Light Chain (AL) Amyloidosis for Nephrologists – Treatment Standard

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Light-chain (AL) amyloidosis for nephrologists—treatment standard

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ABSTRACT

Amyloidosis is a group of complex diseases caused by the misfolding and aggregation of proteins into amyloid fibrils. Light-chain (AL) amyloidosis is one of the most prevalent forms of amyloidosis, characterized by the gradual proliferation of light chains from plasma cell clones. A growing body of evidence has contributed to our understanding of its pathogenesis, presentation and clinical course. Increased recognition of its clinical sequelae has increased the prevalence of AL amyloidosis. Renal involvement, seen in up to 70% of cases, is particularly challenging due to its impact on quality of life and access to treatment options. Thus, early recognition of its unique sequelae, appropriate staging and a comprehensive understanding of treatment options balanced by their organ toxicities are crucial to managing this disease. We review the current treatment standards and discuss novel developments in the pathophysiology, diagnosis, outcome prediction and management of AL amyloidosis for the Nephrologist.

Keywords: AL amyloidosis, biomarker, chemotherapy, proteinuria, renal amyloidosis

'IN A NUTSHELL'

1. The pathophysiology and multi-system involvement of light-chain (AL) amyloidosis deems that early recognition, staging and treatment of the disease is crucial. Renal involvement has a high morbidity and requires multidisciplinary management.
2. Proteinuria and progressive renal dysfunction are key symptoms in renal amyloidosis. If suspected, a work-up for monoclonal protein, tissue biopsy (surrogate or target site) with mass spectrometry if available or immunofluorescence to type the precursor protein should be pursued. Novel, blood-based immunoassays are on the horizon for diagnosis.
3. Staging systems exist for both mortality and progression to end-stage kidney disease, typically based on proteinuria and estimated glomerular filtration rate. Close following for renal progression criteria is key for nephrologists.
4. Daratumumab-containing regimens are first-line treatment regimens for most patients and typically do not require vast adjustments for renal dysfunction.
5. Novel agents, including novel anti-plasma cell targeted therapies, venetoclax and anti-fibril antibodies, are on the horizon for AL amyloidosis.

INTRODUCTION

Amyloidosis encompasses a group of complex diseases initiated by the misfolding and subsequent aggregation of proteins into cross-β-sheet quaternary structure amyloid fibrils [1]. As a systemic disease, amyloidosis can deposit in nearly any organ in the body, including the kidneys, heart, gastrointestinal tract, liver and peripheral nervous system [2]. AL amyloidosis is one of the most prevalent and severe forms of amyloidosis, with up to 40.5 cases per million as of 2015 [3]. Its pathogenesis is characterized by the gradual proliferation of an indolent plasma cell clone that produces pathogenic, immunoglobulin light chains [3]. Renal AL amyloidosis typically presents with nephrotic-range proteinuria and is an important manifestation to recognize early and pursue rigorous work-up early as it can cause irreversible progression to end-stage kidney disease (ESKD) and limit treatment future options.

The approach to treating AL amyloidosis centers around addressing the underlying clonal plasma cell dyscrasia. The clinical goal is achieving rapid and profound hematologic response (HR), a strong surrogate for overall survival [4]. Daratumumab-containing regimens have recently emerged and can elicit profound hematologic and organ responses [5]. Thus, the median overall survival of AL amyloidosis has steadily increased from 1.4 to 4.6 years from 1980 to 2020 [6]. Additionally, many new therapies exist for relapsed-refractory treatment, including venetoclax and bi-specific antibodies, and may be considered. We review the

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pathophysiology of AL amyloidosis, renal manifestations, staging systems, progression and response criteria, and recent evidence regarding management for the Nephrology audience.

TREATMENT STANDARDS

Pathophysiology

Systemic light-chain (AL) amyloidosis is typically caused by a bone marrow plasma cell clone secreting pathogenic immunoglobulin light chains. These free light chains (FLCs) aggregate into amyloid fibrils and deposit in nearly every organ system except the central nervous system, causing multi-organ dysfunction and failure if untreated.

In the kidneys, AL amyloidogenic fibrils typically deposit in the glomeruli and cause substantial proteinuria [7]. With rapid fibril deposition, patients may experience intratubular amyloid cast nephropathy resulting in acute kidney injury most likely secondary to cast nephropathy or amyloid deposition in the tubulointerstial compartment [8]. Other amyloidosis fibrils, such as ALECT2 or AApoAI/IV amyloidosis, typically accumulate in the tubulointerstitial compartment, causing progressive renal dysfunction [9, 10]. Standardized histopathological scoring systems have been developed for renal amyloidosis that correlate with progression to ESKD [11–13]. Rubinstein *et al.* [12] recently defined an amyloid deposit score on renal biopsy, including glomerular and nonglomerular deposits. The score is a semi-quantitative evaluation of amyloid deposits in the mesangium, capillary wall, interstitium and vasculature for renal biopsy, and has since been validated in AL amyloidosis [13].

Renal AL amyloid deposits typically have slowed, gradual immunologic clearance [14]. Thus, the bulk of treatment for AL amyloidosis focuses on decreasing the production of the light chains to allow gradual renal recovery. Newer treatments are now targeting the pathogenic fibrils themselves, ultimately hastening this process of fibril clearing.

Presentation

The initial presentation of AL amyloidosis is typically non-specific, with generalized symptoms, such as fatigue, weight loss and paresthesia. Unfortunately, this often results in delays in diagnosing AL amyloidosis. One study showed a median time from symptom start to diagnosis of 7 months, with significantly worse mortality if patients were diagnosed >12 months after symptom onset [15]. One study reported that at the time of diagnosis of AL amyloidosis, 69% of patients had more than one organ involved [16]. Thus, recognition of all possible organ manifestations is key for early diagnosis.

Kidney involvement is seen in approximately 70% of patients with AL amyloidosis [7]. This typically presents with nephrotic-range proteinuria, peripheral edema or reduced kidney function. Urinary sediment often lacks casts and typically presents with only fat and oval bodies [8]. As the disease progresses, roughly 19%–24% of patients may require kidney replacement therapy [7, 17].

