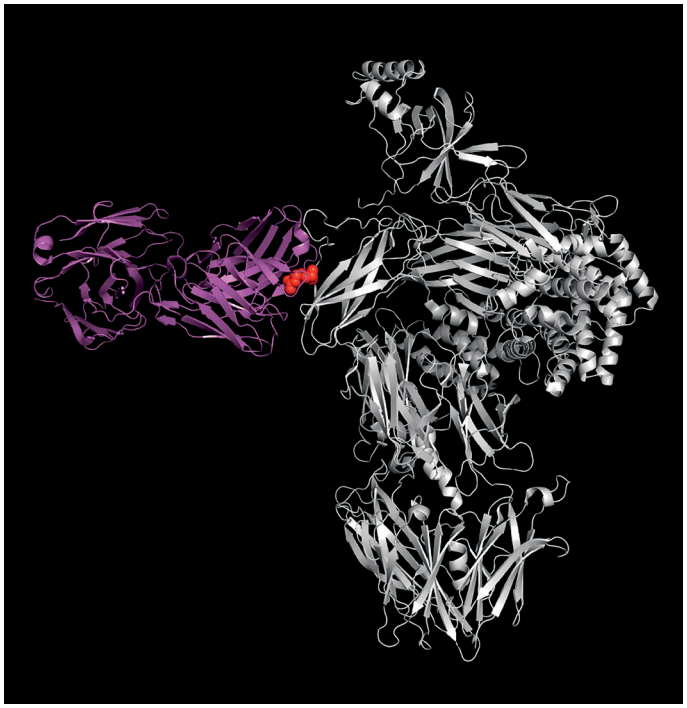
Standard sequencing of the complement genes factor H, factor I, CD46, C3 and factor B is undertaken on all patients referred to the National aHUS Service. Many complement genes are found on chromosome 1 in a region called The Regulators of Complement Activation (RCA) gene cluster. This region is thought 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)

1.7.4 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 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.

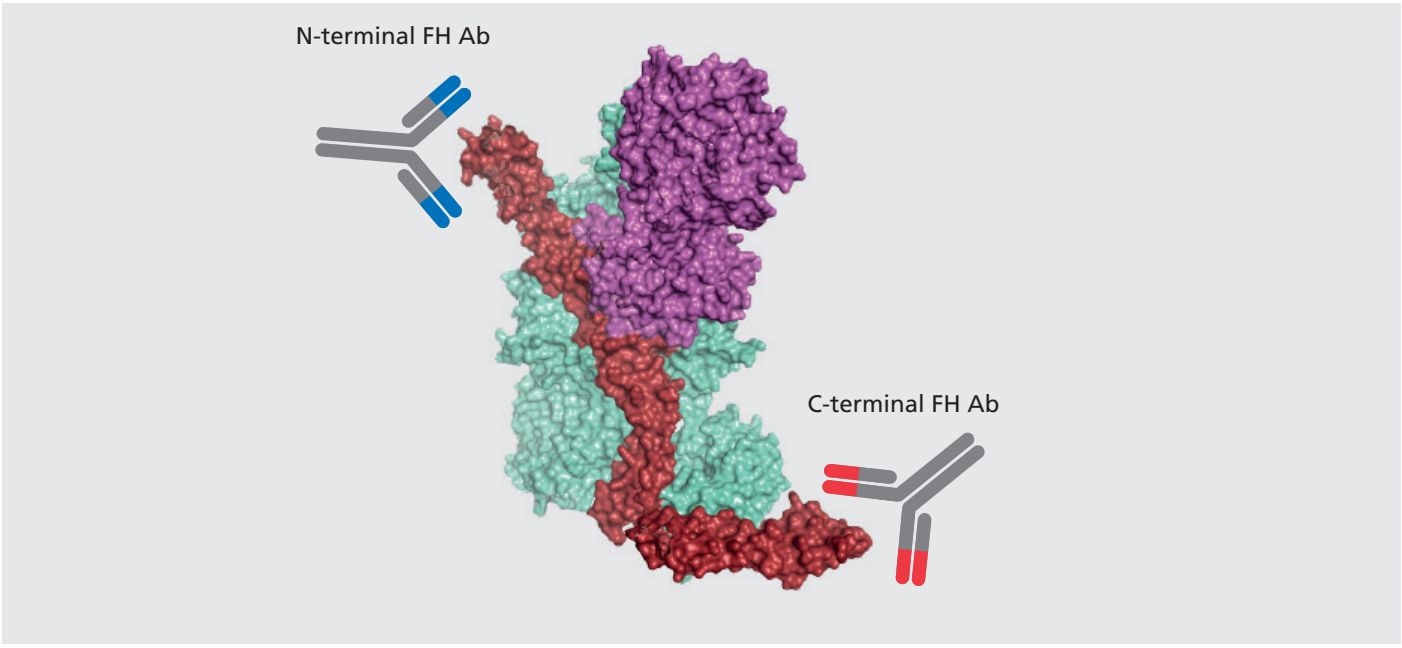
1.7.5 Complement Analysis in aHUS & C3G

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

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.*

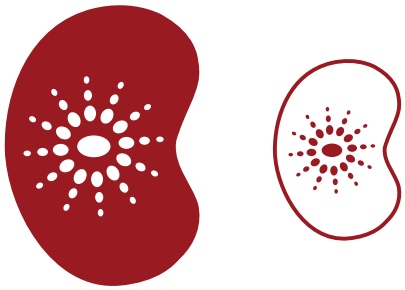
In C3G, C3 Nephritic factors are routinely measured and C4 and C5 Nephritic factor assays are also under development in David Kavanagh's group. These autoantibodies are historically difficult to identify and analyse. The research group is working towards a set of simplified and streamlined assays to enable rapid and semi-automated detection of nephritic factors.

