ASH Draft Recommendations for Diagnosis of Amyloidosis

INTRODUCTION

American Society of Hematology (ASH) guidelines are based on a systematic review of available evidence. Through a structured process, a guideline panel makes judgements about the evidence and forms recommendations.

The public comment period occurs after recommendations are formed but before a manuscript report of the guidelines has been finalized and before ASH organizational approval of the guidelines. Comments collected during the open comment period are provided to the guideline panel for review prior to finalizing the guidelines.

These draft recommendations are not final and therefore are not intended for use or citation.

To submit comments on the draft recommendations, **please email guidelines@hematology.org**. Only comments submitted via email will be reviewed by the guideline panel. Evidence Profiles and Evidence to Decision Frameworks are available via links to Dropbox below. If you are unable to access these links, please email Meghin Brooks at mbrooks@hematology.org.

The public comment period for these draft recommendations is **June 10 – July 10, 2024**.

RECOMMENDATIONS

DEFINITIONS

- IFE – serum immunofixation
- UIFE – urine immunofixation
- FLC – free light chain levels and ratio
- SPEP – serum protein electrophoresis
- UPEP – urine protein electrophoresis
- DPD – 3,3-diphosphono-1,2-propanodicarboxylic acid
- HMPD – Hydroxymethylene Diphosphonate
- PYP – pyrophosphate

SCREENING

- Question 1: *Should IFE/UIFE/FLC be used to increase suspicion of light chain amyloidosis in patients with cardiac symptoms?*
  - **Recommendation 1**: For patients with suspected cardiac amyloidosis, the ASH Guideline Panel *recommends* performing paraprotein testing (IFE/UIFE/FLC) to increase clinical suspicion of light chain amyloidosis. (Strong recommendation based on moderate certainty in the evidence about effects).
  - **Good Practice Statement:** Serum and Urine protein electrophoresis should not be the screening tests or only tests for suspected or confirmed light chain amyloidosis. A combination of

electrophoresis and immunofixation on serum and urine along with serum immunoglobulin free light chains testing are required.
    - **Remarks:** Clinical suspicion is enhanced if any one of the proposed tests (SPEP/IFE, UPEP/IFE, FLC assay) is positive for monoclonal gammopathy.
    - Evidence Profile
    - Evidence to Decision Framework
- Question 2: *Should IFE/UIFE/FLC be used to increase suspicion of light chain amyloidosis in patients with unexplained proteinuria?*
    - **Recommendation 2:** For patients with unexplained proteinuria, the ASH Guideline Panel *suggests* performing paraprotein testing (IFE/UIFE/FLC) to increase clinical suspicion of light chain amyloidosis (conditional recommendation based on low certainty in the evidence about effects).
    - **Good Practice Statement:** Serum and Urine protein electrophoresis should not be the screening tests or only tests for suspected or confirmed light chain amyloidosis. A combination of electrophoresis and immunofixation on serum and urine along with serum immunoglobulin free light chains testing are required.
    - **Remarks**:
        - Clinical suspicion is enhanced if any one of the proposed tests (SIFE, UIFE, FLC assay) is positive for monoclonal gammopathy.
        - A 24-hour urine collection for UIFE is desirable, but a concentrated spot urine is acceptable.
        - FLC values should be interpreted with caution in patients with renal impairment and auto immune conditions. Monoclonal protein testing may also help to increase the suspicion of other kidney diseases associated with monoclonal gammopathy.
    - Evidence Profile
    - Evidence to Decision Framework

ENHANCING CLINICAL SUSPICION

- Question 3: *Should cardiac MRI (CMR) be used to diagnose cardiac light chain amyloidosis in patients suspected of having cardiac amyloidosis (positivity in any of the following studies: IFE, UIFE, or FLC, abnormal cardiac biomarkers, and non-diagnostic echocardiographic findings)?*
    - **Recommendation 3:** For patients with positivity in any of the following studies IFE, UIFE, or FLC, and abnormal cardiac biomarkers, and non-diagnostic echocardiography, the ASH Guideline Panel *suggests* performing cardiac magnetic resonance (CMR) rather than not performing CMR to increase clinical suspicion of cardiac amyloidosis. (conditional recommendation based on a moderate certainty in the evidence about effects).
    - **Remarks:** Diagnostic echocardiographic findings that increase clinical suspicion for cardiac amyloidosis include unexplained left ventricular hypertrophy, reduced left ventricular global longitudinal strain (especially when accompanied by an apical sparring pattern), worsening degrees of diastolic dysfunction, elevation in left ventricular filling pressures, elevations in right heart pressures, and presence of varying degrees of pericardial effusion.
    - Evidence Profile
    - Evidence to Decision Framework

