GI Connect
NEWS

Amyloidosis EDITION

Proceedings Snapshot for Gastroenterology Providers

As part of the 2025 GI ReConnect Conference, 3 gastroenterologists convened in June 2025 to discuss current evidence and understanding of gastrointestinal (GI) involvement in amyloidosis. The key messages from these discussions are summarized in this issue.

Understanding amyloidosis

Spreading like graffiti
GI symptoms in amyloidosis

Time matters
Maintaining a low threshold of suspicion

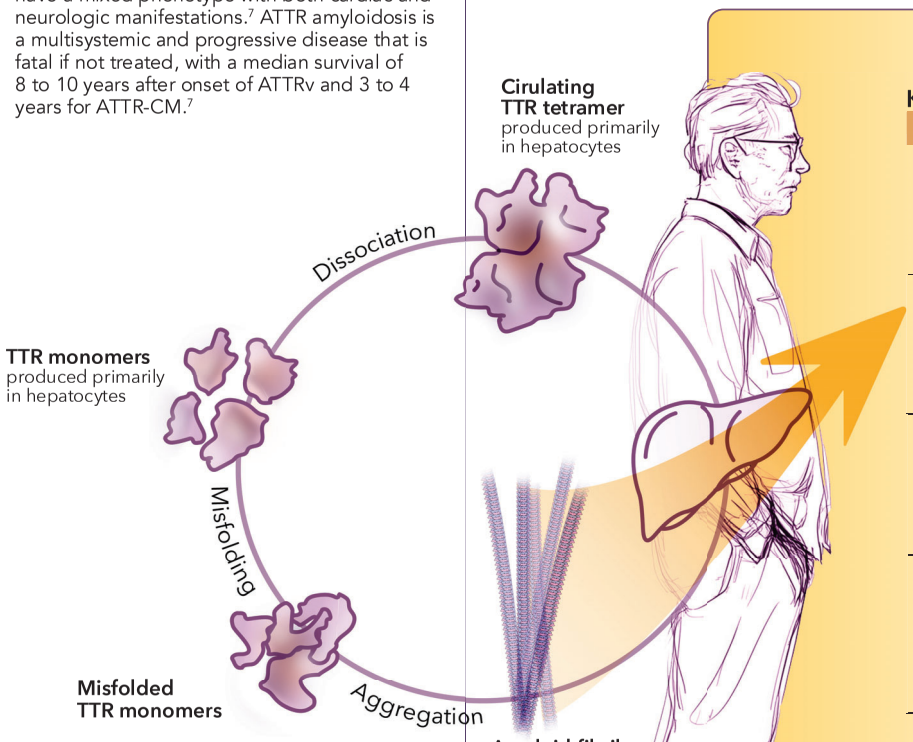
A new era of treatment
Current and emerging treatment options

Gi GastroIntestinal Health Foundation

Amyloidosis

is a group of progressive disorders characterized by the accumulation of insoluble, misfolded protein as amyloid fibrils in tissues, leading to structural and functional impairment.[1-3] The majority (98%) of cases manifest as either light chain amyloidosis (AL), involving monoclonal immunoglobulin light chains, or transthyretin amyloidosis (ATTR), involving transthyretin produced by the liver.4 In ATTR, either destabilizing mutations in hereditary ATTR (hATTR or ATTRv; v for variant) or an age-associated mechanism in wild-type ATTR (wtATTR) lead to dissociation of the transporter of thyroxine- and retinol-binding protein (TTR) from a stable tetramer into monomers, which polymerize into amyloid fibrils.[5-7] Amyloid fibrils are rigid, linear structures dominated by β-pleated sheets that bind to Congo red dye to produce a characteristic "apple-green" birefringence under polarized light microscopy.[8,9] More than 40 different amyloid proteins that cause amyloidosis in humans have been identified, with 19 associated with systemic deposition.[7] Organ dysfunction results from both the circulating oligomers, which are cytotoxic, and the distortion of tissue architecture from deposition of the amyloid fibrils in the extracelluar spaces of various tissues and organs.[7,8,10]

Although amyloidosis can affect any organ, cardiac involvement is among the most common and severe manifestation. Known as ATTR amyloid cardiomyopathy (ATTR-CM), this condition is associated with heart failure, arrhythmias, and a poor life expectancy.[4,11,12] Other commonly involved organs and their manifestation include the kidneys (proteinuria, renal failure); autonomic and peripheral nervous system (polyneuropathy, neuropathic pain, muscle weakness, autonomic dysfunction); liver (hepatomegaly, weight loss, elevated liver enzymes, liver failure); and GI tract (bowel dysmotility, anorexia, weight loss, nausea, vomiting, malabsorption, ulceration, bleeding).[11,13,14] Although traditionally phenotyped into ATTR-CM or ATTR-PN, approximately one-third of symptomatic patients have a mixed phenotype with both cardiac and neurologic manifestations.[7] ATTR amyloidosis is a multisystemic and progressive disease that is fatal if not treated, with a median survival of 8 to 10 years after onset of ATTRv and 3 to 4 years for ATTR-CM.[7]



