Chapter 1

Overview of Amyloidosis

Author:Peter D Gorevic, MD
Section Editor:Helen J Lachmann, MA, MB, BChir, MD, FRCP, FRCPath
Deputy Editor:Siobhan M Case, MD, MHS, Contributor Disclosures
All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Aug 2023. This topic last updated: Jul 24, 2023.

INTRODUCTION

Amyloidosis is the general term used to refer to the extracellular tissue deposition of highly ordered fibrils composed of low molecular weight subunits of a variety of proteins, many of which, in their native form, circulate as normal constituents of plasma. Amyloid deposits may result in a wide range of clinical manifestations depending upon their type, location, and amount. In the genesis of amyloid deposits, previously soluble precursor peptides undergo conformational changes that lead to the adoption of a predominantly antiparallel beta-pleated sheet configuration, allowing them to stack as protofilaments in a twisted fibrillar configuration (figure 1).

At least 38 different human protein precursors of amyloid fibrils are known. Some are produced at the site of amyloid formation (localized amyloid) and some circulate in the blood to deposit in a variety of tissues and organs (systemic amyloidosis). Amyloid has a characteristic gross pathologic and microscopic appearance, demonstrating birefringence with polarized light microscopy of Congo red stained tissue, which may have a typical "apple-green" dichroic appearance [1,2]. (See 'Pathology' below.)

A general overview of the pathogenesis, clinical manifestations, diagnosis, and treatment of the different amyloid disorders is presented here. The role of genetic factors in amyloidosis is discussed in detail elsewhere (see "Genetic factors in the amyloid diseases" and "Genetics of Alzheimer disease"). More detailed discussions of the individual disorders are also presented separately. (See appropriate topic reviews as indicated in the relevant sections below.)

PATHOLOGY

The presence of amyloid is associated with characteristic histopathologic findings, including apple-green birefringence with Congo red staining on polarized light microscopy (picture 1A-D). The term "amyloid," first introduced by Schleiden in 1838 to describe plant starch, was adopted by Rudolf Virchow in 1854 to refer to tissue deposits of material that stained in a similar manner to cellulose when exposed to iodine [3]. In these original descriptions, amyloid deposits were noted by Rokitansky to have a "waxy" or "lardaceous" appearance grossly and by Virchow to be amorphous and hyaline on light microscopy. Congo red, a direct cotton dye and pH indicator that was developed by Paul Böttinger in 1883, was later shown to confer typical apple-green birefringence with polarized microscopy and introduced in the 1920s by Bennhold for the better demonstration of amyloid [4]. The use of thioflavin T, producing an intense yellow-green fluorescence, was popularized in the 1950s [3]. Virchow recorded the prescient observation in his Cellular Pathology (1858) that "I am as yet much more inclined to admit, that the blood in this disease undergoes a chemical alteration in its fluid constituents, than that it contains the pathological substances in a material form."

Electron microscopic examination of amyloid deposits, first performed in 1959, generally demonstrates straight and unbranching fibrils 8 to 10 nm in width, which may be composed of protofilaments at higher resolution [5,6]. Transmission electron, atomic force, and cryo-electron microscopy have had a role in elucidating the three-dimensional structure of these macromolecular aggregates in fibril preparations extracted from tissue or created in vitro and in defining folding intermediates, including small oligomers and amorphous aggregates [1,7,8]. In many instances, the type of amyloid fibril unit can be further defined by immunohistology (immunofluorescence or immunoenzymatic techniques) or by immunoelectron microscopy [9-11] and in subsequent developments by proteomics on fixed tissue using laser-capture microdissection and mass spectroscopy [12].

PATHOGENESIS

Overview of amyloidogenesis — Amyloidosis results from the predominantly extracellular tissue deposition of fibrils composed of low molecular weight subunits of a variety of proteins, typically in the range of 5 to 25 kD; many of these proteins normally circulate as constituents of plasma. Genetic factors play an important role in many forms of amyloidosis. Point mutations, deletions, and premature stop codons may result in structural changes predisposing to fibril formation (fibrillogenesis) by these proteins and the development of amyloid.

Depending upon the type of amyloidosis, factors affecting protein folding and stability, including molecular chaperones and failure of disaggregating pathways, may be operative [13]. There are also major contributions from non-fibrillar components found in all types of amyloid, including serum amyloid P component (SAP), apolipoprotein E, and glycosaminoglycans. Disorders leading to increased production or reduced clearance of potential amyloid precursor proteins (APPs), including chronic inflammation, plasma cell dyscrasias, and chronic renal failure, are important, particularly in systemic amyloidoses. (See 'Fibril formation' below and 'Genetics' below.)

Fibril formation — Amyloid fibrils are insoluble polymers comprised of low molecular weight protein subunits. These subunits are derived from soluble precursors and undergo conformational changes that lead to the adoption of a predominantly antiparallel beta-pleated sheet configuration (figure 1) in which state they auto-aggregate in highly ordered fibrils [14-17]. Oligomeric intermediates that are pre-fibrillar may contribute to tissue toxicity and disease pathogenesis in certain amyloid related disorders [18].

Routes to fibrillogenesis include partial folding or unfolding of the precursor protein that may be facilitated by acidification or proteolysis and accelerated by nucleation [19]. In vivo fibril formation is associated with codeposition of non-fibrillar substances, notably including glycosaminoglycans (particularly heparan sulfate), SAP (a member of the pentraxin family that includes C-reactive protein [CRP]), and specific apolipoproteins (E and J) [20,21]. Cofactors may significantly modulate fibrillogenesis at any of several steps involved in the conversion of soluble precursors to fibrils and may potentially influence the deposition phase of amyloid in tissue, as well as resorption [22].

Circulating precursors are presumed to deposit as amyloid in the systemic forms of disease (see 'Organ-specific amyloid' below). By contrast, in localized immunoglobulin light chain (AL) amyloidosis (which can involve sites such as the conjunctiva, lungs, skin, gastrointestinal or genitourinary tract), the precursor protein (immunoglobulin light chain) is thought to be synthesized and processed at local sites contiguous to amyloid deposition [23-25]. This model for amyloid formation at the sites of protein synthesis has been corroborated in some in vitro models of AA amyloid, in which deposition occurs around cell types such as monocytes, macrophages, or mesangial cells in tissue culture [26].

Genetics — At least 38 different human and 10 different animal protein precursors of amyloid fibrils are now known, and the corresponding amyloid diseases

associated with each of the affected molecules and nomenclature for the subunit proteins have been described (table 1) [27-29].

Several types of amyloidosis are clearly hereditary, and clinical disease has been linked in most familial forms to missense mutations of the precursor proteins. In some instances, deletions or premature stop codon mutations have been described [14,30]. Heritable factors in amyloidosis include the following, which are discussed in greater detail separately (see "Genetic factors in the amyloid diseases"):

●Genetic variants resulting in protein products that are more prone to aggregation and fibrillogenesis than their wild-type counterparts.

●Polymorphisms of cofactors (eg, apolipoprotein E) or of subunit proteins (eg, serum amyloid A, leukocyte cell-derived chemotaxin-2 [LECT2]).

●Heritable disorders that affect the level or accumulation of precursor proteins (eg, presenilin mutations in familial Alzheimer disease).

●Heritable disorders that may result in chronic inflammation and deposition of wild-type precursor serum amyloid A protein as AA amyloidosis in susceptible populations (eg, pyrin and cryopyrin mutations in familial Mediterranean fever [FMF] and cryopyrin-associated periodic syndrome [CAPS], respectively, and tumor necrosis factor [TNF] receptor mutations in the TNF receptor-associated periodic syndrome [TRAPS]).

Virtually all heredofamilial amyloidoses associated with nephropathic, neuropathic, or cardiopathic disease are dominantly inherited heterozygous disorders, and both the wild-type and mutant molecules can be identified in the amyloid deposits. In some instances (eg, transthyretin [TTR], apolipoprotein A-I [ApoAI], Alzheimer APP, and prion protein [PRP]), both the wild-type and mutant molecules are able to form amyloid fibrils under different circumstances, with the wild-type protein implicated in aging-associated diseases. As an example, wild-type TTR; ApoAI; and the beta protein, A-beta, a cleavage product of APPs, may form deposits in association with organ-specific pathology in the aging heart, aorta, and brain, respectively [30-32]. (See "Genetic factors in the amyloid diseases".)

TYPES OF AMYLOIDOSIS

Major forms of systemic amyloidosis — There are 18 different types of systemic and 22 localized forms of amyloidosis [27]. The principal systemic types seen in tertiary

referral centers and inpatient medical services are the primary (immunoglobulin light chain [AL]) and transthyretin (ATTR) types. However, other types of amyloid (eg, secondary [AA]) are clinically important, some of which are common and others rare. A review of more than 11,000 patients seen at a single center from 1987 through 2019 showed that systemic AL amyloidosis accounted for 56 percent, ATTR 21 percent, and AA 8 percent of typed cases [33]; in particular, there has been a substantial increase in the recognition of systemic amyloid due to ATTR in major referral centers. Nomenclature for amyloid subunit proteins includes the letter "A," followed by the abbreviation of the name of the precursor protein (table 1). Major forms include:

●**AL amyloid** – AL amyloid, caused by a plasma cell dyscrasia, is due to deposition of protein derived from immunoglobulin light chain fragments. (See 'AL amyloidosis' below.)

●**ATTR amyloid** – ATTR amyloid may occur as a "wild-type" (ATTRwt) associated with aging or as mutant proteins (ATTRv or hATTR [where v indicates a variant and h indicates hereditary; these were formerly termed ATTRm, to indicate a mutant protein]) associated with familial neuropathy and/or cardiomyopathy [27]. (See 'Wild-type transthyretin systemic amyloidosis' below and 'Heritable amyloidoses' below.)

●**AA amyloidosis** – AA amyloidosis is a potential complication of chronic diseases in which there is ongoing or recurring inflammation that results in sustained high-level production of serum amyloid A protein, an acute phase reactant, which can form amyloid deposits. (See 'AA amyloidosis' below.)

●**Other types of amyloidosis** – Additional forms of amyloid seen clinically include dialysis-related amyloidosis (see 'Dialysis-related amyloidosis' below), heritable amyloidoses (see 'Heritable amyloidoses' below), organ-specific amyloid (see 'Organ-specific amyloid' below), leukocyte cell-derived chemotaxin-2 (LECT2) amyloid (see 'Systemic amyloidosis of poorly understood etiology' below), insulin amyloid [34], and others.

AL amyloidosis — AL amyloidosis is due to deposition of protein derived from immunoglobulin light chain fragments. It is a potential complication of any plasma cell dyscrasia that produces monoclonal immunoglobulin light chains. These can be subtle, but a monoclonal protein is detectable in urine and/or serum in >95 percent of affected patients if both serum and urine immunofixation and a free light chain

(FLC) assay (which is most commonly done on serum) are performed [35]. (See "Monoclonal immunoglobulin deposition disease".)

AL amyloidosis is a systemic disorder that can present with a variety of symptoms or signs, including heavy proteinuria (usually in the nephrotic range) and edema (see 'Renal disease' below), hepatosplenomegaly (see 'Gastrointestinal disease' below), otherwise unexplained heart failure (see 'Cardiomyopathy' below), and the carpal tunnel syndrome (see 'Neurologic abnormalities' below). Although virtually all patients have multisystem amyloid deposition, it is not uncommon to present with evidence of mainly one organ being affected. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis".)

AL amyloidosis usually complicates lower-grade plasma cell clones but can occur in association with multiple myeloma or, much less often, Waldenström macroglobulinemia, non-Hodgkin lymphoma, or chronic lymphocytic leukemia [36]. Light chain deposition disease has a similar pathogenesis and shares some clinical manifestations with AL amyloidosis; the primary difference is that deposited light chain fragments generally do not form fibrils and do not engender deposition of amyloid cofactors [37]. In rare instances, AL amyloid and non-amyloid light chain deposition may coexist in the same organ [38]. The recognition that B cell or plasma cell clones can cause renal disease related to the production of monoclonal immunoglobulin in the absence of direct tumor complications and without reaching current hematologic criteria for specific therapy led to the concept of monoclonal gammopathy of renal significance (MGRS), and renal AL amyloidosis remains the best characterized of these disorders [39]. (See "Monoclonal immunoglobulin deposition disease" and "Epidemiology, pathogenesis, clinical manifestations, and diagnosis of Waldenström macroglobulinemia", section on 'Amyloidosis' and "Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis", section on 'AL amyloidosis and light chain deposition disease' and "Diagnosis and treatment of monoclonal gammopathy of renal significance".)

Amyloid can be derived from immunoglobulin heavy chain fragments [40]. In this case, it is designated AH amyloidosis. Coexisting AH and AL amyloid occurs rarely.

Wild-type transthyretin systemic amyloidosis — Deposition of otherwise normal (wild-type) TTR in myocardium and other sites may result in a form of amyloidosis that is now referred to as wild-type transthyretin systemic amyloidosis (ATTRwt), superseding the previous terminology of systemic senile amyloidosis (SSA) [41,42]. Some experts prefer to reserve use of the term TTR amyloid cardiomyopathy for

those patients who develop cardiomegaly and heart failure from the infiltrative cardiomyopathy, as asymptomatic amyloid deposition in the heart is a common autopsy finding, often without clinical consequence.

Compared with patients with cardiac involvement from AL amyloidosis, heart failure due to ATTR is less severe than that in AL, and those with the ATTRwt disease survive longer (75 versus 11 months) despite having ventricular free wall and septal thickening due to amyloid deposits [43]. In this study, all 18 affected patients were older men. A history of carpal tunnel syndrome is common and spinal stenosis well recognized [44], but significant renal involvement is very rare in the systemic disorder. Amyloid cardiomyopathies are discussed in detail separately. (See "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis".)

There may be considerable overlap clinically between cardiac amyloidosis due to deposition of wild-type TTR, and late-onset cardiomyopathy due to mutant TTR (see 'Heritable amyloidoses' below). A family history may not be apparent, and a screen for informative mutations (notably Ile122, particularly in African American patients) may be necessary to distinguish the two causes of restrictive cardiomyopathy in older adults [45]. Differentiation from cardiac AL amyloidosis is of vital importance, and there are published consensus criteria to aid both disease recognition and diagnosis [46,47]. (See 'Organ-specific amyloid' below and "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis".)

AA amyloidosis — AA amyloidosis may complicate chronic diseases in which there is ongoing or recurring inflammation, such as rheumatoid arthritis (RA), spondyloarthritis, or inflammatory bowel disease; chronic infections; and heredofamilial periodic fever syndromes (eg, familial Mediterranean fever [FMF]). It may occur in association with other causes, including neoplasms, and in a significant proportion of patients is idiopathic [48]. The fibrils are composed of fragments of the acute phase reactant serum amyloid A protein. (See "Pathogenesis of AA amyloidosis" and "Causes and diagnosis of AA amyloidosis and relation to rheumatic diseases".)

The most common organ affected by AA amyloid is the kidney (approximately 80 percent of patients). This is usually characterized by glomerular amyloid deposition, typically leading to the nephrotic syndrome, although the renal presentation may vary (see 'Renal disease' below and "Renal amyloidosis", section on 'AA amyloidosis'). Cardiac and other organ involvement may also be seen, although generally in very advanced disease. (See 'Cardiomyopathy' below and 'Clinical manifestations' below.)

Dialysis-related amyloidosis — Dialysis-related amyloidosis is due to deposition of fibrils derived from beta2-microglobulin, which accumulate in patients with end-stage kidney disease who are being maintained for prolonged periods of time by dialysis. This disorder has a predilection for osteoarticular structures [49,50]. Patients with dialysis-related amyloidosis most commonly complain of shoulder pain related to scapulohumeral periarthritis and rotator cuff infiltration by amyloid, neck pain due to a destructive spondyloarthropathy, and of symptoms of carpal tunnel syndrome. (See "Dialysis-related amyloidosis" and 'Musculoskeletal disease' below and 'Neurologic abnormalities' below.)

Heritable amyloidoses — Many mutations lead to at least 10 heritable types of systemic amyloidosis, each of which has a characteristic pattern of clinical features (table 1). An example of this heterogeneous group of disorders is heritable neuropathic and/or cardiomyopathic amyloidosis due to deposition of fibrils derived from transthyretin (TTR; also referred to as prealbumin) [51]. (See "Genetic factors in the amyloid diseases" and "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis", section on 'Types of amyloidosis'.)

In addition to heritable forms due to mutations in proteins that may form amyloid subunits or changes that may otherwise promote fibrillogenesis, patients with systemic autoinflammatory diseases (also termed hereditary periodic fever syndromes) are also susceptible to AA amyloidosis [52]. (See "Causes and diagnosis of AA amyloidosis and relation to rheumatic diseases", section on ''Hereditary' AA amyloidosis'.)

Systemic amyloidosis of poorly understood etiology — Some types of late-onset amyloid are not associated with either recognized underlying diseases or rare pathogenic mutations in the precursor protein. One example is LECT2-associated amyloidosis. It may account for approximately one-quarter of cases of hepatic amyloid in the United States and has also been reported as the second most common cause of renal amyloidosis [53,54]. Another example is apolipoprotein A-IV (ApoAIV)-derived amyloidosis, which is commonly a constituent of the amyloid proteome in various forms of the disease, but may also be associated with clinically significant renal and cardiac amyloidosis [55,56]. In these cases, the amyloid may be associated with polymorphisms of the precursor proteins, but these are sufficiently common in the population that they are clearly not the sole cause of these rare diseases. (See "Gastrointestinal amyloidosis: Clinical manifestations, diagnosis, and management", section on 'Hepatic amyloidosis' and "Renal amyloidosis", section on 'Introduction'.)

Organ-specific amyloid — Amyloid deposition can be isolated to a single organ, such as the skin, eye, heart, pancreas, and gastrointestinal or genitourinary tract, resulting in specific syndromes. Locally produced proteins (eg, immunoglobulin light chain from plasma cells) rather than circulating forms of the relevant subunit protein tend to be the precursors of the fibril in several forms of localized or organ-specific amyloidosis, in contrast with the systemic amyloids in which such circulating forms are presumed to be the precursors.

Examples of organ-specific amyloid include the following:

●**Alzheimer disease-associated amyloid** – The most common clinically important form of organ-specific amyloid occurs in patients with Alzheimer disease in which plaques and amyloid-laden cerebral vessels are composed of the beta protein (A-beta), a 39 to 43 residue polypeptide that is cleaved out of the much larger amyloid precursor protein (APP) by secretases that are specific for its amino (beta-secretase) and carboxy (gamma-secretase) terminal residues. Similar to other forms of amyloidosis, A-beta polypeptides may exist in soluble forms, oligomers, and amyloid fibrils. The role of amyloid in Alzheimer disease is discussed in detail separately. (See "Genetics of Alzheimer disease", section on 'Early-onset Alzheimer disease' and "Cerebral amyloid angiopathy" and "Epidemiology, pathology, and pathogenesis of Alzheimer disease".)

●**Cutaneous amyloid** – Forms of primary localized cutaneous amyloidosis include macular, nodular, and lichen amyloidosis, with the last occurring in some families with multiple endocrine neoplasia type 2 [23,57-59]. The major fibril subunit proteins for the overlapping syndromes of lichen and macular amyloid are keratins 5 and 14 [60]. (See "Cutaneous manifestations of amyloidosis" and "Clinical manifestations and diagnosis of multiple endocrine neoplasia type 2" and "Cutaneous manifestations of internal malignancy", section on 'Amyloidosis' and "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Localized amyloidosis'.)

●**Bladder amyloid** – Isolated bladder amyloidosis can be the cause of symptoms varying from life-threatening hemorrhage to subclinical hematuria or irritative voiding symptoms; in most instances, this appears to be a localized form of AL amyloid disease [61], although it may also be an extracardiac site of deposition in ATTR. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Localized amyloidosis'.)

●**Ocular amyloid** – Isolated ocular amyloidosis, most commonly presenting as conjunctival lesions biopsied to exclude the diagnosis of lymphoma, may also be a localized form of AL; it is more rarely a presenting manifestation of systemic AL [62].

●**Laryngeal amyloid** – Laryngeal amyloid is a particularly common form of localized amyloidosis, most often due to AL [63] and rarely to hereditary apolipoprotein A-I (ApoAI) amyloidosis and as an incidental finding in ATTR amyloidosis [64,65]. This form of amyloid may involve supra-, infra- or subglottic sites, is frequently multifocal, and is typically locally recurrent [65]. (See "Hoarseness in adults", section on 'Laryngeal amyloidosis'.)

VARIATION IN GEOGRAPHIC DISTRIBUTIONThe prevalence of the most common types of amyloidosis varies between different parts of the world. In resource-abundant countries, primary (AL) and transthyretin (ATTR) are the most common types of systemic amyloidosis, while in resource-limited countries, secondary (AA) amyloid is more frequent.

This variation likely results from a higher burden of chronic infectious diseases such as tuberculosis, leprosy, and osteomyelitis in resource-limited countries and regions [66]. By contrast, advances in resource-intensive diagnostics, most strikingly increased availability of cardiac magnetic resonance imaging (MRI), has led to increasing recognition of ATTR as a cause of amyloid cardiomyopathy in older individuals [67,68].

CLINICAL MANIFESTATIONS

Overview of common clinical features — The type of precursor protein, the tissue distribution, and the amount of amyloid deposited largely determine clinical manifestations. Some clinical and laboratory features that suggest amyloidosis include waxy skin and easy bruising (see 'Skin manifestations' below), enlarged muscles (eg, tongue, deltoids) (see 'Musculoskeletal disease' below), symptoms and signs of heart failure and cardiac conduction abnormalities (see 'Cardiomyopathy' below), hepatomegaly (see 'Gastrointestinal disease' below), evidence of heavy proteinuria or the nephrotic syndrome (see 'Renal disease' below), peripheral and/or autonomic neuropathy (see 'Neurologic abnormalities' below), and impaired coagulation (see 'Hematologic abnormalities' below). Coexistence of any of these features, particularly in combination with nonspecific symptoms such as fatigue, change in taste, dry mouth, or weight loss, should further raise suspicion of amyloidosis and prompt specific investigations. (See 'Diagnosis' below.)

In immunoglobulin light chain (AL) amyloidosis, the major sites of clinically important amyloid deposition are in the kidneys, heart, and liver; and in AA amyloidosis, kidneys, liver, and intestines; whereas in ATTR amyloidosis, heart and nervous system involvement predominate. In some disorders, clinically important amyloid deposition is limited to one organ. (See 'Types of amyloidosis' above and 'Organ-specific amyloid' above and 'Renal disease' below and 'Cardiomyopathy' below and 'Gastrointestinal disease' below.)

Renal disease — Renal involvement most often presents as asymptomatic proteinuria or clinically apparent nephrotic syndrome. However, if amyloid deposition predominantly affects the renal blood vessels or tubules, patients may present with advanced renal failure with little or no proteinuria [69]. The renal manifestations of amyloidosis are discussed in detail separately. (See "Renal amyloidosis".)

Amyloid nephropathy is common in AA and AL amyloidosis, but is rare in ATTR. Leukocyte cell-derived chemotaxin-2 (LECT2), fibrinogen A-alpha chain, and apolipoproteins A-I, A-II, and A-IV are rarer causes of predominantly nephropathic amyloidosis worldwide [70]. (See 'AA amyloidosis' above and 'AL amyloidosis' above.)

Familial or sporadic disease may be important in certain countries or regions. As examples, mutations in the fibrinogen alpha chain were the most common form of hereditary nephropathic amyloid in a large survey from the United Kingdom, and LECT2 disproportionately affects specific populations including Punjabi, North African, and Hispanic [71].

Cardiomyopathy — At least 11 biochemically distinct forms of amyloidosis affect the heart, two of which (wild-type ATTR [ATTRwt] and isolated atrial amyloidosis [atrial natriuretic factor amyloidosis (AANF)]) are considered to be diseases of aging. Cardiac involvement can lead to diastolic or, usually later in the disease course, systolic dysfunction and symptoms of heart failure. Other manifestations include palpitations, syncope due to arrhythmia or heart block, and angina or infarction due to accumulation of amyloid in the coronary arteries [72,73]. The cardiac manifestations of amyloidosis are discussed in detail separately. (See "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis".)

Cardiac amyloidosis is common in ATTR and AL amyloidosis and can rarely complicate AA amyloidosis; it is rare in A-beta2-microglobulin (dialysis-related) amyloidosis. Familial forms of amyloid in which cardiac disease may be significant

include those due to a wide variety of transthyretin (TTR) variants (hATTR or ATTRv, formerly termed ATTRm), as well as apolipoproteins A-I and A-II. Lastly, isolated atrial amyloidosis due to atrial natriuretic peptide is a common, often asymptomatic, concomitant of aging that may be associated with atrial fibrillation [74].

Gastrointestinal disease — Hepatomegaly with or without splenomegaly is a common finding in some forms of amyloidosis. Other gastrointestinal manifestations include bleeding (due to vascular fragility, loss of vasomotor responses to injury, and coagulopathy in some cases of AL), gastroparesis, constipation, bacterial overgrowth, malabsorption, and intestinal pseudo-obstruction resulting from dysmotility [75]. The gastrointestinal manifestations of amyloidosis are discussed in detail separately. (See "Gastrointestinal amyloidosis: Clinical manifestations, diagnosis, and management".)

AL and AA amyloidosis commonly affect the gastrointestinal tract; ATTR may cause dysfunction either directly or via concomitant autonomic neuropathy; familial amyloid due to variant lysozyme may have significant gastrointestinal manifestations [76].

Neurologic abnormalities — Several forms of neurologic involvement may occur, including peripheral and autonomic neuropathy, central nervous system (CNS) involvement, and ischemic stroke:

●**Peripheral and autonomic neuropathy** – Length-dependent mixed sensory and motor peripheral neuropathy and/or autonomic neuropathy may occur and are prominent features in some of the heritable amyloidoses (called familial amyloidotic polyneuropathy) and in AL amyloidosis.

Symptoms of numbness, paresthesia, and pain are frequently noted, as in peripheral neuropathy of many other etiologies. Compression of peripheral nerves, especially the median nerve within the carpal tunnel, can cause more localized sensory changes. Symptoms of bowel or bladder dysfunction and findings of orthostatic hypotension may be due to autonomic nervous system damage [77,78].

●**Central nervous system disease** – CNS involvement is unusual in patients with the more common AL and AA amyloidoses. Amyloid deposits can lead to extensive cortical pathology and dementia in patients with sporadic or familial Alzheimer disease, while cerebral amyloid angiopathy can cause spontaneous cortical and subcortical intracranial bleeding, primarily in older adults [79]. ATTRv amyloidoses

due to several different mutations associated with peripheral neuropathy may have prominent CNS manifestations [80]. (See "Genetics of Alzheimer disease" and "Cerebral amyloid angiopathy".)

●**Ischemic stroke** – Ischemic embolic stroke may be the initial manifestation of amyloid cardiomyopathy of any type. Atrial fibrillation and/or echocardiographic evidence of myocardial or valvular involvement are often present, supporting a cardioembolic source in the majority [81]. (See "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis", section on 'Cardiac involvement'.)

Musculoskeletal disease — Amyloid deposition may affect the muscles, joints, and periarticular soft tissues. The musculoskeletal and rheumatologic manifestations of amyloidosis are discussed in detail separately. (See "Musculoskeletal manifestations of amyloidosis" and "Causes and diagnosis of AA amyloidosis and relation to rheumatic diseases".)

Briefly, infiltration of muscles may cause visible enlargement (ie, pseudohypertrophy). A large tongue (ie, macroglossia) or lateral scalloping of the tongue from impingement on the teeth is characteristic of AL amyloid. Arthropathy may be due to amyloid deposition in joints and surrounding structures. The "shoulder pad" sign is visible enlargement of the anterior shoulder due to fluid in the glenohumeral joint and/or amyloid infiltration of the synovial membrane and surrounding structures. Synovial fluid in AL and A-beta2-microglobulin amyloid is typically noninflammatory; it can be identified by Congo red staining of spun sediment [82].

Shoulder involvement is characteristic of AL amyloid and dialysis-related amyloidosis due to deposition of beta2-microglobulin. Other musculoskeletal features of dialysis-related amyloidosis include scapulohumeral periarthritis, spondyloarthritis, large amyloid-containing bone cysts that may fracture, and carpal tunnel syndrome [83]. (See "Dialysis-related amyloidosis".)

Musculoskeletal disease including carpal tunnel syndrome, lumbar spinal stenosis, and requirement for hip or knee arthroplasty may precede the diagnosis of ATTRwt amyloidosis by considerably more than a decade and may provide an opportunity for early diagnosis by histologic examination of tenosynovial or ligamentum flavum biopsies [84].

Hematologic abnormalities — Increased bleeding may occur in patients with amyloidosis due to one or more of several causes, including reduced activity of

factor X, vascular infiltration with amyloid, and abnormal liver function due to amyloid deposition [85-87].

In one report of 337 patients, abnormal bleeding and abnormal coagulation tests were seen in 28 and 51 percent, respectively [86]. Two major mechanisms have been described: factor X deficiency due to binding on amyloid fibrils primarily in the liver and spleen and decreased synthesis of coagulation factors in patients with advanced liver disease. Amyloid-associated **isolated** factor X deficiency resulting from the binding of factor X to amyloid fibrils has also been described [88-91]. In a series of 368 consecutive patients with AL amyloidosis, 32 and 12 patients had factor X levels below 50 and 25 percent of normal, respectively [89]. Bleeding was noted in 18 patients and was more severe in the 12 patients whose factor X levels were <25 percent of normal. Factor X levels improved following high-dose melphalan chemotherapy and autologous hematopoietic cell transplantation in four of four patients obtaining complete remission and in one of two obtaining partial remission. However, some patients with abnormal bleeding have no abnormalities in any coagulation test [85]. In such patients, amyloid infiltration of blood vessels may contribute to the bleeding diathesis. Bleeding due to acquired von Willebrand disease or factor IX deficiency has also been described in AL amyloidosis [92,93].

Other hematologic manifestations are related to the degree of organ involvement. These include anemia in patients with renal failure, gastrointestinal bleeding, or multiple myeloma and thrombocytopenia due to splenomegaly. Instances of bone marrow replacement by amyloid associated with pathologic fractures have also been described [94]. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Systemic presentations' and "Acquired hemophilia A (and other acquired coagulation factor inhibitors)", section on 'Factor X inhibitors'.)

Pulmonary disease — Pulmonary manifestations of amyloidosis include tracheobronchial infiltration, persistent pleural effusions, parenchymal nodules (amyloidomas), and, rarely, pulmonary hypertension [95-104]. The pleuropulmonary manifestations of amyloidosis are discussed in detail separately. (See "Pleuropulmonary manifestations of amyloidosis".)

Briefly, pulmonary involvement by amyloid is particularly important for AL amyloidosis, which may be systemic or occur in localized forms sometimes associated with Sjögren's disease. Tracheobronchial amyloid infiltration can cause hoarseness, stridor, airway obstruction, and dysphagia; bronchoscopic or surgical resection of airway abnormalities may be required [105-110]. ATTR amyloidosis

due to variant (mutant) protein or in aging patients with ATTRwt (systemic senile amyloidosis [SSA]) or familial amyloid polyneuropathy (FAP), respectively, may also result in alveolar deposits; these are generally asymptomatic and identified incidentally [111]. (See "Clinical presentation, diagnostic evaluation, and management of malignant central airway obstruction in adults".)

Persistent pleural effusions develop in 1 to 2 percent of patients with systemic amyloidosis and appear to be caused by pleural infiltration with amyloid deposits [97,112,113]. However, it is difficult to distinguish primary effusions from those caused by amyloid-induced cardiomyopathy on the basis of echocardiographic findings alone, and the sensitivity of pleural biopsy in this setting has not been studied extensively [97]. They are associated with a poor prognosis and limited response to treatment, although pleurodesis has been useful in some cases [97]. (See "Pleural fluid analysis in adults with a pleural effusion" and "Management of nonmalignant pleural effusions in adults".)

Skin manifestations — Signs of skin involvement in systemic amyloidosis include waxy thickening, easy bruising (ecchymoses), and subcutaneous nodules or plaques. Purpura, characteristically elicited in a periorbital distribution (raccoon eyes) by a Valsalva maneuver or minor trauma, is present in only a minority of patients but is highly characteristic of AL amyloidosis (picture 2) [114]. More subtle purpuric manifestations can also be seen in other types of systemic amyloidosis including inherited ATTRv [115], as well as amyloid associated with variants of lysozyme and apolipoprotein A-I (ApoAI) where a propensity to bruising may predate other symptoms by several decades. Infiltration of the subcutaneous fat is generally asymptomatic but is common and can be a convenient site for biopsy [59]. Amyloidosis limited to the skin may also occur [58]. (See 'Organ-specific amyloid' above.)

Cutaneous manifestations of amyloidosis are described in detail separately. (See "Cutaneous manifestations of amyloidosis".)

Other — Other manifestations include dry eyes and visual and hearing loss in some heritable amyloidoses [116,117]. Bladder deposition may cause hematuria, which can be gross, albeit rarely, and irritative urinary symptoms [24,61]. Ischemic symptoms and tissue infarction due to vascular infiltration have also been reported. Additional manifestations include jaw claudication suggestive of giant cell (temporal) arteritis, which can occur in AL amyloidosis [118], and symptomatic ischemic coronary heart disease, which is associated with the presence of obstructive intramural deposits of AL amyloid [119].

DIAGNOSIS

When to suspect amyloidosis — The different forms of amyloidosis may affect any tissue and organ systems, with a spectrum of clinical manifestations. These in turn can coexist both within a single patient and between different types of amyloidosis. Early diagnosis of amyloidosis relies upon a high index of suspicion, and the following features, particularly the coexistence of two or more clinical features in the context of predisposing conditions, should prompt urgent specific investigation:

●"Red flag" clinical features (see 'Overview of common clinical features' above):

•Non-organ specific: unintentional weight loss, loss of appetite, severe fatigue

•Visible tissue infiltration: macroglossia, easy bruising, skin fragility, nail dystrophy, waxy or thickened skin

•Proteinuria with or without nephrotic syndrome

•Heart failure

•Orthostatic hypotension, arrhythmia

•Carpal tunnel syndrome and/or progressive "glove and stocking" peripheral neuropathy

•Features of autonomic dysfunction including constipation and/or diarrhea, orthostatic hypotension, erectile dysfunction, gustatory sweating

•Hepatosplenomegaly

●Known underlying predisposing conditions:

•Monoclonal gammopathy, multiple myeloma, or other lymphoplasmacytic disorders known to result in production of monoclonal immunoglobulins

•Persistent uncontrolled inflammatory diseases such as autoinflammatory disease (eg, familial Mediterranean fever [FMF]), inflammatory arthritis (eg, rheumatoid arthritis [RA]), inflammatory bowel disease (eg, Crohn disease or ulcerative colitis), or chronic infection (eg, bronchiectasis, urosepsis, or skin sepsis complicating spinal injury)

•A family history of amyloidosis, neuropathy, renal disease, or cardiomyopathy, raising the possibility of dominantly inherited amyloidosis or of kappa AL (which can very rarely be inherited [120]); or of inflammatory symptoms, suggesting inherited autoinflammatory diseases that carry a high risk of AA amyloidosis

Diagnostic approaches — The definitive method for diagnosis of amyloidosis is tissue biopsy, although the presence of amyloidosis may be suggested by the history and clinical manifestations (eg, nephrotic syndrome in a patient with multiple myeloma or longstanding, active RA) (see 'When to suspect amyloidosis' above). In many patients, the biopsy need not be from the known affected organ but can be from another site likely to have deposits, most often the bone marrow or abdominal fat pad (see 'Selection of biopsy site' below). In some patients, the presence of amyloid is demonstrated by findings on imaging (see 'Imaging' below). In some patients, a biopsy result consistent with amyloid is an unexpected diagnosis following routine laboratory Congo Red staining. As an example, AA amyloidosis is only one cause of the nephrotic syndrome in patients with RA; other causes include drug side effects, immune-complex disease, or an unrelated disorder. (See "Overview of the systemic and nonarticular manifestations of rheumatoid arthritis", section on 'Kidney disease' and "Mixed cryoglobulinemia syndrome: Clinical manifestations and diagnosis" and "Minimal change disease: Etiology, clinical features, and diagnosis in adults", section on 'Drugs' and "Membranous nephropathy: Pathogenesis and etiology", section on 'Drugs'.)

Even when amyloidosis is expected, tissue biopsy is important because assumptions regarding the type of amyloid may be incorrect.

Depending upon the presentation and findings, consultation with relevant specialists (eg, a hematologist, nephrologist, cardiologist, neurologist, clinical geneticist, others) and a coordinated multidisciplinary evaluation are important. Referral to a specialized center for the evaluation and management of amyloidosis is preferred, whenever feasible, to access experts in the interpretation and further processing of pathologic specimens, identification of the type of amyloid, detailed characterization of the distribution and extent of disease, and determination of optimal management approaches.

For most patients, the diagnostic evaluation is based upon the clinical presentation and the suspected type of amyloidosis, as described in detail separately for different types of amyloid disorders:

•Initial evaluation in all patients with suspected amyloidosis

Any patient with suspected amyloidosis, whether before or concurrent with scheduling a biopsy or after detection of amyloid as an unexpected biopsy finding, should undergo the following initial evaluation:

•Detailed history to define the presence of underlying conditions known to predispose individuals to developing amyloidosis (such as a hematologic disorder resulting in production of monoclonal immunoglobulin, a chronic inflammatory disorder, or end-stage renal failure) and to ascertain the onset and rate of progression of signs and symptoms systemically and/or related to specific organ system involvement.

•Detailed family history with attention to sex (in hereditary transthyretin amyloidosis [ATTR], inheritance down the female line may be associated with greater penetrance), ancestry, and specific organ involvement.

•Thorough physical examination for cutaneous findings (eg, pinch purpura, skin fragility or thickening, nail fragility), macroglossia, organomegaly, adenopathy, and neuropathy suggestive of amyloidosis.

•Review of recent and past laboratory testing, to include immunoglobulin abnormalities, renal and liver function, and inflammatory (C-reactive protein [CRP], serum amyloid A, and erythrocyte sedimentation rate [ESR]) and cardiac (N-terminal pro-brain natriuretic peptide [NT-proBNP] and troponin) biomarkers.

•Review of recent and past radiographic studies, including computed tomography (CT) scans and echocardiograms.

•Initial evaluation includes a complete blood count, comprehensive metabolic panel, thyroid function tests, and urinalysis.

•Inflammation is screened with an ESR and CRP and may be further defined by a serum amyloid A protein level and proinflammatory cytokine (tumor necrosis factor [TNF] alpha, interleukin [IL] 6) measurements.

•Monoclonal gammopathy is sought by obtaining all quantitative immunoglobulins, serum and urine immunofixation, and measurement of immunoglobulin free light chains (FLC) as elevated levels and/or skewed kappa/lambda ratio in serum.

•Cardiac function is screened with measurements of brain natriuretic peptide (BNP or proBNP) and troponin (T or I).

•Transthyretin (TTR) can be quantitated directly and assessed indirectly by quantitation of retinol binding protein 4 (RBP4) and vitamin A.

●**Suspected AL amyloidosis** – The clinical presentation in immunoglobulin light chain (AL) amyloidosis depends on the number and nature of the organs affected (see 'AL amyloidosis' above). As AL is the most frequently seen type of systemic amyloidosis and is potentially both life threatening and treatable, it should be suspected in all patients with amyloid demonstrated on biopsy until proven otherwise, even with a coexistent history of chronic infectious or inflammatory disease, end-stage kidney disease, or a family history of neuropathy or solid organ failure. Patients should undergo evaluation to determine if paraproteins and a plasma cell dyscrasia are present (see 'Search for monoclonal immunoglobulin' below), including bone marrow aspiration and biopsy. The diagnostic evaluation for AL amyloidosis (algorithm 1) is described in detail separately. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis".).

●**Suspected AA amyloidosis** – Patients with clinical features of systemic amyloidosis and medical conditions that convey an increased risk of AA amyloidosis require a diagnostic evaluation, including a biopsy, to document and determine the extent of disease. Staining with anti-AA antibodies may be helpful. The evaluation and diagnosis of AA amyloidosis is described in detail separately. (See "Causes and diagnosis of AA amyloidosis and relation to rheumatic diseases".)

●**Suspected hereditary amyloidosis** – Patients with a family history of amyloidosis or of neuropathy or cardiac, renal, or liver failure should be suspected of having a heritable form of the disease. A biopsy to document the presence of amyloidosis and detailed analysis to identify the form of amyloid that is present should be performed. A thorough family history and exclusion of these heritable disorders are also warranted if a plasma cell dyscrasia or a cause of AA amyloid cannot be documented [71,121]. (See "Genetic factors in the amyloid diseases".)

●**Suspected amyloid cardiomyopathy** – Amyloid cardiomyopathy should be distinguished from other causes of apparent left ventricular hypertrophy, including hypertensive heart disease, hypertrophic cardiomyopathy, and infiltrative cardiomyopathies such as sarcoidosis and Fabry disease. Multiple forms of amyloidosis can affect the heart, particularly AL and ATTR (both variant [ATTRv] and wild-type [ATTRwt]), as well as rarer hereditary forms, apolipoprotein A-IV (ApoAIV) and AA type. Amyloid cardiomyopathy may be suspected based on apical sparing on strain doppler echocardiograms, typical late gadolinium enhancement

(LGE) on cardiac MRI, or uptake over the heart by bone tracer scintigraphy performed with technetium 99 (99Tc)-pyrophosphate (PYP), 99Tc-3,3 diphosphono-1,2-propanodicarboxylic acid (DPD), or 99Tc-hydroxymethylene diphosphonate (HDMP); the last has been rendered specific for myocardial uptake by single-photon emission CT (SPECT), and graded in quantitative scans as 0 to 3, with grades 2 and 3 being acceptable criteria for diagnosis in lieu of endomyocardial biopsy, and grade 0 making ATTR or AL cardiac amyloidosis unlikely. (See "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis", section on 'Diagnosis'.)

●**Dialysis-related amyloidosis** – Patients with end-stage kidney disease who are suspected of amyloidosis based upon clinical findings (see 'Dialysis-related amyloidosis' above) should undergo a diagnostic evaluation, as described in detail separately. (See "Dialysis-related amyloidosis".)

Biopsy and related analyses

Selection of biopsy site — Biopsies can be obtained from either clinically uninvolved sites, such as subcutaneous fat, minor salivary glands, or rectal mucosa; or from dysfunctional organs (eg, kidney, nerve). We suggest a fat pad aspiration or biopsy as the initial sampling technique for patients with other than single organ involvement because this procedure is less likely than liver, renal, or rectal biopsy to be complicated by serious bleeding; however, biopsy of other tissues may have greater sensitivity. (See 'Abdominal fat pad biopsy' below.)

●**Sensitivity and specificity of fat pad biopsy** – Aspiration or biopsy of subcutaneous fat with Congo red staining and examination using polarized microscopy has an overall sensitivity of 57 to 85 percent and a specificity of 92 to 100 percent for AL or AA amyloidosis [122-125]. The diagnostic sensitivity is higher in those with multiorgan involvement who are suspected of having systemic amyloidosis due to immunoglobulin light chain (primary, or AL), AA protein (secondary), or ATTR (senile cardiac or familial amyloid polyneuropathy [FAP]) deposition [126]. Fat pad aspiration or biopsy has a low sensitivity for amyloidosis in patients with a single involved organ. (See 'Abdominal fat pad biopsy' below.)

Combination of fat pad biopsy and bone marrow biopsy has been shown to have an overall diagnostic sensitivity of 83 percent in AL amyloidosis [127].

●**Patients with few affected organs** – Biopsy of a specifically involved site, rather than an abdominal fat pad biopsy, is suggested for patients with a limited number of

affected organs because patients with single-organ involvement are less likely to have biopsies of unaffected tissues reveal amyloid. This was illustrated by a study of 450 patients with peripheral neuropathy who had fat pad aspiration biopsies performed; among the 143 who had only peripheral neuropathy, none had amyloid deposits noted in the aspiration biopsy [128].

●**Sensitivity and specificity of other biopsy sites** – The sensitivity of rectal biopsy in one large series composed predominantly of patients with systemic amyloid ("primary amyloid" and myeloma associated in 193 patients, "secondary" or localized to a single organ in 41 patients) was 84 percent [129]. The sensitivity of kidney, liver, and carpal-tunnel biopsies were all 90 percent or more in this cohort. Although liver biopsy is rarely complicated by life-threatening bleeding, alternative approaches (eg, transjugular sampling) to diagnosis other than percutaneous liver biopsy are generally preferred. (See "Approach to liver biopsy", section on 'Patients with amyloidosis'.)

Biopsy of the minor salivary glands of the lip, as may be performed for the diagnosis of primary Sjögren's disease, also has a significant yield for both AA and AL amyloidosis, particularly in a subgroup of the latter with major soft tissue manifestations, such as macroglossia, submandibular adenopathy, and arthropathy [130].

Timing of the biopsy — Some patients are under follow-up for a known predisposing underlying disorder, and screening biopsies are performed as soon as there is an index of suspicion, while others present unexpectedly with an amyloid manifestation such as otherwise unexplained heart failure or nephrotic syndrome. In the latter, the diagnosis of amyloidosis comes first, followed by an evaluation for a cause (eg, plasma cell dyscrasia for AL, chronic inflammatory disease for AA).

Abdominal fat pad biopsy — Sampling of subcutaneous tissue was introduced in the 1970s as a diagnostic technique for some systemic forms of amyloidosis and remains a valuable tool, either as an aspiration of the abdominal fat pad or as a deep biopsy of the subcutaneous fat, usually performed by a dermatologist or surgeon [131]. Initial studies involved fine needle aspiration, which has subsequently been used in some studies in combination with ultrastructural and immunohistologic analysis of tissue [132,133].

A protocol has been utilized in clinical studies that involves repeated aspirations carried out at sites approximately 10 cm lateral to the umbilicus using 10 mL syringes with negative pressure through a 16-gauge needle. This procedure is

simple and can be performed in the office over 20 to 30 minutes, but the critical steps for analysis are proper preparation of glass slides for microscopic analysis by Congo red birefringence and for immunohistology, which should be carried out by a pathology laboratory that is experienced with appropriate antibodies and that regularly carries out controls to validate testing. The aim of repeated aspiration, which may be done on both sides of the umbilicus as necessary, is to obtain adequate fat (approximately 30 mg) for routine studies, which may be increased to incorporate quantitation of subunit proteins by methods such as enzyme-linked immunoassay [134] and/or proteomic studies (mass spectroscopy, two-dimensional gel electrophoresis, protein sequence analysis). By contrast, skin biopsy has the potential to distinguish patterns of deposition in the various systemic amyloids [135] and to enhance isolation by laser-capture microdissection [136].

Histopathology and protein analysis — Amyloid deposits appear as amorphous hyaline material on light microscopy (picture 1A-D). The fibrils bind Congo red (leading to green birefringence under polarized light) and thioflavin T (producing an intense yellow-green fluorescence). On electron microscopy, they are 8 to 10 nm in width and are straight and unbranching [3,5].

In patients with a pathologic diagnosis of amyloidosis, the following evaluation will help to confirm and characterize the disorder:

●Slides should be independently reviewed by a pathologist familiar with the evaluation of amyloid in tissue, including metachromasia with dyes such as Congo red or crystal violet, thioflavin T fluorescence, and/or typical apple-green birefringence after staining with Congo red.

●Specific review of the localization of amyloid within biopsied tissue (eg, glomerular, interstitial, or medullary in kidney), with general attention to the presence of congophilic angiopathy and lymphoplasmacytic infiltrates contiguous to amyloid deposits.

●Immunohistochemistry with amyloid type-specific (eg anti-AA/anti-TTR) and generic (eg, anti-serum amyloid P component [SAP]) antisera, with special attention to titration and controls.

●Electron microscopy, particularly with reference to renal tissue, as it can help distinguish amyloid from other renal lesions in monoclonal gammopathy of renal significance (MGRS) [39]. Tissue must be processed specifically for electron microscopy at the time of biopsy.

●Laser-capture microdissection and mass spectroscopy to define the proteomics of amyloid deposits, thereby identifying the fibril subunit protein. Note that although this protocol is best carried out in a major referral center, samples can be obtained from stored tissue blocks or slides.

●In patients with suspected amyloid in whom further biopsies are relatively contraindicated, retrieval of biopsies previously taken for other indications may be performed for re-staining for amyloid; if positive for amyloid, mass spectroscopy may provide a histologic diagnosis and amyloid type.

In some cases, immunohistochemistry can be used to identify the type of protein subunit [10,137,138]. This is most reliable for AA and ATTR amyloid and is less so for AL amyloid; variable staining of AL deposits with standard antisera to kappa or lambda constant region determinants is due to loss of antigenic epitopes in the course of proteolytic processing of the constant region that is presumed to precede fibrillogenesis. Variable region-specific antibodies to immunoglobulin light chain subclass determinants may provide an approach to circumventing this limitation [139,140]. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Differential diagnosis'.)

Direct identification of the proteins present in the amyloid deposits, either by amino acid sequencing or mass spectroscopy, is the most definitive way to characterize the type of amyloid present in the biopsy specimen [141]. This method is performed using laser-capture microdissection of amyloid from formalin-fixed amyloidotic tissue, followed by trypsin digestion, mass spectroscopy, and direct sequence analysis of peptides [136]. This approach, which was originally used for the analysis of the proteomics of AL amyloid, has also been validated for AA; specific tissues, including nerve in patients with amyloid neuropathy and renal biopsies [70]; and for abdominal fat pad aspirates [142]. It has also been adapted for the identification of pathogenic mutations in cases of hereditary amyloid [143] and for the identification of light chain subgroups in AL amyloidosis [144]. The technique is available at a number of specialist centers and requires biopsy blocks or slides, which may be sent for review after a diagnosis of amyloid is made locally.

Search for monoclonal immunoglobulin — In patients without a history of plasma cell dyscrasia, initial testing is aimed at determining whether a monoclonal population of plasma cells is present. This should be accomplished by testing for a monoclonal protein by serum and urine protein electrophoresis (figure 2 and figure 3) and immunofixation (figure 4 and figure 5) and measurement of serum free immunoglobulin light chains. Quantitation of serum FLCs has been utilized as an

adjunctive diagnostic modality that may demonstrate clonality in patients with AL amyloid who do not have monoclonal proteins by immunofixation; this assay may also be used to follow response to treatment [145,146]. (See "Laboratory methods for analyzing monoclonal proteins", section on 'Serum free light chains'.)

The evaluation of a potential plasma cell dyscrasia in patients with suspected AL amyloidosis is described separately. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis".)

However, the presence of a monoclonal protein alone is not sufficient to make a diagnosis of AL amyloid in a patient with documented amyloidosis unless light chains have been demonstrated in the amyloid deposits by histologic, mass spectroscopy, or protein sequencing techniques [71,147]. In particular, monoclonal gammopathies occur in a significant percent of patients with ATTR, in some cases causing coexisting AL and ATTR amyloidosis [148,149]. The potential for misdiagnosis based upon a serum or urine monoclonal protein alone was illustrated in a study of 350 patients suspected of having AL amyloidosis by clinical and laboratory findings and the absence of a family history [71]. Ten percent of these patients had a mutant gene for an "amyloidogenic" protein, most often involving the alpha chain of fibrinogen A or TTR. In 8 of these 34 patients, the presence of low concentrations of monoclonal immunoglobulins (all less than 0.2 g/dL) contributed to the misdiagnosis. (See "Genetic factors in the amyloid diseases".)

Imaging — Some noninvasive tests can provide supportive but not definitive findings. Imaging studies are particularly useful in the evaluation of cardiac disease thought to be related to amyloidosis, but imaging is also useful in other patients, including those with cystic bone lesions in dialysis-related amyloidosis. (See "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis" and "Dialysis-related amyloidosis".)

Scintigraphy with radioisotope-labeled SAP can identify the distribution of amyloid and provide an estimate of the total body burden of fibrillar deposits [150]. However, the availability of SAP scintigraphy is limited as SAP is obtained from blood donors and the technique is not licensed by the US Food and Drug Administration (FDA). It is less helpful in detecting cardiac amyloid. Sensitivity of SAP scanning of 90 percent for AA and AL amyloid is contrasted with 48 percent for hereditary ATTR amyloidosis; the specificity is 93 percent in all three conditions [151]. Positron emission tomography-CT (PET-CT) with tracers with avidity for systemic amyloid deposits has been explored with ^{18}F-florbetapir, ^{18}F-florbetaben, ^{11}C-Pittsburgh compound B, and peptide p5+14 [2]. (See "Clinical presentation,

laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Serum amyloid P component scintigraphy'.)

Systemic versus localized disease — Several approaches will help to distinguish systemic from local disease. Their application is individualized depending upon the clinical presentation, physical findings, presence of underlying disorders predisposing to amyloidosis, and index of suspicion of systemic disease:

●Systemic disease may be suggested by imaging studies, which include:

•CT scans of the chest and abdomen showing organomegaly and/or significant lymphadenopathy.

•Echocardiograms showing wall infiltration and heart failure with or without preserved ejection fraction.

•Cardiac MRI, which has very high sensitivity and specificity for cardiac amyloidosis.

•Whole-body 99Tc-PYP scans looking for uptake over the heart or relevant musculoskeletal disease (wrist and hand for arthropathy or relevant to carpal tunnel syndrome; axial skeleton relevant to lumbar stenosis) is most sensitive for ATTR but is not completely specific and can also be positive in other types of amyloid. Uptake in the spleen is a rare but well-recognized finding in AL type.

●Localized forms of amyloidosis may be evaluated and biopsied by subspecialists (eg, otorhinolaryngologists for laryngeal amyloid, dermatologists for cutaneous amyloid) with specific relevant expertise.

●Tissue sampling for systemic disease may include abdominal fat pad, minor salivary gland, and gastrointestinal (gastric, rectal) biopsies.

●Cardiac biomarkers NT-proBNP and troponin have prognostic significance in systemic disease but can also be used in combination with clinical assessment to screen for the presence of cardiac involvement and to select patients for cardiac imaging as above.

●Assessment of renal function, including proteinuria and liver function, should be performed in all cases.

TREATMENT

General overview — Treatment of the different types of amyloidosis generally varies with the cause of fibril precursor production (eg, treatment of the plasma cell dyscrasia in patients with immunoglobulin light chain [AL] amyloidosis, control of underlying inflammatory or infectious disease in AA amyloidosis).

Strategies to facilitate the clearance of amyloid deposits in tissue are under development in clinical trials. Novel therapies have been developed for hereditary transthyretin (TTR) amyloid to reduce protein transcription, and these latter techniques may have potential for other hereditary amyloidoses in which the mutant amyloid precursor protein (APP) is produced by the liver (eg, apolipoprotein A-I [ApoAI] and fibrinogen Aa); liver transplantation has been used in such patients as an intervention that may prevent further deposition of amyloid and in some cases, can result in regression of established deposits [152-156].

Treatment protocols utilized in AL amyloidosis (eg, chemotherapy, hematopoietic cell transplantation) have no role in patients with hereditary forms of amyloidosis.

A range of novel approaches to treatment are also being investigated (see 'Other approaches and investigational strategies' below).

Therapies for individual amyloid types — The treatment approaches for major forms of amyloidosis are described in more detail separately:

●**AL amyloidosis** – In AL amyloidosis, treatment is directed primarily at suppressing the underlying plasma cell dyscrasia. The treatment of AL amyloidosis is described in detail separately. (See "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis".)

●**AA amyloidosis** – In AA amyloidosis, therapy is aimed primarily at suppressing the underlying infectious or inflammatory disorder, some biologic agents (eg, tumor necrosis factor [TNF], interleukin [IL] 6, and IL-1 inhibitors) have shown particular benefit. The treatment of AA amyloidosis is described in detail separately. (See "Treatment of AA (secondary) amyloidosis".)

●**Dialysis-related amyloidosis** – In patients with dialysis-related amyloidosis, treatment is directed at either altering the mode of dialysis or considering renal transplantation. The treatment of dialysis-related amyloidosis, which is due to beta2-microglobulin amyloid, is described in detail separately. (See "Dialysis-related amyloidosis", section on 'Treatment'.)

●**Transthyretin amyloidosis** – Several approaches have become available for the treatment of hereditary TTR amyloidosis (ATTR). These include the use of ribonucleic acid (RNA)-targeted therapies that interfere with hepatic TTR synthesis and other agents that reduce formation of TTR amyloid through stabilization of the tetramer configuration, preventing release of amyloidogenic monomers.

Liver transplantation has also been used for the treatment of hereditary (variant or mutant) ATTR (ATTRv) as a form of "surgical gene therapy." Liver transplantation is not applicable to wild-type ATTR (ATTRwt), and in most cases, access to heart transplantation is limited by the advanced age of the patient. Treatments for ATTR are discussed briefly below, particularly with respect to the treatment of familial amyloid polyneuropathy (FAP), and are also discussed separately, with a focus on amyloid heart disease (see "Amyloid cardiomyopathy: Treatment and prognosis"):

•**RNA-targeted therapies** – RNA-targeted therapies for ATTR amyloidosis-related cardiomyopathy and neuropathy have become available that interfere with hepatic TTR synthesis and the resultant availability of misfolded monomers to aggregate and form amyloid deposits; these include patisiran, inotersen, and vutrisiran [157-159] (see "Amyloid cardiomyopathy: Treatment and prognosis"):

-**Patisiran** – Patisiran is a TTR-specific small interfering RNA (siRNA) formulation in lipid nanoparticles, which has been shown to substantially reduce the production of both variant and wild-type forms of TTR in patients with hereditary ATTR and in healthy individuals [157,160,161]. Benefit has been shown in clinical trials in patients with FAP due to ATTR [157] and for patients with amyloid cardiomyopathy due to ATTR. Patisiran is administered every three weeks by intravenous infusion.

-**Vutrisiran** – Vutrisiran is a transthyretin-directed siRNA for treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults as an every-three-month subcutaneous injection [159]. It is a chemically modified double-stranded siRNA that targets mutant and wild-type TTR messenger RNA (mRNA) and is covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes, which causes degradation of mutant and wild-type TTR mRNA through RNA interference, resulting in a reduction of serum TTR protein and TTR protein deposits in tissues. Benefits have also been shown in patients with amyloid cardiomyopathy due to ATTR.

-**Inotersen** – Inotersen is an antisense oligonucleotide (ASO) construct that inhibits hepatic production of TTR, resulting in reduced levels of TTR in both healthy

controls and in patients with hereditary ATTR with polyneuropathy [158,162,163]. Moderate to severe thrombocytopenia and bleeding complications have been reported with this agent. Benefits have also been shown for amyloid cardiomyopathy due to ATTR. Inotersen is administered once weekly by subcutaneous injection.

•**Stabilization of transthyretin tetramers** – Tafamidis and diflunisal each can reduce formation of TTR amyloid through stabilization of the TTR tetramer configuration, preventing release of amyloidogenic monomers. The use of tafamidis in amyloid cardiomyopathy is described separately (see "Amyloid cardiomyopathy: Treatment and prognosis"); both tafamidis and diflunisal have also been studied in patients with FAP [164-166].

•**Other agents** – Other agents under investigation for ATTR amyloidosis include AG10, a TTR stabilizer that mimics the effect of the protective TTR T119M variant [167]; tolcapone, a previously licensed drug for Parkinson disease, which was shown to be a potent stabilizer in preclinical studies [168,169]; palindromic bivalent cross-linkers that deplete TTR; covalent stabilizers such as beta-aminoxypropionic acids; cyclic oligosaccharides (cyclodextrins); and polyamidoamine (PAMAM) dendrimers that inhibit formation and disrupt fibrils [170].

●**Isolated organ involvement** – The management of patients with isolated organ involvement depends upon the affected region, organ function, and amyloid type and is discussed separately. (See "Gastrointestinal amyloidosis: Clinical manifestations, diagnosis, and management", section on 'Management' and "Cutaneous manifestations of amyloidosis" and "Pleuropulmonary manifestations of amyloidosis" and "Musculoskeletal manifestations of amyloidosis" and "Cerebral amyloid angiopathy".)

Other approaches and investigational strategies — A range of novel approaches to treatment are being investigated by screening of drug libraries and in animal models. They include agents that interfere with fibril formation; that inhibit the production of amyloidogenic precursors (eg, AL, ATTR, AA); gene editing of mutations, which is being tested for ATTRv; therapeutics that neutralize oligomers, non-amyloid aggregates or protofibrils; agents that promote clearance or degradation of existing amyloid deposits (eg, immunotherapy); and molecules that disrupt the interaction between amyloidogenic proteins and accessory molecules, including chaperones [1,171-177].

The following approaches have been of particular interest:

●**RNA silencing** – In addition to their use for ATTR amyloidosis, RNA silencing using siRNA and ASOs have potential uses as treatment for other amyloidoses. Silencing strategies are potentially applicable to every type of amyloidosis in which reduction in the level of precursor protein has been shown to decrease deposition and fibril formation. A limitation of this approach is that it depends upon being able to knock out a protein so it may not be applicable when the protein has essential functions that cannot be compensated for. The experience with ATTR provides a model for silencing of other amyloidogenic proteins primarily made in the liver, such as acute phase serum amyloid A protein isoforms, and leukocyte cell-derived chemotaxin-2 (LECT2) and has also been examined at the proof-of-concept level for AL amyloidosis [178,179].

●**Gene editing** – Gene editing designed to knock out TTR production is under investigation in a small group of patients with hereditary ATTR amyloidosis with polyneuropathy by use of an in vivo gene-editing agent based on the clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease (CRISPR-Cas9) system [171]; the agent is composed of a lipid nanoparticle encapsulating mRNA for Cas9 protein and a single guide RNA (sgRNA) targeting *TTR*. In the first part of this ongoing phase 1 clinical study, administration of a single infusion of this agent, NTLA-2001, substantially reduced serum levels of TTR with only mild adverse effects. While consistent with clinical proof of concept for this approach, the study is ongoing with further examination of optimal dosing and monitoring of treatment outcomes. No off-target effects of the gene editing have been detected in preclinical studies and in the phase 1 study.

●**Inhibition of proteolysis** – Direct extraction and macromolecular characterization of fibrils have identified cleavage products generated at specific amino acids (eg, position 76 for serum amyloid A protein, position 49 for TTR) that have been shown to be more intrinsically amyloidogenic and/or toxic [180,181] or, in the case of ATTR, that generate a distinct fibrillar and phenotypic morphology [182]. The presence in some amyloid deposits of both the intact precursor and proteolytic cleavage products raises the question of whether proteolysis is a pre- or post-fibrillar event [183]. These considerations have led to the concept that protease inhibition might be a target for therapy (eg, gamma-secretase inhibitors for Alzheimer disease; nanobodies directed against furin active sites for familial polyneuropathy due to gelsolin mutations) [184,185].

●**Immunotherapy** – Recognition that the fibrillar configuration might be accessible to antibodies with conformational specificities shared between different precursor proteins was an observation made a number of years ago [186,187]. Strategies for immunotherapy have included (a) vaccination with antigen preparations that mimic cryptic epitopes, oligomeric or fibrillar configurations, or (b) passive immunotherapy with intravenous gammaglobulin shown to contain amyloid-binding antibody activity, or with monoclonal antibodies that target oligomers, protofibrils, or fibrillar conformations. Active vaccination and passive immunotherapy have been most intensively explored as a strategy for clearance of amyloid for A-beta and tau central nervous system (CNS) diseases [188-190], and remain an area of interest for AL and ATTR [191]. Monoclonal antibodies to ATTR conformational or cryptic epitopes exposed during fibrillogenesis are also under study [192,193].

●**Targeting of serum amyloid P component** – Targeting of serum amyloid P component (SAP), a normal plasma protein common to all forms of systemic amyloid (including AA, AL, and hereditary forms), may be effective for the reduction or removal of tissue deposits of amyloid. Sequential treatment with the drug (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC), which depletes SAP from the plasma but only partly depletes SAP from tissues, followed by administration of an anti-SAP monoclonal antibody, triggered the clearance of amyloid deposits from liver, kidney, and other organs in animal studies and in patients with AL, AA, and hereditary forms of systemic amyloidosis in early-phase clinical trials [194-198].

●**Agents that disrupt fibrils** – Fibril disrupters that have progressed to clinical testing include doxycycline (targeting ATTR, AL, and beta2-microglobulin), which disrupts fibril formation and mature fibrils, as well as inhibiting MMP-9; the nutraceuticals [199] epigallocatechin-3-gallate (green tea; targeting ATTR, A-beta, apolipoprotein A-II [ApoAII], and ATGF-beta1), which disrupts mature fibrils and suppresses markers of oxidative stress [200], and curcumin (targeting ATTR and A-beta), which induces oligomerization to a nontoxic "off pathway" [201]. Low molecular weight aggregation inhibitors include beta sheet breaker peptides, antigen-binding fragment (Fab), scFv or single-chain camelid nanobodies, and peptide inhibitors of adhesive segments [201]. (See "Treatment of AA (secondary) amyloidosis", section on 'Investigational approaches' and "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis", section on 'Clinical trials'.)

INFORMATION FOR PATIENTSUpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

●Basics topics (see "Patient education: AL amyloidosis (The Basics)")

SUMMARY AND RECOMMENDATIONS

●**Types of amyloidosis** – Amyloidosis is a generic term for the extracellular tissue deposition of fibrils composed of low molecular weight subunits of a variety of proteins, many of which circulate as constituents of plasma. These subunit proteins are derived from soluble precursors that undergo conformational changes that lead to the adoption of a predominantly antiparallel beta-pleated sheet configuration. At least 38 different human protein precursors of amyloid fibrils are known (table 1). (See 'Pathogenesis' above.)

Major forms of amyloidosis include:

•**AL amyloidosis** – Due to deposition of protein derived from immunoglobulin light chain fragments. It is a potential complication of any plasma cell dyscrasia that produces monoclonal immunoglobulin. (See 'AL amyloidosis' above and 'Clinical manifestations' above.)

•**Transthyretin amyloidosis (ATTR)** – Due to either specific heritable mutations, which are associated with familial amyloid polyneuropathy (FAP) and/or familial amyloid cardiomyopathy, or which more often may occur in a nonfamilial form as a concomitant of aging without apparent mutations (wild-type transthyretin [TTR] amyloidosis [ATTRwt]). (See 'Heritable amyloidoses' above and 'Wild-type transthyretin systemic amyloidosis' above and 'Clinical manifestations' above.)

•**AA amyloidosis** – The most common form in resource-limited countries, it may complicate chronic diseases associated with ongoing or recurring inflammation, such as chronic infections; rheumatoid arthritis (RA), spondyloarthritis, or inflammatory bowel disease; or periodic fever syndromes. (See 'AA amyloidosis' above and 'Clinical manifestations' above.)

Additional major forms include dialysis-related amyloidosis, other heritable amyloidoses, other age-related amyloidoses, organ-specific amyloid, and others. (See 'Dialysis-related amyloidosis' above and 'Heritable amyloidoses' above and 'Organ-specific amyloid' above and 'Clinical manifestations' above.)

●**Clinical manifestations** – Clinical manifestations vary depending upon the type of amyloid and the distribution of deposition. Some features that suggest amyloidosis include waxy skin and easy bruising, enlarged muscles (eg, tongue, deltoids), carpal tunnel syndrome, heart failure, cardiac conduction abnormalities, hepatomegaly, heavy proteinuria or the nephrotic syndrome, peripheral and/or autonomic neuropathy, and impaired coagulation. (See 'Types of amyloidosis' above and 'Clinical manifestations' above.)

●**Diagnosis** – Tissue biopsy should be used to confirm the diagnosis in all cases. Fat pad aspiration biopsy is less likely than liver, renal, or rectal biopsy to be complicated by serious bleeding; we thus suggest it as the initial biopsy technique for patients with other than single-organ involvement. In patients with single-organ involvement, biopsy of the clinically involved site is suggested because fat pad aspiration biopsy has a low sensitivity for amyloidosis in such patients. (See 'Selection of biopsy site' above.)

●**Monoclonal protein testing** – Patients with biopsy-documented amyloidosis and a well-defined plasma cell dyscrasia (eg, multiple myeloma or Waldenström macroglobulinemia) need not undergo further testing for an underlying hematologic disorder. Patients without a known plasma cell disorder should be tested to determine whether a monoclonal protein is present in serum, urine, or both using a combination of serum and urine protein electrophoresis, followed by immunofixation. Quantitation of serum free light chains (FLCs) is suggested for AL patients who do not have monoclonal proteins by immunofixation. (See 'Search for monoclonal immunoglobulin' above.)

The presence of a monoclonal protein alone is not sufficient to make a diagnosis of AL amyloid unless light chains have been demonstrated within the amyloid deposits. Heritable types of amyloidosis should be excluded if a plasma cell

dyscrasia cannot be documented. (See 'Search for monoclonal immunoglobulin' above.)

●**Treatment** – Treatment of amyloidosis generally varies with the cause of fibril production. As examples, treatment is aimed at the underlying infectious or inflammatory disorder in AA amyloidosis, at the underlying plasma cell dyscrasia in AL amyloidosis, and at either altering the mode of dialysis or considering renal transplantation in patients with dialysis-related amyloidosis. Liver transplantation may be effective in certain of the hereditary amyloidoses. Therapies to decrease TTR production are available, and treatments that promote the clearance of amyloid deposits of different types are in development. (See 'Treatment' above.)

REFERENCES

1. Ke PC, Zhou R, Serpell LC, et al. Half a century of amyloids: past, present and future. Chem Soc Rev 2020; 49:5473.
2. Muchtar E, Dispenzieri A, Magen H, et al. Systemic amyloidosis from A (AA) to T (ATTR): a review. J Intern Med 2021; 289:268.
3. Kyle RA. Amyloidosis: a convoluted story. Br J Haematol 2001; 114:529.
4. Yakupova EI, Bobyleva LG, Vikhlyantsev IM, Bobylev AG. Congo Red and amyloids: history and relationship. Biosci Rep 2019; 39.
5. COHEN AS, CALKINS E. Electron microscopic observations on a fibrous component in amyloid of diverse origins. Nature 1959; 183:1202.
6. Iadanza MG, Jackson MP, Hewitt EW, et al. A new era for understanding amyloid structures and disease. Nat Rev Mol Cell Biol 2018; 19:755.
7. Gosal WS, Myers SL, Radford SE, Thomson NH. Amyloid under the atomic force microscope. Protein Pept Lett 2006; 13:261.
8. Dasari AKR, Hughes RM, Wi S, et al. Transthyretin Aggregation Pathway toward the Formation of Distinct Cytotoxic Oligomers. Sci Rep 2019; 9:33.
9. Picken MM, Westermark P. Amyloid detection and typing: summary of current practice and recommendations of the consensus group. Amyloid 2011; 18 Suppl 1:48.
10. Schönland SO, Hegenbart U, Bochtler T, et al. Immunohistochemistry in the classification of systemic forms of amyloidosis: a systematic investigation of 117 patients. Blood 2012; 119:488.
11. Fernández de Larrea C, Verga L, Morbini P, et al. A practical approach to the diagnosis of systemic amyloidoses. Blood 2015; 125:2239.
12. Hill MM, Dasari S, Mollee P, et al. The Clinical Impact of Proteomics in Amyloid Typing. Mayo Clin Proc 2021; 96:1122.

13. Arosio P, Michaels TC, Linse S, et al. Kinetic analysis reveals the diversity of microscopic mechanisms through which molecular chaperones suppress amyloid formation. Nat Commun 2016; 7:10948.
14. Bellotti V, Nuvolone M, Giorgetti S, et al. The workings of the amyloid diseases. Ann Med 2007; 39:200.
15. Eisenberg D, Jucker M. The amyloid state of proteins in human diseases. Cell 2012; 148:1188.
16. Knowles TP, Vendruscolo M, Dobson CM. The amyloid state and its association with protein misfolding diseases. Nat Rev Mol Cell Biol 2014; 15:384.
17. Chiti F, Dobson CM. Protein Misfolding, Amyloid Formation, and Human Disease: A Summary of Progress Over the Last Decade. Annu Rev Biochem 2017; 86:27.
18. Bemporad F, Chiti F. Protein misfolded oligomers: experimental approaches, mechanism of formation, and structure-toxicity relationships. Chem Biol 2012; 19:315.
19. Rochet JC, Lansbury PT Jr. Amyloid fibrillogenesis: themes and variations. Curr Opin Struct Biol 2000; 10:60.
20. Kisilevsky R. The relation of proteoglycans, serum amyloid P and apo E to amyloidosis current status, 2000. Amyloid 2000; 7:23.
21. Nishitsuji K, Uchimura K. Sulfated glycosaminoglycans in protein aggregation diseases. Glycoconj J 2017; 34:453.
22. Dergunov AD. Role of ApoE in conformation-prone diseases and atherosclerosis. Biochemistry (Mosc) 2006; 71:707.
23. Meijer JM, Schonland SO, Palladini G, et al. Sjögren's syndrome and localized nodular cutaneous amyloidosis: coincidence or a distinct clinical entity? Arthritis Rheum 2008; 58:1992.
24. Hamidi Asl K, Liepnieks JJ, Nakamura M, Benson MD. Organ-specific (localized) synthesis of Ig light chain amyloid. J Immunol 1999; 162:5556.
25. Westermark P. Localized AL amyloidosis: a suicidal neoplasm? Ups J Med Sci 2012; 117:244.
26. Ishii W, Liepnieks JJ, Yamada T, et al. Human SAA1-derived amyloid deposition in cell culture: a consistent model utilizing human peripheral blood mononuclear cells and serum-free medium. Amyloid 2013; 20:61.
27. Benson MD, Buxbaum JN, Eisenberg DS, et al. Amyloid nomenclature 2020: update and recommendations by the International Society of Amyloidosis (ISA) nomenclature committee. Amyloid 2020; 27:217.
28. Basu A, Boczek NJ, Robertson NG, et al. First Report of Bilateral External Auditory Canal Cochlin Aggregates ("Cochlinomas") with Multifocal Amyloid-

Like Deposits, Associated with Sensorineural Hearing Loss and a Novel Genetic Variant in COCH Encoding Cochlin. Head Neck Pathol 2020; 14:808.
29. Dao LN, Kurtin PJ, Smyrk TC, et al. The novel form of amyloidosis derived from EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1) preferentially affects the lower gastrointestinal tract of elderly femalesa. Histopathology 2021; 78:459.
30. Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. Muscle Nerve 2007; 36:411.
31. Mucchiano GI, Häggqvist B, Sletten K, Westermark P. Apolipoprotein A-1-derived amyloid in atherosclerotic plaques of the human aorta. J Pathol 2001; 193:270.
32. Yazaki M, Liepnieks JJ, Kincaid JC, Benson MD. Contribution of wild-type transthyretin to hereditary peripheral nerve amyloid. Muscle Nerve 2003; 28:438.
33. Ravichandran S, Lachmann HJ, Wechalekar AD. Epidemiologic and Survival Trends in Amyloidosis, 1987-2019. N Engl J Med 2020; 382:1567.
34. Nilsson MR. Insulin amyloid at injection sites of patients with diabetes. Amyloid 2016; 23:139.
35. Gertz MA. Immunoglobulin light chain amyloidosis: 2020 update on diagnosis, prognosis, and treatment. Am J Hematol 2020; 95:848.
36. Milani P, Merlini G, Palladini G. Light Chain Amyloidosis. Mediterr J Hematol Infect Dis 2018; 10:e2018022.
37. Jimenez-Zepeda VH. Light chain deposition disease: novel biological insights and treatment advances. Int J Lab Hematol 2012; 34:347.
38. Sobue Y, Takemura G, Kawamura S, et al. Coexistence of amyloidosis and light chain deposition disease in the heart. Cardiovasc Pathol 2021; 51:107315.
39. Leung N, Bridoux F, Nasr SH. Monoclonal Gammopathy of Renal Significance. N Engl J Med 2021; 384:1931.
40. Oe Y, Soma J, Sato H, Ito S. Heavy chain deposition disease: an overview. Clin Exp Nephrol 2013; 17:771.
41. Westermark P, Bergström J, Solomon A, et al. Transthyretin-derived senile systemic amyloidosis: clinicopathologic and structural considerations. Amyloid 2003; 10 Suppl 1:48.
42. Sekijima Y, Yazaki M, Ueda M, et al. First nationwide survey on systemic wild-type ATTR amyloidosis in Japan. Amyloid 2018; 25:8.
43. Ng B, Connors LH, Davidoff R, et al. Senile systemic amyloidosis presenting with heart failure: a comparison with light chain-associated amyloidosis. Arch Intern Med 2005; 165:1425.

