BMJ Best Practice

Amyloidosis

Straight to the point of care

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Summary

Amyloidosis is a rare disease. Immunoglobulin light chain (AL) amyloidosis (also called primary systemic amyloidosis) is the most common type of amyloidosis.

Amyloidosis occurs when amyloid proteins are deposited in tissue and organs. It may have a primary cause, may be inherited, or may be secondary to other diseases.

Amyloidosis usually presents with unexplained weight loss, fatigue, and oedema resistant to diuretic therapy.

Serum and urine immunofixation electrophoresis confirms the presence of monoclonal light chains in AL amyloidosis. Biopsy verification of amyloid deposits is essential for diagnosis. Accurate classification of amyloid deposit in tissues is necessary prior to initiating appropriate therapy.

Resulting clinical syndromes of amyloidosis include nephrotic syndrome, neuropathy, cardiomyopathy, and conduction abnormalities.

Treatment for AL amyloidosis is high-dose myeloablative chemotherapy with autologous stem cell transplantation (in eligible patients) or systemic therapy, or both.

Definition

Amyloidosis is caused by the deposition of amyloid proteins in tissue and organs. Any histological tissue specimen that binds Congo red and demonstrates green birefringence when viewed under polarised light is, by definition, an amyloid deposit.

Deposits of amyloid may be localised in tissue or part of a systemic process. Progressive deposition of amyloid is disruptive to tissue and organ function and manifests its clinical sequelae by the dysfunction of those organs in which it deposits.[1] [2]

Epidemiology

Amyloidosis is rare. Immunoglobulin light chain (AL) amyloidosis is the most common type.[4]

Worldwide, the crude annual incidence of AL amyloidosis is estimated at 10.44 cases per million population (PMP), ranging from 6.72 PMP in Brazil to 14.3 PMP in Japan.[5]

One US-based study reported an increase in prevalence of AL amyloidosis from 15.5 cases per million in 2007 to 40.5 cases per million in 2015.[6] The prevalence and incidence of AL amyloidosis is higher in males than in females.[6] Average age at diagnosis is reported to be between 63 and 65 years, but patients can present at any age.[6] [7]

Studies assessing ethnic disparities in AL amyloidosis are sparse. Potential underdetection of cardiac amyloidosis among black Americans has been reported in one cohort study.[8] In another cohort of US patients with AL amyloidosis, self-identified ethnic minorities (including non-Hispanic black and Hispanic) accounted for 334 (14%) of 2416 patients from a single referral centre. This percentage is lower than the reported >36% representation of racial/ethnic minorities in the US general population, suggesting underdetection of AL amyloidosis among ethnic minorities.[9] Of note, the incidence of multiple myeloma and monoclonal gammopathy of undetermined significance (MGUS), both closely related to amyloidosis, is approximately two- to threefold greater in black people than in white people.[10] [11] [12] The incidence of monoclonal gammopathy disorders is lower in Asian people compared with white people.[12]

Transthyretin (TTR) amyloidosis has historically been considered a rare condition. Precise estimates of incidence and prevalence are not available, but growing evidence suggests that it is more common than previously assumed and often goes undiagnosed in patients with cardiomyopathy.[13] [14]

The incidence of secondary (AA) amyloidosis in the Western world has been falling, possibly due to advances in treatment for chronic inflammatory diseases.[15] [16] [17] Epidemiological study data indicate that, in 2008, AA amyloidosis accounted for approximately 18% of incident systemic amyloidoses in England.[18]

Aetiology

Systemic amyloidosis is characterised by considerable aetiological heterogeneity, but clinical manifestations of the different amyloidoses may overlap.[19]

Immunoglobulin light chain (AL) amyloidosis

Aetiology is unknown; however, AL amyloidosis is associated with a clonal plasma cell dyscrasia, and is closely related to multiple myeloma. Less than 0.5% of patients diagnosed with AL amyloidosis will progress to overt multiple myeloma.[20]

Patients with AL amyloidosis and co-existing multiple myeloma have a poor prognosis (median overall survival <16 months).[21]

Secondary (AA) amyloidosis (non-familial)

Inflammatory polyarthropathies account for 60% of cases; conditions include rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis.[16] The risk of developing AA amyloidosis from chronic

inflammatory arthritides is decreasing, possibly due to advances in treatment for chronic inflammatory diseases.[15] [16] [17]

Inflammatory bowel disease (specifically Crohn's disease), bronchiectasis, tuberculosis, subcutaneous injection of illicit drugs, decubitus ulcers, chronic urinary tract infections, and osteomyelitis can result in AA amyloidosis.[16] Castleman's disease is a non-cancerous lymphoproliferative disorder, where the plasma cell variant can cause AA amyloidosis.[22] [23]

The likelihood of developing AA amyloidosis in the absence of one of these non-familial inflammatory disorders is extremely small.

Familial periodic fever syndromes leading to AA amyloidosis

Familial Mediterranean fever, tumour necrosis factor (TNF) receptor-associated periodic fever syndromes (TRAPS), cryopyrin-associated periodic syndromes (CAPS; e.g., Muckle-Wells syndrome), and mevalonate kinase deficiency (formerly known as hyper-IgD syndrome) have been implicated.[24] [25] [26] [27]

The likelihood of developing AA amyloidosis in the absence of one of these familial inflammatory disorders is extremely small.

Hereditary (familial) amyloidosis

Aetiology of hereditary (familial) amyloidosis includes mutations of:[3]

- Transthyretin (TTR), leading to progressive cardiomyopathy or progressive neuropathy or both
- Fibrinogen A alpha-chain, mainly leading to renal involvement
- Apolipoprotein A, mainly leading to renal involvement
- Lysozyme, mainly leading to renal involvement

A monoclonal gammopathy may be present in patients with hereditary amyloidosis, which can lead to a misdiagnosis of AL amyloidosis.[28] [29] Clinical awareness, a careful family history, and laboratory/pathological evaluation (including genetic testing) are essential to avoid a misdiagnosis of AL amyloidosis in this setting.[30]

Leukocyte chemotactic factor 2 (LECT2) amyloidosis

LECT2 amyloidosis mainly affects the kidney.[3] It is common among certain ethnicities (e.g., Egyptian, Indian, Pakistani, Hispanic).[31] [32] [33] Aetiology is unknown; genetics may have a role but pathogenic mutations have not been identified.[32] [33][34]

Pathophysiology

Amyloidosis comprises a group of disorders that contribute to tissue damage, and organ dysfunction, through the deposition of amyloid proteins.

Immunoglobulin light chain (AL) amyloidosis

- AL amyloidosis is caused by clonal plasma cells that produce abnormal immunoglobulin light chains that are inherently prone to misfolding from a native alpha-helical state into an insoluble beta-pleated sheet configuration.[35]

- The development of amyloidosis is linked both to the quantity of light chain that is produced, as well as a qualitative thermodynamic tendency for the light chain fragment to misfold into the amyloid configuration.[36] [37]
- The kidney and the heart are the primary target organs in AL amyloidosis. The liver and nerves can also be targeted.
- Significant differences in gene usage are found in AL amyloidosis.[38] Patients with AL clones derived from 6aV lambda VI germline gene usage are more likely to present with dominant renal involvement. Those with clones derived from 1c, 2a2, and 3r V lambda genes are more likely to present with cardiac and multisystem disease.[39]
- Renal involvement is reported in approximately 55% of patients with AL amyloidosis.[40] The light chains interact with mesangial cells, which catabolise them into fragments that form amyloid fibrils.[41] Amyloid fibrils deposit extracellularly in the mesangium and capillary loops, resulting in disruption of the glomerular basement membrane.[41]
- Cardiac involvement is reported in 55% to 76% of patients with AL amyloidosis, and is the main cause of death in these patients.[42] [43] [44] Amyloid fibrils deposit extracellularly within the myocardium, which disrupts myocardial contractility and relaxation, and electrical conductance.[45] [46] Cardiac amyloidosis resembles idiopathic restrictive cardiomyopathy, but ventricular long axis function is depressed in all patients with cardiac amyloidosis compared with only 36% of patients with idiopathic restrictive cardiomyopathy.[47]
- Liver involvement is reported in approximately 15% of patients with AL amyloidosis.[48] Approximately 10% of patients have palpable hepatomegaly (>5 cm below the right costal margin).[16] [49]
- Nerve involvement is reported in 10% of patients with AL amyloidosis.[48] Amyloid deposits in the vasa nervorum result in clinical findings similar to ischaemic neuropathy and lead to a mixed axonal demyelinating picture. Carpal tunnel syndrome occurs in approximately 50% of patients.[50] The presence of autonomic neuropathy (e.g., signs of erectile dysfunction, orthostatic hypotension, gastrointestinal dysfunction, or urinary dysfunction) is an important clue.[51]

Secondary (AA) amyloidosis (non-familial) and familial periodic fever syndromes

- AA amyloidosis results from impaired proteolysis of the acute phase reactant, serum amyloid A protein (SAA). N-terminal fragments of SAA, termed amyloid A, are deposited as fibrils in tissue and organs, causing organ damage. Amyloid A is common to AA amyloidosis (non-familial) and familial periodic fever syndromes.
- AA amyloidosis most commonly affects the kidney and less commonly the gastrointestinal tract and thyroid.[52] [53] The most common late sequela of sustained production of AA amyloid is dialysis-dependent renal failure.
- Long-term survivors of AA amyloidosis (non-familial) can develop cardiac amyloidosis, but with a frequency much lower than that seen in AL amyloidosis and familial periodic fever syndromes.

Hereditary (familial) amyloidosis

- Most forms of hereditary amyloidosis are a consequence of misfolding of an inherited mutant transthyretin (TTR) molecule.
- Rarer forms of hereditary amyloidosis are due to mutations of apolipoprotein A1, apolipoprotein A2, fibrinogen, gelsolin, and lysozyme.
- Hereditary TTR amyloidosis usually presents as cardiomyopathy and/or neuropathy (peripheral and autonomic).[54] [55]

Wild-type transthyretin (ATTRwt) amyloidosis

- Occurs in the elderly and is sometimes referred to as senile systemic amyloidosis or senile cardiac amyloidosis.[54]
- Amyloid deposition occurs predominantly in the heart. Up to 20% of patients may have mild peripheral neuropathy.[56]

Leukocyte chemotactic factor 2 (LECT2) amyloidosis

- Caused by abnormal LECT2 protein.[57]
- Amyloid deposition occurs mainly in the kidney.[3][33] Other organs may be involved (e.g., liver)

Classification

Types of amyloidosis[3]

- Localised
- Systemic
    - Derived from immunoglobulin light chains (referred to as AL amyloidosis or primary systemic amyloidosis)
    - Derived from amyloid A protein (referred to as AA amyloidosis or secondary amyloidosis)
    - Derived from other proteins (e.g., leukocyte chemotactic factor 2 [LECT2])
- Familial periodic fever syndromes causing AA amyloidosis
    - Familial Mediterranean fever
    - Tumour necrosis factor (TNF) receptor-associated periodic fever syndromes (TRAPS)
    - Cryopyrin-associated periodic syndromes (CAPS; e.g., Muckle-Wells syndrome)
    - Mevalonate kinase deficiency (formerly known as hyper-IgD syndrome)
- Hereditary (familial) amyloidosis
    - Hereditary transthyretin (TTR) amyloidosis (referred to as variant or ATTRv amyloidosis)
        - Neuropathy
        - Cardiomyopathy
    - Fibrinogen amyloidosis
    - Apolipoprotein amyloidosis
    - Gelsolin amyloidosis
    - Lysozyme amyloidosis
- Wild-type TTR amyloidosis (referred to as ATTRwt amyloidosis)
- Dialysis-related amyloidosis (beta-2 microglobulin amyloidosis)

Case history

Case history #1

A 79-year-old man presents with dyspnoea on exertion for 1 year and lower extremity oedema. As part of a cardiac evaluation, the echocardiogram shows concentric left ventricular hypertrophy. Cardiac catheterisation shows normal coronary arteries and he is referred for further evaluation of non-cardiac dyspnoea.

Case history #2

A 62-year-old man is referred for management of atypical multiple myeloma. He has mild anaemia (haemoglobin 12 g/dL) and urinary protein loss of 2.2 g/day. Urine immunofixation electrophoresis shows free lambda light chains. Bone marrow examination shows 5% plasma cells and does not fulfil criteria for multiple myeloma.

Other presentations

Patients with amyloidosis may present with unexplained cardiomyopathy, non-diabetic proteinuria, unexplained hepatomegaly, axonal or demyelinating peripheral neuropathy with autonomic features, or atypical multiple myeloma.

Approach

The diagnostic work-up of amyloidosis includes a detailed history and physical examination; laboratory and pathological evaluation (including studies to confirm the presence and type of amyloid deposits in tissue); and imaging studies.

It is important to determine amyloidosis type when making a diagnosis, as this guides treatment.

History

A detailed history should be carried out to help to determine the potential cause and type of amyloidosis.

History may reveal a prior diagnosis of monoclonal gammopathy of undetermined significance (MGUS).[58] Patients with MGUS have a relative risk of progression to AL amyloidosis (the most common type of amyloidosis) of eight- to ninefold.[4] [58] [59] It is important to note, however, that an incidental monoclonal gammopathy may be present in patients with other types of amyloidosis (e.g., hereditary amyloidosis, wild-type transthyretin [ATTRwt] amyloidosis), which can lead to a misdiagnosis of AL amyloidosis.[28] [29] [61] Clinical awareness together with a careful family history and laboratory/pathological evaluation (including genetic testing) are essential to avoid a misdiagnosis.[30] [62]

Secondary (AA) amyloidosis is associated with:[16] [22] [23] [24] [25] [26] [27]

- chronic inflammatory conditions (e.g., inflammatory polyarthropathy, inflammatory bowel disease [specifically Crohn's disease])
- chronic infections (e.g., bronchiectasis, tuberculosis, subcutaneous injection of illicit drugs, decubitus ulcers, chronic urinary tract infections, osteomyelitis)
- familial periodic fever syndromes (e.g., familial Mediterranean fever, tumour necrosis factor [TNF] receptor-associated periodic fever syndromes [TRAPS], cryopyrin-associated periodic syndromes [CAPS; such as Muckle-Wells syndrome], mevalonate kinase deficiency [formerly known as hyper-IgD syndrome])
- Castleman disease (plasma cell variant), a noncancerous lymphoproliferative disorder, but this is rare.

ATTRwt is associated with ageing and affects mainly elderly men. History often includes cardiomyopathy, carpal tunnel syndrome, and spinal stenosis.[63]

Symptoms

Patients with amyloidosis frequently present with symptoms relating to a clinical syndrome of the affected organ (e.g., cardiomyopathy, nephrotic syndrome, neuropathy).[64]

Fatigue, weight loss, paraesthesias, and dyspnoea on exertion are the most common symptoms associated with amyloidosis and are common to all systemic forms.[42] However, these complaints are non-specific.

Extreme weight loss (e.g., >9 kg) is common (particularly in patients with cardiac and hepatic involvement) and is suggestive of amyloidosis if associated with oedema or neuropathy.[49]

Cardiac symptoms

Cardiac involvement is most commonly associated with AL amyloidosis and transthyretin (TTR)-related amyloidosis (hereditary and wild type).[42] [43] [49] [54] [55] [65]

Lightheadedness can be a symptom of cardiac amyloidosis (low cardiac output with preserved ejection fraction). Patients may have jaw claudication, calf and limb claudication, and rarely angina if there is involvement of the coronary arterioles.

Fatigue and dyspnoea on exertion caused by early cardiac involvement are generally not recognised as symptoms of overt heart failure and can be misdiagnosed as being stress-related or functional.

Renal involvement

Most commonly associated with AL amyloidosis, AA amyloidosis, non-TTR hereditary amyloidosis (e.g., fibrinogen A alpha-chain, apolipoprotein A), and leukocyte chemotactic factor 2 (LECT2) amyloidosis.[3] [16] [33] [40] [52] [60]

Fatigue and lightheadedness are symptoms of nephrotic syndrome (hypoalbuminemia and intravascular volume contraction).

Neurologic symptoms

Nerve involvement can lead to peripheral and autonomic neuropathy, and is most commonly associated with AL amyloidosis and hereditary TTR (ATTRv) amyloidosis.[19] [49] [66] [67] [68] [69] Mild peripheral neuropathy may occur in patients with ATTRwt amyloidosis (up to 20%).[56]

Nerve involvement is not a typical feature of AA amyloidosis, non-TTR hereditary amyloidosis, or LECT2 amyloidosis.[3]

Initial presentation of peripheral neuropathy is usually distal symmetric sensory loss (i.e., loss of temperature and pain perceptions, followed by proprioceptive loss).[51] Patients usually report dysaesthesia and paraesthesia of the feet and lower legs, which progress to the hands and arms over time.

Patients with autonomic neuropathy may have erectile dysfunction, orthostatic hypotension, gastrointestinal dysfunction, or urinary dysfunction.[19] [69] Sweating abnormalities and failure of heart rate to change when body position is changed are signs of autonomic dysfunction.

Peripheral and autonomic neuropathy are important diagnostic clues for AL amyloidosis and ATTRv amyloidosis.[51]

Carpal tunnel syndrome prevalence is greatest in patients with TTR cardiac amyloidosis (20.3% vs. 4.1% in the general population), but it is also a manifestation of AL amyloidosis.[70] Tinel's sign (tapping over the carpal nerve at the wrist produces tingling in the thumb, index, and middle finger) and Phalen's manoeuvre (holding the dorsal surface of both hands together in forced flexion for around 1 minute produces tingling in the thumb, index, and middle finger) should be performed to test for carpal tunnel syndrome involvement in patients reporting paraesthesia in the hands.

Gastrointestinal symptoms

Steatorrhoea is typical of intestinal involvement. Severe faecal incontinence alternating with 3-4 days of constipation may be present.

Pseudo-obstructive symptoms (including nausea, vomiting, post-prandial abdominal cramping) and gastroparesis may be present if there is upper gastrointestinal tract involvement.