Cardiac amyloidosis typically presents with heart failure with preserved ejection fraction (HFpEF) and associated symptoms (i.e. dyspnea, fatigue). Echocardiography may show concentric thickening of the left ventricle, enlarged septal diameter and abnormal global longitudinal strain [18]. The liver is another common site of deposition, with one autopsy series suggesting up to 70% of liver involvement [19]. Hepatic AL amyloidosis may present with hepatomegaly, elevated alkaline phosphatase (ALP) or progressive hepatic dysfunction, which is particularly rapid in the rare cases with hyperbilirubinemia [20].

Other amyloid-presenting systems include organomegaly from amyloid deposition (e.g. macroglossia, enlarged salivary glands), neurogenic symptoms (peripheral neuropathy, postural hypotension), constitutional symptoms (fatigue, weight loss), gastrointestinal symptoms (motility disorders, ageusia), musculoskeletal symptoms (bilateral carpal tunnel) and dermatologic symptoms (ecchymosis, petechiae) [21]. Factor X deficiency is a hematologic sequela specific to AL amyloidosis thought to be due to amyloid fibrils or serum amyloid protein (SAP) binding factor X. Thus, patients with AL amyloidosis may present with prolonged prothrombin time and partial thromboplastin time [22].

Patients with monoclonal gammopathy of undetermined significance (MGUS) are at particularly high risk for developing AL amyloidosis. Multiple societal guidelines exist for monitoring patients with MGUS, depending on risk level [23]. These patients should be monitored for early signs of organ involvement before symptoms develop: N-terminal pro-brain natriuretic peptide (NT-proBNP) for cardiac involvement, albuminuria for kidney involvement and alkaline phosphatase (ALP) for hepatic involvement [24].

Diagnosis

For patients who present with albuminuria, peripheral edema and progressive kidney dysfunction, the question of how to "not miss" renal AL amyloid is of great interest. In the setting of non-specific symptoms (dyspnea, fatigue) and an elevated spot urine protein excretion, a 24-h urine protein is the most robust test for diagnostics and future staging [25]. A basic metabolic panel, complete blood count and urinalysis should be done to assess for other causes. Urine microscopy to assess for dysmorphic red blood cells and casts can also be done, although renal amyloid is typically benign under microscopy, as previously discussed. Given the broad differential for glomerular disease, a low threshold exists to test for monoclonal protein in blood and urine.

If AL amyloidosis continues to be suspected, serum/urine immunofixation, serum/urine electrophoresis and measurement of serum-free light chains should be completed to rule out an underlying plasma cell dyscrasia. Of note, serum FLC levels are impacted by chronic kidney disease, and adjusted thresholds proposed by the iSTOPMM consortium are important for the nephrologist to consider [26]. Mass spectrometry has also been proposed as a newer approach for identifying M-protein [27].

If an M-protein is found with concern for amyloidosis, histopathology is needed to diagnose and type the amyloid. Surrogate fat pad and lip biopsies have sensitivity up to 70%–80% and are an appealing first step [28]. Bone marrow biopsy is another avenue for confirmation and is necessary to exclude multiple myeloma and obtain fluorescence *in situ* hybridization (FISH) genetics. Particularly, detection of the t(11;14) translocation is relevant for the treatment of AL amyloidosis (see section Treatment of relapsed/refractory patients) [29]. If amyloid is found on bone marrow biopsy, it is considered localized unless found elsewhere in the body. If a surrogate site biopsy is negative, a kidney biopsy may be unavoidable. Relative contraindications (i.e. small and contracted kidneys with thin cortex, solitary kidney) and absolute contraindications (i.e. uncontrolled bleeding disorders, pyelonephritis, skin infection and patient inability to tolerate) make kidney biopsy challenging in certain patients, and further specialist consultation or referral may be required in these cases [30].

Table 1: Cardiac Staging Systems of AL amyloidosis.

Model	Criteria	Score	Stage
Mayo 2004 [33]	TnT > 0.035 µg/L NT-proBNP > 332 ng/L	+1 +1	0 = Stage I 1 = Stage II 2 = Stage III
European 2015 [34]	TnT >0.035 mcg/L NT-proBNP > 332 ng/L NT-proBNP > 8500 ng/L	+1 +1 +1 if score = 2	0 = Stage I 1 = Stage II 2 = Stage IIIa 3 = Stage IIIb
Mayo 2012 [36]	TnT ≥0.025 ng/mL NT-proBNP ≥1800 pg/mL dFLC ≥18 mg/dL	+1 +1 +1	0 = Stage I 1 = Stage II 2 = Stage III 3 = Stage IV
Boston University 2019 [37]	TnI ≥0.1 ng/mL BNP ≥81 pg/mL BNP ≥700 pg/mL	+1 +1 +1 if score = 2	0 = Stage I 1 = Stage II 2 = Stage III 3 = Stage IIIb

Histopathology of amyloid deposits will display green birefringence when subject to polarized light when stained with Congo red or yellow-green fluorescence with Thioflavin T staining [31]. Confirmation of the subunit protein composition in Congo Red tissue specimens may be done through immunohistochemistry, electron microscopy and mass spectrometry–based analysis. Mass spectrometry has the highest sensitivity (88%) and specificity (96%) for amyloidogenic typing and is considered the gold standard [32]. Organ-specific biomarkers should also be collected at baseline, including 24-h urine protein, serum creatinine, estimated glomerular filtration rate (eGFR), NT-proBNP, troponin and ALP, along with a baseline echocardiogram.

Staging

Following diagnosis, staging is imperative to assess the severity of AL amyloidosis and determine treatment course. Given mortality is primarily driven by cardiac involvement, the first staging system created by the Mayo group in 2004 used Troponin T (TnT) and NT-proBNP with thresholds of TnT <0.035 µg/L and NT-proBNP <332 ng/L [33]. In 2015, a European group modified the Mayo 2004 model to stratify Stage III patients into Stage III vs IIIb if they had NT-proBNP >8500 pg/mL [34]. This modified staging system best detects severe cardiac involvement [35]. In 2012, the Mayo Group revised its model to evaluate plasma clone burden, assessed by the difference between involved and uninvolved circulated free-light chains (dFLC) [36]. In 2019, Boston University created a model that utilizes BNP and Troponin I (TnI) to allow centers without access to NT-proBNP and TnT to stage patients [37]. Thresholds for BNP (81 pg/mL, 700 pg/mL) in the Boston University model were selected by correlation to NT-proBNP from the Mayo 2004 model [37]. The aforementioned staging criteria are summarized in Table 1. Importantly, these staging systems were developed before modern treatment regimens for AL amyloidosis. For example, the utility of dFLC in the Mayo 2012 model has since been questioned as plasma cell–directed therapy has improved [38].