Key symptoms of ATTR amyloidosis[16,17]

Site	Key symptoms
Cardiac	Heart failure Atrial fibrillation Bradyarrhythmias Conduction abnormalities
Musculoskeletal	Carpal tunnel syndrome Back bain/lumbar spinal stenosis Ruptured distal biceps tendon Shoulder, knee, and/or hip pain Trigger finger
Polyneuropathy	Painful neuropathy and paresthesias in hands and feet Muscle weakness Difficulty walking Falls
Autonomic dysfunction	Orthostatic hypotension Chronic diarrhea/constipation/weight loss Erectile dysfunction Urinary retention or incontinence Sweating abnormalities

ATTR amyloidosis is caused by the deposition of amyloid fibrils in extracellular tissues.[1,15]

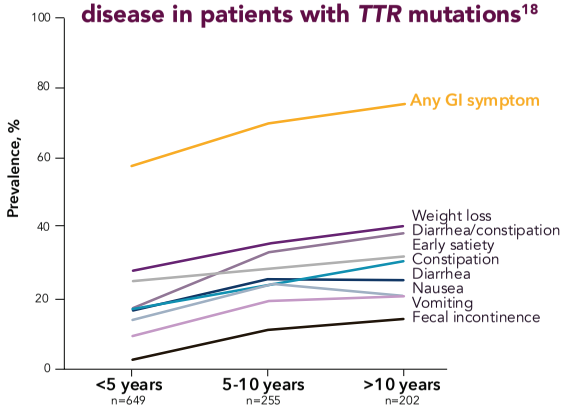
Transthyretin, a transport protein that carries thyroxine and retinol, is produced by the liver and normally exists in the serum as a soluble tetramer protein.[15] In ATTR amyloidosis, the TTR tetramer becomes unstable and dissociates into monomers that misfold, aggregate, and form amyloid fibrils over time.

Potential symptoms of systemic amyloidosis based on location of deposition in the GI tract[9,19-21]

Site	Potential symptoms
Mouth	Macroglossia
Esophagus	Dysphagia Reflux Food impaction Varices
Stomach	Abdominal pain Early satiety Nausea Vomiting Distension
Small bowel	Malabsorption Diarrhea Dysmotility Pseudo-obstruction SIBO
Colon	Diarrhea Constipation Fecal incontinence Bleeding

Gastrointestinal symptoms are common in ATTR amyloidosis. Although the heart is the most commonly involved organ, gastrointestinal (GI) symptoms are common in patients with ATTR amyloidosis.[18] Analysis of 1744 patients enrolled in the Transthyretin Amyloidosis Outcomes Survey (THAOS), a global, longitudinal patient registry, found that 59% of patients reported at least 1 GI symptom.[18] The most commonly reported symptom was unintentional weight loss (28.3%), followed by early satiety (22.9%) and alternative diarrhea and constipation (22.9%). Most patients experienced GI symptoms even in the early stages of disease, and the symptom increased significantly with disease duration.[18]

GI symptoms in relation to duration of disease in patients with *TTR* mutations[18]



Despite these trends, the GI symptoms of amyloidosis can vary considerably by the site and degree of amyloid deposition,[14] which can occur in the luminal GI mucosal, the muscular layers of the gut, the GI vasculature, and/or the enteric nervous system.[19] When discussing this heterogeneity, the faculty likened the scattering of misfolded proteins in the body to graffiti, noting its characteristic patchy and erratic distribution across multiple organs. They explained that amyloidosis can affect the GI tract in different ways depending on the sites involved. For example, stomach involvement may result in gastroparesis, nausea, and vomiting, whereas involvement in the small bowel and/or colon may lead to dysmotility, malnutrition, constipation, diarrhea, ulceration, and/or bleeding. Abnormal bowel function can substantially contribute to the development of malnutrition that characterizes later stage disease.[20] Amyloid deposition involving the enteric nervous system, even without direct mucosal or muscular deposition, can lead to significant GI dysfunction mediated by polyneuropathy and dysautonomia.[19] Weight loss can result from involvement anywhere along the GI tract, and importantly, it can occur before other GI or neuropathic symptoms present. Gastrointestinal symptoms in amyloidosis have a profoundly negative impact on patient quality of life and symptom burden and have been associated with an increased mortality risk.[20]