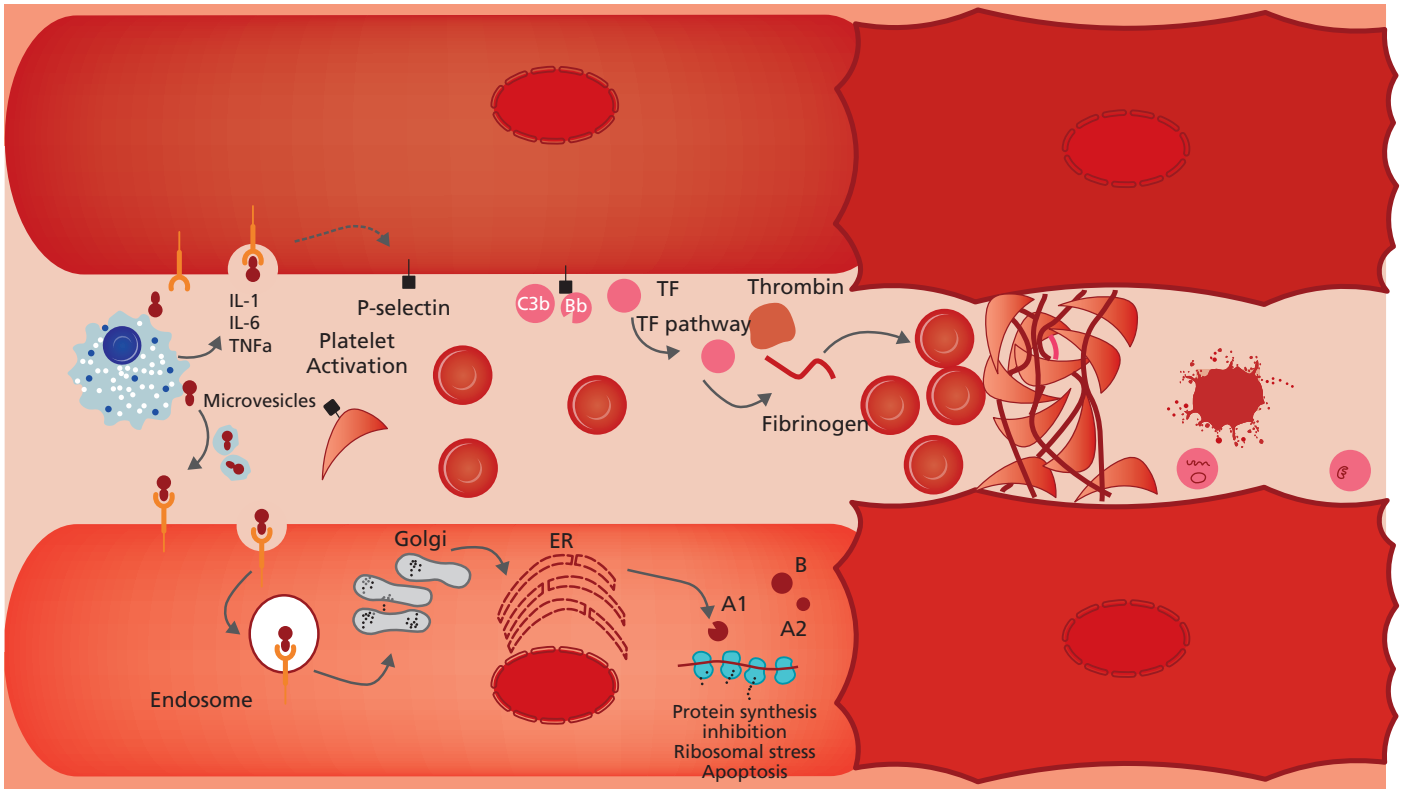
1.7.7 Microbiology Specialist Laboratories

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- 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 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.





Thrombus formation in STEC HUS

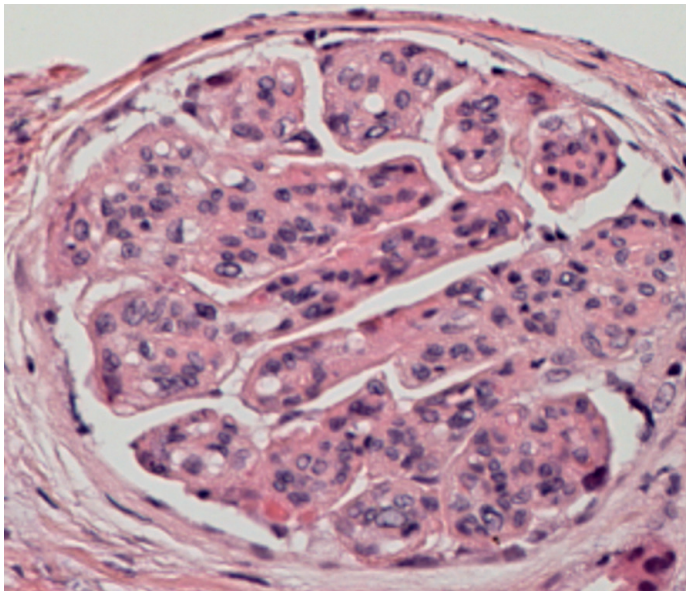
Meningococcal vaccination response

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 UK Health Security Agency 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

1.7.8 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.. 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. Previous European Reference Network collaboration in Thrombotic Microangiopathy Workgroup of ERKNet continues in the form of external partnership of several members of NRCTC despite the leave consequent to Brexit in 2021.

The NRCTC has hosted several prominent European nephrology leaders and HUS experts visits. These were used to exchange ideas and showcase the model of the centralised care for aHUS. The NRCTC is approached regularly for clinical consultations not only across Europe but also Asia, Africa and North and South America. Members of the NRCTC team are regularly invited to disseminate the centre experience on International congresses and teaching events.

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 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.

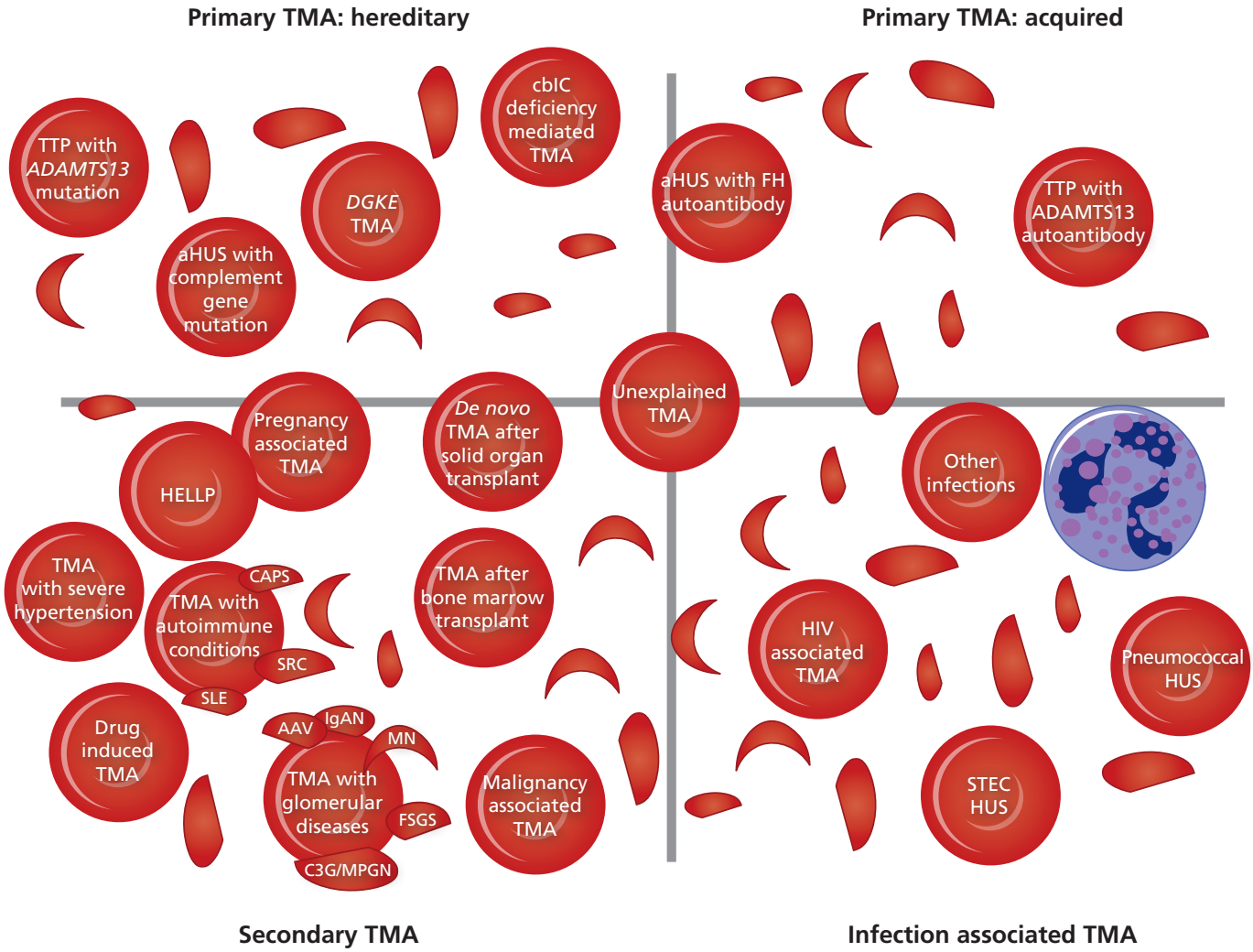
The NRCTC continues to host specialist staff from other units to share experiences of managing these rare diseases of the kidney and developing key links to further develop our practice. Again, due to COVID-19, these have been held virtually.

