



# Clinical Practice Guideline

# **SYSTEMIC AL**

# **AMYLOIDOSIS**

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# 1 INTRODUCTION

In 2010, the first Clinical Practice Guidelines on the Management of Systemic AL Amyloidosis were published on behalf of the Medical Scientific Advisory Group of the Myeloma Foundation of Australia.<sup>1</sup> Although more common than chronic myeloid leukaemia,<sup>2</sup> systemic AL amyloidosis has limited high quality evidence to guide management and therefore limited consensus on what constitutes ‘standard’ treatment. The following guidelines have been prepared by the MSAG to provide Australian clinicians with a current, practical and evidence-based approach to the management of AL amyloidosis.

Please note that management of other non-AL types of amyloidosis and monoclonal immunoglobulin deposition diseases is not covered by this review.

Levels of evidence and grades of recommendations used in these guidelines are listed in Table 1.

**Table 1: Levels of evidence and grades of recommendations**

LEVELS OF EVIDENCE	
1A	Evidence from meta-analysis of randomised controlled trials.
1B	Evidence from at least one randomised controlled trial.
2A	Evidence from at least one well-designed non-randomised trial, including phase II trials and case-control studies.
2B	Evidence from at least one other type of well-designed, quasi-experimental study such as observational studies.
3	Evidence from well-designed non-experimental descriptive studies.
4	Evidence obtained from expert committee reports or opinions and/or of respected authorities.
GRADES OF RECOMMENDATIONS	
A	Recommendation based on at least randomised controlled trial of good quality addressing specific recommendation (Evidence level 1A and 1B).
B	Recommendation based on well-conducted studies but no randomised controlled trial on topic of recommendation (Evidence level 2A, 2B, and 3).
C	Recommendation based on expert opinions or reports (Evidence level 4).

## 2 BACKGROUND

Systemic AL amyloidosis, previously called primary amyloidosis, is a protein misfolding and deposition disorder associated with a monoclonal gammopathy. The precursor protein is an immunoglobulin light chain fragment (most commonly the lambda chain) produced by a monoclonal plasma cell population in the bone marrow. Rarely, the precursor protein may be an immunoglobulin heavy chain (referred to as AH amyloidosis) or be produced by an indolent B cell lymphoma. These precursor proteins fold abnormally to form fibrils with a beta pleated sheet structure. The fibrils associate with serum amyloid P protein (SAP) and other components such as glycosaminoglycans to form amyloid deposits in extracellular tissues that progressively accumulate and disrupt organ function. Whilst most monoclonal light chains are not amyloidogenic, it is currently not possible to predict those that are.

AL amyloidosis most commonly affects the heart, kidney, liver, gastrointestinal tract, carpal tunnels and nerves, with variable involvement of other organs (see Table 2). Progressive infiltration leads to organ dysfunction and end-stage complications including restrictive cardiomyopathy and nephrotic syndrome. Involvement of the peripheral nervous system occurs in more than 20% of cases, causing a predominantly sensory peripheral neuropathy. Autonomic dysfunction may manifest various symptoms including orthostatic hypotension, gastrointestinal dysmotility, early satiety and nausea, and erectile dysfunction. Although generally considered to be pathognomonic of AL amyloidosis, macroglossia, periorbital ecchymoses (“raccoon eyes”), Factor X deficiency and amyloid nail dystrophy are often absent.

The annual incidence of AL in the Australian population is approximately 12 cases per million.<sup>2</sup> The majority of cases are diagnosed over the age of 50 and there is a slight male predominance.

**Table 2: Incidence and updated definitions of organ involvement in AL amyloidosis (adapted from Merlini<sup>3</sup>, Gertz<sup>4,5</sup>)**

ORGAN	% OF PATIENTS WITH INVOLVEMENT AT DIAGNOSIS	DEFINITION
Kidney	65% (nephrotic 42%)	24-hr urine protein > 500 mg/day, predominantly albumin
Heart	74% (heart failure 47%)	Echocardiogram: mean wall thickness > 12 mm, no other cardiac cause, or NT-proBNP ≥332ng/L in the absence of renal failure or atrial fibrillation.
Liver	17%	Total liver span > 15 cm in the absence of heart failure or alkaline phosphatase > 1.5 times institutional upper limit of normal
Gastrointestinal tract	8%	Direct biopsy verification with symptoms
Peripheral nervous system	Peripheral 15% Autonomic 14%	Peripheral: clinical diagnosis of symmetric lower extremity sensorimotor peripheral neuropathy Autonomic: gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration
Lung	NA	Direct biopsy verification with symptoms Interstitial radiographic pattern in absence of pulmonary oedema
Soft tissue	17%	Macroglossia Nail dystrophy Periorbital bruising (“raccoon eye” sign) Arthropathy Jaw claudication with eating Lymphadenopathy Skin Myopathy by biopsy or pseudohypertrophy Carpal tunnel syndrome

NT-proBNP, N-terminal pro-brain natriuretic peptide; NA, not available.

### 3 LOCALISED AL AMYLOIDOSIS

Immunoglobulin light chain amyloidosis is most often systemic, i.e. the production of the amyloid-forming light chain is distant to the amyloid deposits. Localised amyloidosis, in which amyloid deposits occur only at the site of light chain production, is another well-recognized entity. Localised AL amyloidosis is usually a non-life threatening disease with rare progression to systemic disease but local recurrences are often seen.<sup>6-8</sup> AL-type deposits are thought to be produced by foci of low-grade monoclonal or oligoclonal B-cells or plasma cells which secrete monoclonal immunoglobulin light chains in the immediate vicinity although in the majority of cases, no histologically evident lymphoproliferative disease is present.<sup>7-9</sup>

These localized amyloid deposits are commonly located in the **tracheobronchial tree** causing dysphonia, cough, haemoptysis, **orbit and adnexae, lung, bladder** causing haematuria, **gastrointestinal tract, lymph nodes** and **skin** resulting in plaques and nodules. **Prostate** deposits can be localized AL or part of a systemic transthyretin (TTR) amyloidosis.

It is vital that any patient who presents with presumed localized disease has a full work-up to investigate for the presence of systemic disease, including cardiac biomarkers, NT proBNP and troponin T; urine assessment for proteinuria; and a thorough examination looking for any signs of a peripheral or autonomic neuropathy, or soft tissue infiltration. Localised AL amyloidosis can occur in almost any organ of the body. It is also seen infiltrating plasmacytomas or lymphomas and in this situation, is not necessarily indicative of systemic disease.

Localised AL amyloidosis is treated with observation only or local surgical measures<sup>7-9</sup> and is usually associated with an excellent prognosis, although significant infiltration and distortion of the involved organ can occur. There is no proven role for radiotherapy or chemotherapy in the routine management of these patients, although certain severe presentations (e.g. unresectable airway obstruction) may justify a trial of local radiotherapy.<sup>7</sup>

# 4 DIAGNOSTIC WORK-UP

## A DIAGNOSIS OF SYSTEMIC AL AMYLOIDOSIS REQUIRES 4 KEY ELEMENTS:

- 1) histological confirmation of the diagnosis of amyloidosis with positive Congo Red staining of biopsies and apple-green birefringence under polarized light
- 2) confirmation of AL subtype - and exclusion of other subtypes – via a full panel of immunohistochemistry on biopsies +/- genetic studies;
- 3) evaluation of the plasma cell clone; and
- 4) evaluation of the extent and severity of organ involvement (see Figure 1).

### 1. Confirmation of the diagnosis of amyloidosis, and the AL subtype

The diagnosis of AL amyloidosis can be complex and a detailed discussion is beyond the scope of these guidelines.<sup>10,11</sup>

A few points are worth emphasizing:

- Early diagnosis is the key to effective management so the diagnosis of amyloidosis requires a high index of clinical suspicion when patients present with compatible systemic symptoms or monoclonal gammopathies of undetermined significance (MGUS). Proactive screening of MGUS patients with annual urine dipsticks and troponin checks can be one way to assist early diagnosis.<sup>10,11</sup>
- Secondly, Congo Red staining of a biopsy sample remains the essential diagnostic test for AL amyloidosis, and must demonstrate apple-green birefringence under polarized light (positive cardiac uptake on bone scintigraphy with a detectable plasma cell dyscrasia is insufficient to diagnose AL).
- Lastly, correct subtyping of amyloidosis is critical in all cases. Note that AL, AA, transthyretin (TTR), LECT2 and hereditary forms of amyloidosis, such as lysozyme and fibrinogen A-alpha chain amyloidosis, often have overlapping clinical features.

**Immunohistochemistry (IHC)** must be performed on all biopsies to exclude other amyloid subtypes, especially TTR staining on cardiac biopsy specimens, and AA staining on renal biopsy specimens. Note that biopsies of the amyloidotic organ, rather than a “screening” fat or deep rectal tissue, have a lower false negative rate, and are easier to subtype on IHC.<sup>12,13</sup>

Two recent Australian studies<sup>14,15</sup> of 302 amyloid biopsies undergoing expert reviews highlight the difficulties with IHC in amyloidosis subtyping. Abou-Seif *et al* noted an initial false negative rate for Congo red staining of 9%.<sup>14</sup> Both studies report insufficient use of IHC to identify the amyloid subtype, with only half of cases reviewed having had any IHC, and in those that did undergo IHC, the panel was often incomplete. Of concern, the interpretation of the histology, and thus the amyloid subtype was revised in 15% of cases on expert review.

An unrelated monoclonal gammopathy can be detected in an surprisingly high percentage of non-AL amyloidosis, including 25-30% of wildtype TTR amyloidosis.<sup>16,17</sup> However, frustratingly, interpretation of IHC can be difficult and at times unreliable.<sup>10,11,18</sup>

**Biopsy review at an Australian Amyloidosis Network (AAN) service** is encouraged (see Appendix 2), especially in cases when the amyloid typed according to IHC does not match the clinical phenotype, or if there is significant residual doubt as to the interpretation of the IHC.<sup>14,15</sup> Examples include amyloid deposits with IHC staining for both a light chain and TTR, or lack of clear light chain restriction. **Tandem mass spectrometry**<sup>18,19</sup> is offered in cases where the subtype is still in doubt after expert review, however, this method of diagnosis can be expensive with significant time delays for final results.

**Genetic studies** - looking for amyloidogenic mutations that can lead to hereditary forms of disease - should also be considered in complex cases, especially if there is a peripheral or autonomic neuropathy; suggestive family history; or renal amyloidosis without a monoclonal gammopathy; or history of chronic inflammation.<sup>20</sup>

**Bone scintigraphy** is an extremely helpful diagnostic tool, and allows confident diagnosis of cardiac amyloidosis if there is uptake of the tracer in the heart. Bone scintigraphy can detect cardiac involvement in almost every patient with ATTR cardiac amyloidosis and up to a third of patient with cardiac AL amyloidosis.<sup>21</sup> A Perugini score of 3 (whereby the cardiac signal is more intense than that of the bony skeleton) in patients without a detectable plasma cell clone is diagnostic of ATTR, not AL, amyloidosis, avoiding the need for a biopsy. Such patients should have their ATTR amyloidosis treated accordingly. However, patients with a detectable plasma cell dyscrasia still require a histological diagnosis.

Bone scintigraphy is especially recommended for men aged over 60 with clinical suspicion of cardiac amyloidosis given the high rate at ATTR amyloidosis in this population. The three bone complexing molecules validated in this setting are 99m-technecium-labelled agents;

- a) 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD),
- b) pyrophosphate (PYP), and
- c) hydroxymethylene diphosphonate (HMDP).

PYP is a TGA registered agent, whereas DPD and HMDP need to be prescribed under the TGAs SAS program.

Readers are referred to the Australian Guidelines on “How to diagnose amyloidosis”.<sup>11</sup>

## 2. Evaluation of the plasma cell clone

As a disorder resulting from the proliferation of monoclonal plasma cells, AL amyloidosis can be considered a “forme fruste” of myeloma. Typical plasma cell myeloma (i.e. bone disease, hypercalcaemia, anaemia, renal impairment, marked marrow plasmacytosis >30%) is complicated by systemic AL amyloidosis in 10-15% of cases, but very few patients with AL amyloidosis will go on to develop symptomatic myeloma. Whilst nearly all AL patients will have a detectable monoclonal immunoglobulin or serum free light chain at diagnosis, the absolute value is usually small and, in contrast to that seen in myeloma, typically remains stable over time.

Bone marrow biopsy to enumerate clonal plasma cells and perform ancillary tests is recommended. Up to 90% of cases have cytogenetic abnormalities, particularly t(11;14) which is present in up to 50% of patients. Karyotypic abnormalities and mutational profiles in AL amyloidosis are considered more akin to smouldering myeloma than MGUS.<sup>22-24</sup> As with myeloma, del 17p in AL amyloidosis is associated with an inferior prognosis.<sup>25</sup>

IgM-related AL amyloidosis accounts for 5%-7% of all cases of AL cases, and is a distinct clinical entity.<sup>26,27</sup> The pattern of organ involvement is peculiar, with higher frequencies of lung, lymph nodes, and peripheral nervous system involvement. IgD-related AL amyloidosis accounts for only 0.7% of cases, with a similar phenotype to non-IgM AL amyloidosis, but has a higher plasma cell burden and higher rate of transformation to symptomatic myeloma than other AL amyloidoses.<sup>28</sup>

Occasionally, patients will have an underlying lymphoproliferative disorder rather than a plasma cell dyscrasia and treatment should be targeted against this clone rather than a plasma cell clone.<sup>26,27</sup> Bone marrow aspirate and trephine examination is therefore important to define the underlying haematologic disease and to provide a baseline for response evaluation and prognostication. This will often have been performed as part of the diagnostic work-up.

Using currently available assays, almost all cases of AL amyloidosis will have a detectable circulating monoclonal protein. The combination of serum protein electrophoresis with immunofixation (SPEP/IFE), urine protein electrophoresis with immunofixation (UPEP/IFE), and serum free light chain assay (FLC) has a sensitivity > 98% for the detection of an abnormal plasma cell clone.<sup>29</sup> All three assays should be performed in all cases.

Patients should be investigated to exclude end organ damage associated with multiple myeloma (refer to MSAG Clinical Practice Guideline: Multiple Myeloma).<sup>30</sup> Skeletal imaging and assessment of bone marrow plasma cell percentage and clonality, serum biochemistry, renal function, and full blood count at diagnosis are recommended. Those patients with underlying lymphoproliferative disease (e.g. Waldenström macroglobulinaemia) should be investigated accordingly.

