ATTR Disease Management

MED-US-DZSTATE-2400019

ATTR Disease State Slide Deck

- This resource provides information about ATTR.
- This resource is intended to be viewed in its entirety to support scientific exchange and is not intended as recommendations for clinical practice.
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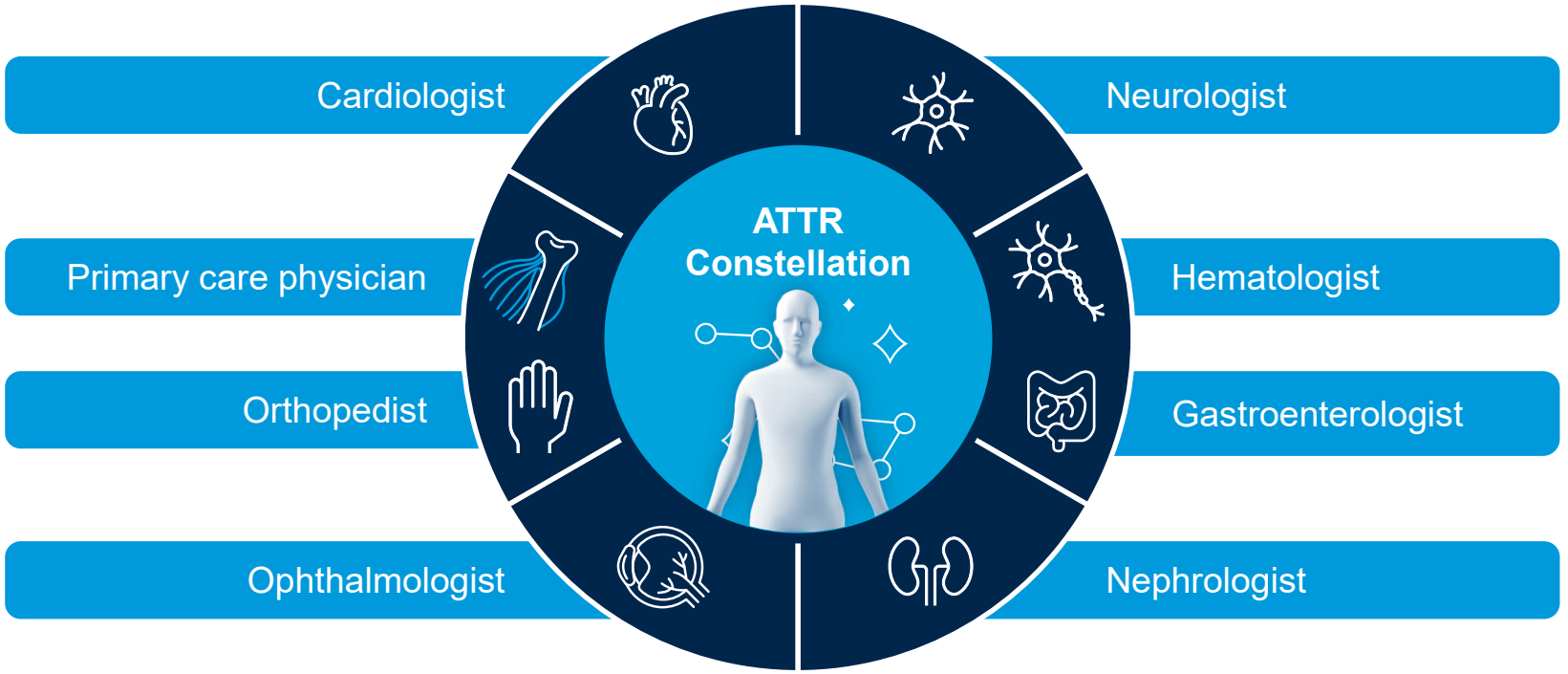
Management

The Multisystemic Nature of ATTR Requires a Multidisciplinary Approach for Assessment, Diagnosis, and Management[1-3]



Advanced-practice providers, for example nurses, pharmacists, dieticians, geneticists, and social workers, also contribute to the treatment and care of amyloidosis patients.[4,5]

ATTR, transthyretin amyloidosis.