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 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.



Causes of TMA

1.10 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 has been 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 has since reopened and completed recruitment. Aside from minimising treatment burden to the patient, we estimate a projected saving to the NHS of over £17 million to date.

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:

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) 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.

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).

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.

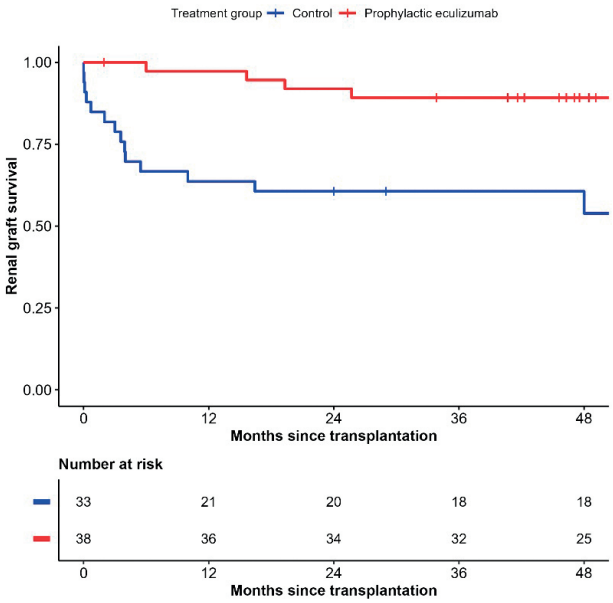
We welcome collaboration with industry in order to support drug development, whether external or within Newcastle. Our preclinical work is supported by development of novel in vivo experimental models of renal disease, such as aHUS. These models provide unparalleled opportunities to improve patient care, 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.

Generation of Real World Evidence

We reviewed 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 below].

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 post-transplant aHUS recurrence.

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



Scan here for the original article

The full data described here is from Glover et al. Assessing the Impact of Prophylactic Eculizumab on Renal Graft Survival in Atypical Hemolytic Uremic Syndrome. Transplantation DOI: 10.1097/TP.0000000000004355

1.11 Meet the team

DR SALLY JOHNSON

Dr Sally Johnson is a paediatric nephrologist and head of department in the paediatric nephrology service 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 Membrano-proliferative 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 CI 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.

DR MICHAL MALINA

Michal Malina is a consultant for paediatric nephrology at Newcastle upon Tyne Hospitals NHS Foundation Trust where his time is divided between the National Renal Complement Therapeutics Centre and Paediatric Services.

DR EMMA MONTGOMERY

Dr Montgomery is an adult nephrologist and divides her time between the National Renal Complement Therapeutics Centre and the Freeman Hospital.

PROFESSOR NEIL SHEERIN

Neil Sheerin is the Professor of Nephrology at Newcastle University, a Consultant Nephrologist 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.

Neil is academic vice president of the UK Kidney Association. He has held several roles in Newcastle University including Associate Dean for postgraduate studies and senior tutor responsible for intercalated studies.

DR EDWIN WONG

Dr Wong is a Consultant Nephrologist at the National Renal Complement Therapeutics Centre and Renal Services. He was a Medical Research Council Clinical Research Training Fellow from 2013 until 2016 during which time he obtained his PhD, having studied complement abnormalities in MPGN and C3G. He is the lead clinician at the NRCTC for C3 glomerulopathy and is chair of the MPGN, DDD and C3G rare disease group. He also is chief investigator on several trials of novel complement therapeutics in C3G.

1.11 Meet the team continued

aHUS Nurse Specialists

GEMMA ALLEN

Gemma 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 qualified as children's nurse (Registered Nurse, Diploma in Higher Education (Child) in 1996, first working as a Staff Nurse on a children's surgical ward at the RVI in Newcastle-upon-Tyne. Whilst working as a Staff Nurse, Christine obtained a BSc (Hons) in Nursing Science. In 2004-2006, Christine then undertook additional academic (BSc Hons, Public Health Nursing) and professional training to become a Specialist Community Public Health Nurse (Health Visitor), managing a caseload of families with young children. From 2009 – 2020, Christine worked as a senior Children and Young People's Clinical Nurse Specialist, managing a sizeable cohort of children and young people with inflammatory bowel disease. Within this role, she undertook additional professional training to be able to practice as a prescriber, and managed her own clinics – independently assessing patients, and recommending and prescribing treatment changes. Part of this role involved therapeutic drug monitoring to ensure patients' treatment was fully optimised to promote remission of the condition. Christine has extensive experience of managing and coordinating the care of patients who have a chronic illness.

In August 2020, Christine joined the team at the National Renal Complement Therapeutics Centre (NRCTC) as a Clinical Nurse Specialist. 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. She and her colleagues presented this quality improvement at UK Kidney week in June 2022. 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.