## 3. Evaluation of extent and severity of organ involvement.

AL amyloidosis is a multisystem disease and accurate baseline assessment plays an important role in determining prognosis and planning treatment. Criteria for organ involvement in AL amyloidosis are listed in Table 2. A thorough clinical history and examination should be followed by relevant organ-specific investigations including:

### Cardiac assessment:

- Electrocardiography should be performed in all patients. Typical features of cardiac amyloid on ECG include low voltages, poor R wave progression and a “pseudoinfarct” pattern suggestive of myocardial infarction. Conduction abnormalities are also common. However, these features are far from universal and a normal ECG does not exclude cardiac amyloidosis.<sup>31</sup>
- Serum cardiac biomarkers should be performed in all patients. Due to the variable availability of investigations, it is recommended that each institution choose a locally available serum biomarker combination of either NT-ProBNP or BNP, and high sensitivity troponin (hsTnT), cTnI or cTnT for cardiac assessment.<sup>32</sup> An elevated troponin is typical of cardiac amyloidosis, and is often initially mistaken for a myocardial infarction. Physicians should note that the NT proBNP concentration can be expressed as either ng/ml or pmol/L (N.B. ng/ml x 0.1182 = pmol/L concentration).
- Echocardiography should be performed in all patients, and whenever possible with global longitudinal strain. A reduced global longitudinal strain pattern with apical sparing is highly suggestive of cardiac amyloidosis. Concentric left ventricular hypertrophy without left ventricular dilatation but with preserved ejection fraction are typical findings. Non-specific valvular thickening, atrial dilatation and a small pericardial effusion are often present. Restrictive filling patterns are often seen on Doppler studies suggesting

significant diastolic dysfunction. It should be noted that the classic ‘speckled’ appearance in the myocardium is a late feature and its absence by no means excludes significant cardiac involvement.<sup>33,34</sup>

- Cardiac MRI can be a useful adjunct to the diagnosis of cardiac amyloidosis, particularly when other potential causes for left ventricular hypertrophy are possible (e.g. hypertrophic cardiomyopathy, hypertension); the characteristic pattern of global subendocardial late gadolinium enhancement is seen in up to 70% of cases.<sup>35,36</sup> However, MRI is unable to reliably discriminate between amyloid subtypes, and other disorders can mimic the pattern of late gadolinium enhancement.
- A baseline 24 hour Holter monitor study can be considered in patients with cardiac involvement to assess the risk of clinically significant arrhythmias.<sup>37</sup>
- The utility of bone scintigraphy in patients with normal cardiac biomarkers has not been extensively studied, however, it is recognized that bone scintigraphy is more sensitive at detecting cardiac amyloid deposition than cardiac biomarkers alone. For that reason, bone scintigraphy is encouraged to be performed in all new patients aged >60 years, as ATTR is more common in this age group.<sup>21</sup>

#### **Renal assessment:**

- 24 hour urine protein studies (including total protein and immunofixation electrophoresis), serum albumin and serum creatinine and calculated glomerular filtration rate (GFR) should be performed in all patients.

#### **Hepatic and gastrointestinal assessment:**

- Liver function tests (particularly alkaline phosphatase) and clinical or imaging assessment of liver size are recommended at baseline. Patients presenting with gastrointestinal symptoms, particularly bleeding, should be assessed with endoscopy and colonoscopy both by direct visualization and with random biopsies.

#### **Neurological assessment:**

- The diagnosis of amyloid neuropathy can be made on clinical grounds in a patient with other organ involvement, but nerve conduction studies and electromyography are recommended if there is diagnostic uncertainty.

#### **Coagulation assessment:**

- A coagulation profile is recommended at baseline. Measurement of Factor X levels are indicated in those with abnormal coagulation test results as acquired factor X deficiency may occur, thought to be due to adsorption of factor X onto amyloid fibrils.<sup>38</sup>

#### **Respiratory assessment:**

- Patients presenting with pulmonary symptoms such as haemoptysis, cough and dyspnea should be investigated with computed tomography, respiratory function testing and, in selected cases, bronchoscopy with biopsy.<sup>39</sup>

#### **Hormonal assessment:**

- Blood sugar measurements should be routine, especially those with proteinuria to exclude diabetes and as a baseline before the introduction of steroids.
- Patients with AL amyloidosis rarely have hypothyroidism or hypogonadism.<sup>40</sup> However, thyroid function testing should be conducted at baseline; sex hormone assessments if hypogonadism is suspected; and a short Synacthen test if hypoadrenalism is suspected.

#### **SAP scintigraphy:**

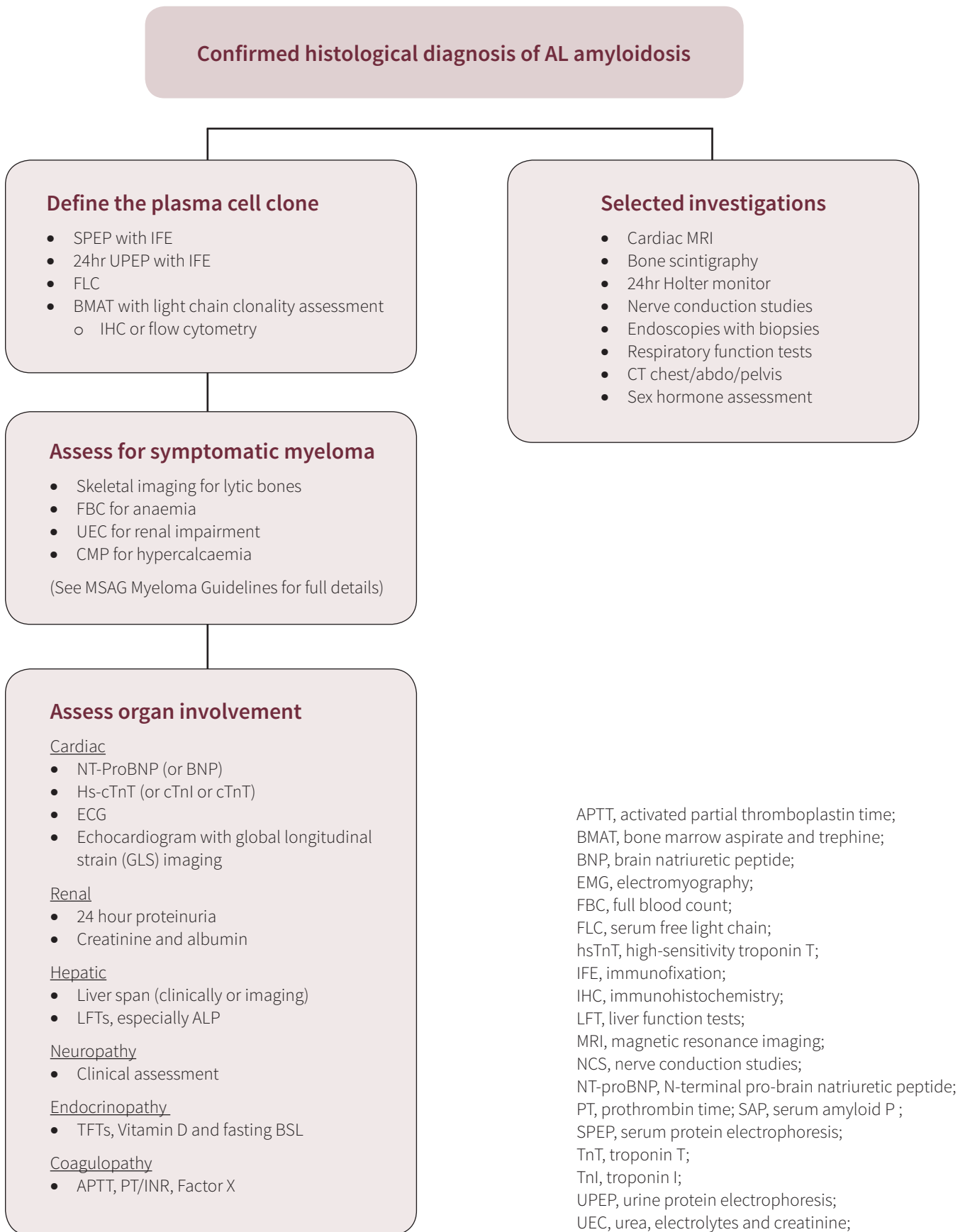
- Scintigraphy with radionuclide-labelled serum amyloid P protein (SAP) is a functional imaging technique with a sensitivity and specificity of >90% in AL amyloidosis.<sup>41,42</sup> Although it cannot demonstrate cardiac, gastrointestinal or pulmonary involvement, SAP scintigraphy can provide an assessment of disease burden in the liver, spleen kidneys, adrenal glands and bones and may have applications in response evaluation.<sup>37</sup> However, this technique is not currently available in Australia and the majority of diagnostic and monitoring information required for patient management can be gained from other investigations.

#### **Review at an Australian Amyloidosis Network Clinic:**

- Newly diagnosed patients should be considered for review at an Australian Amyloidosis Network multi-disciplinary team meeting or clinic, including review of diagnostic biopsies and imaging, and consideration of clinical trials. This is particularly relevant for men over 60 with cardiac amyloidosis given the high rate of ATTR in this population and the high frequency of an unrelated MGUS in this amyloid subtype.<sup>16,17</sup>



**Figure 1: Evaluation of newly-diagnosed AL amyloidosis**



# 5 PROGNOSTIC FACTORS

Prognostication in AL amyloidosis has evolved significantly in the past decade and forms an important basis for management decisions. Cardiac complications account for the majority of deaths in this population, whether by sudden cardiac death from an arrhythmia or asystole, or progression to end-stage, unsalvageable cardiac failure. Patients with cardiac involvement experience shorter overall survival and higher rates of morbidity compared to patients with amyloid limited to other organs.<sup>32,43-50</sup> Thus, all patients should have a thorough cardiac assessment at diagnosis.

The key prognostic determinants in patients with AL amyloidosis are:

- a) the presence and severity of cardiac involvement, best assessed by the cardiac biomarkers N-terminal pro-brain natriuretic peptide (NT-ProBNP) or brain natriuretic peptide (BNP); and troponin T (cTnT), high sensitivity troponin (hs-cTnT) or troponin I (cTnI), and
- b) the clonal plasma cell burden, measured by the difference in the involved and uninvolved serum free light chain class (dFLC).

There are two types of prognostic staging systems in use: two are based on cardiac biomarkers alone (Mayo 2004<sup>45</sup> and Boston University 2019<sup>46</sup> systems); and the third is based on both cardiac biomarkers and the free light chain assay (Revised Mayo system 2012).<sup>47</sup> While other prognostic markers have been identified in previous years (see Table 5), these have largely been superseded by these three staging systems.

Attention must be paid to the units of concentration reported with cardiac biomarkers when assessing disease stage. NT-ProBNP and BNP can be reported as ng/L, pg/ml or pmol/L. Note that pg/ml is the same as ng/L, and to convert these concentrations as pmol/L, multiply by 0.1182. Note that NT-ProBNP and BNP levels are also raised in the presence of renal impairment.<sup>48</sup>

The three staging systems allow determination of patients as low risk (eligible for aggressive therapies such as autologous stem cell transplantation), intermediate risk, and high risk (increased likelihood of early mortality before response to therapy).

## 1. Mayo Staging System 2004

The original Mayo 2004 Staging System was devised by Dispenzieri *et al*<sup>45</sup> and utilises a troponin and NT-ProBNP to provide a prognostic system that reflects the degree of cardiac involvement (Table 3). It is particularly useful for laboratories not offering cTnT as it has been validated for both cardiac troponin I (cTnI) and high sensitivity cTnT (hs-cTnT).

Wechalekar *et al* modified this staging system to identify very poor prognostic patients (Stage IIIB), identified as NT proBNP >8500pg/ml (>1000pmol/L).<sup>49</sup>

**Table 3: Mayo Staging System for AL amyloidosis (Dispenzieri et al, JCO, 2004)<sup>45</sup>**

BIOMARKERS		THRESHOLD
Troponin	Troponin T (cTnT)	<0.035mcg/L
	Troponin I (cTnI)	<0.1mcg/L
N-terminal Pro-Brain Natriuretic Peptide	NT-ProBNP	<332ng/L (<39pmol/L)
STAGE	DEFINITION	MEDIAN SURVIVAL (MO)
Stage I	Both troponin T AND NT-ProBNP below threshold	26.4
Stage II	Either troponin OR NT-ProBNP above threshold	10.5
Stage III	Both troponin AND NT-ProBNP above threshold	3.5

## 2. Revised Mayo Staging System 2012

The Revised Mayo Staging System devised by Kumar *et al*<sup>47</sup> uses a reproducible assessment of cardiac function based on cTnT, NT-proBNP, as well as incorporating clonal plasma burden using the dFLC (see Table 4), and this has been widely validated.<sup>50</sup> In a multivariate analysis incorporating cardiac biomarkers, Kumar *et al* found patients with a dFLC > 180mg/L experienced significantly higher mortality (HR 1.4, p=0.01).

It should be noted that this staging system was validated using the Freelite FLC assay and cannot be applied to FLC results generated by the NLatex assay, although local data suggests that a threshold dFLC of 150mg/L measured by the NLatex assay provides similar prognostic discrimination.<sup>51</sup>

**Table 4: Revised 2012 Mayo Staging System for AL amyloidosis (Kumar *et al*, JCO 2012)<sup>47</sup>**

BIOMARKERS		THRESHOLD
Troponin	Troponin T (cTnT)	<0.025mcg/L
N-terminus Brain Natriuretic Peptide	NT-ProBNP	<1800ng/L (<330pmol/L)
Difference between involved and uninvolved serum free light chains	dFLC	<180mg/L
STAGE	DEFINITION	MEDIAN SURVIVAL (MO)
Stage 0	Troponin T, NT-ProBNP AND dFLC below threshold	Not reached
Stage I	One of Troponin T, NT-ProBNP OR dFLC above threshold	68.8
Stage II	Two of Troponin T, NT-ProBNP AND dFLC above threshold	16.7
Stage III	Troponin T, NT-ProBNP AND dFLC ALL above threshold	6.7

## 3. Boston University Staging System 2019

Boston University has recently validated the staging system incorporating BNP, instead of NT-ProBNP, allowing the physician to easily stage the newly diagnosed patient, irrespective of which cardiac biomarkers are available to a physician's practice.

**Table 5: Boston University Staging System for AL amyloidosis (Lilleness *et al*, Blood 2019)<sup>46</sup>**

BIOMARKERS		THRESHOLD
Troponin	Troponin I (cTnI)	<0.1mcg/L
Brain Natriuretic Peptide	BNP	≤81ng/L (≤9.5pmol/L)
STAGE	DEFINITION	MEDIAN SURVIVAL (MO)
Stage I	Both troponin AND BNP below threshold	Not reached
Stage II	Either troponin OR BNP above threshold	9.4 years
Stage IIIa	Both troponin AND BNP above threshold	4.3 years
Stage IIIb	Both troponin AND BNP above threshold, with BNP >700ng/L (>83pmol/L)	1.0 years

Whilst these staging systems provide the most validated and robust methods to assess prognosis, almost any measure of the severity of cardiac involvement predicts overall survival.<sup>43-50,52-54</sup> This includes clinical parameters (New York Heart Association classification, systolic hypotension, clinical heart failure, pleural effusions), echocardiographic parameters (low ejection fraction, thickened interventricular septum, global longitudinal strain) and ventricular arrhythmias.

### Renal prognosis

While advanced cardiac involvement and the underlying clonal plasma cell burden are the strongest predictors of overall survival, assessment of the severity of renal involvement is also important in order to predict and possibly help prevent, end stage renal failure. A renal staging system devised by Palladini *et al*,<sup>55</sup> based on proteinuria and glomerular filtration rate, is able to separate patients at different risk of progression to dialysis.