- Question 4: *Should cardiac MRI (CMR) be used to diagnose cardiac light chain amyloidosis in patients with abnormal cardiac biomarkers, echocardiography, and positivity in any of the following studies: IFE, UIFE, or FLC?*
    - **Recommendation 4:** For patients with positivity in any of the following studies IFE, UIFE, or FLC, and abnormal cardiac biomarkers, and echocardiography consistent with amyloidosis, the ASH Guideline Panel *suggests against* performing cardiac magnetic resonance (CMR) and instead performing tissue biopsy to diagnose cardiac light chain amyloidosis (conditional recommendation based on a very low certainty in the evidence about effects).
    - **Remarks**:
        - In patients with high suspicion for cardiac amyloidosis, we advise proceeding to tissue biopsy without delay.
        - Diagnostic echocardiographic findings that increase clinical suspicion for cardiac amyloidosis include unexplained left ventricular hypertrophy, reduced left ventricular global longitudinal strain (especially when accompanied by an apical sparring pattern), worsening degrees of diastolic dysfunction, elevation in left ventricular filling pressures, elevations in right heart pressures, and presence of varying degrees of pericardial effusion.
    - Evidence Profile
    - Evidence to Decision Framework

DIAGNOSIS

- Question 5: *Should Bone Scintigraphy (PYP, DPD, HMDP) be used to diagnose light chain Amyloidosis in suspected patients?*
    - **Recommendation 5:** For patients with a suspicion of light chain amyloidosis, the ASH Guideline Panel *recommends against* the use of bone scintigraphy (PYP, DPD, HMDP) for the diagnosis of AL cardiac amyloidosis (strong recommendation based on moderate certainty in the evidence about effects).
    - **Remarks:** Clinical suspicion for light chain cardiac amyloidosis is increased in patients with positive biomarkers (NT-proBNP, BNP, high sensitivity troponin), imaging (echocardiography/cardiac MRI compatible with cardiac amyloidosis), and immunological assays (serum free light chains, serum/urine immunofixation) indicating the presence of a monoclonal gammopathy.
    - Evidence Profile
    - Evidence to Decision Framework
- Question 6: *Should Bone Scintigraphy (PYP, DPD, HMDP) be used to diagnose ATTR Amyloidosis in suspected patients?*
    - **Recommendation 6:** For patients without evidence of a plasma cell disorder (normal serum free light chain levels and no monoclonal proteins on serum and urine immunofixation), the ASH Guideline Panel *recommends* the use of bone scintigraphy (PYP, DPD, HMDP) for the diagnosis of Cardiac ATTR amyloidosis (strong recommendation based on moderate certainty in the evidence about effects)
    - **Remarks:**
        - Bone scintigraphy should be performed with single photon emission tomography (SPECT) rather than planar only imaging to verify myocardial uptake to improve diagnostic accuracy.

        - In patients with suspected or confirmed ATTR amyloidosis, family history needs to be assessed and once diagnosis is confirmed genetic counselling offered.
    - Evidence Profile
    - Evidence to Decision Framework

ORGAN INVOLVEMENT

- Question 7: *Should surrogate biopsy vs cardiac biopsy be used to diagnose light chain amyloidosis in suspected patients?*
    - **Recommendation 7:** For patients with suspected light chain cardiac amyloidosis and positive cardiac biomarkers, echocardiogram, and positivity in any of the following studies: IFE, UIFE, or FLC, the ASH Guideline Panel *suggests* either starting with performing both fat pad sampling and bone marrow biopsy or with endomyocardial biopsy. (conditional recommendation based on low certainty in the evidence about effects)
    - **Good Practice Statement:** The ASH panel agreed that the technique for abdominal fat pad sampling should be optimal to allow for subtyping using a validated method.
    - **Good Practice Statement:** The ASH panel agreed that in patients with proven amyloid deposits on histology, amyloid subtyping using a validated method must be performed in a timely fashion.
    - **Good Practice Statement:** The ASH panel agreed that for patients highly suspected of having AL amyloidosis with absence of amyloid deposits in the fat pad and bone marrow biopsy, consider performing biopsy of the affected organ.
    - **Good Practice Statement:** In patients with suspected light chain amyloidosis, testing of historical pathology samples (within last 3 years) for amyloidosis could be done.
    - **Remarks:**
        - Bone marrow biopsy should not be performed in isolation, and results of the bone marrow biopsy should not be awaited before performing another biopsy method.
        - In cases of suspected cardiac light chain amyloidosis, it is imperative to obtain diagnostic tissue biopsy with a validated subtyping method, whether through fat pad sampling or endomyocardial biopsy.
        - In certain cases, endomyocardial biopsy may be favored over fat pad sampling, such as in patients with risk factors for hereditary cardiac ATTR amyloidosis.
        - Proceeding directly to an endomyocardial biopsy relies on ease of access and available expertise. The associated risk of myocardial perforation may be lower in amyloidosis patients given the concomitant left ventricular hypertrophy.
    - Evidence to Decision Framework/Evidence Profile
- Question 8: *Should surrogate biopsy vs renal biopsy be used to diagnose light chain amyloidosis in suspected patients?*
    - **Recommendation 8:** For patients with suspected light chain renal amyloidosis and positivity in any of the following studies IFE, UIFE, or FLC, the ASH Guideline Panel *suggests* starting with performing both abdominal fat pad sampling and bone marrow biopsy over renal biopsy. (conditional recommendation based on moderate certainty in the evidence about effects)
    - **Good Practice Statement:** The ASH panel agreed that the technique for abdominal fat pad sampling should be optimal to allow for subtyping using a validated method.
    - **Good Practice Statement**: The ASH panel agreed that in patients with proven amyloid deposits on histology, amyloid subtyping using a validated method must be performed in a timely fashion.

