E13/S(HSS)/c

2013/14 NHS STANDARD CONTRACT
FOR DIAGNOSTIC SERVICE FOR AMYLOIDOSIS (ALL AGES)

PARTICULARS, SCHEDULE 2- THE SERVICES, A- SERVICE SPECIFICATIONS

Service Specification No.	E13/S(HSS)/c
Service	Diagnostic Service for Amyloidosis (All Ages)
Commissioner Lead	
Provider Lead	
Period	12 months
Date of Review	

1. Population Needs

1.1 National/local context and evidence base

Amyloidosis is a disorder of protein folding in which normally soluble blood proteins are deposited in the extracellular space as insoluble fibrils that progressively disrupt tissue structure and function and lead to vital organ failure and death within a few years. Amyloid deposition is remarkable in its diversity; it can affect one or many organs, be acquired or hereditary, and be life-threatening or merely an incidental pathological finding. There are many different types of amyloidosis, the commonest of which, are associated with chronic inflammatory diseases (e.g. rheumatoid arthritis), haematological diseases (e.g. myeloma), and old age respectively.

Symptoms are extremely variable and amyloidosis remains difficult to diagnose. There are no specific treatments other than treatment of the associated underlying disorder, but advances in understanding the pathogenesis of the disease have led to improved diagnosis, and better supportive care including haemodialysis and solid organ transplantation. These combined with aggressive treatment of underlying disorders have significantly improved the prognosis in recent years.

The inherited periodic fever syndromes, also known as autoinflammatory diseases, are disorders of innate immunity that cause recurrent bouts of seemingly spontaneous systemic inflammation and fever, and ultimately lead to early death through AA amyloidosis in about 25% of cases. Features include rashes, arthritis, inflammation of the eye, brain, and other vital organs. There has been much recent progress in elucidating their aetiologies and treatment, including seminal pathogenic and therapeutic studies by the team at the National Amyloidosis Centre (NAC) that have led to extremely effective treatments with biologic and other drugs in most cases, with the potential to restore completely normal quality of life and prevent the risk of amyloidosis.

Amyloidosis and inherited fever syndromes are very rare diseases that have been of mainstream interest anywhere in the world.

The service at the Royal Free London NHS Foundation Trust was and remains the only specialist clinical service in these areas in the UK, and one of only a handful in the world. The service evolved from the longstanding Medical Research Council (MRC) funded research programme dating back several decades.

The centre's research including development of diagnostic Amyloid P component serum (SAP) scintigraphy and precise biochemical and genetic characterisation has led to substantial improvements in clinical management that now facilitate rational treatment in most patients. Close interplay between research and clinical practice has enabled the translation of advances in the molecular knowledge of amyloid rapidly and seamlessly into the clinic. Since the NHS NAC was commissioned by The National Specialist Clinical Advisory Group (NSCAG) at the Royal Free in 1999, the amyloidosis practice has become the largest and most diverse in the world, enabling knowledge and study of these diseases to further develop at an ever accelerating pace.

SAP scintigraphy is a non-invasive diagnostic and quantitative method for imaging amyloid deposits, which is used to monitor the disease and its response to treatment. Contrary to previous expectations, serial SAP scintigraphy has shown that amyloid deposits exist in a state of dynamic turnover and frequently regress when underlying disorders are suppressed. SAP scintigraphy is offered to patients attending the National Amyloidosis Centre in conjunction with high sensitivity clinical chemistry assays that monitor amyloid precursor protein production, and hence enable anti-inflammatory treatment and chemotherapy to be given in a rational and much safer manner.