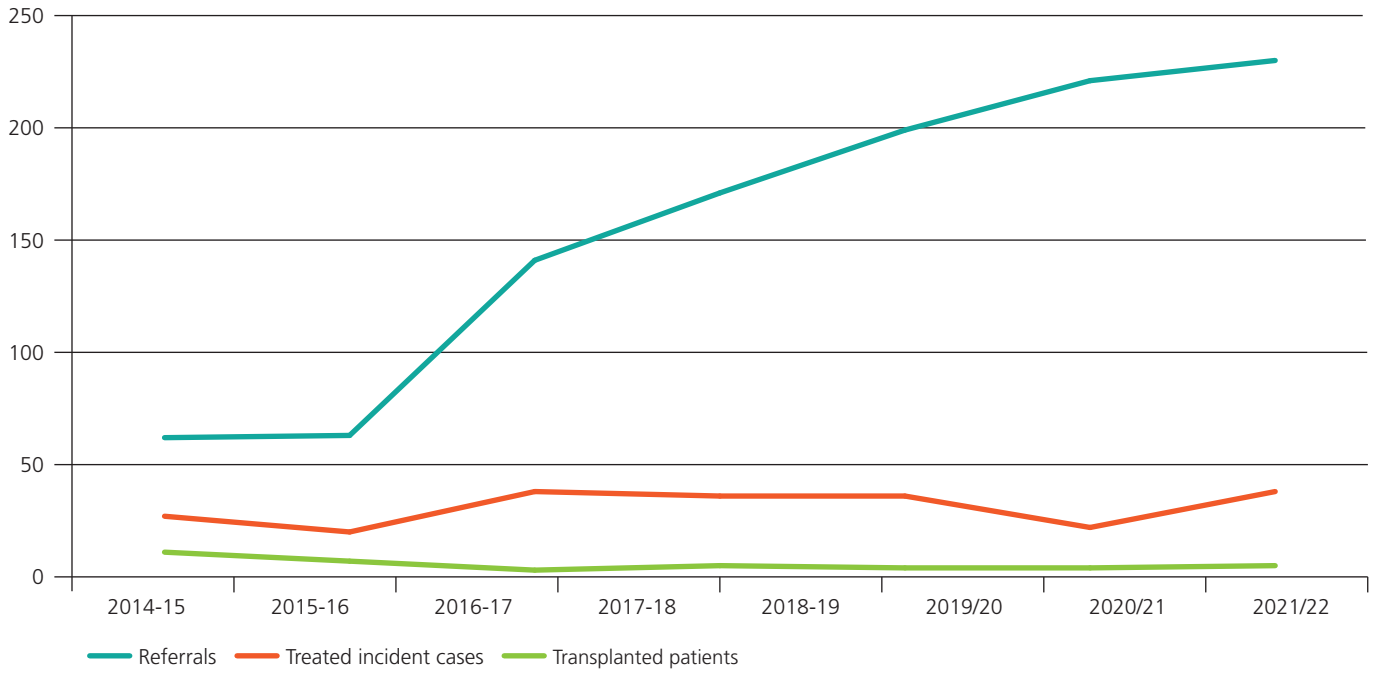
2. Service Activity

This report refers to the activity of the National aHUS Service and the National C3G service. The reporting period described is from April 1st 2021 until March 31st 2022.

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 8 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 8 complete financial years.*

Referrals during the 2020-2021 reporting period

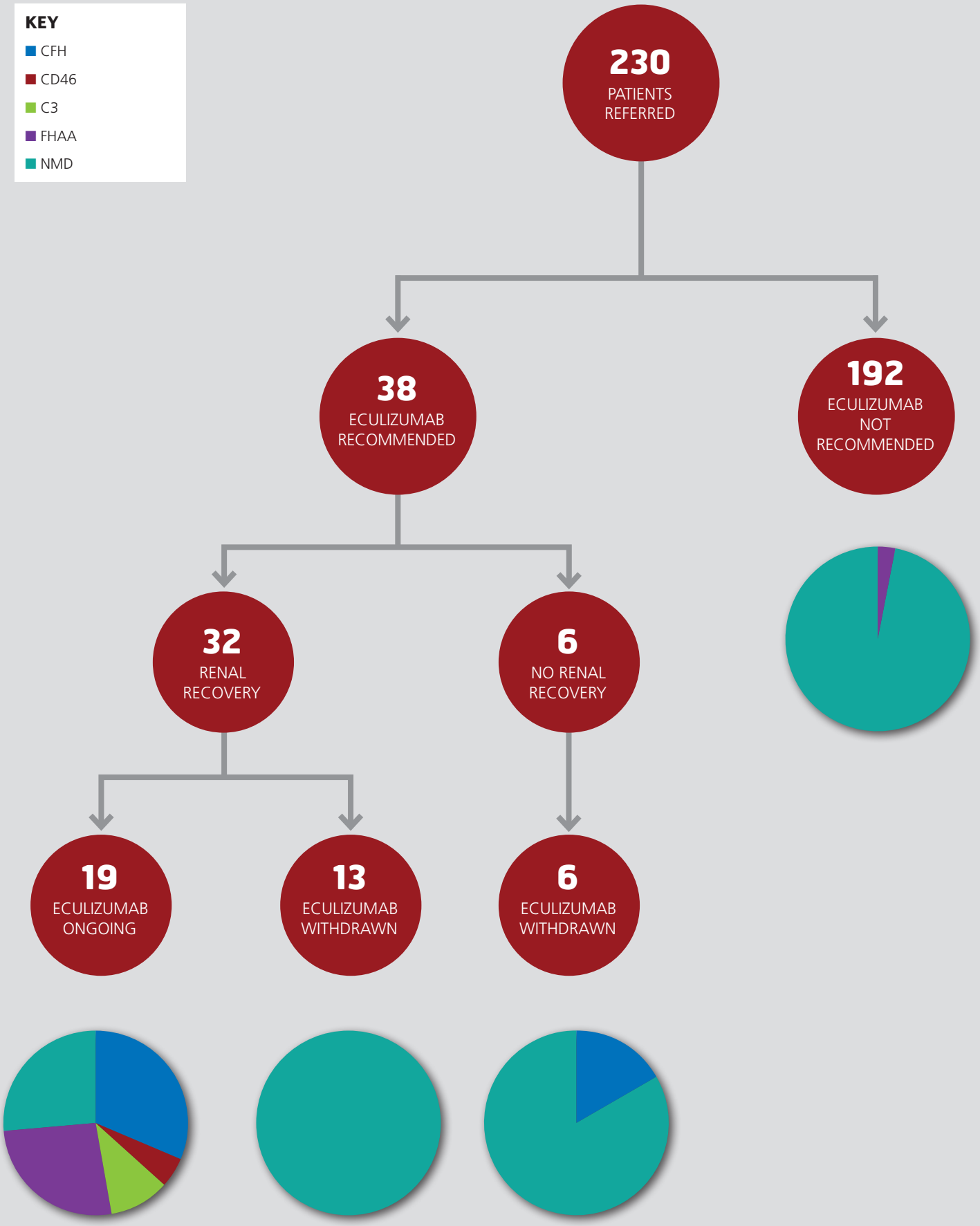
In the 2021/22 reporting period, the National aHUS Service received 230 referrals for new patients for consideration of a diagnosis of aHUS. During the same reporting period, Eculizumab was initially recommended in a total of 38 patients.

We have reported outcomes correct as of 30th June 2022. Of the patients treated with eculizumab during this period, 19 patients improved and remained on Eculizumab. Of these, 73.7% had a pathogenic mutation or acquired complement abnormality on Eculizumab. In a further 13 patients who also showed improvement, a decision to stop eculizumab was subsequently made following review. In one case, the diagnosis was attributed to aHUS – eculizumab was stopped in the setting of a clinical trial.

Six patients showed no significant improvement in renal function. In all of these patients, ongoing ecuilzumab was not recommended.

A diagnosis of aHUS was considered in a further 192 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 were not thought to have aHUS, or if the clinical presentation indicated that would be likely to be little or no clinical benefit. Reasons for this include likely or confirmed alternative diagnosis and/or clinical improvement, or likely futility of treatment based upon evidence of advanced / irreversible renal disease. We subsequently identified an acquired or genetic complement abnormality in six patients (3.1%) from this group. This process of screening for complement abnormalities identifies patients who might benefit with eculizumab in the future, including those who presented at end-stage and can then be recommended pre-emptive treatment at time of transplantation.

National aHUS Service activity from April 2021 until March 2022.
Eculizumab was recommended in 38 patients. The proportion of patients with a mutation in each of the genes (CFH, CD46 and C3) for each treatment arm is shown. [FHAA=Autoantibodies to factor H, NMD=no mutation detected].



2.2 C3G service activity

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.

Since the clinical commissioning policy for Eculizumab in recurrent C3G was introduced, 6 patients have been treated in the period until March 2022. No patient was commenced on treatment in the 12 months prior to March 2022.

