Systemic Amyloidosis

Tamer Rezk and Philip N. Hawkins

Abstract

Amyloidosis describes a group of rare diseases caused by abnormal fibrillar protein aggregation within the interstitium of tissues and organs throughout the body. This chapter focuses upon the pathogenesis, epidemiology, diagnosis and management of these heterogeneous disorders. AA amyloidosis is one of the most feared complications of autoinflammatory syndromes but it is becoming increasingly rare with the advent of effective anti-inflammatory therapy. The most common of the systemic amyloidoses are immunoglobulin light chain (AL) type and wildtype transthyretin (wtATTR) amyloidosis, the latter a probably much underdiagnosed cause of heart failure in the elderly. Precise diagnosis, confirmation of amyloid type, evaluation of amyloidotic organ involvement and associated underlying disorders are imperative for optimal patient care. Although histology has long been the diagnostic gold standard, new technologies including mass spectrometry of tiny tissue samples and highly specific imaging comprising; I^{123} labelled serum amyloid P (SAP) component scintigraphy, ^{99m}Tc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy and cardiac MRI (CMR), have lately transformed the evaluation of patients. A multidisciplinary approach to management is key. Treatment comprises support of failing amyloidotic organs, measures to reduce production of the respective amyloid fibril protein such as suppression of serum amyloid A (SAA) in systemic AA amyloidosis, and recently, novel therapies aimed at enhancing clearing of existing amyloid deposits.

Keywords

Amyloidosis · Autoinflammatory · Systemic Suppression · Nephrotic syndrome · Heart failure · Chemotherapy · Neuropathy

T. Rezk
National Amyloidosis Centre, UCL Division of Medicine, Royal Free Campus, London, UK

UCL Centre for Nephrology, Division of Medicine, University College London, Royal Free Campus, London, UK
e-mail: t.rezk@ucl.ac.uk

P. N. Hawkins (✉)
National Amyloidosis Centre, UCL Division of Medicine, Royal Free Campus, London, UK
e-mail: p.hawkins@ucl.ac.uk

Abbreviations

ACE	Angiotensin-converting enzyme
AEF	Amyloid-enhancing factor
ARB	Angiotensin receptor blockers
ASCT	Autologous stem cell transplantation
BJP	Bence Jones proteinuria

CAPS	Cryopyrin-associated autoinflammatory syndrome
CINCA	Chronic inflammatory neurological cutaneous articular
CKD	Chronic kidney disease
CMR	Cardiac MRI
CPHPC	((R)-1-(6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexa-noyl) pyrrolidine-2 carboxylic acid), a novel bis (D-proline)
DPD	^{99m}Tc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD)
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
ESRF	End stage renal failure
FAP	Familial amyloid polyneuropathy
FCAS	Familial cold autoinflammatory syndrome
FLC	Free light chains
FMF	Familial Mediterranean fever
GAG	Glycosaminoglycans
IHC	Immunohistochemical
IVSD	Interventricular septal diameter
MGUS	Monoclonal gammopathy of unknown significance
MKD	Mevalonate kinase deficiency
MM	Multiple myeloma
MWS	Muckle-Wells syndrome
NAC	National Amyloidosis Centre
NOMID	Neonatal onset multisystem inflammatory disease
NT-proBNP	N terminal pro brain natriuretic peptide
SAA	Serum amyloid A
SAP	Serum amyloid P
TNF	Tumor necrosis factor
TRAPS	TNF receptor-associated periodic syndrome
TTR	Transthyretin
UK	United Kingdom
USA	United States of America

Key Points

- **Systemic amyloidosis is a heterogeneous multisystem disease caused by extracellular deposition of protein in a specific highly ordered fibrillar form**
- **The natural history of systemic amyloidosis is invariably progressive, usually with a fatal outcome**
- **Optimal characterisation of systemic amyloidosis requires clinical assessment, serum and urine biochemistry and multidisciplinary laboratory investigations including histology, proteomics, genetic testing and various imaging modalities, notably including cardiac MRI (CMR) for assessment of cardiac amyloidosis**
- **The presence of a monoclonal gammopathy or a chronic inflammatory disorder may be gravely misleading in suggesting systemic amyloidosis is of AL or reactive AA type, respectively, since these conditions are common in the general population and may be incidental to the type of amyloid**
- **Treatment of systemic amyloidosis includes best supportive care, maximal possible reduction of the supply of the amyloid fibril precursor protein such as suppression of serum amyloid A (SAA) in AA amyloidosis; novel therapies aimed at removing existing amyloid deposits are in development**

15.1 Introduction

- **Amyloidosis is a heterogeneous disease caused by extracellular deposition of protein**
- **The most common circumstance in which amyloid deposition occurs is the presence of an abnormal protein such as monoclonal immunoglobulin light chains in AL amyloidosis**
- **Untreated systemic amyloidosis is invariably progressive, typically leading to organ failure and death**

Amyloidosis comprises a group of rare diseases caused by the extracellular accumulation of amyloid, a highly ordered, insoluble and remarkably stable fibrillar protein material. Amyloid fibrils are derived from a diverse collection of soluble precursor proteins that have a specific propensity to misfold and aggregate in a highly abnormal cross β sheet conformation [1]. Amyloid deposits cause disease by accumulating at a rate that exceeds the body's capacity to clear them, progressively disrupting the structure and function of tissues and organs throughout the body [2]. Amyloid type is classified according to the respective fibril protein, of which more than 30 have been identified in vivo (Table 15.1) [3]. Amyloid deposits have a pathognomonic histologic appearance comprising apple-green dichroism (birefringence) in tissue sections that have been stained with Congo red dye and visualized under cross-polarized light (Fig. 15.1). On electron microscopy, amyloid fibrils appear as rigid non-branching fibrils with a diameter of ~10 nm [4]. Amyloid deposition is highly heterogeneous, ranging from small incidental deposits, through localised accumulations that can cause disease through an infiltrative or mass effect, to systemic (generalized) forms of amyloidosis that can affect almost any organ in the body with fatal consequences. Precise diagnosis, typing and evaluation of the organ distribution, severity and adverse effects of amyloid are imperative to ensure best clinical care.

15.2 Fibril Formation and Amyloid Proteins

Amyloid fibrillogenesis remains poorly understood. Under certain laboratory conditions all sorts of proteins can be induced to misfold and aggregate, but relatively few have the specific properties to form genuine amyloid fibrils *in vivo*. Despite the heterogeneity of those proteins that form amyloid in vivo, the resultant fibrils have remarkably similar morphological ultrastructure and histological properties. The common core structure is one of anti-parallel β-strands that form sheets (Fig. 15.2) [5, 6].

These β-sheets run parallel to the axis of the protofilament with their component β strands perpendicular to the fibril axis, which appear on electron microscopy as non-branching structures 7–10 nm in diameter [7].

All amyloid deposits additionally contain certain non-fibrillary constituents including glycosaminoglycans (GAGs), sulphated proteoglycans, heparin sulphate, apolipoproteins E and A4, type IV collagen and serum amyloid P component (SAP) [8]. GAGs are located primarily on the cell surface in the extracellular matrix and although universal to all amyloid deposits, their role remains unclear. SAP is a normal plasma protein that binds in a reversible calcium dependant manner to a ligand present on all amyloid fibrils, its presence in vivo being an essential amyloid defining characteristic. It is a member of the pentraxin group of plasma proteins that is relatively resistant to proteolysis, and for which there is evidence it both promotes amyloid fibril formation and inhibits their degradation by phagocytic cells and proteolytic enzymes. In vivo, circulating SAP exists in a dynamic equilibrium with SAP bound to amyloid fibrils, forming the basis for diagnostic radiolabelled SAP scintigraphy. SAP knock-out mice are relatively resistant to induction of experimentally induced amyloidosis [9].

There are essentially three circumstances in which amyloid deposition occurs. The most common is the presence of an abnormal protein with pronounced amyloidogenic properties such as the monoclonal immunoglobulin light chains that form AL amyloid and genetic variants of transthyretin (TTR), fibrinogen A-a chain, apolipoprotein AI, apolipoprotein A2, apolipoprotein C3, apolipoprotein C2, gelsolin and lysozyme in hereditary amyloidosis. A second situation is the presence of an abnormally high concentration of a 'normal' protein, examples of which are elevated serum amyloid A protein (SAA) in chronic inflammatory disorders predisposing to AA amyloidosis, and elevated β2M microglobulin in dialysis-related amyloidosis. Third, amyloid deposition can occur in advanced age in the presence of a 'normal' protein that is present in normal abundance, such as the case with wildtype transthyretin in non-hereditary ATTR amyloidosis.

**Table 15.1** Classification of systemic amyloidosis by precursor protein

Fibril protein	Precursor protein	Systemic (S) and/or localized (L)	Acquired (A) or hereditary (H)	Target organs
AL	Immunoglobulin light chain	S, L	A	All organs except CNS
AH	Immunoglobulin heavy chain	S, L	A	All organs except CNS
AA	(Apo) Serum amyloid A	S	A	All organs except CNS
ATTR	Transthyretin, wild type	S	A	Heart mainly in males, ligaments, tenosynovium
	Transthyretin, variants	S	H	PNS, ANS, heart, eye, leptomeningeal
Aβ2M	β2-Microglobulin, wild type	L	A	Musculoskeletal system
	β2-Microglobulin, variant	S	H	ANS
AApoAI	Apolipoprotein A I, variants	S	H	Heart, liver, kidney, PNS, testis, larynx (C-terminal variants), skin (C-terminal variants)
AApoAII	Apolipoprotein A II, variants	S	H	Kidney
AApoAIV	Apolipoprotein A IV, wild type	S	A	Kidney medulla and systemic
AGel	Gelsolin, variants	S	H	PNS, cornea
ALys	Lysozyme, variants	S	H	Kidney
ALECT2	Leukocyte chemotactic factor-2	S	A	Kidney, primarily
AFib	Fibrinogen α, variants	S	H	Kidney, primarily
ACys	Cystatin C, variants	S	H	PNS, skin
ABri	ABriPP, variants	S	H	CNS
ADan	ADanPP, variants	L	H	CNS
Aβ	Aβ protein precursor, wild type	L	A	CNS
	Aβ protein precursor, variant	L	H	CNS
APrP	Prion protein, wild type	L	A	CJD, fatal insomnia
	Prion protein variants	L	H	CJD, GSS syndrome, fatal insomnia
ACal	(Pro)calcitonin	L	A	C-cell thyroid tumors
AIAPP	Islet amyloid polypeptide	L	A	Islets of Langerhans, insulinomas
AANF	Atrial natriuretic factor	L	A	Cardiac atria
APro	Prolactin	L	A	Pituitary prolactinomas, aging pituitary
AIns	Insulin	L	A	Iatrogenic, local injection
ASPC‡	Lung surfactant protein C	L	A	Lung
AGal7	Galectin 7	L	A	Skin
ACor	Corneodesmosin	L	A	Cornified epithelia, hair follicles
AMed	Lactadherin	L	A	Senile, aortic media
Aker	Kerato-epithelin	L	A	Cornea, hereditary
ALac	Lactoferrin	L	A	Cornea
AOAAP	Odontogenic ameloblast-associated protein	L	A	Odontogenic tumors
ASem1	Semenogelin 1	L	A	Vesicula seminalis
AEnf	Enfuvirtide	L	A	Iatrogenic

