The Identification of a Center of Excellence (COE) for the treatment of Amyloidosis: An International Cardio-Oncology Society (IC-OS) Survey and Position Statement

Introduction and rationale

Amyloidosis has historically been thought to be a rare disease and the general perception was that the options for treatment were very limited at best. With growing awareness, the emergence of noninvasive diagnostic pathways for transthyretin amyloid (ATTR) , and the development of effective treatments for both ATTR and light chain amyloid (AL) over the last decade, the prevalence of patients with amyloidosis is steadily increasing (1-3).

A critical concept that has emerged as therapies have become more effective in treating both ATTR and AL amyloidosis is the early initiation of disease modifying therapy. In the case of AL amyloidosis, early diagnosis and institution of appropriate treatment drastically improves outcomes (4). Similarly, for ATTR cardiomyopathy, data has shown that earlier initiation of stabilizers improves long-term survival (5). Given these specific concerns, rapid evaluation and accurate ascertainment of diagnosis is crucial in patients suspected of having amyloidosis, particularly cardiac amyloidosis (CA).

In addition to the attempts to achieve an earlier diagnosis, misclassifying the subtype of amyloidosis can lead to exposure to unnecessary treatment and/or lack of appropriate, effective treatment. In cardiology, there has been a strong educational focus on ATTR cardiomyopathy (ATTR-CM) and many centers now offer nuclear bone scintigraphy as a diagnostic test in response to this growing recognition of ATTR-CM. However, appropriate diagnostic algorithms are not always followed, such as excluding AL amyloidosis before performing bone scintigraphy (6,7). Conversely, it is established that advanced age typically characterizes the diagnosis of wild-type ATTR cardiomyopathy (ATTRwt-CM) and it is not uncommon that older patients with ATTRwt-CM may have concomitant monoclonal gammopathy of undetermined significance (MGUS) with abnormalities in their serum free light chain measurements. As such, this clinical conundrum frequently presents a diagnostic challenge to define MGUS without expert hematologic input. The results of specific diagnostic tools that may be confusing in many situations could lead to a misinterpreted diagnosis of AL amyloidosis. Additionally, rarer familial amyloidosis may be misdiagnosed as they can mimic the presenting features of both AL and ATTR amyloidosis (especially apoliprotein E (cardiac), apolipoprotein A1 (heart, liver and kidneys) and hereditary fibrinogen amyloid (renal)). Hence, centralized expert providers that are experienced in carefully delineating the nuances of specific testing are necessary to have an accurate confirmation of subtype of amyloidosis as well as developing the optimal strategies for treatment.

There is a wide variation in models of care for amyloidosis by country and region. For example, the United Kingdom National Amyloidosis Center (NAC), the amyloidosis center in Pavia, Italy, the amyloidosis centerin Heidelberg University, Germany, the Boston University Amyloidosis Center, and the Mayo Clinic Amyloidosis Program provide consolidated state of the art clinical and research teams for diagnosing and monitoring the treatment of divergent amyloid subtypes (8). Of particular importance is that this aggregated patient cohort places these centers at the forefront of clinical trials and breakthroughs in treatment. Furthermore, with the increased availability of participants and streamlining the trial process in a relatively uncommon disease state, ongoing clinical research can be performed at a very high level.
In most countries, there are substantial gaps in care for patients with suspected or confirmed amyloidosis primarily due to limited resources and expertise in any region.

The purpose of this position statement is to identify those essential elements necessary for highly effective clinical care and develop a general standard with which practices or institutions could be recognized as a COE. By raising the expected standards of patient care, the evaluation and management provided at each center can be improved.