STAGE	DEFINITION	DIALYSIS DEPENDENCY AT 3 YEARS
Stage 1	Proteinuria $\leq 5$ g/24 h and eGFR $\geq 50$ mL/min per 1.73m <sup>2</sup> .	0%
Stage 2	Either proteinuria $> 5$ g/24 h or eGFR $< 50$ mL/min per 1.73 m	17%
Stage 3	Proteinuria $> 5$ g/24 h and eGFR $< 50$ mL/min per 1.73 m	60%

### IgM associated AL amyloidosis

Systemic AL amyloidosis associated with an IgM papaprotein is a relatively rare variant,<sup>26,27</sup> accounting for only 6% of all cases of AL. Sachchithanantham *et al* have suggested a separate staging system for patients with IgM-related amyloidosis, based on the presence of elevated cardiac biomarkers, liver and peripheral nerve involvement. Patients with none of these features have a median overall survival of 90 months, compared with 33 months for one factor and 16 months for two or more factors. The authors confirmed that a deeper HR translates to an overall survival advantage.

### Characteristics of the underlying plasma cell clone

The serum free light chain concentration at diagnosis has been established as a predictor of overall survival (OS),<sup>21,27,56</sup> best measured as the absolute difference between the involved and uninvolved FLC (dFLC).<sup>47</sup>

Other plasma cell factors including the percentage of bone marrow plasma cells,<sup>53</sup> bone marrow plasma cell cyclin D1 expression<sup>57</sup> and the presence of cytogenetic abnormalities known to affect prognosis in multiple myeloma have also been shown to be prognostically significant. The t(11;14) translocation is seen in up to 50% of AL patients, a much higher rate than multiple myeloma, and is associated with a poorer clonal response to bortezomib and inferior OS.<sup>22-24,57,58</sup> Del 17p is also associated with inferior outcomes in AL.<sup>25</sup>

## Other prognostic factors

Various other factors have been associated with poor outcome as outlined in Table 5.

**Table 5: Prognostic factors in AL amyloidosis**<sup>23-27,43-50,52-74</sup>

POOR PROGNOSTIC FACTORS	FAVOURABLE PROGNOSTIC FACTORS
<b>Cardiac factors</b>	<ul style="list-style-type: none"> <li>• Isolated peripheral, non-autonomic neuropathy</li> <li>• Isolated renal involvement</li> </ul>
<ul style="list-style-type: none"> <li>• High cardiac biomarkers (see Table 2)</li> <li>• Worse NYHA Classification score</li> <li>• Syncope</li> <li>• Systolic blood pressure &lt;100mmHg</li> <li>• Clinical heart failure</li> <li>• Pleural effusions</li> <li>• Reduced ejection fraction</li> <li>• Interventricular wall thickness &gt;15mm</li> <li>• Ventricular arrhythmias</li> </ul>	
<b>Measures of the plasma cell clone</b>	
<ul style="list-style-type: none"> <li>• dFLC &gt; 180mg/L</li> <li>• Marrow plasmacytosis</li> <li>• High marrow plasma cell cyclin D1 expression</li> <li>• Cytogenetic abnormalities, eg. del17p</li> </ul>	
<b>Other factors</b>	
<ul style="list-style-type: none"> <li>• Worse performance status</li> <li>• &gt; Two organs involved by amyloidosis</li> <li>• Elevated urate</li> <li>• Elevated beta-2- microglobulin</li> <li>• Liver involvement</li> <li>• Advanced renal stage</li> <li>• Renal impairment (Cr Cl &lt;50mls/min)</li> <li>• Autonomic neuropathy</li> <li>• Elevated von Willebrand factor levels</li> <li>• Low ADAMTS-13 levels</li> <li>• High Growth differentiation factor-15</li> </ul>	

# 6 MANAGEMENT

## a. General considerations

Due to the rarity of AL amyloidosis, there is a paucity of randomized controlled trial data on which to base treatment recommendations, although this is slowly improving. The evidence reviewed in this section is based primarily on the few available phase III trials, as well as phase I and II studies, retrospective analyses and expert opinion. There is a need for further well-designed clinical trials in this field. Enrollment of patients in such trials is strongly recommended.

Another difficulty to note is that there has been variability in the literature on how treatment responses are reported. Some have all the patient's responses reported (so called "intent-to-treat" analysis where those who die before response assessment are not excluded from response assessment), whereas others only report evaluable patients (reflecting treatment efficacy but ignoring treatment toxicity). In the following sections, we have calculated responses based on the "intent-to-treat" approach wherever possible to give some consistency to the data.

Because of the complexity, multi-disciplinary nature and rarity of this disease, referral of patients to centres that are highly experienced in the management of AL amyloidosis is recommended. The management of these patients should be coordinated by a haematologist and conducted in a multidisciplinary setting with involvement from relevant medical, allied health and other services including diagnostic histopathology and radiology, cardiology, nephrology, gastroenterology, neurology, palliative care, pharmacy, nutrition/dietetics, haematology clinical nurses, and the primary care physician.

There are now four specialist amyloidosis centres within Australia,<sup>75,76</sup> designed to coordinate or assist with the diagnosis and management of systemic AL amyloidosis:

- a) Westmead Amyloidosis Clinic in Sydney,
- b) Princess Alexandra Hospital Amyloidosis Centre in Brisbane,
- c) Victorian and Tasmanian Amyloidosis Service at Eastern Health in Melbourne,
- d) Fiona Stanley Hospital Amyloidosis Clinic in Perth

These services make up the Australian Amyloidosis Network (AAN).

Each service provides diagnostic and management advice to physicians through patient and biopsy reviews. Complex case discussions and teleconferences with the referring physician are an integral part of these services. (Refer to <http://amyloidosis.net.au> for further details).

### RECOMMENDATIONS

- Referral of patients to an Australian Amyloidosis Network (AAN) service should be considered for confirmation of the amyloid subtype, and for multi-disciplinary advice on optimal treatment at diagnosis and relapse, clinical trials and supportive care. This is especially the case for patients over 60 years of age, to exclude ATTR.
- Treatment within the context of clinical trials is highly recommended where possible in all newly diagnosed and relapsed/refractory patients.
- Treatment should be conducted in, or in collaboration with, a tertiary centre with extensive experience in the management of AL amyloidosis
- Treatment within a multidisciplinary model incorporating multiple medical specialties, allied health and specialized nursing staff is highly recommended.

## b. Response evaluation

Survival in AL amyloidosis depends upon rapid reduction of the pathological immunoglobulin free light chain and stabilization or recovery of organ function, especially cardiac function. Improvements in organ function can take many months to several years to occur, so the initial assessment of treatment efficacy relies on measurement of haematologic response (HR).

### Haematologic response

Absolute reductions in involved FLC levels have been shown to correlate with improved survival, regardless of treatment strategy.<sup>77-80</sup> Left ventricular systolic function and serum NT-proBNP have been demonstrated to improve with lowering of the FLC,<sup>81</sup> and histologic and SAP scintigraphy regression of amyloid deposits has been observed in patients who achieve normalization of the involved FLC post-treatment.<sup>82</sup> Whilst earlier studies demonstrated a survival benefit with  $\geq 50\%$  reduction in the involved FLC (PR), subsequent analyses reported superior survival when FLC responses of at least a very good partial response (VGPR) are achieved, now defined as an absolute dFLC reduction to  $< 40\text{mg/L}$ .<sup>83,84</sup>

Minimal residual disease (MRD) assessment has not been studied in enough detail in AL amyloidosis to make recommendations of routine use to predict prognosis, although Palladini *et al* have argued that MRD positivity in patients achieving CR “can hinder recovery of organ damage.”<sup>85</sup> In the treatment of multiple myeloma, we know that the deeper the pathogenic clone is suppressed, the longer will PFS be. In AL amyloidosis, it seems intuitive that the same would apply, but with the added benefit of prolonged opportunity for an organ response and recovery.

Haematologic response criteria, produced by the International Symposium on Amyloid and Amyloidosis<sup>83</sup> and recently updated and validated in a multicentre analysis of 1190 patients,<sup>84</sup> are summarized in Table 6. These are somewhat similar to those used in myeloma with the categories Complete Response (CR), Very Good Partial Response (VGPR), Partial Response (PR) and No Response (NR). Change in dFLC is the principal measure of haematologic response in AL amyloidosis. The change in whole paraprotein level is far less important and not included as part of the response assessment. The threshold for measurable disease has been a dFLC  $\geq 50$ mg/L. Negative serum and urine immunofixation electrophoresis is still required to meet criteria for CR.

A further sub-category has recently been suggested for those patients with a low dFLC at diagnosis of 20-50mg/L, with a haematological partial response is defined as dFLC <10mg/L (“Low-dFLC response”),<sup>86</sup> however this is yet to be fully validated.

It should be noted that all clinical validation of the utility of the FLC assay in monitoring response in AL has been done with the Freelite (The Binding Site) assay. New FLC assays have recently been introduced and, while the NLatex (Seimens) assay is now validated for use in AL amyloidosis as a screening and prognostic tool, it has not yet been validated in response assessment. Care must be taken during response assessments that the same FLC assay, either Freelite or NLatex, is used when comparing baseline and post-treatment dFLC measurements.<sup>51</sup>

## Organ Response

Organ Response Criteria are summarized in Table 6. Of particular importance is the role of NT-ProBNP (or BNP) in assessing cardiac response. A reduction in the NT-ProBNP (or BNP) of >30% and at least 300ng/L (or 50ng/L for BNP) is associated with significantly better overall survival.<sup>84</sup> Care must be taken with the interpretation of changes in NT-ProBNP, ensuring matching units of concentration are used (pmol/L or ng/L), and noting that immunomodulatory drug (IMiD) therapy typically raise NT-ProBNP concentrations through an unknown mechanism of action.<sup>87,88</sup> Fluid status, atrial fibrillation and change in renal function can also affect the assays. Thus, assessment of response is best left until therapy is complete and the patient has recovered from any therapy related complications.

Note also that organ responses lag behind clonal responses, with renal responses taking 12 to 18 months to achieve after an adequate clonal response. A recent publication has proposed a grading system for the depth of organ response,<sup>89</sup> much like the depth of clonal responses, although this has yet to be universally adopted.

General recommendations for the frequency and timing of response assessments are presented in Table 7.

**Table 6: Updated Haematologic and Organ Response Criteria<sup>84</sup>**

HAEMATOLOGIC CRITERIA	RESPONSE	
Complete response (CR)	Negative SPEP/IFE, UPEP/IFE, normal FLC ratio	
Very good partial response (VGPR)	dFLC<40mg/L	
Partial response (PR)	dFLC decrease ≥50% (assessable in patients with baseline dFLC≥50mg/L).	
No response (NR)	Less than PR	
Progression	From CR, any detectable monoclonal protein or abnormal free light chain ratio (involved free light chain must be at least a doubling from the normal range) From PR, 50% increase in serum M protein to >5g/L or 50% increase in urine M protein to >200 mg/day (a visible peak must be present). Or, FLC increase of 50% to >100 mg/l at any time.	
ORGAN CRITERIA	RESPONSE	PROGRESSION
Heart	NT-proBNP response (>30% and >300ng/l decrease in patients with baseline NT-proBNP ≥650ng/l) or NYHA class response (≥2 class decrease in subjects with baseline NYHA class 3 or 4)	NT-proBNP increase (>30% and >300ng/l), <b>or</b> cTn increase ≥ 33%, <b>or</b> EF decrease ≥ 10%
Renal	Decrease in proteinuria by ≥30% or below 0.5 g/24 h without renal progression	≥25% decrease in eGFR
Liver	50% decrease in abnormal alkaline phosphatase value Decrease in liver size radiographically at least 2cm	50% increase in alkaline phosphatase above the lowest value.
Peripheral nervous system	Improvement in electromyogram nerve conduction velocity	Progressive neuropathy by EMG or nerve conduction velocity.

cTn, cardiac troponin; dFLC, difference in free light chain concentration; EF, ejection fraction; FLC, free light chain concentration; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SPEP/IFE, serum protein electrophoresis and immunofixation; UPEP/IFE, urine protein electrophoresis and immunofixation.



**Table 7: Recommended frequency of response assessments**

Assessment	DURING CHEMOTHERAPY		ASCT PATIENTS	DURING FOLLOW-UP (ALL PATIENTS)		
	On completion of each cycle	End of treatment	Day 100	2 monthly	6 monthly	Annual
Full blood count	X	X	X	X	X	X
Serum creatinine/urea	X	X	X	X	X	X
LFTs	X	X	X	X	X	X
SPEP/IFE	X		X	X		X
UPEP/IFE (24 hr urine)		X	X		X	X
FLC	X	X	X	X		X
cTnT I (or cTnIT)		X	X		X	X
NT-proBNP (or BNP)		X	X			
24hr urinary total protein		X	X		X	
Clinical assessment	X	X	X	X	X	X
TTE		X				X

ASCT, autologous stem cell transplant; LFTs, liver function tests; SPEP/IFE, serum protein electrophoresis and immunofixation; UPEP/IFE, urine protein electrophoresis and immunofixation; FLC, serum free light chain concentration; dFLC, difference in free light chain concentration; TnT, troponin T; TnI, troponin I; NT-proBNP, N-terminal of pro-brain natriuretic peptide; BNP, brain natriuretic peptide; TTE, transthoracic echocardiogram.

### c. Principles of treatment

The goals of treatment of AL amyloidosis can be summarised as follows:

- To reduce monoclonal protein production as deeply, as quickly and as long as possible to retard further amyloid fibrillogenesis and deposition.
- To tailor therapy to the individual patient, taking into account the anticipated toxicities of various agents as they relate to the extent and degree of organ involvement, as well as the availability of various agents.
- To provide optimal organ-specific supportive care to maximize quality of life and minimize treatment-related morbidity and mortality.

Broadly speaking, any chemotherapy regimen with activity in multiple myeloma is likely to be effective in AL amyloidosis by the suppression of the pathogenic clonal light chains. As with myeloma, the increased number and availability of novel agents that effectively target plasma cell clones has seen the median OS in AL amyloidosis significantly improve over the last two decades.

Along with chemotherapy, compounds that could potentially inhibit fibrillogenesis, or promote amyloid fibril remodeling or clearance, such as monoclonal antibodies against fibrillar deposits,<sup>90-91</sup> doxycycline<sup>92</sup> and epigallocatechin-3-gallate (green tea extract; EGCG),<sup>93,94</sup> have been examined in several small studies. However, these trials have so far either failed to produce significant additional benefit to chemotherapy, been deemed too toxic, or have been of insufficient size or significance to recommend routine use. In particular, EGCG has been shown *in vitro* to antagonize the cytotoxic effect of bortezomib on malignant plasma cells.<sup>95</sup> Thus, chemotherapy against the plasma cell clone - with aggressive supportive care - remains the mainstay of treatment of systemic AL amyloidosis.