CNS central nervous system, *PNS* peripheral nervous system, *ANS* autonomic nervous system, *CJD* Creutzfeldt-Jakob disease, *GSS* Gerstmann–Sträussler–Scheinker
‡Lung surfactant protein C
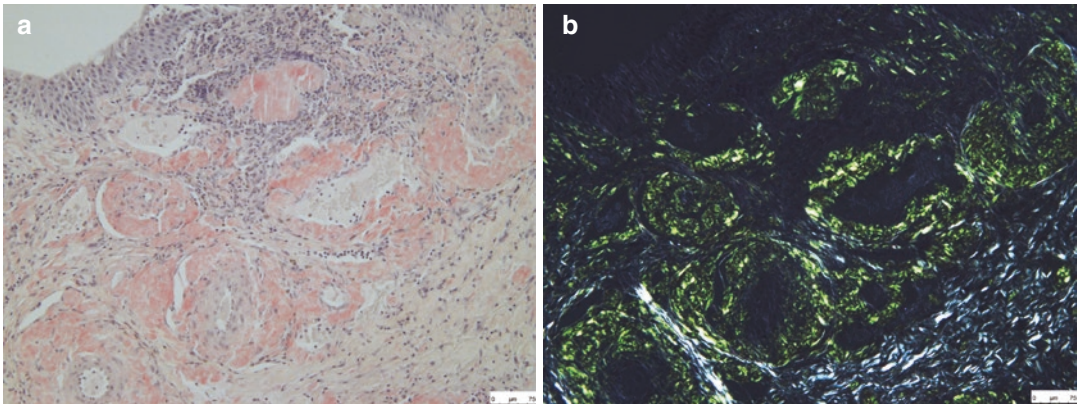
Fig. 15.1 (**a**) Congo red staining of AA amyloid deposition in a biopsy of the bladder. (**b**) Apple green birefringence when viewed under cross polarised light
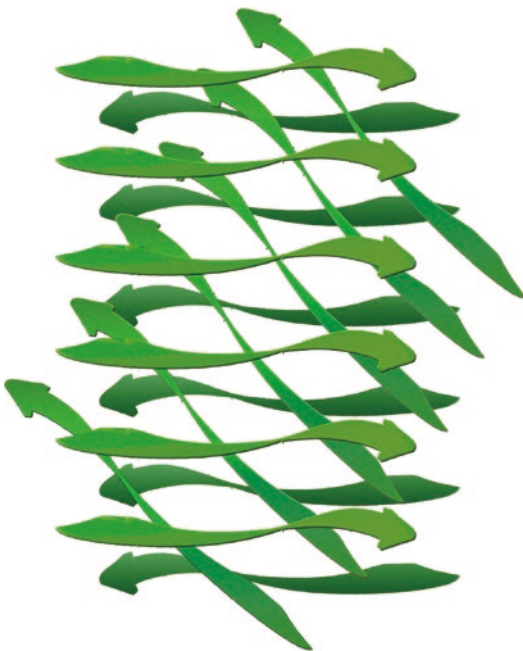
Fig. 15.2 Image depicting anti-parallel β-strands that form sheets

15.3 Pathogenesis of Amyloidosis Accumulation and Degradation

Amyloid deposition causes organ dysfunction due to physical replacement of parenchymal tissue and cellular injury. Pre-fibrillar oligomers may also exert direct toxicity; the strongest evidence for this is derived from observations in cardiac AL amyloid although it has also been postulated in ATTR amyloidosis [10]. Organ damage is ultimately due to a combination of mechanisms that depend on both the type of amyloidosis and the organ in question.

The factors that govern the pattern of organ involvement in different types of amyloidosis, or indeed different patients with the exact same type, remain poorly understood. For example, there can be major phenotypic differences in close family members with the same type of hereditary amyloidosis.

A potential amyloid precursor protein can be present for very prolonged periods without formation of amyloid but, once started, it will continue indefinitely as long as the supply of the precursor protein persists, and at a rate that depends on the abundance of the latter. The notion of 'amyloid-enhancing factor' (AEF) initiating amyloid formation was established many decades ago. In studies of experimentally induced AA amyloid in mice, microscopic amounts of ex vivo amyloidotic material parenterally administered into mice with elevated SAA concentrations were found to trigger substantial AA amyloid deposition within only a few hours [11]. It is now clear that this extraordinarily potent phenomenon is mirrored in patients. Once amyloid formation has begun, it will be forever propagated so long as there

remains a supply of the amyloid precursor protein in question. It is likely that the initiating event is a stochastic protein misfolding/aggregation phenomenon that may only occur after decades of an amyloidogenic protein having been present. The extremely rapid (within weeks) recurrence of nephrotic syndrome following relapse of inflammatory activity in patients with previous apparently resolved AA amyloidosis is an example underlining the rapidity with which amyloid can accumulate [12]. Another example is the rapid progression of hereditary cardiac ATTR amyloidosis following liver transplantation performed to remove the source of the genetic TTR variant, but which is now known to result in enhanced deposition of wildtype TTR on a template of amyloid derived from variant TTR [13].

Untreated systemic amyloidosis is almost always progressive, typically leading to organ failure and death within months to a few years. However, amyloid deposits are constantly being cleared away to a minor and variable extent, such that substantial suppression of the fibril precursor protein supply can gradually result in net regression of the amyloid burden [14]. This slow natural and very inefficient clearance of amyloid is thought to be mediated by macrophages, which can occasionally be identified in amyloidotic tissue, sometimes in sufficient numbers to form multinucleate giant cells that surround and engulf the amyloid material. Depletion of macrophages with liposomal clodronate inhibits amyloid regression in mice [15]. Serial SAP scintigraphy in patients whose amyloid precursor protein production has been halted indicates that the rate of amyloid clearance, i.e. regression, varies widely between individuals and between different organs; typically, clearance of amyloid is substantially slower in the kidneys than the liver, and very slow in the heart.

It is striking, given the highly abnormal and acquired nature of amyloid, that this material does not evoke a significant host response. Pepys hypothesised that the coating of amyloid by SAP, a normal plasma protein, may act as an anti-opsonin, which is supported by inhibited amyloidogenesis in SAP knockout mice. CPHPC, ((R)-1-(6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexa-noyl) pyrrolidine-2 carboxylic acid), a novel bis (D-proline) drug was developed with the aim of removing SAP from amyloid and thus potentially promote removal of amyloid via macrophage infiltration of amyloid deposits.

15.4   Epidemiology

Amyloidosis is a rare condition for which there is a paucity of epidemiological data. It has been estimated to cause 0.5–1.0 deaths per 1000 in the United Kingdom (UK) [16]. The most common type diagnosed in the UK is systemic AL amyloidosis, studies suggesting an incidence of 5.1–12.8 per million person-years. Currently about 800 new patients with various types of amyloidosis are evaluated each year at the National Amyloidosis Centre (NAC). Previous work in our centre in 2008 estimated a minimum incidence of systemic amyloidosis in England of 0.4/100,000 of the population. The incidence peaked at 60–79 years with systemic AL amyloidosis being the most common type, with a minimum incidence of 0.3/100,000 [17].

Non-hereditary, i.e. wildtype, transthyretin amyloidosis, which predominantly causes a cardiomyopathy in older individuals and was previously known as senile systemic/cardiac amyloidosis, is lately being diagnosed much more frequently than hitherto. This reflects the remarkable diagnostic value of cardiac MRI (CMR) and repurposing of bone scintigraphy for this indication. The true prevalence of cardiac ATTR amyloidosis remains unknown, but may be much higher than is currently apparent since post-mortem studies have long demonstrated that some ATTR deposits are present in the hearts of up to 20% of people over the age of 80 years [18]. Diagnosis of wildtype ATTR amyloidosis at the NAC has risen exponentially in recent years and currently exceeds 200 patients per year.

15.5   Types of Amyloidosis

- **AL amyloidosis is the most common form of systemic amyloidosis in the western world**
- **Wildtype transthyretin cardiac amyloidosis (previously known as senile systemic/cardiac amyloidosis) is an increasingly recognised cause of heart failure with preserved ejection fraction (HFPEF)**
- **AA amyloidosis, once the most common form of systemic amyloidosis, is now rare with the advent of improved treatments for chronic inflammatory disorders**
- **Systemic amyloidosis has a varying prognosis depending on both the type and pattern of organ involvement, with survival ranging from months to many years**

15.5.1 Systemic AA Amyloidosis

Reactive systemic (AA) amyloidosis, in which the fibrils are composed of AA protein derived from the acute phase protein SAA, occurs as a rare complication of many chronic inflammatory disorders. The AA amyloid precursor protein is the N terminal fragment of the acute phase reactant SAA, an apolipoprotein constituent of high-density lipoprotein. SAA is synthesized by hepatocytes and its concentration may rise 1000-fold from healthy values of less than 3 mg/L in response to inflammation. Gene transcription of SAA is regulated by cytokines, in particular interleukin (IL)-1 and IL-6.

