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Systemic Light-Chain Amyloidosis: Evolving Diagnostic Paradigms and Emerging Therapeutic Strategies Beyond ANDROMEDA

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ABSTRACT

Background: Systemic light-chain (AL) amyloidosis is a clonal plasma-cell disorder whose prognosis hinges on early diagnosis and rapid deepening of haematologic response. The ANDROMEDA trial established daratumumab plus bortezomib, cyclophosphamide, and dexamethasone (CyBorD) as a new standard of first-line care, yet diagnostic delays persist and relapsed/refractory disease remains therapeutically challenging. This systematic review and meta-analysis synthesizes evolving diagnostic paradigms and evaluates emerging therapeutic strategies beyond ANDROMEDA.

Methods: This review was conducted per PRISMA 2020. Randomized trials, cohort studies, and case series ($n \geq 10$) reporting on diagnostic modalities or therapies for AL amyloidosis in adults were eligible. Two independent reviewers performed screening, data extraction, and risk-of-bias assessment (RoB 2, ROBINS-I). Random-effects meta-analysis pooled [complete haematologic response (CHR), organ response, overall survival (OS), and grade ≥ 3 adverse events]; heterogeneity was evaluated with I^2, and certainty appraised with GRADE.

Result and Conclusions: Diagnostic innovation is central to improving outcomes in AL amyloidosis, and post-ANDROMEDA strategies show promising efficacy and acceptable safety. Standardization of response criteria and prospective comparative data are needed. These findings support a biomarker-guided, risk-adapted therapeutic framework.

Keywords: AL amyloidosis; systemic amyloidosis; daratumumab; ANDROMEDA; plasma cell dyscrasia; light chain; cardiac amyloidosis; amyloid fibril; CAR-T therapy; bispecific antibody; venetoclax; autologous stem cell transplantation; minimal residual disease; proteasome inhibitor; organ response

1. INTRODUCTION TO SYSTEMIC AMYLOIDOSIS

Amyloidosis includes a variety of protein misfolding disorders characterized by the buildup of insoluble fibrillar aggregates in the extracellular space, known collectively as amyloid [1]. These fibrils are characterized by a conserved cross-β-sheet quaternary structure, which shows distinctive apple-green birefringence under polarized light after Congo red staining, a hallmark histopathological criterion for diagnosis.[2] The International Society of Amyloidosis now recognises over 36 distinct precursor proteins that can trigger this condition.[3] Systemic manifestations including light-chain, transthyretin, and serum amyloid A forms, alongside rarer hereditary variants, result in multisystem organ dysfunction that critically informs prognosis and therapeutic strategy. Among these, AL amyloidosis is the predominant subtype in developed nations, constituting approximately 65–70% of cases encountered at specialised referral centres. The pathophysiological hallmark of AL amyloidosis is the clonal proliferation of bone marrow plasma cells secreting structurally unstable immunoglobulin light chains. [4, 5]These proteins undergo misfolding, oligomerisation, and subsequent assembly into insoluble fibrils, which infiltrate tissues to induce functional impairment through both mechanical disruption and direct parenchymal proteotoxicity. You will find that clinical symptoms vary widely, but the main factor determining survival is which organs are involved, especially when the heart is affected.[6]

AL amyloidosis is classified as a rare disease, with an estimated incidence of approximately 8–14 cases per million person-years in Western populations, translating to roughly 4,000–5,000 new diagnoses annually in the United States[7]. Real-world epidemiological studies using claims databases have revealed that the true incidence may be underestimated due to diagnostic misclassification and delays, with a median diagnostic lag of 12–24 months from symptom onset to confirmed diagnosis[8]. The disorder affects predominantly middle-aged to older adults, with a median age at diagnosis of approximately 63–64 years and exhibits a slight male predominance (approximately 60:40 male-to-female ratio). Racial disparities have been documented, with African American patients potentially experiencing differential access to specialised care and diagnostic workup. Approximately 10–15% of AL amyloidosis cases arise in the setting of underlying symptomatic multiple myeloma, while the majority originate from a low-burden clonal plasma cell proliferation indistinguishable from monoclonal gammopathy of undetermined significance (MGUS)[9, 10].

The impact of AL amyloidosis goes well beyond its rarity. Untreated or inadequately treated disease carries a median overall survival of less than 12 months in patients with advanced cardiac involvement, with some stage III–IV patients surviving fewer than 6 months from diagnosis. Historically, fewer than 20% of patients were eligible for high-dose melphalan and autologous stem cell transplantation (HDM-ASCT) due to organ dysfunction at presentation. Even today, AL amyloidosis places a severe burden on your quality of life. Symptoms—like shortness of breath, swelling, fatigue, dizziness, and pain can profoundly limit what you can do. The disease also exerts substantial economic burden, with high rates of hospitalisation, specialised investigations, and long-term follow-up requirements[11].

The history of AL amyloidosis treatment mirrors broader advances in plasma cell dyscrasia management. For decades, oral melphalan and prednisone represented the standard of care, yielding modest hematologic responses and minimal improvement in survival. [12, 13] In the 1990s, high-dose melphalan and stem cell transplants changed the game. They showed for the first time that deep hematologic remissions could help organs recover and extend survival. [14]However, strict transplant rules meant most patients were excluded. New drugs thalidomide, bortezomib, lenalidomide, and later pomalidomide opened up options, allowing treatment of patients with significant organ damage. Bortezomib-based combinations, particularly cyclophosphamide-bortezomib-dexamethasone (CyBorD), emerged as a broadly applicable frontline regimen with acceptable toxicity and meaningful hematologic response rates of 60–80%. [15, 16] More recently, the approval of daratumumab, a monoclonal antibody targeting CD38, has further refined the standard of care by significantly increasing the depth and durability of haematological responses in both transplant-eligible and ineligible cohorts [17]. Despite these therapeutic advancements, early mortality remains a critical clinical challenge, particularly among patients presenting with advanced cardiac staging where survival outcomes have shown limited improvement over recent decades [18, 19].

The approval of daratumumab, a human anti-CD38 IgG1κ monoclonal antibody previously established in multiple myeloma, for AL amyloidosis based on the ANDROMEDA trial marked the most significant therapeutic advance in the field's history. The ANDROMEDA study showed that adding daratumumab to CyBorD (Dara-CyBorD) more than doubled the rate of complete hematologic response (53% vs 18%) and significantly improved cardiac and renal organ response rates, while reducing mortality at 6 months compared with CyBorD alone. This result catalysed a shift in the standard of care and stimulated a new wave of clinical investigation, with ongoing trials exploring BCMA-directed bispecific antibodies, CAR-T cell therapies, anti-fibril strategies, and precision medicine approaches based on cytogenetic profiling and measurable residual disease. This review examines the full spectrum of AL amyloidosis management, focusing on post-ANDROMEDA developments and unmet clinical needs [20, 21, 22, 23]. Additional supporting information, including the detailed literature search strategy and supplementary materials, is provided in *Supplementary File 1*

2. PATHOBIOLOGY OF AL AMYLOIDOSIS

2.1 PLASMA CELL DYSCRASIA AND LIGHT CHAIN PRODUCTION

AL amyloidosis originates from a clonal proliferation of bone marrow plasma cells that synthesise and secrete a structurally unstable immunoglobulin light chain[4]. Unlike multiple myeloma, where damage comes from having too many plasma cells, the problem in AL amyloidosis is the toxic light chain itself, rather than the amount of cancer cells. [24] The plasma cell clone in AL amyloidosis is typically small, constituting fewer than 10% of bone marrow cells in the majority of patients, and bone lesions are typically absent. Lambda light chains are implicated in approximately 70–75% of cases, consistent with the preferential amyloidogenicity of certain lambda variable domain gene segments, particularly those encoded by IGLV2, IGLV3, and IGLV6 family genes compared with kappa light chains. Mass spectrometry-based proteomics has substantially refined understanding of light-chain variable domain usage in AL amyloidosis, demonstrating recurrent overrepresentation of specific germline gene segments that encode light chains with intrinsic thermodynamic instability. [5, 25, 26] These misfolded proteins turn into insoluble, sticky fibres. These fibres build up and damage tissue by poisoning cells and disrupting their communication pathways [27],[28].

2.2 MECHANISMS OF LIGHT CHAIN MISFOLDING

Light chains usually float freely, but they can turn into insoluble amyloid fibrils. This transformation depends on the structural stability of the light chain variable (VL) domain. These proteins often struggle to hold their shape. They unfold slightly, exposing sticky core areas that cause them to clump together in patterns called β-sheets. Key molecular determinants of amyloidogenicity include somatic hypermutations in framework and complementarity-determining regions that destabilise the native fold, the length and composition of the CDR3 loop, and the propensity for domain-swapping oligomerisation. Environmental factors in the tissue microenvironment, including serum amyloid P component (SAP), glycosaminoglycans, apolipoprotein E, and metal ions, act as cofactors that accelerate fibril nucleation and propagation. The conformational landscape of amyloidogenic light chains is highly heterogeneous, and the specific fibril structure formed influences both the tissue tropism and the degree of proteotoxic injury observed clinically.[29, 30, 31]

2.3 AMYLOID FIBRIL FORMATION AND TISSUE DEPOSITION

Amyloid formation happens in stages. First, there is a slow 'lag phase' where soluble chains cluster together to form nuclei. Once that is done, they quickly grow into mature fibrils by adding more building blocks.[32] These resulting fibrils are incredibly tough. They resist the body's natural disposal systems, which explains why they build up tissues over time. Tissue deposition shows preferential tropism for the extracellular matrix of specific organs, most prominently the interstitium of the cardiac myocardium, glomerular mesangium, vasa nervorum of peripheral nerves, hepatic sinusoids, and lamina propria of the gastrointestinal tract. The mechanisms governing organ tropism remain incompletely understood but likely involve interactions between specific light chain sequences and tissue-specific matrix components, including heparan sulfate proteoglycans and collagen.[5, 25, 33]

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2.4 ORGAN TOXICITY AND PROTEOTOXIC EFFECTS

Organ damage in AL amyloidosis results from two complementary mechanisms: (1) amyloid deposits acting as physical clutter that stiffens organs and blocks tiny blood vessels; and (2) toxic protein fragments that directly harm cells before they even settle into deposits. In heart muscle cells, these fragments trigger toxic stress signals that disrupt the electrical and mechanical activity needed for the heart to pump. These cell-autonomous toxic effects explain why clinical biomarkers of myocardial injury (troponin) correlate with circulating free light chain concentration and why hematologic responses achieved by suppressing light chain production are associated with rapid improvement in cardiac biomarkers even before structural amyloid clearance. In renal podocytes and tubular cells, light chain-induced oxidative injury promotes proteinuria, tubulointerstitial fibrosis, and progressive nephron loss. Understanding these dual pathogenic mechanisms has underpinned the rationale for pursuing both clone-directed therapy to stop ongoing light chain production and fibril-directed strategies to clear existing amyloid deposits[24, 27, 34] (Table 1).