- **Good Practice Statement:** The ASH panel agreed that for patients highly suspected of having AL amyloidosis with absence of amyloid deposits in the fat pad and bone marrow biopsy, consider performing biopsy of the affected organ.
- **Good Practice Statement:** In patients with suspected light chain amyloidosis, testing of historical pathology samples (within last 3 years) for amyloidosis could be done.
- **Remarks:**
  - Bone marrow biopsy should not be performed in isolation, and results of the bone marrow biopsy should not be awaited before performing another biopsy method.
  - A positive abdominal fat pad sampling or bone marrow biopsy with subtyping makes renal biopsy unnecessary. However, in the case of a negative fat pad sampling and bone marrow biopsy, a renal biopsy is necessary to look for amyloidosis or other pathology.
  - If there is a high clinical suspicion for other renal pathology which can mimic a presentation similar to renal amyloidosis or other plasma cell disorders, then an upfront kidney biopsy is preferred.
  - If subtyping of the abdominal fat pad is not feasible, the patient should be referred for a kidney biopsy.
  - The panel placed a high value on safety; however, despite the procedure-related risks, it remains important to perform a kidney biopsy when appropriate.
- Evidence to Decision Framework/Evidence Profile

- Question 9: *Should surrogate biopsy vs peripheral nerve biopsy be used to diagnose light chain amyloidosis in suspected patients?*
  - **Recommendation 9:** For patients with a monoclonal gammopathy and generalized small or large fiber peripheral neuropathy or autonomic neuropathy suspected of having light chain amyloidosis, the ASH Guideline Panel *suggests* performing both fat pad sampling and bone marrow biopsy over nerve biopsy (conditional recommendation based on very low certainty in the evidence about effects)
  - **Good Practice Statement:** The ASH panel agreed that in patients with proven amyloid deposits on histology, amyloid subtyping using a validated method must be performed in a timely fashion.
  - **Good Practice Statement:** The ASH panel agreed that for patients highly suspected of having AL amyloidosis with absence of amyloid deposits in the fat pad and bone marrow biopsy, consider performing biopsy of the affected organ.
  - **Good Practice Statement:** In patients with suspected light chain amyloidosis, testing of historical pathology samples (within last 3 years) for amyloidosis could be done.
  - **Remarks:**
    - Bone marrow biopsy should not be performed in isolation, and results of the bone marrow biopsy should not be awaited before performing another biopsy method.
    - In cases with high clinical suspicion, if abdominal fat pad sampling and bone marrow biopsy yield negative results for light chain amyloidosis, a nerve biopsy or other organ-specific biopsy should be performed.
    - If there is a high clinical suspicion for other nerve pathologies which can mimic presentations similar to nerve amyloidosis or other plasma cell disorders, then an upfront nerve biopsy can be considered.
    - If a nerve biopsy is performed, the panel recommends ensuring that that technique and handling is optimized to allow for an adequate diagnostic yield.
    - The neuropathy observed in light chain amyloidosis strongly resembles diabetic neuropathy, which is more frequent at a population level.

        - A skin biopsy is undertaken for assessment of intraepidermal nerve fiber density to confirm a small fiber or autonomic neuropathy, as well as confirmation of congophiliic deposits. Such skin biopsies need special handling and referral to a reference center for analysis.
    - Evidence to Decision Framework/Evidence Profile
- Question 10: *Should surrogate biopsy vs target organ biopsy be used to diagnose light chain amyloidosis in individuals suspected with multiorgan presentation?*
    - **Recommendation 10:** For individuals with suspected multiorgan light chain amyloidosis, the ASH Guideline Panel *suggests* starting with surrogate biopsies (combination of fat pad sampling and bone marrow biopsy) over target organ biopsy if surrogate biopsies can be performed expeditiously. If endomyocardial biopsy or renal biopsy are more feasible than fat pad sampling and bone marrow biopsy, these symptomatic target tissues should be preferentially biopsied (conditional recommendation based on low certainty in the evidence about effects)
    - **Good Practice Statement:** The ASH panel agreed that the technique for abdominal fat pad sampling should be optimal to allow for subtyping using a validated method.
    - **Good Practice Statement:** The ASH panel agreed that in patients with proven amyloid deposits on histology, amyloid subtyping using a validated method must be performed in a timely fashion.
    - **Good Practice Statement:** The ASH panel agreed that for patients highly suspected of having AL amyloidosis with absence of amyloid deposits in the fat pad and bone marrow biopsy, consider performing biopsy of the affected organ.
    - **Good Practice Statement:** In patients with suspected light chain amyloidosis, testing of historical pathology samples (within last 3 years) for amyloidosis could be done.
    - **Remarks:**
        - Promptly obtaining a tissue biopsy with subtyping is imperative, especially when there is suspected cardiac involvement.
        - On repeat biopsies:
            - If surrogate biopsies are negative and suspicion is high for amyloidosis, a target organ should be biopsied.
            - Although not systematically studied, repeat fat pad sampling at an amyloidosis center with greater experience performing such tests may be helpful to reach a diagnosis.
        - In patients suspected of having GI amyloid a more generous and deeper (enclosing submucosal layers) biopsy should be obtained.
    - Evidence to Decision Framework/Evidence Profile
- Question 11: *Should Congo Red Staining on bone marrow biopsy already performed be used to diagnose light chain Amyloidosis in patients with Multiple Myeloma and Smoldering Myeloma?*
    - **Recommendation 11:** For patients with plasma cell dyscrasias (multiple myeloma, smoldering multiple myeloma), the ASH Guideline Panel *suggests* performing Congo red staining on bone marrow biopsies that may have already been performed (conditional recommendation based on a very low certainty in the evidence about effects).
    - **Good Practice Statement:** In patients with suspected light chain amyloidosis, testing of historical pathology samples (within last 3 years) for amyloidosis could be done.
    - **Good Practice Statement:** The ASH panel agreed that in patients with proven amyloid deposits on histology, amyloid subtyping using a validated method must be performed in a timely fashion.

- **Remarks:**
  - Patients with positive Congo Red staining should be re-evaluated for signs and symptoms of systemic light chain amyloidosis.
- Evidence Profile
- Evidence to Decision Framework

➢ Question 12: *In people with light chain amyloidosis with no cardiac symptoms, should we use cardiac biomarkers/investigations (BNP, NT ProBNP, troponin (I,C,T, Highly Sensitive), 2D Echo with strain, Cardiac MRI) or not to evaluate for cardiac involvement?*

- **Recommendation 12:** For patients with proven light chain amyloidosis and with no cardiac symptoms, the ASH Guideline Panel *recommends* performing cardiac biomarkers (high sensitivity troponin, and BNP or NT-proBNP) and cardiac imaging rather than not performing these tests to define the presence and extent of cardiac involvement at diagnosis. (strong recommendation based on low certainty evidence)
- **Remarks:**
  - The ASH panel recognizes that "cardiac involvement" has historically been defined by ECHO (Gertz 2005); however, CMR is a more accurate test with better performance albeit sometimes limited by cost and availability.
  - Echocardiography should be performed with measurement of left ventricular global longitudinal strain to evaluate for reduction in longitudinal shortening and sparing of the apex.
  - The panel recognizes that NT-ProBNP has been studied more than BNP in light chain amyloidosis, but if not available BNP is an acceptable alternative cardiac biomarker.
  - The panel recognizes that cardiac biomarkers (troponin, BNP, NT-pro BNP) results may be affected by kidney function and pre-existing cardiac conditions.
  - The panel recognizes that most evidence in amyloidosis is using hsTroponin T, but we recognize that some centers may not have access to it and other troponin measures that are less extensively evaluated in light chain amyloidosis can be used.
  - The panel recognizes that an hsTroponin T cut-off of 35 ng/L has a sensitivity of 83% and a specificity of 86% for detecting cardiac involvement. On the other hand, a cut-off of 14 ng/L has a sensitivity of 94% but a specificity of only 11%. Therefore, a 35 ng/L cut-off is more specific, while a 14 ng/L cut-off is more sensitive for cardiac involvement.
- Evidence Profiles
  - BNP
  - NT-proBNP
  - CMR
  - Troponin
  - Echo
- Evidence to Decision Frameworks
  - BNP
  - NT-proBNP
  - CMR
  - Troponin
  - Echo

Good Practice Statements

- The ASH panel agreed that it is essential to assess for major organ involvement in patients with confirmed light chain amyloidosis, as this guides further management and risk stratification.
- A multidisciplinary team is often required for the timely and accurate diagnosis and management of light chain amyloidosis.