Plan for ASH Clinical Practice Guidelines on Diagnosis of Systemic Amyloidosis

Background and Rationale

Amyloidosis is a multisystem protein deposition disease often associated with delays in diagnosis, and therefore in appropriate treatment. Recent advances in radioisotope scintigraphy, monoclonal protein testing, mass spectrometry and cardiac testing have improved the speed and accuracy of the diagnosis of the main sub-types of amyloidosis, immunoglobulin light-chain [AL] and transthyretin type [ATTR].

Fast, accurate diagnosis can improve patient outcomes because of the availability of effective treatments. In recent years, new therapies such as proteasome inhibitors, immunomodulators, and monoclonal antibodies have improved the lives of people with amyloidosis. There are multiple studies demonstrating the efficacy of these therapies in AL amyloidosis, and median overall survival for patients exceeds a decade. In the case of the ATTR sub-type of amyloidosis, prognosis for patients with both age-related and hereditary types has improved. This is due to the availability of new drugs such as tafamidis and the RNA-interference agents patisiran and inotersen.

AL amyloidosis is commonly treated by hematologists, while ATTR amyloidosis is commonly treated by cardiologists.

Existing guidelines on amyloidosis include the following:

1. Mayo Clinic: guidelines on workup and management of amyloidosis (Mayo Clinic 1998-2022)
2. British Society for Haematology, Committee for Standards in Haematology: workup and management of AL amyloidosis (Wechalekar et al. 2014)
3. National Comprehensive Cancer Network (NCCN): Guidelines on workup and management of AL amyloidosis (NCCN 2018)
4. European Society of Haematology/International Society of Amyloidosis: Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis (Sanchorawala et al. 2021)

Despite the above guidelines, there is substantial clinical uncertainty about the diagnosis and treatment of amyloidosis, including which diagnostic testing strategies to use, when to consider organ biopsy, and when to use genetic testing. Diagnostic guidelines by ASH are expected to contribute to faster access to therapeutics and hence better clinical outcomes for patients. Guidelines by ASH about the treatment of AL amyloidosis will support clinical decision-making around the use of new therapies.

Scope and Number of Guideline Panels

These guidelines will provide recommendations about alternative screening and diagnostic tests and testing strategies that are used during the intitial evaluation and workup of amyloidosis, inclusive both AL and ATTR subtypes. A single guideline panel will address approximately 10 such questions about alternative tests or testing strategies.

The recommendations will address patient populations for whom there should be "high" clinical suspicion for amyloidosis. This includes individuals with monoclonal gammopathy of undetermined significance (MGUS) and individuals with specific and nonspecific signs and symptoms, such as organ dysfunction, to be described within the guidelines. Generally, amyloidosis is suspected in adults rather than children.

Generally, each guideline question will address a well-defined patient population, a well-defined test or testing strategy, and a comparative test or testing strategy (which could include not testing). Multiple comparisons are also possible but may result in fewer (<10) total questions. A single question may lead to multiple recommendations, e.g., for subpopulations such as patients for whom there are different levels of clinical suspicion for amyloidosis.

While important, the following are out of scope for this project: secondary amyloidosis [AA].

These guidelines will provide recommendations for higher resource settings, taking an individual patient perspective (i.e., rather than the perspective of a health system or of policymakers). It is expected that these recommendations may need to be adapted for other settings or perspectives.

To provide recommendations about screening and diagnostic alternatives, it will be necessary to estimate the effects of available treatments in patients who are correctly or incorrectly diagnosed as having or not having amyloidosis. However, these diagnostic guidelines will *not* offer specific recommendations about treatment. Instead, ASH will develop guidelines on the treatment of amyloidosis, probably by forming another guideline panel, in a future year. Timing of ASH treatment guidelines will depend on current evidence and coordination with other organizations that have previously issued treatment guidelines, such as the European Society of Haematology and the International Society of Amyloidosis.