2.3 Scotland

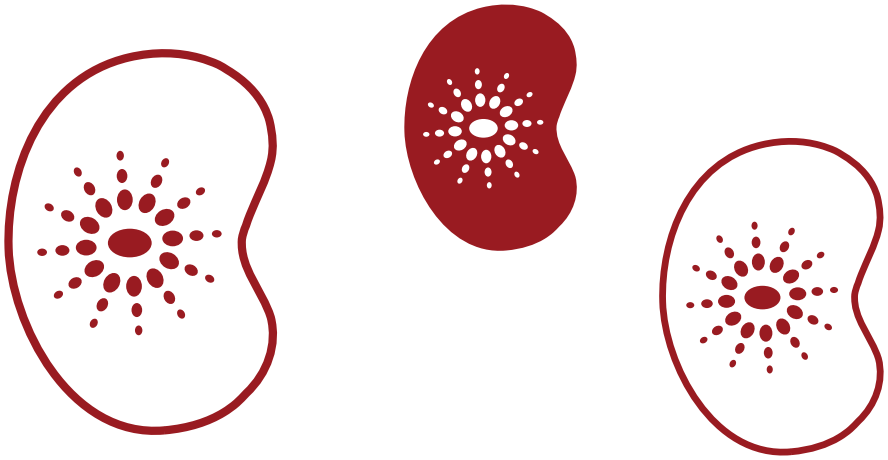
In the period 2021-22, we have a service level agreement to provide diagnostic testing and management advice for patients referred from Scotland with a suspected diagnosis of AHUS and C3 glomerulopathy. Eculizumab may be commenced following discussions with the national aHUS service and treatment costs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

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 2021/2022

As of 31st March 2022 there were 148 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 and Ravulizumab

- Eculizumab and ravulizumab treatment increases susceptibility to meningococcal infection by 500-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:

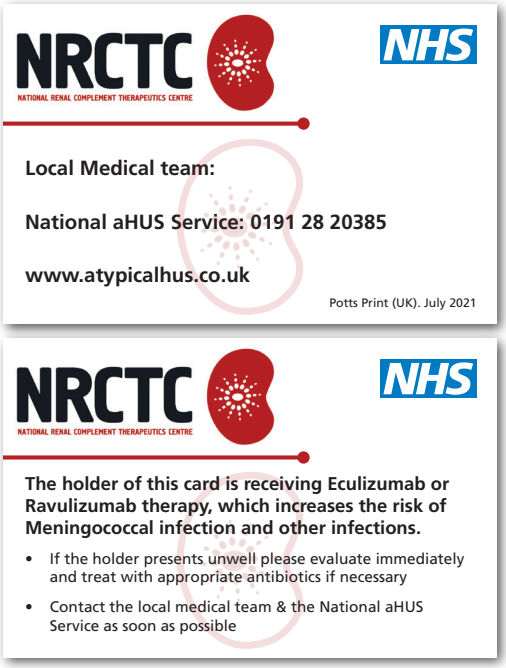
- are vaccinated against serogroups ACWY and B – we follow up all patients to ensure they are vaccinated appropriately and liaise with local teams throughout. We communicate the need for further vaccination when needed via local teams or primary care. [performance metrics relating to this are summarised in domain 4, page 14].
- are started on long-term antibiotic prophylaxis for the duration of eculizumab / ravulizumab therapy, for a specified period after stopping either of these therapies.

Guidelines regarding reducing risk of contracting meningitis

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

Counselling regarding meningitis risk

- We also 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 Eculizumab/ Ravulizumab, particularly those who work in the homecare sector, so we can alert them to the risk and provide them with information on escalation and how / when to seek advice.



Patient-held alert card - meningococcal risk

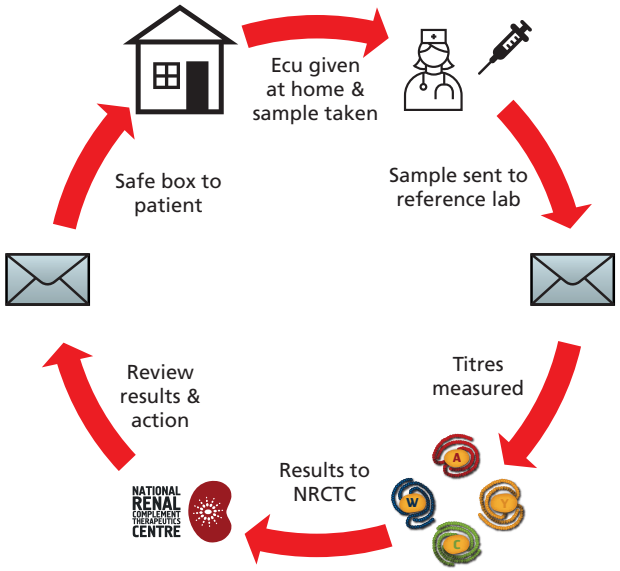
Meningococcal titre monitoring

We recommend annual titre measurement for meningococcal serotypes C, W and Y.

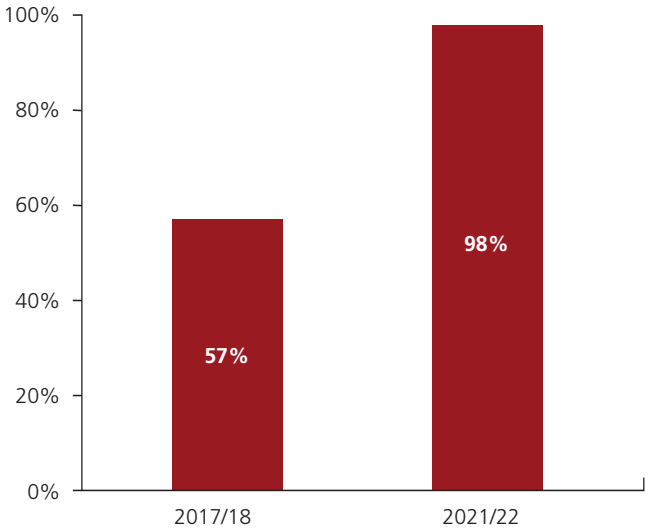
The rationale for this is to identify patients whose titres are considered to be below the protective range and offer meningitis booster vaccinations. We hope that by offering a booster, immunity may be enhanced to help reduce the patient's risk of contracting meningitis on eculizumab or ravulizumab.

This year 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.

- We have worked with the drug manufacturer of eculizumab and ravulizumab in addition to homecare companies so that blood tests can be taken at the point of the patient being cannulated, which helps to ensure bloods are done, and in a timely fashion.
- We post kits to patients along with an explanatory letter, stating that titres are due with the next home infusion. The kit contains a pre-paid, pre-addressed Safebox, blood bottle, and blood form. Once bloods have been taken, the box is 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



Completeness of annual meningococcal titre monitoring increased from 57% in 2017/18 to 98% in 2021/22 as a result of a centralised approach to monitoring



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.

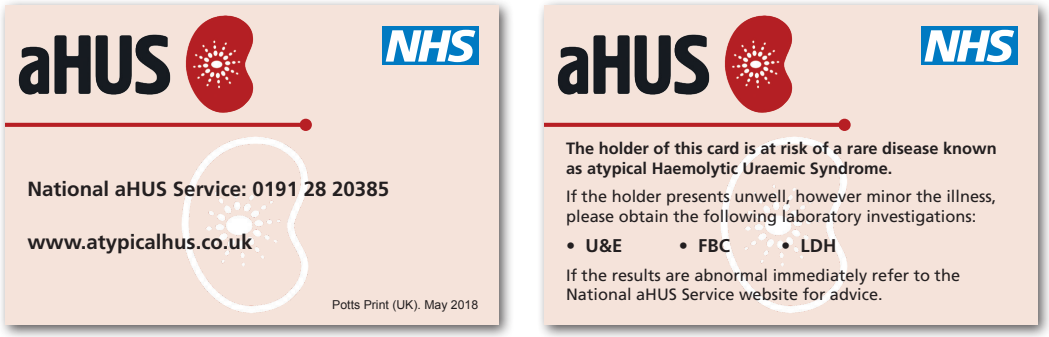
For patients identified as being due a B-strain booster, we:

- 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

This year we have recommended a Bexsero booster to 33% of our patient cohort.

