# Gastrointestinal Amyloidosis: Diagnostic Approach and Treatment

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## ABSTRACT

*Amyloidosis is a disease marked by deposition of misfolded proteins, known as amyloids, in the extracellular space, including gastrointestinal tract. According to the precursor protein, amyloidosis is classified into six types; all of which can be involved in the gastrointestinal tract. Amyloidosis has weight loss and gastrointestinal bleeding as the most frequent symptoms. Gastrointestinal tract biopsy is diagnostic in most cases of amyloidosis and Congo red stain is used to confirm the amyloid proteins deposit. Treatment of amyloidosis consists of controlling symptoms, terminating protein formation and deposit, and treating the underlying diseases. Chemotherapy might be applied depends on the type of amyloidosis.*

***Keywords:*** *amyloidosis, diagnostic, treatment*

## ABSTRAK

*Amiloidosis adalah suatu penyakit yang ditandai oleh penumpukan protein yang mengalami kesalahan pelipatan, yakni amiloid, di ruang ekstraselular, termasuk di saluran cerna. Berdasarkan protein prekursor, amiloidosis dibagi menjadi enam tipe, dimana setiap tipe tersebut dapat terlibat dalam saluran cerna. Penurunan berat badan dan perdarahan saluran cerna merupakan gejala klinis amiloidosis tersering. Biopsi saluran cerna bersifat diagnostik pada kebanyakan kasus amiloidosis dan pewarnaan Congo merah digunakan untuk memastikan adanya penimbunan protein amiloid. Tatalaksana amiloidosis terdiri dari pengontrolan gejala, penghentian pembentukan dan penimbunan protein, dan pengobatan dari penyakit yang mendasari. Kemoterapi dapat digunakan tergantung pada tipe amiloidosis.*

***Kata kunci:*** *amiloidosis, diagnosis, tatalaksana*

## INTRODUCTION

Amyloidosis is a pathologic process caused by deposit of fibrillar amyloid protein in the extracellular space.[1] Amyloid protein has antiparallel ß-pleated sheet configuration and can be identified in biopsy specimen using electron microscope or red Congo stain or thioflavine T.[2] Amyloidosis can occur in various organs, such as heart, kidney, nerve, or gastrointestinal tract.[1,2]

The worldwide yearly incidence of amyloidosis is 0.5-1.3/100,000 people with distribution as follow: 80% primary amyloidosis, 5-10% hereditary amyloidosis,

2-3% secondary amyloidosis, 2% senile amyloidosis, and 8% localized amyloidosis. Sixty percent of primary amyloidosis patients are 50 to 70 years old patients. Secondary amyloidosis is more common in women, probably due to rheumatoid arthritis disease is more common in women.[7]

The frequency of gastrointestinal tract involvement varies with the type of amyloidosis. Gastrointestinal involvement is 55% in patient with secondary amyloidosis and 70% in patient with primary amyloidosis.[3] Only 10-20% of gastrointestinal amyloidosis are localized.[8] In other recent research, within 60 systemic amyloidosis cases, 50 (83%) cases are primary amyloidosis, 5 (8%) cases are hereditary amyloidosis with precursor protein, and 5 (8%) cases are senile amyloidosis.[9]

## AMYLOIDOSIS CLASSIFICATION

Amyloid protein is a transformed low molecular weight protein. According to the precursor protein, amyloidosis is divided into 6 types. Amyloidosis nomenclature starts with letter "A" (for amyloid), followed by precursor protein description.[3] The types of amyloidosis are as follow:

**Primary amyloidosis or AL**

The precursor proteins are light-chain monoclonal immunoglobulins (κ and λ). Amyloidosis can occur individually or coincidently with plasm cell malignancy, such as multiple myeloma or waldenstorm macroglobulinemia.[2,3]