3. CLINICAL MANIFESTATIONS OF AL AMYLOIDOSIS

AL amyloidosis produces a diverse and often insidious clinical syndrome that reflects the organ distribution of amyloid deposition. In large groups of patients, cardiac involvement appears in 70–80% of cases at diagnosis. Renal involvement follows at 50–70%, nerve problems in 15–35%, and liver involvement in 15–20%, often with significant overlap.

3.1 CARDIAC INVOLVEMENT

Cardiac involvement is the most important determinant of prognosis in patients with AL amyloidosis. When amyloid protein invades your heart muscle, it causes a condition called restrictive cardiomyopathy. Amyloid infiltration increases myocardial stiffness, resulting in impaired ventricular relaxation and diastolic filling. Symptoms include exertional dyspnea, orthopnea, peripheral oedema, and, in advanced disease, low-output heart failure with fatigue and syncope. Characteristic electrocardiographic findings include low-voltage QRS complexes that contrast with the increased wall thickness on echocardiography (a 'pseudoinfarct' pattern) and conduction abnormalities including atrioventricular block and atrial fibrillation. Echocardiography reveals concentric wall thickening with a 'granular sparkling' appearance of the myocardium, biatrial enlargement, diastolic dysfunction (typically grade II–III), and pericardial effusion in severe cases. Cardiac biomarkers N-terminal pro-brain natriuretic peptide (NT-proBNP), BNP, and high-sensitivity cardiac troponin T or I are essential for staging, response assessment, and prognostication.[35, 36]

3.2 RENAL INVOLVEMENT

In the kidneys, AL amyloidosis often causes nephrotic syndrome. This is characterised by marked proteinuria, often losing 10–15 grams into your urine every 24 hours. The amyloid typically builds up in the kidney's tiny filters, known as glomeruli. Over time, this causes scarring and eventually stops the kidneys from filtering your blood properly. Renal insufficiency is present at diagnosis in a significant minority, and progressive deterioration leading to end-stage renal disease requiring dialysis occurs in 20–30% of patients within 5 years of diagnosis. The clinical consequence is profound: hypoalbuminemia from urinary protein loss leads to peripheral oedema, poor drug binding, malnutrition, and increased susceptibility to infection. Renal staging systems, including the Palladini renal staging system, incorporate 24-hour urine protein and estimated glomerular filtration rate to predict renal outcomes and likelihood of renal response following treatment. [37, 38]

3.3 PERIPHERAL AND AUTONOMIC NEUROPATHY

Peripheral neuropathy affects 15–35% of patients. It usually starts as a sensory issue causing burning pain, numbness, and balance problems that spreads in a specific pattern. This can mimic the neuropathy seen in hereditary transthyretin amyloidosis. Motor involvement is less common but may occur in advanced disease. Autonomic neuropathy is particularly debilitating. It may cause severe orthostatic hypotension, severe enough to stop you from walking, alongside digestive issues, sweat gland problems, urinary retention, and erectile dysfunction. Autonomic involvement complicates treatment. For instance, severe orthostatic hypotension limits the use of diuretics, which are essential for managing fluid overload in cardiac amyloidosis and worsen fainting risks, which significantly impairs quality of life.. The presence of neuropathy often presents a diagnostic challenge as it may be attributed to diabetes mellitus, Charcot-Marie-Tooth disease, or other common causes before AL amyloidosis is considered.[39, 40]

3.4 GASTROINTESTINAL AND HEPATIC DISEASE

Gastrointestinal amyloidosis may manifest at any level from the oropharynx to the anorectum. The tongue is a characteristic site. Macroglossia an enlarged, stiff, or ribbed tongue is a signature finding present in 10–15% of patients, and it is almost exclusively seen in AL amyloidosis. Gastrointestinal motility disturbances, including gastroparesis, intestinal pseudo-obstruction, and severe diarrhoea alternating with constipation, are common and arise from autonomic dysfunction, smooth muscle infiltration, and enteric nervous system involvement. Malabsorption leading to severe weight loss may mimic inflammatory bowel disease or small bowel lymphoma. Hepatic amyloidosis often shows as an enlarged liver. Characteristic laboratory findings include elevated alkaline phosphatase levels (alkaline phosphatase) that are higher than expected; in advanced cases, it leads to portal hypertension and liver failure. Splenic infiltration may occur concurrently, and spontaneous splenic rupture, though rare, has been reported.[41, 42]

3.5 MUSCULOSKELETAL AND SOFT TISSUE INVOLVEMENT

Amyloid deposits in soft tissues often provide vital diagnostic clues. Periorbital purpura —often called 'raccoon eyes'—is a classic sign of systemic amyloidosis, seen in 10–15% of patients. It happens because amyloid weakens small capillaries around the eyes, which can then rupture after minor trauma or the Valsalva manoeuvre. Carpal tunnel syndrome is another early warning sign. It results from amyloid buildup in the flexor tenosynovium (the tendon sheath), sometimes appearing years before a systemic diagnosis. In fact, bilateral carpal tunnel syndrome in a middle-aged patient should prompt evaluation for systemic amyloidosis. Shoulder pad sign: diffuse amyloid infiltration of the periarticular tissues producing a characteristic rounded fullness of the shoulders, and claudication from vascular amyloid infiltration may also be observed.[43, 44, 45] Furthermore, subcutaneous amyloid deposition may manifest as localised amyloidomas or firm, waxy plaques in the skin, which can occasionally be mistaken for dermatological malignancies or inflammatory conditions [46, 47]. Similarly, musculoskeletal manifestations in ATTR amyloidosis may occur years before other systemic symptoms, with amyloid deposits frequently identified in the rotator cuff tendons and ligamentum flavum during orthopaedic interventions [48].

3.6 RARE AND ATYPICAL PRESENTATIONS

Some atypical signs can cause diagnostic confusion and delays. Pulmonary amyloidosis may be localised (tracheobronchial nodules, parenchymal nodules) or diffuse (alveolar-septal pattern), with diffuse alveolar involvement portending a poor prognosis. Coagulation factor X deficiency is a rare but life-threatening complication. It happens when factor X sticks to amyloid fibrils in the spleen and liver, leading to purpura and major bleeding. Skin amyloid deposits, nodular lymphadenopathy due to nodal amyloid, and adrenal infiltration with secondary hypoadrenalism are additional described presentations. Rarely, localised AL amyloidosis confined to a single organ (most commonly the bladder, lung, or skin) occurs without an identifiable systemic plasma cell clone and carries a favourable prognosis distinct from systemic disease; accurate typing is essential to distinguish these entities.[5, 49, 50]

4. DIAGNOSTIC CHALLENGES IN AL AMYLOIDOSIS

4.1 CAUSES OF DIAGNOSTIC DELAY

Even with modern tools, it typically takes 12–24 months to diagnose AL amyloidosis, with some patients waiting over 3–4 years. Multiple factors contribute to this diagnostic lag. First, the initial symptoms of AL amyloidosis fatigue, dyspnea, peripheral oedema, and weight loss are nonspecific and frequently attributed to common conditions, including heart failure from other causes, nephrotic syndrome from diabetic nephropathy, or neuropathy from diabetes or vitamin B12 deficiency. Second, the rarity of the disease means that many clinicians lack familiarity with its diverse presentations, particularly in non-specialised settings. Third, the absence of a reliable non-invasive screening biomarker means that diagnosis requires a combination of laboratory tests, imaging, and tissue biopsy, which may be pursued sequentially rather than as a coordinated workup. Fourth, patient surveys have documented that many individuals consult multiple specialists' cardiologists, nephrologists, neurologists, and gastroenterologists before a unifying diagnosis is entertained, reflecting the siloed nature of subspecialty evaluation that may prevent recognition of multiorgan disease[48, 51, 52].

4.2 CLINICAL RED FLAGS

Spotting 'red flags' is key to speeding up the diagnosis. The presence of involvement of two or more organ systems, particularly heart failure with proteinuria, hepatomegaly, or neuropathy, should immediately raise suspicion for systemic amyloidosis. Specific findings that should prompt urgent investigation include: macroglossia, periorbital purpura, carpal tunnel syndrome (particularly bilateral or in a middle-aged individual without an occupational cause), unexplained low voltage on ECG in a patient with echocardiographic left ventricular hypertrophy, monoclonal protein detectable on serum or urine protein electrophoresis or immunofixation, and a plasma cell dyscrasia in a patient with multisystem disease. The presence of a monoclonal protein in any patient presenting with unexplained heart failure, nephrotic syndrome, or neuropathy mandates complete workup for AL amyloidosis before attributing the organ disease to other etiologies.[39, 40]

4.3 DIFFERENTIAL DIAGNOSIS

When evaluating systemic amyloidosis, other forms of amyloidosis and non-amyloid conditions that produce similar symptoms must be ruled out. Transthyretin amyloidosis (ATTR) is most critical differential diagnosis. It primarily affects older men and often impacts the heart, as its management differs fundamentally from AL amyloidosis and its incidence has increased with greater recognition. ATTR cardiac amyloidosis tends to produce a more slowly progressive cardiomyopathy with a greater degree of LV wall thickening and a higher frequency of aortic stenosis coexistence compared with AL cardiac amyloidosis. Technetium pyrophosphate scintigraphy has transformed the non-invasive diagnosis of ATTR cardiac amyloidosis, with grade 2–3 cardiac uptake in the absence of a monoclonal protein being highly specific for ATTR; however, low-grade uptake can occasionally occur in AL amyloidosis. Reliable AL/ATTR differentiation requires accurate amyloid typing, most definitively by mass spectrometry-based laser microdissection proteomics.[51, 53, 54]

4.4 IMPORTANCE OF EARLY DETECTION

The importance of early diagnosis in AL amyloidosis cannot be overstated. Organ damage, especially to the heart, is often irreversible once it happens. If the disease reaches advanced cardiac staging (Mayo Stage III–IV), median survival is less than 6 months, even with effective treatment. Early studies from the Mayo Clinic showed that survival rates improved over time not just because of better drugs, but because treatment is started before critical organ damage occurred. More recent data confirm that achieving an early and deep hematologic response- ideally, a complete response is the strongest predictor of organ recovery and long-term survival. The recognition that effective treatment can halt and, in some cases, reverse organ damage provides a powerful rationale for implementing systematic screening strategies in high-risk populations, including patients diagnosed with MGUS undergoing surveillance, and for education campaigns targeting primary care physicians and subspecialists who may first encounter patients with atypical presentations.[55, 56] (Table 3).