Musculoskeletal symptoms

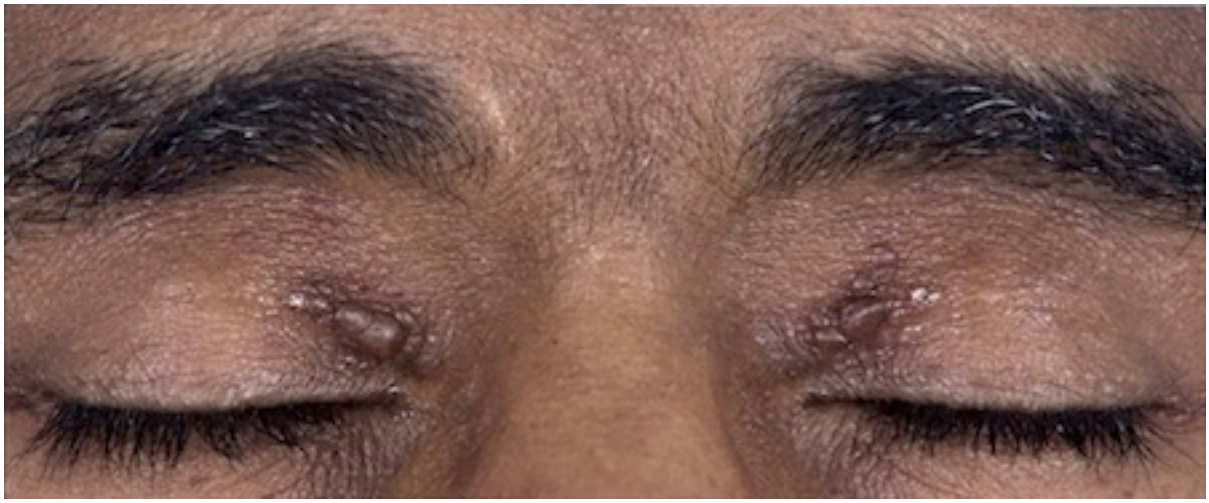
Musculoskeletal disorders (e.g., biceps tendon rupture, hip and knee osteoarthritis, trigger finger, and spinal stenosis) are typically associated with TTR amyloidosis, and may precede cardiac or neurological manifestations.[71] [72]

Physical examination

Common physical findings include lower extremity oedema and elevated jugular venous distention (due to high right-sided filling pressure).[73] [74]

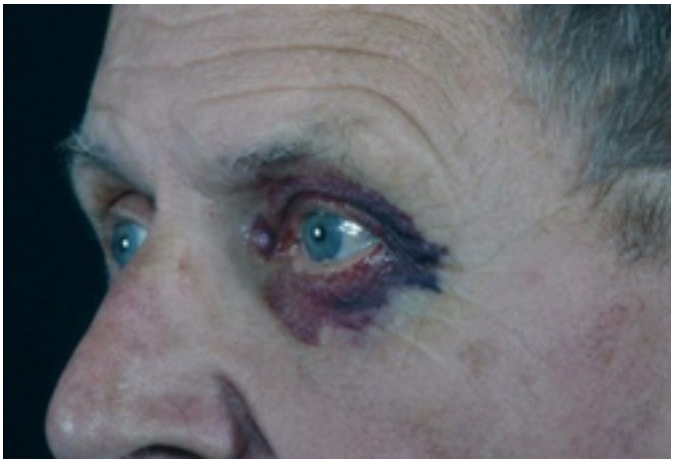
Many physical findings of amyloidosis are specific and diagnostic for amyloidosis, but are present in ≤15% of patients.[49]

- Amyloid purpura: occurs in approximately 15% of patients with AL amyloidosis.[49] Typically periorbital but can occur anywhere above the nipple line.
- Eyelid petechiae: common, but evident only when the patient's eyes are closed.
- Macroglossia: specific and diagnostic for AL amyloidosis.[49] Occurs in approximately 10% of patients but is easily overlooked because the most common presentation is dental indentations on the underside of the tongue.
- Enlargement of the submandibular salivary glands: specific for AL amyloidosis. It may be misinterpreted as lymphadenopathy. Salivary gland involvement results in a sicca syndrome. These patients are often misdiagnosed as having Sjögren's syndrome.
- Palpable hepatomegaly: >5 cm below the right costal margin, most commonly reported in AL amyloidosis (approximately 10% of patients).[16] [49] Splenomegaly is usually of modest degree. Palpable hepatomegaly is uncommon in AA amyloidosis, but histopathological changes in the liver may be evident. Liver involvement is rare in patients with hereditary amyloidosis.
- Shoulder pad sign: rare, due to periarticular infiltration with amyloid; pseudohypertrophy is specific for AL amyloidosis.
- Diffuse muscular weakness: amyloid myopathy can occur with muscle hypertrophy due to extracellular amyloid infiltration in the muscle, or can occur with muscular atrophy due to vascular occlusion leading to muscle ischaemia and claudication.
- Orthostatic hypotension with syncope: can occur if autonomic neuropathy is present (e.g., in AL amyloidosis or ATTRv amyloidosis).



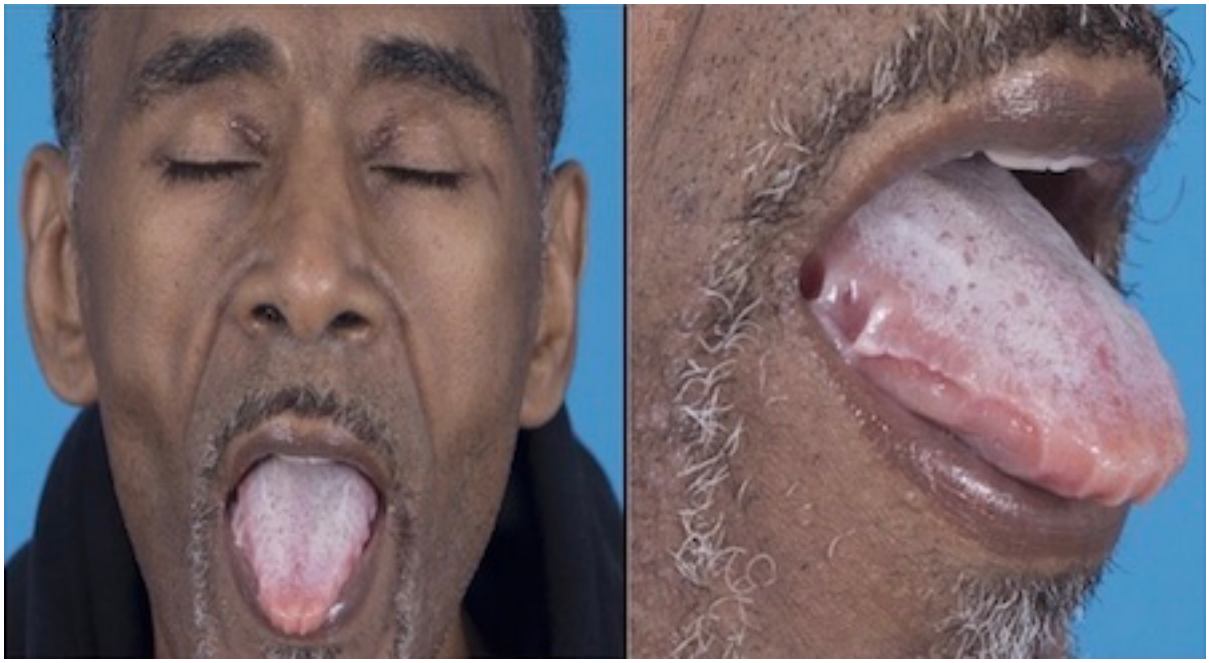
Bilateral periorbital ecchymosis (amyloid purpura) in a patient with AL amyloidosis

Williams#MU, Murphy#CE, Gore#RS, et#al. BMJ Case Rep 2018;11:e225923. doi:10.1136/bcr-2018- 225923



Classic periorbital purpura

Morie A. Gertz, MD; courtesy of Mayo Clinic



Macroglossia in a patient with AL amyloidosis

Williams#MU, Murphy#CE, Gore#RS, et#al. BMJ Case Rep 2018;11:e225923. doi:10.1136/bcr-2018- 225923

Key diagnostic tests

The first tests to order in patients with clinically suspected amyloidosis are immunofixation electrophoresis of the serum and urine (using 24-hour urine collection), and serum immunoglobulin free light chain assay.[62][75]

Positive immunofixation (presence of a monoclonal protein in the serum or urine) and/or an abnormal serum immunoglobulin free light chain assay is reported in 99% of patients with AL amyloidosis.[76]

A diagnosis of AL amyloidosis should be confirmed histologically (e.g., biopsy with amyloid typing) to avoid a misdiagnosis because an incidental monoclonal gammopathy may be present in other types of amyloidosis (e.g., hereditary amyloidosis, ATTRwt amyloidosis).[28] [29] [61] [62] [77]

A diagnosis of AL amyloidosis is unlikely if immunofixation and serum immunoglobulin free light chain assay are normal. Patients with clinically suspected amyloidosis with equivocal or normal immunofixation and serum immunoglobulin free light chain assay should undergo a careful and prompt evaluation (including genetic testing) for other types of amyloidosis (e.g., AA amyloidosis, TTR amyloidosis, localised amyloidosis).

Biopsy studies

Histological confirmation of amyloid deposits in tissue is essential for establishing a diagnosis of amyloidosis.

Bone marrow aspirate and biopsy, and subcutaneous fat aspirate (e.g., abdominal fat pad) are recommended in patients with suspected amyloidosis (e.g., if a monoclonal protein is present).[62] Other tissues that can be biopsied include lip (minor salivary gland) and rectum.[62]

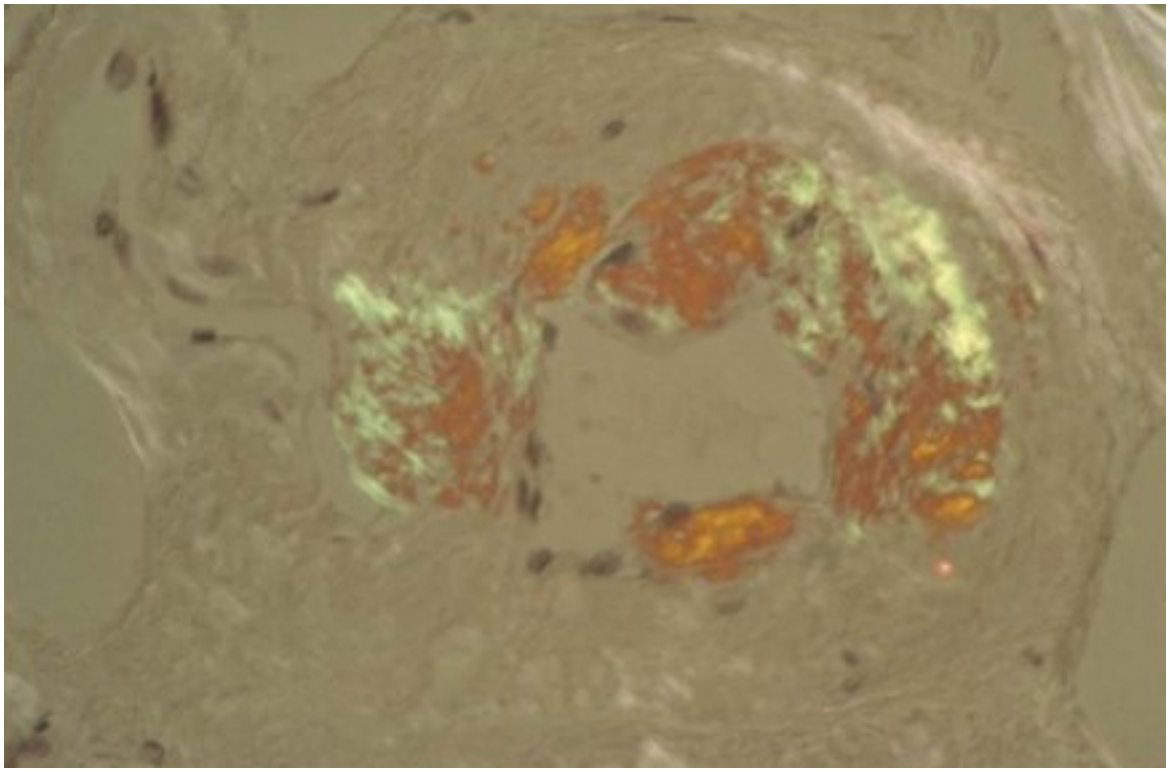
Bone marrow aspirate and biopsy can also be used to identify clonal plasma cells and assess for coexistent multiple myeloma. See Multiple myeloma .

If bone marrow and tissue biopsy studies are negative, biopsy of an involved organ (e.g., heart, liver, kidney, nerve) should be performed as clinically indicated.[62]

Multiple tissue or organ biopsies are potentially hazardous and are not recommended.[78] Bone marrow biopsy combined with subcutaneous fat aspirate (e.g., abdominal fat pad) will identify amyloid deposits in most (85%) patients with amyloidosis.[79]

Apple-green birefringence on a Congo red stained aspirate or biopsy specimen is required for diagnosis.[80] Apple-green birefringence after Congo red staining confirms the presence of amyloid deposits but does not differentiate between different types of amyloid.[62] Amyloid typing and/or immunohistochemical studies should be carried out to confirm the type of amyloid.

Fluorescence in situ hybridisation (FISH) studies should be done on bone marrow aspirate to identify molecular markers that can guide prognosis and treatment e.g., t(11;14) translocation.[81] [82]



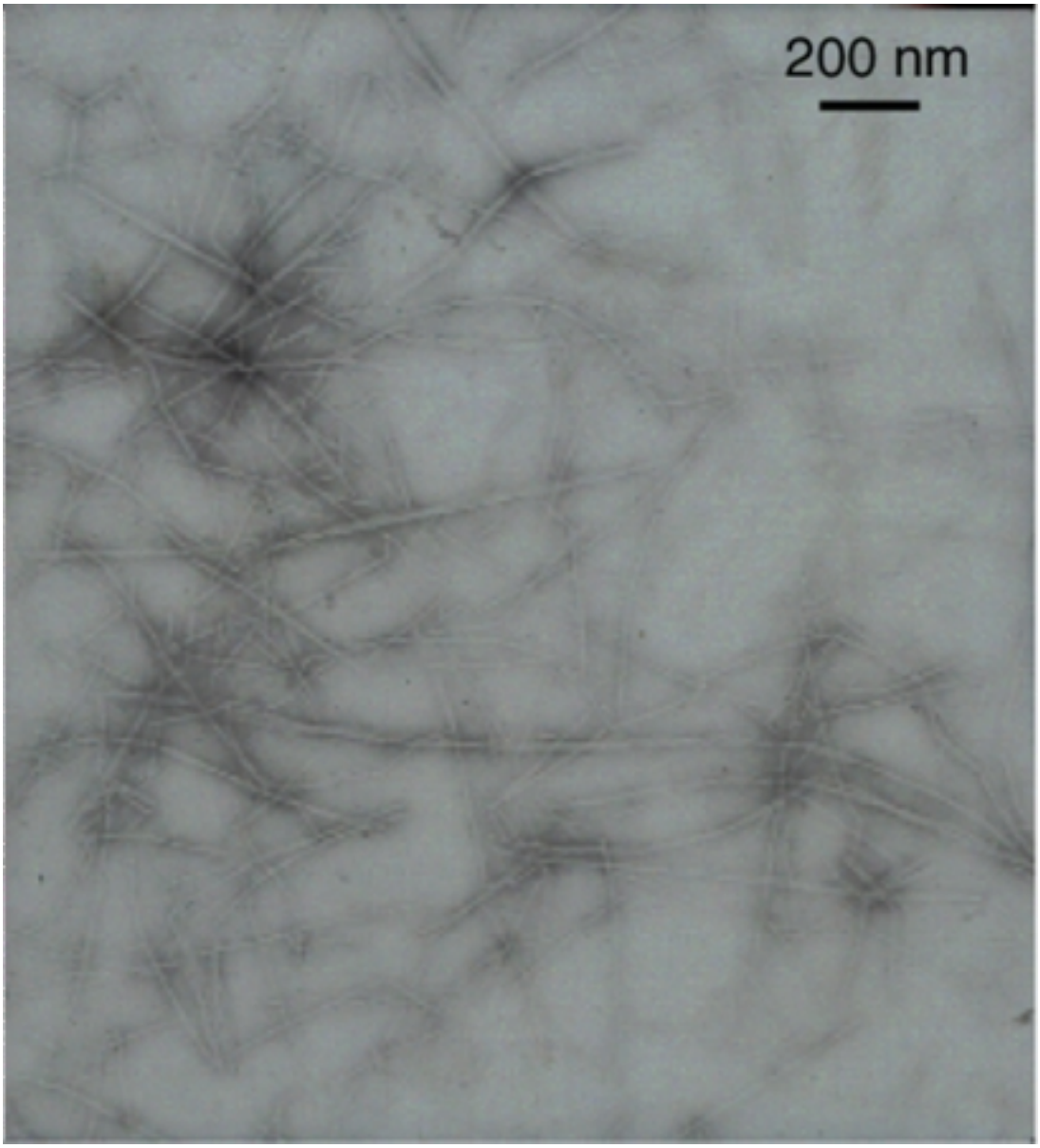
Congo red stain blood vessel in a bone marrow biopsy demonstrating green birefringence pathognomonic of amyloidosis

Morie A. Gertz, MD; courtesy of Mayo Clinic

Amyloid typing

Mass spectrometry-based proteomic analysis is currently the gold standard for amyloid typing. It is the most direct method of confirming the amyloid type (e.g., light chain, serum amyloid A [SAA; associated with AA amyloidosis], TTR).

Immuno-electron microscopy can be used on renal biopsy specimens to clarify the fibrillar nature of the amyloid, but is not part of routine clinical practice for other biopsy material.



Electron micrograph demonstrating classical amyloid fibrils

Morie A. Gertz, MD; courtesy of Mayo Clinic

Immunohistochemical studies

Immunohistochemical staining of amyloid deposits can be attempted to distinguish the various forms of systemic amyloidosis. Commercially available antisera to immunoglobulin light chains, SAA, and TTR are typically used but may lack specificity and sensitivity.

Immunohistochemistry has lower diagnostic accuracy than mass spectrometry.[62]

Genetic testing

Genetic testing can be used to assess for hereditary amyloidosis (e.g., ATTRv, fibrinogen A alpha-chain, apolipoprotein A, lysozyme) and familial periodic fever syndromes associated with AA amyloidosis (e.g., familial Mediterranean fever, TRAPS, CAPS [Muckle-Wells syndrome], mevalonate kinase deficiency [hyper-IgD syndrome]).[83][84]

Use of genetic testing is important to avoid a misdiagnosis (e.g., AL amyloidosis) in patients with hereditary amyloidosis.[30] [62]

Ancillary tests

Patients should have the following tests to guide diagnosis and prognosis, and to assess organ involvement:[62]

- FBC with differential
- Peripheral blood smear, serum quantitative immunoglobulins, and serum protein electrophoresis, to assess for a plasma cell disorder
- N-terminal pro-B-type natriuretic peptide (NT-proBNP; B-type natriuretic peptide [BNP] if NT-proBNP is unavailable), serum troponin T (troponin I if troponin T is unavailable), and lipid panel, to assess for heart involvement and for prognostication
- Urine total protein and urine protein electrophoresis (from the 24-hour urine sample)
- Comprehensive metabolic profile (including serum urea, serum creatinine, electrolytes, serum albumin, serum calcium, serum uric acid, serum lactate dehydrogenase [LDH], beta-2 microglobulin; liver function tests [LFTs]), to assess for renal and liver involvement
- Coagulation studies (including prothrombin time [PT], partial thromboplastin time [PTT], factor X), to assess for amyloid-related coagulation abnormalities
- Orthostatic vital sign assessment and electromyogram (if clinically significant peripheral neuropathy is present)/nerve conduction studies, to assess for nerve involvement
- Thyroid-stimulating hormone and cortisol levels, to assess for endocrine involvement
- Pulmonary function tests, to assess for lung involvement

Cardiac evaluation

Cardiac involvement commonly occurs in AL, ATTRv, and ATTRwt amyloidosis.[42] [43] [49][54] [55] [65] Late diagnosis of cardiac involvement is associated with poor outcomes.[85]

An ECG and echocardiogram (with tissue Doppler and global longitudinal strain) should be carried out in all patients (symptomatic or asymptomatic) with suspected or confirmed cardiac amyloidosis.[55] [71] [86] Increased left ventricular (LV) wall thickness, typical LV longitudinal strain pattern, and reduced tissue Doppler velocities are highly suggestive of cardiac amyloidosis.[55] [86]

Cardiac MRI may be useful if an echocardiogram is suggestive or indeterminate. However, it is not diagnostic and cannot distinguish between AL and TTR cardiac amyloidosis.[71] [86] Cardiac MRI parameters should be combined with electrocardiographic, clinical, biomarker, and other imaging findings to maximise diagnostic accuracy.[86]

Cardiac scintigraphy with technetium-labelled bone tracers (99mTc-PYP or 99mTc-DPD) should be performed if TTR cardiac amyloidosis is suspected.[30] Scintigraphy is sensitive for the detection of TTR cardiac amyloidosis and enables non-invasive clinical diagnosis.[71] [86] [87] [88] However, it lacks specificity, therefore false positives may be seen. A negative monoclonal protein result alongside scintigraphy cardiac uptake (grade 2 or 3) confirms a diagnosis of TTR amyloidosis (without requiring biopsy).[62] [71] If scintigraphy cardiac uptake is 1 or 0, a biopsy is required (cardiac or non-cardiac, depending on presentation).[62]

In older men with an echocardiogram consistent with cardiac amyloidosis, a cardiac scintigraphy showing uptake of 99mTc-PYP or 99mTc-DPD in myocardial tissue increases suspicion for ATTRwt amyloidosis.

Cardiac work-up for coronary artery disease is invariably normal.[89]

Imaging studies

Whole-body low-dose computed tomography (CT) or 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT can be used to detect osteolytic bone lesions if a monoclonal protein is detected. A skeletal survey can be used if these advanced imaging modalites are unavailable, but sensitivity is significantly lower.[62]

A chest CT can be used to evaluate lung involvement, if clinically indicated.[62]

Gastric emptying scan (if gastroparesis is present) and abdominal ultrasound or CT (as clinically indicated) can be used to evaluate liver and gastrointestinal involvement.[62] Upper and lower endoscopies can be performed if symptoms suggest gastrointestinal involvement.

123I-labelled serum amyloid P (SAP) scintigraphy can be used to assess the extent of organ involvement and dysfunction at diagnosis and during follow-up. SAP scintigraphy is standard practice in the UK and the Netherlands, but use in other countries may vary.[78] [90]

Prognostication

Prognostic biomarkers for amyloidosis include: serum troponin T (troponin I if troponin T is unavailable); NT-proBNP (BNP if NT-proBNP is unavailable); and the difference between involved and uninvolved serum free light chains (dFLC).

Serum troponin level is a sensitive marker for myocardial injury in amyloidosis; NT-proBNP is a sensitive marker for myocardial stretch and congestive heart failure.[91] [92] Troponin, NT-proBNP, and dFLC are used in the Mayo staging criteria for AL amyloidosis.[93] [94] [95] See Criteria .

Beta-2-microglobulin is predictive of survival in patients with AL amyloidosis.[96] [97]

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include monoclonal gammopathy of undetermined significance (MGUS), inflammatory conditions, chronic infections, and a positive family history.

jugular venous distention (common)

- High right-sided filling pressure produces dramatic levels of jugular venous distention.[74]

lower extremity oedema (common)

- Occurs due to hypoalbuminaemia from nephrotic syndrome and may occur due to high right-sided filling pressures in the presence of restrictive cardiomyopathy. Present in approximately 50% of patients.[73]

history of monoclonal gammopathy of undetermined significance (MGUS) (uncommon)

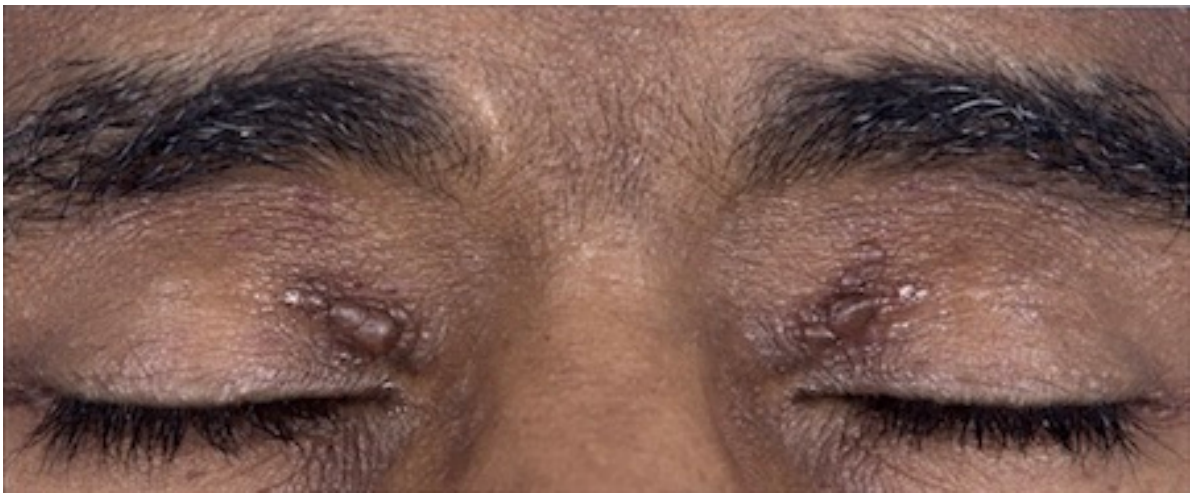
- History may reveal a prior diagnosis of MGUS.[58]
- Patients with MGUS have a relative risk of progression to AL amyloidosis (the most common type of amyloidosis) of eight- to ninefold.[4] [58] [59]
- It is important to note, however, that an incidental monoclonal gammopathy may be present in patients with other types of amyloidosis (e.g., hereditary amyloidosis, wild-type transthyretin [ATTRwt] amyloidosis), which can lead to a misdiagnosis of AL amyloidosis.[28] [29] [61]

history of a chronic inflammatory condition, chronic infection, familial periodic fever syndrome (uncommon)

- Secondary (AA) amyloidosis is typically associated with: chronic inflammatory conditions (e.g., inflammatory polyarthropathy, inflammatory bowel disease [specifically Crohn's disease]); chronic infections (e.g., bronchiectasis, tuberculosis, subcutaneous injection of illicit drugs, decubitus ulcers, chronic urinary tract infections osteomyelitis); familial periodic fever syndromes (e.g., familial Mediterranean fever, tumour necrosis factor (TNF) receptor-associated periodic fever syndromes [TRAPS], cryopyrin-associated periodic syndromes [CAPS; such as Muckle-Wells syndrome], mevalonate kinase deficiency [formerly known as hyper-IgD syndrome]).[16] [24] [25] [26] [27]

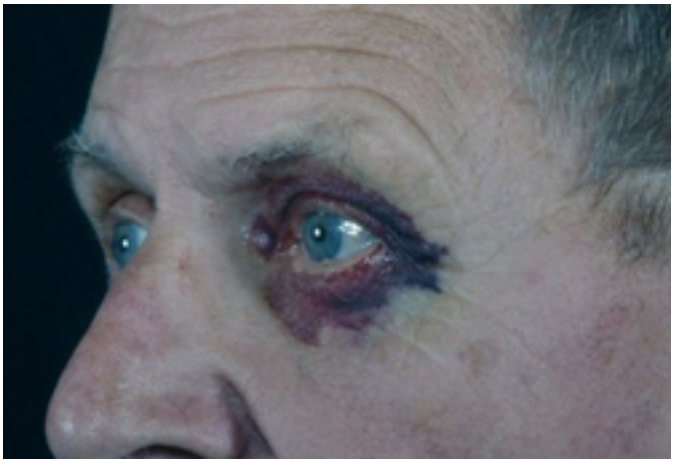
periorbital purpura (uncommon)

- Amyloid purpura occurs in approximately 15% of patients with AL amyloidosis.[49] It is typically periorbital, but can occur anywhere above the nipple line.



Bilateral periorbital ecchymosis (amyloid purpura) in a patient with AL amyloidosis

Williams#MU, Murphy#CE, Gore#RS, et#al. BMJ Case Rep 2018;11:e225923. doi:10.1136/bcr-2018- 225923



Classic periorbital purpura

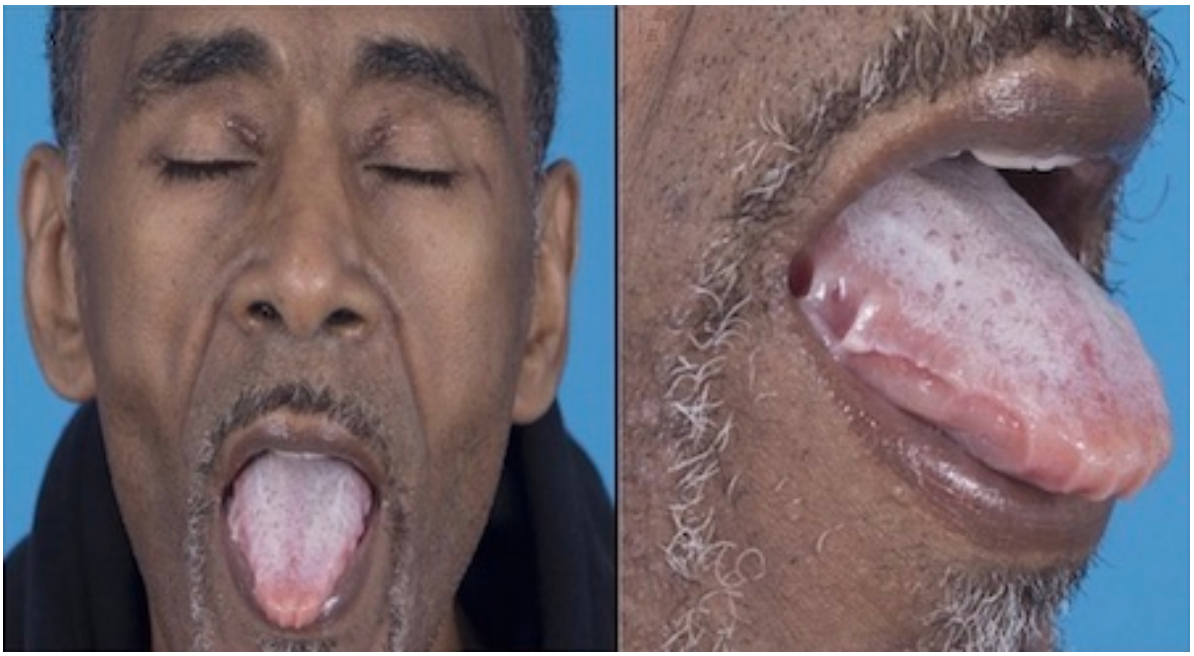
Morie A. Gertz, MD; courtesy of Mayo Clinic

eyelid petechiae (uncommon)

- Eyelid petechiae are common; only evident when eyes are closed. May be confused with immune thrombocytopenia (ITP) or coagulopathy, but is highly specific for amyloidosis.

macroglossia (uncommon)

- Specific and diagnostic sign for AL amyloidosis.[49] Occurs in approximately 10% of patients, but is easily overlooked because the most common presentation is dental indentations on the underside of the tongue.



Macroglossia in a patient with AL amyloidosis

Williams#MU, Murphy#CE, Gore#RS, et#al. BMJ Case Rep 2018;11:e225923. doi:10.1136/bcr-2018- 225923

Other diagnostic factors

fatigue (common)

- Manifestation of systemic disease and is commonly present in patients with early amyloid cardiomyopathy and nephrotic syndrome. Present in approximately 60% of patients.[42]

weight loss (common)

- Extreme weight loss (e.g., >9 kg) is common (particularly in patients with cardiac and hepatic involvement) and is suggestive of amyloidosis if associated with oedema or neuropathy.[49]
- The history may have prompted a detailed search for occult malignancy.

dyspnoea on exertion (common)

- Dyspnoea on exertion is a common finding in patients with amyloid cardiomyopathy. Associated with oedema when right-sided filling pressures are elevated. Present in approximately 40% of patients.[49]

peripheral neuropathy (uncommon)

- Nerve involvement can lead to peripheral neuropathy, and is most commonly associated with immunoglobulin light chain (AL) amyloidosis and hereditary transthyretin (ATTRv) amyloidosis. Mild peripheral neuropathy may occur in patients with wild-type transthyretin (ATTRwt) amyloidosis (up to 20%).[56]
- Nerve involvement is not a typical feature of secondary (AA) amyloidosis, non-TTR hereditary amyloidosis, or LECT2 amyloidosis.[3]
- Initial presentation is usually distal symmetric sensory loss (i.e., loss of temperature and pain perceptions, followed by proprioceptive loss).[51] Patients usually report dysaesthesia and paraesthesia of the feet and lower legs, which progress to the hands and arms over time.
- Peripheral neuropathy is an important diagnostic clue for AL amyloidosis and ATTRv amyloidosis.[51]

autonomic neuropathy (uncommon)

- Nerve involvement can lead to autonomic neuropathy, and is most commonly associated with AL amyloidosis and ATTRv amyloidosis.
- Nerve involvement is not a typical feature of AA amyloidosis, non-TTR hereditary amyloidosis, or LECT2 amyloidosis.[3]
- Patients with autonomic neuropathy may have erectile dysfunction, orthostatic hypotension, gastrointestinal dysfunction, or urinary dysfunction.[19] [69] Sweating abnormalities and failure of heart rate to change when body position is changed are signs of autonomic dysfunction.
- Autonomic neuropathy is an important diagnostic clue for AL amyloidosis and ATTRv amyloidosis.[51]

claudication (uncommon)

- Consequence of amyloid involvement of the small vessels in the peripheral arteries. Results in jaw, calf, and limb claudication. Rarely, patients may have angina.

nausea or vomiting (uncommon)

- If upper gastrointestinal tract is involved, nausea or vomiting may be present (pseudo-obstructive symptoms).

abdominal cramps (uncommon)

- If upper gastrointestinal tract is involved, post-prandial abdominal cramping may occur (pseudo-obstructive symptoms).

alternating bowel habit (uncommon)

- Severe faecal incontinence alternating with 3-4 days of constipation may be present.

steatorrhea (uncommon)

- Typical sign of intestinal involvement.

light-headed (uncommon)

- Lightheadedness can be a consequence of cardiac amyloidosis (low cardiac output with preserved ejection fraction on the echocardiogram) or nephrotic syndrome (hypoalbuminaemia and intravascular volume contraction).

submandibular salivary gland enlargement (uncommon)

- Specific for AL amyloidosis. May be misinterpreted as lymphadenopathy. Salivary gland involvement results in a sicca syndrome. These patients often are misdiagnosed as having Sjögren's syndrome.

hepatomegaly (uncommon)

- Palpable hepatomegaly >5 cm below the right costal margin, most commonly reported in AL amyloidosis (approximately 10% of patients).[16] [49]
- Palpable hepatomegaly is uncommon in AA amyloidosis, but histopathological changes in the liver may be evident. Liver involvement is rare in patients with hereditary amyloidosis.

shoulder pad sign (uncommon)

- A rare sign, specific for AL amyloidosis. Periarticular infiltration with amyloid produces pseudohypertrophy, resulting in enlargement of the musculature of the shoulder and hip girdles.

diffuse muscular weakness (uncommon)

- Can occur due to extracellular amyloid infiltration in the muscle (muscle hypertrophy) or due to vascular occlusion leading to muscle ischaemia and claudication (muscular atrophy).

orthostatic hypotension (uncommon)

- Orthostatic hypotension with syncope can occur if autonomic neuropathy is present (e.g., in AL amyloidosis or ATTRv amyloidosis).

carpal tunnel syndrome (uncommon)

- Carpal tunnel syndrome prevalence is greatest in patients with TTR cardiac amyloidosis (20.3% vs. 4.1% in the general population), but it is also a manifestation of AL amyloidosis.[70]
- Tinel's sign (tapping over the carpal nerve at the wrist produces tingling in the thumb, index, and middle finger) and Phalen's manoeuvre (holding the dorsal surface of both hands together in forced flexion for around 1 minute produces tingling in the thumb, index, and middle finger) should be performed to test for carpal tunnel syndrome involvement in patients reporting paresthaesia in the hands.

musculoskeletal disorders (uncommon)

- Musculoskeletal disorders (e.g., biceps tendon rupture, hip and knee osteoarthritis, trigger finger, and spinal stenosis) are typically associated with transthyretin (TTR) amyloidosis, and may precede cardiac or neurological manifestations.[71] [72]

Risk factors

Strong

monoclonal gammopathy of undetermined significance (MGUS)

- Patients with MGUS have a relative risk of progression to AL amyloidosis of eight- to ninefold.[58] [59]

inflammatory polyarthropathy

- Most common underlying cause of secondary (AA) amyloidosis.
- Includes patients with rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis.[16]

chronic infections

- Risk for secondary (AA) amyloidosis.
- Causes include bronchiectasis, tuberculosis, subcutaneous injection of illicit drugs, decubitus ulcers, chronic urinary tract infections, and osteomyelitis.[16]

inflammatory bowel disease

- Risk for secondary (AA) amyloidosis.
- In particular Crohn's disease.[16]

familial periodic fever syndromes

- Familial Mediterranean fever, tumour necrosis factor (TNF) receptor-associated periodic fever syndromes (TRAPS), cryopyrin-associated periodic syndromes (CAPS; e.g., Muckle-Wells syndrome), and mevalonate kinase deficiency (formerly known as hyper-IgD syndrome) have been implicated in secondary (AA) amyloidosis.[24] [25] [26] [27]

Weak

Castleman's disease

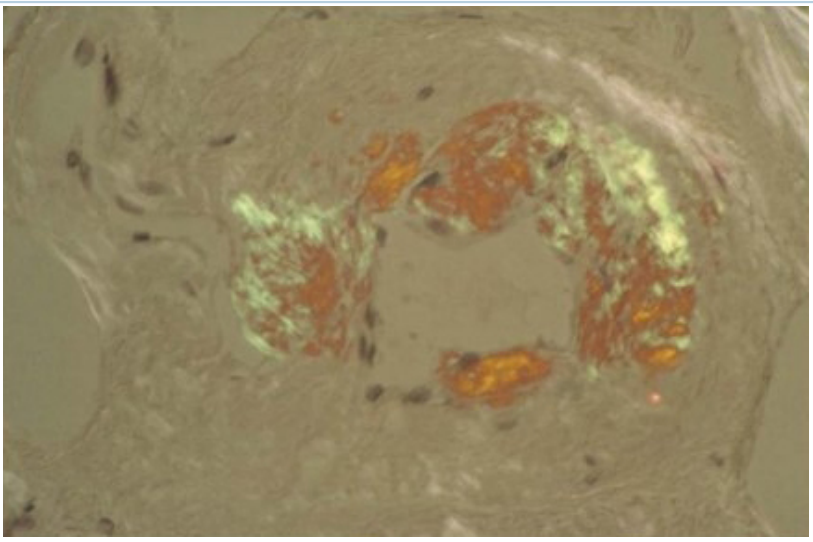
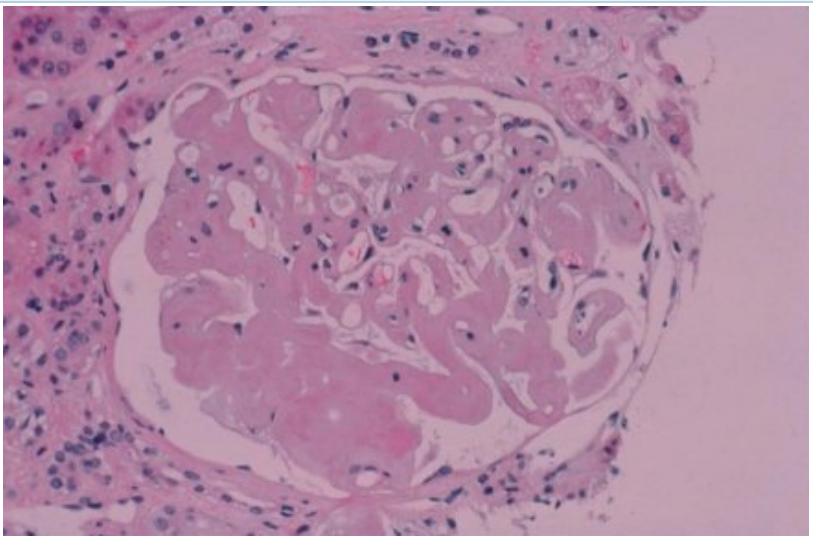
- Non-cancerous tumours of lymphoid tissue.
- The plasma cell variant is a rare cause of secondary (AA) amyloidosis.[22] [23]

Investigations

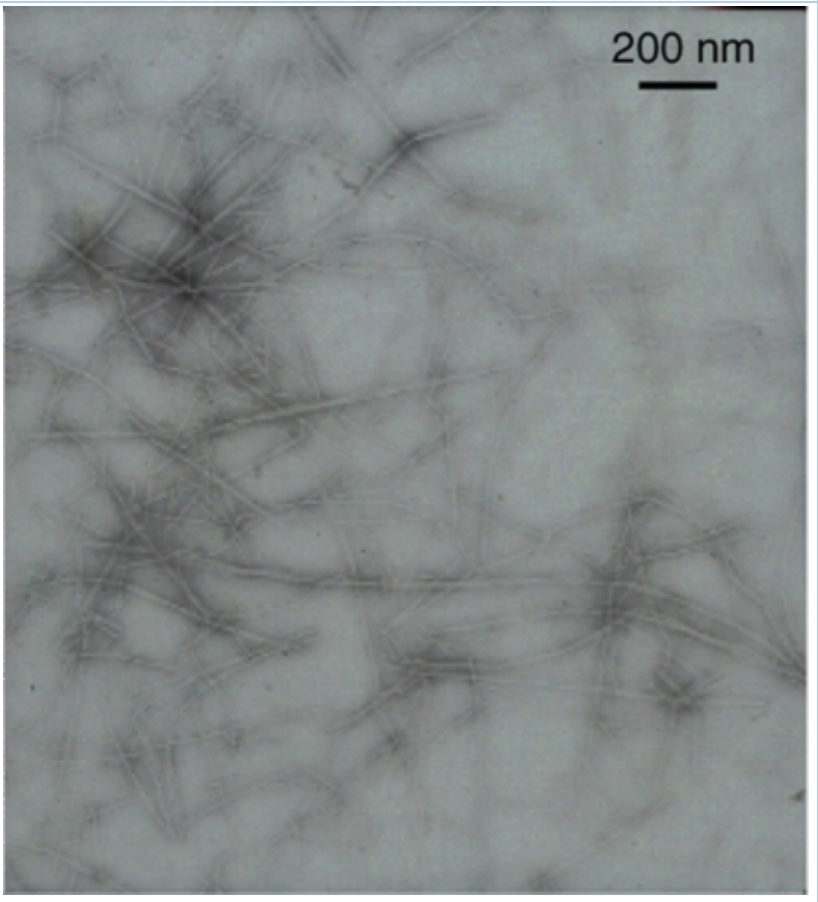
1st test to order

Test	Result
serum immunofixation electrophoresis • Positive immunofixation (presence of a monoclonal protein in the serum or urine) and/or an abnormal serum immunoglobulin free light chain assay is reported in 99% of patients with AL amyloidosis.[76] • A diagnosis of AL amyloidosis should always be confirmed histologically (e.g., biopsy with amyloid typing) to avoid a misdiagnosis because an incidental monoclonal gammopathy may be present in other types of amyloidosis (e.g., hereditary amyloidosis, wild-type transthyretin [ATTRwt] amyloidosis).[28] [29] [61] [62] [77] • A diagnosis of AL amyloidosis is unlikely if immunofixation and serum immunoglobulin free light chain assay are normal.	**may be positive for a monoclonal protein**
urine immunofixation electrophoresis (using 24-hour urine collection) • Positive immunofixation (presence of a monoclonal protein in the serum or urine) and/or an abnormal serum immunoglobulin free light chain assay is reported in 99% of patients with AL amyloidosis.[76] • The finding of a light chain protein in the urine is suggestive of multiple myeloma and AL amyloidosis. • A diagnosis of AL amyloidosis should always be confirmed histologically (e.g., biopsy with amyloid typing) to avoid a misdiagnosis because an incidental monoclonal gammopathy may be present in other types of amyloidosis (e.g., hereditary amyloidosis, wild-type transthyretin [ATTRwt] amyloidosis).[28] [29] [61] [62] [77] • A diagnosis of AL amyloidosis is unlikely if immunofixation and serum immunoglobulin free light chain assay are normal.	**may be positive for a monoclonal protein**
sreum immunoglobulin free light chain assay • Extremely high sensitivity (>95%) for identifying AL amyloidosis.[98] • Positive immunofixation (presence of a monoclonal protein in the serum or urine) and/or an abnormal serum immunoglobulin free light chain assay is reported in 99% of patients with AL amyloidosis.[76] • A diagnosis of AL amyloidosis should always be confirmed histologically (e.g., biopsy with amyloid typing) to avoid a misdiagnosis because an incidental monoclonal gammopathy may be present in other types of amyloidosis (e.g., hereditary amyloidosis, wild-type transthyretin [ATTRwt] amyloidosis).[28] [29] [61] [62] [77] • A diagnosis of AL amyloidosis is unlikely if immunofixation and serum immunoglobulin free light chain assay are normal.	**may show abnormal kappa to lambda light chain ratio**
FBC with differential • Anaemia is seen generally in those patients with renal insufficiency or gastrointestinal blood loss. • Thrombocythaemia is seen as a consequence of hepatic involvement and hypersplenism.	**usually normal**
peripheral blood smear • Ordered to assess for a plasma cell disorder.[62] • May show stacked red blood cells (Rouleaux formation) due to elevated immunoglobulins in serum (associated with AL amyloidosis).	**may show rouleaux formation**

Test	Result
serum quantitative immunoglobulins • Ordered to assess for a plasma cell disorder.[62] • Quantifies the amount of immunoglobulins in the serum, but does not differentiate between polyclonal (normal) and monoclonal (abnormal) immunoglobulins.	**may show increased concentration of immunoglobulins**
serum protein electrophoresis • Ordered to assess for a plasma cell disorder.[62] • Can identify a monoclonal immunoglobulin in the serum, although sensitivity is low without immunofixation.	**may show monoclonal immunoglobulin**
comprehensive metabolic profile • Includes serum urea, serum creatinine, electrolytes, serum albumin, serum calcium, serum uric acid, serum lactate dehydrogenase (LDH), beta-2 microglobulin, and liver function tests (LFTs).[62] • Ordered to assess for renal and liver involvement.[62] • Hepatic amyloid is characterised by elevations of the serum alkaline phosphatase. • Most patients with early renal amyloidosis have preserved clearance of creatinine but can have significant degrees of hypoalbuminaemia due to the urinary protein loss. • Beta-2-microglobulin is predictive of survival in patients with AL amyloidosis.[96] [97]	**may be normal or abnormal (e.g., hypoalbuminaemia; elevated alkaline phosphatase; low calcium [due to hypoalbuminaemia]; elevated beta-2-microglobulin)**
urine protein electrophoresis (using 24-hour urine collection) • Ordered to assess for renal involvement.[62] • May show elevated proteins in the urine (including a monoclonal immunoglobulin, although sensitivity is low without immunofixation)	**urine protein may be elevated (proteinuria); may reveal a monoclonal immunoglobulin**
24-hour total urine protein • Ordered to assess for renal involvement.[62] • Patients with amyloidosis who have a urinary albumin excretion of >1 g/24 hours are considered to have renal involvement. • A level of >3 g/24 hours defines nephrotic range proteinuria.	**may show elevated urinary protein**
orthostatic vital sign assessment • Carried out to assess for nerve involvement.[62] • Orthostatic hypotension with syncope can occur if autonomic neuropathy is present (e.g., in AL amyloidosis or ATTRv amyloidosis)	**may indicate orthostatic hypotension**
tissue biopsy • Histological confirmation of amyloid deposits in tissue is essential for establishing a diagnosis of amyloidosis. • Bone marrow aspirate and biopsy, and subcutaneous fat aspirate (e.g., abdominal fat pad) are recommended in patients with suspected amyloidosis (e.g., if a monoclonal protein is present).[62] Other tissues that can be biopsied include lip (minor salivary gland) and rectum.[62] • Bone marrow aspirate and biopsy can also be used to identify clonal plasma cells and assess for coexistent multiple myeloma. See Multiple myeloma . • If bone marrow and tissue biopsy studies are negative, biopsy of an involved organ (e.g., heart, liver, kidney, nerve) should be performed as clinically indicated.[62] • Multiple tissue or organ biopsies are potentially hazardous and are not recommended.[78] Bone marrow biopsy combined with	**positive apple-green birefringence when aspirate or biopsy specimen is stained with Congo red; may show presence of clonal plasma cells in bone marrow biopsy if multiple myeloma is present**

Test	Result
subcutaneous fat aspirate (e.g., abdominal fat pad) will identify amyloid deposits in most (85%) patients with amyloidosis.[79] • Apple-green birefringence on a Congo red stained aspirate or biopsy specimen is required for diagnosis.[80] Apple-green birefringence after Congo red staining confirms the presence of amyloid deposits but does not differentiate between different types of amyloid.[62] Amyloid typing and/or immunohistochemical studies should be carried out to confirm the type of amyloid. • Amyloid deposits are always extracellular and appear amorphous.  *Congo red stain blood vessel in a bone marrow biopsy demonstrating green birefringence pathognomonic of amyloidosis* *Morie A. Gertz, MD; courtesy of Mayo Clinic*  *Renal biopsy demonstrating amyloid deposits as amorphous replacement of the glomerular architecture* *Morie A. Gertz, MD; courtesy of Mayo Clinic*	
fluorescence in situ hybridisation (FISH) • FISH studies should be done on bone marrow aspirate to identify molecular markers that can guide prognosis and treatment e.g., t(11;14) translocation.[81] [82]	**may show molecular abnormalities e.g., t(11;14)**

Other tests to consider

Test	Result
mass spectrometry • Used to confirm amyloid type by analysing amyloid protein composition in biopsy tissue. Has high sensitivity (90%). Currently the gold standard for amyloid typing. • Mass spectrometry has higher diagnostic accuracy than immunohistochemistry.[62]	**confirms amyloid protein type (e.g., light chain, serum amyloid A, or transthyretin)**
immuno-electron microscopy • All forms of amyloid have a fibrillar appearance under the electron microscope and are rigid and non-branching, but all fibrils are not necessarily amyloid. • Immuno-electron microscopy can be used on renal biopsy specimens to clarify the fibrillar nature of the amyloid, but is not part of routine clinical practice for other biopsy material.  *Electron micrograph demonstrating classical amyloid fibrils* *Morie A. Gertz, MD; courtesy of Mayo Clinic*	**amyloids appear fibrillar, rigid, and non-branching**
immunohistochemical studies • Can be attempted to distinguish the various forms of systemic amyloidosis. Commercially available antisera to immunoglobulin light	**may identify immunoglobulin light chains, serum amyloid A, or transthyretin**

Test	Result
chains, serum amyloid A, and transthyretin are typically used but may lack specificity and sensitivity. • Immunohistochemistry has lower diagnostic accuracy than mass spectrometry.[62] • In most cases, mass spectrometry and immuno-electron microscopy are required to determine the underlying type of amyloid.	
genetic testing • Patients with clinically suspected amyloidosis with equivocal or normal immunofixation and serum immunoglobulin free light chain assay should undergo genetic testing. • Genetic testing can be used to assess for hereditary amyloidosis (e.g., transthyretin variants [ATTRv], fibrinogen A alpha-chain, apolipoprotein A, lysozyme) and familial periodic fever syndromes associated with secondary (AA) amyloidosis (e.g., familial Mediterranean fever, tumour necrosis factor [TNF] receptor-associated periodic fever syndromes [TRAPS], cryopyrin-associated periodic syndromes [CAPS; such as Muckle-Wells syndrome], mevalonate kinase deficiency [formerly known as hyper-IgD syndrome]).[83] [84] • Use of genetic testing is important to avoid a misdiagnosis (e.g., AL amyloidosis) in patients with hereditary amyloidosis.[30] [62]	**may be positive for hereditary amyloidosis or familial periodic fever syndromes**
serum amyloid P (SAP) scintigraphy scan • SAP scintigraphy is standard practice in the UK and the Netherlands, but is not available elsewhere.	**uptake at sites of amyloid deposition**
serum troponin T or I • Used to assess for heart involvement and for prognostication; performed in all patients.[62] Sensitive test of myocardial injury in amyloidosis. • Troponin I can be used if troponin T is unavailable. • Troponin level is incorporated into the staging criteria for AL amyloidosis.[93] [94] [95] See Criteria . • Patients with a detectable troponin level have a worse prognosis than those with undetectable values.[91] •	**may be elevated**
N-terminal pro-B-type natriuretic peptide (NT-proBNP) • Used to assess for heart involvement and for prognostication; performed in all patients.[62] B-type natriuretic peptide (BNP) can be performed if NT-proBNP is unavailable. • A sensitive marker for myocardial stretch and congestive heart failure.[91] [92] Has been shown to have important prognostic value in the management of amyloidosis.[92] • NT-proBNP is incorporated into the staging criteria for AL amyloidosis.[93] [94] [95] See Criteria . • Levels >300 ng/L (>300 pg/mL) are highly suggestive of myocardial involvement with amyloid.[98] • Patients with <170 ng/L (<170 pg/mL) have a significantly longer survival than patients with >170 ng/L (>170 pg/mL).	**may be elevated**
lipid panel • Ordered to assess for heart involvement.[62]	**may be abnormal**

Test	Result
coagulation studies • Includes prothrombin time (PT), partial thromboplastin time (PTT), and factor X, as clinically indicated. • Ordered to assess for amyloid-related coagulation abnormalities.[62] • Patients with AL amyloidosis may develop acquired factor X deficiency due to adsorption of factor X to amyloid fibrils.[99]	**may be abnormal**
ECG • Should be performed in all patients (symptomatic or asymptomatic) with suspected or confirmed amyloidosis.[55] [71] [86] Late diagnosis of cardiac involvement is associated with poor outcomes.[85] • Cardiac involvement is reported in 55% to 76% of patients with AL amyloidosis.[42] [43] [49] [65] Cardiac involvement may also occur in patients with hereditary amyloidosis (e.g., ATTRv amyloidosis) or wild-type transthyretin (ATTRwt) amyloidosis.[54] [55]	**may show conduction abnormalities; atrial fibrillation**
echocardiogram (with tissue Doppler and global longitudinal strain) • Should be performed in all patients (symptomatic or asymptomatic) with suspected (e.g., elevated NT-proBNP) or confirmed amyloidosis.[55] [71] [86] Late diagnosis of cardiac involvement is associated with poor outcomes.[85] • Cardiac involvement is reported in 55% to 76% of patients with AL amyloidosis.[42] [43] [49] [65] Cardiac involvement may also occur in patients with hereditary amyloidosis (e.g., ATTRv amyloidosis) or wild-type transthyretin (ATTRwt) amyloidosis.[54] [55] • Echocardiography with tissue Doppler and global longitudinal strain imaging may identify patterns highly suggestive of cardiac amyloidosis.[55] [86] • Myocardial strain is defined as the percentage change in myocardial fiber length per unit length, and the strain rate is the derivative over time of strain.[100] [101]	**may show diastolic dysfunction (restrictive filling of the ventricular chambers); thickening of the interventricular septum; decreased ejection fraction;#ncreased left ventricular (LV) wall thickness; typical LV longitudinal strain pattern; reduced tissue Doppler velocities**
cardiac MRI • Cardiac MRI may be useful if an echocardiogram is suggestive or indeterminate. However, it is not diagnostic and cannot distinguish between AL amyloidosis and TTR amyloidosis.[71] [86] • Cardiac MRI parameters should be combined with electrocardiographic, clinical, biomarker, and other imaging findings to maximise diagnostic accuracy.[86] • Myocardial nulling after gadolinium injection is highly specific for cardiac amyloidosis.	**may show significantly elevated T1 and T2 relaxation times compared with age-matched controls**
cardiac scintigraphy • Cardiac scintigraphy with technetium-labelled bone tracers (99mTc-PYP or 99mTc-DPD) should be performed if transthyretin (TTR) cardiac amyloidosis is suspected.[30] Scintigraphy is sensitive for the detection of TTR cardiac amyloidosis and enables non-invasive clinical diagnosis.[71] [86] [87] [88] However, it lacks specificity; therefore false positives may be seen. A negative monoclonal protein result alongside scintigraphy cardiac uptake (grade 2 or 3) confirms a diagnosis of TTR amyloidosis (without needing biopsy).[62] [71] If scintigraphy cardiac uptake is 1 or 0, a biopsy is required (cardiac or non-cardiac, depending on presentation).[62] • In older men with an echocardiogram consistent with cardiac amyloidosis, a cardiac scintigraphy showing uptake of 99mTc-PYP or	**may show myocardial uptake of 99mTc-PYP or 99mTc-DPD**

Test	Result
99mTc-DPD in myocardial tissue increases the suspicion of wild-type TTR (ATTRwt) amyloidosis.	
electromyogram/nerve conduction studies • Ordered to assess for nerve involvement (e.g., if significant peripheral neuropathy is present).[62]	**may be abnormal**
endocrine tests • Includes thyroid-stimulating hormone and cortisol levels. • Ordered to assess for endocrine involvement.[62]	**may be abnormal**
pulmonary function tests • Ordered to assess for lung involvement.[62]	**may be abnormal**
computed tomography (CT) scan • Whole-body low-dose CT (WBLD-CT) can be used to detect osteolytic bone lesions if a monoclonal protein is detected.[62] • Abdominal CT can be used to evaluate liver involvement, as clinically indicated.[62] • Chest CT can be used to evaluate lung involvement, if clinically indicated.[62]	**WBLD-CT may detect osteolytic bone lesions; abdominal CT may show liver involvement (hepatomegaly); chest CT may show lung involvement**
fluorodeoxyglucose positron emission tomography (FDG-PET)/CT • Can be used to detect osteolytic bone lesions if a monoclonal protein is detected.	**may detect osteolytic bone lesions**
skeletal survey • Can be used to detect osteolytic bone lesions if a monoclonal protein is detected, but only if advanced imaging modalites (CT, FDG-PET/CT) are unavailable.[62] • Sensitivity is significantly lower than CT and FDG-PET/CT.	**may detect osteolytic bone lesions**
abdominal ultrasound • Ordered to evaluate liver involvement, as clinically indicated.[62]	**may show liver involvement (hepatomegaly)**
gastric emptying scan • Ordered to evaluate gastrointestinal involvement, if gastroparesis is present.[62] • Delayed gastric emptying and gastric retention have been reported in patients with AL and ATTRv amyloidosis.[102] [103] [104]	**may show delayed gastric emptying or gastric retention**
upper and lower endoscopy • Ordered if symptoms suggest gastrointestinal involvement.[62]	**may identify features of amyloid deposits (e.g., polypoid protrusions, erosions, ulcerations)**
123I-labelled serum amyloid P (SAP) scintigraphy • Can be used to assess the extent of organ involvement and dysfunction at diagnosis and during follow-up. • SAP scintigraphy is standard practice in the UK and the Netherlands, but use in other countries may vary.[78] [90]	**shows organ involvement (including quantification of amyloid load)**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Hypertrophic cardiomyopathy (HCM)	• Clinically difficult to distinguish HCM from amyloidosis.	• Echocardiogram meets diagnostic criteria for HCM, such as asymmetric septal hypertrophy. • Doppler echo with global longitudinal strain to exclude features of amyloidosis (i.e., restrictive filling changes). • Cardiac MRI with gadolinium: myocardial nulling after gadolinium injection is highly specific for cardiac amyloidosis.
Membranous glomerulopathy	• Clinically similar presentation in patients who present with nephrotic syndrome.	• Renal biopsy does not stain with Congo red.
Monoclonal gammopathy of undetermined significance (MGUS)-associated neuropathy	• Patients do not have significant degrees of proteinuria, hepatomegaly, or cardiomyopathy. Autonomic neuropathy is absent.	• Sural nerve biopsy does not stain with Congo red.
Multiple myeloma	• Bone pain and symptoms of anaemia.	• Plain x-rays show lytic bone lesions, compression fractures, diffuse osteoporosis. • Low haemoglobin.

Criteria

Mayo staging system for immunoglobulin light chain (AL) amyloidosis (2012)[94]

Based on the following three prognostic markers:

- N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥1800 ng/L
- Cardiac troponin T (cTnT) ≥0.025 micrograms/L
- Difference between involved and uninvolved serum free light chains (dFLC) ≥180 mg/L.

Each prognostic marker is assigned a score of 1. Stage is determined based on the total score:

- Stage I: total score = 0
- Stage II: total score = 1
- Stage III: total score = 2
- Stage IV: total score = 3

Conversion tables for use of B-type natriuretic peptide (BNP) instead of NT-proBNP, and for use of cardiac troponin I (cTnI) or high-sensitivity cTnT (hs-cTnT) instead of cTnT, have been published.[62] [105]

Mayo staging system for immunoglobulin light chain (AL) amyloidosis (2004) with European modifications[93] [95]

Based on the following risk factors:

- N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥332 ng/L
- Cardiac troponin T (cTnT) ≥0.035 microgram/L; or cardiac troponin I (cTnI) ≥0.1 microgram/L

Stage is determined based on the presence of these risk factors (an NT-proBNP cutoff of 8500 ng/L is used to subclassify stage III):

- Stage I: no risk factors
- Stage II: 1 risk factor
- Stage IIIA: 2 risk factors (with NT-proBNP 332 to <8500 ng/L)
- Stage IIIB: 2 risk factors (with NT-proBNP ≥8500 ng/L)

Conversion tables for use of B-type natriuretic peptide (BNP) instead of NT-proBNP, and high-sensitivity cTnT (hs-cTnT) instead of cTnT or cTnI, have been published.[62] [105]

Haematological treatment response criteria for AL amyloidosis[106]

- Complete response (CR): normal serum free light chain (FLC) levels with a normal kappa/lambda ratio and negative serum and urine immunofixation
- Very good partial response (VGPR): difference between involved and uninvolved serum FLC (dFLC) <40 mg/L
- Partial response (PR): dFLC decrease ≥50%
- No response: response is less than PR

A modification to this criteria has been proposed that uses negative serum and urine immunofixation, along with involved FLC ≤20 mg/L or dFLC ≤10 mg/L, as a criteria for CR (i.e., instead of a normal serum FLC ratio), which may provide improved survival discrimination.[107]

ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/ SNMMI expert consensus recommendations: diagnostic criteria[108]

Histological diagnosis of cardiac amyloidosis: Endomyocardial biopsy (amyloidogenic light chain, amyloidogenic transthyretin [ATTR], other subtypes)

- Endomyocardial biopsy positive for cardiac amyloidosis with Congo red staining with apple-green birefringence under polarised light; typing by immunohistochemistry and/or mass spectrometry at specialised centres.

Histological diagnosis of cardiac amyloidosis: Extracardiac biopsy (ATTR)

- ATTR cardiac amyloidosis is diagnosed when the following criteria are met:
  - Extracardiac biopsy proven AL amyloidosis, and
  - Typical cardiac imaging features.

Histological diagnosis of cardiac amyloidosis: Extracardiac biopsy (amyloidogenic light chain)

- Amyloidogenic light chain cardiac amyloidosis is diagnosed when the following criteria are met:
  - Extracardiac biopsy proven AL amyloidosis, and

- Typical cardiac imaging features, or
- Abnormal cardiac biomarkers: abnormal age-adjusted NT-pro BNP or abnormal Troponin T/I/Hs-Troponin (with all other causes for these changes excluded).

Clinical diagnosis of ATTR cardiac amyloidosis: 99mTc-PYP, DPD, HMDP

- ATTR cardiac amyloidosis is diagnosed when the following criteria are met:
  - 99mTc-PYP, DPD, HMDP Grade 2 or 3 myocardial uptake of radiotracer, and
  - Absence of a clonal plasma cell process as assessed by serum FLCs and serum and urine immunofixation, and
  - Typical cardiac imaging features.

Typical imaging features of cardiac amyloidosis: any of the following imaging features (with all other causes for these cardiac manifestations, including hypertension, reasonably excluded)

- Echocardiography (ATTR/amyloidogenic light chain)
  - Left ventricular (LV) wall thickness >12 mm
  - Relative apical sparing of global LS ratio (average of apical LS/average of combined mid+basal LS >1)
  - ≥ Grade 2 diastolic dysfunction.
- Cardiac magnetic resonance (ATTR/amyloidogenic light chain)
  - LV wall thickness >upper limit of normal for sex
  - Global extracellular volume >0.40
  - Diffuse late gadolinium enhancement
  - Abnormal gadolinium kinetics typical for amyloidosis, myocardial nulling prior to blood pool nulling.
- PET: 18F-florbetapir or 18F-florbetaben PET (ATTR/amyloidogenic light chain)
  - Target to background (LV myocardium to blood pool) ratio >1.5
  - Retention index >0.030 minute^-1.

European society of cardiology working group on myocardial and pericardial disease: invasive (all types) cardiac amyloidosis diagnostic criteria[109]

- Cardiac biopsy positive for amyloid, or
- Extracardiac biopsy positive for amyloid, plus
- Echocardiographic/cardiac magnetic resonance criteria.

Echocardiographic and cardiac magnetic resonance criteria are:

- Echocardiography; unexplained LV thickness (≥12 mm) plus 1 or 2:
  1. Characteristic echocardiography findings (≥2 of the following must be present):
     - Grade 2 or worse diastolic dysfunction
     - Reduced tissue Doppler s', e', and a' waves velocities (<5 cm/second)
     - Decreased global longitudinal LV strain (absolute value <-15%).
  2. Multiparametric echocardiographic score ≥8 points:
     - Relative LV wall thickness (IVS+PWT)/LVEDD >0.6 (3 points)

- Doppler E wave/e′ wave velocities >11 (1 point)
- Tricuspid annular plane systolic excursion ≤19 mm (2 points)
- Left ventricular global longitudinal strain absolute value ≤-13% (1 point)
- Systolic longitudinal strain apex to base ratio >2.9 (3 points).

- Cardiac magnetic resonance

1. Characteristic CMR findings (a and b must be present):

    - Diffuse subendocardial or transmural late gadolinium enhancement
    - Abnormal gadolinium kinetics
    - ECV ≥0.40% (strongly supportive, but not essential/diagnostic).

European society of cardiology working group on myocardial and pericardial disease: non-invasive (ATTR only) cardiac amyloidosis diagnostic criteria[109]#

- Grade 2 or 3 cardiac uptake at diphosphonate scintigraphy, plus
- Negative serum free light chains and negative serum and urine immunofixation, plus
- Echocardiographic/cardiac magnetic resonance criteria (per European society of cardiology working group on myocardial and pericardial disease: invasive (all types) cardiac amyloidosis diagnostic criteria).

Approach

Treatment of amyloidosis depends on the type of amyloidosis present. There is no cure for amyloidosis.

Patients should be managed in a specialist amyloidosis centre by a multidisciplinary team (including haematology, cardiology, nephrology, gastroenterology, and neurology specialists).[110] Treatment (including supportive care measures) should be personalised, and all treatment decisions should involve the patient.[110]

Patients should be screened for hepatitis B and C, and HIV (as clinically indicated), before initiating systemic therapy.[62] Herpes zoster prophylaxis is recommended if treatment includes a proteasome inhibitor (e.g., bortezomib) or daratumumab (an anti-CD38 monoclonal antibody).[62]

Immunoglobulin light chain (AL) amyloidosis: treatment aim and approaches

The goal of treatment is to achieve a haematological complete response (CR).[62] [110]

See Criteria for haematological response criteria.

Treatment for AL amyloidosis is aimed at suppressing the plasma cell clone responsible for producing the immunoglobulin light chain causing amyloidosis. Interruption of light chain deposition allows the body to solubilise and eliminate the amyloid deposit. This prevents further amyloid deposition, which would result in progressive organ failure.

All patients with newly diagnosed AL amyloidosis who have organ involvement (i.e., heart, liver, kidney, nerve, lung, or intestine) should be considered for treatment with autologous stem cell transplantation (ASCT) or systemic therapy, or both.[62] [110] [111] Enrolment in a clinical trial should be considered wherever possible.

Patients with an incidental finding of amyloid deposits in the bone marrow and no organ involvement do not require immediate treatment.[112] These patients can be closely observed with monitoring for progression in haematological parameters and vital organ function.[112]

AL amyloidosis: autologous stem cell transplantation (ASCT)

Patients should be carefully assessed for eligibility for ASCT so that treatment-related complications and mortality are minimised.

Eligibility criteria for ASCT in patients with AL amyloidosis are:[111] [112] [113]

- Age ≤70 years
- ≥1 major vital organ involvement
- Performance score ≤2
- Systolic blood pressure ≥90 mmHg (supine)
- Troponin T <0.06 microgram/L (or high-sensitivity troponin T <75 microgram/L)
- N-terminal pro-B-type natriuretic peptide (NT-proBNP) <5000 ng/L
- Left ventricular ejection fraction ≥40%; New York Heart Association (NYHA) class <III
- Oxygen saturation 95% on room air; diffusing capacity of the lungs for carbon monoxide (DLCO) >50%
- Creatinine clearance ≥30 mL/min (unless undergoing long-term dialysis)

- Bilirubin <2 mg/dL

Observational data suggest that ASCT may be safe and effective in carefully selected patients aged 70-75 years.[114] Therefore, patients aged >70 years should be evaluated for eligibility for ASCT by a multi-disciplinary team at a specialist amyloidosis centre.[111]

Definite exclusions for ASCT include:[62] [111]

- Symptomatic and/or medically refractory arrhythmias (ventricular and atrial) or pleural effusions
- Uncompensated heart failure
- Medically refractory orthostatic hypotension
- Factor X deficiency with factor X level <25% or/and evidence of active bleeding
- Extensive gastrointestinal involvement with evidence of active gastrointestinal bleeding or risk of bleeding

Most patients (approximately 80%) will not be eligible for ASCT.[49] [64] Eligibility criteria for SCT may vary depending on the individual centre.

There is a preponderance of observational data suggesting that ASCT is effective in AL amyloidosis.[115] [116] [117] [118] Randomised trials comparing ASCT with systemic therapy are lacking.[119] [120] [121]

Risks associated with ASCT include sudden cardiac death, gastrointestinal tract bleeding, and renal failure. The treatment-related mortality rate is <3%.[122] [123]

Stem cell harvesting and conditioning

Stem cell harvesting (with use of growth factors for mobilisation) should be performed before administering conditioning regimens for ASCT.[111]

The standard conditioning regimen for ASCT is a single administration of high-dose melphalan. One longitudinal study reported that high-dose melphalan plus ASCT induces durable haematological responses and prolonged survival in selected patients.[124]

Dosing of melphalan can be modified based on factors such as age, performance status, renal function, number of organs involved, and cardiac involvement; however, evidence for dose modifications is limited.[62] [125] [126]

Induction therapy

Use of induction therapy prior to ASCT should be considered for all patients to reduce disease burden and improve response rate.[62] [111] [112]

Use of induction therapy may also permit certain patients to undergo ASCT who would otherwise be ineligible.[127]

The recommended regimen for induction therapy is daratumumab plus cyclophosphamide plus bortezomib plus dexamethasone (Dara-CyBorD) for 2-4 cycles.[62] [111] [112] Daratumumab is available as an intravenous formulation, or a subcutaneous formulation (daratumumab/hyaluronidase). Dosing and administration are different for each formulation, but either formulation can be used in daratumumab-containing regimens (in all settings).[62]

If a haematological CR is achieved with induction therapy, ASCT may be deferred.[62] [111] [112]

Consolidation and maintenance therapy

Consolidation and maintenance therapy following ASCT are not routinely recommended due to lack of evidence.[62]

Consolidation therapy may, however, be considered if only a haematological partial response (PR) or very good partial response (VGPR) is achieved after ASCT, and there is no improvement in organ function.[62] [111] [112] [128] [129]

Achieving a rapid and deep haematological response is associated with improved outcomes (including improved organ function and survival).[106] [107] [130] [131] [132] Patients can be observed (without consolidation) if they achieve a haematological VGPR or CR and improved organ function with ASCT. [112] [122]

Maintenance therapy, to prevent haematological progression and organ deterioration after ASCT with minimal toxicity, may be considered in patients with:[62] [111] [112]

- concurrent multiple myeloma,
- bone marrow plasma cells ≥20%, or
- high-risk cytogenetic abnormalities (e.g., del(17p), t(4;14), t(14;16), t(14;20), 1q gain/amplification).

Consolidation and maintenance regimens include bortezomib or lenalidomide, or both combined.[129] [133] However, if bortezomib was used for induction therapy and did not result in a deep haematological response after 4 months, then using it after ASCT is unlikely to provide any incremental value. Lenalidomide is not well-tolerated in patients with AL amyloidosis at doses used for multiple myeloma patients. Dose-adjustment and continuous renal function monitoring are required.[62] [112] [134] [135] [136] Lenalidomide should not be used in patients with advanced heart or autonomic nerve involvement.

Treatment of refractory or relapsed AL amyloidosis post-ASCT

Salvage therapy can be given if there is no response to ASCT (i.e., less than a haematological PR), or if relapse occurs after ASCT (i.e., reappearance of a detectable monoclonal protein or an abnormal immunoglobulin free light chain [FLC] ratio after having achieved a haematological CR). Salvage regimens include:[62] [112]

- Melphalan plus dexamethasone
- Bortezomib plus dexamethasone
- Pomalidomide plus dexamethasone
- Lenalidomide plus dexamethasone
- Bortezomib alone

The salvage therapy regimen should differ from that used for induction therapy (and consolidation or maintenance therapy, if used). The optimal approach for salvage therapy is unknown; it should be guided by prior treatments, depth and duration of response to prior treatments, safety and efficacy of alternative regimens, and patient factors (e.g., fitness, frailty). Enrolment in a clinical trial should be considered wherever possible.

AL amyloidosis: systemic therapy

All patients with newly diagnosed AL amyloidosis and organ involvement are considered candidates for systemic therapy.

The goal of systemic therapy is to achieve a haematological CR.[62] [110]

Initial treatment

Recommended regimens for patients undergoing initial systemic therapy (e.g., those ineligible or declining ASCT) include:[62] [110]

- Daratumumab plus cyclophosphamide plus bortezomib plus dexamethasone (Dara-CyBorD): overall haematological response rate >90% (CR rate: 53%).[137] Dose modification may be required depending on stage (e.g., Mayo stage IIIb), presence of neuropathy, fluid retention status, and patient functional status.
- Daratumumab alone (for Mayo stage IIIb patients): overall haematological response rate 67% (at median follow-up of 8 months) in stage IIIb patients.[138]
- Melphalan plus dexamethasone: overall haematological response rate >65% and long-lasting remission.[139] [140] May be considered for patients with significant neuropathy who are ineligible for ASCT.[62]

Other regimens that may be considered for initial systemic therapy include:[62] [110]

- Cyclophosphamide plus bortezomib plus dexamethasone (CyBorD): haematological response rate of 60% to 80%.[141] [142] [143] [144] [145] Dose modification may be required depending on stage (e.g., Mayo stage IIIb), presence of neuropathy, fluid retention status, and patient functional status.
- Bortezomib plus melphalan plus dexamethasone (BMDex): improved haematological response rate (79% vs. 52%; CR or VGPR rate: 64% vs. 39%) and improved overall survival (hazard ratio: 0.5) compared with melphalan plus dexamethasone.[146]
- Lenalidomide plus dexamethasone: reported to be efficacious, but lenalidomide is not well-tolerated in patients with AL amyloidosis at doses used for multiple myeloma patients. Dose-adjustment and continuous renal function monitoring are required.[62] [112] [134] [135] [136] Lenalidomide should not be used in patients with advanced heart or autonomic nerve involvement.
- Carfilzomib plus dexamethasone: reported to be efficacious in patients with neuropathy, but associated with cardiac and pulmonary toxicity.[147] May be considered for patients with significant neuropathy who do not have advanced cardiac involvement.

Refractory or relapsed disease following initial systemic therapy

Salvage therapy should be considered if:[62] [110] [112]

- haematological response to initial systemic therapy is less than PR by cycle 2 or less than VGPR by cycle 3, or
- relapse occurs after initial systemic therapy (i.e., reappearance of a detectable monoclonal protein or an abnormal immunoglobulin FLC ratio after having achieved a haematological CR).

Salvage therapy should be a different regimen to that used for initial treatment. Repeating the initial treatment regimen may be an option for patients with relapsed disease who have had a long relapse-free period (at least several years) following initial treatment.[62]

The optimal approach for salvage therapy is unknown; therefore, it should be guided by prior treatments, depth and duration of response to prior treatments, safety and efficacy of alternative regimens, and patient factors (e.g., fitness, frailty). For example, if salvage therapy is required after initial treatment with Dara-CyBorD, then pomalidomide plus dexamethasone, or lenalidomide plus dexamethasone, or bendamustine (with or without dexamethasone) can be considered.[134] [136] [148] [149] [150] Ixazomib may be considered in combination with dexamethasone, or with dexamethasone plus lenalidomide.[62] [151] [152] Venetoclax (an oral BCL-2 inhibitor) alone or in combination with dexamethasone can be considered in the relapsed/refractory setting for patients with the t(11;14) chromosome abnormality.[62] [110][112]

There are no approved treatments for salvage therapy for patients with AL amyloidosis. Enrolment in a clinical trial should be considered wherever possible.

Secondary (AA) amyloidosis

Treatment generally involves control of the underlying systemic inflammatory process.

AA amyloidosis (non-familial)

Tumour necrosis factor (TNF)-alpha inhibitors (e.g., infliximab, etanercept) are used to treat inflammatory arthropathies, with a mean duration of therapy of 20 months.[153] Interleukin-1 inhibitors (e.g., anakinra, canakinumab, rilonacept) and interleukin-6 inhibitors (e.g., tocilizumab) may be considered if TNF-alpha inhibitors are not effective or not tolerated.[153] [154] [155]

When AA amyloidosis is due to Castleman's disease, resection of the tumour is effective.[23] [156]

Familial periodic fever syndromes leading to AA amyloidosis

Colchicine effectively reduces the frequency and duration of attacks (including abdominal pain, swollen joints, fever) and prevents the development of AA amyloidosis in patients with familial Mediterranean fever.[157] [158]

Interleukin-1 and interleukin-6 inhibitors improve clinical signs and symptoms of familial periodic fever syndromes.[159] [160] [161] [162] [163] [164] [165] [166] [167]

Canakinumab (an interleukin-1 inhibitor) is approved for the treatment of familial periodic fever syndromes (including familial Mediterranean fever, TNF-receptor-associated periodic fever syndromes [TRAPS], cryopyrin-associated periodic syndromes [CAPS; e.g., Muckle-Wells syndrome], and mevalonate kinase deficiency [formerly known as hyper-IgD syndrome]).

Rilonacept (an interleukin-1 inhibitor) is approved for the treatment of CAPS (including Muckle-Wells syndrome).

Transthyretin (TTR) amyloidosis

Liver transplantation is the most established treatment for hereditary TTR (ATTRv) amyloidosis.[168] [169]

ATTRv amyloidosis with polyneuropathy

Long-term regression of amyloid deposits, and long-term improvements in clinical outcomes (e.g., nerve function) and survival, have been reported after liver transplantation in patients with ATTRv amyloidosis with polyneuropathy, particularly those with Val30Met mutations.[170] [171] [172] [173] However, the number of liver transplantations performed is declining due to the increasing availability of systemic therapies for this condition.[174]

Systemic therapies for ATTRv amyloidosis with polyneuropathy includes:

- Patisiran and vutrisiran: small interfering ribonucleic acids (siRNAs) that inhibit the production of TTR in the liver. In an 18-month randomised controlled trial, patisiran reduced neurological impairment and improved quality of life compared with placebo in patients with ATTRv amyloidosis with polyneuropathy.[175] Longer-term data suggest that efficacy and safety are maintained.[176] Vutrisiran has similar efficacy to patisiran; non-inferiority to patisiran has been reported.[177] Patisiran is administered as an intravenous infusion every 3 weeks; pre-medication with a

corticosteroid, paracetamol, and an antihistamine is recommended to reduce the risk of infusion-related reactions. Vutrisiran is administered by subcutaneous injection at 3-month intervals and does not require additional monitoring.

- Inotersen: a subcutaneously administered antisense oligonucleotide drug that inhibits the production of TTR in the liver. Inotersen is available in the US only through a Risk Evaluation and Mitigation Strategy (REMS) programme. In a 15-month randomised controlled trial, inotersen reduced neurological impairment and improved quality of life compared with placebo in patients with TTR amyloidosis with polyneuropathy.[178] Severe thrombocytopenia and glomerulonephritis have been reported with this agent. Longer-term data suggest that efficacy and safety are maintained.[179]
- Tafamidis: an orally administered TTR stabiliser drug that interferes with the misfolding of TTR and reduces amyloid formation. Available as a free acid (tafamidis) or salt formulation (tafamidis meglumine); the dose for each formulation is different, and they are not interchangeable on a per mg basis. Tafamidis meglumine did not meet the primary end points of reducing neurological impairment and improving quality of life in an 18-month placebo-controlled randomised clinical trial.[180] Long-term tafamidis meglumine was associated with a continued reduction in neurological progression.[181] In the US, both tafamidis and tafamidis meglumine are approved for the treatment of TTR amyloidosis with cardiac involvement, but not for TTR amyloidosis with polyneuropathy (see ATTRv and wild-type [ATTRwt] amyloidosis with cardiac involvement below). Tafamidis meglumine is approved in Europe for the treatment of stage 1 symptomatic polyneuropathy in adults with TTR amyloidosis.
- Diflunisal: a non-steroidal anti-inflammatory drug that stabilises TTR.[182] In one randomised controlled trial, diflunisal given for 2 years reduced the rate of progression of neurological impairment and preserved quality of life compared with placebo in patients with ATTRv amyloidosis with polyneuropathy.[183] Renal function and blood cell counts should be carefully monitored.[184] Use of diflunisal for ATTRv amyloidosis is off-label.

ATTRv and wild-type (ATTRwt) amyloidosis with cardiac involvement

Progression of cardiac disease may occur after liver transplantation in patients with ATTRv amyloidosis with cardiac involvement.[185] [186] Systemic therapies are increasingly available for patients with ATTRv amyloidosis, which means the number of liver transplants performed will likely fall.[174]

In one 30-month randomised controlled trial of patients with TTR cardiac amyloidosis (ATTRv or ATTRwt), tafamidis significantly reduced all-cause mortality and cardiac-related hospitalisations (approximately 30% reduction for each outcome) compared with placebo.[187] Results from an extension study and pre-specified analysis indicate that tafamidis is effective for both ATTRv and ATTRwt cardiac amyloidosis, and that benefit is maintained in the long term.[188] [189]

In the US, both tafamidis and tafamidis meglumine are approved for the treatment of TTR cardiac amyloidosis. In Europe, only tafamidis is approved for TTR cardiac amyloidosis. The dose for each tafamidis formulation is different, and they are not interchangeable on a per mg basis.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
immunoglobulin light chain (AL) amyloidosis		
without organ involvement	**1st**	**observation**
with organ involvement, and eligible for stem cell transplantation	**1st**	**high-dose melphalan plus stem cell transplantation**
	plus	**induction therapy (pre-stem cell transplantation)**
	adjunct	**consolidation and maintenance therapy (post-stem cell transplantation)**
with organ involvement, and not eligible or declining stem cell transplantation	**1st**	**systemic therapy**
secondary (AA) amyloidosis (non-familial)		
	1st	**treatment of underlying condition**
familial periodic fever syndromes		
	1st	**colchicine or canakinumab or rilonacept**
transthyretin (TTR) amyloidosis		
with polyneuropathy	**1st**	**liver transplantation or pharmacotherapy**
with cardiac involvement	**1st**	**liver transplantation or pharmacotherapy**

Ongoing (summary)		
refractory or relapsed AL amyloidosis		
following initial stem cell transplantation	**1st**	**salvage therapy**
following initial systemic therapy	**1st**	**salvage therapy**

MANAGEMENT

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

immunoglobulin light chain (AL) amyloidosis

without organ involvement — 1st — **observation**

» Patients with an incidental finding of amyloid deposits in the bone marrow and no organ involvement do not require immediate treatment.[112]

» Patients can be closely observed with monitoring for progression in haematological parameters and vital organ function.[112]

with organ involvement, and eligible for stem cell transplantation — 1st — **high-dose melphalan plus stem cell transplantation**

Primary options

» melphalan

» Patients should be managed in a specialist amyloidosis centre by a multidisciplinary team (including haematology, cardiology, nephrology, gastroenterology, and neurology specialists).[110]

» Treatment (including supportive care measures) should be personalised, and all treatment decisions should involve the patient.[110]

» All patients with newly diagnosed AL amyloidosis who have organ involvement (i.e., heart, liver, kidney, nerve, lung, or intestine) should be considered for treatment with autologous stem cell transplantation (ASCT) or systemic therapy, or both.[62] [110] [111]

» Patients should be carefully assessed for eligibility for ASCT so that treatment-related complications and mortality are minimised.

» Eligibility criteria for ASCT in patients with AL amyloidosis are: age ≤70 years; ≥1 major vital organ involvement; performance score ≤2; systolic blood pressure ≥90 mmHg (supine); troponin T <0.06 microgram/L (or high-sensitivity troponin T <75 microgram/L); N-terminal pro-B-type natriuretic peptide (NT-proBNP) <5000 ng/L; left ventricular ejection fraction ≥40%; New York Heart Association (NYHA) class <III;

Acute

oxygen saturation 95% on room air; diffusing capacity of the lungs for carbon monoxide (DLCO) >50%; creatinine clearance ≥30 mL/min (unless undergoing long-term dialysis), and bilirubin <2 mg/dL.[111] [112] [113]

» Observational data suggest that ASCT may be safe and effective in carefully selected patients aged 70-75 years.[114] Therefore, patients aged >70 years should be evaluated for eligibility for ASCT by a multi-disciplinary team at a specialist amyloidosis centre.[111]

» Definite exclusions for ASCT include: symptomatic and/or medically refractory arrhythmias (ventricular and atrial) or pleural effusions; uncompensated heart failure; medically refractory orthostatic hypotension; factor X deficiency with factor X level <25% or/and evidence of active bleeding; extensive gastrointestinal involvement with evidence of active gastrointestinal bleeding or risk of bleeding.[62] [111]

» Most patients (approximately 80%) will not be eligible for ASCT.[49] [64] Eligibility criteria for ASCT may vary depending on the individual centre.

» There is a preponderance of observational data suggesting that ASCT is effective in AL amyloidosis.[115] [116] [117] [118] Randomised trials comparing ASCT with systemic therapy are lacking.[119] [120] [121]

» Risks associated with ASCT include sudden cardiac death, gastrointestinal tract bleeding, and renal failure. The treatment-related mortality rate is <3%.[122] [123]

» Stem cell harvesting (with use of growth factors for mobilisation) should be performed before administering conditioning regimens for ASCT.[111]

» The standard conditioning regimen for ASCT is a single administration of high-dose melphalan. One longitudinal study reported that high-dose melphalan plus ASCT induces durable haematological responses and prolonged survival in selected patients.[124]

» Dosing of melphalan can be modified based on factors such as age, performance status, renal function, number of organs involved, and cardiac involvement; however, evidence for dose modifications is limited.[62] [125] [126]

Acute

» See local specialist protocol for dosing guidelines.

plus **induction therapy (pre-stem cell transplantation)**

Treatment recommended for ALL patients in selected patient group

Primary options

» daratumumab
-or-
» daratumumab/hyaluronidase
--AND--
» cyclophosphamide
--AND--
» bortezomib
--AND--
» dexamethasone

» Use of induction therapy prior to autologous stem cell transplantation (ASCT) should be considered for all patients to reduce disease burden and improve response rate.[62] [111] [112]

» Use of induction therapy may also permit certain patients to undergo ASCT who would otherwise be ineligible.[127]

» The recommended regimen for induction therapy is daratumumab plus cyclophosphamide plus bortezomib plus dexamethasone (Dara-CyBorD) for 2-4 cycles.[62] [111] [112]

» Daratumumab (an anti-CD38 monoclonal antibody) is available as an intravenous formulation, or a subcutaneous formulation (daratumumab/hyaluronidase). Dosing and administration are different for each formulation, but either formulation can be used in daratumumab-containing regimens (in all settings).[62]

» If a haematological complete response (CR) is achieved with induction therapy, ASCT may be deferred.[62] [111] [112] See Criteria for haematological response criteria.

» Patients should be screened for hepatitis B and C and HIV (as clinically indicated) before initiating systemic therapy.[62] Herpes zoster prophylaxis is recommended if treatment includes a proteasome inhibitor (e.g., bortezomib) or daratumumab.[62]

Acute

» Enrolment in a clinical trial should be considered wherever possible.[62]

» See local specialist protocol for dosing guidelines.

adjunct **consolidation and maintenance therapy (post-stem cell transplantation)**

Treatment recommended for SOME patients in selected patient group

Primary options

» bortezomib

OR

» lenalidomide

OR

» bortezomib
-and-
» lenalidomide

» Consolidation and maintenance therapy following autologous stem cell transplantation (ASCT) are not routinely recommended due to lack of evidence.[62]

» Consolidation therapy may, however, be considered if only a haematological partial response (PR) or very good partial response (VGPR) is achieved after ASCT, and there is no improvement in organ function.[62] [111] [112] [128] [129]

» Achieving a rapid and deep haematological response is associated with improved outcomes (including improved organ function and survival).[106] [107] [130] [131] [132] Patients can be observed (without consolidation) if they achieve a haematological VGPR or CR and improved organ function with ASCT.[112] [122]

» Maintenance therapy, to prevent haematological progression and organ deterioration after ASCT with minimal toxicity, may be considered in patients with concurrent multiple myeloma, bone marrow plasma cells ≥20%, or high-risk cytogenetic abnormalities (e.g., del(17p), t(4;14), t(14;16), t(14;20), 1q gain/amplification).[62] [111] [112]

» Consolidation and maintenance regimens include bortezomib or lenalidomide, or both combined.[129] [133] However, if bortezomib was used for induction therapy and did not

Acute

result in a deep haematological response after 4 months, then using it after ASCT is unlikely to provide any incremental value. Lenalidomide is not well-tolerated in patients with AL amyloidosis at doses used for multiple myeloma patients. Dose-adjustment and continuous renal function monitoring are required.[62] [112] [134] [135] [136] Lenalidomide should not be used in patients with advanced heart or autonomic nerve involvement.

» Patients should be screened for hepatitis B and C and HIV (as clinically indicated) before initiating systemic therapy.[62] Herpes zoster prophylaxis is recommended if treatment includes a proteasome inhibitor (e.g., bortezomib).[62]

» Enrolment in a clinical trial should be considered wherever possible.

» See local specialist protocol for dosing guidelines.

with organ involvement, and not eligible or declining stem cell transplantation — **1st**

systemic therapy

Primary options

» daratumumab
-or-
» daratumumab/hyaluronidase
--AND--
» cyclophosphamide
--AND--
» bortezomib
--AND--
» dexamethasone

OR

» daratumumab

OR

» daratumumab/hyaluronidase

OR

» melphalan
-and-
» dexamethasone

Secondary options

» cyclophosphamide
-and-

Acute

» bortezomib
-and-
» dexamethasone

OR

» bortezomib
-and-
» melphalan
-and-
» dexamethasone

OR

» lenalidomide
-and-
» dexamethasone

OR

» carfilzomib
-and-
» dexamethasone

» Patients should be managed in a specialist amyloidosis centre by a multidisciplinary team (including haematology, cardiology, nephrology, gastroenterology, and neurology specialists).[110]

» Treatment (including supportive care measures) should be personalised, and all treatment decisions should involve the patient.[110]

» All patients with newly diagnosed AL amyloidosis and organ involvement (i.e., heart, liver, kidney, nerve, lung, or intestine) are considered candidates for systemic therapy.[62] [110] [111]

» The goal of systemic therapy is to achieve a haematological CR.[62] [110]

» Recommended regimens for patients undergoing initial systemic therapy (e.g., those ineligible or declining autologous stem cell transplantation [ASCT]) include: daratumumab plus cyclophosphamide plus bortezomib plus dexamethasone (Dara-CyBorD); daratumumab alone (for Mayo stage IIIb patients); and melphalan plus dexamethasone (for patients with AL amyloidosis with significant neuropathy who are ineligible for ASCT).[62] [110]

» Other regimens that may be considered for initial systemic therapy include:

Acute

cyclophosphamide plus bortezomib plus dexamethasone (CyBorD); bortezomib plus melphalan plus dexamethasone (BMDex); lenalidomide plus dexamethasone; and carfilzomib plus dexamethasone (for patients with significant neuropathy who do not have advanced cardiac involvement).[62] [110]

» Dara-CyBorD and CyBorD may require dose modification depending on stage (e.g., Mayo stage IIIb), presence of neuropathy, fluid retention status, and patient functional status.[62] [110]

» Daratumumab (an anti-CD38 monoclonal antibody) is available as an intravenous formulation, or a subcutaneous formulation (daratumumab/hyaluronidase). Dosing and administration are different for each formulation, but either formulation can be used in daratumumab-containing regimens (in all settings).[62]

» Patients should be screened for hepatitis B and C and HIV (as clinically indicated) before initiating systemic therapy.[62] Herpes zoster prophylaxis is recommended if treatment includes a proteasome inhibitor (e.g., bortezomib) or daratumumab.[62]

» Enrolment in a clinical trial should be considered wherever possible.

» See local specialist protocol for dosing guidelines.

secondary (AA) amyloidosis (non-familial)

1st **treatment of underlying condition**

Primary options

» infliximab

OR

» etanercept

Secondary options

» anakinra

OR

» canakinumab

OR

Acute

» rilonacept

OR

» tocilizumab

» Treatment generally involves control of the underlying systemic inflammatory process.

» Tumour necrosis factor (TNF)-alpha inhibitors (e.g., infliximab, etanercept) are used to treat inflammatory arthropathies, with a mean duration of therapy of 20 months.[153]

» Interleukin-1 inhibitors (e.g., anakinra, canakinumab, rilonacept) and interleukin-6 inhibitors (e.g., tocilizumab) may be considered if TNF-alpha inhibitors are not effective or not tolerated.[153] [154] [155]

» When AA amyloidosis is due to Castleman's disease, resection of the tumour is effective.[23] [156]

» Consult specialist for guidance on dose.

familial periodic fever syndromes

1st **colchicine or canakinumab or rilonacept**

Primary options

» colchicine

OR

» canakinumab

OR

» rilonacept

» Colchicine effectively reduces the frequency and duration of attacks (including abdominal pain, swollen joints, fever) and prevents the development of secondary (AA) amyloidosis in patients with familial Mediterranean fever.[157] [158]

» Interleukin-1 and interleukin-6 inhibitors improve clinical signs and symptoms of familial periodic fever syndromes.[159] [160] [161] [162] [163] [164] [165] [166] [167]

» Canakinumab (an interleukin-1 inhibitor) is approved for the treatment of familial periodic fever syndromes (including familial Mediterranean fever, tumour necrosis factor

MANAGEMENT

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[TNF] receptor-associated periodic fever syndromes [TRAPS], cryopyrin-associated periodic syndromes [CAPS; e.g., Muckle-Wells syndrome], and mevalonate kinase deficiency [formerly known as hyper-IgD syndrome]).

» Rilonacept (an interleukin-1 inhibitor) is approved for the treatment of CAPS (including Muckle-Wells syndrome).

» Consult specialist for guidance on dose.

transthyretin (TTR) amyloidosis

with polyneuropathy — **1st** — **liver transplantation or pharmacotherapy**

Primary options

» patisiran

OR

» vutrisiran

OR

» inotersen

OR

» tafamidis meglumine

Secondary options

» diflunisal

» Liver transplantation is the most established treatment for hereditary TTR (ATTRv) amyloidosis.[168] [169]

» Long-term regression of amyloid deposits, and long-term improvements in clinical outcomes (e.g., nerve function) and survival, have been reported after liver transplantation in patients with ATTRv amyloidosis with polyneuropathy, particularly those with Val30Met mutations.[170] [171] [172] [173] However, the number of liver transplantations performed is declining due to the increasing availability of systemic therapies for this condition (e.g., patisiran, vutrisiran, inotersen, tafamidis, and diflunisal).[174]

» Patisiran and vutrisiran: small interfering ribonucleic acids (siRNAs) that inhibit the production of TTR in the liver. In an 18-month randomised controlled trial, patisiran reduced neurological impairment and

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improved quality of life compared with placebo in patients with ATTRv amyloidosis with polyneuropathy.[175] Longer-term data suggest that efficacy and safety are maintained.[176] Vutrisiran has similar efficacy to patisiran; non-inferiority to patisiran has been reported.[177] Patisiran is administered as an intravenous infusion every 3 weeks; pre-medication with a corticosteroid, paracetamol, and an antihistamine is recommended to reduce the risk of infusion-related reactions. Vutrisiran is administered by subcutaneous injection at 3-month intervals and does not require additional monitoring.

» Inotersen: a subcutaneously administered antisense oligonucleotide drug that inhibits the production of TTR in the liver. Inotersen is available in the US only through a Risk Evaluation and Mitigation Strategy (REMS) programme. In Europe, inotersen is approved for the treatment of stage 1 or stage 2 polyneuropathy in adults with ATTRv amyloidosis. In a 15-month randomised controlled trial, inotersen reduced neurological impairment and improved quality of life compared with placebo in patients with TTR amyloidosis with polyneuropathy.[178] Severe thrombocytopenia and glomerulonephritis have been reported with this agent. Longer-term data suggest that efficacy and safety are maintained.[179]

» Tafamidis: an orally administered TTR stabiliser drug that interferes with the misfolding of TTR and reduces amyloid formation. Available as a free acid (tafamidis) or salt formulation (tafamidis meglumine); the dose for each formulation is different, and they are not interchangeable on a per mg basis. Tafamidis meglumine did not meet the primary end points of reducing neurological impairment and improving quality of life in an 18-month placebo-controlled randomised clinical trial.[180] Long-term tafamidis meglumine was associated with a continued reduction in neurological progression.[181] In the US, both tafamidis and tafamidis meglumine are approved for the treatment of TTR amyloidosis with cardiac involvement, but not for TTR amyloidosis with polyneuropathy. Tafamidis meglumine is approved in Europe for the treatment of stage 1 symptomatic polyneuropathy in adults with TTR amyloidosis.

» Diflunisal: a non-steroidal anti-inflammatory drug that stabilises TTR. In one randomised

Acute

controlled trial, diflunisal given for 2 years reduced the rate of progression of neurological impairment and preserved quality of life compared with placebo in patients with ATTRv amyloidosis with polyneuropathy.[183] Renal function and blood cell counts should be carefully monitored.[184] Use of diflunisal for ATTRv amyloidosis is off-label.

» Consult specialist for guidance on dose.

with cardiac involvement — **1st** — **liver transplantation or pharmacotherapy**

Primary options

» tafamidis

OR

» tafamidis meglumine

» Liver transplantation is the most established treatment for hereditary TTR (ATTRv) amyloidosis.[168] [169]

» Progression of cardiac disease may occur after liver transplantation in patients with ATTRv amyloidosis with cardiac involvement.[185] [186]

» Systemic therapies are increasingly available for patients with ATTRv amyloidosis, which means the number of liver transplants performed will likely fall.[174]

» In one 30-month randomised controlled trial of patients with TTR cardiac amyloidosis (ATTRv or ATTRwt), tafamidis (a TTR stabiliser that is administered orally) significantly reduced all-cause mortality and cardiac-related hospitalisations (approximately 30% reduction for each outcome) compared with placebo.[187] Results from an extension study and pre-specified analysis indicate that tafamidis is effective for both ATTRv and ATTRwt cardiac amyloidosis, and that benefit is maintained in the long term.[188] [189]

» Tafamidis is available as a free acid or salt formulation (tafamidis meglumine); the dose for each formulation is different, and they are not interchangeable on a per mg basis. In the US, both tafamidis and tafamidis meglumine are approved for the treatment of TTR cardiac amyloidosis. In Europe, only tafamidis is approved for TTR cardiac amyloidosis.

» Consult specialist for guidance on dose.

Ongoing

refractory or relapsed AL amyloidosis

following initial stem cell transplantation | **1st** | **salvage therapy**

Primary options

» melphalan
-and-
» dexamethasone

OR

» bortezomib
-and-
» dexamethasone

OR

» pomalidomide
-and-
» dexamethasone

OR

» lenalidomide
-and-
» dexamethasone

OR

» bortezomib

» Salvage therapy can be given if there is no response to autologous stem cell transplantation (i.e., less than a haematological partial response [PR]), or if relapse occurs after stem cell transplantation (i.e., reappearance of a detectable monoclonal protein or an abnormal immunoglobulin free light chain [FLC] ratio after having achieved a haematological complete response [CR]).

» Salvage regimens include: melphalan plus dexamethasone; bortezomib plus dexamethasone; pomalidomide plus dexamethasone; lenalidomide plus dexamethasone; bortezomib alone.[62] [112]

» The salvage therapy regimen should differ from that used for induction therapy (and consolidation or maintenance therapy, if used).

» The optimal approach for salvage therapy is unknown; it should be guided by prior

Ongoing

treatments, depth and duration of response to prior treatments, safety and efficacy of alternative regimens, and patient factors (e.g., fitness, frailty).

» Lenalidomide is not well-tolerated in patients with AL amyloidosis at doses used for multiple myeloma patients. Dose-adjustment and continuous renal function monitoring are required.[62] [112] [134] [135] [136] Lenalidomide should not be used in patients with advanced heart or autonomic nerve involvement.

» There are no approved treatments for salvage therapy for patients with AL amyloidosis. Enrolment in a clinical trial should be considered wherever possible.

» See local specialist protocol for dosing guidelines.

following initial systemic therapy | **1st** | **salvage therapy**

» Salvage therapy should be considered if: haematological response to initial systemic therapy is less than a partial response (PR) by cycle 2 or less than a very good partial response (VGPR) by cycle 3, or relapse occurs after initial systemic therapy (i.e., reappearance of a detectable monoclonal protein or an abnormal immunoglobulin free light chain [FLC] ratio after having achieved a haematological complete response [CR]).

» Salvage therapy should be a different regimen to that used for initial treatment.

» Repeating the initial treatment regimen may be an option for patients with relapsed disease who have had a long relapse-free period (at least several years) following initial treatment.[62]

» The optimal approach for salvage therapy is unknown; therefore, it should be guided by prior treatments, depth and duration of response to prior treatments, safety and efficacy of alternative regimens, and patient factors (e.g., fitness, frailty). For example, if salvage therapy is required after initial treatment with daratumumab plus cyclophosphamide plus bortezomib plus dexamethasone (Dara-CyBorD), then pomalidomide plus dexamethasone, or lenalidomide plus dexamethasone, or bendamustine (with or without dexamethasone) can be considered.[134] [136] [148] [149] [150] Ixazomib may be considered in combination with dexamethasone, or with dexamethasone plus lenalidomide.[62] [151] [152] Venetoclax (an oral BCL-2 inhibitor) alone or in combination

Ongoing

with dexamethasone can be considered in the relapsed/refractory setting for patients with the t(11;14) chromosome abnormality.[62] [110] [112]

» There are no approved treatments for salvage therapy for patients with AL amyloidosis. Enrolment in a clinical trial should be considered wherever possible.

Emerging

Acoramidis

In a phase 3 trial of patients with transthyretin amyloid cardiomyopathy (ATTR-CM), acoramidis (an oral investigational transthyretin stabiliser) was superior to placebo with respect to a hierarchical composite primary endpoint (all-cause mortality, cumulative frequency of cardiovascular [CV]-related hospitalisation, change from baseline in NT-proBNP, and change from baseline in 6-minute walk distance).[190] [191] In an earlier phase 2 study, acoramidis was well-tolerated and demonstrated a near-complete stabilisation of TTR tetramers (at the highest dose tested).[192]

CAEL-101

A fibril-reactive monoclonal antibody, CAEL-101 targets an epitope on human light-chain amyloid fibrils, resulting in the reduction and/or elimination of amyloid deposits.[193] [194] Results from phase I and II clinical trials of CAEL-101 in patients with AL amyloidosis are promising.[195] [196]

Isatuximab

An anti-CD38 monoclonal antibody approved for multiple myeloma, isatuximab may be effective in patients with previously treated AL amyloidosis.[197]

Eplontersen

Eplontersen, an investigational ligand-conjugated antisense drug, has been granted orphan drug designation in the US for the treatment of transthyretin-mediated amyloidosis. It is currently in phase 3 clinical trials for amyloid transthyretin cardiomyopathy and polyneuropathy.[198] [199]

NTLA-2001

NTLA-2001 is the first investigational CRISPR therapy candidate to be administered systemically, and could potentially be curative for ATTR amyloidosis. NTLA-2001 is an in vivo gene-editing therapeutic that is designed to reduce serum transthyretin levels. The treatment uses lipid nanoparticles to deliver a two-part genome editing system to the liver consisting of single-guide RNAs targeting transthyretin, and mRNAs for the Cas9 protein. Preclinical studies have shown durable knockout of the transthyretin protein after a single intravenous dose.[200] A phase 1 trial is ongoing.[201] NTLA-2001 has been granted orphan drug designation in the US for the treatment of transthyretin amyloidosis.

Primary prevention

Immunoglobulin light chain (AL) amyloidosis is sporadic and no preventive interventions are recognised.

Development of secondary (AA) amyloidosis in a chronic inflammatory state is directly related to uncontrolled inflammation and hepatic production of serum amyloid A protein.[60] Treatment of the underlying condition to suppress the inflammation reduces the subsequent risk of AA amyloidosis.

Secondary prevention

Patients with multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) should have regular clinical assessment. Repeat serum protein electrophoresis testing is indicated annually.

Routine screening for amyloidosis is not indicated unless the patient has increasing fatigue or oedema, or if urinalysis shows proteinuria.

Patient discussions

Excellent patient-related websites exist that allow for networking with other patients with amyloidosis. [Amyloidosis Foundation] (http://www.amyloidosis.org) [Amyloidosis Support Groups] (http://www.amyloidosissupport.org) [Myeloma UK] (http://www.myeloma.org.uk) [Amyloidosis UK] (https://amyloidosisuk.org)

FOLLOW UP

Monitoring

Monitoring

Long-term monitoring of AL amyloidosis involves serialised measurements of serum immunoglobulin free light chain, repeated serum and urine immunofixation electrophoresis, serum creatinine, and 24-hour total urinary protein.

Echocardiogram should be repeated every 6 months.

Serialised measurements of serum troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are useful in assessing the status of the heart, with rising levels indicating worsening cardiac status.

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
treatment-related complications	**short term**	**medium**
Treatment-related mortality associated with autologous stem cell transplantation (ASCT) for AL amyloidosis is <3%.[122][123] Because of pre-existing organ dysfunction in AL amyloidosis, the complication rate associated with high-dose chemotherapy and ASCT is greater than that for transplantation for multiple myeloma or lymphoma.[202] Patients are at high risk of developing infections (including reactivation or worsening of viral infections) following systemic therapy for AL amyloidosis. Patients should be screened for hepatitis B and C and HIV (as clinically indicated) before initiating systemic therapy.[62] Herpes zoster prophylaxis is recommended if treatment includes a proteasome inhibitor (e.g., bortezomib) or daratumumab (an anti-CD38 monoclonal antibody).[62] Dexamethasone is associated with fluid retention, particularly in patients with cardiac and renal amyloidosis, and may require concomitant diuretic therapy. Bortezomib is associated with peripheral and autonomic neuropathy, Carfilzomib is associated with cardiac and pulmonary toxicity.		
chronic renal failure	**long term**	**medium**
The protracted excretion of albumin at levels in excess of 5 g/24 hours eventually results in tubular damage and dialysis-dependent renal insufficiency. Although lisinopril has been used to reduce diabetic proteinuria, its value in amyloid nephrotic syndrome remains unproven. Case studies report the use of tocilizumab in the management of serum A amyloidosis proteinuria secondary to rheumatoid arthritis.[206] [207] Patients who are on dialysis tend not to do as well as patients with primary renal disease because of associated cardiomyopathy. Rarely, patients have received myeloablative chemotherapy followed by a kidney transplant.		
progressive cardiomyopathy	**long term**	**medium**
Progressive cardiomyopathy is the most common cause of death in amyloidosis and, because it is a restrictive cardiomyopathy, tends to respond poorly to conventional therapy. Calcium-channel blockers, beta-blockers, and ACE inhibitors have not been systematically studied for their ability to improve cardiac disease. Patients frequently suffer clinical deterioration following exposure to these agents.		
conduction abnormalities	**long term**	**medium**
May require use of amiodarone for the prevention of high-grade arrhythmias and pacing therapy for patients with conduction system abnormality.		

Complications	Timeframe	Likelihood
progressive painful peripheral neuropathy	**long term**	**low**
Increased likelihood if bortezomib is used in treatment. Standard agents such as gabapentin and amitriptyline have significant adverse effects (e.g., sedation) that make their use at standard doses difficult. Narcotics are often required.		
obstruction related to an enlarged tongue (macroglossia)	**long term**	**low**
Obstructive sleep apnoea and progressive difficulty in the deglutition of solid foods occurs as a consequence of progressive tongue enlargement. Surgical intervention on the tongue is generally contra-indicated due to bleeding complications. Patients may respond to continuous positive airway pressure. Rarely, a tracheostomy is required or a feeding oesophagostomy is required to overcome obstruction of the airway and upper digestive tract.		
factor X deficiency	**long term**	**low**
This is characteristic of patients with advanced hepatic amyloidosis. Deficiency of factor X results in significant prolongation of the prothrombin time, which can lead to spontaneous bleeding.		
splenic rupture	**long term**	**low**
Amyloid renders the spleen rigid. A tear in the capsule can result in extensive haemorrhage, particularly because patients may also have factor X deficiency. This is considered an acute surgical emergency. Pre-operatively, management includes administration of activated factor VII or infusion of factor X concentrate.		

Prognosis

Immunoglobulin light chain (AL) amyloidosis

The prognosis for patients with AL amyloidosis following treatment is dependent on therapeutic suppression of light chain synthesis. Outcome is also determined by the severity of cardiac involvement.[202]

Survival statistics among 2337 individuals with AL amyloidosis referred to the Boston University Amyloidosis Center have been reported according to date of diagnosis.[203]

- 1980-1989: 1.4 years overall median survival; 15% 5-year overall survival (OS); 7% 10-year OS

- 1990-1999: 2.6 years overall median survival; 36% 5-year OS; 18% 10-year OS
- 2000-2009: 3.3 years overall median survival; 40% 5-year OS; 22% 10-year OS
- 2010-2019: 4.6 years overall median survival; 48% 5-year OS; non-evaluable 10-year OS.

Cardiac failure was the leading cause of death (32%). Individuals without cardiac involvement experienced the greatest improvement in overall survival (median OS increasing >6 years over the study period).[203] Mortality unrelated to AL amyloidosis increased with time (3% [1980-1989], 8% [1990-1999], 8% [2000-2009], 16% [2010-2019]), and with long-term survival (29% for deaths occurring >10 years after diagnosis).[203]

In another institution, 25% of patients with AL amyloidosis who were diagnosed after 2004 survived for over a decade.[44] Of these long-term survivors, 67% had a complete haematological response and 30% had a very good partial response. Long-term survivors had more limited organ involvement and were less likely to have cardiac, liver, and nerve involvement.

Staging systems may be used to prognosticate survival at diagnosis and at relapse in patients with AL amyloidosis. The European modification of the original Mayo staging system (which utilises a higher threshold for NT-proBNP) may be preferred to other staging criteria because of its discriminative accuracy in detecting patients with the best and worst prognoses, and its applicability in high-risk patients (eGFR <50 or atrial arrhythmia).[204] [205] Adding dFLC (difference between the involved to the uninvolved light chain) to a cardiac biomarker-based model increases ability to predict for long-term survival.[204]

Secondary (AA) amyloidosis

The prognosis for patients with AA amyloidosis depends on the control of the underlying disease.

Serum amyloid A (SAA) protein levels are highly predictive of survival.