1. Nativi-Nicolau et al. *Heart Fail Rev.* 2022;27(3):785–93; 2. Ando et al. *Amyloid.* 2022;29(3):143–55; 3. Karam et al. *Meeting of the International Society of Amyloidosis* 2022; Poster P192; 4. Kittleson et al. *JACC.* 2023; 81(11):1076–176; 5. Nativi-Nicolau et al. *Clin Med Insights Cardiol.* 2021;15:1–10.

hATTR ISA Guideline Recommendations for Symptomatic Therapy

Symptom	Therapy
Neuropathic pain	• **First line:** SNRI, gabapentinoids, trialed in 4-6-week period with 2 weeks at max tolerated dose • **Second line:** weak opioid analgesics, topical agents • **Third line:** strong opioids
Gastrointestinal disturbances	• Dietary changes • Prokinetics with erythromycin or domperidone • Metoclopramide for acute attacks of recurrent vomiting • Osmotic laxatives and polyethylene glycol • Linaclotide, lubiprostone, and prucalopride when laxatives have failed • Rifaximin followed by probiotics • Octreotide or opium tincture for chronic diarrhea refractory to loperamide
Cardiac involvement	• Low dose loop diuretics or mineralocorticoid receptor antagonists in case loop diuretics fail • Beta blockers, ACE inhibitors, or angiotensin receptor blockers if no clear contraindications • Anticoagulation with warfarin or other oral anticoagulant for rhythm disturbances • Pacing for significant bradycardia and certain AV blocks • ICD is not indicated as sudden cardiac death in ATTR-CM may result
Orthostatic hypotension	• **Nonpharmacologic interventions:** compression stockings, removal of aggravating hypotensive medications, increasing water intake • **Pharmacologic:** norepinephrine replacers, fludrocortisone, octreotide • In case of CHF, avoid fludrocortisone
Ocular involvement	• Ocular lubrication, vitrectomy or trabeculectomy
Renal failure	• Treatment in line with guidelines for chronic kidney failure • Hemodialysis for end stage disease

Symptomatic management in hATTR is of major importance due to its impact on patient quality of life as well as social, economic, and psychological well-being.

ACE, angiotensin-converting enzyme; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; AV, atrial-ventricular; CHF, congestive heart failure; hATTR, hereditary ATTR; ICD, implantable cardioverter defibrillator; ISA, International Society of Amyloidosis; SNRI, serotonin-norepinephrine reuptake inhibitors.

1. Ando et al. *Amyloid.* 2022; 29(3):143–55.

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Current Therapeutic Strategies for ATTR

Strategies include both approved therapies and investigational treatments in clinical trials

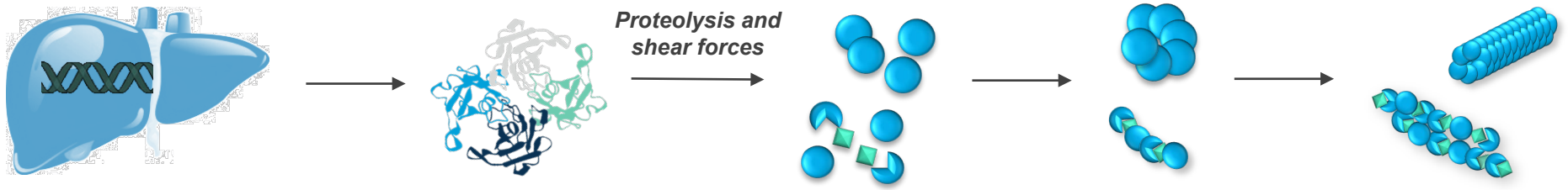
Suppression of TTR synthesis:

Liver transplantation
Gene silencing (siRNA, ASO)
Gene editing (CRISPR-Cas9)

TTR stabilizers

Amyloid fibril degradation/reabsorption:

Anti-TTR misfolded monoclonal antibody



TTR* gene expressed in liver** → **TTR tetramer** → ***Proteolysis and shear forces → **TTR monomers** → **Truncated and misfolded TTR** → **Amyloid fibrils**

Image adapted from Ando et al. 2022[1]

ASO, antisense oligonucleotide; ATTR, transthyretin amyloidosis; CRISPR, clustered regularly interspaced short palindromic repeats; siRNA, small interfering ribonucleic acid; TTR, transthyretin.