A seminal discovery has been that 10% of patients with apparent sporadic amyloidosis actually have hereditary forms. This has a major impact on clinical management, and DNA analysis is now performed routinely. Notable findings have included identification of many new amyloidogenic transthyretin (TTR), apolipoprotein AI and fibrinogen A alpha chain mutations. The team instigated the first liver transplants to correct the underlying metabolic defect in each of these forms of hereditary amyloidosis, and the first 'domino' liver transplants in which functionally normal livers removed from patients with variant TTR and fibrinogen amyloidosis were re-utilised in patients ineligible for life-saving grafts of normal livers. The Centre's discovery of hereditary lysozyme amyloidosis has been of pivotal importance as a model for elucidating the mechanisms of amyloidogenesis generally

Studies in the inherited periodic fever syndromes have included identification of numerous new mutations in patients with familial Mediterranean fever (FMF) and the TNF receptor-associated periodic fever syndrome, elucidation of the genetics of dominant FMF, and characterisation of the inflammation/apoptosis gene.

2. Scope

2.1 Aims and objectives of service

The aim of the service is to provide a national diagnostic and management advice for patients with amyloidosis and inherited periodic fever syndromes. The multidisciplinary service offers comprehensive diagnostic clinical and pathological investigations and expert opinion, facilitating optimal patient management on a shared-care basis with referring clinicians and other specialist services including liver, kidney and heart transplantation. The goals of the service are to achieve accurate diagnosis as early as possible with a view to patients accessing the most effective therapies available, which frequently have the capacity to preserve vital organ function and prolong survival among patients with this group of very rare, incurable and usually fatal disorders.

The service is required due to the rarity of the amyloid diseases and lack of any other specialist clinical, pathological or diagnostic / imaging services in the UK for patients with amyloidosis and inherited periodic fever syndromes.

The NAC was commissioned by NSCAG in 1999, and provides the only specialist services for patients with amyloidosis and related disorders in the UK. A multidisciplinary team provide a comprehensive range of diagnostic, staging and disease monitoring investigations along with expert clinical advice on treatment that ranges from biologic immune modulating agents to chemotherapy and stem cell transplantation to solid organ transplantation. Many of the diagnostic tests provided by the service were developed there, notably including SAP scintigraphy, and are not available at all elsewhere.

The centre is based in University College London (UCL) Medical School at the Royal Free London NHS Foundation Trust, and is allied to a basic and translational research programme of leading international repute; together, they have contributed to almost all significant clinical developments in the field of amyloidosis during their existence.

The target population is all English and Scottish patients with suspected and histologically demonstrated amyloidosis and inherited fever syndromes, of all ages. Both are exceptionally rare diseases - there are less than 600 new cases of amyloidosis per year in the UK, and inherited periodic fever syndromes affect less than 1 per 100,000 of the population. The service has grown more than five-fold since 1999 reflecting increased awareness and demand for improved diagnosis and optimal state of the art treatment.

The objectives of the service are to ensure that patients with amyloidosis and inherited periodic fever syndromes receive an accurate diagnosis and optimal clinical management that can be delivered on a shared-care basis. Systemic amyloidosis is a progressive fatal disease that is rare and falls outside organ-based clinical specialties. Most physicians see only a few cases during their careers.

The potential for amyloid deposits to regress following aggressive intervention, which variously may comprise biologic anti-inflammatory drugs, chemotherapy, stem cell transplantation or solid organ transplantation, is still not fully appreciated. Moreover, the idiosyncratic multi-system nature of amyloidosis means that definitive diagnosis, staging and direct quantitative monitoring of the amyloid deposits themselves are essential in guiding the choice, intensity and on-going requirement for treatment.

The purposes and goals of the service are therefore to offer comprehensive diagnostic investigations, monitoring and expert clinical opinion for the national caseload of patients with systemic amyloidosis and related disorders. Treatment can usually be administered by the referring unit or at a regional hospital, with regular follow-up at 6-12 monthly interval intervals.

The desired high level outcomes of the service are: accurate, definitive diagnosis of amyloidosis and inherited periodic fever syndromes; access to and therapy with the most effective treatments; avoidance of inappropriate therapies and reduction in treatment related morbidity and mortality; improved quality of life; improved survival.