**Secondary/reactive amyloidosisor AA**

The precursor protein are acute-phase serum amyloid A proteins (A-SAAs), secreted during acute phase of inflammation. This amyloidosis occurred in diseases with high level of acute-phase reactant, such as inflammatory diseases. Forty eight percent of AA patients have rheumatoid arthritis; in contrary, the incidence of amyloidosis in rheumatoid arthritis is 7-21%. AA may also occur in other inflammatory diseases, such as: Crohn's disease, ankylosing spondylitis, Reiter syndrome, psoriasis, progresive systemic sclerosis, primary biliary cirrhosis, systemic lupus erythematosus, or chronic infection (tuberculosis, syphilis, pyelonephritis, osteomyelitis, parasite infection).[3,4]

**Amyloidosis associated with hemodialysis**

Precursor protein is ß2 microglobulin, which is a molecular component of class I MHC in all nucleated cells. ß2 microglobulin is detained in the circulation due to decrease renal function of excretion, then transformed into amyloid protein. ß2 microglobulin just able be cleared by the kidney and cannot pass through dialysis membrane. The symptoms usually happen after 5 years.[3,5]

**Hereditary amyloidosis**

Precursor protein is an abnormal protein due to gen mutation.The most common type of this amyloidosis is ATTR (precursor protein is abnormal transthyretin) and AFib (precursor protein is abnormal αfibrinogen chain). The mutation can occurred in gen encoding apolipoprotein AI and lysozyme.[3,6]

**Senile amyloidosis**

Precursor protein is transthyretin, which is not abnormal inherited transthyretin. This amyloidosis mainly found in patients aged over 80 years. The protein deposition is in the heart or gastrointestinal tract.[3,6]

**Localized amyloidosis**

Precursor protein is hormonal or pro-hormonal protein. This amyloidosis is in the malignancy producing hormonal or pro-hormonal protein such as medullary thyroid carcinoma, prolactinoma, or insulinoma.[6,7]

## PATHOGENESIS OF AMYLOIDOSIS

Precursor protein is stimulated to be transformed into amyloid protein due to high level in serum or gene mutation which is prone to misfolding.There are also protein having intrinsic tendency to be amyloid protein with slower late, such as transthyretin in senile amyloidosis. Once stimulated protein interacts with extracellular environment, proteolysis might occur and it binds to matrix component (glycosaminoglycan and collagen), facilitating aggregation into fibrilar amyloid protein. In this mechanism, extracellular chaperone protein act to prevent aggregation and serum P amyloid will bind to amyloid protein and protect it from reabsorption[10]

The amyloid protein will result in cell injury, tissue damage, and organ dysfunction through mechanism that is not fully understood. The damage might be due to direct precursor protein before being amyloid protein (e.g. light chain immunoglobulin) or after being amyloid protein deposit.[10] In gastrointestinal amyloid, the amyloid protein can infiltrate either mucosa or neuromuscular structure. Mucosal infiltration most commoly occur in the descendent part of duodenum (100%), stomach and colorectum (more than 90%), and esophagus (around 70%).[11]Blood vessel is usually

affected in the small bowel. Occlusion of the vessel will result in bowel ischemia and infarct.[3,11]

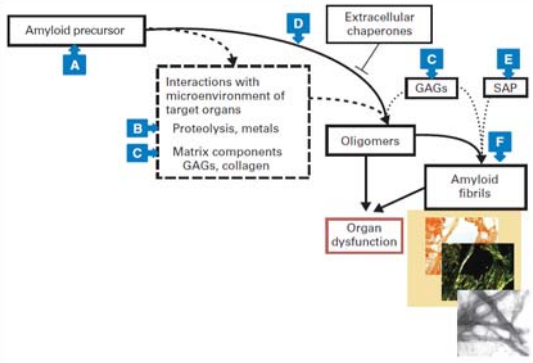


**Figure 1. Pathogenesis of amyloidosis[10]**

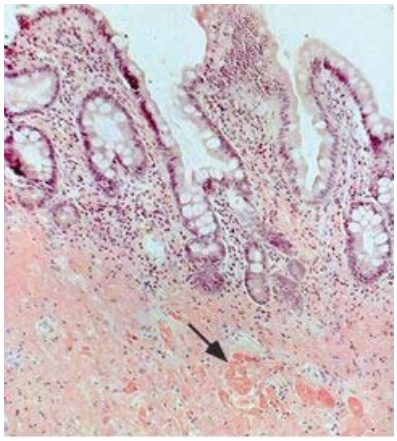

**Figure 2. Biopsy result of duodenum mucosa endoscopy using red Congo stain – arrow: positive staining at lamina propria and blood vessel[11]**