The optimal haematologic endpoint after chemotherapy is CR. A VGPR (reduction in dFLC to <40mg/L) is also associated with improved likelihood of an organ response and improved overall survival,<sup>96-98</sup> although some authors believe that this is a suboptimal response due to inferior PFS with VGPR.<sup>96,97</sup> For patients with a dFLC between 20-50mg/L at diagnosis, a reduction in dFLC to <10mg/L is associated with improved OS and renal survival.<sup>99</sup> If neither CR or VGPR are possible, PR (≥50% reduction in dFLC) with an organ response may be sufficient in some cases. Because of the biological and analytical variability of the FLC assay, care should be taken with decisions to change therapy based on haematologic response when the baseline dFLC is low.

An important caveat in the management of AL is that these patients are frailer and experience significantly higher treatment-related toxicity and mortality than patients with myeloma. Patients with AL amyloidosis more commonly present with multi-organ dysfunction, impaired nutrition and limited physiologic reserve that can make delivery of high dose, effective chemotherapy extremely difficult. Therefore, treatment decisions should be made by careful assessment of patient-specific risks and benefits for each therapeutic strategy. Optimising organ support with specialist assistance while embarking on chemotherapy is critical, such as addressing early satiety and nausea with prokinetic agents; aggressive management of fluid retention from cardiac failure or nephrotic syndrome with diuretics, fluid and salt restriction; and malnutrition with dietary supplements (see “Supportive care” section).

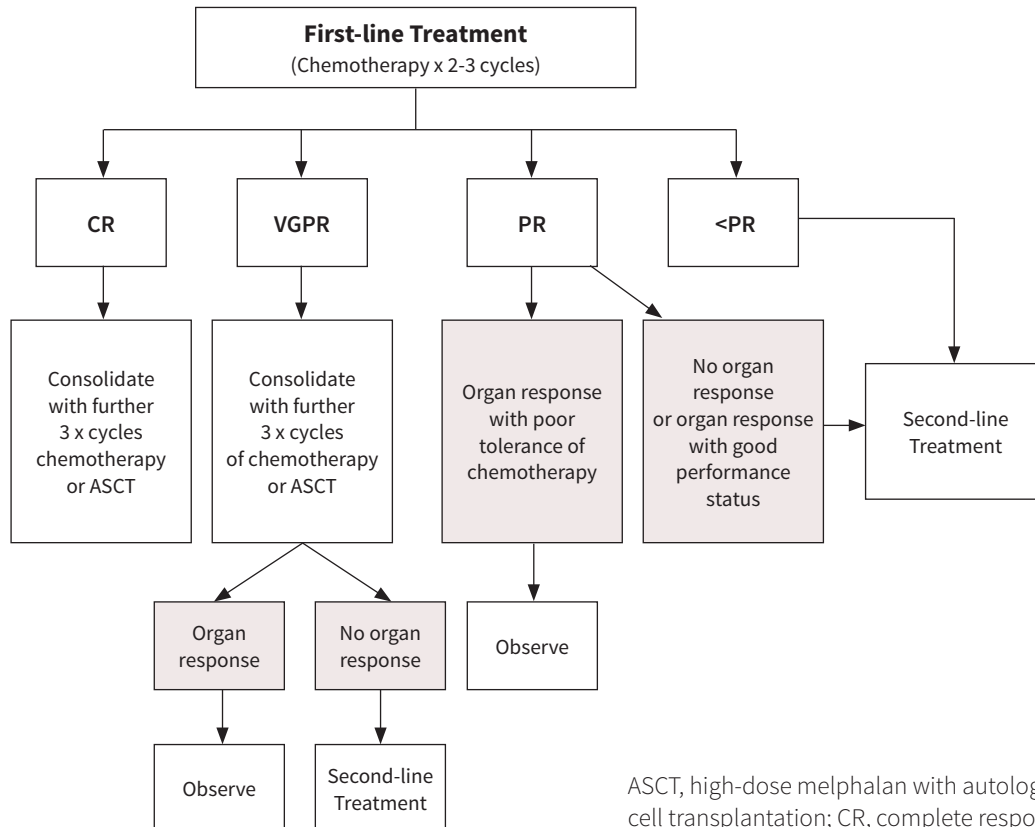
A prospective UK study of 91 patients, presented in abstract form only, has reported that early switch to second-line treatment in patients who fail to achieve at least VGPR after 3 cycles of initial therapy,<sup>100</sup> was associated with improved clonal response in 52%, but no meaningful survival data was supplied. We recommend clinical discretion when considering adding in an additional therapy - such as thalidomide to bortezomib, cyclophosphamide and dexamethasone (CyBORd) - or changing to second-line therapy, influenced in part by the organ impaired with amyloid and whether there is any evidence of an early organ or clinical response. For example, patients with cardiac involvement who achieve less than a PR after 2 cycles have a greater urgency to achieve prompt reduction in the pathologic light chain compared to patients with non-critical organ involvement. Likewise, in cases where a stable VGPR is achieved and treatment toxicities have been minimal but there has been no organ response, it is reasonable to proceed to second line therapy in an attempt to achieve CR. In cases where second line agents are relatively contraindicated due to deteriorating performance status, a PR with an organ response is a reasonable treatment outcome. The challenge with AL amyloidosis is to find the balance between achieving the most effective control of the pathogenic clone, while not significantly adding further insult to organs already impaired by amyloid deposition, or to the patient's quality of life.

As the plasma cell burden is generally small in AL amyloidosis, there is no need for protracted duration of treatment as in myeloma. Generally six cycles of bortezomib-based treatment (see Figure 2) or continuing treatment for two cycles beyond maximal response is usually adequate. Thalidomide "maintenance" or consolidation therapy in AL patients has been studied in a small retrospective analysis,<sup>101</sup> suggesting minor improvement in clonal response rates and longer PFS but with a significant increase in toxicity, thus is not routinely recommended. Lenalidomide is generally continued until CR or progression if well tolerated.

Patients who suffer from both symptomatic myeloma and systemic AL amyloidosis should be managed according to the principles of both conditions. For example, a patient under 70 years of age without contraindication to transplantation should receive induction, ASCT and maintenance in addition to bisphosphonates, whereas a patient under 70 years of age with significant cardiac or autonomic nervous system involvement, should not undergo ASCT, but may require a longer duration of therapy than if underlying symptomatic myeloma was not present. Of note, patients without symptomatic myeloma, especially no evidence of lytic bone disease, do not require bisphosphonates as a routine.

An overview of the approach to initial treatment of AL amyloidosis is presented in Figure 2.

**Figure 2: General treatment approach**



ASCT, high-dose melphalan with autologous stem cell transplantation; CR, complete response; VGPR, very good partial response; PR, partial response.

## Choice of Upfront Therapy

Bortezomib-based regimens are the preferred front-line therapy with multiple studies demonstrating brisk and deep clonal responses,<sup>102-105</sup> coupled with superior HR and PFS when compared to historical MDex and CTD controls.<sup>106,107</sup> Recently, a Phase III trial comparing bortezomib with MDex (BMD) to MDex alone has cemented bortezomib as the standard of care upfront treatment of choice, confirming superior haematologic response rates, PFS and OS with the bortezomib-containing arm.<sup>108</sup> Practically speaking, the most commonly used first-line treatment internationally is bortezomib, cyclophosphamide and dexamethasone (CyBorD).<sup>109-111</sup> The cyclophosphamide is stem cell sparing compared to melphalan, thus CyBorD can allow greater treatment flexibility to BMD, including the possibility of future high-dose melphalan with autologous stem cell transplant (HDM/ASCT) in eligible patients.

Traditional chemotherapy approaches using oral melphalan and prednisolone produce modest survival benefit<sup>112-114</sup> and have been superseded by the melphalan and dexamethasone (MDex) combination.<sup>115-117</sup> Cyclophosphamide with thalidomide and dexamethasone (CTD) emerged as an alternative to MDex, achieving similar but more rapid clonal responses than MDex, with the advantage of being stem cell sparing regimen that has superior tolerability in renal impairment.<sup>118,119</sup>

If there are contraindications to bortezomib, such as pre-existing autonomic neuropathy, MDex is a reasonable alternative.<sup>115,116</sup> CTD can also be considered if access to bortezomib is unavailable.

Lastly, in appropriately selected patients, initial HDM/ASCT either with or without induction chemotherapy remains a therapeutic option (see later section). While in previous years there was a trend for upfront HDM/ASCT in transplant-eligible newly diagnosed AL patients without induction, a retrospective analysis by the Mayo group has suggested that patients with Mayo 2012 Stage III disease and those with a bone marrow plasmacytosis of >10% at diagnosis have inferior OS if they do not receive induction therapy before HDM/ASCT.<sup>120</sup> A small RCT of HDM/ASCT with or without bortezomib induction in patients with renal AL amyloidosis also reported superior outcomes for the bortezomib induction arm.<sup>121</sup> Other non-randomized studies of bortezomib induction suggest a benefit compared to historical data of HDM/ASCT without induction therapy.<sup>122-125</sup> Thus, a trial of bortezomib-based induction chemotherapy should be considered in most cases. Such an approach allows the option of deferral of HDM/ASCT in the event of good clonal control or alternatively may lead to an organ response by the time the HDM/ASCT is delivered – thus, decreasing the likelihood of TRM or further organ damage. Patients should have response assessment prior to ASCT as persistent cardiac or renal involvement and < VGPR is associated with poorer prognosis (see Figure 2). There have been several reports of patients who were considered ineligible for ASCT at diagnosis subsequently being reassessed as eligible after induction therapy with VCD, due to improvements in organ function after suppression of the pathogenic clone.<sup>126</sup>

Patients with IgM-related AL amyloidosis require therapy more akin to treatment of Waldenström Macroglobulinaemia. The MSAG guidelines on Waldenström Macroglobulinaemia recommend that patients who have concomitant symptomatic amyloidosis be considered candidates for treatment.<sup>127</sup> Bendamustine and rituximab, and dexamethasone with rituximab and cyclophosphamide (DRC) are recommended as first line treatment and HDM/ASCT has also been reported to have activity against the pathogenic IgM clone.<sup>26,127-129</sup> HDM/ASCT is reported to have an HR of 92%, with VGPR or greater responses of 76% in a retrospective study of 38 patients.<sup>129</sup>

The choices to consider in initial treatment are summarized in Table 7. The various chemotherapy regimens are discussed in the following sections, and are detailed in Appendix 1.

In common with many orphan diseases, access to all therapies is not universal in Australia due to both registration and reimbursement issues.<sup>76</sup>

## Treatment of relapsed systemic AL amyloidosis

A common issue is when to restart therapy at clonal relapse. Should one restart therapy at the first signs of clonal progression or wait until evidence of organ progression? What is the threshold at which asymptomatic clonal relapse should be addressed? There are no prospective data to clearly answer this question. Recently, Palladini *et al* put forward the concept of patients with “high-risk dFLC progression”<sup>130</sup> which was defined as a dFLC of >20 mg/L, a level >20% of baseline value, and a >50% increase from the value reached at best response. A recent publication of two counter arguments on this point has also recently been published, one advocating for early therapy at clonal relapse to prevent organ progression,<sup>131</sup> the other cautioning over-enthusiastic resumption of chemotherapy in frail patients at the first sign of clonal relapse.<sup>132</sup> International opinion remains mixed.<sup>133</sup> Thus, objective guidelines on this controversial area are not available, however, it seems reasonable to consider therapy when the dFLC has reached 50% of the diagnostic level, or if a patient qualifies as a Palladini “high-risk dFLC-progressor”,<sup>130</sup> especially in those patients with significant cardiac or autonomic amyloid disease.

Second- and third-generation proteasome inhibitors and IMiDs have activity in relapsed/refractory disease, and are summarized in the individual sections. Bendamustine has also been used, especially in IgM-related amyloidosis, and while haematological response rates are encouraging in the relapsed setting, prolonged cytopenias have limited its use. Bortezomib-based therapies may be reused if there was a deep and prolonged clonal response with acceptable toxicity at induction. HDM/ASCT can also be used as salvage therapy rather than consolidation in eligible patients.<sup>134</sup> Daratumumab has been reported to have excellent activity in the relapsed/refractory setting and is well tolerated.

**Table 8: Choice of initial therapy in AL amyloidosis**

- CyBorD and BMD are the optimal initial treatment regimens for newly-diagnosed AL amyloidosis (Level 1B, Grade A)\*
- Bortezomib and thalidomide-based regimens should be avoided in patients with Grade 3 peripheral sensory neuropathy, painful neuropathy or significant autonomic neuropathy (Level 2B, Grade B)
- Bortezomib-based regimens are preferred in patients with renal impairment (Level 2B, Grade C)
- HDM/ASCT should be considered in patients with no or mild cardiac disease and adequate renal function (GFR>50ml/min) (Level 2A, Grade B), preferably after a trial of induction chemotherapy (Level 3, Grade B)
- In patients who may become candidates for ASCT, consideration should be given to the collection of PBSC prior to extensive melphalan exposure (Level 2B, Grade C)
- MDex or lenalidomide/dex can be considered in patients with significant autonomic and/or peripheral neuropathy, but have inferior and slower clonal response rates than BMD or CyBorD (Level 3, Grade B)
- Lenalidomide at a maximum dose of 15mg daily is recommended (Level 3, Grade B)
- In the rare cases of IgM-associated or a lymphoproliferative-associated AL amyloidosis, treatment should be directed at the pathogenic clone, such as with bendamustine/rituximab, DRC or HDM/ASCT (Level 3, Grade B)

\*At the time of writing, access to all recommended therapies is not universal in Australia

CyBorD – cyclophosphamide, bortezomib and dexamethasone

BMD – bortezomib, melphalan and dexamethasone

DRC – dexamethasone, rituximab and cyclophosphamide

## d. Chemotherapy and novel agents

### Bortezomib

Current data suggests that bortezomib is the most active agent in AL amyloidosis. The high response rates seen with this drug are postulated to occur due to the particular susceptibility of clonal AL plasma cells to the effects of proteasome inhibition, resulting in endoplasmic reticulum stress induced by accumulation of toxic unfolded amyloidogenic light chains.<sup>135</sup>

Major trials of bortezomib in AL amyloidosis are summarized in Table 9. Haematologic response rates with single agent or combined therapy are not only high but also rapid, with median time to HR of 52 days.<sup>102-107</sup> Patients with significant (Grade 3) or painful sensory neuropathy and significant autonomic neuropathy were excluded from these trials. Because of neuropathic effects, autonomic complications including postural hypotension and diarrhoea can be problematic and need careful monitoring and should prompt early dose modification of bortezomib. Whilst twice weekly dosing may improve the speed of response, this is often at the expense of increased toxicity, especially neuropathy.<sup>103</sup> One study reports inferior long-term OS with full-dose bortezomib and dexamethasone compared to risk-adapted dosing.<sup>110</sup> Clonal response rates are similar, whether using once or twice weekly bortezomib, although time to first clonal response was more rapid in the twice-weekly cohort (0.7 vs 2.1 months).<sup>103</sup> Thus, if an urgent clonal response is required, an initial cycle of twice weekly bortezomib, then reverting to once weekly once a clonal response is obtained, may be considered. Subcutaneous (SC) bortezomib has similar efficacy to the IV formulation.<sup>111</sup> Given that the SC form has been shown to have reduced neurotoxicity in myeloma,<sup>30</sup> it is recommended that the SC form is used in AL amyloidosis, unless there are significant concerns about absorption due to excessive oedema.