Example Guideline Questions

The approximately 10 questions about alternative tests and testing strategies will be determined by the guideline panel through a brainstorming and prioritization process. Each question will be addressed by systematic evidence review. Randomized, controlled trials comparing alternative tests and testing strategies are not expected to be found. Therefore, the consequences of testing will most likely need to be modeled based on best estimates of the pretest probability of disease in patients for whom there is "high" clinical suspicion of

amyloidosis, the diagnostic accuracy of tests and test strategies in such patients, and the effects of treatment. Different bodies of evidence will inform these estimates.

Populations with "high" clinical suspicion of amyloidosis may be defined by presence of other conditions or diseases (e.g., MGUS, multiple myeloma), family or genetic history, clinical symptoms, imaging findings (e.g., cardiac), and physical exam findings. Estimates of the pretest probability of disease in such patients will not only inform modeling for specific recommendations; the estimates may also support discussion within the guidelines of the initial evalution and workup of patients presenting for evaluation by a hematologist or other medical specialist, e.g., in an introductory section of the guidelines or in good practice statements. Discussion or good practice statements may also address the optimal model of care for timely diagnosis of amyloidosis, e.g., evaluation and testing within comprehensive centers/tertiary care centers versus community centers.

Tests or strategies for which diagnostic accuracy may be reviewed and compared include the following:

- Tissue diagnosis of amyloid of a target involved organ versus a surrogate site
- Tissue diagnosis of amyloid across various organs, e.g., if multiple organs are involved
- Tissue diagnosis of amyloid across surrogate sites
- Imaging, e.g., cardiac investigations
- Mass spectrometry
- Pathological analysis, e.g., immunogold, electron microscopy
- Strategies without tissue diagnosis, e.g., use of cardiac nuclear testing if there is a paraprotein

Some tests used in the workup and diagnosis of amyloidosis are expensive, e.g., cardiac MRI versus 2D echo, EMG/NCS. Cost or resource use will be considered by the guideline panel when determining recommendations. Cost-effectiveness studies will be used, if available. If not available, cost and resource use will be estimated by pragmatic review of typical costs of alternative tests and test strategies within higher resource care settings.

The consequences of testing will be patient-important outcomes. Benefits may include survival or improved timeliness of treatment. Harms may include disease outcomes such as mortality, direct harms of testing, and adverse effects of treatments.

Good Practice Statements

In addition to graded recommendations, the guideline panels may offer "good practice statements." Good practice statements are strong recommendations that are *not* based on a systematic review of evidence and are formed outside of the evidence-to-decision process used to develop graded recommendations for ASH guidelines. Under the GRADE approach, such statements endorse interventions for which the net benefit is overwhelmingly clear, such that it would be a poor use of resources to systematically review the evidence and apply a guideline process just to offer an obvious recommendation (Izcovich et al. 2020, Guyatt et al. 2016). As defined by GRADE, good practice

statements should be valuable for clinicians and patients and should be clear and actionable. For example, as described above, a good practice statement could address components of an initial evaluation and workup, such as physical exam and history.

Panel Composition

The guideline panel will include experts in the diagnosis and treatment of amyloidosis as well as patient representatives, i.e., individuals with lived experience of the disease, such as a patient or a caregiver. Experts may include hematologist/oncologists, pathologists, and cardiologists. At least one early career hematologist will be included, and at least one community-based hematologist or other clinician.

A member of the ASH Guideline Oversight Subcommittee will serve on the panel as an ex officio member. This individual's role will be to ensure that the guideline development process is conducted in accordance with this project plan and ASH policies and procedures, including ensuring that questions are within scope, reviewing participant disclosures and ensuring adherence to ASH COI policies, and critically reviewing the guideline report for publication.

A member of the guideline panel will be asked to serve in a "writer" role. Responsibilities of this role will include drafting background clinical content, recording panel decisions and discussion points, drafting the guideline report, integrating edits by authors into the guideline report, and addressing comments receiving during public review. At the beginning of the project, panel leadership will discuss and agree with writers how to appropriately recognize their contributions on publication.

