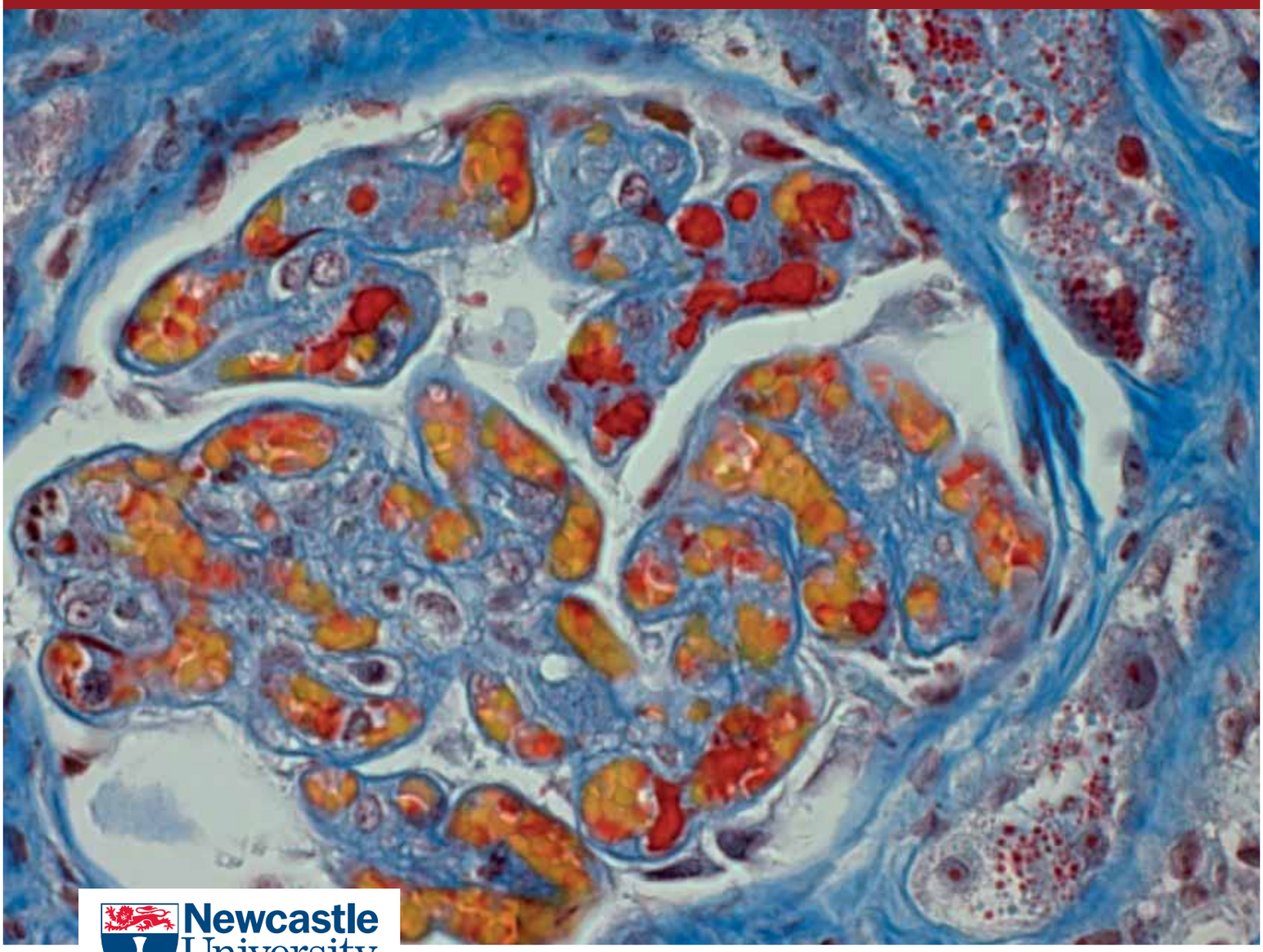
NATIONAL RENAL COMPLEMENT THERAPEUTICS CENTRE

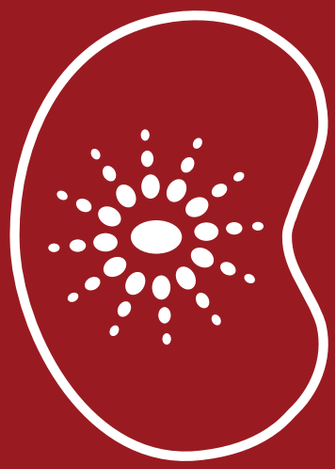
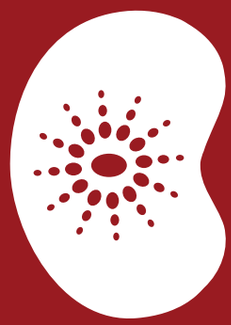
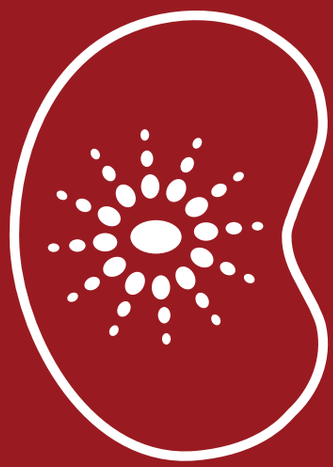
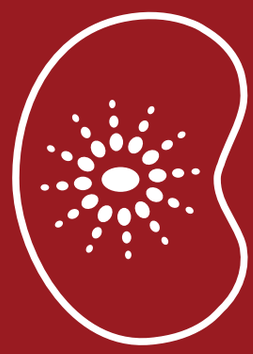
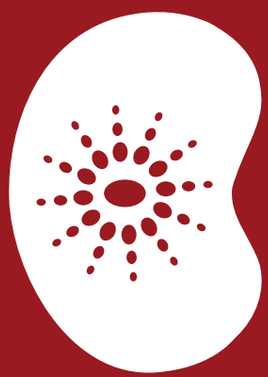
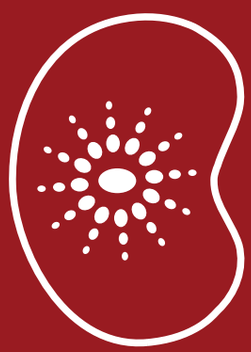
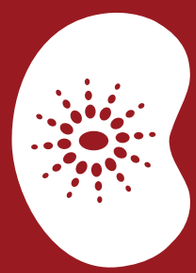
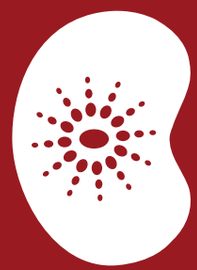
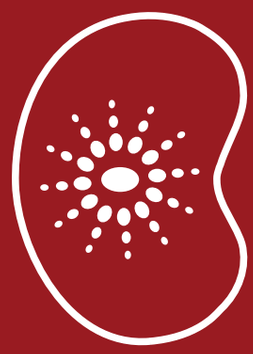
NHS
The Newcastle upon Tyne Hospitals
NHS Foundation Trust

The Annual Report of the **National Renal Complement Therapeutics Centre** 2017/18



Newcastle University

www.atypicalhus.co.uk

Authors
Edwin Wong
Joanne Stout
Jalibani Ndebele
Angela Watt
Michal Malina
Sally Johnson
Neil Sheerin
David Kavanagh

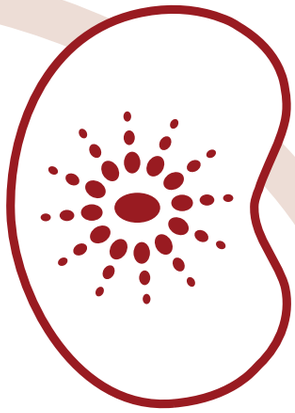
The Annual Report of the **National Renal Complement Therapeutics Centre** 2017/18

aHUS
ATYPICAL HAEMOLYTIC URAEMIC SYNDROME

NATIONAL RENAL COMPLEMENT THERAPEUTICS CENTRE

C3G
C3 Glomerulopathy

Contents



1. Service Overview

1.1 The National Service

The National atypical Haemolytic Uraemic Syndrome (aHUS) Service was commissioned in May 2016 by NHS England (NHSE) to co-ordinate the management of patients with aHUS and other thrombotic microangiopathies. The National C3G/MPGN Service was added to our portfolio in February 2017 to manage the investigation and treatment of these diseases recurring after kidney transplantation. The aim of our service is to provide a combined clinical, diagnostic, research and treatment centre for these complement mediated diseases. 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.

The National aHUS Service and the National C3G Service are part of the National Renal Complement Therapeutics Centre (NRCTC), and are based at the Newcastle upon Tyne Hospitals NHS Foundation Trust.

Our core team currently comprises five consultant nephrologists (3 adult and 2 paediatric), two nurse specialists and the administration team. To provide cutting edge diagnostics we also have six dedicated clinical scientists and two consultants working across genetics, haematology and immunology. 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, "putting patients at the heart of everything we do." 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

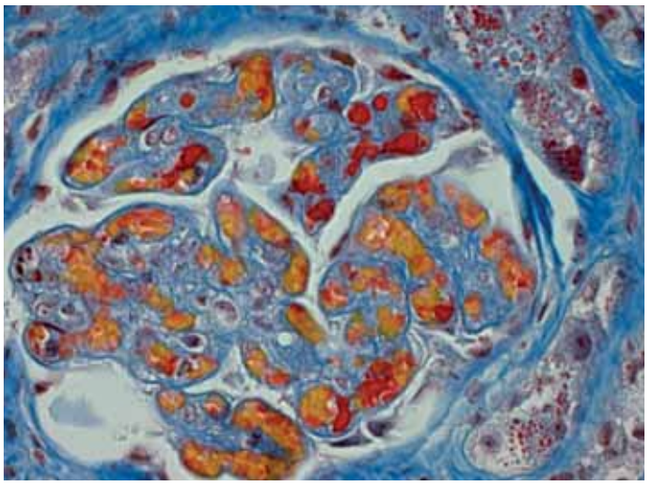
"putting patients at the heart of everything we do"

1.3 Disease Context

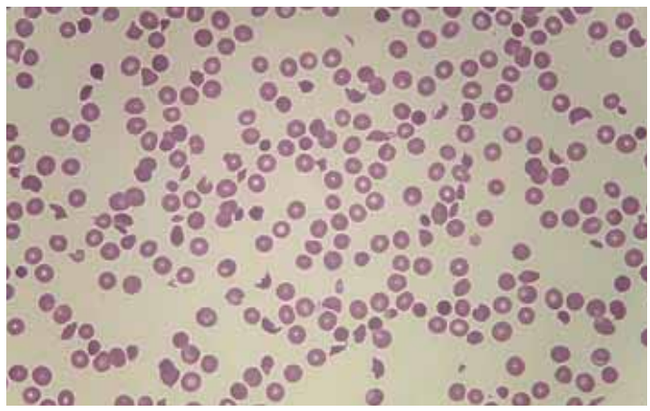
1.3.1 What is aHUS?

Atypical HUS 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 is poor with 50% of patients developing renal 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



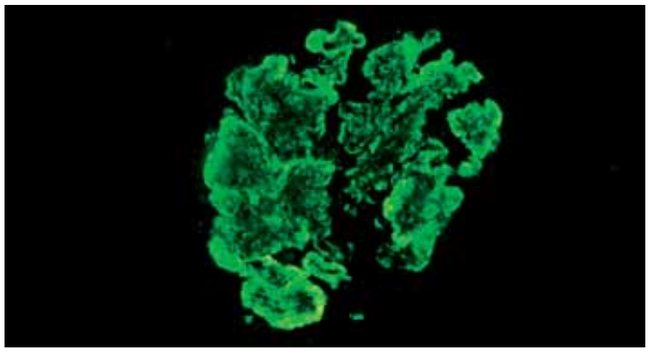
Blood film from aHUS patient showing schistocytes

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.

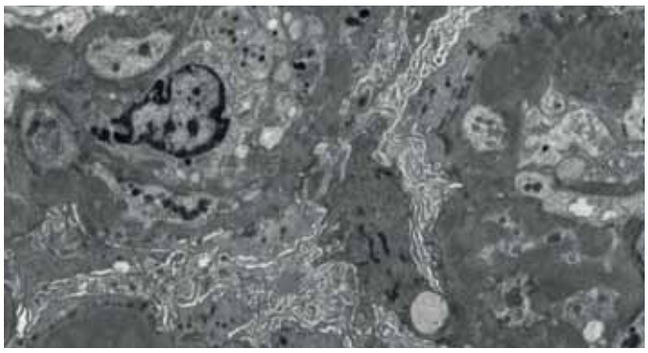
Since 2016, the National aHUS Service has been available 7 days a week 24 hours a day to provide advice on diagnosis and management from consultants experienced in the management of aHUS. We also provide rapid diagnostic testing and support for clinicians to exclude other forms of Thrombotic Microangiopathy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

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.



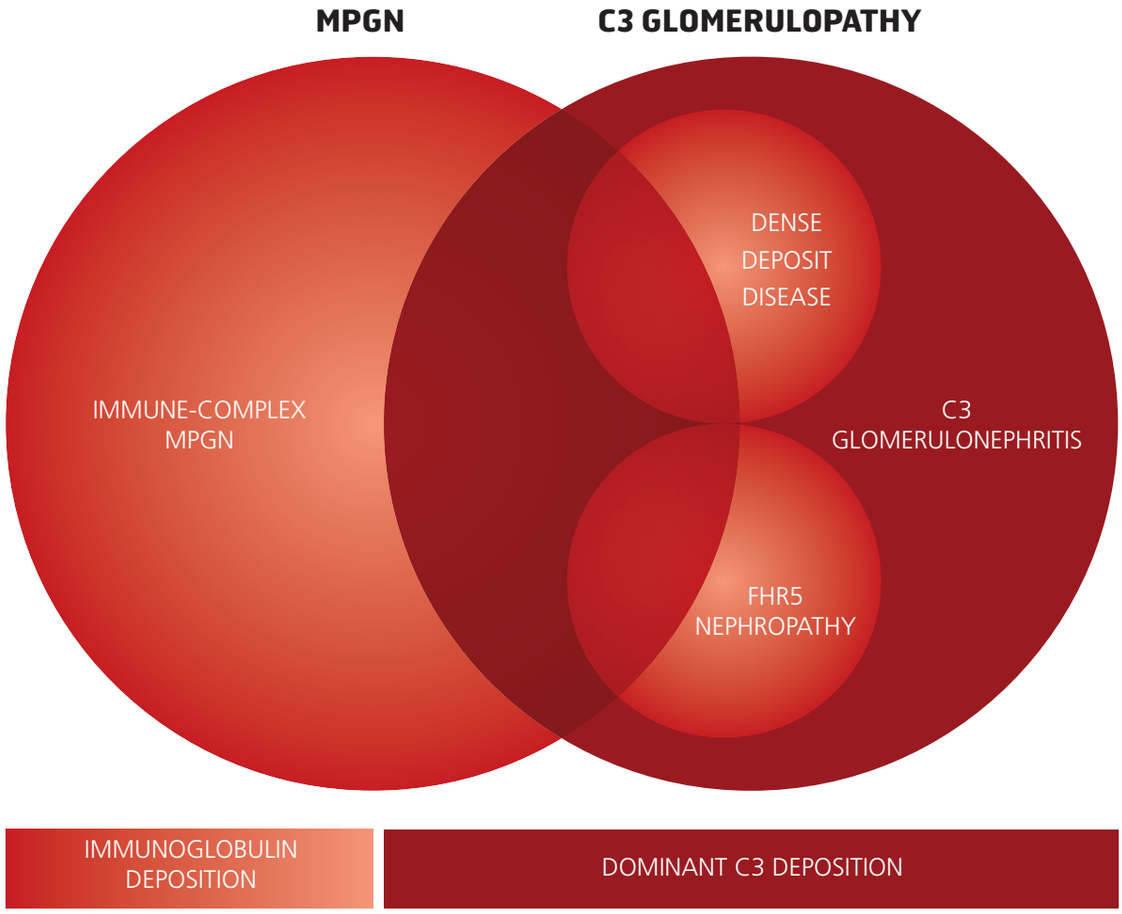
Strong C3 staining in C3GN



Sub-endothelial deposits in C3GN

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. Current classifications distinguish C3G from immune-complex MPGN though abnormalities in complement regulation can be found in both.

Eculizumab is not licenced for treatment of C3G but a review of the available evidence of its use in C3G led to a Clinical Commissioning Policy (NHSE 16054/P) published in February 2017 and possible use in recurrent C3G following renal transplantation. 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

During this current reporting period the following developments have occurred:

- Implementation of NHS England policy for Eculizumab in the treatment of recurrent C3G following renal transplantation
- Appointment of an adult and a paediatric nephrologist
- Development of disease specific information for patients and carers
- Creation of a patient focus group to promote service development and launch a patient support network
- Establishment of aHUS roadshows for patients
- Continuous improvements to the National aHUS Service website, providing information for clinicians and patients
- Refinement of patient flow and follow up processes
- Winner of the Bright Ideas in Health Award for Research Delivery Impact

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 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

Our team have been very active in eliciting the views of our patients, keeping them informed of our service developments and producing patient information.

In October 2017 we held the first patient focus group, with representation from all regions of England. Key themes from the focus group can be viewed below. The focus group agreed to meet annually to ensure our patients' needs continue to be met.

Hand held records have been developed in order to empower our patients to take ownership of their care. These records were given to a group of patients for comments. Their feedback was positive and we have incorporated their ideas and patients will start receiving these as part of our referral pathway.