High rates of renal involvement and its clinical impact have led to the development of renal-specific staging and progression models. In 2014, Palladini *et al.* created a renal staging system for AL amyloidosis that included proteinuria (>5 g/24 h) and eGFR (<50 mL/min/1.73 m^2) as high-risk factors predictive of progression to dialysis. However, renal staging and response were not significantly associated with survival [39]. Recently, newer renal staging models have been developed. Kastritis *et al.* developed a model with 24-h proteinuria (UPr) to eGFR ratio (UPr/eGFR) to avoid renal progression criteria that rely solely on eGFR reduction [40]. A more recent renal staging proposed by Basset *et al.* avoids the difficulty of collecting a 24-h urine protein and uses urinary albumin to creatinine ratio (UACR) [41]. However, a separate cohort study by the Boston Medical Center group suggests that urine protein-to-creatinine ratio (UPCR) instead of 24-h UPr changes renal staging in up to 20% of patients and should be used cautiously [25]. The Palladini criteria is the best validated and most used. All renal staging, response and progression criteria are summarized in Table 2.

Staging systems typically describe renal response as >30% reduction in 24-h urine protein without worsening eGFR [42]. More recently, graded response criteria have been described: in the absence of renal progression (≥25% decrease in eGFR): renal complete response (renCR, 24-h proteinuria ≤200 mg/day), very good partial response (renVGPR, >60% reduction in 24-h proteinuria), partial response (renPR, 31%–60% reduction in 24-h proteinuria) and no response (renNR, ≤30% reduction in 24-h proteinuria) [43]. These were validated in renal AL amyloidosis and may help when assessing response to therapy. Graded renal response criteria and organ response criteria are included in Table 3.

Treatment of newly diagnosed patients

Following diagnosis and staging, induction chemotherapy with a four-drug regimen of daratumumab, cyclophosphamide (an alkylating agent), bortezomib (a proteasome inhibitor) and dexamethasone (a steroid) (Dara-CyBorD) is typically indicated for AL amyloidosis [44]. These drugs collectively target the amyloidogenic plasma cell clone, aiming to eradicate the source of pathogenic light chains. The ANDROMEDA trial demonstrated that Dara-CyBorD had higher complete remission rates (53% vs 17%) and HR (92% vs 77%) compared with standard of care [44]. Daratumumab is a monoclonal antibody targeting the plasma cell marker CD38 and is relatively well tolerated [45]. Premedication with steroids, H2 blockers and leukotriene receptor antagonists is recommended to decrease daratumumab-related infusion reactions for the first cycle [45].

Dosing per the ANDROMEDA trial is based on a 28-day cycle: weekly in cycles 1 to 2, every 2 weeks in cycles 3 to 6, and every 4 weeks thereafter for up to 2 years [46]. Cyclophosphamide 300 mg/m^2 orally or intravenously and bortezomib 1.3 mg/m^2 subcutaneously were given weekly for up to six cycles [46]. Finally, dexamethasone is administered weekly, with a starting dose of 40 mg, and the dose is reduced in certain patient populations (elderly age, low body mass index, hypervolemia, poorly controlled type 2 diabetes or prior adverse reaction to steroids) [46].

Current recommendations suggest induction with two to four cycles of Dara-CyBorD and assessing HR. If the patient has VGPR or CR, completing six total cycles of Dara-CyBorD followed by single-agent Daratumumab for 2 years is recommended [44]. However, if the patient has <VGPR, it is reasonable to consider other chemotherapy regimens or referral for high-dose melphalan and autologous stem cell transplantation (HDM/SCT).

Alternative chemotherapy options include bortezomib, melphalan (an alkylating agent) and dexamethasone (BMDex) triplet therapy, found to be useful in cardiac disease. However, this requires renal dose adjustment and has a higher myelotoxicity risk than cyclophosphamide as the alkylating agent [47, 48]. If daratumumab is not available for newly diagnosed, transplant-ineligible

Table 2: Renal staging systems for AL amyloidosis.

Model	Criteria	Score	Stage	Response	Progression
Palladini *et al.* (2014) [39]	UPr >5 g/24 h eGFR <50 mL/min	+1 +1	0 = Stage I 1 = Stage II 2 = Stage III	>30% decrease in 24 h urine protein in absence of kidney progression	≥25% decrease in eGFR
Kastritis *et al.* (2017)	24 h UPr/eGFR <30 24 h UPr/eGFR 30–99 24 h UPr/eGFR ≥100		Stage I Stage II Stage III	≥25% decrease in 24 h UPr/eGFR OR 24 UPr/eGFR <1000 if initially >100	≥25% increase in 24 h UPr/eGFR ratio or ratio ≥100
Basset *et al.* (2022)	eGFR <50 mL/min UACR ≥3600	+1 +1	0 = Stage I 1 = Stage II 2 = Stage III	≥30% decrease in UACR in absence of kidney progression	≥25% decrease in eGFR

Table 3: Response definitions for AL amyloidosis.

Organ		Response	Progression
Hematologic [97]	CR	Normalization of FLC and ratio[a] AND negative serum and urine immunofixation	From CR, any detectable monoclonal protein or abnormal FLC ratio
	VGPR PR	dFLC <40 mg/L dFLC decrease >50%	From PR, 50% increase in serum M protein to >0.5 g/dL or 50% increase in urine M protein to >200 mg/day For patients with stable disease or partial response, serum FLC increase of 50% to >100 mg/L "High-risk dFLC progression:" dFLC >20 mg/L, level >20 % of baseline value, and >50% increase from value reached at best response [98]
	No response (NR)	Less than partial response	
Cardiac [97]		Decrease of NT-proBNP of >30% and 300 ng/L (baseline NT-proBNP ≥650 ng/L)[b] NYHA class response (≥2 class decrease in subjects with baseline NYHA class 3 or 4)	>30% and >300 ng/L increase NT-proBNP ≥33% increase in cTnT ≥10% decrease in ejection fraction
Renal [39, 43]	renCR renVGPR renPR No response (renNR)	24-h proteinuria ≤200 mg/day >60% reduction in 24-h proteinuria 31–60% reduction in 24-hour proteinuria 30% or less reduction in 24-h proteinuria	≥25% decrease in eGFR
Hepatic [99][c]		50% decrease in abnormal ALP OR Decrease in radiographic liver size by 2 cm	50% increase of ALP above lowest value
Peripheral nervous system		Improvement in electromyogram nerve conduction velocity	Progressive neuropathy by electromyography