1. Ando et al. *Amyloid.* 2022; 29(3):143–55.

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Monitoring Patients With hATTR Following Diagnosis and Treatment Initiation

Patients presenting with one class of symptoms should schedule a yearly follow-up with appropriate specialists to monitor the other classes of hATTR symptoms.

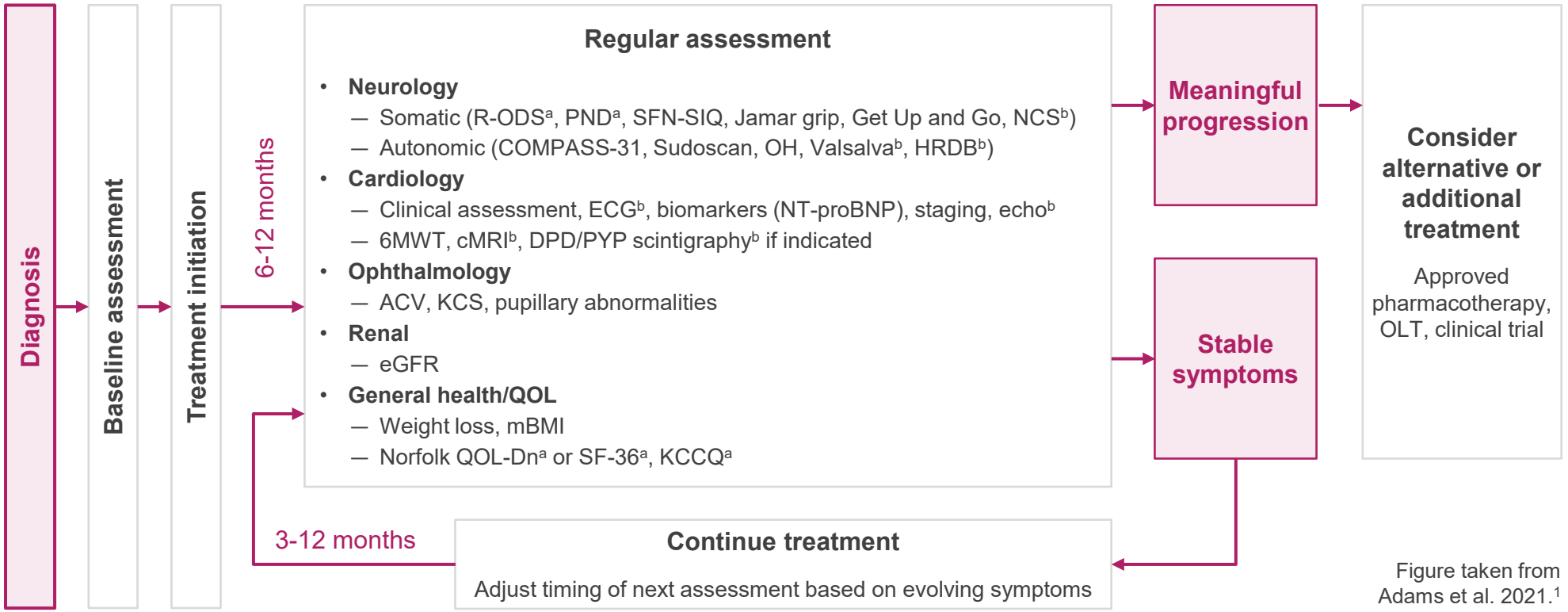

Figure taken from Adams et al. 2021.[1]