An annual report will be made to commissioners on diagnostic test turnaround times. The service will also report on agreed quality of life measures.

2.2 Service description/care pathway

The centre uniquely provides a one-stop comprehensive clinical and laboratory evaluation of amyloidosis and related disorders for about 500 new patients per year, and follow-up at 6-12 months for about 1,750 patients each year. The clinical service includes:

- Clinical consultation with expertise gained from experience of over 4000 patients with amyloidosis and related disorders, the largest experience anywhere in the world
- Whole body SAP scintigraphy, a nuclear medicine scan, to diagnose, quantify and serially monitor amyloid deposits throughout the body. Radiolabelled SAP scintigraphy is not available anywhere else and is the only means of quantitatively monitoring amyloid
- Definitive amyloid fibril protein immunohistochemistry; independent
- Clinical chemistry immunoassays for amyloid fibril precursor proteins to assist diagnosis and monitoring treatment; samples posted in during treatment and follow-up
- Specialised echocardiography and evaluation of cardiac amyloidosis;
- Extraction of amyloid fibril proteins from tissues, and biochemical / proteomic characterisation
- DNA analysis and genetic counselling for all types of hereditary amyloidosis (10% of cases) and inherited periodic fever syndromes
- Open telephone access, counselling and provision of information to patients and their local medical teams
- Liaison and work with the patient organization MyelomaUK, to improve

information and access to state of the art treatments
- Leadership and organisational support for UK Amyloidosis Network
- Affiliation with UCL Medical School's Centre for amyloidosis and acute phase proteins.

The service is predominantly but not exclusively a tertiary referral service opens to all NHS patients in England and Scotland (and elsewhere in the EU via the overseas visitor regulations) with suspected or proven amyloidosis and/or inherited periodic fever syndromes. The NAC is located within the medical school at the Royal Free London NHS Foundation Trust, and comprises a purpose built self-contained space comprising clinical consultation rooms, an echocardiography suite, a nuclear medicine computerised topography (CT) – single-photon emission computed tomography (SPECT) gamma camera suite, a diagnostic laboratory and associated offices.

Approximately 50 patients attend the centre per week for clinical evaluation and in addition, about 200 blood, DNA and histopathology samples are sent each week for specialist investigations. Clinical evaluation of patients is usually completed over one to two days, during which hospital or hotel accommodation is arranged. Investigations include whole body SAP scanning to establish the distribution and quantity of amyloid in the body, blood and urine tests, a detailed echocardiogram, and specific additional tests that may include DNA analysis and possibly a bone marrow examination or other biopsies under local anaesthesia. Other investigations for nerve or lung function can also be performed. A medical consultation is carried out at the end of the assessment, at which time the majority of blood, urine, scan and echo results will be presented, and a clinical management plan will be formulated. Each case is reviewed the following Monday afternoon by the NAC multi-disciplinary team, and a medical report is compiled, and is made available to the patient. Follow-up assessments are typically scheduled 6-12 monthly.

The product of the service is accurate diagnosis, provision of information to patients, and clinical management advice to referring physicians with on-going interim monitoring through blood samples sent through the post.

The provider will work with NHS England to ensure sufficient considerations are given to communications.

Service model and care pathways

Patients are referred predominantly by hospital consultants, but the service is open to all medical practitioners within the NHS in England and Scotland. Referrals are assessed by the NAC consultants to be urgent, soon or routine, and an appointments officer liaises directly with the patients, most of whom are seen within two weeks. Urgent cases are aimed to be scheduled within one week. Patients visiting for evaluation of amyloidosis are required to attend the centre for 2 consecutive days in most cases, though all investigation can be performed in a single day in a minority of cases.