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 2021 and 31st March 2022. Patients approved for pre-emptive Eculizumab are reviewed at regular meetings. As of 31st March 2022, there were 24 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 97.4% of treated patients in the period from April 2021 to March 2022.

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

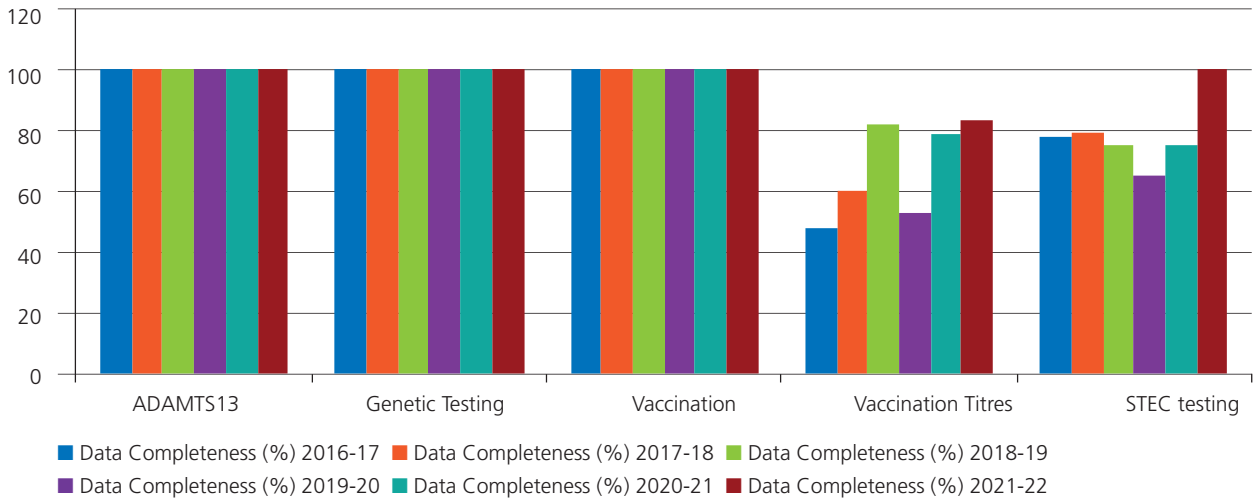
97% data completeness in 5 audited domains

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 period on all patients treated. Data for genetic testing, vaccination, STEC testing and ADAMTS13 was above the 90% quality standard Vaccination titres 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 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 86.2% of patients who had remained on treatment beyond the timepoint that titres could be recommended. Of the patients from whom we were unable to get a titre, all were recommended concurrent antibiotic use and all subsequently stopped treatment with eculizumab. 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 understand the problems we have had in the past with obtaining samples for STEC testing. We contact local teams and their microbiology labs to directly to explain 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 expediate reporting of any results that they receive. We were able to obtain samples for STEC testing in 100% of patients in whom testing was indicated.

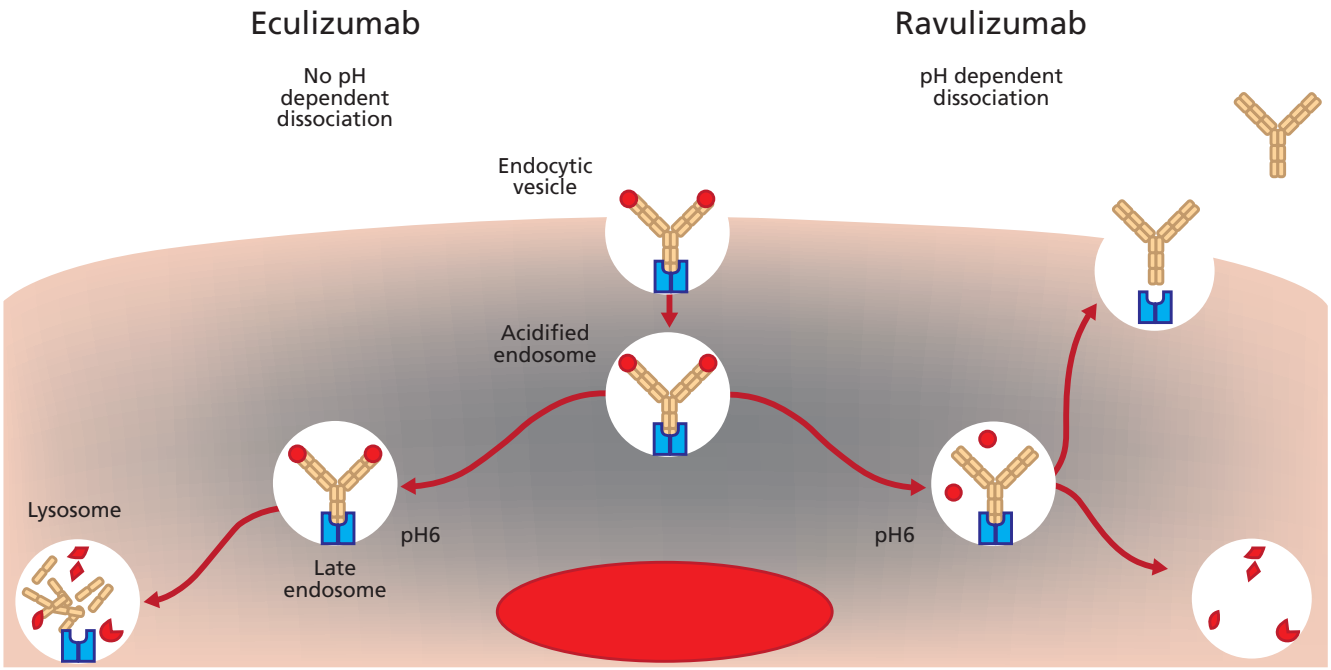
Summary of our previous implementation in this domain

- 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

Out Patients 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 2021-22, 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. We also utilised outpatient attendances to discuss possible switch from eculizumab to ravulizumab – this is described further in section 5.6

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.

Rollout of Ravulizumab

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

Patient consultations

The NRCTC wrote to all patients 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.

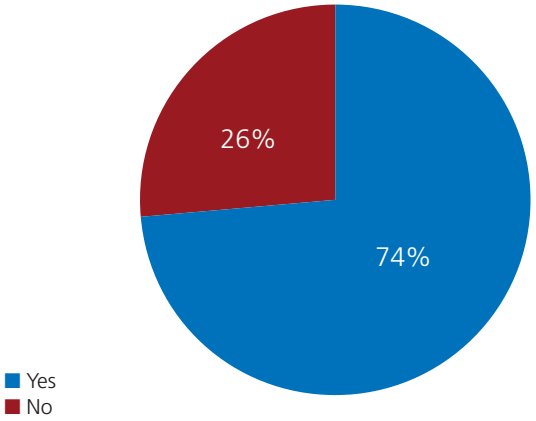
We also follow up on all patients who have decided to switch, linking in with local clinicians and pharmacists to confirm date of switch.