44. Maurer MS, Ruberg FL. Early Diagnosis of Cardiac Amyloidosis by Carpal Tunnel Surgery: Is it All in the Wrist? J Am Coll Cardiol 2018; 72:2051.
45. Pinney JH, Whelan CJ, Petrie A, et al. Senile systemic amyloidosis: clinical features at presentation and outcome. J Am Heart Assoc 2013; 2:e000098.
46. Maurer MS, Bokhari S, Damy T, et al. Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis. Circ Heart Fail 2019; 12:e006075.
47. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation 2016; 133:2404.
48. Papa R, Lachmann HJ. Secondary, AA, Amyloidosis. Rheum Dis Clin North Am 2018; 44:585.
49. Stoppini M, Bellotti V. Systemic amyloidosis: lessons from β2-microglobulin. J Biol Chem 2015; 290:9951.
50. Kaneko S, Yamagata K. Hemodialysis-related amyloidosis: Is it still relevant? Semin Dial 2018; 31:612.
51. Koike H, Katsuno M. Transthyretin Amyloidosis: Update on the Clinical Spectrum, Pathogenesis, and Disease-Modifying Therapies. Neurol Ther 2020; 9:317.
52. Obici L, Merlini G. Amyloidosis in autoinflammatory syndromes. Autoimmun Rev 2012; 12:14.
53. Mereuta OM, Theis JD, Vrana JA, et al. Leukocyte cell-derived chemotaxin 2 (LECT2)-associated amyloidosis is a frequent cause of hepatic amyloidosis in the United States. Blood 2014; 123:1479.
54. Larsen CP, Kossmann RJ, Beggs ML, et al. Clinical, morphologic, and genetic features of renal leukocyte chemotactic factor 2 amyloidosis. Kidney Int 2014; 86:378.
55. Sethi S, Theis JD, Shiller SM, et al. Medullary amyloidosis associated with apolipoprotein A-IV deposition. Kidney Int 2012; 81:201.
56. Martins E, Urbano J, Leite S, et al. Cardiac Amyloidosis Associated with Apolipoprotein A-IV Deposition Diagnosed by Mass Spectrometry-Based Proteomic Analysis. Eur J Case Rep Intern Med 2019; 6:001237.
57. Baykal C, Buyukbabani N, Boztepe H, et al. Multiple cutaneous neuromas and macular amyloidosis associated with medullary thyroid carcinoma. J Am Acad Dermatol 2007; 56:S33.
58. Miura Y, Harumiya S, Ono K, et al. Galectin-7 and actin are components of amyloid deposit of localized cutaneous amyloidosis. Exp Dermatol 2013; 22:36.

59. Phelps RG, Gorevic PD. Cutaneous amyloidosis. In: Fitzpatrick's Dermatology, 9th ed, Kang S, Amagai M, Bruckner AL, et al (Eds), McGraw-Hill Education, 2019.
60. Chapman JR, Liu A, Yi SS, et al. Proteomic analysis shows that the main constituent of subepidermal localised cutaneous amyloidosis is not galectin-7. Amyloid 2021; 28:35.
61. Monge M, Chauveau D, Cordonnier C, et al. Localized amyloidosis of the genitourinary tract: report of 5 new cases and review of the literature. Medicine (Baltimore) 2011; 90:212.
62. Dammacco R, Merlini G, Lisch W, et al. Amyloidosis and Ocular Involvement: an Overview. Semin Ophthalmol 2020; 35:7.
63. Kourelis TV, Kyle RA, Dingli D, et al. Presentation and Outcomes of Localized Immunoglobulin Light Chain Amyloidosis: The Mayo Clinic Experience. Mayo Clin Proc 2017; 92:908.
64. Gaglione R, Smaldone G, Di Girolamo R, et al. Cell milieu significantly affects the fate of AApoAI amyloidogenic variants: predestination or serendipity? Biochim Biophys Acta Gen Subj 2018; 1862:377.
65. Harris G, Lachmann H, Hawkins P, Sandhu G. One Hundred Cases of Localized Laryngeal Amyloidosis - Evidence for Future Management. Laryngoscope 2021; 131:E1912.
66. Westermark P, Westermark GT. Review. Reflections on amyloidosis in Papua New Guinea. Philos Trans R Soc Lond B Biol Sci 2008; 363:3701.
67. Porcari A, Merlo M, Rapezzi C, Sinagra G. Transthyretin amyloid cardiomyopathy: An uncharted territory awaiting discovery. Eur J Intern Med 2020; 82:7.
68. Waddington-Cruz M, Schmidt H, Botteman MF, et al. Epidemiological and clinical characteristics of symptomatic hereditary transthyretin amyloid polyneuropathy: a global case series. Orphanet J Rare Dis 2019; 14:34.
69. Kurita N, Kotera N, Ishimoto Y, et al. AA amyloid nephropathy with predominant vascular deposition in Crohn's disease. Clin Nephrol 2013; 79:229.
70. Said SM, Sethi S, Valeri AM, et al. Renal amyloidosis: origin and clinicopathologic correlations of 474 recent cases. Clin J Am Soc Nephrol 2013; 8:1515.
71. Lachmann HJ, Booth DR, Booth SE, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. N Engl J Med 2002; 346:1786.
72. Rubin J, Maurer MS. Cardiac Amyloidosis: Overlooked, Underappreciated, and Treatable. Annu Rev Med 2020; 71:203.

73. Cheung CC, Roston TM, Andrade JG, et al. Arrhythmias in Cardiac Amyloidosis: Challenges in Risk Stratification and Treatment. Can J Cardiol 2020; 36:416.
74. Sukhacheva TV, Eremeeva MV, Ibragimova AG, et al. Isolated Atrial Amyloidosis in Patients with Various Types of Atrial Fibrillation. Bull Exp Biol Med 2016; 160:844.
75. Sattianayagam P, Hawkins P, Gillmore J. Amyloid and the GI tract. Expert Rev Gastroenterol Hepatol 2009; 3:615.
76. Syed U, Ching Companioni RA, Alkhawam H, Walfish A. Amyloidosis of the gastrointestinal tract and the liver: clinical context, diagnosis and management. Eur J Gastroenterol Hepatol 2016; 28:1109.
77. Shin SC, Robinson-Papp J. Amyloid neuropathies. Mt Sinai J Med 2012; 79:733.
78. Kaku M, Berk JL. Neuropathy Associated with Systemic Amyloidosis. Semin Neurol 2019; 39:578.
79. Revesz T, Holton JL, Lashley T, et al. Genetics and molecular pathogenesis of sporadic and hereditary cerebral amyloid angiopathies. Acta Neuropathol 2009; 118:115.
80. Ikeda SI. [Cerebral amyloid angiopathy with familial transthyretin-derived oculoleptomeningeal amyloidosis]. Brain Nerve 2013; 65:831.
81. Zubkov AY, Rabinstein AA, Dispenzieri A, Wijdicks EF. Primary systemic amyloidosis with ischemic stroke as a presenting complication. Neurology 2007; 69:1136.
82. Cohen AS, Canoso JJ. Rheumatological aspects of amyloid disease. Clin Rheum Dis 1975; 1:149.
83. M'bappé P, Grateau G. Osteo-articular manifestations of amyloidosis. Best Pract Res Clin Rheumatol 2012; 26:459.
84. Wininger AE, Phelps BM, Le JT, et al. Musculoskeletal pathology as an early warning sign of systemic amyloidosis: a systematic review of amyloid deposition and orthopedic surgery. BMC Musculoskelet Disord 2021; 22:51.
85. Yood RA, Skinner M, Rubinow A, et al. Bleeding manifestations in 100 patients with amyloidosis. JAMA 1983; 249:1322.
86. Mumford AD, O'Donnell J, Gillmore JD, et al. Bleeding symptoms and coagulation abnormalities in 337 patients with AL-amyloidosis. Br J Haematol 2000; 110:454.
87. Sucker C, Hetzel GR, Grabensee B, et al. Amyloidosis and bleeding: pathophysiology, diagnosis, and therapy. Am J Kidney Dis 2006; 47:947.

88. Furie B, Greene E, Furie BC. Syndrome of acquired factor X deficiency and systemic amyloidosis in vivo studies of the metabolic fate of factor X. N Engl J Med 1977; 297:81.
89. Choufani EB, Sanchorawala V, Ernst T, et al. Acquired factor X deficiency in patients with amyloid light-chain amyloidosis: incidence, bleeding manifestations, and response to high-dose chemotherapy. Blood 2001; 97:1885.
90. Boggio L, Green D. Recombinant human factor VIIa in the management of amyloid-associated factor X deficiency. Br J Haematol 2001; 112:1074.
91. Thompson CA, Kyle R, Gertz M, et al. Systemic AL amyloidosis with acquired factor X deficiency: A study of perioperative bleeding risk and treatment outcomes in 60 patients. Am J Hematol 2010; 85:171.
92. Kos CA, Ward JE, Malek K, et al. Association of acquired von Willebrand syndrome with AL amyloidosis. Am J Hematol 2007; 82:363.
93. Ericson S, Shah N, Liberman J, Aboulafia DM. Fatal bleeding due to acquired factor IX and X deficiency: a rare complication of primary amyloidosis; case report and review of the literature. Clin Lymphoma Myeloma Leuk 2014; 14:e81.
94. Hoffman JE, Dempsey NG, Sanchorawala V. Systemic Amyloidosis Caused by Monoclonal Immunoglobulins: Soft Tissue and Vascular Involvement. Hematol Oncol Clin North Am 2020; 34:1099.
95. Ross P Jr, Magro CM. Clonal light chain restricted primary intrapulmonary nodular amyloidosis. Ann Thorac Surg 2005; 80:344.
96. Howard ME, Ireton J, Daniels F, et al. Pulmonary presentations of amyloidosis. Respirology 2001; 6:61.
97. Berk JL, Keane J, Seldin DC, et al. Persistent pleural effusions in primary systemic amyloidosis: etiology and prognosis. Chest 2003; 124:969.
98. Maeno T, Sando Y, Tsukagoshi M, et al. Pleural amyloidosis in a patient with intractable pleural effusion and multiple myeloma. Respirology 2000; 5:79.
99. Ikeda S, Takabayashi Y, Maejima Y, et al. Nodular lung disease with five year survival and unilateral pleural effusion in AL amyloidosis. Amyloid 1999; 6:292.
100. Utz JP, Swensen SJ, Gertz MA. Pulmonary amyloidosis. The Mayo Clinic experience from 1980 to 1993. Ann Intern Med 1996; 124:407.
101. Dingli D, Utz JP, Gertz MA. Pulmonary hypertension in patients with amyloidosis. Chest 2001; 120:1735.
102. Onozato ML, Tojo A, Ogura S, et al. Primary amyloidosis with multiple pulmonary nodular lesions and IgA nephropathy-like renal involvement. Clin Nephrol 2003; 60:134.

103. Fujimoto N, Masuoka H, Kosaka H, et al. Primary amyloidosis with pulmonary involvement which presented exudative pleural effusion and high fever. Intern Med 2003; 42:756.
104. BoydKing A, Sharma O, Stevenson K. Localized interstitial pulmonary amyloid: a case report and review of the literature. Curr Opin Pulm Med 2009; 15:517.
105. Dahl KA, Kernstine KH, Vannatta TL, et al. Tracheobronchial amyloidosis: a surgical disease with long-term consequences. J Thorac Cardiovasc Surg 2004; 128:789.
106. O'Regan A, Fenlon HM, Beamis JF Jr, et al. Tracheobronchial amyloidosis. The Boston University experience from 1984 to 1999. Medicine (Baltimore) 2000; 79:69.
107. Capizzi SA, Betancourt E, Prakash UB. Tracheobronchial amyloidosis. Mayo Clin Proc 2000; 75:1148.
108. Pribitkin E, Friedman O, O'Hara B, et al. Amyloidosis of the upper aerodigestive tract. Laryngoscope 2003; 113:2095.
109. Monroe AT, Walia R, Zlotecki RA, Jantz MA. Tracheobronchial amyloidosis: a case report of successful treatment with external beam radiation therapy. Chest 2004; 125:784.
110. Dedo HH, Izdebski K. Laryngeal amyloidosis in 10 patients. Laryngoscope 2004; 114:1742.
111. Ueda M, Ando Y, Haraoka K, et al. Aging and transthyretin-related amyloidosis: pathologic examinations in pulmonary amyloidosis. Amyloid 2006; 13:24.
112. Berk JL. Pleural effusions in systemic amyloidosis. Curr Opin Pulm Med 2005; 11:324.
113. Khoor A, Colby TV. Amyloidosis of the Lung. Arch Pathol Lab Med 2017; 141:247.
114. Eder L, Bitterman H. Image in clinical medicine. Amyloid purpura. N Engl J Med 2007; 356:2406.
115. Lanoue J, Wei N, Gorevic P, Phelps RG. Cutaneous Manifestations of Familial Transthyretin Amyloid Polyneuropathy. Am J Dermatopathol 2016; 38:719.
116. Martins AC, Rosa AM, Costa E, et al. Ocular Manifestations and Therapeutic Options in Patients with Familial Amyloid Polyneuropathy: A Systematic Review. Biomed Res Int 2015; 2015:282405.
117. Tran TA. Muckle-Wells syndrome: clinical perspectives. Open Access Rheumatol 2017; 9:123.

118. Gertz MA, Kyle RA, Griffing WL, Hunder GG. Jaw claudication in primary systemic amyloidosis. Medicine (Baltimore) 1986; 65:173.
119. Neben-Wittich MA, Wittich CM, Mueller PS, et al. Obstructive intramural coronary amyloidosis and myocardial ischemia are common in primary amyloidosis. Am J Med 2005; 118:1287.
120. Benson MD, Liepnieks JJ, Kluve-Beckerman B. Hereditary systemic immunoglobulin light-chain amyloidosis. Blood 2015; 125:3281.
121. Saraiva MJ. Sporadic cases of hereditary systemic amyloidosis. N Engl J Med 2002; 346:1818.
122. Duston MA, Skinner M, Meenan RF, Cohen AS. Sensitivity, specificity, and predictive value of abdominal fat aspiration for the diagnosis of amyloidosis. Arthritis Rheum 1989; 32:82.
123. van Gameren II, Hazenberg BP, Bijzet J, van Rijswijk MH. Diagnostic accuracy of subcutaneous abdominal fat tissue aspiration for detecting systemic amyloidosis and its utility in clinical practice. Arthritis Rheum 2006; 54:2015.
124. Dhingra S, Krishnani N, Kumari N, Pandey R. Evaluation of abdominal fat pad aspiration cytology and grading for detection in systemic amyloidosis. Acta Cytol 2007; 51:860.
125. Westermark P. Subcutaneous adipose tissue biopsy for amyloid protein studies. Methods Mol Biol 2012; 849:363.
126. Paulsson Rokke H, Sadat Gousheh N, Westermark P, et al. Abdominal fat pad biopsies exhibit good diagnostic accuracy in patients with suspected transthyretin amyloidosis. Orphanet J Rare Dis 2020; 15:278.
127. Cohen OC, Sharpley F, Gilbertson JA, et al. The value of screening biopsies in light-chain (AL) and transthyretin (ATTR) amyloidosis. Eur J Haematol 2020; 105:352.
128. Andrews TR, Colon-Otero G, Calamia KT, et al. Utility of subcutaneous fat aspiration for diagnosing amyloidosis in patients with isolated peripheral neuropathy. Mayo Clin Proc 2002; 77:1287.
129. Kyle RA, Bayrd ED. Amyloidosis: review of 236 cases. Medicine (Baltimore) 1975; 54:271.
130. Foli A, Palladini G, Caporali R, et al. The role of minor salivary gland biopsy in the diagnosis of systemic amyloidosis: results of a prospective study in 62 patients. Amyloid 2011; 18 Suppl 1:80.
131. Westermark P. Amyloid diagnosis, subcutaneous adipose tissue, immunohistochemistry and mass spectrometry. Amyloid 2011; 18:175.

132. Devata S, Hari P, Markelova N, et al. Detection of amyloid in abdominal fat pad aspirates in early amyloidosis: Role of electron microscopy and Congo red stained cell block sections. Cytojournal 2011; 8:11.
133. Wang D, Wang Y, Liu B, et al. Diagnostic value of electron microscopy detection using abdominal fat pad biopsy in systemic amyloidosis. Clin Nephrol 2021; 95:201.
134. Hazenberg BP, Limburg PC, Bijzet J, van Rijswijk MH. A quantitative method for detecting deposits of amyloid A protein in aspirated fat tissue of patients with arthritis. Ann Rheum Dis 1999; 58:96.
135. Ikeda S, Sekijima Y, Tojo K, Koyama J. Diagnostic value of abdominal wall fat pad biopsy in senile systemic amyloidosis. Amyloid 2011; 18:211.
136. Vrana JA, Gamez JD, Madden BJ, et al. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood 2009; 114:4957.
137. Arbustini E, Morbini P, Verga L, Merlini G. Light and electron microscopy immunohistochemical characterization of amyloid deposits. Amyloid 1997; 4:157.
138. Linke RP. On typing amyloidosis using immunohistochemistry. Detailled illustrations, review and a note on mass spectrometry. Prog Histochem Cytochem 2012; 47:61.
139. Davern S, Tang LX, Williams TK, et al. Immunodiagnostic capabilities of anti-free immunoglobulin light chain monoclonal antibodies. Am J Clin Pathol 2008; 130:702.
140. Picken MM. The Pathology of Amyloidosis in Classification: A Review. Acta Haematol 2020; 143:322.
141. Wisniowski B, Wechalekar A. Confirming the Diagnosis of Amyloidosis. Acta Haematol 2020; 143:312.
142. Klein CJ, Vrana JA, Theis JD, et al. Mass spectrometric-based proteomic analysis of amyloid neuropathy type in nerve tissue. Arch Neurol 2011; 68:195.
143. Dasari S, Theis JD, Vrana JA, et al. Clinical proteome informatics workbench detects pathogenic mutations in hereditary amyloidoses. J Proteome Res 2014; 13:2352.
144. Dasari S, Theis JD, Vrana JA, et al. Proteomic detection of immunoglobulin light chain variable region peptides from amyloidosis patient biopsies. J Proteome Res 2015; 14:1957.
145. Kumar S, Dispenzieri A, Katzmann JA, et al. Serum immunoglobulin free light-chain measurement in primary amyloidosis: prognostic value and correlations with clinical features. Blood 2010; 116:5126.

146. Mollee P, Merlini G. Free light chain testing for the diagnosis, monitoring and prognostication of AL amyloidosis. Clin Chem Lab Med 2016; 54:921.
147. Comenzo RL, Zhou P, Fleisher M, et al. Seeking confidence in the diagnosis of systemic AL (Ig light-chain) amyloidosis: patients can have both monoclonal gammopathies and hereditary amyloid proteins. Blood 2006; 107:3489.
148. Phull P, Sanchorawala V, Connors LH, et al. Monoclonal gammopathy of undetermined significance in systemic transthyretin amyloidosis (ATTR). Amyloid 2018; 25:62.
149. Sidiqi MH, McPhail ED, Theis JD, et al. Two types of amyloidosis presenting in a single patient: a case series. Blood Cancer J 2019; 9:30.
150. Hawkins PN. Serum amyloid P component scintigraphy for diagnosis and monitoring amyloidosis. Curr Opin Nephrol Hypertens 2002; 11:649.
151. Hazenberg BP, van Rijswijk MH, Piers DA, et al. Diagnostic performance of 123I-labeled serum amyloid P component scintigraphy in patients with amyloidosis. Am J Med 2006; 119:355.e15.
152. Herlenius G, Wilczek HE, Larsson M, et al. Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. Transplantation 2004; 77:64.
153. Tsuchiya A, Yazaki M, Kametani F, et al. Marked regression of abdominal fat amyloid in patients with familial amyloid polyneuropathy during long-term follow-up after liver transplantation. Liver Transpl 2008; 14:563.
154. Benson MD. Liver transplantation and transthyretin amyloidosis. Muscle Nerve 2013; 47:157.
155. Rizvi SSA, Challapalli J, Maynes EJ, et al. Indications and outcomes of combined heart-liver transplant: A systematic review and met-analysis. Transplant Rev (Orlando) 2020; 34:100517.
156. Meyer L, Ulrich M, Ducloux D, et al. Organ Transplantation in Hereditary Fibrinogen A α-Chain Amyloidosis: A Case Series of French Patients. Am J Kidney Dis 2020; 76:384.
157. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med 2018; 379:11.
158. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med 2018; 379:22.

159. FULL PRESCRIBING INFORMATION for AMVUTTRA (vutrisiran) injection, for subcutaneous use. Initial U.S. Approval: 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215515s000lbl.pdf (Accessed on June 15, 2022).
160. Coelho T, Adams D, Silva A, et al. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. N Engl J Med 2013; 369:819.
161. Suhr OB, Coelho T, Buades J, et al. Efficacy and safety of patisiran for familial amyloidotic polyneuropathy: a phase II multi-dose study. Orphanet J Rare Dis 2015; 10:109.
162. Ackermann EJ, Guo S, Benson MD, et al. Suppressing transthyretin production in mice, monkeys and humans using 2nd-Generation antisense oligonucleotides. Amyloid 2016; 23:148.
163. Brannagan TH, Wang AK, Coelho T, et al. Early data on long-term efficacy and safety of inotersen in patients with hereditary transthyretin amyloidosis: a 2-year update from the open-label extension of the NEURO-TTR trial. Eur J Neurol 2020; 27:1374.
164. Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology 2012; 79:785.
165. Coelho T, Maia LF, da Silva AM, et al. Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy. J Neurol 2013; 260:2802.
166. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. JAMA 2013; 310:2658.
167. Judge DP, Heitner SB, Falk RH, et al. Transthyretin Stabilization by AG10 in Symptomatic Transthyretin Amyloid Cardiomyopathy. J Am Coll Cardiol 2019; 74:285.
168. Sant'Anna R, Gallego P, Robinson LZ, et al. Repositioning tolcapone as a potent inhibitor of transthyretin amyloidogenesis and associated cellular toxicity. Nat Commun 2016; 7:10787.
169. Pinheiro F, Varejão N, Esperante S, et al. Tolcapone, a potent aggregation inhibitor for the treatment of familial leptomeningeal amyloidosis. FEBS J 2021; 288:310.
170. Dohrn MF, Ihne S, Hegenbart U, et al. Targeting transthyretin - Mechanism-based treatment approaches and future perspectives in hereditary amyloidosis. J Neurochem 2021; 156:802.
171. Gillmore JD, Gane E, Taubel J, et al. CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis. N Engl J Med 2021; 385:493.

172. Kolstoe SE, Wood SP. Drug targets for amyloidosis. Biochem Soc Trans 2010; 38:466.
173. Merlini G, Seldin DC, Gertz MA. Amyloidosis: pathogenesis and new therapeutic options. J Clin Oncol 2011; 29:1924.
174. De Genst E, Messer A, Dobson CM. Antibodies and protein misfolding: From structural research tools to therapeutic strategies. Biochim Biophys Acta 2014; 1844:1907.
175. Ankarcrona M, Winblad B, Monteiro C, et al. Current and future treatment of amyloid diseases. J Intern Med 2016; 280:177.
176. Morgan GJ, Yan NL, Mortenson DE, et al. Stabilization of amyloidogenic immunoglobulin light chains by small molecules. Proc Natl Acad Sci U S A 2019; 116:8360.
177. Finn JD, Smith AR, Patel MC, et al. A Single Administration of CRISPR/Cas9 Lipid Nanoparticles Achieves Robust and Persistent In Vivo Genome Editing. Cell Rep 2018; 22:2227.
178. Gorevic PD. Amyloid and inflammation. Proc Natl Acad Sci U S A 2013; 110:16291.
179. Phipps JE, Kestler DP, Foster JS, et al. Inhibition of pathologic immunoglobulin-free light chain production by small interfering RNA molecules. Exp Hematol 2010; 38:1006.
180. Wang W, Khatua P, Hansmann UHE. Cleavage, Downregulation, and Aggregation of Serum Amyloid A. J Phys Chem B 2020; 124:1009.
181. Dasari AKR, Arreola J, Michael B, et al. Disruption of the CD Loop by Enzymatic Cleavage Promotes the Formation of Toxic Transthyretin Oligomers through a Common Transthyretin Misfolding Pathway. Biochemistry 2020; 59:2319.
182. Bergström J, Gustavsson A, Hellman U, et al. Amyloid deposits in transthyretin-derived amyloidosis: cleaved transthyretin is associated with distinct amyloid morphology. J Pathol 2005; 206:224.
183. Enqvist S, Sletten K, Westermark P. Fibril protein fragmentation pattern in systemic AL-amyloidosis. J Pathol 2009; 219:473.
184. Wolfe MS. Probing Mechanisms and Therapeutic Potential of γ-Secretase in Alzheimer's Disease. Molecules 2021; 26.
185. Giorgino T, Mattioni D, Hassan A, et al. Nanobody interaction unveils structure, dynamics and proteotoxicity of the Finnish-type amyloidogenic gelsolin variant. Biochim Biophys Acta Mol Basis Dis 2019; 1865:648.
186. Franklin EC, Zucker-Franklin D. Antisera specific for human amyloid reactive with conformational antigens. Proc Soc Exp Biol Med 1972; 140:565.

187. O'Nuallain B, Wetzel R. Conformational Abs recognizing a generic amyloid fibril epitope. Proc Natl Acad Sci U S A 2002; 99:1485.
188. Sigurdsson EM, Wisniewski T, Frangione B. A safer vaccine for Alzheimer's disease? Neurobiol Aging 2002; 23:1001.
189. Zampar S, Wirths O. Immunotherapy targeting amyloid-β peptides in Alzheimer's disease. In: Alzheimer's Disease: Drug Discovery, Huang X (Ed), Exon Publications, 2020.
190. Sigurdsson EM. Tau Immunotherapies for Alzheimer's Disease and Related Tauopathies: Progress and Potential Pitfalls. J Alzheimers Dis 2018; 64:S555.
191. Garcia-Pavia P, Aus dem Siepen F, Donal E, et al. Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid. N Engl J Med 2023; 389:239.
192. Hosoi A, Su Y, Torikai M, et al. Novel Antibody for the Treatment of Transthyretin Amyloidosis. J Biol Chem 2016; 291:25096.
193. Goldsteins G, Persson H, Andersson K, et al. Exposure of cryptic epitopes on transthyretin only in amyloid and in amyloidogenic mutants. Proc Natl Acad Sci U S A 1999; 96:3108.
194. Pepys MB, Herbert J, Hutchinson WL, et al. Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. Nature 2002; 417:254.
195. Bodin K, Ellmerich S, Kahan MC, et al. Antibodies to human serum amyloid P component eliminate visceral amyloid deposits. Nature 2010; 468:93.
196. Gillmore JD, Tennent GA, Hutchinson WL, et al. Sustained pharmacological depletion of serum amyloid P component in patients with systemic amyloidosis. Br J Haematol 2010; 148:760.
197. Richards DB, Cookson LM, Berges AC, et al. Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component. N Engl J Med 2015; 373:1106.
198. Richards DB, Cookson LM, Barton SV, et al. Repeat doses of antibody to serum amyloid P component clear amyloid deposits in patients with systemic amyloidosis. Sci Transl Med 2018; 10.
199. Stoilova T, Colombo L, Forloni G, et al. A new face for old antibiotics: tetracyclines in treatment of amyloidoses. J Med Chem 2013; 56:5987.
200. Cappelli F, Martone R, Taborchi G, et al. Epigallocatechin-3-gallate tolerability and impact on survival in a cohort of patients with transthyretin-related cardiac amyloidosis. A single-center retrospective study. Intern Emerg Med 2018; 13:873.

201. Zaidi FK, Bhat R. Two polyphenols with diverse mechanisms towards amyloidosis: differential modulation of the fibrillation pathway of human lysozyme by curcumin and EGCG. J Biomol Struct Dyn 2022; 40:4593.

Topic 5589 Version 47.0

Chapter 2

CLINICAL PRESENTATION, LABORATORY MANIFESTATIONS, AND DIAGNOSIS OF IMMUNOGLOBULIN LIGHT CHAIN (AL) AMYLOIDOSIS

Author:Angela Dispenzieri, MD
Section Editors:S Vincent Rajkumar, MD, Richard J Glassock, MD, MACP
Deputy Editor:Rebecca F Connor, MD
Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Aug 2023. This topic last updated: Apr 14, 2022.

INTRODUCTIONAmyloidosis is a generic term that refers to the extracellular tissue deposition of fibrils composed of subunits of a variety of normal serum proteins. These fibrils have a predominantly antiparallel beta-pleated sheet configuration (noted on x-ray diffraction), and can be identified on biopsy specimens both by their characteristic appearance on electron microscopy and by their ability to bind Congo red (leading to green birefringence under polarized light) and thioflavine T (producing an intense yellow-green fluorescence).

More than 30 distinct low molecular weight proteins are recognized to form amyloid fibrils. The four most common causes of systemic amyloid deposition are:

●Immunoglobulin light chain (AL) amyloidosis (historically referred to as primary amyloidosis) in which the fibrils are composed of fragments of monoclonal light chains. Affected patients may have amyloidosis alone or in association with other plasma cell dyscrasias (multiple myeloma, Waldenström macroglobulinemia). All forms of systemic amyloidosis in which the fibrils are derived from monoclonal light chains, regardless of the nature of the underlying plasma cell disorder (eg, monoclonal gammopathy of undetermined significance, multiple myeloma, or Waldenström macroglobulinemia) are considered AL amyloidosis.

●Wild type transthyretin amyloidosis (ATTRwt, historically referred to as age-related [senile] amyloidosis) typically involves the heart and causes a restrictive cardiomyopathy. It is caused by deposition of normal unmutated transthyretin

(TTR), which appears to be an inherently amyloidogenic protein. (See "Overview of amyloidosis", section on 'Wild-type transthyretin systemic amyloidosis'.)

●Hereditary (familial) amyloidosis (ATTRmt) are the result of mutations in genes coding for several different proteins that are normally present in the body. The most common "amyloidogenic proteins" implicated in hereditary amyloidosis are mutated forms of TTR, the alpha chain of fibrinogen A, apolipoprotein AI and AII, lysozyme, and gelsolin. (See "Genetic factors in the amyloid diseases".)

●AA amyloidosis in which the fibrils are composed of fragments of the acute phase reactant serum amyloid A. AA amyloidosis is typically reactive (secondary) to chronic inflammation. (See "Pathogenesis of AA amyloidosis".)

Because AL amyloidosis is a clonal plasma cell disorder, it is treated with chemotherapy to eradicate the underlying clone. AL amyloidosis must be differentiated from other forms of amyloidosis (eg, AA amyloidosis, ATTRmt amyloidosis, and ATTRwt amyloidosis) since the latter are non-neoplastic and will not benefit from chemotherapy.

AL amyloidosis is a systemic disorder that can present with a variety of symptoms or signs, including heavy proteinuria (usually in the nephrotic range), edema, hepatosplenomegaly, otherwise unexplained heart failure, and the carpal tunnel syndrome. Although virtually all patients have multisystem amyloid deposition, it is not uncommon to present with evidence of mainly one organ being affected. (See "Renal amyloidosis" and "Gastrointestinal amyloidosis: Clinical manifestations, diagnosis, and management" and "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis".)

The clinical presentation, diagnosis, and differential diagnosis of AL amyloidosis will be discussed here. An overview of the amyloid disorders as well as the pathogenesis, prognosis, and treatment of AL amyloidosis are presented separately.

●(See "Overview of amyloidosis".)

●(See "Monoclonal immunoglobulin deposition disease".)

●(See "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis".)

EPIDEMIOLOGYAL amyloidosis is an uncommon disorder and the exact incidence is unknown. In the United States, the incidence appears to be stable at approximately 9 to 14 cases per million person-years [1-3].

AL amyloidosis is a disease of older adults. As with other plasma cell dyscrasias, the age-specific incidence rates increase in each decade of life after age 40 years [1]. The median age at diagnosis is 64 years, and less than 5 percent of patients are under the age of 40 [4-8]. There is a male predominance with men accounting for 65 to 70 percent of patients.

AL amyloidosis occurs in all races and all geographic locations; however, there are few data regarding whether the incidence varies by ethnicity or geography.

Relation to other plasma cell disorders — Some patients who ultimately show clinical evidence of AL amyloidosis present with what appeared to be monoclonal gammopathy of undetermined significance (MGUS). Once a diagnosis of AL amyloidosis is made, such patients are no longer considered to have MGUS. Over time, a small number of patients with MGUS eventually develop symptoms or signs of AL amyloidosis, multiple myeloma (MM), or Waldenström macroglobulinemia (WM), at a rate of approximately 1 percent per year [9]. (See "Clinical course and management of monoclonal gammopathy of undetermined significance", section on 'Disease progression'.)

AL amyloidosis can also occur in patients with other plasma cell dyscrasias, including MM and WM, which are malignant disorders of plasma cells or lymphoplasmacytic cells, respectively. Less frequently, AL amyloidosis may be associated with marginal zone lymphoma or another non-Hodgkin lymphoma subtype [10].

When MM and AL amyloidosis are diagnosed in the same patient, the myeloma is typically diagnosed before or around the time of the amyloidosis diagnosis. Less commonly, myeloma develops more than six months after the diagnosis of amyloidosis (delayed progression):

●In a series of 1596 patients with AL amyloidosis seen at the Mayo Clinic between 1960 and 1994, only six (0.4 percent) showed delayed progression (at 10 to 81 months) to overt myeloma [11]. This usually occurred in patients without cardiac or hepatic amyloidosis who lived long enough to develop myeloma.

●In a series of 4319 patients seen at the Mayo Clinic between 1990 and 2008 with a diagnosis of myeloma who had at least six months of follow-up, there were 47 patients (1.1 percent) in whom the diagnosis of AL amyloidosis followed the diagnosis of myeloma by at least six months [12]. Outcome of these patients was poor, especially in those with cardiac involvement, with a median survival after the diagnosis of AL amyloidosis of nine months (95% CI 4-14 months).

In patients with AL amyloidosis, hypercalcemia, bone pain, or lytic bone lesions is suggestive of the combination of clinical myeloma and amyloidosis. The diagnosis of coexisting MM is reserved for patients with amyloidosis who would otherwise meet diagnostic criteria for MM, usually with clonal bone marrow plasmacytosis ≥10 percent and one or more myeloma-defining events (MDEs) such as osteolytic bone lesions [13]. (See "Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis", section on 'Diagnostic criteria'.)

Although AL amyloidosis is not an MDE, outcomes of patients with AL amyloidosis who have clonal bone marrow plasmacytosis ≥10 percent are comparable to patients meeting criteria for coexisting MM due to the presence of MDEs [14]. Therefore, such patients with AL amyloidosis without clinical myeloma who have a higher plasma cell burden (≥10 percent) should be managed more intensively than their low tumor burden counterparts. Although typical myeloma regimens are often not well tolerated in patients with AL amyloidosis, induction and maintenance strategies should be considered for those who meet the current criteria for coexistent myeloma.

CLINICAL PRESENTATION

Systemic presentations — The clinical presentation in AL amyloidosis depends on the number and nature of the organs affected. In some patients only one organ is affected, while in others there is extensive multi-system involvement. However, even in patients with more than one organ affected, it is usually possible to identify one organ as the "dominant" site of involvement. A more complete overview of the clinical manifestations of amyloidosis in general can be found elsewhere. (See "Overview of amyloidosis", section on 'Clinical manifestations'.)

Non-specific systemic symptoms, including fatigue and unintentional weight loss, are common in patients with AL amyloidosis [15]. Other common clinical presentations of AL amyloidosis include the following:

●**Nephrotic syndrome** – Renal involvement occurs in approximately 70 percent of patients and most often presents as asymptomatic proteinuria or clinically apparent nephrotic syndrome (50 percent). (See "Renal amyloidosis".)

●**Restrictive cardiomyopathy** – Cardiac involvement is seen in approximately 60 percent of patients and is typically characterized by thickening of the interventricular septum and ventricular wall (movie 1). This can lead to systolic or diastolic dysfunction and the symptoms of heart failure. Other manifestations that can occur include sudden death or syncope due to arrhythmia or heart block, and rarely angina or infarction due to accumulation of amyloid in the coronary arteries. Elevations in N-terminal serum brain natriuretic peptide (BNP) in patients with AL amyloidosis are seen before the onset of clinical heart failure and are a marker of cardiac involvement. (See "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis".)

●**Peripheral neuropathy** – Mixed sensory and motor peripheral neuropathy (20 percent) and/or autonomic neuropathy (15 percent) is a prominent feature in AL amyloidosis. Symptoms of numbness, paresthesia, and pain are frequently noted, as in peripheral neuropathy of many other causes. Compression of peripheral nerves, especially the median nerve within the carpal tunnel, can cause more localized sensory changes. Symptoms of bowel or bladder dysfunction and findings of orthostatic hypotension may be due to autonomic nervous system damage.

●**Hepatomegaly, with elevated liver enzyme levels** – Hepatomegaly with or without splenomegaly is seen in as many as 70 percent of patients. A cholestatic pattern with elevated liver enzymes is seen in approximately 25 percent. Clinical gastrointestinal involvement appears to be less common than in other forms of amyloidosis, with clinically apparent disease occurring in only 1 percent of patients [16]. Because amyloidosis is a systemic disease, rates of positive gastrointestinal biopsies are much higher; in days past, rectal biopsy was considered a safe and simple method of diagnosing systemic amyloidosis with a sensitivity of 75 percent [15]. For symptomatic patients potential gastrointestinal manifestations include bleeding (due to vascular fragility and loss of vasomotor responses to injury), gastroparesis, constipation, bacterial overgrowth, malabsorption, and intestinal pseudo-obstruction resulting from dysmotility. (See "Gastrointestinal amyloidosis: Clinical manifestations, diagnosis, and management".)

●**Macroglossia and involvement of other muscles** – Amyloid infiltration of skeletal muscles may cause visible enlargement (ie, pseudohypertrophy). A large tongue (ie, macroglossia), or lateral scalloping of the tongue from impingement on

the teeth, is characteristic of AL amyloidosis (picture 1). Arthropathy may be due to amyloid deposition in joints and surrounding structures. The "shoulder pad" sign is visible enlargement of the anterior shoulder due to fluid in the glenohumeral joint and/or amyloid infiltration of the synovial membrane and surrounding structures. (See "Musculoskeletal manifestations of amyloidosis", section on 'Muscle involvement in AL amyloid'.)

●**Purpura and other skin manifestations** – Purpura, characteristically elicited in a periorbital distribution (raccoon eyes) by a Valsalva maneuver or minor trauma, is present in only a minority of patients, but is highly characteristic of AL amyloidosis (picture 2) [17]. Other signs of skin involvement include waxy thickening, easy bruising (ecchymoses) (picture 3), and subcutaneous nodules or plaques. Infiltration of the subcutaneous fat is generally asymptomatic but provides a convenient site for biopsy.

●**Bleeding diathesis** – Amyloidosis may be directly associated with a bleeding diathesis [18-22]. In one report of 337 patients, abnormal bleeding and abnormal coagulation tests were seen in 28 and 51 percent, respectively [19]. Proposed mechanisms include factor X deficiency due to binding to amyloid fibrils primarily in the liver and spleen; decreased synthesis of coagulation factors in patients with advanced liver disease; and acquired von Willebrand disease. However, some patients with abnormal bleeding have no abnormality in any coagulation test [18]. In such patients, amyloid infiltration of blood vessels may contribute to the bleeding diathesis. (See "Acquired von Willebrand syndrome" and "Pathophysiology of von Willebrand disease", section on 'Causes of reduced VWF in acquired VWS'.)

Nearly 10 percent of patients will have clinical manifestations of coexisting MM characterized by anemia, hypercalcemia, and/or lytic bone lesions [14]. Such patients may present with signs and symptoms related to the MM, such as bone pain and infection. (See 'Relation to other plasma cell disorders' above and "Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis", section on 'Clinical presentation'.)

IgM-associated AL amyloidosis — AL amyloidosis is an uncommon complication of immunoglobulin M (IgM)-associated monoclonal gammopathies, such as Waldenström macroglobulinemia [23-28]. IgM-related AL amyloidosis appears to be a distinct clinical entity with less cardiac involvement and a higher incidence of lymph node and soft tissue involvement (eg, liver damage, peripheral and autonomic neuropathy) when compared with non-IgM-related AL amyloidosis. (See

"Epidemiology, pathogenesis, clinical manifestations, and diagnosis of Waldenström macroglobulinemia", section on 'Amyloidosis'.)

In the largest retrospective study, 131 of 250 patients with IgM-associated systemic AL amyloidosis had a clearly identified lymphoproliferative disorder, 39 of which predated the amyloidosis diagnosis [27]. The most common identified conditions were lymphoplasmacytic lymphoma and non-Hodgkin lymphoma, not specifically classified. Rare cases of associated chronic lymphocytic leukemia and follicular lymphoma were seen. The involved light chain was kappa in 40 percent. The most commonly involved organs were:

●Kidney (68 percent)

●Soft tissue (35 percent, including lymph nodes in 20 percent)

●Liver (17 percent)

●Peripheral nervous system (15 percent)

●Autonomic nervous system (13 percent)

●Gastrointestinal system (9 percent)

On multivariate analysis, adverse prognostic features included older age, high NT-proBNP, elevated troponin T, liver involvement, and the presence of neuropathy. These features were combined into a novel prognostic score.

IgD-associated AL amyloidosis — It is extremely rare for patients with AL amyloidosis to have a monoclonal immunoglobulin D (IgD) at the time of diagnosis. The largest single center retrospective case series of 3955 patients with Ig light chain amyloidosis identified 53 patients (1.3 percent) with a serum IgD monoclonal protein [29]. When compared with non-IgD AL amyloidosis, patients appeared to have a lower frequency of renal and cardiac involvement. At the time of presentation, the most common signs and symptoms were fatigue (60 percent), lower extremity edema (43 percent), paresthesias (32 percent), weight loss (32 percent), dyspnea on exertion (28 percent), and carpal tunnel syndrome (26 percent). Survival appeared similar to that of non-IgD AL amyloidosis.

PATHOLOGIC FEATURES

Tissue biopsy

Choosing a biopsy site — The diagnosis of AL amyloidosis requires the demonstration of amyloid fibrils upon histologic evaluation of an affected organ (eg, kidney, liver) or a surrogate site (eg, abdominal fat pad, bone marrow). We suggest initial evaluation with an abdominal fat pad aspirate and bone marrow biopsy because of their ease, convenience, and high yield (algorithm 1). Either or both are positive in 90 percent of patients with AL amyloidosis. If AL amyloidosis is still suspected in the setting of negative fat pad aspirate and bone marrow biopsy, then the affected organ should be biopsied.

The choice of initial biopsy site must take into consideration the expected yield, accessibility of the site, and the risks associated with the procedure. Kidney or liver biopsy is positive in over 90 percent of cases; however, a high success rate can also be achieved by less invasive procedures, such as abdominal fat pad aspirate (60 to 80 percent), rectal biopsy (50 to 70 percent), bone marrow biopsy (50 to 55 percent), or skin biopsy (50 percent) [15,30-33].

We do not perform gingival biopsy because it is uncomfortable for the patient, and skin biopsies are generally negative unless there is clinical involvement or if a considerable amount of fat is taken with the skin. In addition, some patients have a bleeding diathesis (eg, acquired factor X deficiency), which may limit the safety of biopsy of major internal organs. (See "Overview of amyloidosis", section on 'Hematologic abnormalities'.)

Identifying amyloid — On hematoxylin- and eosin-stained biopsy sections, amyloid appears as a pink, amorphous, waxy substance with a characteristic 'cracking' artifact (picture 4) [34]. The presence of amyloid fibrils can be confirmed by their characteristic appearance on electron microscopy (picture 5) and by their ability to bind Congo red (leading to green birefringence under polarized light) (picture 6A-B) or thioflavine-T (producing an intense yellow-green fluorescence) [35]. The estimated sensitivity and specificity of Congo red staining on light microscopy for amyloid are 79 and 80 percent, respectively [36]. The sensitivity for kappa (74 percent) is lower than that for lambda (84 percent). Of importance, biopsy sections that are very thin (ie, 6 microns or less) may not stain appropriately with Congo red despite the presence of amyloid fibrils on electron microscopy.

Determining the type of amyloid — Once the histologic diagnosis of amyloid is made (typically based on the Congo red stain), there are a number of laboratory and histologic findings that may distinguish AL amyloidosis from other forms of

amyloidosis on tissue specimens. Mass spectrometry is the preferred method since immunohistochemistry and immunofluorescence have a greater risk of false positive and false negative results. However, this test is not widely available, and appropriate tissue samples need to be sent to referral centers for such testing. If available, immunoelectron microscopy is an acceptable alternative to mass spectrometry.

The following describes the use of each of these methods:

●Laser microdissection with mass spectrometry (MS) combines tissue sampling by laser microdissection along with tandem mass spectrometry-based proteomic analysis [37-40]. This technique is able to efficiently and accurately identify all types of amyloid, including rare subtypes, with 100 percent specificity [8]. In a study of 50 cases of amyloidosis well-characterized by gold standard clinicopathologic criteria (training set) and an independent validation set comprising 41 cases of cardiac amyloidosis, this technique identified the amyloid type with 100 percent specificity and sensitivity in the training set and 98 percent in the validation set [37].

●Immunohistochemical staining (eg, for kappa and lambda light chains, transthyretin, and serum amyloid A component) of the amyloid can determine the type of amyloidosis [41]. Positive staining for kappa or lambda indicates AL amyloidosis; positive staining for transthyretin indicates hereditary or wild type transthyretin (ATTRmt or ATTRwt) amyloidosis; positive staining for serum amyloid A component occurs with secondary (AA) amyloidosis. However, immunohistochemical staining should only be done at centers with considerable expertise with the antibodies since false negatives and false positives are common in inexperienced hands.

●Immunoelectron microscopy combines immunohistochemistry and electron microscopy to confirm amyloid deposition and identify the protein within the amyloid fibrils. In one study, when compared with Congo red staining, immunoelectron microscopy had similar sensitivity (76 percent) and higher specificity (100 percent) for amyloid [36]. The sensitivity for kappa (71 percent) was lower than for lambda (83 percent).

●Immunofluorescence microscopy in the kidney or other affected tissue (picture 7) may show deposition of a monoclonal (lambda or kappa) light chain in AL amyloidosis, although some have reported a low sensitivity with renal biopsies (65 percent in one series) [42]. Immunofluorescence using light-chain specific antisera

and other specialized techniques can also be used with other tissue specimens to help diagnose AL amyloidosis (picture 8) [43,44].

Chromosomal changes — Patients with AL amyloidosis frequently have chromosomal abnormalities, but there is no single chromosomal change that is diagnostic of this disease. The monotypic plasma cell population in the bone marrow has elements of a neoplastic nature as shown by the frequent finding of numerical chromosomal abnormalities. In a study of bone marrow samples with fluorescence in situ hybridization (FISH) from 21 patients with AL amyloidosis, monosomy of chromosome 18 was the most common abnormality, occurring in 72 percent of cases, but trisomy of a variety of chromosomes was also common [45]. Similar prevalences were found in 19 patients with monoclonal gammopathy of undetermined significance (MGUS). (See "Diagnosis of monoclonal gammopathy of undetermined significance".)

When a myeloma FISH panel is applied to patients with AL amyloidosis, t(11;14)(q13;q32) is the most common abnormality, seen in nearly 50 percent of patients; other commonly seen abnormalities include del(13q14) and gain of 1q21 [46-50]. High-risk FISH abnormalities (eg, 17p13 deletion) are distinctively uncommon. (See "Multiple myeloma: Pathobiology", section on 'Cytogenetic abnormalities' and "Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis", section on 'Cytogenetics'.)

Evidence of monoclonal plasma cells — The diagnosis of AL amyloidosis requires evidence of a monoclonal plasma cell proliferative disorder as displayed by the presence of a serum or urine monoclonal (M) protein, an abnormal serum free light chain ratio, or clonal plasma cells in the bone marrow.

A monoclonal plasma cell proliferative disorder can be assumed if an M protein is detected in the serum or urine. The M protein in AL amyloidosis is IgG in approximately 35 percent, IgA in 10 percent, IgM in 5 percent, IgD in 1 percent, and light chain (lambda or kappa) in the remaining patients [51]. Most patients with AL amyloidosis have little or no intact monoclonal immunoglobulin, but are characterized by the presence of monoclonal free light chain. The monoclonal light chain type is lambda in approximately 70 percent of cases, kappa in 25 percent, and biclonal in 5 percent [52]. Evaluation with serum and urine immunofixation plus a serum free light chain ratio analysis provides the most sensitive measure for this M protein:

●Serum protein electrophoresis (SPEP), which detects intact monoclonal immunoglobulin, will demonstrate a localized band or peak in less than 50 percent of patients with AL amyloidosis. (See "Laboratory methods for analyzing monoclonal proteins", section on 'Serum protein electrophoresis (SPEP)'.)

●Immunofixation techniques designed to identify light chains will detect a serum or urinary M protein in nearly 90 percent of cases of AL amyloidosis [7]. Of importance, a subset of patients has very small M protein levels that may only be detected by immunofixation (eg, monoclonal IgD) [29]. (See "Laboratory methods for analyzing monoclonal proteins", section on 'Serum immunofixation'.)

●When serum and urine immunofixation is combined with serum free light chain ratio analysis, an M protein can be detected in virtually all cases [7,52]. (See "Laboratory methods for analyzing monoclonal proteins", section on 'Serum free light chains'.)

Clonal plasma cells can also be identified in the bone marrow. Bone marrow biopsy specimens typically demonstrate a slightly increased percentage of plasma cells that may appear morphologically normal [34]. Less commonly, the bone marrow demonstrates overt myeloma or lymphoplasmacytic lymphoma. A clonal excess of plasma cells (lambda or kappa) can also be demonstrated by immunoperoxidase staining or flow cytometric analysis of specimens of involved bone marrow (picture 7) [53,54]. However, a monoclonal plasma cell staining pattern typical of AL amyloidosis may be missed if the clone is small and masked by normal polyclonal plasma cells.

IMAGING

Serum amyloid P component scintigraphy — Serum amyloid P component (SAP) scintigraphy is a method of measuring the extent of amyloid involvement by using a radiolabeled variant of the SAP found in all amyloid deposits [55,56]. Tissue amyloid deposits are identified by scintigraphy following the intravenous injection of technetium-labeled SAP [57,58]. This test is more accurate in secondary amyloidosis [59] and may be positive even when tissue biopsy has been negative [55].

The value of SAP scintigraphy is limited because it is inconvenient, costly, not widely available, and is less helpful in detecting cardiac amyloidosis. Another limitation is that the SAP is currently obtained from blood donors, thereby carrying a potential infectious risk.

DIAGNOSIS

Evaluation — AL amyloidosis is suspected in a patient presenting with any one of the following (algorithm 1):

●Non-diabetic nephrotic range proteinuria

●Restrictive cardiomyopathy or otherwise unexplained congestive heart failure

●Increased NT-proBNP in the absence of known primary heart disease

●Unexplained edema, hepatosplenomegaly, or carpal tunnel syndrome

●Unexplained facial or neck purpura

●Macroglossia

The initial evaluation of a patient suspected of having AL amyloidosis should consist of serum and urine protein electrophoresis with immunofixation, serum free light chain ratio analysis, and an abdominal fat pad aspirate and bone marrow biopsy [60]. (See 'Choosing a biopsy site' above.)

If AL amyloidosis is still suspected in the setting of negative fat pad aspirate and bone marrow biopsy, then the affected organ (eg, kidney, liver) should be biopsied. Some patients have a bleeding diathesis, which may limit the safety of biopsy of major internal organs. (See "Overview of amyloidosis", section on 'Hematologic abnormalities'.)

The following tests are performed to assess for clinical organ involvement:

●Kidney – 24-hour urine for protein electrophoresis, creatinine, estimated glomerular filtration rate, and serum albumin.

●Heart – Troponin T, NT-proBNP, echocardiography, and electrocardiogram.

●Liver – Alkaline phosphatase; if involvement is suspected clinically, ultrasound or computed tomography to assess liver size.

●Coagulation system – Factor X levels; alternatively, clinicians may choose to check prothrombin time (PT) and partial thromboplastin time (PTT) with plans to check factor X levels in patients with abnormal bleeding or abnormal testing.

●Neuropathy – Patients with neurologic symptoms should be evaluated with electromyography (EMG) and nerve conduction studies. Since the neuropathy is most typically a small fiber neuropathy, these tests are often normal despite patient's complaint of paresthesia or dysesthesia.

Additional testing is performed after diagnosis as part of the pretreatment evaluation. This described in more detail separately. (See "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis", section on 'Pretreatment evaluation'.)

Diagnostic criteria — Diagnostic criteria for AL amyloidosis have been developed by the Mayo Clinic and the International Myeloma Working Group and require the presence of **all** of the following four criteria (table 1) [13,61,62]:

●Presence of an amyloid-related systemic syndrome (eg, renal, liver, heart, gastrointestinal tract or peripheral nerve involvement). In order to be included as a diagnostic criterion, the organ damage must be felt to be related to amyloid deposition and not to another common disease, such as diabetes or hypertension. (See 'Systemic presentations' above.)

●Positive amyloid staining by Congo red in any tissue (eg, fat aspirate, bone marrow or organ biopsy) or the presence of amyloid fibrils on electron microscopy. (See 'Identifying amyloid' above.)

●Evidence that the amyloid is light chain-related established by direct examination of the amyloid using spectrometry-based proteomic analysis or immunoelectron microscopy. (See 'Determining the type of amyloid' above.)

●Evidence of a monoclonal plasma cell proliferative disorder (eg, presence of a serum or urine M protein, abnormal serum free light chain ratio, or clonal plasma cells in the bone marrow). (See "Laboratory methods for analyzing monoclonal proteins", section on 'Serum free light chains'.)

Approximately 2 to 3 percent of patients with AL amyloidosis will **not** meet the requirement for evidence of a monoclonal plasma cell disorder listed above; the diagnosis of AL amyloidosis must be made with caution in these patients.

Given the common occurrence of monoclonal gammopathy of undetermined significance (MGUS) in the general population, especially in the elderly, the presence of a monoclonal protein in conjunction with the demonstration of amyloid deposition may not always indicate that the amyloidosis is of the AL type. As an example, a patient may have wild type transthyretin amyloidosis and a concomitant unrelated MGUS, which can be potentially misdiagnosed as AL amyloidosis. As such, the amyloid itself should be examined directly for light chains rather than assuming a diagnosis of AL amyloidosis based on the presence of monoclonal light chains in the serum of a patient with amyloidosis. (See "Diagnosis of monoclonal gammopathy of undetermined significance".)

Patients with AL amyloidosis who have hypercalcemia, bone pain, or lytic bone lesions should be evaluated for coexisting multiple myeloma. (See 'Relation to other plasma cell disorders' above and "Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis", section on 'Evaluation'.)

DIFFERENTIAL DIAGNOSISAL amyloidosis should be distinguished from other forms of amyloidosis, from localized amyloidosis, and from other types of monoclonal immunoglobulin deposition diseases, because the clinical course and therapy are markedly different.

Other forms of amyloidosis — Other forms of amyloidosis include wild type transthyretin amyloidosis, hereditary amyloidosis, and AA amyloidosis. All of these entities will demonstrate staining with Congo red (a characteristic of amyloid), but direct examination of the amyloid material will not reveal immunoglobulin light chains (as seen in AL amyloidosis). A diagnosis of AL amyloidosis cannot be assumed based on the presence of monoclonal light chains in the serum of a patient with amyloid since it is not uncommon for a patient with another form of amyloid to have a concomitant and unrelated monoclonal gammopathy of undetermined significance (MGUS).

ATTRwt amyloidosis (age-related amyloidosis) — Wild type transthyretin amyloidosis (ATTRwt) refers to the deposition of otherwise normal (wild-type) transthyretin (TTR) in the myocardium and other sites of older adults [63,64]. ATTRwt has historically been referred to as age-related or senile amyloidosis. Patients may present with heart failure or an arrhythmia. Recognition is important because survival is better than with AL amyloidosis, and chemotherapy or hematopoietic cell transplantation are contraindicated. Unlike AL amyloidosis, direct examination of the amyloid material in ATTRwt does not reveal

immunoglobulin light chains, but rather reveals TTR deposits. (See "Overview of amyloidosis", section on 'Wild-type transthyretin systemic amyloidosis'.)

Hereditary (familial) amyloidosis — Heritable, autosomal dominant amyloidosis results from mutations in genes coding for several different proteins. The most common "amyloidogenic proteins" implicated in hereditary amyloidosis are mutated forms of transthyretin (TTR), the alpha chain of fibrinogen A, apolipoprotein AI and AII, lysozyme, and gelsolin. Hereditary systemic AL amyloidosis not due to a plasma cell dyscrasia has been described in one family [65].

Sporadic cases of hereditary amyloidosis may be confused with AL amyloidosis, and diagnosis requires careful assessment to determine the chemical nature of the amyloid deposits by mass spectroscopy. The frequency with which this might occur was illustrated in a study of 350 patients suspected of having AL amyloidosis by clinical and laboratory findings and the absence of a family history; 34 (9.7 percent) had a mutant gene for an "amyloidogenic" protein, most often involving the alpha chain of fibrinogen A or transthyretin [66]. The presence of low concentrations of monoclonal immunoglobulins (less than 0.2 g/dL) in 8 of these 34 patients may have contributed to the misdiagnosis. (See "Genetic factors in the amyloid diseases".)

A thorough family history and exclusion of these heritable disorders is important, since the treatment used in AL amyloidosis (eg, chemotherapy, hematopoietic cell transplantation) has no role in the treatment of the hereditary amyloidoses, and is dangerous. Unlike AL amyloidosis, direct examination of the amyloid material in hereditary amyloidosis does not reveal immunoglobulin light chains. (See "Overview of amyloidosis", section on 'Diagnosis'.)

AA amyloidosis — AA amyloidosis (previously referred to as secondary amyloidosis) occurs as a complication of a variety of chronic inflammatory conditions, such as rheumatoid arthritis and its variants, bronchiectasis, Crohn's disease and other inflammatory bowel diseases, osteomyelitis, and familial Mediterranean fever. Inflammation leads to increased hepatic production of the acute phase reactant serum amyloid A, which is then degraded in circulating macrophages into smaller amyloid A fragments that are then deposited as fibrils in the tissues. A distinction between AA amyloidosis and AL amyloidosis can be made based on the identification of immunoglobulin light chains upon the direct examination of the amyloid material in AL amyloidosis, a feature that is not seen in

secondary amyloidosis. (See "Pathogenesis of AA amyloidosis" and "Causes and diagnosis of AA amyloidosis and relation to rheumatic diseases".)

A diagnosis of AL amyloidosis cannot be assumed based on the presence of monoclonal light chains in the serum of a patient with amyloid since it is not uncommon for a patient with other forms of amyloidosis to have a concomitant and unrelated MGUS.

Localized amyloidosis — Localized amyloidosis is the term used for local amyloid deposits in tissues such as the tracheobronchial tree, urinary tract, or skin; these deposits are derived from monoclonal light chains, but are not due to an underlying **systemic** clonal plasma cell disorder. Patients with localized amyloidosis do not develop systemic disease (ie, cardiac, renal, hepatic, or nerve involvement) and do not require chemotherapy [67].

Localized AL amyloidosis is most commonly found in the upper respiratory tract (nasopharynx), urinary bladder, colon, skin and nails, and orbit [68-74]. In most of these patients, monoclonal immunoglobulins cannot be found in serum or urine, although the amyloid fibrils are usually light chain-derived. These light chains are usually derived from more than one light chain variable family and may not be clonal [8]. While damage to the affected site may occur (eg, nasal or colonic bleeding, tracheobronchial obstruction, hematuria), the clinical course is usually benign and surgical excision may be the only treatment needed [70,75,76]. If there is evidence of a circulating monoclonal protein in patients with localized amyloidosis, it is important to confirm the absence of systemic AL amyloidosis with an investigation for sites of additional disease (ie, liver function tests, 24-hour urine protein, serum creatinine and echocardiography) to ensure appropriate management. (See 'Evaluation' above.)

Other forms of systemic monoclonal immunoglobulin deposition disease — The monoclonal immunoglobulin deposition diseases (MIDD) are a group of disorders characterized by the accumulation of intact or fragmented abnormal immunoglobulin in visceral and soft tissues resulting in organ damage. The MIDD are plasma cell dyscrasias with abnormal immunoglobulin components secreted by plasma cells or a lymphoplasmacytic neoplasm. There are four major groups of MIDD:

- AL amyloidosis

- Light chain deposition disease

●Light and heavy chain deposition disease

●Heavy chain deposition disease

All of these entities will have evidence of a monoclonal plasma cell proliferative disorder and many will demonstrate light chains in the serum. However, only AL amyloidosis will demonstrate staining with Congo red.

Light chain deposition disease — Light chain deposition disease (LCDD) is a monoclonal immunoglobulin deposition disease related to AL amyloidosis in which fibril formation does not occur, but fragments of monoclonal light chains are deposited in the tissues [4,35]. LCDD typically presents as nephrotic syndrome and/or renal insufficiency [77]. Most patients with renal involvement progress to end-stage kidney disease requiring dialysis [78-80]. Less frequently, liver involvement can occur with hepatomegaly and liver dysfunction, either alone or in combination with renal involvement. Rarely, LCDD may involve the heart and lead to cardiomyopathy and heart failure or involve the peripheral nerves, salivary glands, gastrointestinal tract, and/or skin. Patients may progress to overt multiple myeloma; some patients may have coexisting multiple myeloma at initial diagnosis. Unlike AL amyloidosis, LCDD does not stain with Congo red. (See "Monoclonal immunoglobulin deposition disease".)

Heavy chain deposition disease — Heavy chain deposition disease (HCDD) is a rare monoclonal immunoglobulin deposition disease that has clinical characteristics that are similar to AL amyloidosis and LCDD. Deposits in HCDD are heavy chains or short (truncated) heavy chains, granular, and do not stain positive with Congo red. (See "Monoclonal immunoglobulin deposition disease".)

SOCIETY GUIDELINE LINKSLinks to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Immunoglobulin light chain (AL) amyloidosis".)

INFORMATION FOR PATIENTSUpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade

reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient education" and the keyword(s) of interest.)

●Basics topics (see "Patient education: AL amyloidosis (The Basics)")

SUMMARY AND RECOMMENDATIONS

●**Relation to other plasma cell disorders** – Amyloidosis is a generic term that refers to the extracellular tissue deposition of fibrils composed of subunits of a variety of normal serum proteins. AL amyloidosis (previously called primary amyloidosis) is a clonal plasma cell proliferative disorder in which fibrils of monoclonal light chains are deposited in the kidneys, heart, and other tissues. Affected patients may have AL amyloidosis alone or in association with other plasma cell dyscrasias (multiple myeloma, Waldenström macroglobulinemia). (See 'Epidemiology' above.)

●**Clinical presentation** – The clinical presentation in AL amyloidosis depends on the number and nature of the organs affected. Non-specific systemic symptoms, including fatigue and unintentional weight loss, are common. Other common clinical presentations include nephrotic syndrome, restrictive cardiomyopathy, peripheral neuropathy, and hepatomegaly with elevated liver enzymes. Other less common but suggestive signs are macroglossia, purpura, and an unexplained bleeding diathesis. (See 'Systemic presentations' above.)

●**Tissue biopsy** – The diagnosis of AL amyloidosis requires a biopsy. An abdominal fat pad aspirate and bone marrow biopsy are the preferred sites to biopsy in patients with suspected AL amyloidosis due to the ease of access and safety of accessing these sites (algorithm 1). Either or both are positive in 90 percent of patients with AL amyloidosis. (See 'Tissue biopsy' above.)

●**Diagnostic criteria** – Diagnostic criteria for systemic AL amyloidosis require the presence of **all** of the following (table 1) (see 'Diagnostic criteria' above):

•Presence of an amyloid-related systemic syndrome (eg, renal, liver, heart, gastrointestinal tract or peripheral nerve involvement). (See 'Systemic presentations' above.)

•Positive amyloid staining by Congo red in any tissue (eg, fat aspirate, bone marrow or organ biopsy). (See 'Identifying amyloid' above.)

•Evidence that the amyloid is light chain-related established by direct examination of the amyloid (eg, using mass spectrometry based proteomic analysis; note that immunohistochemistry results to type amyloid may be unreliable). (See 'Determining the type of amyloid' above.)

•Evidence of a monoclonal plasma cell proliferative disorder (eg, presence of a serum or urine M protein, abnormal serum free light chain ratio, or clonal plasma cells in the bone marrow). (See "Laboratory methods for analyzing monoclonal proteins", section on 'Serum free light chains'.)

●**Differential diagnosis** – AL amyloidosis should be distinguished from other forms of amyloidosis, from localized amyloidosis, and from other types of monoclonal immunoglobulin deposition diseases (MIDD) because the clinical course and therapy are markedly different.

Other forms of amyloidosis will demonstrate staining with Congo red (a characteristic of amyloid), but direct examination of the amyloid material will not reveal immunoglobulin light chains (as seen in AL amyloidosis). (See 'Other forms of amyloidosis' above.)

Other forms of MIDD will have evidence of a monoclonal plasma cell proliferative disorder and many will demonstrate light chains in the serum. However, AL amyloidosis is the only MIDD that will demonstrate staining with Congo red. (See 'Other forms of systemic monoclonal immunoglobulin deposition disease' above.)

ACKNOWLEDGMENTThe UpToDate editorial staff acknowledges Robert A Kyle, MD, who contributed as a Section Editor to an earlier version of this topic review.

REFERENCES

1. Kyle RA, Linos A, Beard CM, et al. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. Blood 1992; 79:1817.
2. Quock TP, Yan T, Chang E, et al. Epidemiology of AL amyloidosis: a real-world study using US claims data. Blood Adv 2018; 2:1046.
3. Kyle RA, Larson DR, Kurtin PJ, et al. Incidence of AL Amyloidosis in Olmsted County, Minnesota, 1990 through 2015. Mayo Clin Proc 2019; 94:465.
4. Kyle RA, Greipp PR. Amyloidosis (AL). Clinical and laboratory features in 229 cases. Mayo Clin Proc 1983; 58:665.
5. Kyle RA, Greipp PR, O'Fallon WM. Primary systemic amyloidosis: multivariate analysis for prognostic factors in 168 cases. Blood 1986; 68:220.
6. Shimazaki C, Hata H, Iida S, et al. Nationwide Survey of 741 Patients with Systemic Amyloid Light-chain Amyloidosis in Japan. Intern Med 2018; 57:181.
7. Muchtar E, Gertz MA, Kyle RA, et al. A Modern Primer on Light Chain Amyloidosis in 592 Patients With Mass Spectrometry-Verified Typing. Mayo Clin Proc 2019; 94:472.
8. Dasari S, Theis JD, Vrana JA, et al. Amyloid Typing by Mass Spectrometry in Clinical Practice: a Comprehensive Review of 16,175 Samples. Mayo Clin Proc 2020; 95:1852.
9. Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med 2002; 346:564.
10. Basset M, Defrancesco I, Milani P, et al. Nonlymphoplasmacytic lymphomas associated with light-chain amyloidosis. Blood 2020; 135:293.
11. Rajkumar SV, Gertz MA, Kyle RA. Primary systemic amyloidosis with delayed progression to multiple myeloma. Cancer 1998; 82:1501.
12. Madan S, Dispenzieri A, Lacy MQ, et al. Clinical features and treatment response of light chain (AL) amyloidosis diagnosed in patients with previous diagnosis of multiple myeloma. Mayo Clin Proc 2010; 85:232.
13. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014; 15:e538.
14. Kourelis TV, Kumar SK, Gertz MA, et al. Coexistent multiple myeloma or increased bone marrow plasma cells define equally high-risk populations in patients with immunoglobulin light chain amyloidosis. J Clin Oncol 2013; 31:4319.
15. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol 1995; 32:45.
16. Menke DM, Kyle RA, Fleming CR, et al. Symptomatic gastric amyloidosis in patients with primary systemic amyloidosis. Mayo Clin Proc 1993; 68:763.
17. Eder L, Bitterman H. Image in clinical medicine. Amyloid purpura. N Engl J Med 2007; 356:2406.
18. Yood RA, Skinner M, Rubinow A, et al. Bleeding manifestations in 100 patients with amyloidosis. JAMA 1983; 249:1322.

19. Mumford AD, O'Donnell J, Gillmore JD, et al. Bleeding symptoms and coagulation abnormalities in 337 patients with AL-amyloidosis. Br J Haematol 2000; 110:454.
20. Sucker C, Hetzel GR, Grabensee B, et al. Amyloidosis and bleeding: pathophysiology, diagnosis, and therapy. Am J Kidney Dis 2006; 47:947.
21. Greipp PR, Kyle RA, Bowie EJ. Factor X deficiency in primary amyloidosis: resolution after splenectomy. N Engl J Med 1979; 301:1050.
22. Greipp PR, Kyle RA, Bowie EJ. Factor-X deficiency in amyloidosis: a critical review. Am J Hematol 1981; 11:443.
23. Gertz MA, Kyle RA, Noel P. Primary systemic amyloidosis: a rare complication of immunoglobulin M monoclonal gammopathies and Waldenström's macroglobulinemia. J Clin Oncol 1993; 11:914.
24. Gertz MA, Kyle RA. Amyloidosis with IgM monoclonal gammopathies. Semin Oncol 2003; 30:325.
25. Terrier B, Jaccard A, Harousseau JL, et al. The clinical spectrum of IgM-related amyloidosis: a French nationwide retrospective study of 72 patients. Medicine (Baltimore) 2008; 87:99.
26. Wechalekar AD, Lachmann HJ, Goodman HJ, et al. AL amyloidosis associated with IgM paraproteinemia: clinical profile and treatment outcome. Blood 2008; 112:4009.
27. Sachchithanantham S, Roussel M, Palladini G, et al. European Collaborative Study Defining Clinical Profile Outcomes and Novel Prognostic Criteria in Monoclonal Immunoglobulin M-Related Light Chain Amyloidosis. J Clin Oncol 2016; 34:2037.
28. Sissoko M, Sanchorawala V, Seldin D, et al. Clinical presentation and treatment responses in IgM-related AL amyloidosis. Amyloid 2015; 22:229.
29. Gertz MA, Buadi FK, Hayman SR, et al. Immunoglobulin D amyloidosis: a distinct entity. Blood 2012; 119:44.
30. Duston MA, Skinner M, Shirahama T, Cohen AS. Diagnosis of amyloidosis by abdominal fat aspiration. Analysis of four years' experience. Am J Med 1987; 82:412.
31. Duston MA, Skinner M, Meenan RF, Cohen AS. Sensitivity, specificity, and predictive value of abdominal fat aspiration for the diagnosis of amyloidosis. Arthritis Rheum 1989; 32:82.
32. Sungur C, Sungur A, Ruacan S, et al. Diagnostic value of bone marrow biopsy in patients with renal disease secondary to familial Mediterranean fever. Kidney Int 1993; 44:834.
33. Garcia Y, Collins AB, Stone JR. Abdominal fat pad excisional biopsy for the diagnosis and typing of systemic amyloidosis. Hum Pathol 2018; 72:71.
34. World health organization classification of tumours of haematopoietic and lymphoid tissues, revised 4th edition, Swerdlow SH, Campo E, Harris NL, et al. (Eds), IARC, Lyon 2017.
35. Glenner GG. Amyloid deposits and amyloidosis. The beta-fibrilloses (first of two parts). N Engl J Med 1980; 302:1283.
36. Fernández de Larrea C, Verga L, Morbini P, et al. A practical approach to the diagnosis of systemic amyloidoses. Blood 2015; 125:2239.