Most patients are accommodated in a neighbouring hotel, though sicker patients are admitted to one of two designated amyloidosis beds on ward 2 North. Patients are sent a 24 hr urine container prior to visiting the NAC, and are requested to collect a complete 24 hr urine collection beginning one day before their appointments. On arrival in the NAC patients are received by the receptionist, a nurse or a healthcare assistant, and are directed or escorted to the main waiting area. Patients initially undergo an electrocardiogram (ECG), urinalysis and pregnancy test if indicated, height and weight measurements, and postural blood pressure measurements by a nurse or a healthcare assistant in a consulting room. Detailed echocardiography, taking about 45 minutes, will be scheduled either at this stage, or occasionally later on following isotope injection. Patients are then seen formally by a clinic nurse, who provides written information on amyloidosis and the NAC, and on the investigations that will be performed. Written consent is obtained for investigation and retention of any remaining unused blood. This is followed by placement of an intravenous butterfly line to draw blood and to be administered radio-iodinated SAP tracer. A doctor is available to assess patients and assist the nurse as indicated. In some cases a biopsy procedure, typically either a bone marrow or fat biopsy, will then be performed by a doctor in a consulting room. Patients are then able to leave the centre for either ~ 6hr or 24 hr when SAP scintigraphy is performed. Following whole body SAP scintigraphy, a medical consultation is carried out, at which time the majority of blood, urine, scan and echo results will be presented, and a clinical management plan will be formulated. Each case is reviewed the following Monday afternoon by the NAC multi-disciplinary team, and a medical report that aims to provide a definitive diagnosis and recommendations for treatment containing is compiled, and is made available to the patient.

The service does not provide treatment, which is delivered by the referring physician and specialist colleagues as required at local centres.

Follow-up evaluations are scheduled six monthly in patients with AL amyloidosis and 12 monthly in other types, though with some flexibility according to patients' individual requirements. Patients receiving chemotherapy for AL amyloidosis at their referring hospitals send in blood samples to the NAC monthly for serial monitoring of response with serum free light chain measurements, and those with AA amyloidosis send in blood samples monthly for serial monitoring of response to anti-inflammatory treatment with serum amyloid A protein (SAA) measurements. Results are sent out to the referring doctors and to the patients.

Patients and their local doctors are routinely invited to contact the NAC at any time for additional discussion and advice, and feedback.

2.3 Population covered

Every effort is maintained to promote equal access to the service regardless of culture, disability, gender sensitive issues or where patients live, although the difficulties of funding the cost of travel to access the service are recognised.

Demand for the service has increased ~ five-fold in the first 10 years since national designation and commissioning of the service reflecting increasing recognition and support from referring physicians throughout England and Scotland.

2.4 Any acceptance and exclusion criteria

There are no specific exclusion criteria for referral. The centre welcomes prior telephone discussion of prospective referrals.

In suspected cases of hereditary periodic fever syndromes, many of which are eminently treatable, samples may be sent to the NAC for genetic analysis before a decision to evaluate the patient is taken.

Patients are referred predominantly by hospital consultants, but the service is open to all medical practitioners within the NHS in England and Scotland.

This service covers patients registered with an English GP, resident in Scotland, resident in the European Union and eligible for treatment in the NHS under reciprocal arrangements.

Patients from Wales and Northern Ireland are not part of this commissioned service and the trust must have separate arrangements in place for patients from these and other non EU referrers.

The service has achieved equitable geographic access across England, with referral rates of ~ 12 per million per year in each SHA. Demographical audits have been categorized by disease for AL, AA, hereditary, localised, senile amyloid and fever disorders for each region. Most differences between regions in the can be accounted for by differing incidence of disease in different parts of the country; for example, certain fever conditions are more prevalent in certain London immigrant communities, and the incidence of different types of hereditary amyloidosis varies across the country.

Referral criteria, sources and routes

The NAC provides a diagnostic and management advisory service for all patients with suspected or histologically proven non-central nervous system (CNS) amyloidosis, and patients with suspected or genetically confirmed periodic fever syndromes. It also provides genetic counselling and testing for relatives of patients with hereditary amyloidosis and periodic fever syndromes.