The National aHUS Service hosted members of the aHUS alliance, the umbrella organisation of aHUS patient groups from around the world. As part of their European tour of expert aHUS centres, they were able to visit three centres in six days; their visit to Newcastle was sandwiched between Paris and Milan. Linda Burke (USA) and Len Woodward (UK) presented the work the aHUS alliance is involved in, including patient information the alliance has produced, the purpose for the tour of expert centres and their vision for aHUS patients across the globe.

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.

The NRCTC have held a seminar series during the year hosting specialist staff from the Public Health England (PHE) reference laboratories in London and Manchester. Staff from Royal Liverpool and Broadgreen University Hospitals presented their experience of developing a regional highly specialised service for TTP.

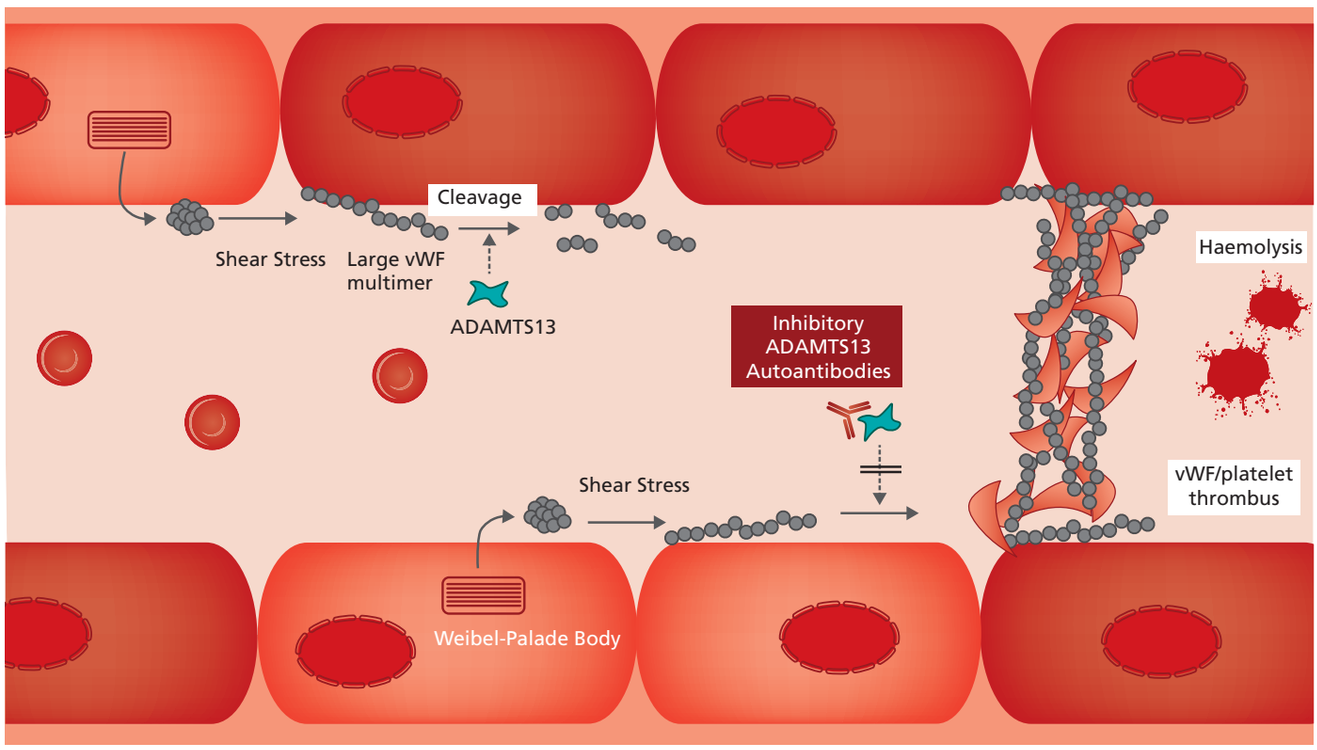
1.8 Ensuring High Quality Care that Delivers Optimal Use of Eculizumab

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.

Complement Genetics

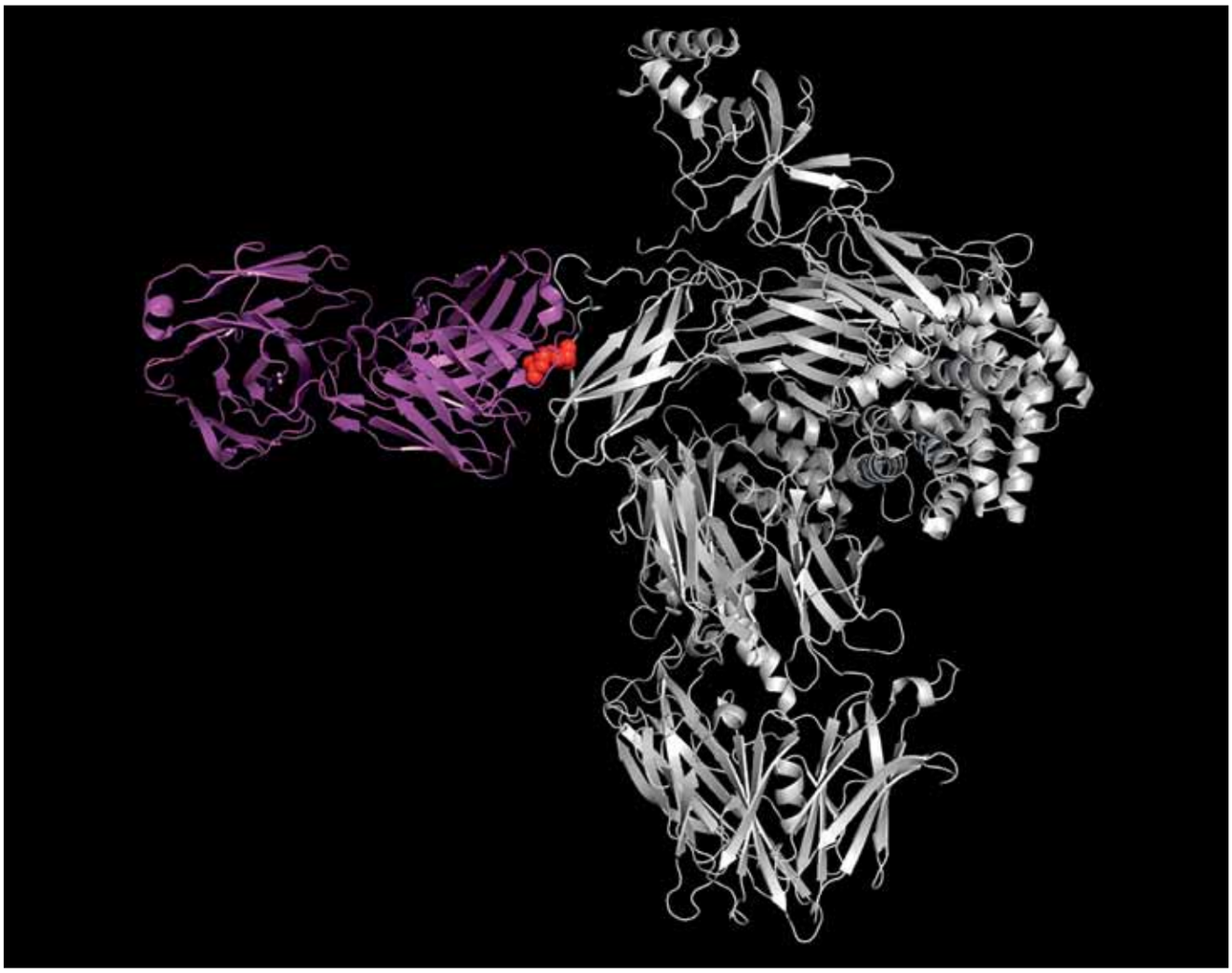
Standard sequencing of the complement genes factor H, factor I, *CD46*, *C3* and factor B is undertaken on all patients referred to the National aHUS Service. Many complement genes are found on chromosome 1 in a region called The Regulators of Complement Activation (RCA) gene cluster. This region is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

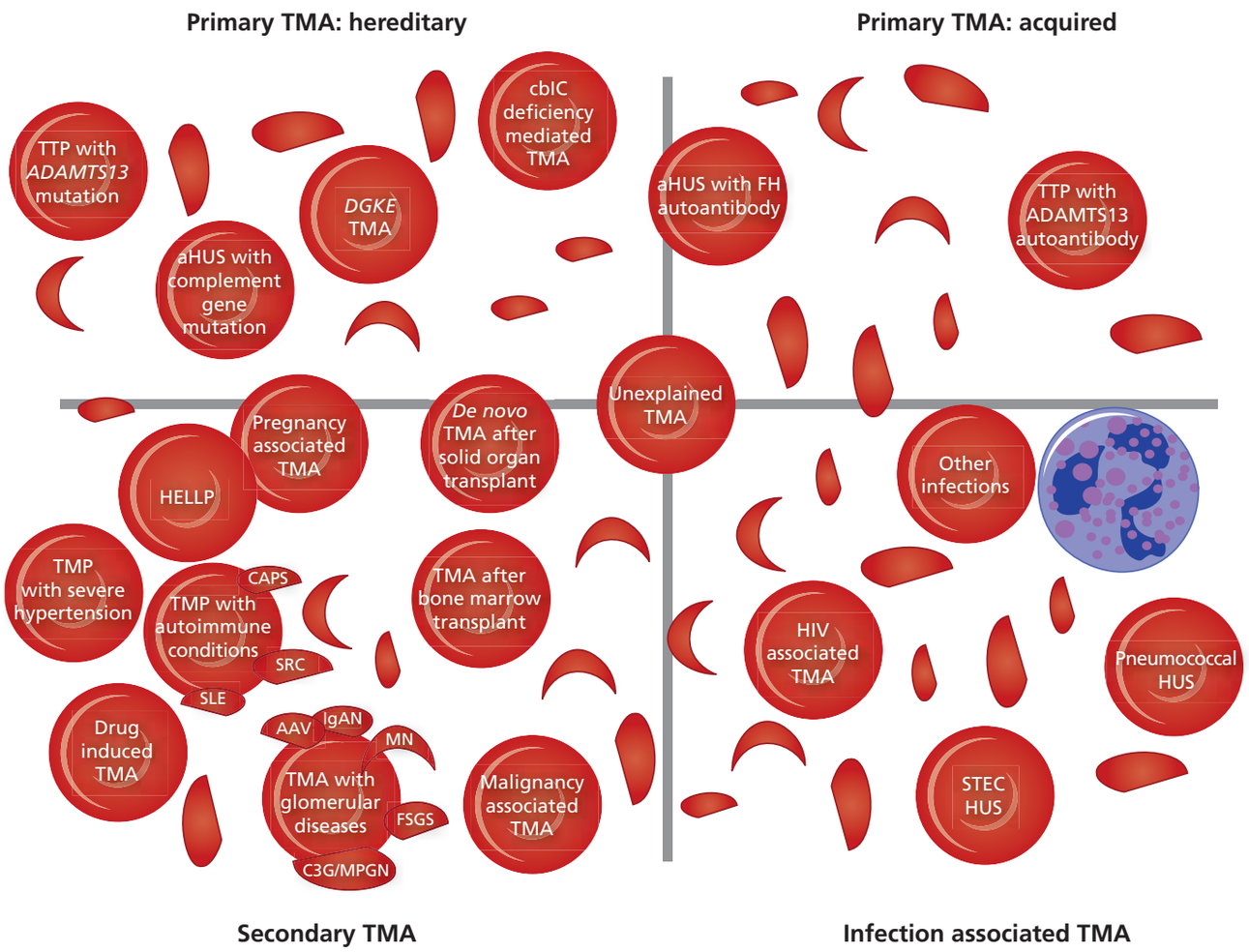
Complement assays are a key part of the diagnostic toolkit, providing evidence of complement activation, validation of genetic findings and allowing therapeutic profiling. The Newcastle upon Tyne Hospitals Blood Sciences' Complement Immunology laboratory overseen by Dr Adrian Heaps and Professor Claire Harris' 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, CH100, AP100 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.

In C3G, C3 Nephritic factors are routinely measured and C4 and C5 Nephritic factor assays are under development in Professor Claire Harris' group.



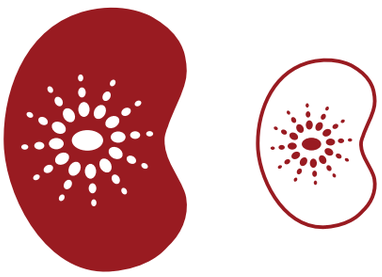
Causes of TMA

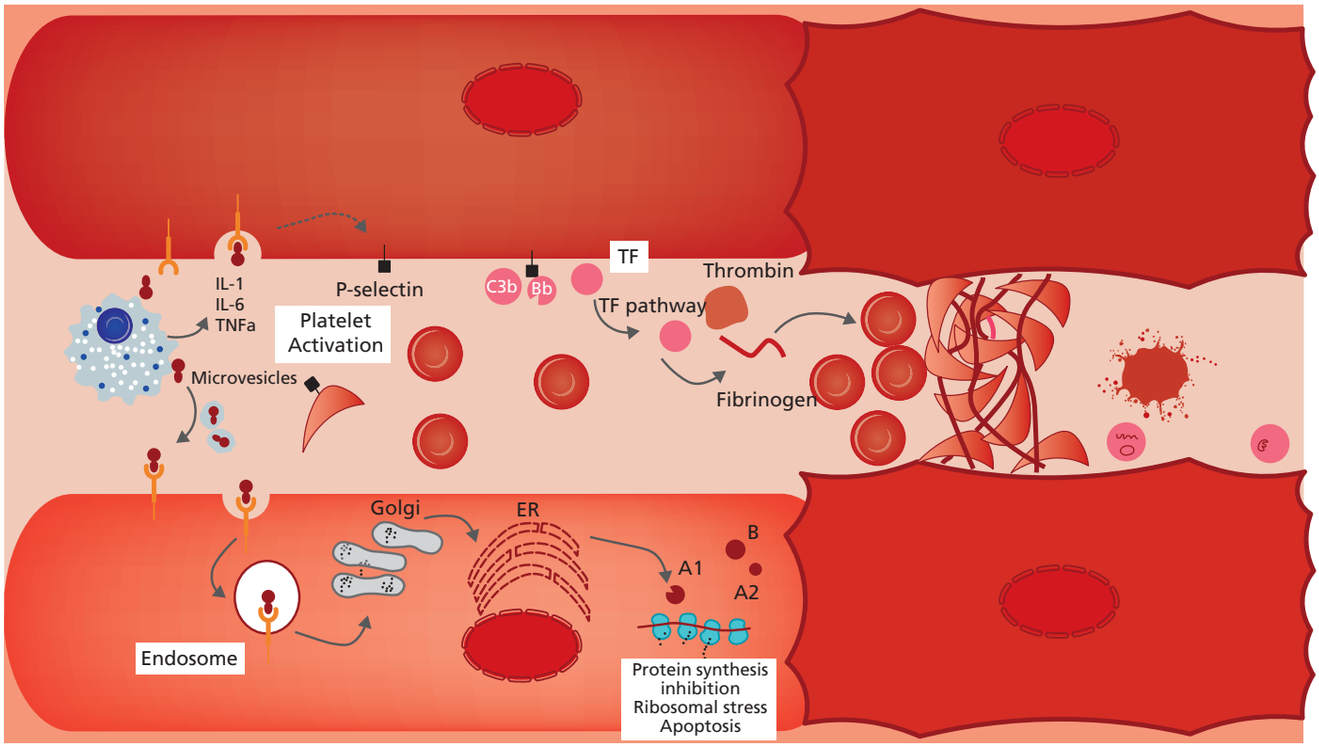
1.8.7 Microbiology Specialist Laboratories

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

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.





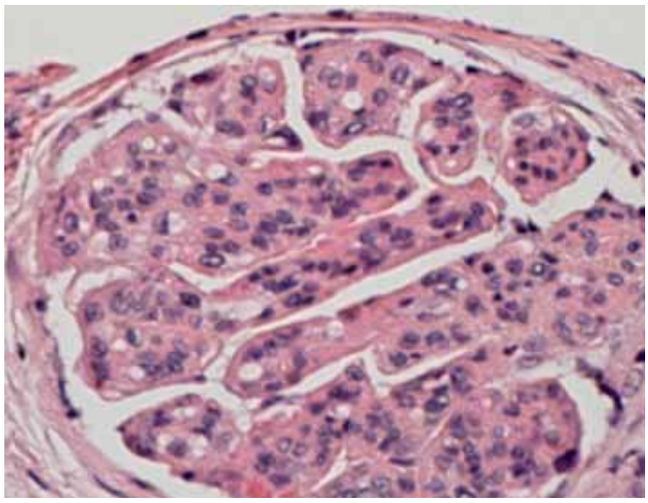
Thrombus formation in STEC HUS

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 current policy is to vaccinate against Meningococcal serotypes ACWY and B. 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.

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. Eligibility for treatment with Eculizumab is dependent on confirmation of C3G as the original cause of kidney failure and its recurrence in the transplanted 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 Healthcare NHS Trust.