Maintaining a low threshold

Time matters

Endoscopy and colonoscopy with standard biopsies are the gold standard for diagnosing GI involvement in amyloidosis, although this approach detects mucosal involvement rather than primarily neuropathic or muscular involvement.[22,23] Given the broad, nonspecific endoscopic findings associated with GI amyloidosis, histopathological examination with Congo red staining is required to identify amyloid deposition, thus confirming the diagnosis, and to identify the type of amyloid fibril present.[21,22,24] Although limited data have demonstrated the highest diagnostic yield in the duodenum,[24,25] multiple biopsies are usually performed throughout the GI tract, targeting any areas of mucosal irregularity or those most implicated by symptoms. Several studies have suggested that AL and ATTR proteins tend to accumulate in the submucosa, highlighting the need for adequate sampling of the submucosa to avoid misdiagnosis due to superficial sampling.[16,23] Submucosal rectal biopsy has been found to have high diagnostic yield even in the absence of endoscopic abnormalities.[26]

Early diagnosis of amyloidosis is critical as prognosis worsens rapidly with accumulating amyloid deposition and organ dysfunction.[27] Recognizing and diagnosing patients at an early stage of the disease is especially important in light of the availability of treatment options that have a favorable impact on survival and/or prevent potentially irreversible loss of physical function and quality of life.[22] With that in mind, the presence of non-cardiac symptoms such as unexplained diarrhea or weight loss clustered with cardiac and/or neurologic symptoms, particularly in the presence of family history of amyloidosis, should prompt diagnostic testing and referral for multidisciplinary assessment at an amyloidosis expert center.[16,28] Gastroenterologists are encouraged to have a low threshold for performing biopsy in patients with unexplained GI symptoms.[23] Expanding on this, the faculty emphasized the importance maintaining a low threshold for Congo red staining and of informing the pathologist that amyloidosis is suspected when appropriate.

Maintain a low threshold for requesting Congo red staining when biopsying the gut for patients with unexplained diarrhea or malnutrition, and maintain curiosity for systemic conditions that could be driving these things.

A new era of treatment

Liver transplantation and symptom management have historically been the mainstay of treatment for ATTR amyloidosis, with heart or combined heart-liver transplantation reserved for select patients.[29] However, the development of treatments that target key steps in ATTR fibril formation and clearance has revolutionized the management of this disease, improving the prognosis and offering new hope for patients.[1,30] Over the past decade, multiple disease-modifying therapies have been approved by the US Food and Drug Administration (FDA) for ATTR-CM and/or ATTR-PN.[31-35] These therapies either stabilize circulating TTR (TTR stabilizers) or reduce the production of TTR (small interfering RNA [siRNA] inhibitors and antisense oligonucleotides).[6]

Tafamidis and acoramidis are TTR stabilizers that slow the dissociation of TTR and thus fibril formation and cardiac deposition.[22] In contrast, TTR gene silencing therapies such as patisiran and vutrisiran aim to reduce the production of TTR protein by hepatocytes.[1] Antisense oligonucleotides such as eplontersen represent another approach to silencing TTR gene expression that works by binding to and initiating mRNA degradation, inhibiting gene expression and silencing TTR precursor production.[11] Overall, the TTR stabilizers and TTR gene silencers have been found to improve outcomes in ATTR-CM[36-39] and/or ATTR-PN,[40,41] including slowing disease progression and improving survival. These therapies are considered relatively safe, although their long-term safety and durability remain under active investigation.[11,42]

Anti-amyloid therapies, also known as TTR depleters, are an evolving strategy for TTR amyloidosis that work by binding to and extracting misfolded TTR and amyloid deposits from affected organs and tissues.[29,42] Several monoclonal antibodies are currently under investigation, and early results suggest potential for these therapies to significantly reduce amyloid burden, improve clinical outcomes and potentially slow disease progression in ATTR amyloidosis.[29] Gene editing is another investigational approach for ATTR amyloidosis, with nexiguran ziclumeran (formerly NTLA-2001) currently in late-stage clinical trials for ATTR-CM.[43] Based on CRISPR-Cas9 -technology, this single-dose therapy is designed to permanently edit the TTR gene in hepatocytes, thereby inhibiting TTR production.[1,29] With potential to offer a one-time, permanent solution, this therapy could represent a revolutionary approach to TTR amyloidosis.[1]