Neuromuscular infiltration starts with nerve infiltration, resulting in contraction abnormality with normal amplitude and uncoordinated frequency. As the disease progresses, the muscle is infiltrated, leading to muscle atrophy and decreased in contraction amplitude. Therefore, the bowel transit time is longer. Although there is no study in gastrointestinal motility in amyloidosis patient available at present, neuromuscular infiltration usually induces stasis syndrome.[3,12,13]

The level of nerve and muscle infiltration varies depend on the type of amyloidosis. One study evaluated 16 patients having amyloidosis and intestinal pseudo obstruction (13 AA, 2 AL,1 dialysis associated amyloidosis). Patients with AA had tendency of having amyloid protein deposit in Auerbach plexus without muscle infiltration, while other patients had diffuse and extensive infiltration of muscle layer along the gastrointestinal tract. The etiology of this finding is still unknown.[13]

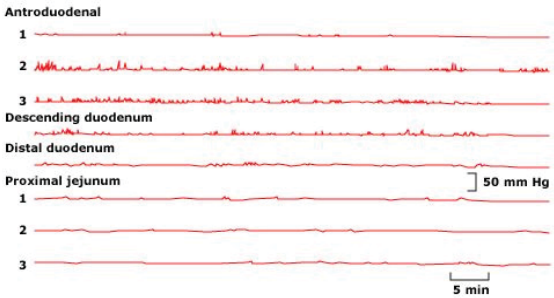


**Figure 3. Gastrointestinal manometry in 60-year primary amyloidosis patient – low amplitude of contraction in all level[12]**

## CLINICAL MANIFESTATION

A symptomatic gastrointestinal amyloidosis patient usually come with one of these four syndomes: (1) Gastrointestinal hemorrhage due to fragile blood vessel or mucosal lesion; (2) Chronic intestinal dismotility due to infiltration of smooth muscle in the gastrointestinal tract. The clinical manifestation consists of dysphagia, gastroparesis, constipation, or chronic intestinal pseudo obstruction. Dysmotility causing shortening of intestinal transit time might also cause diarrhea; (3) Malabsorption due to neuromuscular infiltration, ischemia, bacterial overgrowth, pancreatic insuffieciency (amyloid protein infiltration in blood vessel or pancreatic acini tissue). This syndrome is found in 8.5% AL patient and 23% AA patient. The clinical manifestation consists of weight loss, diarrhea, steatorrhea, anorexia, hypotension or orthostatic changes; (4) Gastroenteropathy with protein loss with edema as the clinical manifestation.[3,8,14]

The most frequent clinical manifestation in all patients are weigh loss (45%) and gastrointestinal bleeding (36%).[6,14] Esophageal disease in amyloidosis has symptoms such as dysphagia, chest pain, heart burn, and hematemesis. The most common radiography finding are atony and widening esophagus with decreased peristaltic, sometimes with narrowing in the distal part and widening in the proximal part, linked with tracheobronchial aspiration. Less common finding is ulcer or mass. Various manometry abnormality can bee seen in esophagus. Frequent manometry abnormality can be seen in the esophagus. The pressure of lower esophageal sphincter is usually normal or low, and accompanied with heart burn. The prevalence of esophageal amyloidosis varies from 13% in a radiology study to 22% in an autopsy report.[6]

In amyloidosis patient, stomach involvement occur in 8% of patients according to biopsy and 12% of patients according to autopsy, with only 1% of patients are symptomatic. The symptoms of stomach involvement are nausea, vomiting, hematemesis, and epigastric pain. Obstruction of gastric outlet, thickening of gastric fold, gastric ulcer, hematoma, artery vein malformation, granular appearance of mucosa, plaque-like lesion, and gastroparesis can occur infrequently.[6] Stomach amyloidosis may also manifest as gastric perforation, gastro-colon fistula, and gastric malignancy.[15]