5. CONTEMPORARY DIAGNOSTIC APPROACH

5.1 LABORATORY EVALUATION

In patients with suspected AL amyloidosis, laboratory evaluation should include, a coordinated panel of tests to find and identify the underlying plasma cell growth. Serum protein electrophoresis (SPEP) identifies an M-protein as a discrete band or spike in the gamma globulin region in approximately 50% of cases; critically, SPEP alone misses monoclonal proteins in up to 50% of cases because the clonal burden is low.[57] Urine protein electrophoresis (UPEP) on a 24-hour specimen further enhances detection of Bence Jones proteinuria. Serum and urine immunofixation electrophoresis (IFE) are substantially more sensitive than SPEP/UPEP and should be performed in all patients with suspected amyloidosis; combined serum and urine IFE detects a monoclonal protein in approximately 90% of AL amyloidosis patients. Serum free light chain (sFLC) assay (Freelite; The Binding Site) is the most sensitive assay for detecting clonal light chains, capable of detecting concentrations as low as 1–2 mg/dL and also provides quantitative assessment critical for treatment response monitoring. An abnormal sFLC ratio (kappa: lambda <0.26 or >1.65) occurs in approximately 96–98% of AL amyloidosis patients. The combination of SPEP, serum IFE, and sFLC assay detects a clonal abnormality in nearly 99% of patients with AL amyloidosis, making this triple-test strategy the recommended

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initial evaluation in all suspected cases.[4, 58, 59] Beyond initial diagnostic screening, recent investigations have begun to use next-generation flow cytometry to track minimal residual disease in patients who achieve a complete hematologic response [60, 61]. Furthermore, assessing renal function through creatinine, serum albumin, and comprehensive urinalysis remains essential, as these parameters are frequently compromised and indicate the extent of end-organ involvement [62] (Table 2).

5.2 HISTOPATHOLOGICAL DIAGNOSIS

Histopathological confirmation of amyloid deposition remains an absolute prerequisite for the diagnosis of AL amyloidosis no clinical or laboratory combination is sufficient for diagnosis without tissue confirmation[4]. Congo red staining performed by an experienced pathologist demonstrates characteristic apple-green birefringence under polarised light. This result is 100% specific for amyloid. The preferred initial biopsy site is abdominal subcutaneous fat pad aspiration, a minimally invasive outpatient procedure with a diagnostic sensitivity of approximately 70–80% in AL amyloidosis and negligible risk of serious complications. Bone marrow biopsy, performed in virtually all patients to assess plasma cell burden, has a sensitivity of approximately 50–60% for amyloid detection and should be interpreted in conjunction with fat pad aspiration: combined sensitivity exceeds 85%[63, 64]. Directly biopsying an organ like the kidney, heart, liver, or nerve gives the highest yield (nearly 100% in affected organs). This approach is used when non-invasive tests are inconclusive but clinical suspicion remains high. Renal biopsy for investigation of proteinuria frequently establishes the diagnosis. Cardiac biopsy carries procedural risks but may be necessary in select cases where cardiac imaging is highly suggestive and fat/bone marrow biopsies are non-diagnostic[51].

5.3 AMYLOID TYPING

Amyloid typing should always be performed—identifying the specific precursor protein—even if you have already identified a monoclonal protein, because approximately 10% of patients with a detectable M-protein and amyloid deposition have ATTR or AA amyloidosis, not AL amyloidosis[4]. Treating a patient with ATTR amyloidosis as AL amyloidosis exposes them to unnecessary toxicity from chemotherapy without benefit. Immunohistochemistry (IHC) using antibodies against AL lambda/kappa light chains, transthyretin, AA, and other precursors represents the first-line typing method in most centers; however, sensitivity is suboptimal (~75–80%) due to antigenic masking within mature fibrils and is highly dependent on antibody quality and laboratory experience[39]. Immunofluorescence on fresh-frozen tissue provides somewhat better antibody penetration but requires specialized tissue handling. Mass spectrometry (MS)-based proteomics following laser capture microdissection of Congo red-stained tissue deposits has emerged as the gold standard for amyloid typing, with diagnostic sensitivity and specificity exceeding 97–98% and the ability to simultaneously identify the specific immunoglobulin variable gene segments contributing to fibril formation. Referral of tissue to specialized amyloid typing centers (such as Mayo Clinic) is strongly recommended when local IHC is inconclusive, and MS-based typing should be the standard in all specialised amyloidosis centers[65].

5.4 CARDIAC IMAGING

A multimodality imaging approach is recommended to characterise heart involvement, guide therapy, and monitor progress. Start with a standard echocardiogram; look for signs of cardiac amyloidosis, such as increased left ventricular wall thickness (IVSd ≥12 mm in the absence of hypertension or aortic stenosis), a granular sparkling echogenic texture, diastolic dysfunction, reduced longitudinal strain (with relative apical sparing pattern on global longitudinal strain—a highly specific feature of cardiac amyloidosis), biatrial enlargement, and pericardial effusion[51]. The combination of IVSd >12 mm with relative apical sparing on GLS has high sensitivity and specificity for cardiac amyloidosis. [94] Cardiac MRI provides a more detailed look at heart tissue than echocardiography. It uses late gadolinium enhancement (LGE) usually diffuse subendocardial or transmural in a non-coronary distribution along with native T1 mapping and extracellular volume (ECV) quantification to measure amyloid buildup and predict outcomes. Nuclear scans, like PYP or DPD scintigraphy, are key tools for diagnosing ATTR cardiac amyloidosis. However, interpret AL amyloidosis results carefully, as low-grade cardiac uptake can sometimes occur. Fluorodeoxyglucose (FDG) PET is not routinely used in AL amyloidosis cardiac evaluation; investigational PET tracers targeting amyloid fibrils remain experimental[66, 67].

5.5 DIAGNOSTIC ALGORITHMS AND CLINICAL WORKFLOW

Evaluation of suspected AL amyloidosis begins by recognising signs of multiorgan involvement. Follow this with a structured laboratory evaluation (SPEP, UPEP, serum and urine IFE, sFLC assay, CBC, comprehensive metabolic panel, 24-hour urine protein, NT-proBNP, troponin)[4]. If you detect a clonal abnormality alongside unexplained organ dysfunction, refer the patient immediately to a specialised amyloidosis center. Tissue biopsy (fat pad aspiration ± bone marrow) provides histological confirmation, with definitive amyloid typing by MS-based proteomics. Comprehensive cardiac evaluation (echocardiography, CMR in selected cases, biomarkers) and renal evaluation (24-hour urine protein and eGFR) quantify organ involvement and guide staging. Bone marrow biopsy with plasma cell enumeration, cytogenetics (including FISH for t(11;14), del(17p), and 1q21 amplification), and immunophenotyping completes the evaluation and identifies cytogenetic risk factors that influence treatment selection[37].

6. STAGING AND RISK STRATIFICATION

6.1 MAYO 2004 STAGING

The original Mayo Clinic staging system for AL amyloidosis, published in 2004 by Dispenzieri and colleagues, established cardiac biomarkers as the preeminent prognostic factors in this disease. The system uses two biomarkers—serum cardiac troponin T (cTnT; threshold ≥0.035 µg/L) and N-terminal pro-BNP (NT-proBNP; threshold ≥332 ng/L)—to define three stages: Stage I (both biomarkers below threshold), Stage II (one biomarker elevated), and Stage III (both biomarkers elevated). Median overall survival in the original cohort was 26.4 months for Stage I, 10.5 months for Stage II, and 3.5 months for Stage III, demonstrating the extreme prognostic gradient across stages[68, 69].

6.2 MAYO 2012 STAGING

With the introduction of high-sensitivity cardiac troponin assays and recognition that the difference between involved and uninvolved free light chains (dFLC) provides independent prognostic information, Kumar and colleagues revised the staging system in 2012 to incorporate three biomarkers: NT-proBNP (≥1800 ng/L), high-sensitivity troponin T (≥25 ng/L), and dFLC (≥180 mg/L). This four-stage system (Stage I: 0 risk factors; Stage II: 1 factor; Stage III: 2 factors; Stage IV: 3 factors) yielded median survivals of 94.1 months, 40.3 months, 14 months, and 5.8 months respectively, more granularly stratifying patients and showing that Stage IV patients survived fewer than 6 months with the treatments available at the time. The 2012 staging system has been widely adopted for clinical trial stratification and is the de facto standard in current practice, with validation in multiple independent cohorts[70, 71].

6.3 EUROPEAN MODIFICATION

Wechalekar and colleagues, in a European Collaborative Study of 346 patients with Stage III (2004 staging) AL amyloidosis, identified that systolic blood pressure <100 mmHg and NT-proBNP >8500 ng/L further substratified Stage III patients into two distinct groups (Stage IIIa and Stage IIIb) with markedly different early mortality. Stage IIIb patients defined by NT-proBNP >8500 ng/L—had a median survival of only 3 months, largely owing to early mortality from refractory heart failure that precluded sustained treatment. This European modification changes the clinical approach, as Stage IIIb patients require specialised supportive strategies, are often ineligible for standard treatment, and may warrant consideration for urgent cardiac interventions or, in exceptional cases, heart transplantation before systemic therapy[72].

6.4 RENAL STAGING SYSTEMS

Palladini and colleagues developed a dedicated renal staging system incorporating baseline eGFR and 24-hour urine protein to predict renal outcomes—specifically progression to end-stage renal disease requiring dialysis. Stage I (eGFR ≥50 mL/min/1.73m² and urine protein <5 g/24h), Stage II (either criterion not meeting Stage I thresholds), and Stage III (eGFR <50 mL/min/1.73m² and urine protein ≥5 g/24h) yielded 3-year risk of progression to dialysis of 0%, 11%, and 60%, respectively. This system helps identify patients at high risk of renal failure and guides decisions regarding renal transplantation following the achievement of haematologic remission [37, 38].

6.5 CYTOGENETIC RISK FACTORS

Using fluorescence in situ hybridisation (FISH) on bone marrow plasma cells helps to determine the patient's prognosis and predict outcomes in AL amyloidosis. The translocation t(11;14)(q13;q32), juxtaposing CCND1 with the IGH locus, is the most common recurrent cytogenetic abnormality in AL amyloidosis, occurring in approximately 40–50% of cases—substantially more frequently than in multiple myeloma (15–20%). In AL amyloidosis, t(11;14) is associated with predominant lambda light chain production and, in several studies, with inferior outcomes when treated with bortezomib-based regimens. Conversely, t(11;14) predicts sensitivity to venetoclax, a BCL-2 inhibitor, providing a precision medicine opportunity in this subgroup. Deletion 17p13 (TP53 deletion) and gain of 1q21 represent additional high-risk features associated with shortened survival, though their therapeutic implications in AL amyloidosis specifically are less well defined than in multiple myeloma[73, 74].

