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# Diagnosis and Treatment of AA Amyloidosis with Rheumatoid Arthritis: State of the Art

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## 1. Introduction

Amyloidosis is a term applied to a heterogeneous group of rare diseases characterized by extracellular deposition of amyloid, causing target-organ dysfunction and a wide range of clinical symptoms [1]. These symptoms depend on the organ involved, and include nephrotic syndrome, hepatosplenomegaly, congestive heart failure, carpal tunnel syndrome, gastrointestinal (GI) symptoms and macroglossia [2]. Amyloidosis is clinically classified into several types depending on the precursor of the amyloid fibril. The disease involves amyloid fibrils formed in vivo by 27 different types of protein [3] (Table 1). Reactive amyloid A (AA) amyloidosis is the representative systemic condition that develops in patients with chronic inflammatory diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis, ankylosing spondylitis, inflammatory bowel disease, familial periodic fever syndrome, and chronic infections [4,5,6,7]. In some parts of the world, hereditary causes and infections are responsible for a larger proportion of cases of AA amyloidosis. In Turkey, familial Mediterranean fever (FMF) is the cause of more than 60 percent of cases [8]. Other conditions that may be associated with AA amyloidosis include neoplasms, particularly renal cell carcinoma [9], non-Hodgkin lymphoma [10], Castleman's disease [11], and cystic fibrosis [12]. Recently, therapy with biologic agents including anti-tumor necrosis factor (anti-TNF) and anti-interleukin-6 (IL-6) is now employed routinely for the management of RA in patients for whom traditional disease-modifying anti-rheumatic drugs (DMARDs) have failed. In parallel with this shift of treatment strategy, the treatment of amyloidosis has also changed. This article discusses current concepts of AA amyloidosis that is mainly secondary to RA, and addresses various strategies for prophylaxis, diagnosis, and therapy of this important complication in the light of changes in clinical management, especially hemodialysis (HD).

## 2. Prevalence

Epidemiological data for AA amyloidosis, extrapolated from autopsy records in Western nations, has indicated that the prevalence varies from about 0.5% to 0.86% according to environmental risk factors and geographic clustering [13,14]. The incidence of AA

amyloidosis in RA is still undefined, and is considered to be underestimated. In Europe, 5-20% of patients with RA develop amyloidosis, with the highest incidence in Finland [15], where reevaluation of autopsy materials for the period 1952-1991 yielded a 30% incidence of AA amyloidosis compared with 18% detected by routine testing, indicating that a significant proportion of cases may not be detected by standard histologic analysis [16]. Japanese autopsy reports have revealed that about 30% of autopsied RA patients have amyloid deposits [17]. Some Japanese medical centers have reported the incidence of amyloidosis in consecutive patients undergoing GI biopsy. The frequency of amyloidosis in RA has been reported to vary between 5% and 13.3% in cases confirmed by biopsy, and from 14% to 26% in cases confirmed at autopsy [18,19,20,21].

Amyloid protein	Precursor	Systemic (S) or localized, organ restricted (L)	Syndrome or involved tissues
AL	Immunoglobulin light chain	S, L	Primary Myeloma-associated
AH	Immunoglobulin heavy chain	S, L	Primary Myeloma-associated
A $\beta_2$ M	$\beta_2$ -microglobulin	S L?	Hemodialysis-associated Joints
ATTR	Transthyretin	S L?	Familial Senile systemic Tenosynovium
AA	(Apo)serumAA	S	Secondary, reactive
AApoAI	Apolipoprotein AI	S L	Familial Aorta, meniscus
AApoAII	Apolipoprotein AII	S	Familial
AApoAIV	Apolipoprotein AIV	S	Sporadic, associated with aging
AGel	Gelsolin	S	Familial (Finnish)
ALys	Lysozyme	S	Familial
AFib	Fibrinogen $\alpha$ -chain	S	Familial
ACys	Cystatin C	S	Familial
ABri	ABriPP	S	Familial dementia, British
ALect2	Leukocyte chemotactic factor 2	S	Mainly kidney
ADan*	ADanPP	L	Familial dementia, Danish
A $\beta$	A $\beta$ protein precursor (A $\beta$ PP)	L	Alzheimer's disease, aging
APrP	Prion protein	L	Spongiform encephalopathies
ACal	(Pro) calcitonin	L	C-cell thyroid tumors
AIAPP	Islet amyloid polypeptide**	L	Islets of Langerhans Insulinomas
AANF	Atrial natriuretic factor	L	Cardiac atria
APro	Prolactin	L	Aging pituitary Prolactinomas
Ains	Insulin	L	Iatrogenic
AMed	Lactadherin	L	Senile aortic, media
AKer	Kerato-epithelin	L	Cornea, familial
ALac	Lactoferrin	L	Cornea
AOaap	Odontogenic ameloblast-associated protein	L	Odontogenic tumors
ASemI	Semenogelin I	L	Vesicula seminalis

\*Proteins are listed, when possible, according to relationship. Thus, apolipoproteins are grouped together, as are polypeptide hormones.

\*ADan comes from the same gene as ABri. \*\*Also called 'amylin'.