Referrals will be accepted from colleagues in primary and secondary care (predominantly the latter in practice); genetic counselling services, or by self-referral in the case of individuals who may be at risk of hereditary disease but who wish to be seen initially in complete confidence.

All referrals are triaged by consultant medical staff, who will occasionally seek

additional information from referrers to clarify the indication for assessment.

Response time, detail and prioritisation

Referrals are graded as urgent, soon or routine by one of the NAC consultants within one day of receipt. Target waiting times set by the NAC are seven days, 14 days and 31 days respectively, and at last audit were met on 80%, 79% and 94% of occasions. However none were delayed by more than four days.

No specific patients/indicators are used for prioritisation, which is made at the consultants' judgement, but all patients with advanced cardiac amyloidosis or clinical significant liver impairment are assessed urgently.

2.5 Interdependencies with other services

There are no other specialist clinical services available that focus specifically on amyloidosis. It is a multi-system disease that can affect almost any organ or multiple organs throughout the body other than the brain. Symptoms are non-specific, and patients typically have advanced amyloid disease causing significant dysfunction of at least one organ system when the diagnosis is suspected. As a result, patients are referred to the NAC from many different organ based specialties, notably including nephrology, cardiology, gastroenterology, dermatology and neurology, along with haematology, immunology, genetics, paediatrics and rheumatology. A small proportion of patients are referred from primary care, a significant proportion of who have a family history of hereditary amyloidosis and require genetic screening.

The clinical, nuclear medicine, echocardiography, histology and genetic facilities at the NAC are to a large extent self-contained and self-sufficient, but the service and multi-disciplinary staff nevertheless depend on support from the routine haematology, clinical chemistry and nuclear medicine departments at the Royal Free London NHS Foundation Trust.

In addition to direct patient services, the NAC provides specialised histological, genetic and clinical chemistry services to external NHS laboratories through England and Scotland on receipt of blood, DNA and tissue samples. No other specialist services of these types are available within the NHS.

Treatment differs according to type of amyloid, organ involvement and severity, and includes anti-inflammatory therapy, chemotherapy and stem cell transplantation, and solid organ transplantation. Supportive treatment of many kinds is also vital, often requiring input from many different specialties. The NAC provides a diagnosis and management advisory service, and treatment for most patients is delivered by local secondary care facilities, with primary care support in standard fashion. Patients with amyloidosis therefore tend to require on-going care from several specialists, with whom the amyloidosis service liaises on an individual, tailored basis.

MyelomaUK is an organisation that provides information and support to people affected by myeloma and related diseases including amyloidosis, with the aim to

improve standards of treatment and care through research, education, campaigning, and raising awareness.

The amyloidosis service works closely with MyelomaUK to provide information leaflets, information websites (*www.myeloma.org.uk/amyloidosis*), telephone support and patient education 'Infodays'.

The UK Amyloidosis Network was created in 2008 as a forum for all clinicians, nurses, researchers and allied individuals who have an interest in this multisystem disease. The network aims to foster better communication and sharing of ideas between interested parties and promote better co-ordinated care of patients with amyloidosis, as well as serving as a forum for developing and implementing research. It is organised and led by the consultants at the NAC.

ALchemy (AL amyloidosis chemotherapy project) - This is a MyelomaUK-funded programme to record quality of life before, during and after chemotherapy, response to treatment, chemotherapy-related side effects and toxicities. A nurse practitioner in the amyloidosis centre is co-ordinating the programme, which involves intensive monitoring, with the aim of developing of an improved model of shared care with local referring haematologists and their teams. The ALchemy project supports the amyloidosis network.

3. Applicable Service Standards

The governance and risk arrangements for the Royal Free London NHS Foundation Trust were reviewed by the trust Board in support of establishing a new divisional structure in April 2009. This structure was proposed in order to develop and facilitate a more integrated approach to systems of quality improvement. The integrated approach represents a move from a centrally managed process to one in which each of the four clinical divisions manage the devolved system of quality assurance through divisional governance and risk processes.