6.6 PROGNOSTIC BIOMARKERS

Beyond the established staging biomarkers (NT-proBNP, troponin, dFLC), several additional biomarkers have prognostic value in AL amyloidosis. Soluble suppression of tumorigenicity 2 (sST2) a decoy receptor for interleukin-33 reflecting cardiac stress provides prognostic information independent of troponin and NT-proBNP. Circulating tumour DNA (ctDNA) assessment, next-generation sequencing of bone marrow plasma cells, and mass spectrometry-based minimal residual disease (MRD) monitoring are emerging tools with prognostic potential. High-sensitivity troponin I assays and new candidate biomarkers reflecting renal tubular injury, hepatic amyloid burden, and oxidative stress are under investigation. The field increasingly recognises that integrated biomarker profiling combining hematologic, cardiac, renal, and cytogenetic data will be required for optimal prognostication and individualised treatment planning[4, 49].

7. TREATMENT RESPONSE ASSESSMENT

7.1 HEMATOLOGIC RESPONSE CRITERIA

The International Society of Amyloidosis and the Amyloidosis Research Consortium update consensus criteria for hematologic response in AL amyloidosis. These criteria focus on suppressing the clonal light chain. Complete response (CR) is defined as normalisation of the sFLC ratio, a negative serum and urine immunofixation, and negative bone marrow evaluation where tested[4, 75]. Very good partial response (VGPR) requires a dFLC <40 mg/L. Partial response (PR) requires a ≥50% reduction in dFLC. No response (NR) is defined as a <50% reduction in dFLC. These criteria, validated in large retrospective series, demonstrate that the depth of hematologic response robustly predicts organ response and survival: patients achieving CR have median survival exceeding 10 years in some cohorts, while those with NR have a median survival of approximately 10–14 months. The incorporation of bone marrow MRD assessment by next-generation flow cytometry and next-generation sequencing analogous to MRD criteria in multiple myeloma is an emerging area of active investigation with potential to identify candidates for treatment de-escalation or, conversely, intensification[76, 77].

7.2 ORGAN RESPONSE CRITERIA

Organ response as a sustained improvement in organ function caused by amyloid regression, rather than non-specific effects. Cardiac response is defined as a ≥30% and ≥300 ng/L reduction in NT-proBNP in patients with a baseline NT-proBNP ≥650 ng/L, or improvement in mean left ventricular wall thickness by ≥2 mm on echocardiography. Renal response requires a ≥30% reduction in 24-hour urine protein (to <500 mg/24h) without a concomitant ≥25% reduction in eGFR. Hepatic response requires a ≥50% reduction in elevated alkaline phosphatase or reduction in liver span by ≥2 cm on imaging. Organ responses lag behind hematologic responses. Even with effective treatment, they typically take 6–12 months to appear. Recent work has refined organ response criteria and introduced the concept of 'organ progression,' which is defined as a ≥30% increase in NT-proBNP (and by ≥300 ng/L) or a ≥25% increase in serum creatinine or serum urine protein, enabling earlier identification of treatment failure[78, 79].

7.3 MINIMAL/MEASURABLE RESIDUAL DISEASE

Minimal residual disease (MRD) testing is increasingly being incorporated into the management of AL amyloidosis, informed by experience gained in multiple myeloma. This approach checks for tiny traces of disease that standard tests miss. Like in myeloma, 'MRD negativity' is a strong sign of better long-term survival. Techniques applicable to AL amyloidosis include multiparameter flow cytometry (MFC) of bone marrow aspirates at sensitivities of 10^{-4} to 10^{-5}, next-generation sequencing (NGS)-based clonotype tracking, and mass spectrometry-based detection of clonotypic light chains in serum or bone

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marrow. Preliminary data from cohorts of patients achieving CR following HDM-ASCT and daratumumab-based therapy suggest that MRD negativity predicts superior outcomes; however, the optimal assay, timepoint, and sensitivity threshold for clinical decision-making in AL amyloidosis remain areas of active investigation. Importantly, the relationship between bone marrow MRD and circulating light chain levels requires further elucidation, given that sFLC provides a direct measure of clonal protein production that may partly parallel MRD status[80, 81].

7.4 MONITORING RELAPSE AND PROGRESSION

Once a patient responds to treatment, continued monitoring is essential to detect relapse, including a rise in dFLC meeting progression criteria or haematologic progression, even in patients with stable organ function. Monitoring of sFLC levels and urine protein **every 1–3 months during treatment and every 3–6 months thereafter is recommended**, together with cardiac biomarkers (NT-proBNP and troponin) and assessment of kidney function at the same intervals. Clinical relapse, characterised by organ progression (worsening NT-proBNP, increasing proteinuria, or deteriorating hepatic function) in the absence of hematologic progression, may reflect progressive amyloid accumulation from persisting low-level clonal activity or structural irreversibility of established organ damage; distinguishing between these possibilities is clinically challenging and guides re-treatment decisions. Surveillance bone marrow biopsies are typically performed at the time of suspected hematologic progression to confirm and characterise the relapsing clone[82, 83].

8. CURRENT TREATMENT LANDSCAPE

8.1 PRINCIPLES OF THERAPY

The main goal in AL amyloidosis is to rapidly and durably suppress the plasma cell clone that creates amyloid. This halts organ injury and helps the body clear existing deposits over time. [The depth of hematologic response specifically achieving a complete (CR) or very good partial (VGPR) response is the strongest modifiable predictor of organ response and survival, establishing complete or near-complete hematologic remission as the primary treatment endpoint[4]. Treatment decisions are individualised based on Mayo staging, PS, organ function, cytogenetic risk, and patient preference. A central tension in AL amyloidosis management is the need for rapid, aggressive treatment (to minimise ongoing organ injury) balanced against the vulnerability of compromised organs (particularly heart and kidneys) to treatment-related toxicity. Specialised centres now use a 'risk-adapted' approach, where the adjusted treatment intensity is based on the patient's stage, organ function, and individual fitness [84].

8.2 ORGAN-SPECIFIC SUPPORTIVE CARE

Supportive management of organ dysfunction is an essential component of AL amyloidosis care, often requiring the coordinated expertise of cardiology, nephrology, neurology, hepatology, and palliative care in addition to haematology. Cardiac management centres on volume optimisation using diuretics loop diuretics [furosemide or bumetanide] and aldosterone antagonists while avoiding agents that may be poorly tolerated in amyloid cardiomyopathy: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium channel blockers may precipitate hypotension and hemodynamic deterioration in patients with restrictive physiology and should be used with extreme caution or avoided. Atrial fibrillation, which carries a high thromboembolic risk in amyloid cardiomyopathy, requires anticoagulation (preferably direct oral anticoagulants, though data on their safety in amyloid-associated coagulopathy are limited). Renal supportive care includes diuretic management of edema, aggressive treatment of hypoalbuminemia with dietary protein supplementation, and planning for renal replacement therapy or renal transplantation in eligible patients achieving deep hematologic remission. Compression stockings, midodrine, and fludrocortisone may be used to manage orthostatic hypotension from autonomic neuropathy[85, 86].

8.3 FRONTLINE MANAGEMENT STRATEGIES

Before the ANDROMEDA trial, CyBorD (cyclophosphamide 300 mg/m² PO weekly, bortezomib 1.3 mg/m² SC weekly, dexamethasone 40 mg weekly) was the most widely used frontline regimen, based on its high response rates (~65–75% overall hematologic response, 25–35% CR), broad applicability across cardiac stage groups, and manageable toxicity profile with subcutaneous bortezomib administration[16, 47]. Oral melphalan-dexamethasone (MDex) remains a valid option for fragile or elderly patients with advanced organ dysfunction that are not suitable for intensive regimens, with a long track record of safety and efficacy. High-dose melphalan and autologous stem cell transplantation (HDM-ASCT) is the preferred strategy for transplant-eligible patients, generally those with Mayo Stage I–II disease, ECOG PS 0–2, eGFR ≥30 mL/min/1.73m², NT-proBNP <5000 ng/L, and troponin below threshold with reports of 5-year survival rates of 55–65% in carefully selected patients. However, the emergence of Dara-CyBorD as the new standard of care has prompted re-evaluation of the role of upfront ASCT versus non-transplant strategies, with ongoing trials directly addressing this question[87, 88].

9. DARATUMUMAB ERA: IMPACT OF THE ANDROMEDA TRIAL

9.1 STUDY DESIGN

The phase 3 ANDROMEDA trial (ClinicalTrials.gov NCT03201965) compared subcutaneous daratumumab plus CyBorD (Dara-CyBorD) against CyBorD alone in newly diagnosed AL amyloidosis. A total of 388 patients across 21 countries were enrolled, randomly assigned 1:1 to receive either Dara-CyBorD (n=195) or CyBorD (n=193). Subcutaneous daratumumab (1800 mg co-formulated with recombinant human hyaluronidase) was administered weekly for cycles 1–2, every 2 weeks for cycles 3–6, and then every 4 weeks thereafter until organ response criteria were met or disease progression occurred. CyBorD was administered for 6 cycles as cyclophosphamide 300 mg/m² orally weekly, bortezomib 1.3 mg/m² SC on days 1, 8, 15, and 22, and dexamethasone 40 mg weekly. Key eligibility criteria included newly diagnosed biopsy-proven AL amyloidosis, at least one measurable organ involvement, and cardiac stage I–IIIa by 2004 Mayo staging; patients with Stage IIIb disease (NT-proBNP >8500 ng/L) were excluded. The primary endpoint was the rate of complete hematologic response (CR)[89, 90].

9.2 KEY FINDINGS

In the primary analysis, the trial found that the complete response (CR) rate was 53.3% in the Dara-CyBorD arm versus 18.1% in the CyBorD arm (OR 5.1; 95% CI, 3.2–8.2; p<0.001). This is nearly three times the response rate in the standard arm. The overall hematologic response rate was 92.3% vs 76.9%, achieved a very good partial response (VGPR) or better in 79.0% vs 49.7% of patients in the Dara-CyBorD and CyBorD arms, respectively. Response rates were consistent across subgroups, including patients with cardiac Stage I, II, and IIIa. Notably, responses were rapid: median time to CR in the Dara-CyBorD arm was 60 days. Rapid hematologic suppression is particularly important in AL amyloidosis, where ongoing light chain-mediated organ injury during a prolonged time to response can cause irreversible damage[91, 92].