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.

Key outcomes of our Ravulizumab switch process

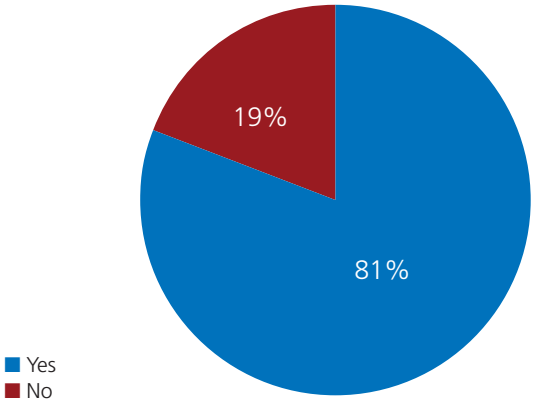
- 74% of patients (to date) have decided to switch to Ravulizumab

Patients deciding to switch to Ravulizumab



- After deciding to switch, 81% of patients (to date) have switched to Ravulizumab – the remainder will complete the switch to Ravulizumab as part of the process described above.

Patients who have successfully switched



Nurse-led monitoring

The aHUS Nurse Specialists at the NRCTC also support the monitoring of patients with aHUS in relation to Factor H autoantibody titre measurement and complement blockade.

Factor H autoantibodies

For patients in whom we have detected factor H autoantibodies (a known cause of aHUS), we send blood forms to local clinicians to help as part of our systematic process for measuring these antibodies on a six monthly basis.

In patients for whom the finding of anti-FH antibodies was the sole cause of aHUS (ie no genetic mutations as a cause of their aHUS), changes in anti-FH titres eg if they become undetectable, could lead to changes in treatment recommendations with eculizumab or ravulizumab. Decisions are taken in consideration with the clinical course and shared with local clinical teams and their patients.

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 2021 to 31st March 2022. 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%	97.4%
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 2021 until 31st March 2022.
Performance targets for all domains were met.

5. Improving the Patient Experience

5.1 Patient engagement

We recognise the importance of engaging patients and families to help shape the service we provide. The NRCTC team are involved with a number of patient engagement activities which are described in more detail below.

Patient questionnaires

We previously sought patient feedback from a patient questionnaire in 2017 – a number of changes were made in direct response to the feedback and suggestions provided. Some of these are summarised.

54.5% said were given enough info about aHUS

We now offer clinics to all newly diagnosed patients

Only half the respondents were clear on their care plan and how it is used

Each clinic appointment is summarised with a letter, that is sent to the patient, GP and local clinician, each letter details the current plan of care

We have written customised letters for patients who are activated on the transplant list and have been pre-approved to receive eculizumab at the point of transplantation. The letter is a plan of care for that individual patient in relation to their atypical HUS, which is copied to the whole clinical team involved with that patient (local nephrologist, transplant nephrologist, transplant co-ordinators in local and transplant centres, pharmacists at local and transplant centres, and a transplant surgeon). We ask the local teams to ensure there is an alert placed against the patient stating they have aHUS and refers them to look at this letter if patient called in for transplant.

We also provide an abridged version of this letter to the patient, and ask them to take it with them if attending for a deceased donor transplant so they can show it to the clinicians at the time. This should ensure that the managing teams have all relevant information about the patient to hand, and act upon this.

Only half of respondents felt able to go on holiday or travel as much as they like to.

Expedite the switch process giving most patients a longer window between infusions

In response to this, the aHUS Nurses have worked with the drug manufacturer to ensure that timely advice can be given to patients planning holidays, who require eculizumab infusions, so care is more streamlined.

40% of respondents reported that the healthcare professional provided enough information to college, school or nursery about condition.

The aHUS Nurses have adopted a systematic approach to offering to liaise with nurseries, schools and colleges for all newly diagnosed children and young people with parental consent. We have also extended this to employers for adult patients.

The majority of respondents preferred to receive new information relating to aHUS via newsletters from the NRCTC. The NRCTC website, newsletters, patient roadshows, patient consultations and genetic testing was positively received when patients were aware of these services.

The aHUS Nurses now highlight all of these things in our patient packs and introductory letters as well as during consultations.

This year we conducted a new survey to allow us to revisited some of the core service delivery indicators such as communication, quality of care received and access to information and support. We have also asked patients about their understanding of the shared care model, their perceptions of the role of social media, and how they would like to interact with our team and other aHUS patients and families.

The survey was shared via email, with a QR code and link provided. For those patients who prefer not to receive communication electronically, a paper copy and freepost envelope was provided.

The survey was open from July to September 2022 and we use the results to continue to develop the service to further benefit our patients.

Patient Panel

Patient Panel September 2022

The aHUS nurses have held the first patient panel since the covid pandemic. The intention of the panel was to create a forum for patients and their carers/ parents to explore in depth their opinions in relation to aHUS, with a view that it will ultimately help to shape the care of this group of patients. Invitation to the panel was voluntary and patients were invited to express their interest in communication sent out within our newsletter.

We were delighted to have 11 volunteers, both patients and parents of patients, that now comprise our new aHUS patient panel with representation from across the country depicted below.

Nationwide reach of patient panel

This patient panel was held virtually on Thursday 8th September 2022.The topic on the agenda for this first session focused on access to information and the discussion centred around the types of information patients received, when they received it and the quality and quantity of the information provided.

The experiences shared by the panel reinforced the need for good quality accessible information from a variety of sources. The members provided a rich insight into the types of information they currently find supportive at the point of diagnosis and what they feel is missing. This qualitative data will be built upon to help shape the types of information which is available to aHUS patients.

The next panel meeting will be held December 2022.

5.2 Patient Roadshows

Webinar November 2021

We hosted our second Webinar in November 2021. The format involved a series of talks delivered by the NRCTC consultants, on topics patients had suggested. There was then the opportunity for patients and parents to ask questions, during the "Question and Answer" session.'

Feedback from this event was very positive:

- 100% of those who responded said they felt the webinar was helpful
- 100% of respondents said they felt their questions during the Q&A had been answered

Some individual comments included:

I find these sessions so interesting & it's reassuring to know that there are others who have the same questions!

It was perfect for us as a family

Useful topics, good format, thank you

Edinburgh May 2022

We were able to hold our first face-to-face patient roadshow post-Covid 19 pandemic outbreak. We felt it was important to host this in Scotland because the NRCTC was formally commissioned to provide a service to Scotland in relation to aHUS and C3 Glomerulopathy in 2021. This provided an opportunity to meet some of our Scottish patients in person.

The format included a "meet and greet" session, followed by talks from the NRCTC consultants and aHUS Nurses. There was an opportunity for an open question and answer session, followed by small group sessions which were facilitated by members of our team

The feedback obtained from this event was wholly positive, and highlighted the value of patient roadshows in promoting relationships between patients and the NRCTC, as well an opportunity for patients and parents to meet others in a similar situation to themselves.

Patients and their families felt that the talks presented provided them with a better understanding of atypical HUS and helped them to make informed decisions about their care. The feedback identified that the information provided in the talks was easy to understand and attendees felt encouraged to ask questions. All those attending would recommend our roadshow to another patient or family member with atypical HUS.

Direct comments included:

The information provided about complement was useful and informative

My highlight was meeting the team, consultants and nurses and the other families

It was so useful meeting the whole team. You are all great and really care about your patients.