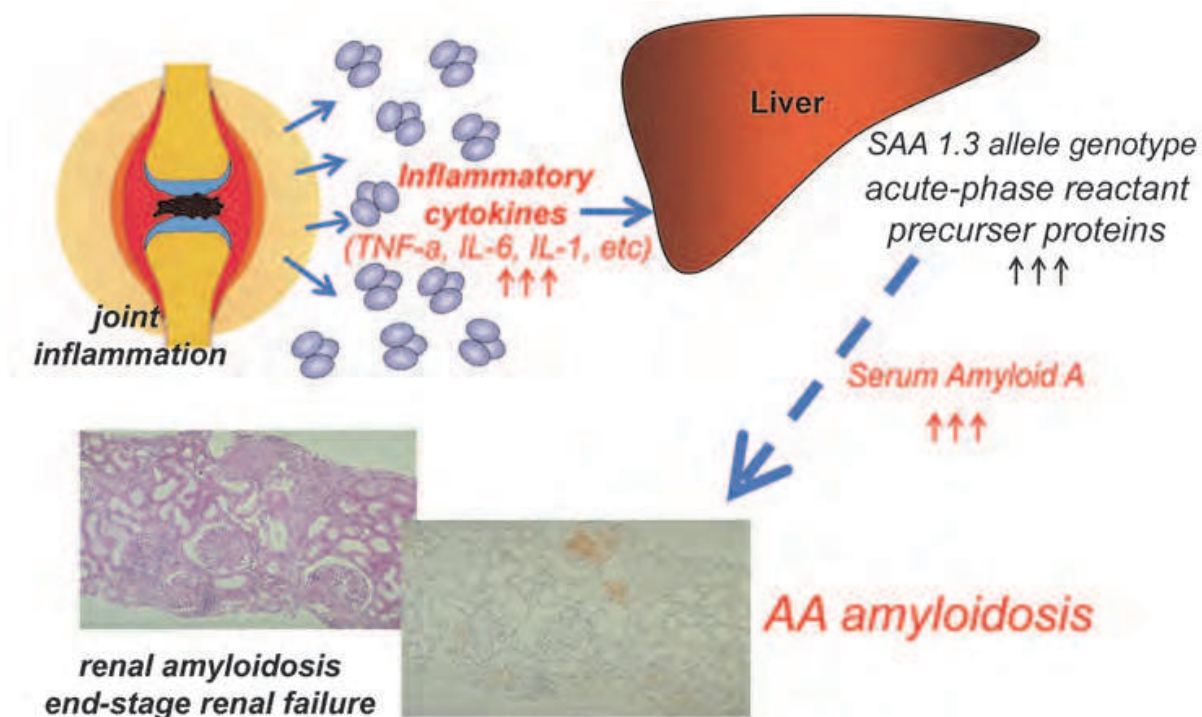
Table 1. Amyloid fibril proteins and their precursors in humans.\*

Although the subclinical phase of AA amyloidosis is defined by the formation of amyloid deposits in tissue without any clinical manifestation, it is very difficult to distinguish between the clinical and subclinical phases. Obviously, it is difficult to evaluate the natural history of amyloid deposition and to know the length of this phase and its final outcome. In contrast, the prevalence of clinical amyloidosis is likely to be lower; at least half of amyloidosis patients have subclinical disease, and AA amyloidosis is clinically overt in only 25-50%, even after longer periods of follow-up sampling. Considering this discrepancy between the prevalence rates of clinical and subclinical AA amyloidosis, the wide variation

in the prevalence of AA amyloidosis secondary to RA is due partly to marked geographic differences worldwide, possibly including genetic factors, and to the lack of unified statistical studies of AA amyloidosis among races and districts. In view of these factors, the prevalence of AA amyloidosis associated with RA is probably higher than that estimated so far.

### 3. Pathogenesis of amyloid fibril formation and genetic background

Precise details of the mechanism of amyloid fibril formation are unknown, and may differ among the various types of amyloid [22, 23]. Factors that contribute to fibrillogenesis include a variant or unstable protein structure, extensive  $\beta$ -conformation of the precursor protein, association with components of the serum or extracellular matrix, and physical properties including the pH of the tissue site. Extracellular matrix components include the amyloid P component, amyloid enhancing factor (AEF), apolipoprotein E, and glycosaminoglycans (GAG). Amyloidosis is classified clinically into several types according to the precursor of the amyloid fibril and the type of amyloid fibril protein. Any complete definition of amyloidosis includes the amyloid fibril protein precursor, the protein type or variant, and the clinical setting at diagnosis [3]. Table 1 shows the types of amyloid protein, precursor proteins, localization and syndrome, or the involved tissues. Reactive systemic AA (secondary) amyloidosis complicates many chronic inflammatory diseases and has been studied most widely in experimental animal models. AA amyloid also occurs spontaneously in various animal species, and can be induced by chronic inflammatory stimuli. The best-known model of this disease is amyloid induction by injection of casein/azocasein in certain genetically susceptible strains of mice. AA fibril formation can be accelerated by an AEF in murine models present at high concentration in the spleen, by basement membrane heparan sulfate proteoglycan, or by seeding with AA or heterologous fibrils [24,25]. (AEF has not yet been detected in humans.) Therefore, sustained overproduction of SAA is a prerequisite for the development of AA amyloidosis. The mechanism of amyloidosis is initiated by overproduction of SAA as a consequence of acute and chronic inflammation. Next, SAA is internalized by macrophages, followed by intracellular proteolysis, and subsequent release of amyloidogenic peptides into the extracellular space, apparently preceding fibril formation [26]. AA amyloidosis is caused by organ deposition of AA fibrils, which are formed from an N-terminal cleavage fragment of SAA [27]. SAA is a 104-amino-acid protein produced in the liver under transcriptional regulation by proinflammatory cytokines, and transported by a high-density lipoprotein (HDL), HDL3, in plasma [28,29,30,31]. SAA is encoded by a family of SAA genes, which are responsive to proinflammatory cytokines [32,33]. A major factor responsible for the development of AA amyloidosis is increased synthesis and subsequent degeneration of SAA under conditions of chronic inflammation. AA amyloidosis is a rare but serious complication of diseases that stimulate a sustained and substantial acute-phase response, and foremost of which is RA. In RA, there is increased synthesis of SAA accompanied by inflammation, which may be due to elevated levels of proinflammatory cytokines. The increased cytokine levels are correlated with synovitis, which may stimulate synoviocytes to produce SAA [26,34,35] (Figure 1). These mechanisms lead to elevated levels of SAA in joint fluid relative to serum [35], sometimes reaching up to 1,000 times the baseline level [36], thus facilitating the development of AA amyloidosis.