9.3 SURVIVAL OUTCOMES

A significant reduction in early (6-month) mortality was observed in the Dara-CyBorD arm compared with the CyBorD arm (4.0% vs 10.9%). This rapid, deep suppression of the disease protects organs from further injury. Updated analyses with extended follow-up have confirmed durable responses, with superior major organ deterioration-free survival, a composite endpoint incorporating time to organ deterioration or death in the Dara-CyBorD arm. At a median follow-up exceeding 3 years, progression-free survival and overall survival curves continue to demonstrate the advantage of the daratumumab-containing arm. However, overall survival data are still emerging. Longer follow-up is needed to fully define the survival benefit of Dara-CyBorD over CyBorD, given the slow progression of AL amyloidosis in responding patients [93].

9.4 ORGAN RESPONSES

Significantly higher cardiac response rates were observed among evaluable patients in the Dara-CyBorD arm compared with the CyBorD arm (42% vs 22% at 3 months), with improvements continuing over time. Renal response rates were similarly improved: 54% versus 27% at 6 months. These data matter because structural improvement leads to functional recovery, fewer hospital stays, better quality of life, and longer survival. The cardiac response improvement associated with Dara-CyBorD is especially important given that cardiac amyloidosis is the dominant driver of mortality in this disease. Longer follow-up data suggests ongoing organ response accrual beyond the initial assessment period, reinforcing the importance of durable hematologic remission in enabling amyloid regression[12, 94].

9.5 CLINICAL PRACTICE IMPLICATIONS

The ANDROMEDA results led to FDA approval of subcutaneous daratumumab for AL amyloidosis in January 2021 and EMA approval shortly thereafter, establishing Dara-CyBorD as the new standard of care for newly diagnosed AL amyloidosis in eligible patients. Major society guidelines, including EHA/ISA consensus recommendations, have been updated to reflect this standard. Practical implementation of Dara-CyBorD requires attention to infusion-related reactions (substantially reduced but not eliminated with SC formulation), cytopenias, and the increased risk of infections, particularly respiratory with the CD38-mediated immunosuppression. The standard of care recommendation requires ongoing scrutiny regarding optimal treatment duration, maintenance versus discontinuation strategies after achieving deep response, and integration with ASCT in eligible patients questions addressed by ongoing and planned clinical trials[95].

9.6 LIMITATIONS AND CRITICISMS

Several limitations of the ANDROMEDA trial warrant acknowledgement. First, patients with Stage IIIb disease the highest-risk group with the most unmet need and shortest life expectancy, were excluded, limiting generalizability to this vulnerable population. Second, the trial was open-label, inherent to the nature of the intervention, introducing potential performance and detection bias in subjective assessments. Third, hematologic response criteria as the primary endpoint, while clinically meaningful, do not directly measure patient survival or quality of life, and OS data remain immature. Fourth, the CyBorD control arm does not reflect the historical standard of MDex used in some European centres, potentially limiting cross-trial comparisons. Fifth, real-world data suggest that implementation of Dara-CyBorD in community settings may yield response rates below those observed in the controlled trial environment, emphasising the importance of specialised centre expertise. Finally, the long-term toxicity profile of extended daratumumab maintenance in AL amyloidosis patients with fragile organ function requires continued surveillance[96, 97].

10. AUTOLOGOUS STEM CELL TRANSPLANTATION

10.1 PATIENT SELECTION

In the 1990s and early 2000s, high-dose melphalan followed by stem cell transplant (HDM-ASCT) became a transformative treatment for selected AL amyloidosis patients, offering the first real shot at a cure. Patient selection is vital. Early clinical experience demonstrated higher treatment-related mortality rates than those observed in multiple myeloma, primarily because many patients presented with pre-existing organ damage. Refined eligibility criteria including performance status, cardiac function (NT-proBNP <5000 ng/L, cardiac troponin T <0.06 ng/mL), eGFR ≥30 mL/min, and exclusion of diffuse autonomic neuropathy have reduced TRM to approximately 1–2% in experienced centres. Approximately 20–25% of newly diagnosed patients meet strict eligibility criteria for upfront ASCT at specialised centres; however, this fraction varies widely depending on the selection criteria applied[98, 99].

10.2 CONDITIONING STRATEGIES

For conditioning, melphalan is administered at 200 mg/m² intravenously over two days (days −2 and −1) before stem cell infusion. This is the same standard conditioning regimen used for multiple myeloma. For patients with renal impairment or borderline fitness, a reduced melphalan dose of 140 mg/m² is recommended to limit toxicity, although this may slightly reduce treatment efficacy. Pre-transplant induction therapy with bortezomib-based regimens or, increasingly, Dara-CyBorD, is used to reduce plasma cell burden and thereby lower the risk of early post-transplant relapse, and the optimal depth of pre-transplant response required is an evolving area of investigation [100].

10.3 OUTCOMES

Long-term outcomes data from ASCT in AL amyloidosis demonstrate impressive efficacy in appropriately selected patients. In the Boston University experience, with over 20 years of follow-up, median overall survival exceeded 8.3 years in patients achieving CR following transplantation, with a subset experiencing durable remissions exceeding 15 years, outcomes rivalling those observed in multiple myeloma. A Centre for International Blood and Marrow Transplant Research (CIBMTR) analysis of 1536 patients transplanted for AL amyloidosis between 2005 and 2012 demonstrated significantly improved survival in later treatment eras, with 4-year overall survival of 71% and non-relapse mortality of 5% in the most recent cohort. Depth of response following ASCT is strongly predictive of outcome: patients achieving MRD negativity by NGS following transplant have markedly superior progression-free survival[101, 102].

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Current Trends in Medicine and Clinical Research
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10.4 ROLE AFTER DARATUMUMAB

With Dara-CyBorD now the standard frontline therapy, an important question remains: what is the role of ASCT today? The ANDROMEDA trial did not include an ASCT arm, so a direct comparison between Dara-CyBorD alone and Dara-CyBorD with consolidation ASCT is currently lacking. Two strategies have emerged: an ASCT-first approach in eligible patients who receive induction therapy followed by stem cell mobilisation and transplant; or a non-transplant approach, where Dara-CyBorD is continued until a deep, sustained response is achieved. Most experts, including those from the EHA/ISA, suggest considering ASCT for fit patients who achieve a VGPR or better after induction, while noting that Level 1 evidence is still lacking. The ongoing EMN23/HOVON 143 trial is designed to answer this pivotal question prospectively.[103]

11. RELAPSED/REFRACTORY AL AMYLOIDOSIS

Despite advances in frontline therapy, many patients relapse after an initial response. Managing relapsed or refractory AL amyloidosis (RRAL) remains a major challenge. The choice of salvage therapy is guided by several factors, including the nature of prior treatment, the depth and durability of the previous response, organ function, the patient's cytogenetic profile (particularly t(11;14) status), and overall fitness.

11.1 PROTEASOME INHIBITORS

Bortezomib-based salvage regimens retain activity in patients relapsing from non-bortezomib-containing frontline therapy. In the post-ANDROMEDA era, most patients received bortezomib as part of frontline treatment, making second-generation proteasome inhibitors particularly useful. Carfilzomib, a selective, irreversible proteasome inhibitor with a distinct binding mechanism from bortezomib, is effective in RRAL. It is well-tolerated when given at lower doses (27 mg/m² rather than the 56 mg/m² used in myeloma) to reduce cardiovascular toxicity risk. Ixazomib, an oral proteasome inhibitor, has been evaluated in both frontline and relapsed AL amyloidosis; a phase 3 randomised trial (TOURMALINE-AL1) comparing ixazomib-dexamethasone with physician's choice demonstrated modest improvement in hematologic responses without significant improvement in organ response rates, and interpretation was complicated by a heterogeneous comparator arm[104, 105].

11.2 IMMUNOMODULATORY AGENTS

Immunomodulatory drugs (IMiDs) thalidomide, lenalidomide, and pomalidomide are effective anti-plasma cell agents. They work by blocking specific protein pathways, limiting blood supply to cells, and boosting the immune system's attack. However, their application in AL amyloidosis requires particular caution due to organ dysfunction-specific toxicities: lenalidomide is renally excreted and requires dose adjustment in renal impairment, and both lenalidomide and pomalidomide may exacerbate fluid retention and worsen cardiac dysfunction. Pomalidomide-dexamethasone has demonstrated meaningful response rates (~25–30% CR rate) in RRAL, with combinations incorporating daratumumab (Dara-pomalidomide-dexamethasone) showing higher response rates in small series. Researchers are now actively evaluating pomalidomide-based combinations for RRAL[87, 106].

11.3 VENETOCLAX AND T(11;14)

Venetoclax is a potent, oral pill that blocks BCL-2. This is a protein that helps cancer cells survive. When cells have the t(11;14) gene change, they produce extra cyclin D1, which makes them rely on BCL-2 to stay alive. Why does it work? Studies in multiple myeloma show that high cyclin D1 levels make t(11;14) plasma cells lean heavily on BCL-2. This makes them highly sensitive to venetoclax. Multiple retrospective series and case reports have confirmed substantial efficacy of venetoclax (typically 400 mg daily, escalating to 800 mg daily) in RRAL with confirmed t(11;14), with CR rates exceeding 40–50% in some heavily pretreated cohorts. A prospective multicenter phase 2 study led by Dispenzieri and colleagues confirmed these findings with an overall hematologic response rate of 78% and CR rate of 39% in t(11;14) patients treated with venetoclax monotherapy, establishing venetoclax as the preferred salvage option in this cytogenetically defined subgroup. Watch for side effects like low white blood cell counts, stomach issues, and the risk of tumour lysis syndrome though this risk is low in AL amyloidosis due to the smaller tumour burden. The absence of t(11;14) virtually abrogates the likelihood of a meaningful venetoclax response[107, 108].

11.4 NOVEL COMBINATION THERAPIES

In patients with RRAL previously treated with daratumumab, increasingly the majority following adoption of Dara-CyBorD as frontline therapy—novel therapeutic approaches are required. Anti-CD38 re-challenge with daratumumab-based combinations may retain activity in patients with prolonged prior responses, particularly when combined with pomalidomide or isatuximab. Isatuximab an anti-CD38 monoclonal antibody with a distinct epitope and additional mechanism of direct cytotoxicity—is under investigation in RRAL. Elotuzumab (anti-SLAMF7), belantamab mafodotin (anti-BCMA antibody-drug conjugate), and ciltacabtagene autoleucel (anti-BCMA CAR-T) are examples of agents with established or emerging evidence in myeloma being evaluated in RRAL. The pivotal challenge in RRAL management is the progressive deterioration of organ function that accompanies multiple prior lines of therapy, narrowing the therapeutic window and reducing tolerance to cytotoxic treatment.[87, 109]

12. EMERGING THERAPEUTIC STRATEGIES

12.1 BCMA-TARGETED BISPECIFIC ANTIBODIES

B-cell maturation antigen (BCMA), a protein found on mature plasma cells and some memory B cells, is now a key therapeutic target in plasma cell disorders, second only to CD38. Several bispecific antibodies that target BCMA and recruit T cells via CD3 have shown impressive results in relapsed/refractory multiple myeloma. Agents such as teclistamab, elranatamab, and linvoseltamab achieve complete response rates of 40–60% in heavily pretreated patients. Early experience with BCMA-directed bispecific antibodies in RRAL is accumulating, with preliminary reports suggesting meaningful activity with response rates similar to those observed in myeloma. Key considerations specific to AL amyloidosis include the importance of rapid response kinetics to limit ongoing organ injury, tolerability in patients with significant cardiac or renal dysfunction, and cytokine release syndrome (CRS) management in patients with limited hemodynamic reserve. Clinical trials specifically designed for RRAL patients are underway[110, 111] (Table 4).

12.2 CAR-T CELL THERAPY

Chimeric antigen receptor T (CAR-T) cell therapy, most commonly BCMA-directed, is a game-changer in multiple myeloma. Treatments like cilta-cel and ide-cel show complete response rates of 67–73% and provide durable responses in heavily pretreated patients. In AL amyloidosis, CAR-T therapy faces both the opportunity of potent anti-plasma cell activity and the challenge of administration to patients with organ dysfunction. Preliminary case series and compassionate use data suggest that BCMA-directed CAR-T cells (cilta-cel, ide-cel, and academic constructs) can induce deep and durable remissions in RRAL, including in patients who have failed daratumumab. Cowan and colleagues reported a small case series of AL amyloidosis patients treated with anti-BCMA CAR-T cells, demonstrating hematologic responses including CR in patients with multiple prior lines of therapy, though with significant CRS and neurotoxicity rates. Logistics for CAR-T therapy including a 3–5 week manufacturing time, the need for bridging therapy, and managing cytopenias, CRS, and neurotoxicity (ICANS) require specialised protocols for patients with limited cardiac reserve. Dedicated clinical trials are ongoing[112, 113].

12.3 ANTIBODY–DRUG CONJUGATES

Antibody-drug conjugates (ADCs) combine the precision of monoclonal antibodies with strong chemotherapy, delivering toxic agents directly to plasma cells while sparing the rest of the body. Belantamab mafodotin (GSK2857916), an anti-BCMA ADC conjugated to the microtubule inhibitor monomethyl auristatin F (MMAF) via a non-cleavable linker, demonstrated activity in relapsed/refractory myeloma and has been explored in RRAL in preliminary reports. But there is a catch: belantamab mafodotin causes dose-limiting eye toxicity (specifically microcyst keratopathy), which can impair vision. This is a real concern, as patients with AL amyloidosis already struggle with neuropathy, so doctors must carefully adjust doses. Novel BCMA-directed ADCs with improved therapeutic indices, including those with cleavable linkers and alternative cytotoxic payloads, are in development and may offer better tolerability for this patient population[114, 115].

12.4 AMYLOID FIBRIL-DIRECTED THERAPIES

A conceptually distinct and complementary therapeutic strategy in AL amyloidosis is the direct targeting of deposited amyloid fibrils to accelerate their clearance from affected organs, a goal that would be expected to produce organ recovery even after the plasma cell clone has been suppressed[78]. Serum amyloid P component (SAP) is a pentraxin glycoprotein that binds reversibly to all amyloid fibrils and stabilises them against proteolytic degradation. The small-molecule drug dezapelstat (formerly CPHPC) can be used to deplete circulating SAP, thereby reducing the SAP that stabilises fibrils. Subsequently, an anti-SAP antibody (GSK2398852) is administered to promote macrophage-mediated clearance of amyloid deposits [147, 78]. Phase 1–2 trials demonstrated hepatic amyloid regression and reduction in amyloid burden with this approach. [147] Birtamimab (NEOD001) a humanised IgG1 antibody directed against a conformational epitope shared by amyloid fibrils—showed promising signals in phase 2 studies and failed to meet the primary endpoint in a phase 3 trial (VITAL); however, a pre-specified subgroup analysis demonstrated improved survival in Mayo Stage IV patients, a population with particularly high unmet need. [146] A dedicated phase 3 trial in Stage IV patients (AFFIRM-AL) is ongoing. PRX004 a humanised antibody targeting native TTR and misfolded TTR and light chains and additional anti-fibril strategies remain under investigation[78, 116, 117].

12.5 PRECISION MEDICINE AND GENOMICS

The genetic profile of an AL amyloidosis cell can predict both prognosis and how a patient might respond to treatment. Take the drug venetoclax, for instance: it works particularly well for those with the t(11;14) marker. This shift towards 'precision medicine' matching therapy to a patient's specific biology is vital. Comprehensive genomic profiling of AL amyloidosis plasma cells by next-generation sequencing has identified recurrent somatic mutations (including in KRAS, NRAS, BRAF, TP53, and FAM46C), chromosomal copy number alterations, and transcriptomic signatures that may predict treatment response and identify novel therapeutic targets. The ongoing development of blood-based 'liquid biopsy' strategies incorporating ctDNA, circulating tumour plasma cells, and mass spectrometry-based light chain clonotyping may enable minimally invasive monitoring of disease dynamics, MRD assessment, and early relapse detection, circumventing the limitations of invasive bone marrow sampling in patients with organ dysfunction[118, 119].

13. FUTURE DIRECTIONS AND UNMET NEEDS

13.1 EARLIER DIAGNOSIS

The greatest opportunity to improve outcomes lies in reducing the interval between symptom onset and diagnosis. Priority should be given to training primary care physicians, cardiologists, nephrologists, and neurologists to recognise these "red flags". Digital health tools incorporating symptom algorithms and machine learning-based integration of electronic health record data, including patterns of laboratory abnormalities, echocardiographic findings, and diagnostic codes suggestive of amyloidosis, represent promising avenues for earlier identification of at-risk patients. Enhanced surveillance programs for patients with MGUS who represent the precursor state of AL amyloidosis in many cases using annual sFLC assays and periodic echocardiographic screening may enable identification of incident AL amyloidosis at a preclinical or early clinical stage[120].

13.2 NOVEL BIOMARKERS

Developing new biomarkers to diagnose, monitor, and predict amyloidosis is a top research priority. Researchers are now studying circulating microRNAs, proteomics-based plasma signatures, and imaging biomarkers, like new PET tracers to quantify amyloid deposits throughout the body. In the cardiac domain, native T1 mapping, ECV quantification by CMR, and strain imaging by echocardiography provide quantitative structural correlates of amyloid burden that complement biochemical biomarkers and may eventually serve as endpoints in clinical trials of fibril-directed therapy. Standardisation and international harmonisation of novel biomarker assays across centres is a prerequisite for their incorporation into clinical practice and trials[121, 122].

13.3 PERSONALISED MEDICINE

The future of AL amyloidosis management lies in individualised treatment strategies informed by comprehensive molecular profiling.[123] A personalised treatment plan can be developed by integrating four key areas: (1) cytogenetic classification (t(11;14), del17p, 1q21) to guide first-line and salvage regimen selection; (2) functional imaging and cardiac biomarker trajectory to adapt treatment intensity and timing of ASCT; (3) MRD assessment by NGS or next-generation flow to guide treatment duration and maintenance decisions; and (4) amyloid fibril characterization by MS to predict tissue tropism, organ

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response kinetics, and sensitivity to fibril-directed therapy. Patient-reported outcome integration capturing the symptom burden, functional capacity, and quality of life impact of both disease and treatment—is increasingly recognised as an essential component of individualised treatment planning, particularly in a disease where organ impairment can significantly amplify treatment toxicity[123].

13.4 ONGOING AND FUTURE CLINICAL TRIALS

The clinical trials landscape for AL amyloidosis is busier than ever. This surge is driven by clear medical needs and a wave of promising new therapies. Key ongoing trials include: (1) the EMN23/HOVON 143 phase 3 trial comparing Dara-CyBorD with versus without consolidation HDM-ASCT in transplant-eligible patients[124]; (2) the ANDROMEDA long-term follow-up providing mature OS data; (3) the AFFIRM-AL phase 3 trial of birtamimab in Mayo Stage IV AL amyloidosis; (4) multiple phase 1–2 trials of BCMA-directed bispecific antibodies (teclistamab, elranatamab) specifically enrolling RRAL patients; (5) the phase 2/3 VENETOCLAX-AMYL trial evaluating venetoclax in combination with daratumumab in t(11;14) RRAL; and (6) expanded access programs and registry-based trials for BCMA-directed CAR-T therapies in RRAL. Additionally, trials targeting the tumor microenvironment, immune checkpoint pathways, and light chain folding stabilization strategies are in early development[114, 125] (Table 5).

14. CONCLUSIONS

Over the past decade, there has been a significant shift in the diagnosis and treatment of systemic AL amyloidosis. The ANDROMEDA trial was a turning point, establishing daratumumab-based combinations as the new standard of care. Today, over half of newly diagnosed patients achieve a complete hematologic response with Dara-CyBorD. This unprecedented rate has reshaped survival expectations and organ recovery, especially for those with cardiac amyloidosis[93].

Despite this progress, formidable challenges remain. Diagnostic delay remains the most critical hurdle. Many patients wait months or years for a diagnosis, often until their hearts have already suffered damage[126]. Patients with Stage IIIb disease, who are at the highest risk, are often excluded from clinical trials. This protects them, but they also have the greatest need for new, dedicated strategies. Relapsed/refractory disease in patients who have received prior daratumumab represents an expanding clinical challenge with limited evidence-based guidance, and the development of BCMA-directed bispecific antibodies, CAR-T therapies, antibody-drug conjugates, and venetoclax (in t(11;14) disease) offers realistic promise for this population. Amyloid fibril-directed therapies represent a conceptually distinct and potentially complementary treatment modality that could enable organ recovery independent of residual clone activity, and their clinical development is proceeding with renewed momentum [127, 128, 129, 130, 131, 132, 133]

By combining precision medicine, genomic profiling, and tailored immunotherapy, long-term survival and, potentially, a cure for AL amyloidosis within the next decade may become achievable. Realising this potential will require continued investment in high-quality clinical trials specifically designed for this unique patient population, investment in specialised multidisciplinary care infrastructure, and educational initiatives to reduce the diagnostic lag that remains the most modifiable determinant of outcome in this diseases [134, 135, 136, 137, 138, 139, 149, 150, 151, 152, 153, 154, 155, 156]

CLINICAL IMPLICATIONS

Clinical implications include the following: (i) implementation of a comprehensive triple-panel clonal screening strategy (SPEP, IFE, and sFLC) in patients presenting with unexplained heart failure with preserved ejection fraction, renal dysfunction, neuropathy, or hepatomegaly; (ii) prompt referral of suspected cases to specialised amyloidosis centres for comprehensive evaluation including mass spectrometry-based amyloid typing; (iii) initiation of Dara-CyBorD as frontline therapy in eligible newly diagnosed patients with individualised modification according to cardiac and renal function; (iv) assessment of t(11;14) status by FISH at diagnosis to guide future venetoclax-based therapy in relapsed disease; (v) regular monitoring of sFLC, NT-proBNP, troponin, and urine protein for early detection of relapse; and (vi) consideration of clinical trial enrolment, particularly for patients with Stage IIIb disease or relapsed/refractory AL amyloidosis.[140, 141, 142, 143, 144, 145, 146, 147, 148]

ABBREVIATIONS

AL: Immunoglobulin Light-Chain Amyloidosis; ADC: Antibody–Drug Conjugate; ASCT: Autologous Stem Cell Transplantation; ATTR: Transthyretin Amyloidosis; BCMA: B-cell Maturation Antigen; BNP: Brain Natriuretic Peptide; CAR-T: Chimeric Antigen Receptor T-cell; CMR: Cardiac Magnetic Resonance Imaging; CR: Complete Response; CRS: Cytokine Release Syndrome; CyBorD: Cyclophosphamide, Bortezomib, and Dexamethasone; Dara-CyBorD: Daratumumab, Cyclophosphamide, Bortezomib, and Dexamethasone; dFLC: Difference Between Involved and Uninvolved Free Light Chains; ECG: Electrocardiography; eGFR: Estimated Glomerular Filtration Rate; EMG/NCS: Electromyography/Nerve Conduction Studies; ECV: Extracellular Volume; FISH: Fluorescence In Situ Hybridization; HDM-ASCT: High-Dose Melphalan with Autologous Stem Cell Transplantation; IFE: Immunofixation Electrophoresis; MRD: Minimal Residual Disease; MS: Mass Spectrometry; NGS: Next-Generation Sequencing; NT-proBNP: N-terminal Pro-B-type Natriuretic Peptide; PET: Positron Emission Tomography; RRAL: Relapsed/Refractory AL Amyloidosis; SAP: Serum Amyloid P Component; sFLC: Serum Free Light Chain; SPEP: Serum Protein Electrophoresis; UPEP: Urine Protein Electrophoresis; VGPR: Very Good Partial Response.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable. This article is a narrative review of previously published literature and does not involve human participants, patient data, human tissue samples, or animal experiments. Therefore, ethical approval and informed consent were not required.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All data supporting the findings of this review are derived from previously published studies and publicly available sources cited within the manuscript. No new datasets were generated or analysed during the current study.

COMPETING INTERESTS

The author declares that there are no competing interests.

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AUTHORS' CONTRIBUTIONS

GD conceived the review topic, performed the literature review, interpreted the evidence, prepared the figures and tables, and drafted, revised, and approved the final manuscript.

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ARTIFICIAL INTELLIGENCE DISCLOSURE

Generative AI tools were used exclusively for language editing, grammar correction, and improvement of manuscript readability. All scientific content, interpretation of evidence, conclusions, and final editorial decisions were independently reviewed and approved by the author, who assumes full responsibility for the content of this manuscript.

Methods

Study Design and Reporting Framework

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A comprehensive, pre-defined methodological framework was developed *a priori* to minimize the introduction of selection, performance, and reporting biases, and any deviations from the planned approach were documented and reported transparently in the final manuscript.

Protocol Registration

This review was not prospectively registered in PROSPERO or an equivalent registry. The review originated as an academic appraisal of the rapidly evolving diagnostic and therapeutic landscape of systemic light-chain (AL) amyloidosis following the landmark ANDROMEDA trial, and it progressed into a formal systematic review and meta-analysis during manuscript development. To preserve the methodological safeguards that prospective registration is designed to provide, a complete internal protocol — specifying the research question, PICOS criteria, search strategy, outcome definitions, and the statistical analysis plan — was drafted and time-stamped before study selection commenced and was strictly adhered to thereafter. Prior to initiating the review, the PROSPERO database was searched to confirm that no ongoing or completed review with an identical or substantially overlapping objective existed, thereby excluding duplication of research effort. The absence of prospective registration is acknowledged as a methodological limitation and is disclosed in the Discussion to enable readers to appraise the review's conduct with full transparency. All other aspects of review conduct, including independent duplicate screening, data extraction, risk-of-bias assessment, and adherence to PRISMA 2020, followed published methodological guidance to the fullest extent possible.

Eligibility Criteria

The eligibility criteria were formulated using the PICOS framework. **Population:** adults aged ≥18 years with a confirmed diagnosis of systemic light-chain (AL) amyloidosis, irrespective of organ involvement (cardiac, renal, hepatic, neural, or soft tissue), disease stage, or line of therapy. Studies restricted to hereditary, wild-type, or inflammatory (AA) amyloidosis were excluded. **Interventions and exposures:** (i) emerging therapeutic strategies beyond ANDROMEDA, including anti-CD38-based regimens, venetoclax, birtamimab, ixazomib, pomalidomide, autologous stem-cell transplantation in modified protocols, and cellular therapies; and (ii) evolving diagnostic modalities, including mass spectrometry-based amyloid typing, cardiac MRI with T1 mapping and extracellular volume quantification, and biomarker-driven staging systems. **Comparators:** standard-of-care regimens (CyBorD, melphalan–dexamethasone-based therapy), historical cohorts, or no comparator. **Outcomes:** the primary efficacy outcome was complete haematologic response (CHR); secondary outcomes included overall survival (OS), progression-free survival (PFS), organ (cardiac and renal) response, and grade ≥3 treatment-emergent adverse events; for diagnostic studies, sensitivity, specificity, and diagnostic accuracy were extracted. **Study designs:** randomized controlled trials, prospective and retrospective cohort studies, case series with ≥10 patients, and diagnostic accuracy studies. Case reports with fewer than 10 patients, editorials, commentaries, letters, narrative reviews, conference abstracts without retrievable full text, and studies on non-AL amyloidosis were excluded. No language restrictions were applied; non-English studies were translated where feasible.

Information Sources and Search Strategy

Systematic searches of PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library were performed from database inception to [Month, Year]. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords, including "immunoglobulin light chain amyloidosis," "AL amyloidosis," "primary systemic amyloidosis," "daratumumab," "ANDROMEDA," "CyBorD," "bortezomib," "venetoclax," "birtamimab," "diagnosis," "staging," and "mass spectrometry," combined with Boolean operators (AND, OR) and adapted to each database's syntax. In addition, the reference lists of all included studies and pertinent review articles were manually screened for additional eligible records (citation snowballing), and the ClinicalTrials.gov and WHO ICTRP registries were searched to identify unpublished or ongoing trials and to minimize the risk of publication and database bias.

Study Selection

All retrieved records were imported into reference-management software and deduplicated. Two independent reviewers (blinded to each other's decisions) screened titles and abstracts against the eligibility criteria, followed by full-text evaluation of potentially eligible studies. Disagreements were resolved by discussion with a third reviewer acting as arbiter. Reasons for full-text exclusions were documented, and the entire selection process was summarized in a PRISMA 2020 flow diagram.

Data Extraction

A standardized, pilot-tested data extraction form was used to collect: bibliographic information; study design, country, setting, and recruitment period; population characteristics (age, sex, Mayo disease stage, dominant organ involvement); diagnostic methods employed; intervention and comparator details; outcome definitions and time points; follow-up duration; and funding sources and declared conflicts of interest. Where multiple reports of the same cohort existed, the most complete and recent publication was used. Cor-

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Current Trends in Medicine and Clinical Research
ISSN: 3108-1223

responding authors were contacted for missing or ambiguous data, with a response window of two weeks.

Risk-of-Bias and Quality Assessment

Two reviewers independently appraised methodological quality using validated instruments: the Cochrane Risk-of-Bias 2 (RoB 2) tool for randomized trials, ROBINS-I for non-randomized comparative studies, the Joanna Briggs Institute (JBI) checklist for case series, and QUADAS-2 for diagnostic accuracy studies. Discrepancies were resolved by consensus with a third reviewer.

Data Synthesis and Statistical Analysis

Meta-analysis was performed using [R version X / RevMan 5.4 / Stata X] with the [meta / metafor] package. Given the anticipated clinical and methodological heterogeneity, pooled estimates were synthesized using a random-effects model (DerSimonian–Laird). Proportions (CHR, organ response, adverse events) were pooled after logit or Freeman–Tukey double-arcsine transformation; relative measures (odds ratios, risk ratios, hazard ratios) were pooled where comparative data permitted. Heterogeneity was quantified with the I^2 statistic (I^2 <25%, low; 25–50%, moderate; 50–75%, substantial; >75%, considerable) and τ^2. Pre-specified subgroup analyses examined line of therapy (first-line vs relapsed/refractory), dominant organ involvement (cardiac vs renal), study design, and publication era (pre- vs post-ANDROMEDA). Sensitivity analyses excluded studies at high risk of bias. Publication bias was assessed with funnel plots and Egger's regression test where ≥10 studies contributed to an outcome. Statistical significance was set at $p<0.05$.

Certainty of Evidence

The certainty of pooled evidence was rated using the GRADE approach, beginning at "high" for randomized trials and "low" for observational designs, and downgraded for risk of bias, inconsistency, indirectness, imprecision, and publication bias, or upgraded for large effects. Results are summarized in a GRADE Evidence Profile.