37. Vrana JA, Gamez JD, Madden BJ, et al. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood 2009; 114:4957.
38. Sethi S, Theis JD, Leung N, et al. Mass spectrometry-based proteomic diagnosis of renal immunoglobulin heavy chain amyloidosis. Clin J Am Soc Nephrol 2010; 5:2180.
39. Klein CJ, Vrana JA, Theis JD, et al. Mass spectrometric-based proteomic analysis of amyloid neuropathy type in nerve tissue. Arch Neurol 2011; 68:195.
40. Brambilla F, Lavatelli F, Di Silvestre D, et al. Reliable typing of systemic amyloidoses through proteomic analysis of subcutaneous adipose tissue. Blood 2012; 119:1844.
41. Schönland SO, Hegenbart U, Bochtler T, et al. Immunohistochemistry in the classification of systemic forms of amyloidosis: a systematic investigation of 117 patients. Blood 2012; 119:488.
42. Novak L, Cook WJ, Herrera GA, Sanders PW. AL-amyloidosis is underdiagnosed in renal biopsies. Nephrol Dial Transplant 2004; 19:3050.
43. Anesi E, Palladini G, Perfetti V, et al. Therapeutic advances demand accurate typing of amyloid deposits. Am J Med 2001; 111:243.
44. Herrera GA, Sanders PW, Reddy BV, et al. Ultrastructural immunolabeling: a unique diagnostic tool in monoclonal light chain-related renal diseases. Ultrastruct Pathol 1994; 18:401.
45. Fonseca R, Ahmann GJ, Jalal SM, et al. Chromosomal abnormalities in systemic amyloidosis. Br J Haematol 1998; 103:704.
46. Hayman SR, Bailey RJ, Jalal SM, et al. Translocations involving the immunoglobulin heavy-chain locus are possible early genetic events in patients with primary systemic amyloidosis. Blood 2001; 98:2266.
47. Harrison CJ, Mazzullo H, Ross FM, et al. Translocations of 14q32 and deletions of 13q14 are common chromosomal abnormalities in systemic amyloidosis. Br J Haematol 2002; 117:427.
48. Bochtler T, Hegenbart U, Cremer FW, et al. Evaluation of the cytogenetic aberration pattern in amyloid light chain amyloidosis as compared with monoclonal gammopathy of undetermined significance reveals common pathways of karyotypic instability. Blood 2008; 111:4700.
49. Bryce AH, Ketterling RP, Gertz MA, et al. Translocation t(11;14) and survival of patients with light chain (AL) amyloidosis. Haematologica 2009; 94:380.
50. Bochtler T, Merz M, Hielscher T, et al. Cytogenetic intraclonal heterogeneity of plasma cell dyscrasia in AL amyloidosis as compared with multiple myeloma. Blood Adv 2018; 2:2607.
51. Kyle RA, Gertz MA, Greipp PR, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. N Engl J Med 1997; 336:1202.
52. Palladini G, Russo P, Bosoni T, et al. Identification of amyloidogenic light chains requires the combination of serum-free light chain assay with immunofixation of serum and urine. Clin Chem 2009; 55:499.

53. Paiva B, Vídriales MB, Pérez JJ, et al. The clinical utility and prognostic value of multiparameter flow cytometry immunophenotyping in light-chain amyloidosis. Blood 2011; 117:3613.
54. Muchtar E, Jevremovic D, Dispenzieri A, et al. The prognostic value of multiparametric flow cytometry in AL amyloidosis at diagnosis and at the end of first-line treatment. Blood 2017; 129:82.
55. Hawkins PN, Lavender JP, Pepys MB. Evaluation of systemic amyloidosis by scintigraphy with 123I-labeled serum amyloid P component. N Engl J Med 1990; 323:508.
56. Gallo G, Wisniewski T, Choi-Miura NH, et al. Potential role of apolipoprotein-E in fibrillogenesis. Am J Pathol 1994; 145:526.
57. Hawkins PN, Pepys MB. Imaging amyloidosis with radiolabelled SAP. Eur J Nucl Med 1995; 22:595.
58. Jager PL, Hazenberg BP, Franssen EJ, et al. Kinetic studies with iodine-123-labeled serum amyloid P component in patients with systemic AA and AL amyloidosis and assessment of clinical value. J Nucl Med 1998; 39:699.
59. Tan SY, Pepys MB, Hawkins PN. Treatment of amyloidosis. Am J Kidney Dis 1995; 26:267.
60. Gillmore JD, Wechalekar A, Bird J, et al. Guidelines on the diagnosis and investigation of AL amyloidosis. Br J Haematol 2015; 168:207.
61. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia 2009; 23:3.
62. Rajkumar SV. Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol 2016; 91:719.
63. Gertz MA, Kyle RA, Edwards WD. Recognition of congestive heart failure due to senile cardiac amyloidosis. Biomed Pharmacother 1989; 43:101.
64. Ng B, Connors LH, Davidoff R, et al. Senile systemic amyloidosis presenting with heart failure: a comparison with light chain-associated amyloidosis. Arch Intern Med 2005; 165:1425.
65. Benson MD, Liepnieks JJ, Kluve-Beckerman B. Hereditary systemic immunoglobulin light-chain amyloidosis. Blood 2015; 125:3281.
66. Lachmann HJ, Booth DR, Booth SE, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. N Engl J Med 2002; 346:1786.
67. Mahmood S, Bridoux F, Venner CP, et al. Natural history and outcomes in localised immunoglobulin light-chain amyloidosis: a long-term observational study. Lancet Haematol 2015; 2:e241.
68. Guidelines Working Group of UK Myeloma Forum, British Commitee for Standards in Haematology, British Society for Haematology. Guidelines on the diagnosis and management of AL amyloidosis. Br J Haematol 2004; 125:681.
69. Fujita Y, Tsuji-Abe Y, Sato-Matsumura KC, et al. Nail dystrophy and blisters as sole manifestations in myeloma-associated amyloidosis. J Am Acad Dermatol 2006; 54:712.

70. Kyle RA, Gertz MA, Lacy MQ, Dispenzieri A. Localized AL amyloidosis of the colon: an unrecognized entity. Amyloid 2003; 10:36.
71. Tirzaman O, Wahner-Roedler DL, Malek RS, et al. Primary localized amyloidosis of the urinary bladder: a case series of 31 patients. Mayo Clin Proc 2000; 75:1264.
72. Kourelis TV, Kyle RA, Dingli D, et al. Presentation and Outcomes of Localized Immunoglobulin Light Chain Amyloidosis: The Mayo Clinic Experience. Mayo Clin Proc 2017; 92:908.
73. Grogg KL, Aubry MC, Vrana JA, et al. Nodular pulmonary amyloidosis is characterized by localized immunoglobulin deposition and is frequently associated with an indolent B-cell lymphoproliferative disorder. Am J Surg Pathol 2013; 37:406.
74. Basset M, Hummedah K, Kimmich C, et al. Localized immunoglobulin light chain amyloidosis: Novel insights including prognostic factors for local progression. Am J Hematol 2020.
75. Domínguez S, Wienberg P, Clarós P, et al. Primary localized nasopharyngeal amyloidosis. A case report. Int J Pediatr Otorhinolaryngol 1996; 36:61.
76. Zeiser R, Mikesch K, Fisch P, et al. Extramedullary plasmocytoma with local amyloidosis presenting as a lump on the lip. Br J Haematol 2004; 125:679.
77. Nasr SH, Valeri AM, Cornell LD, et al. Renal monoclonal immunoglobulin deposition disease: a report of 64 patients from a single institution. Clin J Am Soc Nephrol 2012; 7:231.
78. Pozzi C, D'Amico M, Fogazzi GB, et al. Light chain deposition disease with renal involvement: clinical characteristics and prognostic factors. Am J Kidney Dis 2003; 42:1154.
79. Sayed RH, Wechalekar AD, Gilbertson JA, et al. Natural history and outcome of light chain deposition disease. Blood 2015; 126:2805.
80. Joly F, Cohen C, Javaugue V, et al. Randall-type monoclonal immunoglobulin deposition disease: novel insights from a nationwide cohort study. Blood 2019; 133:576.

Topic 6668 Version 44.0

Chapter 3

CARDIAC AMYLOIDOSIS: EPIDEMIOLOGY, CLINICAL MANIFESTATIONS, AND DIAGNOSIS

Author:Marianna Fontana, MD
Section Editor:Donna Mancini, MD
Deputy Editor:Todd F Dardas, MD, MS, Contributor Disclosures
All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Aug 2023. This topic last updated: Aug 16, 2022.

INTRODUCTIONCardiac amyloidosis is a disorder caused by amyloid fibril deposition in the extracellular space of the heart. It can present with cardiac signs or symptoms or may be diagnosed as the result of screening in patients who manifest extracardiac signs of amyloidosis. The approach to diagnosis depends upon the clinical presentation and the results of initial testing.

This topic will review the epidemiology, clinical manifestations, and diagnosis of cardiac amyloidosis. The treatment of cardiac amyloidosis and an overview of amyloidosis are discussed separately. (See "Amyloid cardiomyopathy: Treatment and prognosis" and "Overview of amyloidosis".)

TYPES OF AMYLOIDOSISThe clinical syndrome associated with cardiac amyloid infiltration in the heart is referred to as "cardiac amyloidosis" [1]. Two of the most common types of cardiac amyloidosis are transthyretin amyloidosis (ATTR amyloidosis) and light chain amyloidosis (AL amyloidosis), which are named after the precursor protein of the amyloid deposit:

●**Transthyretin amyloidosis (ATTR amyloidosis)** – Transthyretin amyloidosis results from the misfolding and deposition of transthyretin (TTR, formerly known as prealbumin), a tetrameric protein synthesized by the liver that normally functions to transport thyroid hormone and retinol (vitamin A). ATTR amyloidosis can be further divided into two subtypes:

•**Wild-type amyloidosis (wtATTR amyloidosis)** – Wild-type transthyretin amyloidosis (previously known as senile systemic amyloidosis) is caused by the

deposition of misfolded wild-type (normal) transthyretin. The mechanism by which normal transthyretin causes pathogenic deposits is unclear.

•**Hereditary amyloidosis (hATTR amyloidosis)** – Hereditary transthyretin amyloidosis is caused by gene mutations in the transthyretin gene (*TTR*) that predispose the tetrameric structure of transthyretin to instability, misfolding, and deposition. The typical transmission of hATTR is autosomal dominant inheritance with variable penetrance, and there are more than 120 known mutations of *TTR* associated with hATTR amyloidosis [2]. (See 'Epidemiology' below.)

●**Light chain amyloidosis (AL amyloidosis)** – Light chain amyloidosis (AL amyloidosis; also known as primary systemic amyloidosis) results from deposition of misfolded immunoglobulin light chains from a plasma cell dyscrasia. (See "Overview of amyloidosis", section on 'AL amyloidosis'.)

●**Other types of amyloid** – Rare causes of cardiac amyloidosis include serum amyloid A amyloidosis (AA), hereditary apolipoprotein A-1 (AApoA-1), and apolipoprotein A-4 (AApoA-4) amyloidosis (table 1). (See "Overview of amyloidosis", section on 'AA amyloidosis'.)

EPIDEMIOLOGYCardiac amyloidosis is a rare form of cardiomyopathy. Approximately 95 percent of cases of cardiac amyloidosis are caused by the deposition of transthyretin (TTR) or immunoglobulin light chains [3-5]. The epidemiology of common causes of cardiac amyloidosis is described below:

●**Wild-type transthyretin amyloidosis** – The overall prevalence of cardiac ATTR amyloidosis is unknown. However, studies in which patients were systematically screened for cardiac wild-type transthyretin amyloidosis (wtATTR amyloidosis) suggest that it is relatively common in populations of older adult patients with heart failure with preserved ejection fraction (HFpEF) and severe aortic stenosis. As examples:

•In a study of patients >60 years of age with HFpEF who underwent screening for cardiac ATTR amyloidosis, the prevalence of cardiac ATTR amyloidosis was relatively high (6 percent) and higher than in patients who did not undergo dedicated amyloid screening (1 percent) [6]. This study suggests that cardiac ATTR amyloidosis may be underdiagnosed in patients with HFpEF.

•In another study of 120 patients with HFpEF (age >60 years old) who were admitted to a hospital with HF and screened for amyloidosis with bone scintigraphy,

genetic testing, and cardiac biopsy, the prevalence of cardiac wtATTR amyloidosis was 13 percent [7]. No cases of cardiac hATTR amyloidosis were detected.

•In a cohort of 151 patients with aortic stenosis who underwent transcatheter aortic valve implantation, screening with bone scintigraphy identified cardiac wtATTR amyloidosis in 16 percent [8].

●**Hereditary transthyretin amyloidosis** – The prevalence of hereditary transthyretin amyloidosis (hATTR amyloidosis) is unknown. There are over 120 pathogenic gene variants known to be associated with cardiac hATTR amyloidosis. Some of these variants are more prevalent in specific geographic regions or ethnic groups, while others are more widely distributed [9-18]. Across populations, some of the most common variants are Val122Ile, Val30Met, Thr60Ala, Glu89Gln, Leu111Met, Ile68Leu, and Ser77Tyr [19,20].

●**Light chain amyloidosis** – Cardiac light chain amyloidosis (AL amyloidosis) is a rare condition associated with plasma cell dyscrasias that has an annual incidence of approximately 1 per 100,000 people in the United States [9].

CLINICAL MANIFESTATIONSThe clinical manifestations of amyloidosis are diverse, depending on the pattern of organ involvement. The variable clinical phenotype and generally nonspecific clinical features makes diagnosis difficult and contributes to diagnostic delays.

Age of onset and disease distribution — The usual age of onset of symptoms and disease distribution varies among the various types of amyloidosis [9].

Patients with light chain cardiac amyloidosis (AL amyloidosis) typically present at age ≥40 years. Systemic AL amyloidosis is a multisystem disorder which commonly affects the liver, kidneys, spleen, the autonomic and peripheral nervous systems, lungs, and heart. Cardiac amyloid infiltration is present in most patients with AL amyloidosis (50 to 70 percent) and it is the main determinant of prognosis [21,22]. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Clinical presentation'.)

Patients with transthyretin cardiac amyloidosis (ATTR amyloidosis) typically present at age ≥60 years, and most commonly >70 years. Various transthyretin mutations are associated with differing ages of onset (ranging from 30 to 70 years) and differing risks of cardiomyopathy. Cardiac amyloidosis is the dominant feature

of wild-type ATTR amyloidosis (ATTRwt amyloidosis) and for some ATTR variants (eg, Val122Ile, Thr60Ala, Ile58Leu, and Leu111Met) [9,16-18].

Cardiac involvement — Cardiac amyloidosis typically presents with symptoms and signs such as dyspnea, lower extremity edema, elevated jugular venous pressure, hepatic congestion, and ascites, which are caused by restrictive cardiomyopathy with predominantly right ventricular failure; symptoms and signs of low cardiac output (eg, diminished pulse pressure and diminished capillary refill) are features of advanced disease. Angina is uncommon, although microvascular dysfunction is a frequent finding. Amyloidogenic light chains may be toxic to myocardial cells as suggested by in vitro studies [23,24] as well as clinical observation of worse symptoms in patients with AL amyloidosis compared with patients with ATTR amyloidosis with similar degrees of cardiac involvement.

Patients with cardiac amyloidosis also frequently present with syncope or presyncope [25]. Syncope is frequently caused by bradyarrhythmias or advanced atrioventricular block and is infrequently caused by ventricular arrhythmia. Patients with ATTR amyloidosis (wild-type or hereditary) often develop progressive conduction system disease and pacemaker implantation is often required. In contrast, patients with AL amyloidosis infrequently develop high-degree atrioventricular block or symptomatic sinus node dysfunction [26]. Other conditions may contribute to the risk of syncope in patients with amyloid cardiomyopathy including postural or exertional hypotension caused by excessive diuresis or autonomic neuropathy.

Patients with amyloid cardiomyopathy, particularly those with AL amyloidosis or atrial fibrillation, are at risk for cardiac thromboembolism. Amyloid deposits in atrial as well as ventricular walls and thus causes atrial dysfunction including atrial electromechanical dissociation during sinus rhythm with associated risk of atrial thrombus formation [27-29].

Patients who develop wtATTR amyloidosis and aortic stenosis have similar demographic features, and some patients have both cardiac wtATTR amyloidosis and aortic stenosis [8,23-25]. Cardiac ATTR amyloidosis has been identified in a substantial minority of patients with severe aortic stenosis undergoing surgical valve replacement (6 to 12 percent [30,31]) or transcatheter aortic valve implantation (TAVI; 16 percent [32]). It has been postulated that ATTR amyloidosis with associated restrictive cardiomyopathy may be a contributing cause of low-flow, low-gradient aortic stenosis [8]. (See "Clinical manifestations and diagnosis of low gradient severe aortic stenosis".)

Extracardiac involvement — Extracardiac involvement varies among the types of amyloidosis.

Al amyloidosis — The clinical manifestations of AL amyloidosis include nonspecific symptoms (fatigue, poor appetite, early satiety, and weight loss) as well as more specific symptoms and signs of the following disorders: kidney disease (including asymptomatic proteinuria and nephrotic syndrome), peripheral neuropathy, carpal tunnel syndrome, gastrointestinal involvement (including hepatomegaly and gastrointestinal bleeding), macroglossia (which is nearly pathognomonic), purpura (including periorbital purpura, which is nearly pathognomonic), and bleeding diathesis. These clinical manifestations are discussed in detail separately. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Clinical presentation'.)

ATTR amyloidosis — Patients with ATTR amyloidosis (wild-type or hereditary) can develop autonomic or peripheral nerve disease. Wild-type TTR amyloid deposits are found in about one-third of older adults undergoing carpal tunnel decompression [26]. Spinal stenosis and biceps tendon rupture are also relatively common in patients with wtATTR amyloidosis.

Initial tests

Initial laboratory tests — Laboratory test abnormalities in patients with cardiac amyloidosis include proteinuria which may or may not be accompanied by elevations of serum BUN and creatinine in patients with kidney disease and liver biochemical abnormalities (eg, elevation in serum bilirubin) in patients with congestive hepatopathy. (See "Renal amyloidosis" and "Congestive hepatopathy", section on 'Laboratory testing'.)

Natriuretic peptides and troponin T and I levels are commonly elevated in patients with cardiac amyloidosis [27,28]. (See "Amyloid cardiomyopathy: Treatment and prognosis".)

Electrocardiogram — A hallmark of cardiac amyloidosis is discordance between increased left ventricular (LV) wall thickness (identified by cardiac imaging such as echocardiography) and QRS voltage, which is often reduced. However, this feature of cardiac amyloidosis has low sensitivity and the prevalence of low voltage varies markedly with etiology, with higher frequency in patients with AL amyloidosis (60 percent) than in patients with ATTR amyloidosis (20 percent) [29,33]. Thus, the

absence of low QRS voltage does not exclude cardiac amyloidosis, particularly in patients with wtATTR amyloidosis.

Among patients with wtATTR amyloidosis, 30 percent have voltage criteria for LV hypertrophy (LVH) or left bundle branch block, and 70 percent have pseudo-infarction patterns; conduction abnormalities affecting the sinus node and His-Purkinje systems are also common [34]. Thus, the presence of atrioventricular (AV) block in an older patient with LVH should prompt consideration of cardiac amyloidosis. (See 'Cardiac involvement' above.)

Atrial fibrillation is common in patients with cardiac amyloidosis (15 percent in one series), with highest prevalence in patients with wtATTR amyloidosis (40 percent) and lower prevalence with hATTR amyloidosis (11 percent) and AL amyloidosis (9 percent) [30].

DIAGNOSIS

When to suspect cardiac amyloidosis — The following are clinical settings in which cardiac amyloidosis should be suspected:

●Patients with unexplained LV hypertrophy (LVH; with or without HF).

●Patients with HF and unexplained LVH – Echocardiography is the first-line cardiac imaging test for patients presenting with HF and may identify LVH (as well as other abnormalities), which should raise suspicion of cardiac amyloidosis. (See "Heart failure: Clinical manifestations and diagnosis in adults", section on 'Echocardiography' and "Determining the etiology and severity of heart failure or cardiomyopathy", section on 'Echocardiography'.)

●Patients with presyncope, syncope, angina, or no cardiac symptoms with unexplained LVH – Echocardiography is commonly performed in patients with presyncope and syncope, as well as for other indications such as suspected valve disease, and may identify LVH.

●Patients with aortic stenosis with features associated with cardiac amyloidosis, such as presence of low-flow, low-gradient aortic stenosis and/or echocardiographic detection of impaired longitudinal strain (eg, mitral annular S' ≤6 cm/s) [8,31]. (See "Clinical manifestations and diagnosis of low gradient severe aortic stenosis", section on 'Additional evaluation based upon type of low gradient AS'.)

●Patients with HF and symptoms or signs commonly seen in AL and/or ATTR amyloidosis. For example, a history of bilateral carpel tunnel syndrome prior to development of unexplained symptoms of HF in an older adult should prompt evaluation for possible cardiac ATTR amyloidosis.

●Patients with a condition highly associated with cardiac amyloidosis (eg, systemic AL amyloidosis, ATTR-related peripheral neuropathy or ATTR mutation carrier state).

How to diagnose cardiac amyloidosis — We recommend the following approach to diagnosis of cardiac amyloidosis.

●The initial diagnostic evaluation of the patient with suspected cardiac amyloidosis includes a clinical examination to identify and assess cardiac and extracardiac symptoms and signs, laboratory tests, and an electrocardiogram, as described above. (See 'Clinical manifestations' above.)

●An echocardiogram is the initial cardiac imaging test for patients with suspected cardiac amyloidosis. While nearly all echocardiographic findings are non-specific, some findings are highly suggestive of cardiac amyloidosis in the appropriate clinical setting (particularly the finding of relative apical sparing of longitudinal strain) [23]. (See 'Echocardiography' below.)

Further evaluation with imaging is based upon the patient's clinical presentation (reason for suspecting cardiac amyloidosis) (figure 1):

●**For patients with unexplained LVH, aortic stenosis with features associated with cardiac amyloidosis, or HF with symptoms or signs typical of amyloidosis (consistent with AL amyloidosis or with both ATTR and AL amyloidosis)**, we recommend cardiovascular magnetic resonance (CMR) imaging. (See 'Cardiovascular magnetic resonance' below.)

•If CMR findings are consistent with cardiac amyloidosis, all three tests for evidence of monoclonal protein are performed (serum kappa/lambda free light chain ratio analysis, serum protein immunofixation, **and** urine protein immunofixation) (see "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Evidence of monoclonal plasma cells' and "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Diagnosis'):

-If monoclonal protein is identified by one or more of these tests, referral to a hematologist is recommended for evaluation and further assessment. Bone marrow biopsy is generally performed. Additional tissue biopsy may be required such as fat pad aspirate or biopsy of other tissues. Noncardiac biopsy with amyloid of AL type and a CMR consistent with cardiac amyloidosis is sufficient in the majority of cases for the diagnosis of cardiac AL amyloidosis. Tissue specimens are examined to determine the type of amyloid. While the presence of monoclonal protein is suggestive of AL amyloidosis, other causes include ATTR with a monoclonal gammopathy of undetermined significance (MGUS), or other type of amyloidosis (eg, AApoA-1 or AA) with MGUS [24,25]. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Tissue biopsy' and "Diagnosis of monoclonal gammopathy of undetermined significance".)

-If monoclonal protein is not identified by any of these three tests, management is based upon the results of bone tracer cardiac scintigraphy performed with 99mtechnetium pyrophosphate (99mTc-pyrophosphate [PYP]), 99mTc 3,3-diphosphono-1,2-propanodicarboxylic acid [DPD], or 99mTc-hydroxymethylene diphosphonate [HMDP] to identify the presence and extent of cardiac uptake:

Grade 0 scintigraphy in this setting suggests the CMR images should be reviewed. If the CMR images are highly suggestive of cardiac amyloidosis or if the clinical suspicion remains high, an endomyocardial biopsy may be helpful to exclude cardiac AL amyloidosis, cardiac ATTR amyloidosis caused by rare TTR gene variants, and rare forms of cardiac amyloidosis such as AApoA-1, AApoA-4 amyloidosis, and AA amyloidosis. Other nonamyloid diagnoses should also be considered. (See 'Differential diagnosis' below.)

Grade 1 scintigraphy is seen with various types of cardiac amyloidosis. Further evaluation includes peripheral or endomyocardial biopsy for confirmation and typing. Possible diagnoses include early ATTR cardiac amyloidosis (hereditary or wild-type) or AL cardiac amyloidosis, or less commonly, other types of amyloidosis (eg, AApoA-1 and AApoA-4).

Grade 2 or 3 scintigraphy, coupled with lack of evidence of a plasma cell dyscrasia, is highly specific for ATTR cardiac disease, so tissue biopsy is not required [32]. In patients diagnosed with cardiac ATTR amyloidosis, genetic testing is performed to distinguish hATTR from wtATTR amyloidosis.

•If CMR findings are not consistent with cardiac amyloidosis, cardiac amyloidosis is unlikely and other causes of LVH should be considered. (See 'Differential diagnosis' below.)

●**For patients with systemic AL amyloidosis or HF with symptoms or signs typical for AL** (but not ATTR) **amyloidosis,** we recommend CMR. (See 'Cardiovascular magnetic resonance' below.)

•If CMR findings suggest cardiac amyloidosis and confirmed systemic AL amyloidosis is present, the diagnosis of cardiac amyloidosis is confirmed, as studies have shown high specificity and sensitivity in this clinical setting [35-39]. Bone scintigraphy is not very useful in patients with systemic AL amyloidosis as it is negative in approximately 60 percent of patients with cardiac AL amyloidosis, with the remainder showing only grade 1 uptake (grade 2 and 3 cardiac uptake is a rare occurrence) [34].

If CMR findings suggest cardiac amyloidosis and AL amyloidosis is suspected, evaluation includes testing for monoclonal protein (by performing serum protein immunofixation, urine protein immunofixation, **and** serum free light chain ratio analysis); if one or more of these tests is positive, tissue biopsy (including bone marrow) is indicated. While the presence of monoclonal protein is suggestive of AL amyloidosis, tissue biopsy is important because other possible causes include ATTR with a monoclonal gammopathy of undetermined significance (MGUS), or other type of amyloidosis (eg, AApoA-1, AApoA-4, or AA) with MGUS. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis".)

•If CMR findings are not consistent with cardiac amyloidosis, the diagnosis is unlikely. If LVH or HF is present, other causes should be considered. (See 'Differential diagnosis' below.)

●**For patients with ATTR-associated polyneuropathy, ATTR mutation carrier state, or HF with symptoms and signs typical for ATTR** (but not AL) **amyloidosis**, we suggest either bone scintigraphy or CMR as the next step to evaluate for cardiac infiltration with evaluation similar to that described above for unexplained LVH. Further is needed as there are limited data to guide the choice of tests in this setting.

Diagnostic tests

Echocardiography — Echocardiography is the initial imaging test of choice for diagnosis of cardiac amyloidosis.

Relative apical sparing of longitudinal strain is a key feature — Reduction in global longitudinal strain (a measure of systolic function) is one of the earliest markers of cardiac amyloidosis and presents with a characteristic pattern of relative apical sparing of longitudinal strain (ie, the ratio of apical longitudinal strain/average of mid and basal longitudinal strain >1.0) [40]. This pattern of longitudinal strain alteration has high sensitivity (93 percent) and specificity (82 percent) for cardiac amyloidosis with proven utility in differentiating cardiac amyloidosis from other hypertrophic phenocopies [40,41].

General features — Infiltration of the ventricular walls produces an appearance of hypertrophy (commonly biventricular) with nondilated or small ventricles; a dilated phenotype is rare. Common findings include thickening of the valves and the interatrial septum. The atria are almost invariably dilated. There are some structural and functional differences between AL and ATTR amyloidosis (including greater increase in LV and right ventricular [RV] mass and more systolic dysfunction with ATTR than AL amyloidosis) but there is significant overlap between these types [40]. LVH is typically symmetric in AL amyloidosis but asymmetric with predominantly septal hypertrophy in ATTR amyloidosis; in ATTR amyloidosis, asymmetric septal hypertrophy is associated with a sigmoid septum (in 70 percent of cases) or reverse septal curvature (in 30 percent) [41]. LV outflow obstruction is rare [23].

While echocardiographic findings of unexplained LVH raise suspicion of cardiac amyloidosis, identification of LVH is not required to proceed with CMR in patients with AL amyloidosis, ATTR-related peripheral neuropathy, or ATTR mutation carrier state. In patients with cardiac amyloidosis, CMR abnormalities may be identified prior to the development of LVH [41].

Cardiac amyloidosis is one of the conditions in the differential diagnosis for HF with preserved systolic function. This terminology does not fully characterize the functional phenotype for cardiac amyloidosis, which typically involves diastolic as well as systolic impairment although the LV ejection fraction (LVEF) is typically normal until end-stage, in which it is typically is only mildly reduced [42]. Stroke volume index (stroke volume divided by body surface area) is a better marker of systolic function in this clinical setting, and is invariably reduced, even at very early stages of infiltration [42]. Reduction in peak systolic wall motion velocities,

disproportionally affecting the longitudinal rather than the radial axes, are also an early disease marker.

Diastolic dysfunction is almost invariably affected with early impaired relaxation, which then invariably progresses to typical restrictive physiology [42]. Similar changes are present in the structure and systolic and diastolic function of the RV. (See "Tests to evaluate left ventricular systolic function" and "Echocardiographic evaluation of left ventricular diastolic function in adults" and "Echocardiographic assessment of the right heart".)

The pulmonary artery systolic pressure, as estimated from the peak velocity of the tricuspid valve regurgitant jet, may indicate moderate pulmonary hypertension (estimated pulmonary artery pressure of 40 to 50 mmHg). This is almost invariably secondary to the markedly elevated LV diastolic pressure and does not indicate primary pulmonary hypertension or cor pulmonale.

Pericardial and pleural effusions are common findings, especially in AL amyloidosis.

Cardiovascular magnetic resonance — CMR is a key test in the diagnosis of cardiac amyloidosis and is generally performed with contrast [43]. CMR provides a detailed assessment of cardiac structure (including identification and quantification of LVH) and function as well as unique information on the characteristics of the myocardial tissue. CMR can detect early cardiac amyloidosis before the development of LVH. However, CMR cannot distinguish cardiac AL from ATTR amyloidosis [44,45].

Cardiac amyloidosis has a highly characteristic appearance on CMR imaging performed with late gadolinium enhancement (LGE): Initially, there may be diffuse subendocardial LGE, while later in the course of disease, there is a transmural myocardial LGE pattern [35]. The three progressive LGE patterns identified in cardiac amyloidosis (none, subendocardial, and transmural) correlate with the degree of myocardial infiltration [46]. In a systematic review of studies comparing LGE with endomyocardial biopsy and/or echocardiography and other clinical features, the pooled sensitivity of LGE for cardiac amyloidosis was 85 percent (95% CI 77-91 percent) and the pooled specificity was 92 percent (95% CI 83-97 percent) [47]. Limitations of LGE include lack of quantitative results (which limits the ability to track changes over time) and limited applicability since gadolinium-based contrast agents are relatively contraindicated in patients with a severe reduction in renal function (which is relatively common in patients with AL amyloidosis). (See "Patient evaluation before gadolinium contrast administration for magnetic

resonance imaging" and "Nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy in advanced kidney disease".)

T1 mapping can overcome some of the limitations of LGE but center-specific reference ranges are required for early disease detection [48]. T1 mapping provides quantitative measures of myocardial T1 relaxation time (precontrast [native] or postcontrast). Native myocardial T1 increases with cardiac amyloid infiltration and correlated with markers of systolic and diastolic dysfunction [49]. Native myocardial T1 elevation is an early disease marker with high diagnostic accuracy for cardiac amyloidosis when the pretest probability is high [50]. In a study of 868 patients with suspected cardiac amyloidosis (222 with cardiac AL amyloidosis, 214 patients with cardiac ATTR amyloidosis, and 427 with no cardiac involvement), T1 mapping diagnosed cardiac amyloidosis with a sensitivity of 85 percent and specificity of 87 percent [51]. T1 mapping may be particularly helpful in patients with severely impaired kidney function, in whom gadolinium contrast is contraindicated (see "Patient evaluation before gadolinium contrast administration for magnetic resonance imaging", section on 'Approach to preventing nephrogenic systemic fibrosis'). However, native T1 is a composite myocardial signal from both interstitium and myocytes that does not distinguish among the underlying processes (fibrosis, edema, amyloid, myocyte volume) and while the T1 elevation is marked with advanced disease, the lower elevations in early disease can be accurately identified only by referencing the center-specific normal range.

Extracellular volume (ECV) fraction measurement using intravenous gadolinium-based contrast agent is an ancillary method for identification and assessment of cardiac amyloidosis that helps to quantify the amount of cardiac amyloid. ECV elevation may be detected early before the development of LV hypertrophy, LGE or elevation in serum biomarkers [52]. ECV elevation correlates with markers of disease activity, including cardiac function, serum biomarkers, patient functional performance [53], and prognosis [41,54]. Native T2 mapping is another technique that may be helpful; T2 elevations demonstrate that edema is part of cardiac amyloidosis (particularly AL) and is linked to prognosis [55].

Bone tracer cardiac scintigraphy — Bone tracer cardiac scintigraphy (using 99m technetium [Tc]-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid [DPD], 99mTc-labeled pyrophosphate [PYP], or 99mTc-labeled hydroxymethylene diphosphonate [HMDP]) is a pivotal test for identifying ATTR amyloidosis (figure 2). The diagnostic utility of 99mTc-PYP imaging for ATTR cardiac amyloidosis was demonstrated using the Perugini staging system based on simple visual scoring of

the three-hour planar image: grade 0 being negative (no cardiac uptake) and grades 1 to 3 defined as detection of progressively greater cardiac uptake and decrease in the bone uptake [56]. A subsequent multicenter study showed that ATTR cardiac amyloidosis is particularly avid for bone tracers (the mechanism is not understood); in contrast, in cardiac AL amyloidosis, there is either absent or only grade 1 uptake (grade 1 being present in approximately 40 percent of patients) [32]. As illustrated by a systematic review, the presence of grade 1, 2, or 3 scintigraphy had high sensitivity (pooled value of 82 percent) and specificity (98.8 percent) for cardiac amyloidosis as compared with tissue biopsy in studies evaluating the diagnostic performance of scintigraphy for cardiac amyloidosis [44]. Presence of grade 2 or 3 positive bone tracer cardiac scintigraphy in a patient without monoclonal protein (ie, free light chain ratio is normal and serum and urine immunofixation results are both normal) is highly specific for ATTR cardiac amyloid and thus sufficient for diagnosis of this condition without tissue biopsy [32].

The main limitation of bone tracer scintigraphy is lack of quantification of amyloid burden, a parameter that might prove useful for assessing response to therapy in the era of disease modifying agents. Novel quantitative positron emission tomography (PET) imaging using bone or amyloid binding tracers might prove useful in this context [57].

Monoclonal protein — Identification of monoclonal protein (by serum protein immunofixation, urine protein immunofixation, or serum free light chain ratio analysis) along with echocardiographic or CMR findings consistent with cardiac amyloidosis is suggestive of AL amyloidosis but may also be caused by ATTR (or a rarer cause of cardiac amyloidosis) with an unrelated monoclonal gammopathy of undetermined significance (MGUS) [58]. Thus it is important to identify the specific cause of cardiac amyloidosis even when monoclonal protein has been identified, particularly in patients with features that are atypical for AL amyloidosis. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis" and "Laboratory methods for analyzing monoclonal proteins" and "Diagnosis of monoclonal gammopathy of undetermined significance".)

Tissue biopsy — Tissue biopsy is required for some, but not all, patients undergoing diagnostic evaluation of cardiac amyloidosis, as described above. (See 'How to diagnose cardiac amyloidosis' above.)

Tissue biopsy is not required when other findings are diagnostic for the presence and type of cardiac amyloidosis. As described above, the presence of grade 2 or 3

positive bone tracer cardiac scintigraphy in the absence of monoclonal protein is diagnostic for cardiac ATTR amyloidosis, and thus no tissue biopsy is required. The presence of CMR findings consistent with cardiac amyloidosis in a patient with previously confirmed systemic AL amyloidosis is diagnostic for cardiac AL amyloidosis, so endomyocardial biopsy is not indicated.

In patients with suspected AL amyloidosis, evaluation typically includes bone marrow biopsy and other tissue biopsy (eg, fat pad aspirate, endomyocardial) as discussed separately. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis".)

Low power microscopic examination of tissue with amyloid infiltration shows amorphous hyaline deposits seen predominantly in the extracellular space. Diagnostic characteristics of extracellular amyloid deposits include typical apple-green birefringence with Congo red dye under polarized light microscopy and unique cross–β-pleated sheets under electron microscopy. The fibrils also bind thioflavine T (producing an intense yellow-green fluorescence), and sulfated Alcian blue (producing a green color) (picture 1A-B). The type of amyloid fibril may be identified using immunohistochemistry, immunofluorescence or immunoelectron microscopy but laser microdissection with mass spectrometry is considered the gold standard for identifying the precursor protein and amyloidosis type [59]. (See 'Types of amyloidosis' above and "Overview of amyloidosis", section on 'Pathology' and "Overview of amyloidosis", section on 'Types of amyloidosis'.)

DIFFERENTIAL DIAGNOSISIn patients with LV hypertrophy (LVH), the differential diagnosis includes hypertrophic cardiomyopathy, LVH associated with hypertension, HF with preserved ejection fraction (HFpEF; which overlaps with hypertensive LVH) and Anderson Fabry disease.

Echocardiography is helpful since the finding of relative apical sparing of longitudinal strain is suggestive of cardiac amyloidosis. Additional imaging with CMR is helpful as CMR has high sensitivity for both AL and ATTR types of cardiac amyloidosis and typical LGE findings are specific for cardiac amyloidosis. Although late gadolinium enhancement (LGE) is frequently seen in patients with hypertrophic cardiomyopathy or Fabry disease, the pattern of LGE in those conditions differs from that seen with cardiac amyloidosis. (See 'Cardiovascular magnetic resonance' above and "Hypertrophic cardiomyopathy: Clinical manifestations, diagnosis, and evaluation", section on 'Cardiovascular magnetic resonance' and "Fabry disease: Cardiovascular disease", section on 'Cardiovascular magnetic resonance'.)

Patients with cardiac amyloidosis with HF typically have preserved LVEF until advanced stages, and other causes of this presentation should be excluded (table 2). Many of the alterative causes of HF with a normal ejection fraction can be identified by echocardiography, including valvular heart disease, right HF, and pericardial disease. The differential diagnosis of HFpEF, including non-HF and HF conditions, is discussed separately (see "Heart failure with preserved ejection fraction: Clinical manifestations and diagnosis", section on 'Differential diagnosis'). Evaluation of the cause of HF (with reduced or preserved ejection fraction) is discussed separately. (See "Determining the etiology and severity of heart failure or cardiomyopathy".)

SOCIETY GUIDELINE LINKSLinks to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cardiac amyloidosis" and "Society guideline links: Cardiomyopathy" and "Society guideline links: Heart failure in adults" and "Society guideline links: Immunoglobulin light chain (AL) amyloidosis".)

INFORMATION FOR PATIENTSUpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

●Basics topics (see "Patient education: AL amyloidosis (The Basics)")

SUMMARY AND RECOMMENDATIONS

●**Types of amyloidosis** – Classification of amyloidosis is based upon the type of precursor protein (table 1). The common types of cardiac amyloidosis are transthyretin amyloidosis (ATTR amyloidosis), which includes the wild-type (wtATTR amyloidosis) and hereditary (hATTR amyloidosis) subtypes, and light chain amyloidosis (AL amyloidosis). (See 'Types of amyloidosis' above.)

●**Epidemiology** – Cardiac amyloidosis is a rare form of cardiomyopathy whose overall frequency in the population is not well described, though more is known about the epidemiology of specific types of cardiac amyloidosis. Among patients who have cardiac amyloidosis, approximately 95 percent of cases are caused by the deposition of transthyretin (ATTR amyloidosis) or immunoglobulin light chains (AL amyloidosis). (See 'Epidemiology' above.)

●**Clinical manifestations** – Clinical manifestations in patients with cardiac amyloidosis are diverse, depending on the pattern of organ involvement. The variable clinical phenotype and generally nonspecific clinical features makes diagnosis difficult and contributes to diagnostic delays. (See 'Clinical manifestations' above.)

•Patients with AL cardiac amyloidosis typically present at age ≥40 years. Systemic AL amyloidosis is a multisystem disorder which commonly affects the liver, kidneys, the autonomic and peripheral nervous systems, lung as well as heart. Cardiac amyloid infiltration is present in most patients (50 to 70 percent) and is the main determinant of prognosis.

•Patients with ATTR cardiac amyloidosis typically present at age ≥60 years, and most commonly >70 years. Various transthyretin mutations are associated with differing ages of onset (ranging from 30 to 70 years) and differing risks of cardiomyopathy. Cardiac amyloidosis is the dominant feature of wtATTR amyloidosis and for some ATTR variants.

●**Electrocardiogram** – A hallmark of cardiac amyloidosis is discordance between increased left ventricular (LV) wall thickness (identified by cardiac imaging such as echocardiography) and QRS voltage, which is often reduced. However, this is feature of cardiac amyloidosis has low sensitivity and the prevalence of low voltage varies markedly with etiology, with higher frequency in patients with AL amyloidosis (60 percent) than in patents with ATTR amyloidosis (20 percent). (See 'Electrocardiogram' above.)

●**When to suspect cardiac amyloidosis** – Cardiac amyloidosis should be suspected in patients with unexplained LV hypertrophy (LVH; with or without heart failure [HF]), patients with aortic stenosis with features associated with cardiac amyloidosis (such as presence of low-flow, low-gradient aortic stenosis and/or echocardiographic detection of impaired longitudinal strain [eg, mitral annular S' ≤6 m/sec]), patients with symptoms or signs typical of AL or ATTR amyloidosis and HF, and patients with a condition highly associated with cardiac amyloidosis (eg,

systemic AL amyloidosis, ATTR-related peripheral neuropathy, or ATTR mutation carrier state). (See 'When to suspect cardiac amyloidosis' above.)

●**How to diagnose cardiac amyloidosis** – The diagnostic evaluation for cardiac amyloidosis starts with an initial clinical examination to assess cardiac and extracardiac symptoms and signs, initial laboratory tests, an electrocardiogram, and an echocardiogram. Further evaluation is based upon the patient's clinical presentation. (See 'How to diagnose cardiac amyloidosis' above.)

•**Suspected cardiac amyloidosis without known systemic amyloidosis** – For patients with unexplained LVH, aortic stenosis with features associated with cardiac amyloidosis, or HF with symptoms or signs typical of amyloidosis (consistent with AL and ATTR amyloidosis), we recommend cardiovascular magnetic resonance (CMR) imaging. (See 'Cardiovascular magnetic resonance' above.)

-If CMR findings suggest cardiac amyloidosis, we recommend testing for evidence of monoclonal protein (by serum protein immunofixation, urine protein immunofixation, and serum free light chain ratio analysis). If monoclonal protein is identified, hematology referral and tissue biopsy (including bone marrow biopsy) are indicated. If monoclonal protein is not identified, further evaluation is based upon the results of bone tracer cardiac scintigraphy . (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Evidence of monoclonal plasma cells' and "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Diagnosis'.)

-If CMR is not suggestive of cardiac amyloidosis, cardiac amyloidosis is unlikely and other causes of LVH and/or HF should be considered. (See 'Differential diagnosis' above.)

•**Known systemic amyloidosis** – For patients with systemic AL amyloidosis, we recommend CMR. (See 'Cardiovascular magnetic resonance' above.)

-If CMR findings suggest cardiac amyloidosis, the diagnosis of cardiac amyloidosis is confirmed.

-If CMR findings do not suggest cardiac amyloidosis, the diagnosis is unlikely. Other causes of LVH and/or HF should be considered. (See 'Differential diagnosis' above.)

•**Patients at high-risk for cardiac ATTR** – For patients with ATTR-associated polyneuropathy or ATTR mutation carrier state, we suggest either bone scintigraphy or CMR as the next step to evaluate for cardiac infiltration. Further studies are needed to determine the optimum diagnostic approach in this setting. (See 'How to diagnose cardiac amyloidosis' above.)

REFERENCES

1. Fontana M, Ćorović A, Scully P, Moon JC. Myocardial Amyloidosis: The Exemplar Interstitial Disease. JACC Cardiovasc Imaging 2019; 12:2345.
2. Finsterer J, Iglseder S, Wanschitz J, et al. Hereditary transthyretin-related amyloidosis. Acta Neurol Scand 2019; 139:92.
3. Falk RH, Alexander KM, Liao R, Dorbala S. AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy. J Am Coll Cardiol 2016; 68:1323.
4. Gertz MA, Benson MD, Dyck PJ, et al. Diagnosis, Prognosis, and Therapy of Transthyretin Amyloidosis. J Am Coll Cardiol 2015; 66:2451.
5. Sipe JD, Benson MD, Buxbaum JN, et al. Amyloid fibril proteins and amyloidosis: chemical identification and clinical classification International Society of Amyloidosis 2016 Nomenclature Guidelines. Amyloid 2016; 23:209.
6. AbouEzzeddine OF, Davies DR, Scott CG, et al. Prevalence of Transthyretin Amyloid Cardiomyopathy in Heart Failure With Preserved Ejection Fraction. JAMA Cardiol 2021; 6:1267.
7. González-López E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J 2015; 36:2585.
8. Castaño A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J 2017; 38:2879.
9. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet 2016; 387:2641.
10. Ohmori H, Ando Y, Makita Y, et al. Common origin of the Val30Met mutation responsible for the amyloidogenic transthyretin type of familial amyloidotic polyneuropathy. J Med Genet 2004; 41:e51.
11. Soares ML, Coelho T, Sousa A, et al. Haplotypes and DNA sequence variation within and surrounding the transthyretin gene: genotype-phenotype correlations in familial amyloid polyneuropathy (V30M) in Portugal and Sweden. Eur J Hum Genet 2004; 12:225.
12. Zaros C, Genin E, Hellman U, et al. On the origin of the transthyretin Val30Met familial amyloid polyneuropathy. Ann Hum Genet 2008; 72:478.
13. Conceição I, De Carvalho M. Clinical variability in type I familial amyloid polyneuropathy (Val30Met): comparison between late- and early-onset cases in Portugal. Muscle Nerve 2007; 35:116.

14. Reilly MM, Staunton H, Harding AE. Familial amyloid polyneuropathy (TTR ala 60) in north west Ireland: a clinical, genetic, and epidemiological study. J Neurol Neurosurg Psychiatry 1995; 59:45.
15. Jacobson DR, Alexander AA, Tagoe C, Buxbaum JN. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African-Americans. Amyloid 2015; 22:171.
16. Rapezzi C, Quarta CC, Obici L, et al. Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an Italian perspective. Eur Heart J 2013; 34:520.
17. Gagliardi C, Perfetto F, Lorenzini M, et al. Phenotypic profile of Ile68Leu transthyretin amyloidosis: an underdiagnosed cause of heart failure. Eur J Heart Fail 2018; 20:1417.
18. Suhr OB, Svendsen IH, Andersson R, et al. Hereditary transthyretin amyloidosis from a Scandinavian perspective. J Intern Med 2003; 254:225.
19. Swiecicki PL, Zhen DB, Mauermann ML, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. Amyloid 2015; 22:123.
20. Coelho T, Maurer MS, Suhr OB. THAOS - The Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. Curr Med Res Opin 2013; 29:63.
21. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med 2003; 349:583.
22. Kyle RA, Linos A, Beard CM, et al. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. Blood 1992; 79:1817.
23. Boldrini M, Cappelli F, Chacko L, et al. Multiparametric Echocardiography Scores for the Diagnosis of Cardiac Amyloidosis. JACC Cardiovasc Imaging 2020; 13:909.
24. Ruberg FL, Grogan M, Hanna M, et al. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol 2019; 73:2872.
25. Cuddy SAM, Dorbala S, Falk RH. Complexities and Pitfalls in Cardiac Amyloidosis. Circulation 2020; 142:409.
26. Sekijima Y, Uchiyama S, Tojo K, et al. High prevalence of wild-type transthyretin deposition in patients with idiopathic carpal tunnel syndrome: a common cause of carpal tunnel syndrome in the elderly. Hum Pathol 2011; 42:1785.
27. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J 2018; 39:2799.
28. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol 2004; 22:3751.
29. Cyrille NB, Goldsmith J, Alvarez J, Maurer MS. Prevalence and prognostic significance of low QRS voltage among the three main types of cardiac amyloidosis. Am J Cardiol 2014; 114:1089.

30. Longhi S, Quarta CC, Milandri A, et al. Atrial fibrillation in amyloidotic cardiomyopathy: prevalence, incidence, risk factors and prognostic role. Amyloid 2015; 22:147.
31. Cavalcante JL, Rijal S, Abdelkarim I, et al. Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis. J Cardiovasc Magn Reson 2017; 19:98.
32. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation 2016; 133:2404.
33. Mussinelli R, Salinaro F, Alogna A, et al. Diagnostic and prognostic value of low QRS voltages in cardiac AL amyloidosis. Ann Noninvasive Electrocardiol 2013; 18:271.
34. Quarta CC, Zheng J, Hutt D, et al. 99mTc-DPD scintigraphy in immunoglobulin light chain (AL) cardiac amyloidosis. Eur Heart J Cardiovasc Imaging 2021; 22:1304.
35. Maceira AM, Joshi J, Prasad SK, et al. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation 2005; 111:186.
36. Vogelsberg H, Mahrholdt H, Deluigi CC, et al. Cardiovascular magnetic resonance in clinically suspected cardiac amyloidosis: noninvasive imaging compared to endomyocardial biopsy. J Am Coll Cardiol 2008; 51:1022.
37. Austin BA, Tang WH, Rodriguez ER, et al. Delayed hyper-enhancement magnetic resonance imaging provides incremental diagnostic and prognostic utility in suspected cardiac amyloidosis. JACC Cardiovasc Imaging 2009; 2:1369.
38. Ruberg FL, Appelbaum E, Davidoff R, et al. Diagnostic and prognostic utility of cardiovascular magnetic resonance imaging in light-chain cardiac amyloidosis. Am J Cardiol 2009; 103:544.
39. Syed IS, Glockner JF, Feng D, et al. Role of cardiac magnetic resonance imaging in the detection of cardiac amyloidosis. JACC Cardiovasc Imaging 2010; 3:155.
40. Maurer MS, Elliott P, Comenzo R, et al. Addressing Common Questions Encountered in the Diagnosis and Management of Cardiac Amyloidosis. Circulation 2017; 135:1357.
41. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, et al. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. J Am Coll Cardiol 2017; 70:466.
42. Knight DS, Zumbo G, Barcella W, et al. Cardiac Structural and Functional Consequences of Amyloid Deposition by Cardiac Magnetic Resonance and Echocardiography and Their Prognostic Roles. JACC Cardiovasc Imaging 2019; 12:823.
43. Carvalho FP, Erthal F, Azevedo CF. The Role of Cardiac MR Imaging in the Assessment of Patients with Cardiac Amyloidosis. Magn Reson Imaging Clin N Am 2019; 27:453.
44. Brownrigg J, Lorenzini M, Lumley M, Elliott P. Diagnostic performance of imaging investigations in detecting and differentiating cardiac amyloidosis: a systematic review and meta-analysis. ESC Heart Fail 2019; 6:1041.
45. Dorbala S, Cuddy S, Falk RH. How to Image Cardiac Amyloidosis: A Practical Approach. JACC Cardiovasc Imaging 2020; 13:1368.

46. Fontana M, Pica S, Reant P, et al. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. Circulation 2015; 132:1570.
47. Zhao L, Tian Z, Fang Q. Diagnostic accuracy of cardiovascular magnetic resonance for patients with suspected cardiac amyloidosis: a systematic review and meta-analysis. BMC Cardiovasc Disord 2016; 16:129.
48. Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson 2017; 19:75.
49. Karamitsos TD, Piechnik SK, Banypersad SM, et al. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. JACC Cardiovasc Imaging 2013; 6:488.
50. Fontana M, Banypersad SM, Treibel TA, et al. Native T1 mapping in transthyretin amyloidosis. JACC Cardiovasc Imaging 2014; 7:157.
51. Baggiano A, Boldrini M, Martinez-Naharro A, et al. Noncontrast Magnetic Resonance for the Diagnosis of Cardiac Amyloidosis. JACC Cardiovasc Imaging 2020; 13:69.
52. Banypersad SM, Sado DM, Flett AS, et al. Quantification of myocardial extracellular volume fraction in systemic AL amyloidosis: an equilibrium contrast cardiovascular magnetic resonance study. Circ Cardiovasc Imaging 2013; 6:34.
53. Fontana M, Banypersad S, Triebel T, et al. AL and ATTR cardiac amyloid are different: native T1 mapping and ECV detect different biology. J Cardiovasc Magn Reson 2014; 16:341.
54. Banypersad SM, Fontana M, Maestrini V, et al. T1 mapping and survival in systemic light-chain amyloidosis. Eur Heart J 2015; 36:244.
55. Kotecha T, Martinez-Naharro A, Treibel TA, et al. Myocardial Edema and Prognosis in Amyloidosis. J Am Coll Cardiol 2018; 71:2919.
56. Perugini E, Guidalotti PL, Salvi F, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. J Am Coll Cardiol 2005; 46:1076.
57. Trivieri MG, Dweck MR, Abgral R, et al. 18F-Sodium Fluoride PET/MR for the Assessment of Cardiac Amyloidosis. J Am Coll Cardiol 2016; 68:2712.
58. Lachmann HJ, Booth DR, Booth SE, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. N Engl J Med 2002; 346:1786.
59. Nativi-Nicolau J, Maurer MS. Amyloidosis cardiomyopathy: update in the diagnosis and treatment of the most common types. Curr Opin Cardiol 2018; 33:571.

This generalized information is a limited summary of diagnosis, treatment, and/or medication information. It is not meant to be comprehensive and should be used as a tool to help the user understand and/or assess potential diagnostic and treatment options. It does NOT include all information about conditions, treatments, medications, side effects, or risks that may apply to a specific patient. It is not intended to be medical advice or a substitute

Topic 122846 Version 8.0

Chapter 4

Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis

Author:Angela Dispenzieri, MD
Section Editors:S Vincent Rajkumar, MD, Richard J Glassock, MD, MACP, Steve J Schwab, MD, FACP, FASN
Deputy Editor:Rebecca F Connor, MD, Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Aug 2023. This topic last updated: Mar 13, 2023.

INTRODUCTIONImmunoglobulin light chain (AL) amyloidosis (previously referred to as primary amyloidosis), is a monoclonal plasma cell proliferative disorder characterized by tissue deposits of fibrils composed of monoclonal light chain fragments, leading to organ dysfunction.

The incidence of AL amyloidosis is approximately one-fifth that of multiple myeloma (MM). At the time of diagnosis, approximately 10 percent of patients with AL amyloidosis will meet diagnostic criteria for MM as defined by CRAB (hypercalcemia, renal insufficiency, anemia, or bone disease) criteria; nearly another 40 percent of patients with AL do not meet criteria for MM but have 10 percent or more bone marrow plasmacytosis at diagnosis. The clinical course and treatment of these patients is dependent on which of the two diseases is dominant in terms of end-organ damage and symptoms. Less than 1 percent of patients with isolated AL amyloidosis at diagnosis develop MM at a future time point.

The treatment and prognosis of AL amyloidosis will be reviewed in detail here. The pathogenesis, clinical features, and diagnosis of these disorders and the diagnosis and management of amyloid cardiomyopathy and renal amyloid are discussed in detail separately.

●(See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis".)

●(See "Monoclonal immunoglobulin deposition disease".)

●(See "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis".)

●(See "Amyloid cardiomyopathy: Treatment and prognosis".)

●(See "Renal amyloidosis".)

PRETREATMENT EVALUATION

Assessment — To best treat patients with AL amyloidosis, the initial evaluation must confirm the diagnosis, establish the extent and sites of disease, and evaluate for comorbidities that are likely to have an impact on treatment options. The diagnosis of AL amyloidosis is presented separately. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis".)

In addition to a history and physical examination, it is our practice to perform the following pretreatment studies in patients with AL amyloidosis some of which will have already been performed as part of the diagnostic evaluation:

●Laboratory studies include a complete blood count with differential, chemistries with liver and renal function and electrolytes, electrophoresis of the serum and urine, immunofixation of the serum and urine, serum free light chain assay, 24-hour urinary protein and creatinine clearance, troponin T, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and thyroid stimulating hormone (TSH). We measure factor X levels for all patients; alternatively, clinicians may choose to check prothrombin time (PT) and partial thromboplastin time (PTT) with plans to check factor X levels in patients with abnormal bleeding or abnormal PT/PTT testing.

●Unilateral bone marrow aspirate and biopsy with immunohistochemical staining for kappa and lambda and Congo red staining for amyloid. The prognostic value of fluorescence in situ hybridization (FISH) studies is not well established. We perform FISH to identify t(11;14), t(4;14), t(6;14), t(14;16), t(14;20), trisomies, 1q+, and del17p. While there are data that patients with t(11;14) are less likely to respond to bortezomib-based therapy [1,2], this poor prognosis may be abrogated partially by the use of transplant, daratumumab, or low dose alkylator, but these data need further confirmation [3,4]. (See "Multiple myeloma: Staging and prognostic studies".)

●Bone imaging should be performed in patients with ≥10 percent bone marrow plasma cells. As with other patients with suspected multiple myeloma, cross sectional imaging is preferred over plain radiographs. This is discussed in more detail separately. (See "Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis", section on 'Choice of modality'.)

●Electrocardiogram, echocardiogram, and chest radiograph. A cardiac magnetic resonance imaging (MRI) study may be valuable in certain circumstances. Late gadolinium enhancement can diagnose cardiac involvement, but it is not independently prognostic of other cardiac measures [5]. Equilibrium contrast cardiovascular magnetic resonance can be used to quantify the cardiac interstitial compartment, measured as myocardial extracellular volume (ECV) fraction [6].

●Blood pressure should be measured while the patient is seated and standing to assess for orthostatic (postural) hypotension due to autonomic neuropathy. Patients with neurologic symptoms should be evaluated with electromyography (EMG) and nerve conduction studies (NCS). Since the neuropathy is most typically a small fiber neuropathy, EMG/NCS are often normal despite symptoms of paresthesia or dysesthesia. (See "Musculoskeletal manifestations of amyloidosis" and "Myopathies of systemic disease", section on 'Amyloid myopathy'.)

●Craniocaudal liver span should be documented with an ultrasound or computed tomography. Patients with symptoms of gastroparesis should undergo a study of gastric emptying. (See "Gastroparesis: Etiology, clinical manifestations, and diagnosis", section on 'Scintigraphic gastric emptying'.)

●Men and women with child-bearing potential should receive counseling about the potential effect of treatment on their fertility and options for fertility-preserving measures. Given the urgent need for treatment, options for women are limited, but men can often participate in sperm banking. (See "Fertility and reproductive hormone preservation: Overview of care prior to gonadotoxic therapy or surgery".)

Organ involvement defined — For treatment purposes, organ involvement by amyloidosis is defined by consensus criteria created in 2005 at the 10th International Symposium on Amyloid and Amyloidosis and revised in 2011 [7,8]:

●Kidney – Direct biopsy verification with clinical or laboratory evidence of organ dysfunction or, if amyloid deposits have been confirmed at another site, 24-hour urine protein >0.5 g/day, predominantly albumin. Other causes of proteinuria (eg, poorly controlled diabetes mellitus or uncontrolled hypertension) should be excluded. (See "Renal amyloidosis".)

The likelihood of requiring dialysis can be predicted using two risk factors: 24-hour urinary protein excretion ≥5 g/24 hours and estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 [9]. In one study, among patients with previously

untreated AL amyloidosis, dialysis was required within two years in 0 to 3, 11 to 25, and 60 to 75 percent of those with none, one, or both risk factors, respectively.

●Heart – Direct biopsy verification with clinical or laboratory evidence of organ dysfunction or, if amyloid deposits have been confirmed at another site, echocardiogram with mean wall thickness (interventricular septum and posterior wall) >12 mm with no other cardiac cause or an elevated NT-proBNP (>332 ng/L) in the absence of renal failure or atrial fibrillation. NT-proBNP is highly sensitive for cardiac involvement in patients with AL amyloidosis and a normal NT-proBNP rules out the possibility of clinically meaningful cardiac involvement [10]. (See "Amyloid cardiomyopathy: Treatment and prognosis" and "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis".)

●Liver – Direct biopsy verification with laboratory evidence of organ dysfunction or, if amyloid deposits have been confirmed at another site, total liver span >15 cm in the absence of heart failure or alkaline phosphatase >1.5 times institutional upper limit of normal. (See "Gastrointestinal amyloidosis: Clinical manifestations, diagnosis, and management", section on 'Hepatic amyloidosis'.)

●Nerve – Clinical symmetric lower extremity sensorimotor peripheral neuropathy or gastric-emptying disorder, intestinal pseudo-obstruction, voiding dysfunction not related to direct organ infiltration.

●Gastrointestinal tract – Direct biopsy verification with symptoms (eg, diarrhea, motility disturbances, and weight loss). Identification of vascular-only amyloid deposits without symptoms should not be considered intestinal organ involvement. (See "Gastrointestinal amyloidosis: Clinical manifestations, diagnosis, and management", section on 'Gastrointestinal tract amyloidosis'.)

●Lung – Direct biopsy verification with symptoms and an interstitial radiographic pattern is included in the consensus criteria; however, we do not consider direct biopsies to be necessary in most of these patients.

●Soft tissue – Clinical tongue enlargement, arthropathy, claudication (presumed vascular amyloid), skin involvement, myopathy by biopsy or muscle pseudohypertrophy, lymph node involvement (may be localized), carpal tunnel syndrome.

Staging — While multiple prognostic models have been proposed for patients with amyloidosis, simple staging models that incorporate N-terminal prohormone of

brain natriuretic peptide (NT-proBNP) and cardiac troponin are easily applied in clinical practice (table 1). The systems below can used to assess prognosis at diagnosis, and to compare clinical trials. The Mayo 2004 and revised Mayo system can also be used for restaging at three and six months from treatment initiation and at the time of second-line therapy [11,12].

●**NT-proBNP plus cardiac troponin T (Mayo 2004 Stage with European Modification)** – The Mayo 2004 staging system uses cardiac troponin and NT-proBNP to determine stage as follows (table 1) [13]:

•Stage I – Cardiac troponin <0.035 mcg/L and NT-proBNP <332 ng/L

•Stage II – Cardiac troponin ≥0.035 mcg/L or NT-proBNP ≥332 ng/L (not both)

•Stage III – Cardiac troponin ≥0.035 mcg/L and NT-proBNP ≥332 ng/L

In 2015, the Europeans proposed splitting the stage III patients into IIIa and IIIb based on the absence or presence of NT-proBNP >8500 ng/L, respectively [14]:

•Stage IIIA – Cardiac troponin ≥0.035 mcg/L and NT-proBNP 332 to <8500 ng/L

•Stage IIIB – Cardiac troponin ≥0.035 mcg/L and NT-proBNP ≥8500 ng/L

Of note, some laboratories measure cardiac troponin I instead of T. If cardiac troponin I is used instead of T, a value of ≥0.10 mcg/L is considered a risk factor in this model [15].

The Mayo 2004 staging system was originally derived using clinical information from 242 patients with newly diagnosed AL amyloidosis seen at a single institution [13]. Median survivals for those not undergoing hematopoietic cell transplantation (HCT) with stage I, II, and III AL amyloidosis were 26, 11, and 4 months, respectively. Another study reported that this model predicted prognosis in patients with AL amyloidosis undergoing HCT, with stage III patients having a median survival of less than one year despite HCT [16].

●**BNP plus cardiac troponin I (Boston University Staging System)** – The Boston University staging system uses cardiac troponin I and brain natriuretic peptide (BNP) as risk factors (table 1) [17]:

•Stage I – Cardiac troponin I ≤0.10 ng/mL and BNP ≤81 pg/mL

•Stage II – Cardiac troponin I >0.10 ng/mL or BNP >81 pg/mL (not both)

•Stage IIIA – Cardiac troponin I >0.10 ng/mL and BNP >81 to 700 pg/mL

•Stage IIIB – Cardiac troponin I >0.10 ng/mL and BNP >700 pg/mL

When applied to a cohort of 250 consecutive patients referred to their center in 2016, corresponding estimated median overall survival times were not reached, 9.4 years, 4.3 years, and 1 year [17]. This system has not yet been validated by other groups. Importantly, a variety of clinical immunoassays are available for plasma BNP and they are not completely interchangeable.

•NT-proBNP, cardiac troponin T, and serum free light chains (Mayo 2012 Stage) – The Mayo 2012 staging system uses NT-proBNP ≥1800 ng/L, cardiac troponin T ≥0.025 mcg/L, and the difference between involved and uninvolved serum free light chains (dFLC) ≥18 mg/dL as risk factors (table 1) [18]:

•Stage I – None elevated

•Stage II – One elevated

•Stage III – Two elevated

•Stage IV – Three elevated

If cardiac troponin T is measured using a high sensitivity assay, a cutoff of 40 pg/mL should be used [15,19].

The Mayo 2012 staging system was developed using data from 810 patients with newly diagnosed AL amyloidosis seen at a single institution and validated in another 303 patients undergoing HCT and 103 patients enrolled onto different clinical trials [18]. For patients classified as having stage I, II, III, or IV disease, median overall survival from diagnosis was 94, 40, 14, and 6 months, respectively. For patients undergoing HCT, the four-year estimated overall survival rates were 87, 72, 56, and 46 percent, respectively, with median overall survivals of not reached, 97, 58, and 22 months.

GENERAL CONCEPTS

Goals of therapy — Patients with systemic AL amyloidosis are not cured with conventional treatment. However, early mortality rates have decreased and survival has improved as there has been a shift toward earlier diagnosis and therapy aimed at achieving deep remissions [20]. (See 'Prognosis' below.)

While remissions can be attained, relapses are common. Treatment directed at the plasma cells aims to decrease amyloid production, limit further organ damage, and allow for regression of tissue amyloid deposits. With this approach, regression of tissue amyloid deposits is uncommon; as such, symptoms due to these deposits are likely not reversible. Management is multidisciplinary, often involving the collaboration of experts in hematology, cardiology, nephrology, gastroenterology, and neurology.

Indications for systemic therapy — Virtually all patients with systemic AL amyloidosis require treatment at the time of diagnosis. An important exception is patients with AL amyloid in the bone marrow discovered incidentally as part of the evaluation of monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma in whom initial therapy can be postponed until the first sign of organ involvement. Such patients are seen in clinic every three months. At these visits we perform a focused review of systems and examination along with laboratory studies to detect progression (serum immunoglobulin, free light chains, alkaline phosphatase, troponin, NT-proBNP, creatinine, and spot urine for albumin).

Systemic therapy is also not necessary for patients with localized forms of AL amyloidosis (eg, tracheobronchial, genitourinary, isolated carpal tunnel and non-purpuric cutaneous lesions). These deposits are not due to an underlying systemic clonal plasma cell disorder and do not progress to systemic disease [21]. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Localized amyloidosis'.)

Amyloid cardiomyopathy — Patients with amyloid cardiomyopathy due to AL amyloidosis need careful management of cardiac complications including heart failure (HF), atrial fibrillation, and conduction disease. In particular, treatment of HF in patients with cardiac amyloidosis differs from the therapy generally recommended in patients with diastolic or systolic HF. This is described in more detail separately. (See "Amyloid cardiomyopathy: Treatment and prognosis".)

INITIAL TREATMENT

Determining transplant eligibility — All patients with newly diagnosed AL amyloidosis need to be assessed to determine eligibility for autologous hematopoietic cell transplantation (HCT). Eligibility for autologous HCT in AL amyloidosis varies across countries and institutions. Autologous HCT is offered primarily to patients less than 70 years of age. However, a strict age-limit is not used and retrospective analyses suggest that carefully selected patients over age 70 years may have good outcomes with HCT [22]. As such, decisions are made on a case-by-case basis based on "physiologic age" and vary across institutions. Over 80 percent of newly diagnosed patients will be ineligible for transplant due to advanced age, renal insufficiency, advanced heart failure, or multiorgan involvement [23]. (See "Determining eligibility for autologous hematopoietic cell transplantation".)

In general, patients should meet all of the following criteria in order to be eligible for autologous HCT in AL amyloidosis [24,25]:

●Physiologic age ≤70 years

●Troponin T <0.06 ng/mL (or hs-Troponin T <75 ng/mL)

●Systolic blood pressure ≥90 mmHg

●Creatinine clearance ≥30 mL/min (unless on chronic stable dialysis)

●Eastern Cooperative Oncology Group (ECOG) performance status ≤2 (table 2)

●New York Heart Association (NYHA) functional status class I or II (table 3)

●No more than two organs significantly involved (liver, heart, kidney, or autonomic nerve)

●No large pleural effusions

●No dependency on oxygen therapy

These are guidelines; the decision on transplant eligibility should be made based on a risk-benefit assessment and the needs and wishes of the patient. Of importance, patients with severe (<25 percent) factor X deficiency have a transplant-related mortality (TRM) rate that approaches 50 percent [26]. Splenectomy may be performed in such patients in an effort to increase factor X levels prior to HCT [27].

Cardiac and renal transplantation followed by HCT has been used in selected patients with cardiac and renal amyloidosis, respectively, and is discussed separately. (See "Renal amyloidosis", section on 'Dialysis and kidney transplantation' and "Amyloid cardiomyopathy: Treatment and prognosis".)

Support for the use of these transplant eligibility criteria comes from retrospective analyses and small prospective series that have demonstrated the adverse prognostic importance of organ involvement in patients with AL amyloidosis undergoing HCT [28-33]. As an example, in a series of 21 transplanted patients, the most striking finding was the prognostic value of the number of clinical manifestations of amyloidosis at the time of transplantation [28]. The criteria used included creatinine clearance <30 mL/min, nephrotic syndrome, heart failure, neuropathy, or hepatomegaly associated with an alkaline phosphatase concentration >200 international units (IU)/L. Patients with less than two of these manifestations had a much higher overall (92 versus 11 percent) and event-free (46 versus 11 percent) survival than those with two or more manifestations. The poor outcomes in the latter group were primarily due to a greater than 75 percent incidence of toxic death with intensive therapy.

Patients eligible for transplant

Choice of therapy — There is uncertainty regarding the preferred management of patients who are eligible for HCT, and participation in clinical trials should be encouraged. Outside of a clinical trial, we suggest the use of induction therapy followed by high dose melphalan and autologous HCT for patients who are fit enough, rather than HCT or chemotherapy alone (algorithm 1). HCT should be performed at a center with specific expertise in AL amyloidosis. Other experts offer induction therapy and defer HCT in those with a satisfactory response [25].

Our preference for HCT is based on low quality data that suggest HCT can result in longer remissions, though data using daratumumab-based inductions may eventually challenge that paradigm [34]. As with any therapy that results in deep hematologic response, HCT stops amyloid production, amyloid deposits are slowly resorbed, and organ function, performance status, and quality of life improve. However, careful selection of patients is critical since there is an increased risk of TRM from compromised organ reserve due to amyloid deposition. (See 'HCT efficacy and toxicity' below.)

Emerging data suggest better outcomes for patients who receive two to four cycles of bortezomib-based induction therapy prior to stem cell mobilization and

transplantation. Our preferred induction therapy is subcutaneous daratumumab plus cyclophosphamide, bortezomib, and dexamethasone (CyBorD). If daratumumab is not available, we offer induction with CyBorD alone. (See 'Bortezomib-based regimens' below.)

Treatment regimens that include immunomodulatory derivatives (eg, lenalidomide, thalidomide) are generally avoided as these drugs are typically less well-tolerated in patients with AL amyloidosis [35-39]. Following HCT, we consider further therapy based on the degree of response achieved. This is discussed in more detail below. (See 'Monitoring response' below.)

Maintenance therapy is offered after HCT to all patients with overt multiple myeloma (MM), and to selected patients without overt MM but with at least 20 percent bone marrow plasma cells and/or high-risk findings on fluorescence in situ hybridization (FISH; ie, del17p, t(4;14), t(14;16), and t(14;20)). (See "Multiple myeloma: Use of hematopoietic cell transplantation", section on 'Maintenance'.)

Although one study has suggested that there might be a component of graft-versus-tumor effect in patients receiving myeloablative or nonmyeloablative allogeneic HCT, allogeneic HCT is **not** considered a treatment option given an extremely high incidence of TRM [40].

HCT efficacy and toxicity — Autologous HCT allows for the delivery of myeloablative doses of melphalan aimed at the underlying plasma cell dyscrasia. Delivery of higher melphalan doses is associated with deeper responses and better clinical outcomes [28,29,41-45]. When successful, HCT stops amyloid production, amyloid deposits are slowly resorbed, and organ function, performance status, and quality of life improve [46]. However, careful selection of patients is critical since there is an increased risk of TRM from compromised organ reserve due to amyloid deposition.

Patients with AL amyloidosis are at increased risk for early TRM due to cardiac arrhythmias, sepsis, intractable hypotension, gastrointestinal bleeding, and multiorgan failure. Experienced referral centers have multidisciplinary teams that are well equipped to manage these complicated patients. At these centers, early TRM is <5 percent [47-50].

Studies that have compared HCT with conventional chemotherapy have had mixed results [42,51-58].

While the results of a small randomized trial suggested no benefit from HCT, a number of flaws in study design question the applicability of these results to this patient population [59]. Retrospective studies have suggested improved overall survival (OS) and improved quality of life among patients with AL amyloidosis undergoing HCT when compared with similar patients undergoing chemotherapy alone [51,60]. Results may be even better with careful patient selection and implementation of a risk-adapted approach [42,51,52,54-56,61].

The following studies illustrate outcomes seen with HCT:

●A retrospective analysis of the International Blood and Marrow Transplant Research database identified 1536 patients with AL amyloidosis who underwent autologous HCT between 1995 and 2012 [47]. Over the study time-period there was a decline in early mortality and improvement in OS. Among the 800 patients transplanted from 2007 to 2012, the mortality rate at 100 days was 5 percent; the estimated OS rate at five years was 77 percent. Outcomes were better at centers that performed more transplants. Factors associated with worse outcomes included cardiac involvement, poor performance status, and increased creatinine. It is unknown whether the improved outcomes over time were a result of improved patient selection, changes in the transplant protocols, better supportive care, or a combination of these factors.

●A series of 629 patients treated with high dose melphalan (100 to 200 mg/m^2) followed by autologous HCT at Boston University School of Medicine reported the following [48,62,63]:

•The 100-day TRM was 7.5 percent. The TRM in patients transplanted after 2005 was lower at 3.4 percent, probably reflecting better patient selection and improvements in supportive care. Median survival was 7.6 years.

•Complete response (CR) was obtained in 40 percent. Patients who attained a CR had superior median OS (not reached at 8 years follow-up versus 6.3 years) and estimated rates of survival at 1 (100 versus 94 percent), 5 (88 versus 60 percent), 10 (72 versus 34 percent), and 15 (57 versus 18 percent) years. The median survival following hematologic relapse was 4.3 years.

•TRM, rates of CR, and median survivals were similar in older (65 to 79 years) and younger (<65 years) patients eligible for, and receiving, HCT [64].

•A higher dose of melphalan (200 mg/m^2) was associated with a higher CR rate and improved OS.

•Improvement in the function of at least one organ system (eg, hepatic, renal, cardiac, neurologic) occurred in 79 percent of those achieving a CR, and in 39 percent of those who did not achieve CR status.