The lifetime incidence of AA amyloidosis in patients with chronic inflammatory conditions is less than 1–5% [19]. In Western Europe and the United States of America (USA) the most frequent predisposing conditions are idiopathic rheumatic diseases, notably rheumatoid arthritis and juvenile idiopathic arthritis (Table 15.2). AA amyloidosis has become increasingly rare, reflecting improved treatment of chronic inflammatory disorders, and for reasons that are not clear, the incidence is lower in the United States than in Europe. Amyloidosis is exceptionally rare in systemic lupus erythematosus, related connec-

Table 15.2 Conditions associated with reactive systemic amyloid AA amyloidosis

Chronic inflammatory disorders
Rheumatoid arthritis
Juvenile idiopathic arthritis
Ankylosing spondylitis
Psoriasis and psoriatic arthropathy
Reactive arthritis
Adult onset Still disease
Behçet syndrome
Crohn disease
Whipple disease
Hereditary autoinflammatory/periodic fever syndromes
Familial Mediterranean fever
Tumor necrosis factor receptor-associated periodic syndrome
Cryopyrin-associated periodic syndromes
Mevalonate kinase deficiency
Chronic microbial infections
Leprosy
Tuberculosis
Bronchiectasis
Decubitus ulcers
Chronic pyelonephritis in paraplegics
Chronic infected burns
Chronic osteomyelitis
Malignant neoplasms
Hodgkin disease
Renal cell carcinoma
Carcinomas of gut, lung, urogenital tract
Basal cell carcinoma
Hairy cell leukemia
Unknown etiology

tive tissue diseases, and in ulcerative colitis in which there is a blunted acute phase response of SAA. Longstanding, though not necessarily constant elevation of SAA, is a prerequisite to the development of AA amyloidosis. Tuberculosis and leprosy are important causes of AA amyloidosis where these infections remain endemic. Chronic osteomyelitis, bronchiectasis, chronically infected burns, and decubitus ulcers are other well-recognized associations (Table 15.2). Hodgkin disease and renal cell carcinoma, which often cause an acute phase response, are the malignancies most commonly associated with systemic AA amyloidosis.

Intriguingly, at least 10% of patients with AA amyloidosis do not have a clinically obvious

chronic inflammatory disease, and may erroneously be assumed to have AL amyloidosis. The most common identifiable diseases found in our experience in such cases are inherited autoinflammatory syndromes and cytokine-secreting Castleman disease tumors of the solitary plasma cell type, located either in the mediastinum or the gut mesentery. However, in the majority of these challenging patients the precise nature of the causative inflammatory disorder cannot be determined.

15.5.1.1 Autoinflammatory Diseases and Amyloidosis

The hereditary periodic fever/autoinflammatory syndromes are a well-described cause of AA amyloidosis, among which four are most commonly implicated. These are familial Mediterranean fever (FMF), Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), the cryopyrin-associated autoinflammatory syndrome (CAPS) and to a lesser extent mevalonate kinase deficiency (MKD) (see Chaps. 16–19). FMF is the most common of these diseases. It is characterised by recurrent self-limiting attacks of fever, serositis and sometimes arthritis or rash [20]. There is a clear ethnic preponderance, with FMF being prevalent in the Eastern Mediterranean, where it is the most common monogenic autoinflammatory disease. CAPS comprises a continuous spectrum of three disorders, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic inflammatory neurological cutaneous articular syndrome (CINCA).

It is important to recognise that genetic associations with the development of amyloidosis are weak and not useful predictors of risk in individual patients. The remarkably high risk of AA amyloidosis in systemic autoinflammatory diseases reflects persistent and uncontrolled inflammation. Although small series have identified increased risks with specific genotypes in FMF and perhaps with mutations affecting cysteine residues in TRAPS (see below) there are no guaranteed 'safe' mutations and all patients should be treated to completely suppress chronic inflammatory disease and SAA production. The same is true for the data on SAA polymorphisms and risk of the development of AA amyloidosis.

Serum Amyloid A (SAA) Polymorphisms

While persistent and sustained inflammation is the key risk factor for the development of AA amyloidosis in autoinflammatory diseases, studies have shown (predominantly in FMF) the contribution of serum amyloid A1 (SAA1) polymorphisms, differing gene mutations and birthplace. Most of these studies are small and subject to confounding influences such as increased investigation of patients who present with AA amyloidosis and more recently, a significant impact from the availability of effective long-term prophylactic treatment.

SAA1 has 5 polymorphic coding alleles, SAA1.1, SAA1.2, SAA1.3, SAA1.4 and SAA1.5 [21]. The gene products of these coding alleles vary by only a few amino acids at different positions of the mature SAA1 protein. Despite these minor differences, the allelic variants of SAA1 have shown differences in both in vitro assays as well as correlation with various diseases [22]. The importance of polymorphisms in SAA1 differs between populations. In Japan homozygosity for SAA1.3 has been known to increase the risk of AA amyloid in rheumatoid arthritis for many years [23]. In other populations with a different distribution of polymorphism, homozygosity for SAA1.1 is a risk factor. This is the case in Turkish patients with FMF who have an increased incidence of SAA1.1 homozygosity in FMF patients with amyloidosis (56%) compared to FMF patients without amyloidosis (31%), a 2.5 fold increased risk [24].

Risk Factors for Amyloidosis in Familial Mediterranean Fever (FMF)

The *MEFV* M694V variant has been associated with the most severe form of FMF and a higher risk of AA amyloidosis [25]. In 170 Armenian patients with FMF; 60% had a concurrent diagnosis of AA amyloidosis. The most common genotype in this cohort was M694V/M694V homozygosity which was present in 36% of

patients and was associated with an increased risk of AA amyloidosis when compared to M694V heterozygosity [26].

While M694V was previously thought to be the key risk factor for AA amyloidosis; in a large online study of 35 centres in 14 countries, 2482 cases of FMF were identified of whom 260 developed renal amyloidosis. Interestingly, country of recruitment rather than the *MEFV* genotype was the leading risk factor for the manifestation of renal amyloidosis which may indicate a potential environmental origin of amyloidosis susceptibility [27].

Risk Factors for Amyloidosis in the Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS)

In TRAPS, the international Eurofever/Eurotraps registry identified 158 patients in whom the most common variant of *TNFRSF1SA* was R92Q (34% of cases) and T50M (10%) with disrupted cysteine residues in 27% of cases. AA amyloidosis developed in 16 (10%) patients at a median age of 43 years. This group included 7 patients with cysteine variants (44%), two with T50M (13%) and none with R92Q. Patients who developed AA amyloidosis had significantly longer disease duration than those who did not [28].

Risk Factors for Amyloidosis in the Cryopyrin-Associated Periodic Syndrome (CAPS)

Retrospective literature review of all cases of CAPS from the French network for rare diseases identified 67 patients diagnosed with CAPS who developed AA amyloidosis. While AA amyloidosis was seen in all CAPS phenotypes it appeared to be more common in MWS [29]. Due to the rarity and severity of disease with high mortality rates there is less data on amyloidosis in patients with NOMID.

15.5.1.2   Clinical Features

AA amyloid involves the viscera, but may be widely distributed without causing symptoms. It predominantly affects the kidneys with more than 95% of patients presenting with proteinuria and

around 10% having already reached end-stage renal failure (ESRF) at diagnosis [12].

The predominant presentation is nephrotic syndrome with non-selective proteinuria from glomerular deposition of amyloid and or chronic kidney disease (CKD). Splenic involvement is evident on SAP scintigraphy in almost all cases and while deposits commonly occur in the adrenal gland and gastrointestinal tract, this is usually without associated organ dysfunction. Liver involvement in AA amyloidosis is a feature of advanced disease and confers a poor prognosis [30]. Cardiac amyloidosis and amyloid-related neuropathy are rare manifestations of AA amyloidosis and are seen only in advanced cases.

15.5.2 Systemic AL Amyloidosis

This is the most common form of amyloidosis in the developed world and is associated with dyscrasias of cells within the B-lymphocyte lineage, including multiple myeloma (MM), malignant lymphomas and macroglobulinemia. Most cases develop in the context of what would otherwise be a low grade monoclonal gammopathy of unknown significance (MGUS). The age adjusted incidence in the USA is 8.9 per million person-years [31]. Amyloidosis occurs in up to 10% of cases of MM and in a lower proportion of other malignant B-cell disorders. Approximately 2% of patients with an MGUS eventually develop AL amyloidosis [31]. The fibrils are formed from the N terminal domain of monoclonal lambda (more common) or kappa immunoglobulin light chains, and consist of the whole or part of the variable (VL) domain.

A monoclonal immunoglobulin can be detected in the serum or urine by immunofixation electrophoresis in 65% and 86% of patients, respectively. A monoclonal excess of free light chains (FLC) can be identified at baseline in 98% of patients with systemic AL amyloidosis. Subnormal levels of some or all serum immunoglobulins, or increased numbers of marrow plasma cells may provide less direct clues to the underlying etiology. Until recently, it has been the practice to consider apparent primary cases of

amyloidosis, with no previous predisposing inflammatory condition or family history of amyloidosis, as AL type. However, it has now been recognized that some patients with mutations associated with autosomal dominant hereditary non-neuropathic amyloidosis, particularly that caused by variant fibrinogen α-chain, do not develop fibrinogen α-chain amyloidosis. The coincident occurrence of a monoclonal gammopathy, which occurs in more than 10% of the healthy older population, may then be gravely misleading and it is essential to exclude other forms of amyloidosis by genotyping all known amyloidogenic mutations, and to seek definitive immunohistochemical or proteomic identification of the amyloid fibril protein in all cases.

15.5.2.1 Clinical Manifestations

Clinical suspicion of AL amyloidosis should be raised in any patient with unexplained nephropathy, cardiac failure, peripheral and/or autonomic neuropathy or any other multisystem disease. Potentially all organs can be directly affected by amyloid deposits in systemic AL amyloidosis except the central nervous system. Renal involvement is the most common manifestation with approximately 70% of patients presenting with either proteinuria or elevated serum creatinine. Cardiac amyloidosis is present in 50% of patients at baseline and is the key determinant of mortality. Cardiac amyloidosis typically manifests with a restrictive cardiomyopathy; concentric ventricular wall thickening resulting in diastolic dysfunction manifesting with congestive cardiac failure and, more often than not, hypotension. Autonomic nervous system involvement presents variably and is often challenging to diagnose. It can lead to orthostatic hypotension, erectile dysfunction, urinary retention and fecal incontinence. In patients in whom a peripheral neuropathy is present there is most commonly a distal sensory deficit which can be subclinical at presentation. Systemic chemotherapy aimed at suppressing the monoclonal light chain can cause worsening of peripheral and autonomic neuropathy depending upon the neurotoxicity of therapy. Liver involvement as a presenting feature is rare but is a quite common finding at post mortem examination and on SAP

scintigraphy. Hepatomegaly and obstructed liver function tests are the most common clinical findings but can be absent in patients despite the presence of significant hepatic amyloid deposits [32].

There are a plethora of soft tissue features in AL amyloidosis with macroglossia and periorbital bruising thought to be pathognomonic for AL type. Gastrointestinal involvement can result in malabsorption, altered bowel habit and gastrointestinal hemorrhage [33].