Each division has a number of specialist boards that monitor governance and risk arrangements within their clinical directorate or speciality. A number of these report directly to the trust operations board, although most such Boards provide updates to their respective divisional board meetings.

There is also a small corporate governance team comprises of: a central risk & safety team managed by the deputy director of risk & safety, and the clinical effectiveness & quality standards manager managed by the deputy director of clinical governance. Each of the four clinical divisions has aligned governance partners responsible for coordinating and managing locally the governance and risk processes. The governance partners are accountable to the divisional nurse directors with responsibilities to the central governance and risk leads.

Each clinical specialty is required to provide ratings to the divisional board meetings by means of a 'quality scorecard' in three areas of review: do no harm, effectiveness

and patient experience. Corporately the quality scorecard provides disaggregated information for those target areas.

The quality scorecard is also populated with information from divisional 'audit scorecards', which are used as a monitoring tool and to collate information on clinical audit activity required for reporting the 'engagement in clinical audits' national priority indictor to the Care Quality Commission (CQC).

The audit scorecard is reviewed monthly at the clinical audit & effectiveness committee (CAEC). The role of CAEC is to enable the effective delivery of the local and national clinical audit and effectiveness agenda, support the delivery of significant improvements in the quality of patient care and improve patient safety through clinical audit and clinical effectiveness.

There is an expectation that practitioners will participate in continuous professional development and networking. Provide assurance that this will be built into roles within the service.

The amyloidosis service has evolved enormously since its inception in 1999. It has expanded over five-fold, made substantial strides in its histological, DNA and diagnostic imaging facilities, and has become recognised as that countries national referral centre for inherited periodic fever syndromes. It has an exemplary record of translating novel academic advances into clinical practice, and continues to work in very close alliance with UCL's centre for amyloidosis and acute phase proteins, which has a world-leading basic and translational amyloidosis research programme.

The service is committed to continually improving the service and react to innovative and dynamic ideas, and to respond to

- Complaints
- Regular audits
- Ad hoc and organised feedback through the UK Amyloidosis Network
- Observation from other amyloidosis services in the EU and US
- Needs assessments
- Service user feedback / patient and public involvement
- Research
- Policy / guidance on best practice e.g. NHS Institute for Innovation and Improvement.

Risk management

It is widely recognised that an effectively planned, organised and controlled approach to the risk management process is the cornerstone of sound management practice, which aims to anticipate and wherever possible prevent, or manage risks to patients, staff, visitors and the organisation. Good risk management awareness and practice embedded in the service is an essential success factor in ensuring that risks are managed systematically and consistently.

The NAC recognises that identifying risks and managing these well provides invaluable opportunities to improve patient care and there are formal arrangements

in place to support these principles.

Risk management is covered in mandatory training programmes for staff and the monthly directorate risk and governance meeting provides the opportunity to review all clinical incidents and to ensure processes are revisited as a part of managing risk. This is also achieved by promoting a policy of openness and accountability and by effective communication both within the service and with the external community.

The service recognises that in the absence of a peer review opportunities from which shared learning can occur, this may create a risk element for the service and therefore it recognises the importance of having a sound risk management processes in place which allows the service to continually review performance and learning needs and to respond to these appropriately.

4. Key Service Outcomes

Diagnostic test turnaround times

Significant variation from the national average or, in services with one or two national centres, significant variation from the outcomes achieved in the previous three years.

5. Location of Provider Premises

The service is delivered in purpose built premises at the Royal Free London NHS Foundation Trust.

The amyloidosis service is substantially provided by UCL Medical School staff, which holds honorary contracts with the Royal Free London NHS Foundation Trust. A sub-contracting agreement, subject to annual review, has been drawn up between the two institutions, principally to define allocation of the budget. The Royal Free London NHS Foundation Trust is the legal entity responsible for the clinical amyloidosis service. No sub-contracts are held externally to the Royal Free – UCL Partnertship.