●In a series of 672 patients undergoing autologous HCT at the Mayo Clinic, the 100-day TRM declined over time (14.5 percent from 1996 to 2002; 8.6 percent from 2003 to 2009; 2.4 percent from 2010 to 2016) [49]. CR was obtained in 40 percent and a partial response (PR) or better was seen in 80 percent. Median OS was 122 months. For the most recent cohort, over 85 percent were alive at one year and the estimated rate of survival at five years exceeded 80 percent. Earlier disease stage and deeper responses were associated with superior survival.

Other experts offer bortezomib-based therapy (eg, daratumumab plus CyBorD, cyclophosphamide, bortezomib, dexamethasone) to all patients with deferral of HCT in those who achieve a satisfactory response (eg, CR or organ response plus an at least partial response) [25]. This approach places a higher value on the avoidance of HCT-related toxicity, while recognizing the risk that some patients may become ineligible for HCT. While most studies evaluated this approach with CyBorD alone, daratumumab plus CyBorD is the preferred induction regimen, if available, based on the Andromeda study [4].

●In a report from one center that used this approach, 63 of 139 patients (45 percent) achieved a satisfactory response and were treated with CyBorD alone; of the 76 patients with unsatisfactory response, 55 patients proceeded with HCT, 16 patients lost eligibility for HCT, and 5 patients refused HCT [58]. The estimated five-year OS was similar among the patients treated with HCT or CyBorD alone (86 versus 84 percent); however, five-year OS was 51 percent among the patients with unsatisfactory response who did not undergo HCT.

●A retrospective analysis of >650 patients who underwent stem cell collection at a large referral center reported similar OS among patients who underwent HCT within 90 days of collection and those who had not undergone HCT by 90 days [65]. Median OS was similar among patients who achieved an at least very good partial response at the time of collection and underwent early HCT or deferred HCT (14.2 versus 13.4 years). However, when the analysis was limited to patients who received induction therapy prior to stem cell collection, there was a trend for better

OS among those who underwent early HCT, although this difference did not reach statistical significance.

Melphalan dosing — The standard preparative (conditioning) regimen used for HCT in AL amyloidosis is melphalan at a dose of 200 mg/m^2. Even in transplant-eligible patients, the TRM is higher in AL amyloidosis than in myeloma [66]. Although a risk-adapted dosing strategy using lower conditioning doses of melphalan has been evaluated in an attempt to reduce TRM, this has been associated with lower efficacy [42,44,62,67]. Patients who are considered to be ineligible to receive a melphalan dose of 200 mg/m^2 are probably best treated with nontransplant approaches. One exception is patients who are on chronic stable dialysis and are being considered for transplantation in whom a reduced melphalan dose of 140 mg/m^2 is used. (See "Multiple myeloma: Use of hematopoietic cell transplantation", section on 'Preparative chemotherapy'.)

Patients not eligible for transplant

Choice of therapy — The preferred management of patients who are not eligible for HCT is unclear, and participation in clinical trials should be encouraged. Outside of a clinical trial, we offer combination therapy with daratumumab, bortezomib, cyclophosphamide, dexamethasone (dara-CyBorD), or a triplet like CyBorD or bortezomib, melphalan, and dexamethasone (BMD) (algorithm 1). This preference is based on clinical trials and large case series with these regimens demonstrating encouraging response rates and tolerability. If the patient is not a candidate for bortezomib, we offer daratumumab as a single agent or in combination with cyclophosphamide and dexamethasone. This includes patients with sensory neuropathy that is painful or limiting self-care.

Support for the use of bortezomib-based regimens comes from a randomized trial that showed an OS benefit for the addition of bortezomib to melphalan plus dexamethasone [68]. BMD has not been directly compared with CyBorD in randomized trials; retrospective analyses suggest equipoise [69]. In another randomized trial, the addition of daratumumab to CyBorD deepened responses and delayed major organ deterioration [70]. Our approach for patients who are not candidates for transplantation is to initiate therapy with one of these regimens, assess response each cycle, and modify therapy if an optimal response is not achieved. Better treatments are needed and patients, especially those with advanced cardiac involvement, should be encouraged to participate in clinical trials. (See 'Clinical trials' below.)

We offer alternative systemic therapy if the initial therapy fails to achieve >50 percent reduction in the difference between involved free light chain (FLC) levels and uninvolved FLC levels (dFLC) after two cycles; or dFLC ≥40 mg/L after four to six cycles; or if there is disease progression at any time. (See 'Response assessment' below.)

Although for many years melphalan and prednisone was the standard treatment of patients with AL amyloidosis who were not candidates for HCT [53,71-76], this has been replaced by regimens described below as front-line therapy in these patients.

Bortezomib-based regimens — For most patients who are not candidates for HCT, we recommend a bortezomib-based regimen. If available, we prefer the combination of daratumumab, cyclophosphamide, bortezomib, and dexamethasone (dara-CyBorD) based on the Andromeda trial which demonstrated that the addition of daratumumab to CyBorD resulted in deeper responses and delayed major organ deterioration [4]. If daratumumab is not available, we prefer cyclophosphamide, bortezomib, and dexamethasone (CyBorD) or bortezomib, melphalan, and dexamethasone (BMD), rather than melphalan plus dexamethasone. Rapid responses are seen in a majority of patients and the most common toxicities are vomiting, diarrhea, and cytopenias [14,69,77-81]. Neuropathy can be dose limiting, but is abrogated by subcutaneous administration.

CyBorD with or without daratumumab — For AL amyloidosis, CyBorD is usually administered on a 28-day cycle as follows:

- Bortezomib 1.3 to 1.5 mg/m^2 subcutaneous administration once a week

- Cyclophosphamide 500 mg (total dose) by mouth once a week

- Dexamethasone 20 to 40 mg by mouth once a week

If available, daratumumab-hyaluronidase (1800 mg daratumumab with 30,000 units hyaluronidase) is administered subcutaneously once a week for cycles 1 and 2, then every two weeks for cycles 3 through 6, then every four weeks until disease progression or for a maximum of two years. Given concerns about cardiac toxicity, approval of daratumumab-hyaluronidase by the US Food and Drug Administration does not include patients with NYHA class IIIB or class IV cardiac disease or Mayo 2004 stage IIIB.

Depending on the degree of cytopenias and other side effects, an alternative CyBorD schedule is to administer bortezomib, cyclophosphamide, and dexamethasone for three consecutive weeks followed by a one-week break before proceeding with subsequent cycles. Note that the doses used are different than those used in multiple myeloma. Dose modifications may be needed for patients with renal and/or hepatic dysfunction. This regimen has a low or very low risk of emesis and antiemetic prophylaxis is not necessary. Patients should be encouraged to maintain adequate oral hydration to void every two to three hours to reduce the risk of hemorrhagic cystitis. Bortezomib therapy may be associated with an increased risk of herpes zoster and infections not related to neutropenia. Antiviral prophylaxis (eg, acyclovir 400 mg orally twice a day) should be administered to all patients receiving CyBorD. Some clinicians also administer trimethoprim-sulfamethoxazole double strength once daily on Mondays, Wednesdays, and Fridays during treatment.

In a phase 3 trial (ANDROMEDA), 388 patients with newly diagnosed AL amyloidosis were randomly assigned to receive six cycles of CyBorD with or without subcutaneous daratumumab [4]. Those assigned to daratumumab also received maintenance with single-agent daratumumab monthly for up to two years. After a median follow-up of 11.4 months, the addition of daratumumab to CyBorD resulted in higher rates of hematologic complete response at any time (53 versus 18 percent); higher rates of cardiac response (42 versus 22 percent) and renal response (53 versus 24 percent) at six months; and delayed a composite endpoint of major organ deterioration, hematologic progression, or death (hazard ratio 0.58; 95% CI 0.36-0.93).

Toxicity was also increased with higher rates of grade 3 or 4 adverse events (17 versus 10 percent) but a similar percentage of patients discontinuing therapy due to adverse events (4.1 versus 4.3 percent). Daratumumab increased the rates of lymphopenia (19 versus 15 percent), upper respiratory tract infections (26 versus 11 percent), and peripheral sensory neuropathy (31 versus 20 percent). A minority of patients have died in the two arms (27 and 29 patients, respectively); those assigned to daratumumab had a numerically higher percentage of deaths attributed to adverse events (11.9 versus 7.4 percent) and lower percentage of deaths attributed to disease progression (1 versus 4.8 percent) or other reasons (1 versus 2.7 percent). Most deaths, including those attributed to adverse events, occurred in patients with cardiac involvement at baseline. Longer follow-up is needed to assess impact on overall survival.

These results led to accelerated approval by the US Food and Drug Administration of subcutaneous daratumumab-hyaluronidase in combination with CyBorD for newly diagnosed AL amyloidosis [82]. In patients with AL amyloidosis, the prescribing information describes cardiac failure and/or cardiac arrest in 16 percent and fatal cardiac disorders in 10 percent. Patients with baseline cardiac involvement may be at higher risk and should be monitored closely for cardiac adverse reactions; daratumumab-hyaluronidase should not be used for patients with AL amyloidosis who have NYHA class IIIB or class IV cardiac disease or Mayo stage IIIB. Additional administration considerations are described separately. (See "Multiple myeloma: Administration considerations for common therapies", section on 'Anti-CD38 monoclonal antibodies'.)

The strongest data regarding the efficacy of CyBorD as initial treatment for AL amyloidosis comes from two large series, which included over 1000 patients [14,69]. Hematologic responses were seen in 60 to 65 percent (approximately 25 percent complete). Cardiac (17 to 33 percent), renal (15 to 25 percent), and liver (30 percent) responses were also reported. Survival correlated with Mayo Stage and degree of response. For the larger study, estimated median OS was 72 months for the entire population and not reached, 80, 36, and 4 months for patients with Mayo Stage I, II, IIIa (stage III with NT-proBNP ≤8500 ng/L), and IIIb (stage III with NT-proBNP >8500 ng/L), respectively. Stringent dFLC response (<10 mg/L) correlated with superior survival. Most toxicities were grade 1 to 2 with the most common being lethargy (56 percent), constipation (26 percent), fluid overload (24 percent), and sensory neuropathy (21 percent).

Bortezomib, melphalan, and dexamethasone — For AL amyloidosis, BMD is can be administered as follows [68]:

●Bortezomib 1.3 mg/m^2 subcutaneous administration on days 1, 4, 8, and 11 of cycles 1 and 2 (cycle length = 28 days), and on days 1, 8, 15, and 22 of subsequent cycles (cycle length = 35 days)

●Melphalan 0.22 mg/kg by mouth for four consecutive days each cycle

●Dexamethasone 40 mg by mouth for four consecutive days each cycle

Dose modifications may be needed for patients with renal and/or hepatic dysfunction. This regimen has a low or very low risk of emesis and antiemetic prophylaxis is not necessary. Bortezomib therapy may be associated with an increased risk of herpes zoster and infections not related to neutropenia. Antiviral

prophylaxis (eg, acyclovir 400 mg orally twice a day) should be administered to all patients receiving BMD. Some clinicians also administer trimethoprim-sulfamethoxazole double strength once daily on Mondays, Wednesdays, and Fridays during treatment. Primary prophylaxis with granulocyte-stimulating factor is not indicated. While the above schedule was used for the trial described below, prior studies have demonstrated better tolerability and higher effective doses of bortezomib delivered when using weekly bortezomib [77].

Data supporting the use of BMD comes from a phase III international, open-label trial in which 109 transplant-ineligible patients with previously untreated AL amyloidosis were randomly assigned to receive BMD versus melphalan plus dexamethasone alone [68]. The trial excluded patients with advanced cardiac stage (stage IIIb) amyloidosis. After a median follow-up of 50 months, BMD resulted in improved response rates (hematologic response at three months 79 versus 52 percent; very good partial response [VGPR] plus CR rate 64 versus 39 percent) and superior OS (median OS not reached versus 34 months; HR 0.50, 95% CI 0.27-0.90). BMD also increased the percentage of treatment cycles with grade 3 or 4 adverse events (20 versus 10 percent), although patient-reported quality of life after three cycles was similar between the two arms. The most common nonhematologic adverse events with BMD were peripheral sensory neuropathy (52 percent); gastrointestinal disorders (40 percent); and fluid retention, fatigue, and fever (approximately 20 percent each). Approximately 20 percent of patients in this trial received intravenous bortezomib; rates of peripheral neuropathy are lower with subcutaneous bortezomib administration. As this was a highly selected cohort, toxicities are likely to be more common in a broader population.

Melphalan and dexamethasone — Melphalan and dexamethasone is an option for patients with AL amyloidosis who are not candidates for HCT, cannot receive bortezomib, and do not have access to daratumumab. This regimen is well tolerated with cytopenias being the most common dose-limiting toxicity. Approximately 60 percent of patients will demonstrate an at least partial hematologic response, although response rates are much lower in patients with advanced cardiac involvement [83-85]. A hematologic response is required for functional improvement of involved organs (organ response).

Melphalan plus dexamethasone is administered in 28-day cycles as follows:

- Melphalan 0.22 mg/kg by mouth daily on days 1 through 4

- Dexamethasone 40 mg by mouth daily on days 1 through 4

This regimen has low or very low risks of emesis and infection and does not require prophylaxis for either. The melphalan dose can be reduced by 25 to 30 percent for patients with renal failure.

Support for the use of melphalan plus dexamethasone in this population comes from case series of patients treated at amyloid referral centers. Differences in response rates and survival have been largely attributed to the different proportions of high-risk patients.

In an early study, 46 patients with AL amyloidosis who did not meet criteria for HCT because of severe organ damage were treated with this regimen [86]. Prophylactic omeprazole (20 mg/day by mouth), ciprofloxacin (250 mg by mouth twice per day), and itraconazole (100 mg/day by mouth), were also given for the first 10 days of each cycle. Treatment was continued for up to nine courses. The following findings were noted [86]:

●CRs and overall response rates were noted in 33 and 67 percent of the patients, respectively, following a median of four treatment courses (4.5 months).

●Seventy-one percent of the 31 responding patients (ie, monoclonal protein decreased by at least 50 percent), achieved significant functional improvement of involved organs. No functional improvement was noted in the 15 patients not responding to treatment.

●At a median follow-up of five years, median progression-free survival (PFS) and OS were 3.8 and 5.1 years, respectively [87].

●CRs were durable, being maintained for at least three years in 70 percent of patients. In relapsing patients, the amyloid-producing clone remained sensitive to this regimen, and CR could be restored by repeat treatment [87].

In a subsequent report of 119 HCT-ineligible patients treated with this regimen at this center, hematologic and CR rates were 76 and 31 percent with a median survival of 7.4 years [85]. The same center used a lower dexamethasone dose (20 mg) in combination with standard melphalan to treat 140 patients with AL amyloidosis and advanced cardiac disease (eg, those with repetitive ventricular arrhythmias or fluid retention >3 percent of body weight). This higher risk population had hematologic and CR rates of 51 and 12 percent, respectively, and a median survival of 20 months. It is not clear whether these inferior outcomes were

related to the increased baseline risk of the population, the lower dexamethasone dose, or a combination of the two.

Comparable results have been demonstrated by the French [59], but other studies have demonstrated inferior results, which are thought to be at least partially explained by a higher incidence of cardiac involvement in the patient populations [88,89].

RESPONSE ASSESSMENT

Monitoring response — Patients are monitored to determine whether the disease is responding appropriately to therapy and whether a change in management is needed (algorithm 1). In general, we offer alternative systemic therapy in the following scenarios [90] (see 'Relapsed or refractory disease' below):

●Hematologic or organ progression at any time

●<50 percent reduction in the difference between involved free light chain (FLC) levels and uninvolved FLC levels (dFLC) after two cycles of chemotherapy

●dFLC ≥40 mg/L after four to six cycles of chemotherapy or on day 100 after transplant [90] (see 'Relapsed or refractory disease' below)

We follow patients monthly for the first year and while on active therapy. At these monthly visits, we routinely perform serum protein electrophoresis and serum FLC assay.

For organ response, we select among the following tests depending on the type of existing organ involvement and any new suspected organ involvement based on clinical features: serum troponin, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), creatinine, 24-hour urine protein electrophoresis, liver function tests, electrocardiography, and echocardiography. The frequency of the tests used to assess organ response varies according to the clinical condition, but is usually every three months.

Response criteria — Hematologic (table 4) and organ (table 5) response is determined by the criteria validated by the Roundtable on Clinical Research in Immunoglobulin Light Chain Amyloidosis [7,91,92]. Response to treatment correlates with overall survival (OS) (figure 1 and figure 2) [23,90-93].

The dFLC values used in these response criteria do not apply to the approximately 20 percent of patients with a pretreatment dFLC <50 mg/L. In patients with a pretreatment dFLC between 20 and 50 mg/L, two studies demonstrated superior OS among those achieving a post-treatment dFLC <10 mg/L [94,95].

There is uncertainty regarding the best definition for progressive disease. Interpretation of FLC values for identifying progression should consider the FLC value at diagnosis (baseline FLC), the lowest FLC achieved (nadir FLC), and limitations of the FLC assay [96]. A nadir FLC <20 mg/L is associated with higher organ response rates and superior progression-free and overall survival [97]. Outcomes are also better if treatment is reinstated before cardiac progression [98].

While initial retrospective studies suggest that the addition of multiparametric flow cytometry of the bone marrow to the hematologic response assessment may improve the distinction of prognostic groups, further study is needed to validate these findings and determine how to incorporate them into practice [99-101].

RELAPSED OR REFRACTORY DISEASEFor patients who relapse after or are refractory to initial therapy (bortezomib-based regimen, melphalan plus dexamethasone, or hematopoietic cell transplantation [HCT]), treatment options include daratumumab, proteasome inhibitor-based regimens, and immunomodulatory-based regimens [78,102-104].

There are no good data to determine which of these regimens will be of most benefit; the choice will be dictated by prior therapy, patient and physician preferences, expected toxicity, drug availability, and insurance coverage. As an example, daratumumab may be preferred for patients with severe cardiac involvement, while a lenalidomide-based regimen may be preferred for patients with peripheral neuropathy. Lenalidomide-based regimens are also preferred for patients who received bortezomib as part of their original therapy. We typically reserve bendamustine-based regimens for patients who have received multiple prior regimens, or for those with toxicities that limit the use of other agents.

Our experience and other case series suggest that venetoclax is very effective in patients with t(11;14) [105-112]. Clinical trials are in progress to fully evaluate the safety and efficacy of this drug as a single agent or in combination.

Daratumumab-based regimens — The anti-CD38 monoclonal antibody daratumumab and daratumumab-based combination regimens are treatment options that have demonstrated activity in AL amyloidosis. While off-label for this

population, these regimens may be particularly attractive for patients with severe cardiac involvement. Use in newly diagnosed AL amyloidosis is discussed separately. (See 'CyBorD with or without daratumumab' above.)

Daratumumab can be administered subcutaneously (daratumumab 1800 mg with hyaluronidase 30,000 units) or intravenously (daratumumab 16 mg/kg) depending on formulation availability. Subcutaneous administration has fewer infusion-related reactions and a faster administration time. Either formulation is administered weekly for eight weeks, then every two weeks for 16 weeks, and then every four weeks for up to a maximum of two years [113,114]. Administration requires premedication to minimize infusion-related reactions, and antimicrobial prophylaxis to reduce viral reactivation. Daratumumab can interfere with cross-matching and red blood cell antibody screening. These and other administration considerations are discussed separately and in the prescribing information. (See "Multiple myeloma: Administration considerations for common therapies", section on 'Anti-CD38 monoclonal antibodies'.)

Retrospective studies and small phase 2 trials have described the safety and efficacy of daratumumab in patients with relapsed or refractory AL amyloidosis [113-122]. In the retrospective studies, single-agent daratumumab was associated with high rates of hematologic response (76 to 78 percent), with median times to first response less than three months. Toxicity was similar to that seen in patients with multiple myeloma, although infection may be more common in the AL amyloidosis population [121].

Further data come from two prospective trials that evaluated single-agent daratumumab in patients with previously treated AL amyloidosis [113,114]. In a single-center phase 2 trial that enrolled 22 patients with a median of two prior therapies, hematologic very good partial response (VGPR) or better was seen in 86 percent of patients with a median time to first response of four weeks and a median progression-free survival (PFS) of 28 months [114]. In a multicenter phase 2 trial that enrolled 40 patients with a median of three prior therapies, hematologic VGPR or better was seen in 48 percent with a median time to first response of one week, and median PFS of 25 months [113]. Both studies reported renal and cardiac responses. Further response was unlikely in those without response after four doses. Adverse events were mostly low grade and similar to those reported in other populations; the most common were infections (55 percent), infusion reactions (53 percent), and gastrointestinal disorders (43 percent).

Retrospective analyses suggest that response rates may be even higher when daratumumab is used in combination with dexamethasone and other therapies such as lenalidomide, pomalidomide, or bortezomib [117,119,123].

Proteasome inhibitor-based regimens — The proteasome inhibitor bortezomib is frequently used as part of an initial treatment regimen for patients with AL amyloidosis based on prospective trials that have demonstrated efficacy. Ixazomib is an oral proteasome inhibitor with demonstrated efficacy in relapsed disease [124,125]; we consider its off-label use in this setting. Cardiovascular toxicities with carfilzomib are expected to limit its use in this population. (See 'Bortezomib-based regimens' above.)

Data regarding the use of ixazomib come from a phase 3 trial (TOURMALINE-AL1) of 168 patients with relapsed or refractory AL amyloidosis following one to two prior lines of therapy who were randomly assigned to ixazomib plus dexamethasone or to physician's choice of a non-proteasome inhibitor containing regimen from a prespecified list [126]. The most common physician's choice regimens were lenalidomide plus dexamethasone (47 patients), melphalan plus dexamethasone (24 patients), and cyclophosphamide plus dexamethasone (10 patients). The following results were reported:

●Approximately half of patients in each treatment arm had a hematologic response to treatment.

●Patients assigned to ixazomib plus dexamethasone had a longer treatment duration (median 11.7 versus 5.0 months) and median time to vital organ deterioration or mortality (35 versus 26 months; HR 0.53, 95% CI 0.32-0.87).

●Adverse effects included diarrhea (34 versus 30 percent), rash (33 versus 20 percent), cardiac arrhythmias (26 versus 15 percent), and nausea (24 versus 14 percent).

These results suggest that ixazomib plus dexamethasone provides more durable responses than non-proteasome inhibitor based therapies despite similar response rates.

Bortezomib has been studied in the relapsed setting. In retrospective studies and small prospective single-arm trials of bortezomib in relapsed AL amyloidosis, overall response rates (ORRs) were 70 to 80 percent with complete responses (CRs) in 25 to 40 percent [77,127]. Expected toxicities include cytopenias, gastrointestinal

distress, and peripheral neuropathy. When used to treat relapsed disease, once-weekly bortezomib is better tolerated and has similar efficacy to twice-weekly bortezomib.

Once-weekly bortezomib is usually preferred over twice-weekly bortezomib. While the response time appears slower with once-weekly administration, the toxicities are markedly less and may reduce the risk of neuropathy and neuropathic pain. Bortezomib has also been administered in combination with cyclophosphamide and dexamethasone (CyBorD) with rapid responses in patients with and without cardiac involvement. (See 'Bortezomib-based regimens' above.)

The incorporation of bortezomib-based consolidation was investigated in a phase II trial of 40 patients with AL amyloidosis who underwent initial treatment with high dose melphalan and autologous HCT [128]. Consolidation with six cycles of bortezomib plus dexamethasone was offered to patients with less than a complete hematologic response at three months. At a median follow-up of 45 months, the estimated PFS and overall survival (OS) rates at two years were 69 and 82 percent, respectively. The most common severe (grade 3/4) toxicities during consolidation were thrombocytopenia (40 percent), cardiac toxicity (17 percent), and anemia (13 percent). The majority (57 percent) experienced grade 2 or greater neuropathy.

Immunomodulatory derivatives — The immunomodulatory derivatives (IMiDs), lenalidomide, pomalidomide, and thalidomide, have demonstrated efficacy among patients with relapsed AL amyloidosis but have not been compared with other regimens in this setting. Of importance, the dosing used is lower than that used in patients with multiple myeloma. In general, pomalidomide- and lenalidomide-based regimens are preferred to thalidomide-based regimens. IMiDs have been associated with a rise in cardiac biomarkers. This is sometimes asymptomatic, but other times associated with worsening symptoms.

Lenalidomide-based regimens — The combination of lenalidomide plus low dose dexamethasone with or without cyclophosphamide is a reasonable option for patients with relapsed AL amyloidosis.

Lenalidomide plus dexamethasone is administered in a 28-day cycle as follows:

- Lenalidomide 15 mg by mouth daily for 21 days

- Dexamethasone 40 mg by mouth once per week

Of importance, the initial dose of lenalidomide as used in multiple myeloma (ie, 25 mg/day) is poorly tolerated in those with AL amyloidosis [35,36,129]. A lower dose, in the range of 5 to 15 mg/day, has been better tolerated [129]. Cardiac and renal toxicity have been reported, so the use of this drug should be reassessed in the setting of worsening clinical status [37,130,131]. This regimen has low or very low risks of emesis and infection and does not require prophylaxis for either. The combination of lenalidomide plus dexamethasone is associated with an increased risk of thrombosis and therefore requires thromboprophylaxis. (See "Multiple myeloma: Prevention of venous thromboembolism in patients receiving immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide)".)

●Two studies evaluated the efficacy of lenalidomide (initial dose 25 mg/day by mouth for 21 days of a 28-day cycle) with or without dexamethasone in patients with AL amyloid [35,36]. ORRs for subjects taking both medications were 67 to 75 percent, with CRs in 16 percent [129]. In one of the studies, organ responses were seen in 42 percent of patients who received at least three cycles of therapy [35].

●A phase I/II dose-escalation study in 26 patients with de novo AL amyloidosis reported complete hematologic responses in 42 percent of patients when lenalidomide 15 mg per day was combined with melphalan and dexamethasone [132]. At a median follow-up of 19 months, the estimated rates of OS and event-free survival (EFS) at two years were 81 and 54 percent, respectively. It is notable that only patients with a performance status (PS) of 0 or 1 were eligible for this trial. Two other trials that allowed patients with PS 2 or better have had nearly comparable results with hematologic responses in 44 to 68 percent of patients, hematologic CR in fewer than 20 percent of patients and approximate two-year OS and EFS of 7 and 50 percent, respectively [133,134]. One study that allowed patients with advanced cardiac disease had far inferior results [135].

●In phase II trials of lenalidomide, cyclophosphamide, and dexamethasone administered at different doses, hematologic responses were seen in 46 to 77 percent [38,136,137]. Estimated two-year survival rates were 41 to 59 percent. The most common toxicities were cytopenias, fatigue, edema, gastrointestinal, and rash.

Together, these studies suggest that lenalidomide-based regimens are active in patients with relapsed AL amyloidosis and associated with acceptable toxicity. The low levels of neurotoxicity make them particularly attractive for patients with baseline neuropathy.

Pomalidomide-based regimens — Small prospective trials have evaluated the use of pomalidomide plus dexamethasone (Pd) in patients with previously treated AL amyloidosis [138-140]. Pomalidomide appears to be well tolerated, and hematologic responses are seen in approximately half of patients. When used for AL amyloidosis, the starting dose is pomalidomide 2 mg daily for 28-day cycles with dose adjustments made based on toxicity and efficacy. If the drug is tolerated and there is no response after a two-month trial, we increase the dose to 4 mg daily.

In a phase 2 trial of pomalidomide (2 mg daily for 28-day cycles) and low dose dexamethasone in 33 patients with previously treated AL amyloidosis, hematologic responses were seen in 48 percent with a median time to response of 1.9 months [138]. Five patients had improvement in organ involvement. The median OS and PFS times were 28 and 14 months, respectively. Estimated OS and PFS at one year were 76 and 59 percent, respectively. The most common severe toxicities were neutropenia and fatigue. Two additional trials of Pd in previously treated AL amyloidosis reported hematologic response rates of 50 and 68 percent [139,140].

Thalidomide-based regimens — The combination of thalidomide plus low dose dexamethasone with or without cyclophosphamide is an option for patients with relapsed AL amyloidosis that has demonstrated efficacy [141,142]. However, pomalidomide- and lenalidomide-based regimens are generally preferred to thalidomide-based regimens due to the toxicity of the latter.

Cyclophosphamide, thalidomide, and dexamethasone is administered as follows:

●Cyclophosphamide 500 mg once weekly

●Thalidomide 50 mg by mouth daily starting dose, and increased to a maximum dose of 200 mg/day over the course of four weeks

●Dexamethasone 20 to 40 mg by mouth once weekly

Of importance, higher doses of thalidomide such as those used in multiple myeloma are poorly tolerated in patients with AL amyloid [143,144]. Starting at a lower dose (50 mg daily) and slowly titrating minimizes toxicities. The combination of thalidomide plus dexamethasone is associated with an increased risk of thrombosis and therefore requires thromboprophylaxis. Treatment may be complicated by bradycardia, worsening heart failure, and neuropathy. (See "Multiple myeloma: Prevention of venous thromboembolism in patients receiving immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide)", section on 'Thalidomide'.)

Bendamustine-based regimens — Bendamustine plus dexamethasone is moderately effective in AL amyloidosis without significant cardiac, renal, or pulmonary toxicities. We typically reserve bendamustine-based regimens for patients who have received multiple prior regimens, or for those with toxicities that limit the use of other agents.

A multicenter phase 2 trial evaluated bendamustine (100 mg/m^2 on days 1 and 2) and dexamethasone (40 mg weekly) administered in 28-day cycles in 31 patients with persistent or progressive AL amyloidosis after at least one prior therapy [145]. Hematologic responses were seen in 57 percent with a median time to first response of 1.9 months. Seven patients had improvement in organ involvement. The median PFS and OS were 11 months and 18 months, respectively. OS was better among those with a hematologic response. Grade ≥3 adverse events were reported in 65 percent of patients. The most common adverse events were myelosuppression, fatigue, nausea, and vomiting.

In contrast, in a retrospective study of 122 patients with AL amyloidosis treated with bendamustine and prednisone with or without rituximab, the hematologic response rate was only 32 percent, and the median PFS among previously treated patients was eight months [146]. Response rates appeared to be higher among patients with AL amyloidosis and IgM monoclonal proteins. However, interpretation is limited by the inclusion of newly diagnosed and relapsed/refractory patients and the retrospective nature of the analysis. Prospective studies are needed to better evaluate the role of this combination.

PROGNOSIS

Impact of organ involvement — The prognosis of AL amyloidosis varies considerably depending on the nature, number, and extent of organ involvement (table 1). As such, prognosis is intimately tied to:

●Assessment of organ involvement (see 'Organ involvement defined' above)

●Staging with cardiac biomarkers (see 'Staging' above)

AL amyloidosis has a poor long-term prognosis when detected at an advanced stage [53,71,73,84,147,148]. Median survival may be as short as four to six months, with cardiac or hepatic failure and infection being the major causes of death. In one series, heart failure accounted for 51 percent of deaths, with renal failure and infection accounting for 15 percent each [53].

On the other hand, patients with limited organ involvement can expect a median survival in excess of five years with current therapy [60,149]. In approximately 15 to 20 percent of patients, the difference between the involved and uninvolved free light chains (dFLC) is <50 mg/L [94,95]. Such patients have superior survival rates and a different pattern of organ damage with less severe heart involvement and more frequent kidney involvement.

Since the early 2000s, we have observed a shift toward earlier diagnosis, with a reduction in early mortality and improvement in survival [20].

Coexisting myeloma — AL amyloidosis can occur in patients with other plasma cell dyscrasias, including multiple myeloma (MM) and Waldenström macroglobulinemia. When MM and AL amyloidosis are diagnosed in the same patient, the MM is typically diagnosed before or around the time of the amyloid diagnosis. Less commonly, MM develops more than six months after the diagnosis of amyloid. Patients that have a coexisting MM have a worse prognosis than patients who do not. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Relation to other plasma cell disorders'.)

A single-center retrospective analysis evaluated the prognostic impact of bone marrow plasma cells and MM-related end-organ damage (ie, CRAB) in 1255 patients diagnosed with AL amyloidosis between 2000 and 2010 [150]. The majority (679 patients) had AL amyloidosis without signs or symptoms of MM at the time of diagnosis and had a median overall survival of 46 months. MM-related end-organ damage was present in 100 patients, while 476 patients had bone marrow plasma cells >10 percent (without evidence of end-organ damage). Both of these latter findings were associated with advanced stage disease, increased cardiac biomarkers, and inferior median overall survival (10.6 and 16 months, respectively). The negative prognostic value of plasma cells >10 percent and of end-organ damage was independent of other prognostic factors.

In a retrospective analysis of 147 patients with biopsy-proven AL amyloidosis who also had specialized testing for determination of circulating plasma cells, 20 patients had concurrent MM [151]. Of the subset of patients with ≥2 percent circulating plasma cells, 50 percent had clinical MM, a rate significantly higher than the 12 percent incidence seen in those with fewer circulating plasma cells. Patients with both AL amyloidosis and MM had a significantly worse prognosis than those with AL amyloidosis alone (14 versus 32 months). (See "Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis", section on 'Peripheral smear'.)

IgM-related amyloidosis — Approximately 5 percent of AL amyloidosis is associated with an IgM monoclonal protein produced by a lymphoproliferative disorder such as lymphoplasmacytic lymphoma [152]. IgM-related AL amyloidosis appears to be a distinct clinical entity with less cardiac involvement and a higher incidence of lymph node and soft tissue involvement (eg, liver damage, peripheral and autonomic neuropathy). A relatively lower light chain clonal burden makes the application of standard response assessment criteria and prognostic tools challenging. Serial IgM measurements can be followed to help monitor response. In addition, a novel prognostic score has been proposed that incorporates liver and nerve involvement in addition to age and cardiac stage [152]. Overall, patients with IgM-related AL amyloidosis have had worse outcomes than non-IgM-related AL amyloidosis since they are less likely to respond to plasma cell-directed treatments. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'IgM-associated AL amyloidosis'.)

CLINICAL TRIALSOften there is no better therapy to offer a patient than enrollment onto a well-designed, scientifically valid, peer-reviewed clinical trial. Additional information and instructions for referring a patient to an appropriate research center can be obtained from the United States National Institutes of Health (www.clinicaltrials.gov).

Areas of interest include the use of hematopoietic cell transplantation, new combinations of available agents, the use of novel agents studied in related diseases, and experimental agents designed to degrade or interfere with the formation of amyloid fibrils [153,154]. (See "Treatment of AA (secondary) amyloidosis", section on 'Investigational approaches'.)

SOCIETY GUIDELINE LINKSLinks to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Immunoglobulin light chain (AL) amyloidosis".)

INFORMATION FOR PATIENTSUpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient education" and the keyword(s) of interest.)

●Basics topics (see "Patient education: AL amyloidosis (The Basics)")

SUMMARY AND RECOMMENDATIONS

●**Definitions** – Immunoglobulin light chain (AL) amyloidosis is a monoclonal plasma cell proliferative disorder characterized by tissue deposits of fibrils composed of monoclonal light chain fragments, leading to organ dysfunction. This disorder has a poor long-term prognosis, with cardiac or hepatic failure, and infection being the major causes of death. (See "Renal amyloidosis" and "Gastrointestinal amyloidosis: Clinical manifestations, diagnosis, and management", section on 'Hepatic amyloidosis' and "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis".)

●**Pretreatment evaluation** – To best treat patients with AL amyloidosis, the initial evaluation must confirm the diagnosis, establish the extent and sites of disease, and evaluate for comorbidities that are likely to have an impact on prognosis and treatment options. Simple staging systems that incorporate NT-proBNP and cardiac troponin are easily applied at the point of care (table 1). (See 'Pretreatment evaluation' above.)

●**Initial therapy** – Our approach to the initial management of patients with AL amyloidosis varies depending on whether patients are eligible to pursue high dose melphalan followed by autologous hematopoietic cell transplantation (HCT) (algorithm 1). Eligibility for autologous HCT in AL amyloidosis varies across countries and institutions. In general, patients with poor performance status, major comorbidities, involvement of three or more organs, and advanced cardiac amyloidosis are not considered transplant candidates. Participation in a well-conducted research trial is always a reasonable alternative. (See 'Determining transplant eligibility' above.)

•**HCT-eligible patients** – For patients eligible for HCT, we suggest induction therapy followed by high dose melphalan and autologous HCT rather than chemotherapy alone, provided that HCT can be performed in referral centers with adequate expertise in the procedure for this group of patients (Grade 2C). With better patient selection, and by using a risk-adapted approach, results with HCT may

be superior to those obtained following chemotherapy. (See 'Choice of therapy' above.)

As induction therapy, we offer two to four cycles of a bortezomib-based regimen. Our preferred regimen is daratumumab plus cyclophosphamide, bortezomib, and dexamethasone (CyBorD). If daratumumab is not available, we offer induction with CyBorD alone. (See 'Bortezomib-based regimens' above.)

•**Not eligible for HCT** – For patients not eligible for HCT, we recommend a bortezomib-based regimen rather than melphalan plus dexamethasone (Grade 1B). Daratumumab plus CyBorD is our preferred regimen. If daratumumab is not available, acceptable alternatives are CyBorD alone or bortezomib, melphalan, and dexamethasone. Daratumumab is offered as a single agent or in combination with cyclophosphamide and dexamethasone to patients who are not candidates for bortezomib. (See 'Choice of therapy' above.)

●**Monitoring response** – Patients are monitored to determine whether the disease is responding appropriately to therapy and whether a change in management is needed (algorithm 1). In general, we offer alternative systemic therapy if there is hematologic or organ progression at any time; if there is <50 percent reduction in the difference between the involved and uninvolved free light chain levels (dFLC) after two cycles of chemotherapy; or if dFLC is ≥40 mg/L after four to six cycles of chemotherapy or on day 100 after transplant. (See 'Monitoring response' above.)

●**Relapsed or refractory disease** – For patients with relapsed or refractory disease, reasonable approaches include treatment with proteasome inhibitor-based regimens, immunomodulatory derivative-based regimens, daratumumab, or enrollment on a clinical trial. There are no good data to determine which of these regimens will be of most benefit; the choice will be dictated by prior therapy, patient and physician preferences, expected toxicity, drug availability, and insurance coverage. As an example, daratumumab may be preferred for patients with severe cardiac involvement while a lenalidomide-based regimen may be preferred for patients with peripheral neuropathy. We typically reserve bendamustine-based regimens for patients who have received multiple prior regimens, or for those with toxicities that limit the use of other agents. (See 'Relapsed or refractory disease' above.)

●**Prognosis** – The prognosis of AL amyloidosis varies considerably depending on the nature, number, and extent of organ involvement. AL amyloidosis has a poor long-term prognosis when detected at an advanced stage. Earlier diagnosis is

associated with lower early mortality and improved survival. (See 'Prognosis' above.)

ACKNOWLEDGMENTThe UpToDate editorial staff acknowledges Robert A Kyle, MD, who contributed as a Section Editor to earlier versions of this topic review.

REFERENCES

1. Bryce AH, Ketterling RP, Gertz MA, et al. Translocation t(11;14) and survival of patients with light chain (AL) amyloidosis. Haematologica 2009; 94:380.
2. Bochtler T, Hegenbart U, Kunz C, et al. Translocation t(11;14) is associated with adverse outcome in patients with newly diagnosed AL amyloidosis when treated with bortezomib-based regimens. J Clin Oncol 2015; 33:1371.
3. Bochtler T, Hegenbart U, Kunz C, et al. Prognostic impact of cytogenetic aberrations in AL amyloidosis patients after high-dose melphalan: a long-term follow-up study. Blood 2016; 128:594.
4. Kastritis E, Palladini G, Minnema MC, et al. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. N Engl J Med 2021; 385:46.
5. Vogelsberg H, Mahrholdt H, Deluigi CC, et al. Cardiovascular magnetic resonance in clinically suspected cardiac amyloidosis: noninvasive imaging compared to endomyocardial biopsy. J Am Coll Cardiol 2008; 51:1022.
6. Banypersad SM, Sado DM, Flett AS, et al. Quantification of myocardial extracellular volume fraction in systemic AL amyloidosis: an equilibrium contrast cardiovascular magnetic resonance study. Circ Cardiovasc Imaging 2013; 6:34.
7. Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol 2005; 79:319.
8. Merlini G, Seldin DC, Gertz MA. Amyloidosis: pathogenesis and new therapeutic options. J Clin Oncol 2011; 29:1924.
9. Dispenzieri A. Renal risk and response in amyloidosis. Blood 2014; 124:2315.
10. Aljama MA, Sidiqi MH, Dispenzieri A, et al. Comparison of different techniques to identify cardiac involvement in immunoglobulin light chain (AL) amyloidosis. Blood Adv 2019; 3:1226.
11. Hwa YL, Gertz MA, Kumar SK, et al. Prognostic restaging at the time of second-line therapy in patients with AL amyloidosis. Leukemia 2019; 33:1268.
12. Abdallah N, Dispenzieri A, Muchtar E, et al. Prognostic restaging after treatment initiation in patients with AL amyloidosis. Blood Adv 2021; 5:1029.
13. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol 2004; 22:3751.

14. Palladini G, Sachchithanantham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood 2015; 126:612.
15. Muchtar E, Kumar SK, Gertz MA, et al. Staging systems use for risk stratification of systemic amyloidosis in the era of high-sensitivity troponin T assay. Blood 2019; 133:763.
16. Dispenzieri A, Gertz MA, Kyle RA, et al. Prognostication of survival using cardiac troponins and N-terminal pro-brain natriuretic peptide in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation. Blood 2004; 104:1881.
17. Lilleness B, Ruberg FL, Mussinelli R, et al. Development and validation of a survival staging system incorporating BNP in patients with light chain amyloidosis. Blood 2019; 133:215.
18. Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol 2012; 30:989.
19. Kumar SK, Gertz MA, Dispenzieri A. Validation of Mayo Clinic Staging System for Light Chain Amyloidosis With High-Sensitivity Troponin. J Clin Oncol 2019; 37:171.
20. Muchtar E, Gertz MA, Kumar SK, et al. Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: cracking the glass ceiling of early death. Blood 2017; 129:2111.
21. Kourelis TV, Kyle RA, Dingli D, et al. Presentation and Outcomes of Localized Immunoglobulin Light Chain Amyloidosis: The Mayo Clinic Experience. Mayo Clin Proc 2017; 92:908.
22. Sidiqi MH, Aljama MA, Muchtar E, et al. Autologous Stem Cell Transplant for Immunoglobulin Light Chain Amyloidosis Patients Aged 70 to 75. Biol Blood Marrow Transplant 2018; 24:2157.
23. Dispenzieri A, Seenithamby K, Lacy MQ, et al. Patients with immunoglobulin light chain amyloidosis undergoing autologous stem cell transplantation have superior outcomes compared with patients with multiple myeloma: a retrospective review from a tertiary referral center. Bone Marrow Transplant 2013; 48:1302.
24. mSMART: Mayo Consensus on AL Amyloidosis: Diagnosis, Treatment and Prognosis. https://static1.squarespace.com/static/5b44f08ac258b493a25098a3/t/5fad7f650e8bbf646ff5c9cf/1605205862155/Amyloid+Treatment+mSMART+2020+revision+October+2020.pdf (Accessed on October 10, 2022).
25. Sanchorawala V, Boccadoro M, Gertz M, et al. Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis: EHA-ISA working group guidelines. Amyloid 2022; 29:1.
26. Choufani EB, Sanchorawala V, Ernst T, et al. Acquired factor X deficiency in patients with amyloid light-chain amyloidosis: incidence, bleeding manifestations, and response to high-dose chemotherapy. Blood 2001; 97:1885.
27. Comenzo RL. How I treat amyloidosis. Blood 2009; 114:3147.

28. Moreau P, Leblond V, Bourquelot P, et al. Prognostic factors for survival and response after high-dose therapy and autologous stem cell transplantation in systemic AL amyloidosis: a report on 21 patients. Br J Haematol 1998; 101:766.
29. Comenzo RL, Vosburgh E, Falk RH, et al. Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: survival and responses in 25 patients. Blood 1998; 91:3662.
30. Goodman HJ, Gillmore JD, Lachmann HJ, et al. Outcome of autologous stem cell transplantation for AL amyloidosis in the UK. Br J Haematol 2006; 134:417.
31. Porrata LF, Gertz MA, Litzow MR, et al. Early lymphocyte recovery predicts superior survival after autologous hematopoietic stem cell transplantation for patients with primary systemic amyloidosis. Clin Cancer Res 2005; 11:1210.
32. Leung N, Slezak JM, Bergstralh EJ, et al. Acute renal insufficiency after high-dose melphalan in patients with primary systemic amyloidosis during stem cell transplantation. Am J Kidney Dis 2005; 45:102.
33. Cordes S, Dispenzieri A, Lacy MQ, et al. Ten-year survival after autologous stem cell transplantation for immunoglobulin light chain amyloidosis. Cancer 2012; 118:6105.
34. Palladini G, Kastritis E, Maurer MS, et al. Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. Blood 2020; 136:71.
35. Dispenzieri A, Lacy MQ, Zeldenrust SR, et al. The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. Blood 2007; 109:465.
36. Sanchorawala V, Wright DG, Rosenzweig M, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. Blood 2007; 109:492.
37. Specter R, Sanchorawala V, Seldin DC, et al. Kidney dysfunction during lenalidomide treatment for AL amyloidosis. Nephrol Dial Transplant 2011; 26:881.
38. Kastritis E, Terpos E, Roussou M, et al. A phase 1/2 study of lenalidomide with low-dose oral cyclophosphamide and low-dose dexamethasone (RdC) in AL amyloidosis. Blood 2012; 119:5384.
39. Kastritis E, Dialoupi I, Gavriatopoulou M, et al. Primary treatment of light-chain amyloidosis with bortezomib, lenalidomide, and dexamethasone. Blood Adv 2019; 3:3002.
40. Schönland SO, Lokhorst H, Buzyn A, et al. Allogeneic and syngeneic hematopoietic cell transplantation in patients with amyloid light-chain amyloidosis: a report from the European Group for Blood and Marrow Transplantation. Blood 2006; 107:2578.
41. Comenzo RL, Sanchorawala V, Fisher C, et al. Intermediate-dose intravenous melphalan and blood stem cells mobilized with sequential GM+G-CSF or G-CSF alone to treat AL (amyloid light chain) amyloidosis. Br J Haematol 1999; 104:553.
42. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. Blood 2002; 99:4276.

43. Casserly LF, Fadia A, Sanchorawala V, et al. High-dose intravenous melphalan with autologous stem cell transplantation in AL amyloidosis-associated end-stage renal disease. Kidney Int 2003; 63:1051.
44. Gertz MA, Lacy MQ, Dispenzieri A, et al. Risk-adjusted manipulation of melphalan dose before stem cell transplantation in patients with amyloidosis is associated with a lower response rate. Bone Marrow Transplant 2004; 34:1025.
45. Szalat R, Sarosiek S, Havasi A, et al. Organ responses after highdose melphalan and stemcell transplantation in AL amyloidosis. Leukemia 2021; 35:916.
46. Seldin DC, Anderson JJ, Sanchorawala V, et al. Improvement in quality of life of patients with AL amyloidosis treated with high-dose melphalan and autologous stem cell transplantation. Blood 2004; 104:1888.
47. D'Souza A, Dispenzieri A, Wirk B, et al. Improved Outcomes After Autologous Hematopoietic Cell Transplantation for Light Chain Amyloidosis: A Center for International Blood and Marrow Transplant Research Study. J Clin Oncol 2015; 33:3741.
48. Sanchorawala V, Sun F, Quillen K, et al. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem cell transplantation: 20-year experience. Blood 2015; 126:2345.
49. Sidiqi MH, Aljama MA, Buadi FK, et al. Stem Cell Transplantation for Light Chain Amyloidosis: Decreased Early Mortality Over Time. J Clin Oncol 2018; 36:1323.
50. Sharpley FA, Petrie A, Mahmood S, et al. A 24-year experience of autologous stem cell transplantation for light chain amyloidosis patients in the United Kingdom. Br J Haematol 2019; 187:642.
51. Dispenzieri A, Kyle RA, Lacy MQ, et al. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study. Blood 2004; 103:3960.
52. Dispenzieri A, Lacy MQ, Kyle RA, et al. Eligibility for hematopoietic stem-cell transplantation for primary systemic amyloidosis is a favorable prognostic factor for survival. J Clin Oncol 2001; 19:3350.
53. Kyle RA, Gertz MA, Greipp PR, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. N Engl J Med 1997; 336:1202.
54. Gertz MA, Lacy MQ, Dispenzieri A, et al. Trends in day 100 and 2-year survival after auto-SCT for AL amyloidosis: outcomes before and after 2006. Bone Marrow Transplant 2011; 46:970.
55. Gertz MA, Lacy MQ, Dispenzieri A, et al. Autologous stem cell transplant for immunoglobulin light chain amyloidosis: a status report. Leuk Lymphoma 2010; 51:2181.
56. Rosengren S, Mellqvist UH, Nahi H, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation in Sweden, long-term results from all patients treated in 1994-2009. Bone Marrow Transplant 2016; 51:1569.

57. Gertz MA, Lacy MQ, Dispenzieri A, et al. Stem cell transplantation compared with melphalan plus dexamethasone in the treatment of immunoglobulin light-chain amyloidosis. Cancer 2016; 122:2197.
58. Basset M, Milani P, Nuvolone M, et al. Sequential response-driven bortezomib-based therapy followed by autologous stem cell transplant in AL amyloidosis. Blood Adv 2020; 4:4175.
59. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med 2007; 357:1083.
60. Muchtar E, Gertz MA, Lacy MQ, et al. Ten-year survivors in AL amyloidosis: characteristics and treatment pattern. Br J Haematol 2019; 187:588.
61. Sidana S, Sidiqi MH, Dispenzieri A, et al. Fifteen year overall survival rates after autologous stem cell transplantation for AL amyloidosis. Am J Hematol 2019; 94:1020.
62. Skinner M, Sanchorawala V, Seldin DC, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. Ann Intern Med 2004; 140:85.
63. Cibeira MT, Sanchorawala V, Seldin DC, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. Blood 2011; 118:4346.
64. Seldin DC, Anderson JJ, Skinner M, et al. Successful treatment of AL amyloidosis with high-dose melphalan and autologous stem cell transplantation in patients over age 65. Blood 2006; 108:3945.
65. Abdallah N, Sidana S, Dispenzieri A, et al. Outcomes with early vs. deferred stem cell transplantation in light chain amyloidosis. Bone Marrow Transplant 2020; 55:1297.
66. Wechalekar AD, Hawkins PN, Gillmore JD. Perspectives in treatment of AL amyloidosis. Br J Haematol 2008; 140:365.
67. Perfetti V, Siena S, Palladini G, et al. Long-term results of a risk-adapted approach to melphalan conditioning in autologous peripheral blood stem cell transplantation for primary (AL) amyloidosis. Haematologica 2006; 91:1635.
68. Kastritis E, Leleu X, Arnulf B, et al. Bortezomib, Melphalan, and Dexamethasone for Light-Chain Amyloidosis. J Clin Oncol 2020; 38:3252.
69. Manwani R, Cohen O, Sharpley F, et al. A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. Blood 2019; 134:2271.
70. Comenzo RL, Kastritis E, Palladini G, et al. Reduction in Absolute Involved Free Light Chain and Difference between Involved and Uninvolved Free Light Chain Is Associated with Prolonged Major Organ Deterioration Progression-Free Survival in Patients with Newly Diagnosed AL Amyloidosis Receiving Bortezomib, Cyclophosphamide, and Dexamethasone with or without Daratumumab: Results from Andromeda [Abstract #552]. Blood (ASH Annual Meeting Abstracts) 2020; 136.
71. Kyle RA, Gertz MA, Greipp PR, et al. Long-term survival (10 years or more) in 30 patients with primary amyloidosis. Blood 1999; 93:1062.

72. Tan SY, Pepys MB, Hawkins PN. Treatment of amyloidosis. Am J Kidney Dis 1995; 26:267.
73. Skinner M, Anderson J, Simms R, et al. Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. Am J Med 1996; 100:290.
74. Sanchorawala V, Wright DG, Seldin DC, et al. Low-dose continuous oral melphalan for the treatment of primary systemic (AL) amyloidosis. Br J Haematol 2002; 117:886.
75. Kyle RA, Wagoner RD, Holley KE. Primary systemic amyloidosis: resolution of the nephrotic syndrome with melphalan and prednisone. Arch Intern Med 1982; 142:1445.
76. Gertz MA, Kyle RA. Acute leukemia and cytogenetic abnormalities complicating melphalan treatment of primary systemic amyloidosis. Arch Intern Med 1990; 150:629.
77. Reece DE, Hegenbart U, Sanchorawala V, et al. Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: results of a phase 1/2 study. Blood 2011; 118:865.
78. Reece DE, Sanchorawala V, Hegenbart U, et al. Weekly and twice-weekly bortezomib in patients with systemic AL amyloidosis: results of a phase 1 dose-escalation study. Blood 2009; 114:1489.
79. Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Blood 2012; 119:4387.
80. Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood 2012; 119:4391.
81. Palladini G, Milani P, Foli A, et al. Melphalan and dexamethasone with or without bortezomib in newly diagnosed AL amyloidosis: a matched case-control study on 174 patients. Leukemia 2014; 28:2311.
82. US prescribing information daratumumab-hyaluronidase https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761145s008lbl.pdf (Accessed on February 17, 2021).
83. Gertz MA. How to manage primary amyloidosis. Leukemia 2012; 26:191.
84. Wechalekar AD, Schonland SO, Kastritis E, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood 2013; 121:3420.
85. Palladini G, Milani P, Foli A, et al. Oral melphalan and dexamethasone grants extended survival with minimal toxicity in AL amyloidosis: long-term results of a risk-adapted approach. Haematologica 2014; 99:743.
86. Palladini G, Perfetti V, Obici L, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. Blood 2004; 103:2936.

87. Palladini G, Russo P, Nuvolone M, et al. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. Blood 2007; 110:787.
88. Lebovic D, Hoffman J, Levine BM, et al. Predictors of survival in patients with systemic light-chain amyloidosis and cardiac involvement initially ineligible for stem cell transplantation and treated with oral melphalan and dexamethasone. Br J Haematol 2008; 143:369.
89. Dietrich S, Schönland SO, Benner A, et al. Treatment with intravenous melphalan and dexamethasone is not able to overcome the poor prognosis of patients with newly diagnosed systemic light chain amyloidosis and severe cardiac involvement. Blood 2010; 116:522.
90. Al Saleh AS, Sidiqi MH, Sidana S, et al. Impact of consolidation therapy post autologous stem cell transplant in patients with light chain amyloidosis. Am J Hematol 2019; 94:1066.
91. Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia 2012; 26:2317.
92. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol 2012; 30:4541.
93. Muchtar E, Dispenzieri A, Wisniowski B, et al. Graded Cardiac Response Criteria for Patients With Systemic Light Chain Amyloidosis. J Clin Oncol 2023; 41:1393.
94. Milani P, Basset M, Russo F, et al. Patients with light-chain amyloidosis and low free light-chain burden have distinct clinical features and outcome. Blood 2017; 130:625.
95. Dittrich T, Bochtler T, Kimmich C, et al. AL amyloidosis patients with low amyloidogenic free light chain levels at first diagnosis have an excellent prognosis. Blood 2017; 130:632.
96. Dispenzieri A. Opening a can of worms in AL progression. Blood 2018; 131:475.
97. Muchtar E, Dispenzieri A, Leung N, et al. Optimizing deep response assessment for AL amyloidosis using involved free light chain level at end of therapy: failure of the serum free light chain ratio. Leukemia 2019; 33:527.
98. Palladini G, Milani P, Foli A, et al. Presentation and outcome with second-line treatment in AL amyloidosis previously sensitive to nontransplant therapies. Blood 2018; 131:525.
99. Muchtar E, Jevremovic D, Dispenzieri A, et al. The prognostic value of multiparametric flow cytometry in AL amyloidosis at diagnosis and at the end of first-line treatment. Blood 2017; 129:82.
100. Paiva B, Vídriales MB, Pérez JJ, et al. The clinical utility and prognostic value of multiparameter flow cytometry immunophenotyping in light-chain amyloidosis. Blood 2011; 117:3613.
101. Staron A, Burks EJ, Lee JC, et al. Assessment of minimal residual disease using multiparametric flow cytometry in patients with AL amyloidosis. Blood Adv 2020; 4:880.

102. Kastritis E, Wechalekar AD, Dimopoulos MA, et al. Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis. J Clin Oncol 2010; 28:1031.
103. Wechalekar AD, Lachmann HJ, Offer M, et al. Efficacy of bortezomib in systemic AL amyloidosis with relapsed/refractory clonal disease. Haematologica 2008; 93:295.
104. Browning S, Quillen K, Sloan JM, et al. Hematologic relapse in AL amyloidosis after high-dose melphalan and stem cell transplantation. Blood 2017; 130:1383.
105. Leung N, Thomé SD, Dispenzieri A. Venetoclax induced a complete response in a patient with immunoglobulin light chain amyloidosis plateaued on cyclophosphamide, bortezomib and dexamethasone. Haematologica 2018; 103:e135.
106. Gran C, Borg Bruchfeld J, Ellin F, Nahi H. Rapid Complete Response to Single-Agent Bcl-2 Inhibitor Venetoclax in a Heart-Transplanted Patient with Triple Refractory Immunoglobulin Light-Chain Amyloidosis. Acta Haematol 2020; 143:500.
107. Ghilardi G, Stussi G, Mazzucchelli L, et al. Venetoclax plus daratumumab induce hematological CR and organ response in an AL amyloidosis patient with t(11;14). Amyloid 2019; 26:173.
108. Premkumar V, Comenzo R, Lentzsch S. Venetoclax in Immunoglobulin Light Chain Amyloidosis: Is This the Beginning or the End? Clin Lymphoma Myeloma Leuk 2019; 19:686.
109. Nahi H, Kashif M, Klimkowska M, et al. Low dose venetoclax as a single agent treatment of plasma cell malignancies harboring t(11;14). Am J Hematol 2021; 96:925.
110. Pasquer H, Belhadj K, Dupuis J, et al. Venetoclax induces profound and sustained responses in patients with relapsed/refractory light-chain amyloidosis. Br J Haematol 2021; 193:674.
111. Premkumar VJ, Lentzsch S, Pan S, et al. Venetoclax induces deep hematologic remissions in t(11;14) relapsed/refractory AL amyloidosis. Blood Cancer J 2021; 11:10.
112. Sidiqi MH, Al Saleh AS, Leung N, et al. Venetoclax for the treatment of translocation (11;14) AL amyloidosis. Blood Cancer J 2020; 10:55.
113. Roussel M, Merlini G, Chevret S, et al. A prospective phase 2 trial of daratumumab in patients with previously treated systemic light-chain amyloidosis. Blood 2020; 135:1531.
114. Sanchorawala V, Sarosiek S, Schulman A, et al. Safety, tolerability, and response rates of daratumumab in relapsed AL amyloidosis: results of a phase 2 study. Blood 2020; 135:1541.
115. Sher T, Fenton B, Akhtar A, Gertz MA. First report of safety and efficacy of daratumumab in 2 cases of advanced immunoglobulin light chain amyloidosis. Blood 2016; 128:1987.

116. Kaufman GP, Schrier SL, Lafayette RA, et al. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. Blood 2017; 130:900.
117. Abeykoon JP, Zanwar S, Dispenzieri A, et al. Daratumumab-based therapy in patients with heavily-pretreated AL amyloidosis. Leukemia 2019; 33:531.
118. Chung A, Kaufman GP, Sidana S, et al. Organ responses with daratumumab therapy in previously treated AL amyloidosis. Blood Adv 2020; 4:458.
119. Kimmich CR, Terzer T, Benner A, et al. Daratumumab for systemic AL amyloidosis: prognostic factors and adverse outcome with nephrotic-range albuminuria. Blood 2020; 135:1517.
120. Lecumberri R, Krsnik I, Askari E, et al. Treatment with daratumumab in patients with relapsed/refractory AL amyloidosis: a multicentric retrospective study and review of the literature. Amyloid 2020; 27:163.
121. Van de Wyngaert Z, Carpentier B, Pascal L, et al. Daratumumab is effective in the relapsed or refractory systemic light-chain amyloidosis but associated with high infection burden in a frail real-life population. Br J Haematol 2020; 188:e24.
122. Canichella M, Serrao A, Annechini G, et al. Long-term response to daratumumab in a patient with advanced immunoglobulin light-chain (AL) amyloidosis with organ damage. Ann Hematol 2019; 98:1047.
123. Milani P, Fazio F, Basset M, et al. High rate of profound clonal and renal responses with daratumumab treatment in heavily pre-treated patients with light chain (AL) amyloidosis and high bone marrow plasma cell infiltrate. Am J Hematol 2020; 95:900.
124. Sanchorawala V, Palladini G, Kukreti V, et al. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis. Blood 2017; 130:597.
125. Cohen OC, Sharpley F, Gillmore JD, et al. Use of ixazomib, lenalidomide and dexamethasone in patients with relapsed amyloid light-chain amyloidosis. Br J Haematol 2020; 189:643.
126. Dispenzieri A, Kastritis E, Wechalekar AD, et al. A randomized phase 3 study of ixazomib-dexamethasone versus physician's choice in relapsed or refractory AL amyloidosis. Leukemia 2021.
127. Reece DE, Hegenbart U, Sanchorawala V, et al. Long-term follow-up from a phase 1/2 study of single-agent bortezomib in relapsed systemic AL amyloidosis. Blood 2014; 124:2498.
128. Landau H, Hassoun H, Rosenzweig MA, et al. Bortezomib and dexamethasone consolidation following risk-adapted melphalan and stem cell transplantation for patients with newly diagnosed light-chain amyloidosis. Leukemia 2013; 27:823.
129. Sanchorawala V, Finn KT, Fennessey S, et al. Durable hematologic complete responses can be achieved with lenalidomide in AL amyloidosis. Blood 2010; 116:1990.

130. Dispenzieri A, Dingli D, Kumar SK, et al. Discordance between serum cardiac biomarker and immunoglobulin-free light-chain response in patients with immunoglobulin light-chain amyloidosis treated with immune modulatory drugs. Am J Hematol 2010; 85:757.
131. Basset M, Kimmich CR, Schreck N, et al. Lenalidomide and dexamethasone in relapsed/refractory immunoglobulin light chain (AL) amyloidosis: results from a large cohort of patients with long follow-up. Br J Haematol 2021; 195:230.
132. Moreau P, Jaccard A, Benboubker L, et al. Lenalidomide in combination with melphalan and dexamethasone in patients with newly diagnosed AL amyloidosis: a multicenter phase 1/2 dose-escalation study. Blood 2010; 116:4777.
133. Sanchorawala V, Patel JM, Sloan JM, et al. Melphalan, lenalidomide and dexamethasone for the treatment of immunoglobulin light chain amyloidosis: results of a phase II trial. Haematologica 2013; 98:789.
134. Hegenbart U, Bochtler T, Benner A, et al. Lenalidomide/melphalan/dexamethasone in newly diagnosed patients with immunoglobulin light chain amyloidosis: results of a prospective phase 2 study with long-term follow up. Haematologica 2017; 102:1424.
135. Dinner S, Witteles W, Afghahi A, et al. Lenalidomide, melphalan and dexamethasone in a population of patients with immunoglobulin light chain amyloidosis with high rates of advanced cardiac involvement. Haematologica 2013; 98:1593.
136. Kumar SK, Hayman SR, Buadi FK, et al. Lenalidomide, cyclophosphamide, and dexamethasone (CRd) for light-chain amyloidosis: long-term results from a phase 2 trial. Blood 2012; 119:4860.
137. Cibeira MT, Oriol A, Lahuerta JJ, et al. A phase II trial of lenalidomide, dexamethasone and cyclophosphamide for newly diagnosed patients with systemic immunoglobulin light chain amyloidosis. Br J Haematol 2015; 170:804.
138. Dispenzieri A, Buadi F, Laumann K, et al. Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis. Blood 2012; 119:5397.
139. Sanchorawala V, Shelton AC, Lo S, et al. Pomalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 1 and 2 trial. Blood 2016; 128:1059.
140. Palladini G, Milani P, Foli A, et al. A phase 2 trial of pomalidomide and dexamethasone rescue treatment in patients with AL amyloidosis. Blood 2017; 129:2120.
141. Palladini G, Perfetti V, Perlini S, et al. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). Blood 2005; 105:2949.
142. Wechalekar AD, Goodman HJ, Lachmann HJ, et al. Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. Blood 2007; 109:457.

143. Seldin DC, Choufani EB, Dember LM, et al. Tolerability and efficacy of thalidomide for the treatment of patients with light chain-associated (AL) amyloidosis. Clin Lymphoma 2003; 3:241.
144. Dispenzieri A, Lacy MQ, Rajkumar SV, et al. Poor tolerance to high doses of thalidomide in patients with primary systemic amyloidosis. Amyloid 2003; 10:257.
145. Lentzsch S, Lagos GG, Comenzo RL, et al. Bendamustine With Dexamethasone in Relapsed/Refractory Systemic Light-Chain Amyloidosis: Results of a Phase II Study. J Clin Oncol 2020; 38:1455.
146. Milani P, Schönland S, Merlini G, et al. Treatment of AL amyloidosis with bendamustine: a study of 122 patients. Blood 2018; 132:1988.
147. Cohen AS, Rubinow A, Anderson JJ, et al. Survival of patients with primary (AL) amyloidosis. Colchicine-treated cases from 1976 to 1983 compared with cases seen in previous years (1961 to 1973). Am J Med 1987; 82:1182.
148. Kyle RA, Greipp PR. Amyloidosis (AL). Clinical and laboratory features in 229 cases. Mayo Clin Proc 1983; 58:665.
149. Ravichandran S, Lachmann HJ, Wechalekar AD. Epidemiologic and Survival Trends in Amyloidosis, 1987-2019. N Engl J Med 2020; 382:1567.
150. Kourelis TV, Kumar SK, Gertz MA, et al. Coexistent multiple myeloma or increased bone marrow plasma cells define equally high-risk populations in patients with immunoglobulin light chain amyloidosis. J Clin Oncol 2013; 31:4319.
151. Pardanani A, Witzig TE, Schroeder G, et al. Circulating peripheral blood plasma cells as a prognostic indicator in patients with primary systemic amyloidosis. Blood 2003; 101:827.
152. Sachchithanantham S, Roussel M, Palladini G, et al. European Collaborative Study Defining Clinical Profile Outcomes and Novel Prognostic Criteria in Monoclonal Immunoglobulin M-Related Light Chain Amyloidosis. J Clin Oncol 2016; 34:2037.
153. Edwards CV, Bhutani D, Mapara M, et al. One year follow up analysis of the phase 1a/b study of chimeric fibril-reactive monoclonal antibody 11-1F4 in patients with AL amyloidosis. Amyloid 2019; 26:115.
154. Edwards CV, Rao N, Bhutani D, et al. Phase 1a/b study of monoclonal antibody CAEL-101 (11-1F4) in patients with AL amyloidosis. Blood 2021; 138:2632.

This generalized information is a limited summary of diagnosis, treatment, and/or medication information. It is not meant to be comprehensive and should be used as a tool to help the user understand and/or assess potential diagnostic and treatment options. It does NOT include all information about conditions, treatments, medications, side effects, or risks that may apply to a specific patient. It is not intended to be medical advice or a substitute for the medical advice, diagnosis, or treatment of a health care provider based on the health care provider's examination and assessment of a patient's specific and unique circumstances. Patients must speak with a health care provider for complete information

about their health, medical questions, and treatment options, including any risks or benefits regarding use of medications. This information does not endorse any treatments or medications as safe, effective, or approved for treating a specific patient. UpToDate, Inc. and its affiliates disclaim any warranty or liability relating to this information or the use thereof. The use of this information is governed by the Terms of Use, available at https://www.wolterskluwer.com/en/know/clinical-effectiveness-terms
Topic 6666 Version 90.0

CHAPTER 5

Gastrointestinal amyloidosis: Clinical manifestations, diagnosis, and management

Author:Michael Camilleri, MD
Section Editor:Lawrence S Friedman, MD
Deputy Editor:Shilpa Grover, MD, MPH, AGAF, Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Aug 2023. This topic last updated: Oct 24, 2022.

INTRODUCTIONAmyloidosis is a generic term that refers to the extracellular tissue deposition of fibrils composed of low molecular weight subunits (5 to 25 kD) of a variety of serum proteins, many of which circulate as constituents of plasma [1]. The subunit proteins forming amyloid deposits are derived from soluble precursors which have undergone conformational changes that lead to the adoption of a predominantly antiparallel beta-pleated sheet configuration. Deposition into tissues results in organ dysfunction. These fibrils can be identified on biopsy specimens both by their characteristic appearance on electron microscopy and by their ability to bind Congo red (leading to green birefringence under polarized light) and thioflavine T (producing an intense yellow-green fluorescence). These deposits may result in a wide range of clinical manifestations depending upon their type, location, and the amount of deposition.

This topic will review the clinical manifestations, diagnosis, and management of gastrointestinal amyloidosis. A general overview of the genetics, pathogenesis, clinical manifestations, diagnosis, and treatment of the different amyloid disorders is discussed in detail, separately. (See "Genetic factors in the amyloid diseases" and "Overview of amyloidosis" and "Renal amyloidosis" and "Amyloid cardiomyopathy: Treatment and prognosis" and "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis" and "Dialysis-related amyloidosis" and "Musculoskeletal manifestations of amyloidosis" and "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis".)

TYPES OF AMYLOIDThere are several major forms of amyloidosis. Amyloidosis is classified based on the fibril precursor protein. Nomenclature for amyloid subunit proteins includes the letter "A," followed by the abbreviation of the name of the precursor protein [2]. (See "Overview of amyloidosis", section on 'Types of amyloidosis'.)

The most common causes of systemic amyloid deposition are as follows:

●AL amyloid (also called immunoglobulin light chain amyloidosis), caused by a plasma cell dyscrasia, is due to deposition of protein derived from immunoglobulin light chain fragments. AL amyloidosis is the most prevalent type of amyloidosis [3]. The prognosis of patients with AL amyloidosis and gastrointestinal (GI) involvement appears to be worse than in patients without GI involvement; in addition, those with GI involvement may have more other organs involved and more advanced disease than those without organ involvement [4].

●AA amyloidosis is a potential complication of chronic diseases in which there is ongoing or recurring inflammation that results in the production of serum amyloid A protein, a normal acute phase reactant protein sometimes referred to as SAA, which can form amyloid deposits (eg, chronic degenerative arthropathies, particularly rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, inflammatory bowel disease).

●Other major forms of amyloid seen clinically include dialysis-related amyloidosis (in which the non-glycosylated protein, beta 2-microglobulin, is deposited in organs), age-related (also called senile amyloidosis) systemic amyloidosis, and organ-specific amyloid.

●A rare form of hereditary amyloidosis is hereditary transthyretin amyloidosis that results from a single amino acid substitution in TTR gene, was previously called transthyretin familial amyloid polyneuropathy (TTR-FAP) or familial amyloid cardiomyopathy (TTR-FAC). Although, there are 120 amyloidogenic TTR mutations identified. The most common mutations in the United States are Val122Ile, Thr60Ala, and Val30Met [5]. The phenotype is variable (as in other types of amyloidosis), although polyneuropathy or cardiomyopathy may be more likely with certain TTR mutations. The following table summarizes the commonest forms of systemic amyloidosis, with their associated parent protein, distribution, and organs involved (table 1) [6].

EPIDEMIOLOGYAmyloidosis of the gastrointestinal tract may be limited to the gut or part of systemic involvement. In a retrospective review of 2334 patients with amyloidosis, 76 patients (3 percent) had biopsy-proven amyloid involvement of the gastrointestinal tract of which approximately 80 percent had systemic amyloidosis and 20 percent had amyloidosis of the gastrointestinal tract without evidence of an associated plasma cell dyscrasia or other organ involvement [6].

The distribution of clinically apparent gastrointestinal involvement varies with the type of amyloidosis [7]. Gastrointestinal disease is present in as many as 60 percent of patients with AA amyloidosis [8]. In contrast, gastrointestinal tract involvement appears to be less common in AL amyloidosis, with biopsy diagnosed disease and clinically apparent disease occurring in 8 and 1 percent of patients, respectively [9]. In autopsy series, 56 to 95 percent of patients with amyloidosis have hepatic involvement [10,11]. Hepatic amyloid has been reported in up to 90 percent of patients with AL amyloid and 60 percent of patients with AA amyloid.

The prevalence of dialysis-related amyloidosis has not been well studied but clinically apparent disease does not appear to be common [12]. Senile amyloidosis is found in 10 to 36 percent of patients over 80 years old and mainly involves the heart, but can also be seen throughout the gastrointestinal tract. Amyloid has been reported in subserosal veins of 41 to 44 percent of older adult patients, mainly in the large and small bowel [13].

PATHOGENESISGastrointestinal disease in amyloidosis results from either mucosal infiltration or neuromuscular infiltration. In addition, an extrinsic autonomic neuropathy may also affect gut function.

●**Mucosal infiltration** – The most common sites of mucosal infiltration are the second part of the duodenum (100 percent), the stomach and colorectum (>90 percent), and the esophagus (approximately 70 percent) (picture 1A-C) [14].

•In AL amyloidosis, amyloid deposition in the muscularis mucosae, submucosa, and muscularis propria leads to polypoid protrusions and thickening of the valvulae conniventes. As a result, AL amyloidosis usually presents with constipation, mechanical obstruction, or chronic intestinal pseudo-obstruction.

•In AA amyloidosis, granular amyloid deposition occurs mainly in the mucosa, resulting in the fine granular appearance, mucosal friability, and erosions. As a result, AA amyloidosis presents with diarrhea and malabsorption [15].

•In patients with dialysis-related amyloid, the development of gastrointestinal amyloidosis is associated with the length of time on dialysis [12]. Vascular deposition can range from subtle hyalinization of the vascular intima and media within submucosal vessels to significant thickening of the vessel wall with resultant mucosal ischemia. Interstitial deposits are usually localized to the mucosa, submucosa, and muscularis propria but can range from immunoreactive beta2-

microglobulin amyloid without mural expansion to macroscopic nodular deposits (amyloid tumors) within the muscularis propria.