There are many potential benefits of a COE designation for the treatment of amyloidosis including recognition of institutions that have been leading the way for the optimal treatment of this condition, elevation of the expectation for any center who is engaging in the treatment of amyloidosis and developing cooperative groups to allow more effective research in this disease space. An example of the cooperation by leading centers resulting in an improved treatment paradigm is demonstrated by the recent report highlighting that early treatment of ATTR-CM could prevent the development of symptomatic heart failure(9). By centralizing care at specific institutions, and improving access to dedicated teams of multidisciplinary specialists, clinicians can rapidly provide comprehensive evaluation of patients to arrive at a definitive diagnosis in an efficient manner. Once the diagnosis is established, centralized care coordination can improve access to appropriate treatment options including pharmacologic therapy and the need for solid organ or stem cell transplantation, if indicated. Commonly, there is substantial financial toxicity associated with the high cost of therapies for both ATTR and AL amyloidosis, and centers experienced at working through the financial approval process can expedite access to treatment(10,11). Additionally, the goal is that a COE may serve as leading sites for clinical trials and development of novel diagnostic strategies, prognostic algorithms, and advances in treatment. Standardizing the expectations and criteria for these centers is essential for ensuring the highest quality of clinical care and community education.

In an attempt to better understand what constitutes a COE for the treatment of amyloidosis, the International Cardio-Oncology Society (IC-OS) established an amyloidosis working group (AWG) to focus on the diagnosis and treatment of all forms of amyloidosis. The IC-OS AWG developed a survey of practitioners who actively diagnose and treat patients with amyloidosis to obtain their input on what they feel would represent the key components of a COE. Utilizing an electronic database with access worldwide (REDCAP), the survey results are provided in this document. Additionally, direct feedback from these international experts is consolidated to formulate a blueprint for establishing a COE designation for the treatment of amyloidosis.

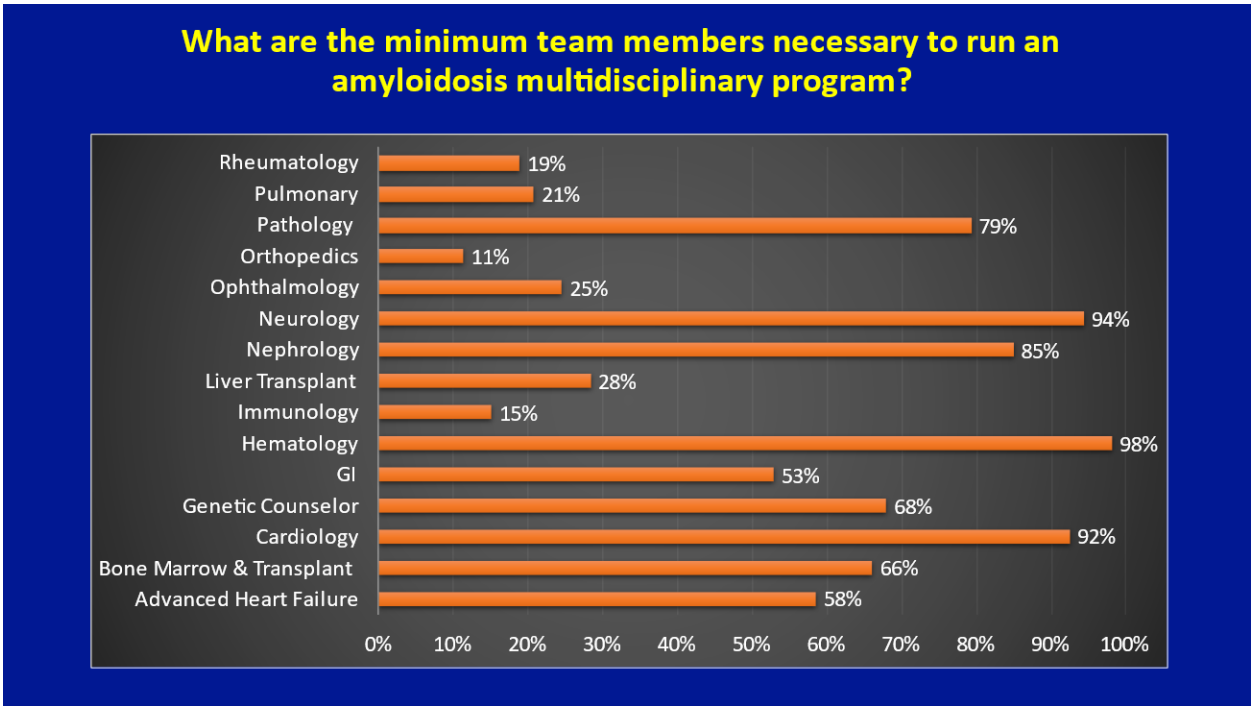
What are the necessary components of a COE?