MPGN on Renal Biopsy

1.9 Global Reach for Optimal Patient Care

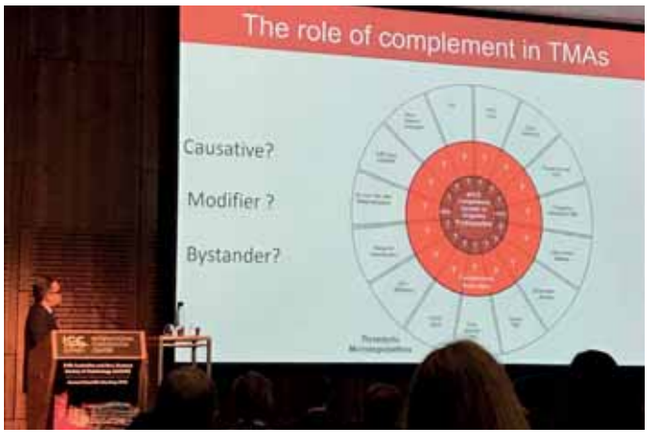
European Reference Network on Rare Kidney Disease (ERKNet)

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 is proud to have been selected as a reference centre for TMA for ERKNet. ERKNet offers virtual consultation services to physicians throughout Europe who need advice for challenging cases with a rare kidney disease. The NRCTC has already demonstrated its global reach 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.



Ongoing Audit and Review of Practice

The NRCTC undertakes constant audit and research to optimise practice. In the last year we have reviewed all cases of *DGKE* mediated aHUS and bone marrow transplant associated TMA and this data was presented at UK Kidney week by two of our research fellows.

Nurse Education

Our specialist nurses have continued to present at a number of nursing study days in the UK and internationally to raise the awareness of the National aHUS Service, the disease process and its treatment options. Regular updates are held for nurses working in the teams delivering treatment to our patients in their home. Our specialist nurses also presented at the Trust's Nursing and Midwifery Conference and at UK Kidney Week.

Our specialist Nurses are also enrolled on the post graduate certificate course in Genomic Medicine and have completed several modules, including genetic counselling.

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 of 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.

The protocol has ethical and MHRA approval and will open for recruitment later this year.

Professor David Kavanagh is the Chief investigator in the UK for:

CL011_168 Trial

The CL011_168 Trial is a randomised, double-blind placebo-controlled phase 2 study evaluating the safety and efficacy of Avacopan (CCX168) in patients with C3 Glomerulopathy.

Dr. Sally Johnson is the Chief Investigator for two multicentre studies in the UK.

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

ECUSTEC is a randomised, double-blind, placebo-controlled trial which aims to determine whether Eculizumab reduces the severity of STEC-HUS in children. The trial opened in July 2017 and will recruit 134 children with STEC-HUS over 4 years. Twelve paediatric renal units across the UK are participating in the trial. If effective, Eculizumab may reduce the number of children requiring dialysis or developing severe multi-system complications from STEC-HUS.

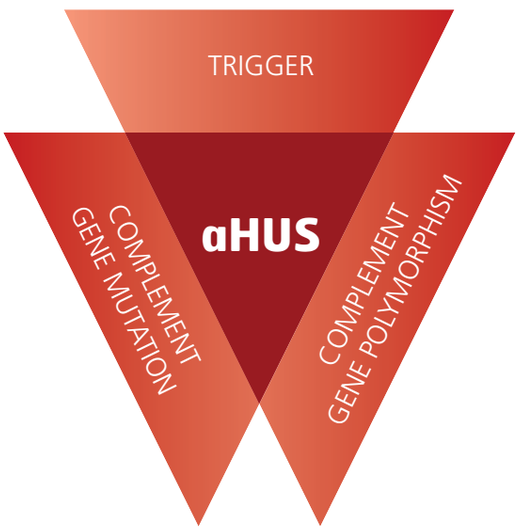
National Study of MPGN and C3G:

The National Study of MPGN and C3G was a longitudinal cohort study which brought together clinical, pathological, genetic and functional data of patients with these rare but devastating complement-mediated renal conditions. The aims of the study are to understand genotype/phenotype correlation, identify novel pathogenic mechanisms and identify factors associated with disease severity. Funding has been provided by Kids Kidney Research and the NIHR Rare Disease Translational Research Collaboration. Nearly 300 patients, both adult and paediatric patients have been recruited from 31 centres over 5 years. Recruitment has now closed and work is ongoing to fully characterise this cohort and to stratify patients in preparation for potential trials of therapeutic complement inhibition.

Translational Research at the Newcastle University Complement Therapeutics Research Group

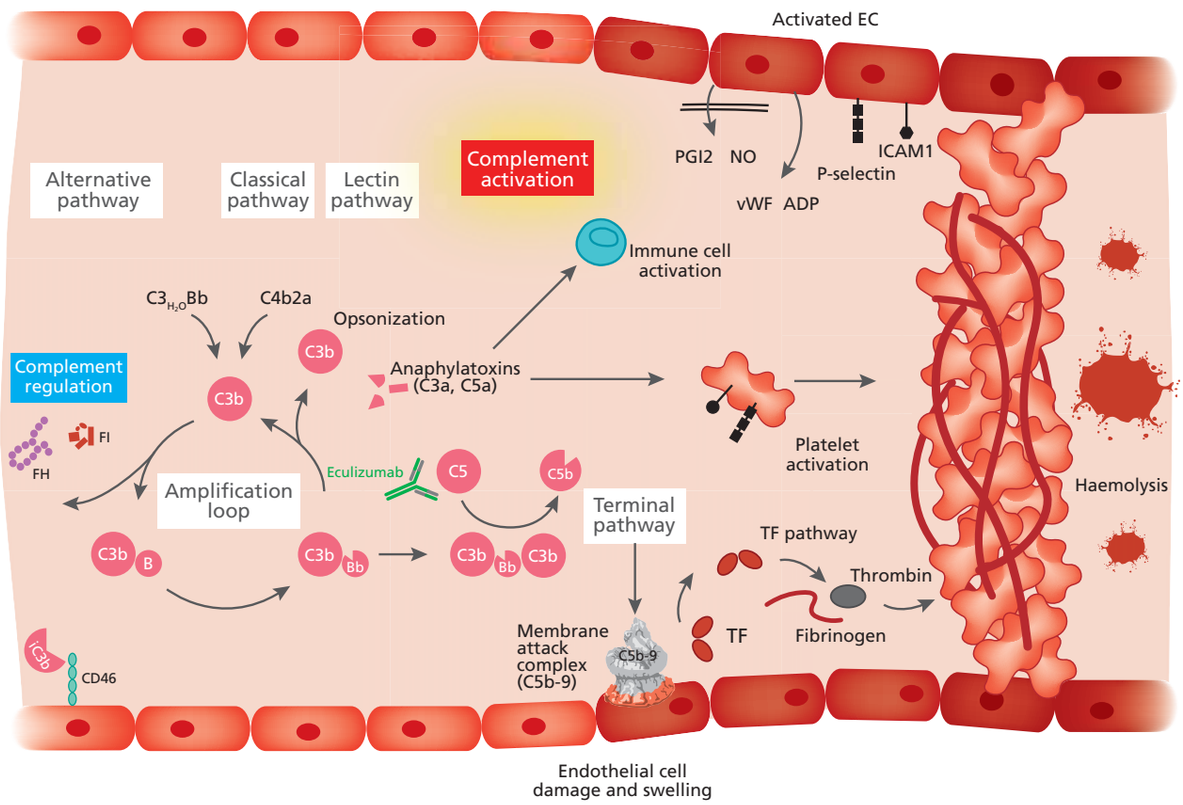
Dr Marchbank, Professor Harris and Professor Kavanagh also oversee an active bench to bedside research programme within the NRCTC. Research in the group encompasses basic, translational and clinical science, ranging from deciphering of disease mechanisms using intricate in vitro assays, through animal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

Thriving collaboration between the scientific and clinical teams in 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 multiplexed 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, University of Southampton, University Washington School Of Medicine, St Louis, and Tufts University School of Medicine, Boston.



Thrombus formation in patients with aHUS

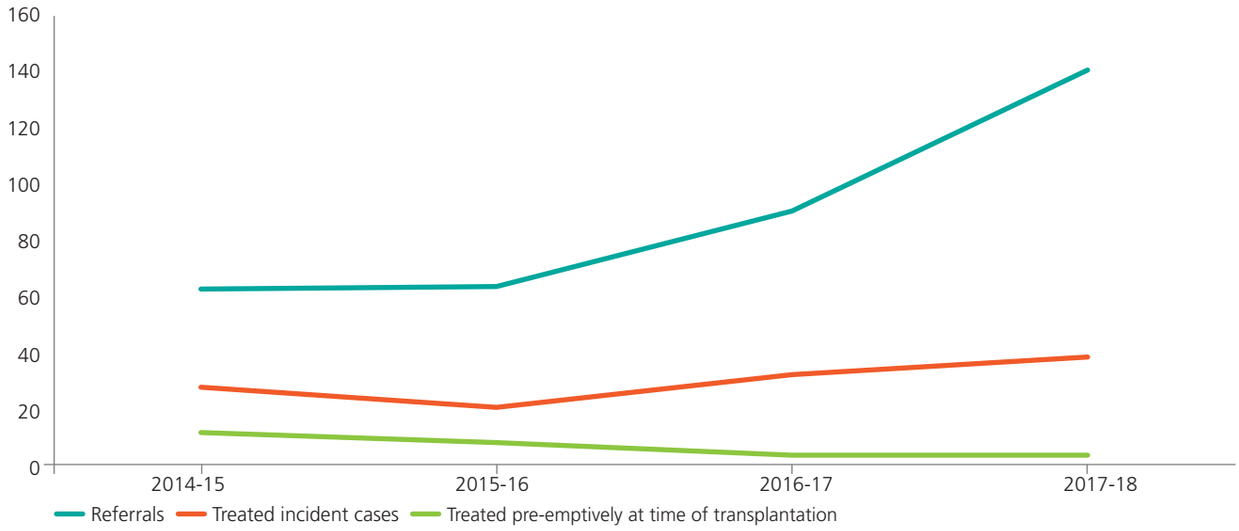
2. Service Activity

The National aHUS Service and the National C3G Service have had referrals from throughout England since they were commissioned in 2016. The reporting period of this report is from April 1st 2017 until March 31st 2018.

2.1 aHUS service activity

Increasing annual activity

Referrals to the National aHUS Service have been increasing year on year. The annual referral numbers to the service in each of the last 4 complete financial years are summarised in below. During the same reporting period, the number of incident patients with aHUS treated with Eculizumab remains broadly unchanged. However, pre-emptive use of Eculizumab at time of transplantation in prevalent aHUS patients to prevent recurrent disease has decreased. The higher numbers of patients transplanted with pre-emptive Eculizumab in the earlier years of the service reflects the accumulation of patients who were unable to have transplants, due to the risk of life threatening aHUS relapse before Eculizumab was available. It also emphasises the success of Eculizumab in preventing patients going to end-stage renal failure and requiring transplantation.



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 4 complete financial years.*

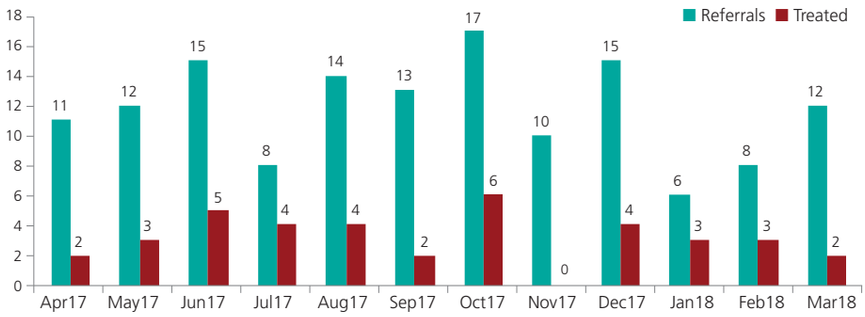
Referrals during the 2017-2018 reporting period

In the 2017/18 reporting period, the National aHUS Service has received 141 referrals for Eculizumab in patients with a potential diagnosis of aHUS. During the same reporting period, Eculizumab was recommended in a total of 38 patients. The monthly activity is summarised in the chart below.

Of the patients referred during this period, as of 31st March 2018, 17 patients improved clinically and remained on Eculizumab. Of these, 29% had a complement genetic variant. An additional 11 patients improved clinically but Eculizumab was subsequently withdrawn. In 4 cases, an alternative diagnosis was identified. Eculizumab was also withdrawn in another 10 patients who did not recover renal function.

In total, 77 patients that were referred to the National aHUS Service for assessment were not recommended for treatment with Eculizumab. Seven cases (9%) of this cohort had a rare genetic variant, but were not treated due to spontaneous recovery, ineligibility for Eculizumab or irreversible kidney damage.

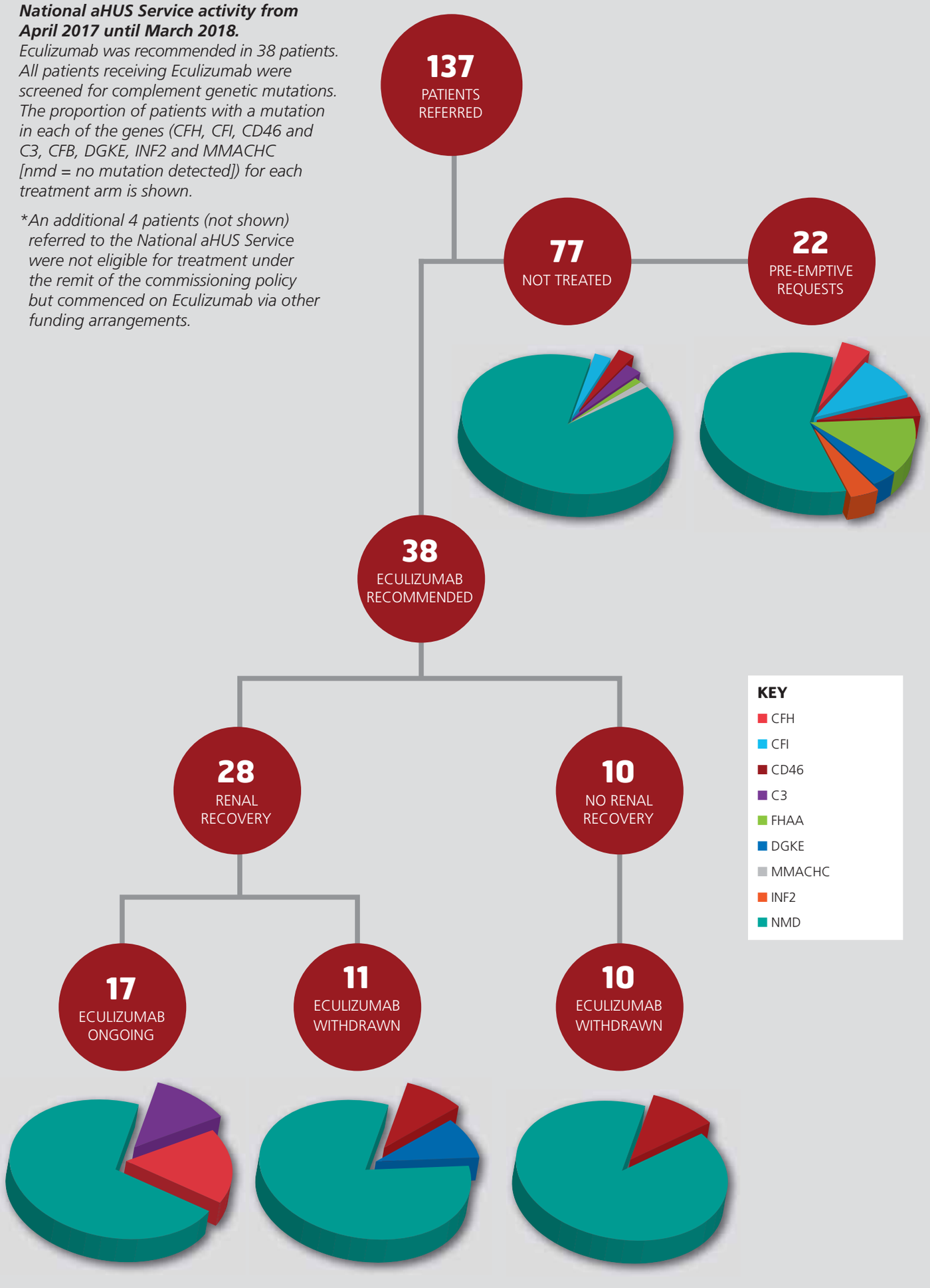
An additional 22 patients were referred to the National aHUS Service for consideration of Eculizumab pre-emptively in case of disease relapse or recurrence. Following genetic testing, any patients who are at end-stage renal failure and considered high risk of recurrent disease are approved for pre-emptive treatment with Eculizumab at time of transplantation. Details of the incident and prevalent patients approved for pre-emptive treatment with Eculizumab during this reporting period can be found in section 3.2.



National aHUS Service monthly activity. *Bar chart shows number of patients referred to the National aHUS Service and number of patients recommended for treatment with Eculizumab in the reporting period from April 2017 until March 2018.*

National aHUS Service activity from April 2017 until March 2018.
Eculizumab was recommended in 38 patients. All patients receiving Eculizumab were screened for complement genetic mutations. The proportion of patients with a mutation in each of the genes (CFH, CFI, CD46 and C3, CFB, DGKE, INF2 and MMACHC [nmd = no mutation detected]) for each treatment arm is shown.