The most common site of amyloid deposit is in the small intestine, which is 31% of patients according to autopsy. Patient with small intestine amyloid might come with diarrhea, steatorrhea, protein loss, bleeding, obstruction, infarct, perforation, intussusception, intestinal pneumatosis, and constipation. Some amyloid patients may also have malabsorption symptom.[6,16] Clinical manifestation of amyloid deposit in colon can resemble other diseases including inflammatory bowel disease, malignancy, ischemic colon, and collagenous colitis. The complications are colon dilatation, pseudo obstruction, stricture formation, rectal bleeding, submucosal bleeding, volvulus, infarct, and perforation.[6,14]

## DIAGNOSIS OF GASTROINTESTINAL AMYLOIDOSIS

Diagnosis of gastrointestinal amyloidosis is quite difficult. Gastrointestinal amyloidosis is suspected in the following conditions: (1) Patient having disease which is known associated with amyloidosis, such as: multiple myeloma, chronic inflammation disease, chronic kidney failure on hemodialysis treatment; (2) Patient having organ disorder typically for accumulation of amyloid protein, such as: nephritic syndrome, unexplained heart failure, carpal tunnel syndrome, joint inflammation in dialysis patient.

Since AL is the most frequent etiology of gastrointestinal amyloidosis, it is suggested that initial examination includes light chain immunoglobulin examination. This, can be done through urine or serum protein electrophoresis, urine or serum immunofixation, or serum light chain immune nephelometry method. Using these 3 methods of examination will yield 99% of sensitivity.[15] Bone marrow aspiration and biopsy might be performed to look for plasm cell malignancy if AL is suspected in negative urine and serum protein electrophoresis.[16]

Endoscopic biopsy of gastrointestinal tract is diagnostic in most cases of amyloidosis. The highest degree of amyloid protein deposit over all of gastrointestinal tract is in the duodenum. Various mucosal abnormalities are found in endoscopy of gastrointestinal tract. Lesion may appear as fine granular, mucosal granular and nodular, polypoid protrusion, erosion, ulceration, fragile mucosa and thickening of bowel wall. Macroscopically, AL usually has polypoid protrusion while AA has granular mucosa.[17] Some patients have deposit of amyloid protein forming a tumor called amyloidoma. Amyloidoma can be found at anywhere in the gastrointestinal tract. Focal amyloidoma in duodenum and jejunum have ever been described as extensive deposit of amyloid involving all layers of the bowel wall.[18]

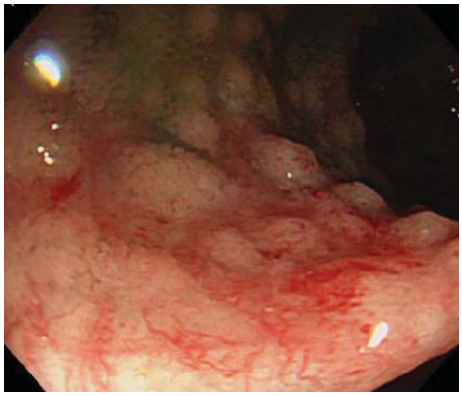

**Figure 4. Granular and nodular lesion in the duodenum. The mucosa is fragile and easily bleed.[6]**

Confirmation of amyloid protein deposit in the biopsy specimen can be done using Conge red staining. Direct fast scarlet staining can show typical red appearance in normal lighting and birefringens green apple in light polarization. Both indicate a prominent mucosal deposit of amyloid.[6] The biopsy must be deep enough (especially for AL) in order to acquire the lamina propria layer since birefringens is best identified at blood vessel wall.[16]

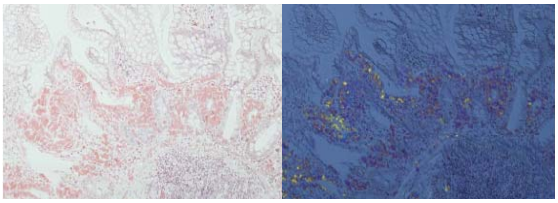

**Figure 5. Direct fast scarlet staining shows a typical red appearance in normal lighting (left) and birefringens green apple in light polarization (right)[6]**

To get overall image of amyloid deposit in the body, serum amyloid P with $I^{123}$ label can be injected into the circulation. It binds with body fibrilar amyloid protein. The sensitivity of this scintigraphy diagnostic is 90% for AA and AL.[6]

Radiography examination using Barium has limited diagnostic value due to unspecific finding for amyloidosis, such as: (1) AA: coarse mucosal pattern with fine granular elevation mostly due to expansion of lamina propria due to deposition of amyloid protein; (2) AL: polypoid protrusion and thick folding which reflect massive amyloid protein deposit in the smoot muscle layer; (3) Amyloid associated with dialysis: small bowel and colon dilatation due to smooth muscle deposit of amyloid protein causing prolonged transit time.[19]

Proper classification is an important thing. Systemic chemotherapy can effectively treat AL patient. Localized amyloidosis does not require systemic therapy due to good long term prognosis.[15] Organ such as bone marrow, kidney, heart, intestine, lung, and joint are almost involved in the systemic amyloidosis. Therefore, systemic amyloidosis can be excluded if no amyloid protein deposit found in organ biopsy. Moreover, to diagnose localized amyloidosis, paraproteinemia is best to be excluded through immunofixation.[8]

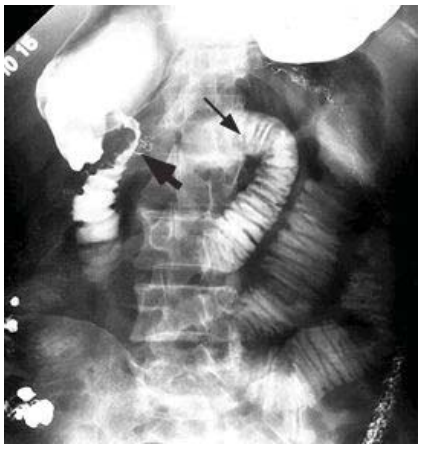

**Figure 6. Non-specific small intestine loop dilatation (thin arrow) and stricture at duodenal loop (thick arrow) in AA patient[19]**

## TREATMENT OF AMYLOIDOSIS

Gastrointestinal complication can cause significant pain but usually will not cause death. Mortality is more common due to kidney failure, restrictive cardiomyopathy, or ischemic heart disease. The principle of management of amyloidosis should be directed at controlling gastrointestinal symptoms using symptomatic therapy, stopping the formation and deposit of amyloid protein, and treating the

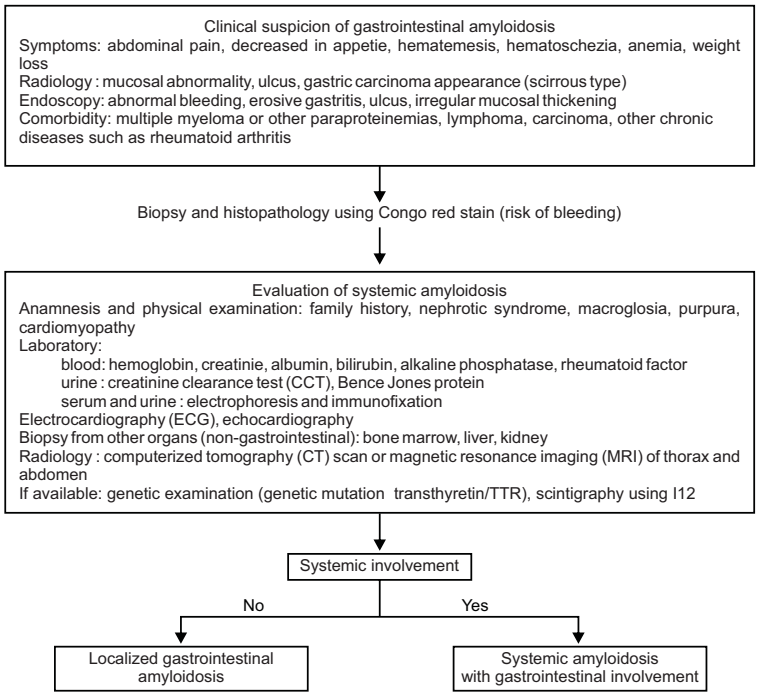


**Figure 7. Diagnosis algorithm of gastric localized amyloidosis8**

underlying diseases. This approach can result stabilization or improvement of function of the affected organ.[6] The goal in AL treatment is to reduce light chain immunoglobulin production through chemotherapy. Recently, high dose chemotherapy using melphalan 200 mg/m$^2$ and prednisone combined with stem cell transplantation to treat AL resulted in increase of survival rate.[15]