Suppression of SAA levels to normal (<10 mg/L) is commonly associated with survival in excess of 10 years. However, the relative risk of death increases fivefold for SAA levels between 9 mg/L and 16.6 mg/L, and 17-fold for SAA levels between 87 mg/L and 154 mg/L.[16]

Diagnostic guidelines

United Kingdom

Guidelines on the diagnosis and investigation of AL amyloidosis (https://b-s-h.org.uk/guidelines)

Published by: British Committee for Standards in Haematology **Last published:** 2014

Europe

Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC working group on myocardial and pericardial disease (https://www.escardio.org/Guidelines/Consensus-and-Position-Papers)

Published by: European Society of Cardiology **Last published:** 2021

First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy (https://journals.lww.com/co-neurology/fulltext/2016/02001/First_European_consensus_for_diagnosis,.3.aspx)

Published by: European Network for TTR-FAP (ATTReuNET) **Last published:** 2016

International

Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy (https://arci.org/resources-category/publications)

Published by: Amyloidosis Research Consortium **Last published:** 2020

Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis (https://arci.org/resources-category/publications)

Published by: Amyloidosis Research Consortium **Last published:** 2019

International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders (https://www.myeloma.org/resource-library/international-myeloma-working-group-imwg-guidelines-serum-free-light-chain)

Published by: International Myeloma Working Group **Last published:** 2009

North America

NCCN clinical practice guidelines in oncology: systemic light chain amyloidosis (https://www.nccn.org/professionals/physician_gls)

Published by: National Comprehensive Cancer Network **Last published:** 2024

Expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis (https://www.acc.org/Guidelines)

Published by: American College of Cardiology **Last published:** 2023

Expert consensus recommendations for multimodality imaging in cardiac amyloidosis (https://www.asnc.org/guidelinesandstandards)

Published by: American Society of Nuclear Cardiology **Last published:** 2021

Treatment guidelines

Europe

Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC working group on myocardial and pericardial disease (https://www.escardio.org/Guidelines/Consensus-and-Position-Papers)

Published by: European Society of Cardiology **Last published:** 2021

First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy (https://journals.lww.com/co-neurology/fulltext/2016/02001/First_European_consensus_for_diagnosis,.3.aspx)

Published by: European Network for TTR-FAP (ATTReuNET) **Last published:** 2015

International

Guidelines for non-transplant chemotherapy for treatment of systemic AL amyloidosis: EHA-ISA working group (https://www.isaamyloidosis.org/isa-guidelines)

Published by: European Haematology Association; International Society of Amyloidosis **Last published:** 2023

Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis: EHA-ISA working group guidelines (https://www.isaamyloidosis.org/isa-guidelines)

Published by: European Haematology Association; International Society of Amyloidosis **Last published:** 2022

North America

NCCN clinical practice guidelines in oncology: systemic light chain amyloidosis (https://www.nccn.org/professionals/physician_gls)

Published by: National Comprehensive Cancer Network **Last published:** 2024

NCCN clinical practice guidelines in oncology: hematopoietic cell transplantation (HCT) (https://www.nccn.org/guidelines/category_1)

Published by: National Comprehensive Cancer Network **Last published:** 2024

Expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis (https://www.acc.org/Guidelines)

Published by: American College of Cardiology **Last published:** 2023

Treatment of AL amyloidosis: Mayo stratification of myeloma and risk-adapted therapy (mSMART) consensus statement (https://www.mayoclinicproceedings.org/article/S0025-6196(21)00228-7/fulltext)

Published by: Mayo Clinic Proceedings **Last published:** 2021

Online resources

1. Amyloidosis Foundation (http://www.amyloidosis.org) *(external link)*
2. Amyloidosis Support Groups (http://www.amyloidosissupport.org) *(external link)*
3. Myeloma UK (http://www.myeloma.org.uk) *(external link)*
4. Amyloidosis UK (https://amyloidosisuk.org) *(external link)*

Key articles

- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: systemic light chain amyloidosis [internet publication]. Full text (https://www.nccn.org/guidelines/category_1)
- Wechalekar AD, Cibeira MT, Gibbs SD, et al. Guidelines for non-transplant chemotherapy for treatment of systemic AL amyloidosis: EHA-ISA working group. Amyloid. 2023 Mar;30(1):3-17. Full text (https://www.tandfonline.com/doi/full/10.1080/13506129.2022.2093635#d1e326) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35838162?tool=bestpractice.bmj.com)
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Images

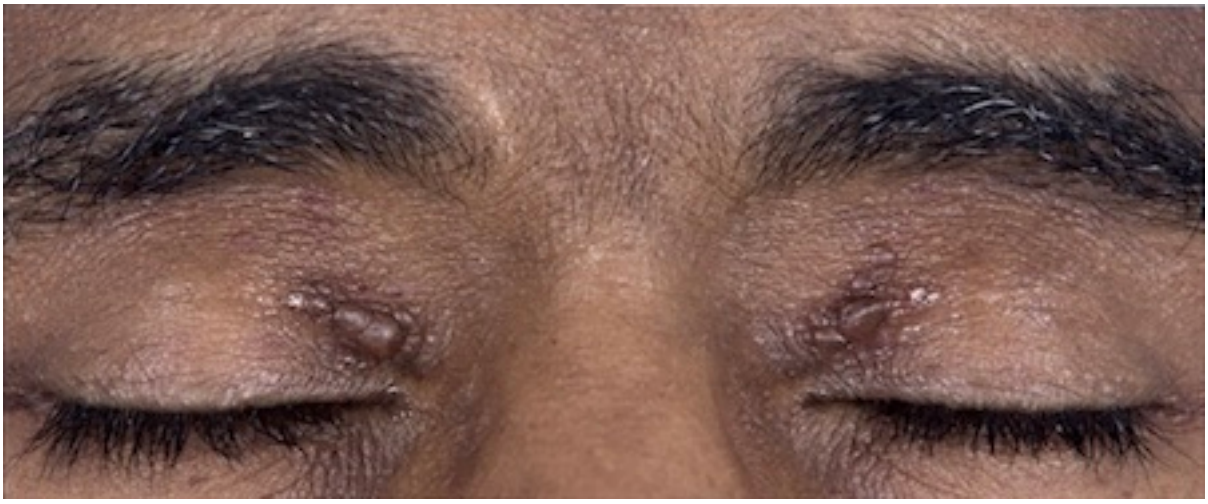

Figure 1: Bilateral periorbital ecchymosis (amyloid purpura) in a patient with AL amyloidosis

Williams#MU, Murphy#CE, Gore#RS, et#al. BMJ Case Rep 2018;11:e225923. doi:10.1136/bcr-2018- 225923

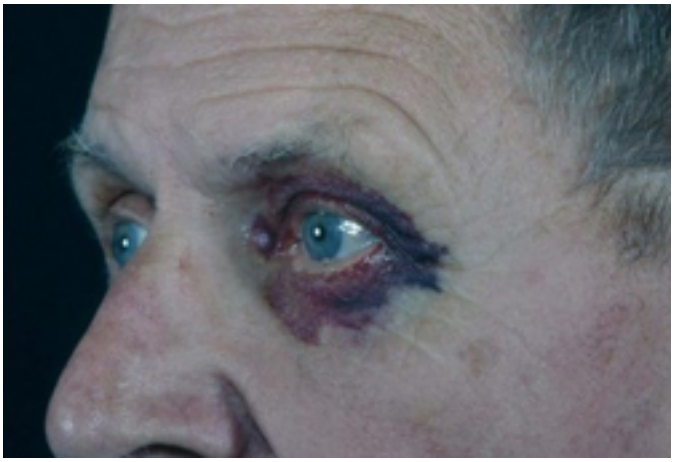

Figure 2: Classic periorbital purpura

Morie A. Gertz, MD; courtesy of Mayo Clinic

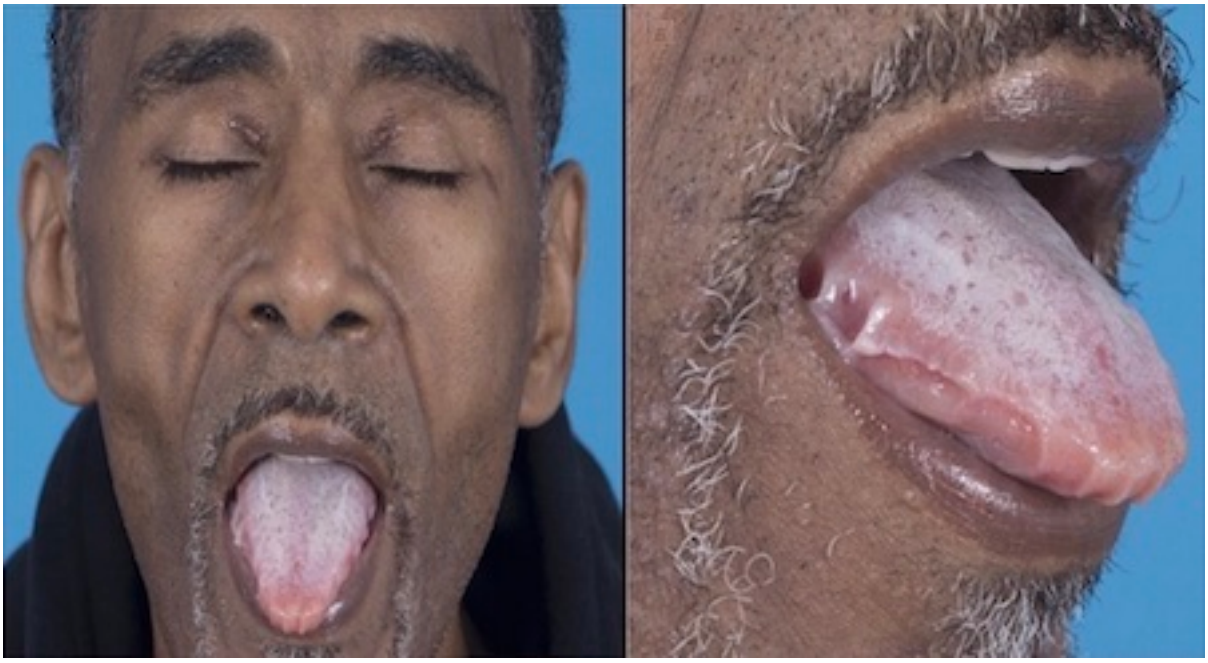

Figure 3: Macroglossia in a patient with AL amyloidosis

Williams#MU, Murphy#CE, Gore#RS, et#al. BMJ Case Rep 2018;11:e225923. doi:10.1136/bcr-2018- 225923

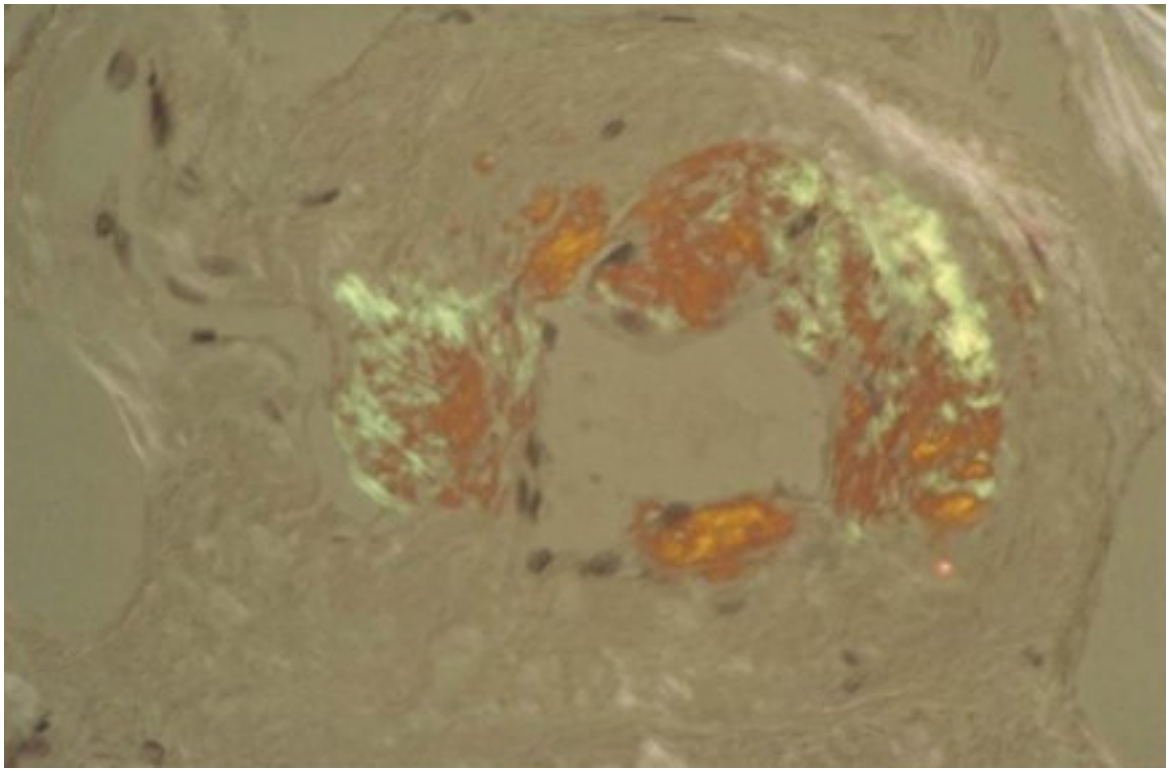

Figure 4: Congo red stain blood vessel in a bone marrow biopsy demonstrating green birefringence pathognomonic of amyloidosis

Morie A. Gertz, MD; courtesy of Mayo Clinic

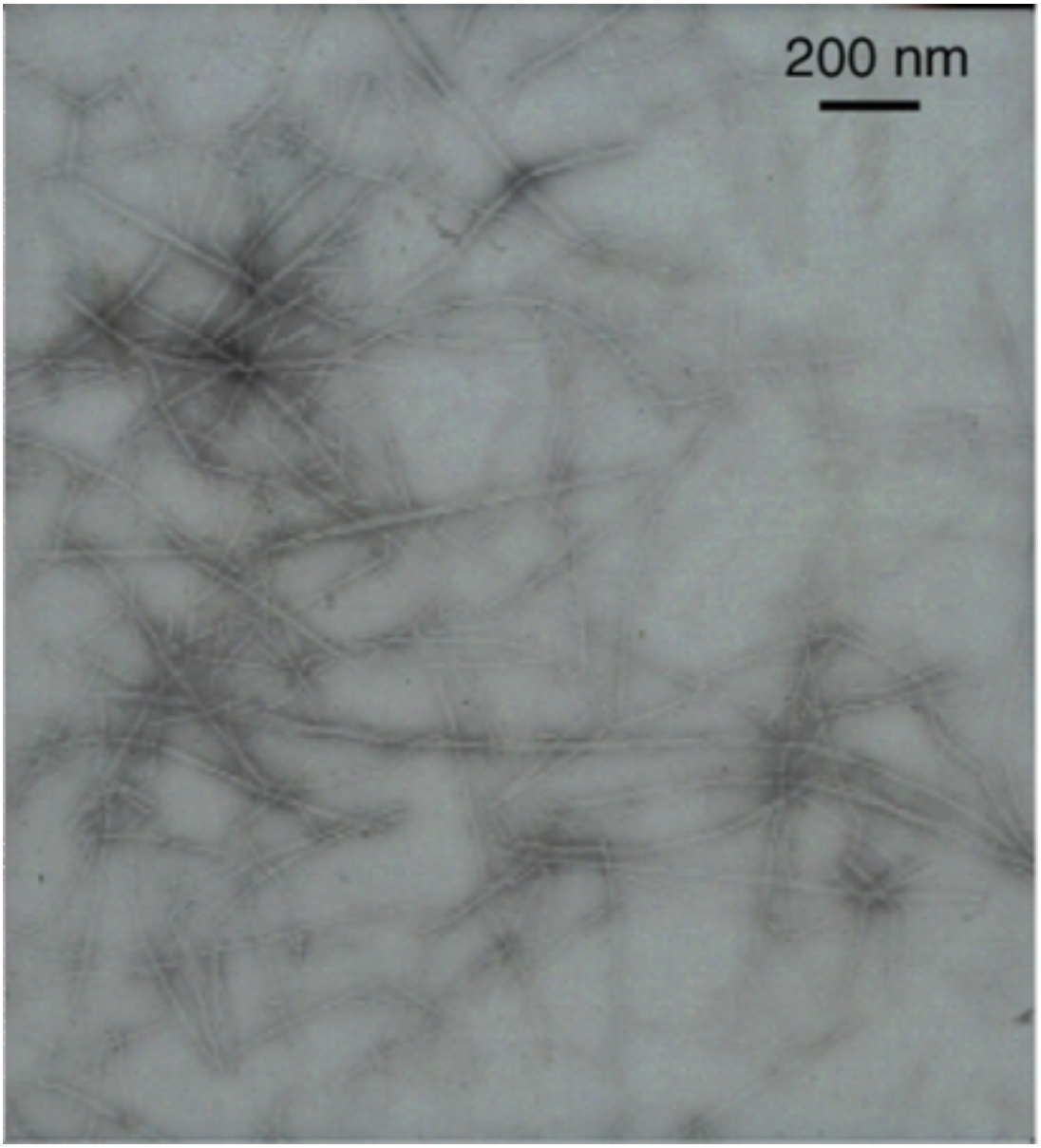

Figure 5: Electron micrograph demonstrating classical amyloid fibrils

Morie A. Gertz, MD; courtesy of Mayo Clinic

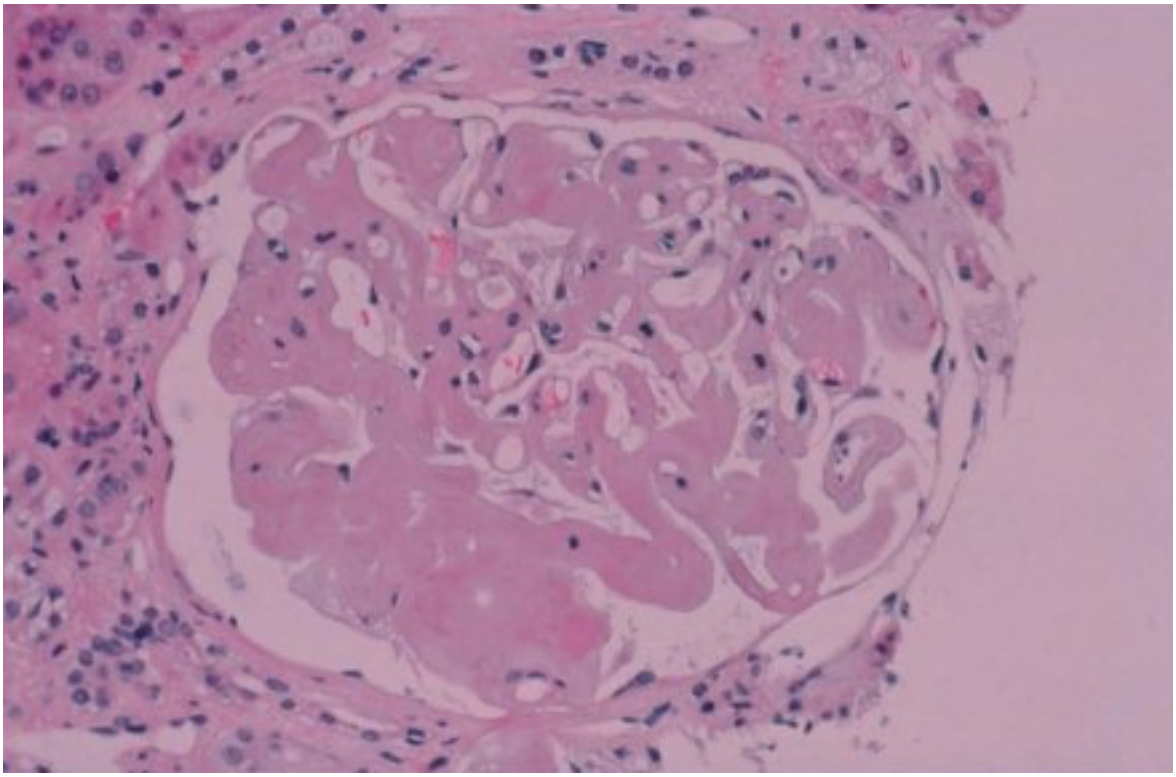

Figure 6: Renal biopsy demonstrating amyloid deposits as amorphous replacement of the glomerular architecture

Morie A. Gertz, MD; courtesy of Mayo Clinic

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