In an effort to define what components are necessary to have a vibrant and effective COE for the treatment of amyloidosis, we prepared a survey in cooperation with a multidisciplinary panel of amyloidosis experts representing an international consortium. Many of the components of the survey were drawn from an existing model for COE, the United Kingdom (UK) National Amyloidosis Centre (NAC(12))(12). The multidisciplinary clinical service is delivered by specialists in rheumatology, immunology, nephrology, neurology, imaging, pathology and cardiology. The NAC's amyloidosis practice is the world's largest and most diverse, with a current referral rate of 1, 400 new patients per year from the UK and internationally.

Survey elements included are summarized in appendix A, and comprise the minimum necessary team of multidisciplinary members, diagnostic modalities, and therapeutic interventions for an amyloidosis COE. The survey was provided electronically to 95 clinicians identified by IC-OS over a 2-month period from December 2021 to February 2022. There were 53 total respondents (55% response rate) with not all demographic questions answered. Practitioners from the USA, Brazil, Italy, Denmark, Vietnam, and

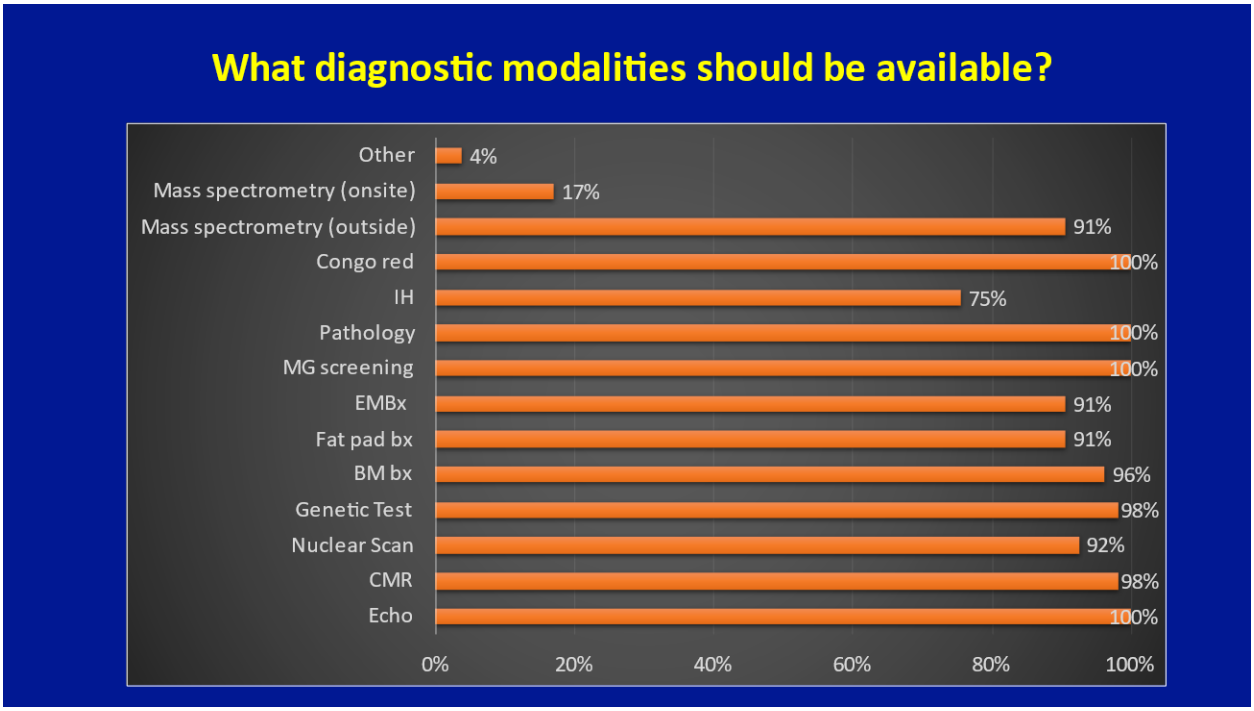
Turkey indicated their location while only half of the respondents indicated their specialty. The majority who answered this survey were cardiologists (46%) or HF specialists (19%), hematologists (19%), oncologists (8%) with 1 respondent each indicating neurology (4%) or nephrology (4%) as a specialty.