RA begins with joint synovitis, and serum amyloid A protein (SAA) is synthesized in the liver chiefly as a result of stimulation with proinflammatory cytokines. Genetic background factors such as the SAA 1.3 allele genotype are a risk factor for amyloidosis. Amyloid fibrils are deposited in tissues of various organs, leading to organ failure. TNF- $\alpha$ : tumor necrosis factor- $\alpha$ , IL-6: interleukin-6, IL-1: interleukin-1, SAA1.3: one of the SAA1 gene polymorphisms.

Fig. 1. Pathogenesis of AA amyloidosis secondary to RA

However, a high concentration of SAA alone is not sufficient for development of amyloidosis. Several genetic factors have been evaluated. Recent studies have focused on SAA polymorphism as a genetic background factor linked to amyloidogenesis. Allelic variants include acute phase SAAs (SAA1 and SAA2) and SAA4, and post-translational modifications of these gene products. SAA3 is a pseudogene with no product, and the serum concentration of SAA4 does not change during an acute-phase response [29]. The acute-phase proteins SAA1 and SAA2 are apolipoproteins, primarily associated with specific high-density lipoprotein (HDL), and are expressed extrahepatically in the absence of HDL [37]. SAA1 and SAA2 are inducible by interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)- $\alpha$ , lipopolysaccharide (LPS), and several transcription factors, notably SAA activating factor (SAF-1) [38,39]. Both SAA1 and SAA2 are polymorphic proteins, and amyloid fibrils are considered to be formed in tissues from both SAAs1 and 2, but predominantly from SAA1 in humans [40]. Synthesis of amyloid protein from SAAs1 and 2 is strongly induced by inflammatory cytokines such as IL-6 in the liver, in parallel with the disease activity of RA [41]. SAA1 is the most important precursor for tissue AA deposition, because this isotype is predominant in plasma, and AA proteins are derived largely from it. SAA1 has three alleles, designated SAA1.1, SAA1.3, and SAA1.5, defined by amino acid substitutions at positions 52 and 57 of the molecule [3]. SAA2 has two alleles, SAA2.1 and 2.2. The frequency of these alleles varies among populations, and may be associated with the occurrence of AA amyloidosis in diseases such as RA, and also with the level of SAA in blood, efficacy of clearance, susceptibility to proteolytic cleavage by specific

metalloproteinases, disease severity, and response to treatment [42]. The SAA1 alleles 1.1 and 1.3 have been proposed as positive risk factors in Caucasian and Japanese patients, respectively [43,44,45,46,47,48,49,50].

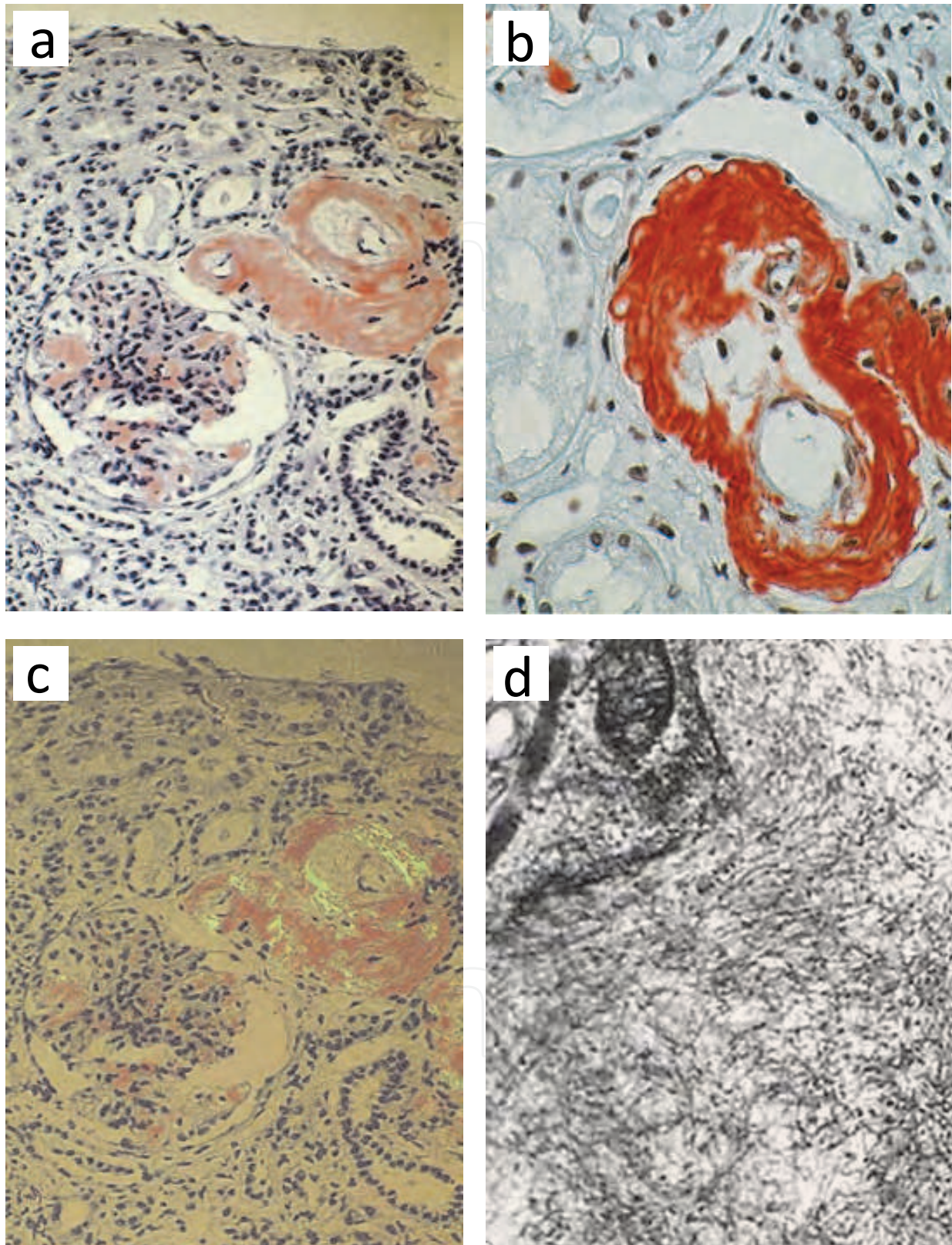
While the SAA1.1 allele was found to have a negative association with amyloidosis in Japanese subjects, it showed a positive association in Caucasians. Similarly, SAA1.3 showed an inverse association between Japanese and Caucasians. Recent new data have indicated that the -13T/C single nucleotide polymorphism in the 50-flanking region of SAA1 is a better marker of AA amyloidosis than the exon-3-based haplotype in both Japanese and American Caucasian populations [48,51,52].

Polymorphism of apolipoprotein E has been investigated as a potentially relevant genetic background factor, as this molecule is generally involved in the process of amyloid deposition [28]. According to several recent reports, apolipoprotein E4 is positively related to the development of AA amyloidosis in patients with RA [53]. Amyloid fibrils associate with other moieties, including GAG, serum amyloid P component (SAP) and apoprotein A-II of which are related to the onset of amyloidosis [30, 54]. The fibrils bind Congo red and exhibit green birefringence when viewed by polarization light microscopy, although the deposits can also be recognized in hematoxylin and eosin-stained sections [55, 56]. Electron microscopy demonstrates deposits of amyloid fibril protein in tissues as rigid, non-branching fibrils approximately 8 to 10 nm wide and of varying length, with a 2.5 to 3.5 nm filamentous subunit arranged with a slow twist along the long axis of the fibril [57]. When isolated and analysed by X-ray diffraction, the fibrils exhibit a characteristically abnormal  $\beta$ -sheet pattern [58]. Typing of amyloid deposits can be done by conventional immunohistochemical staining.

#### 4. Diagnosis

A cohort study of patients with RA has shown that deposits of fat AA fibrils are not uncommon (16.3%) [59]. Any patient with long-standing active inflammatory disease, such as RA, who develops proteinuria or intractable diarrhea must first be investigated for AA amyloidosis. No blood test is specially diagnostic for amyloidosis. Results of tests confirming the presence of chronic inflammatory disease, such as increased levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and SAA, are not necessarily discriminatory, because most patients with chronic inflammation do not develop amyloidosis. The next step for diagnosis is to perform a biopsy and histopathological examination. In order to begin intensive treatment as early as possible before organ function worsens, it is important to choose a high-sensitivity biopsy site and employ a safe technique. In general, subcutaneous fat, spleen, adrenal gland, liver, labial salivary gland, and sites in the alimentary canal ranging from the tongue and gingiva to the rectum, are frequent sites of AA amyloid deposition [60,61,62,63,64,65,66,67,68,69]. Many non-invasive techniques are useful for assessing organ involvement, but cannot establish whether the findings are related to amyloid. The definitive diagnostic test is biopsy of either an accessible tissue expected to contain amyloid, or a clinically affected organ. GI, rectal and subcutaneous fat biopsies are the procedures of choice, because the methodology is simple [18,70,71,72]. Aspiration biopsy of abdominal fat is recommended for screening in outpatient clinics because it is easy to perform in that setting, requires no specialty consultation or technical experience, has a high yield, and results in only minimal side effects [59]. As experience has shown that the amount of amyloid in fat tissue is low, the operator should aspirate as large a

sample as possible. If possible, GI and rectal biopsies are also recommended because their sensitivity is high and they can also be performed at hospitals in an outpatient setting. Generally, in AA amyloidosis, the GI is a more sensitive site for biopsy than subcutaneous fat aspiration [18,61]. The detection rate is higher in the duodenal bulb and second portion of the small intestine than in the stomach. Additionally, the incidence of amyloidosis in GI biopsies is highly correlated with that in renal biopsies [19]. If GI biopsy reveals amyloid deposition, the presence of renal amyloidosis should be considered [19]. However, a more recent study has revealed that the amounts of amyloid deposition in GI and renal biopsies are not correlated. GI amyloid-positive areas are larger than renal amyloid-positive areas [73]. If a fat biopsy proves negative, biopsy of the clinically involved site is suggested for patients with a limited number of affected organs. More organ-specific biopsies, such as heart, kidney and liver, are recommended, and it is useful to determine the type of amyloidosis. However, such biopsy sites carry a relatively higher risk than GI, rectal or subcutaneous fat biopsies. In such cases, clinicians should weigh the risks and benefits of biopsy. In Japan, however, GI biopsy is commonly performed for screening, rather than fat biopsy. If amyloidosis is strongly suspected clinically in association with marked inflammation, annual screening biopsy is recommended. The many reports of renal biopsy results for RA patients have suggested that renal amyloidosis is the most serious complication. In RA patients, renal biopsy can sometimes be hazardous, because of difficulties in maintaining a fixed body position, osteoporosis, or advanced age [74]. Renal involvement tends to determine the clinical course in such patients. Renal biopsy can also reveal underlying renal disorder such as mesangial proliferative glomerulonephritis (MesPGN), membranous nephropathy (MN), and thin basement membrane disease (TBMD). Pathological information on such underlying conditions is sometimes very important for the treatment of concomitant amyloidosis. Amyloid cardiomyopathy and autonomic neuropathy have been extremely rare in previously reported series [66], but should be kept in mind when interpreting biopsy results. The third step is histological diagnosis of amyloidosis, which can be established by light microscopy using special staining for amyloid. Alkaline Congo red has long been the standard method of staining for amyloid [55,56,63]. Deposits of amyloid bind Congo red and exhibit apple-green birefringence when viewed by polarization light microscopy. This provides definitive diagnosis of amyloidosis. However, Dylon stain is more sensitive, and is therefore more useful for the detection of small amounts of amyloid [68, 69]. The use of Dylon stain, also known as direct fast scarlet, has recently become more popular. However, it requires more careful observation because of a tendency for over-staining (Figure 2). Thioflavin T is also more sensitive than Congo red, but less specific [75,76,77]. Although it yields a more intense fluorescent reaction, over-staining often hinders accurate diagnosis. If biopsy samples show a positive reaction, the type of amyloidosis should then be determined. Immunohistochemistry with fluorescent antibodies specific for precursor proteins, such as light chain j, k, SAA, etc., is a reliable diagnostic complement. Additional testing of serum and urine samples for monoclonal immunoglobulins, and of serum for free light chains, should be performed to exclude AL amyloidosis. Amino acid sequencing and mass spectroscopy of amyloid deposits have been utilized to identify the precursor protein in some cases, but these techniques are not used routinely. Electron microscopy demonstrates straight, unbranched amyloid fibrils 8 to 10 nm in width. Scintigraphy using radio-labeled SAP can identify the distribution of amyloid, and provide an estimate of the total body burden of fibrillar deposits [78]. However, the value of SAP scintigraphy is limited because



Amyloid substance is reactive with Congo red stain (a) and Dylon stain (b), and shows apple-green fluorescence under a polarizing microscope (c). Electron microscopy shows thin amyloid fibrils with a diameter of about 10 nm in AA and AL amyloidosis.

Fig. 2. Histological diagnosis of renal amyloidosis



it is obtained from blood donors, and it is possible to perform limited facilities. Additionally, it is less helpful for detecting cardiac amyloid. The fourth step is to initiate treatment. If AA amyloid is revealed in any organ, the treatment should be focused on systemic amyloidosis, while giving due attention to any underlying chronic inflammatory diseases. If AA amyloidosis is related to tuberculosis or FMF, treatment of these underlying diseases should also be started. It is important to introduce specific therapies for individual diseases in such cases.

## 5. Clinical features

The clinical features of amyloidosis are compatible with the infiltration of amyloid deposits. AA amyloidosis is a serious disease with a significant mortality due to end-stage renal disease, heart failure, bowel perforation, or GI bleeding [70,79]. Common clinical features of AA amyloidosis are proteinuria, loss of renal function, and gastrointestinal disorders. A clinical diagnosis of amyloidosis is usually suspected if proteinuria, renal insufficiency, or intractable diarrhea is present. Attention should also be paid to long-lasting and high inflammatory disease activity. Although AA amyloid can sometimes be detected in patients with arthritis in the absence of other clinical features, the clinical importance of such “silent” deposits remains to be determined. Renal involvement is a well-known complication of amyloidosis with RA. It is usually manifested as proteinuria or nephrotic syndrome with a variable degree of renal impairment that may progress to end-stage renal disease (ESRD). If proteinuria worsens to about 0.5 g/day, amyloidosis should be suspected even if other reasons are plausible. In RA, several underlying renal disorders accompanying renal amyloidosis have been observed [80], including MesPGN, MN, TBMD, and interstitial nephritis [80]. Crescentic glomerulonephritis is a rare underlying disease in RA patients, and can result in rupture of the fragile glomerular basement membrane due to amyloid deposition [81]. Usually, MesPGN and interstitial nephritis are associated with mild to moderate proteinuria, and MN with severe proteinuria. TBMD shows no proteinuria, and usually hematuria alone is evident. Histological investigation frequently demonstrates renal amyloidosis concomitant with these underlying diseases [80]. In renal tissue, primary amyloid deposition may be limited to the blood vessels or tubules. Such patients present with renal failure but little or no proteinuria [82]. These deposits lead to narrowing of the vascular lumina [83]. Glomerular deposits are more common, and are associated with a poor renal outcome in patients with AA and RA. One report has described that 27 patients with renal amyloidosis due to RA had glomerular deposits, and that 85 percent of them showed progression to ESRD during a five-year observation period. However, patients with vascular and tubular amyloid deposits showed no deterioration of renal function [84]. Such patients with vascular and tubular amyloid deposits usually present with slowly progressive chronic kidney disease with little or no proteinuria, and their prognosis appears to be more favorable [84]. The kidneys are usually enlarged slightly when nephrotic, but show a decrease in size as ESRD ensues.

GI symptoms, such as alternating periods of constipation and diarrhea or bleeding, may frequently suggest early localization of amyloid deposits and warrant further investigation. Abdominal distention and appetite loss are also frequently observed. Diminished peristalsis and malabsorption are common results of amyloid deposition, and can lead to nausea, vomiting, diarrhea, or hypoalbuminemia [85]. Endoscopy may demonstrate erosion, ulceration, mucosal weakness, or micro-polyposis, but sometimes no abnormality is evident

in patients with mild amyloid deposition [61,86]. Fatal pancreatitis can sometimes occur at the end-stage of renal disease, and this is due to vascular obstruction in the pancreas by amyloid deposits [87]. Liver involvement can be manifested as weight loss, fatigue, and abdominal pain. About one-fourth of patients with amyloidosis have hepatic disease. Clinical signs may include only mild hepatomegaly with elevation of the serum alkaline phosphatase level [88]. However, most patients show concurrent extrahepatic manifestations.

In the cardiovascular system, amyloid deposition is limited to the heart. In cases of unexplained heart failure, only small amounts of amyloid deposition are observed around the vascular walls. In contrast, in AL amyloidosis, massive cardiac involvement is invariably evident. Unlike the situation in AL amyloidosis, cardiac involvement in reactive AA amyloidosis is not so common, affecting only about 10% of patients, and clinically overt heart failure is usually present in the terminal phase of the disease course, in addition to ESRD [89]. Restrictive cardiomyopathy or ischemic heart disease is rarely the cause of death [90]. Hypertension is frequent, and hypotension is rare in such patients, except in those with end-stage renal failure. Hypothyroidism due to amyloid deposition is sometimes observed [91]. In AA amyloidosis, involvement of the musculoskeletal system is rare. Usually, most of the symptoms are due to RA itself, and amyloid deposits do not elicit musculoskeletal symptoms. Central nervous system involvement is also unusual. Infiltration of subcutaneous fat is generally asymptomatic, but provides a convenient site for biopsy.

## 6. Management and treatment

Clinicians should remain vigilant for early signs of amyloidosis. For this purpose, patients with chronic rheumatic disorders, including those with elevated levels of inflammatory markers despite adequate symptom control by specific therapy, should undergo periodic urinalysis or assessments of 24-hour urinary protein excretion. If proteinuria exceeds 1(+) or increases to 0.5 g/day, screening for amyloidosis should be performed, including abdominal fat aspiration, or GI or rectal biopsy, to search for amyloid deposits [42]. Occasionally, GI symptoms, such as alternating periods of constipation and diarrhea or bleeding, may suggest early localization of amyloid deposits and warrant further investigation. If possible, GI endoscopy is recommended, because of its diagnostic yield. If a positive biopsy result is obtained after Congo red staining, accurate immunohistochemical characterization of amyloid as the AA type is mandatory. Once amyloidosis has developed, the SAA concentration over the course of the disease represents the main factor affecting renal progression and survival [36,92]. A previous study has revealed a relationship between turnover and regression of amyloid deposits and the corresponding clinical benefit, in terms of both organ function and survival [36].

AA amyloidosis occurs in patients who have persistently high plasma SAA concentrations, as part of the acute-phase response to a wide range of diseases. The natural history of AA amyloidosis is typically progressive, leading to organ failure and death, in patients whose underlying inflammatory disease remains active. By contrast, patients in whom the serum SAA concentration falls to within the reference range as a result of anti-inflammatory therapy show regression of amyloid deposits, stabilisation or recovery of amyloidotic organ function, and excellent long-term survival [93]. The therapeutic approach to AA involves treatment of the RA inflammatory process. It is important to control the level of SAA protein, which is

the precursor of AA amyloid. It appears that reduction of the SAA level to less than 10 mg/L allows resorption of the deposits and prevents further accumulation [92]. Frequent monitoring of SAA, when available, is therefore recommended in patients with AA amyloidosis as a guide to treatment strategy and follow-up. Alternatively, quantification of CRP may provide a valid marker for monitoring the effective suppression of underlying inflammation in these patients. The therapeutic strategy is shown in Table 2. It may be assumed that tight control of RA with any other DMARDs such as methotrexate (MTX), cyclophosphamide, azathioprine, tacrolimus, mycophenolate mofetil, and a combination of DMARDs would have a similar impact. A small retrospective study has indicated that cyclophosphamide may confer a significant survival benefit in patients with RA and renal AA amyloidosis [94]. In that study, six of 15 patients received monthly pulse cyclophosphamide following confirmation of renal involvement. These patients treated with cyclophosphamide survived longer than those administered non-alkylating drugs [94]. Trends toward decreased proteinuria and maintenance of renal function have also been noted with cyclophosphamide. Similar results have been confirmed in a cohort study reported from Japan [95]. Prospective studies are required to properly assess the role and toxicity of this agent in this setting. Recent studies have indicated the therapeutic benefit of anti-TNF or anti-IL-6 agents for AA amyloidosis secondary to inflammatory arthritides, including RA [93,96,97,98,99,100]. These agents strongly inhibit the production of SAA. If possible, for the treatment of reabsorption of amyloid deposits, and, possibly, recovery of target organ function, treatment with biologics has been recommended. Tocilizumab has an excellent inhibitory effect on disease activity and joint destruction, and is therapeutically beneficial for the symptoms of AA amyloidosis, especially intractable diarrhea [101]. Although there are no data for the effect of abatacept on AA amyloidosis, it may be effective in theory. AA amyloid deposits exist in a state of dynamic turnover, and the outcome is favorable when the SAA concentration is maintained at below 10 mg/L. The potential for amyloid to regress and for the function of amyloidotic organs to recover support the use of therapeutic strategies to decrease the supply of amyloid fibril precursor proteins in amyloidosis generally [36]. The use of biologics is not part of the conventional treatment approach, and they are chosen according to the conditions in individual patients, such as renal and pulmonary function. If there is any risk of infection, short-acting biologics are desirable. Especially, in the case of tocilizumab, infection may be difficult to find, and clinicians need to be vigilant. Treatment with biologic agents is prohibited in certain circumstances, such as severe infections or demyelinating diseases. The treatment of patients with coexisting RA and hepatitis B poses a difficult therapeutic challenge because of the risk that treatment of the RA could aggravate hepatic disease and increase viremia. In general, the use of biologics such as anti-TNF and anti-IL-6 is contraindicated in patients who are HBV carriers or have chronic hepatitis B. However, in clinical practice, it is necessary to use anti-TNF in these patients. The existing data suggest that treatment of such patients with etanercept and tocilizumab co-administered with lamivudine or entecavir is safe [102,103]. If treatments for the organ damage, such as immunosuppressive agents or anti-cytokine therapy, are unavailable, medium-dose steroid (prednisolone 10~40 mg daily) is effective. However, it is important to establish a diagnosis in the early stage without organ damage, and robust treatment for RA is the most reasonable approach. A recent report has indicated that eprodisate is a useful antifibril compound for treatment of AA amyloidosis, significantly delaying progression to HD or ESRD [104].

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 Control SAA synthesis

## (1) Tight control of disease activity of RA

- a) DMARDs: MTX as the anchor drug
- b) Immunosuppressant: cyclophosphamide, azathiopurine, tacrolimus, MMF
- c) Biologics: anti-TNF, anti-IL-6, abatacept
- d) Antifibril drug: eprosinate

## Supportive treatment

## (1) Cardiac

- a) Congestive heart failure\*: Salt restriction, Diuretics
- b) Arrhythmia: Pacemaker, Automatic implantable cardiac defibrillator, Antiarrhythmics

## (2) Renal

- a) Nephrotic syndrome: Salt restriction, Maintain dietary protein, ACE inhibitor, ARB
- b) Renal failure: Dialysis (HD, CAPD) : Programmed initiation\*\*

## (3) Gastrointestinal

- a) Diarrhea: Steroid, codeine phosphate, lactate bacteria, octreotide, parenteral nutrition, anti-IL-6

## (4) Others

- a) DMSO: resolvable amyloid deposits (very limited)
  - b) HB carrier : Etanercept with anti-viral agents is relatively safe.
- 

SAA serum amyloid A protein, RA rheumatoid arthritis, DMARDs disease-modifying antirheumatic Drugs, MTX methotrexate, MMF mycophenolate mofetil, TNF tumor necrosis factor, IL-6 interleukin-6, ACE angiotensin converting enzyme, ARB angiotensin receptor blocker, HD hemodialysis, CAPD continuous ambulatory peritoneal dialysis, DMSO dimethyl sulfoxide

\*If co-existence of renal failure, CHDF (Continuous hemodiafiltration) is effective.

\*\* To avoid the trouble for the HD initiation, programmed initiation is recommended

Table 2. Treatment for AA amyloidosis

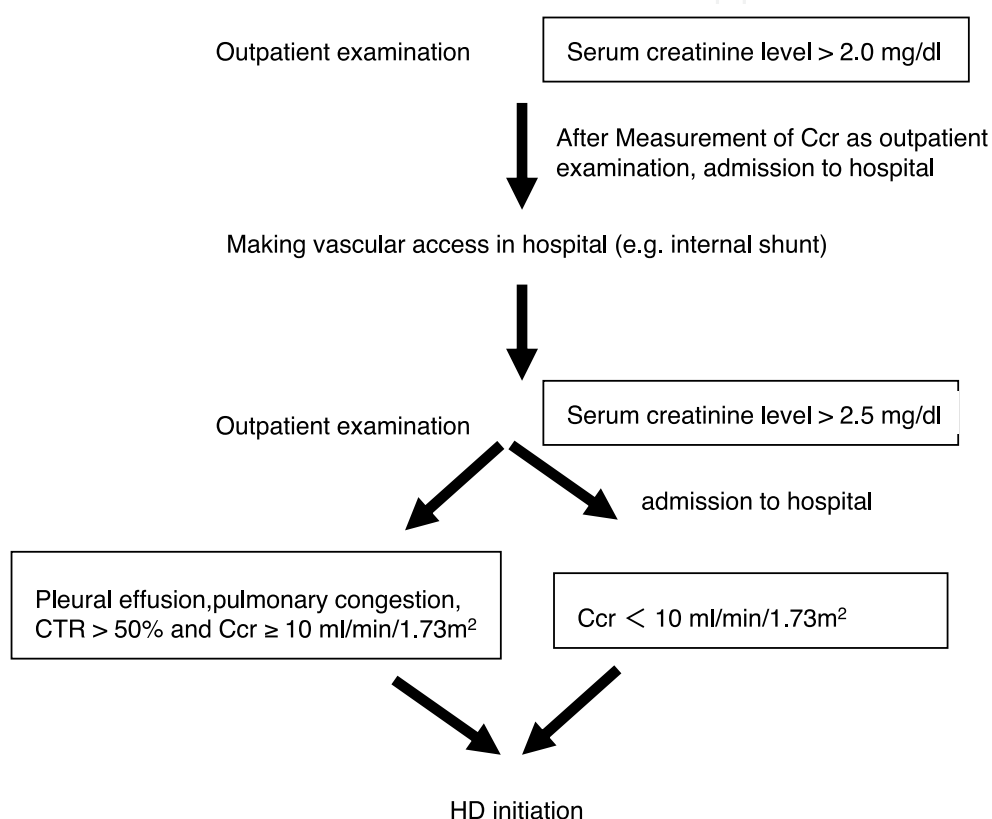
When considering supplementary treatment, cardiac amyloidosis is major therapeutic problem. Loop diuretics are the main therapeutic agents for the managements of volume overload. However, many patients with cardiac amyloidosis mostly have concomitant renal amyloidosis, making it difficult to maintain a balance between edema and intravascular contraction. Antihypertensive treatment is also important. A recent report has indicated that etanercept was effective in a patient with cardiac amyloidosis associated with RA [100]. Heart failure is known to be a contraindication for the heart failure [105], but the condition under the control of heart failure, biologics may be effective. With regard to renal impairment in patients with RA and amyloidosis, the serum creatinine (Cr) level is relatively low because of reduced muscle volume. Gender, long-lasting inflammation and RA, together with a low level of serum protein, may be associated with a decrease of muscle volume, and these in turn affect the level of serum Cr. This may partly explain why the serum Cr level is not elevated in comparison with creatinine clearance (Ccr) in patients with RA-associated amyloidosis [106]. Measurement of the serum Cr level is convenient in an outpatient setting, and is considered useful for accurate estimation of renal function even in these states. Measurement of cystatin C and calculation of estimated glomerular filtration rate (eGFR) are also useful [107]. Care must be taken not to underestimate the level of Cr. If renal dysfunction has progressed to some extent, almost all cases will follow a final common pathway to renal failure. Clinicians should always be mindful of the serum Cr level, and initiate treatment of renal amyloidosis as early as possible [97]. For the treatment of renal amyloidosis, it is important to estimate renal function accurately. Because the muscle