[a]Either FLC ratio within reference range OR uninvolved FLC > involved FLC with or without abnormal FLC ratio [100].
[b]Graded cardiac criteria described recently [101].
[c]Hematologic, cardiac and renal response criteria have been validated, while hepatic has been obtained by consensus.
NYHA, New York Heart Association.

cases, CyBorD alone may be administered. Combinations of bortezomib and Immunomodulatory agents (IMiDs), such as lenalidomide or pomalidomide, may also be tried. Finally, venetoclax for patients with the t(11;14) translocation and bi-specific antibodies are newer, promising options, and are further discussed in the section Treatment of relapsed/refractory patients.

During induction, assessing eligibility for HDM/SCT is recommended, given its possibility as a treatment option (Table 4). An eGFR >30 mL/min/1.73 m^2 is typically recommended, although if patients meet all other criteria, one may still proceed. Treatment-related mortality with HDM/SCT has fallen from 20% to 5% due to careful patient selection [49]. However, the rapidly changing chemotherapy landscape is decreasing this practice. Eligibility criteria for HDM/SCT (Table 4), pre/post-treatment HDM/SCT guidelines (Table 5) and chemotherapy options for AL amyloidosis and their side effects (Table 6) are included in this review.

It is important to monitor treatment carefully to obtain the best hematologic possible (Table 3). Specifically, patients with cardiac Stage IIIB AL amyloidosis should be closely monitored, given rapid hematologic recovery within 1 month is strongly associated with survival in this population [50]. However, some patients who experience hematologic CR may not have a durable organ response. Next-generation flow cytometry of bone marrow aspirates has been used to detect minimal residual disease (MRD) in multiple myeloma as a surrogate endpoint for clinical trials and to guide treatment [51]. MRD has recently shown promise in AL

Table 4: Transplant inclusion and exclusion criteria [48, 102].

		Criteria
Inclusion criteria	Presentation	Biopsy-proven with accurate typing Evidence of plasma cell dyscrasia Involvement of >1 major organ
	Age	18–70 years
Exclusion criteria	Performance	Southwest Oncology Group performance status score ≥3 Significant exercise limitations (<2–3 flights of stairs during pulmonary function testing)
	Cardiac	LVEF <40% Arrhythmias resistant to medical management Decompensated heart failure (NYHA class III or greater) Troponin T ≥0.06 ng/mL NT-proBNP ≥5000 pg/mL Hemodynamic instability (systolic blood pressure <90 mm Hg) Orthostatic hypotension refractory to medical therapy
	Pulmonary	Oxygen saturation <95% on room air Lung diffusion capacity <50% predicted Persistent pleural effusions refractory to medical management
	Gastrointestinal	Direct hyperbilirubinemia ≥2 mg/dL Active or risk of GI bleeding
	Kidney	eGFR <30 mL/min/1.73 m^2 Note: patients on renal replacement therapy are not excluded if all other eligibility criteria are met
	Hematologic	Factor X level <25% or active bleeding

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; GI, gastrointestinal.

amyloidosis [52, 53]. Undetectable MRD at least 5 months after achieving CR in one study was associated with higher rates of renal (90% vs 62%) and cardiac (95% vs 75%) response; MRD-positive patients had higher rates of hematologic progression [53]. More recently, mass-spectrometry of serum FLC (FLC-MS) at 12 months after treatment has shown utility for assessing the progression of AL amyloidosis [54]. These newer techniques may be a new standard for response assessment in patients with AL amyloidosis. Figure 1 shows the comprehensive treatment algorithm for patients with newly diagnosed AL amyloidosis.

Consolidation and maintenance

Consolidation therapy (to increase the depth of HR) and maintenance therapy (to prevent hematologic progression) are open research areas in AL amyloidosis. Two Phase II trials suggest consolidation therapy with thalidomide/dexamethasone (TD) [55] or bortezomib/dexamethasone (BD) [56] may be effective in deepening HR post-ASCT. A retrospective study of 471 patients at the Mayo Clinic suggested consolidation therapy with proteasome inhibitors (PIs), IMiDs or a combination had improved rates of CR and progression-free survival (PFS) in patients with <VGPR [57].

A clinical trial is underway (NCT03618537) to investigate the use of ixazomib, a second-generation proteasome inhibitor, as maintenance post-ASCT in patients with high burden (>10% Bone Marrow Plasma-Cell Percentage). A small series investigated consolidation therapy with daratumumab (4 weekly cycles) following chemotherapy without CR in transplant-ineligible patients, demonstrating improved CR and MRD compared with controls [47, 48]. Ultimately, the benefits of consolidation therapy must be balanced with toxicity, and consensus guidelines suggest one may consider a short course of a PI- or IMiD-based regimen in patients with <VGPR following ASCT [58].

Maintenance therapy has not been well studied in AL amyloidosis and is not routinely recommended. One exception is patients with background symptomatic myeloma for which there is evidence for maintenance therapy [47, 48]. A retrospective study of 50 patients with AL amyloidosis who received IMiD-based maintenance, primarily lenalidomide, had no impact on outcome [59]. Ongoing studies may demonstrate the emerging role of ixazomib and daratumumab in this setting.

Special considerations

Renal disease: patients with chronic kidney disease (CKD) are often treated similarly and require only renal dose adjustment for chemotherapy. Standard bortezomib, cyclophosphamide, and dexamethasone has been used for years in patients with acute or chronic renal failure for plasma cell disorders. Bortezomib does not require dose adjustment for patients receiving dialysis but should be administered after dialysis [48]. Daratumumab is generally thought to be well tolerated. However, special consideration should be given to patients with heavy proteinuria as this may lead to higher clearance of the antibody and lower efficacy of therapy [48]. Lenalidomide is the only IMiD that requires dose adjustment based on eGFR. Melphalan needs dose adjustment to 140 mg/m^2 when eGFR is <30 mL/min /1.73 m^2.