Regarding minimum team members necessary to run an amyloidosis multidisciplinary program, the majority (over 50%) of respondents felt that necessary members included specialists from cardiology, hematology, neurology, nephrology, pathology, genetic counseling, advanced heart failure, and gastroenterology. This array of specialists would appropriately aid in the accurate diagnosis as well as management of the most common manifestations of amyloidosis with the greatest morbidity. Respondents were less likely (30% or less) to require specialists in liver transplantation, ophthalmology, orthopedic surgery, pulmonology, rheumatology, or immunology. The lack of enthusiasm for including these specialists is in part explained by several clinical realities in the present day: 1. their expertise being no longer necessary due to amyloid-specific therapeutic advances (in the case of liver transplantation which is rarely indicated with the advent of TTR silencer therapy); 2. amyloid-related clinical manifestations do not warrant amyloid-specific interventions (as in the case of carpal tunnel syndrome or spinal stenosis which can be managed by an orthopedist without amyloid expertise); or because relevant amyloid-related clinical manifestations involving that particular organ system are less common clinically (rheumatology, ophthalmology, pulmonology, immunology).



Among the array of diagnostic and therapeutic modalities included in the survey, the majority of respondents felt that almost every option was necessary to designate a COE. The ability to perform reliable and accurate monoclonal protein screens and technetium pyrophosphate scans forms the cornerstone of non-invasive cardiac amyloidosis diagnosis. In cases in which there may be an abnormal monoclonal protein screens or equivocal technetium pyrophosphate scanning and there is a high index of suspicion, a tissue biopsy may be required for diagnosis. These can be obtained at either a surrogate site, such as fat pad or bone marrow, or the gold standard of the affected organ (commonly heart or

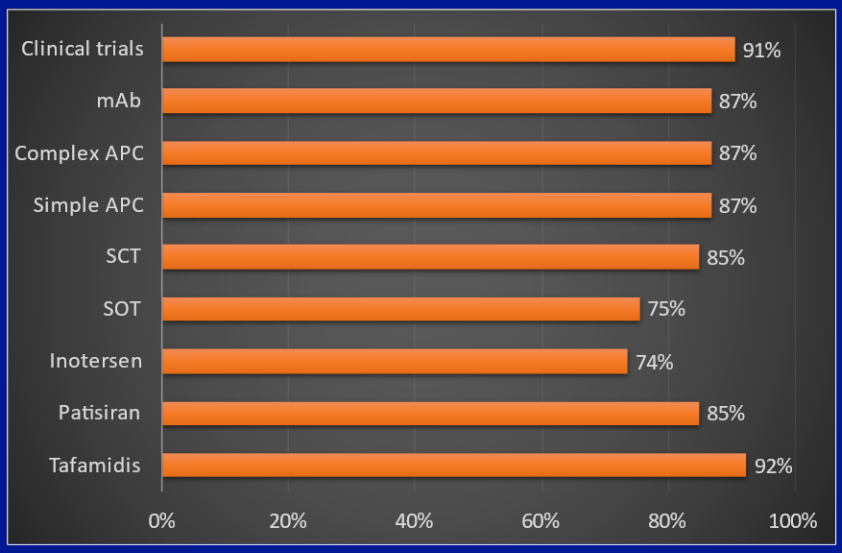
kidney). Of note, onsite mass spectrometry was not felt to be necessary by the majority (83%) of respondents, which is reasonable as this is often a send-out test to a specialty laboratory such as the Mayo Clinic or Cleveland Clinic in the USA. Cardiac MRI is neither necessary nor sufficient for the diagnosis of the specific type of amyloidosis, but it certainly is a useful diagnostic test to delineate the extent and severity of cardiac involvement. In certain situations in which a diagnosis has not been confirmed, such as biopsy-proven AL amyloidosis of another organ, an endomyocardial biopsy may be necessary.



