

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

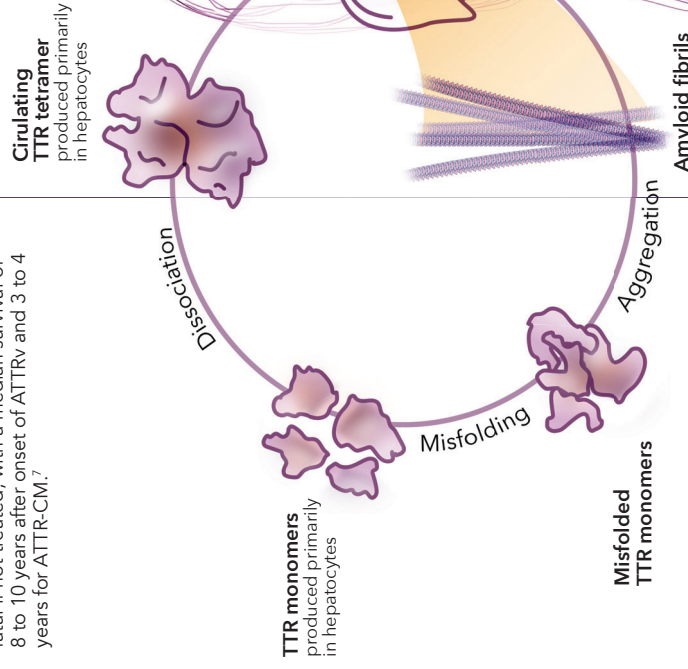
A new era of treatment

Current and emerging
treatment options

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 (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 extracellular 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



Cardiac

Key symptoms of ATTR amyloidosis^{16,17}

Site	Key symptoms
Cardiac	Heart failure Atrial fibrillation Bradyarrhythmias Conduction abnormalities
Musculoskeletal	Carpal tunnel syndrome Back pain/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

Autonomic dysfunction

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.



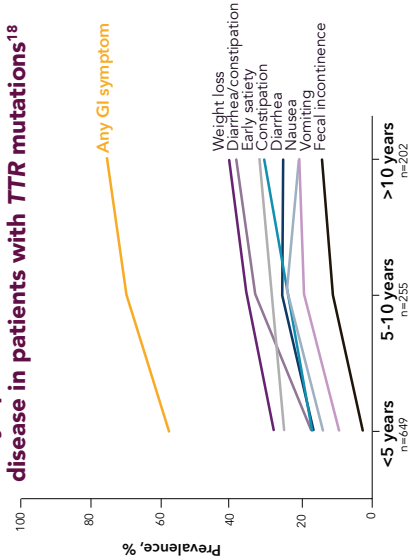
Spreading like

Potential symptoms of systemic amyloidosis based on location of deposition in the GI tract^{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 mutations¹⁸



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 mucosa, 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

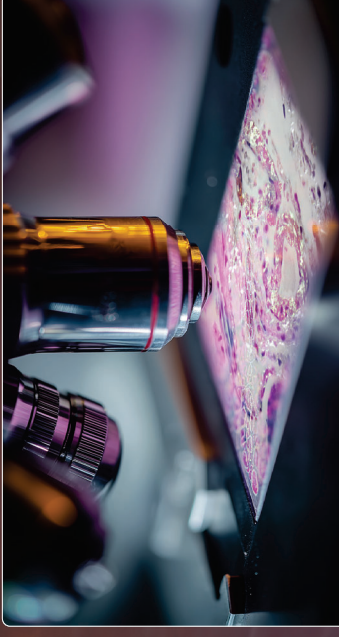
or muscular deposition, can lead to significant GI dysfunction mediated by polyneuropathy and dysautonomia.¹⁹ Weight loss can result from involvement anywhere along the GI tract, and importantly, it can occur before other GI or neuropathic symptoms present. Gastrointestinal symptoms in amyloidosis have 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 of 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.^{23,42} 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) 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		Most common adverse events	Other considerations
			ATTR-CM	ATTR-PN		
TTR stabilizers	Acoramidis ²² (Atruby TM)	2024	✓		Diarrhea, upper abdominal pain	
	Tafamidis ⁴⁴ (Vyndaqel TM), Vyndaqel [®])	2019	✓		Oral capsules, once daily	
TTR siRNAs	Patisiran ³³ (Onpattro [®])	2018	✓		IV infusion every 3 weeks	Need for vitamin A supplementation
	Vutrisiran ³¹ (Amvuttra [®])	2022	✓	✓	SC injection every 3 months	Need for vitamin A supplementation
TTR ASO	Eplontersen ³⁵ (Wainua [®])	2023	✓		SC injection once monthly	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.