Alkylator-bortezomib combinations appear to provide higher response rates, in both untreated and relapsed patients.<sup>104-109</sup> Additionally, there is evidence that patients with advanced cardiac disease, who traditionally do very badly regardless of treatment choice, may enjoy prolonged OS with the CyBorD regimen if a rapid VGPR/CR is achieved.

A multicentre, randomized phase III trial comparing Mel-Dex with or without bortezomib in untreated, transplant-ineligible patients has demonstrated a higher clonal response rate ( $p=0.005$ ), and improved PFS and OS with the addition of bortezomib.<sup>108</sup> Of interest, there was no definite difference in the rate of cardiac or renal responses, although there was a slightly higher rates of responses in the bortezomib-containing groups ( $p=0.37$  for cardiac;  $p=0.26$  for renal), and follow-up is still ongoing.

Venner *et al* performed a matched comparison of 69 patients with CyBorD and CTD, and found that while 1 year OS was virtually identical between these two treatment regimens, CR rates were higher (40.5% vs. 24.6%,  $p = 0.046$ ), and PFS longer with CyBorD (not reached vs. 19.2 months,  $p = 0.028$ ).<sup>107</sup>

Recently, a study examining the combination of bortezomib with lenalidomide suggested similar HR rates to CyBorD, however, 43% of patients required lenalidomide dose reduction due to toxicity.<sup>136</sup>

Further study is required to determine the true PFS, both in terms of the pathogenic clone and organ involvement, with bortezomib-containing regimens. The role of a “consolidation” HDM/ASCT in transplant-eligible patients remains uncertain. Those with a more typical myeloma burden of disease at diagnosis may benefit from the consolidation approach, although there is limited data to support this.

**Table 9: Major trials of bortezomib in AL amyloidosis**

AUTHOR	INTERVENTION	STUDY DESIGN	N	HR (CR) % <sup>A</sup>	OR % <sup>A</sup>	MEDIAN OS	COMMENTS
Kastritis 2010 <sup>102</sup>	Bortezomib/dexamethasone	Retro, multi-centre	94	72 (25)	30	NR	76% 1yr OS No difference in toxicity between weekly and twice weekly schedules
Reece 2011 <sup>103</sup>	Bortezomib	Prospective phase I/II	52	67 (29)	44	NR	89% 1yr OS Higher toxicity in twice weekly schedule
Mikhael 2012 <sup>104</sup>	CyBorD	Retro, single centre	17	94 (71)	50% (renal) 71% (cardiac)	NR	88% received weekly bortezomib; no grade 3/4 peripheral neuropathy
Venner 2012 <sup>105</sup>	CyBorD	Retro, single centre	43	81 (42)	46	NR	46% stage III 2yr OS 98% (94% for stage III patients) 14% discontinued due to neuropathy
Palladini 2015 <sup>106</sup>	CyBorD	Retro, multi-centre	230	60 (23)	21	NR	
Kastritis 2018 <sup>136</sup>	BLD	Phase II	30	88 (24)	21	NR	First-line treatment 43% required lenalidomide dose reduction
Zonder 2009 <sup>137</sup>	BMD	Prospective phase II	30	94 (63)	40	NR	7 had improvement in neuropathy
Kastritis 2016 <sup>103</sup>	BMD	Prospective phase III	53	81 (64% VGPR)	43	NR	Improved PFS and OS in bortezomib-containing arm

<sup>a</sup> Calculated by intention-to-treat; NR = not reached.

HR, haematologic response; CR, complete response; OR, organ response; OS, overall survival; TRM, treatment-related mortality; PFS, progression-free survival; Retro, retrospective

CyBorD – cyclophosphamide, bortezomib and dexamethasone

BLD – bortezomib, lenalidomide and dexamethasone

BMD – bortezomib, melphalan and dexamethasone

#### RECOMMENDATIONS\*<sup>^</sup>

- Bortezomib-based chemotherapy regimens are effective in patients with untreated or relapsed/refractory disease (Level 1B, Grade A).
- SC bortezomib administration is preferred to IV, except if there is significant tissue oedema (Level 2B, Grade B).
- Combination regimens incorporating alkylating agents, such as CyBorD or BMD, produce higher response rates than monotherapy and are the preferred upfront treatment strategy (Level 2B, Grade B).
- Weekly dosing schedules are better tolerated with similar clonal response rates and improved OS compared to twice-weekly dosing, although initial twice-weekly dosing may result in quicker clonal responses (Level 2A, Grade C).
- Bortezomib should be avoided in patients with Grade 3 peripheral sensory neuropathy, painful neuropathy or significant autonomic neuropathy (Level 2A, Grade C).
- Early dose modification is required in the event of worsening neuropathy of autonomic symptoms (Level 2A, Grade B)

\*At the time of writing, access to all recommended therapies is not universal in Australia

<sup>^</sup> In the absence of toxicity, therapy duration is generally for six cycles (see Figure 2) or continuing treatment for two cycles beyond maximal response

## Melphalan

Clinical trials of melphalan in AL amyloidosis were first reported in 1978. Melphalan and prednisolone (MP) demonstrated superior haematologic and organ responses with minor survival improvement in prospective randomized trials when compared to placebo or colchicine.<sup>112-114</sup> Following recognition of the efficacy of high-dose dexamethasone in AL amyloidosis, the melphalan-dexamethasone regimen (Mel-Dex) was developed.<sup>115-117</sup>

Due to concerns about the potential for erratic absorption of oral melphalan in AL patients, some centres have used intravenous administration. A phase II Australian study assessed monthly IV melphalan and oral dexamethasone in patients ineligible for HDM/ASCT. IV melphalan at a dose of 20mg/m<sup>2</sup> was associated with high rates of Grade 3 and 4 myelosuppression and corresponding high treatment-related mortality rates, with no improvements in response.<sup>138</sup> IV melphalan at 16mg/m<sup>2</sup> appears to be more tolerable, but in practice, this is now only recommended in patients with peripheral or autonomic neuropathy who have issues with gastrointestinal absorption.

**Table 10: Major trials of conventional dose melphalan in AL amyloidosis**

AUTHOR	INTERVENTION	STUDY DESIGN	N	HR (CR) % <sup>A</sup>	OR % <sup>A</sup>	MEDIAN OS (MONTHS)	TRM	COMMENTS
Kyle 1997 <sup>113</sup>	MP ±colchicine	RCT	220	28	17	18	-	Myelodysplasia occurred in ~5% of Mel group
Palladini 2004, 2007 <sup>105,116</sup>	Mel-Dex	Phase II single centre	46	67 (33)	48	61.2	4%	Pts ineligible for ASCT; Median 4 cycles completed
Jaccard 2007 <sup>139</sup>	Mel-Dex	Phase III RCT	50	52 (18)	34	57	0	
Mollee 2012 <sup>138</sup>	IV Mel-Dex	Phase II, multi-centre	14	21 (7)	7	6.8	50% at 6 mo	
Lebovic 2008 <sup>140</sup>	Mel-Dex	Retrospective, single centre	40	58 (13)	-	10.5	-	Pts ineligible for ASCT

<sup>a</sup> Calculated by intention-to-treat

ASCT, autologous stem cell transplant; HR, haematologic response; CR, complete response; OR, organ response; OS, overall survival; RCT, randomized controlled trial; TRM, treatment-related mortality.

RECOMMENDATIONS* <sup>^</sup>
<ul style="list-style-type: none"> <li>• Oral melphalan-dexamethasone is a suitable first-line regimen (Level 1B, Grade A) when bortezomib is contraindicated or not accessible.</li> <li>• Oral melphalan-dexamethasone is a suitable second-line regimen, although combining with a novel agent may enhance clonal and organ response rates and PFS (Level 4, Grade C)</li> </ul>

\*At the time of writing, access to all recommended therapies is not universal in Australia

<sup>^</sup>In the absence of toxicity, therapy duration is generally for six cycles (see Figure 2) or continuing treatment for two cycles beyond maximal response

## Thalidomide

Thalidomide has been studied as a single agent or in combination with other agents in a number of small single-centre trials (see Table 11).<sup>100,101,107,118,119,141,142</sup> Significant treatment-limiting toxicity has been observed with doses above 100mg daily, including symptomatic bradycardia, severe peripheral oedema, constipation, rash and cognitive side-effects. Attenuated dose thalidomide in combination with cyclophosphamide and low-dose dexamethasone (CTDa) appears to produce the highest response rates with acceptable toxicity.<sup>118</sup> A retrospective comparison of MDex and CTD found no difference in efficacy between the two regimens.<sup>119</sup> Due to cumulative neurotoxicity, the use of thalidomide as maintenance therapy is not routinely recommended,<sup>101</sup> although may have a role as short-term consolidation therapy. Thalidomide-based regimens should be avoided in patients with Grade 3 or 4 peripheral sensory neuropathy, painful neuropathy or significant autonomic neuropathy. The NT-ProBNP is typically elevated with IMiDs so interpretation of a cardiac response should be interpreted with caution in patients during therapy with these agents.<sup>87,88</sup>

**Table 11: Major studies of thalidomide in AL amyloidosis**

AUTHOR	INTERVENTION	STUDY DESIGN	N	HR (CR) % <sup>A</sup>	OR % <sup>A</sup>	MEDIAN OS (MONTHS)	COMMENTS
Palladini 2005 <sup>141</sup>	Thal-dex	Phase I/II	31	48 (19)	26	-	≥Grade 3 toxicity in 65%, most commonly symptomatic bradycardia
Wechalekar 2007 <sup>118</sup>	CTD/CTDa	Phase II	75	74 (21)	26	NR	Non-significant difference between CTD and CTDa. ≥Grade 3 toxicity in 32%
Palladini 2009 <sup>142</sup>	MTD	Phase II	22	36 (5)	18	5.3	100% of patients were NYHA Class IV

<sup>a</sup> Calculated by intention-to-treat; NR = not reached.

HR, haematologic response; CR, complete response; OR, organ response; OS, overall survival; TRM, treatment-related mortality.

CTD – cyclophosphamide, thalidomide and dexamethasone (full dose)

CTDa – cyclophosphamide, thalidomide and dexamethasone (attenuated dose)

MTD – melphalan, thalidomide and dexamethasone

RECOMMENDATIONS <sup>A</sup>
<ul style="list-style-type: none"> <li>• CTD/CTDa is a suitable first-line regimen (Level 2A, Grade B) if bortezomib is not accessible.</li> <li>• The maximum daily recommended thalidomide dose, regardless of regimen, is 100mg (Level 2B, Grade C).</li> <li>• Thalidomide maintenance is not recommended (Level 2B, Grade C)</li> </ul>

<sup>A</sup> In the absence of toxicity, therapy duration is generally for six cycles (see Figure 2) or continuing treatment for two cycles beyond maximal response.

## Lenalidomide

While poor results were seen with lenalidomide monotherapy in early studies, doublet and triplet combinations have shown response rates similar to CTD or MDex (see Table 12). Early trials of lenalidomide using ‘myeloma’ doses (ie 25mg daily) in combination with dexamethasone demonstrated HR rates around 40-50% but with significant haematologic, renal and skin toxicity.<sup>143, 144</sup> Subsequently, a daily lenalidomide dose of 15mg was established as the maximum tolerated dose in a phase I/II dose escalation study.<sup>145</sup> Using this lower dose, HR rates around 60% have been reported when combined with cyclophosphamide, and dexamethasone<sup>146,147</sup> although the CR rate has remained disappointingly low. Median time to haematologic response is 3 months<sup>148</sup>

There is preliminary evidence that lenalidomide should be continued after achievement of maximal response in a maintenance fashion to improve organ responses.<sup>148</sup> Combining lenalidomide with bortezomib and dexamethasone (LBD) appears to enhance clonal response rates, up to 88%, but these results are similar to those obtained with CyBorD, and at a cost of significant additional toxicity requiring dose adjustments in the majority of patients.<sup>136</sup> A Phase I trial of front-line pomalidomide, bortezomib and dexamethasone was terminated early due to perceived excessive toxicity.

Lenalidomide does not appear to induce or exacerbate neuropathy in the majority of AL patients, thus lenalidomide-based regimens can be considered for patients with amyloid neuropathy. Finally, like thalidomide, lenalidomide increases BNP and NT-proBNP levels. This is independent of changes in renal function and FLC, and may interfere with the assessment of cardiac response.<sup>87,88</sup>

**Table 12: Major trials of lenalidomide in AL amyloidosis**

AUTHOR	INTERVENTION	STUDY DESIGN	N	HR (CR) % <sup>A</sup>	OR % <sup>A</sup>	MEDIAN OS (MONTHS)	COMMENTS
Santhorawala 2007 <sup>143</sup>	Len-Dex	Phase II	34	47 (21)	21	NR	35% ≥Grade 3 myelosuppression
Dispenzieri 2007 <sup>144</sup>	Len-Dex	Phase II	22	41 (5)	23	NR	Only 55% completed >3 cycles; ≥Grade 3 toxicity in 86% 50% 2yr OS
Moreau 2010 <sup>145</sup>	MLD	Phase I/II	26	58 (23)	50	NR	Untreated patients; No DLT observed at len doses ≤15mg/day 81% 2yr OS
Kumar 2012 <sup>146</sup>	CLD	Phase II	35	60 (11)	31	37.8	Mixture of treated and untreated patients; 43% stage III. 2 treatment-related deaths.
Kastritis 2012 <sup>147</sup>	LcD	Phase I/II	37	55 (8)	22	17	65% untreated. 35% stage III. 2 treatment-related deaths (coronary events).
Mahmood 2014 <sup>148</sup>	Len-Dex	Retrospective, single centre	84	61 (20)	16	NR	2 year OS 74%
Kastritis 2018 <sup>136</sup>	LBD	Phase II	30	88 (24)	21	NR	First-line treatment 43% required lenalidomide dose reduction

<sup>a</sup> Calculated by intention-to-treat; NR= not reached. NRp = not reported

CR, complete response; DLT, dose-limiting toxicity; HR, haematologic response; OR, organ response; OS, overall survival; TRM, treatment-related mortality.

Len-Dex – Lenalidomide and dexamethasone

MLD – Melphalan, lenalidomide and dexamethasone

CLD – Cyclophosphamide, lenalidomide and weekly dexamethasone

LcD – Lenalidomide, low dose cyclophosphamide and pulse dexamethasone

LBD – Lenalidomide, bortezomib and dexamethasone

#### RECOMMENDATIONS\*

- Lenalidomide-based combination chemotherapy regimens are effective in patients with untreated or relapsed/refractory disease. Single agent lenalidomide has limited activity (Level 2A, Grade B).
- Combination regimens incorporating alkylating agents, such as CLD and MLD, are a reasonable treatment strategy for relapsed patients, subject to local availability of lenalidomide (Level 2A, Grade B).
- Lenalidomide-based therapy can be considered in patients with peripheral or autonomic neuropathy that would preclude the use of other neurotoxic agents.
- The maximum recommended daily dose of lenalidomide in AL, regardless of regimen, is 15mg for 21 days of a 28 day cycle (Level 2A, Grade B).

\*At the time of writing, access to all recommended therapies is not universal in Australia

#### Other agents

Second and third-generation proteasome inhibitors and IMiDs have been used in AL amyloidosis, as in myeloma, however, there are no available Phase III trials in this space. Early stage trials have limited follow-up data, with no meaningful overall survival data. However, they do offer additional treatment options for the relapsed patient. Daratumumab in particular seems well tolerated and highly effective. There are no studies of CAR-T cells, histone deacetylase inhibitors or other plasma-cell directed monoclonal antibodies currently available in the treatment of AL amyloidosis in the literature.



## Pomalidomide

This third-generation immunomodulatory agent has been tested in AL amyloidosis over the last decade. One phase II trial of pomalidomide in combination with weekly dexamethasone in previously treated patients with AL amyloid showed a HR rate of 48% with organ responses in 5/33 patients.<sup>149</sup> The most common adverse effects were fatigue and neutropenia. Two other early phase trials have revealed similar results, with the maximum tolerated dose confirmed at 4mg daily.<sup>150,151</sup>

## Carfilzomib

Cohen *et al* have reported in abstract form the only available data on carfilzomib.<sup>152</sup> This is as a Phase I/II trial in 2016, involving 28 patients with relapsed/refractory Mayo cardiac stage I or II disease. The 20/36 mg/m<sup>2</sup> dosing was determined as the MTD. While the haematologic response rate of 63% is comparable to most other therapies for relapsed/refractory disease, the CR was low at 11%. 20 patients experienced Grade III/IV toxicity, many cardiac or pulmonary in type, and 40% of patients had rises in NT proBNP that would qualify for organ progression. While five (21%) patients had organ responses, none were cardiac. Overall, it is the advice of the authors that carfilzomib has some safety concerns, especially cardiac and renal, and we advice caution and close monitoring with its use, and to consider alternate therapies first if available until further data is collected.

## Ixazomib

The Phase I/II study of ixazomib in relapsed/refractory disease involved 27 patients.<sup>153</sup> Patients received ixazomib on days 1, 8, and 15 of 28-day cycles, for up to 12 cycles. Patients with less than partial response after 3 cycles received oral dexamethasone (40 mg, days 1-4). The MTD was determined as 4.0 mg. A HR was observed in 52%, but a CR was only achieved in 2 patients. Organ responses were seen in 56%; 5 cardiac, 5 renal. 1-year PFS and OS was 60% and 85%, respectively (median follow-up, 16.9 months).

The Phase 3 TOURMALINE-AL1 study, comparing ixazomib and dexamethasone with physicians choice (typically lenalidomide and dexamethasone) for relapsed AL amyloidosis was terminated early as interim analysis suggested that the trial would not meet its primary end-point of improvement in overall haematologic response. No safety concerns were raised with the ixazomib/dexamethasone combination.<sup>154</sup>

Thus, weekly oral ixazomib appears to be active in patients with relapsed/refractory AL amyloidosis, albeit with low CR rates.

## Daratumumab

Daratumumab has demonstrated high rates of clonal responses in relapsed/refractory disease as monotherapy in several retrospective analyses.<sup>155-159</sup> A recent prospective Phase 2 trial of 40 relapsed/refractory patients receiving daratumumab monotherapy demonstrated overall HR of 59% with VGPR or greater seen in 44%.<sup>159</sup> Haematologic responses were brisk, typically within one cycle, and well tolerated, with all cause >Grade 2 toxicity of only 25%. Thus, daratumumab has relatively high response rates with good tolerance in relapsed/refractory disease.

## Bendamustine

Bendamustine/rituximab demonstrated excellent HR on an intention to treat basis of 59% of patients with IgM-associated AL amyloidosis.<sup>128</sup> Two studies of bendamustine with dexamethasone have suggested good clonal response rates in heavily pre-treated patients, but the significant haematologic toxicity observed prevents routine use of this agent.<sup>160,161</sup>

## Venetoclax

Venetoclax has the theoretical advantage in AL amyloidosis of targeting the t(11;14) translocation present in 50% of patients. However, there is no trial data to support its use in AL amyloidosis; in fact, only one case report had been published<sup>162</sup> at the time of this guideline's release, and one small case series of 12 patients from the Mayo Clinic reported in abstract form.<sup>163</sup> Toxicity assessment in the setting of AL amyloidosis has been minimal. Thus, venetoclax is not recommended outside the clinical trial context.

## Doxycycline

Doxycycline has been studied *in vitro* and in mouse models as a possible anti-fibrillogenic agent to slow the progression of AL amyloidosis.<sup>164</sup> A clinical benefit has also been suggested by two retrospective cohort studies.<sup>165,166</sup> Doxycycline has been used at the Mayo Clinic at a dose of 100mg twice daily as infection prophylaxis in the penicillin allergic after HDM/ASCT in AL. In a retrospective study of 455 patients,<sup>165</sup> Kumar *et al* report that patients who received doxycycline post HDM/ASCT demonstrated superior OS when compared to those who received penicillin prophylaxis (not reached vs. 113 months, p=0.09).

Thus, doxycycline is a useful prophylactic antibiotic in AL amyloidosis, and while early data from prospective studies are encouraging,<sup>167</sup> routine use of this agent has yet to be proven.

**Table 13: Major trials of novel therapies in AL amyloidosis**

AUTHOR	INTERVENTION	STUDY DESIGN	N	HR (CR) % <sup>A</sup>	OR % <sup>A</sup>	MEDIAN OS (MONTHS)	COMMENTS
Kaufman 2017 <sup>156</sup>	Daratumumab	Retro, single centre	25	76 (36)	NRp	NR	16mg/kg weekly for 8 doses, then 2 weekly for 8 then 4 weekly
Khouri 2019 <sup>157</sup>	Daratumumab	Retro, single centre	15	82 (7)	55	NR	73% VGPR rate
Kimmich 2018 <sup>155</sup>	Daratumumab	Retro, single centre	49	65 (10)	NRp	NR	82% OS at 6 months in a heavily pre-treated population
Jaccard 2018 <sup>159</sup>	Daratumumab	Phase II	36	59 (NRp)	50	NR	VGPR or greater in 44%
Cohen 2016 <sup>152</sup>	Carfilzomib	Phase I/II	28	63 (11)	21	NR	20mg added with each carfilzomib dose if no VGPR after 4 cycles MTD was 20/36mg/m <sup>2</sup>
Sanchorawala 2017 <sup>153</sup>	Ixazomib	Phase I/II	27	52 (7)	56	NR	1 year PFS 60%, OS 85%
Milani 2017 <sup>160</sup>	Bendamustine	Retro, single centre	125	36(2)	14	NR	1 year OS 85%
Lagos 2016 <sup>161</sup>	Bendamustine/ dexamethasone	Phase II	31	41 (3)	31	NR	8 discontinued due to AEs
Manwani 2018 <sup>128</sup>	Bendamustine/ rituximab	Retro, single centre	27	59 (11)	15	NR	IgM AL amyloidosis 11% cardiac responses 18% renal responses First-line therapy in 22
Kumar 2012 <sup>163</sup>	Doxycycline	Retro, single centre	106	NA	NRp	NR	1 year duration post-ASCT = improved OS vs. penicillin (p=0.09)
D'Souza 2018 <sup>164</sup>	Doxycycline	Phase II	25	NA	36	NR	All received concurrent VCD. OS 80% at 1year
Dispenzieri 2012 <sup>149</sup>	Pomalidomide/ dexamethasone	Phase II	33	48	15	28	Common toxicities were neutropenia and fatigue
Sanchorawala 2016 <sup>150</sup>	Pomalidomide/ dexamethasone	Phase I/II	27	50	NRp	NR	PFS 18 months
Palladini 2017 <sup>151</sup>	Pomalidomide/ dexamethasone	Phase II	28	68	29	NR	Pom was 2mg/day 15 had Grade III/IV toxicity

<sup>a</sup> Calculated by intention-to-treat; NR= not reached; NRp = not reported; NA = not applicable  
CR, complete response; DLT, dose-limiting toxicity; HR, haematologic response; OR, organ response; OS, overall survival;  
TRM, treatment-related mortality; Retro, retrospective.

## RECOMMENDATIONS\*

- Pomalidomide-based combination chemotherapy regimens (max dose 4mg daily) are effective in patients with relapsed/refractory disease. (Level 2A, Grade B).
- Carfilzomib should be used with caution, especially with cardiac disease, with a maximum dose of 36mg/m<sup>2</sup> (Level 3, Grade B)
- Ixazomib is effective therapy at doses 4mg weekly in relapsed/refractory disease (Level 2A, Grade B)
- Daratumumab at 16mg/kg weekly dosing IV is effective as monotherapy in relapsed/refractory disease, with an acceptable toxicity profile (Level 2A, Grade B)
- Bendamustine 90mg/m<sup>2</sup> D1 and 2, with rituximab 375mg/m<sup>2</sup> D1 every 28 days is effective first-line in the treatment of IgM AL amyloidosis (Level 3, Grade B)
- Bendamustine/dexamethasone is effective in AL, but limited by toxicity (Level 2A, Grade B)

\*At the time of writing, access to all recommended therapies is not universal in Australia

## e. Autologous stem cell transplantation

### Background

Evidence supporting the use of high-dose therapy with autologous stem cell transplantation for AL amyloidosis first emerged in 1996. The current literature base is limited, with the majority of evidence derived from single-centre case series and small phase II trials.<sup>168-184</sup> Until 2010, overall response rates were considered around 60% and median OS around 5 years. However, treatment-related mortality (TRM) was significantly higher than that observed in the myeloma population, with figures varying between 20-40%.

Over the last 20 years, larger, more experienced centres have achieved improvements in TRM (5% or lower) with careful patient selection.<sup>185-192</sup> In 2018, Sidiqi et al reported a retrospective study of 672 consecutive patients in a single centre,<sup>192</sup> highlighting improved HR (84%), markedly reduced TRM (2.4%) and improved OS (not reached) since 2012, presumably due to improved patient selection and supportive care (see Table 12). 'Risk-adapted' conditioning with reduced-dose melphalan (100-140mg/m<sup>2</sup>) had been trialled in patients who are considered to be at higher risk from transplant-related complications, traditionally because of advanced age, renal impairment or cardiac dysfunction. Retrospective analyses from two large centres have shown that such dose reductions produce inferior response rates with similar toxicities compared with high-dose melphalan.<sup>172,175</sup> This was further supported by the Sidiqi report, which reported that on multivariate analysis, the conditioning dose, Mayo Stage 2012 and HR were the only independent predictors of OS. Thus, reduced-dose melphalan conditioning is not recommended in HDM/ASCT for treatment of AL amyloidosis.

Transplant centres that perform four or more HDM/ASCT annually for AL amyloidosis have less early mortality and improved OS compared to those centres that conduct fewer such transplants. In a study of >300 patients, D'Souza *et al* observed early mortality was worse among 81 centers that performed fewer than four HDM/ASCT for AL per year.<sup>187</sup> Their mortality rate of 5% (95% CI, 3% to 7%) at 30 days and 7% (95% CI, 5% to 10%) at 100 days compared with 1% (95%CI, 0.4% to 3%) at 30 days and 3% (95% CI 2% to 6%) at 100 days for centers that performed four or more such transplants annually. Thus, it is the recommendation of the authors that, where possible, HDM/ASCT should be conducted in a centre with extensive experience and frequency in conducting HDM/ASCT specifically in AL amyloidosis patients.

The only randomized trial to date comparing HDM/ASCT and chemotherapy with MDex was published by Jaccard *et al* in 2007.<sup>139</sup> One hundred patients aged 18-70 were randomized to each treatment arm. Baseline characteristics were similar between groups, with cardiac involvement in approximately 50% of patients. Of 37/50 patients who underwent ASCT, 10 received modified dose conditioning with melphalan 140mg/m<sup>2</sup>; the overall TRM in the transplant arm was 24%. No significant difference in response rates was observed between the two groups. On intention-to-treat analysis, overall survival was significantly longer in the MDex arm (56.9mo vs. 22.2mo, p=0.04). The authors concluded that outcomes with HDM/ASCT were not superior to those with MDex. Subsequently, a meta-analysis of 12 studies comparing ASCT with conventional chemotherapy concluded that while ASCT does not appear to confer an overall survival benefit, the low quality of available evidence indicates that further studies are needed to resolve the question.<sup>173</sup> Critics of the study by Jaccard *et al* pointed out that the reported TRM is considerably higher than that reported by experienced transplant centres. However, a subsequent 6 month landmark analysis demonstrated that after excluding early deaths in the transplant arm, there was still no survival difference between the two groups.<sup>193</sup> The use of dose-attenuated melphalan conditioning was labeled inappropriate due to its demonstrated inferiority compared with high-dose treatment, as well as the lack of cardiac biomarker assessment. Nonetheless, this study has raised important questions about the need to assess risk carefully when considering HDM/ASCT versus conventional chemotherapy upfront.

**Table 14: Major trials of HDM/ASCT in AL amyloidosis**

AUTHOR	STUDY DESIGN	N	HR (CR) % <sup>A</sup>	OR % <sup>A</sup>	MEDIAN OS (MONTHS)	TRM %	COMMENTS
Sidiqi 2018 <sup>192</sup>	Retrospective single centre,	672	84 (39)	NRp	122	2.4 after 2010	Reduced-dose melphalan patients had inferior OS
Skinner, 2004 <sup>171</sup> ; Cibeira 2011 <sup>175</sup>	Single centre, prospective	421	(34)	51	75.6 158 (CR)	11	45% received modified dose melphalan
Jaccard 2007 <sup>139</sup>	Phase III RCT	50	36 (22)	26	22	24	13/50 (26%) did not receive assigned intervention in HDM/ASCT arm 27% received modified dose melphalan; 58% 3yr OS
Mangatter 2008 <sup>176</sup>	Retrospective, single centre	100	79 (44)	43	NR	3	55 patients received VAD or high-dose dexamethasone induction pre-ASCT
Vesole 2006 <sup>177</sup>	Registry study	107	32 (16)	-	47.2	27	
Goodman 2006 <sup>178</sup>	Retrospective, multicentre	92	37 (20)	-	63.6	23	
Moreau, 1998 <sup>173</sup>	Retrospective, multicentre	21	(14)	48		43	
Mollee, 2004 <sup>54</sup>	Retrospective, single centre	20	56 (28)	-	60	35	

<sup>a</sup> Calculated by intention-to-treat;

HDM/ASCT, high dose melphalan with autologous stem cell transplantation; HR, haematologic response; CR, complete response; OR, organ response; OS, overall survival; TRM, treatment-related mortality; NR, not reached; NRp, not reported

### Eligibility criteria for autologous stem cell transplantation

Selection criteria for HDM/ASCT vary between institutions and consensus guidelines have not been devised. In general, conventional eligibility criteria for ASCT, such as age and performance status, should be assessed in conjunction with amyloid-specific factors including amyloidotic organ involvement (especially cardiac, gastrointestinal with bleeding and symptomatic autonomic neuropathy) and susceptibility to treatment toxicity.

Commonly used eligibility criteria for HDM/ASCT are listed in Table 15. The presence and degree of cardiac involvement is the most significant parameter in predicting TRM. Traditional markers such as left ventricular ejection fraction and interventricular septal thickness have been superseded by the use of cardiac biomarkers. The Mayo Clinic showed significantly higher 100-day all-cause mortality (28% vs 7%) in patients with baseline cTnT  $\geq 0.06$ mcg/L compared to those with cTnT  $< 0.06$ mcg/L.<sup>184</sup> In essence, patients with significant cardiac involvement are not candidates for upfront HDM/ASCT.

Patients with significant nephrotic syndrome at time of HDM/ASCT have also been reported to be at greater risk of renal complications.<sup>179,194</sup> Given that organ responses may lag significantly behind clonal responses (up to 2 years), caution is advised in those patient in VGPR or CR but with ongoing nephrotic syndrome, and consideration given to delaying HDM/ASCT until any signs of clonal or organ progression.

**Table 15: Commonly used eligibility criteria for autologous stem cell transplantation**<sup>187-192</sup>

<p><b>Clinical factors</b></p> <ul style="list-style-type: none"><li>• Age &lt;70</li><li>• NYHA class I-II</li><li>• ECOG performance status ≤ 2</li><li>• Systolic blood pressure ≥90mmHg</li></ul> <p><b>Organ function</b></p> <ul style="list-style-type: none"><li>• cTnT &lt;0.06mcg/L or cTnl &lt;0.1mcg/L</li><li>• NT-proBNP &lt;590pmol/L</li><li>• Creatinine clearance &gt;50ml/min</li><li>• Bilirubin &lt;1.5 x ULN with preserved hepatic synthetic function</li></ul>
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### Stem cell collection

Patients with AL amyloidosis experience higher rates of complications and mortality during peripheral blood stem cell mobilization and collection, with the overall complication rate around 15%. Peripheral and pulmonary oedema, symptomatic hypocalcaemia and hypoxia are all more common and can jeopardise the collection procedure. Cyclophosphamide use is associated with more toxicity and higher rates of hospitalization and cardiac complications than G-CSF alone. Therefore, stem cell mobilization with G-CSF 10mcg/kg alone is recommended, given in twice daily divided doses with collection beginning on day 5. Plerixafor has been reported in small series to be effective and well tolerated when used upfront or as rescue for stem cell mobilization in AL amyloidosis in patients with cardiac involvement.<sup>195</sup>

### Peri-transplant care

Precautions specific to this patient group include:

- **Arrhythmia prophylaxis**

Patients with cardiac involvement are at high risk of life-threatening arrhythmias including atrial tachycardias and non-sustained ventricular tachycardia around the time of stem cell collection, reinfusion and cytopenic phase.<sup>196-198</sup> Cardiac monitoring during stem cell reinfusion is recommended in these patients. The use of prophylactic antiarrhythmics, such as amiodarone, can be considered, although only weak data support routine use of this approach.

- **Fluid balance**

G-CSF should be avoided in patients with nephrotic syndrome and cardiac involvement due to risk of fluid retention; albumin replacement should be considered if serum albumin <20g/L, both for oedema management and blood pressure support if required.

- **Gastrointestinal bleeding risk**

Careful pre-transplant assessment is required, including stool fecal occult blood testing and targeted endoscopic evaluation of the upper and lower bowel if GIT involvement is suspected. During the cytopenic phase, routine proton-pump inhibitor therapy, higher platelet transfusion threshold (>20 to 50 x 10<sup>9</sup>/L) and daily testing of the faeces for blood are recommended.

- **Nausea and vomiting**

Higher rates are seen in ASCT compared to myeloma patients, and this is thought to result from impaired gastric emptying. Higher doses of antiemetics for a longer duration, especially prokinetic agents, are often required with appropriate nutritional support.

- **Infection prophylaxis**

As per local guidelines, although doxycycline post-ASCT may be the preferred prophylactic agent (see earlier section).<sup>165</sup>

## f. Allogeneic stem cell transplantation

A study by Schonland *et al* retrospectively studied 19 patients with AL amyloidosis who underwent allogeneic (n = 15) or syngeneic (n = 4) hematopoietic stem cell transplantation between 1991 and 2003.<sup>199</sup> 40% of patients died of TRM. In 5 of 7 evaluable patients in CR, chronic graft-versus-host disease was observed, suggesting a contribution of immune effects to disease control. The main clinical problem was cardiac failure in patients with poor performance status due to amyloidosis or in combination with severe infections. Patients with renal impairment or significant proteinuria are also susceptible to increased TRM.

Allogeneic transplantation should not be considered standard therapy, given the unacceptably high rate of TRM, and the increased availability of novel agents since publication of this study.

## RECOMMENDATIONS

- High-dose melphalan (200mg/m<sup>2</sup>) with autologous stem cell transplantation is an effective front-line therapy in selected untreated patients (Level 2B, Grade B).
- Dose-attenuated melphalan regimens are not recommended (Level 2B, Grade C).
- Eligibility criteria for HDM/ASCT should be based primarily on cardiac status; patients with elevated cardiac biomarkers (cTnT >0.06mcg/L, cTnI >0.1mcg/L, BNP >300ng/L, NT proBNP >590pmol/L) should be excluded. (Level 2B, Grade B)
- Renal impairment (GFR <50mls/min) and a history of autonomic neuropathy or GI bleeding are also a relative contraindications (Level 2B, Grade B)
- Peripheral blood progenitor cell mobilization should be performed with G-CSF alone, there is insufficient evidence regarding plerixafor to issue a recommendation (Level 3, Grade C).
- During stem cell reinfusion, cardiac monitoring is recommended for patients with cardiac involvement. Arrhythmia prophylaxis with amiodarone can be considered (Level 3, Grade C).
- Routine G-CSF is not recommended during the cytopenic period (Level 3, Grade C).
- Higher platelet transfusion thresholds (>20 x 10<sup>9</sup>/L) during the cytopenic period is recommended (Level 3, Grade C).
- Multi-disciplinary care, particularly with Cardiology and Nephrology support, is essential.
- HDM/ASCT should be conducted in a tertiary centre with experience in AL amyloidosis, such as an AAN service (Level 2, Grade B)
- Doxycycline 100mg twice-daily is the preferred prophylactic antibiotic during chemotherapy and after HDM/ASCT (Level 2A, Grade B)
- Allogeneic stem cell transplantation is not recommended (Level 3, Grade B)

### g. Supportive care

Careful medical management of amyloidosis-related complications is critical for the improvement of patient quality of life and the achievement of organ response.

#### Cardiac amyloidosis

As in other infiltrative cardiomyopathies, cardiac amyloidosis is characterized by diastolic dysfunction that, with time, progresses to produce a restrictive cardiomyopathy, with abnormal systolic function usually only seen in the terminal phases. The mainstay of supportive care in cardiac amyloid is the management of fluid overload using loop diuretics and/or spironolactone.<sup>200</sup> Thiazide diuretics can be used as an adjunct sparingly in refractory cases. IV diuresis should be considered in patients with severe fluid retention where gastrointestinal absorption of oral diuretics is ineffective or in doubt. Patients should be reminded that basic measures such as a 1.5 litre fluid restriction, a low salt diet, and adjustment of diuretics according to daily morning weights are paramount to heart failure management. A heart failure nurse can be particularly helpful.

Supporting the blood pressure with midodrine at a dose of 5mg to 10mg thrice daily should be considered in difficult cases. Salt-poor albumin infusions can also assist in mobilizing extra-vascular fluid and maintaining blood pressure in patients with serum albumin concentrations less than 20g/L.

Diuretics should be used with caution in patients with concomitant autonomic neuropathy due to the risk of worsening orthostatic hypotension. Excessive diuresis can also exacerbate renal dysfunction in patients with renal amyloid. Although angiotensin-converting enzyme (ACE) inhibitors are used frequently in the management of heart failure with reduced ejection fraction,<sup>200</sup> patients with cardiac amyloidosis rely on angiotensin for maintenance of blood pressure and the use of these agents can induce severe hypotension, and are not recommended.<sup>201,202</sup> Similarly, calcium-channel blockers are contraindicated due to the risk of hypotension and syncope relating to their negative inotropic effects.

Cardiac amyloid deposition within electrical pathways frequently causes conduction disturbances. Atrial fibrillation (AF) is particularly common. Beta-blockers are often used as rate control in patients with AF. However, the minimum effective dose of beta blocker should be used, given the problems of hypotension and negative inotropic effects, and the fact that patients with restrictive cardiomyopathies often rely on adequate heart rate to maintain cardiac output. Amiodarone is generally well tolerated. Patients with cardiac amyloidosis are also highly sensitive to digoxin and are at increased risk of life-threatening arrhythmias, even at therapeutic concentrations, due to the high avidity of digoxin for amyloid fibrils resulting in increased intra-cardiac drug concentrations.<sup>201-203</sup> However, a recent study showed digoxin can be used cautiously in refractory cases of rapid AF in low dose with frequent drug level and clinical monitoring.<sup>203</sup> Patients in AF may benefit from electric cardioversion, although recurrence is common. Ablations should be considered only in refractory cases due to inconsistent results.<sup>204,205</sup>

A study of implanted cardiac rhythm recorders found that sudden death in AL amyloidosis is commonly due to pulseless electrical activity, often preceded by bradycardia.<sup>206</sup> No randomized trial data is available to support the use of prophylactic antiarrhythmics in cardiac amyloidosis; some groups, however, advocate amiodarone 200mg/day if ventricular couplets or non-sustained ventricular tachycardia are detected on Holter monitor testing due to the association of these abnormalities with sudden death.<sup>69</sup> The routine use of defibrillators is consequently not recommended, though may benefit selected cases with evidence of ventricular arrhythmias.<sup>207,208</sup>

**Cardiac transplantation** for AL amyloidosis is rarely practiced due to the contraindications of significant extra-cardiac organ involvement. Nevertheless, small case series have been reported. It is clear from these studies that patients who do not undergo therapy to eradicate the plasma cell clone following transplantation will develop amyloid involvement and failure of the graft. Studies from various centres employing this approach have reported 1-year OS around 80% with survival at 5 years dropping to around 60%, most often due to recurrent multi-organ amyloidosis.<sup>209-211</sup> Consolidation with effective chemotherapy and/or HDM/ASCT is integral to the management approach to avoid recurrence of amyloidosis, and an Australian Phase II trial is currently underway examining this approach.

### RECOMMENDATIONS

- Symptomatic cardiac failure should be managed with fluid restriction, a low salt diet, loop diuretics and potassium-sparing diuretics (Level 3, Grade C).
- ACE inhibitors and calcium-channel blockers should be avoided, particularly in patients with autonomic neuropathy, impaired renal function and baseline hypotension (Level 3, Grade C).
- Digoxin is relatively contraindicated for atrial fibrillation control (Level 3, Grade C).
- Beta-blockers are poorly tolerated, and if required for arrhythmia management, the lowest possible dose should be used (Level 4, Grade C)
- Primary arrhythmia prophylaxis with amiodarone may be considered in patients with high-risk features on Holter monitor testing. (Level 4, Grade C).
- The use of midodrine and/or salt-poor albumin infusions can be considered as an adjunct to allow effective diuresis in overloaded patients. (Level 4, Grade C)
- IV frusemide can be considered in patients where gastrointestinal absorption of oral diuretics is in question (Level 4, Grade C)
- Pacemakers and implantable defibrillators are not recommended routinely, but may be of benefit in selected patients (Level 3, Grade C)
- DC cardioversions can be considered in some patient in atrial fibrillation, however, atrial fibrillation ablation therapy is relatively contraindicated and has a high recurrence rate. (Level 3 Grade C)
- Cardiac transplantation may be considered for highly selected patients with severe cardiac disease and without other organ involvement, and should be followed by chemotherapy and/or HDM/ASCT with the intention of achieving a VGPR/CR haematologic response (Level 3, Grade C).

## Renal amyloidosis

The most common renal manifestation of AL amyloidosis is the nephrotic syndrome. While the glomerular filtration rate may be preserved in early-stage disease, progressive tubular damage from uncontrolled proteinuria may eventually lead to end-stage kidney disease.

The medical management of the nephrotic syndrome generally relies on diuretic therapy to control symptomatic oedema and fluid overload. Loop diuretics are usually first-line, but spironolactone and thiazides may also be required. ACE inhibitors may be used in patients without significant cardiac involvement or autonomic neuropathy with the hope of minimizing proteinuria, although there is no evidence that ACE inhibitors accelerate the resolution of proteinuria in AL amyloidosis. Strict fluid and salt restriction, and control of blood pressure are also recommended. The increased risk of venous thromboembolism in the nephrotic syndrome should be carefully considered prior to the use of immunomodulatory agents (including thalidomide, lenalidomide and pomalidomide), which are known to potentiate venous thrombosis. Prophylactic anticoagulation should be considered on a case-by-case basis in patients with nephrotic syndrome treated with an immunomodulatory drug considering both benefits of thrombosis prevention and the bleeding diathesis that sometimes occur in AL amyloidosis. Measuring serum antithrombin III levels has not been proven to be predictive of venous thromboembolism in AL-associated nephrotic syndrome.

Approximately one third of patients with amyloid-related nephrotic syndrome will proceed to dialysis. Overall survival is improved (particularly in younger patients with renal replacement therapy compared to supportive care only) and outcomes do not appear to differ between haemodialysis and peritoneal dialysis.<sup>211,212</sup> Patients with cardiac involvement are more prone to hypotension and other complications related to volume changes during haemodialysis. Survival following initiation of dialysis is shorter in amyloidosis compared with other renal diseases, the vast majority of patients dying from progressive cardiac involvement.

**Renal transplantation** for amyloid-related end-stage kidney disease is infrequently performed. There are several case series that suggest that renal transplantation in patients with clonal responses of CR for 12 months or more, especially following ASCT, may be able to improve dialysis-free and overall survival in selected groups<sup>209,213</sup> as well as patient quality of life. Whether a lesser degree of haematological response, such as VGPR, is sufficient to allow renal transplantation is unknown.

RECOMMENDATIONS
<ul style="list-style-type: none"> <li>• Nephrotic syndrome should be managed supportively with diuretic therapy, salt and fluid restriction (Level 4, Grade C).</li> <li>• The use of ACE inhibitors should be limited to patients who do not have significant cardiac or autonomic nervous system involvement (Level 4, Grade C).</li> <li>• The risks and benefits of prophylactic anticoagulation in patients with nephrotic syndrome should be considered on an individual basis (Level 4, Grade C).</li> <li>• Renal replacement therapy should be considered in patients with end-stage kidney disease, taking into account age, severity of other organ involvement and fitness for chemotherapy (Level 3, Grade C).</li> <li>• Renal transplantation may be considered on an individual basis in those with clonal responses of CR for more than one year (Level 3, Grade C).</li> </ul>

### Orthostatic hypotension

The mechanisms underlying this common and disabling symptom relate to both impaired autonomic function and cardiac dysfunction. Inappropriate antihypertensive use and fluid depletion from diuretics may also contribute. Amyloid infiltration causing primary adrenal failure is uncommon but patients should be screened with the short Synacthen test. For symptomatic orthostatic hypotension, lower limb compression garments can be used to augment venous return and assist in reducing peripheral oedema.<sup>202</sup> Midodrine is an orally-active alpha-adrenergic agonist that can be started at 2.5mg thrice daily and titrated to a maximum total dose of 30mg daily. Side-effects may include tachycardia, supine hypertension and restlessness. Fludrocortisone 100-200mcg/day is less effective and often poorly tolerated due to fluid retention, and not routinely recommended. Those patients with an albumin level of <20g/L should be considered for 20% concentrated albumin infusions to help mobilise retained fluid while maintaining a satisfactory blood pressure.