Regarding the array of treatment options that were felt to be essential, nearly all respondents included clinical trials, tafamidis, complex anti-plasma-cell therapies, stem cell transplantation, and solid organ transplantation. One could imagine centers that are expert in the diagnosis of amyloidosis with an appropriate complement of reliable and accurate diagnostic testing as well as standard therapeutics but without the spectrum of advanced therapies for complex disease. All centers may not necessarily be able to provide stem cell transplantation or solid organ transplantation, but very capably diagnose and initiate therapies that are available. If the disease process for an individual patient is more complex or involved than this scenario, a major comprehensive referral center could then become involved. There may be the need for primary (bronze or silver) versus comprehensive (gold) designation for the COE defined by their level of expertise in diagnosis alone versus diagnosis and management, similar to the hypertrophic cardiomyopathy centers as outlined in the 2020 ACC/AHA Guideline for the Management of Hypertrophic Cardiomyopathy(13).

Finally, the administrative components to keep a large multidisciplinary program running smoothly must be considered, including a centralized intake system for referrals, the ability to care for patients using telemedicine, and adequate volume. The most commonly chosen critical element for quality care was multidisciplinary meetings, whichaligns with the disease state given the multiorgan involvement that impacts patients' quality of life and survival.

What therapies should be offered to be considered a COE?



SOT = solid organ transplant

SCT = stem cell transplant

APC = anti-plasma cell
- Simple = outpatient or PO/SQ
- Complex = inpatient or IV

mAb = monoclonal antibody

What are specific clinical goals when considering a practice as a COE?

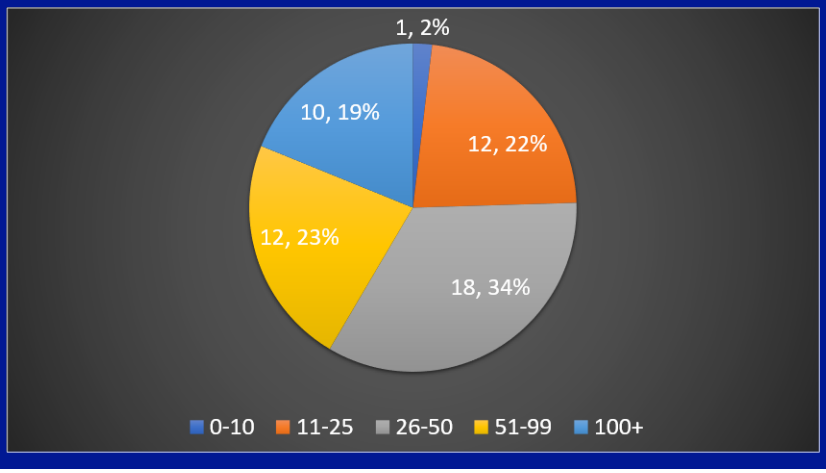
From an amyloid disease management standpoint, several clinical milestones are critical. The intent of designating COE status is to ensure the highest quality clinical care from experts in amyloidosis to facilitate rapid diagnosis ascertainment, appropriate and effective treatment initiation and provide longitudinal care. A centralized intake system can expedite getting patients into clinic; in our survey, 64% of sites had a centralized process that can enable scheduling with multiple subspecialists.