[a]Questionnaire to be performed prior to consultation. [b]Additional test.
6MWT, 6-min walk test; ACV, abnormal conjunctival vessel; cMRI cardiac magnetic resonance imaging; COMPASS-31, Composite Autonomic Symptom Score-31; DPD, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid; ECG, electrocardiogram; eGFR estimated glomerular filtration rate; HRDB, heart rate deep breathing; KCCQ, Kansas City Cardiac Questionnaire; KCS, keratoconjunctivitis sicca; mBMI, modified body mass index; NCS, nerve conduction study; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal prohormone of brain-type natriuretic peptide; OH, orthostatic hypotension; OLT, orthotopic liver transplantation; PND, polyneuropathy disability; PYP, ^{99m}Tc-pyrophosphate; QOL, quality of life; R-ODS, Rasch-built Overall Disability Scale; SF-36, 36-item Short-Form Healthy Survey; SFN-SIQ, small-fiber neuropathy and symptom inventory questionnaire.

1. Adams et al. *Orphanet J Rare Dis.* 2021;16:411

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Summary

- ATTR is a multisystemic, rapidly progressive, debilitating, and fatal disease caused by misfolded TTR accumulating as amyloid deposits in multiple organs and tissues including nerves, heart, and GI tract [1-4]
  - Patients diagnosed with hATTR and wtATTR amyloidosis have a median survival of 4.7[5] and 2.5-5.5 years,[6-8] respectively
- ATTR remains underdiagnosed or misdiagnosed[4,9,10]
- Patients with ATTR experience substantial burden, including reduced QoL[11-14] and functional impairment[6,15]

There remains a need for health care professionals to:

1	2	3	4
Recognize the constellation of red-flag symptoms of ATTR[16,17]	**Collaborate with a multidisciplinary team for a potential diagnosis[16,17]**	**Employ the diagnostic algorithm and confirmatory diagnostic tools to verify diagnosis[17-19]**	**Assess progression of disease following treatment and provide patient with holistic care (mental, physical, and social support)[20,21]**

ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR; wtATTR, wild-type ATTR; GI, gastrointestinal; QoL, quality of life; TTR, transthyretin.

1. Hanna. *Curr Heart Fail Rep.* 2014;11:50–7; 2. Mohty et al. *Arch Cardiovasc Dis.* 2013;106:528–40; 3. Adams et al. *Neurology.* 2015;85:675–82; 4. Maurer et al. *Circ Heart Fail.* 2019;12:e006075; 5. Swiecicki et al. *Amyloid.* 2015;22:123–31; 6. Lane et al. *Circulation.* 2019;140:16–26; 7. Aus dem Siepen et al. *Clin Res Cardiol.* 2018;107(2):158–69; 8. Givens et al. *Aging health.* 2013;9(2):229–35; 9. Hawkins et al. *Ann Med.* 2015;47:625–38; 10. Castano et al. *Heart Fail Rev.* 2015;20:163–78; 11. Coehlo et al. *Muscle Nerve.* 2017;55:323–32; 12. Vinik et al. *J Peripher Nerv Syst.* 2014;19:104–14; 13. Ines et al. *ISPOR Congress* 2015. Poster N21; 14. Obici et al. *Amyloid.* 2020;27:153–62; 15. Bolte et al. *Orphanet J Rare Dis* 2020;15:287; 16. Nativi-Nicolau et al. *Heart Fail Rev.* 2022;27(3):785–93; 17. Kittleson et al. *JACC.* 2023; 81(11):1076–176; 18. Namiranian and Geisler. *Am J Med.* 2022;135 Suppl 1:S13–19; 19. Ando et al. *Orphanet J Rare Dis.* 2013;8:31; 20. Adams et al. *Orphanet J Rare Dis.* 2021;16:411; 21. Obici et al. *BMJ Open.* 2023;13:e073130.

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