Regarding ASCT, there are important considerations for the Nephrologist. Multiple case studies have demonstrated that dialysis during ASCT or chemotherapy for AL amyloidosis did not worsen prognosis, although ESKD patients, in aggregate, had worse outcomes [60]. Current consensus eligibility criteria for ASCT include an eGFR >30 mL/min/1.73 m^2, but patients on hemodialysis (HD) or peritoneal dialysis (PD) should not be excluded if they meet other criteria (Table 5). One study of 408 ASCT patients from 1996 to 2010 found that patients needing dialysis within 30 days of ASCT had the highest treatment-related mortality (44.4%). This study suggested screening for hypoalbuminemia (<2.5 g/dL) and eGFR (<40 mL/min/1.73 m^2) could identify these at-risk patients [61]. Acute kidney injury is a common complication of HDM/SCT, and the Boston University group

Table 5: Stem cell transplant pre/post-guidelines.

Stage	Agent	Guidelines
Induction	Dara-CyBorD	Administer for 2–4 cycles, assess response; defer ASCT if hematologic CR is achieved
Stem cell mobilization	G-CSF (10–16 μg/kg/day)	Single or two divided doses 3–4 days prior to ASCT
	Plerixafor	May be considered to aid in mobilization; use with abbreviated G-CSF dosing in patients with significant cardiac involvement or CHF
	Cyclophosphamide	Myeloma-associated AL amyloidosis, recommend mesna to prevent hemorrhagic cystitis
Conditioning	Melphalan (200 mg/m^2)	Age <65 AND cardiac Stage I AND eGFR >50 mL/min/m^2
	Melphalan (100–140 mg/m^2)	Age ≥70 OR cardiac Stage III OR eGFR ≤30 mL/min/m^2
Peri ASCT phase	Antimicrobial prophylaxis: fluoroquinolone, acyclovir or valacyclovir, fluconazole GI prophylaxis w/PPI Transfusion parameters: Hgb <8 g/dL, platelets <10k or 20k if bleeding and with fever	
	Renal involvement: Albumin infusion if serum albumin <2 g/dL in advanced nephrotic syndrome	
	Cardiac involvement: Telemetry Avoid beta blockers and calcium channel blockers for atrial fibrillation Consider amiodarone prophylaxis in patients with arrhythmias Midodrine for blood pressure support	
Post ASCT phase	VZV prophylaxis for 12 months Pneumocystis pneumonia prophylaxis for 3 months Immunizations	
Consolidation	PI, IMiD or combination	Limited data available; short course may be considered in patients with <VGPR post-ASCT
Maintenance	No role demonstrated in observational studies	
Follow-up	Assess HR 3–6 months post-ASCT BM aspiration and biopsy only required for assessment of MRD	

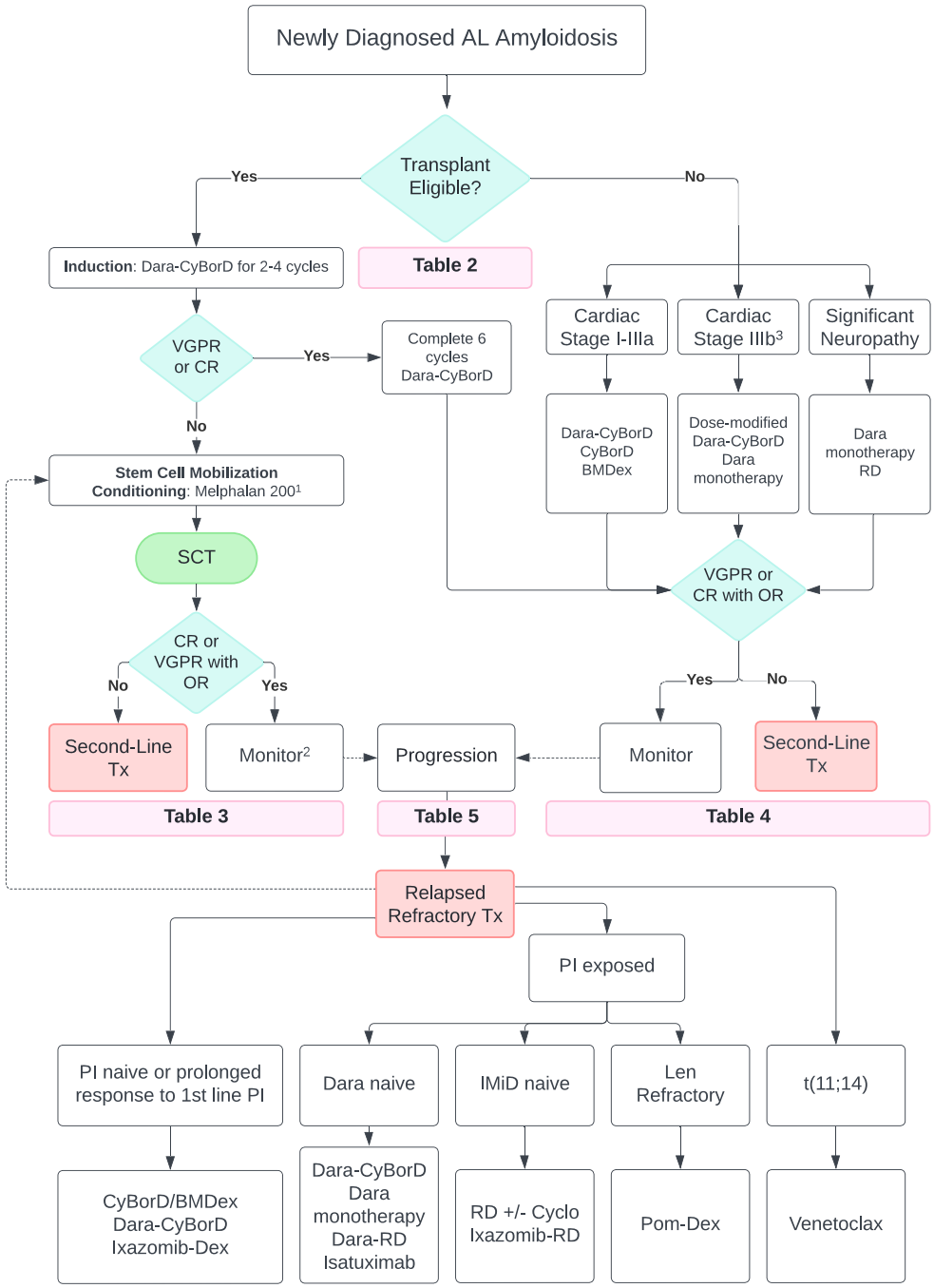
Special considerations: kidney transplantation may be done before or after ASCT; cardiac or liver transplantation must be done prior to ASCT; and patients on renal replacement therapy can safely undergo ASCT [60, 103].
G-CSF, granulocyte colony-stimulating factor; CHF, congestive heart failure; GI, gastrointestinal; PPI, proton pump inhibitor; Hgb, hemoglobin.