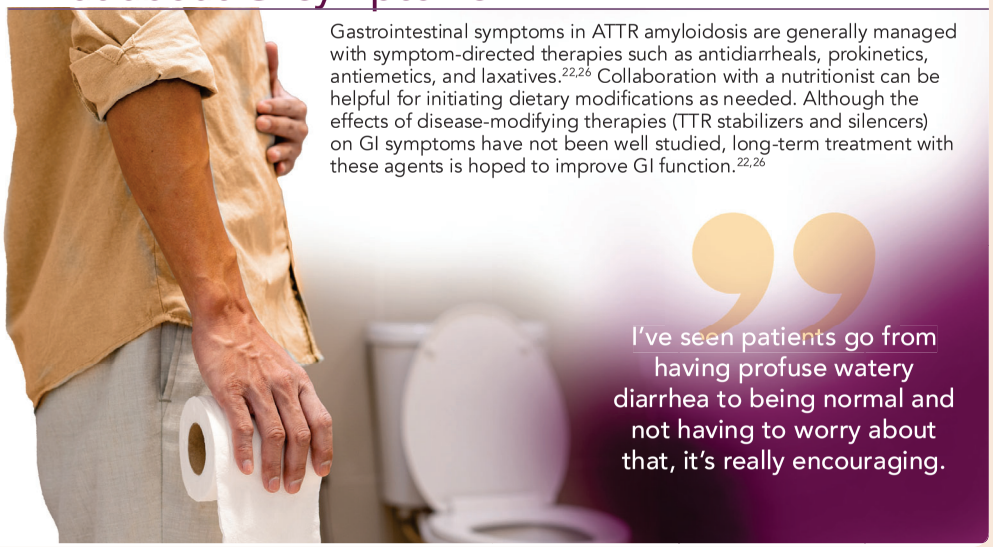
"In training amyloidosis was a fire that couldn't be put out and we had to manage the smoke, but now we have treatments that can stop new misfolded proteins from being spun out."

FDA-approved therapies for ATTR amyloidosis

Mechanism	Drug	FDA approval	Approved indications		Dosage regimen	Most common adverse events	Other considerations
			ATTR-CM	ATTR-PN			
TTR stabilizers	**Acoramidis**[32] (Attruby™)	2024	✓		Oral tablets, twice daily	Diarrhea, upper abdominal pain	
	Tafamidis[34] (Vyndamax™), Vyndaqel®)	2019	✓		Oral capsules, once daily		
TTR siRNAs	**Patisiran**[33] (Onpattro®)	2018		✓	IV infusion every 3 weeks	URT infections, infusion-related reactions	Need for vitamin A supplementation
	Vutrisiran[31] (Amvuttra®)	2022	✓	✓	SC injection every 3 months	Pain in extremity, arthralgia, dyspnea, decreased vitamin A	Need for vitamin A supplementation
TTR ASO	**Eplontersen**[35] (Wainua®)	2023		✓	SC injection once monthly	Decreased vitamin A, vomiting	Need for vitamin A supplementation

ASO, antisense oligonucleotide; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTR-PN, transthyretin amyloid polyneuropathy; IV, intravenous: SC, subcutaneous; siRNA, small interfering RNA; TTR, transthyretin; URT, upper respiratory tract.

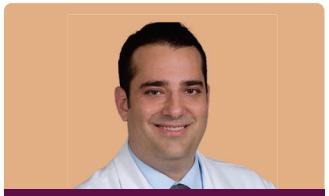
What about GI symptoms?



Gastrointestinal symptoms in ATTR amyloidosis are generally managed with symptom-directed therapies such as antidiarrheals, prokinetics, antiemetics, and laxatives.[22,26] Collaboration with a nutritionist can be helpful for initiating dietary modifications as needed. Although the effects of disease-modifying therapies (TTR stabilizers and silencers) on GI symptoms have not been well studied, long-term treatment with these agents is hoped to improve GI function.[22,26]

"I've seen patients go from having profuse watery diarrhea to being normal and not having to worry about that, it's really encouraging.

Faculty



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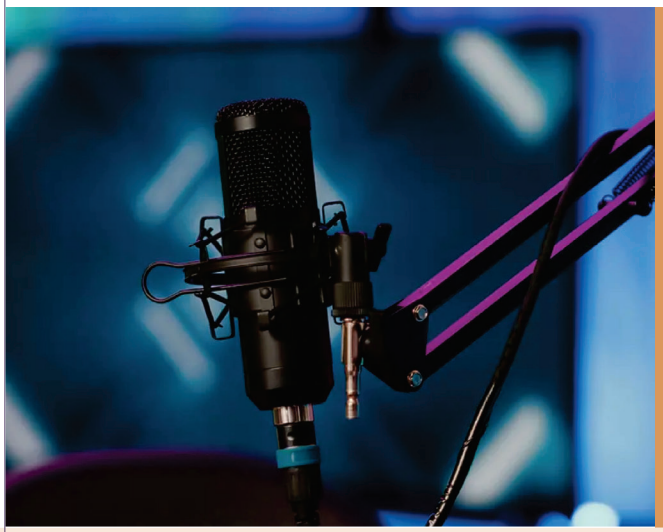

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