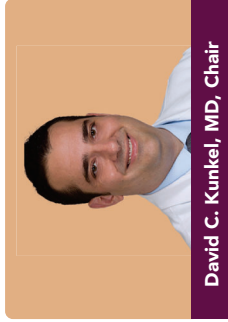
What about GI symptoms?

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



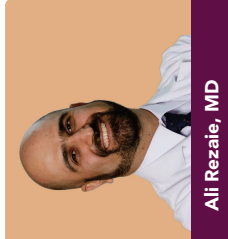
David C. Kunkel, MD, Chair

UC San Diego Health
San Diego, CA



Lucinda A. Harris, MD

Mayo Clinic
Phoenix, AZ



Ali Rezaie, MD

Cedars-Sinai Medical Center
Los Angeles, CA

References

- Castiglione V, Montuoro S, Orlando G, Almo A, Vergaro G, Emidin M. Cardiac amyloidosis: Innovations in diagnosis and treatment. *Eur Heart J Suppl.* 2025;27(Suppl 1):188-197.
- Senecal JB, Abou-Akl R, Allevato P et al. Amyloidosis: a case series and review of the literature. *J Med Case Rep.* 2023;17(1):184.
- Delgado D, Dabbous F, Shivappa N et al. Epidemiology of transthyretin (ATTR) amyloidosis: a systematic literature review. *Orphanet J Rare Dis.* 2025;20(1):29.
- O'Sullivan M, Osman W, Krishnagopal A, Parry M, Davis M, Chu CH. Integrated specialty care for amyloidosis: a scoping review using the Consolidated Framework for Implementation Research. *BMC Health Serv Res.* 2025;25(1):415.
- Gertz MA, Dispenzieri A. Systemic amyloidosis recognition, prognosis, and therapy: a systematic review. *JAMA.* 2020;324(1):79-89.
- Prata AA, Katsuyama ES, Scardini PG et al. The efficacy and safety of specific therapies for cardiac transthyretin-mediated amyloidosis: a systematic review and meta-analysis of randomized trials. *BMC Cardiovasc Disord.* 2025;25(1):296.
- Karam C, Mauremman ML, Gonzalez-Duarte A et al. Diagnosis and treatment of hereditary transthyretin amyloidosis with polyneuropathy in the United States: Recommendations from a panel of experts. *Muscle Nerve.* 2024;69(3):273-287.
- Domelly JP, Hanna M. Cardiac amyloidosis: An update on diagnosis and treatment. *Cleve Clin J Med.* 2017;84(12 Suppl 3): 12-26.
- Dahiya DS, Kichloo A, Singh J, Albosta M, Wani F. Gastrointestinal amyloidosis: a focused review. *World J Gastrointest Endosc.* 2021;13(1):1-12.
- Nakov N, Sarotov S, Nakov V et al. Fecal calprotectin levels are elevated in transthyretin amyloidosis patients with gastrointestinal manifestations. *Malacarne (Milano).* 2020;49(11):e1950.
- Hallgren EL, Rodighiero AJ, Rodriguez-Carrión MC, Krishna H, DiDonato RJ. Current and emerging therapies for amyloid transthyretin cardiomyopathy. *Current and emerging medications. Pharmacotherapy.* 2025;45(2):124-144.
- Maurer MS, Bokhari S, Dany T et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. *Circ Heart Fail.* 2019;12(9):e006075.
- Muchtar E, Dispenzieri A, Magen H et al. Systemic amyloidosis from A (AA) to T (ATTR): a review. *J Intern Med.* 2021;289(3):268-292.
- Ramachandran R, Grantham T, Isaac-Coss G, Etienne D, Reddy M. Gastrointestinal involvement in AL amyloidosis: case report and literature review. *J Investig Med High Impact Case Rep.* 2024;12:23247096241237759.
- Nativi-Nicolau J, Maurer MS. Amyloidosis cardiomyopathy: update in the diagnosis and treatment of the most common types. *Curr Opin Cardiol.* 2018;33(5):571-579.
- Nativi-Nicolau JN, Karam C, Khella S, Maurer MS. Screening for ATTR amyloidosis in the clinic: overlapping disorders, misdiagnosis, and multicourse awareness. *Heart Fail Rev.* 2022;27(3):785-793.
- Tschöpe C, Elanhoury A, Kristen AV. Transthyretin Amyloid Cardiomyopathy-2025 Update: Current Diagnostic Approaches and Emerging Therapeutic Options. *J Clin Med.* 2025;14(13):4785.
- Wiener J, Mundayar R, Karayal ON et al. THAOS: gastrointestinal manifestations of transthyretin amyloidosis - common complications of a rare disease. *Orphanet J Rare Dis.* 2014;9:61.
- Muchtar E, Grogan M, Aus dem Siepen F et al. Supportive care for systemic amyloidosis: International Society of Amyloidosis (ISA) expert panel guidelines. *Amyloid.* 2025;32(2):93-116.
- Obici L, Suhr OB. Diagnosis and treatment of gastrointestinal dysfunction in hereditary TTR amyloidosis. *Clin Auton Res.* 2019;29(Suppl 1):55-63.
- Syed U, Ching Compantoni RA, Alkhatwam H, Wallish A. Amyloidosis of the gastrointestinal tract and the liver: clinical context, diagnosis and management. *Eur J Gastroenterol Hepatol.* 2016;28(10):1109-1121.
- Writing Committee, Kittleson MM, Ruberg FL et al. 2023 ACC Expert Consensus Decision Pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2023;81(11):1076-1126.
- Hagen CE, D'Saai S, Theis JD et al. Gastrointestinal amyloidosis: an often unexpected finding with systemic implications. *Hum Pathol.* 2023;135:27-36.
- Niu Z, Ling Y, Shen Y, Zhang H, Xue Y, Ding S. Endoscopic and pathological characteristics of gastrointestinal amyloidosis: a retrospective analysis. *BMC Gastroenterol.* 2025;25(1):81.
- Ishii T, Kikuchi M, Nakase H, Saito H. Systemic amyloidosis and gastrointestinal involvement: Dismiss from endoscopic and histological views. *J Gastroenterol Hepatol.* 2018;33(3):583-590.
- Fritz CDJ, Blaney E. Evaluation and management strategies for GI involvement with amyloidosis. *Am J Med.* 2022;135 Suppl 1:S20-S23.
- Witeles RM, Bokhari S, Dany T et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *JACC Heart Fail.* 2019;7(8):709-716.
- Cappelli M, Barbara G, Bellini M et al. Identification and management of gastrointestinal manifestations of hereditary transthyretin amyloidosis: recommendations from an Italian group of experts. *Dig Liver Dis.* 2024;56(6):1014-1020.
- Patel AGM, Li P, Badrish N, Kesari A, Shah KB. Transthyretin cardiac amyloidosis: current and emerging therapies. *Curr Cardiol Rep.* 2025;27(1):33.