Table 6: Chemotherapy for AL amyloidosis.

Therapy class	Agent	Side effect profile/special considerations
Alkylating Agents	Cyclophosphamide	Immunosuppression, cytopenias
	Melphalan	Requires renal adjustment, myelotoxicity → myelodysplastic
Proteasome inhibitors	Bortezomib	Pulmonary toxicity (small risk), neuropathy, signal of cardiotoxicity, atrial arrhythmias when given IV vs SubQ
	Carfilzomib, irreversible second-generation	Renal toxicity, cardiovascular toxicity
	Ixazomib, second-generation	Oral administration, lower neurotoxicity, thrombocytopenia, diarrhea
Immunomodulatory agents	Lenalidomide	Poorly tolerated at full dose, skin rashes, thrombotic complications, infections, fatigue and deteriorating kidney function
	Pomalidomide	Better tolerated, can cause transient increase in NT-proBNP
Monoclonal antibody	Daratumumab, anti-CD38	Immunosuppression, higher risk of infection

developed a prediction model (eGFR <60 mL/min/1.73 m^2, interventricular septal thickness in diastole >12 mm, serum albumin <3 g/dL) to identify patients at high risk of this treatment complication [62].

Cardiac Stage IIIB: the high risk of mortality in this patient population complicates therapy selection. Early initiation of first-line Dara-CyBorD remains the favored therapy, with dose reductions of bortezomib and/or dexamethasone due to cardiac toxicity [63]. If the patient cannot tolerate these, single-agent subcutaneous daratumumab can be given, with promising results in a Phase II study [64]. If volume overload is of concern, daratumumab may be administered in divided intravenous doses [48].



[1] Dose adjusted conditioning (ie Mel140) in specific patient populations
[2] Role of maintainence only in myeloma-associated AL amyloidosis
[3] May consider heart transplant

Abbreivations: Stem cell transplant (SCT); Daratumumab (Dara); Cyclophosphamide+Bortezomib+Dexamethasone (CyBorD); Lenalidomide-Dexamethasone (RD); Pomalidomide (Pom); Dexamethasone (Dex); Cyclophosphamide (Cyclo); proteasome inhibitor (PI); treatment (Tx); complete response (CR), very good partial response (VGPR), organ reponse (OR)

Figure 1: Treatment algorithm for patients with newly diagnosed AL amyloidosis.

Peripheral neuropathy: given bortezomib's side-effect profile, it may be dose-reduced for patients with mild neuropathy and entirely omitted for patients with severe neuropathy. In these patients, single-agent daratumumab, alkylating agent-steroid dual therapy or IMiDs can be considered [48].

Liver failure: patients with severe hepatic dysfunction are uniquely challenging to treat as many therapies undergo hepatic metabolism and, therefore, require substantial dose adjustment [48]. Bortezomib dose modification in liver dysfunction remains poorly studied and is complicated by case reports of

bortezomib-related liver toxicity [48]. Cyclophosphamide relies on hepatic metabolism and activation, which is unfavorable in this patient population [48]. Daratumumab has not been studied in patients with liver dysfunction [48]. Based on these limited data, daratumumab with dexamethasone is likely the preferred therapy in patients with liver failure.

Supportive care

Kidney

The focus of supportive care in patients with AL amyloidosis and kidney involvement is volume status management [65]. The mainstay therapies are loop diuretics and strict fluid and salt restriction. Renin–angiotensin–aldosterone system blockers should be used cautiously in patients with AL amyloidosis as they can exacerbate autonomic dysfunction and perpetuate hypotension. Dietary sodium and protein restriction should be considered while managing dyslipidemia. Large-volume proteinuria can lead to loss of antithrombin III and hypercoagulable states, and anticoagulation should be considered if there is a thromboembolic event [65].

In patients with AL amyloidosis, approximately 25% progress to ESKD [17, 39]. For these patients, the choice between intermittent HD and PD depends on several factors, including cardiac involvement, autonomic dysfunction, risks associated with each modality and patient preferences. Survival in patients with AL amyloidosis and ESKD is generally shorter than in those with ESKD from other causes [104]. In patients with AL amyloidosis, cardiac involvement is a strong predictor of mortality with in first year of dialysis [105]. In cases where cardiac and autonomic involvement are significant, HD can be challenging due to the risk of hypotension. However, for patients with severe volume overload, HD may be better suited, and the use of midodrine can help manage hemodynamic instability. On the other hand, PD may be a preferable option for patients with cardiac and autonomic dysfunction, as it avoids the rapid fluid shifts seen in HD. However, PD can be less effective in advanced cases of abdominal amyloid deposition, which can impair peritoneal function. No significant differences in survival outcomes have been observed between HD and PD in these patients [104, 106]. Given the complexities of AL amyloidosis, the choice of dialysis modality should be individualized, based on each patient's clinical presentation and comorbidities.

Additionally, kidney transplantation has shown extended overall and kidney graft survival in patients with AL amyloidosis who experience at least VGPR [66–68]. In a recent, large, multicenter study of 237 patients, the median overall survival from kidney transplant was 9 years in patients with hematologic CR and VGPR vs 6.8 years for patients with partial and no response at time of transplantation [67]. Similarly, median graft survival was 8.3 vs 5.7 years in these two populations. Thus, it is recommended to refer AL amyloidosis patients with ESKD for kidney transplant who achieve at least VGPR and do not exhibit significant cardiac involvement or contraindications to kidney transplant.