15.5.3 Hereditary Systemic Amyloidosis

15.5.3.1 Familial Amyloid Polyneuropathy

Familial amyloid polyneuropathy (FAP) is associated with more than 100 mutations in the gene encoding TTR. TTR is predominantly synthesized in the liver and is a tetrameric protein which has a role in the transport of thyroxine and retinol binding protein. FAP is an autosomal dominant syndrome with onset of symptoms at any point from the second decade onwards. It was first described in 1952 in Portuguese kindreds [34]. It is characterised by progressive peripheral and autonomic neuropathy alongside varying involvement of visceral organs. Extra-neural manifestations predominantly include cardiomyopathy as well as more rarely vitreous amyloid, renal involvement and oculoleptomeningeal amyloid deposition leading to encephalopathy, seizures and dementia. The combination of neuropathy and cardiomyopathy leads to muscle wasting and malnutrition that usually results in death within 9–13 years [35]. The most common encoding mutation is a valine for methionine substitution at position 30 (V30M) and quite numerous cases are seen in Sweden, Japan and Portugal. The T60A variant is most common in the UK, and the low penetrance V122I variant associated with predominant cardiomyopathy occurs in 3–4% of black individuals. Proposed mechanisms of ATTR amyloidogenesis include dissociation of the TTR tetramer into monomers and mechano-enzymatic cleavage with resulting destabilising of the tetrameric TTR protein [36].

15.5.3.2 Non neuropathic Systemic Amyloidosis

The non-neuropathic forms of hereditary systemic amyloidosis were first described in 1932 and are derived from variants of apolipoprotein AI, apolipoprotein AII, lysozyme and fibrinogen A-α chain. Renal involvement is often the most common manifestation however the heart, spleen, liver and bowel may all also be involved. Presentation can vary both within and between kindreds. Clinical presentation is usually around the sixth decade although can occur in early adulthood or before. Following clinical presentation, there is an inexorable progression to organ failure requiring dialysis, organ (renal/cardiac) transplantation or death. In fibrinogen A-α chain amyloidosis the median time from presentation to end stage renal disease (ESRD) is approximately 5 years [37]. The progression of renal disease is much more gradual in apolipoprotein AI and lysozyme amyloidosis with a median time from presentation to ESRD of greater than 10 years.

15.5.3.3 Wildtype Transthyretin Amyloidosis (Previously Known as Senile Systemic Cardiac Amyloidosis)

Wild type transthyretin amyloidosis (ATTRwt) also known as senile systemic/cardiac amyloidosis is a disease of older people with a strong male preponderance. The amyloid deposits are composed of wildtype TTR [38]. The clinical phenotype comprises predominantly of cardiac amyloidosis manifesting as congestive cardiac failure. ATTR deposits are present in other sites including the lungs, gut and bladder, where they can occasionally cause symptoms [39]. Carpal tunnel syndrome is common and often precedes cardiac manifestations by up to a decade or more [40].

15.6 Diagnosis

- **Congo red staining and immunohistochemistry are the standard methods for identification and typing of amyloid deposits in clinical practice**
- **Due to the high prevalence (up to 10%) of monoclonal gammopathies of unknown significance (MGUS) in older populations,**

presence of a monoclonal immunoglobulin is not sufficient to infer that amyloid is of AL type
- **Cardiac MRI (CMR) is a sensitive and very specific method for the diagnosis of cardiac amyloidosis**

15.6.1 Histology

The diagnosis of amyloidosis is frequently made late in its natural history, often months or years after the onset of first symptoms. Delays in diagnosis are due to a combination of the heterogeneous nature of the disease, its perceived rarity and the need for histological confirmation. The gold standard for diagnosis is staining of the deposits with Congo-red and pathognomonic apple green birefringence when the tissue sections are observed under cross polarised light microscopy [41] (Fig. 15.1). Congo red staining has a variable sensitivity depending on user experience with very high specificity when performed optimally [42, 43]. Nonetheless, our own experience of many thousands of cases has been at least 10% false positive and false negative rate when Congo red staining has been performed in nonspecialist laboratories.

Target organ biopsies such as renal, cardiac and gastrointestinal tissue are usually diagnostic. Rectal biopsies have been used in the past as a screening tool for systemic amyloidosis with a published sensitivity of 75–94% [44]. Abdominal fat pad fine needle aspiration is a quick, simple, minimally invasive bedside test that has limited diagnostic sensitivity and experience is required in its interpretation. One recent study reported that abdominal fat aspiration is a useful test in cardiac amyloidosis often sparing the need for an endomyocardial biopsy [45]. In patients with cardiac AL amyloidosis, abdominal fat aspiration sensitivity correlated with whole-body amyloid burden as assessed by SAP component scintigraphy with a sensitivity of 100%, 97% and 78% of those with a large, moderate and small whole body amyloid load, respectively [45]. It was less useful in ATTR cardiac amyloidosis with a diagnostic sensitivity of 45% in variant ATTR and 15% in wildtype ATTR cardiac amyloidosis [45].

15.6.2 Determining the Fibril Precursor Protein

Immunohistochemical (IHC) staining of amyloidotic tissue is widely available for identifying the amyloid fibril protein, but requires specific expertise. It is relatively quick and is the preferred method in clinical practice [41]. An alternative method for diagnosis and typing of amyloid is immuno-electron microscopy [46] but this method is not routinely available, is expensive and performed only in a few centres.

IHC has variable sensitivity and specificity for typing amyloid. Deposits often fail to stain definitively with a panel of antibodies. This is especially problematic in AL amyloid, in which approximately 30% of samples fail to stain definitively with antibodies to kappa or lambda light chains [47].

15.6.3 Proteomics and Mass Spectrometry

Proteomic analyses comprising mass spectrometry on amyloid deposits cut from tissue sections using laser dissection is increasingly used to confirm the presence of amyloid and identify its type. Expert centres estimate between 98 to 100% specificity and sensitivity [48]. A key advantage over traditional IHC is that it can be performed on tiny amounts of formalin fixed tissue, such as a single glomerulus. Experience to date has mainly been with organ biopsies, but the role of proteomics in identifying amyloid in fat aspirates has lately been reported to have sensitivity for diagnosis and identifying the type of amyloid in up to 90% of cases [49].

A challenge in proteomics typing of amyloid is the detection of more than one potentially amyloidogenic protein in the sample, notably both immunoglobulin and TTR, which are abundant plasma proteins. One study has shown that in cases where more than one amyloidogenic protein is detected, decellularisation of amyloid tissue biopsies can increase the accuracy of proteomic typing and substantially enhance the specificity of detecting the culprit protein [50].

15.6.4 Genetic Sequencing

Five to ten percent of systemic amyloidosis is hereditary [51]. Genetic testing is often key to identifying the type of amyloid but the results need to be interpreted in clinical context and with due caution. The phenotype of hereditary forms of amyloid can vary a great deal within a single family, and novel mutations may be completely incidental (i.e. non-disease causing) (see Chap. 12). Conversely, the presence of a known pathogenic and amyloidogenic mutation may also be incidental; for example, the TTR T60A mutation was present in one study in 1 of 100 apparently healthy Irish individuals, and a case was reported in which the presence of this mutation resulted in delayed treatment of AL amyloidosis [52]. The prevalence of MGUS has been estimated at over 5% in patients aged greater than 70 years and 7.5% in those 85 years or older [53]. The frequency of incidental MGUS has been much higher among patients with ATTR amyloidosis referred to our centre, presumably due to referral bias, i.e. the presence of MGUS having erroneously increased the suspicion of amyloidosis.

15.7 Assessment of Organ Involvement and Function

15.7.1 Imaging

15.7.1.1 Serum Amyloid P (SAP) Component Scintigraphy

I^{123} labelled SAP scintigraphy is a specialised imaging technique developed at the NAC which is not generally available. It identifies amyloid deposits in visceral organs such as the spleen, liver, kidneys and adrenal glands [54]. Organ involvement by SAP scintigraphy can be pathognomonic of amyloid subtype. For example, bone uptake is almost always diagnostic of AL amyloidosis (Fig. 15.3). A major limitation of SAP scintigraphy is its inability to identify cardiac or pulmonary amyloid deposits due to movement and blood pool background in the heart and lungs. Also, there is insufficient resolution to identify deposits in hollow, diffuse or very small
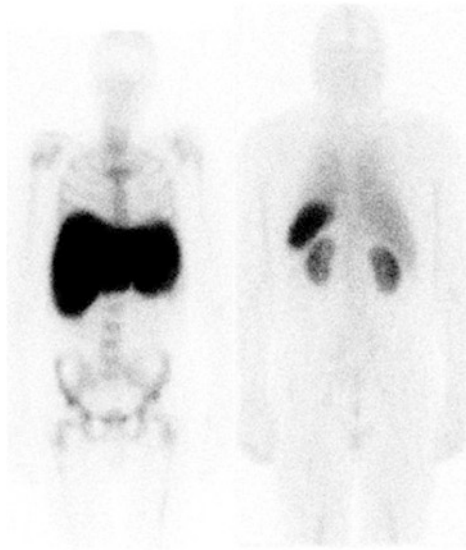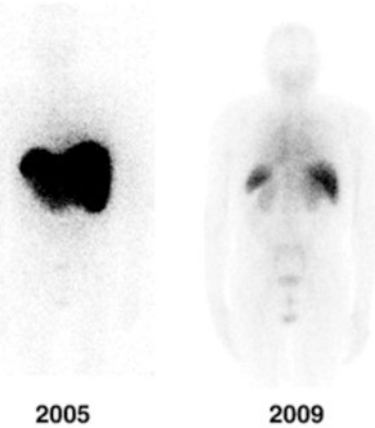
Fig. 15.3 (Left) Anterior whole body scintigraphic image following intravenous injection of ^{123}I-human serum amyloid P (SAP) in a patient with AL amyloidosis. Uptake is seen in the bones, a finding which is pathognomonic for AL amyloidosis and uptake is also present in the liver and spleen. (Right) Posterior whole body SAP scintigraphic image in a patient with hereditary fibrinogen amyloidosis. Uptake is seen in the spleen and kidneys

Fig. 15.4 Posterior whole body images of serum amyloid P (SAP) scintigraphy scans of a patient with systemic monoclonal immunoglobulin type (AL) amyloidosis who presented with major liver involvement and proteinuria in 2005. He responded well to chemotherapy with substantial regression of amyloid by 2009 when his liver and renal function had returned to normal

structures such as the gastrointestinal tract, skin and nerves. However, SAP scintigraphy is a powerful and uniquely informative tool that can determine organ distribution, progression and regression of visceral amyloid deposits. It reveals the dynamic nature of amyloid deposits and remains the only method for estimating organ and whole body load of amyloid as well as the response to treatment (Fig. 15.4) [55].