Thank you

There was nothing I would change. It was a highlight to meet everyone from Newcastle after 2 years

I would change absolutely nothing at all. It was excellent

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. Evaluation of the effectiveness of these clinics will be discussed with the current patient panel and we are currently working alongside the trust patient engagement team to progress how we can evaluate these further.

5.4 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.

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.

We are currently in the process of working with a website design company to update and refresh our website to improve accessibility and navigation.

5.5 Patient Stories

Frederico's Story: aHUS adventures

After feeling dizzy and unwell for a week I finally went to the hospital thinking I had covid, despite negative tests. Doctors told me I had kidney failure to which I thought it was impossible! After a few days I was transferred to another hospital where they suspected it was aHUS, something I didn't even know existed. From that day onwards all I heard was dialysis for life, kidney transplants and being in such a fragile state and alone, not being able to see my family/ partner due to covid restrictions. I can say I wasn't too optimistic, but the team was there for me the whole time and that was like having my guardian angel looking after me times 10! Even today, just by putting pen to paper it made me cry, not for the pain or fear I had those weeks but because I really felt I could trust them and will be forever grateful to all of the doctors and nurses who looked after me locally and the Newcastle Team.

The organisation I work for was amazing as they gave me full support and also stood by me through it all, reassuring me that they would give me all the time I needed and contacting me every single day. That gave me a boost, as it also made me feel like I was ready to face this new challenge that life put in my way.

Going back home was daunting but needed to progress, dialysis for 2 months on the midnight shift to be able to start doing some work and getting back into a routine once I was strong enough to even go up the stairs without feeling dizzy and breathless (needed to lose some weight before so not all was bad!).

My advice to others, is to set short term goals and believe in them full heartedly going through this type of process. Simple wins that you can achieve and keep you motivated:

1 Be able to walk for longer periods without interruptions

2 Find simple routine exercises that can help you focus on a task that will allow your brain to relax

3 Use any creative outlets you want to create something new and exciting (paint, write, try a musical instrument, try a new hobby, be bold!). The sky is literally the limit!

Sometimes time makes you drop your shoulders a bit, but we need to get them back up and take every day as an opportunity to live our life the best way we can!

I became a new person, readjusted my expectations, adapted to my new possibilities (forget about limitations and see it as a way to challenge your ability to succeed and improve your life)! My Family, partner and friends helped me stay positive!

aHUS is now a part of my life, but I'll never let it define who I am!

We set the rules, we just need to look after our body better and listen to our amazing team of consultants and nurses for advice and help!

Always Be strong!

6. NRCTC Key Service Development Goals

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:

Developing Current Patient Pathways

Continuing to offer all patients under shared care for aHUS appointments to discuss diagnosis and ongoing treatment options [NB specific ongoing discussions regarding ravulizumab / prospect of eculizumab withdrawal / meningococcal risk]

Drug ordering –The transition to delivery of Eculizumab therapy from hospital to the patients' homes has resulted is reduced stock of drugs in hospital for acute aHUS cases. This necessitated a review of practice. We are working alongside pharmaceutical industry to improve the experience of ordering drug, particularly in emergency/ OOH scenarios and develop a process of reimbursement for drug for patients pre-approved for complement inhibition, which should be in place by December 2022.

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".

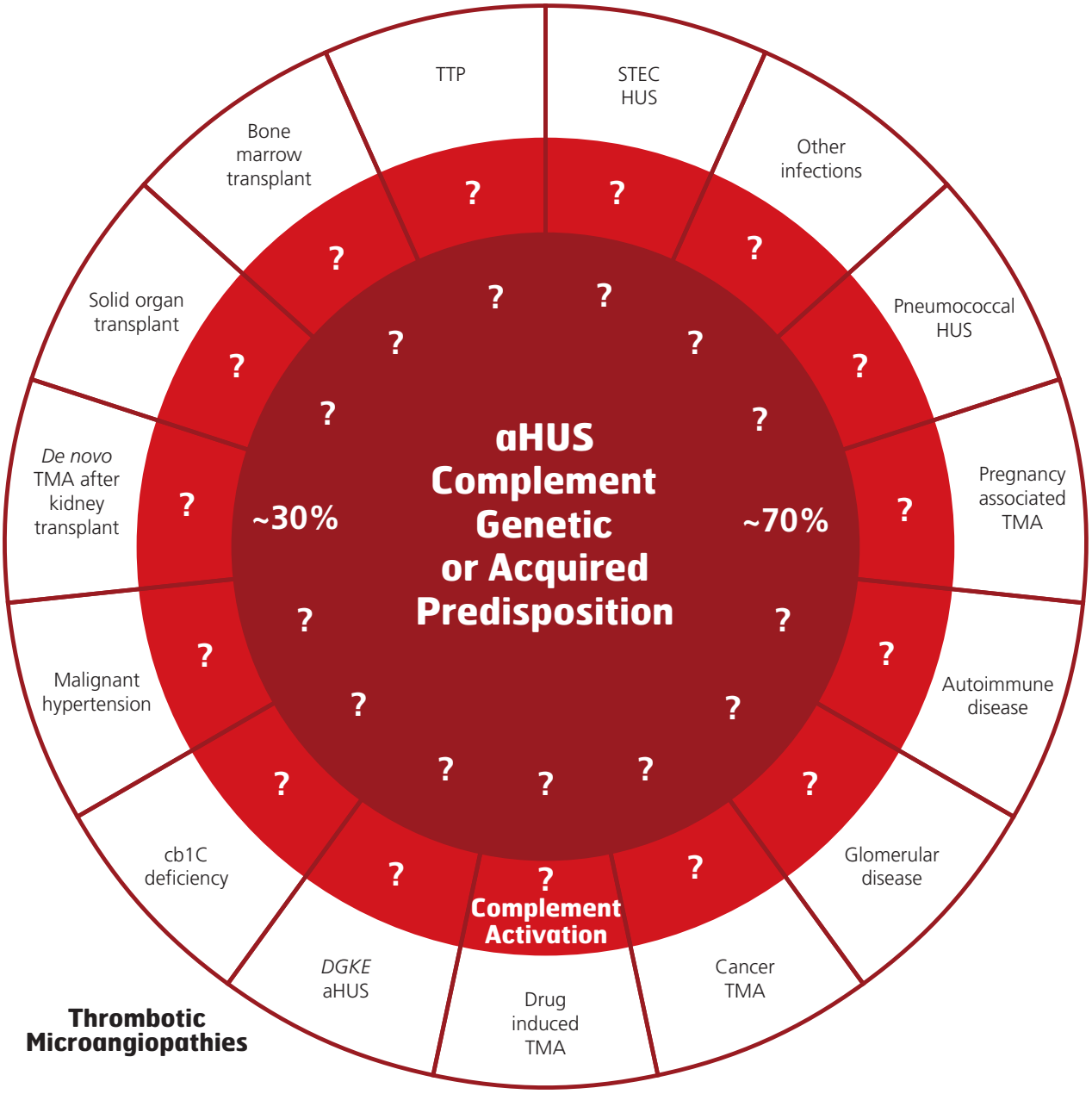
Patient packs and alert cards – updating current and developing new online resources & interactive applications, in addition to the written materials we send out.

Peer support network – formalise our peer support network and identify a range of patients across the cohort that represent all patient groups.

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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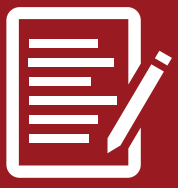

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