The question of when to refer AL amyloidosis patients for kidney transplant is important and an open area of research. A time lag often naturally occurs following initiation of therapy until evaluating HR before one may consider kidney transplant. From our center experience at Boston University, typically 6 months after treatment initiation allows for durable HR to evaluate for kidney transplant. If the patient is being considered for ASCT, kidney transplant may occur before or after HDM/SCT, while other solid-organ transplantation (i.e. heart, liver) is exclusively recommended before ASCT [67]. Importantly, protocol states one must obtain kidney allograft biopsy with Congo Red staining to exclude amyloid prior to transplant.

Cardiac

Heart failure symptoms in AL amyloid patients can be difficult to control as sinus tachycardia is required to maintain cardiac output due to restrictive infiltrative cardiomyopathy [65]. The mainstay therapies are loop diuretics and aldosterone receptor blockers; however, patients must be monitored for symptomatic hypotension [65]. Negative inotropic agents such as calcium channel blockers and beta-blockers should be avoided. High-fitness patients with severe cardiac AL amyloidosis may be suitable for heart transplant with comparable outcomes to non-amyloid heart transplant patients in multiple case studies [69]. Additionally, bortezomib-based induction therapy would be recommended to reduce risk of amyloid deposition in the transplanted heart [65]. Ultimately, data for these patient populations is limited, and a multi-disciplinary team evaluation is warranted.

Neuropathy

Peripheral neuropathy in AL amyloidosis typically presents with sensory-dominant impairment, early involvement of lower limbs and loss of sensations. In advanced stages, orthostatic hypotension is frequently observed. Treatment of neuropathy includes anticonvulsants (gabapentin and pregabalin) and serotonin–norepinephrine reuptake inhibitors (duloxetine and venlafaxine) [65]. Tricyclic antidepressants (amitriptyline and nortriptyline) should be avoided as they can worsen orthostatic hypotension and urinary retention [65]. Lidocaine patches and high-dose capsaicin can be considered as topical agents, and compression stockings for symptom management. For autonomic dysfunction, midodrine is used for first-line management [70]. Additionally, droxidopa in conjunction with midodrine may be used for orthostatic hypotension and should also be considered for these patients [71].

Treatment of relapsed/refractory patients

Unfortunately, most patients with AL amyloidosis will relapse after treatment with chemotherapy or ASCT. Progression criteria across organ systems are included in Table 3. It is reasonable to consider restarting therapy when dFLC is 50% of diagnostic level in a patient with limited vital organ involvement or utilize "high-risk" dFLC-progression criteria in patients with significant end organ dysfunction [72]. For patients with relapse ≥2 years since the last therapy, patients may retry their original efficacious therapy. If patients had severe disease at diagnosis, such as Stage IIIB, treatment should be initiated as soon as hematologic relapse is detected. HDM/SCT is always an option (either first transplant or repeat) based on patient eligibility and availability of alternative agents.

Multiple retrospective and prospective studies have demonstrated high response rates for daratumumab in the relapsed setting [73]. A Phase II study of daratumumab monotherapy dosed 16 mg/kg was administered by IV infusion once weekly for Weeks 1–8, every 2 weeks for Weeks 9–24, and every 4 weeks thereafter until progression or unacceptable toxicity for up to 24 months in this setting had hematologic CR or VGPR in 86% of patients and was well tolerated [74]. A small retrospective study suggested Dara-RD [75]. Isatuximab, another anti-CD38 monoclonal

antibody, is under Phase II trial investigation in the relapsed setting (NCT03499808). Taken together, for relapsed AL amyloidosis patients who are PI-exposed but daratumumab naive, daratumumab monotherapy, Dara-V(C)D, Dara-RD and isatuximab are options [48].

Another option for relapsed patients is ixazomib, a second-generation PI [76, 77], with dexamethasone (Ixazomib-Dex) demonstrated by the TOURMALINE-AL1 study [78]. Ixazomib is typically well tolerated with minimal neuropathy. The data for carfilzomib in the relapsed setting, however, are limited. A Phase I/II study of carfilzomib demonstrated promising HR in bortezomib-exposed population, although cardiac toxicity is a concern [79]. Other options for PI-naïve patients or those with prolonged response to first-line PI in addition to Ixazomib-Dex include CyBorD/VMDex B and Dara-CyBorD [48].

IMiDs (lenalidomide and pomalidomide) have also been studied in relapsed AL amyloidosis [80]. Daily 15 mg lenalidomide has been established in Phase I/II dose escalation, with HR rates at 60% when combined with cyclophosphamide and dexamethasone (CRd) [81, 82]. Of note, IMiDs have potential to increase NT-proBNP and worsen kidney function, but lenalidomide does not appear to worsen neuropathy and can be considered with amyloid neuropathy. Pomalidomide, at a maximum tolerated dose as 4 mg daily, with dexamethasone (Pom-Dex) has also been explored in the relapsed setting in a recent retrospective study and is appealing in lenalidomide-refractory cases [83]. For patients that are PI exposed yet IMiD naïve, options include CRd or ixazomib–lenalidomide dexamethasone, and for lenalidomide refractory cases, one may consider Pom-Dex [48].

An exciting area of interest is BCL-2 inhibition for patients with the t(11;14) translocation (~50% of AL amyloidosis cases) [84]. Cyclin D1 is constitutively expressed in the t(11;14) translocation causing clonal proliferation. BCL-2 inhibition removes anti-apoptotic protections to kill these clones. Venetoclax is the best-studied BCL-2 inhibitor demonstrated in t(11;14) multiple myeloma. Retrospective data suggests venetoclax has up to an 88% overall response rate in t(11;14) AL amyloid patients and thus should be considered as a first-line relapse treatment in t(11;14) patients when possible [29, 85, 86]. Single agent venetoclax, venetoclax–bortezomib–dexamethasone or melphalan–dexamethasone may also be considered for these patients [48].

Recently, teclistimab, a bi-specific T-cell engager (BiTE) antibody targeting B-cell maturation antigen (BCMA) and CD3 (found on T cells), has shown a strong response in a multinational retrospective case series of 17 patients [87]. Deep and rapid responses, as early as 14 days, with a median HR of 1 month was reported. Step up dosing of 0.06 mg/kg at Day 1, 0.3 mg/kg at Day 4, 1.5 mg/kg at Day 8 and then 1.5 mg/kg weekly and dexamethasone per local practice was used. Eighty-eight percent of these patients experienced VGPR or better, and 41% had CR. Importantly, BiTEs have unique toxicities, including cytokine release syndrome (CRS), seen in 53% of patients, and immune effector cell–associated neurotoxicity syndrome (ICANS), and these adverse effects must be monitored carefully as more studies are done. No cardiac toxicity was reported in this limited study which is appealing in AL amyloidosis [87].