●**Neuromuscular infiltration** – Neuromuscular infiltration has been reported in patients with AL, AA, and dialysis-related amyloid and usually induces stasis syndromes. Neuromuscular infiltration initially affects the intrinsic nervous system and results in a neuropathic process that is characterized by normal amplitude but uncoordinated contractions [16,17]. Tissue wall infiltration results in a myopathic process with low amplitude contractions that are typically associated with significantly prolonged transit (waveform 1) [18]. The preferential site of amyloid infiltration varies by the type of amyloidosis [19,20]. In one study that evaluated 16 patients with amyloidosis and intestinal pseudo-obstruction (13 with AA, 2 with AL, and 1 with dialysis-related amyloidosis), extensive infiltration and replacement of the muscularis propria by amyloid deposits throughout the gastrointestinal tract, especially the small intestine, were found in AL and dialysis-related amyloidosis cases. In contrast, in patients with AA amyloidosis, there was amyloid infiltration in the myenteric plexus without appreciable muscle infiltration.

CLINICAL MANIFESTATIONS

Clinical presentation

Gastrointestinal tract amyloidosis — Patients with symptomatic gastrointestinal amyloidosis usually present with one of four syndromes [9,21-26]:

●**Gastrointestinal bleeding** – Bleeding is the presenting symptom in 25 to 45 percent of patients with gastrointestinal tract amyloidosis [27,28]. Bleeding may be due to ischemia or infarction, vascular friability, or mucosal lesions (ulcers, nodularity or polypoid lesions, erosions, submucosal hematomas, and small mucosal hemorrhages) [6,29-31]. Occult bleeding is the most commonly reported gastrointestinal (GI) presentation of B2M-amyloidosis [32]. (See 'Types of amyloid' above.)

●**Malabsorption** – Patients with amyloidosis may develop malabsorption due to mucosal infiltration, pancreatic insufficiency or bacterial overgrowth and present with weight loss (median 13.6 kg in one series), diarrhea, or steatorrhea [33,34]. Less common features included anorexia, dizziness, hypotension, or orthostatic changes in blood pressure. (See "Approach to the adult patient with suspected malabsorption", section on 'Clinical manifestations'.)

●**Protein-losing gastroenteropathy** – Patients with protein-losing gastroenteropathy usually present with diarrhea, edema, ascites, pleural or pericardial effusion and have laboratory evidence of hypoalbuminemia [35]. (See "Protein-losing gastroenteropathy", section on 'Clinical features'.)

●**Chronic gastrointestinal dysmotility** – Less often, patients may present with constipation, or nausea, vomiting, abdominal pain, bloating, or chronic intestinal pseudo-obstruction [16,19]. Dysmotility can also result in rapid intestinal transit and cause diarrhea [36]. In hereditary transthyretin amyloidosis, 24-hour, small, intestinal motility studies show more daytime phase III migrating motor complexes than patient controls (which may be a feature of vagal denervation) and a lower amplitude of small intestinal contractions; together these features would be consistent with a combined neuromyopathic disorder [37]. (See 'Types of amyloid' above.)

●Other rare symptoms of amyloidosis include:

•Cholangitis due amyloid deposition at the ampulla of Vater [38].

•Bowel obstruction due to encapsulating peritonitis or extraluminal amyloidoma [39,40].

•Bowel perforation in light chain amyloidosis, which may occur after the initiation of anti-AL therapy (eg, bortezomib, lenalidomide or thalidomide-based therapy) [41].

•Esophageal involvement due to amyloid deposition in nerves and resulting in dysphagia, heartburn, dysmotility (up to aperistalsis that may mimic achalasia), dilatation, and low lower esophageal sphincter (LES) pressure.

•Pneumatosis intestinalis [42].

While patients with AA amyloidosis usually present with diarrhea and malabsorption, patients with AL amyloidosis usually present with constipation, mechanical obstruction, or chronic intestinal pseudo-obstruction [15].

When there is involvement of the GI tract in senile systemic amyloidosis, it is usually discovered incidentally on histological examination within subserosal veins of the large and small bowel. It is present in about 40 percent of those >80 years of age [43].

Amyloidosis secondary to inflammatory bowel disease — AA amyloidosis is a rare complication of inflammatory bowel disease (~1 in 200 cases), and is 10 to 15 times more likely in Crohn disease than ulcerative colitis, presumably because of the greater systemic inflammation. Typically, AA amyloidosis occurs in association with male sex, fistulizing behavior, extraintestinal manifestations, perianal disease, and ileocolic anatomical location. Renal disease is the most common organ involved in AA amyloidosis associated with inflammatory bowel disease [43].

Hepatic amyloidosis — Clinical manifestations of hepatic amyloid deposition are usually mild with hepatomegaly and elevated alkaline phosphatase being the most frequent findings [44]. Patients with hepatic amyloidosis often have concurrent symptoms of fatigue, weight loss, and anorexia due to systemic amyloidosis.

Hepatomegaly is present in 57 to 83 percent of patients with hepatic amyloidosis and does not correlate with the amount of amyloid deposition [10,45]. While patients may have associated ascites, this is more likely due to concurrent heart failure or hypoalbuminemia. Chronic liver disease and portal hypertension are rare. The most frequently abnormal test of hepatic function is an elevated serum alkaline phosphatase level. In one study that included 98 patients with hepatic amyloidosis, an elevated alkaline phosphatase was noted in 86 percent of patients, of which 61 percent had values of 500 int. units/L or more [46]. The serum aspartate aminotransferase (AST) was more than twice the upper limit of normal in 37 percent of patients.

Hepatic involvement can be seen in up to 90 percent of patients with AL amyloid and 60 percent of patients with AA amyloidosis [10,11,47]. Clinical features of hepatic involvement in AA amyloidosis are similar to those seen in AL amyloidosis. Although histologic differences between AL and AA amyloidosis have been described, there is considerable overlap making the significance of these observations unclear [47-49].

Although some case reports have suggested that patients with hepatic amyloidosis have an increased risk of bleeding and/or hepatic rupture following the biopsy, this has not been consistently demonstrated [21]. (See "Approach to liver biopsy".) Rarely, ascites may result from peritoneal amyloidosis [50].

Imaging findings — Radiologic and endoscopic findings of gastrointestinal amyloidosis are nonspecific [51] and the diagnosis typically requires biopsy and special stains to identify the amyloid infiltration and the specific nature of the amyloid protein infiltration [52].

●**Gastrointestinal tract amyloidosis** – On small bowel follow-through and cross sectional imaging with computed tomographic (CT) scan or magnetic resonance imaging (MRI) in patients with AA amyloid, the mucosa may have a coarse mucosal pattern with innumerable fine granular elevations due to expansion of the lamina propria by amyloid deposits [53]. In patients with AL amyloid, findings include polypoid protrusions or masses that may mimic cancer, thickening of the folds, luminal narrowing, loss of haustrations, thickened mucosal folds, mucosal nodularity, and ulceration. Dilatation of the small bowel or colon may be seen in patients with neuromuscular amyloid infiltration (image 1). Rarely mesenteric thickening or adenopathy may be seen on CT scan [53]. The appearance of primary amyloidosis in the intestine may mimic Crohn disease [54].

●**Hepatic amyloidosis** – Ultrasonographic findings of hepatic amyloidosis include heterogeneous echogenicity [51]. On CT scan, diffuse or focal regions of decreased parenchymal attenuation with or without extensive calcification may be seen. MRI demonstrates significantly increased signal intensity on T1-weighted images of the liver without significantly altered signal intensity on T2-weighted images; the reason for high signal intensity on T1 is unclear.

DIAGNOSISGastrointestinal amyloidosis should be suspected in patients with diarrhea, weight loss, or gastrointestinal bleeding and disorders known to be associated with amyloidosis (eg, plasma cell dyscrasia, chronic inflammatory disease, and chronic renal failure on maintenance dialysis). Amyloidosis should also be suspected when there is involvement of other organs characteristic of systemic amyloid deposition (eg, proteinuria, hepatomegaly and elevated alkaline phosphatase, restrictive cardiomyopathy, neuropathy, unexplained edema, carpal tunnel syndrome, unexplained facial or neck purpura, or macroglossia). The diagnosis of gastrointestinal amyloid requires a tissue biopsy with positive staining of amyloid by Congo red or the presence of amyloid fibrils on electron microscopy. (See "Overview of amyloidosis", section on 'Clinical manifestations'.)

●**Tissue biopsy** – Based on the gastrointestinal symptoms, we perform a colonoscopy and/or an upper endoscopy to obtain rectal or duodenal mucosal biopsies in patients with suspected amyloidosis and to exclude other etiologies. In patients with unexplained hepatomegaly and elevated alkaline phosphatase, a liver biopsy serves to establish the diagnosis of hepatic amyloid and rule out other infiltrative liver diseases. (See 'Differential diagnosis' below.)

•**Endoscopy** – The endoscopic appearance of amyloidosis is not specific. The gastrointestinal tract mucosa may have a fine granular appearance, polypoid

protrusions, erosions, ulcerations, friability, and thickening of the wall [14,55]. Rarely, patients have tumor-forming deposits of amyloid, called amyloidomas [56-58].

•**Histology** – On hematoxylin and eosin stained biopsy sections, amyloid appears as a pink, amorphous, waxy substance with a characteristic 'cracking' artifact (picture 1A-C). In the gastrointestinal tract, amyloid deposits may be seen in the mucosa and submucosa and are best identified in the wall of blood vessels. In patients with hepatic amyloid, deposits are usually seen periportally in the space of Disse but the deposits are occasionally centrilobular. Atrophy of hepatocytes may be seen due to compression by amyloid fibrils [59].

The presence of amyloid fibrils can be confirmed by their characteristic appearance on electron microscopy and by their ability to bind Congo red (leading to green birefringence under polarized light) or thioflavine-T (producing an intense yellow-green fluorescence) [2]. It is important to note that biopsy sections that are very thin (ie, 6 microns or less) may not stain appropriately with Congo red despite the presence of amyloid fibrils on electron microscopy. AL, Aβ2M, and ATTR amyloids are likely to deposit submucosally, while AA amyloid is easily deposited in the superficial layer of the mucous membrane [60]. Among 521 patients with biopsies from the gastrointestinal tract, the type of amyloid deposition was ALλ amyloid in 286 (52.8 percent), ATTR in 88 (16.2 percent), ALκ in 74 (13.7 percent), AA in 58 (10.7 percent), and apolipoprotein A- amyloid in four (0.7 percent) patients [7].

•**Determining the type of amyloid and underlying etiology** – Once the histologic diagnosis of amyloidosis is made, it is important to determine the type of amyloid and the underlying cause [61]. This evaluation is discussed in detail, separately. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Determining the type of amyloid' and "Overview of amyloidosis", section on 'Histopathology and protein analysis'.)

DIFFERENTIAL DIAGNOSISThe differential diagnosis of gastrointestinal amyloidosis varies based on the clinical presentation. Other causes of diarrhea with mucosal erosions include inflammatory bowel disease (ulcerative colitis and Crohn disease), radiation colitis, gastrointestinal malignancies, and medication-induced enteropathy. Gastrointestinal tract amyloidosis can be differentiated from these by a history which may be suggestive of the underlying cause and by histology. The differential diagnosis for chronic diarrhea and the evaluation of diarrhea are discussed in detail, separately. (See "Clinical manifestations, diagnosis, and

prognosis of ulcerative colitis in adults", section on 'Differential diagnosis' and "Approach to the adult with chronic diarrhea in resource-abundant settings".)

The differential diagnosis of hepatomegaly and elevated alkaline phosphatase includes other infiltrative disorders of the liver including sarcoidosis, tuberculosis, malignancy, and glycogen storage diseases. These can be distinguished from hepatic amyloidosis by liver biopsy. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated alkaline phosphatase'.)

MANAGEMENTTherapy is directed at the gastrointestinal manifestations and at the underlying cause of amyloidosis.

Symptomatic treatment — In patients with nausea and vomiting or abdominal pain, which is often due to amyloid-related dysmotility, management consists of dietary modification, hydration, and pharmacologic therapy with prokinetics (eg, metoclopramide, and, where approved, domperidone) and anti-emetics (eg, promethazine, dimenhydrinate, ondansetron). Small meals consisting of liquid or homogenized foods are better tolerated than solids. Hypercaloric liquid formulations should be used in patients with low caloric intake. Parenteral nutrition may be necessary for patients with severe dysmotility who have failed enteral nutrition together with prokinetics and antiemetic therapy [19]. (See "Treatment of gastroparesis", section on 'Prokinetics' and "Chronic intestinal pseudo-obstruction: Management", section on 'Symptomatic management'.)

In patients with diarrhea and bloating and demonstrated small intestinal bacterial overgrowth, we suggest empiric treatment with antibiotics for small intestinal bacterial overgrowth (eg, quinolones, doxycycline, metronidazole). In case reports, patients with severe diarrhea and hypoalbuminemia due to a protein-losing enteropathy have responded to glucocorticoids and octreotide [62,63]. (See "Small intestinal bacterial overgrowth: Management", section on 'Antibiotic therapy' and "Protein-losing gastroenteropathy", section on 'Management'.)

The initial management of patients with gastrointestinal bleeding includes triage to the appropriate setting for management (outpatient, inpatient, intensive care unit), general supportive measures (eg, oxygen, establishment of adequate intravenous access), appropriate fluid and blood product resuscitation, and management of coagulopathies, anticoagulants, and antiplatelet agents. In many cases, the bleeding can be controlled with therapies applied at the time of endoscopy or angiography. The management of gastrointestinal bleeding is discussed in detail, separately. (See

"Approach to acute lower gastrointestinal bleeding in adults" and "Approach to acute upper gastrointestinal bleeding in adults".)

Treatment of the underlying disorder — Treatment of the underlying disease has been associated with regression of gastrointestinal amyloid (table 2) [64-68]. As examples, therapy is aimed at the underlying infectious or inflammatory disorder in secondary AA amyloidosis (eg, anti-TNF therapy in Crohn disease), at the underlying plasma cell dyscrasia in AL amyloidosis, and at either altering the mode of dialysis or considering renal transplantation in patients with dialysis-related amyloidosis. The management of underlying cause of amyloidosis is discussed in detail, separately [69-76]. (See "Overview of amyloidosis", section on 'Treatment' and "Treatment of AA (secondary) amyloidosis" and "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis".)

PROGNOSISAlthough the gastrointestinal complications can result in significant morbidity, they are not usually the cause of death, which is most often due to renal failure, restrictive cardiomyopathy, or ischemic heart disease. However, the presence of hepatic manifestations has a poor prognosis as it likely reflects relatively severe systemic disease [44,77]. In one series of 98 patients with hepatic amyloidosis, the median survival in patients with hepatic amyloidosis was nine months [46]. Independent predictors of shortened survival included heart failure, a total bilirubin >2 mg/dL, and a platelet count >500,000/microL. Novel agents (proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, venetoclax) and autologous stem cell transplantation, used for eliminating the underlying plasma cell clone, have improved the outcome for low- and intermediate-risk patients, but the prognosis for high-risk patients is still grave [78]. There is an ongoing search for novel treatment approaches to AL amyloidosis. Early diagnosis is of paramount importance for effective treatment and prognosis due to the progressive nature of this disease.

SUMMARY AND RECOMMENDATIONS

●Amyloidosis is a generic term that refers to the extracellular tissue deposition of a variety of serum proteins, many of which circulate as constituents of plasma. The most common causes of systemic amyloid deposition are AL amyloid caused by a plasma cell dyscrasia and AA amyloidosis due to ongoing or recurring inflammation from chronic disease. Other major forms of amyloid seen clinically include dialysis-related amyloidosis, heritable amyloidosis, age-related systemic amyloidosis, and organ-specific amyloidosis. (See 'Introduction' above and 'Types of amyloid' above.)

●Gastrointestinal disease in amyloidosis results from either mucosal or neuromuscular infiltration. In addition, an extrinsic autonomic neuropathy may also affect gut function. (See 'Pathogenesis' above.)

●Patients with symptomatic gastrointestinal amyloidosis usually present with one of four syndromes: gastrointestinal bleeding, malabsorption, protein-losing gastroenteropathy, and, less often, gastrointestinal dysmotility. While patients with AA amyloidosis usually present with diarrhea and weight loss, patients with AL amyloidosis usually present with constipation, mechanical obstruction, or chronic intestinal pseudo-obstruction.

Clinical manifestations of hepatic amyloid deposition are usually mild with hepatomegaly and elevated alkaline phosphatase being the most frequent findings. However, patients usually have weight loss, fatigue, and anorexia due to systemic involvement. (See 'Clinical presentation' above.)

●Gastrointestinal amyloidosis should be suspected in patients with diarrhea, weight loss, or gastrointestinal bleeding and disorders known to be associated with amyloidosis (eg, plasma cell dyscrasia, chronic inflammatory disease, and chronic renal failure on maintenance dialysis). Amyloidosis should also be suspected when there is involvement of other organs characteristic of systemic amyloid deposition (eg, proteinuria, hepatomegaly and elevated alkaline phosphatase, restrictive cardiomyopathy, neuropathy, unexplained edema, carpal tunnel syndrome, unexplained facial or neck purpura, or macroglossia). The diagnosis of gastrointestinal amyloid requires a tissue biopsy with positive staining of amyloid by Congo red or the presence of amyloid fibrils on electron microscopy. (See 'Diagnosis' above.)

●Although the gastrointestinal complications can result in significant morbidity, they are not usually the cause of death, which is most often due to renal failure, restrictive cardiomyopathy, or ischemic heart disease. However, the presence of hepatic manifestations has a poor prognosis as it likely reflects relatively severe systemic disease. Therapy is directed at the gastrointestinal manifestations and at the underlying cause of amyloidosis. Early diagnosis is of paramount importance for effective treatment and prognosis due to the progressive nature of this disease. (See 'Management' above and 'Prognosis' above.)

REFERENCES

1. Nordling E, Abraham-Nordling M. Colonic amyloidosis, computational analysis of the major amyloidogenic species, Serum Amyloid A. Comput Biol Chem 2012; 39:29.
2. Glenner GG. Amyloid deposits and amyloidosis. The beta-fibrilloses (first of two parts). N Engl J Med 1980; 302:1283.
3. Nienhuis HL, Bijzet J, Hazenberg BP. The Prevalence and Management of Systemic Amyloidosis in Western Countries. Kidney Dis (Basel) 2016; 2:10.
4. Lim AY, Lee JH, Jung KS, et al. Clinical features and outcomes of systemic amyloidosis with gastrointestinal involvement: a single-center experience. Korean J Intern Med 2015; 30:496.
5. Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. Am J Manag Care 2017; 23:S107.
6. Cowan AJ, Skinner M, Seldin DC, et al. Amyloidosis of the gastrointestinal tract: a 13-year, single-center, referral experience. Haematologica 2013; 98:141.
7. Freudenthaler S, Hegenbart U, Schönland S, et al. Amyloid in biopsies of the gastrointestinal tract-a retrospective observational study on 542 patients. Virchows Arch 2016; 468:569.
8. Okuda Y, Takasugi K, Oyama T, et al. [Amyloidosis in rheumatoid arthritis--clinical study of 124 histologically proven cases]. Ryumachi 1994; 34:939.
9. Menke DM, Kyle RA, Fleming CR, et al. Symptomatic gastric amyloidosis in patients with primary systemic amyloidosis. Mayo Clin Proc 1993; 68:763.
10. LEVINE RA. Amyloid disease of the liver. Correlation of clinical, functional and morphologic features in forty-seven patients. Am J Med 1962; 33:349.
11. Iwata T, Hoshii Y, Kawano H, et al. Hepatic amyloidosis in Japan: histological and morphometric analysis based on amyloid proteins. Hum Pathol 1995; 26:1148.
12. Jimenez RE, Price DA, Pinkus GS, et al. Development of gastrointestinal beta2-microglobulin amyloidosis correlates with time on dialysis. Am J Surg Pathol 1998; 22:729.
13. Ueda M, Horibata Y, Shono M, et al. Clinicopathological features of senile systemic amyloidosis: an ante- and post-mortem study. Mod Pathol 2011; 24:1533.
14. Tada S, Iida M, Iwashita A, et al. Endoscopic and biopsy findings of the upper digestive tract in patients with amyloidosis. Gastrointest Endosc 1990; 36:10.
15. Tada S, Iida M, Yao T, et al. Endoscopic features in amyloidosis of the small intestine: clinical and morphologic differences between chemical types of amyloid protein. Gastrointest Endosc 1994; 40:45.
16. Battle WM, Rubin MR, Cohen S, Snape WJ Jr. Gastrointestinal-motility dysfunction in amyloidosis. N Engl J Med 1979; 301:24.
17. Camilleri M, Malagelada JR, Stanghellini V, et al. Gastrointestinal motility disturbances in patients with orthostatic hypotension. Gastroenterology 1985; 88:1852.
18. Malagelada JR, Camilleri M, Stanghellini V. Manometric Diagnosis of Gastrointestinal Motility Disorders, Thieme Medical Publishers, New York 1986.

19. Tada S, Iida M, Yao T, et al. Intestinal pseudo-obstruction in patients with amyloidosis: clinicopathologic differences between chemical types of amyloid protein. Gut 1993; 34:1412.
20. Tada S, Iida M, Yao T, et al. Gastrointestinal amyloidosis: radiologic features by chemical types. Radiology 1994; 190:37.
21. Ebert EC, Nagar M. Gastrointestinal manifestations of amyloidosis. Am J Gastroenterol 2008; 103:776.
22. Petre S, Shah IA, Gilani N. Review article: gastrointestinal amyloidosis - clinical features, diagnosis and therapy. Aliment Pharmacol Ther 2008; 27:1006.
23. Reddy MB, Poppers DM, Uram-Tuculescu C. Recurrent obscure gastrointestinal bleeding in a patient with gastric amyloid. Clin Gastroenterol Hepatol 2009; 7:e1.
24. Kim SH, Kang EJ, Park JW, et al. Gastrointestinal amyloidosis presenting with multiple episodes of gastrointestinal bleeding. Cardiovasc Intervent Radiol 2009; 32:577.
25. Baldewijns M, Ectors N, Verbeeck G, et al. Intermittent subobstruction and cholestasis as complications of duodenal amyloid tumours. Gastroenterol Clin Biol 1995; 19:218.
26. Hemmer PR, Topazian MD, Gertz MA, Abraham SC. Globular amyloid deposits isolated to the small bowel: a rare association with AL amyloidosis. Am J Surg Pathol 2007; 31:141.
27. Brandt K, Cathcart ES, Cohen AS. A clinical analysis of the course and prognosis of forty-two patients with amyloidosis. Am J Med 1968; 44:955.
28. Levy DJ, Franklin GO, Rosenthal WS. Gastrointestinal bleeding and amyloidosis. Am J Gastroenterol 1982; 77:422.
29. Chang HS, Myung SJ, Yang SK, et al. Massive small bowel bleeding in a patient with amyloidosis. Gastrointest Endosc 2004; 59:126.
30. James DG, Zuckerman GR, Sayuk GS, et al. Clinical recognition of Al type amyloidosis of the luminal gastrointestinal tract. Clin Gastroenterol Hepatol 2007; 5:582.
31. Yumoto S, Doi K, Higashi T, et al. Intra-abdominal bleeding caused by amyloid transthyretin amyloidosis in the gastrointestinal tract: a case report. Clin J Gastroenterol 2022; 15:140.
32. Maher ER, Dutoit SH, Baillod RA, et al. Gastrointestinal complications of dialysis related amyloidosis. BMJ 1988; 297:265.
33. Hayman SR, Lacy MQ, Kyle RA, Gertz MA. Primary systemic amyloidosis: a cause of malabsorption syndrome. Am J Med 2001; 111:535.
34. Madsen LG, Gimsing P, Schiødt FV. Primary (AL) amyloidosis with gastrointestinal involvement. Scand J Gastroenterol 2009; 44:708.
35. Suzuki C, Higaki S, Nishiaki M, et al. 99mTc-HSA-D scintigraphy in the diagnosis of protein-losing gastroenteropathy due to secondary amyloidosis. J Gastroenterol 1997; 32:78.
36. Guirl MJ, Högenauer C, Santa Ana CA, et al. Rapid intestinal transit as a primary cause of severe chronic diarrhea in patients with amyloidosis. Am J Gastroenterol 2003; 98:2219.

37. Wixner J, Törnblom H, Karling P, et al. Abnormal small bowel motility in patients with hereditary transthyretin amyloidosis. Neurogastroenterol Motil 2018; 30:e13354.
38. Yoshiki Y, Yamamoto G, Takazawa Y, et al. AL amyloidosis with severe gastrointestinal invasion and acute obstructive suppurative cholangitis. Ann Hematol 2012; 91:467.
39. Jones J, VanRosendaal G, Cleary C, et al. Primary amyloidosis presenting as small bowel encapsulation. Can J Gastroenterol 2004; 18:169.
40. Willson TD, Bird J, Azizi R, et al. Extraluminal amyloidoma of the pelvic cavity causing large bowel obstruction. Case Rep Gastroenterol 2011; 5:315.
41. Shaulov A, Avivi I, Cohen Y, et al. Gastrointestinal perforation in light chain amyloidosis in the era of novel agent therapy - a case series and review of the literature. Amyloid 2018; 25:11.
42. Raghunathan V, Louis D, Wirk B. Gastrointestinal Tract Amyloidosis Presenting With Pneumatosis Intestinalis. J Clin Med Res 2017; 9:654.
43. Syed U, Ching Companioni RA, Alkhawam H, Walfish A. Amyloidosis of the gastrointestinal tract and the liver: clinical context, diagnosis and management. Eur J Gastroenterol Hepatol 2016; 28:1109.
44. Gertz MA, Kyle RA. Hepatic amyloidosis (primary [AL], immunoglobulin light chain): the natural history in 80 patients. Am J Med 1988; 85:73.
45. Kyle RA, Bayrd ED. Amyloidosis: review of 236 cases. Medicine (Baltimore) 1975; 54:271.
46. Park MA, Mueller PS, Kyle RA, et al. Primary (AL) hepatic amyloidosis: clinical features and natural history in 98 patients. Medicine (Baltimore) 2003; 82:291.
47. Buck FS, Koss MN. Hepatic amyloidosis: morphologic differences between systemic AL and AA types. Hum Pathol 1991; 22:904.
48. Chopra S, Rubinow A, Koff RS, Cohen AS. Hepatic amyloidosis. A histopathologic analysis of primary (AL) and secondary (AA) forms. Am J Pathol 1984; 115:186.
49. Looi LM, Sumithran E. Morphologic differences in the pattern of liver infiltration between systemic AL and AA amyloidosis. Hum Pathol 1988; 19:732.
50. Stofer F, Barretto MF, Gouvea AL, et al. A Rare Case of Ascites due to Peritoneal Amyloidosis. Am J Case Rep 2016; 17:439.
51. Kim SH, Han JK, Lee KH, et al. Abdominal amyloidosis: spectrum of radiological findings. Clin Radiol 2003; 58:610.
52. Iida T, Yamashita K, Nakase H. Localized Gastrointestinal ALλ Amyloidosis. Clin Gastroenterol Hepatol 2018; 16:e93.
53. Araoz PA, Batts KP, MacCarty RL. Amyloidosis of the alimentary canal: radiologic-pathologic correlation of CT findings. Abdom Imaging 2000; 25:38.
54. Wang Z, Huang C, Ji F. Primary amyloidosis mimicking Crohn's disease: a case report. Int J Clin Exp Med 2015; 8:16137.
55. Bighi S, Trevisani L, Lupi L, et al. Amyloidosis of the gastric stump: radiographic and CT findings. Gastrointest Radiol 1990; 15:197.

56. Kahi CJ, Vakili S, Liepnieks JJ, Benson M. Amyloidoma of the esophagus. Am J Gastroenterol 2007; 102:910.
57. Saindane AM, Losada M, Macari M. Focal amyloidoma of the small bowel mimicking adenocarcinoma on CT. AJR Am J Roentgenol 2005; 185:1187.
58. Peny MO, Debongnie JC, Haot J, Van Gossum A. Localized amyloid tumor in small bowel. Dig Dis Sci 2000; 45:1850.
59. World health organization classification of tumours of haematopoietic and lymphoid tissues, revised 4th edition, Swerdlow SH, Campo E, Harris NL, et al. (Eds), IARC, Lyon 2017.
60. Iida T, Yamano H, Nakase H. Systemic amyloidosis with gastrointestinal involvement: Diagnosis from endoscopic and histological views. J Gastroenterol Hepatol 2018; 33:583.
61. Said SM, Grogg KL, Smyrk TC. Gastric amyloidosis: clinicopathological correlations in 79 cases from a single institution. Hum Pathol 2015; 46:491.
62. Fushimi T, Takahashi Y, Kashima Y, et al. Severe protein losing enteropathy with intractable diarrhea due to systemic AA amyloidosis, successfully treated with corticosteroid and octreotide. Amyloid 2005; 12:48.
63. Shin JK, Jung YH, Bae MN, et al. Successful treatment of protein-losing enteropathy due to AA amyloidosis with octreotide in a patient with rheumatoid arthritis. Mod Rheumatol 2013; 23:406.
64. Okuda Y, Takasugi K. Successful use of a humanized anti-interleukin-6 receptor antibody, tocilizumab, to treat amyloid A amyloidosis complicating juvenile idiopathic arthritis. Arthritis Rheum 2006; 54:2997.
65. Sato H, Sakai T, Sugaya T, et al. Tocilizumab dramatically ameliorated life-threatening diarrhea due to secondary amyloidosis associated with rheumatoid arthritis. Clin Rheumatol 2009; 28:1113.
66. Dainaka K, Isozaki Y, Kunieda K, et al. [A case of gastrointestinal amyloidosis and hypoproteinemia improved by tocilizumab]. Nihon Shokakibyo Gakkai Zasshi 2016; 113:245.
67. Inoue D, Arima H, Kawanami C, et al. Excellent therapeutic effect of tocilizumab on intestinal amyloid a deposition secondary to active rheumatoid arthritis. Clin Rheumatol 2010; 29:1195.
68. Kuroda T, Otaki Y, Sato H, et al. A case of AA amyloidosis associated with rheumatoid arthritis effectively treated with Infliximab. Rheumatol Int 2008; 28:1155.
69. Wixner J, Mundayat R, Karayal ON, et al. THAOS: gastrointestinal manifestations of transthyretin amyloidosis - common complications of a rare disease. Orphanet J Rare Dis 2014; 9:61.
70. Dhodapkar MV, Jagannath S, Vesole D, et al. Treatment of AL-amyloidosis with dexamethasone plus alpha interferon. Leuk Lymphoma 1997; 27:351.
71. Gertz MA, Lacy MQ, Dispenzieri A. Myeloablative chemotherapy with stem cell rescue for the treatment of primary systemic amyloidosis: a status report. Bone Marrow Transplant 2000; 25:465.

72. Gertz MA, Lacy MQ, Dispenzieri A, et al. Transplantation for amyloidosis. Curr Opin Oncol 2007; 19:136.
73. Suhr OB, Holmgren G, Steen L, et al. Liver transplantation in familial amyloidotic polyneuropathy. Follow-up of the first 20 Swedish patients. Transplantation 1995; 60:933.
74. Mejhert M, Hast R, Sandstedt B, Janczewska I. Ten-year follow-up after autologous stem cell transplantation of a patient with immunoglobulin light-chain (AL) amyloidosis with deposits in the heart, liver and gastrointestinal tract. BMJ Case Rep 2011; 2011.
75. Landau H, Hassoun H, Rosenzweig MA, et al. Bortezomib and dexamethasone consolidation following risk-adapted melphalan and stem cell transplantation for patients with newly diagnosed light-chain amyloidosis. Leukemia 2013; 27:823.
76. Gottenberg JE, Merle-Vincent F, Bentaberry F, et al. Anti-tumor necrosis factor alpha therapy in fifteen patients with AA amyloidosis secondary to inflammatory arthritides: a followup report of tolerability and efficacy. Arthritis Rheum 2003; 48:2019.
77. Levy M, Fryd CH, Eliakim M. Intrahepatic obstructive jaundice due to amyloidosis of the liver. A case report and review of the literature. Gastroenterology 1971; 61:234.
78. Vaxman I, Gertz M. Recent Advances in the Diagnosis, Risk Stratification, and Management of Systemic Light-Chain Amyloidosis. Acta Haematol 2019; 141:93.

Topic 2642 Version 21.0

CHAPTER 6

Renal amyloidosis

Authors:Nelson Leung, MD, Gerald B Appel, MD
Section Editor:Richard J Glassock, MD, MACP
Deputy Editor:Albert Q Lam, MD, Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Aug 2023. This topic last updated: May 17, 2023.

INTRODUCTIONAmyloidosis is a group of diseases characterized by extracellular deposition of beta-sheet fibrils. In the systemic forms, the amyloid protein causes progressive organ dysfunction, which may lead to death of the patients. Over 35 proteins capable of amyloid formation have been identified.

Clinically evident kidney involvement most commonly occurs in AL (immunoglobulin light chain) or AA (previously referred to as secondary) amyloidosis but can also occur in other forms of amyloidosis. The deposition of beta-2 microglobulin occurs in patients on prolonged maintenance dialysis; deposition in the kidney has been reported in autopsies but has no clinical significance. (See "Dialysis-related amyloidosis".)

This topic will review the pathology, pathogenesis, clinical manifestations, diagnosis, management, and prognosis of renal amyloidosis. A broad overview of amyloidosis and the specific treatment of AL and AA amyloidosis are presented elsewhere.

- (See "Overview of amyloidosis".)

- (See "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis".)

- (See "Treatment of AA (secondary) amyloidosis".)

EPIDEMIOLOGYThe prevalence of renal amyloidosis in native kidney biopsies is approximately 2 percent [1,2]. In a large biopsy series of 474 cases of renal amyloidosis, the most common type was immunoglobulin-associated (light chain [AL], heavy chain [AH], or both [AHL]) amyloidosis (86 percent), followed by AA amyloidosis (7 percent) and leukocyte cell-derived chemotaxin 2 (ALECT2) amyloidosis (3 percent) [1]. (See 'Types of renal amyloidosis' below.)

The prevalence of the various types of amyloid varies by geographic location and population studied [3-9]. As an example, in resource-limited countries, the prevalence of AA amyloidosis is higher than that of AL amyloidosis due to the high incidence of infectious diseases [3,4,6]. In the Southwest of the United States, where there is a large Mexican population, ALECT2 amyloidosis is more frequent, accounting for over 50 percent of the cases of amyloidosis found in patients of Mexican descent [10]. By contrast, in Egypt, AA amyloidosis predominates, and ALECT2 amyloidosis is the second most common cause of amyloidosis [11,12]. Other countries (eg, Sweden) have a high prevalence of hereditary amyloidosis [13,14].

Kidney involvement is present in approximately 50 to 80 percent of patients with AL amyloidosis [15-17] and is the predominant clinical manifestation (97 percent of patients) among patients with AA amyloidosis [18].

TYPES OF RENAL AMYLOIDOSIS

AL amyloidosis — The amyloid fibrils in AL amyloidosis (previously referred to as primary amyloidosis) consist of monoclonal immunoglobulin light chains [19]. The composition of deposits is confirmed by immunofluorescence microscopy with either anti-lambda or anti-kappa light chain antibodies in most cases. Staining for only a single type of light chain should suggest a monoclonal gammopathy such as AL amyloidosis or myeloma. In cases where the immunofluorescence is equivocal, laser microdissection and tandem mass spectrometry, when available, should be used to establish the diagnosis [20]. Although AL amyloidosis is the result of clonal proliferation of plasma cells, most patients do not meet criteria for multiple myeloma. These patients are best categorized as having monoclonal gammopathy of renal significance [21]. Furthermore, most patients with myeloma and overproduction of light chains (light chain myeloma) do not develop systemic amyloidosis. (See "Kidney disease in multiple myeloma and other monoclonal gammopathies: Etiology and evaluation" and "Diagnosis and treatment of monoclonal gammopathy of renal significance".)

Intrinsic factors of the pathogenic light chain are responsible for amyloid formation. Renal AL amyloidosis most frequently involves V lambda 6 light chains with several peculiarities, including somatic mutations in variable domains, hydrophobicity, posttranslational modifications (glycosylation), and aggregation features. Another property is the ability to be taken up by macrophages, where the intact light chains are metabolized to preamyloid fragments; these fragments must then have the biochemical properties that allow them to form amyloid fibrils [19]. The pathogenic

nature of the light chain may determine the post-uptake trafficking and modification [22], resulting in either amyloid formation or light chain deposition disease. Amyloidogenic light chains induce phenotypic changes in the mesangial cells that make them resemble macrophages [23]. (See "Monoclonal immunoglobulin deposition disease", section on 'Pathogenesis'.)

In AL amyloidosis, lambda light chains are more amyloidogenic than kappa light chains. In one study of 145 patients with biopsy-proven AL amyloidosis, the ratio of patients with lambda versus kappa light chains was much higher among patients who had kidney involvement (12:1) compared with those who did not (4:1). Among 84 patients with known renal amyloidosis, those with lambda light chains had greater urinary protein loss compared with those with kappa light chains (7 versus 3 g/day, respectively) [24].

AA amyloidosis — AA amyloidosis (previously referred to as secondary amyloidosis), also called reactive amyloidosis or amyloidosis AA, occurs in patients with chronic inflammation due to chronic infections, autoimmune diseases, or genetic autoinflammatory diseases (table 1) [18]. In the United States and many resource-abundant countries, rheumatoid arthritis (adult or juvenile) currently accounts for up to 40 percent of cases [19,25]. (See "Causes and diagnosis of AA amyloidosis and relation to rheumatic diseases".)

AA amyloidosis is associated with increased hepatocyte production of the acute phase reactant serum amyloid A (SAA); this process may be stimulated by the release of cytokines (perhaps interleukin 1 [IL-1] and IL-6) from activated macrophages [19]. Cleavage in circulating monocytes/macrophages results in the generation of smaller fragments, called AA protein, which can then deposit in the tissues. (See "Pathogenesis of AA amyloidosis".)

AA amyloidosis often leads to end-stage kidney disease (ESKD), particularly in patients whose inflammatory etiology has not been altered and who have persistently high circulating levels of SAA.

ALECT2 amyloidosis — Leukocyte cell-derived chemotaxin 2 (ALECT2)-associated amyloidosis is a systemic form of amyloidosis with predominantly kidney and liver involvement [26-28]. Most reported cases in North America (88 to 92 percent) occur in older adults of Mexican origin, although Punjabis, First Nations people in British Columbia, and Native Americans also have a predisposition for this disorder [29-32]. In one study of renal amyloidosis among Egyptians, ALECT2 amyloidosis was the second most common form of renal amyloidosis behind AA and ahead of AL

amyloidosis [11]. Cases have also been reported in Pakistani, Sudanese, and Chinese patients [33].

The pathogenesis of ALECT2 amyloidosis is not well understood. Patients typically present with chronic kidney disease (CKD) and variable proteinuria; nephrotic syndrome is uncommon [29,31]. A kidney biopsy, preferably with laser microdissection and mass spectrometry, is required to make the diagnosis. Patients with ALECT2 amyloidosis characteristically have diffuse Congo red-positive amyloid deposition in the cortical interstitium, with variable glomerular and vascular involvement [26,27,31]. In general, patients with ALECT2 amyloidosis have better overall survival than those with AL or AA amyloidosis, possibly due to the absence or rare occurrence of cardiac involvement. However, kidney survival is relatively poor, with up to 39 percent of patients progressing to ESKD [31]. There are no specific therapies for ALECT2 amyloidosis.

Apolipoprotein A-IV amyloidosis — Apolipoprotein A-IV (AApoAIV) amyloidosis is a rare form of renal amyloidosis that has been described in patients presenting with slowly progressive kidney function impairment and minimal or absent proteinuria [34,35]. In contrast with AApoAI and AApoAII amyloidoses, which are both hereditary forms of amyloidosis, no genetic mutations have yet been identified among patients with AApoAIV amyloidosis. Similar to patients with AApoAI amyloidosis, patients with AApoAIV amyloidosis have Congo red-positive amyloid deposits that are restricted to the renal medulla (mostly peritubular and interstitial) and spare the cortex.

Hereditary renal amyloidosis — Hereditary renal amyloidosis is an uncommon disorder in which amyloid deposition is most prominent in the kidneys. Although uncommon, one series reported that 10 percent of patients at an amyloidosis referral center who were thought to have AL amyloidosis actually had a hereditary form of the disease [36]. Mutations in a number of proteins can result in kidney deposition. These include the following:

●Fibrinogen A alpha chain [37-39]

●Lysozyme [40,41]

●Apolipoprotein A-I [42,43]

●Apolipoprotein A-II

●Apolipoprotein C-II

●Apolipoprotein C-III

●Gelsolin

●Transthyretin (ATTR) [44]

CLINICAL MANIFESTATIONSThe clinical manifestations of renal amyloidosis vary with the type of amyloid protein and the site and degree of amyloid deposition (table 2).

●**Proteinuria and nephrotic syndrome** – Proteinuria is the most common manifestation and is generally associated with glomerular deposition of amyloid. As an example, approximately 75 percent of patients with AL amyloidosis (most of whom have predominant glomerular deposition) present with proteinuria, often accompanied by edema [45,46]. The degree of proteinuria can range from mild to massive (>20 g/day), depending upon the extent of glomerular involvement. Patients with AL amyloidosis frequently present with heavy proteinuria (mean of 6.2 g/day in one study [1]), and approximately two-thirds present with the nephrotic syndrome [1]. The urine sediment is typically bland (reflecting the lack of glomerular inflammation), and the plasma creatinine concentration may be normal or only moderately elevated. End-stage kidney disease (ESKD) develops in approximately 20 percent of those with the nephrotic syndrome [45,46].

●**Slowly progressive CKD with little or no proteinuria** – Slowly progressive chronic kidney disease (CKD) with little or no proteinuria is the usual presentation of patients with AA amyloidosis who have amyloid deposits primarily limited to the vessels and tubulointerstitial areas (picture 1) [47,48]. Why this occurs is unclear, but the site of deposition may be determined at least in part by the size of the amyloid A fragment that is formed [48]. Prognosis in such patients appears to be more favorable [47,49]. Similar findings have also been reported in 5 percent of patients with AL amyloidosis [50].

Kidney function impairment without significant proteinuria is also the primary manifestation of patients with predominantly tubulointerstitial amyloid deposition, such as those with ALECT2 [28], apolipoprotein A-I (AApoAI) amyloidosis associated with the Leu75Pro mutation [43], or AApoAIV [35] amyloidosis. In ALECT2, the cortical interstitium is typically involved, and in some patients with AA,

AApoAI, AApoAIV, or transthyretin (ATTR)-associated amyloidosis, amyloid deposits are limited to the medullary interstitium [44,51].

●**Tubular dysfunction** – Tubular dysfunction such as type 1 (distal) renal tubular acidosis or polyuria due to arginine vasopressin resistance (previously called nephrogenic diabetes insipidus) can be the presenting features in patients with heavy tubular deposition (picture 2) [52]. Acquired Fanconi syndrome has been reported in rare cases of AL amyloidosis [53].

●**Crescentic glomerulonephritis** – Crescentic glomerulonephritis is a very rare presentation in patients with renal AA amyloidosis [54,55]. Almost all reported patients have had AA amyloidosis due to rheumatoid arthritis or its variants. A possible mechanism is amyloid fibril-induced ruptures in the capillary loops, leading to fibrin entry into Bowman space.

●**Acute kidney injury** – In rare cases, patients with AL amyloidosis can present with acute kidney injury due to intratubular amyloid cast nephropathy [56,57]. In such patients, the immunoglobulin light chain can precipitate to form intratubular casts resembling those in myeloma light chain cast nephropathy. However, these casts are congophilic and display fibrillar structures under electron microscopy.

PATHOLOGYCharacteristic histologic findings of renal amyloidosis on kidney biopsy include the following:

●**Light microscopy** – Light microscopy in renal amyloidosis typically reveals diffuse glomerular deposition of amorphous hyaline Congo red-positive material, initially in the mesangium and then along the capillary loops (picture 3A-D). These nodules stain weakly with periodic acid-Schiff and methenamine silver stain because they are composed mostly of amyloid fibrils and not extracellular matrix as in diabetes mellitus [58]. Scanty deposits of amyloid may go undetected by light microscopy. In some patients, amyloid is deposited primarily in the interstitium and along the tubular basement membranes or in the small arteries and arterioles (table 2).

There are multiple other causes of nodular glomerulosclerosis observed by light microscopy, most of which are identified by characteristic findings observed by immunofluorescence or electron microscopy. (See "Diabetic kidney disease: Manifestations, evaluation, and diagnosis", section on 'Pathology'.)

●**Immunofluorescence** – Immunofluorescence microscopy is negative for immunoglobulins and complement in non-AL amyloidosis but is positive for lambda

or kappa light chain in AL amyloidosis. The finding of only one light chain type, lambda or kappa, is required to confirm the diagnosis of AL amyloid. False negatives with immunofluorescence can occur in 25 to 35 percent of cases, especially if the antisera against kappa and lambda light chains used for immunofluorescence are obtained from only a single vendor. To increase sensitivity in this setting, the antisera from multiple vendors may be used, and immunoperoxidase can also be helpful. False-positive immunofluorescence has also been reported in some cases of AA amyloidosis thought to be the result of nonspecific immunoglobulin trapping.

Laser dissection of the tissue followed by tandem mass spectrometry-based proteomic analysis is the gold standard but is not needed in most patients for a diagnosis and is only available in specialized laboratories [20,59].

●**Electron microscopy** – Electron microscopy demonstrates straight, nonbranching fibrils that are randomly arranged and measure 8 to 12 nm in diameter, typically in the mesangium and along the glomerular capillary walls. The size of the fibrils distinguishes renal amyloidosis from other kidney diseases with organized immunoglobulin deposits, such as fibrillary glomerulonephritis. Immunoelectron microscopy has a high diagnostic accuracy for typing amyloidosis, but this technique is not widely available. (See "Glomerular diseases due to nonamyloid fibrillar deposits", section on 'Pathology and pathogenesis'.)

DIAGNOSISRenal amyloidosis should be suspected in any patient presenting with proteinuria with or without the nephrotic syndrome. Suspicion is even higher if other systemic symptoms (such as heart failure, gastrointestinal symptoms, or neuropathy) are also present. The evaluation of patients presenting with proteinuria with or without the nephrotic syndrome is discussed in detail elsewhere. (See "Glomerular disease: Evaluation and differential diagnosis in adults".)

A kidney biopsy is generally required to make a definitive diagnosis of renal amyloidosis. However, a kidney biopsy may be deferred if amyloidosis is suspected in a patient with a monoclonal gammopathy, in which case an abdominal fat pad aspirate may secure the diagnosis of systemic AL amyloidosis. If the fat pad aspirate is negative and the diagnosis of renal AL amyloidosis is still suspected, then a kidney biopsy should be performed. Of note, AL amyloidosis may be present in the bone marrow biopsy of patients with a monoclonal gammopathy; however, this is considered localized amyloidosis unless amyloid is discovered elsewhere in the body. (See "Overview of amyloidosis", section on 'Selection of biopsy site' and

"Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Choosing a biopsy site'.)

Once amyloidosis is confirmed by biopsy, the underlying etiology should be determined by typing the amyloid. This point cannot be overemphasized. Even when amyloid deposits are identified, the presence of a monoclonal gammopathy does not ensure the diagnosis of AL amyloidosis. One study showed that approximately 10 percent of patients at an amyloid referral center initially thought to have AL amyloidosis had hereditary amyloidosis [36]. Misdiagnosis not only results in exposure to unnecessary cytotoxic agents but also prevents the patient from receiving the appropriate therapy. It is also important to note that two different types of amyloid have sometimes been identified in a single organ. Biopsy of the affected organ is important to make sure the correct type of amyloid is being targeted by therapy [60]. A discussion of the methods used to determine the type of amyloid is presented elsewhere. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Determining the type of amyloid'.)

MANAGEMENTIn the absence of treatment, ongoing deposition of amyloid protein in the kidney results in a progressive decline in kidney function and ultimately end-stage kidney disease (ESKD) in most patients. Treatment of renal amyloidosis involves therapies targeting the production of amyloid protein as well as supportive measures. The goal of therapy is to achieve the best possible reduction in the amyloid protein precursor in order to limit further kidney injury and to preserve or improve kidney function.

Treatment of specific amyloid types — Specific therapy of renal amyloidosis is guided by the type of amyloid. However, there are no specific therapies for ALECT2, apolipoprotein A-IV (AApoAIV), or any of the hereditary renal amyloidoses. A novel approach using gene editing technology has been shown to reduce the production of transthyretin (ATTR) in patients with the mutant form of ATTR amyloidosis [61], suggesting that a similar approach might be applied to other forms of hereditary amyloidosis.

●**AL amyloidosis** – The approach to the treatment of AL amyloidosis is discussed in detail elsewhere. (See "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis".)

Factors that influence kidney response to therapy include the degree of baseline proteinuria and the serum creatinine [24,62]. This was shown in a study of 122

patients with AL amyloidosis [62]. At a median follow-up of 45 months posttherapy, multivariate analysis found that low baseline proteinuria (and cardiac troponin T) levels predicted a kidney response, which was defined as greater than 50 percent reduction in proteinuria with less than 25 percent decline in kidney function. A hematologic response (72 percent of patients) also correlated significantly with kidney response (43 percent of patients). Ninety-six percent of kidney responders also had a hematologic response versus only 54 percent of kidney nonresponders.

Elimination of the monoclonal protein and the plasma cell clone may lead to reversal of organ damage [17,62]. However, the small size of the monoclonal protein and low clonal plasma cells load often makes determination of hematologic response difficult. This process has been made easier with the serum-free light chain assay, which has a sensitivity more than 1000 times that of serum protein electrophoresis and 300 times that of immunofixation. In separate studies, significant (>90 percent) reduction or normalization of serum-free light chain levels after autologous stem cell transplantation was associated with better organ response and improved overall survival [63,64]. However, a 50 percent reduction in proteinuria can take up to 12 months to occur. In one study, a 30 percent reduction in proteinuria with less than 25 percent decline in estimated glomerular filtration rate (eGFR) was shown to predict response and avoidance of ESKD in two separate cohorts [65]. (See "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis", section on 'Prognosis'.)

A hematologic response to therapy is strongly associated with improved outcomes, even in patients with advanced amyloid-related kidney disease at the time of diagnosis. This was shown in a study of 84 patients with AL amyloidosis and an eGFR of <20 mL/min/1.73 m^2 at the time of diagnosis [66]. Forty-five patients had renal-limited amyloidosis, and 39 had both kidney and cardiac involvement. At baseline, median eGFR and 24-hour urine protein excretion were 10 mL/min/1.73 m^2 and 6.2 grams, respectively. Among the 78 patients who received chemotherapy, 55 percent received a bortezomib-based regimen as first-line therapy. Patients who achieved ≥90 percent reduction in the amyloidogenic free light chain (defined as the difference between the involved and uninvolved free light chain [dFLC]) within three months of baseline had better median overall survival and a prolonged time to dialysis (23 months versus 6.1 months) compared with those who achieved a lesser degree of clonal response. However, achieving the same reduction in dFLC after three months from baseline was not associated with a benefit in kidney survival. Thus, patients with AL amyloidosis and advanced chronic kidney disease (CKD) at

presentation may benefit from treatment, but the magnitude and speed of hematologic response appear to be critical factors in determining outcome.

●**AA amyloidosis** – Treatment of AA amyloidosis is targeted at the underlying chronic inflammatory disease responsible for the production of serum amyloid A (SAA). The treatment of AA amyloidosis is discussed in detail elsewhere. (See "Treatment of AA (secondary) amyloidosis".)

Supportive measures in all patients — General supportive measures in all patients with renal amyloidosis include dietary sodium and protein restriction, blood pressure control, treatment of dyslipidemia, and, in selected patients, anticoagulation. Other aspects of therapy include diuretics to control edema and maintenance of adequate nutrition. Importantly, patients with amyloidosis may experience hypotension and intolerance to diuretics related to cardiac involvement and autonomic dysregulation; thus, angiotensin inhibitors and diuretics should be used with caution. This approach is consistent with the 2021 Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for the Management of Glomerular Diseases [67]. These issues are discussed in greater detail elsewhere:

●Dietary sodium and protein restriction (see "Dietary recommendations for patients with nondialysis chronic kidney disease", section on 'Salt intake' and "Dietary recommendations for patients with nondialysis chronic kidney disease", section on 'Protein intake')

●Antihypertensive therapy (see "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults")

●Renin-angiotensin system inhibition (see "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Renin-angiotensin system inhibitors')

●Lipid lowering (see "Lipid abnormalities in nephrotic syndrome", section on 'Management')

●Anticoagulation (see "Hypercoagulability in nephrotic syndrome", section on 'Patients with other causes of nephrotic syndrome')

●Treatment of edema (see "Overview of the management of chronic kidney disease in adults", section on 'Volume overload')

DIALYSIS AND KIDNEY TRANSPLANTATIONPatients with renal amyloidosis who progress to end-stage kidney disease (ESKD) can be treated with either dialysis or kidney transplantation.

Outcomes in AL amyloidosis

●**Dialysis** – In general, outcomes among patients with AL amyloidosis who require dialysis are not as good as those for patients with other kidney diseases who require dialysis [16,68-70]. In earlier studies, median survival ranged from 8 to 26 months [16,68,69]. Subsequent studies have shown a modest improvement in outcomes. As an example, a United Kingdom study of 222 patients with AL amyloidosis on dialysis reported a mean survival of 39 months [71].

●**Transplantation** – By contrast, outcomes with kidney transplantation appear to be more favorable, especially in selected patients without other severe organ failure and who have a complete or very good partial hematologic response prior to transplantation [71-75]:

•The largest study included 237 patients with AL amyloidosis who underwent kidney transplantation and were followed for a median of 8.5 years [75]. Median overall survival from kidney transplantation was 8.6 years and was longer in patients with complete or very good partial hematologic responses compared with those who had less than very good partial response at the time of transplant (9 versus 6.8 years, respectively). Median graft survival was 7.8 years and greater in patients with complete or very good partial response (8.3 versus 5.7 years, respectively).

•Similar findings were reported in a study of 60 patients with AL amyloidosis who underwent kidney transplantation and were followed for a median of 61 months [73]. Prior to transplantation, 37 had achieved a complete hematologic response, 6 had a very good partial response, 5 had a partial response, 3 had no response, and 9 were treatment-naïve (never treated). Median overall survival for the group was 123 months. Median overall survival was not reached in the complete response group and was 8, 47, 81, and 117 months for the no response, partial response, very good partial response, and treatment-naïve groups, respectively. Death-censored graft survival at one and five years was 98 and 96 percent, respectively. Three patients (5 percent) developed graft failure, 19 (32 percent) died with a functioning graft, and 13 (22 percent) had amyloid recurrence.

•In another study of 49 patients who underwent kidney transplantation, median patient survival was 15.4 years from the time of diagnosis and 10.5 years from the time of transplant [72]. One-, three-, and five-year graft survival were 94, 89, and 81 percent, respectively. Patient survival was better among patients with hematologic complete response or very good partial response prior to transplant compared with those who had partial or no response.

Recurrence is a problem in AL amyloidosis. Two separate strategies have been used to address this issue, both of which have been shown to produce similar outcomes [76]. One restores kidney function first with a living donor kidney transplant prior to an autologous stem cell transplantation to treat the plasma cell dyscrasia [77]. This approach was evaluated in a report from the Mayo Clinic, which described their experience with the first eight patients with ESKD treated with this regimen [77]. Of eight patients who received a living donor kidney transplant, five subsequently underwent successful autologous stem cell transplantation, two died (one prior to stem cell transplantation and one after stem cell transplantation), and one patient elected not to undergo stem cell transplantation. At follow-up 0.4 to 2.3 years post-stem cell transplantation, kidney function was adequate in the five survivors who underwent both procedures (serum creatinine concentration ranging from 0.9 to 1.9 mg/dL [80 to 168 micromol/L]).

Alternatively, autologous stem cell transplantation can be performed first in patients with AL amyloidosis and ESKD, and kidney transplantation can be considered once hematologic complete response is achieved. Boston University reported their experience of this approach with 15 patients [78]. While toxicity, especially mucositis, and transfusion requirement were greater in those with ESKD, overall survival and response were similar to those in patients without ESKD. One advantage of this approach is avoidance of immunosuppression during autologous stem cell transplantation, which can be challenging.

Outcomes in AA amyloidosis

●**Dialysis** – Outcomes among patients with AA amyloidosis who require dialysis are generally unfavorable although much of the data are from older studies [68,69,79]. As examples:

•In a retrospective study of 73 patients with AA amyloidosis, of whom 45 developed ESKD and required dialysis (41 with hemodialysis, 4 with peritoneal dialysis), median survival on dialysis was 20 months [79]. Among patients receiving dialysis, one- and two-year patient survival were 64 and 56 percent, respectively, compared

with 84 and 74 percent, respectively, among patients who did not require dialysis. Survival on dialysis did not differ significantly with regards to the underlying etiology of AA amyloidosis (mostly Familial Mediterranean fever and tuberculosis).

•In another retrospective study that included 20 patients with AA amyloidosis requiring dialysis, three patients (15 percent) died over a mean of 32 months [69].

●**Transplantation** – The experience with kidney transplantation may be more favorable than that of dialysis [74,80-83]:

•In a study of 43 patients with AA amyloidosis who underwent kidney transplantation, 5- and 10-year graft survival rates were 86 and 59 percent, respectively [84]. Sixteen patients (37 percent) died over a median of 5 years, mostly from infectious causes. Recurrence of amyloidosis in the allograft occurred in nine patients (21 percent), two of whom experienced graft failure as a result. Similar graft survival rates have been reported in other studies [82].

•In another study that compared long-term transplant outcomes between 24 patients with ESKD secondary to amyloidosis (22 with AA amyloidosis, 2 with AL amyloidosis) and 24 control patients with ESKD from other causes, rates of biopsy-proven acute rejection and graft failure were similar between the groups [83]. However, patient survival rates were lower among patients with AA amyloidosis compared with those with ESKD due to other causes (68 versus 86 percent, respectively, at 10 years and 37 versus 60 percent, respectively, at 20 years).

Outcomes in other types of amyloidosis — Data on dialysis or transplant outcomes in patients with other forms of amyloidosis are more limited.

Recurrence appears to be common in patients with fibrinogen A alpha-chain amyloidosis who received kidney transplantation alone. In the largest series to date, recurrence was noted in four of eight successful kidney allografts [85]. Three of the grafts were lost as a direct result of recurrence (median of six years), with one remaining functional after 12 years. By comparison, seven patients have undergone combined liver-kidney transplantation and no recurrence has been found in the six surviving patients.

SOCIETY GUIDELINE LINKSLinks to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Glomerular disease in adults" and "Society guideline links: Immunoglobulin light chain (AL) amyloidosis".)

INFORMATION FOR PATIENTSUpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

●Basics topics (see "Patient education: AL amyloidosis (The Basics)")

SUMMARY AND RECOMMENDATIONS

●**Overview** – Amyloidosis is a group of diseases characterized by extracellular deposition of beta-sheet fibrils. Kidney involvement occurs in AL amyloidosis, characterized by the deposition of immunoglobulin light chains, or AA amyloidosis, characterized by the deposition of amyloid A. Kidney involvement is also the dominant presentation in some hereditary forms of amyloidosis. (See 'Introduction' above and 'Epidemiology' above.)

●**Types of renal amyloidosis** – The etiology of renal amyloidosis depends upon the type (table 2). An abnormal clonal proliferation of plasma cells causes AL amyloidosis. Chronic inflammatory diseases (such as rheumatoid arthritis) cause AA amyloidosis. Other major conditions associated with AA amyloidosis include ankylosing spondylitis, psoriatic arthritis, chronic pyogenic infections, inflammatory bowel disease, cystic fibrosis, some neoplasms, Familial Mediterranean fever, and other genetic autoinflammatory diseases. Less commonly, genetic disorders associated with chronic inflammation may cause AA amyloidosis. (See 'Types of renal amyloidosis' above.)

●**Clinical manifestations** – Clinical manifestations of renal amyloidosis vary with the site and degree of involvement (table 2). The most common presentation of AL and AA amyloidosis is heavy proteinuria which is associated with glomerular deposits. Patients with tubulointerstitial or vascular deposits present with slowly

progressive chronic kidney disease (CKD) with little or no proteinuria. Less commonly, patients with pure tubular deposits present with tubular dysfunction such as type 1 (distal) renal tubular acidosis or polyuria due to arginine vasopressin resistance (previously called nephrogenic diabetes insipidus), and, in rare cases, Fanconi syndrome. Crescentic glomerulonephritis is extremely rare. (See 'Clinical manifestations' above.)

●**Diagnosis** – Renal amyloidosis should be suspected in any patient presenting with proteinuria with or without the nephrotic syndrome. A kidney biopsy is generally required to make a definitive diagnosis. However, a kidney biopsy may be deferred if amyloidosis is suspected in a patient with a monoclonal gammopathy, in which case an abdominal fat pad aspirate may secure the diagnosis of systemic AL amyloidosis. Once amyloidosis is confirmed by biopsy, the underlying etiology should be determined by typing the amyloid. (See 'Diagnosis' above.)

●**Management** – In the absence of treatment, ongoing deposition of amyloid protein in the kidney results in a progressive decline in kidney function and ultimately end-stage kidney disease (ESKD) in most patients. Treatment of renal amyloidosis involves therapies targeting the production of amyloid protein as well as supportive measures. The goal of therapy is to decrease the burden of amyloid protein in order to limit further kidney injury and to preserve or improve kidney function. (See 'Management' above.)

●**End-stage kidney disease** – Patients with renal amyloidosis who progress to end-stage kidney disease (ESKD) can be treated with either dialysis or kidney transplantation. In general, outcomes among patients with amyloidosis who require dialysis are not as good as those for patients with other kidney diseases who require dialysis. Outcomes with kidney transplantation in selected patients appear to be more favorable. (See 'Dialysis and kidney transplantation' above.)

ACKNOWLEDGMENTThe UpToDate editorial staff acknowledges Robert A Kyle, MD, who contributed to earlier versions of this topic review.

REFERENCES

1. Said SM, Sethi S, Valeri AM, et al. Renal amyloidosis: origin and clinicopathologic correlations of 474 recent cases. Clin J Am Soc Nephrol 2013; 8:1515.
2. von Hutten H, Mihatsch M, Lobeck H, et al. Prevalence and origin of amyloid in kidney biopsies. Am J Surg Pathol 2009; 33:1198.

3. Mehta HJ, Talwalkar NC, Merchant MR, et al. Pattern of renal amyloidosis in western India. A study of 104 cases. J Assoc Physicians India 1990; 38:407.
4. Prakash J, Brojen T, Rathore SS, et al. The changing pattern of renal amyloidosis in Indian subcontinent: two decades of experience from a single center. Ren Fail 2012; 34:1212.
5. Bergesio F, Ciciani AM, Santostefano M, et al. Renal involvement in systemic amyloidosis--an Italian retrospective study on epidemiological and clinical data at diagnosis. Nephrol Dial Transplant 2007; 22:1608.
6. Oliveira-Silva C, Marques N, Pinho A, et al. Lessons from Four Decades of Systemic Amyloidosis with Renal Involvement. Nephron 2023; 147:158.
7. Damy T, Adams D, Bridoux F, et al. Amyloidosis from the patient perspective: the French daily impact of amyloidosis study. Amyloid 2022; 29:165.
8. Pinney JH, Smith CJ, Taube JB, et al. Systemic amyloidosis in England: an epidemiological study. Br J Haematol 2013; 161:525.
9. Nienhuis HL, Bijzet J, Hazenberg BP. The Prevalence and Management of Systemic Amyloidosis in Western Countries. Kidney Dis (Basel) 2016; 2:10.
10. Larsen CP, Beggs ML, Wilson JD, Lathrop SL. Prevalence and organ distribution of leukocyte chemotactic factor 2 amyloidosis (ALECT2) among decedents in New Mexico. Amyloid 2016; 23:119.
11. Larsen CP, Ismail W, Kurtin PJ, et al. Leukocyte chemotactic factor 2 amyloidosis (ALECT2) is a common form of renal amyloidosis among Egyptians. Mod Pathol 2016; 29:416.
12. Abdallah E, Waked E. Incidence and clinical outcome of renal amyloidosis: a retrospective study. Saudi J Kidney Dis Transpl 2013; 24:950.
13. Hemminki K, Li X, Försti A, et al. Incidence of hereditary amyloidosis and autoinflammatory diseases in Sweden: endemic and imported diseases. BMC Med Genet 2013; 14:88.
14. Hemminki K, Li X, Försti A, et al. Incidence and survival in non-hereditary amyloidosis in Sweden. BMC Public Health 2012; 12:974.
15. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol 1995; 32:45.
16. Gertz MA, Kyle RA, O'Fallon WM. Dialysis support of patients with primary systemic amyloidosis. A study of 211 patients. Arch Intern Med 1992; 152:2245.
17. Skinner M, Sanchorawala V, Seldin DC, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. Ann Intern Med 2004; 140:85.
18. Lachmann HJ, Goodman HJ, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. N Engl J Med 2007; 356:2361.
19. Glenner GG. Amyloid deposits and amyloidosis. The beta-fibrilloses (first of two parts). N Engl J Med 1980; 302:1283.
20. Vrana JA, Gamez JD, Madden BJ, et al. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood 2009; 114:4957.

21. Leung N, Bridoux F, Nasr SH. Monoclonal Gammopathy of Renal Significance. N Engl J Med 2021; 384:1931.
22. Herrera GA, Del Pozo-Yauner L, Teng J, et al. Glomerulopathic Light Chain-Mesangial Cell Interactions: Sortilin-Related Receptor (SORL1) and Signaling. Kidney Int Rep 2021; 6:1379.
23. Poshusta TL, Sikkink LA, Leung N, et al. Mutations in specific structural regions of immunoglobulin light chains are associated with free light chain levels in patients with AL amyloidosis. PLoS One 2009; 4:e5169.
24. Gertz MA, Leung N, Lacy MQ, et al. Clinical outcome of immunoglobulin light chain amyloidosis affecting the kidney. Nephrol Dial Transplant 2009; 24:3132.
25. Gertz MA, Kyle RA. Secondary systemic amyloidosis: response and survival in 64 patients. Medicine (Baltimore) 1991; 70:246.
26. Benson MD, James S, Scott K, et al. Leukocyte chemotactic factor 2: A novel renal amyloid protein. Kidney Int 2008; 74:218.
27. Murphy CL, Wang S, Kestler D, et al. Leukocyte chemotactic factor 2 (LECT2)-associated renal amyloidosis: a case series. Am J Kidney Dis 2010; 56:1100.
28. Nasr SH, Dogan A, Larsen CP. Leukocyte Cell-Derived Chemotaxin 2-Associated Amyloidosis: A Recently Recognized Disease with Distinct Clinicopathologic Characteristics. Clin J Am Soc Nephrol 2015; 10:2084.
29. Larsen CP, Kossmann RJ, Beggs ML, et al. Clinical, morphologic, and genetic features of renal leukocyte chemotactic factor 2 amyloidosis. Kidney Int 2014; 86:378.
30. Mereuta OM, Theis JD, Vrana JA, et al. Leukocyte cell-derived chemotaxin 2 (LECT2)-associated amyloidosis is a frequent cause of hepatic amyloidosis in the United States. Blood 2014; 123:1479.
31. Said SM, Sethi S, Valeri AM, et al. Characterization and outcomes of renal leukocyte chemotactic factor 2-associated amyloidosis. Kidney Int 2014; 86:370.
32. Hutton HL, DeMarco ML, Magil AB, Taylor P. Renal leukocyte chemotactic factor 2 (LECT2) amyloidosis in First Nations people in Northern British Columbia, Canada: a report of 4 cases. Am J Kidney Dis 2014; 64:790.
33. Rezk T, Gilbertson JA, Rowczenio D, et al. Diagnosis, pathogenesis and outcome in leucocyte chemotactic factor 2 (ALECT2) amyloidosis. Nephrol Dial Transplant 2018; 33:241.
34. Sethi S, Theis JD, Shiller SM, et al. Medullary amyloidosis associated with apolipoprotein A-IV deposition. Kidney Int 2012; 81:201.
35. Dasari S, Amin MS, Kurtin PJ, et al. Clinical, biopsy, and mass spectrometry characteristics of renal apolipoprotein A-IV amyloidosis. Kidney Int 2016; 90:658.
36. Lachmann HJ, Booth DR, Booth SE, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. N Engl J Med 2002; 346:1786.
37. Uemichi T, Liepnieks JJ, Benson MD. Hereditary renal amyloidosis with a novel variant fibrinogen. J Clin Invest 1994; 93:731.
38. Picken MM, Linke RP. Nephrotic syndrome due to an amyloidogenic mutation in fibrinogen A alpha chain. J Am Soc Nephrol 2009; 20:1681.

39. Tavares I, Oliveira JP, Pinho A, et al. Unrecognized Fibrinogen A α-Chain Amyloidosis: Results From Targeted Genetic Testing. Am J Kidney Dis 2017; 70:235.
40. Valleix S, Drunat S, Philit JB, et al. Hereditary renal amyloidosis caused by a new variant lysozyme W64R in a French family. Kidney Int 2002; 61:907.
41. Yazaki M, Farrell SA, Benson MD. A novel lysozyme mutation Phe57Ile associated with hereditary renal amyloidosis. Kidney Int 2003; 63:1652.
42. Vigushin DM, Gough J, Allan D, et al. Familial nephropathic systemic amyloidosis caused by apolipoprotein AI variant Arg26. Q J Med 1994; 87:149.
43. Gregorini G, Izzi C, Obici L, et al. Renal apolipoprotein A-I amyloidosis: a rare and usually ignored cause of hereditary tubulointerstitial nephritis. J Am Soc Nephrol 2005; 16:3680.
44. Lobato L, Rocha A. Transthyretin amyloidosis and the kidney. Clin J Am Soc Nephrol 2012; 7:1337.
45. Palladini G, Merlini G. Current treatment of AL amyloidosis. Haematologica 2009; 94:1044.
46. Wechalekar AD, Hawkins PN, Gillmore JD. Perspectives in treatment of AL amyloidosis. Br J Haematol 2008; 140:365.
47. Falck HM, Törnroth T, Wegelius O. Predominantly vascular amyloid deposition in the kidney in patients with minimal or no proteinuria. Clin Nephrol 1983; 19:137.
48. Westermark GT, Sletten K, Grubb A, Westermark P. AA-amyloidosis. Tissue component-specific association of various protein AA subspecies and evidence of a fourth SAA gene product. Am J Pathol 1990; 137:377.
49. Uda H, Yokota A, Kobayashi K, et al. Two distinct clinical courses of renal involvement in rheumatoid patients with AA amyloidosis. J Rheumatol 2006; 33:1482.
50. Eirin A, Irazabal MV, Gertz MA, et al. Clinical features of patients with immunoglobulin light chain amyloidosis (AL) with vascular-limited deposition in the kidney. Nephrol Dial Transplant 2012; 27:1097.
51. Sethi S, Theis JD. Pathology and diagnosis of renal non-AL amyloidosis. J Nephrol 2018; 31:343.
52. Neugarten J, Gallo GR, Buxbaum J, et al. Amyloidosis in subcutaneous heroin abusers ("skin poppers' amyloidosis"). Am J Med 1986; 81:635.
53. Orfila C, Lepert JC, Modesto A, et al. Fanconi's syndrome, kappa light-chain myeloma, non-amyloid fibrils and cytoplasmic crystals in renal tubular epithelium. Am J Nephrol 1991; 11:345.
54. Moroni G, Banfi G, Maccario M, et al. Extracapillary glomerulonephritis and renal amyloidosis. Am J Kidney Dis 1996; 28:695.
55. Verine J, Mourad N, Desseaux K, et al. Clinical and histological characteristics of renal AA amyloidosis: a retrospective study of 68 cases with a special interest to amyloid-associated inflammatory response. Hum Pathol 2007; 38:1798.
56. Sharma A, Bansal S, Jain R. Unique morphology of intratubular light chain casts in multiple myeloma: the amyloid cast nephropathy. Indian J Pathol Microbiol 2014; 57:629.

57. Kato H, Fujigaki Y, Asakawa S, et al. Rapid Deterioration of the Renal Function Caused by the Coexistence of Intratubular Amyloidosis and Myeloma Cast Nephropathy. Intern Med 2015; 54:3023.
58. Dember LM. Amyloidosis-associated kidney disease. J Am Soc Nephrol 2006; 17:3458.
59. Sethi S, Theis JD, Leung N, et al. Mass spectrometry-based proteomic diagnosis of renal immunoglobulin heavy chain amyloidosis. Clin J Am Soc Nephrol 2010; 5:2180.
60. Papa R, Gilbertson JA, Rendell N, et al. Two types of systemic amyloidosis in a single patient. Amyloid 2020; 27:275.
61. Gillmore JD, Gane E, Taubel J, et al. CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis. N Engl J Med 2021; 385:493.
62. Leung N, Dispenzieri A, Lacy MQ, et al. Severity of baseline proteinuria predicts renal response in immunoglobulin light chain-associated amyloidosis after autologous stem cell transplantation. Clin J Am Soc Nephrol 2007; 2:440.
63. Sanchorawala V, Seldin DC, Magnani B, et al. Serum free light-chain responses after high-dose intravenous melphalan and autologous stem cell transplantation for AL (primary) amyloidosis. Bone Marrow Transplant 2005; 36:597.
64. Dispenzieri A, Lacy MQ, Katzmann JA, et al. Absolute values of immunoglobulin free light chains are prognostic in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation. Blood 2006; 107:3378.
65. Palladini G, Hegenbart U, Milani P, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood 2014; 124:2325.
66. Rezk T, Lachmann HJ, Fontana M, et al. Prolonged renal survival in light chain amyloidosis: speed and magnitude of light chain reduction is the crucial factor. Kidney Int 2017; 92:1476.
67. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int 2021; 100:S1.
68. Moroni G, Banfi G, Montoli A, et al. Chronic dialysis in patients with systemic amyloidosis: the experience in northern Italy. Clin Nephrol 1992; 38:81.
69. Bollée G, Guery B, Joly D, et al. Presentation and outcome of patients with systemic amyloidosis undergoing dialysis. Clin J Am Soc Nephrol 2008; 3:375.
70. Tang W, McDonald SP, Hawley CM, et al. End-stage renal failure due to amyloidosis: outcomes in 490 ANZDATA registry cases. Nephrol Dial Transplant 2013; 28:455.
71. Pinney JH, Lachmann HJ, Bansi L, et al. Outcome in renal Al amyloidosis after chemotherapy. J Clin Oncol 2011; 29:674.
72. Angel-Korman A, Stern L, Sarosiek S, et al. Long-term outcome of kidney transplantation in AL amyloidosis. Kidney Int 2019; 95:405.
73. Heybeli C, Bentall A, Wen J, et al. Corrigendum to Heybeli C, Bentall A, Wen J, et al. A study from The Mayo Clinic evaluated long-term outcomes of kidney transplantation

in patients with immunoglobulin light chain amyloidosis. Kidney Int. 2021;99:707-715. Kidney Int 2021; 100:1348.
74. Law S, Cohen O, Lachmann HJ, et al. Renal transplant outcomes in amyloidosis. Nephrol Dial Transplant 2021; 36:355.
75. Havasi A, Heybeli C, Leung N, et al. Outcomes of renal transplantation in patients with AL amyloidosis: an international collaboration through The International Kidney and Monoclonal Gammopathy Research Group. Blood Cancer J 2022; 12:119.
76. Herrmann SM, Gertz MA, Stegall MD, et al. Long-term outcomes of patients with light chain amyloidosis (AL) after renal transplantation with or without stem cell transplantation. Nephrol Dial Transplant 2011; 26:2032.
77. Leung N, Griffin MD, Dispenzieri A, et al. Living donor kidney and autologous stem cell transplantation for primary systemic amyloidosis (AL) with predominant renal involvement. Am J Transplant 2005; 5:1660.
78. Casserly LF, Fadia A, Sanchorawala V, et al. High-dose intravenous melphalan with autologous stem cell transplantation in AL amyloidosis-associated end-stage renal disease. Kidney Int 2003; 63:1051.
79. Yilmaz M, Unsal A, Sokmen M, et al. Renal involvement in AA amyloidosis: clinical outcomes and survival. Kidney Blood Press Res 2013; 37:33.
80. Pasternack A, Ahonen J, Kuhlbäck B. Renal transplantation in 45 patients with amyloidosis. Transplantation 1986; 42:598.
81. Sobh M, Refaie A, Moustafa F, et al. Study of live donor kidney transplantation outcome in recipients with renal amyloidosis. Nephrol Dial Transplant 1994; 9:704.
82. Sherif AM, Refaie AF, Sobh MA, et al. Long-term outcome of live donor kidney transplantation for renal amyloidosis. Am J Kidney Dis 2003; 42:370.
83. Heybeli C, Yildiz S, Oktan MA, et al. Long-Term Outcomes of Patients With Amyloidosis Following Kidney Transplant. Exp Clin Transplant 2023; 21:324.
84. Pinney JH, Lachmann HJ, Sattianayagam PT, et al. Renal transplantation in systemic amyloidosis-importance of amyloid fibril type and precursor protein abundance. Am J Transplant 2013; 13:433.
85. Gillmore JD, Lachmann HJ, Rowczenio D, et al. Diagnosis, pathogenesis, treatment, and prognosis of hereditary fibrinogen A alpha-chain amyloidosis. J Am Soc Nephrol 2009; 20:444.

Topic 3120 Version 26.0

CHAPTER 7

Amyloid cardiomyopathy: Treatment and prognosis

Author:Marianna Fontana, MD
Section Editors:S Vincent Rajkumar, MD, William J McKenna, MD
Deputy Editor:Todd F Dardas, MD, MS
Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Aug 2023. This topic last updated: Mar 23, 2021.

INTRODUCTIONAmyloidosis refers to the extracellular deposition of fibrils that are composed of low molecular weight subunits (5 to 25 kD) of a variety of serum proteins. These fibrils adopt a beta-pleated sheet configuration that leads to characteristic histologic changes. Amyloid deposits can occur in a variety of organs, with involvement of the heart, kidney, liver, and autonomic nervous system most often being responsible for morbidity and mortality. (See "Overview of amyloidosis".)

The frequency of cardiac involvement varies among types of amyloidosis. The prognosis of amyloid cardiomyopathy also varies among types of amyloidosis, with high mortality rates particularly in light-chain (AL) amyloidosis.

This topic will review the treatment of amyloid cardiomyopathy. The clinical manifestations and diagnosis of amyloid cardiomyopathy are discussed separately. (See "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis".)

NATURAL HISTORY AND PROGNOSIS

Cardiac ATTR amyloidosis

Wild-type ATTR amyloidosis — Original reports of wild-type transthyretin amyloidosis (ATTRwt) suggested a median survival of >5 years [1]; later studies [2-4] have reported worse outcomes, with median survival of 3.5 years [5].

Hereditary ATTR amyloidosis — The clinical phenotype of hereditary ATTR (ATTRm) varies among TTR variants and includes primary polyneuropathy (Val30Met), cardiomyopathy (Val122Ile, Leu111Met, Ile68Leu), and mixed phenotype (T60A). Peripheral neuropathy and autonomic dysfunction have a

significant impact on quality of life, but cardiac involvement is the main determinant of prognosis with a median survival of four to five years when cardiac amyloidosis is present [6].

Cardiac AL amyloidosis — Natural history studies found that patients with cardiac AL amyloidosis and heart failure (HF) without disease-specific treatment had an overall median survival of only six months [7]. With contemporary management, the median survival for AL amyloidosis with cardiac involvement has significantly improved (eg, 5.5 years after diagnosis [8]). (See "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis".)

STAGING

AL amyloidosis — Multiple staging systems have been proposed for AL amyloidosis, as discussed separately (table 1). (See "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis", section on 'Staging'.)

As an example, the Revised Mayo Stage system is based on serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), cardiac troponin T, and free light chains [9]. The scoring system assigns 1 point for NT-pro-BNP ≥1800 pg/mL, troponin T ≥0.025 ng/mL, and difference between the kappa and lambda free light chains ≥18 mg/dL. Median survival for stage III patients was 14 months and for stage IV patients was 5.8 months [9]. Within stage III, NT-proBNP >8500 pg/mL combined with a systolic blood pressure <100 mmHg identifies a group of patients with the highest mortality (IIIb).

In AL amyloidosis, changes in NT-proBNP have also been used to predict response to treatment and disease progression (table 2), with a decrease in NT-proBNP of >30 percent and >300 ng/L from a baseline value ≥650 ng/L associated with better prognosis [10].

ATTR amyloidosis — Two staging systems have been proposed in patients with ATTR amyloidosis:

●The first published staging system for ATTRwt is based on serum levels of NT-proBNP and cardiac troponin T [5]. Thresholds of troponin T (0.05 ng/ml) and NT-proBNP (3000 pg/ml) were used. The respective four-year overall survival estimates were 57, 42, and 18 percent for stage I (both values below cutoff), stage II (one above), and stage III (both above), respectively.

●The second staging system, validated in both ATTRwt and ATTRm, is based on serum levels of NT-proBNP and estimated glomerular filtration rate (eGFR) [11]. Stage I is defined as NT-proBNP ≤3000 ng/L and eGFR ≥45 mL/min, Stage III is defined as NT-proBNP >3000 ng/L and eGFR <45 mL/min, and the remainder were Stage II. Median survival among Stage I patients was 69.2 months, Stage II patients 46.7 months, and Stage III patients 24.1 months [11].

TREATMENT

General considerations — The treatment of symptomatic cardiac amyloidosis is twofold: therapy for HF and treatment of the underlying disease. Patients with ATTRm or ATTRwt generally respond better to HF therapy than patients with AL amyloidosis. However, there are more therapeutic options for addressing the underlying disease in AL amyloidosis, and if the plasma cell dyscrasia can be controlled, there is often a relatively rapid decrease in serum biomarkers of HF [12].

Heart failure therapy

Approach to heart failure — Treatment of HF in patients with cardiac amyloidosis differs from the therapy generally recommended in patients with diastolic or systolic HF. While loop diuretics are a mainstay of treatment of cardiac amyloidosis, there is no evidence that beta blockers and angiotensin-converting enzyme (ACE) inhibitors are associated with prognostic benefit in cardiac amyloidosis despite their efficacy in other types of systolic HF. Furthermore, they are usually poorly tolerated, especially in AL amyloidosis. Similarly, calcium channel blockers that may be useful in treatment of diastolic HF are contraindicated in amyloid cardiomyopathy. Adverse responses to drugs in cardiac amyloidosis are likely due to its unique pathophysiologic features.

HF in patients with cardiac amyloidosis is secondary to complex pathophysiologic alterations. The pathologic changes that result from extensive amyloid infiltration result in a nondilated normal to small biventricular cavity size, with significant diastolic dysfunction because of decreased compliance. Systolic dysfunction is almost invariably present, and this usually affects first the longitudinal contraction (better assessed with longitudinal strain) and, in later stages, the radial contraction (reduced ejection fraction). In addition, the infiltration of the atria may severely impair atrial contraction, further decreasing ventricular filling. This combination results in a decreased stroke volume and cardiac output and marked elevation of intracardiac pressures with frequent occurrence of functional mitral and tricuspid regurgitation. In addition, there is experimental evidence that excessive circulating

free light chains in AL amyloidosis are cardiotoxic, possibly explaining the worse prognosis in cardiac AL amyloidosis compared with ATTR. (See "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis", section on 'Types of amyloidosis'.)

Medical therapy — Loop diuretics are a mainstay of the management of HF. If edema is severe, hospitalization and a course of intravenous diuretics should be strongly considered. This should be accompanied by careful monitoring of blood pressure and renal function, as overvigorous diuresis may result in progressive azotemia. Aldosterone antagonist therapy (eg, spironolactone) in conjunction with loop diuretics is generally tolerated without the development of excessive hypotension.

Although beta blockers reduce morbidity and mortality in patients with systolic HF generally, they have no proven benefit in patients with HF due to cardiac amyloidosis. Indeed, they are poorly tolerated in patients with cardiac amyloidosis in whom cardiac output is dependent on heart rate due to presence of a low, fixed stroke volume.

The safety and efficacy of ACE inhibitors or angiotensin receptor blockers (ARBs) in patients with cardiac amyloidosis is uncertain. There are no clinical trials of ACE inhibitors or ARBs in amyloidosis, but clinical experience has shown that these agents often provoke profound hypotension in AL amyloidosis, possibly by exposing a subclinical autonomic neuropathy. ACE inhibitors and ARBs appear to be better tolerated in patients with ATTRwt amyloidosis, in whom autonomic neuropathy is rare. Tolerability of ACE inhibitors and ARBs in ATTR cardiomyopathy due to a mutant protein depends on the presence or absence of concomitant autonomic dysfunction. If a trial of ACE inhibition is attempted in a patient with AL amyloidosis, initiation should be with a very low dose of captopril with careful blood pressure monitoring and slow, carefully monitored up-titration of the dose if tolerated.

Amyloid fibrils bind to digoxin and this interaction may account for increased susceptibility to digitalis toxicity [13]. Although digoxin has no role in treating HF due to amyloid cardiomyopathy, careful use of digoxin may be of value in a patient with atrial fibrillation and a rapid ventricular response, particularly when hypotension makes beta blocker use untenable [14]. (See "Atrial fibrillation: Overview and management of new-onset atrial fibrillation" and "Control of ventricular rate in patients with atrial fibrillation who do not have heart failure: Pharmacologic therapy".)

Calcium channel blockers such as verapamil or diltiazem that are used to slow heart rate and that may possibly improve ventricular relaxation in diastolic HF (eg, in hypertensive heart disease or hypertrophic cardiomyopathy) have not been proven to be effective in cardiac amyloidosis, and this is probably related to the different mechanism leading to diastolic dysfunction, as the diastolic dysfunction is due to the amyloid and not to myocardial cellular dysfunction. Indeed, these drugs are contraindicated, as their negative inotropic effects may be profound, possibly because of an abnormal binding to amyloid fibrils, and may depress compensatory heart rate responses to low stroke volume and cardiac output [13,15,16].

Heart transplantation and ventricular assist devices — The great majority of patients with cardiac AL amyloidosis have significant noncardiac amyloidosis and are not suitable candidates for heart transplantation. For example, in one series, only 4 percent of patients had clinically isolated cardiac disease [17]. Early experience with cardiac transplantation in AL amyloidosis did not address the importance of a sustained clonal response and, not surprisingly, when the disease relapsed, the disease progressed in other organs and/or returned in the transplanted heart [18,19]. The few major centers that accept patients with AL amyloidosis for cardiac transplantation accept only those who have disease clinically isolated to the heart. Heart transplantation for AL amyloidosis in these centers is followed by high-dose chemotherapy and autologous hematopoietic stem cell transplantation within a 12-month period. Long-term follow-up data in these patients are not yet available, but several appear to have had excellent cardiac results and a durable hematologic response [20-24].

Patients with ATTRwt amyloidosis generally have the disease clinically isolated to the heart and as such would appear to be more suitable candidates. However, most patients are diagnosed in their seventh or eighth decade of life and are excluded based on their age. Nevertheless, successful heart transplantation has been carried out in a few patients with ATTRwt amyloidosis who presented at a younger age [25].

Patients with ATTRm cardiac amyloidosis are often younger than ATTRwt patients, and may be candidates for heart transplantation if amyloid neuropathy is absent or mild. However, since the mutant TTR is produced in the liver, most mutations may need a combined liver and heart transplant to prevent recurrence in the transplanted heart. Fourteen patients in a single center in Italy had combined liver-heart transplantation for familial amyloid cardiomyopathy between 1999 and 2012. Actuarial survival at one and five years was 93 and 82 percent, respectively, and the explanted liver was retransplanted into another (nonamyloid) recipient in 8 of 14

cases. No recurrent amyloid was reported in heart-liver recipients [26]. An exception to the requirement of liver transplantation is probably the Val122Ile mutation, common in African-Americans, in which isolated heart transplantation has been performed without documentation of recurrent disease [27].

Ventricular assist devices have been used very infrequently in cardiac amyloidosis, owing to technical difficulties when used in a restrictive cardiomyopathy as well as the presence of coexisting noncardiac amyloidosis [28].

Treatment of atrial fibrillation — If atrial fibrillation with a rapid ventricular response develops in a patient with AL or ATTR amyloidosis, low-dose beta blockade and careful digoxin use may help with rate control (notwithstanding the above concerns about beta blocker and digoxin use in amyloid cardiomyopathy generally). Despite severely impaired atrial contractile function, clinical improvement may occur after restoration of sinus rhythm in a patient with atrial fibrillation of recent onset, possibly due to a regularization of the heart rate. Amiodarone use to maintain sinus rhythm appears to be well tolerated without specific amyloidosis-related side effects. Experience with catheter ablation for atrial arrhythmias in patients with cardiac amyloidosis is limited. Results in 26 patients over two decades indicate symptomatic improvement but without evidence of change in disease-related mortality [29]. (See "Atrial fibrillation: Overview and management of new-onset atrial fibrillation".)

Anticoagulation — Amyloid cardiomyopathy is associated with high risk of intracardiac thrombus, predominantly in the atria [30]. (See "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis", section on 'Cardiac involvement'.)

Anticoagulation is indicated if a patient with amyloid develops atrial fibrillation, since the risk of intracardiac thrombus is very high. The role of anticoagulation in patients in sinus rhythm is uncertain. Atrial failure, even in the presence of sinus rhythm, is very common in amyloidosis and is associated with atrial thrombus formation, particularly in patients with AL-type amyloidosis [30-32].

Although amyloidosis is associated with increased hemorrhagic risk due to amyloid angiopathy, intestinal or bladder amyloid, or coagulopathy, major bleeding in anticoagulated patients does not seem to exceed that seen in other patients with similar nonamyloid degrees of illness, so anticoagulation should not be withheld if indicated unless a clear-cut contraindication exists. There are no controlled data on bleeding risk of oral anticoagulants in cardiac amyloidosis, but bleeding has not

been found to be excessive, and warfarin or one of the newer oral anticoagulants have been used (oral direct thrombin inhibitor or direct factor Xa inhibitor) without unanticipated problems. (See "Atrial fibrillation in adults: Use of oral anticoagulants".)

Conduction disease — Patients with amyloid cardiomyopathy are at risk of conduction system disease with the potential requirement for pacemaker therapy; general indications for cardiac pacing should be applied. (See "Permanent cardiac pacing: Overview of devices and indications".)

Implantable cardioverter-defibrillator — The efficacy of implantable cardioverter-defibrillator (ICD) therapy in patients with cardiac amyloidosis is uncertain. Sudden cardiac death (SCD) is common in patients with cardiac AL amyloidosis and prophylactic ICDs have been suggested as an option to reduce this risk. However, electromechanical dissociation appears to be a significant cause of SCD in these patients, so the role of ICD therapy in preventing SCD in this population is unclear.

This issue was illustrated by a study in which 19 cardiac AL amyloidosis patients with history of syncope (n = 4) or high-grade ventricular arrhythmias (n = 10), or both (n = 5) received an ICD [33]. Two subsequently underwent cardiac transplant, and one died of an unrelated disease. There were six cardiac deaths, all sudden despite the ICD. One patient received appropriate shocks but later died of electromechanical dissociation, which was also the cause of death in the other five. Only one patient received appropriate ICD shocks with long-term survival.

Similar findings were reported in a retrospective analysis of a cohort of 53 patients with amyloid cardiomyopathy (33 with cardiac AL amyloidosis confirmed by endomyocardial biopsy) who had undergone ICD implantation (77 percent for primary prevention) at a single center between 2000 and 2009 [34]. Over a mean follow-up of 23 months, 15 patients (12 with cardiac AL amyloidosis) received at least one appropriate ICD shock, with none of these shocks occurring in patients who received the ICD strictly for primary prevention due to a reduced left ventricular ejection fraction. However, there was no significant difference in survival between patients who received an appropriate ICD shock and those who did not receive ICD shock.

Thus, the limited available clinical data do not support use of ICDs for primary prevention of SCD in patients with cardiac amyloidosis of any etiology. In the patient with cardiac amyloidosis who is resuscitated from a life-threatening ventricular arrhythmia, implantation of an ICD should be considered.

TREATMENT OF THE UNDERLYING PROTEIN MISFOLDING DISORDERTreatment of the underlying protein misfolding disorder varies with the cause of excess fibril production.

Specific therapy for AL amyloidosis — As discussed in detail separately, survival in patients with AL amyloidosis varies with the extent of organ involvement, and median survival is as short as four to six months in those with HF (see "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis", section on 'Prognosis' and "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis"). However, with earlier diagnosis, careful patient selection, and use of currently available chemotherapeutic regimens, survival can be significantly prolonged [12]. The available medical regimens are discussed separately, but the basic principles will be reviewed here. (See "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis".)

In general, therapy involves the administration of chemotherapy and/or autologous stem cell transplantation (ASCT) in an attempt to treat the underlying plasma cell clone responsible for AL amyloid formation. The goal of therapy in patients with cardiac involvement is to achieve a 90 percent or greater reduction in serum free light chain levels, but not all patients may be able to attain this level of response. The intensity and type of therapy chosen is affected by the number and extent of organ involvement. The most common initial chemotherapy regimens used are now bortezomib-based regimens such as daratumumab, cyclophosphamide, bortezomib, dexamethasone (dara-CyBorD) or cyclophosphamide, bortezomib, dexamethasone (CyBorD). For patients who are candidates for stem cell transplantation, ASCT involves administration of high-dose melphalan followed by stem cell rescue. The risk of treatment-related mortality associated with ASCT in AL amyloidosis restricts the use of this procedure to a small group of selected patients.

New York Heart Association (NYHA) functional class III or IV HF is generally considered a contraindication to ASCT in patients with AL amyloidosis. These patients have also been classified as stage III AL amyloidosis (table 1). (See "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis".)

The prognosis of such individuals, who have been excluded from many of the clinical therapeutic studies, was evaluated in a study of 346 Stage III patients treated with standard chemotherapeutic regimens. The median survival was seven months, with 24 percent surviving until 24 months [35]. The overall hematologic response rate was 33 percent, including a complete response rate of 12 percent. N-terminal pro-B-type natriuretic peptide (NT-proBNP) >8500 ng/L and systolic blood pressure <100

mmHg predicted a poor outcome. However, these patients were treated before the widespread use of bortezomib, and it is likely that current regimens are superior in terms of survival [36].

Specific therapy for ATTR amyloidosis — For ATTR cardiomyopathy, options include:

●For patients with ATTR cardiomyopathy with NYHA functional class I to III, we recommend treatment with tafamidis. In this population, a randomized trial found that tafamidis therapy reduced mortality as well as cardiovascular-related hospitalizations, and reduced declines in functional capacity and quality of life [37]. (See 'Tafamidis' below.)

●In addition, patients diagnosed with ATTRm cardiomyopathy should undergo evaluation for liver transplantation, as this can be curative in selected patients with ATTRm but not in ATTRwt, as discussed below.

Tafamidis — The multicenter randomized ATTR-ACT trial demonstrated that tafamidis is an effective therapy for patients with ATTR cardiomyopathy [37]. Tafamidis stabilizes the transthyretin tetramer and may thus reduce formation of TTR amyloid [38,39]. In the ATTR-ACT trial, 441 patients with ATTR (variant or wild-type) amyloid cardiomyopathy were randomly assigned in a 2:1:2 ratio to receive tafamidis 80 mg, tafamidis 20 mg, or placebo once daily for 30 months [37]. Exclusion criteria included NYHA functional class IV HF or an estimated glomerular filtration rate less than 25 mL per minute per 1.73 m^2 of body-surface area. Tafamidis reduced mortality compared with placebo (29.5 versus 42.9 percent; hazard ratio 0.70, 95% CI 0.51-0.96) and also reduced cardiovascular-related hospitalizations (0.48 versus 0.70 per year; risk ratio 0.68, 95% CI 0.56-0.81). Tafamidis also reduced the rate of decline in six-minute walk distance and Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS). The incidence of adverse events was similar in the tafamidis and placebo groups.

Consistent effects on mortality and cardiovascular hospitalization were observed across subgroups of TTR type, tafamidis dose, and NYHA functional class at baseline, except for patients with NYHA class III at baseline, for whom the risk of cardiovascular-related hospitalization was higher with tafamidis. This finding may be due to longer survival in severely symptomatic patients.

The US Food and Drug Administration (FDA) approved doses and formulations of tafamidis for amyloid cardiomyopathy are an 80 mg daily dose of tafamidis

meglumine (Vyndaqel) for amyloid cardiomyopathy, or alternatively, a 61 mg daily dose of tafamidis (Vyndamax). The 80 mg dose of tafamidis meglumine was approved by the FDA because a pooled analysis of 11 studies found that ex vivo stabilization of transthyretin tetramers was greater with the 80 mg dose than with the 20 mg dose, and safety results were similar for the two doses [40]; the clinical significance of this surrogate endpoint is uncertain.

Liver transplantation — In ATTR amyloidosis, the source of the amyloidogenic protein is the liver. Transplantation of the liver removes the mutant amyloidogenic TTR in ATTRm, but in ATTRwt the precursor protein is native TTR, and thus liver transplantation is not indicated. Unfortunately, cardiac disease has progressed after liver transplantation in some patients with familial ATTR, even though deposits elsewhere may stabilize [41]. Examination of the composition of TTR in the heart of patients with progressive cardiomyopathy after liver transplantation reveals that the mechanism is enhanced deposition of wild-type TTR on a template of amyloid derived from variant TTR. Patients with advanced heart disease may be treated with combined heart and liver transplantation [42].

Once a patient with a transthyretin mutation is found to have a positive biopsy for amyloid, he or she should undergo evaluation for liver transplantation, with the goal to receive the transplant as early in the disease as possible. If an amyloid cardiomyopathy is present with significant HF, isolated liver transplantation is contraindicated and consideration should be given to a combined liver-heart transplant or just heart alone.

This appears to be particularly true in patients with the Ala60 mutation in whom cardiomyopathy is almost always present and in whom liver transplant alone does not stop progressive cardiomyopathy [43].

Investigational agents — Several investigational agents for ATTR amyloidosis are in active trials, but effects on cardiovascular outcomes have not been established. RNA-targeted therapies that interfere with hepatic TTR synthesis and thus reduce the availability of misfolded monomer to form amyloid deposits include patisiran and inotersen, which are discussed further separately (see "Overview of amyloidosis", section on 'Treatment'):

●Patisiran is an anti-TTR small interfering ribonucleic acid (siRNA) formulation of lipid nanoparticles. A randomized trial comparing patisiran with placebo in patients with ATTRm amyloidosis with polyneuropathy found that patisiran significantly reduced symptoms and impairment from neuropathy and improved quality of life

[44]. In a cardiac subgroup, patisiran significantly reduced NT-proBNP levels and LV wall thickness and reduced worsening of longitudinal strain. The drug was generally well tolerated.

●Inotersen is an antisense oligonucleotide construct that inhibits hepatic production of TTR. A randomized trial comparing inotersen with placebo found that inotersen significantly reduced symptoms and impairment from neuropathy and improved quality of life [45]. The most frequent serious adverse events were glomerulonephritis and severe thrombocytopenia.

SOCIETY GUIDELINE LINKSLinks to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cardiac amyloidosis" and "Society guideline links: Arrhythmias in adults" and "Society guideline links: Heart failure in adults" and "Society guideline links: Immunoglobulin light chain (AL) amyloidosis".)

INFORMATION FOR PATIENTSUpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

●Basics topics (see "Patient education: AL amyloidosis (The Basics)")

SUMMARY AND RECOMMENDATIONS

●The treatment of symptomatic cardiac amyloidosis is twofold: therapy for heart failure (HF) and treatment of the underlying disease. (See 'General considerations' above.)

●Treatment of HF in patients with cardiac amyloidosis differs from the therapy generally recommended in patients with diastolic or systolic HF. While loop diuretics are a mainstay of treatment of cardiac amyloidosis, beta blockers and angiotensin-converting enzyme inhibitors are often not tolerated despite their efficacy in other types of systolic HF. Similarly, calcium channel blockers that may be useful in treatment of diastolic HF are contraindicated in amyloid cardiomyopathy. (See 'Heart failure therapy' above.)

●Anticoagulation is recommended in patients with amyloid cardiomyopathy with atrial fibrillation, intracardiac thrombi, or an embolic event. (See 'Anticoagulation' above.)

●The efficacy of implantable cardioverter-defibrillator therapy in patients with severe cardiac amyloidosis is unclear. (See 'Implantable cardioverter-defibrillator' above.)

●The main treatment option in patients with light-chain (AL) amyloidosis is chemotherapy. A variety of regimens are used, including high-dose melphalan with autologous hematopoietic stem cell transplantation. Bortezomib-based regimens are first-line therapy for most patients who are not candidates for hematopoietic stem cell transplantation, even in patients with advanced cardiac disease (New York Heart Association [NYHA] functional class III or IV) (table 3). (See 'Specific therapy for AL amyloidosis' above.)

●For transthyretin amyloidosis (ATTR) cardiomyopathy, options include (see 'Specific therapy for ATTR amyloidosis' above):

•For patients with ATTR cardiomyopathy with NYHA functional class I to III, we recommend treatment with tafamidis (Grade 1B). In this population, a randomized trial found that tafamidis therapy reduced mortality as well as cardiovascular-related hospitalizations, and reduced declines in functional capacity and quality of life. (See 'Tafamidis' above.)

•In addition, patients diagnosed with familial ATTR (ATTRm) cardiomyopathy should undergo evaluation for liver transplantation, as this can be curative in selected patients with ATTRm but not in those with wild-type ATTR (ATTRwt) amyloidosis. However, cardiac disease has progressed after liver transplantation in some patients with ATTRm. Patients with advanced heart disease with ATTRm may be treated with combined heart and liver transplantation. (See 'Liver transplantation' above.)

ACKNOWLEDGMENTThe UpToDate editorial staff acknowledge Rodney H Falk, MD, who contributed to earlier versions of this topic review.

REFERENCES

1. Rapezzi C, Merlini G, Quarta CC, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. Circulation 2009; 120:1203.
2. Connors LH, Sam F, Skinner M, et al. Heart Failure Resulting From Age-Related Cardiac Amyloid Disease Associated With Wild-Type Transthyretin: A Prospective, Observational Cohort Study. Circulation 2016; 133:282.
3. Ruberg FL, Maurer MS, Judge DP, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). Am Heart J 2012; 164:222.
4. Pinney JH, Whelan CJ, Petrie A, et al. Senile systemic amyloidosis: clinical features at presentation and outcome. J Am Heart Assoc 2013; 2:e000098.
5. Grogan M, Scott CG, Kyle RA, et al. Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. J Am Coll Cardiol 2016; 68:1014.
6. Fontana M, Ćorović A, Scully P, Moon JC. Myocardial Amyloidosis: The Exemplar Interstitial Disease. JACC Cardiovasc Imaging 2019; 12:2345.
7. Kyle RA, Linos A, Beard CM, et al. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. Blood 1992; 79:1817.
8. Madan S, Kumar SK, Dispenzieri A, et al. High-dose melphalan and peripheral blood stem cell transplantation for light-chain amyloidosis with cardiac involvement. Blood 2012; 119:1117.
9. Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol 2012; 30:989.
10. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol 2012; 30:4541.
11. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J 2018; 39:2799.
12. Maurer MS, Elliott P, Comenzo R, et al. Addressing Common Questions Encountered in the Diagnosis and Management of Cardiac Amyloidosis. Circulation 2017; 135:1357.
13. Griffiths BE, Hughes P, Dowdle R, Stephens MR. Cardiac amyloidosis with asymmetrical septal hypertrophy and deterioration after nifedipine. Thorax 1982; 37:711.
14. Muchtar E, Gertz MA, Kumar SK, et al. Digoxin use in systemic light-chain (AL) amyloidosis: contra-indicated or cautious use? Amyloid 2018; 25:86.

15. Gertz MA, Skinner M, Connors LH, et al. Selective binding of nifedipine to amyloid fibrils. Am J Cardiol 1985; 55:1646.
16. Pollak A, Falk RH. Left ventricular systolic dysfunction precipitated by verapamil in cardiac amyloidosis. Chest 1993; 104:618.
17. Dubrey SW, Cha K, Anderson J, et al. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. QJM 1998; 91:141.
18. Dubrey S, Simms RW, Skinner M, Falk RH. Recurrence of primary (AL) amyloidosis in a transplanted heart with four-year survival. Am J Cardiol 1995; 76:739.
19. Hosenpud JD, DeMarco T, Frazier OH, et al. Progression of systemic disease and reduced long-term survival in patients with cardiac amyloidosis undergoing heart transplantation. Follow-up results of a multicenter survey. Circulation 1991; 84:III338.
20. Kpodonu J, Massad MG, Caines A, Geha AS. Outcome of heart transplantation in patients with amyloid cardiomyopathy. J Heart Lung Transplant 2005; 24:1763.
21. Dubrey SW, Burke MM, Hawkins PN, Banner NR. Cardiac transplantation for amyloid heart disease: the United Kingdom experience. J Heart Lung Transplant 2004; 23:1142.
22. Pelosi F Jr, Capehart J, Roberts WC. Effectiveness of cardiac transplantation for primary (AL) cardiac amyloidosis. Am J Cardiol 1997; 79:532.
23. Maurer MS, Raina A, Hesdorffer C, et al. Cardiac transplantation using extended-donor criteria organs for systemic amyloidosis complicated by heart failure. Transplantation 2007; 83:539.
24. Davis MK, Kale P, Liedtke M, et al. Outcomes after heart transplantation for amyloid cardiomyopathy in the modern era. Am J Transplant 2015; 15:650.
25. Fuchs U, Zittermann A, Suhr O, et al. Heart transplantation in a 68-year-old patient with senile systemic amyloidosis. Am J Transplant 2005; 5:1159.
26. Careddu L, Zanfi C, Pantaleo A, et al. Combined heart-liver transplantation: a single-center experience. Transpl Int 2015; 28:828.
27. Thenappan T, Fedson S, Rich J, et al. Isolated heart transplantation for familial transthyretin (TTR) V122I cardiac amyloidosis. Amyloid 2014; 21:120.
28. Frazier OH, Cohn WE. Continuous-flow total heart replacement device implanted in a 55-year-old man with end-stage heart failure and severe amyloidosis. Tex Heart Inst J 2012; 39:542.
29. Tan NY, Mohsin Y, Hodge DO, et al. Catheter Ablation for Atrial Arrhythmias in Patients With Cardiac Amyloidosis. J Cardiovasc Electrophysiol 2016; 27:1167.
30. Martinez-Naharro A, Gonzalez-Lopez E, Corovic A, et al. High Prevalence of Intracardiac Thrombi in Cardiac Amyloidosis. J Am Coll Cardiol 2019; 73:1733.
31. Feng D, Edwards WD, Oh JK, et al. Intracardiac thrombosis and embolism in patients with cardiac amyloidosis. Circulation 2007; 116:2420.
32. Feng D, Syed IS, Martinez M, et al. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. Circulation 2009; 119:2490.

33. Kristen AV, Dengler TJ, Hegenbart U, et al. Prophylactic implantation of cardioverter-defibrillator in patients with severe cardiac amyloidosis and high risk for sudden cardiac death. Heart Rhythm 2008; 5:235.
34. Lin G, Dispenzieri A, Kyle R, et al. Implantable cardioverter defibrillators in patients with cardiac amyloidosis. J Cardiovasc Electrophysiol 2013; 24:793.
35. Wechalekar AD, Schonland SO, Kastritis E, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood 2013; 121:3420.
36. Kastritis E, Roussou M, Gavriatopoulou M, et al. Long-term outcomes of primary systemic light chain (AL) amyloidosis in patients treated upfront with bortezomib or lenalidomide and the importance of risk adapted strategies. Am J Hematol 2015; 90:E60.
37. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med 2018; 379:1007.
38. Bulawa CE, Connelly S, Devit M, et al. Tafamidis, a potent and selective transthyretin kinetic stabilizer that inhibits the amyloid cascade. Proc Natl Acad Sci U S A 2012; 109:9629.
39. Said G, Grippon S, Kirkpatrick P. Tafamidis. Nat Rev Drug Discov 2012; 11:185.
40. FDA summary review. Vyndaqel (tafamidis meglumine). http://bit.ly/2RO4s7F (Accessed on January 07, 2020).
41. Dubrey SW, Davidoff R, Skinner M, et al. Progression of ventricular wall thickening after liver transplantation for familial amyloidosis. Transplantation 1997; 64:74.
42. Raichlin E, Daly RC, Rosen CB, et al. Combined heart and liver transplantation: a single-center experience. Transplantation 2009; 88:219.
43. Sattianayagam PT, Hahn AF, Whelan CJ, et al. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant. Eur Heart J 2012; 33:1120.
44. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med 2018; 379:11.
45. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med 2018; 379:22.

Topic 85952 Version 22.0

CHAPTER 8

Cutaneous manifestations of amyloidosis

Authors:Kim Bohjanen, MD, Daniel D Miller, MD
Section Editor:Jeffrey Callen, MD, FACP, FAAD
Deputy Editor:Abena O Ofori, MD, Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Aug 2023. This topic last updated: Feb 28, 2023.

INTRODUCTIONAmyloidosis is the abnormal deposition of amyloid (insoluble fibrils comprised of beta-pleated sheets of protein) in extracellular tissues. Amyloid appears microscopically as globules of eosinophilic, homogeneous, hyaline material.

The deposition of amyloid in the skin can occur as a skin-limited disorder (primary localized cutaneous amyloidosis and secondary localized cutaneous amyloidosis). Cutaneous amyloidosis may also occur as a manifestation of systemic amyloidosis, most often in immunoglobulin light chain (AL) amyloidosis.

The clinical manifestations, diagnosis, and management of cutaneous amyloidosis, with a focus on primary localized cutaneous amyloidosis, will be reviewed here. Systemic amyloidosis is reviewed in detail separately.

●(See "Overview of amyloidosis".)

●(See "Monoclonal immunoglobulin deposition disease".)

●(See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis".)

●(See "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis".)

●(See "Causes and diagnosis of AA amyloidosis and relation to rheumatic diseases".)

●(See "Treatment of AA (secondary) amyloidosis".)

●(See "Genetic factors in the amyloid diseases".)

OVERVIEWThe pathogenesis of amyloidosis involves the extracellular deposition of insoluble amyloid fibrils comprised of soluble precursor proteins that undergo conformational changes to form a predominantly antiparallel beta-sheet configuration [1]. A wide variety of normal and abnormal precursor proteins can lead to amyloid formation, resulting in multiple amyloid types (table 1). The principles of fibril formation are reviewed separately. (See "Overview of amyloidosis", section on 'Pathogenesis'.)

Of the many types of amyloid described (table 1), only some are associated with cutaneous manifestations (eg, amyloid K [AK], amyloid light chain [AL], amyloid A [AA], A beta-2 microglobulin, and amyloid transthyretin [ATTR]). The major cutaneous manifestations of amyloidosis (and their associated subtypes of amyloid) can be subdivided as follows [2]:

●**Localized cutaneous amyloidosis**:

•Primary localized cutaneous amyloidosis:

-Macular amyloidosis (AK)

-Lichen amyloidosis (AK)

-Nodular amyloidosis (AL)

-Pharmaceutical (injection site) amyloidosis (AIns)

-Familial primary localized cutaneous amyloidosis (AK)

•Secondary localized cutaneous amyloidosis (predominantly AK)

●**Systemic amyloidosis with cutaneous involvement**:

•Immunoglobulin light chain (AL) amyloidosis (previously referred to as primary amyloidosis)

•Secondary (AA) amyloidosis

•Dialysis-related amyloidosis (A beta-2 microglobulin amyloid)

•Heredofamilial amyloidoses (eg, ATTR amyloid [most common])

While the various types of amyloid appear similar on light microscopic examination and exhibit similar properties on special stains (metachromatic staining with crystal violet and methyl violet, green birefringence with Congo red viewed under polarized light, and yellow-green fluorescence with thioflavin T), they represent vastly different diseases with pronounced differences in prognosis and treatment [1,3,4]. As examples, macular and lichen amyloidosis are skin-limited diseases with no potential for visceral involvement. Nodular amyloidosis is skin limited but represents a localized plasma cell dyscrasia and carries a small risk of progression to systemic disease. AL amyloidosis is a plasma cell dyscrasia with significant morbidity and mortality.

LOCALIZED CUTANEOUS AMYLOIDOSISThe major types of localized cutaneous amyloidosis include macular amyloidosis, lichen amyloidosis, nodular amyloidosis, familial primary localized cutaneous amyloidosis (PLCA), and secondary localized cutaneous amyloidosis. Rare variants of cutaneous amyloidosis include poikiloderma-like cutaneous amyloidosis and amyloidosis cutis dyschromica. (See 'Rare variants' below.)

Macular and lichen amyloidosis — Macular amyloidosis and lichen amyloidosis are uncommon skin-limited conditions that may represent a clinical spectrum of a single disease process. These clinical presentations may be most likely to occur in South American, Asian, or Middle Eastern individuals [5-7] and usually arise in adulthood [5].

Most cases are sporadic. However, macular amyloidosis and lichen amyloidosis also represent the most common manifestations of familial PLCA [8]. In a series of 794 Chinese patients with primary cutaneous amyloidosis (primarily lichenoid, biphasic, and macular amyloidosis), 7 percent had a positive family history of cutaneous amyloidosis [5]. (See 'Familial primary localized cutaneous amyloidosis' below.)

Pathogenesis — The amyloid deposits in macular amyloidosis and lichen amyloidosis are derived from keratin intermediate filament proteins. Degeneration of basal keratinocytes in the overlying epidermis likely plays a role. In one theory, cytokeratin released from apoptotic basal keratinocytes is covered with autoantibodies, phagocytosed by macrophages, and enzymatically degraded to form amyloid K [4]. In addition, sweat gland or sweat duct dysfunction leading to leakage of sweat into the dermoepidermal junction, an inflammatory response, epidermal damage, and amyloid deposition has been proposed as a pathogenic mechanism for lichen amyloidosis [9].

A cycle of chronic pruritus and scratching may contribute to amyloid production and deposition. Pruritic conditions such as chronic kidney disease and biliary cirrhosis are potential triggers.

Clinical features — Macular amyloidosis classically appears as hyperpigmented, thin plaques, often containing "rippled" linear gray-tan streaks (picture 1A-B). Typical sites of involvement are the upper back (scapula region) and extensor surfaces of extremities. Macular amyloidosis is usually, but not always, pruritic.

Lichen amyloidosis is pruritic and appears as discrete, skin-colored to hyperpigmented, scaly, domed, 2 to 4 mm papules that coalesce to form persistent plaques with a rippled appearance (picture 2A-E). The plaques are most commonly found on the extensor surfaces, such as the shins. Lichen amyloidosis usually begins unilaterally but may progress to symmetric involvement. Bullae occur in rare cases [10].

The typical anatomic locations for lichen amyloidosis may correlate with areas that can be easily scratched or rubbed. Patients with pretibial lichen amyloidosis often acknowledge chronic rubbing of the heel of the contralateral leg along the shin.

Some patients exhibit overlapping features of macular and lichen amyloidosis. This phenomenon has been termed biphasic amyloidosis [10].

Histopathology — The various subtypes of disease are distinguished in skin biopsies by the pattern and location of amyloid deposition and immunohistochemical properties. In both macular amyloidosis and lichen amyloidosis, small globules of pink material (amyloid) are present in the superficial dermis, mostly in dermal papillae between epidermal rete ridges [3]. The overlying epidermis may demonstrate degeneration of basal keratinocytes with cytoplasmic vacuolization. Pigment incontinence is also common, with admixed melanophages, which may have a dendritic morphology.

In addition, lichen amyloidosis demonstrates hyperkeratosis and epidermal acanthosis that may resemble lichen simplex chronicus. The epidermis of macular amyloidosis typically appears normal.

Amyloid deposition is not present around blood vessel walls or deeper in the dermis in either disorder, and plasma cells are generally not increased in affected skin [4]. The keratinocyte-derived amyloid stains with Congo red, crystal violet, and

thioflavin T stains and is positive on keratin-specific immunohistochemical stains such as cytokeratin 5 [11].

Diagnosis — A diagnosis of macular amyloidosis or lichen amyloidosis is suspected based upon the recognition of consistent clinical findings (hyperpigmented, rippled, thin plaques for macular amyloidosis and skin-colored or hyperpigmented, dome-shaped papules coalescing into plaques for lichen amyloidosis), particularly when found in a characteristic location (eg, upper back for macular amyloidosis, shins for lichen amyloidosis). There is often a history of pruritus and scratching in the affected area.

The diagnosis is confirmed by the detection of amyloid with a skin biopsy. A punch biopsy is the preferred type of biopsy. (See "Skin biopsy techniques", section on 'Punch biopsy' and 'Histopathology' above.)

Differential diagnosis — A careful skin examination will often identify features that suggest alternative diagnoses. A skin biopsy demonstrating amyloid deposits distinguishes amyloidosis from other disorders.

The differential diagnosis of macular amyloidosis often includes:

●**Notalgia paresthetica** – Notalgia paresthetica is considered a form of neuropathic itch that occurs on the back, medial to the scapular border (picture 3). The pruritus is usually unilateral and may be in a dermatomal distribution. Hyperpigmentation often occurs secondary to scratching or rubbing the skin. Amyloid deposits are not a primary histologic feature of notalgia paresthetica; however, chronic scratching of the affected area may contribute to the development of associated macular amyloidosis. (See "Pruritus: Etiology and patient evaluation", section on 'Notalgia paresthetica'.)

●**Tinea versicolor** – Tinea versicolor is a common cutaneous fungal infection that manifests as hyperpigmented or hypopigmented scaly patches on the skin, particularly the trunk (picture 4). A potassium hydroxide preparation will show fungal hyphae and spores. (See "Tinea versicolor (pityriasis versicolor)".)

●**Confluent and reticulated papillomatosis** – Confluent and reticulated papillomatosis is an uncommon disorder that usually occurs in young adults and manifests as reticulated hyperpigmented keratotic papules on the trunk (picture 5). A skin biopsy can differentiate between confluent and reticular papillomatosis and macular amyloidosis. (See "Confluent and reticulated papillomatosis".)

Other disorders that may be mistaken for macular amyloidosis include drug-induced pigmentation and other cutaneous dyschromias, such as erythema dyschromicum perstans (ashy dermatosis) and actinic lichen planus (picture 6A-B). These conditions typically lack the rippled appearance often present in macular amyloidosis.

The differential diagnosis of lichen amyloidosis primarily consists of disorders that may manifest with plaques on the extensor surfaces of the extremities. Examples of disorders in the differential diagnosis include:

●**Lichen simplex chronicus** – Lichen simplex chronicus is a reactive thickening of the skin related to chronic pruritus and scratching (picture 7). Often, there is an underlying pruritic dermatosis, such as atopic dermatitis. Clinically, lichen amyloidosis has a more rippled appearance than lichen simplex chronicus.

●**Prurigo nodularis** – Prurigo nodularis is characterized by pruritic, scaly nodules and commonly occurs on the extensor surfaces of the extremities (picture 8). As with lichen amyloidosis, the itch-scratch cycle plays an important role in development. Prurigo nodularis is commonly associated with other pruritic skin disorders, such as atopic dermatitis. (See "Prurigo nodularis".)

●**Hypertrophic lichen planus** – Hypertrophic lichen planus classically presents as hypertrophic, violaceous, thick plaques with overlying scale (picture 9). The shins are common sites for this disorder. A distinctive histologic finding of lichen planus is a band-like lymphocytic infiltrate in the superficial dermis. (See "Lichen planus", section on 'Cutaneous variants'.)

●**Localized lichen myxedematosus** – Localized lichen myxedematosus is a rare disorder that presents with multiple waxy papules in a linear arrangement or coalescing into plaques. A skin biopsy will demonstrate abundant mucin. (See "Localized lichen myxedematosus".)

●**Pretibial myxedema** – Pretibial myxedema is an infiltrative mucinosis of the skin that usually occurs in association with Graves' disease. Pretibial myxedema commonly presents as thickened nodules or plaques on the shins (picture 10). An association with thyroid disease and a skin biopsy demonstrating abundant mucin define this entity. (See "Pretibial myxedema (thyroid dermopathy) in autoimmune thyroid disease".)

●**Elephantiasis nostras verrucosa** – Chronic lymphedema may lead to sclerotic thickening of the skin with a "mossy" and papillomatous appearance. The chronic lymphedema should alert the clinician to this entity. (See "Clinical features and diagnosis of peripheral lymphedema".)

Treatment — Macular amyloidosis and lichen amyloidosis are skin-limited diseases with no potential for visceral involvement; therefore, the goals of treatment are to improve associated symptoms and cosmesis. Although a variety of treatments have been employed, efficacy data are limited and high-quality randomized trials are lacking, leaving the best approach to treatment unclear. No treatment is consistently effective or curative:

●**First-line therapy** – Given the benign nature of these disorders, a conservative initial approach to treatment is preferred. Clinical experience suggests that interventions to break the itch-scratch cycle can be helpful. Patients should be encouraged to avoid scratching or rubbing affected areas; occlusive dressings are helpful when needed. In addition, a potent (group 1 or 2) topical corticosteroid can be applied once or twice daily (table 2). For thick plaques of lichen amyloidosis, the topical corticosteroid can be applied under occlusion to augment drug penetration.

If there is no improvement after one month, topical corticosteroid therapy should be discontinued. Cutaneous atrophy is a potential side effect of topical corticosteroid use.

Clinical experience suggests that intralesional corticosteroid therapy (eg, triamcinolone acetonide 10 mg/mL) can be a useful alternative to topical corticosteroid therapy for patients with small, localized areas of lichen amyloidosis [4]. As with topical corticosteroids, there is a risk of cutaneous atrophy. A case report suggests that topical tacrolimus may be a topical alternative; treatment with tacrolimus 0.1% ointment twice daily for two months was associated with improved pruritus and reduced thickness of plaques in a patient with lichen amyloidosis [12]. An advantage of topical tacrolimus is the absence of risk for cutaneous atrophy.

Topical keratolytic agents, such as salicylic acid or urea, are helpful for removing associated scale.

●**Other therapies** – Limited data primarily from case reports, case series, and small, uncontrolled studies suggest that skin moisturizers applied under occlusion [9], physical interventions (eg, phototherapy [13-18], laser therapy [19], and dermabrasion [20,21]), and systemic medications (eg, oral retinoids [22],

cyclosporine [15,23,24], cyclophosphamide [25], and thalidomide [26]) may improve macular amyloidosis or lichen amyloidosis. Use of these therapies is usually reserved for patients who fail to respond to first-line interventions. Associated risks should be carefully considered prior to treatment.

Few studies have directly compared interventions, leaving uncertainty about relative efficacy. An open left-right comparison study that compared the efficacy of moderate to potent topical corticosteroids with the efficacy of ultraviolet B (UVB) or psoralen plus ultraviolet A (PUVA) phototherapy in 20 patients with a clinical diagnosis of lichen amyloidosis found a trend towards greater reductions in patient-reported itch and skin roughness with phototherapy, but the difference was not statistically significant [13]. In a single-blind randomized trial that compared treatment with superficial and deep modes of a fractional carbon dioxide laser in 16 patients with macular amyloidosis and nine patients with lichen amyloidosis, both modes were associated with reduced pigmentation, thickness, itching, and amyloid deposits in treated areas [27]. The superficial mode induced less pain.

Nodular amyloidosis — Nodular amyloidosis (also known as tumefactive amyloidosis) is rare, occurring less often than macular amyloidosis and lichen amyloidosis [28]. Nodular amyloidosis usually occurs in adults [29]. There does not appear to be a sex predilection [29].

Nodular amyloidosis is skin limited but represents a localized plasma cell dyscrasia. There is a small risk of progression to systemic amyloidosis (between 1 and 7 percent in different series) [30-32]. An association with Sjögren's disease has been proposed [29,31].

Pathogenesis — The amyloid in nodular amyloidosis is immunoglobulin derived and contains either lambda (most common) or kappa light chains [33]. The immunoglobulins appear to be derived from a clonal population of skin-homing plasma cells [10].

Clinical features — Nodular amyloidosis presents as asymptomatic, solitary or multiple, waxy nodules or plaques on the head, trunk, or extremities (picture 11A-B). There is a predilection for acral sites. The color of nodules is usually yellow to brown, and the diameter of nodules typically ranges from 0.5 to 7 cm [29]. The overlying skin may appear atrophic, and the nodules may have associated purpura.

Histopathology — The classic histologic findings of nodular amyloidosis are diffuse infiltrates of amyloid in the dermis, subcutis, and blood vessel walls [32]. Plasma cell

infiltrates are found in close proximity to the amyloid deposits [3]. Kappa and lambda light chain immunostains or in situ hybridization studies may demonstrate plasma cell clonality. Antikeratin antibody stains are negative [3].

Diagnosis and evaluation — The clinical features of nodular amyloidosis overlap with multiple other disorders. A skin biopsy demonstrating amyloid is required to confirm the diagnosis. A deep shave biopsy or a punch biopsy is usually sufficient. (See "Skin biopsy techniques".)

An evaluation for systemic amyloidosis is recommended at the time of diagnosis because of the risk for progression of nodular amyloidosis to systemic disease. The initial workup should include a complete review of systems and full physical examination. Studies should include:

●Complete blood count

●Comprehensive metabolic panel

●Serum protein electrophoresis and immunofixation

●Urine protein electrophoresis and immunofixation

●Electrocardiogram

The clinical features and diagnosis of immunoglobulin light chain amyloidosis are reviewed in detail separately. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis".)

The potential for progression of nodular amyloidosis to systemic amyloidosis warrants ongoing follow-up. Periodic assessments with a review of systems, complete physical examination, and laboratory tests are indicated after diagnosis. We reevaluate patients at least once yearly.

Differential diagnosis — The differential diagnosis of nodular amyloidosis includes other disorders that may present with smooth nodules or nonscaly plaques on the skin. Examples of disorders in the differential diagnosis include cutaneous lymphoma, leukemia cutis, pseudolymphoma, sarcoidosis, and granuloma annulare. A biopsy will distinguish nodular amyloidosis from other conditions.

Treatment — Treatment of nodular amyloidosis is not mandatory but can be employed for the purpose of improving the appearance of lesions. Treatment involves physical removal or destruction of the nodules. Recurrences are common after treatment.

Surgical excision is a common removal technique. Shave excisions have yielded favorable results for facial nodular amyloidosis in case reports [34]. Other treatments described as beneficial in case reports include electrodesiccation [35], dermabrasion [32,36], and laser treatment with carbon dioxide or pulsed dye lasers [19]. Some of the risks of these procedures include pain, dyspigmentation, infection, and scarring.

Pharmaceutical (injection site) amyloidosis — Injections of certain medications may result in subcutaneous amyloid deposits, believed to represent complexes of amyloid and the injected material, which resemble nodular amyloidosis clinically and microscopically. This phenomenon has been most commonly reported in association with insulin (both porcine and recombinant human forms) and has been alternately referred to as pharmaceutical amyloidosis, amyloidoma, or "insulin ball" [37-40]. Repeated subcutaneous injections of insulin into the same soft tissue site is reported as a risk factor for development. Enfuvirtide, an antiretroviral medication known to commonly cause injection site reactions, has also been implicated in this phenomenon [40-42].

Clinical features for both medications include subcutaneous nodules or firm, nodular plaques with overlying hyperpigmentation and/or ecchymosis, which appear in areas of soft tissue such as the abdominal pannus and thighs. Microscopic features include amorphous deposits of hyaline pink, homogenous material within the deep dermis and subcutaneous fat lobules that exhibit typical apple green birefringence on polariscopic examination with Congo red staining [37,42]. These deposits do not stain positively for AA amyloid or kappa or lambda light chains but may exhibit apolipoprotein expression [37,42].

Local treatment is preferred; surgical excision is reported as curative [40]. Patients should take care to avoid prior sites of involvement when performing future injections.

Familial primary localized cutaneous amyloidosis — The clinical manifestations of familial primary localized amyloidosis (PLCA), a rare hereditary disorder, typically resemble sporadic macular amyloidosis and sporadic lichen amyloidosis [8]. Familial PLCA usually presents between the ages of 5 and 18 years. An autosomal

dominant pattern of inheritance has been detected in families in Japan, China, Taiwan, and Brazil. Mutations in the oncostatin M receptor beta (*OSMRB*) and interleukin-31 receptor A (*IL31RA*) genes have been found in affected families [43].

Familial cases of macular amyloidosis and lichen amyloidosis may also occur in association with multiple endocrine neoplasia type 2A with mutations in the *RET* proto-oncogene [44]. The approach to treatment is similar to sporadic disease. (See "Clinical manifestations and diagnosis of multiple endocrine neoplasia type 2" and 'Treatment' above.)

Secondary localized cutaneous amyloidosis — Secondary localized cutaneous amyloidosis is the incidental finding of small amounts of amyloid in diseased skin. Secondary localized cutaneous amyloidosis is usually found in cutaneous tumors but has also occurred in other cutaneous diseases [45,46]. The amyloid in secondary localized cutaneous amyloidosis is thought to be derived from keratinocytes [45]. Immunostaining for cytokeratin is usually positive [6].

Rare variants — Rare clinical variants of primary cutaneous amyloidosis include poikiloderma-like cutaneous amyloidosis and amyloidosis cutis dyschromica:

●**Poikiloderma-like cutaneous amyloidosis** – Poikiloderma-like cutaneous amyloidosis is characterized by poikiloderma-like skin changes, lichenoid papules, and blisters. Most reported cases have occurred on the extremities; however, involvement of the trunk is documented [47]. Skin biopsies show amyloid deposits in the papillary dermis. A syndromic form of poikiloderma-like cutaneous amyloidosis is associated with photosensitivity, short stature, and occasional palmoplantar keratosis [47].

●**Amyloidosis cutis dyschromica** – Amyloidosis cutis dyschromica is a rare sporadic or familial form of cutaneous amyloidosis that manifests as widespread, symmetric, macular or reticulate hyperpigmentation mixed with guttate hypopigmented macules (picture 12) [48]. The disorder may be asymptomatic or pruritic. Skin biopsies demonstrate amyloid deposits in the papillary dermis. Improvement with oral acitretin therapy has been reported [48].

SYSTEMIC AMYLOIDOSES WITH CUTANEOUS INVOLVEMENTCutaneous findings may occur in immunoglobulin light chain (AL) amyloidosis, secondary systemic (AA) amyloidosis, dialysis-associated systemic amyloidosis, and some hereditary amyloidoses:

●**AL amyloidosis** – Approximately 40 percent of patients with AL amyloidosis have cutaneous findings (picture 13A-B). Fundamental skin lesions include domed, shiny or waxy-appearing papules, which appear translucent and may resemble vesicles or small bullae. These lesions tend to aggregate around mucocutaneous junctions such as the orbits, the nares, cutaneous lips, and genital skin. Patients may also develop nodules resembling nodular amyloidosis. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis".)

Purpura is another common skin finding. Purpura result from blood vessel fragility due to vascular amyloid deposition and preferentially affect sites of thin skin, such as the eyelids. Purpura may be triggered by light trauma or increased hydrostatic pressure, such as the Valsalva maneuver. Patients may also exhibit nonspecific skin findings seen in depositional disorders (eg, alopecia, nail dystrophies, macroglossia) (picture 14A-B) [2].

Histopathologic findings include amyloid deposits in the dermis that may extend into the subcutis, where amyloid deposits may surround individual fat cells [3]. Purpuric areas may exhibit amyloid deposits in the walls of dermal blood vessels. More than 50 percent of biopsies of normal skin demonstrate amyloid deposits in the dermis [3,49].

●**AA amyloidosis** – Cutaneous involvement in AA amyloidosis is rare [50]. Petechiae, purpura, and alopecia have been reported [49]. In addition, amyloid deposits may be detected in clinically normal skin. In one series, 5 of 12 patients with this form of systemic amyloidosis had amyloid deposits in normal-appearing skin [49]. (See "Causes and diagnosis of AA amyloidosis and relation to rheumatic diseases".)

●**Dialysis-associated amyloidosis** – Cutaneous involvement in dialysis-associated amyloidosis is rare. Potential manifestations include hyperpigmentation, lichenoid eruptions, or nodules that demonstrate amyloid deposits on histopathologic examination [51]. (See "Dialysis-related amyloidosis".)

●**Heredofamilial amyloidosis** – The most common hereditary variant of systemic amyloidosis is hereditary transthyretin amyloidosis, which is related to the deposition of amyloid transthyretin (ATTR). Cutaneous manifestations can include atrophic scars, persistent ulcers, or petechiae [4]. Cutaneous findings may also occur in other hereditary systemic amyloidoses, such as hereditary apolipoprotein A1 amyloidosis (maculopapular eruptions and petechiae), tumor necrosis factor-receptor 1 associated periodic fever syndrome (migrating cutaneous erythemas),

hereditary gelsolin amyloidosis (cutis laxa, pruritus, petechiae, ecchymoses, hypotrichosis, and alopecia), and Muckle-Wells syndrome (pruritus and cold urticaria-like eruptions) [4]. (See "Genetic factors in the amyloid diseases", section on 'AA amyloid and the inherited systemic autoinflammatory diseases'.)

INFORMATION FOR PATIENTSUpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

●Basics topics (see "Patient education: AL amyloidosis (The Basics)")

SUMMARY AND RECOMMENDATIONS

●**Overview** – The cutaneous manifestations of amyloidosis include skin-limited disorders (primary localized cutaneous amyloidosis and secondary localized cutaneous amyloidosis) as well as cutaneous manifestations of systemic amyloidoses. (See 'Overview' above.)

●**Localized cutaneous amyloidosis** – The primary localized cutaneous amyloidoses include macular amyloidosis, lichen amyloidosis, and nodular amyloidosis. Macular amyloidosis and lichen amyloidosis are the most common types of primary localized cutaneous amyloidosis. Secondary localized cutaneous amyloidosis is the presence of incidental amyloid deposits in cutaneous tumors or other cutaneous diseases. (See 'Localized cutaneous amyloidosis' above.)

•**Macular amyloidosis and lichen amyloidosis** – Macular amyloidosis and lichen amyloidosis may represent a clinical spectrum of a single disease process. Amyloid in these disorders is derived from keratin intermediate filament proteins and likely results from the degeneration of basal keratinocytes. A cycle of chronic pruritus and

scratching may contribute to the development of macular amyloidosis and lichen amyloidosis. (See 'Macular and lichen amyloidosis' above.)

Macular amyloidosis classically presents as hyperpigmented, thin plaques with rippled linear streaks (picture 1A-B). The upper back and extensor surfaces of extremities are common sites. Lichen amyloidosis characteristically presents with skin-colored to hyperpigmented scaly, dome-shaped papules that coalesce to form plaques with a rippled appearance (picture 2A-E). Lichen amyloidosis usually occurs on the extensor surfaces of extremities. (See 'Macular and lichen amyloidosis' above.)

•**Nodular amyloidosis** – Nodular amyloidosis typically presents with single or multiple, asymptomatic, yellow-brown, waxy nodules or plaques on the trunk or extremities. The amyloid in nodular amyloidosis is composed of immunoglobulin light chains. In contrast to macular amyloidosis and lichen amyloidosis, nodular amyloidosis is associated with risk of progression to systemic amyloidosis. Patients with nodular amyloidosis should be evaluated for systemic disease. (See 'Nodular amyloidosis' above.)

•**Diagnosis of localized cutaneous amyloidosis** – A skin biopsy is necessary to confirm a diagnosis of macular amyloidosis, lichen amyloidosis, or nodular amyloidosis. (See 'Diagnosis' above and 'Diagnosis and evaluation' above.)

•**Treatment of localized cutaneous amyloidosis** – Treatment of primary localized cutaneous amyloidosis is not mandatory. Treatment is performed to improve symptoms and/or cosmesis. (See 'Treatment' above and 'Treatment' above.)

-**Macular amyloidosis and lichen amyloidosis** – No treatment is consistently effective for macular amyloidosis and lichen amyloidosis. We suggest interventions to minimize pruritus and scratching as initial treatment (Grade 2C). Our initial treatment approach consists of local corticosteroid therapy to reduce pruritus. Other interventions that may be useful for patients who fail to improve with these conservative measures include phototherapy, laser, dermabrasion, and systemic medications. (See 'Treatment' above.)

-**Nodular amyloidosis** – Nodular amyloidosis can be treated with surgical excision or other destructive procedures. Recurrence is common. (See 'Treatment' above.)

•**Systemic amyloidosis** – Systemic amyloidoses with cutaneous manifestations include immunoglobulin (AL) light chain amyloidosis, secondary systemic (AA)

amyloidosis (rare skin involvement), dialysis-related amyloidosis (rare skin involvement), and various hereditary variants of systemic amyloidosis. (See 'Systemic amyloidoses with cutaneous involvement' above.)

REFERENCES

1. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet 2016; 387:2641.
2. James W, Berger T, Elston D. Errors in metabolism. In: Andrews' Diseases of the Skin Clinical Dermatology, 11th ed, James W, Berger T, Elston D (Eds), Saunders Elsevier, 2011. p.506.
3. Molina-Ruiz AM, Cerroni L, Kutzner H, Requena L. Cutaneous deposits. Am J Dermatopathol 2014; 36:1.
4. Schreml S, Szeimies RM, Vogt T, et al. Cutaneous amyloidoses and systemic amyloidoses with cutaneous involvement. Eur J Dermatol 2010; 20:152.
5. Wang WJ, Chang YT, Huang CY, Lee DD. Clinical and histopathological characteristics of primary cutaneous amyloidosis in 794 Chinese patients. Zhonghua Yi Xue Za Zhi (Taipei) 2001; 64:101.
6. Fernandez-Flores A. Cutaneous amyloidosis: a concept review. Am J Dermatopathol 2012; 34:1.
7. Rasi A, Khatami A, Javaheri SM. Macular amyloidosis: an assessment of prevalence, sex, and age. Int J Dermatol 2004; 43:898.
8. Wali A, Liu L, Takeichi T, et al. Familial primary localized cutaneous amyloidosis results from either dominant or recessive mutations in OSMR. Acta Derm Venereol 2015; 95:1005.
9. Shimoda Y, Sato Y, Hayashida Y, et al. Lichen amyloidosus as a sweat gland/duct-related disorder: resolution associated with restoration of sweating disturbance. Br J Dermatol 2017; 176:1308.
10. Groves R, Black M. Amyloidosis. In: Dermatology, 3rd ed, Bolognia J, Jorizzo J, Schaffer J (Eds), Saunders Elsevier, 2012. p.699.
11. Devata S, Hari P, Markelova N, et al. Detection of amyloid in abdominal fat pad aspirates in early amyloidosis: Role of electron microscopy and Congo red stained cell block sections. Cytojournal 2011; 8:11.
12. Castanedo-Cazares JP, Lepe V, Moncada B. Lichen amyloidosis improved by 0.1% topical tacrolimus. Dermatology 2002; 205:420.
13. Jin AG, Por A, Wee LK, et al. Comparative study of phototherapy (UVB) vs. photochemotherapy (PUVA) vs. topical steroids in the treatment of primary cutaneous lichen amyloidosis. Photodermatol Photoimmunol Photomed 2001; 17:42.
14. Oiso N, Yudate T, Kawara S, Kawada A. Successful treatment of lichen amyloidosus associated with atopic dermatitis using a combination of narrowband ultraviolet B phototherapy, topical corticosteroids and an antihistamine. Clin Exp Dermatol 2009; 34:e833.

15. Kang MJ, Kim HS, Kim HO, Park YM. A case of atopic dermatitis-associated lichen amyloidosis successfully treated with oral cyclosporine and narrow band UVB therapy in succession. J Dermatolog Treat 2009; 20:368.
16. Hudson LD. Macular amyloidosis: treatment with ultraviolet B. Cutis 1986; 38:61.
17. Grimmer J, Weiss T, Weber L, et al. Successful treatment of lichen amyloidosis with combined bath PUVA photochemotherapy and oral acitretin. Clin Exp Dermatol 2007; 32:39.
18. Kalkan G, Markoç F, Bas Y. An alternative treatment model: the combination therapy of narrow band ultraviolet B phototherapy and tacrolimus ointment 0.1% in biphasic amyloidosis. J Pak Med Assoc 2014; 64:579.
19. Al Yahya RS. Treatment of primary cutaneous amyloidosis with laser: a review of the literature. Lasers Med Sci 2016; 31:1027.
20. Wong CK, Li WM. Dermabrasion for lichen amyloidosus. Report of a long-term study. Arch Dermatol 1982; 118:302.
21. Savant SS. Therapeutic regional dermabrasion in papular lichen amyloidosis of shins. Indian J Dermatol Venereol Leprol 1995; 61:196.
22. Hernández-Núñez A, Daudén E, Moreno de Vega MJ, et al. Widespread biphasic amyloidosis: response to acitretin. Clin Exp Dermatol 2001; 26:256.
23. Behr FD, Levine N, Bangert J. Lichen amyloidosis associated with atopic dermatitis: clinical resolution with cyclosporine. Arch Dermatol 2001; 137:553.
24. Teraki Y, Katsuta M, Shiohara T. Lichen amyloidosus associated with Kimura's disease: successful treatment with cyclosporine. Dermatology 2002; 204:133.
25. Das J, Gogoi RK. Treatment of primary localised cutaneous amyloidosis with cyclophosphamide. Indian J Dermatol Venereol Leprol 2003; 69:163.
26. An Q, Zhang L, Zheng S, et al. Thalidomide improves clinical symptoms of primary cutaneous amyloidosis: report of familiar and sporadic cases. Dermatol Ther 2013; 26:263.
27. Esmat SM, Fawzi MM, Gawdat HI, et al. Efficacy of different modes of fractional CO2 laser in the treatment of primary cutaneous amyloidosis: A randomized clinical trial. Lasers Surg Med 2015; 47:388.
28. Borowicz J, Gillespie M, Miller R. Cutaneous amyloidosis. Skinmed 2011; 9:96.
29. Konopinski JC, Seyfer SJ, Robbins KL, Hsu S. A case of nodular cutaneous amyloidosis and review of the literature. Dermatol Online J 2013; 19:10.
30. Kaltoft B, Schmidt G, Lauritzen AF, Gimsing P. Primary localised cutaneous amyloidosis--a systematic review. Dan Med J 2013; 60:A4727.
31. Moon AO, Calamia KT, Walsh JS. Nodular amyloidosis: review and long-term follow-up of 16 cases. Arch Dermatol 2003; 139:1157.
32. Woollons A, Black MM. Nodular localized primary cutaneous amyloidosis: a long-term follow-up study. Br J Dermatol 2001; 145:105.
33. Flowers J, Miller R. Nodular cutaneous amyloidosis: A rare case and review of amyloidosis classification. J Am Acad Dermatol 2010; 62:AB92.

34. Grattan CE, Burton JL, Dahl MG. Two cases of nodular cutaneous amyloid with positive organ-specific antibodies, treated by shave excision. Clin Exp Dermatol 1988; 13:187.
35. Vestey JP, Tidman MJ, Mclaren KM. Primary nodular cutaneous amyloidosis--long-term follow-up and treatment. Clin Exp Dermatol 1994; 19:159.
36. Lien MH, Railan D, Nelson BR. The efficacy of dermabrasion in the treatment of nodular amyloidosis. J Am Acad Dermatol 1997; 36:315.
37. Yumlu S, Barany R, Eriksson M, Röcken C. Localized insulin-derived amyloidosis in patients with diabetes mellitus: a case report. Hum Pathol 2009; 40:1655.
38. Endo JO, Röcken C, Lamb S, et al. Nodular amyloidosis in a diabetic patient with frequent hypoglycemia: sequelae of repeatedly injecting insulin without site rotation. J Am Acad Dermatol 2010; 63:e113.
39. Samlaska C, Reber S, Murry T. Insulin-derived amyloidosis: The insulin ball, amyloidoma. JAAD Case Rep 2020; 6:351.
40. D'Souza A, Theis JD, Vrana JA, Dogan A. Pharmaceutical amyloidosis associated with subcutaneous insulin and enfuvirtide administration. Amyloid 2014; 21:71.
41. Morilla ME, Kocher J, Harmaty M. Localized amyloidosis at the site of enfuvirtide injection. Ann Intern Med 2009; 151:515.
42. Naujokas A, Vidal CI, Mercer SE, et al. A novel form of amyloid deposited at the site of enfuvirtide injection. J Cutan Pathol 2012; 39:220.
43. Lin MW, Lee DD, Liu TT, et al. Novel IL31RA gene mutation and ancestral OSMR mutant allele in familial primary cutaneous amyloidosis. Eur J Hum Genet 2010; 18:26.
44. Scapineli JO, Ceolin L, Puñales MK, et al. MEN 2A-related cutaneous lichen amyloidosis: report of three kindred and systematic literature review of clinical, biochemical and molecular characteristics. Fam Cancer 2016; 15:625.
45. Powell AM, Albert S, Bhogal B, Black MM. Discoid lupus erythematosus with secondary amyloidosis. Br J Dermatol 2005; 153:746.
46. Nanda V, Garg BK, Chittoria R, et al. Amyloidosis complicating rhinophyma. Aesthetic Plast Surg 2004; 28:98.
47. Heng JK, Ho SA, Tan KB. Poikiloderma-like cutaneous amyloidosis--a rare presentation of primary localized cutaneous amyloidosis. Dermatol Online J 2016; 22.
48. Mahon C, Oliver F, Purvis D, Agnew K. Amyloidosis cutis dyschromica in two siblings and review of the epidemiology, clinical features and management in 48 cases. Australas J Dermatol 2016; 57:307.
49. Rubinow A, Cohen AS. Skin involvement in generalized amyloidosis. A study of clinically involved and uninvolved skin in 50 patients with primary and secondary amyloidosis. Ann Intern Med 1978; 88:781.
50. Breathnach SM. Amyloid and amyloidosis. J Am Acad Dermatol 1988; 18:1.
51. Takayama K, Satoh T, Maruyama R, Yokozeki H. Dialysis-related amyloidosis on the buttocks. Acta Derm Venereol 2008; 88:72.

CHAPTER 9

Causes and diagnosis of AA amyloidosis and relation to rheumatic diseases

Author:Peter D Gorevic, MD
Section Editor:Helen J Lachmann, MA, MB, BChir, MD, FRCP, FRCPath
Deputy Editor:Siobhan M Case, MD, MHS
Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Aug 2023. This topic last updated: May 22, 2022.

INTRODUCTIONAA amyloidosis (previously known as secondary [AA] amyloidosis) is a disorder characterized by the extracellular tissue deposition of fibrils that are composed of fragments of and/or intact serum amyloid A protein (SAA), a hepatic acute phase reactant. (See "Pathogenesis of AA amyloidosis".)

AA amyloidosis may complicate any chronic inflammatory condition, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), inflammatory bowel disease, familial periodic fever syndromes, chronic infections, and certain neoplasms (table 1).

The major causes and approach to diagnosis of AA amyloidosis are presented here. The clinical manifestations and treatment of AA amyloidosis and the musculoskeletal and renal manifestations of amyloid diseases are discussed separately. (See "Overview of amyloidosis", section on 'Clinical manifestations' and "Treatment of AA (secondary) amyloidosis" and "Musculoskeletal manifestations of amyloidosis" and "Renal amyloidosis".)

CAUSES AND RELATION TO RHEUMATIC DISEASESMultiple chronic inflammatory conditions, among them rheumatologic, autoinflammatory, chronic infectious, and other disorders, have been associated with the development of AA amyloid [1,2]. The most common organ system involved in this form of amyloidosis is the kidney, although other organ systems are often also affected. (See 'Clinical manifestations' below and "Overview of amyloidosis", section on 'Clinical manifestations'.)

Epidemiology — The disorders most often identified as underlying AA amyloidosis have varied over time and geographically, reflecting the prevalent chronic inflammatory conditions. During the 20th century, AA amyloidosis has become less common and the contribution of AA amyloid to large series of amyloidosis has

gradually decreased. The underlying causes of chronic inflammation have also changed; inflammatory arthritides have become the most common underlying disease, replacing chronic infections, particularly tuberculosis [3] and osteomyelitis, which had historically been the predominant causes. With widespread availability of highly effective antimicrobial agents, the infectious causes have become less common in much of the world [4], and it is anticipated that therapeutic advances in the treatment of rheumatologic and other inflammatory disorders with highly effective biologic agents will result in fewer patients developing amyloidosis [5].

Both the annual incidence and population prevalence of AA amyloidosis appear to be decreasing in national surveys from some western countries, presumably reflecting advances in therapeutics of the underlying disorders [6-8]. The overall autopsy incidence of AA amyloidosis in western nations ranges from 0.5 to 0.86 percent [9,10]. In the United Kingdom, the estimated incidence of AA amyloidosis was 0.166 per 100,000 in 2008 [8].

The list of chronic inflammatory conditions reported in association with AA amyloidosis is extensive, including chronic inflammatory arthritides, vasculitides, inflammatory bowel disease, periodic fever syndromes, chronic infections, neoplasms, and other disorders (table 1).

The following frequencies of underlying disorders have been found in large series of patients with AA amyloidosis from two large centers in the United States [9,11,12]:

●Idiopathic – 21 to 29 percent

●Rheumatoid arthritis (RA) or juvenile idiopathic arthritis (JIA) – 12 to 21 percent

●Inflammatory bowel disease – 16 to 17 percent

●Spondyloarthritis/psoriasis – 10 to 12 percent

●Familial Mediterranean fever – 4 to 5 percent

Two series of patients with AA amyloidosis in the United Kingdom, the larger of which included 374 subjects, found the following associated diseases [13-15]:

●Adult RA – 23 to 51 percent

●JIA – 11 to 17 percent

●Chronic infection – 9 to 15 percent

●Hereditary periodic fever syndromes (eg, familial Mediterranean fever) – 9 to 11 percent

●Ankylosing spondylitis (AS) – 0 to 12 percent

●Psoriatic arthritis – 4 percent

●Crohn disease – 2 to 5 percent

In some other parts of the world, hereditary periodic fevers and infections are responsible for a larger proportion of cases of AA amyloid [16]. As an example, in Turkey, familial Mediterranean fever is the cause of more than 60 percent of cases [17]. In Armenia, and among Armenian populations in surrounding countries, familial Mediterranean fever is common, and the carrier rate for *MEFV* gene mutations approaches one in five individuals. Further genetic work in this population has shown that *MEFV* M694V (the commonest mutation underlying familial Mediterranean fever) is associated with a greater risk of developing AA amyloidosis. A further genetic contribution to the risk of AA amyloidosis is homozygosity for the SAA1.1 allele, and patients who are homozygous for both *MEFV* M694V and SAA1.1 have a sevenfold increased risk of developing renal amyloidosis, compared with other *SAA1* genotypes [18,19].

Other conditions that may be associated with AA amyloid include neoplasms, particularly renal cell carcinoma [20], non-Hodgkin lymphoma [21], Waldenström macroglobulinemia [22] and other gammopathies [23], Castleman disease [24-26], and non-neoplastic conditions such as cystic fibrosis [27,28], abuse of injected drugs [29], and hidradenitis suppurativa [30,31]. In the United Kingdom experience, the contribution of AA amyloidosis due to chronic infection due to recreational drug use rose from 1 percent in 1990 to 1997 to 13 percent in 2007 to 2014 [8], an experience mirrored in a series of intravenous drug users in San Francisco [29].

A striking change since 1990 has been the increasing proportion of patients with underlying inflammation of unknown etiology even after extensive investigation by experienced centers. In a study of the changes in causation over 25 years, AA amyloidosis of unknown etiology rose from 10 to 27 percent of new cases [8]. Some of this might be explained by the obesity epidemic, as this has been identified as an emerging cause of AA amyloid, with resultant renal disease, in association with

findings suggesting low-grade but chronic inflammation probably due to cytokine production by adipocytes [32,33].

Geographic variation may result from additional factors beyond causative or associated disease prevalence and the availability of effective therapies. Studies of the prevalence of AA amyloidosis complicating juvenile arthritis from the 1960s and 1970s reported an almost 100-fold variation between the United States and Poland [34-36]. As a subsequent example, in familial Mediterranean fever, the development of AA amyloidosis is related to severity and duration of disease and homozygosity for the M694V variant, but in a large study, geography was identified as the leading risk factor [37]. Whether the country of origin reflects genetic factors associated with ethnicity or environmental factors is not yet clear. (See "Clinical manifestations and diagnosis of familial Mediterranean fever".)

Rheumatoid arthritis — Susceptibility to AA amyloidosis in RA is related to duration of the disease activity, greater disability, and higher levels of inflammation. Amyloidosis is more likely to occur in patients with poorly controlled, seropositive, severe, and longstanding disease occurring in association with other extraarticular manifestations. Renal, gastrointestinal, and cardiac manifestations of amyloidosis are most common, but in the majority of patients, the disease remains subclinical.

The reported postmortem incidence of amyloid complicating adult RA has generally ranged from 10 to 25 percent, although studies of patients from the 1930s and 1940s reported 60 percent involvement [38]. Similar values of 7.1 to 29 percent have been found with subcutaneous fat pad aspirates or gastrointestinal biopsies in living patients with RA in studies published between 1993 and 2004 [39-44]. In these studies, AA amyloid was clinically overt in only 25 to 50 percent, even after long periods of follow-up sampling, indicating the majority of cases were subclinical [40,42].

Symptomatic disease diagnosed pre-mortem has been reported in 2 to 11 percent, with considerable variation among geographic areas [38,42]. In a 1999 population-based series of 1666 subjects with RA who had died in Finland, the prevalence of amyloidosis was 5.8 percent [45]. The yield of amyloid among patients with RA and renal disease ranges from 10 to 30 percent [46-48].

The clinical spectrum of amyloidosis in RA was evaluated in a report of 124 patients from Japan [41]. The following observations were noted:

●Major manifestations and their frequency included:

•Nephropathy – 59 percent (see "Renal amyloidosis")

•Gastrointestinal symptoms – 58 percent (see "Gastrointestinal amyloidosis: Clinical manifestations, diagnosis, and management")

•Cardiomyopathy – 40 percent (see "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis")

●The mean duration of RA at diagnosis of amyloidosis was 15.4 years

Similar findings were noted in a retrospective review of 91 Dutch patients with AA amyloidosis due to RA [49]. Nephropathy was the most common presenting symptom, being manifested as proteinuria (70 percent) or impaired renal function. Other organ systems were less frequently involved: cardiomyopathy (9 percent), gastrointestinal symptoms (24 percent), and hepatomegaly (19 percent).

The development of amyloidosis has traditionally been associated with a relatively poor prognosis, unless the underlying RA can be effectively treated. It has been estimated to be the cause of death of 2 to 8 percent of adult patients coming to autopsy [38]. A 1994 report from Japan found a four-year survival rate of 58 percent from the time of diagnosis of amyloidosis, with renal failure contributing to 39 percent of deaths [41]; a subsequent series over a decade later reported an improvement to 67 months in the mean survival following the diagnosis of AA amyloidosis [50]. Prognosis may be significantly impacted by whether amyloid deposition is glomerular or purely vascular in RA patients with AA deposition [51].

Similarly, a study from Finland found that the diagnosis of amyloidosis shortened the lifespan of RA patients by 7.7 years [45]; a reevaluation of autopsy material for the period from 1952 to 1991 from Finland reported a 30 percent incidence of AA amyloid compared with 18 percent detected on routine testing, indicating that a significant proportion of patients may not have been appreciated by standard histologic analysis [52,53]. In contrast with the time period sampled above, subsequent (1987 to 1997) surveys from Finland appeared to confirm a decreasing incidence of AA amyloid among RA patients, possibly reflecting the impact of newer drugs and treatment regimens and of more aggressive treatment standards for early disease [6].

Juvenile idiopathic arthritis — In early reviews, juvenile chronic polyarthritis, also known as juvenile idiopathic arthritis (JIA), accounted for 43 percent of cases of

amyloidosis occurring under age 18, with a 4 to 6 percent incidence reported among 389 cases of systemic JIA (Still's disease) followed over a 10-year period [34].

Renal involvement, manifested clinically as proteinuria, occurs in almost all affected patients. Symptomatic disease is also relatively common. One report, for example, found the following frequency of symptoms [54]:

●Edema – 53 percent

●Hypertension – 25 percent

●End-stage kidney disease – 2.5 percent

●Severe abdominal pain, hepatomegaly, and splenomegaly – approximately 20 percent each

●Diarrhea – 13 percent

●Ascites – 2.5 percent

Amyloidosis had been estimated to be the cause of death of 43 to 47 percent of European patients with JIA in the mid-20th century, but the introduction of more effective treatments that lessen the chronic inflammation associated with systemic JIA has been associated with a dramatic reduction in the incidence of JIA-associated AA amyloidosis. Serial retrospective reviews from the United Kingdom's National Amyloidosis Centre showed a drop in JIA as an association for AA amyloid from 25 percent for the period 1990 to 1997 to 2 percent for 2007 to 2014 [8]; similarly, no cases have been documented in the Finnish registry since 1991 [38,55]. (See "Systemic juvenile idiopathic arthritis: Treatment".)

Ankylosing spondylitis — AS, a form of axial spondyloarthritis, is a well-established cause of AA amyloidosis, and AA amyloidosis was more common among AS patients than RA patients in a multicenter study from Turkey [56]. Renal involvement is the primary clinical manifestation.

The Medical Research Council studies, performed in Britain in the 1950s, found a 6 percent incidence of amyloidosis in patients dying with AS; the diagnosis was made pre-mortem in only 11 of 25 affected patients [57]. A 7 to 9 percent incidence has been reported in a series in which random rectal or fat pad biopsies were

performed [58,59]. Subsequently, a 4.3 percent incidence was reported, primarily in patients with severe chronic disease [59,60].

Systemic lupus erythematosus — AA amyloidosis has been described in only a small number of patients with systemic lupus erythematosus (SLE) [61]. The reason for the lower incidence of amyloidosis in SLE relative to RA is unknown but may be due to characteristically lower serum amyloid A protein (SAA) levels [62]. An increased predilection for circulating SAA to undergo proteolytic cleavage in RA compared with SLE has also been proposed [63].

Other rheumatic diseases — Scattered case reports have noted AA amyloidosis in a number of other rheumatic diseases. These include reactive arthritis (formerly Reiter syndrome) [64], psoriatic arthritis [65], Behçet syndrome [66], Takayasu arteritis [67,68], Whipple's disease [69], polymyalgia rheumatica [70], giant cell (temporal) arteritis [71], polyarteritis nodosa [72], gout [73], Sjögren's disease [74], and immunoglobulin (Ig)G4-related disease [75].

'Hereditary' AA amyloidosis — AA amyloidosis is not directly inherited, but there is evidence for genetic predisposition; in children with familial Mediterranean fever, multivariate analysis has shown that the presence of a family history of amyloidosis plus consanguinity was associated with a sixfold increased risk of developing AA amyloidosis [76] (see "The autoinflammatory diseases: An overview"). In one well-described family, AA amyloid occurred over multiple generations linked to a variant in the *SAA1* promoter [77].

AA amyloidosis in the spectrum of autoinflammatory diseases — AA amyloidosis may complicate autoinflammatory diseases characterized by monogenic inheritance.

These include familial Mediterranean fever and other periodic fever syndromes, which may also have rheumatic symptoms, and are discussed separately:

●Familial Mediterranean fever (see "Clinical manifestations and diagnosis of familial Mediterranean fever")

●Cryopyrin-associated periodic syndromes (see "Cryopyrin-associated periodic syndromes and related disorders")

●Tumor necrosis factor receptor-1 (TNFR1) associated periodic syndrome (see "Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS)")

●Mevalonate kinase deficiency (see "Hyperimmunoglobulin D syndrome: Clinical manifestations and diagnosis")

In these syndromes, AA amyloidosis may precede the characteristic clinical phenotype [78,79], which for familial Mediterranean fever has been designated "phenotype 2." Overlap between inflammation, IgM kappa gammopathy, and the occasional development of AA amyloid may also be found in Schnitzler syndrome, characterized by recurrent episodes of urticarial rash [80]. Lastly, AA amyloid may complicate sporadic autoinflammatory diseases that include JIA [81], adult-onset Still's disease [82], gout [73], and there has been one case report of AA amyloidosis in the newly described disease VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic), which is due to an acquired somatic mutation in *UBA1* [83].

Idiopathic AA amyloidosis — In small but increasing numbers, the underlying cause of the chronic inflammatory state remains obscure, despite an extensive evaluation for underlying inflammatory or infectious causes [14]. In three well-characterized single-center series of patients with AA amyloidosis from the United States, approximately 20 percent of cases were found to be idiopathic at diagnosis, with a small percentage revealing a known association later in the course [11,12,84]. In two subsequent large series of patients with AA amyloid seen at referral centers in the United Kingdom and Italy, the underlying disease remained unknown in 19 and 32 percent, respectively [8,85].

Changing face of disease and survival — The observation that AA amyloidosis is becoming less common [8] may be a reflection of advances in treatment of inflammatory arthritis in the era of biologic agents. This has both reduced the incidence of AA amyloidosis, and, when it does develop, has improved outcomes in what were previously the commonest pathologies underlying AA amyloidosis. In addition, the older age of the United Kingdom cohort (62 years in 2007 to 2014 versus 54 years in 1990 to 1997) may well reflect both the impact of better treatments, such as biologics, and more willingness to aggressively investigate and manage older patients. In the latest cohort, there was a significantly increased proportion of patients in end-stage kidney disease (29 versus 15 percent) compared with the earliest – a both unexpected and disappointing observation. Possible explanations include age-related decreased renal reserve resulting in more rapid loss of renal function in the presence of AA amyloidosis. While overall survival does not appear to have changed despite new effective therapies, age at death has

increased significantly over the last 25 years, suggesting improved general management and supportive care, including renal transplantation [8].

The median survival among cohorts of patients with AA amyloidosis has improved from 24.5 months in a series of 64 in 1991 from the United States [86] to 140 months in 375 patients from the United Kingdom in 2007 [14] and 143 months for 200 patients in Italy in 2017 [85].

CLINICAL MANIFESTATIONSAA amyloidosis can affect a variety of organs, including the kidneys and heart. These and other manifestations are discussed in detail elsewhere. (See "Overview of amyloidosis", section on 'Clinical manifestations'.)

The most common organ system involved in AA amyloid is the kidney (approximately 90 percent). This is usually characterized by glomerular amyloid deposition, typically leading to the nephrotic syndrome (picture 1A-D) [8,11-15]. However, variant forms occur in which the deposits are predominantly vascular [87] or tubular [88], with some evidence indicating that the AA protein in these forms is biochemically distinct (picture 2A-B) [87-89]. Patients with these variant forms of renal amyloid may present with progressive renal failure, a relatively bland urinary sediment, and little proteinuria, or they may show signs of primary tubular dysfunction such as arginine vasopressin resistance (AVP-R, previously called nephrogenic diabetes insipidus) [51]. (See "Renal amyloidosis".)

DIAGNOSISTissue biopsy is necessary to confirm the presence of amyloid, although the diagnosis of AA amyloidosis may be suggested by clinical features and by the presence of a predisposing rheumatic or a chronic inflammatory disease (eg, nephrotic syndrome occurring in the setting of longstanding rheumatoid arthritis [RA]), and additional laboratory testing may be needed to exclude other conditions. (See "Overview of amyloidosis", section on 'Diagnosis' and 'Differential diagnosis' below.)

Diagnostic approach — We take the following approach to diagnosis:

●In all patients with suspected AA amyloidosis, we recommend tissue biopsy to confirm the presence of amyloid. The abdominal fat is a generally safe and reasonably sensitive site for initial biopsy. In patients with a negative fat aspiration biopsy, we perform a biopsy of a clinically involved organ. (See 'Biopsy' below and "Overview of amyloidosis", section on 'Selection of biopsy site'.)

Alternatives to abdominal fat biopsies for screening include rectal and gingival biopsies. Amyloidosis is very unlikely in a patient with a negative screening biopsy and a negative biopsy of adequate tissue from an affected organ by a laboratory with expertise in these techniques.

Scintigraphy with radioisotope labeled serum amyloid P component (SAP) is also a useful screening technique for suspected amyloidosis, but its availability has been limited to the United Kingdom and the Netherlands, and it is not available in the United States. (See 'Serum amyloid P component scintigraphy' below and "Overview of amyloidosis", section on 'Imaging'.)

●In patients in whom amyloid is present on biopsy, further immunofluorescence or immunohistochemical staining for AA protein and for kappa and lambda light chains is indicated to confirm the diagnosis of AA amyloidosis and to exclude immunoglobulin light chain (AL; primary) amyloidosis. (See 'Biopsy' below.)

●Positive immunohistochemical staining of amyloid deposits with monospecific anti-AA protein antiserum is highly specific for AA amyloidosis when performed in expert centers. For confirmation of the diagnosis, to exclude AL amyloidosis, and if immunohistochemistry is equivocal or unavailable, we test serum and urine for monoclonal immunoglobulins by performing serum immunofixation and test serum for free light chains. (See 'Laboratory testing' below.)

Biopsy — Biopsy of the subcutaneous fat, rectal or gingival tissue, or a clinically involved organ is used to document the presence of amyloid. These individual techniques are discussed in more detail elsewhere. (See "Overview of amyloidosis", section on 'Selection of biopsy site'.)

The fat pad biopsy can establish the diagnosis in up to 80 percent of cases and can be combined with immunoelectron microscopy and mass spectroscopy.

Numerous studies support the use of a biopsy of the rectal mucosa and submucosa, with a sensitivity of approximately 75 to 85 percent for the detection of amyloid deposits. However, some series have shown lower sensitivity than abdominal fat aspiration. Considering that the involvement of the gastrointestinal tract may be focal, vascular, and subtle, sampling of multiple locations in the gastrointestinal tract (eg, stomach, small bowel, or colon) may also be useful for diagnosis [90].

Immunofluorescence (as well as immunohistochemical and immunoelectron) microscopy with a monospecific anti-AA protein antiserum is typically markedly

positive in AA amyloidosis (picture 1D) [91,92] (see 'Diagnosis' above). Absence of staining for lambda or kappa light chains further helps to distinguish AA from AL amyloidosis. These analyses should be performed by centers with expertise in these techniques.

For further analysis, amino acid sequencing and mass spectroscopy of amyloid deposits have been utilized to identify the precursor protein [93-95] and are available commercially [96]. Quantitation of AA amyloid in abdominal fat pad aspirates has been demonstrated using an enzyme-linked immunosorbent assay (ELISA); this approach may have utility for comparing patient population and for monitoring AA deposition serially [94]. A full proteomics approach combined with immunoelectron microscopy of fat pad aspirates establishes the diagnosis of AA amyloidosis in 70 to 80 percent of cases [97].

Laboratory testing — We obtain a serum C-reactive protein (CRP) level and an erythrocyte sedimentation rate (ESR) to assess the acute phase response for evidence of an inflammatory state. These are sometimes useful for monitoring of therapy [12]. However, other than the biopsy-related studies (see 'Biopsy' above), laboratory testing has little role in confirming the presence of AA amyloidosis. An important limitation regarding the ESR as a measure of inflammation in some patients with amyloidosis is the elevation seen in this assay in patients with chronic kidney disease and proteinuria, even in the absence of inflammation.

Demonstration of a sustained inflammation with a raised CRP, ESR (except in patients with chronic kidney disease, in whom the test may be elevated without inflammation), or other hepatic acute phase response testing is suggestive of chronic inflammation that might result in AA amyloidosis. We typically perform such testing every two to four weeks over at least a two-month period to assess inflammatory activity. It would be very unusual to have AA amyloidosis with a normal ESR and CRP. Serum amyloid A protein (SAA), which is also predominantly synthesized in the liver, would be an alternative (and superior) marker for AA amyloid. However, SAA quantitation is not always available outside specialist centers. In the United States, it is available through the multi-biomarker disease activity (MBDA) test (Vectra DA) or inflammatory bowel disease diagnostic panels. Proinflammatory cytokine measurements can be obtained either individually or as part biomarker screens [12].

Tests for monoclonal immunoglobulins in serum, such as immunofixation and measurement of free immunoglobulin light chains, are useful in excluding AL amyloidosis but must be interpreted with caution, as incidental monoclonal

gammopathies are present in 5 to 8 percent of patients over 70 years of age, and in some cases of AL amyloidosis, the clone may not be detected in the serum. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis" and "Laboratory methods for analyzing monoclonal proteins".)

Serum amyloid P component scintigraphy — Amyloid fibrils avidly bind both apolipoprotein E and serum amyloid P component (SAP). Tissue amyloid deposits may be identifiable by scintigraphy following the intravenous injection of technetium- or radioiodine-labeled SAP. The sensitivity and specificity of SAP scanning are discussed in detail elsewhere. This test is available in the United Kingdom and the Netherlands but is not available in the United States. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Serum amyloid P component scintigraphy'.)

Other imaging modalities — Potential ligands for imaging of AA amyloid include antibodies with reactivity to the subunit protein, peptides that bind to tissue AA, and 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) [98-100].

DIFFERENTIAL DIAGNOSISIn the presence of biopsy-established amyloidosis, the differential diagnosis of AA amyloidosis includes the following:

●**Immunoglobulin light chain amyloidosis** – Immunoglobulin light chain (AL; primary) amyloidosis is due to the tissue deposition of fragments of monoclonal immunoglobulin light chains. The plasma cell proliferation in this disorder leads to the presence of a paraprotein in the serum (as an M protein on protein immunoelectrophoresis or immunofixation or as evidenced by increased serum free light chains) or urine (as monoclonal light chains) in approximately 90 percent of cases. Although virtually all patients have multisystem amyloid deposition, it is not uncommon to present with organ-dominant disease. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis".)

Patients who have a monoclonal gammopathy of undetermined significance (MGUS) may require additional diagnostic studies, as approximately 10 percent of such patients have been found to have a type of amyloidosis other than AL amyloid.

●**Hereditary amyloidosis** – Heritable amyloidoses result from mutations in gene coding for one of several different proteins. A thorough family history aids in the

exclusion of these heritable disorders. AA-specific immunohistochemical staining on biopsy will confirm AA amyloidosis and thus exclude a hereditary form. (See ''Hereditary' AA amyloidosis' above and "Genetic factors in the amyloid diseases".)

●**Dialysis-related amyloidosis** – Dialysis-related amyloidosis is due to deposition of fibrils derived from beta-2 microglobulin, which accumulates in patients with end-stage kidney disease who are being maintained for prolonged periods of time by dialysis. This disorder has a predilection for osteoarticular structures. Although dialysis-related amyloidosis is associated with chronic hemo- or peritoneal dialysis, the amyloid rarely involves the kidney itself. Dialysis-related amyloidosis is almost exclusively a disease of patients on long-term renal replacement therapy. (See "Dialysis-related amyloidosis".)

●**Age-related (senile) systemic amyloidosis** – Deposition of otherwise normal (wild-type) transthyretin in myocardium and other sites is referred to as age-related (senile) systemic amyloidosis. Age-related systemic amyloidosis very rarely affects the kidney, the major target organ being the heart. Localization of amyloid deposition to the myocardium, immunohistochemistry with antibodies to transthyretin, and proteomic testing may also be used to distinguish this form of amyloid from AA. (See "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis" and "Overview of amyloidosis", section on 'Wild-type transthyretin systemic amyloidosis'.)

●**Organ-specific localized amyloidosis** – The coincidental occurrence of organ-specific amyloidosis in a patient with a systemic rheumatic or chronic inflammatory disorder could cause confusion with AA amyloidosis, but localized AA amyloid is rare. When found, localized amyloidosis is usually AL-type amyloidosis that is diagnosed on histology or mass spectrometry; it is very rarely hereditary. It has been reported in association with sarcoidosis, Sjögren's disease, and occasionally other conditions. (See "Overview of amyloidosis", section on 'Organ-specific amyloid'.)

SUMMARY AND RECOMMENDATIONS

●AA amyloidosis (previously known as secondary [AA] amyloidosis) is a disorder characterized by the extracellular tissue deposition of fibrils that are predominantly composed of fragments of serum amyloid A (SAA) protein, an acute phase reactant. AA amyloidosis may complicate a number of chronic inflammatory conditions. The incidence appears to be falling and in western nations ranges from 0.5 to 0.86

percent. (See 'Introduction' above and 'Causes and relation to rheumatic diseases' above.)

●The most common underlying disorders associated with AA amyloidosis in the United States and Europe include rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), inflammatory bowel disease, psoriatic arthritis, familial periodic fever syndromes, chronic infections, and certain neoplasms. Inflammation of unknown etiology appears to be responsible for an increasing proportion, perhaps reflecting more effective treatment of the inflammatory arthritides and inflammatory bowel disease with biologic agents. (See 'Causes and relation to rheumatic diseases' above.)

In some eastern Mediterranean countries (eg, Turkey, Armenia), familial Mediterranean fever and certain *MEFV* mutations are more common causes and associations with AA amyloidosis than in North America and Europe. Chronic infections are responsible for a larger proportion of patients with AA amyloid in the developing world than in the United States and Europe. It may precede and/or complicate familial Mediterranean fever and tumor necrosis factor receptor-1 (TNFR1) associated periodic syndrome monogenic autoinflammatory diseases, as well as complicate sporadic and hereditary diseases such as Schnitzler syndrome, JIA, and adult-onset Still's disease. Susceptibility to AA amyloidosis among the various rheumatic diseases is determined by duration and severity of inflammation with contributions from additional genetic and environmental factors. (See 'Causes and relation to rheumatic diseases' above.)

●We recommend tissue biopsy in all cases of suspected AA amyloidosis to confirm the presence of amyloid. The abdominal fat is a generally safe and reasonably sensitive site for initial biopsy. If a fat aspiration biopsy is negative, then we obtain a biopsy of a clinically involved organ. Alternative sites to the abdominal fat pad for the screening biopsy include the rectum and gingiva. (See 'Diagnosis' above and "Overview of amyloidosis", section on 'Selection of biopsy site'.)

●In patients in whom amyloid is present on biopsy, further immunofluorescence or immunochemical staining is indicated for identification of AA protein and, in some cases, for kappa and lambda light chains. (See 'Diagnosis' above and 'Biopsy' above.)

●We perform testing of serum and urine for monoclonal immunoglobulins and of serum for free light chains to help exclude immunoglobulin light chain (AL; primary) amyloidosis. (See 'Diagnosis' above and 'Laboratory testing' above.)

●In the presence of biopsy-established amyloidosis, the differential diagnosis of AA amyloidosis includes AL amyloidosis, hereditary amyloidosis, dialysis-related amyloidosis, age-related systemic amyloidosis, and organ-specific amyloidosis. (See 'Differential diagnosis' above.)

REFERENCES

1. Papa R, Lachmann HJ. Secondary, AA, Amyloidosis. Rheum Dis Clin North Am 2018; 44:585.
2. Brunger AF, Nienhuis HLA, Bijzet J, Hazenberg BPC. Causes of AA amyloidosis: a systematic review. Amyloid 2020; 27:1.
3. Westermark P, Nilsson GT. Demonstration of amyloid protein AA in old museum specimens. Arch Pathol Lab Med 1984; 108:217.
4. Deshayes S, Aouba A, Grateau G, Georgin-Lavialle S. Infections and AA amyloidosis: An overview. Int J Clin Pract 2021; 75:e13966.
5. Nienhuis HL, Bijzet J, Hazenberg BP. The Prevalence and Management of Systemic Amyloidosis in Western Countries. Kidney Dis (Basel) 2016; 2:10.
6. Laiho K, Tiitinen S, Kaarela K, et al. Secondary amyloidosis has decreased in patients with inflammatory joint disease in Finland. Clin Rheumatol 1999; 18:122.
7. Panizo N, Rivera F, López-Gómez JM, Spanish Registry of Glomerulonephritis. Decreasing incidence of AA amyloidosis in Spain. Eur J Clin Invest 2013; 43:767.
8. Lane T, Pinney JH, Gilbertson JA, et al. Changing epidemiology of AA amyloidosis: clinical observations over 25 years at a single national referral centre. Amyloid 2017; 24:162.
9. Simms RW, Prout MN, Cohen AS. The epidemiology of AL and AA amyloidosis. Baillieres Clin Rheumatol 1994; 8:627.
10. Real de Asúa D, Costa R, Galván JM, et al. Systemic AA amyloidosis: epidemiology, diagnosis, and management. Clin Epidemiol 2014; 6:369.
11. Girnius S, Dember L, Doros G, Skinner M. The changing face of AA amyloidosis: a single center experience. Amyloid 2011; 18 Suppl 1:226.
12. Bunker D, Gorevic P. AA amyloidosis: Mount Sinai experience, 1997-2012. Mt Sinai J Med 2012; 79:749.
13. Gillmore JD, Lovat LB, Persey MR, et al. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. Lancet 2001; 358:24.
14. Lachmann HJ, Goodman HJ, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. N Engl J Med 2007; 356:2361.
15. Hunter J, McGregor L. Do inflammatory rheumatic diseases still cause as much harm through amyloidosis? Amyloid 2011; 18 Suppl 1:208.
16. Westermark P, Westermark GT. Review. Reflections on amyloidosis in Papua New Guinea. Philos Trans R Soc Lond B Biol Sci 2008; 363:3701.

17. Ensari C, Ensari A, Tümer N, Ertug E. Clinicopathological and epidemiological analysis of amyloidosis in Turkish patients. Nephrol Dial Transplant 2005; 20:1721.
18. Cazeneuve C, Sarkisian T, Pêcheux C, et al. MEFV-Gene analysis in armenian patients with Familial Mediterranean fever: diagnostic value and unfavorable renal prognosis of the M694V homozygous genotype-genetic and therapeutic implications. Am J Hum Genet 1999; 65:88.
19. Atoyan S, Hayrapetyan H, Sarkisian T, Ben-Chetrit E. MEFV and SAA1 genotype associations with clinical features of familial Mediterranean fever and amyloidosis in Armenia. Clin Exp Rheumatol 2016; 34:72.
20. Pras M, Franklin EC, Shibolet S, Frangione B. Amyloidosis associated with renal cell carcinoma of the AA type. Am J Med 1982; 73:426.
21. Piskin O, Alacacioglu I, Ozkal S, et al. A patient with diffuse large B-cell non-Hodgkin's lymphoma and AA type amyloidosis. J BUON 2008; 13:113.
22. Muzaffar J, Katragadda L, Haider S, et al. Waldenström's macroglobulinemia associated with serum amyloid A protein amyloidosis: pitfalls in diagnosis and successful treatment with melphalan-based autologous stem cell transplant. Acta Haematol 2013; 130:146.
23. Terré A, Colombat M, Cez A, et al. AA amyloidosis complicating monoclonal gammopathies, an unusual feature validating the concept of "monoclonal gammopathy of inflammatory significance"? Int J Clin Pract 2021; 75:e14817.
24. Shimojima Y, Takei Y, Tazawa K, et al. Histopathological regression of systemic AA amyloidosis after surgical treatment of a localized Castleman's disease. Amyloid 2006; 13:184.
25. Ogita M, Hoshino J, Sogawa Y, et al. Multicentric Castleman disease with secondary AA renal amyloidosis, nephrotic syndrome and chronic renal failure, remission after high-dose melphalan and autologous stem cell transplantation. Clin Nephrol 2007; 68:171.
26. Fayand A, Boutboul D, Galicier L, et al. Epidemiology of Castleman disease associated with AA amyloidosis: description of 2 new cases and literature review. Amyloid 2019; 26:197.
27. Skinner M, Pinnette A, Travis WD, et al. Isolation and sequence analysis of amyloid protein AA from a patient with cystic fibrosis. J Lab Clin Med 1988; 112:413.
28. Stankovic Stojanovic K, Hubert D, Leroy S, et al. Cystic fibrosis and AA amyloidosis: a survey in the French cystic fibrosis network. Amyloid 2014; 21:231.
29. Lejmi H, Jen KY, Olson JL, et al. Characteristics of AA amyloidosis patients in San Francisco. Nephrology (Carlton) 2016; 21:308.
30. Girouard SD, Falk RH, Rennke HG, Merola JF. Hidradenitis suppurativa resulting in systemic amyloid A amyloidosis: a case report and review of the literature. Dermatol Online J 2012; 18:2.
31. Schandorff KD, Miller IM, Krustrup D, et al. Renal amyloid A amyloidosis as a complication of hidradenitis suppurativa. Clin Nephrol 2016; 86:51.
32. Stankovic Stojanovic K, Georgin-Lavialle S, Poitou C, et al. AA amyloidosis is an emerging cause of nephropathy in obese patients. Eur J Intern Med 2017; 39:e18.

33. Blank N, Hegenbart U, Dietrich S, et al. Obesity is a significant susceptibility factor for idiopathic AA amyloidosis. Amyloid 2018; 25:37.
34. Smith ME, Ansell BM, Bywaters EG. Mortality and prognosis related to the amyloidosis of Still's disease. Ann Rheum Dis 1968; 27:137.
35. Roztropowicz-Denisiewicz K, Madyk E, Romicka A, Szymanska-Jagiello W. Variability of the course of amyloidosis in children with rheumatoid arthritis. Ped Pol 1974; 49:10.
36. Filipowicz-Sosnowska AM, Roztropowicz-Denisiewicz K, Rosenthal CJ, Baum J. The amyloidosis of juvenile rheumatoid arthritis--comparative studies in Polish and American children. I. Levels of serum SAA protein. Arthritis Rheum 1978; 21:699.
37. Touitou I, Sarkisian T, Medlej-Hashim M, et al. Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. Arthritis Rheum 2007; 56:1706.
38. Husby G. Amyloidosis and rheumatoid arthritis. Clin Exp Rheumatol 1985; 3:173.
39. Päi S, Helin H, Isomäki H. Frequency of amyloidosis in Estonian patients with rheumatoid arthritis. Scand J Rheumatol 1993; 22:248.
40. Gómez-Casanovas E, Sanmartí R, Solé M, et al. The clinical significance of amyloid fat deposits in rheumatoid arthritis: a systematic long-term followup study using abdominal fat aspiration. Arthritis Rheum 2001; 44:66.
41. Okuda Y, Takasugi K, Oyama T, et al. [Amyloidosis in rheumatoid arthritis--clinical study of 124 histologically proven cases]. Ryumachi 1994; 34:939.
42. Wakhlu A, Krisnani N, Hissaria P, et al. Prevalence of secondary amyloidosis in Asian North Indian patients with rheumatoid arthritis. J Rheumatol 2003; 30:948.
43. El Mansoury TM, Hazenberg BP, El Badawy SA, et al. Screening for amyloid in subcutaneous fat tissue of Egyptian patients with rheumatoid arthritis: clinical and laboratory characteristics. Ann Rheum Dis 2002; 61:42.
44. Wiland P, Wojtala R, Goodacre J, Szechinski J. The prevalence of subclinical amyloidosis in Polish patients with rheumatoid arthritis. Clin Rheumatol 2004; 23:193.
45. Myllykangas-Luosujärvi R, Aho K, Kautiainen H, Hakala M. Amyloidosis in a nationwide series of 1666 subjects with rheumatoid arthritis who died during 1989 in Finland. Rheumatology (Oxford) 1999; 38:499.
46. Sellars L, Siamopoulos K, Wilkinson R, et al. Renal biopsy appearances in rheumatoid disease. Clin Nephrol 1983; 20:114.
47. Bourke BE, Woodrow DF, Scott JT. Proteinuria in rheumatoid arthritis--drug-induced or amyloid? Ann Rheum Dis 1981; 40:240.
48. Ludwin D, Alexopoulou I, Esdaile JM, Tugwell P. Renal biopsy specimens from patients with rheumatoid arthritis and apparently normal renal function after therapy with cyclosporine. Canadian Multicentre Rheumatology Group. Am J Kidney Dis 1994; 23:260.
49. Hazenberg BP, van Rijswijk MH. Where has secondary amyloid gone? Ann Rheum Dis 2000; 59:577.

50. Kuroda T, Tanabe N, Harada T, et al. Long-term mortality outcome in patients with reactive amyloidosis associated with rheumatoid arthritis. Clin Rheumatol 2006; 25:498.
51. Uda H, Yokota A, Kobayashi K, et al. Two distinct clinical courses of renal involvement in rheumatoid patients with AA amyloidosis. J Rheumatol 2006; 33:1482.
52. Koivuniemi R, Paimela L, Suomalainen R, Leirisalo-Repo M. Amyloidosis as a cause of death in patients with rheumatoid arthritis. Clin Exp Rheumatol 2008; 26:408.
53. Koivuniemi R, Paimela L, Suomalainen R, et al. Amyloidosis is frequently undetected in patients with rheumatoid arthritis. Amyloid 2008; 15:262.
54. Woo P. Amyloidosis in children. Baillieres Clin Rheumatol 1994; 8:691.
55. Immonen K, Savolainen A, Kautiainen H, Hakala M. Longterm outcome of amyloidosis associated with juvenile idiopathic arthritis. J Rheumatol 2008; 35:907.
56. Pamuk ÖN, Kalyoncu U, Aksu K, et al. A multicenter report of biologic agents for the treatment of secondary amyloidosis in Turkish rheumatoid arthritis and ankylosing spondylitis patients. Rheumatol Int 2016; 36:945.
57. CRUICKSHANK B. Pathology of ankylosing spondylitis. Bull Rheum Dis 1960; 10:211.
58. Gratacos J, Orellana C, Sanmarti R, et al. Secondary amyloidosis in ankylosing spondylitis. A systematic survey of 137 patients using abdominal fat aspiration. J Rheumatol 1997; 24:912.
59. Kovacsovics-Bankowski M, Zufferey P, So AK, Gerster JC. Secondary amyloidosis: a severe complication of ankylosing spondylitis. Two case-reports. Joint Bone Spine 2000; 67:129.
60. Singh G, Kumari N, Aggarwal A, et al. Prevalence of subclinical amyloidosis in ankylosing spondylitis. J Rheumatol 2007; 34:371.
61. Aktas Yilmaz B, Düzgün N, Mete T, et al. AA amyloidosis associated with systemic lupus erythematosus: impact on clinical course and outcome. Rheumatol Int 2008; 28:367.
62. Pepys MB. Serum C-reactive protein, serum amyloid P-component and serum amyloid A protein in autoimmune disease. Clin Immunol Allergy 1981; 1:77.
63. Migita K, Eguchi K, Tsukada T, et al. Increased circulating serum amyloid A protein derivatives in rheumatoid arthritis patients with secondary amyloidosis. Lab Invest 1996; 75:371.
64. Anderson CJ, Gregory MC, Groggel GC, Clegg DO. Amyloidosis and Reiter's syndrome: report of a case and review of the literature. Am J Kidney Dis 1989; 14:319.
65. Mpofu S, Teh LS, Smith PJ, et al. Cytostatic therapy for AA amyloidosis complicating psoriatic spondyloarthropathy. Rheumatology (Oxford) 2003; 42:362.
66. Kosemehmetoglu K, Baydar DE. Renal amyloidosis in Behçet's disease: clinicopathologic features of 8 cases. Int Urol Nephrol 2013; 45:785.
67. Wada Y, Nishida H, Kohno K, et al. AA amyloidosis in Takayasu's arteritis--long-term survival on maintenance haemodialysis. Nephrol Dial Transplant 1999; 14:2478.

68. Nakamura S, Morishita M, Yang CL, et al. An elderly female who survived more than 30 years following a diagnosis of Takayasu's arteritis, complicated by fatal intestinal amyloidosis. Clin Rheumatol 2006; 25:907.
69. Cruz I, Oliveira AP, Lopes JM, et al. Whipple's disease and renal amyloidosis. Am J Gastroenterol 1993; 88:1954.
70. Escribá A, Morales E, Albizúa E, et al. Secondary (AA-type) amyloidosis in patients with polymyalgia rheumatica. Am J Kidney Dis 2000; 35:137.
71. Moraga, Sicilia JJ, Blanco J, Ubeda I. Giant cell arteritis and renal amyloidosis: report of a case. Clin Nephrol 2001; 56:402.
72. Hočevar A, Lestan B, Šemrl SS, et al. AA amyloidosis in a polyarteritis nodosa patient treated with tocilizumab. Amyloid 2013; 20:275.
73. Ter Borg EJ, Wegewijs MA, de Bruin P. Gout and AA Amyloidosis: A Case Report and Review of the Literature. J Clin Rheumatol 2017; 23:233.
74. Wong BC, Wong KL, Ip MS, et al. Sjögren's syndrome with amyloid A presenting as multiple pulmonary nodules. J Rheumatol 1994; 21:165.
75. Karim F, Clahsen-van Groningen M, van Laar JA. AA Amyloidosis and IgG4-Related Disease. N Engl J Med 2017; 376:599.
76. Saatçi U, Ozen S, Ozdemir S, et al. Familial Mediterranean fever in children: report of a large series and discussion of the risk and prognostic factors of amyloidosis. Eur J Pediatr 1997; 156:619.
77. Sikora J, Kmochová T, Mušálková D, et al. A mutation in the SAA1 promoter causes hereditary amyloid A amyloidosis. Kidney Int 2022; 101:349.
78. Soriano A, Manna R. Familial Mediterranean fever: new phenotypes. Autoimmun Rev 2012; 12:31.
79. Delaleu J, Deshayes S, Rodrigues F, et al. Tumour necrosis factor receptor-1 associated periodic syndrome (TRAPS)-related AA amyloidosis: a national case series and systematic review. Rheumatology (Oxford) 2021; 60:5775.
80. Palladini G, Merlini G. The elusive pathogenesis of Schnitzler syndrome. Blood 2018; 131:944.
81. Saha A, Chopra Y, Theis JD, et al. AA amyloidosis associated with systemic-onset juvenile idiopathic arthritis. Am J Kidney Dis 2013; 62:834.
82. Delplanque M, Pouchot J, Ducharme-Bénard S, et al. AA amyloidosis secondary to adult onset Still's disease: About 19 cases. Semin Arthritis Rheum 2020; 50:156.
83. Euvrard R, Fournier T, Georgescu D, et al. VEXAS syndrome-related AA amyloidosis: a case report. Rheumatology (Oxford) 2021; 61:e15.
84. Kluve-Beckerman B, Benson MD. AA amyloidosis in patients with no known inflammatory condition. Abstract PB15. XIII Intl Symposium on Amyloidosis, May 6-10, 2012.
85. Palladini G, Riva E, Basset M, et al. Prognostication of survival and progression to dialysis in AA amyloidosis. Amyloid 2017; 24:136.
86. Gertz MA, Kyle RA. Secondary systemic amyloidosis: response and survival in 64 patients. Medicine (Baltimore) 1991; 70:246.

87. Westermark GT, Sletten K, Westermark P. Massive vascular AA-amyloidosis: a histologically and biochemically distinctive subtype of reactive systemic amyloidosis. Scand J Immunol 1989; 30:605.
88. Hiki Y, Horii A, Kokubo T, et al. A case of rheumatoid arthritis with renal tubular amyloidosis. Nephron 1994; 68:394.
89. Westermark GT, Sletten K, Grubb A, Westermark P. AA-amyloidosis. Tissue component-specific association of various protein AA subspecies and evidence of a fourth SAA gene product. Am J Pathol 1990; 137:377.
90. Hachulla E, Grateau G. Diagnostic tools for amyloidosis. Joint Bone Spine 2002; 69:538.
91. Yang GC, Gallo GR. Protein A-gold immunoelectron microscopic study of amyloid fibrils, granular deposits, and fibrillar luminal aggregates in renal amyloidosis. Am J Pathol 1990; 137:1223.
92. Picken MM, Pelton K, Frangione B, Gallo G. Primary amyloidosis A. Immunohistochemical and biochemical characterization. Am J Pathol 1987; 129:536.
93. Murphy CL, Wang S, Williams T, et al. Characterization of systemic amyloid deposits by mass spectrometry. Methods Enzymol 2006; 412:48.
94. Hazenberg BP, Bijzet J, Limburg PC, et al. Diagnostic performance of amyloid A protein quantification in fat tissue of patients with clinical AA amyloidosis. Amyloid 2007; 14:133.
95. Lavatelli F, Perlman DH, Spencer B, et al. Amyloidogenic and associated proteins in systemic amyloidosis proteome of adipose tissue. Mol Cell Proteomics 2008; 7:1570.
96. Dogan A. Classification of amyloidosis by mass spectometry-based proteomics. In: Amyloid & Related Disorders: Surgical Pathology & Clinical Correlations, Pickens MM, et al (Eds), Springer, 2012. p.261.
97. Brambilla F, Lavatelli F, Di Silvestre D, et al. Reliable typing of systemic amyloidoses through proteomic analysis of subcutaneous adipose tissue. Blood 2012; 119:1844.
98. Marshall J, McNally W, Muller D, et al. In vivo radioimmunodetection of amyloid deposits in experimental amyloidosis. In: Amyloidosis, Glenner GG, Osserman EF, Benditt EP, et al (Eds), Plenum Press, 1986. p.163.
99. Martin EB, Williams A, Richey T, et al. Comparative evaluation of p5+14 with SAP and peptide p5 by dual-energy SPECT imaging of mice with AA amyloidosis. Sci Rep 2016; 6:22695.
100. Wang J, Zhao B, Song T, Sun J. Lung cancer combined with diffuse peritoneal and mesenteric amyloidosis detected on 18F-FDG PET/CT: A case report. Medicine (Baltimore) 2021; 100:e25961.

This generalized information is a limited summary of diagnosis, treatment, and/or medication information. It is not meant to be comprehensive and should be used as a tool to help the user understand and/or assess potential diagnostic and treatment options. It does NOT include all information about conditions, treatments, medications, side effects, or risks

Topic 5602 Version 26.0

CHAPTER 10

Pathogenesis of AA amyloidosis

Author:Peter D Gorevic, MD
Section Editor:Helen J Lachmann, MA, MB, BChir, MD, FRCP, FRCPath
Deputy Editor:Siobhan M Case, MD, MHS
Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Aug 2023. This topic last updated: Mar 04, 2022.

INTRODUCTIONAA amyloid results from the deposition in tissue of serum amyloid A (SAA) protein, which is a major acute phase reactant. Amyloidosis encompasses a group of diseases caused by misfolding and extracellular accumulation of proteins as fibrillar deposits [1,2]. These fibrils stain with Congo red and produce pathognomonic green birefringence when viewed by microscopy under crossed polarized light. The process of amyloid formation and deposition causes tissue toxicity and progressive organ dysfunction.

The pathogenesis of AA amyloidosis is presented here. The clinical manifestations, diagnosis, and treatment of this disorder, an overview of amyloidosis, and the pathogenesis of other forms of amyloidosis are discussed separately. (See "Causes and diagnosis of AA amyloidosis and relation to rheumatic diseases" and "Treatment of AA (secondary) amyloidosis" and "Overview of amyloidosis".)

AMYLOID PRECURSORS AND AMYLOIDOGENESISAll forms of amyloidosis, including AA amyloidosis, are characterized by codeposition of other molecules, including:

●Serum amyloid P component (SAP), a member of the pentraxin family that includes C-reactive protein [2]

●Glycosaminoglycans, notably heparan sulfate [3]

●Apolipoproteins (E and A4) [4]

There are 36 different human precursor proteins known to be deposited in a fibrillar configuration as amyloid, 14 associated with systemic disease [5]. Common examples include:

●Serum amyloid A (SAA) protein in AA amyloidosis

●Monoclonal immunoglobulin light chains in primary or immunoglobulin light chain (AL) amyloidosis (see "Monoclonal immunoglobulin deposition disease")

●Beta-2 microglobulin in dialysis-related amyloidosis (see "Dialysis-related amyloidosis")

●Transthyretin in wild-type transthyretin (TTR) amyloidosis (previously known as senile cardiac amyloidosis)

●Several different apolipoproteins among the hereditary amyloidoses (see "Genetic factors in the amyloid diseases")

A number of factors have been identified that contribute to the pathogenesis of AA amyloid:

●Sustained increase in the serum concentration of SAA in chronic inflammatory states [6]

●Post-translational modifications that may influence synthesis or destabilize SAA and favor its misfolding and aggregation [7]

●Interruption of ligand binding to various receptors as a result of proteolysis at position 76 of SAA [8]

●The intrinsic propensity of SAA subsequences to misfolding [9]

A combination of these factors may determine the amyloidogenicity. Nonetheless, undetermined environmental and genetic factors must also be involved as only a minority of patients with sustained inflammation and persistent elevation of SAA levels develop AA amyloidosis [2].

Cofactors, such as glycosaminoglycans and SAP, may play a role in predisposition to amyloid formation via one or more of the following effects [10-14]:

●Modulation of fibrillogenesis by direct binding to specific domains of subunit proteins or their precursors

●Stabilization of the fibril and protection from degradation

●Localization to specific organs or tissue sites by binding to matrix components or receptor molecules

●Secondary effects on the metabolism of precursor protein, leading to the accumulation of degradation products with amyloidogenic potential

●Modulation of proteolytic events that may facilitate fibril formation

SERUM AMYLOID A PROTEINAA amyloid results from the deposition in tissue of serum amyloid A (SAA) protein, which is a major acute phase reactant [7,15]. (See "Acute phase reactants".)

Types — Several forms of SAA have been identified in serum. These include acute phase (SAA1 and SAA2) and constitutive (SAA4) isoforms, allelic variants, and post-translational modifications of these gene products [1,7,15]. Acute phase SAA proteins (SAA1 and SAA2) are apolipoproteins, primarily associated with high-density lipoprotein (HDL), and are also expressed extrahepatically (eg, synovial membrane) in the absence of HDL [16]. However, during the inflammatory response, SAA may exchange with low-density lipoproteins [17], and a small fraction binds to retinol-binding protein and indirectly to transthyretin [18].

Expression of SAA1 and SAA2 is induced by a number of factors, particularly interleukin (IL) 6, but also IL-1, tumor necrosis factor (TNF), lipopolysaccharide (LPS), and several transcription factors (pERK1/2, pjNK, p38), notably including SAA-activating factor (SAF)-1 [19-21].

●SAA1 is the precursor protein in most individuals with AA amyloid [22].

●Binding of heparin to SAA1 displaces it from HDL, perhaps contributing to the mechanism by which heparin and heparan sulfate facilitate formation of AA amyloid [3].

●SAA1 has three alleles, designated SAA1.1, SAA1.3, and SAA1.5, defined by amino acid substitutions at positions 52 and 57 of the molecule [23]. SAA2 has two alleles (alpha and beta) that differ from each other by a single base pair substitution at codon 71 resulting in an adenine substitution of guanine [24].

●The frequency of these alleles varies between populations and homozygosity for SAA1. SAA1 has been associated with an increased risk of AA amyloidosis in diseases such as rheumatoid arthritis and familial Mediterranean fever in White

individuals, perhaps because of increased susceptibility to proteolytic cleavage by specific metalloproteinases [25,26].

●In the Japanese population, specific single nucleotide polymorphisms (SNPs) of the gene for SAA1.3 have been associated with increased gene transcription, AA amyloidosis complicating rheumatoid arthritis, adult-onset Still's disease, and susceptibility to familial Mediterranean fever [27,28].

●The carrier frequency for *MEFV* variants and familial Mediterranean fever in Armenia ranges up to one in three persons; Armenian patients homozygous for SAA1-alpha have a sevenfold higher risk of developing renal AA amyloidosis [29].

Possible function — The acute phase response, as reflected in the *SAA* gene, has been conserved for half a billion years throughout vertebrate evolution. Whereas SAA1 and SAA2 genes are found in most mammalian species due to conversion/duplication of an ancestral gene, fowl and fish have only a single acute phase response SAA, yet some species (eg, Pekin duck, some dolphins) are still susceptible to developing AA amyloid [21]. In humans, SAA is one of the most dynamic components with a potential increase in circulating concentration of more than 1000-fold, implying that it has important functions in the inflammatory response. Nonetheless, the exact contributions SAA proteins play in host defense remain somewhat opaque [7].

SAA proteins may increase the affinity of HDLs for macrophages and adipocytes during the acute phase response, a property termed "reverse cholesterol metabolism" [15,30,31]. Other properties include extracellular matrix binding [32]; opsonization of Gram-negative bacteria [33]; chemoattractant activity for monocytes, neutrophils, and lymphocytes [34]; induction of the release of proinflammatory cytokines from neutrophils [35,36]; and platelet effects [37,38]. Pro- and antiinflammatory effects of SAA vary with regard to the blood pool of hepatically derived acute phase SAA; local effects of tissue- and macrophage-derived SAA; the use of recombinant SAA for many in vitro studies; and whether SAA is bound to HDL or delipidated [39].

Ligands — SAA interacts specifically with a wide range of ligands, either bound to the surface of HDLs or in a lipid-free form [40]. The former include cholesterol (residues 1 to 18 and 40 to 63 of SAA), HDL (residues 1 to 18), calcium (residues 48 to 51), laminin (residues 29 to 33), fibronectin (residues 39 to 41), cystatin c (residues 86 to 104), and heparin/heparan sulfate (two binding sites within residues 17 to 49 and 77 to 103) [21]; the last ligand, in particular, has been

targeted for the development of therapeutic agents for the treatment of AA amyloid [41]. (See "Treatment of AA (secondary) amyloidosis".)

Some SAA binding may occur selectively within the joint space of patients with rheumatoid arthritis, as both acute phase and constitutive isoforms of SAA appear to be synthesized by synovial tissue [16,42]. High levels of both SAA and its receptor, formyl peptide receptor-like 1 (FPRL1), have been demonstrated in the rheumatoid synovium, and a link to leukocyte infiltration, including the influx of CCR6-expressing Th17 cells, was confirmed by the ability of SAA to upregulate CCR20 expression of rheumatoid arthritis synoviocytes [43]. Acute phase SAA may directly stimulate the production of TNF-alpha and acute phase pentraxin production by synoviocytes [44]; SAA can mediate inflammatory and angiogenic effects by interaction with toll-like receptors (TLR2 and TLR4) [39,45]. Inhibition of IL-6-mediated induction of acute phase SAA in rheumatoid synovium by JAK/STAT (Janus kinase/signal transducer and activator of transcription) inhibitors being developed for clinical use provides another mechanism for abrogating SAA that may have potential for use in inflammatory arthritis, as well as in AA amyloidosis [46].

PATHOGENESIS OF AA AMYLOIDOSISCommon causes of AA amyloidosis are rheumatoid arthritis, chronic infections (particularly in resource-limited countries), and autoinflammatory disorders [47,48]. (See "Causes and diagnosis of AA amyloidosis and relation to rheumatic diseases".)

AA amyloid occurs in various mammalian and avian species and can be induced by chronic inflammatory stimuli. The best-studied model for this disease is amyloid induction by casein/azocasein injections in certain genetically susceptible strains of mice [49]. Although most animal models for AA amyloid parallel human disease with predominant fibril deposition in spleen, liver, and kidney, chickens develop a unique articular amyloidosis when injected with *Enterococcus faecalis* [50,51]. Transmissibility of systemic AA amyloidosis by a seeding-nucleation process (so-called amyloid-enhancing factor [AEF]) has been identified in the pathogenesis of bovine, avian, mouse, and cheetah AA amyloid [52].

Principal pathogenic factors — Based upon findings in these animal models and results in patients, the principal pathogenic factors in AA amyloidosis (figure 1) appear to be the following [1,53,54]:

●Overproduction of both high-density lipoprotein (HDL)-associated and lipid-free serum amyloid A (SAA) as a consequence of acute and chronic inflammation.

●Proteolytic processing of SAA to AA, with a major cleavage occurring at position 76, thereby releasing the carboxyterminal third of the molecule [55]. The in vitro demonstration of internalization of SAA by macrophages, followed by intracellular proteolysis, and later by release of amyloidogenic peptides into the extracellular space [56], suggests that these events precede fibril formation. However, there is still uncertainty about the order of events in vivo [12,13].

●Focus on the intralysosomal pathway and acidification as promoting SAA aggregation has provided evidence for oligomers and other prefibrillar soluble aggregates of SAA as contributing to disease pathogenesis, toxicity, and the potential value of therapies that can inhibit aggregation and clear oligomers [57,58]

●Intrinsic fibrillogenic properties of SAA subsequences, particularly involving the amino-terminal end of the molecule [59,60].

Increased synthesis — There is increased synthesis of SAA with inflammation due to elevated levels of proinflammatory cytokines. With rheumatoid arthritis, for example, this increase in cytokine levels correlates with synovitis, which, in turn, may stimulate synoviocytes to produce SAA [16,34,42,61]. These events lead to elevated levels in joint fluid relative to serum [42]. In addition, SAA may directly potentiate rheumatoid inflammation via the induction of matrix metalloproteinases (MMP1 and MMP3) by synovial cells and chondrocytes [42,44,62].

Although most acute phase response SAA originates in the liver, SAA1/2 may also be produced by macrophages, kidney, lung, adipocytes, mammary glands, synovial cells, and intestinal epithelial cells (IECs) (figure 1). Early studies demonstrated SAA to be a major adipokine [63], relevant to the lipoprotein redistribution in obesity [64], inflammation [24], and in some instances, the development of AA amyloidosis [65]. Studies of SAA upregulation in mice and zebrafish, and the development of double and triple SAA knockout mice, have focused attention on possible roles in regulating inflammation and facilitating autoimmunity in inflammatory bowel disease (IBD). In mice, acute phase response SAA production by IECs may be induced by intra-ileal colonization by specific segmented filamentous microbes, triggered by interleukin (IL) 22-producing type 3 innate lymphoid cells, with SAA in turn promoting T helper (Th) 17 differentiation and increased IL-17 produced by these Th cells. This scenario provides a mechanism for SAA modulation of the inflammasome response in IBD, as well as autoimmune disease systemically [66-70].

The importance of increased SAA synthesis has been demonstrated by the correlation between the serum SAA concentration and disease course in patients with established AA amyloidosis. This was illustrated in a report of 80 patients with AA amyloid (mostly due to juvenile idiopathic arthritis or to rheumatoid arthritis) who were prospectively followed for a median of four years; the systemic amyloid load was assessed by yearly serum amyloid P component (SAP) scintigraphy [71]. The following findings were noted (see "Treatment of AA (secondary) amyloidosis"):

●Forty-two patients had median serum SAA concentration within the reference range (<10 mg/L); amyloid deposits regressed in 25 and stabilized in 14. Among patients with renal disease at baseline, proteinuria typically fell while the serum creatinine concentration was either stable or improved. Two patients who required dialysis remained on dialysis.

●The outcomes were variable in the other patients. However, among those in whom the serum SAA was persistently above 50 mg/L, the amyloid load usually increased and organ function deteriorated. In one patient who underwent renal transplantation, proteinuria and renal amyloid deposits recurred within 36 months.

●Amyloid deposition increased rapidly in patients with relapse of the underlying inflammatory disease. This observation is consistent with an underlying susceptibility to amyloidosis.

Processing — All forms of AA amyloidosis are associated with increased levels of SAA in blood [72]. In rheumatoid arthritis, however, SAA levels are increased in patients both with and without amyloidosis [73]. This indicates that additional factors (perhaps genetic and environmental) must be involved in pathogenesis [74,75], a feature of pathogenesis underscored by the variable incidence of AA amyloidosis complicating hereditary autoinflammatory disorders [76]. Other factors potentially include aberrant degradation of SAA to AA protein [77] and the accumulation of proteolytic cleavage products attributable to specific enzymes (eg, MMP1) in blood and/or tissue [78].

Intrinsic properties — The type and size of the fragments that are formed may also determine both the amyloidogenic potential and the site of tissue deposition [79,80]. Biochemical analysis has shown that smaller fragments are more likely to deposit in the glomeruli, while larger fragments may preferentially deposit in the blood vessels [80]. Cryogenic electron microscopy (CryoEM) studies of AA amyloid fibrils purified from tissue compared with those formed from recombinant peptides

suggest that proteolytic selection may be responsible for the dominance of morphologies more likely to damage tissue [81].

Accelerated deposition — In murine models of amyloidosis, the deposition phase of disease can be greatly accelerated by injection of AEF, an activity that is probably due to the AA fibrils, peptides, and oligomers that provide a template for amyloid deposition and that is transmissible between animals [1,52,82,83]. The relevance of these observations to the role of SAA in inflammation and the induction of AA amyloid in susceptible individuals with inflammatory diseases remains to be determined [52,84].

SUMMARY

●Amyloidosis is a general term that refers to the predominantly extracellular tissue deposition of fibrils composed of low molecular weight subunits (5 to 25 kD) derived from any of more than 30 diverse serum proteins; these proteins have little in common with regard to their primary structure or metabolism. The fibrils have a predominantly antiparallel beta-pleated sheet configuration; they can be identified on biopsy specimens by tinctorial properties that result from the binding of specific dyes, such as Congo red. All forms of amyloidosis are characterized by codeposition of other substances, and cofactors may play a role in amyloid formation. (See 'Introduction' above.)

●Systemic AA amyloid results from the deposition in tissue of serum amyloid A (SAA) protein, which is a major acute phase reactant. SAA proteins may function to increase the affinity of high-density lipoproteins (HDLs) for macrophages and adipocytes during the acute phase response. SAA binds specifically to several ligands, including cholesterol, HDL, calcium, laminin, and heparin/heparan sulfate. (See 'Serum amyloid A protein' above.)

●Common causes of AA amyloidosis are rheumatoid arthritis, chronic infections (particularly in underdeveloped countries), and autoinflammatory disorders. (See 'Pathogenesis of AA amyloidosis' above.)

●The principal pathogenic factors in AA amyloidosis include overproduction of both HDL-associated and lipid-free SAA in both blood and tissue as a consequence of acute and chronic inflammation; proteolytic processing of SAA to AA, which releases the carboxyterminal third of the molecule and which may involve internalization of SAA by macrophages, intracellular proteolysis, and release of amyloidogenic

peptides into the extracellular space; and intrinsic fibrillogenic properties of the molecule (figure 1). (See 'Principal pathogenic factors' above.)

REFERENCES

1. Westermark GT, Fändrich M, Westermark P. AA amyloidosis: pathogenesis and targeted therapy. Annu Rev Pathol 2015; 10:321.
2. Papa R, Lachmann HJ. Secondary, AA, Amyloidosis. Rheum Dis Clin North Am 2018; 44:585.
3. Takase H, Tanaka M, Yamamoto A, et al. Structural requirements of glycosaminoglycans for facilitating amyloid fibril formation of human serum amyloid A. Amyloid 2016; 23:67.
4. Ogawa M, Shintani-Domoto Y, Nagashima Y, et al. Mass spectrometry-based absolute quantification of amyloid proteins in pathology tissue specimens: Merits and limitations. PLoS One 2020; 15:e0235143.
5. Benson MD, Buxbaum JN, Eisenberg DS, et al. Amyloid nomenclature 2020: update and recommendations by the International Society of Amyloidosis (ISA) nomenclature committee. Amyloid 2020; 27:217.
6. Sorić Hosman I, Kos I, Lamot L. Serum Amyloid A in Inflammatory Rheumatic Diseases: A Compendious Review of a Renowned Biomarker. Front Immunol 2020; 11:631299.
7. Sack GH Jr. Serum Amyloid A (SAA) Proteins. Subcell Biochem 2020; 94:421.
8. Frame NM, Gursky O. Structure of serum amyloid A suggests a mechanism for selective lipoprotein binding and functions: SAA as a hub in macromolecular interaction networks. FEBS Lett 2016; 590:866.
9. Lu J, Yu Y, Zhu I, et al. Structural mechanism of serum amyloid A-mediated inflammatory amyloidosis. Proc Natl Acad Sci U S A 2014; 111:5189.
10. Gallo G, Wisniewski T, Choi-Miura NH, et al. Potential role of apolipoprotein-E in fibrillogenesis. Am J Pathol 1994; 145:526.
11. Kisilevsky R, Ancsin JB, Szarek WA, Petanceska S. Heparan sulfate as a therapeutic target in amyloidogenesis: prospects and possible complications. Amyloid 2007; 14:21.
12. Husby G, Stenstad T, Magnus JH, et al. Interaction between circulating amyloid fibril protein precursors and extracellular tissue matrix components in the pathogenesis of systemic amyloidosis. Clin Immunol Immunopathol 1994; 70:2.
13. Tennent GA, Lovat LB, Pepys MB. Serum amyloid P component prevents proteolysis of the amyloid fibrils of Alzheimer disease and systemic amyloidosis. Proc Natl Acad Sci U S A 1995; 92:4299.
14. Pinney JH, Lachmann HJ. Systemic AA amyloidosis. Subcell Biochem 2012; 65:541.
15. Kisilevsky R, Manley PN. Acute-phase serum amyloid A: perspectives on its physiological and pathological roles. Amyloid 2012; 19:5.
16. O'Hara R, Murphy EP, Whitehead AS, et al. Local expression of the serum amyloid A and formyl peptide receptor-like 1 genes in synovial tissue is associated with matrix

metalloproteinase production in patients with inflammatory arthritis. Arthritis Rheum 2004; 50:1788.
17. Wilson PG, Thompson JC, Shridas P, et al. Serum Amyloid A Is an Exchangeable Apolipoprotein. Arterioscler Thromb Vasc Biol 2018; 38:1890.
18. Hu Z, Bang YJ, Ruhn KA, Hooper LV. Molecular basis for retinol binding by serum amyloid A during infection. Proc Natl Acad Sci U S A 2019; 116:19077.
19. Thorn CF, Lu ZY, Whitehead AS. Regulation of the human acute phase serum amyloid A genes by tumour necrosis factor-alpha, interleukin-6 and glucocorticoids in hepatic and epithelial cell lines. Scand J Immunol 2004; 59:152.
20. Ray A, Shakya A, Kumar D, et al. Inflammation-responsive transcription factor SAF-1 activity is linked to the development of amyloid A amyloidosis. J Immunol 2006; 177:2601.
21. Sack GH Jr. Serum amyloid A - a review. Mol Med 2018; 24:46.
22. Sun L, Ye RD. Serum amyloid A1: Structure, function and gene polymorphism. Gene 2016; 583:48.
23. Sipe J. Revised nomenclature for serum amyloid A (SAA). Nomenclature Committee of the International Society of Amyloidosis. Part 2. Amyloid 1999; 6:67.
24. Zhang Y, Zhang J, Sheng H, et al. Acute phase reactant serum amyloid A in inflammation and other diseases. Adv Clin Chem 2019; 90:25.
25. Obici L, Raimondi S, Lavatelli F, et al. Susceptibility to AA amyloidosis in rheumatic diseases: a critical overview. Arthritis Rheum 2009; 61:1435.
26. van der Hilst JC, Yamada T, Op den Camp HJ, et al. Increased susceptibility of serum amyloid A 1.1 to degradation by MMP-1: potential explanation for higher risk of type AA amyloidosis. Rheumatology (Oxford) 2008; 47:1651.
27. Migita K, Agematsu K, Masumoto J, et al. The contribution of SAA1 polymorphisms to Familial Mediterranean fever susceptibility in the Japanese population. PLoS One 2013; 8:e55227.
28. Yashiro M, Furukawa H, Asano T, et al. Serum amyloid A1 (SAA1) gene polymorphisms in Japanese patients with adult-onset Still's disease. Medicine (Baltimore) 2018; 97:e13394.
29. Atoyan S, Hayrapetyan H, Sarkisian T, Ben-Chetrit E. MEFV and SAA1 genotype associations with clinical features of familial Mediterranean fever and amyloidosis in Armenia. Clin Exp Rheumatol 2016; 34:72.
30. van der Westhuyzen DR, de Beer FC, Webb NR. HDL cholesterol transport during inflammation. Curr Opin Lipidol 2007; 18:147.
31. Poitou C, Divoux A, Faty A, et al. Role of serum amyloid a in adipocyte-macrophage cross talk and adipocyte cholesterol efflux. J Clin Endocrinol Metab 2009; 94:1810.
32. Ancsin JB, Kisilevsky R. Characterization of high affinity binding between laminin and the acute-phase protein, serum amyloid A. J Biol Chem 1997; 272:406.
33. Shah C, Hari-Dass R, Raynes JG. Serum amyloid A is an innate immune opsonin for Gram-negative bacteria. Blood 2006; 108:1751.
34. Mullan RH, Bresnihan B, Golden-Mason L, et al. Acute-phase serum amyloid A stimulation of angiogenesis, leukocyte recruitment, and matrix degradation in

rheumatoid arthritis through an NF-kappaB-dependent signal transduction pathway. Arthritis Rheum 2006; 54:105.
35. Lee HY, Kim SD, Shim JW, et al. LL-37 inhibits serum amyloid A-induced IL-8 production in human neutrophils. Exp Mol Med 2009; 41:325.
36. He RL, Zhou J, Hanson CZ, et al. Serum amyloid A induces G-CSF expression and neutrophilia via Toll-like receptor 2. Blood 2009; 113:429.
37. Urieli-Shoval S, Shubinsky G, Linke RP, et al. Adhesion of human platelets to serum amyloid A. Blood 2002; 99:1224.
38. Page MJ, Thomson GJA, Nunes JM, et al. Serum amyloid A binds to fibrin(ogen), promoting fibrin amyloid formation. Sci Rep 2019; 9:3102.
39. Ye RD, Sun L. Emerging functions of serum amyloid A in inflammation. J Leukoc Biol 2015; 98:923.
40. Webb NR. High-Density Lipoproteins and Serum Amyloid A (SAA). Curr Atheroscler Rep 2021; 23:7.
41. Ancsin JB, Kisilevsky R. The heparin/heparan sulfate-binding site on apo-serum amyloid A. Implications for the therapeutic intervention of amyloidosis. J Biol Chem 1999; 274:7172.
42. Vallon R, Freuler F, Desta-Tsedu N, et al. Serum amyloid A (apoSAA) expression is up-regulated in rheumatoid arthritis and induces transcription of matrix metalloproteinases. J Immunol 2001; 166:2801.
43. Migita K, Koga T, Torigoshi T, et al. Serum amyloid A protein stimulates CCL20 production in rheumatoid synoviocytes. Rheumatology (Oxford) 2009; 48:741.
44. Connolly M, Mullan RH, McCormick J, et al. Acute-phase serum amyloid A regulates tumor necrosis factor α and matrix turnover and predicts disease progression in patients with inflammatory arthritis before and after biologic therapy. Arthritis Rheum 2012; 64:1035.
45. Connolly M, Rooney PR, McGarry T, et al. Acute serum amyloid A is an endogenous TLR2 ligand that mediates inflammatory and angiogenic mechanisms. Ann Rheum Dis 2016; 75:1392.
46. Migita K, Koga T, Komori A, et al. Influence of Janus kinase inhibition on interleukin 6-mediated induction of acute-phase serum amyloid A in rheumatoid synovium. J Rheumatol 2011; 38:2309.
47. Lachmann HJ, Goodman HJ, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. N Engl J Med 2007; 356:2361.
48. Bunker D, Gorevic P. AA amyloidosis: Mount Sinai experience, 1997-2012. Mt Sinai J Med 2012; 79:749.
49. Gruys E, Snel FW. Animal models for reactive amyloidosis. Baillieres Clin Rheumatol 1994; 8:599.
50. Landman WJ. Amyloid arthropathy in chickens. Vet Q 1999; 21:78.
51. Sevimli A, Misirlioğlu D, Yağci A, et al. The role of chicken IL-1beta, IL-6 and TNF-alpha in the occurrence of amyloid arthropathy. Vet Res Commun 2008; 32:499.
52. Murakami T, Ishiguro N, Higuchi K. Transmission of systemic AA amyloidosis in animals. Vet Pathol 2014; 51:363.

53. Grateau G. Musculoskeletal disorders in secondary amyloidosis and hereditary fevers. Best Pract Res Clin Rheumatol 2003; 17:929.
54. van der Hilst JC. Recent insights into the pathogenesis of type AA amyloidosis. ScientificWorldJournal 2011; 11:641.
55. Röcken C, Menard R, Bühling F, et al. Proteolysis of serum amyloid A and AA amyloid proteins by cysteine proteases: cathepsin B generates AA amyloid proteins and cathepsin L may prevent their formation. Ann Rheum Dis 2005; 64:808.
56. Kinkley SM, Bagshaw WL, Tam SP, Kisilevsky R. The path of murine serum amyloid A through peritoneal macrophages. Amyloid 2006; 13:123.
57. Patke S, Srinivasan S, Maheshwari R, et al. Characterization of the oligomerization and aggregation of human Serum Amyloid A. PLoS One 2013; 8:e64974.
58. Jayaraman S, Gantz DL, Haupt C, Gursky O. Serum amyloid A forms stable oligomers that disrupt vesicles at lysosomal pH and contribute to the pathogenesis of reactive amyloidosis. Proc Natl Acad Sci U S A 2017; 114:E6507.
59. Westermark GT, Engström U, Westermark P. The N-terminal segment of protein AA determines its fibrillogenic property. Biochem Biophys Res Commun 1992; 182:27.
60. Yamada T, Kluve-Beckerman B, Liepnieks JJ, Benson MD. Fibril formation from recombinant human serum amyloid A. Biochim Biophys Acta 1994; 1226:323.
61. Ray A, Schatten H, Ray BK. Activation of Sp1 and its functional co-operation with serum amyloid A-activating sequence binding factor in synoviocyte cells trigger synergistic action of interleukin-1 and interleukin-6 in serum amyloid A gene expression. J Biol Chem 1999; 274:4300.
62. Lee HY, Kim MK, Park KS, et al. Serum amyloid A stimulates matrix-metalloproteinase-9 upregulation via formyl peptide receptor like-1-mediated signaling in human monocytic cells. Biochem Biophys Res Commun 2005; 330:989.
63. Sjöholm K, Palming J, Olofsson LE, et al. A microarray search for genes predominantly expressed in human omental adipocytes: adipose tissue as a major production site of serum amyloid A. J Clin Endocrinol Metab 2005; 90:2233.
64. Jahangiri A, Wilson PG, Hou T, et al. Serum amyloid A is found on ApoB-containing lipoproteins in obese humans with diabetes. Obesity (Silver Spring) 2013; 21:993.
65. Beridze Vaktangova N, García Moreira V, García Castañón S, et al. AA amyloidosis associated with morbid obesity (clinical case). Reumatol Clin (Engl Ed) 2020; 16:493.
66. Eckhardt ER, Witta J, Zhong J, et al. Intestinal epithelial serum amyloid A modulates bacterial growth in vitro and pro-inflammatory responses in mouse experimental colitis. BMC Gastroenterol 2010; 10:133.
67. Sano T, Huang W, Hall JA, et al. An IL-23R/IL-22 Circuit Regulates Epithelial Serum Amyloid A to Promote Local Effector Th17 Responses. Cell 2015; 163:381.
68. Murdoch CC, Espenschied ST, Matty MA, et al. Intestinal Serum amyloid A suppresses systemic neutrophil activation and bactericidal activity in response to microbiota colonization. PLoS Pathog 2019; 15:e1007381.
69. Lee JY, Hall JA, Kroehling L, et al. Serum Amyloid A Proteins Induce Pathogenic Th17 Cells and Promote Inflammatory Disease. Cell 2020; 183:2036.