AA patient can have stabilization or improvement if the underlying disease (rheumatoid arthritis, Crohn's disease, etc) is well controlled so that the production of serum amyloid A can be controlled. Patient having severe intestinal amyloidosis due to aggressive rheumatoid arthritis can be treated using tocilizumab, an interleukin 6 anti reseptor antibody. This therapy results in improvement of gastrointestinal symptoms and systemic joint pain. Moreover, AA serum protein level can be reduced back to normal range and repeat endoscopic biopsy show no amyloid accumulation in the colon. Tocilizumab can be the drug of choice in treatment of AA associated with inflammatory arthritis. A new-small molecular inhibitor, R-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexa-noyl] pyrrolidine-2 carboxylic acid (CPHPC) has been developed to specifically attack serum amyloid P component which is a universal constituent of amyloid deposit and contributes to its formation. CPHPC reduced serum amyloid P and ceased the amyloid deposit in a systemic amyloidosis study. Unfortunately, that promising specific agent of treatment has not been yet available in clinical setting. In practical, AA amyloidosis treatment is to control the primary disease. For example, extending anti tuberculosis treatment could reduce amyloidosis in a report. Chlorambucil and tumor necrosis factor-α inhibitor used in inflammatory arthritis therapy would reduce the amyloid deposit. Colchicine, alkaloid extracted from *Colchicum autumnale*, family of lily plant, is prescribed to treat diseases such as gout, Behcet's disease, and primary biliary cirrhosis. This drug inhibits the formation of microtubule, affects cellular mitosis, and interferes with the phagositic ability of PMN cell. Colchicine is presently used as an effective drug to prevent and treat amyloidosis secondary to FMF. In an initial study, colchicine (1.5 mg/day) was given to treat nephropathy amyloid in patient with dystrophic type of inherited bullous epidermolysis. Recently, it is reported that gastrointestinal amyloidosis secondary to bullous epidermolysis was cured using colchicines in the same dose in the next 2 months.[6,10]

Liver transplantation is an effective method to treat hereditary amyloidosis. Abnormal transthyretin in hereditary amyloidosis is produced by liver, so that liver transplantation will result in normal production of transthyretin.[6] Gastrointestinal complication can be treated with symptomatic control. It is important to ensure adequate nutrition and hydration. For example, gastroparesis symptom can be effectively treated using metoclopramide or domperidone. Neostigmine can relieve acute pseudo-obstruction of colon, and can be used as an alternative to decompress the colon in patient with acute medical condition. Diarrhea can be treated using loperamide or octreotide.[3] Total parenteral nutrition can be used in severe dysmotility and patient is in malnutrition. Antibiotic is used to treat bacterial overgrowth. It is better for the patient to get supplementation, especially fat-soluble vitamin. The treatment of gastrointestinal bleeding is the same as in other diseases.[6]

## PROGNOSIS OF AMYLOIDOSIS

Median survival rate of 868 AL patients in Pavia center was 3.8 years, of which 27% of patients died in first 1 year after diagnosed and cumulative proportion of 10-year survival rate was 31%. Mortality was due to cardiac amyloidosis in 75% of dead patients. Therefore, the determinant of amyloidosis output was the magnitude of cardiac involvement.[10]

## CONCLUSION

Amyloidosis is a pathologic process caused by deposit of fibrillar amyloid protein in the extracellular space. Diagnosis of gastrointestinal amyloidosis is quite difficult. Endoscopic biopsy of gastrointestinal tract is diagnostic in most cases of amyloidosis. Confirmation of amyloid protein deposit in the biopsy specimen can be done using Congo red staining. The principle of management of amyloidosis should be directed at controlling gastrointestinal symptoms using symptomatic therapy, stopping the formation and deposit of amyloid protein, and treating the underlying diseases.

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