Bendamustine, an alkylating agent, has been trialed in the relapsed setting with dexamethasone, but significant hematologic toxicity was observed [88]. Its use is reserved in patients with immunoglobulin M–related AL amyloidosis. Aside from these agents, enrollment in clinical trials is also encouraged.

Box: Strategies how to personalize treatments.

➔ Recognize the sequelae of amyloidosis

- ♦ A thorough work-up for proteinuria when symptoms are suspected is key
- ♦ Biopsy is needed to confirm, and often only surrogate site biopsy is needed for diagnosis and amyloid typing

➔ Physical, history and biomarker staging is necessary to understand organ involvement status

- ♦ Staging (cardiac, renal) to assess severity of disease (Tables 1 and 2)

➔ For most fit patients, induction with Dara-CyBorD is recommended:

- ♦ After 2–4 cycles, assess whether there is VGPR or CR; if not, consider alternative chemotherapy or ASCT (Table 6)
- ♦ Severe cardiac amyloidosis (Cardiac IIIb): proceed with a dose-modified regimen
- ♦ For Cardiac I–IIIa, Dara-CyBorD or BMDex
- ♦ Consider dose reduction of bortezomib or avoiding all-together in patients with severe neuropathy
- ♦ Eligibility criteria for ASCT and treatment modifications for renal disease are described (Tables 4 and 5)
- ♦ Dialysis may be administered in conjunction with stem cell transplant
- ♦ Kidney transplant may be before or after stem cell transplant

➔ Relapsed-refractory therapy

- ♦ Consider re-trying therapy if efficacious and >2 years since initial treatment
- ♦ FiSH for translocation t(11;14) is key given the high success of venetoclax in these populations
- ♦ Bi-specific antibodies are also showing great promise
- ♦ ASCT may be considered in all relapsed patients

NEW DEVELOPMENTS

Many novel approaches are underway for both diagnosis and treatment for patients with AL amyloidosis. Recently, a novel immunoassay that detects the dimeric, constant domain of the lambda amyloidogenic light chain was found to be specific to patients with AL amyloidosis compared with healthy, multiple myeloma and MGUS patients [89]. It is currently undergoing validation and shows great promise for diagnosis of lambda (~75% of cases) AL amyloidosis, especially for patients with MGUS and smoldering multiple myeloma.

Regarding treatment, BCMA targeting is of great interest as demonstrated by the interest in bi-specific antibodies. The antibody–drug conjugate belantamab mafodotin, which targets BCMA, has been explored in multiple myeloma [90] and now is being examined in a prospective EMN study (NCT04617925) and a multi-center retrospective study with promising response rates for refractory AL amyloidosis [91]. A notable toxicity of

the drug is its ocular toxicity with keratopathy. BCMA chimeric antigen receptor (CAR)-T cells have similarly strong anti-plasma cell
activity in relapsed/refractory multiple myeloma. However, their use is limited to clinical trials and they harbor similar toxicities to bi-specific antibodies, such as CRS and ICANS. Another anti-plasma cell target is SLAMF7, targeted by the monoclonal antibody elotuzumab. This is approved for multiple myeloma, with some success in small case series for AL amyloidosis [92]. A Phase II study examining elotuzumab, lenalidomide and dexamethasone ± cyclophosphamide is currently underway (NCT03252600).

Finally, direct targeting of amyloid fibrils or the serum amyloid P-component (SAP) are under development for AL amyloidosis. The anti-amyloid light-chain monoclonal antibody, CAEL-101, has promising results in a single-arm study [93]. Randomized trials in cardiac AL amyloidosis are currently in progress (NCT04512235, NCT04504825). The anti-fibril monoclonal antibody birtamimab recently was explored in a Phase III VITAL clinical trial in addition to standard of care, which suggested a survival benefit and improvements in quality of life for Mayo Stage IV patients [94]. Trials of other antibodies including anti-SAP (dezamizumab), SAP-depleting agent (miridesap) were discontinued due to futility or unfavorable side-effect profile.

Doxycycline has also been shown to inhibit amyloid fibril formation *in vivo* in transthyretin amyloid and light-chain amyloid [95]. However, one randomized trial showed doxycycline with CyBorD failed to prolong PFS and cardiac PFS compared with CyBorD in cardiac AL amyloidosis [96]. Another randomized Phase II/III trial in cardiac AL amyloidosis is currently underway (NCT03474458), but currently, there is no role outside of clinical trials for doxycycline in the treatment of AL amyloidosis.

SUMMARY

The pathophysiology of AL amyloidosis guides staging, management and surveillance. This multi-system disease is often underdiagnosed due to its complex presentation and unique presentation by the organ system. Renal involvement, typically presenting with nephrotic-range proteinuria, should be worked up carefully to prevent irreversible organ damage. Less invasive methods of histopathological confirmation, i.e. fat-pad biopsies, have high sensitivity and may avoid renal biopsy. In the past year, blood-based immunoassays have shown great promise as a new, less-invasive avenue of diagnosis.

Following diagnosis, staging based on cardiac biomarkers for mortality and renal biomarkers for progression to ESKD should be done. For ESKD, eGFR and 24-h urine protein are key for assessing stage, risk of ESKD and ultimately response when patients are started on treatment. The use of plasma cell dyscrasia biomarkers (dFLC) for mortality staging is currently being re-examined given better plasma cell–directed therapies.

Finally, daratumumab-containing regimens are now first-line therapy for most newly diagnosed patients and require only minor modifications for patients with CKD or ESKD. ASCT still has a role given the availability of alternative chemotherapies if patients do not respond to induction chemotherapy, and studies have shown it can be safe in patients on dialysis. In the relapsed and refractory setting, newer treatments are also under development, notably anti-fibril antibodies targeting the pathogenic component rather than the plasma cell clone. It is a remarkable time for novel diagnostics, re-examined staging and innovative treatments for AL amyloidosis.

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S.A. and M.N. wrote the first draft. V.S. and A.V. acted as supervisors and edited the first draft.

DATA AVAILABILITY STATEMENT

N/A.

CONFLICT OF INTEREST STATEMENT

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