**An additional 4 patients (not shown) referred to the National aHUS Service were not eligible for treatment under the remit of the commissioning policy but commenced on Eculizumab via other funding arrangements.*

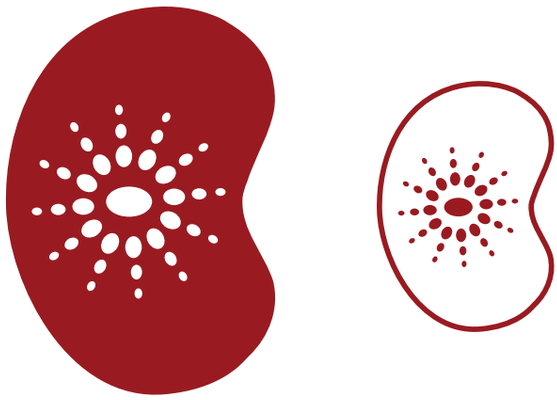


2.2 C3G service activity

In the period between publication of the policy in February 2017 and April 2017, an expert C3G panel was convened between the NRCTC and the Imperial C3G service. A referral pathway was set up for clinicians to refer patients for assessment. The initial point of contact was the NRCTC via email: **C3.glomerulopathy@nhs.net**.

This section reports the activity of the NRCTC with respect to the clinical commissioning policy for Eculizumab in recurrent C3G in the period April 2017 until March 2018. No referrals were made prior to April 2017.

There were 12 referrals to the NRCTC with respect to the C3G policy. Only 2 cases fulfilled the eligibility criteria as set out in the commissioning policy and were commenced on Eculizumab. Both cases demonstrated stabilisation / improvement in graft function and were eligible to be considered for further courses of Eculizumab in the event of further deterioration in graft function.

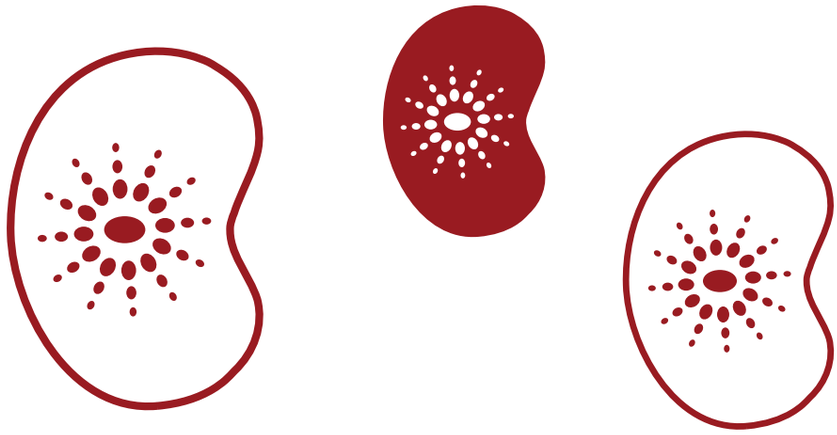


3. Performance Analysis

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 2017/2018

As of the 31st March 2018 there were 114 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 a case review is performed to determine whether aHUS was active at the time and therefore contributed to the death.

The case reviews demonstrated 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. Meningococcal vaccination is required prior to the initiation of 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 vaccination response (see domain 3).

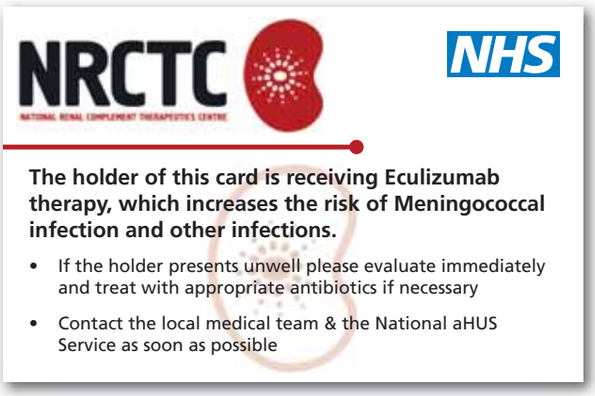
Medical alert cards have been sent to patients receiving treatment to ensure they receive appropriate care when seeking medical treatment. The cards also contain the service website and contact details.

Familial risk of aHUS

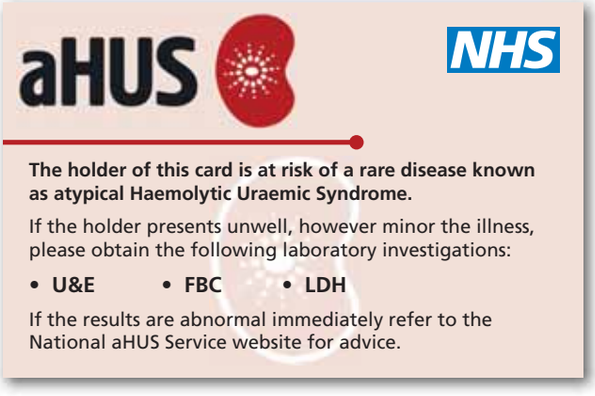
We are now able to offer genetic testing to all relatives of aHUS patients who carry a genetic mutation to identify those who are at risk of developing the disease in the future. Early recognition of the disease is important in preventing the morbidity and mortality associated with aHUS. At risk family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

Recommendations:

- Ongoing regular patient case review meetings
- To continually review our processes for data collection and completion
- Ensure our meningococcal prevention monitoring is accurate with information available on the National aHUS Service website
- Advise all at risk relatives are counselled about the risk of disease and offered genetic screening
- Highlighting risks of meningococcal infection through patient roadshows and newsletters



Patient-held alert card - meningococcal risk



Patient-held alert card at- risk of developing aHUS

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 approved 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 as per our transplantation protocol. We have a database of patients with aHUS who have been assessed for pre-emptive Eculizumab to personalise their management. Our patients undergo extensive genetic and autoimmune testing to characterise their risk of recurrent aHUS at the time of transplant. These patients are at risk of their disease recurring following transplantation and therefore approval is given for Eculizumab to be administered at the time of transplant.

Three patients who had been approved for pre-emptive Eculizumab received a renal transplant between 1st April 2017 and 31st March 2018. In this same period, a further four patients were approved for transplantation with pre-emptive Eculizumab. Patients approved for pre-emptive Eculizumab are reviewed at regular meetings. On 31st March 2018, there were 23 patients pre-approved for Eculizumab to enable listing for renal transplantation.

Recommendations:

- To commence conversations about transplantation with the referring team at the earliest juncture
- Bi monthly MDT reviewing patients placed on the pre-emptive list

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

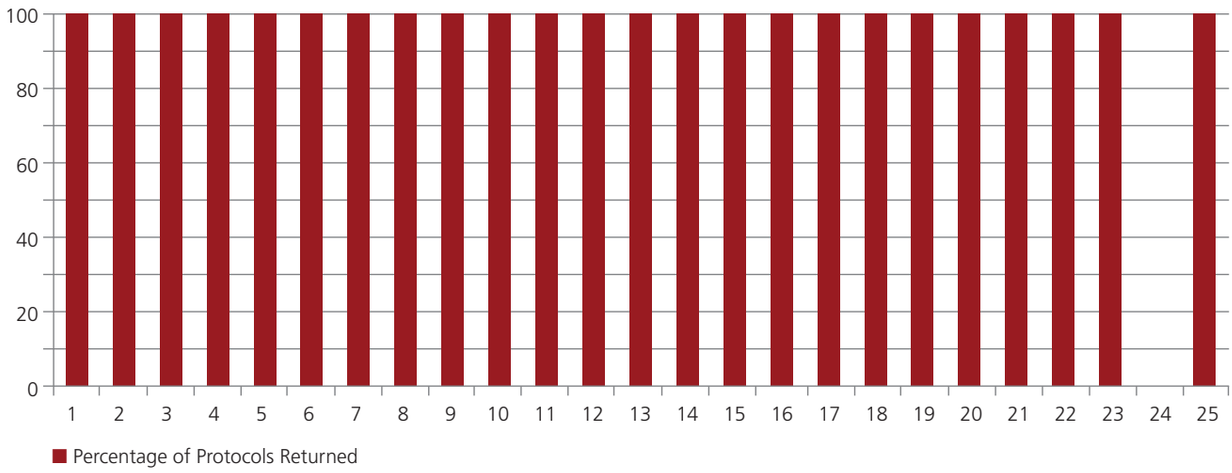
All referrals to the National aHUS Service were answered within 24 hours

We provide a 24 hours, 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.

One hundred and forty one patients were referred to the service in this first full year of commissioning, with a possible diagnosis of aHUS. We achieved 100%, for the quality indicator of providing advice to the referring units within 24 hours; the standard required is 90%.

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 have 100% return rate from all units except for one, resulting in an overall return rate of 76%.



Concordance of return of shared care protocol. There is 100% return rate from all units except for one.

Recommendations:

- Keep service website updated with details of our referral pathway
- Work with NHS England to ensure 100% & concordance

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

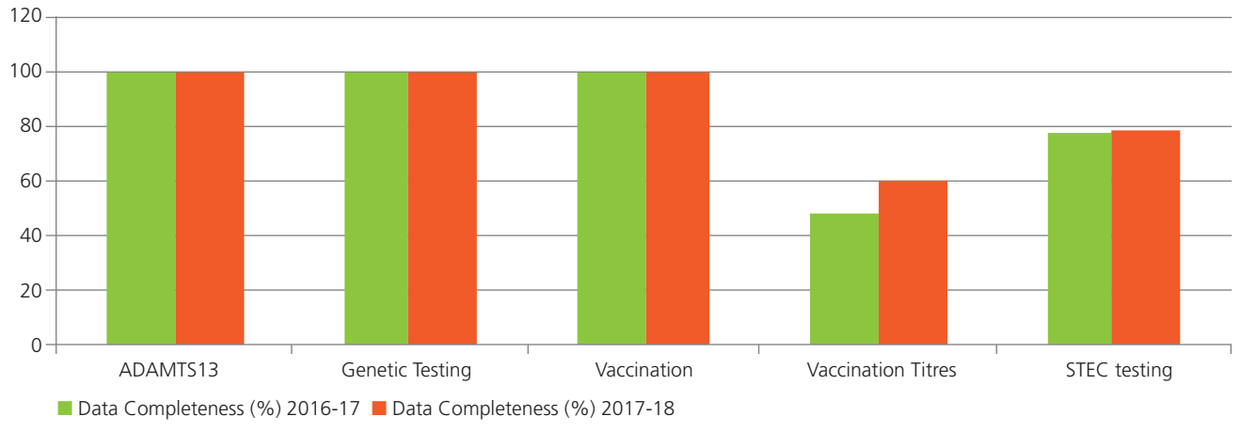
91% data completeness in 5 audited domains

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. A diagnostic checklist is forwarded to the referring clinician for completion to ensure data completeness. To ensure all relevant data is completed for patients commencing treatment, we have introduced a visual referral system which highlights what data is outstanding for the patient. All patients are followed up at one month to review their outcome.

There are five categories of data we measure the standard of data completeness against for those patients approved 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. Data collection in three of the five categories was 100% complete thus achieving the 90% standard.



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 but the data completeness remains less than 90%.*

ADAMTS13 Testing

ADAMTS13 testing was completed on all patients deemed necessary.

Genetic Testing

All patients that we approved for Eculizumab had genetic testing. Genetic testing was also offered to patients referred to the service that were not approved for Eculizumab.

Our specialist nurses completed a short course in 2017 to enable recruitment of patients who do not have a genetic variant and have received Eculizumab treatment, into the 100000 genome project. Recruitment has now closed.

Meningococcal Prevention (Vaccination and Vaccination Titres)

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

In this reporting period, a bespoke laboratory form for measurement of meningococcal vaccination titres was uploaded to our website to allow easy accessibility to the Manchester lab. This has increased our data completeness to 60% from last year's figure of 48%. This was introduced not only to improve our compliance, but to assist local clinicians ordering unfamiliar investigations.

However we continue to have issues obtaining titres at the level of the clinician and/or the patient that will need addressing.

STEC Testing

STEC-HUS is a self-resolving condition that can be quickly distinguished from aHUS following prompt STEC testing. In most patients treated with Eculizumab (excepting post-partum, post-transplant or patients with a known mutation), the results of STEC testing would change our recommendation to treat with eculizumab. Results of STEC testing were available in 79% of such patients.

We have investigated possible reasons for STEC testing not being completed. This revealed microbiology laboratories routinely discard formed stool specimens sent for STEC testing. Therefore to improve compliance when a patient is referred we send the Colindale Public Health Laboratory form and propose the local team liaise with their microbiology laboratory regarding the specimen.

Recommendations

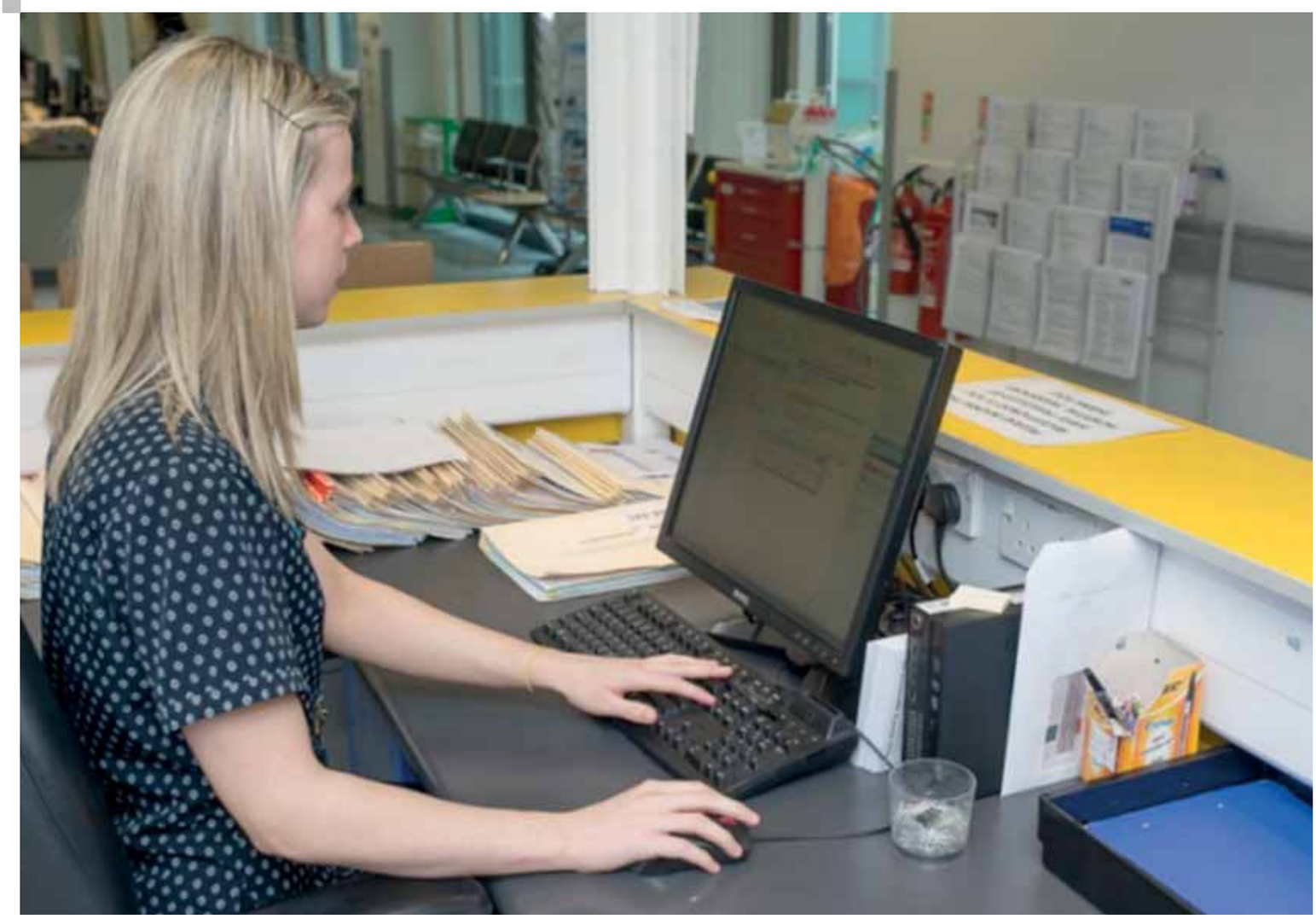
- Continue to investigate methods to improve compliance with vaccination titres and STEC testing
- Clinician engagement and education
- Sending forms direct to patients when discharged
- Work with NHS England to improve compliance with nationally agreed protocols

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 consultation the 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 clinical research trials which may benefit them. Family member are also counselled about the risk to themselves due to their relative's diagnosis. Thirty five patients were reviewed in the aHUS clinic during the year and eleven patients in the C3G clinic.

Recommendations:

- Explore funding streams to assist patients to attend outpatient appointments in Newcastle
- Nurse led clinics
- New patients to be sent a letter from Specialist nurses



4. Achievement of Performance Targets

The results compiled in this section encompass the activity of the National aHUS Service from the 1st April 2017 to 31st March 2018. 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%	76%*
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%	91%

National aHUS Service – Performance during reporting period from 1st April 2017 until 31st March 2018.
*We met the performance targets for domains 1, 2 and 4. * further details are reported in section 3.3.*

5. Online NRCTC

One of our key remits is to provide high quality advice to patients and clinicians about C3G and aHUS. We have previously developed a website **(http://www.atypicalhus.co.uk/)** providing both lay and professional information and advice. This is continually updated with clinical information and access to our newsletters and events throughout the year and is a valuable resource for patients and their families. This year, we have also produced a video that describes the disease mechanisms and treatment of aHUS – this is now featured on our website. We also share news and events via social media on Twitter (**@NationalaHUS**).

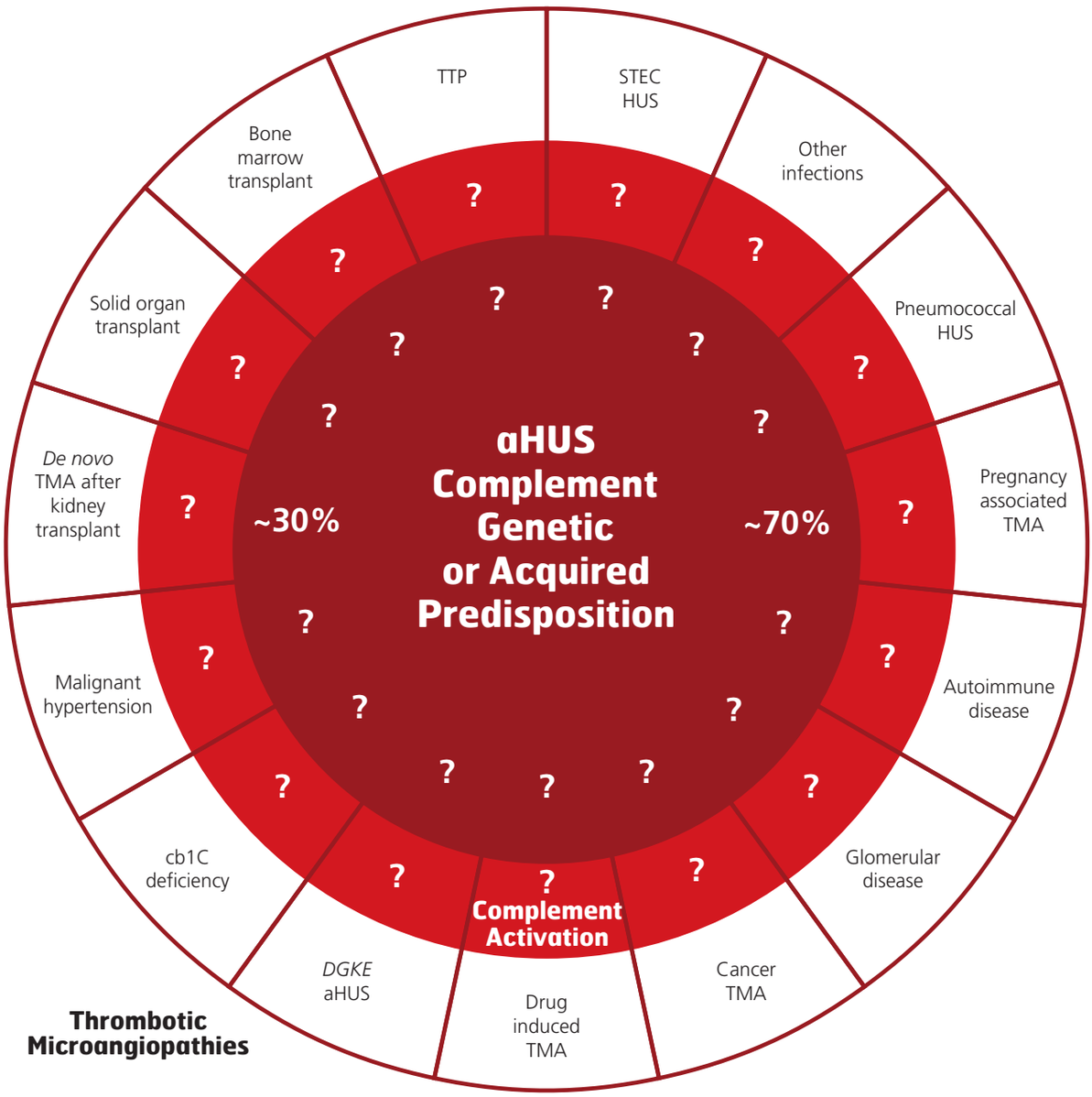
For clinicians the website continues to serve as a portal to access our full range of services as well as providing an up to date summary of complement mediated renal diseases and their treatments. An emergency referrals page **(http://www.atypicalhus.co.uk/emergency-referrals/)** highlights a 24 hour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

Screenshot from the website of the National Renal Complement Therapeutics Centre *depicts our video that describes aHUS 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].*

6. Patient Roadshows

Our first patient roadshow was held in Durham in March 2018. Patients were invited from North East of England and North Yorkshire, the roadshow was also publicised in the newsletter. The feedback from the day was positive. Patients and their families enjoyed talking to the team in an informal setting, listening to the team deliver presentations about their disease and the future and meeting other patients. Contact details were exchanged between the patients during the day. Following the success of Durham we held a second roadshow in Manchester. Patients were invited from the North West and South West Yorkshire. A roadshow in Bristol has been organised for this autumn for patients living in the South West, West Midlands and Hampshire. Dates will be planned for other regions in 2019.

7. Complement Research at the NRCTC



[1] Blaum, B.S., et al., Structural basis for sialic acid-mediated self-recognition by complement factor H. Nat Chem Biol, 2015. 11(1): p. 77-82.

[2] Hunt, D., et al., Thrombotic microangiopathy associated with interferon beta. N Engl J Med, 2014. 370(13): p. 1270-1.

[3] Seddon, J.M., et al., Rare variants in CFI, C3 and C9 are associated with high risk of advanced age-related macular degeneration. Nat Genet, 2013. 45(11): p. 1366-70.

[4] Legendre, C.M., et al., Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med, 2013. 368(23): p. 2169-81.

[5] Morgan, H.P., et al., Structural basis for engagement by complement factor H of C3b on a self surface. Nat Struct Mol Biol, 2011. 18(4): p. 463-70.

[6] Lapeyraque, A.L., et al., Eculizumab in severe Shiga-toxin-associated HUS. N Engl J Med, 2011. 364(26): p. 2561-3.

[7] Hughes, A.E., et al., A common CFH haplotype, with deletion of CFHR1 and CFHR3, is associated with lower risk of age-related macular degeneration. Nat Genet, 2006. 38(10): p. 1173-7.

[8] Brown, K.M., et al., Influence of donor C3 allotype on late renal-transplantation outcome. N Engl J Med, 2006. 354(19): p. 2014-23.

[9] Richards, A., et al., Factor H mutations in hemolytic uremic syndrome cluster in exons 18-20, a domain important for host cell recognition. Am J Hum Genet, 2001. 68(2): p. 485-90.

[10] Buddles, M.R., et al., Complement factor H gene mutation associated with autosomal recessive atypical hemolytic uremic syndrome. Am J Hum Genet, 2000. 66(5): p. 1721-2.

[11] Warwicker, P., J.A. Goodship, and T.H. Goodship, von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med, 1999. 340(17): p. 1368-9.

[12] Schaefer, F., et al., Clinical and genetic predictors of atypical hemolytic uremic syndrome phenotype and outcome. Kidney Int, 2018. 94(2): p. 408-418.

[13] Arbore, G , et al., Complement receptor CD46 co-stimulates optimal human CD8+ T cell effector function via fatty acid metabolism. Nat Commun, 2018. In Press

[14] Goodship, T.H., et al., Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int, 2017. 91(3): p. 539-551.

[15] Challis, R.C., et al., Thrombotic Microangiopathy in Inverted Formin 2-Mediated Renal Disease. J Am Soc Nephrol, 2017. 28(4): p. 1084-1091.

[16] Calippe, B., et al., Complement Factor H Inhibits CD47-Mediated Resolution of Inflammation. Immunity., 2017. 46(2): p. 261-272. doi: 10.1016/j.immuni.2017.01.006.

[17] Bruel, A., et al., Hemolytic Uremic Syndrome in Pregnancy and Postpartum. Clin J Am Soc Nephrol, 2017. 12(8): p. 1237-1247.

[18] Brocklebank, V., K.M. Wood, and D. Kavanagh, Thrombotic Microangiopathy and the Kidney. Clin J Am Soc Nephrol, 2017.

[19] Brocklebank, V., et al., Factor H autoantibody is associated with atypical hemolytic uremic syndrome in children in the United Kingdom and Ireland. Kidney Int, 2017. 92(5): p. 1261-1271.

[20] Kavanagh, D. and K. Smith-Jackson, Eculizumab in children with hemolytic uremic syndrome. Kidney Int, 2016. 89(3): p. 537-8.

[21] Kavanagh, D., et al., Type I interferon causes thrombotic microangiopathy by a dose-dependent toxic effect on the microvasculature. Blood, 2016. 128(24): p. 2824-2833.

[22] Challis, R.C., et al., A De Novo Deletion in the Regulators of Complement Activation Cluster Producing a Hybrid Complement Factor H/Complement Factor H-Related 3 Gene in Atypical Hemolytic Uremic Syndrome. J Am Soc Nephrol, 2016. 27(6): p. 1617-24.

[23] Schramm, E.C., et al., Mapping interactions between complement C3 and regulators using mutations in atypical hemolytic uremic syndrome. Blood, 2015. 125(15): p. 2359-69.

[24] Ruseva, M.M., et al., An anticomplement agent that homes to the damaged brain and promotes recovery after traumatic brain injury in mice. Proc Natl Acad Sci U S A., 2015. 112(46): p. 14319-24. doi: 10.1073/pnas.1513698112. Epub 2015 Nov 2.

[25] Nichols, E.M., et al., An extended mini-complement factor H molecule ameliorates experimental C3 glomerulopathy. Kidney Int, 2015. 88(6): p. 1314-1322.

[26] Licht, C., et al., Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. Kidney Int, 2015. 87(5): p. 1061-73.

[27] Kavanagh, D., et al., Rare genetic variants in the CFI gene are associated with advanced age-related macular degeneration and commonly result in reduced serum factor I levels. Hum Mol Genet, 2015. 24(13): p. 3861-70.

[28] Yu, Y., et al., Whole-exome sequencing identifies rare, functional CFH variants in families with macular degeneration. Hum Mol Genet, 2014. 23(19): p. 5283-93.

[29] Wong, E.K., et al., Characterization of a factor H mutation that perturbs the alternative pathway of complement in a family with membranoproliferative GN. J Am Soc Nephrol, 2014. 25(11): p. 2425-33.

[30] Chen, Q., et al., Complement factor H-related hybrid protein deregulates complement in dense deposit disease. J Clin Invest, 2014. 124(1): p. 145-55.

[31] Tortajada, A., et al., C3 glomerulopathy-associated CFHR1 mutation alters FHR oligomerization and complement regulation. J Clin Invest., 2013. 123(6): p. 2434-46. doi: 10.1172/JCI68280.

[32] Pickering, M.C., et al., C3 glomerulopathy: consensus report. Kidney Int., 2013. 84(6): p. 1079-89. doi: 10.1038/ki.2013.377. Epub 2013 Oct 30.

[33] Goicoechea de Jorge, E., et al., Dimerization of complement factor H-related proteins modulates complement activation in vivo. Proc Natl Acad Sci U S A., 2013. 110(12): p. 4685-90. doi: 10.1073/pnas.1219260110. Epub 2013 Mar 4.

[34] Bresin, E., et al., Combined complement gene mutations in atypical hemolytic uremic syndrome influence clinical phenotype. J Am Soc Nephrol, 2013. 24(3): p. 475-86.

[35] Paixao-Cavalcante, D., et al., Sensitive and specific assays for C3 nephritic factors clarify mechanisms underlying complement dysregulation. Kidney Int., 2012. 82(10): p. 1084-92. doi: 10.1038/ki.2012.250. Epub 2012 Aug 1.

[36] Kavanagh, D., et al., Factor I autoantibodies in patients with atypical hemolytic uremic syndrome: disease-associated or an epiphenomenon? Clin J Am Soc Nephrol, 2012. 7(3): p. 417-26.

[37] Kavanagh, D. and H.E. Anderson, Interpretation of genetic variants of uncertain significance in atypical hemolytic uremic syndrome. Kidney Int, 2012. 81(1): p. 11-3.

[38] Francis, N.J., et al., A novel hybrid CFH/CFHR3 gene generated by a microhomology-mediated deletion in familial atypical hemolytic uremic syndrome. Blood, 2012. 119(2): p. 591-601.

[39] Zhao, J., et al., Association of genetic variants in complement factor H and factor H-related genes with systemic lupus erythematosus susceptibility. PLoS Genet, 2011. 7(5): p. e1002079.

[40] Salmon, J.E., et al., Mutations in complement regulatory proteins predispose to preeclampsia: a genetic analysis of the PROMISSE cohort. PLoS Med, 2011. 8(3): p. e1001013.

[41] Roversi, P., et al., Structural basis for complement factor I control and its disease-associated sequence polymorphisms. Proc Natl Acad Sci U S A., 2011. 108(31): p. 12839-44. doi: 10.1073/pnas.1102167108. Epub 2011 Jul 18.

[42] Lambert, H.J., et al., Primary, nonsyndromic vesicoureteric reflux and nephropathy in sibling pairs: a United Kingdom cohort for a DNA bank. Clin J Am Soc Nephrol, 2011. 6(4): p. 760-6.

[43] Heurich, M., et al., Common polymorphisms in C3, factor B, and factor H collaborate to determine systemic complement activity and disease risk. Proc Natl Acad Sci U S A., 2011. 108(21): p. 8761-6. doi: 10.1073/pnas.1019338108. Epub 2011 May 9.

[44] Alcorlo, M., et al., Unique structure of iC3b resolved at a resolution of 24 A by 3D-electron microscopy. Proc Natl Acad Sci U S A., 2011. 108(32): p. 13236-40. doi: 10.1073/pnas.1106746108. Epub 2011 Jul 25.

[45] Noris, M., et al., Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol, 2010. 5(10): p. 1844-59.

[46] Moore, I., et al., Association of factor H autoantibodies with deletions of CFHR1, CFHR3, CFHR4, and with mutations in CFH, CFI, CD46, and C3 in patients with atypical hemolytic uremic syndrome. Blood, 2010. 115(2): p. 379-87.

[47] Martinez-Barricarte, R., et al., Human C3 mutation reveals a mechanism of dense deposit disease pathogenesis and provides insights into complement activation and regulation. J Clin Invest., 2010. 120(10): p. 3702-12. doi: 10.1172/JCI43343. Epub 2010 Sep 13.

[48] Hakobyan, S., et al., Variant-specific quantification of factor H in plasma identifies null alleles associated with atypical hemolytic uremic syndrome. Kidney Int., 2010. 78(8): p. 782-8. doi: 10.1038/ki.2010.275. Epub 2010 Aug 11.

[49] Goodship, T.H. and D. Kavanagh, Pulling the trigger in atypical hemolytic uremic syndrome: the role of pregnancy. J Am Soc Nephrol, 2010. 21(5): p. 731-2.

[50] Tortajada, A., et al., The disease-protective complement factor H allotypic variant Ile62 shows increased binding affinity for C3b and enhanced cofactor activity. Hum Mol Genet., 2009. 18(18): p. 3452-61. doi: 10.1093/hmg/ddp289. Epub 2009 Jun 23.

[51] Tang, Z., et al., C3a mediates epithelial-to-mesenchymal transition in proteinuric nephropathy. J Am Soc Nephrol, 2009. 20(3): p. 593-603.

[52] Montes, T., et al., Functional basis of protection against age-related macular degeneration conferred by a common

polymorphism in complement factor B. Proc Natl Acad Sci U S A., 2009. 106(11): p. 4366-71. doi: 10.1073/pnas.0812584106. Epub 2009 Mar 2.

[53] Sheerin, N.S., Should complement activation be a target for therapy in renal transplantation? J Am Soc Nephrol, 2008. 19(12): p. 2250-1.

[54] Martinez-Barricarte, R., et al., The complement factor H R1210C mutation is associated with atypical hemolytic uremic syndrome. J Am Soc Nephrol, 2008. 19(3): p. 639-46.

[55] Kavanagh, D., A. Richards, and J. Atkinson, Complement regulatory genes and hemolytic uremic syndromes. Annu Rev Med, 2008. 59: p. 293-309.

[56] Fremeaux-Bacchi, V., et al., Mutations in complement C3 predispose to development of atypical hemolytic uremic syndrome. Blood, 2008. 112(13): p. 4948-52.

[57] Fang, C.J., et al., Membrane cofactor protein mutations in atypical hemolytic uremic syndrome (aHUS), fatal Stx-HUS, C3 glomerulonephritis, and the HELLP syndrome. Blood, 2008. 111(2): p. 624-32.

[58] Zipfel, P.F., et al., Deletion of complement factor H-related genes CFHR1 and CFHR3 is associated with atypical hemolytic uremic syndrome. PLoS Genet, 2007. 3(3): p. e41.

[59] Kavanagh, D., et al., Screening for complement system abnormalities in patients with atypical hemolytic uremic syndrome. Clin J Am Soc Nephrol, 2007. 2(3): p. 591-6.

[60] Goicoechea de Jorge, E., et al., Gain-of-function mutations in complement factor B are associated with atypical hemolytic uremic syndrome. Proc Natl Acad Sci U S A., 2007. 104(1): p. 240-5. doi: 10.1073/pnas.0603420103. Epub 2006 Dec 20.

[61] Venables, J.P., et al., Atypical haemolytic uraemic syndrome associated with a hybrid complement gene. PLoS Med, 2006. 3(10): p. e431.

[62] Sheerin, N.S., et al., Accumulation of immune complexes in glomerular disease is independent of locally synthesized c3. J Am Soc Nephrol, 2006. 17(3): p. 686-96.

[63] Goodship, T.H., Atypical HUS and complement dysregulation. J Am Soc Nephrol, 2006. 17(7): p. 1775-6.