70. Shridas P, De Beer MC, Webb NR. High-density lipoprotein inhibits serum amyloid A-mediated reactive oxygen species generation and NLRP3 inflammasome activation. J Biol Chem 2018; 293:13257.
71. Gillmore JD, Lovat LB, Persey MR, et al. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. Lancet 2001; 358:24.
72. Gertz MA, Skinner M, Sipe JD, et al. Serum amyloid A protein and C-reactive protein in systemic amyloidosis. Clin Exp Rheumatol 1985; 3:317.
73. De Beer FC, Mallya RK, Fagan EA, et al. Serum amyloid-A protein concentration in inflammatory diseases and its relationship to the incidence of reactive systemic amyloidosis. Lancet 1982; 2:231.
74. Ajiro J, Narita I, Sato F, et al. SAA1 gene polymorphisms and the risk of AA amyloidosis in Japanese patients with rheumatoid arthritis. Mod Rheumatol 2006; 16:294.
75. Utku U, Dilek M, Akpolat I, et al. SAA1 alpha/alpha alleles in Behçet's disease related amyloidosis. Clin Rheumatol 2007; 26:927.
76. Ombrello AK, Aksentijevich I. AA amyloidosis. In: Amyloid and Related Disorders: Surgical Pathology and Clinical Correlations, Pickens MM (Ed), Springer, 2012. p.31.
77. Kluve-Beckerman B, Liepnieks JJ, Wang L, Benson MD. A cell culture system for the study of amyloid pathogenesis. Amyloid formation by peritoneal macrophages cultured with recombinant serum amyloid A. Am J Pathol 1999; 155:123.
78. Migita K, Eguchi K, Tsukada T, et al. Increased circulating serum amyloid A protein derivatives in rheumatoid arthritis patients with secondary amyloidosis. Lab Invest 1996; 75:371.
79. Westermark GT, Westermark P, Sletten K. Amyloid fibril protein AA. Characterization of uncommon subspecies from a patient with rheumatoid arthritis. Lab Invest 1987; 57:57.
80. Westermark GT, Sletten K, Westermark P. Massive vascular AA-amyloidosis: a histologically and biochemically distinctive subtype of reactive systemic amyloidosis. Scand J Immunol 1989; 30:605.
81. Bansal A, Schmidt M, Rennegarbe M, et al. AA amyloid fibrils from diseased tissue are structurally different from in vitro formed SAA fibrils. Nat Commun 2021; 12:1013.
82. Senthilkumar S, Chang E, Jayakumar R. Diffusible amyloid oligomers trigger systemic amyloidosis in mice. Biochem J 2008; 415:207.
83. Westermark GT, Westermark P. Serum amyloid A and protein AA: molecular mechanisms of a transmissible amyloidosis. FEBS Lett 2009; 583:2685.
84. Gorevic PD. Amyloid and inflammation. Proc Natl Acad Sci U S A 2013; 110:16291.

This generalized information is a limited summary of diagnosis, treatment, and/or medication information. It is not meant to be comprehensive and should be used as a tool to help the user understand and/or assess potential diagnostic and treatment options. It does NOT include all information about conditions, treatments, medications, side effects, or risks

Topic 5619 Version 18.0

CHAPTER 11

Genetic factors in the amyloid diseases

Author:
Peter D Gorevic, MD
Section Editors:
Helen J Lachmann, MA, MB, BChir, MD, FRCP, FRCPath
Benjamin A Raby, MD, MPH
Deputy Editor:
Siobhan M Case, MD, MHS
Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Aug 2023.
This topic last updated: Apr 11, 2022.

INTRODUCTIONAmyloidosis is the general term used to refer to the extracellular tissue deposition of highly ordered fibrils composed of low molecular weight subunits of a variety of proteins, many of which, in their native form, circulate as normal constituents of plasma. Amyloid deposits may result in a wide range of clinical manifestations depending upon their type, location, and amount. In the genesis of amyloid deposits, previously soluble precursor peptides undergo conformational changes that lead to the adoption of a predominantly antiparallel beta-pleated sheet configuration, allowing them to stack as protofilaments in a twisted fibrillar configuration [1-4]. During fibrillogenesis, amyloid P component, apolipoprotein (Apo) E, and glycosaminoglycans contribute to the formation and persistence of amyloid deposits. These components are found in all amyloid deposits, regardless of the protein type, and therefore serve as universal amyloid signatures [5].

At least 38 different human protein precursors of amyloid fibrils are known. Some are produced at the site of amyloid formation (localized amyloid) and some circulate in the blood to deposit in a variety of tissues and organs (systemic amyloidosis). Amyloid has a characteristic gross pathologic and microscopic appearance, demonstrating birefringence under polarized light microscopy of Congo red stained tissue, which may have a typical "apple-green" dichroic appearance [6].

Over 500 variants and polymorphisms have been associated with heritable and acquired forms of amyloidosis, affecting genes for amyloid subunit proteins and

their precursors, proteins implicated in autoinflammatory diseases in which AA amyloid may occur and presenilins (table 1).

The genetic contributions to various types of amyloidosis will be reviewed here. An overview of the amyloidoses, including pathology, fibrillogenesis, clinical manifestations, diagnosis, and therapies, is presented separately, as is a discussion of the genetics of Alzheimer disease (AD). (See "Overview of amyloidosis" and "Genetics of Alzheimer disease".)

TYPES OF GENETIC ABNORMALITIES IN AMYLOIDOSESThe importance of heredity in the amyloid diseases has been recognized for many years [7]; some amyloid disorders appear to be entirely due to heritable abnormalities in precursor proteins and are inherited in an autosomal dominant fashion. In addition, the expression of acquired amyloidoses may also be affected by genetically determined factors. The name "**hereditary**" rather than "familial" is recommended by the International Society of Amyloidosis (ISA) for amyloid diseases associated with mutations in the amyloidogenic protein itself, thereby making it prone to amyloidogenesis. By contrast, in "**familial**" amyloidoses associated with autoinflammatory diseases, the genetic abnormality affects protein(s) involved in modulation of the inflammatory response, which, in turn, creates an environment that is permissive for AA development [8].

Genetic abnormalities that have been identified as contributors to amyloidogenesis include (table 2):

●Sequence variants, which increase the amyloidogenicity of the protein precursor, in some instances by destabilizing a native fold in the molecule and in others by increasing the intrinsic aggregation rate.

●Variants that alter ligand binding or facilitate proteolytic cleavage.

●Sequence variants that cause premature or late stop of translation, facilitating the accumulation of amyloidogenic variants.

●Genetically determined post-translational modifications.

●Variants in genes for non-amyloidogenic proteins can play a role in amyloid development. Examples include variants causing systemic autoinflammatory diseases that may be complicated by acquired AA amyloidosis and presenilin variants in early-onset Alzheimer disease (AD).

Apolipoprotein (Apo) misfolding has a more general role in the pathogenesis of amyloid diseases, as indicated by the observations that both wild-type and variant proteins may form amyloid fibrils, that specific Apo are part of the protein milieu for a variety of types of amyloidosis (as revealed by mass spectroscopy; eg, ApoE, ApoJ, and ApoAIV), and in the growing number of forms of hereditary amyloid (ApoAI, ApoAII, ApoCII, and ApoCIII) that may be causes of early-onset familial disease [9].

AUTOSOMAL DOMINANT HEREDITARY AMYLOIDOSES

Genetic mechanisms — The various autosomal dominant hereditary amyloidoses are typically associated with missense variants, although variants resulting in deletions and stop codons have also been described. The pathogenic point variant usually affects the part of the precursor molecule that is most aggregation prone; the whole precursor protein can be incorporated into the amyloid fibrils, or domains may be eliminated either prior to or after fibril formation [10-12]. Examining the fibrillogenic potential of recombinant proteins or synthetic peptides has demonstrated that the variant is often intrinsically more unstable and fibrillogenic in vitro than the wild-type peptide [13-15]. A resource for the tabulation of variants associated with the systemic hereditary amyloidoses is Mutations in Hereditary Amyloidosis [16,17].

In three forms of hereditary amyloid disease (hereditary British dementia, hereditary Danish dementia, and apolipoprotein [Apo] AII nephropathy), variants at the site of stop codons lead to carboxyterminal extensions that are not expressed by the wild-type protein [18,19]. Fibril subunit proteins may include an aminoterminal portion of the precursor (eg, ApoAI), a carboxyterminal fragment (eg, fibrinogen A-alpha chain), or the entire molecule (eg, transthyretin [TTR]).

Detection of variants — Variant forms of amyloidogenic proteins have been defined serologically, by immunoblot/immunoelectrophoresis, in the past, but these are challenging techniques; mass spectroscopy offers another means of looking for abnormal precursors or metabolic products in blood [20-22]. Genetic testing for the single base substitution characteristic for the particular amyloid disease was usually carried out by directly sequencing the amplified exon of the relevant gene of interest or targeted panels [23].

Transthyretin

Range of genetic variants — Multiple variants have been identified among patients with TTR amyloidosis. The gene for transthyretin (*TTR* or prealbumin), a protein

involved in the **t**ransport of **t**hyroxine and **r**etinol (hence, TTR), is located on chromosome 18. Until now, at least 138 *TTR* variants have been described, including single variants, compound heterozygotes, and deletions. Nomenclature for missense variants due to a single nucleotide change was updated in 2014 to include the 20 amino acid signal peptide [16,17]. One hundred and thirty-three of these variant *TTR* gene products are amyloidogenic; five are classified as "non-amyloidogenic" but include variants that may represent common polymorphisms [24] or that in trans may in fact be protective from developing amyloidosis [25].

Variants have been identified in approximately 60 percent of residues in this 127 amino acid single chain molecule. Thirty-eight residues have more than one substitution associated with disease; these tend to occur at variant hotspots in the DNA sequence and along portions of the molecule known to adopt a beta-pleated sheet configuration from radiograph crystallography of wild-type TTR [26].

One variant, substitution of methionine for threonine at position 119 (T119M), appears to have a stabilizing effect on the TTR tetramer and confers relative protection from development of TTR amyloidosis. Milder disease has been reported in compound heterozygotes for this variant and for another (R104H) known amyloidogenic variant [27,28]. In addition, this substitution appeared to be associated with increased plasma levels of TTR compared with destabilizing variants. In the Copenhagen General Population Study and Copenhagen City Heart Study involving 68,602 participants, 10,636 of whom developed vascular disease, the T119M variant was associated with a decreased incidence of cerebrovascular disease and increased life expectancy [28]. A more recent study involving approximately 500,000 participants enrolled in the United Kingdom Biobank, however, failed to confirm this association [29].

Major TTR amyloidosis phenotypes — Transthyretin (TTR) amyloidosis can present with peripheral and/or autonomic neuropathy, infiltrative cardiomyopathy, vitreous amyloid, or leptomeningeal disease in any combination [30,31]. Some phenotype-genotype correlation is seen, with subgroups of variants associated with a more neuropathic presentation and others with a later-onset cardiac presentation that more closely resembles wild-type TTR amyloidosis [31]. There may also be non-amyloid associations: A registry-based study in Swedish patients with familial amyloid polyneuropathy (FAP) suggested that patients have increased risk for the development of non-Hodgkin lymphoma [32], and some variants may affect the binding of thyroxine (T4) by TTR, resulting in euthyroid hyperthyroidism (eg, TTR Met 119) [33].

●**Peripheral and autonomic neuropathy and central nervous system disease** – The most common phenotype among the amyloidogenic *TTR* variants is peripheral neuropathy, usually a length-dependent sensorimotor polyneuropathy, which may also present as small fiber neuropathy and/or prominently feature carpal tunnel syndrome (CTS) [34]. CTS is specifically identified in 25 variants and may predate cardiomyopathy by many years within kindreds with a mixed phenotype [35]. Autonomic neuropathy (orthostasis, gastrointestinal dysmotility) is clinically significant in 40 variants and is likely subclinical in others [36]. Leptomeningeal amyloidosis has been reported in 10 variants, and other central nervous system (CNS) manifestations (dementia, cerebellar dysfunction with ataxia, or cerebral hemorrhage) have been reported in some variants [37].

●**Cardiomyopathy** – The other main phenotype of TTR amyloidosis is cardiomyopathy, which is present in 106 different variants, and may be the sole organ system involved in 24 [30]. ATTR variant (ATTRv, formerly termed ATTRm, to indicate a mutant protein) cardiomyopathy is notably late onset in several variants (V20I, E42G, Q92K, T60A), making it an important consideration in the diagnosis of cardiomyopathy in older adults [38]. ATTRv is also sometimes known as hereditary ATTR (hATTR). Presentations for ATTR cardiomyopathy include biventricular infiltrative cardiomyopathy, heart failure with preserved ejection fraction, conduction defects (notably atrial fibrillation), and as a concomitant of severe aortic stenosis [39]. (See "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis".)

●**Vitreous amyloid** – Vitreous amyloid, reflecting production of TTR by the retinal epithelium, has been described with 26 variants, may be the presenting and only disease manifestation in 5, and may develop after liver transplantation as a late manifestation of disease [40-42].

Kidney disease may complicate other organ system involvement or be due to deposition of TTR amyloid in the kidney. The latter has been reported for 15 different *TTR* variants but has been best studied among individuals affected by the V30M variant, in whom kidney involvement has been associated with late-onset neuropathy, families with low-penetrance disease, and patients manifesting cardiac arrhythmias [43].

Additionally, occasional patients with a clinical presentation suggesting immunoglobulin light chain (AL) amyloidosis have been identified in whom the amyloid deposits result from hereditary TTR amyloidosis. (See 'Variable penetrance and expressivity in hereditary amyloidosis' below.)

Populations with increased prevalence of certain variants — Certain populations have an increased prevalence of specific variants. Examples include:

●**Portugal, Sweden, Japan, and other regions** – In endemic areas of Portugal, 1 of every 600 people carries the *TTR* variant *TTR* Val30Met that can result in FAP [44]. The same variant is seen in some other countries such as Sweden and Japan [45,46]. In northern Sweden, the carrier frequency is 8.3-fold higher than in Portugal, but with a lower incidence and prevalence of amyloidosis due to a much lower penetrance (5 versus 87 percent) before age 40 [47]. Although haplotype analysis of contiguous *TTR* gene regions in Swedish, French, Portuguese, and Japanese carriers indicates common founders, these phenotypic differences highlight the importance of additional genetic and epigenetic factors in disease expression [48,49]. National FAP registers from Japan, France, and Italy, as well as the TTR Amyloidosis Outcome Survey (THAOS), have provided additional evidence for genetic and phenotypic heterogeneity for both hereditary and wild-type amyloid [50,51].

●**African American, Afro-Caribbean, and West African populations** – Isolated cardiac amyloidosis presenting virtually exclusively as late-onset (age >65) disease is more common in African Americans than White Americans and White Europeans, and 3 to 4 percent of African Americans and some Afro-Caribbean populations are carriers for a potentially amyloidogenic substitution *TTR* Val122Ile. In addition, the carrier rate is >5 percent in some areas of West Africa. Although the prevalence of the Val122Ile variant is relatively high in these populations, it appears to have low penetrance for causing amyloid cardiomyopathy [52-55]. The male:female ratios reported for both wild-type and *TTR* Val122Ile have ranged up to 25:1; the basis for this sex bias remains to be fully explained. Homozygosity is associated with an earlier age of onset and female sex with a later age of onset and a less aggressive disease trajectory [56,57]. (See "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis", section on 'Types of amyloidosis'.)

Gelsolin — The Meretoja syndrome, also referred to as hereditary amyloidosis, Finnish type, results from variants in the gelsolin gene, which is located on chromosome 9 at q33.2; the most prevalent of these variants are associated with a characteristic triad of:

●Lattice corneal dystrophy

●Neuropathy with progressive facial paresis and largely sensory peripheral symptoms

●Cutis laxa

Variants at codon 654 (residue 187) are called Meretoja substitutions, named after the ophthalmologist who first delineated the disease, and occur within the amyloidogenic fragment of gelsolin [11,15,20,58]. Meretoja syndrome is also referred to as familial amyloidosis, Finnish type, because of the striking clustering of the disease in the southern part of this country, where multiple families have been shown to share an ancestral haplotype [59].

The D187N variant has been found in Finnish, Japanese, American, Dutch, Portuguese, British, and Iranian families, and the D187Y variant was found in Danish, Czech, and Brazilian families with this phenotype; both interfere with calcium binding and increase proteolysis by furin to yield amyloidogenic fragments [15,20,60]. Variants at Glu580Lys and Met544Arg have also been described to have the Meretoja phenotype [61,62]. A novel presentation of fever, rash, and anemia with amyloidosis has been associated with an exon 10 variant [63]. Renal amyloid deposition appears common, but renal dysfunction in hereditary gelsolin amyloidosis is rare and has mostly been described in homozygotes; however, two novel variants, G194R and N211K, were reported to be associated with renal amyloidosis in patients without corneal lattice dystrophy or neuropathies [64].

Apolipoprotein AI — Apo amyloidosis may be hereditary or acquired, the latter due to wild-type protein in the senile forms of pathology that may occur in the aorta in association with atherosclerosis or (like wild-type ATTR) in the osteoarthritic joint [65]. ApoAI amyloidosis is the second most common hereditary systemic amyloidosis, and 22 pathogenic variants in the gene, which is located on chromosome 11, have been described, most of which are single amino acid substitutions resulting from point variants; deletions and insertions may also be associated with amyloid deposition [16,23].

Clinical manifestations of ApoAI amyloidosis vary with the location of variant within the approximately 93 residue fragments that form the fibril protein [12]. Variants in the 75 aminoterminal residues manifest as an interstitial and medullary nephropathy (11 variants) and/or as hepatic involvement (5 variants), and may be early or late onset in nature [66]. A deletion at position 107 (Lys 107 del [pLys 131 del]) is strikingly associated with angina and accelerated atherosclerosis. Glu34Lys was found to present with retinal, glomerular, and hepatic involvement, making it amenable to hepatorenal transplantation [65]. Cutaneous amyloid deposits (two variants), cardiomyopathy (seven variants), neuropathy/CTS (four variants), or laryngeal/palatal dysfunction (six variants) are more characteristic of variants

beyond residue 90 and may present as localized amyloid involving the larynx or skin [23,67]. Hot spots for amyloidogenesis include residues 14 to 22 and the 121 to 142 segment that is particularly susceptible to proteolysis [65].

Apolipoprotein AII — Variants in the gene for ApoAII, which is located on chromosome 1, may cause amyloidosis [18,23,68,69]. Four stop-codon variants have been described at residue 78 in exon 4, leading to a 21 residue extension at the C-terminus of the molecule, with full-length mutant ApoAII depositing as amyloid. The clinical phenotype is a slowly progressive renal (glomerular and interstitial amyloid) disease, with other organ system involvement being less prominent.

Apolipoproteins CII and CIII — Rare cases of amyloidosis affecting the kidney have been described due to variants in the genes for apolipoproteins CII and CIII [70,71]. The gene for ApoCII is located on chromosome 19, and the protein is known from previous studies to be able to generate amyloidogenic peptides. In 2017, there was the first report of nodular glomerular and interstitial amyloid associated with a missense variant Glu69Val [70], with the average age of onset of 70; another variant associated with renal amyloidosis has subsequently been reported from the United States (Lys41Thr) [70,72].

The gene for ApoCIII is on chromosome 11q23-24 as part of a gene cluster with ApoAI and ApoAIV. The Asp25Val variant has been found to be markedly fibrillogenic and associated with severe renal amyloidosis and hypotriglyceridemia in a French family [71].

Lysozyme — Nine variants in the lysozyme gene, which is located on chromosome 12, have been associated with several amyloid phenotypes, including sicca syndrome (three out of nine), renal (six out of nine), hepatic/gastrointestinal (six out of nine), and cardiac (three out of nine) amyloid disease of variable onset [13,73,74]. A novel variant in an American family of Swedish ancestry described chronic abdominal pain, diarrhea, weight loss, malabsorption, and sicca syndrome as common manifestations without apparent renal disease [75], and a complex T88N/W130R variant was associated with significant cardiac involvement [76].

Fibrinogen A-alpha — Variants in the fibrinogen alpha chain gene, which is located on chromosome 4, have been associated with a late-onset renal amyloidosis that is strikingly glomerular, without interstitial or vascular involvement; 15 variants have been described, all clustered near the 5' end of exon 5 and resulting in this clinical phenotype. It is the most common cause of hereditary amyloidosis in the United Kingdom (>70 patients reported) [77]. By contrast, a lower incidence has been

reported in the United States [78]. Overall, only 46 percent of patients with fibrinogen alpha amyloidosis (AFib) have a family history, the majority of cases being sporadic. The rate of progression of AFib amyloid is slow compared with AL amyloid but greater than that seen in ApoAI or lysozyme-type amyloid. Additionally, occasional patients with a clinical presentation suggesting AL amyloidosis have been identified in whom the amyloid deposits result from hereditary AFib amyloidosis. (See 'Variable penetrance and expressivity in hereditary amyloidosis' below.)

The progression to end-stage kidney disease from presentation of renal disease is 4.6 years. Similarly, the time to recurrence in a renal allograft is 4.9 to 6.0 years, and the median transplant survival is 7.3 years. Since virtually all fibrinogen is synthesized in the liver, double allograft (liver-kidney) has also been attempted, albeit with significant perioperative morbidity and mortality [78-80]. (See "Renal amyloidosis".)

Cystatin C — One variant has been described in the cystatin gene, which is located on chromosome 20. This variant is associated with massive amyloid angiopathy, cerebral hemorrhage (Icelandic type), and a fatal outcome in the third to fourth decades of life in approximately 50 percent of affected persons [14,81].

Beta-2 microglobulin — Variant forms of the gene beta-2m for beta-2 microglobulin (beta-2m), which is located on chromosome 15, have been identified as a rare cause of hereditary amyloidosis [82,83]. However, most patients with beta-2m amyloidosis have the wild-type form of beta-2m as the major subunit of the amyloid complicating chronic hemo- or peritoneal dialysis. In the latter situation, defective renal clearance in such patients causes persistent high circulating levels. (See "Dialysis-related amyloidosis".)

The hereditary beta-2m amyloidoses include a novel dominantly inherited Asp76Asn variant of beta-2m, described in association with systemic amyloidosis in a French family, in whom it was manifested as gastrointestinal disease, autonomic neuropathy, and sicca syndrome [82]. In these patients, beta-2m levels in blood were normal, and the variant molecule was found to have striking intrinsic amyloidogenicity in vitro. Another amyloidogenic beta2m variant (V27M) was identified in the amyloid of a patient on hemodialysis [83].

Hereditary AL amyloidosis — A hereditary form of immunoglobulin light chain (AL) amyloidosis has been very rarely described, unlike the far more common AL amyloidosis often associated with plasma cell dyscrasias. An extended family,

multiple members of which had progressive renal amyloidosis, has been described in which each affected member was found to have a single point variant in the constant region of the immunoglobulin kappa light chain [84]. These patients had no evidence of plasma cell dyscrasia, and indeed V-kappa peptides identified in the amyloid came from three different subgroups. This is in contradistinction to very rare instances of more than one member of a family being affected by myeloma and/or AL amyloid, where the amyloid subunit protein is clonal and has only a single V-region sequence.

VARIABLE PENETRANCE AND EXPRESSIVITY IN HEREDITARY AMYLOIDOSISClinical features, age at onset, and progression of disease may be uniform among members of the same kindred carrying specific amyloidogenic variants. However, a consistent course is not universal. Rarely, individuals with an amyloidogenic variant (homozygous or heterozygous) may remain relatively asymptomatic or may have late onset or more severe disease [85-90]. Variations in clinical manifestations of disease between different kindreds carrying the same variants suggest an important role for modifier genes and/or possibly environmental factors in disease expression.

As examples:

●**Uniform expression** – As an example of highly consistent clinical phenotypic expression in family members, in a large kindred of persons with Finnish type of hereditary amyloidosis (caused by a variant in the gelsolin gene), early signs of corneal lattice dystrophy were apparent by the third or fourth decade of life. The characteristic facies, due to cranial neuropathy and cutis laxa, most apparent around the eyes, developed progressively in the fifth and sixth decades [91]. (See 'Gelsolin' above.)

●**Variable expression** – The transthyretin (TTR) Met (30) substitution, which accounts for approximately 60 percent of cases of hereditary amyloid polyneuropathy worldwide due to TTR, may have an onset at different ages or with varying clinical presentations when sampled among large groups of affected patients in Portugal, Sweden, or Japan. Haplotype analysis indicates multiple founders responsible for disease in different endemic geographic areas [47,92].

In addition, anticipation of age at onset, with age at onset becoming younger in patients of successive generations, has been described in pedigrees with TTR Met (30) from two high-prevalence areas in Japan [93]. In a study of 77 Swedish families,

potentially higher penetrance has been described when inherited down the maternal rather than the paternal line [47].

Occasional kindreds have been described in which the onset of neuropathy or cardiomyopathy associated with *TTR* variants occurs late in life [47,86,89,94].

Of more interest has been TTR I122, associated with late-onset amyloid cardiomyopathy, which is a common polymorphism virtually, but not entirely, unique to groups with African ancestry [95]. It has been estimated that 3.9 percent of African Americans (ie, 1.3 million people) are carriers for this variant TTR molecule and are, therefore, at risk for the development of cardiac amyloid [94,95]. (See 'Populations with increased prevalence of certain variants' above and "Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis".)

●**Confusion with AL amyloidosis** – Phenotypically, there is a considerable overlap between immunoglobulin light chain (AL) and ATTR variant (ATTRv) amyloidosis, with both being associated with cardiomyopathy and peripheral neuropathy. Moreover, a substantial proportion of patients with ATTR also have monoclonal gammopathy of undetermined significance (MGUS). In one study, 49 percent of patients with cardiac ATTRv amyloidosis were shown to have a concurrent MGUS [96]. Therefore, sporadic cases of hereditary amyloidoses may be confused with AL amyloidosis, a complication of a plasma cell dyscrasia. This was illustrated in a study of 350 patients suspected of having AL amyloidosis by clinical and laboratory findings and the absence of a family history; 34 (9.7 percent) had a mutant gene for an "amyloidogenic" protein, most often involving fibrinogen A-alpha or TTR [77]. The presence of low concentrations of monoclonal immunoglobulins (less than 0.2 g/dL) in 8 of these 34 patients contributed to the misdiagnosis. Recognition of these heritable conditions is important, since treatment for AL amyloidosis (eg, chemotherapy) has no role in the treatment of the hereditary disorders [97]. (See "Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis".)

ROLE OF GENETIC DETERMINANTS OF AA AMYLOIDOSISMultiple genetic factors may influence the expression of AA amyloid. As examples, in early studies, the frequency of amyloid complicating disorders such as leprosy was noted to sometimes vary strikingly between leprosaria [98]; the frequency of AA amyloid complicating juvenile and adult rheumatoid arthritis (RA) and tuberculosis varied between populations [99,100]; and surveys have indicated a higher incidence of AA amyloidosis among patients with RA in Japan and Finland than in the United States [101]. Genetic factors may have relevance to reports of a declining incidence of AA amyloidosis complicating RA in some populations (eg, Finland) and not others (eg,

Japan), as well as varying incidences of subclinical versus clinical disease, and time to develop overt amyloid [102].

AA amyloidosis complicating chronic inflammatory diseases is a useful model to explore additional genetic contributors in amyloidosis as it remains more prevalent than the individual types of hereditary amyloidosis, and the fibril precursor protein, serum amyloid A protein (SAA), shows much less variability than the clonal light chains that form AL amyloidosis.

The genetics of both the underlying inflammatory disorders and the acute phase amyloidogenic protein, SAA, are relevant:

●**Role of genes influencing inflammatory disease rates** – The population prevalence of AA amyloidosis is significantly increased in specific ethnic groups with higher variant carrier rates in genes predisposing to autoinflammatory diseases [103]. For example, carrier rates for *MEFV* variants have been reported in up to 1 in 5 among Armenian individuals, 1 in 6 among the North African Jewish population, 1 in 8 among Iraqi individuals, and 1 in 12 among the Ashkenazi Jewish population [104]. Increased prevalence of certain *MEFV* variants in certain populations has been related to heightened resistance to *Yersinia pestis* [105]. These diseases may rarely present as what has been termed "phenotype 2," in which (usually) renal amyloid is found without any indication of symptoms of periodic fever [106,107]. (See 'AA amyloid and the inherited systemic autoinflammatory diseases' below.)

In a large database of patients with AA amyloidosis evaluated in the United Kingdom Amyloidosis Referral Center in 2007, approximately 9 percent were associated with known autoinflammatory disease, and approximately 6 percent were found to have "idiopathic" AA, occurring in the absence of any apparent underlying inflammatory disease [108]. These observations may also have relevance to the greatly increased incidence of AA as a cause of renal amyloid in Turkey and Armenia, where carrier rates for pathogenic variants in *MEFV* are high, and autoinflammatory diseases such as familial Mediterranean fever (FMF) and Behçet syndrome are quite prevalent [109]. In this study, surprisingly, country of living was the most important factor in developing AA amyloidosis (rather than FMF genotype), and this may suggest a major role for unknown **environmental factors**.

●**Role of *SAA* gene polymorphisms** – The presence of certain alleles of *SAA* can influence disease expression. AA forms by proteolysis from one of two human acute-phase SAA proteins (SAA1 and SAA2), encoded by members of a gene family on

chromosome 11. The *SAA1* gene has five alleles (1.1 to 1.5), and the *SAA2* gene has two (2.1 to 2.2), based on amino acid substitutions at positions 52, 57, and 60 of the molecule for *SAA1* and at position 71 for *SAA2*. (See "Pathogenesis of AA amyloidosis".)

Among European individuals, the incidence of AA amyloid appears to be increased in persons homozygous for the 1.1 allele [110]. By contrast, the 1.1 allele appears to have an inhibitory effect on the development of AA amyloidosis in Japan and East Asia, where homozygosity of the 1.3 allele correlates positively with renal AA, and an additional single nucleotide polymorphism (SNP) at the 5' flanking region of *SAA1* also confers increased risk [111]. *SAA1* gene polymorphisms, consisting of -13T/C SNP in the 5' flanking region and SNPs within exon 3 (2995C/T and 3010C/T polymorphisms) of the *SAA1* gene, were associated with susceptibility to FMF in the Japanese population [112]. Studies from Turkey have shown that the 1.1 allele is a significant risk factor for AA amyloid complicating Behçet syndrome, and an association between the *SAA* 1-13T/C polymorphism and amyloidosis in FMF patients has been found [113,114]. Conversely, the *SAA* 1 beta/beta polymorphism was associated with relative protection against AA amyloidosis in Armenian FMF patients homozygous for *MEFV* M694V [115]. Additional studies are necessary to reconcile these observations and to establish the significance of *SAA* polymorphisms as predictive risk factors for the development of AA amyloidosis in FMF.

●**Non-genetic determinants of AA amyloidosis** – Non-genetic factors, particularly early diagnosis and treatment in the case of the autoinflammatory disorders, affects the risk of development of AA amyloidosis. Historically, AA amyloid was reported to complicate these diseases with frequencies varying from greater than 60 percent in untreated FMF in certain ethnic populations (eg, Turkish people) to 25 percent in the tumor necrosis factor receptor-1 (TNFR1) associated periodic syndrome (TRAPS) and the cryopyrin-associated periodic syndrome (CAPS), and to less than 5 percent in mevalonate kinase deficiency (MKD) [116]. These rates have decreased dramatically with the advent of earlier diagnosis and the availability of highly effective targeted therapies for these disorders. (See 'AA amyloid and the inherited systemic autoinflammatory diseases' below and "The autoinflammatory diseases: An overview".)

Obesity was added as a significant susceptibility factor for idiopathic AA amyloidosis as the list of conditions associated with AA amyloidosis continues to expand [117]. However, no association with an identifiable underlying disease can be seen in up to 19 percent of patients diagnosed with AA amyloidosis [8].

AA AMYLOID AND THE INHERITED SYSTEMIC AUTOINFLAMMATORY DISEASES

Familial Mediterranean fever — AA amyloidosis occurs in patients with familial Mediterranean fever (FMF), where its occurrence is influenced by genetic factors that influence the development of FMF itself and of amyloidosis in the patients with FMF, but most importantly, by the timing and effectiveness of treatment for the autoinflammatory disorder. FMF is characterized by recurrent episodes of painful serositis associated with fever and sometimes arthritis, typically lasting two to four days. The responsible molecule is pyrin, a neutrophil, mononuclear, and dendritic cell-specific protein that has an important role in regulation of apoptosis and inflammation [118-120]. Pyrin is encoded by a single gene (*MEFV*) on chromosome 16p. Amyloid in these patients typically presents as nephropathy, which may follow a period of active disease (phenotype 1) or which may be the apparent presenting manifestation (phenotype 2) [107,121,122]. FMF and the genetics of FMF itself are discussed in more detail separately. (See 'Role of genetic determinants of AA amyloidosis' above and "Clinical manifestations and diagnosis of familial Mediterranean fever", section on 'Long-term complications' and "Familial Mediterranean fever: Epidemiology, genetics, and pathogenesis".)

The prevalence of specific *MEFV* variants (particularly homozygous M694V) correlates positively with the incidence and severity of disease and AA amyloid in some populations [109,123-126]. It is important to note that severe disease and AA amyloidosis can occur in a variety of genotypes, and variability in expression of the same variant between populations, and even within families, suggests a significant effect for environment and other genes [127]. Several modifying genetic factors influence disease expression, including male sex, *SAA1* polymorphisms, and major histocompatibility complex class 1-related gene A [128,129]. (See "Familial Mediterranean fever: Epidemiology, genetics, and pathogenesis".)

The most frequent variant associated with amyloidosis in some (but not all) studies is homozygous M694V, followed by M690I/M694V compound and M694V heterozygous genotypes [130,131]. R202Q and M680I may also be associated. *MEFV* M694V homozygosity is also associated with more severe disease and poor responsiveness to colchicine.

Variants at positions M680 and M694 are associated with earlier onset of FMF, with more severe disease, and with an increased incidence of AA amyloidosis in all ethnic groups; homozygosity for the M694V variant is significantly associated with phenotype 2 presentation of AA amyloidosis. Phenotype 2 presents as AA amyloidosis in an otherwise asymptomatic individual with *MEFV* genetics consistent

with FMF and/or a family history of FMF. AA amyloidosis has also been described in a typical dominant disease in association with an M694del variant in White Northern European patients, and 3 T577 variants in British, Turkish, and Dutch patients [132].

Tumor necrosis factor receptor-1 associated periodic syndrome — The tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS) is a dominantly inherited disease characterized by recurrent febrile episodes lasting one to four weeks, serositis, myalgia, rash, and periorbital edema; muscle and fascia may be inflamed. It can be complicated by AA amyloidosis. The relevant gene (*TNFR1*) has been mapped to chromosome 12. TRAPS and its genetics and pathogenesis are discussed in detail separately. (See "Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS)".)

AA amyloid may complicate TRAPS with an estimated prevalence of 14 to 25 percent, with considerable variability between families [133]. Variants affecting cysteine residues are accompanied by a higher risk for amyloid than non-cysteine variants [134,135]. Two familial cases of severe amyloidosis were associated with a non-cysteine variant T50M. Homozygous SAA1.1 is also significantly associated with AA amyloidosis in TRAPS patients. (See "Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS)", section on 'Secondary (AA) amyloidosis'.)

Cryopyrin-associated periodic syndromes — AA amyloidosis can occur as a complication of cryopyrin-associated periodic syndromes (CAPS), which are characterized by periodic fever, urticaria, arthralgia, and deafness with variable degrees of chronic meningitis and joint involvement. Mild to mid-spectrum CAPS is transmitted as an autosomal dominant trait. The disease is due to variants in the cryopyrin gene (*NLRP3*) on chromosome 1q44 [136]. Variants in this gene are also associated with the severe CAPS phenotypes of neonatal multisystem inflammatory disease (NOMID)/chronic infantile neurologic, cutaneous, and articular (CINCA) syndromes that are generally sporadic diseases due to de novo variant. Broad spectrum of disease and variable age of onset relate in part to a significant incidence of somatic mosaicism. CAPS and its genetics and pathogenesis are described in detail separately. (See "Cryopyrin-associated periodic syndromes and related disorders", section on 'Cryopyrin-associated periodic syndromes'.)

The incidence of AA amyloid has been reported to be approximately 25 percent in Muckle-Wells syndrome (MWS), approximately 20 percent in CINCA/NOMID, and approximately 2 percent in familial cold autoinflammatory syndrome (FCAS). Heterozygosity for both V198M and R260W was found in one MWS family. An

N475K knock-in mouse recapitulated CAPS and developed amyloid. Cryopyrinopathies are responsive to treatment with interleukin 1 receptor antagonist (IL-1ra) and other IL-1-beta antagonists [137]. (See "Cryopyrin-associated periodic syndromes and related disorders", section on 'Cryopyrin-associated periodic syndromes' and "Cryopyrin-associated periodic syndromes and related disorders", section on 'Treatment of cryopyrinopathies'.)

Mevalonate kinase deficiency — Mevalonate kinase deficiency (MKD), which is also known as hyper-immunoglobulin D (IgD) syndrome (HIDS) in its less severe form, is an autosomal recessive hereditary disease associated with variants in the mevalonate kinase (*MVK*) gene on chromosome 12 and may be rarely (2 to 4 percent) associated with AA amyloidosis [138]. MKD is considered a pyrin inflammasomopathy because of the effect of variants on the pyrin regulatory factor RhoA [115]. The genetics and pathophysiology of HIDS and related conditions and its clinical manifestations are discussed in detail separately. (See "Hyperimmunoglobulin D syndrome: Pathophysiology" and "Hyperimmunoglobulin D syndrome: Clinical manifestations and diagnosis".)

In a review of 114 cases of MKD, AA amyloidosis was found in 5 patients, significantly associated with V377I/I268T compound heterozygosity [139]. In a review of 20 cases of AA complicating MKD, 18 were compound heterozygotes [140]. (See "Autoinflammatory diseases mediated by inflammasomes and related IL-1 family cytokines (inflammasomopathies)", section on 'Hyperimmunoglobulin D syndrome'.)

Coexpression of allelic variants of different autoinflammatory diseases and AA amyloidosis — Allelic variants of two different autoinflammatory diseases may co-associate in some patients presenting with an autoinflammatory disease phenotype, and low penetrance allelic variants have been identified with apparent increased frequency among patients with AA amyloidosis with the advent of whole genome sequencing [141-143].

OCULAR AMYLOIDSAmyloidosis of the eye may be an organ-specific manifestation of a systemic disease or may be localized to this organ; examples of the former include lattice dystrophy type II in familial amyloidosis, Finnish type, due to mutant gelsolin [15,20,91], and amyloidosis, which may be a prominent feature among some kindred associated with mutant transthyretin (TTR) molecules and retinal amyloid with apolipoprotein (Apo) AI variants [17,42,65].

Various phenotypes of corneal amyloidosis occur [144-147]. These phenotypes have been related to variants of gelsolin in lattice corneal dystrophy, type 3, as seen in familial amyloidosis, Finnish type (see 'Gelsolin' above); and to 28 variants of the tumor-associated calcium signal transducer 2 (*TACSTD2*) gene on chromosome 1 in gelatinous drop dystrophy. Additionally, they can present as a result of >50 variants of a gene product variously called keratoepithelin, transforming growth factor beta-induced protein (TGFB1), or BIGH3 on chromosome 5 in lattice corneal dystrophy type 1, granular corneal dystrophies (GCD) type 1 (characterized by amorphous aggregates), GCD type 2 (characterized by a combination of amyloid and amorphous aggregates), and Thiel-Behnke corneal dystrophy (TBCD; in which curly fibers form in the superficial corneal stroma).

LOCALIZED AMYLOIDS ASSOCIATED WITH GENETIC DISORDERSThere are a number of genetic diseases that manifest organ-specific or localized amyloids. These include Alzheimer disease (AD) (see "Genetics of Alzheimer disease"), hereditary cerebral hemorrhage with amyloidosis (HCHWA) syndromes (cystatin C, Bri2), and the lattice corneal dystrophies (see 'Autosomal dominant hereditary amyloidoses' above and 'Ocular amyloids' above). Additional examples include amyloid due to calcitonin associated with medullary carcinoma of the thyroid [148] and cutaneous lichen amyloidosis, associated with familial medullary carcinoma of the thyroid and multiple endocrine neoplasia syndrome 2A (MEN2A) [149-151]. Hypertrichosis of the scalp with amyloid deposition has been associated with nonsense variants of the *CDSN* gene encoding corneodesmosin on chromosome 6; these variants occur in the middle of the coding region, resulting in a truncated protein that is aggregation-prone [152,153].

Dysferlin-deficient muscular dystrophy and anoctamin 5 muscular dystrophy may both be associated with skeletal muscle amyloid deposits, as well as cardiomyopathy with delayed enhancement on cardiac magnetic resonance imaging (MRI) [154]; these conditions are discussed separately. (See "Musculoskeletal manifestations of amyloidosis", section on 'Dysferlin-deficient muscular dystrophy' and "Musculoskeletal manifestations of amyloidosis", section on 'Anoctamin 5 muscular dystrophy'.)

ALZHEIMER DISEASE AND ALZHEIMER AMYLOID PRECURSOR PROTEINMore than 50 variants have been identified within the Alzheimer amyloid precursor protein gene (*APP*) from over 100 families with early-onset Alzheimer disease (AD) [155-158]. *APP* is located on chromosome 21 (21q21.3). The genetics of AD, including the

role of the *APP* gene, presenilins, and apolipoprotein (Apo) E, are reviewed in detail separately. (See "Genetics of Alzheimer disease".)

Variants that have been associated with early-onset or familial cases of AD can occur in the gene for amyloid precursor protein (APP) that cluster within the amyloidogenic Alzheimer beta protein (A-beta) sequence [155,159]. In these cases, it is assumed that diversion of APP processing to an amyloid-producing pathway is the primary mechanism leading to accumulation of fibrillogenic A-beta peptides at the sites of pathology. Striking cerebrovascular amyloidosis has been associated with point mutations in the coding sequence of the A-beta protein sequence, as well as familial British dementia and familial Danish dementia (ABri2-related dementias), hereditary cerebral hemorrhage with amyloidosis of Icelandic type due to a mutation of the cystatin C gene (ACys), transthyretin amyloid (ATTR), and prion protein amyloidosis (APrP) [160].

SUMMARY

●**Amyloid formation** – Amyloidosis is a generic term that refers to the extracellular tissue deposition of fibrils that are insoluble polymers comprised of low molecular weight subunit proteins. These subunits are derived from soluble precursors, which undergo conformational changes that lead to the adoption of a predominantly antiparallel beta-pleated sheet configuration. Some amyloid disorders appear to be entirely due to heritable abnormalities in precursor proteins that render them intrinsically unstable, and the expression of acquired amyloidosis may be affected by genetically determined factors (table 1). (See 'Introduction' above.)

●**Types of genetic abnormalities in amyloidogenic proteins** – Three types of genetic abnormalities have been identified in amyloidogenic proteins: polymorphisms, which are relatively frequent in specific populations; rare gene variants (eg, missense variants, deletions, and premature stop codons); and genetically determined post-translational modifications. In addition, variants in genes for non-amyloidogenic proteins can play a permissive role in amyloid development. (See 'Genetic mechanisms' above.)

●**Autosomal dominant hereditary amyloidoses** – Among the familial diseases associated with missense variants, the point variant that correlates with clinical disease usually occurs in the part of the precursor molecule that actually forms the fibril subunit protein; other precursor domains may be eliminated by metabolism or may be digested away prior to or after fibril formation. Subunit protein variants associated with genetic amyloidoses may occur in genes for transthyretin (TTR),

gelsolin, apolipoprotein (Apo) AI, ApoAII, fibrinogen A-alpha chain, lysozyme, beta-2 microglobulin (beta-2m), and cystatin C. (See 'Autosomal dominant hereditary amyloidoses' above.)

●**Variable disease expression** – Clinical features, age at onset, and progression of disease may be uniform among members of a kindred carrying specific amyloidogenic variants. However, a uniform course is not universal. Rarely, individuals with an amyloidogenic variant (homozygous or heterozygous) may remain relatively asymptomatic, may have late-onset disease, or may have more severe disease. Variations in clinical manifestations between different kindreds carrying the same variants suggest an important role for modifier genes and/or possibly environmental factors in disease expression. (See 'Variable penetrance and expressivity in hereditary amyloidosis' above.)

●**AA amyloidosis**

•**Complicating chronic infectious and systemic rheumatic disorders and related conditions** – The frequency of AA amyloid complicating disorders such as leprosy, juvenile and adult rheumatoid arthritis (RA), and tuberculosis varies considerably between populations. Additional studies are necessary to reconcile these observations and to establish the significance of serum amyloid A (*SAA*) polymorphisms as predictive risk factors for the development of AA amyloid. (See 'Role of genetic determinants of AA amyloidosis' above.)

•**Complicating hereditary autoinflammatory diseases** – AA amyloid complicates hereditary autoinflammatory diseases with varying frequencies: familial Mediterranean fever (FMF), tumor necrosis factor receptor-1 (TNFR1) associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS), and, rarely, mevalonate kinase deficiency (MKD). (See 'AA amyloid and the inherited systemic autoinflammatory diseases' above.)

●**Organ-specific and localized disease** – Genetic forms of amyloidosis affecting the eye or skin may be an organ-specific manifestation of a systemic disease or may be localized to these organs. (See 'Ocular amyloids' above.)

●**Alzheimer disease** – Numerous variants have been found to affect the Alzheimer amyloid precursor protein gene (*APP*) and the presenilin genes, which play a role in Alzheimer disease (AD). The genetics of AD are reviewed in detail separately. (See "Genetics of Alzheimer disease".)

REFERENCES

1. Bustamante JG, Zaidi SRH. Amyloidosis. In: StatPearls, StatPearls Publishing, 2020.
2. Kundu D, Prerna K, Chaurasia R, et al. Advances in protein misfolding, amyloidosis and its correlation with human diseases. 3 Biotech 2020; 10:193.
3. Ke PC, Zhou R, Serpell LC, et al. Half a century of amyloids: past, present and future. Chem Soc Rev 2020; 49:5473.
4. Muchtar E, Dispenzieri A, Magen H, et al. Systemic amyloidosis from A (AA) to T (ATTR): a review. J Intern Med 2021; 289:268.
5. Misra P, Blancas-Mejia LM, Ramirez-Alvarado M. Mechanistic Insights into the Early Events in the Aggregation of Immunoglobulin Light Chains. Biochemistry 2019; 58:3155.
6. Yakupova EI, Bobyleva LG, Vikhlyantsev IM, Bobylev AG. Congo Red and amyloids: history and relationship. Biosci Rep 2019; 39.
7. Thomas PK. Genetic factors in amyloidosis. J Med Genet 1975; 12:317.
8. Ombrello AK, Aksentijevich I. AA amyloidosis. In: Amyloid and Related Disorders: Surgical Pathology and Clinical Correlations, 2nd ed, Picken MM, Herrera GA, Dogan A (Eds), Springer International Publishing, 2015. p.31.
9. Jeraj N, Hegele RA, Berberich AJ. Apolipoprotein genetic variants and hereditary amyloidosis. Curr Opin Lipidol 2021; 32:132.
10. Marcoux J, Mangione PP, Porcari R, et al. A novel mechano-enzymatic cleavage mechanism underlies transthyretin amyloidogenesis. EMBO Mol Med 2015; 7:1337.
11. Huff ME, Balch WE, Kelly JW. Pathological and functional amyloid formation orchestrated by the secretory pathway. Curr Opin Struct Biol 2003; 13:674.
12. Das M, Gursky O. Amyloid-Forming Properties of Human Apolipoproteins: Sequence Analyses and Structural Insights. Adv Exp Med Biol 2015; 855:175.
13. Moraitakis G, Goodfellow JM. Simulations of human lysozyme: probing the conformations triggering amyloidosis. Biophys J 2003; 84:2149.
14. Calero M, Pawlik M, Soto C, et al. Distinct properties of wild-type and the amyloidogenic human cystatin C variant of hereditary cerebral hemorrhage with amyloidosis, Icelandic type. J Neurochem 2001; 77:628.
15. Maury CP, Nurmiaho-Lassila EL, Boysen G, Liljeström M. Fibrillogenesis in gelsolin-related familial amyloidosis. Amyloid 2003; 10 Suppl 1:21.
16. Rowczenio DM, Noor I, Gillmore JD, et al. Online registry for mutations in hereditary amyloidosis including nomenclature recommendations. Hum Mutat 2014; 35:E2403.
17. Connors LH, Lim A, Prokaeva T, et al. Tabulation of human transthyretin (TTR) variants, 2003. Amyloid 2003; 10:160.
18. Yazaki M, Liepnieks JJ, Barats MS, et al. Hereditary systemic amyloidosis associated with a new apolipoprotein AII stop codon mutation Stop78Arg. Kidney Int 2003; 64:11.

19. Ghiso J, Vidal R, Rostagno A, et al. A newly formed amyloidogenic fragment due to a stop codon mutation causes familial British dementia. Ann N Y Acad Sci 2000; 903:129.
20. Maury CP, Sletten K, Totty N, et al. Identification of the circulating amyloid precursor and other gelsolin metabolites in patients with G654A mutation in the gelsolin gene (Finnish familial amyloidosis): pathogenetic and diagnostic implications. Lab Invest 1997; 77:299.
21. Nepomuceno AI, Mason CJ, Muddiman DC, et al. Detection of genetic variants of transthyretin by liquid chromatography-dual electrospray ionization fourier-transform ion-cyclotron-resonance mass spectrometry. Clin Chem 2004; 50:1535.
22. Altland K, Benson MD, Costello CE, et al. Genetic microheterogeneity of human transthyretin detected by IEF. Electrophoresis 2007; 28:2053.
23. Benson MD. The hereditary amyloidoses. In: Amyloid and Related Disorders: Surgical Pathology and Clinical Correlations, Springer, 2012. p.53.
24. Jacobson DR, Alves IL, Saraiva MJ, et al. Transthyretin Ser 6 gene frequency in individuals without amyloidosis. Hum Genet 1995; 95:308.
25. Hammarström P, Schneider F, Kelly JW. Trans-suppression of misfolding in an amyloid disease. Science 2001; 293:2459.
26. Sekijima, Y, Yoshida, et al. Familial Transthyretin Amyloidosis. In: Gene Reviews, Pagon, RA, Bird, TC, Dolan, CR, Stephens, K (Eds), University of Washington, Seattle 2010.
27. Almeida MR, Alves IL, Terazaki H, et al. Comparative studies of two transthyretin variants with protective effects on familial amyloidotic polyneuropathy: TTR R104H and TTR T119M. Biochem Biophys Res Commun 2000; 270:1024.
28. Hornstrup LS, Frikke-Schmidt R, Nordestgaard BG, Tybjærg-Hansen A. Genetic stabilization of transthyretin, cerebrovascular disease, and life expectancy. Arterioscler Thromb Vasc Biol 2013; 33:1441.
29. Parker MM, Ticau S, Butler J, et al. Transthyretin-stabilising mutation T119M is not associated with protection against vascular disease or death in the UK Biobank. Amyloid 2020; 27:184.
30. Manganelli F, Fabrizi GM, Luigetti M, et al. Hereditary transthyretin amyloidosis overview. Neurol Sci 2022; 43:595.
31. Benson MD, Dasgupta NR, Rao R. Diagnosis and Screening of Patients with Hereditary Transthyretin Amyloidosis (hATTR): Current Strategies and Guidelines. Ther Clin Risk Manag 2020; 16:749.
32. Hemminki K, Li X, Försti A, et al. Non-Hodgkin lymphoma in familial amyloid polyneuropathy patients in Sweden. Blood 2013; 122:458.
33. Alves IL, Divino CM, Schussler GC, et al. Thyroxine binding in a TTR Met 119 kindred. J Clin Endocrinol Metab 1993; 77:484.
34. Kaku M, Berk JL. Neuropathy Associated with Systemic Amyloidosis. Semin Neurol 2019; 39:578.

35. Aus dem Siepen F, Hein S, Prestel S, et al. Carpal tunnel syndrome and spinal canal stenosis: harbingers of transthyretin amyloid cardiomyopathy? Clin Res Cardiol 2019; 108:1324.
36. Palma JA, Gonzalez-Duarte A, Kaufmann H. Orthostatic hypotension in hereditary transthyretin amyloidosis: epidemiology, diagnosis and management. Clin Auton Res 2019; 29:33.
37. Kleefeld F, Knebel F, Eurich D, et al. Familial Oculo-Leptomeningeal Transthyretin Amyloidosis Caused by Leu55Arg Mutation. J Neuromuscul Dis 2020; 7:515.
38. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)* cardiac amyloidosis: an age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. Genet Med 2017; 19:733.
39. Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement From the American Heart Association. Circulation 2020; 142:e7.
40. Gorevic PD, Rodrigues MM, Spencer WH, et al. Prealbumin. A major constituent of vitreous amyloid. Ophthalmology 1987; 94:792.
41. Liepnieks JJ, Phan AD, Wise RJ, et al. Biochemical characterization of vitreous amyloid formed after liver transplantation. Amyloid 2016; 23:136.
42. Dammacco R, Merlini G, Lisch W, et al. Amyloidosis and Ocular Involvement: an Overview. Semin Ophthalmol 2020; 35:7.
43. Lobato L, Rocha A. Transthyretin amyloidosis and the kidney. Clin J Am Soc Nephrol 2012; 7:1337.
44. Inês M, Coelho T, Conceição I, et al. Epidemiology of Transthyretin Familial Amyloid Polyneuropathy in Portugal: A Nationwide Study. Neuroepidemiology 2018; 51:177.
45. Kato-Motozaki Y, Ono K, Shima K, et al. Epidemiology of familial amyloid polyneuropathy in Japan: Identification of a novel endemic focus. J Neurol Sci 2008; 270:133.
46. Hellman U, Suhr O. Regional differences and similarities of FAP in Sweden. Amyloid 2012; 19 Suppl 1:53.
47. Hellman U, Alarcon F, Lundgren HE, et al. Heterogeneity of penetrance in familial amyloid polyneuropathy, ATTR Val30Met, in the Swedish population. Amyloid 2008; 15:181.
48. Olsson M, Norgren N, Obayashi K, et al. A possible role for miRNA silencing in disease phenotype variation in Swedish transthyretin V30M carriers. BMC Med Genet 2010; 11:130.
49. De Lillo A, Pathak GA, De Angelis F, et al. Epigenetic profiling of Italian patients identified methylation sites associated with hereditary transthyretin amyloidosis. Clin Epigenetics 2020; 12:176.
50. Coelho T, Maurer MS, Suhr OB. THAOS - The Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. Curr Med Res Opin 2013; 29:63.

51. Parman Y, Adams D, Obici L, et al. Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. Curr Opin Neurol 2016; 29 Suppl 1:S3.
52. Quarta CC, Buxbaum JN, Shah AM, et al. The amyloidogenic V122I transthyretin variant in elderly black Americans. N Engl J Med 2015; 372:21.
53. Jacobson DR, Alexander AA, Tagoe C, et al. The prevalence and distribution of the amyloidogenic transthyretin (TTR) V122I allele in Africa. Mol Genet Genomic Med 2016; 4:548.
54. Damrauer SM, Chaudhary K, Cho JH, et al. Association of the V122I Hereditary Transthyretin Amyloidosis Genetic Variant With Heart Failure Among Individuals of African or Hispanic/Latino Ancestry. JAMA 2019; 322:2191.
55. Agbor-Etang BB, Okafor HE, Farber-Eger EH, Wells QS. Low Prevalence of Clinically Apparent Cardiac Amyloidosis Among Carriers of Transthyretin V122I Variant in a Large Electronic Medical Record. Am J Med 2021; 134:e98.
56. Reddi HV, Jenkins S, Theis J, et al. Homozygosity for the V122I mutation in transthyretin is associated with earlier onset of cardiac amyloidosis in the African American population in the seventh decade of life. J Mol Diagn 2014; 16:68.
57. Batra J, Rosenblum H, Defilippis EM, et al. Sex Differences in the Phenotype of Transthyretin Cardiac Amyloidosis Due to Val122Ile Mutation: Insights from Noninvasive Pressure-Volume Analysis. J Card Fail 2021; 27:67.
58. Kiuru-Enari S, Haltia M. Hereditary gelsolin amyloidosis. Handb Clin Neurol 2013; 115:659.
59. Mustonen T, Schmidt EK, Valori M, et al. Common origin of the gelsolin gene variant in 62 Finnish AGel amyloidosis families. Eur J Hum Genet 2018; 26:117.
60. Zorgati H, Larsson M, Ren W, et al. The role of gelsolin domain 3 in familial amyloidosis (Finnish type). Proc Natl Acad Sci U S A 2019; 116:13958.
61. Potrč M, Volk M, de Rosa M, et al. Clinical and Histopathological Features of Gelsolin Amyloidosis Associated with a Novel GSN Variant p.Glu580Lys. Int J Mol Sci 2021; 22.
62. Cabral-Macias J, Garcia-Montaño LA, Pérezpeña-Díazconti M, et al. Clinical, histopathological, and in silico pathogenicity analyses in a pedigree with familial amyloidosis of the Finnish type (Meretoja syndrome) caused by a novel gelsolin mutation. Mol Vis 2020; 26:345.
63. Oregel KZ, Shouse GP, Oster C, et al. Atypical Presentation of Gelsolin Amyloidosis in a Man of African Descent with a Novel Mutation in the Gelsolin Gene. Am J Case Rep 2018; 19:374.
64. Efebera YA, Sturm A, Baack EC, et al. Novel gelsolin variant as the cause of nephrotic syndrome and renal amyloidosis in a large kindred. Amyloid 2014; 21:110.
65. Gursky O. Novel clinical manifestations and treatment of hereditary apoA-I amyloidosis: when a good protein turns bad. Kidney Int 2020; 98:62.

66. Obici L, Palladini G, Giorgetti S, et al. Liver biopsy discloses a new apolipoprotein A-I hereditary amyloidosis in several unrelated Italian families. Gastroenterology 2004; 126:1416.
67. Rowczenio D, Dogan A, Theis JD, et al. Amyloidogenicity and clinical phenotype associated with five novel mutations in apolipoprotein A-I. Am J Pathol 2011; 179:1978.
68. Magy N, Liepnieks JJ, Yazaki M, et al. Renal transplantation for apolipoprotein AII amyloidosis. Amyloid 2003; 10:224.
69. Benson MD. Ostertag revisited: the inherited systemic amyloidoses without neuropathy. Amyloid 2005; 12:75.
70. Nasr SH, Dasari S, Hasadsri L, et al. Novel Type of Renal Amyloidosis Derived from Apolipoprotein-CII. J Am Soc Nephrol 2017; 28:439.
71. Valleix S, Verona G, Jourde-Chiche N, et al. D25V apolipoprotein C-III variant causes dominant hereditary systemic amyloidosis and confers cardiovascular protective lipoprotein profile. Nat Commun 2016; 7:10353.
72. Sethi S, Dasari S, Plaisier E, et al. Apolipoprotein CII Amyloidosis Associated With p.Lys41Thr Mutation. Kidney Int Rep 2018; 3:1193.
73. Röcken C, Becker K, Fändrich M, et al. ALys amyloidosis caused by compound heterozygosity in exon 2 (Thr70Asn) and exon 4 (Trp112Arg) of the lysozyme gene. Hum Mutat 2006; 27:119.
74. Sattianayagam PT, Gibbs SD, Rowczenio D, et al. Hereditary lysozyme amyloidosis -- phenotypic heterogeneity and the role of solid organ transplantation. J Intern Med 2012; 272:36.
75. Girnius S, Skinner M, Spencer B, et al. A new lysozyme tyr54asn mutation causing amyloidosis in a family of Swedish ancestry with gastrointestinal symptoms. Amyloid 2012; 19:182.
76. Sperry BW, Dispenzieri A, Ikram A, et al. Complex p.T88N/W130R mutation in the lysozyme gene leading to hereditary lysozyme amyloidosis with biopsy-proven cardiac involvement. Amyloid 2017; 24:60.
77. Lachmann HJ, Booth DR, Booth SE, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. N Engl J Med 2002; 346:1786.
78. Zhen DB, Swiecicki PL, Zeldenrust SR, et al. Frequencies and geographic distributions of genetic mutations in transthyretin- and non-transthyretin-related familial amyloidosis. Clin Genet 2015; 88:396.
79. Gillmore JD, Lachmann HJ, Wechalekar A, Hawkins PN. Hereditary fibrinogen A alpha-chain amyloidosis: clinical phenotype and role of liver transplantation. Blood 2010; 115:4313; author reply 4314.
80. Haidinger M, Werzowa J, Kain R, et al. Hereditary amyloidosis caused by R554L fibrinogen Aα-chain mutation in a Spanish family and review of the literature. Amyloid 2013; 20:72.
81. Palsdottir A, Snorradottir AO, Thorsteinsson L. Hereditary cystatin C amyloid angiopathy: genetic, clinical, and pathological aspects. Brain Pathol 2006; 16:55.

82. Valleix S, Gillmore JD, Bridoux F, et al. Hereditary systemic amyloidosis due to Asp76Asn variant β2-microglobulin. N Engl J Med 2012; 366:2276.
83. Mizuno H, Hoshino J, So M, et al. Dialysis-related amyloidosis associated with a novel β2-microglobulin variant. Amyloid 2021; 28:42.
84. Benson MD, Liepnieks JJ, Kluve-Beckerman B. Hereditary systemic immunoglobulin light-chain amyloidosis. Blood 2015; 125:3281.
85. Augustin S, Llige D, Andreu A, et al. Familial amyloidosis in a large Spanish kindred resulting from a D38V mutation in the transthyretin gene. Eur J Clin Invest 2007; 37:673.
86. Kristen AV, Ehlermann P, Helmke B, et al. Transthyretin valine-94-alanine, a novel variant associated with late-onset systemic amyloidosis with cardiac involvement. Amyloid 2007; 14:283.
87. Maurer MS, Hanna M, Grogan M, et al. Genotype and Phenotype of Transthyretin Cardiac Amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). J Am Coll Cardiol 2016; 68:161.
88. Holmgren G, Hellman U, Lundgren HE, et al. Impact of homozygosity for an amyloidogenic transthyretin mutation on phenotype and long term outcome. J Med Genet 2005; 42:953.
89. Sequeiros J, Saraiva MJ. Onset in the seventh decade and lack of symptoms in heterozygotes for the TTRMet30 mutation in hereditary amyloid neuropathy-type I (Portuguese, Andrade). Am J Med Genet 1987; 27:345.
90. Koike H, Sobue G. Late-onset familial amyloid polyneuropathy in Japan. Amyloid 2012; 19 Suppl 1:55.
91. Kiuru S. Gelsolin-related familial amyloidosis, Finnish type (FAF), and its variants found worldwide. Amyloid 1998; 5:55.
92. Zaros C, Genin E, Hellman U, et al. On the origin of the transthyretin Val30Met familial amyloid polyneuropathy. Ann Hum Genet 2008; 72:478.
93. Misu K, Hattori N, Ando Y, et al. Anticipation in early- but not late-onset familial amyloid polyneuropathy (TTR met 30) in Japan. Neurology 2000; 55:451.
94. Jacobson DR, Pastore RD, Yaghoubian R, et al. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans. N Engl J Med 1997; 336:466.
95. Cappelli F, Frusconi S, Bergesio F, et al. The Val142Ile transthyretin cardiac amyloidosis: not only an Afro-American pathogenic variant? A single-centre Italian experience. J Cardiovasc Med (Hagerstown) 2016; 17:122.
96. Phull P, Sanchorawala V, Connors LH, et al. Monoclonal gammopathy of undetermined significance in systemic transthyretin amyloidosis (ATTR). Amyloid 2018; 25:62.
97. Comenzo RL, Zhou P, Fleisher M, et al. Seeking confidence in the diagnosis of systemic AL (Ig light-chain) amyloidosis: patients can have both monoclonal gammopathies and hereditary amyloid proteins. Blood 2006; 107:3489.

98. Williams RC Jr, Cathcart ES, Calkins E, et al. Secondary amyloidosis in lepromatous leprosy. Possible relationships of diet and environment. Ann Intern Med 1965; 62:1000.
99. Filipowicz-Sosnowska AM, Roztropowicz-Denisiewicz K, Rosenthal CJ, Baum J. The amyloidosis of juvenile rheumatoid arthritis--comparative studies in Polish and American children. I. Levels of serum SAA protein. Arthritis Rheum 1978; 21:699.
100. Anders RF. Amyloid fibril proteins found in Papua New Guinean and other amyloidoses. P N G Med J 1978; 21:79.
101. Obici L, Raimondi S, Lavatelli F, et al. Susceptibility to AA amyloidosis in rheumatic diseases: a critical overview. Arthritis Rheum 2009; 61:1435.
102. Pettersson T, Konttinen YT. Amyloidosis-recent developments. Semin Arthritis Rheum 2010; 39:356.
103. Papadopoulos VP, Giaglis S, Mitroulis I, Ritis K. The population genetics of familial mediterranean fever: a meta-analysis study. Ann Hum Genet 2008; 72:752.
104. Koshy R, Sivadas A, Scaria V. Genetic epidemiology of familial Mediterranean fever through integrative analysis of whole genome and exome sequences from Middle East and North Africa. Clin Genet 2018; 93:92.
105. Park YH, Remmers EF, Lee W, et al. Ancient familial Mediterranean fever mutations in human pyrin and resistance to Yersinia pestis. Nat Immunol 2020; 21:857.
106. Tunca M, Akar S, Onen F, et al. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore) 2005; 84:1.
107. Altunoğlu A, Erten Ş, Canoz MB, et al. Phenotype 2 familial mediterranean fever: evaluation of 22 case series and review of the literature on phenotype 2 FMF. Ren Fail 2013; 35:226.
108. Lachmann HJ, Goodman HJ, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. N Engl J Med 2007; 356:2361.
109. Touitou I, Sarkisian T, Medlej-Hashim M, et al. Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. Arthritis Rheum 2007; 56:1706.
110. Booth DR, Booth SE, Gillmore JD, et al. SAA1 alleles as risk factors in reactive systemic AA amyloidosis. Amyloid 1998; 5:262.
111. Ajiro J, Narita I, Sato F, et al. SAA1 gene polymorphisms and the risk of AA amyloidosis in Japanese patients with rheumatoid arthritis. Mod Rheumatol 2006; 16:294.
112. Migita K, Agematsu K, Masumoto J, et al. The contribution of SAA1 polymorphisms to Familial Mediterranean fever susceptibility in the Japanese population. PLoS One 2013; 8:e55227.
113. Utku U, Dilek M, Akpolat I, et al. SAA1 alpha/alpha alleles in Behçet's disease related amyloidosis. Clin Rheumatol 2007; 26:927.
114. Akar N, Hasipek M, Oztürk A, et al. Serum amyloid A1 -13 T/C alleles in Turkish familial Mediterranean fever patients with and without amyloidosis. J Nephrol 2006; 19:318.

115. Kriegshäuser G, Hayrapetyan H, Atoyan S, et al. Serum amyloid A1 genotype associates with adult-onset familial Mediterranean fever in patients homozygous for mutation M694V. Rheumatology (Oxford) 2021; 60:441.
116. Lane T, Loeffler JM, Rowczenio DM, et al. AA amyloidosis complicating the hereditary periodic fever syndromes. Arthritis Rheum 2013; 65:1116.
117. Blank N, Hegenbart U, Dietrich S, et al. Obesity is a significant susceptibility factor for idiopathic AA amyloidosis. Amyloid 2018; 25:37.
118. Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease (*). Annu Rev Immunol 2009; 27:621.
119. Schnappauf O, Chae JJ, Kastner DL, Aksentijevich I. The Pyrin Inflammasome in Health and Disease. Front Immunol 2019; 10:1745.
120. Tufan A, Lachmann HJ. Familial Mediterranean fever, from pathogenesis to treatment: a contemporary review. Turk J Med Sci 2020; 50:1591.
121. Majeed HA, Rawashdeh M, el-Shanti H, et al. Familial Mediterranean fever in children: the expanded clinical profile. QJM 1999; 92:309.
122. Melikoğlu M, Ozdoğan H, Korkmaz C, et al. A survey of phenotype II in familial Mediterranean fever. Ann Rheum Dis 2000; 59:910.
123. Migita K, Agematsu K, Yazaki M, et al. Familial Mediterranean fever: genotype-phenotype correlations in Japanese patients. Medicine (Baltimore) 2014; 93:158.
124. Kriegshäuser G, Enko D, Hayrapetyan H, et al. Clinical and genetic heterogeneity in a large cohort of Armenian patients with late-onset familial Mediterranean fever. Genet Med 2018; 20:1583.
125. Bodur H, Yurdakul FG, Çay HF, et al. Familial mediterranean fever: assessment of clinical manifestations, pregnancy, genetic mutational analyses, and disease severity in a national cohort. Rheumatol Int 2020; 40:29.
126. Atoyan S, Hayrapetyan H, Sarkisian T, Ben-Chetrit E. MEFV and SAA1 genotype associations with clinical features of familial Mediterranean fever and amyloidosis in Armenia. Clin Exp Rheumatol 2016; 34:72.
127. Pras M. Amyloidosis of familial mediterranean fever and the MEFV gene. Amyloid 2000; 7:289.
128. Ozen S, Aktay N, Lainka E, et al. Disease severity in children and adolescents with familial Mediterranean fever: a comparative study to explore environmental effects on a monogenic disease. Ann Rheum Dis 2009; 68:246.
129. Medlej-Hashim M, Delague V, Chouery E, et al. Amyloidosis in familial Mediterranean fever patients: correlation with MEFV genotype and SAA1 and MICA polymorphisms effects. BMC Med Genet 2004; 5:4.
130. Ait-Idir D, Djerdjouri B, Bouldjennet F, et al. The M694I/M694I genotype: A genetic risk factor of AA-amyloidosis in a group of Algerian patients with familial Mediterranean fever. Eur J Med Genet 2017; 60:149.

131. Nursal AF, Tekcan A, Kaya SU, et al. Mutational Spectrum of the MEFV Gene in AA Amyloidosis Associated With Familial Mediterranean Fever. Iran J Kidney Dis 2016; 10:107.
132. Rowczenio DM, Iancu DS, Trojer H, et al. Autosomal dominant familial Mediterranean fever in Northern European Caucasians associated with deletion of p.M694 residue-a case series and genetic exploration. Rheumatology (Oxford) 2017; 56:209.
133. Papa R, Lane T, Minden K, et al. INSAID Variant Classification and Eurofever Criteria Guide Optimal Treatment Strategy in Patients with TRAPS: Data from the Eurofever Registry. J Allergy Clin Immunol Pract 2021; 9:783.
134. van der Hilst JC, Simon A, Drenth JP. Hereditary periodic fever and reactive amyloidosis. Clin Exp Med 2005; 5:87.
135. Lachmann HJ, Papa R, Gerhold K, et al. The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EUROTRAPS international registry. Ann Rheum Dis 2014; 73:2160.
136. Kubota T, Koike R. Cryopyrin-associated periodic syndromes: background and therapeutics. Mod Rheumatol 2010; 20:213.
137. Toker O, Hashkes PJ. Critical appraisal of canakinumab in the treatment of adults and children with cryopyrin-associated periodic syndrome (CAPS). Biologics 2010; 4:131.
138. Obici L, Manno C, Muda AO, et al. First report of systemic reactive (AA) amyloidosis in a patient with the hyperimmunoglobulinemia D with periodic fever syndrome. Arthritis Rheum 2004; 50:2966.
139. Ter Haar NM, Jeyaratnam J, Lachmann HJ, et al. The Phenotype and Genotype of Mevalonate Kinase Deficiency: A Series of 114 Cases From the Eurofever Registry. Arthritis Rheumatol 2016; 68:2795.
140. Rodrigues F, Philit JB, Giurgea I, et al. AA amyloidosis revealing mevalonate kinase deficiency: A report of 20 cases including two new French cases and a comprehensive review of literature. Semin Arthritis Rheum 2020; 50:1370.
141. Aganna E, Hawkins PN, Ozen S, et al. Allelic variants in genes associated with hereditary periodic fever syndromes as susceptibility factors for reactive systemic AA amyloidosis. Genes Immun 2004; 5:289.
142. Bozgeyik E, Mercan R, Arslan A, Tozkir H. Next-generation screening of a panel of genes associated with periodic fever syndromes in patients with Familial Mediterranean Fever and their clinical characteristics. Genomics 2020; 112:2755.
143. Umar M, Megarbane A, Shan J, et al. Genome sequencing unveils mutational landscape of the familial Mediterranean fever: Potential implications of IL33/ST2 signalling. J Cell Mol Med 2020; 24:11294.
144. Klintworth GK. Corneal dystrophies. Orphanet J Rare Dis 2009; 4:7.
145. Kawasaki S, Kinoshita S. Clinical and basic aspects of gelatinous drop-like corneal dystrophy. Dev Ophthalmol 2011; 48:97.

146. Niel-Butschi F, Kantelip B, Iwaszkiewicz J, et al. Genotype-phenotype correlations of TGFBI p.Leu509Pro, p.Leu509Arg, p.Val613Gly, and the allelic association of p.Met502Val-p.Arg555Gln mutations. Mol Vis 2011; 17:1192.
147. Moshirfar M, West W, Ronquillo Y. Lattice Corneal Dystrophy. In: StatPearls, StatPearls Publishing, 2020.
148. Khurana R, Agarwal A, Bajpai VK, et al. Unraveling the amyloid associated with human medullary thyroid carcinoma. Endocrinology 2004; 145:5465.
149. Verga U, Fugazzola L, Cambiaghi S, et al. Frequent association between MEN 2A and cutaneous lichen amyloidosis. Clin Endocrinol (Oxf) 2003; 59:156.
150. Westermark P, Murphy C, Eulitz M, et al. Galectin 7-associated cutaneous amyloidosis. Amyloid 2010; 17(Suppl 1):71.
151. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet 2016; 387:2641.
152. Chiti F, Dobson CM. Protein Misfolding, Amyloid Formation, and Human Disease: A Summary of Progress Over the Last Decade. Annu Rev Biochem 2017; 86:27.
153. Caubet C, Bousset L, Clemmensen O, et al. A new amyloidosis caused by fibrillar aggregates of mutated corneodesmosin. FASEB J 2010; 24:3416.
154. Tan SML, Ong CC, Tan KB, et al. Subclinical Cardiomyopathy in Miyoshi Myopathy Detected by Late Gadolinium Enhancement Cardiac Magnetic Resonance Imaging. Int Heart J 2021; 62:186.
155. Levy E, Prelli F, Frangione B. Studies on the first described Alzheimer's disease amyloid beta mutant, the Dutch variant. J Alzheimers Dis 2006; 9:329.
156. Sahlin C, Lord A, Magnusson K, et al. The Arctic Alzheimer mutation favors intracellular amyloid-beta production by making amyloid precursor protein less available to alpha-secretase. J Neurochem 2007; 101:854.
157. Cruts M, Theuns J, Van Broeckhoven C. Locus-specific mutation databases for neurodegenerative brain diseases. Hum Mutat 2012; 33:1340.
158. Hardy J. The discovery of Alzheimer-causing mutations in the APP gene and the formulation of the "amyloid cascade hypothesis". FEBS J 2017; 284:1040.
159. Trambauer J, Fukumori A, Steiner H. Pathogenic Aβ generation in familial Alzheimer's disease: novel mechanistic insights and therapeutic implications. Curr Opin Neurobiol 2020; 61:73.
160. Revesz T, Holton JL, Lashley T, et al. Genetics and molecular pathogenesis of sporadic and hereditary cerebral amyloid angiopathies. Acta Neuropathol 2009; 118:115.

Chapter 12