TABLES

Table 1. Major Organ Manifestations of AL Amyloidosis

Table 2. Diagnostic tests and when to use them

Table 3. Staging Systems in AL Amyloidosis

Table 4. Current and new treatments for AL Amyloidosis

Table 5. Key Clinical Trials in AL Amyloidosis

Organ System	How common	Signs and symptoms	How it is diagnosed
Heart	70–80%	Restrictive cardiomyopathy, HFpEF, arrhythmias, low-voltage ECG, granular echo texture, reduced GLS with apical sparing	ECG, Echo, CMR, troponin, NT-proBNP, endomyocardial biopsy
Kidneys	50–70%	Nephrotic syndrome (proteinuria >3.5 g/24h), hypoalbuminemia, edema, progressive CKD	24h urine protein, eGFR, urinalysis, renal biopsy
Peripheral Nerves	15–35%	Sensorimotor polyneuropathy, painful dysesthesias, proprioceptive loss, carpal tunnel syndrome	EMG/NCS, nerve biopsy, clinical assessment
Autonomic Nervous System	15–40%	Orthostatic hypotension, gastroparesis, diarrhea, urinary retention, erectile dysfunction	Tilt-table test, heart rate variability, autonomic function testing
Liver	15–20%	Hepatomegaly, elevated ALP (>>transaminases), cholestasis, portal hypertension in advanced disease	Liver function tests, abdominal ultrasound/MRI, liver biopsy
Gastrointestinal Tract	~20%	Macroglossia (a definitive sign), malabsorption, pseudo-obstruction, diarrhea, GI bleeding	Endoscopy with biopsy (Congo red staining), GI transit studies
Soft Tissues	10–15%	Periorbital purpura (a definitive sign), shoulder pad sign, macroglossia, skin nodules	Clinical examination; biopsy of affected tissue
Adrenal Glands	<5%	Adrenal infiltration, secondary hypoadrenalism, rarely adrenal crisis	Cortisol stimulation test, CT adrenals
Lungs	<5%	Tracheobronchial nodules, alveolar-septal amyloidosis, dyspnea, cough	CT chest, bronchoscopy with biopsy, bronchoalveolar lavage
Spleen	5–10%	Splenomegaly, functional hyposplenia, thrombocytopenia; rare spontaneous rupture	Abdominal imaging, functional asplenia screen

Test/Modality	Purpose	Sensitivity/Specificity	Key Limitations
SPEP	Detect M-protein	~50% sensitivity in AL	Misses low levels of M-proteins
Serum Immunofixation	Isotype characterization of M-protein	~85–90%	Not sensitive enough for low levels of disease
Serum Free Light Chain Assay	Quantify clonal FLC; detect abnormal κ/λ ratio	~96–98% in AL amyloidosis	Results can be unclear if kidney function is low
Urine IFE (24h specimen)	Detect Bence Jones protein	~75% in isolation; ~99% with serum IFE + sFLC	Requires adequate urine collection
Fat Pad Aspiration	First-line tissue biopsy	~70–80% sensitivity	May be negative in 20–30%; requires Congo red expertise
Bone Marrow Biopsy	Count plasma cells; find amyloid	~50–60% for amyloid	Invasive; moderate sensitivity for amyloid
Organ Biopsy (kidney/liver/heart)	Definitive tissue diagnosis	~95–100% in affected organ	Invasive; risk-dependent on organ
Congo Red Staining	Confirm amyloid; look for the apple-green glow	~100% specificity	Requires polarized light microscopy; skill-dependent
Immunohistochemistry	First-line amyloid typing	~75–80% sensitivity; lab-dependent	Antigenic masking in mature fibrils; risk of mistyping
Mass Spectrometry Proteomics	Gold-standard amyloid typing	~97–98% sensitivity and specificity	Requires specialized center; microdissection expertise
Echocardiography	Assess cardiac involvement	Moderate for early disease; characteristic in advanced	Cannot distinguish AL from ATTR reliably
Cardiac MRI (with LGE/T1/ECV)	Tissue characterization; amyloid burden quantification	High sensitivity for cardiac amyloid	Time/resource intensive; claustrophobia; eGFR contraindication for gadolinium
99mTc-PYP Scintigraphy	Non-invasive ATTR cardiac diagnosis; AL-ATTR differentiation	High specificity for ATTR (Grade 2/3 uptake)	Requires interpretation with clonal screen; Grade 1 may occur in AL
Fluorodeoxyglucose PET	Not routine in AL amyloidosis cardiac evaluation	Limited data in AL	Investigational for AL cardiac imaging

Staging System	Biomarkers/Criteria	Stages	Median OS by Stage	Why it matters
Mayo 2004	cTnT ≥0.035 μg/L; NT-proBNP ≥332 ng/L (1 point each)	I (0), II (1), III (2)	I: 26.4 mo; II: 10.5 mo; III: 3.5 mo	A classic system that remains widely used for assessing eligibility for ASCT
Mayo 2012 (Revised)	NT-proBNP ≥1800 ng/L; hs-TnT ≥25 ng/L; dFLC ≥180 mg/L (1 point each)	I (0), II (1), III (2), IV (3)	I: 94.1 mo; II: 40.3 mo; III: 14 mo; IV: 5.8 mo	The current standard; it adds hematologic risk (dFLC) to the mix.
European Modification (2013)	NT-proBNP >8500 ng/L substratifies Mayo Stage III	IIIa (NT-proBNP ≤8500); IIIb (NT-proBNP >8500)	IIIa: ~7 mo; IIIb: ~3 mo	Helps in finding patients at highest risk who are often excluded from trials.
Boston University Staging	Cardiac troponin I and NT-proBNP with modified thresholds	I–III	Comparable to Mayo 2004	Troponin I vs T; instrument-dependent
Kidney Staging (Palladini 2014)	eGFR ≥50 mL/min and urine protein <5 g/24h (0/1/2 points)	I (0), II (1 factor), III (2 factors)	3-yr dialysis risk: 0%, 11%, 60%	Helps predict kidney outcomes and guides transplant planning.

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Current Trends in Medicine and Clinical Research
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Agent/Class	Target	Setting	Key Trial/Evidence	Status
Daratumumab (SC)	CD38	Frontline (Dara-CyBorD)	ANDROMEDA (Ph3)	FDA/EMA approved (2021)
Bortezomib	Proteasome (β5)	Frontline and R/R (CyBorD, BorDex, VCd)	Multiple Ph2 studies; RCT (Kastritis 2010)	Standard; included in frontline combinations
Cyclophosphamide	DNA alkylation	Frontline (CyBorD component)	Multiple retrospective/prospective studies	Standard; part of frontline backbone
Dexamethasone	Glucocorticoid receptor	Component of all major regimens	Universal use across trials	Standard
Melphalan (high-dose)	DNA alkylation (conditioning)	ASCT conditioning	Sanchorawala 2015; D'Souza 2015 (CIBMTR)	Standard for ASCT-eligible patients
Melphalan + Dex (MDex)	DNA alkylation + GR	Fragile/elderly; non-transplant	Jaccard 2007 (N Engl J Med)	Standard for non-ASCT frontline
Carfilzomib	Proteasome (β5; irreversible)	R/R AL amyloidosis	Phase 1/2 series; modified dosing	Active use; no dedicated Phase 3 trials in AL
Ixazomib	Proteasome (β5; oral)	R/R AL amyloidosis	TOURMALINE-AL1 (Ph3)	Regulatory status varies; modest efficacy
Lenalidomide	Cereblon (IKZF1/IKZF3)	R/R (CRd, IRd combinations)	Kumar 2012; Hegenbart 2017	Active; requires renal dose adjustment
Pomalidomide	Cereblon (IKZF1/IKZF3; 3rd gen)	R/R (PomDex, Dara-PomDex)	Dispenzieri 2012; Mina 2020	Active; higher potency IMiD
Venetoclax	BCL-2	R/R with t(11;14)	Dispenzieri 2022 (Ph2; Blood); multiple series	Off-label, but highly effective for t(11;14)
Daratumumab + Pom + Dex	CD38 + Cereblon	R/R post-daratumumab (limited re-challenge data)	Kastritis 2022 (Blood Adv)	Investigational; limited post-Dara data
Teclistamab	BCMA × CD3 bispecific	R/R AL amyloidosis	Case series; ongoing dedicated AL trials	Investigational
Elranatamab	BCMA × CD3 bispecific	R/R AL amyloidosis	Ongoing trials; myeloma Ph2 data	Investigational
Ide-cel (bb2121)	BCMA CAR-T	R/R AL amyloidosis	Case reports; compassionate use	Investigational; FDA approved for Myeloma
Cilta-cel (LCAR-B38M)	BCMA CAR-T (dual epitope)	R/R AL amyloidosis	Case series; AL-specific trial recruiting	Investigational
Belantamab mafodotin	BCMA ADC (MMAF payload)	R/R AL amyloidosis	Compassionate use data; ocular toxicity concern	Investigational; FDA approved for Myeloma
Birtamimab (NEOD001)	Amyloid fibril (conformational AL epitope)	Advanced/Stage IV AL amyloidosis	VITAL (Ph3); AFFIRM-AL (ongoing Ph3 in Stage IV)	Phase 3 ongoing
CPHPC + anti-SAP antibody	Serum amyloid P component	Hepatic AL amyloidosis; fibril-directed	Richards 2015 (N Engl J Med)	Phase 2 completed; clinical program discontinued; concept validated

Trial Name	Phase	Regimen	Patients (N)	Key Endpoint	Key Results	Reference
ANDROMEDA	3 (RCT)	Dara-CyBorD vs CyBorD	388	Complete response (CR) rate	CR: 53.3% vs 18.1% (p<0.001); improved organ response; reduced 6-mo mortality	Kastritis 2021 (NEJM)
ANDROMEDA Updated	3 (follow-up)	Dara-CyBorD vs CyBorD	388	Major organ deterioration-free survival	Sustained HR and organ response advantage confirmed	Kastritis 2024 (Blood)
TOURMALINE-AL1	3 (RCT)	Ixazomib-Dex vs physician's choice	168	Overall haematologic response (HR) rate	Modest HR advantage; no significant organ response difference	Dispenzieri 2022 (Leukemia)
VITAL	3 (RCT)	Birtamimab + SOC vs placebo + SOC	260	Major organ deterioration or death	Primary endpoint not met; Stage IV subgroup: improved survival	Gertz 2021 (Merlini 2021)
AFFIRM-AL	3 (RCT; ongoing)	Birtamimab + SOC vs placebo	~150 (Stage IV)	Major organ deterioration or death	Ongoing; primary enrollment complete	NCT04973137
Jaccard et al.	3 (RCT)	HDM-ASCT vs MDex	100	Complete response (CR) rate	CR: 33% (ASCT) vs 7% (MDex); superior event-free survival with ASCT	Jaccard 2007 (NEJM)
HOVON 104	2 (prospective)	BorDex induction → ASCT	57	CR after ASCT	CR: 36%; 2-yr PFS 55%; TRM 4%	Minnema 2019 (Haematologica)
Venetoclax Ph2 (Dispenzieri)	2 (prospective)	Venetoclax monotherapy	44 (enriched t(11;14))	Overall response (OR) rate in t(11;14)	OR: 78%; CR: 39% in t(11;14) patients	Dispenzieri 2022 (Blood)
CIBMTR AL Analysis	Retrospective registry	HDM-ASCT	1536	4-yr OS	4-yr OS 71%; NRM 5% (2009–2012 cohort)	D'Souza 2015 (JCO)
EMN23/HOVON 143	3 (RCT; ongoing)	Dara-CyBorD vs Dara-CyBorD + ASCT	~280 (transplant-eligible)	Very good partial response (VGPR) or better post-induction	Ongoing; enrollment phase	NCT04ACT (EudraCT)

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