Importantly, a rapid and accurate diagnosis is paramount. The diagnosis should be handled by a multidisciplinary team with extensive experience in evaluating and managing amyloidosis. In our survey, most respondents felt that a clinical volume of 26-50 amyloid patients/year is necessary for adequate exposure and expertise. A high level of experience is needed to avoid misclassification because amyloid can have many "mimickers" of disease including hypertrophic cardiomyopathy or hypertensive heart disease(14,15). In individuals with abnormal serum testing for light chain amyloidosis, tissue confirmation is needed to confirm or exclude AL amyloidosis with higher diagnostic yield in experienced centers. While increasingly commonplace in the community, interpretation of nuclear bone scintigraphy should be done by experts to minimize risk for misinterpretation(16) and should follow established guidelines(17). An amyloid COE with a designated team of multifaceted experts can more quickly obtain the necessary diagnostic testing to not only accelerate care once the diagnosis is confirmed, but also to avoid initiating treatment in an individual inappropriately who does not have amyloidosis.

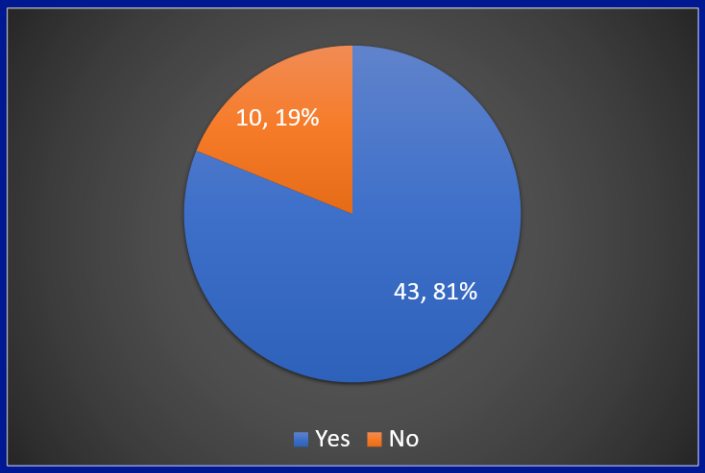
Once the diagnosis is established, urgent initiation of treatment is particularly important for cases of AL amyloidosis, since survival is predicated on timely therapy(18,19). In cases of ATTR amyloidosis, an understanding of the complexities of obtaining approval for disease modifying therapies is helpful due to the difficulties that can occur with navigating the approval and assistance process(20). Beyond targeted therapies, the holistic management of individuals with cardiac amyloidosis differs from other HF cohorts and requires an in-depth understanding of these nuances such as restrictive physiology and vascular-ventricular decoupling(15). The integration of the various providers and patient-decision making into longitudinal care is important, since cardiac amyloidosis is a chronic disease that is frequently accompanied by high levels of patient and caregiver burden.

Standardized follow-up can lay a foundation for routine reassessment of clinical status in individuals with amyloidosis, including the need to adjust chemotherapy doses, assess when one line of therapy is ineffective, or for titration of diuretics, among other considerations. From a patient access standpoint, individuals in rural areas or far away from the COE may have limited access to care that is similar to other disease states(21). The use of telemedicine can abrogate the need for challenging long-distance travel for these individuals, which often require frequent follow-up; in our survey, 81% of programs utilized telemedicine routinely. Ideally, the COE would incorporate remote management into the healthcare model distributed amongst the key stakeholders involved with each case.

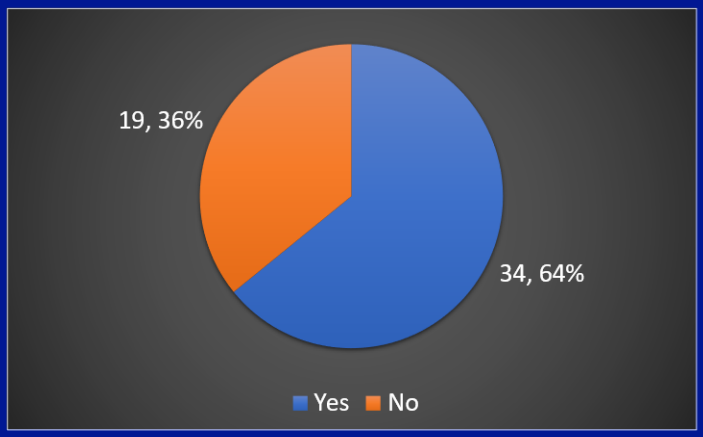
What patient volume (new or follow-up) PER YEAR is necessary to be considered a COE?