[64] Goodship, T.H., Factor H genotype-phenotype correlations: lessons from aHUS, MPGN II, and AMD. Kidney Int, 2006. 70(1): p. 12-3.

[65] Fremeaux-Bacchi, V., et al., Genetic and functional analyses of membrane cofactor protein (CD46) mutations in atypical hemolytic uremic syndrome. J Am Soc Nephrol, 2006. 17(7): p. 2017-25.

[66] Caprioli, J., et al., Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. Blood, 2006. 108(4): p. 1267-79.

[67] Bresin, E., et al., Outcome of renal transplantation in patients with non-Shiga toxin-associated hemolytic uremic syndrome: prognostic significance of genetic background. Clin J Am Soc Nephrol, 2006. 1(1): p. 88-99.

[68] Kavanagh, D., et al., Mutations in complement factor I predispose to development of atypical hemolytic uremic syndrome. J Am Soc Nephrol, 2005. 16(7): p. 2150-5.

[69] Richards, A., et al., Mutations in human complement regulator, membrane cofactor protein (CD46), predispose to development of familial hemolytic uremic syndrome. Proc Natl Acad Sci U S A, 2003. 100(22): p. 12966-71.

[70] Warwicker, P., et al., Genetic studies into inherited and sporadic hemolytic uremic syndrome. Kidney Int, 1998. 53(4): p. 836-44.

[71] Zelek, W.M., et al., Characterizing a pH-switch anti-C5 antibody as a tool for human and mouse complement C5 purification and cross-species inhibition of classical and reactive lysis. Immunology, 2018. 7(10): p. 12982.

[72] Zelek, W.M., C.L. Harris, and B.P. Morgan, Extracting the barbs from complement assays: Identification and optimisation of a safe substitute for traditional buffers. Immunobiology, 2018. 19(18): p. 30057-3.

[73] Wong, E.K.S. and D. Kavanagh, Diseases of complement dysregulation-an overview. Semin Immunopathol, 2018.

[74] Walsh, P.R., et al., Glucose-6-Phosphate Dehydrogenase Deficiency Mimicking Atypical Hemolytic Uremic Syndrome. Am J Kidney Dis, 2018. 71(2): p. 287-290.

[75] Walsh, P.R. and S. Johnson, Treatment and management of children with haemolytic uraemic syndrome. Arch Dis Child, 2018. 103(3): p. 285-291.

[76] Walsh, P.R. and S. Johnson, Eculizumab in the treatment of Shiga toxin haemolytic uraemic syndrome. Pediatr Nephrol, 2018.

[77] Teoh, C.W., et al., Clinical Relapses of Atypical HUS on Eculizumab: Clinical Gap for Monitoring and Individualised Therapy. Case Rep Nephrol, 2018. 2018: p. 2781789.

[78] Osborne, A.J., et al., Statistical Validation of Rare Complement Variants Provides Insights into the Molecular Basis of Atypical Hemolytic Uremic Syndrome and C3 Glomerulopathy. J Immunol, 2018.

[79] Morgan, B.P. and D. Kavanagh, Introduction to complement in health and disease: novel aspects and insights. Semin Immunopathol, 2018.

[80] Loveless, S., et al., Tissue microarray methodology identifies complement pathway activation and dysregulation in progressive multiple sclerosis. Brain Pathol., 2018. 28(4): p. 507-520. doi: 10.1111/bpa.12546. Epub 2017 Jul 30.

[81] Harris, C.L., et al., Developments in anti-complement therapy; from disease to clinical trial. Molecular Immunology, 2018. In press.

[82] Harris, C.L., Expanding horizons in complement drug discovery: challenges and emerging strategies. Semin Immunopathol., 2018. 40(1): p. 125-140. doi: 10.1007/s00281-017-0655-8. Epub 2017 Oct 6.

[83] Walsh, P.R., et al., Glucose-6-Phosphate Dehydrogenase Deficiency Mimicking Atypical Hemolytic Uremic Syndrome. Am J Kidney Dis, 2017.

[84] Pugh, D., et al., Interventions for atypical haemolytic uraemic syndrome. The Cochrane Library, 2017.

[85] Parikh, S.R., et al., Meningococcal B Vaccine Failure With a Penicillin-Resistant Strain in a Young Adult on Long-Term Eculizumab. Pediatrics, 2017. 140(3).

[86] Loveless, S., et al., Tissue microarray methodology identifies complement pathway activation and dysregulation in progressive multiple sclerosis. Brain Pathol, 2017. 14(10): p. 12546.

[87] Legendre, C.M., et al., Outcomes of patients with atypical haemolytic uraemic syndrome with native and transplanted kidneys treated with eculizumab: a pooled post hoc analysis. Transpl Int, 2017. 30(12): p. 1275-1283.

[88] Kerr, H., et al., Disease-linked mutations in factor H reveal pivotal role of cofactor activity in self-surface-selective regulation of complement activation. J Biol Chem, 2017. 292(32): p. 13345-13360.

[89] Hallam, D., et al., An Induced Pluripotent Stem Cell Patient Specific Model of Complement Factor H (Y402H) Polymorphism Displays Characteristic Features of Age-Related Macular Degeneration and Indicates a Beneficial Role for UV Light Exposure. Stem Cells, 2017. 35(11): p. 2305-2320.

[90] Goodship, T.H.J., et al., Use of the complement inhibitor Coversin to treat HSCT-associated TMA. Blood Adv, 2017. 1(16): p. 1254-1258.

[91] Dowen, F., et al., Rare genetic variants in Shiga toxin-associated haemolytic uraemic syndrome: genetic analysis prior to transplantation is essential. Clin Kidney J, 2017. 10(4): p. 490-493.

[92] Brocklebank, V. and D. Kavanagh, Complement C5-inhibiting therapy for the thrombotic microangiopathies: accumulating evidence, but not a panacea. Clin Kidney J, 2017. 10(5): p. 600-624.

[93] Blatt, A.Z., et al., Factor H C-Terminal Domains Are Critical for Regulation of Platelet/Granulocyte Aggregate Formation. Front Immunol, 2017. 8: p. 1586.

[94] Woodward, L., et al., An innovative and collaborative partnership between patients with rare disease and industry-

supported registries: the Global aHUS Registry. Orphanet J Rare Dis, 2016. 11(1): p. 154.

[95] Wong, E., et al., Patient stratification and therapy in atypical haemolytic uraemic syndrome (aHUS). Immunobiology, 2016. 221(6): p. 715-8.

[96] Taton, O., et al., An unusual case of haemolytic uraemic syndrome following endoscopic retrograde cholangiopancreatography rapidly improved with eculizumab. Acta Gastroenterol Belg, 2016. 79(2): p. 257-61.

[97] Sheerin, N.S., et al., A national specialized service in England for atypical haemolytic uraemic syndrome-the first year's experience. QJM, 2016. 109(1): p. 27-33.

[98] Scully, M.A. and D. Kavanagh, Thrombotic Microangiopathies. Practical Haemostasis & Thrombosis. Vol. 183-194. 2016.

[99] Riddell, A., T. Goodship, and C. Bingham, Prevention of recurrence of atypical hemolytic uremic syndrome post renal transplant with the use of higher-dose eculizumab. Clin Nephrol, 2016. 86(10): p. 200-2.

[100] Phillips, E.H., et al., The role of ADAMTS-13 activity and complement mutational analysis in differentiating acute thrombotic microangiopathies. J Thromb Haemost, 2016. 14(1): p. 175-85.

[101] Loirat, C., et al., An international consensus approach to the management of atypical hemolytic uremic syndrome in children. Pediatr Nephrol, 2016. 31(1): p. 15-39.

[102] Hakobyan, S., et al., Complement Biomarkers as Predictors of Disease Progression in Alzheimer's Disease. J Alzheimers Dis., 2016. 54(2): p. 707-16. doi: 10.3233/JAD-160420.

[103] Gleeson, P.J., et al., Chromosomal rearrangement-A rare cause of complement factor I associated atypical haemolytic uraemic syndrome. Immunobiology, 2016. 221(10): p. 1124-30.

[104] Ermini, L., et al., Systematic assessment of the influence of complement gene polymorphisms on kidney transplant outcome. Immunobiology, 2016. 221(4): p. 528-34.

[105] Zipfel, P.F., et al., The role of complement in C3 glomerulopathy. Mol Immunol, 2015. 67(1): p. 21-30.

[106] Wong, E.K. and D. Kavanagh, Anticomplement C5 therapy with eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Transl Res, 2015. 165(2): p. 306-20.

[107] Watson, R., et al., Autoantibodies to CD59, CD55, CD46 or CD35 are not associated with atypical haemolytic uraemic syndrome (aHUS). Mol Immunol, 2015. 63(2): p. 287-96.

[108] Sevinc, M., et al., Plasma resistant atypical hemolytic uremic syndrome associated with a CFH mutation treated with eculizumab: a case report. J Med Case Rep, 2015. 9: p. 92.

[109] Sei, Y., et al., Expression of membrane complement regulators, CD46, CD55 and CD59, in mesothelial cells of patients on peritoneal dialysis therapy. Mol Immunol., 2015. 65(2): p. 302-9. doi: 10.1016/j.molimm.2015.02.005. Epub 2015 Feb 25.

[110] Ring, T., et al., Use of eculizumab in crescentic IgA nephropathy: proof of principle and conundrum? Clin Kidney J, 2015. 8(5): p. 489-91.

[111] Owen, E.P., et al., A complement C5 gene mutation, c.754G>A:p.A252T, is common in the Western Cape, South Africa and found to be homozygous in seven percent of Black African meningococcal disease cases. Mol Immunol., 2015. 64(1): p. 170-6. doi: 10.1016/j.molimm.2014.11.010. Epub 2014 Dec 19.

[112] Nester, C.M., et al., Atypical aHUS: State of the art. Mol Immunol, 2015. 67(1): p. 31-42.

[113] Morgan, B.P. and C.L. Harris, Complement, a target for therapy in inflammatory and degenerative diseases. Nat Rev Drug Discov., 2015. 14(12): p. 857-77. doi: 10.1038/nrd4657. Epub 2015 Oct 23.

[114] Montgomery, E., et al., Novel compound heterozygous mutations in AMN cause Imerslund-Grasbeck syndrome in two half-sisters: a case report. BMC Med Genet, 2015. 16: p. 35.

[115] Martinez-Barricarte, R., et al., The molecular and structural bases for the association of complement C3 mutations with atypical hemolytic uremic syndrome. Mol Immunol., 2015. 66(2): p. 263-73. doi: 10.1016/j.molimm.2015.03.248. Epub 2015 Apr 11.

[116] Iqbal, Z., et al., Thrombotic Microangiopathy as a Cause of Chronic Kidney Transplant Dysfunction: Case Report Demonstrating Successful Treatment with Eculizumab. Transplant Proc, 2015. 47(7): p. 2258-61.

[117] Giles, J.L., et al., Functional analysis of a complement polymorphism (rs17611) associated with rheumatoid arthritis. J Immunol., 2015. 194(7): p. 3029-34. doi: 10.4049/jimmunol.1402956. Epub 2015 Feb 27.

[118] Giles, J.L., et al., Response to Comment on "Functional Analysis of a Complement Polymorphism (rs17611) Associated with Rheumatoid Arthritis". J Immunol., 2015. 195(1): p. 4. doi: 10.4049/jimmunol.1500968.

[119] Fearn, A. and N.S. Sheerin, Complement activation in progressive renal disease. World J Nephrol, 2015. 4(1): p. 31-40.

[120] Cullinan, N., et al., Case report: Benefits and challenges of long-term eculizumab in atypical hemolytic uremic syndrome. Pediatrics, 2015. 135(6): p. e1506-9.

[121] Scully, M. and T. Goodship, How I treat thrombotic thrombocytopenic purpura and atypical haemolytic uraemic syndrome. Br J Haematol, 2014. 164(6): p. 759-66.

[122] Sansbury, F.H., et al., Factors determining penetrance in familial atypical haemolytic uraemic syndrome. J Med Genet, 2014. 51(11): p. 756-64.

[123] Paixao-Cavalcante, D., et al., A humanized antibody that regulates the alternative pathway convertase: potential for therapy of renal disease associated with nephritic factors. J Immunol., 2014. 192(10): p. 4844-51. doi: 10.4049/jimmunol.1303131. Epub 2014 Apr 11.

[124] Kavanagh, D., S. Raman, and N.S. Sheerin, Management of hemolytic uremic syndrome. F1000Prime Rep, 2014. 6: p. 119.

[125] Kavanagh, D., Investment in research can changes lives. Journal of Renal Nursing, 2014. 6: p. 265.

[126] Johnson, S.A., E.K. Wong, and C.M. Taylor, Making sense of the spectrum of glomerular disease associated with complement dysregulation. Pediatr Nephrol, 2014. 29(10): p. 1883-94.

[127] Johnson, S., et al., An audit analysis of a guideline for the investigation and initial therapy of diarrhea negative (atypical) hemolytic uremic syndrome. Pediatr Nephrol, 2014. 29(10): p. 1967-78.

[128] Ingram, G., et al., Complement activation in multiple sclerosis plaques: an immunohistochemical analysis. Acta Neuropathol Commun., 2014. 2:53.(doi): p. 10.1186/2051-5960-2-53.

[129] Brocklebank, V., et al., Atypical haemolytic uraemic syndrome associated with a CD46 mutation triggered by Shigella flexneri. Clin Kidney J, 2014. 7(3): p. 286-288.

[130] Brocklebank, V. and D. Kavanagh, Protecting the kidney from complement: atypical haemolytic uraemic syndrome. Clin Med (Lond), 2014. 14 Suppl 6: p. s89-94.

[131] Blom, A.M., et al., A novel method for direct measurement of complement convertases activity in human serum. Clin Exp Immunol, 2014. 178(1): p. 142-53.

[132] Azukaitis, K., et al., Macrovascular involvement in a child with atypical hemolytic uremic syndrome. Pediatr Nephrol, 2014. 29(7): p. 1273-7.

[133] Wong, E.K., T.H. Goodship, and D. Kavanagh, Complement therapy in atypical haemolytic uraemic syndrome (aHUS). Mol Immunol, 2013. 56(3): p. 199-212.

[134] Wilson, V., et al., Genotype/phenotype correlations in complement factor H deficiency arising from uniparental isodisomy. Am J Kidney Dis., 2013. 62(5): p. 978-83. doi: 10.1053/j.ajkd.2013.05.020. Epub 2013 Jul 16.

[135] Sofat, R., et al., Distribution and determinants of circulating complement factor H concentration determined by a high-throughput immunonephelometric assay. J Immunol Methods, 2013. 390(1-2): p. 63-73.

[136] Reynolds, B.C., et al., One good match permits another-why

HLA-matched blood transfusion makes sense. Clin Kidney J, 2013. 6(4): p. 452.

[137] Malina, M., et al., Peripheral gangrene in children with atypical hemolytic uremic syndrome. Pediatrics, 2013. 131(1): p. e331-5.

[138] Kavanagh, D., T.H. Goodship, and A. Richards, Atypical hemolytic uremic syndrome. Semin Nephrol, 2013. 33(6): p. 508-30.

[139] Holmes, L.V., et al., Determining the population frequency of the CFHR3/CFHR1 deletion at 1q32. PLoS One, 2013. 8(4): p. e60352.

[140] Hamilton, A.J., et al., Prevalence in the General Population of a CFH Sequence Variant Associated with Atypical Haemolytic Uraemic Syndrome in an Extensive Family from Southwest England. Nephron Extra, 2013. 3(1): p. 86-90.

[141] Gustafsson, M.C., et al., Factor H binds to the hypervariable region of many Streptococcus pyogenes M proteins but does not promote phagocytosis resistance or acute virulence. PLoS Pathog, 2013. 9(4): p. e1003323. doi: 10.1371/journal.ppat.1003323. Epub 2013 Apr 18.

[142] Gilbert, R.D., et al., Cisplatin-induced haemolytic uraemic syndrome associated with a novel intronic mutation of CD46 treated with eculizumab. Clin Kidney J, 2013. 6(4): p. 421-425.

[143] Gilbert, R.D., et al., Eculizumab therapy for atypical haemolytic uraemic syndrome due to a gain-of-function mutation of complement factor B. Pediatr Nephrol, 2013. 28(8): p. 1315-8.

[144] Gandhi, V., A. Burns, and T. Goodship, A complementary component to atypical haemolytic uraemic syndrome. BMJ Case Rep, 2013. 2013.

[145] Forbes, T.A., et al., Changing strategies for organ transplantation in atypical haemolytic uraemic syndrome: a tertiary case series. Pediatr Transplant, 2013. 17(3): p. E93-9.

[146] Adriani, K.S., et al., Common polymorphisms in the complement system and susceptiblity to bacterial meningitis. J Infect., 2013. 66(3): p. 255-62. doi: 10.1016/j.jinf.2012.10.008. Epub 2012 Oct 13.

[147] Abdel-Salam, F., et al., Suspected pheochromocytoma in a patient with Guillain-Barre syndrome. Pediatrics, 2013. 131(3): p. e955-8.

[148] Provaznikova, D., et al., Manifestation of atypical hemolytic uremic syndrome caused by novel mutations in MCP. Pediatr Nephrol, 2012. 27(1): p. 73-81.

[149] Mizuno, M., et al., Membrane complement regulators protect against fibrin exudation increases in a severe peritoneal inflammation model in rats. Am J Physiol Renal Physiol., 2012. 302(10): p. F1245-51. doi: 10.1152/ajprenal.00652.2011. Epub 2012 Feb 15.