15.7.1.2 Cardiac Imaging

Cardiac involvement is the key predictor of mortality in systemic amyloidosis [56]. Assessment of cardiac amyloidosis has historically been based on transthoracic echocardiography. This classically demonstrates thickening of the left ventricular free wall and interventricular septal diameter (IVSD) along with restrictive diastolic physiology. A widely used definition of cardiac involvement in systemic AL amyloidosis has been a mean left ventricular wall thickness >12 mm in the absence of an alternative cause of left ventricular hypertrophy

[57]. However, there are many limitations in the use of echocardiography for diagnosis and evaluation of cardiac amyloidosis with studies showing both poor sensitivity and specificity, particularly in differentiating cardiac amyloidosis from other causes of myocardial thickening, such as hypertrophic cardiomyopathy and hypertensive heart disease [58].

CMR in amyloidosis was first reported in 2005 by our group and is now increasingly used in clinical practice to diagnose infiltrative cardiomyopathies. CMR demonstrates the structure of the heart more accurately than echocardiography and contrast studies demonstrate highly characteristic patterns of late gadolinium enhancement, initially in the sub-endocardium and later more diffusely throughout the myocardium, i.e. in a transmural distribution [59]. The dogma that cardiac amyloid causes concentric symmetrical thickening has lately been refuted by CMR studies in ATTR amyloidosis, which demonstrated asymmetrical hypertrophy as the most common pattern of ventricular remodelling [60]. Recently, the role of CMR in systemic amyloidosis has evolved far beyond just diagnostic utility. Amyloid infiltration results in expansion of the extracellular space, which can be measured with

remarkable accuracy using T1 mapping technologies, providing a novel tool to monitor amyloid load in the heart and track response to treatment.

15.7.2 Cardiac Rhythm Analysis

Electrocardiographic changes are common in cardiac amyloidosis. The largest study comprised 127 patients with biopsy proven cardiac AL amyloidosis evaluated at the Mayo Clinic which revealed a characteristic appearance of low QRS voltage (limb leads <5 mm) with poor R wave progression in the chest leads in approximately 50% of patients [61]. Cardiac rhythm analysis is particularly pertinent in patients with cardiac AL amyloidosis where the early mortality rate is very high (30–40%), often within months of diagnosis, due to sudden cardiac death. The prevalence of serious tachyarrhythmias and bradyarrhythmias in patients with cardiac AL amyloidosis has been estimated at up to 30% [62]. A study from our centre using loop recorders in 20 patients with advanced cardiac AL amyloidosis (Mayo Stage 3b) showed that the most frequent preterminal dysrhythmias were bradycardias and complete heart block [63].

Cardiac ATTR amyloidosis is also associated with various electrocardiographic abnormalities, but low QRS voltages occur less often than in cardiac AL amyloidosis [64]. Conduction system disease is common in patients with cardiac ATTR amyloid and atrial fibrillation occurs in 40% of patients [65].

15.7.3 Biochemical Analysis

15.7.3.1 Investigations for Clonal Disease

AL amyloid fibrils are composed of fragments of monoclonal immunoglobulin light chains produced by a clonal B-cell dyscrasia that is often very subtle, but can represent overt MM or lymphoplasmacytoid lymphoma in a small proportion of cases. Characterisation and qualification of the clonal cell dyscrasia requires use of an array of sensitive assays, including serum and urine electrophoresis and immunofixation and serum free light chain assay. Use of the latter technique has greatly improved the sensitivity of detection of an underlying clone [66] but no systemic clone can be identified in approximately 1–2% of patients with systemic AL amyloidosis [67], making both diagnosis and monitoring chemotherapy extremely challenging. All patients should undergo a bone marrow biopsy with aspiration and trephine to assess and further characterize the clonal cell infiltrate. Cytogenetic studies may help predict response to treatment and patient outcome [68]. The translocation t11:14 is present in up to half of patients with systemic AL amyloidosis but fewer than 15% of patients with MM [69]. Traditional skeletal radiographic surveys for bone lesions of MM are now being superseded by more sensitive MRI and low-dose whole-body CT studies [70]. Accurate characterization of the underlying plasma cell disease and determination of where it lies on the spectrum between MGUS and MM is important for both prognosis and treatment options.

15.7.3.2 Cardiac Biomarkers

The two biomarkers used routinely in the diagnosis and monitoring of patients with cardiac amyloidosis are N terminal pro brain natriuretic peptide (NT-proBNP) and high sensitivity cardiac troponin T. Both are part of the widely used Mayo staging system for cardiac AL amyloidosis (Table 15.3) [71]. The Mayo staging provides powerful prognostic information on overall survival in patients with cardiac AL amyloidosis. Median survival is 27 months, 11 months and 4 months in Mayo Stage I, II and III disease, respectively. Further sub-classification of Mayo

Table 15.3 Mayo staging in cardiac AL amyloidosis

Mayo stage	Cardiac biomarkers
Stage 1	NT proBNP <332 ng/L and cardiac troponin T <0.035mcg/L
Stage 2	NT proBNP ≥332 ng/L or cardiac troponin T ≥0.035mcg/L
Stage 3	NT proBNP ≥332 ng/L and cardiac troponin T ≥0.035mcg/L

NT proBNP N terminal pro brain natriuretic peptide

Stage III disease into IIIa and IIIb is used to identify patients at very high risk of early mortality based upon the presence of systolic dysfunction defined as either systolic blood pressure <100 mm/Hg and/or NT-proBNP >8500 ng/L [56]. Both NT-proBNP and cardiac troponin T can be elevated due to other factors including atrial fibrillation, pneumonia and renal failure [72]. The limitations of NT-proBNP in patients with systemic AL amyloidosis and advanced renal excretory impairment have been noted [73]. NT-proBNP may increase substantially during chemotherapy and in response to fluid retention. A greater than 30% fall in NT-proBNP is a key determinant of a cardiac response to treatment in systemic AL amyloidosis, per current consensus criteria [57].

Cardiac ATTR amyloidosis is an increasingly frequently diagnosed progressive cardiomyopathy, the natural history of which can vary significantly. A new staging system for ATTR cardiac amyloidosis based upon a combination of baseline NT-proBNP and estimated glomerular filtration rate (eGFR) identified three disease stages; Stage 1 was defined as NT-proBNP ≤3000 ng/L and eGFR ≥45 mL/min, Stage 3 as an NT-proBNP of ≥3000 ng/L and eGFR ≤45 mL/min and the remainder are stage 2. Median survival in Stage 1, Stage 2 and Stage 3 disease was 69, 46 and 24 months, respectively [65].

15.7.3.3 Renal Biomarkers
Renal involvement in amyloidosis typically manifests with proteinuric CKD, often associated with nephrotic syndrome. Nonetheless the degree of proteinuria varies both between and within different types of renal amyloidosis as well as stage of CKD and/or urinary output. The three key biomarkers for the diagnosis and prognostication of patients with renal amyloidosis are serum albumin, degree of proteinuria and serum creatinine/eGFR. Consensus criteria define renal involvement in systemic AL amyloidosis as non-Bence Jones proteinuria (BJP) of >0.5 g/24 h. Both renal progression and renal response to treatment are dependent upon improvement or worsening of proteinuria in the context of a change in the eGFR.

The monitoring of renal amyloidosis based on proteinuria has its limitations in light of alternative pathologies that can drive urinary protein leak, including diabetes and hypertension. Novel urinary biomarkers have been used in monoclonal gammopathies of renal significance to detect renal insult and may offer improved methods of both diagnosis and monitoring of renal amyloidosis [74].

15.7.3.4 Liver Function Tests
Liver function is often remarkably well preserved despite massive hepatic amyloid infiltration and enlargement. Alkaline phosphatase and γ-glutamyl transferase may rise very substantially before synthetic function is affected, but studies in systemic AL amyloidosis have shown that even a modestly raised bilirubin concentration is associated with a high risk of early death [75].

15.8 Treatment

- **Best supportive care is crucial in the management of systemic amyloidosis**
- **Suppression, or ideally complete elimination, of the supply of the respective amyloid fibril precursor protein is the cornerstone of treatment in amyloidosis**
- **Numerous novel therapies aimed at removing existing amyloid deposits are now in late stage development**

15.8.1 General Management Principles

There are three key principles in the management of systemic amyloidosis. Supportive care to preserve organ function, reduction, or ideally elimination, of the ongoing supply of the respective amyloid fibril precursor protein, and relatively novel therapies aimed at inhibiting the formation of amyloid fibrils or removing existing amyloid deposits.

15.8.1.1 Supportive Care

Best supportive care is vital for patients with all forms of systemic amyloidosis. The aim is to support failing amyloidotic organ function and reduce the risk of complications in vulnerable organs.

Kidneys extensively infiltrated by amyloid are exquisitely vulnerable to intercurrent insults such as hypo/hyper perfusion and nephrotoxic drugs which should be avoided as much as possible. The management of nephrotic syndrome includes meticulous fluid balance encouraging patients to pursue a low salt diet in combination with a total fluid restriction of 1.5 L per day. Diuretic therapy is the mainstay of medical management and loop diuretics are often required at high doses and/or in combination with either thiazide or potassium sparing diuretics [76]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) have been shown to reduce proteinuria and reduce the risk of progression to ESRD in patients with nephrotic syndrome [77]. Nonetheless due to their risk of acute kidney injury they are often not used in the initial setting. One study of 44 patients with systemic AA amyloidosis showed a reduction in proteinuria in patients treated with ARB although there was no clear long-term benefit in reducing the risk of progression to ESRD [78].

Anticoagulation in nephrotic syndrome remains a controversial issue with no clear consensus. Patients with systemic amyloidosis have an increased risk of bleeding due to amyloidotic vascular fragility while patients with heavy proteinuria and associated hypoalbuminemia are at an increased risk of venous thromboembolic disease. Decisions regarding anticoagulation should be made on an individual basis and in high risk patients low molecular weight heparin treatment can offer a suitable option with a short half-life and easy reversal compared to warfarin therapy.