- Stein-Merlob AE, Swier R, Vucelja D. Evolving strategies in cardiac amyloidosis: from mechanistic discoveries to diagnostic and therapeutic advances. *Cardiol Clin.* 2025;43(1):93-110.
- Amvutraf® (vutrisiran). Prescribing information. Anylam Pharmaceuticals, Inc. 2025.
- Attruby™ (acoramidis). Prescribing information. BridgeBio Pharma, Inc. 2024.
- Onpatro® (patisiran). Prescribing information. Anylam Pharmaceuticals, Inc. 2023.
- Vyndamax™ (safamidis mesilamine and tafamidis). Prescribing information. Pfizer Labs, 2025.
- Wanua® (eplontersen). Prescribing information. AstraZeneca Pharmaceuticals LP, 2025.
- Fontana M, Berk JL, Gilmore JD et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med.* 2025;392(1):33-44.
- Gilmore JD, Judge DP, Cappelli F et al. Efficacy and safety of acoramidis in transthyretin amyloid cardiomyopathy. *N Engl J Med.* 2024;390(2):132-142.
- Maurer MS, Schwartz JH, Gundapaneni B et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med.* 2018;379(11):1007-1016.
- Maurer MS, Kale P, Fontana M et al. Patisiran treatment in patients with transthyretin cardiac amyloidosis. *N Engl J Med.* 2023;389(17):1553-1565.
- Adams D, Tournev IL, Taylor MS et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid.* 2023;30(1):1-9.
- Coelho T, Marques V, Dasgupta NR et al. Eplontersen for hereditary transthyretin-mediated amyloidosis with polyneuropathy. *JAMA.* 2023;330(15):1448-1458.
- Avan I. Advances in the treatment of transthyretin amyloidosis. *eGastroenterology.* 2025;3(3):e100198.
- National Library of Medicine. Accessed September 18, 2025. <https://www.clinicaltrials.gov>.

To hear more about amyloidosis from a gastroenterology perspective, visit:

