ISSN 1948-5190 (online)

World Journal of

Gastrointestinal Endoscopy

World J Gastrointest Endosc 2021 January 16; 13(1): 1-32

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Endoscopy

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ABOUT COVER

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INDEXING/ABSTRACTING

The *WJGE* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Anastasios Koulaouzidis, Bing Hu, Sang Chul Lee

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5190/editorialboard.htm

PUBLICATION DATE
January 16, 2021

INSTRUCTIONS TO AUTHORS
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https://www.wjgnet.com/bpg/gerinfo/242

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World Journal of Gastrointestinal Endoscopy

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World J Gastrointest Endosc 2021 January 16; 13(1): 1-12

DOI: 10.4253/wjge.v13.i1.1

ISSN 1948-5190 (online)

MINIREVIEWS

Gastrointestinal amyloidosis: A focused review

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Author contributions: Dahiya DS and Kichloo A are credited with substantial contribution to the design of the work, literature review of all the sections discussed, the revision of critically important intellectual content, final approval of the published version, and agreement of accountability for all aspects of the work; Singh J and Albosta M are credited with significant design of the tables and graphs, literature review of all sections, revision of important intellectual content for the discussion, and agreement of accountability for all parts of the work; Wani F is credited with literature review, final content write up and agreement of accountability for all aspects of the work.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior author or other coauthors who contributed their efforts in this manuscript.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external

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Abstract

Amyloidosis, a heterogenous group of disorders, is characterized by the extracellular deposition of autologous, insoluble, fibrillar misfolded proteins. These extracellular proteins deposit in tissues aggregated in ß-pleated sheets arranged in an antiparallel fashion and cause distortion to the tissue architecture and function. In the current literature, about 60 heterogeneous amyloidogenic proteins have been identified, out of which 27 have been associated with human disease. Classified as a rare disease, amyloidosis is known to have a wide range of possible etiologies and clinical manifestations. The exact incidence and prevalence of the disease is currently unknown. In both systemic and localized amyloidosis, there is infiltration of the abnormal proteins in the layers of the gastrointestinal (GI) tract or the liver parenchyma. The gold standard test for establishing a diagnosis is tissue biopsy followed by Congo Red staining and apple-green birefringence of the Congo Red-stained deposits under polarized light. However, not all patients may have a positive tissue confirmation of the disease. In these cases additional workup and referral to a gastroenterologist may be warranted. Along with symptomatic management, the treatment for GI amyloidosis consists of observation or localized surgical excision in patients with localized disease, and treatment of the underlying pathology in cases of systemic amyloidosis. In this review of the literature, we describe the subtypes of amyloidosis, with a primary focus on the epidemiology, pathogenesis, clinical features, diagnosis and treatment strategies available for GI amyloidosis.

Key Words: Gastroenterology; Hepatology; Amyloidosis; Dysmotility; Endoscopy; Therapeutics

Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

Peer-review report's scientific quality classification
Grade A (Excellent): A, A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

Received: October 23, 2020
Peer-review started: October 23, 2020
First decision: December 1, 2020
Revised: December 16, 2020
Accepted: December 27, 2020
Article in press: December 27, 2020
Published online: January 16, 2021

P-Reviewer: Bratlie SO, Emara MH, Kim GH, Weiss H, Yildiz K
S-Editor: Zhang L
L-Editor: A
P-Editor: Wang LL

Core Tip: This manuscript focuses on a rare disease entity that can cause significant morbidity and mortality, especially amongst the elderly patient population. Lack of awareness regarding the possibility of gastrointestinal amyloidosis, which presents with vague symptoms common to a host of disorders, can lead to unnecessary testing and delays in diagnosis, contributing to poor outcomes. Physicians should consider the presence of gastrointestinal amyloidosis, especially in elderly patients with conditions predisposing them to the development of amyloid deposition.

Citation: Dahiya DS, Kichloo A, Singh J, Albosta M, Wani F. Gastrointestinal amyloidosis: A focused review. *World J Gastrointest Endosc* 2021; 13(1): 1-12
URL: https://www.wjgnet.com/1948-5190/full/v13/i1/1.htm
DOI: https://dx.doi.org/10.4253/wjge.v13.i1.1

INTRODUCTION

In 1853, Rudolf Virchow first used the term "amyloid" to describe tissue deposits which showed close similarity to starch after they were dyed with iodine and sulphuric acid[1]. Amyloidosis encompasses a heterogenous group of disorders characterized by the extracellular deposition of autologous fibrillar proteins, which aggregate into a three-dimensional ß-lamina disposition (ß-pleated sheets aligned in an anti-parallel fashion) in tissues, disrupting normal tissue architecture and function[2,3]. According to the Genetic and Rare Disease Information Center (GARD) of the National Institute of Health (NIH), amyloidosis is a rare disease. It is known to have a wide spectrum of possible etiologies and clinical manifestations, thereby making an accurate assessment of epidemiology extremely difficult. According to the data available from the NIH, AL (amyloid light chain) amyloidosis has an incidence of 1 case per 100000 person-years in Western countries[4]. Systemic amyloidosis is more common than localized disease, and the annual incidence of primary systemic amyloidosis is 78% whereas that of secondary systemic amyloidosis is only 6% every year in the United States[4]. In the literature, about 60 heterogeneous amyloidogenic proteins have been identified, out of which 27 are associated with known disease in humans[5]. Based on the location of production of amyloidogenic precursor protein and its deposition within the tissues, it can be classified into two distinct subtypes: Systemic and localized amyloidosis[6]. GI tract involvement may be a feature of both subtypes[6]. Gastrointestinal (GI) amyloidosis is defined as the presence of GI signs and symptoms along with direct biopsy verification of the disease. However, as per the current literature, GI amyloidosis with direct biopsy verification from the GI tract may be a rare phenomenon. Hence, in this review, we describe the different subtypes of amyloidosis with associated amyloid precursor proteins deposited in tissues. We also describe the incidence rates of amyloidosis reported in different healthcare systems throughout the world. Additionally, we detail the pathogenesis, clinical presentations, methods to establish diagnosis, and the treatment strategies available for GI amyloidosis.

METHODS

A thorough literature search was performed to identify articles on amyloidosis of the GI tract and its clinical presentations. The authors used search engines such as PubMed, Google Scholar, and Ovid MEDLINE to search for published literature on GI amyloidosis between the years 1960 and 2020. A detailed literature search of the articles referenced in the identified publications was also performed. Furthermore, data and statistics available from national organizations such as the GARD were also researched. The keywords used in the literature search included, but are not limited to: "amyloidosis", "gastrointestinal amyloidosis", "localized amyloidosis", "systemic amyloidosis", "amyloid pathogenesis", "hepatic amyloidosis", "amyloidosis treatment", "gastrointestinal amyloidosis treatment", and "gastrointestinal

amyloidosis prognosis". The inclusion criteria set by the authors consisted of articles published between the years 1960 and 2020, published articles available in the English language, data and statistics available from national organizations such as the NIH, and published articles or guidelines related to the therapeutic options available for the management of GI amyloidosis in all clinical settings. The exclusion criteria consisted of duplicate articles or abstracts only, articles published before the year 1950, articles published in a language other than English, and unpublished research on GI amyloidosis. Application of the inclusion and exclusion criteria yielded a total of 3197 articles which were carefully reviewed by all the authors for this review of the literature. A total of 65 references ultimately were used for the purposes of drafting this narrative review.

DISCUSSION

As described earlier, amyloidosis refers to a heterogenous group of disorders characterized by extracellular deposition of fibrillar proteins, which can disrupt tissue structure and function. On electron microscopy, amyloid fibrils are approximately 10 nm in diameter, and on polarized light microscopy after staining with Congo Red (CR) dye, they have the characteristic apple green-birefringence appearance[5]. According to the 2010 recommendations from the Nomenclature Committee of the International Society of Amyloidosis, about 60 heterogeneous amyloidogenic proteins have been identified, out of which 27 have been found to be associated with known human disease[7].

CLASSIFICATION

Amyloidosis can be classified into two main subtypes based on the location of production of the amyloidogenic precursor protein and its deposition within the tissues (Table 1)[6]. The classification is as follows[6,8].

Systemic amyloidosis

The most common subtype. It is characterized by the production of amyloidogenic precursor proteins at a site remote from the organ of amyloid deposition. It can either be due to acquired conditions such as plasma cell dyscrasias, or hereditary conditions due to modifications in the transthyretin (TTR) gene. Table 2 summarizes the common forms of systemic amyloidosis along with organ-specific involvement[8].

Localized amyloidosis

It is characterized by the production of amyloidogenic precursor proteins at the same location as its deposition. It may commonly involve the respiratory tract, urinary bladder, breast, skin, or the GI tract. A single center retrospective analysis by Cowan *et al*[6] reported that out of the 3.3% of patients with biopsy proven amyloidosis, only 21% had amyloidosis restricted to the GI tract[6]. Hence, localized amyloidosis is an uncommon entity.

EPIDEMIOLOGY

According to the GARD, amyloidosis is a rare disease entity. It is known to have a wide spectrum of possible etiologies and clinical manifestations, thereby making an accurate assessment of epidemiology extremely difficult. Furthermore, regional variations in the environment *i.e.*, prevalence of local infections and autoimmune diseases which predispose to chronic inflammation, and genetic factors such as polymorphisms in the genes encoding for amyloid precursors may also contribute significantly to the likelihood of developing the disease[9]. Studies, although limited, have been conducted to evaluate the epidemiology of the disease in the United States and worldwide. According to the latest statistics available from the NIH, AL amyloidosis has an incidence of 1 case per 100000 person-years in Western countries, and in the United States approximately 1275 to 3200 new cases are reported every year[4]. Systemic amyloidosis is more common than localized amyloidosis, and the annual portion of new cases with primary systemic amyloidosis (AL) is 78% whereas secondary systemic amyloidosis (AA) represents only 6% of these cases every year in

Table 1 Differences in systemic and localized gastrointestinal amyloidosis

Systemic gastrointestinal amyloidosis	Localized gastrointestinal amyloidosis
More common subtype	Less common subtype
Amyloid production at a remote location with subsequent deposition in the GI tract	Amyloid production in the GI tract with subsequent deposition locally
Presence of amyloid precursor proteins in the blood	Amyloid precursor proteins absent in the blood
Associated with plasma cell dyscrasia, chronic inflammatory conditions, dialysis, or hereditary conditions	Not associated with an underlying disease pathology
Amyloid precursor protein deposited include AL, AA, Aβ2M and ATTR	Amyloid precursor protein most deposited is AL
Management consists of symptomatic management and treatment of the underlying etiology	Management consists of observation or surgical excision of the localised deposition
Prognosis depends on the type and amount of amyloid deposition	Good prognosis. No transition to systemic type

AL: Monoclonal light chain; AA: Serum amyloid A; Aβ2M: β2-microglobulin amyloid; ATTR: Familial transthyretin-associated amyloidosis; GI: Gastrointestinal.

Table 2 The common forms of systemic amyloidosis with organ involvement

Type of systemic amyloidosis	Causative protein	Organ involvement
Primary systemic amyloidosis	Monoclonal light chain (AL)	Heart, Kidneys, Liver, Peripheral nervous system, Autonomic nervous system, and Gastrointestinal tract
Senile systemic amyloidosis	Wild-type transthyretin (ATTR)	Heart
Hereditary systemic amyloidosis	Mutant transthyretin (ATTR); Apolipoprotein 1 (AApoA1); Mutant fibrinogen A alpha (AFib); Lysozyme (ALys)	Heart; Heart, Kidneys, Liver, Peripheral nervous system, and Skin; Kidneys and Liver; Kidneys and Liver
Isolated Atrial Systemic Amyloidosis	Atrial natriuretic factor (AANF)	Heart
Secondary Systemic Amyloidosis	Serum amyloid A (AA)	Kidneys, Heart, and Gastrointestinal tract
Dialysis-Related Systemic Amyloidosis	β2-microglobulin ($A\beta_2M$)	Osteoarticular tissue, Circulatory system, and Gastrointestinal tract
Finnish-type Systemic Amyloidosis	Gelsolin (AGel)	Lattice dystrophy of cornea, and Corneal neuropathy

the United States[4]. Familial transthyretin-associated amyloidosis, believed to be less common and with a currently unknown incidence rate, constitutes approximately 10% to 20% of diagnosed cases at tertiary hospitals in the United States[4]. Outside the United States, similar trends in incidence have been observed. In the United Kingdom, Pinney *et al*[10] reported a global incidence of amyloidosis of 5 cases per million person-years, out of which 3 cases per million person-years were attributed to the AL amyloidosis and 1 case per million person-years to AA amyloidosis[10]. Similarly, Hemminki *et al*[11] estimated the incidence of amyloidosis to be 8 patients per million person-years in Sweden, from which 3 cases per million person-years were credited to AL amyloidosis and 2 cases per million person-years to AA amyloidosis[11]. Typically, amyloidosis manifests later in life and more commonly affects the older demographic (mean age for the AL subtype is 63 years)[12]. A higher incidence and prevalence of the disease has been reported in males as compared to females[12]. In the United States, the literature also reported a substantial increase in amyloidosis-related mortality from 1.77 to 3.96 per million between 1979 and 2015, with the highest mortality rates noted in the African-American population[13].

Involvement of the GI tract can be seen in both localized (limited only to the gut) and systemic (most commonly AL subtype) amyloidosis. GI amyloidosis is defined as the presence of GI signs and symptoms along with direct biopsy verification of the disease[14]. It is more commonly seen in elderly males. Yen *et al*[15] conducted a single center retrospective cohort study from 2008 to 2017 in 583 amyloid patients and observed that only 96 (16.8%) patients had GI signs and symptoms[15]. Out of these 96

patients, 82 underwent esophagogastroduodenoscopy (EGD) or colonoscopy with biopsy, and it was reported that only 37 (45%) patients had biopsy proven GI amyloidosis, whereas 45 (55%) patients had absence of GI amyloidosis on biopsy[15]. Similarly, another retrospective study which evaluated 2337 patients in a 13-year period using the Boston University Amyloid Treatment and Research Program database reported biopsy proven GI Amyloidosis in only 76 (3.3%) of the patients[6]. Furthermore, on EGD or colonoscopy, the site of highest diagnostic yield from biopsy specimens was found to be the duodenum, followed by the stomach, colon and rectum, and esophagus[6,15]. Hence, it can be concluded that GI amyloidosis with direct biopsy verification from the GI tract is a rare phenomenon. There is also a significant paucity of data on GI amyloidosis with most of it available either from small, retrospective single center studies, or isolated case reports. Therefore, we strongly advocate for the need for additional large multi-center prospective studies to capture the impact of GI amyloidosis globally and its burden on the healthcare system.

PATHOGENESIS

The basic pathogenic mechanism of amyloidosis involves the extracellular deposition of insoluble protein fibrils derived from amyloid precursor proteins in tissues[16]. These are composed of low molecular weight subunits arranged in antiparallel ß-pleated sheets[16]. In GI amyloidosis, infiltration of extracellular misfolded proteins can be seen in the different layers of the GI tract.

Mucosal infiltration

The most common site of mucosal infiltration is the duodenum, followed by the stomach, colorectum and the esophagus[17]. Furthermore, the subtype of amyloid protein deposited governs the clinical presentation[18,19].

AL amyloid deposition is usually seen in the muscularis mucosa, submucosa and muscularis propria, often leading to the formation of protrusions. It may present with symptoms of bowel obstruction.

AA amyloid deposition is seen mainly in the mucosa, which may lead to increased friability and erosions in the involved area. It may present with diarrhea and clinical features of malabsorption.

β2-microglobulin amyloid ($A\beta_2M$) deposition is usually seen in patients on hemodialysis and corresponds to increased mean time on dialysis. $A\beta_2M$ deposits can be seen in the blood vessels of the GI tract, mucosa, submucosa, and muscularis propria. It may present with features of mucosal ulceration.

Neuromuscular infiltration

It is characterized by the deposition of the amyloid proteins in the neuromuscular layer of the GI tract. This can affect the intrinsic nerve plexus (myenteric or submucosal nerve plexus) and the muscularis externa (longitudinal and circular muscles) leading to abnormal peristalsis, abnormal GI transit times and dysmotility[20-22].

Hepatic amyloidosis, a manifestation of systemic amyloidosis, has a similar pathogenic mechanism and is characterized by the extracellular deposition of fibrillar amyloid protein (AL) in the hepatic parenchyma[23]. It is a diagnostic challenge as it shares numerous clinical manifestations with other common chronic liver diseases, and has a poor prognosis particularly in patients with jaundice[23].

CLINICAL MANIFESTATIONS

The clinical manifestations of GI amyloidosis depends on the amount and location of the amyloid deposits, irrespective of whether it is primary or secondary systemic amyloidosis[17]. Patients with localized amyloidosis may have similar clinical features as those with systemic disease. All patients with amyloidosis share common presenting symptoms such as fatigue, light-headedness, anorexia, and weight loss[24]. The common GI-specific abnormalities include.

Gastrointestinal bleeding

May occur from any site of amyloid deposition and can be seen in up to 57% of patients[25]. The underlying cause is commonly mucosal lesions (amyloidoma ulcers,

erosions, polypoid lesions, hematomas or submucosal hemorrhage), vascular friability, or in some cases bowel ischemia[25,26]. Massive occult bleeding from the GI tract is usually seen with dialysis-related amyloidosis[27].

Malabsorption

May present with symptoms such as diarrhea, weight loss, steatorrhea, anorexia, or dizziness and is usually secondary to mucosal infiltration, pancreatic insufficiency, or bacterial overgrowth[28,29].

Protein-losing gastroenteropathy

GI specific manifestations include diarrhea, edema, and ascites. It is secondary to mucosal lesions which may lead to abnormal protein loss from the GI tract[30].

Chronic gastrointestinal dysmotility (Stasis syndrome)

May present with nausea, vomiting, dysphagia, gastroparesis, gastro-oesophageal reflux, loss of appetite, constipation, abdominal pain, bloating, or clinical features of chronic intestinal pseudo-obstruction[20,21,25]. Dysmotility can be secondary to myopathic and neuropathic dysfunction[25]. Some patients may present with persistent diarrhea due to rapid transit times secondary to dysmotility, intestinal inflammation and bacterial overgrowth[25,31,32].

Hepatic amyloidosis

Has no clinical significance in most patients due to mild clinical manifestations[33]. Hepatomegaly and mild elevations in alkaline phosphatase (ALP) are the most frequent findings[34]. Other symptoms include weight loss (72%), fatigue (60%), abdominal discomfort (53%) and anorexia (26%)[25]. Elevated direct serum bilirubin levels (> 2 mg/dL) are often associated with a poor prognosis[25,34].

Uncommon symptoms

Some patients with GI Amyloidosis may have features of cholangitis, pneumatosis intestinalis (gas pockets within the bowel wall), or bowel perforation[35-37].

The physical examination findings in patients with amyloidosis depend on the organ specific infiltration by abnormal proteins[9]. However, from a purely GI perspective, physical examination may reveal macroglossia (enlarged tongue) in up to 50% of the cases[25]. On abdominal examination, hepatosplenomegaly and ascites may be the most frequent findings[34,38].

ESTABLISHING THE DIAGNOSIS

A high degree of clinical suspicion is necessary to establish a definitive diagnosis of GI amyloidosis. Due to the rarity of the condition coupled with non-specific signs and symptoms at the time of presentation, these patients usually undergo extensive and unnecessary testing to identify the cause of clinical presentation. GI amyloidosis should be high on the list of possible differential diagnoses in patients presenting with non-specific GI symptoms and a past medical history of disorders commonly associated with amyloidosis, such as plasma cell dyscrasia, chronic renal failure on hemodialysis, and other chronic inflammatory conditions (*e.g.* rheumatoid arthritis and inflammatory bowel disease). A positive family history of amyloidosis should also alert the provider to suspect GI amyloidosis[9]. Laboratory investigations in these patients may reveal anaemia, mild elevations in ALP levels, elevations of acute phase reactants (due to the underlying chronic inflammatory condition) and deficiencies from malabsorption. Radiological investigations in GI amyloidosis are usually non-specific[39]. Some common features seen on computer tomography (CT) or magnetic resonance imaging (MRI) include[25,39-41]: (1) Diffuse or nodular wall thickening of the involved bowel segment; (2) Dilatation depending upon the degree of hypomotility; (3) Presence of fluid levels in dilated bowel loops; (4) Luminal narrowing secondary to amyloid infiltration or ischemia; (5) Attenuation due to cluster of calcifications or mucosal ulcerations; (6) Presence of polyploid protrusions or masses mimicking cancer; (7) Loss of haustrations; (8) Mesenteric thickening or adenopathy; and (9) Decreased hepatic attenuation with or without areas of calcification (Ultrasound may demonstrate heterogenic hepatic echotexture).

Although radiological investigations may provide a clue to the extent and area of involvement, the gold standard test to establish a diagnosis of GI amyloidosis is tissue

biopsy followed by CR staining and visualization under polarized light microscopy[42]. Based on the patients presenting symptom, an EGD or colonoscopy should be performed to obtain the biopsy specimen. As mentioned earlier, the site of highest diagnostic yield from biopsy specimen in the GI tract has been found to be the duodenum, followed by the stomach, colorectum, and the esophagus[6,15]. A liver biopsy may also be performed to confirm hepatic infiltration of the amyloid proteins; however, a transjugular route should be used to prevent fatal bleeding complications[43,44]. Additionally, the study by Yen *et al*[15] reported biopsy negative disease in 55% of the patients. However, these patients met the Rome IV criteria for several functional bowel disorders, but only 23.2% underwent additional diagnostic studies for functional assessment of the luminal gastrointestinal tract (such as esophageal or anorectal manometry, capsule endoscopy, or gastric emptying studies)[6]. Hence, the authors recommend the need for additional diagnostic studies to evaluate for motility disorders in patients with clinical features of GI amyloidosis but a negative result on biopsy.

Amyloid fibrils appear as amorphous, eosinophilic deposits on routine hematoxylin-eosin stained preparations, which may sometimes be confused with hyaline changes or sclerosis[45]. Hence, CR staining with the characteristic apple-green birefringence of CR-stained deposits under polarized light has been considered the gold standard for a definitive diagnosis since its inception[45]. However, despite a high sensitivity and specificity of the CR-staining method, false negative results may be seen due to the quantity of amyloid deposition in the tissue, the age of the deposits, thickness of the sections for visualization, fixation of the tissues on the slide, or the staining procedure itself[46]. Therefore, newer methods are being developed to act as an adjunct for diagnosis. Digitally reinforced hematoxylin-eosin polarization (DRHEP), a newly introduced technique which uses both routine light microscopy and digital photography, can detect weak birefringence which is not recognized through the microscope objective[45]. Although the use of DRHEP is currently limited to kidney biopsies, its role for GI amyloidosis is currently under investigation[45].

TREATMENT

Once the diagnosis of GI amyloidosis is established, the biopsy specimen needs further analysis to determine the subtype of amyloid deposition which can then help guide therapy[47]. The management of GI Amyloidosis includes:

Symptomatic management

Symptom control in patients with GI amyloidosis is tailored to the clinical presentation. In patients with symptoms of dysmotility (stasis syndrome), dietary modifications, adequate hydration, and the use of pro-kinetic and anti-emetic agents is advised. Dietary modification consists of frequent, small-volume liquid or homogenized foods with low soluble fibre and fat content along with additional nutritional supplementation when necessary[48]. Prokinetic agents such as metoclopramide, erythromycin or domperidone (if indicated) are the mainstay of therapy for dysmotility[48]. Parenteral nutrition is indicated in severe cases of chronic GI dysmotility. Patients with dysphagia may be successfully treated with balloon dilation[49]. For patients with diarrhea or bloating, anti-diarrheal agents such as loperamide should be initiated[50]. Empiric antibiotic therapy should be considered in patients with diarrhea and suspected bacterial overgrowth. In patients with severe diarrhea associated with protein-losing enteropathy, literature reports good response to corticosteroid and octreotide therapy[51,52]. The management for GI bleeding includes triage to appropriate settings, supportive measures, volume resuscitation if needed, and source control through ligation of the bleeding blood vessel. Surgical intervention may be necessary in cases of severe obstruction, uncontrolled GI hemorrhage or bowel ischemia[8,53]. Patients with macroglossia causing airway obstruction or obstructive sleep apnea may need partial resection of the tongue to alleviate symptoms[54].

Treatment of the underlying condition for systemic amyloidosis

No specific treatment protocols currently exist for the management of GI amyloidosis. Therapy varies significantly depending on the cause and type of amyloid protein deposited within the tissues (Table 3). The current management strategies based on the type of amyloid deposits available in literature include:

AL amyloidosis: The therapy is aimed at suppressing the production of monoclonal

Table 3 Management of gastrointestinal amyloidosis based on the amyloid protein

Gastrointestinal amyloidosis	AL amyloidosis	AA amyloidosis	Hereditary amyloidosis	Dialysis-related amyloidosis
Treatment strategy	Systemic: Eligible: Autologous stem cell transplantation (ASCT) for plasma cell dyscrasias. Non-eligible: No standard protocol; combination of Bortezomib, Melphalan and Dexamethasone has shown improved survival. Localized: Observation or localized surgical excision	Chronic inflammatory conditions: Biologics (anti-TNF antibodies, humanized anti-IL6 receptor antibody) and immunosuppressants. Familial mediterranean fever: Colchicine.	Liver production of transthyretin: Orthotopic liver transplantation (OLT). Disease modifying therapy: Transthyretin stabilizers (Tafamidis and Diflunisal), Doxycycline, Patisiran and Inotersen may be used on case-to-case basis	Prevention: Removal of plasmatic β2-microglobulin ($A\beta_2M$) through hemodialysis or peritoneal dialysis. Early renal transplant

immunoglobulin light chains through eradication of the malignant plasma cells[55]. Autologous stem cell transplantation is the standard of care for plasma cell dyscrasias in eligible patients[55]. For patients not eligible to receive autologous stem cell transplantation, the management guidelines are unclear; however, the use of combination therapy with Bortezomib, Melphalan and Dexamethasone has shown improved hematologic response rate and overall survival[56]. The addition of Daratumumab (human monoclonal antibody against CD38) to bortezomib-based therapy has been evaluated but the results are yet to be published[55]. Furthermore, a fully humanized monoclonal IgG1 anti-serum amyloid P component antibody (Dezamizumab) is also under evaluation for AL amyloidosis[57].

AA Amyloidosis: Therapy is specifically directed at controlling the underlying disease which in turn helps reduce the acute phase response and production of serum amyloid A protein. Colchicine is used in the treatment of patients with Familial Mediterranean Fever[58]. Biologic agents (activity against pro-inflammatory cytokines such as TNF-alpha, IL-1, and IL-6), cytotoxic agents and immunosuppressants have a key role to play in the management of underlying chronic inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, and psoriatic arthritis among others.

Hereditary amyloidosis: Therapy is aimed to eliminate the source of production of the genetically variant protein. The liver produces most of the circulating TTR in the body. Orthotopic liver transplantation can be used to significantly reduce the production of the mutant protein in patients where the liver is the culprit[59]. Other disease modifying therapies such as TTR Stabilizers (Tafamidis and Diflunisal), Doxycycline, Patisiran and Inotersen may also be considered on a case-to-case basis[59]

Dialysis-related amyloidosis: No medical or pharmacological therapy currently exists for dialysis-related amyloidosis[60]. The prevention and treatment consists of removal of plasmatic $A\beta_2M$ through hemodialysis or peritoneal dialysis using ultrapure dialysate or with more biocompatible and high-flux membranes[60]. Furthermore, early and successful renal transplantation leads to reduction in $A\beta_2M$ levels, which after a few years may lead to regression of the already deposited amyloid proteins[61].

Treatment of localized amyloidosis: It is characterized by deposition of AL amyloid restricted to the GI tract. For patients who are asymptomatic, no intervention may be needed, and observation may be the key; however, patients with recurrent or severe symptoms may require localized surgical excision.

Moreover, the treatment strategies for GI amyloidosis are consistently evolving with a better understanding of the disease pathology and the development of newer agents with target specific actions. Clinical trials to assess the efficacy and the toxicity profile of newer agents are currently ongoing and available at clinicaltrials.gov[62].

PROGNOSIS

The prognosis of GI amyloidosis depends on the extent of involvement of the GI tract, the quantity of deposition and the type of amyloid deposition. Literature reports that patients with AL amyloidosis and GI tract involvement had a worse prognosis than those without GI involvement[63]. Additionally, patients with GI amyloidosis had involvement of additional organs, an increased number of poor prognostic factors, and

a more advanced disease than those without the involvement of the GI tract[63]. Patients with AA amyloidosis were reported to have better median survival outcomes[64]. Involvement of the liver was associated with poor prognosis and increased mortality, particularly in patients with jaundice at the time of initial presentation and those with elevated direct serum bilirubin levels (> 2 mg/dL)[25,34].

CONCLUSION

Amyloidosis is characterised by the extracellular deposition of autologous fibrillar proteins aggregated into three-dimensional ß-pleated sheets aligned in an anti-parallel fashion. Based on the location of production of amyloidogenic precursor protein and its deposition in tissues, it can be divided into two distinct subtypes, systemic and localized amyloidosis. Involvement of the GI tract (GI amyloidosis) may be seen with both subtypes. Patients with GI amyloidosis commonly present with fatigue, light-headedness, anorexia, weight loss, GI bleeding, features of malabsorption, protein-losing enteropathy, or chronic GI dysmotility. Infiltration of amyloid proteins in the liver may also be seen, often presenting with hepatomegaly and mild elevations of ALP. Presence of jaundice with liver involvement (elevated direct bilirubin levels > 2 mg/dL) is associated with a poor prognosis. Radiological investigations are usually non-specific, and a definitive diagnosis is established with a tissue biopsy followed by CR-staining. The characteristic apple-green birefringence of the CR-stained deposits under polarized light is diagnostic. In patients with a negative biopsy from the GI tract, the authors recommend for the need of additional investigations for motility disorders and referral to a gastroenterologist. The use of DRHEP, a newly introduced technique, is also being explored to aid in diagnosis. For all patients with localized GI amyloidosis, the management consists of observation or localized surgical excision; however, for those with systemic GI amyloidosis, therapy is directed towards the underlying disease pathology. Symptomatic management in these patients is tailored to the presenting symptoms. The overall survival outcome depends on the extent of involvement of the GI tract, the quantity, and type of amyloid deposition.

REFERENCES

1 **Campistol JM**, Amiloidosis En, Rozman C, Cardellach F. Farreras/Rozman, Medicina Interna. 16ª ed. Barcelona: Elsevier España; 2009: 1147-1150

2 **Real de Asúa D**, Costa R, Galván JM, Filigheddu MT, Trujillo D, Cadiñanos J. Systemic AA amyloidosis: epidemiology, diagnosis, and management. *Clin Epidemiol* 2014; **6**: 369-377 [PMID: 25378951 DOI: 10.2147/CLEP.S39981]

3 **Sattianayagam PT**, Hawkins PN, Gillmore JD. Systemic amyloidosis and the gastrointestinal tract. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 608-617 [PMID: 19724253 DOI: 10.1038/nrgastro.2009.147]

4 **Bustamante JG**, Zaidi SRH. Amyloidosis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020 January. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470285/

5 **Merlini G**, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med* 2003; **349**: 583-596 [PMID: 12904524 DOI: 10.1056/NEJMra023144]

6 **Cowan AJ**, Skinner M, Seldin DC, Berk JL, Lichtenstein DR, O'Hara CJ, Doros G, Sanchorawala V. Amyloidosis of the gastrointestinal tract: a 13-year, single-center, referral experience. *Haematologica* 2013; **98**: 141-146 [PMID: 22733017 DOI: 10.3324/haematol.2012.068155]

7 **Sipe JD**, Benson MD, Buxbaum JN, Ikeda S, Merlini G, Saraiva MJ, Westermark P. Amyloid fibril protein nomenclature: 2010 recommendations from the nomenclature committee of the International Society of Amyloidosis. *Amyloid* 2010; **17**: 101-104 [PMID: 21039326 DOI: 10.3109/13506129.2010.526812]

8 **Baker KR**, Rice L. The amyloidoses: clinical features, diagnosis and treatment. *Methodist Debakey Cardiovasc J* 2012; **8**: 3-7 [PMID: 23227278 DOI: 10.14797/mdcj-8-3-3]

9 **Rowe K**, Pankow J, Nehme F, Salyers W. Gastrointestinal Amyloidosis: Review of the Literature. *Cureus* 2017; **9**: e1228 [PMID: 28611935 DOI: 10.7759/cureus.1228]

10 **Pinney JH**, Smith CJ, Taube JB, Lachmann HJ, Venner CP, Gibbs SD, Dungu J, Banypersad SM, Wechalekar AD, Whelan CJ, Hawkins PN, Gillmore JD. Systemic amyloidosis in England: an epidemiological study. *Br J Haematol* 2013; **161**: 525-532 [PMID: 23480608 DOI: 10.1111/bjh.12286]

11 **Hemminki K**, Li X, Försti A, Sundquist J, Sundquist K. Incidence and survival in non-hereditary amyloidosis in Sweden. *BMC Public Health* 2012; **12**: 974 [PMID: 23148499 DOI: 10.1186/1471-2458-12-974]

12 **Quock TP**, Yan T, Chang E, Guthrie S, Broder MS. Epidemiology of AL amyloidosis: a real-world study using US claims data. *Blood Adv* 2018; **2**: 1046-1053 [PMID: 29748430 DOI:

10.1182/bloodadvances.2018016402]
13 **Alexander KM**, Orav J, Singh A, Jacob SA, Menon A, Padera RF, Kijewski MF, Liao R, Di Carli MF, Laubach JP, Falk RH, Dorbala S. Geographic Disparities in Reported US Amyloidosis Mortality From 1979 to 2015: Potential Underdetection of Cardiac Amyloidosis. *JAMA Cardiol* 2018; **3**: 865-870 [PMID: 30046835 DOI: 10.1001/jamacardio.2018.2093]
14 **Gertz MA**, Comenzo R, Falk RH, Fermand JP, Hazenberg BP, Hawkins PN, Merlini G, Moreau P, Ronco P, Sanchorawala V, Sezer O, Solomon A, Grateau G. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. *Am J Hematol* 2005; **79**: 319-328 [PMID: 16044444 DOI: 10.1002/ajh.20381]
15 **Yen T**, Chen FW, Witteles RM, Liedtke M, Nguyen LA. Clinical implications of gastrointestinal symptoms in systemic amyloidosis. *Neurogastroenterol Motil* 2018; **30**: e13229 [PMID: 29024324 DOI: 10.1111/nmo.13229]
16 **Nordling E**, Abraham-Nordling M. Colonic amyloidosis, computational analysis of the major amyloidogenic species, Serum Amyloid A. *Comput Biol Chem* 2012; **39**: 29-34 [PMID: 22885776 DOI: 10.1016/j.compbiolchem.2012.06.005]
17 **Tada S**, Iida M, Iwashita A, Matsui T, Fuchigami T, Yamamoto T, Yao T, Fujishima M. Endoscopic and biopsy findings of the upper digestive tract in patients with amyloidosis. *Gastrointest Endosc* 1990; **36**: 10-14 [PMID: 2311879 DOI: 10.1016/s0016-5107(90)70913-3]
18 **Tada S**, Iida M, Yao T, Kawakubo K, Yao T, Okada M, Fujishima M. Endoscopic features in amyloidosis of the small intestine: clinical and morphologic differences between chemical types of amyloid protein. *Gastrointest Endosc* 1994; **40**: 45-50 [PMID: 8163134 DOI: 10.1016/s0016-5107(94)70008-7]
19 **Jimenez RE**, Price DA, Pinkus GS, Owen WF Jr, Lazarus JM, Kay J, Turner JR. Development of gastrointestinal beta2-microglobulin amyloidosis correlates with time on dialysis. *Am J Surg Pathol* 1998; **22**: 729-735 [PMID: 9630180 DOI: 10.1097/00000478-199806000-00010]
20 **Battle WM**, Rubin MR, Cohen S, Snape WJ Jr. Gastrointestinal-motility dysfunction in amyloidosis. *N Engl J Med* 1979; **301**: 24-25 [PMID: 221808 DOI: 10.1056/NEJM197907053010105]
21 **Tada S**, Iida M, Yao T, Kitamoto T, Yao T, Fujishima M. Intestinal pseudo-obstruction in patients with amyloidosis: clinicopathologic differences between chemical types of amyloid protein. *Gut* 1993; **34**: 1412-1417 [PMID: 8244111 DOI: 10.1136/gut.34.10.1412]
22 **Hirschfield GM**. Amyloidosis: a clinico-pathophysiological synopsis. *Semin Cell Dev Biol* 2004; **15**: 39-44 [PMID: 15036205 DOI: 10.1016/j.semcdb.2003.12.013]
23 **Matsuda S**, Motosugi U, Kato R, Muraoka M, Suzuki Y, Sato M, Shindo K, Nakayama Y, Inoue T, Maekawa S, Sakamoto M, Enomoto N. Hepatic Amyloidosis with an Extremely High Stiffness Value on Magnetic Resonance Elastography. *Magn Reson Med Sci* 2016; **15**: 251-252 [PMID: 27001387 DOI: 10.2463/mrms.ci.2015-0133]
24 **Gertz MA**, Lacy MQ, Dispenzieri A. Amyloidosis. *Hematol Oncol Clin North Am* 1999; **13**: 1211-1233, ix [PMID: 10626146 DOI: 10.1016/s0889-8588(05)70122-2]
25 **Petre S**, Shah IA, Gilani N. Review article: gastrointestinal amyloidosis - clinical features, diagnosis and therapy. *Aliment Pharmacol Ther* 2008; **27**: 1006-1016 [PMID: 18363891 DOI: 10.1111/j.1365-2036.2008.03682.x]
26 **Chang HS**, Myung SJ, Yang SK, Jung HY, Lee GH, Hong WS, Kim JH, Min YI, Kim HC, Ha HK, Kim JS. Massive small bowel bleeding in a patient with amyloidosis. *Gastrointest Endosc* 2004; **59**: 126-129 [PMID: 14722567 DOI: 10.1016/s0016-5107(03)02352-6]
27 **Maher ER**, Dutoit SH, Baillod RA, Sweny P, Moorhead JF. Gastrointestinal complications of dialysis related amyloidosis. *BMJ* 1988; **297**: 265-266 [PMID: 3416145 DOI: 10.1136/bmj.297.6643.265]
28 **Madsen LG**, Gimsing P, Schiødt FV. Primary (AL) amyloidosis with gastrointestinal involvement. *Scand J Gastroenterol* 2009; **44**: 708-711 [PMID: 19242859 DOI: 10.1080/00365520902783717]
29 **Hayman SR**, Lacy MQ, Kyle RA, Gertz MA. Primary systemic amyloidosis: a cause of malabsorption syndrome. *Am J Med* 2001; **111**: 535-540 [PMID: 11705429 DOI: 10.1016/s0002-9343(01)00919-6]
30 **Suzuki C**, Higaki S, Nishiaki M, Mitani N, Yanai H, Tada M, Okita K. 99mTc-HSA-D scintigraphy in the diagnosis of protein-losing gastroenteropathy due to secondary amyloidosis. *J Gastroenterol* 1997; **32**: 78-82 [PMID: 9058299 DOI: 10.1007/BF01213300]
31 **Guirl MJ**, Högenauer C, Santa Ana CA, Porter JL, Little KH, Stone MJ, Fordtran JS. Rapid intestinal transit as a primary cause of severe chronic diarrhea in patients with amyloidosis. *Am J Gastroenterol* 2003; **98**: 2219-2225 [PMID: 14572571 DOI: 10.1111/j.1572-0241.2003.07695.x]
32 **Okuda Y**, Takasugi K, Oyama T, Oyama H, Nanba S, Miyamoto T. Intractable diarrhoea associated with secondary amyloidosis in rheumatoid arthritis. *Ann Rheum Dis* 1997; **56**: 535-541 [PMID: 9370878 DOI: 10.1136/ard.56.9.535]
33 **Buck FS**, Koss MN. Hepatic amyloidosis: morphologic differences between systemic AL and AA types. *Hum Pathol* 1991; **22**: 904-907 [PMID: 1916751 DOI: 10.1016/0046-8177(91)90180-w]
34 **Gertz MA**, Kyle RA. Hepatic amyloidosis (primary [AL], immunoglobulin light chain): the natural history in 80 patients. *Am J Med* 1988; **85**: 73-80 [PMID: 3389383 DOI: 10.1016/0002-9343(88)90505-0]
35 **Yoshiki Y**, Yamamoto G, Takazawa Y, Nannya Y, Ishida J, Nagai R, Fukayama M, Kurokawa M. AL amyloidosis with severe gastrointestinal invasion and acute obstructive suppurative cholangitis.

Ann Hematol 2012; **91**: 467-468 [PMID: 21643678 DOI: 10.1007/s00277-011-1271-7]

36 **Raghunathan V**, Louis D, Wirk B. Gastrointestinal Tract Amyloidosis Presenting With Pneumatosis Intestinalis. *J Clin Med Res* 2017; **9**: 654-658 [PMID: 28611868 DOI: 10.14740/jocmr2957w]

37 **Shaulov A**, Avivi I, Cohen Y, Duek A, Leiba M, Gatt ME. Gastrointestinal perforation in light chain amyloidosis in the era of novel agent therapy - a case series and review of the literature. *Amyloid* 2018; **25**: 11-17 [PMID: 29241368 DOI: 10.1080/13506129.2017.1416350]

38 **Levy M**, Polliack A, Lender M, Eliakim M. The liver in amyloidosis. *Digestion* 1974; **10**: 40-51 [PMID: 4847635 DOI: 10.1159/000197521]

39 **Kim SH**, Han JK, Lee KH, Won HJ, Kim KW, Kim JS, Park CH, Choi BI. Abdominal amyloidosis: spectrum of radiological findings. *Clin Radiol* 2003; **58**: 610-620 [PMID: 12887954 DOI: 10.1016/s0009-9260(03)00142-9]

40 **Özcan HN**, Haliloğlu M, Sökmensüer C, Akata D, Özmen M, Karçaaltıncaba M. Imaging for abdominal involvement in amyloidosis. *Diagn Interv Radiol* 2017; **23**: 282-285 [PMID: 28498108 DOI: 10.5152/dir.2017.16484]

41 **Araoz PA**, Batts KP, MacCarty RL. Amyloidosis of the alimentary canal: radiologic-pathologic correlation of CT findings. *Abdom Imaging* 2000; **25**: 38-44 [PMID: 10652919 DOI: 10.1007/s002619910007]

42 **Kyle RA**. Amyloidosis: a convoluted story. *Br J Haematol* 2001; **114**: 529-538 [PMID: 11552976 DOI: 10.1046/j.1365-2141.2001.02999.x]

43 **LEVINE RA**. Amyloid disease of the liver. Correlation of clinical, functional and morphologic features in forty-seven patients. *Am J Med* 1962; **33**: 349-357 [PMID: 14464647 DOI: 10.1016/0002-9343(62)90231-0]

44 **Vrana JA**, Theis JD, Dasari S, Mereuta OM, Dispenzieri A, Zeldenrust SR, Gertz MA, Kurtin PJ, Grogg KL, Dogan A. Clinical diagnosis and typing of systemic amyloidosis in subcutaneous fat aspirates by mass spectrometry-based proteomics. *Haematologica* 2014; **99**: 1239-1247 [PMID: 24747948 DOI: 10.3324/haematol.2013.102764]

45 **Doganavsargil B**, Buberal GE, Toz H, Sarsik B, Pehlivanoglu B, Sezak M, Sen S. Digitally reinforced hematoxylin-eosin polarization technique in diagnosis of rectal amyloidosis. *World J Gastroenterol* 2015; **21**: 1827-1837 [PMID: 25684948 DOI: 10.3748/wjg.v21.i6.1827]

46 **Puchtler H**, Sweat F, Levine M. On the binding of congo red by amyloid. *J Histochem Cytochem* 1962; **10**: 355-364 [DOI: 10.1177/10.3.355]

47 **Gillmore JD**, Wechalekar A, Bird J, Cavenagh J, Hawkins S, Kazmi M, Lachmann HJ, Hawkins PN, Pratt G; BCSH Committee. Guidelines on the diagnosis and investigation of AL amyloidosis. *Br J Haematol* 2015; **168**: 207-218 [PMID: 25312307 DOI: 10.1111/bjh.13156]

48 **Obici L**, Suhr OB. Diagnosis and treatment of gastrointestinal dysfunction in hereditary TTR amyloidosis. *Clin Auton Res* 2019; **29**: 55-63 [PMID: 31452022 DOI: 10.1007/s10286-019-00628-6]

49 **Costigan DJ**, Clouse RE. Achalasia-like esophagus from amyloidosis. Successful treatment with pneumatic bag dilatation. *Dig Dis Sci* 1983; **28**: 763-765 [PMID: 6872809 DOI: 10.1007/BF01312569]

50 **Wang C**, Li Y, Jin Y, Zhou W, Zhu Y, Yao F, Qian J. Chronic diarrhea as the presenting feature of primary systemic AL amyloidosis: serendipity or delayed diagnosis? *BMC Gastroenterol* 2013; **13**: 71 [PMID: 23617890 DOI: 10.1186/1471-230X-13-71]

51 **Fushimi T**, Takahashi Y, Kashima Y, Fukushima K, Ishii W, Kaneko K, Yazaki M, Nakamura A, Tokuda T, Matsuda M, Furuya R, Ikeda S. Severe protein losing enteropathy with intractable diarrhea due to systemic AA amyloidosis, successfully treated with corticosteroid and octreotide. *Amyloid* 2005; **12**: 48-53 [PMID: 16076611 DOI: 10.1080/13506120500032725]

52 **Shin JK**, Jung YH, Bae MN, Baek IW, Kim KJ, Cho CS. Successful treatment of protein-losing enteropathy due to AA amyloidosis with octreotide in a patient with rheumatoid arthritis. *Mod Rheumatol* 2013; **23**: 406-411 [PMID: 22815005 DOI: 10.1007/s10165-012-0675-0]

53 **Rives S**, Pera M, Rosiñol L, Vidal O, Miquel R, Solé M, García-Valdecasas J, Bladé J. Primary systemic amyloidosis presenting as a colonic stricture: successful treatment with left hemicolectomy followed by autologous hematopoietic stem-cell transplantation: report of a case. *Dis Colon Rectum* 2002; **45**: 1263-1266 [PMID: 12352247 DOI: 10.1007/s10350-004-6403-x]

54 **Jacobs P**, Sellars S, King HS. Massive macroglossia, amyloidosis and myeloma. *Postgrad Med J* 1988; **64**: 696-698 [PMID: 3150784 DOI: 10.1136/pgmj.64.755.696]

55 **Koh Y**. AL amyloidosis: advances in diagnosis and management. *Blood Res* 2020; **55**: S54-S57 [PMID: 32719177 DOI: 10.5045/br.2020.S009]

56 **Kastritis E**, Leleu X, Arnulf B, Zamagni E, Cibeira MT, Kwok F, Mollee P, Hájek R, Moreau P, Jaccard A, Schönland SO, Filshie R, Nicolas-Virelizier E, Augustson B, Mateos MV, Wechalekar A, Hachulla E, Milani P, Dimopoulos MA, Fermand JP, Foli A, Gavriatopoulou M, Klersy C, Palumbo A, Sonneveld P, Johnsen HE, Merlini G, Palladini G. Bortezomib, Melphalan, and Dexamethasone for Light-Chain Amyloidosis. *J Clin Oncol* 2020; **38**: 3252-3260 [PMID: 32730181 DOI: 10.1200/JCO.20.01285]

57 **Zhang KW**, Stockerl-Goldstein KE, Lenihan DJ. Emerging Therapeutics for the Treatment of Light Chain and Transthyretin Amyloidosis. *JACC Basic Transl Sci* 2019; **4**: 438-448 [PMID: 31312767 DOI: 10.1016/j.jacbts.2019.02.002]

58 **Nakamura N**, Fujita T, Murakami R, Kumasaka R, Shimada M, Shimaya Y, Osawa H, Yamabe H, Okumura K, Yachie A. A case of familial Mediterranean fever-associated systemic amyloidosis. *CEN Case Rep* 2012; **1**: 4-6 [PMID: 28509144 DOI: 10.1007/s13730-011-0002-1]

59 **Kapoor M**, Rossor AM, Laura M, Reilly MM. Clinical Presentation, Diagnosis and Treatment of TTR Amyloidosis. *J Neuromuscul Dis* 2019; **6**: 189-199 [PMID: 30829617 DOI: 10.3233/JND-180371]

60 **Scarpioni R**, Ricardi M, Albertazzi V, De Amicis S, Rastelli F, Zerbini L. Dialysis-related amyloidosis: challenges and solutions. *Int J Nephrol Renovasc Dis* 2016; **9**: 319-328 [PMID: 27994478 DOI: 10.2147/IJNRD.S84784]

61 **Campistol JM**. Dialysis-related amyloidosis after renal transplantation. *Semin Dial* 2001; **14**: 99-102 [PMID: 11264775 DOI: 10.1046/j.1525-139x.2001.00038.x]

62 **Oncopeptides AB**. A Clinical Study of Melphalan Flufenamide (Melflufen) and Dexamethasone for Patients with Immunoglobulin Light Chain (AL) Amyloidosis. Available from: https://www.clinicaltrials.gov/ct2/results?cond=Amyloidosis

63 **Lim AY**, Lee JH, Jung KS, Gwag HB, Kim DH, Kim SJ, Lee GY, Kim JS, Kim HJ, Lee SY, Lee JE, Jeon ES, Kim K. Clinical features and outcomes of systemic amyloidosis with gastrointestinal involvement: a single-center experience. *Korean J Intern Med* 2015; **30**: 496-505 [PMID: 26161016 DOI: 10.3904/kjim.2015.30.4.496]

64 **Lachmann HJ**, Goodman HJ, Gilbertson JA, Gallimore JR, Sabin CA, Gillmore JD, Hawkins PN. Natural history and outcome in systemic AA amyloidosis. *N Engl J Med* 2007; **356**: 2361-2371 [PMID: 17554117 DOI: 10.1056/NEJMoa070265]

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