Management of cardiac amyloidosis is challenging. Patients with cardiac amyloidosis do not tolerate hypotension well due to the low cardiac output state and while there are no clear guidelines on the use of traditional heart failure medication, ACE inhibitors and β-blockers are generally best avoided. Arrhythmias are common in AL amyloidosis. The mainstay of therapy is with oral anti-arrhythmias, most commonly amiodarone. There are limited data on the role of implantable intracardiac defibrillators in patients with cardiac amyloidosis. Appropriate device therapy has been reported in a significant proportion of patients and while it has been shown to be lifesaving in the short-term, long-term survival benefit remains unclear [79].

Gastrointestinal involvement can present with chronic diarrhea, malabsorption and cachexia with symptoms often becoming debilitating. Gastrointestinal bleeding can occur manifesting with melena and anemia. Somatostatin analogues have provided relief in some case studies, but if symptoms lead to malnutrition total parenteral nutrition may be needed to support the patient until bowel function improves.

Adrenal involvement in AA amyloidosis is common but frank adrenal insufficiency is rare. Patients are often receiving corticosteroid therapy for their underlying inflammatory condition. Addisonian symptoms can be difficult to identify, particularly orthostatic hypotension which can be explained by alternative pathologies such as nephrotic syndrome and concurrent diuretic use.

Amyloid related autonomic nerve dysfunction is predominantly seen in AL amyloidosis and hereditary ATTR amyloidosis. Autonomic failure often manifests predominantly with postural hypotension but other symptoms include altered bowel habit, incontinence and erectile dysfunction. Anecdotal evidence supports the use of oral inotropes such as midodrine for the treatment of postural hypotension.

15.8.1.2 Organ Transplantation in Hereditary Amyloidosis

Disease modifying treatment for hereditary systemic amyloidosis remains limited. The mainstay of treatment is supportive therapy including organ transplantation for the failing amyloidotic organ. When the liver is the main source of production of variant precursor protein, liver transplantation can be performed to replace the variant protein with the wildtype non amyloidogenic protein.

Fibrinogen, TTR and ApoA1 are predominantly synthesised in the liver. While liver transplantation can be lifesaving in selected patients with hereditary amyloidosis, careful consideration needs to be taken due to the considerable peri-operative risk, long term immunosuppression, renal toxicity and development of secondary malignancies.

Hereditary AFib amyloidosis is a predominantly renal disease leading to ESRD within 5–10 years. Kidney transplantation has been performed in many cases, but recurrence of renal amyloidosis within 7–10 years commonly causes graft failure. While combined liver-kidney transplantation eliminates the source of the amyloidogenic AFib variant, with potential to prevent further amyloid deposition, the procedure is associated with some mortality and is best reserved for younger patients [80].

15.8.2 Treatment of AA Amyloidosis

Treatment depends on the nature of the underlying chronic inflammatory disorder and ranges from potent anti-inflammatory and immunosuppressive biological drugs in patients with rheumatoid arthritis, to lifelong prophylactic colchicine in FMF and surgery in conditions such as refractory osteomyelitis and the cytokine secreting tumors of Castleman disease.

Most patients with AA amyloidosis complicating inflammatory arthritis can now be treated effectively with one or other of the many biological agents now available, i.e. anti-cytokine (TNF, IL-1, IL-6) and anti-CD20 antibodies. Nonetheless, while there have been advances in the use of biologic therapies, progressive renal dysfunction remains common in AA amyloidosis and the need for renal replacement therapy occurs in up to a 40% of patients with a median time to dialysis from diagnosis of 6.5 years. Mortality, amyloid burden and renal prognosis are all significantly correlated with SAA concentration during follow up. In a study of 374 patients with systemic AA amyloidosis, the risk of death was 17.7 times higher in patients with SAA concentrations ≥155 mg/L compared to <4 mg/L. In fact, even in patients with AA amyloidosis and modestly elevated SAA levels (4–9 mg/L), the risk of death was fourfold higher compared to those with SAA <4 mg/L. [12]. Complete suppression of inflammation (SAA concentration persistently <4 mg/L) is frequently associated with gradual regression of amyloid and preservation of renal function [12].

Colchicine (in FMF) at the maximum tolerated dose and IL-1 inhibition with biological agents has revolutionised the management and prognosis of many patients with inherited autoinflammatory/periodic fever syndromes. Work from the NAC in AA amyloidosis complicating hereditary autoinflammatory/periodic fever syndromes has shown that that this diagnosis was not considered in half of patients prior to presentation with AA amyloidosis, almost 25% had evidence of ESRD at presentation and a further 28% developed ESRD over the course of follow-up with a median time of 3.3 years. Of the 46 patients assessed, 24 had FMF (6 were asymptomatic, i.e. phenotype 2-see Chap. 16), 12 TRAPS and 6 CAPS. The majority of patients with FMF (22/24) were treated with high dose colchicine with complete remission in 19 patients and partial remission in one. Of the 12 patients with TRAPS, 6 patients were initially treated with anti-TNF therapy with a transient response seen in 4; all switched to IL-1 blockade. Four patients were treated upfront with IL-1 blockade. Of the 6 patients with CAPS, 4 were treated with IL-1 blockade with dramatic clinical and laboratory improvement and 2 died before the role of IL-1 therapy in CAPS was recognised. Of the total 37 patients from the cohort who were treated successfully, or in whom at least partial remission of the underlying autoinflammatory condition was achieved, 17 (46%) showed amyloid regression, 14 (38%) had a stable amyloid load, and the amyloid deposition increased in 2 (5%) [81].

A Turkish case series of 29 patients with FMF-related amyloidosis receiving IL-1 blockade revealed that in patients with relatively preserved renal excretory function (n = 13) (serum creatinine <130 mmol/L) proteinuria improved dramatically from a median of 3.7 g/24 h to 1.3 g/24 h, while in patients with more advanced CKD at presentation the role of IL-1 blockade was less pronounced [82].

The successful use of IL-6 blockade has been reported in colchicine-resistant FMF and in systemic AA amyloidosis complicating autoinflammatory diseases. IL-6 is a key driver of SAA production, and inhibition of the latter through IL-6 blockade is associated with stabilisation or gradual regression of AA amyloid deposits [83]. In a Turkish series of 12 patients with AA amyloidosis complicating FMF, five of whom had co-existing autoimmune disease, IL-6 blockade reduced the frequency of FMF attacks, suppressed the acute phase response and stabilised renal function [84].

The preferred form of renal replacement therapy in AA amyloidosis remains renal transplantation and suppression of the underlying inflammatory disorder is imperative prior to transplantation and during follow up to prevent recurrence of amyloidosis and graft failure. In a study looking at renal transplantation in 128 patients with AA amyloidosis and ESRF, 43 underwent renal transplantation with a median time from ESRF to transplantation of 1.5 years. The median estimated graft survival non-censored for death was 10.3 years; with 5 and 10-year graft survival of 86% and 59% respectively. Sixteen (37%) patients died, most commonly from infection. Median SAA levels were higher in patients with recurrent amyloid in the graft compared to those in whom amyloid did not recur [85]. In FMF the combination of transplant immunosuppression and prophylactic colchicine remains the mainstay of treatment to prevent systemic inflammation and recurrence of AA amyloidosis. However, there have been case reports of the effective use of IL-1 blockade in patients with colchicine-resistant FMF who underwent renal transplant for AA amyloidosis [86].

No effective specific therapy for AA amyloidosis has yet been developed. A promising agent that ultimately failed to translate into clinical benefit was eprodisate. This is a negatively charged, highly sulphonated molecule that is thought to interfere with the association of AA amyloid fibrils and GAGs, which was shown to inhibit amyloid formation in an experimental murine model of AA amyloidosis [87]. Although a multicentre, international randomised controlled clinical trial of patients with renal impairment due to AA amyloidosis suggested the possibility of clinical benefit [88], a subsequent study designed to confirm and extend these findings found absolutely no benefit, and further development was ceased (results never published).

15.8.3 Treatment of AL Amyloidosis

The current management of AL amyloidosis is aimed at suppressing the underlying B-cell clone as quickly and completely as possible with chemotherapy and novel agents. This in turn halts the production of amyloidogenic light chains. Remission of the underlying clonal disease, i.e. hematologic response, may be associated with preservation of organ function and in some cases improvement in organ function, i.e. organ response, especially when hematologic remission has been sufficient to facilitate some gradual regression of the amyloid deposits.

Consensus criteria to define hematologic and organ response in AL amyloidosis have been devised [89]. Patients who achieve a complete hematologic response have the best clinical outcomes [90]. This is defined by no detectable monoclonal immunoglobulin [M] band in serum or urine by immunofixation and normal free light chains, or a very good partial response, defined as the difference between the involved and uninvolved free light chains (dFLC) <40 mg/L.

Although chemotherapy for AL amyloidosis has very largely been adapted from substantial experience in MM, adverse effects of treatment in patients with amyloidosis are much more frequent and serious, due to the reduced functional reserve of amyloidotic organs and poor performance status of many patients. This has led to risk adapted chemotherapy protocols, with most AL amyloidosis patients being classed as intermediate risk and best suited to cyclic combination chemotherapy regimens. These have historically included oral melphalan with dexamethasone as well as a combination of cyclophosphamide, thalidomide and dexamethasone. More lately, proteasome inhibitors, initially

bortezomib and now others, have become the cornerstone of treatment [91]. First line combination therapy with bortezomib, cyclophosphamide and dexamethasone has been shown to deliver high overall response rates [92]. Ixazomib is the first oral proteasome inhibitor and is available in combination with lenolidamide and dexamethasone after at least one prior line of therapy. Carfilzomib is a novel irreversible proteasome inhibitor approved for relapsed/refractory MM. While Phase I/II studies of its use to treat systemic AL amyloidosis have shown promising hematologic response rates, cardiac, renal and pulmonary toxicity have been noted, warranting close monitoring of side effects and dose reduction.

Autologous stem cell transplantation (ASCT), both in the initial and relapsed disease settings, is an effective treatment for AL amyloidosis leading to deep and durable clonal responses with an excellent median overall survival of over 5 years. However, this high intensity treatment is suitable for only a minority of patients due to significant procedure related morbidity and mortality [93]. Stringent risk stratification has helped improve outcomes, and use of Mayo cardiac staging criteria has resulted recently in procedural mortality rates of 7% or less [93].

Median survival in AL amyloidosis has improved a great deal over the past decade with a current estimated 4-year survival rate of 50%. Sadly, nearly 25% of patients still die from disease related complications within the first few months of treatment and this is primarily due to the presence and severity of cardiac involvement [94].

15.8.4 Novel Therapeutic Approaches in Clinical Trials

A number of different therapies aimed specifically at inhibiting the formation of amyloid fibrils or promoting fibril regression are currently under development, and some have already been clinically evaluated.

In-vitro studies have shown that amyloidogenic misfolding of TTR may be inhibited by compounds that bind TTR in the plasma. Tafamidis, which is a TTR stabiliser, has been developed specifically to treat ATTR amyloidosis and to slow neuropathic disease in patients with V30M familial amyloid polyneuropathy [95]. Diflunisal, a non-steroidal anti-inflammatory drug, has lately been repurposed as an amyloid treatment, unrelated to its anti-inflammatory properties; it also binds to and stabilises TTR in vitro [96]. A randomized controlled trial confirmed that it slows neurological progression in hereditary ATTR amyloidosis [97]. TTR is almost exclusively synthesized by the liver which presents a target for state of the art RNA-inhibiting therapies. Anti-sense oligonucleotide and small interfering RNA therapies have been shown to reduce circulating TTR by 70–85% respectively [98], and phase 3 studies have lately been completed of both class of agents with great success, showing substantial inhibition and even reversal of neuropathic features in FAP [99].

15.8.4.1 Anti-amyloid Antibodies

The role of therapeutic antibodies to directly target existing amyloid deposits is being investigated with vigor. There are currently two monoclonal antibodies that are undergoing testing.

The first antibody approach focuses on the murine monoclonal 11-1F4 antibody prepared against human light chain related fibrils which are recognised as an amyloid-associated conformational epitope [100]. In animal models of mice bearing human amyloidomas, defined as a solitary localised deposit of amyloid, rapid and complete elimination of the masses without toxicity was demonstrated. In an open-label, dose escalation phase I clinical trial, the drug was tolerated well by participants with no grade 4 or 5 adverse events reported. Organ responses were seen in 60% of evaluable patients with a median time to response of only 2 weeks after the start of treatment [101].

The second antibody approach, potentially applicable to all types of amyloidosis, targeted SAP. SAP binds to and is present in all amyloid deposits, which is believed to protect them from degradation by phagocytic cells and proteolytic enzymes [102]. CPHPC, a drug that cross-links pairs of circulating SAP molecules in vivo trigger-

ing their removal by the liver, rapidly and almost completely eliminates SAP from the bloodstream. By contrast, even long term treatment with CPHPC only modestly depletes SAP from amyloid deposits. Subsequent work showed that antibodies to SAP can then target the remaining SAP present in all amyloid deposits, resulting in their rapid clearance by macrophage and complement mediated mechanisms. In an open-label Phase I dose escalation study of 16 patients, a combination of CPHPC and anti-SAP antibody has been shown by ^{123}I-SAP scintigraphy to result in swift and marked removal of liver amyloid deposits with associated improvement in liver function tests [55]. This therapy is currently being tested in a phase 2 trial of patients with cardiac ATTR and cardiac AL amyloidosis.

References

1. Lachmann HJ, Hawkins PN. Systemic amyloidosis. Curr Opin Pharmacol. 2006;6:214–20.
2. Pepys MB. Amyloidosis. In: Frank MM, Austen KF, Claman HN, Unanue ER, editors. Samter's immunologic diseases. 5th ed. Boston: Little, Brown and Company; 1994. p. 637–55.
3. Sipe JD, Benson MD, Buxbaum JN, et al. Nomenclature 2014: Amyloid fibril proteins and clinical classification of the amyloidosis. Amyloid. 2014;21:221–4.
4. Pepys MB. Amyloidosis. Annu Rev Med. 2006;57:223–41.
5. Bonar L, Cohen AS, Skinner MM. Characterization of the amyloid fibril as a cross-beta protein. Proc Soc Exp Biol Med. 1969;131:1373–5.
6. Glenner GG, Eanes ED, Bladen HA, Linke RP, Termine JD. β-pleated sheet fibrils. A comparison of native amyloid with synthetic protein fibrils. Prog Histochem Cytochem. 1974;22:1141–58.
7. Jaroniec CP, MacPhee CE, Bajaj VS, McMahon MT, Dobson CM, Griffin RG. High-resolution molecular structure of a peptide in an amyloid fibril determined by magic angle spinning NMR spectroscopy. Proc Natl Acad Sci U S A. 2004;101:711–6.
8. Pepys MB, Rademacher TW, Amatayakul-Chantler S, et al. Human serum amyloid P component is an invariant constituent of amyloid deposits and has a uniquely homogeneous glycostructure. Proc Natl Acad Sci U S A. 1994;91:5602–6.
9. Botto M, Hawkins PN, Bickerstaff MCM, et al. Amyloid deposition is delayed in mice with targeted deletion of the serum amyloid P component gene. Nat Med. 1997;3:855–9.
10. Reixach N, Deechongkit S, Jiang X, Kelly JW, Buxbaum JN. Tissue damage in the amyloidoses: transthyretin monomers and nonnative oligomers are the major cytotoxic species in tissue culture. Proc Natl Acad Sci U S A. 2004;101:2817–22.
11. Lundmark K, Westermark GT, Nystrom S, Murphy CL, Solomon A, Westermark P. Transmissibility of systemic amyloidosis by a prion-like mechanism. Proc Natl Acad Sci U S A. 2002;99:6979–84.
12. Lachmann HJ, Goodman HJB, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. N Engl J Med. 2007;356:2361–71.
13. Stangou AJ, Hawkins PN, Heaton ND, et al. Progressive cardiac amyloidosis following liver transplantation for familial amyloid polyneuropathy: implications for amyloid fibrillogenesis. Transplantation. 1998;66:229–33.
14. Hawkins PN. Studies with radiolabelled serum amyloid P component provide evidence for turnover and regression of amyloid deposits *in vivo*. Clin Sci. 1994;87:289–95.
15. Van Rooijen N, Sanders A. Liposome mediated depletion of macrophages: mechanism of action, preparation of liposomes and applications. J Immunol Methods. 1994;174:83–93.
16. Pepys MB. Pathogenesis, diagnosis and treatment of systemic amyloidosis. Philos Trans R Soc Lond Ser B Biol Sci. 2001;356:203–10; discussion 10–1.
17. Pinney JH, Smith CJ, Taube JB, et al. Systemic amyloidosis in England: an epidemiological study. Br J Haematol. 2013;161:525–32.
18. Tanskanen M, Peuralinna T, Polvikoski T, et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. Ann Med. 2008;40:232–9.
19. Hawkins PN. Systemic amyloidosis. In: Weinsten WM, Hawkey CJ, Bosch J, editors. Clinical gastroenterology and hepatology. 1st ed. London: Elseiver Health Sciences; 2005. p. 853–8.
20. Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum. 1997;40:1879–85.
21. Sipe J. Revised nomenclature for serum amyloid A (SAA). Nomenclature Committee of the International Society of Amyloidosis. Part 2. Amyloid. 1999;6:67–70.
22. Sun L, Ye RD. Serum amyloid A1: structure, function and gene polymorphism. Gene. 2016;583:48–57.
23. Nakamura T, Higashi S, Tomoda K, Tsukano M, Baba S, Shono M. Significance of SAA1.3 allele genotype in Japanese patients with amyloidosis secondary to rheumatoid arthritis. Rheumatology (Oxford). 2006;45:43–9.
24. Akar N, Hasipek M, Akar E, Ekim M, Yalcinkaya F, Cakar N. Serum amyloid A1 and tumor necrosis factor-alpha alleles in Turkish familial Mediterranean fever patients with and without amyloidosis. Amyloid. 2003;10:12–6.
25. Touitou I. The spectrum of familial Mediterranean fever (FMF) mutations. Eur J Hum Genet. 2001;9:473–83.

26. Mukhin NA, Kozlovskaya LV, Bogdanova MV, Rameev VV, Moiseev SV, Simonyan A. Predictors of AA amyloidosis in familial Mediterranean fever. Rheumatol Int. 2015;35:1257–61.

27. Touitou I, Sarkisian T, Medlej-Hashim M, et al. Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. Arthritis Rheum. 2007;56:1706–12.

28. Lachmann HJ, Papa R, Gerhold K, et al. The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EUROTRAPS international registry. Ann Rheum Dis. 2014;73:2160–7.

29. Georgin-Lavialle S, Stankovic Stojanovic K, Buob D, et al. French Amyloidosis CAPS study: AA Amyloidosis complicating cryopyrin-associated periodic syndrome: a study on 14 cases and review of 53 cases from literature. Pediatr Rheumatol Online J. 2015;13(Suppl 1):P32.

30. Lovat LB, Persey MR, Madhoo S, Pepys MB, Hawkins PN. The liver in systemic amyloidosis: insights from ^{123}I serum amyloid P component scintigraphy in 484 patients. Gut. 1998;42:727–34.

31. Kyle RA, Linos A, Beard CM, et al. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. Blood. 1992;79:1817–22.

32. Kyle RA, Bayrd ED. Amyloidosis: review of 236 cases. Medicine. 1975;54:271–99.

33. Sattianayagam PT, Hawkins PN, Gillmore JD. Systemic amyloidosis and the gastrointestinal tract. Nat Rev Gastroenterol Hepatol. 2009;6:608–17.

34. Dwulet FE, Benson MD. Primary structure of an amyloid prealbumin and its plasma precursor in a heredofamilial polyneuropathy of Swedish origin. Proc Natl Acad Sci U S A. 1984;81:694–8.

35. Suhr O, Danielsson A, Holmgren G, Steen L. Malnutrition and gastrointestinal dysfunction as prognostic factors for survival in familial amyloidotic polyneuropathy. J Intern Med. 1994;235:479–85.

36. Marcoux J, Mangione PP, Porcari R, et al. A novel mechano-enzymatic cleavage mechanism underlies transthyretin amyloidogenesis. EMBO Mol Med. 2015;7:1337–49.

37. Gillmore JD, Lachmann HJ, Rowczenio D, et al. Diagnosis, pathogenesis, treatment, and prognosis of hereditary fibrinogen A alpha-chain amyloidosis. J Am Soc Nephrol. 2009;20:444–51.

38. Westermark P, Sletten K, Johansson B, Cornwell GG. Fibril in senile systemic amyloidosis is derived from normal transthyretin. Proc Natl Acad Sci U S A. 1990;87:2843–5.

39. Westermark P, Bergstrom J, Solomon A, Murphy C, Sletten K. Transthyretin-derived senile systemic amyloidosis: clinicopathologic and structural considerations. Amyloid. 2003;10(Suppl 1):48–54.

40. Youngstein T, Gilbertson JA, Hutt DF, et al. Carpal Tunnel biopsy identifying transthyretin amyloidosis. Arthritis Rheumatol (Hoboken, NJ). 2017;69:2051.

41. Puchtler H, Sweat F, Levine M. On the binding of Congo red by amyloid. J Histochem Cytochem. 1962;10:355–64.

42. van Gameren II, Hazenberg BP, Bijzet J, van Rijswijk MH. Diagnostic accuracy of subcutaneous abdominal fat tissue aspiration for detecting systemic amyloidosis and its utility in clinical practice. Arthritis Rheum. 2006;54:2015–21.

43. Guy CD, Jones CK. Abdominal fat pad aspiration biopsy for tissue confirmation of systemic amyloidosis: specificity, positive predictive value, and diagnostic pitfalls. Diagn Cytopathol. 2001;24:181–5.

44. Ebert EC, Nagar M. Gastrointestinal manifestations of amyloidosis. Am J Gastroenterol. 2008;103:776–87.

45. Quarta CC, Gonzalez-Lopez E, Gilbertson JA, et al. Diagnostic sensitivity of abdominal fat aspiration in cardiac amyloidosis. Eur Heart J. 2017;38:1905–8.

46. Silver MM, Hearn SA, Walton JC, Lines LA, Walley VM. Immunogold quantitation of immunoglobulin light chains in renal amyloidosis and kappa light chain nephropathy. Am J Pathol. 1990;136:997–1007.

47. Gilbertson JA, Theis JD, Vrana JA, et al. A comparison of immunohistochemistry and mass spectrometry for determining the amyloid fibril protein from formalin-fixed biopsy tissue. J Clin Pathol. 2015;68:314–7.

48. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR 3rd, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood. 2009;114:4957–9.

49. Vrana JA, Theis JD, Dasari S, et al. Clinical diagnosis and typing of systemic amyloidosis in subcutaneous fat aspirates by mass spectrometry-based proteomics. Haematologica. 2014;99:1239–47.

50. Mangione PP, Mazza G, Gilbertson JA, et al. Increasing the accuracy of proteomic typing by decellularisation of amyloid tissue biopsies. J Proteome. 2017;165:113–8.

51. Lachmann HJ, Booth DR, Booth SE, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. N Engl J Med. 2002;346:1786–91.

52. Landau HJ, Comenzo RL, Zhou P, et al. Al amyloidosis in a patient with a T60A TTR mutation. XIth International Symposium on Amyloidosis 2008:160–2.

53. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med. 2006;354:1362–9.

54. Hawkins PN, Lavender JP, Pepys MB. Evaluation of systemic amyloidosis by scintigraphy with ^{123}I-labeled serum amyloid P component. N Engl J Med. 1990;323:508–13.

55. Richards DB, Cookson LM, Berges AC, et al. Therapeutic clearance of amyloid by antibodies to serum amyloid P component. N Engl J Med. 2015;373:1106–14.

56. Wechalekar AD, Schonland SO, Kastritis E, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood. 2013;121:3420–7.

57. Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis. Am J Hematol. 2005;79:319–28.

58. Falk RH. Diagnosis and management of the cardiac amyloidoses. Circulation. 2005;112:2047–60.

59. Perugini E, Rapezzi C, Piva T, et al. Non-invasive evaluation of the myocardial substrate of cardiac amyloidosis by gadolinium cardiac magnetic resonance. Heart. 2006;92:343–9.

60. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, et al. Magnetic resonance in transthyretin cardiac amyloidosis. J Am Coll Cardiol. 2017;70:466–77.

61. Murtagh B, Hammill SC, Gertz MA, Kyle RA, Tajik AJ, Grogan M. Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. Am J Cardiol. 2005;95:535–7.

62. Dubrey SW, Cha K, Anderson J, et al. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. QJM. 1998;91:141–57.

63. Sayed RH, Rogers D, Khan F, et al. A study of implanted cardiac rhythm recorders in advanced cardiac AL amyloidosis. Eur Heart J. 2015;36:1098–105.

64. Rapezzi C, Merlini G, Quarta CC, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. Circulation. 2009;120:1203–12.

65. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J. 2018;39:2799–806.

66. Lachmann HJ, Gallimore R, Gillmore JD, et al. Outcome in systemic AL amyloidosis in relation to changes in concentration of circulating free immunoglobulin light chains following chemotherapy. Br J Haematol. 2003;122:78–84.

67. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation. 2016;133:2404–12.

68. Bochtler T, Hegenbart U, Kunz C, et al. Prognostic impact of cytogenetic aberrations in AL amyloidosis patients after high-dose melphalan: a long-term follow-up study. Blood. 2016;128:594–602.

69. Bahlis NJ, Lazarus HM. Multiple myeloma-associated AL amyloidosis: is a distinctive therapeutic approach warranted? Bone Marrow Transplant. 2006;38:7–15.

70. Derlin T, Bannas P. Imaging of multiple myeloma: current concepts. World J Orthop. 2014;5:272–82.

71. Dispenzieri A, Gertz M, Kyle R, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol. 2004;22:3751–7.

72. Mannu GS. The non-cardiac use and significance of cardiac troponins. Scott Med J. 2014;59:172–8.

73. Palladini G, Foli A, Milani P, et al. Best use of cardiac biomarkers in patients with AL amyloidosis and renal failure. Am J Hematol. 2012;87:465–71.

74. Sanders PW. Mechanisms of light chain injury along the tubular nephron. J Am Soc Nephrol. 2012;23:1777–81.

75. Sattianayagam PT. The pathogenesis, investigation and management of systemic amyloidosis. London: UCL Medical School; 2012.

76. Brater DC. Diuretic therapy. N Engl J Med. 1998;339:387–95.

77. Ruggenenti P, Mosconi L, Vendramin G, et al. ACE inhibition improves glomerular size selectivity in patients with idiopathic membranous nephropathy and persistent nephrotic syndrome. Am J Kidney Dis. 2000;35:381–91.

78. Odabas AR, Cetinkaya R, Selcuk Y, Bilen H. Effect of losartan treatment on the proteinuria in normotensive patients having proteinuria due to secondary amyloidosis. Ups J Med Sci. 2001;106:183–8.

79. Rezk T, Whelan CJ, Lachmann HJ, et al. Role of implantable intracardiac defibrillators in patients with cardiac immunoglobulin light chain amyloidosis. Br J Haematol. 2018;182:145–8.

80. Gillmore JD, Lachmann HJ, Wechalekar A, Hawkins PN. Hereditary fibrinogen A alpha-chain amyloidosis: clinical phenotype and role of liver transplantation. Blood. 2010;115:4313; author reply 4–5.

81. Lane T, Loeffler JM, Rowczenio DM, et al. AA amyloidosis complicating the hereditary periodic fever syndromes. Arthritis Rheum 2013;65(4):1116–1121.

82. Ugurlu S, Ergezen B, Hacioglu A, Ozdogan H. Anti-interleukin 1 therapy in FMF amyloidosis: a single center experience (Case Series). Ann Rheum Dis. 2017;76:412.

83. Lane T, Gillmore JD, Wechalekar AD, Hawkins PN, Lachmann HJ. Therapeutic blockade of interleukin-6 by tocilizumab in the management of AA amyloidosis and chronic inflammatory disorders: a case series and review of the literature. Clin Exp Rheumatol. 2015;33(Suppl 94):46–53.

84. Ugurlu S, Hacioglu A, Adibnia Y, Hamuryudan V, Ozdogan H. Tocilizumab in the treatment of twelve cases with aa amyloidosis secondary to familial Mediterranean fever. Orphanet J Rare Dis. 2017;12:105.

85. Pinney JH, Lachmann HJ, Sattianayagam PT, et al. Renal transplantation in systemic amyloidosis-importance of amyloid fibril type and precursor protein abundance. Am J Transplant. 2013;13:433–41.

86. Moser C, Pohl G, Haslinger I, et al. Successful treatment of familial Mediterranean fever with anakinra and outcome after renal transplantation. Nephrol Dial Transplant. 2009;24:676–8.

87. Kisilevsky R, Ancsin JB, Szarek WA, Petanceska S. Heparan sulfate as a therapeutic target in amyloidogenesis: prospects and possible complications. Amyloid. 2007;14:21–32.

88. Dember LM, Hawkins PN, Hazenberg BPC, et al. Eprodisate for the treatment of renal disease in AA amyloidosis. N Engl J Med. 2007;356:2349–60.

89. Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain (AL) amyloidosis. Leukemia. 2012;26:2317–25.

90. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol. 2012;30:4541–9.

91. Dimopoulos MA, Kastritis E. Bortezomib for AL amyloidosis: moving forward. Blood. 2011;118:827–8.

92. Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression free survival. Blood. 2012;119:4387–90.

93. Venner CP, Lane T, Foard D, et al. Stringent patient selection improves outcomes in patients with AL amyloidosis undergoing autologous stem cell transplantation. International Society of Amyloidosis; XIIIth International Symposium on Amyloidosis from misfolded proteins to well-designed treatment. 2012;PC58(May):211.

94. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet. 2016;387:2641–54.

95. Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology. 2012;79:785–92.

96. Sekijima Y, Dendle MA, Kelly JW. Orally administered diflunisal stabilizes transthyretin against dissociation required for amyloidogenesis. Amyloid. 2006;13:236–49.

97. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. JAMA. 2013;310:2658–67.

98. Coelho T, Adams D, Silva A, et al. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. N Engl J Med. 2013;369:819–29.

99. Adams D, Suhr OB, Dyck PJ, et al. Trial design and rationale for APOLLO, a Phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. BMC Neurol. 2017;17:181.

100. Edwards CV, Gould J, Langer AL, et al. Interim analysis of the phase 1a/b study of chimeric fibril-reactive monoclonal antibody 11-1F4 in patients with AL amyloidosis. Amyloid. 2017;24(suppl 1):58–9.

101. Edwards CV, Gould J, Langer AL, et al. Final analysis of the phase 1a/b study of chimeric fibril-reactive monoclonal antibody 11-1f4 in patients with relapsed or refractory AL amyloidosis. Blood. 2017;130:509.

102. Tennent GA, Lovat LB, Pepys MB. Serum amyloid P component prevents proteolysis of the amyloid fibrils of Alzheimer's disease and systemic amyloidosis. Proc Natl Acad Sci U S A. 1995;92:4299–303.