Do you have a system that allows for telemedicine?



Do you have a centralized intake system for specific referrals?



How can a vigorous Research Program improve the standard of care for treatment?

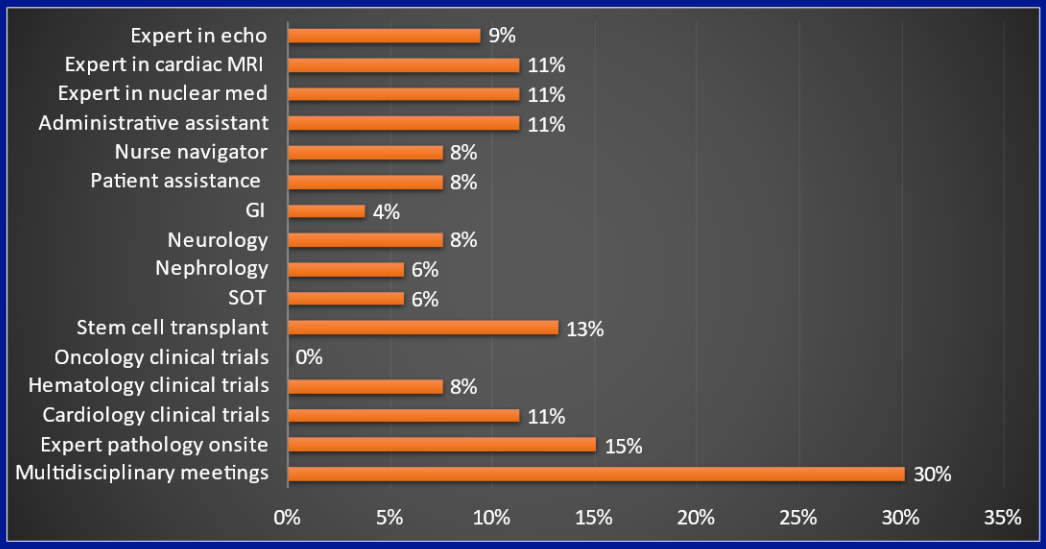
4) Research Mission
-Multidisciplinary team to refine important research questions
-Centralized and standardized management will allow evaluation of efficacy of specific interventions
-Uncommon disease, need centralization of cases
-Access to clinical trials

Ariane, Joao

A well-structured research program plays a crucial role for the treatment of amyloidosis by outlining the best practices, creating a standard of care, and enabling significant advancements in patient care. The core mission of research in COE is to continuously seek new knowledge about the disease to improve patient well-being (22). Therefore, identifying gaps to be explored in this area, such as the best diagnostic and treatment practices, and understanding the underlying mechanisms of amyloidosis, is essential.

Centralization and standardization of amyloidosis management in COE are crucial for evaluating the effectiveness of specific interventions(23). When treatment is carried out in multiple locations, there may be significant variations in the protocols used, making it difficult to compare interventions or outcomes and determine which approaches are most effective. Research allows COE to standardize pathways for diagnostic evaluation and treatment, creating an environment conducive to comparing the effectiveness of different approaches(22). Conducting clinical trials is especially important in this scenario given the rapid developments in the field, as it allows patients to access treatment options while directly contributing to advancing knowledge about amyloidosis.

What are the 3 most critical elements for a COE to have to offer quality care?



The identification of quality and the enhancement of education

5) Quality improvement and education
-How to measure performance of centers – what metrics?
-Standardization of clinical care
-Education to other providers and the community

Courtney, Jose

6) What are the financial considerations intertwined with a COE?