[150] Malina, M., et al., Genetics of hemolytic uremic syndromes. Presse Med, 2012. 41(3 Pt 2): p. e105-14.

[151] Kempshall, E., et al., Complement-induced protection: an explanation for the limitations of cell-based tumour immunotherapies. Immunol Cell Biol., 2012. 90(9): p. 869-71. doi: 10.1038/icb.2012.30. Epub 2012 Jul 10.

[152] Johnson, S. and A. Waters, Is complement a culprit in infection-induced forms of haemolytic uraemic syndrome? Immunobiology, 2012. 217(2): p. 235-43.

[153] Ingram, G., et al., Systemic complement profiling in multiple sclerosis as a biomarker of disease state. Mult Scler., 2012. 18(10): p. 1401-11. doi: 10.1177/1352458512438238. Epub 2012 Feb 21.

[154] Herbert, A.P., et al., Structural and functional characterization of the product of disease-related factor H gene conversion. Biochemistry, 2012. 51(9): p. 1874-84.

[155] Harris, C.L., et al., The complotype: dictating risk for inflammation and infection. Trends Immunol., 2012. 33(10): p. 513-21. doi: 10.1016/j.it.2012.06.001. Epub 2012 Jun 29.

[156] Goodship, T.H., et al., Factor H autoantibodies in membranoproliferative glomerulonephritis. Mol Immunol, 2012. 52(3-4): p. 200-6.

[157] Gibson, J., et al., Variation in complement component C1 inhibitor in age-related macular degeneration. Immunobiology., 2012. 217(2): p. 251-5. doi: 10.1016/j.imbio.2011.07.015. Epub 2011 Jul 23.

[158] Ermini, L., et al., Complement polymorphisms: geographical distribution and relevance to disease. Immunobiology, 2012. 217(2): p. 265-71.

[159] Ermini, L., et al., Common genetic variants in complement genes other than CFH, CD46 and the CFHRs are not associated with aHUS. Mol Immunol, 2012. 49(4): p. 640-8.

[160] de Cordoba, S.R., et al., Complement dysregulation and disease: from genes and proteins to diagnostics and drugs. Immunobiology., 2012. 217(11): p. 1034-46. doi: 10.1016/j.imbio.2012.07.021.

[161] Brown, J.H., et al., Postpartum aHUS secondary to a genetic abnormality in factor H acquired through liver transplantation. Am J Transplant., 2012. 12(6): p. 1632-6. doi: 10.1111/j.1600-6143.2012.03991.x. Epub 2012 Mar 15.

[162] Barbour, T., et al., Thrombotic microangiopathy and associated renal disorders. Nephrol Dial Transplant, 2012. 27(7): p. 2673-85.

[163] Wilson, C.H., et al., Successful treatment of de novo posttransplant thrombotic microangiopathy with eculizumab. Transplantation, 2011. 92(8): p. e42-3.

[164] Wilson, C., et al., Successful simultaneous liver-kidney transplant in an adult with atypical hemolytic uremic syndrome associated with a mutation in complement factor H. Am J Kidney Dis, 2011. 58(1): p. 109-12.

[165] Smith, R.J., C.L. Harris, and M.C. Pickering, Dense deposit disease. Mol Immunol., 2011. 48(14): p. 1604-10. doi: 10.1016/j.molimm.2011.04.005. Epub 2011 May 24.

[166] Roversi, P., et al., Structures of the rat complement regulator CrrY. Acta Crystallogr Sect F Struct Biol Cryst Commun., 2011. 67(Pt 7): p. 739-43. doi: 10.1107/S1744309111016551. Epub 2011 Jun 23.

[167] Rodriguez de Cordoba, S., et al., Lessons from functional and structural analyses of disease-associated genetic variants in the complement alternative pathway. Biochim Biophys Acta., 2011. 1812(1): p. 12-22. doi: 10.1016/j.bbadis.2010.09.002. Epub 2010 Sep 16.

[168] Pechtl, I.C., et al., Disease-associated N-terminal complement factor H mutations perturb cofactor and decay-accelerating activities. J Biol Chem, 2011. 286(13): p. 11082-90.

[169] Morgan, H.P., et al., Crystallographic determination of the disease-associated T1184R variant of complement regulator factor H. Acta Crystallogr D Biol Crystallogr, 2011. 67(Pt 7): p. 593-600.

[170] Kim, J.J., et al., Plasma therapy for atypical haemolytic uraemic syndrome associated with heterozygous factor H mutations. Pediatr Nephrol, 2011. 26(11): p. 2073-6.

[171] Kavanagh, D. and T.H. Goodship, Atypical hemolytic uremic syndrome, genetic basis, and clinical manifestations. Hematology Am Soc Hematol Educ Program, 2011. 2011: p. 15-20.

[172] Kavanagh, D. and T. Goodship, Haemolytic uraemic syndrome. Nephron Clin Pract, 2011. 118(1): p. c37-42.

[173] Davin, J.C., et al., Prevention of large-vessel stenoses in atypical hemolytic uremic syndrome associated with complement dysregulation. Pediatr Nephrol, 2011. 26(1): p. 155-7.

[174] Waters, A.M., et al., Successful renal transplantation in factor H autoantibody associated HUS with CFHR1 and 3 deficiency and CFH variant G2850T. Am J Transplant, 2010. 10(1): p. 168-72.

[175] Taylor, C.M., et al., Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. Br J Haematol, 2010. 148(1): p. 37-47.

[176] Manickam, B., et al., Suppression of complement activation by recombinant Crry inhibits experimental autoimmune anterior uveitis (EAAU). Mol Immunol., 2010. 48(1-3): p. 231-9. doi: 10.1016/j.molimm.2010.08.006. Epub 2010 Sep 16.

[177] Loirat, C., et al., Non-atheromatous arterial stenoses in atypical haemolytic uraemic syndrome associated with complement dysregulation. Nephrol Dial Transplant, 2010. 25(10): p. 3421-5.

[178] Kavanagh, D., et al., Transplantation in atypical hemolytic

uremic syndrome. Semin Thromb Hemost, 2010. 36(6): p. 653-9.
[179] Kavanagh, D. and T.H. Goodship, Atypical hemolytic uremic syndrome. Curr Opin Hematol, 2010. 17(5): p. 432-8.
[180] Kavanagh, D. and T. Goodship, Genetics and complement in atypical HUS. Pediatr Nephrol, 2010. 25(12): p. 2431-42.
[181] Karpman, D., L. Sartz, and S. Johnson, Pathophysiology of typical hemolytic uremic syndrome. Semin Thromb Hemost, 2010. 36(6): p. 575-85.
[182] Johnson, S.A., et al., Impact of compound heterozygous complement factor H mutations on development of atypical hemolytic uremic syndrome-A pedigree revisited. Mol Immunol, 2010. 47(7-8): p. 1585-91.
[183] Ingram, G., et al., Complement regulator factor H as a serum biomarker of multiple sclerosis disease state. Brain., 2010. 133(Pt 6): p. 1602-11. doi: 10.1093/brain/awq085. Epub 2010 Apr 25.
[184] Haller, W., et al., Successful isolated liver transplantation in a child with atypical hemolytic uremic syndrome and a mutation in complement factor H. Am J Transplant, 2010. 10(9): p. 2142-7.
[185] Dhillon, B., et al., Complement factor h autoantibodies and age-related macular degeneration. Invest Ophthalmol Vis Sci, 2010. 51(11): p. 5858-63.
[186] Davin, J.C., et al., Maintenance of kidney function following treatment with eculizumab and discontinuation of plasma exchange after a third kidney transplant for atypical hemolytic uremic syndrome associated with a CFH mutation. Am J Kidney Dis, 2010. 55(4): p. 708-11.
[187] Bento, D., et al., Triggering of atypical hemolytic uremic syndrome by influenza A (H1N1). Ren Fail, 2010. 32(6): p. 753-6.
[188] Ruseva, M.M., et al., Crry deficiency in complement sufficient mice: C3 consumption occurs without associated renal injury. Mol Immunol., 2009. 46(5): p. 803-11. doi: 10.1016/j.molimm.2008.09.003. Epub 2008 Oct 22.
[189] Richards, A. and D. Kavanagh, Pathogenesis of thrombotic microangiopathy: insights from animal models. Nephron Exp Nephrol, 2009. 113(4): p. e97-103.
[190] Mizuno, M., et al., Zymosan, but not lipopolysaccharide, triggers severe and progressive peritoneal injury accompanied by complement activation in a rat peritonitis model. J Immunol., 2009. 183(2): p. 1403-12. doi: 10.4049/jimmunol.0804245. Epub 2009 Jun 24.
[191] Hughes, T.R., et al., Identification of the high affinity binding site in the Streptococcus intermedius toxin intermedilysin for its membrane receptor, the human complement regulator CD59. Mol Immunol., 2009. 46(7): p. 1561-7. doi: 10.1016/j.molimm.2009.01.003. Epub 2009 Feb 6.
[192] Ferreira, V.P., et al., The binding of factor H to a complex of physiological polyanions and C3b on cells is impaired in atypical hemolytic uremic syndrome. J Immunol, 2009. 182(11): p. 7009-18.
[193] Edey, M., et al., Is complement factor H a susceptibility factor for IgA nephropathy? Mol Immunol, 2009. 46(7): p. 1405-8.
[194] Davin, J.C., et al., Prophylactic plasma exchange in CD46-associated atypical haemolytic uremic syndrome. Pediatr Nephrol, 2009. 24(9): p. 1757-60.
[195] Ariceta, G., et al., Guideline for the investigation and initial therapy of diarrhea-negative hemolytic uremic syndrome. Pediatr Nephrol, 2009. 24(4): p. 687-96.
[196] Sheerin, N.S., et al., Synthesis of complement protein C3 in the kidney is an important mediator of local tissue injury. FASEB J, 2008. 22(4): p. 1065-72.
[197] Schmidt, C.Q., et al., A new map of glycosaminoglycan and C3b binding sites on factor H. J Immunol, 2008. 181(4): p. 2610-9.
[198] Li, K., S.H. Sacks, and N.S. Sheerin, The classical complement pathway plays a critical role in the opsonisation of uropathogenic Escherichia coli. Mol Immunol, 2008. 45(4): p. 954-62.
[199] Lapeyraque, A.L., et al., Efficacy of plasma therapy in atypical hemolytic uremic syndrome with complement factor H mutations. Pediatr Nephrol, 2008. 23(8): p. 1363-6.
[200] Kavanagh, D., et al., Characterization of mutations in complement factor I (CFI) associated with hemolytic uremic syndrome. Mol Immunol, 2008. 45(1): p. 95-105.
[201] Johnson, S. and C.M. Taylor, What's new in haemolytic uraemic syndrome? Eur J Pediatr, 2008. 167(9): p. 965-71.
[202] Hocking, H.G., et al., Structure of the N-terminal region of complement factor H and conformational implications of disease-linked sequence variations. J Biol Chem, 2008. 283(14): p. 9475-87.
[203] Hepburn, N.J., et al., Complement, roles in renal disease and modulation for therapy. Clin Nephrol., 2008. 70(5): p. 357-76.
[204] Hepburn, N.J., et al., Prevention of experimental autoimmune myasthenia gravis by rat Crry-Ig: A model agent for long-term complement inhibition in vivo. Mol Immunol., 2008. 45(2): p. 395-405. doi: 10.1016/j.molimm.2007.06.144. Epub 2007 Jul 24.
[205] Hakobyan, S., et al., Complement factor H binds to denatured rather than to native pentameric C-reactive protein. J Biol Chem., 2008. 283(45): p. 30451-60. doi: 10.1074/jbc.M803648200. Epub 2008 Sep 11.
[206] Hakobyan, S., et al., Measurement of factor H variants in plasma using variant-specific monoclonal antibodies: application to assessing risk of age-related macular degeneration. Invest Ophthalmol Vis Sci., 2008. 49(5): p. 1983-90. doi: 10.1167/iovs.07-1523.
[207] Fang, C.J., et al., Advances in understanding of pathogenesis of aHUS and HELLP. Br J Haematol, 2008. 143(3): p. 336-48.
[208] Edey, M.M., et al., Association of a factor H mutation with hemolytic uremic syndrome following a diarrheal illness. Am J Kidney Dis, 2008. 51(3): p. 487-90.
[209] Davin, J.C., L. Strain, and T.H. Goodship, Plasma therapy in atypical haemolytic uremic syndrome: lessons from a family with a factor H mutation. Pediatr Nephrol, 2008. 23(9): p. 1517-21.
[210] Blom, A.M., et al., A novel non-synonymous polymorphism (p.Arg240His) in C4b-binding protein is associated with atypical hemolytic uremic syndrome and leads to impaired alternative pathway cofactor activity. J Immunol, 2008. 180(9): p. 6385-91.
[211] Saunders, R.E., et al., The interactive Factor H-atypical hemolytic uremic syndrome mutation database and website: update and integration of membrane cofactor protein and Factor I mutations with structural models. Hum Mutat, 2007. 28(3): p. 222-34.
[212] Richards, A., D. Kavanagh, and J.P. Atkinson, Inherited complement regulatory protein deficiency predisposes to human disease in acute injury and chronic inflammatory statesthe examples of vascular damage in atypical hemolytic uremic syndrome and debris accumulation in age-related macular degeneration. Adv Immunol, 2007. 96: p. 141-77.
[213] Richards, A., et al., Implications of the initial mutations in membrane cofactor protein (MCP; CD46) leading to atypical hemolytic uremic syndrome. Mol Immunol, 2007. 44(1-3): p. 111-22.
[214] Mizuno, M., C.L. Harris, and B.P. Morgan, Immunization with autologous CD46 generates a strong autoantibody response in rats that targets spermatozoa. J Reprod Immunol., 2007. 73(2): p. 135-147. doi: 10.1016/j.jri.2006.08.001. Epub 2006 Sep 6.
[215] Mizuno, M., et al., CD55 in rat male reproductive tissue: differential expression in testis and expression of a unique truncated isoform on spermatozoa. Mol Immunol., 2007. 44(7): p. 1613-22. doi: 10.1016/j.molimm.2006.08.018. Epub 2006 Sep 27.
[216] Liszewski, M.K., et al., Modeling how CD46 deficiency predisposes to atypical hemolytic uremic syndrome. Mol Immunol, 2007. 44(7): p. 1559-68.
[217] Li, B., et al., Combined yeast {beta}-glucan and antitumor monoclonal antibody therapy requires C5a-mediated neutrophil

chemotaxis via regulation of decay-accelerating factor CD55. Cancer Res., 2007. 67(15): p. 7421-30. doi: 10.1158/0008-5472.CAN-07-1465.

[218] Kavanagh, D. and T.H. Goodship, Update on evaluating complement in hemolytic uremic syndrome. Curr Opin Nephrol Hypertens, 2007. 16(6): p. 565-71.

[219] Kavanagh, D., et al., The decay accelerating factor mutation I197V found in hemolytic uraemic syndrome does not impair complement regulation. Mol Immunol, 2007. 44(12): p. 3162-7.

[220] Karpman, D., et al., Anguish over angiopathy: hemolytic uremic syndrome. Clin Immunol, 2007. 122(2): p. 135-8.

[221] Jokiranta, T.S., et al., Where next with atypical hemolytic uremic syndrome? Mol Immunol, 2007. 44(16): p. 3889-900.

[222] Johnson, S., et al., End-stage renal failure in adolescence with Sjogren's syndrome autoantibodies SSA and SSB. Pediatr Nephrol, 2007. 22(10): p. 1793-7.

[223] Hepburn, N.J., et al., In vivo characterization and therapeutic efficacy of a C5-specific inhibitor from the soft tick Ornithodoros moubata. J Biol Chem., 2007. 282(11): p. 8292-9. doi: 10.1074/jbc.M609858200. Epub 2007 Jan 10.

[224] Harris, C.L., et al., Decay-accelerating factor must bind both components of the complement alternative pathway C3 convertase to mediate efficient decay. J Immunol., 2007. 178(1): p. 352-9.

[225] Brown, K.M., S.H. Sacks, and N.S. Sheerin, Mechanisms of disease: the complement system in renal injury--new ways of looking at an old foe. Nat Clin Pract Nephrol, 2007. 3(5): p. 277-86.

[226] Bora, N.S., et al., CD59, a complement regulatory protein, controls choroidal neovascularization in a mouse model of wet-type age-related macular degeneration. J Immunol., 2007. 178(3): p. 1783-90.

[227] Atkinson, J.P. and T.H. Goodship, Complement factor H and the hemolytic uremic syndrome. J Exp Med, 2007. 204(6): p. 1245-8.

[228] Spendlove, I., et al., Complement decay accelerating factor (DAF)/CD55 in cancer. Cancer Immunol Immunother., 2006. 55(8): p. 987-95. doi: 10.1007/s00262-006-0136-8. Epub 2006 Feb 17.

[229] Saunders, R.E., et al., An interactive web database of factor H-associated hemolytic uremic syndrome mutations: insights into the structural consequences of disease-associated mutations. Hum Mutat, 2006. 27(1): p. 21-30.

[230] Saland, J.M., et al., Favorable long-term outcome after liver-kidney transplant for recurrent hemolytic uremic syndrome associated with a factor H mutation. Am J Transplant, 2006. 6(8): p. 1948-52.

[231] Morgan, B.P., et al., The membrane attack pathway of complement drives pathology in passively induced experimental autoimmune myasthenia gravis in mice. Clin Exp Immunol., 2006. 146(2): p. 294-302. doi: 10.1111/j.1365-2249.2006.03205.x.

[232] Mizuno, M., C.L. Harris, and B.P. Morgan, Spermatogenic cells distal to the blood-testis barrier in rats lack C3 convertase regulators and may be at risk of complement-mediated injury. J Reprod Immunol., 2006. 69(1): p. 23-34. doi: 10.1016/j.jri.2005.11.002. Epub 2005 Dec 27.

[233] Longhi, M.P., et al., Holding T cells in check--a new role for complement regulators? Trends Immunol., 2006. 27(2): p. 102-8. doi: 10.1016/j.it.2005.12.008. Epub 2006 Jan 10.

[234] Lin, T., et al., Deficiency of C4 from donor or recipient mouse fails to prevent renal allograft rejection. Am J Pathol, 2006. 168(4): p. 1241-8.

[235] Li, K., et al., CD46 (membrane cofactor protein) acts as a human epithelial cell receptor for internalization of opsonized uropathogenic Escherichia coli. J Immunol, 2006. 177(4): p. 2543-51.

[236] Kavanagh, D., et al., Does complement factor B have a role in the pathogenesis of atypical HUS? Mol Immunol, 2006. 43(7): p. 856-9.

[237] Kavanagh, D., T.H. Goodship, and A. Richards, Atypical haemolytic uraemic syndrome. Br Med Bull, 2006. 77-78: p. 5-22.

[238] Kavanagh, D. and T.H. Goodship, Membrane cofactor protein and factor I: mutations and transplantation. Semin Thromb Hemost, 2006. 32(2): p. 155-9.

[239] Kavanagh, D. and T. Goodship, Haemolytic Uraemic Syndrome. Horizons in Medicine. Vol. 18. 2006.

[240] Heinen, S., et al., De novo gene conversion in the RCA gene cluster (1q32) causes mutations in complement factor H associated with atypical hemolytic uremic syndrome. Hum Mutat, 2006. 27(3): p. 292-3.

[241] Harris, C.L., M. Mizuno, and B.P. Morgan, Complement and complement regulators in the male reproductive system. Mol Immunol., 2006. 43(1-2): p. 57-67. doi: 10.1016/j.molimm.2005.06.026.

[242] Hageman, G.S., et al., Extended haplotypes in the complement factor H (CFH) and CFH-related (CFHR) family of genes protect against age-related macular degeneration: Characterization, ethnic distribution and evolutionary implications. Ann Med, 2006. 38(8): p. 592-604.

[243] Davin, J.C., et al., Complement factor H-associated atypical hemolytic uremic syndrome in monozygotic twins: concordant presentation, discordant response to treatment. Am J Kidney Dis, 2006. 47(2): p. e27-30.

[244] Chamberlain-Banoub, J., et al., Complement membrane attack is required for endplate damage and clinical disease in passive experimental myasthenia gravis in Lewis rats. Clin Exp Immunol., 2006. 146(2): p. 278-86. doi: 10.1111/j.1365-2249.2006.03198.x.

[245] Wenzel, K., et al., Increased susceptibility to complement attack due to down-regulation of decay-accelerating factor/CD55 in dysferlin-deficient muscular dystrophy. J Immunol., 2005. 175(9): p. 6219-25.

[246] van Beek, J., et al., Decay-accelerating factor (CD55) is expressed by neurons in response to chronic but not acute autoimmune central nervous system inflammation associated with complement activation. J Immunol., 2005. 174(4): p. 2353-65.

[247] Morgan, B.P., et al., Complement: central to innate immunity and bridging to adaptive responses. Immunol Lett., 2005. 97(2): p. 171-9. doi: 10.1016/j.imlet.2004.11.010. Epub 2004 Dec 7.

[248] Morgan, B.P., C.W. Berg, and C.L. Harris, ''Homologous restriction" in complement lysis: roles of membrane complement regulators. Xenotransplantation., 2005. 12(4): p. 258-65. doi: 10.1111/j.1399-3089.2005.00237.x.

[249] Mizuno, M., et al., Expression of CD46 in developing rat spermatozoa: ultrastructural localization and utility as a marker of the various stages of the seminiferous tubuli. Biol Reprod., 2005. 72(4): p. 908-15. doi: 10.1095/biolreprod.104.035485. Epub 2004 Dec 15.

[250] Kemp, E.J., et al., The development of atypical hemolytic uremic syndrome is not influenced by thrombophilia susceptibility factors. J Thromb Haemost, 2005. 3(9): p. 2128-30.

[251] Harris, C.L., et al., Molecular dissection of interactions between components of the alternative pathway of complement and decay accelerating factor (CD55). J Biol Chem., 2005. 280(4): p. 2569-78. doi: 10.1074/jbc.M410179200. Epub 2004 Nov 9.

[252] Fremeaux-Bacchi, V., et al., The development of atypical haemolytic-uraemic syndrome is influenced by susceptibility factors in factor H and membrane cofactor protein: evidence from two independent cohorts. J Med Genet, 2005. 42(11): p. 852-6.

[253] Elward, K., et al., CD46 plays a key role in tailoring innate immune recognition of apoptotic and necrotic cells. J Biol Chem., 2005. 280(43): p. 36342-54. doi: 10.1074/jbc.M506579200. Epub 2005 Aug 8.

[254] Davies, C.S., C.L. Harris, and B.P. Morgan, Glycation of CD59 impairs complement regulation on erythrocytes from diabetic subjects. Immunology., 2005. 114(2): p. 280-6. doi: 10.1111/j.1365-2567.2004.02086.x.

[255] Atkinson, J.P., et al., Hemolytic uremic syndrome: an example of insufficient complement regulation on self-tissue. Ann N Y Acad Sci, 2005. 1056: p. 144-52.

[256] Pirson, Y., et al., Familial hemolytic uremic syndrome: a privileged observation. Bull Mem Acad R Med Belg, 2004. 159(Pt 2): p. 191-4.

[257] Olie, K.H., et al., Atypical relapse of hemolytic uremic syndrome after transplantation. Pediatr Nephrol, 2004. 19(10): p. 1173-6.

[258] Goodship, T.H., et al., Mutations in CD46, a complement regulatory protein, predispose to atypical HUS. Trends Mol Med, 2004. 10(5): p. 226-31.

[259] Goodship, T., Inherited dysregulation of the complement system. Bull Mem Acad R Med Belg, 2004. 159(Pt 2): p. 195-8.

[260] Filler, G., et al., Challenges in the management of infantile factor H associated hemolytic uremic syndrome. Pediatr Nephrol, 2004. 19(8): p. 908-11.

[261] Baalasubramanian, S., et al., CD59a is the primary regulator of membrane attack complex assembly in the mouse. J Immunol., 2004. 173(6): p. 3684-92.

[262] Morgan, B.P. and C.L. Harris, Complement therapeutics; history and current progress. Mol Immunol., 2003. 40(2-4): p. 159-70.

[263] Harris, C.L., et al., Generation of anti-complement "prodrugs": cleavable reagents for specific delivery of complement regulators to disease sites. J Biol Chem., 2003. 278(38): p. 36068-76. doi: 10.1074/jbc.M306351200. Epub 2003 Jul 3.

[264] Harris, C.L., et al., Characterization of the mouse analogues of CD59 using novel monoclonal antibodies: tissue distribution and functional comparison. Immunology., 2003. 109(1): p. 117-26.

[265] Fraser, D.A., et al., Generation of a recombinant, membrane-targeted form of the complement regulator CD59: activity in vitro and in vivo. J Biol Chem., 2003. 278(49): p. 48921-7. doi: 10.1074/jbc.M302598200. Epub 2003 Sep 30.

[266] Clayton, A., et al., Antigen-presenting cell exosomes are protected from complement-mediated lysis by expression of CD55 and CD59. Eur J Immunol., 2003. 33(2): p. 522-31. doi: 10.1002/immu.200310028.

[267] Ahmad, S.R., et al., Decay-accelerating factor induction by tumour necrosis factor-alpha, through a phosphatidylinositol-3 kinase and protein kinase C-dependent pathway, protects murine vascular endothelial cells against complement deposition. Immunology., 2003. 110(2): p. 258-68.

[268] Richards, A., J.A. Goodship, and T.H. Goodship, The genetics and pathogenesis of haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura. Curr Opin Nephrol Hypertens, 2002. 11(4): p. 431-5.

[269] Perkins, S.J. and T.H. Goodship, Molecular modelling of the C-terminal domains of factor H of human complement: a correlation between haemolytic uraemic syndrome and a predicted heparin binding site. J Mol Biol, 2002. 316(2): p. 217-24.

[270] Perkins, S.J., et al., Solution structures of complement components by X-ray and neutron scattering and analytical ultracentrifugation. Biochem Soc Trans, 2002. 30(Pt 6): p. 996-1001.

[271] Johnson, S.A., et al., Primary hyperoxaluria type 2 in children. Pediatr Nephrol, 2002. 17(8): p. 597-601.

[272] Harris, C.L., et al., Coupling complement regulators to immunoglobulin domains generates effective anti-complement reagents with extended half-life in vivo. Clin Exp Immunol., 2002. 129(2): p. 198-207.

[273] Harris, C.L., D.M. Lublin, and B.P. Morgan, Efficient generation of monoclonal antibodies for specific protein domains using recombinant immunoglobulin fusion proteins: pitfalls and solutions. J Immunol Methods., 2002. 268(2): p. 245-58.

[274] Harris, C.L., D.A. Fraser, and B.P. Morgan, Tailoring anti-complement therapeutics. Biochem Soc Trans., 2002. 30(Pt 6): p. 1019-26. doi: 10.1042/.

[275] Fraser, D.A., et al., Bacterial expression and membrane targeting of the rat complement regulator Crry: a new model anticomplement therapeutic. Protein Sci., 2002. 11(10): p. 2512-21. doi: 10.1110/ps.0212402.

[276] Donne, R.L., et al., Recurrence of hemolytic uremic syndrome after live related renal transplantation associated with subsequent de novo disease in the donor. Am J Kidney Dis, 2002. 40(6): p. E22.

[277] Stoiber, H., et al., Enhancement of complement-mediated lysis by a peptide derived from SCR 13 of complement factor H. Immunobiology., 2001. 203(4): p. 670-86.

[278] Miwa, T., et al., Characterization of glycosylphosphatidylinositol-anchored decay accelerating factor (GPI-DAF) and transmembrane DAF gene expression in wild-type and GPI-DAF gene knockout mice using polyclonal and monoclonal antibodies with dual or single specificity. Immunology., 2001. 104(2): p. 207-14.

[279] Maeda, Y., et al., PIG-M transfers the first mannose to glycosylphosphatidylinositol on the lumenal side of the ER. EMBO J., 2001. 20(1-2): p. 250-61. doi: 10.1093/emboj/20.1.250.

[280] Lin, F., et al., Tissue distribution of products of the mouse decay-accelerating factor (DAF) genes. Exploitation of a Daf1 knock-out mouse and site-specific monoclonal antibodies. Immunology., 2001. 104(2): p. 215-25.

[281] Harris, C.L., et al., The lipopolysaccharide co-receptor CD14 is present and functional in seminal plasma and expressed on spermatozoa. Immunology., 2001. 104(3): p. 317-23.

[282] Perez de la Lastra, J.M., et al., Pigs express multiple forms of decay-accelerating factor (CD55), all of which contain only three short consensus repeats. J Immunol., 2000. 165(5): p. 2563-73.

[283] Harris, C.L., O.B. Spiller, and B.P. Morgan, Human and rodent decay-accelerating factors (CD55) are not species restricted in their complement-inhibiting activities. Immunology., 2000. 100(4): p. 462-70.

[284] Harris, C.L., Functional assays for complement regulators. Methods Mol Biol, 2000. 150:83-101.(doi): p. 10.1385/1-59259-056-X:83.

[285] Warwicker, P., et al., Familial relapsing haemolytic uraemic syndrome and complement factor H deficiency. Nephrol Dial Transplant, 1999. 14(5): p. 1229-33.

[286] Spiller, O.B., C.L. Harris, and B.P. Morgan, Efficient generation of monoclonal antibodies against surface-expressed proteins by hyperexpression in rodent cells. J Immunol Methods., 1999. 224(1-2): p. 51-60.

[287] Harris, C.L., N.K. Rushmere, and B.P. Morgan, Molecular and functional analysis of mouse decay accelerating factor (CD55). Biochem J., 1999. 341(Pt 3): p. 821-9.

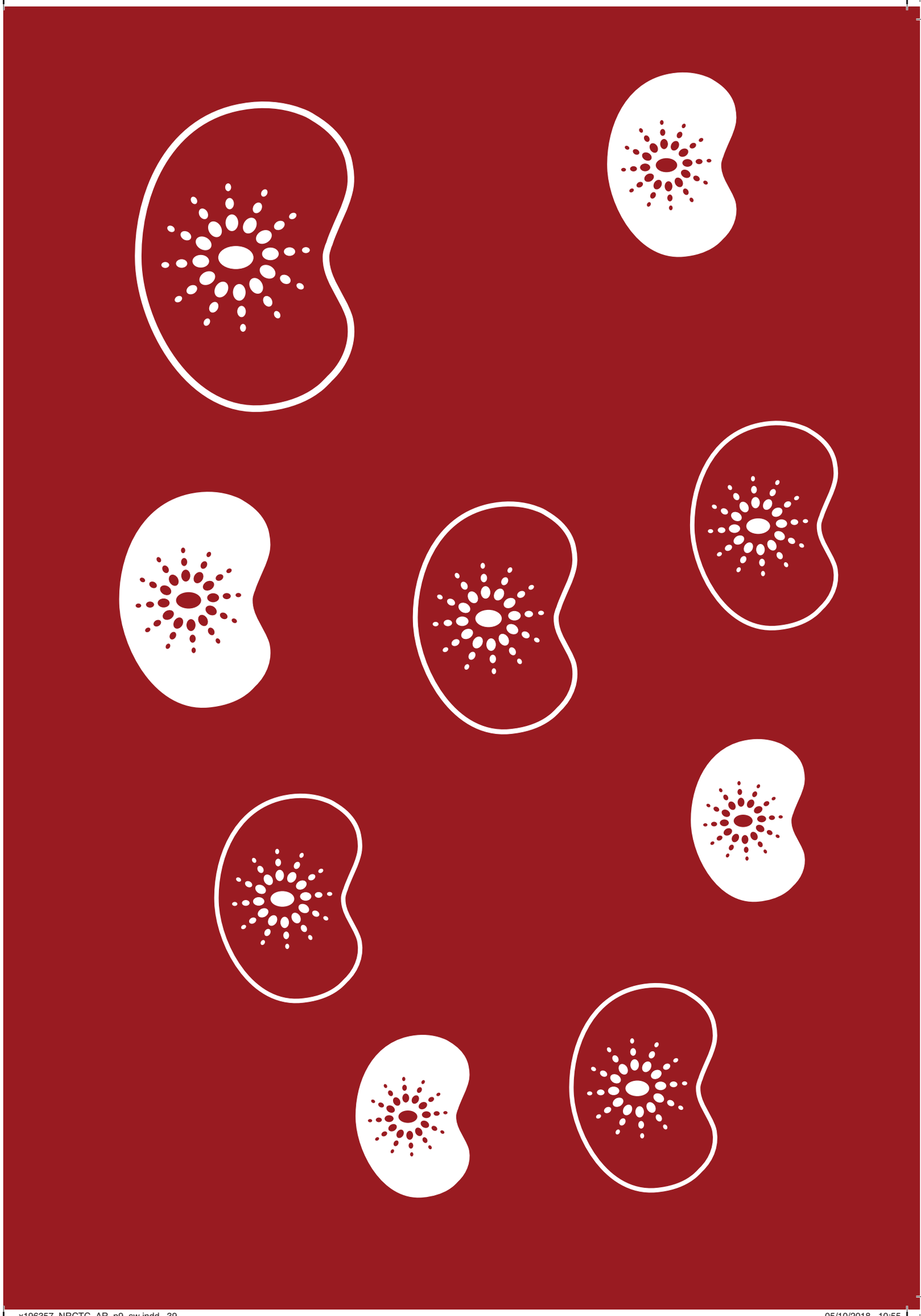
[288] Warwicker, P., J.A. Goodship, and T.H. Goodship, Factor H--US? Nephrol Dial Transplant, 1998. 13(8): p. 1921-3.

[289] Morgan, B.P., N.K. Rushmere, and C.L. Harris, Therapeutic uses of recombinant complement receptors. Biochem Soc Trans., 1998. 26(1): p. 49-54.

[290] Blok, V.T., et al., A bispecific monoclonal antibody directed against both the membrane-bound complement regulator CD55 and the renal tumor-associated antigen G250 enhances C3 deposition and tumor cell lysis by complement. J Immunol., 1998. 160(7): p. 3437-43.

[291] Harris, C.L., et al., Tumour cell killing using chemically engineered antibody constructs specific for tumour cells and the complement inhibitor CD59. Clin Exp Immunol., 1997. 107(2): p. 364-71.

[292] Harris, C.L. and B.P. Morgan, Characterization of a glycosyl-phosphatidylinositol anchor-deficient subline of Raji cells. An analysis of the functional importance of complement inhibitors on the Raji cell line. Immunology., 1995. 86(2): p. 311-8.



National Renal Complement Therapeutics Centre
Building 26, Royal Victoria Infirmary,
Queen Victoria Road, Newcastle upon Tyne NE1 4LP

Tel: **0191 282 0385**
www.atypicalhus.co.uk

ISBN 978-1-5272-3218-1