Vitamin D deficiency is common in patients with AL amyloidosis, especially with nephrotic syndrome, which may lead to proximal myopathy and exacerbation of the symptoms of orthostatic hypotension.<sup>214</sup> However, there are no studies demonstrating that supplementation of vitamin D improves outcomes or overall survival.

### Peripheral neuropathy

Up to 20% of patients present with a sensory neuropathy, which is typically symmetrical, affecting the lower extremities, and may be painful.<sup>215</sup> Motor neuropathy is uncommon. Carpal tunnel syndrome is common and may predate other symptoms by several months.

Many chemotherapies used in AL amyloidosis will result in a peripheral neuropathy that can cause significant distress to the patient if not corrected and treated quickly. Avoidance or dose reduction of neuropathic chemotherapy is important to prevent long-term morbidity. Chemotherapy may unmask an asymptomatic amyloid-related neuropathy so care should be taken in neurological assessment within the first two cycles of treatment.

Most therapies trialed in myeloma for peripheral neuropathy can also be trialed in AL amyloidosis, such as pregabalin, amitriptyline, opiates, menthol creams and TENS machines. Referral to a neurologist or pain service may help with symptoms relief. For patients with neuropathy from carpal tunnel syndrome, releases or braces are of benefit.

RECOMMENDATIONS
<ul style="list-style-type: none"> <li>• Midodrine can be used up to 30mg/day in divided doses for orthostatic hypotension (Level 4, Grade C).</li> <li>• Patients with orthostatic hypotension should be screened for hypoadrenalism with the short Synacthen test (Level 4, Grade C).</li> <li>• Support stockings are an inexpensive and safe intervention that may be effective (Level 4, Grade C).</li> <li>• Once or twice-weekly albumin infusions should be considered in patients with serum albumin &lt;20g/L (Level 4, Grade C).</li> <li>• Peripheral neuropathy should be treated with reduction or cessation of neuropathic chemotherapies, and symptomatic medications such as pregabalin, amitriptyline, opiates or referral to a pain/palliative care team (Level 4, Grade C).</li> </ul>



## Gastrointestinal amyloidosis

Amyloid infiltration of the gastrointestinal tract may be subclinical or may present with weight loss, malabsorption or GI bleeding. It is estimated that up to 25% of AL patients are malnourished, with one study finding that a baseline body mass index <22 and prealbumin <200mg/L represent adverse prognostic indicators.<sup>216,217</sup> Identifying and addressing nutritional needs in these patients is difficult and it is recommended that input and follow-up from a specialist dietitian be offered to patients. Regular domperidone in doses up to 20mg every 6 hours before meals can be used effectively to partially overcome early satiety and nausea from gastrointestinal and autonomic amyloidosis.

Motility disturbance including constipation and diarrhea may result from concomitant autonomic neuropathy. A hierarchical approach using oral antimotility agents including loperamide (up to 32mg daily), codeine (such as 30mg twice daily) and diphenoxylate is often required. Long-acting or continuous subcutaneous octreotide has been used successfully in an outpatient setting in patients with severe diarrhea. Palliative end-ileostomy has also been reported.<sup>202</sup>

Hepatic amyloidosis often presents initially with an asymptomatic elevation in the serum alkaline phosphatase reflecting intrahepatic cholestasis. Progression to cirrhosis and portal hypertension may occur if left untreated. Supportive management of AL liver disease should be along similar lines to other chronic liver diseases. The use of ursodeoxycholic acid has been reported in hepatic amyloidosis but its role is yet to be defined. Liver transplantation is not recommended due to poor outcomes in most patients in small series.<sup>209</sup>

### RECOMMENDATIONS

- Assessment and optimization of nutritional status is recommended in all patients. (Level 4, Grade C)
- Domperidone should be used regular in doses up to 20mg QDS in patient with significant early satiety and nausea (Level 4, Grade C)
- Antimotility agents such as loperamide, codeine, diphenoxylate and octreotide may be used in patients with significant diarrhoea (Level 4, Grade C).

# 7 CONCLUSION

AL amyloidosis is a relatively rare disorder for which the diagnosis and management has evolved considerably in the last decade. New prognostic assessment tools, particularly the cardiac biomarkers, and standardised haematologic and organ response criteria have improved assessment of patients. New treatment options have allowed tailoring of treatment to individual patients, with increased options of treatments for patients with relapsed/refractory disease. This has led to an improvement in overall survival, although advanced stage disease at diagnosis remains the greatest challenge.

The above treatment guidelines from the Australian Myeloma Scientific Advisory Group to the Myeloma Foundation of Australia are based on current published data and clinical experience. We hope these guidelines will assist Australian and New Zealand clinicians and improve the management of patients with AL amyloidosis.

# 8 APPENDICES

## Chemotherapy regimens

REGIMEN	REFERENCE	CHEMOTHERAPY	COMMENTS
<b>Melphalan-based</b>			
MP	Kyle 1997 <sup>114</sup>	Melphalan 0.15 mg/kg po D1-7 Prednisone 0.8mg/kg po D1-7  Cycles repeated every 6 weeks for 2 years or until signs of serious toxicity.	Due to low response rates, MP regimens are now superseded by M-Dex regimens.
MDex	Palladini 2004 <sup>115</sup>  Jaccard 2007 <sup>139</sup>	Melphalan 0.22 mg/kg po D1-4 Dexamethasone 40mg po D1-4  Cycles repeated every 28 days for up to 9 cycles in responders, or until 2 cycles beyond maximal response, progressive disease or serious toxicity. Median number of cycles = 5 (personal communication, Giovanni Palladini)  Melphalan 10mg/m <sup>2</sup> po D1-4 Dexamethasone 40mg po D1-4  Cycles repeated every 28 days for up to 18 cycles in responders (discontinued after 12 cycles in complete responders and sooner if serious toxicity).	Prophylactic omeprazole (20 mg/d), ciprofloxacin (250 mg twice daily), and itraconazole (100 mg/d) given D1-10.  The dose of melphalan was adjusted during the first three courses in order to induce mild mid-cycle leukopenia. Prophylaxis with proton-pump inhibitors and trimethoprim-sulfamethoxazole was recommended.
Mel200	Skinner 2004 <sup>171</sup> Sidiqi 2018 <sup>192</sup> Jaccard 2007 <sup>139</sup>	Melphalan 200mg/m <sup>2</sup> IV, 1-2 days prior to stem cell reinfusion.	Mobilisation with G-CSF 10mcg/kg daily.
<b>Thalidomide-based*</b>			
CTD	Wechalekar 2007 <sup>118</sup>	Cyclophosphamide 500mg po D1, 8, 15 Thalidomide 100mg po D1-21 Dexamethasone 40mg po D1-4, 9-12  Cycles repeated every 21 days until stable clonal response on consecutive samples at least 4 weeks apart.	Thalidomide maintenance therapy was only considered for responders and was decided on by a combination of patient preference and tolerance to treatment.
CTDa		Attenuated regimen for age >70, NYHA class >II or significant fluid overload:  Cyclophosphamide 500mg po D1, 8, and 15 Thalidomide 100 mg po D1-28 (starting dose, 50 mg/day, increased by 50 mg at 4-week intervals as tolerated)  Dexamethasone 20mg po D1-4, D15-18  Cycles repeated every 28 days until stable clonal response on consecutive samples at least 4 weeks apart.	Dose attenuation did not affect haematologic response but significantly reduced grade ≥2 toxicity.

REGIMEN	REFERENCE	CHEMOTHERAPY	COMMENTS
<b>Lenalidomide-based*</b>			
LD	Sanchorawala 2007 <sup>143</sup>	Lenalidomide 15 mg po D1-21 Dexamethasone 10-20 mg po D1-4, D9-12, D17-20 alternate cycles (if no HR by cycle 3)  Cycles repeated every 28 days.	
CLd	Kumar 2012 <sup>146</sup>	Cyclophosphamide 300mg/m <sup>2</sup> po D1, 8, 15 Lenalidomide 15mg po D1-21 Dexamethasone 40mg po D1, 8, 15, 22  Cycles repeated every 28 days for up to 24 cycles (with cessation of cyclophosphamide after cycle 12).	Antimicrobial prophylaxis at investigator discretion.
CLd	Kastritis 2012 <sup>147</sup>	Cyclophosphamide 100mg po D1-10 Lenalidomide 15mg po D1-21 Dexamethasone 20mg po D1-4  Cycles repeated every 28 days for a planned duration of 12 cycles.	
<b>Bortezomib-based*</b>			
Bortezomib and dex	Kastritis 2010 <sup>102</sup>	Bortezomib 1.3mg/m <sup>2</sup> IV D1, 4, 8, 11 Dexamethasone 40mg po D1-4  Cycles repeated every 21 days.	
CyBorD	Mikhael 2012 <sup>104</sup>	Bortezomib 1.5 mg/m <sup>2</sup> IV D1, 8, 15, 22 Cyclophosphamide 300mg/m <sup>2</sup> po D1, 8, 15 Dexamethasone 40mg po D1, 8, 15, 22  Cycles repeated every 28 days for a median of 3 cycles.	Antiviral prophylaxis (agent not specified).
CyBorD	Venner 2012 <sup>105</sup>	Bortezomib 1.0 mg/m <sup>2</sup> IV D1, 4, 8, 11 (increased to 1.3 mg/m <sup>2</sup> if well tolerated) Cyclophosphamide 350 mg/m <sup>2</sup> po D1, 8, 15 Dexamethasone 20 mg po D1, 4, 8, 11 (increased to 20 mg for 2 days if well tolerated)  Cycles repeated every 21 days for up to 8 cycles.	
BMD	Kastritis 2016 <sup>108</sup>	Melphalan 0.22 mg/m <sup>2</sup> PO D1-4 Bortezomib 1.3 mg/m <sup>2</sup> IV D1, 4,8,11 on cycle 1 and 2 D1, 8, 15, 22 Dexamethasone 40 mg PO D1-4  Cycles repeated every 4-6 weeks to 8 cycles.	
<b>Pomalidomide-based*</b>			
Pd	Sanchorawala 2016 <sup>150</sup>	Pomalidomide 4mg po D1-21 Dexamethasone 20mg po D1, 8, 15, 22  Cycles repeated every 28 days.	
<b>Carfilzomib-based*</b>			
Car-Dex	Cohen 2017 <sup>152</sup>	Carfilzomib 20mg/m <sup>2</sup> for D1,2 the 36mg/m <sup>2</sup> Dexamethasone 40mg po D1-4  Cycles repeated every 21 days.	Dexamethasone only added if PR not reached by end of cycle 4.

REGIMEN	REFERENCE	CHEMOTHERAPY	COMMENTS
<b>Ixazomib-based*</b>			
Id	Sanchorawala 2017 <sup>153</sup>	Ixazomib 4mg po D1, 8, 15 Dexamethasone 40mg po D1-4 Cycles repeated every 28 days.	Dexamethasone only added if PR not reached by end of cycle 3.
<b>Daratumumab-based*</b>			
Dara	Jaccard 2018 <sup>159</sup>	Daratumumab 16mg/kg weekly for 8 doses, then 2 weekly for 8 doses, then every 4 weeks until progression	

\*At the time of writing, access to all recommended therapies is not universal in Australia

## Contact details for specialised tests for amyloid diagnosis

### Histology and imaging reviews

**Australia:** *Review, interpretation or assistance with Congo red staining, kappa, lambda, transthyretin, AA and fibrinogen immunohistochemistry*

Dr Patrick Hosking and Dr Simon Gibbs, Victorian and Tasmanian Amyloidosis Service, Eastern Health, Victoria; [Patrick.hosking@monash.edu](mailto:Patrick.hosking@monash.edu); [simon.gibbs@monash.edu](mailto:simon.gibbs@monash.edu)

Dr Peter Mollee, Princess Alexandra Amyloidosis Centre, Brisbane; [Peter.Mollee@health.qld.gov.au](mailto:Peter.Mollee@health.qld.gov.au)

Dr Fiona Kwok, Westmead Amyloidosis Clinic, Westmead Hospital, NSW; [Fiona.kwok@health.nsw.gov.au](mailto:Fiona.kwok@health.nsw.gov.au)

**UK:** As above as well as LECT2 immunohistochemistry

Janet Gilbertson and Professor Philip Hawkins, National Amyloidosis Centre, London, UK; [j.gilbertson@ucl.ac.uk](mailto:j.gilbertson@ucl.ac.uk); [p.hawkins@ucl.ac.uk](mailto:p.hawkins@ucl.ac.uk)

Please refer to <http://amyloidosis.net.au> for further details

### Genetic screening

**Australia:** *Mutation analysis of ATTR, AFib, ApoA1, Alys*

Professor Bruce Bennetts, Department of Molecular Genetics, The Childrens' Hospital at Westmead, Westmead NSW 2152; [bruce.bennetts@health.nsw.gov.au](mailto:bruce.bennetts@health.nsw.gov.au)

*Mutation analysis of ATTR only*  
Path West Laboratories

**New Zealand:** *Mutation analysis of ATTR, AFib*  
Canterbury Health Laboratories, Christchurch, NZ

**UK:** *Mutation analysis of ATTR, AFib, ApoA1, ApoA2, Alys*

Professor Philip Hawkins, National Amyloidosis Centre, London, UK; [p.hawkins@ucl.ac.uk](mailto:p.hawkins@ucl.ac.uk)

### Tandem Mass Spectrometry

**Australia:** A/Prof Peter Mollee, Dept of Haematology Princess Alexandra Hospital, Brisbane; [Peter.Mollee@health.qld.gov.au](mailto:Peter.Mollee@health.qld.gov.au)

**New Zealand:** Dr Hugh Goodman, Haematology Dept, Waikato Hospital, Hamilton; [Hugh.Goodman@waikatodhb.health.nz](mailto:Hugh.Goodman@waikatodhb.health.nz)

**UK:** Janet Gilbertson and Professor Philip Hawkins National Amyloidosis Centre, London, UK; [j.gilbertson@ucl.ac.uk](mailto:j.gilbertson@ucl.ac.uk); [p.hawkins@ucl.ac.uk](mailto:p.hawkins@ucl.ac.uk)

**USA:** Mayo Clinic Laboratories – see <https://www.mayocliniclabs.com/test-catalog/Overview/70356>

### SAP scintigraphy

**UK:** Professor Philip Hawkins, National Amyloidosis Centre, London, UK; [p.hawkins@ucl.ac.uk](mailto:p.hawkins@ucl.ac.uk)

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