The concept of financial toxicity related to the diagnosis and treatment of amyloidosis has become a challenging barrier to effective treatment. There are many examples of this principle and the region of the world in which a patient is receiving treatment has a major influence on the details and magnitude of this obstacle. A recent update of the ACC/AHA/HFSA Guidelines for Heart Failure indicated the extreme cost of tafamidis compared to typical therapy for systolic heart failure(24).

As medication compliance is essential to patient outcomes, treatment of amyloidosis has unique challenges due to the high cost of therapy. For ATTR-CM, tafamidis was brought to market as the most expensive cardiovascular drug ever released at a United States cost of $225,000 per year. Subsequent analysis found that tafamidis would need a 92.6% price reduction in order to achieve cost effectiveness(10).RNA silencer therapy for hATTR neuropathy is even more expensive. With ongoing trials for additional treatments in this space, including the promising results of the AG-10 trial, competition will hopefully bring prices down over time. Yet, in the current environment, cost remains a barrier to treatment in some individuals

Similarly, optimal therapy for AL amyloidosis can be limited in rural areas in the United States or internationally. Socioeconomic factors, including insurance status, in the US are directly related to worsened survival (25). Daratumumab, the only drug specifically approved for AL amyloidosis in the United States, is not available in many countries. For example, in England, the National Health Service initially only approved daratumumab for 4th line treatment for multiple myeloma in 2018. There are recent plans for approval in 2023 for more expanded access after initial results showed prolongation of remission by more than two years (https://www.pharmatimes.com/news/nice_approval_for_janssens_darzalex_combination_1491077). A large obstacle to approval was concern over pricing which limited cost effectiveness. Certainly, in other areas of the world, the cost of the drug still prevents it from being available to patients.

To overcome these limitations, an effective COE will need to have processes in place to maximize insurance approval and patient assistance programs. Cases exist of ATTR-CM patients who were denied insurance approval for their treatment at community clinics and hospitals and were ultimately referred to a COE before they were able to initiate therapy. The expertise of the COE in overcoming these obstacles is crucial towards maximizing patient outcomes. Ideally, COE staff will also be involved in advocacy to lower cost of drugs and improve patient access. These efforts will certainly vary across countries and medical system, but the goal of these efforts will be unified with a goal to improve patient access to treatment. Fortunately, once prescribed and approved, adherence to amyloidosis treatment appears to be high(26).

7) How can professional or support groups improve practice and collaboration?

IC-OS identified the early diagnosis and treatment of amyloidosis as an important societal goal in 2021 and formulated the Amyloidosis Working Group (AWG) with international experts meeting monthly to strategize how to improve the clinical care provided to all patients with amyloidosis. There are many professional groups who have also provided educational, research-related, and clinical practice resources over the years to patients and providers alike. These include, but are not limited to, the Amyloidosis Foundation, Amyloidosis Research Consortium, Amyloidosis Support Group, International Society of Amyloidosis, the Heart Failure Society of America and others. It is also the goal of IC-OS to forge a combined effort from all of these important entities to align the improvements in quality care provided as well as enhancing access in whatever ways this can be achieved. Some of these efforts have already been realized with 2 separate online curricula developed (Steve can you provide a link to those?) and deployed in cooperation with members of several above mentioned groups. Future plans include the establishment of COE designation and a combined clinical database to continue enhancing our clinical research knowledge in a prospective fashion.

Conclusion (we should improve this)

Beyond direct patient care, we anticipate these COE will serve fundamental leadership roles in the field of amyloidosis by establishing and disseminating standards for best practices, providing high quality education and guidance, iteratively redefining the direction and vision for the field, and formalizing performance measures. Further, we anticipate that a network of these centers will foster research collaboration through data sharing,multicenter studies, expedite identification of potential sites for clinical trials, and facilitate knowledge sharing.

Hence, our document represents collective feedback from numerous international expert centers in the field of amyloidosis in an attempt to define what has made them effective, major referral centers.

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