Organizational Collaborators

ASH will not invite other organizations to collaborate in the funding, development, or approval of these guidelines. However, ASH may invite other organizations to recommend experts for the guideline panel, if experts are needed from outside the ASH membership, and to review and endorse the guidelines. ASH will also explore with other relevant organizations opportunities to promote and disseminate the guidelines. In addition to endorsement, this could include announcements, summaries, commentaries, or educational programs about the guidelines. Relevant other organizations for which such opportunities will be explored include Amyloid Research Consortium, Amyloidosis Support, Amyloidosis Foundation, Amyloidosis Alliance, and International Society of Amyloidosis.

Methodology Team

Under a paid agreement with ASH, a methodology team will support the guideline development process, including conducting systematic reviews of available evidence.

Methods

The ASH guideline development process includes the following steps:

1. ASH forms a guideline panel.
2. The panel prioritizes guideline questions.

3. The methodology team in collaboration with experts on the guideline panel systematically reviews available evidence.
4. The guideline panel reviews and finalizes evidence summaries and forms recommendations.
5. ASH makes the recommendations available for public comment.
6. The guideline panel and the methodology team write a report of the guidelines for publication and dissemination.
7. ASH committees and officers review and approve publication of the guidelines under the imprimatur of ASH.
8. Authors submit the guidelines report to *Blood Advances* for review and publication.

The GRADE approach will be used to assess certainty of evidence (Guyatt et al. 2008). The GRADE Evidence-to-Decision framework (Alonso-Coello et al. 2016) will be used to make judgments about the available evidence and form guideline recommendations using standardized language that has well-defined interpretations for clinicians, patients, and policymakers (Izcovich et al. 2020).

Systematic reviews will be conducted according to standards defined by the Cochrane Collaboration or equivalent. Specific methods used will depend upon the nature and quality of the best available evidence. Complex evidence review may affect the project timeline or scope.

Some prioritized questions may include multiple comparisons that may result in multiple recommendations. This may affect the number of questions the panel finally addresses.

Meetings will be planned to occur both virtually and in person. The guideline panel and the methodology team will meet virtually in early 2023 for introductions and orientation. In spring 2023, the panel and team will meet in person to prioritize questions. Evidence review will be accomplished through virtual meetings during 2023. In late 2023 or early 2024, the panel and team will meet again in person to discuss the results of the systematic reviews of evidence and to agree on recommendations.

Online tools including the GRADEPro Guideline Development Tool will be used to summarize evidence, obtain panel voting, and document panel judgments and decisions.

Management of Conflicts of Interest

Conflicts of interest of all participants will be managed in accordance with general ASH policies, as described on the ASH website (https://www.hematology.org/about/governance/conflict-of-interest), and with specific ASH policies and procedures determined by the ASH Guideline Oversight Subcommittee. The most recent version of these policies, dated September 2020, is attached as Appendix A.

Publication Strategy

Publication strategy for the guidelines and any other intellectual property will be determined by ASH, including the ASH Guideline Oversight Subcommittee. The current strategy is to submit and publish all work relating to this project including the guideline reports and systematic reviews within ASH's online-only open access scientific journal, *Blood Advances.* At the beginning of the project, a pre-submission inquiry to the editors of *Blood Advances* will describe all planned work. The inquiry and discussions with the editors will be led by the lead authors and by the GOS ex officio member(s) of the panels.

Systematic reviews may be developed for submission to *Blood Advances* as separate, simultaneous publications. If the reviews are not prepared as separate publications, details about the reviews will be included with the guideline reports as supplements.

Authorship, sponsorship, and acknowledgements of such publications will be in accordance with academic standards and customs and requirements of the journal of publication. ASH authorship criteria for the guidelines are presented as Appendix B.

Dissemination and Implementation

To support understanding and implementation of the guidelines, the panel will be asked to write recommendations and remarks that are clear and actionable.

The chair and panelists will strategize a dissemination and implementation plan that will enhance access, for clinician and patients, to the guideline and support understanding and implementation of the guidelines recommendations. While a formal strategy will be written around the time of public comment, panelists will also be asked to flag recommendations in development for which there are implementation barriers (e.g., insufficient clinician awareness or education, lacking information systems support).

References

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