volume in RA patients is relatively low, the serum Cr concentration does not reflect renal function. Even if the serum Cr level is normal, such patients may still have renal damage. If patients are in a nephrotic state, angiotensin converting enzyme (ACE) inhibitor and/or angiotensin II receptor antagonist (ARB) are effective for reducing the level of urinary protein. For patients with renal failure, dialysis is needed. The prognosis of those who require dialysis is not good, although some data suggest a survival benefit among patients with AA amyloidosis [70]. The poor prognosis of these patients is due mainly to a large number of sudden deaths immediately after introducing HD therapy [108,109]. Additionally, unplanned initiation of HD is significantly associated with poor survival. Therefore, properly planned initiation of HD is highly recommended. To circumvent the problem of HD initiation while ensuring its safety, the procedure for planned introduction is shown in Figure 3. Programmed initiation of HD will improve the prognosis of patients with ESRD [110]. Continuous ambulatory peritoneal dialysis (CAPD) can also be considered for patients with ESRD, as it has an advantage in preserving the functionality of the kidneys and avoiding hypotension associated with HD. However, in RA patients, disability of the hands due to chronic inflammation, and also the risk of peritonitis, should be considered [111]. Renal transplantation has been performed successfully for a number of patients with renal failure and AA amyloidosis, but only on a very limited basis [112]. In the near future, renal transplantation may become a recommended therapy for such patients. For treatment of GI symptoms, mostly intractable diarrhea, medium- to high-dose steroid (prednisolone 10~40 mg daily) is effective. Parenteral nutrition is also effective for this condition. Anti-IL-6 therapy is reportedly highly effective for intractable diarrhea [101]. However, immunosuppressive therapies, including biologics, may be associated with serious infection in amyloidosis patients. Advanced age is an important risk factor for infection in patients with RA. Some of the increased risk may be related to steroid usage. Additionally, such patients generally show low protein levels or hypoalbuminemia. These factors may lead to serious infection and/or opportunistic infection. It is possible that infection may exacerbate elevation of the SAA level and lead to additional organ damage. Preventive therapy against infection should always be borne in mind. Dimethyl sulfoxide (DMSO) has been proposed as a therapeutic agent that may solubilize AA deposits, and a number of patients have been treated with DMSO in an uncontrolled trial. There appeared to be salutary effects in some patients, but the accompanying body odor made the treatment unacceptable [113]. Recently, treatment with DMSO has been very limited. Earlier diagnosis of amyloidosis leads to better treatment and an improved chance of recovery.

## 7. Outcome

Survival after the diagnosis of AA amyloidosis secondary to RA seems to be 4-5 years [108,114]. Recently, however, a median survival period of more than 10 years after diagnosis has been reported [115]. Survival seems to depend on the timing of diagnosis, and this may partly explain the great individual variation in observed survival time, leading to the notion that an active diagnostic attitude for AA amyloidosis should be adopted in patients with RA. Treatment strategy is also important. Infection and renal failure are generally common causes of death in RA patients with AA amyloidosis [116,117]. A higher risk of severe infection is a substantial problem in the management of such patients. Potent immunosuppressive treatment may sometimes result in infection, and in such cases, prophylactic treatment with an antituberculosis agent is recommended. Increased

production of SAA is a strong risk factor for ESRD and death, but this may be ameliorated by anti-inflammatory treatment. A relationship between SAA concentration, renal function and whole-body amyloid burden has been revealed. Outcome has been shown to be favorable in patients with AA amyloidosis when the SAA concentration is maintained below 10 mg/L [115]. Factors associated with poor prognosis are well known to include age at onset of RA and amyloidosis, female gender, a reduced serum albumin concentration, end-stage renal failure, the level of disease activity including serum levels of CRP and IgG, and the SAA concentration during follow-up [117]. Steroid dosage, and markers of renal function that are correlated with renal disease, such as BUN, Cr, and Ccr, at the time of detection of amyloidosis are important factors predictive of survival [108].



Schematic representation of the program used for our patients with end-stage renal disease due to reactive amyloidosis associated with rheumatoid arthritis. Ccr: creatinine clearance, CTR: cardiothoracic ratio

Fig. 3. Program of hemodialysis initiation

The results of dialysis for AA amyloidosis are extremely poor, and trouble with the initiation of HD in fact worsens prognosis, due to a rapid decline of renal function in the year preceding dialysis. Reported median survival after initiation of HD is more than 1 year [118], or more than 5 years [119]. These reports indicate that strict treatment and care will improve the clinical outcome. Amyloidotic cardiac involvement has been shown to be a poor prognostic factor [120,121]. Heart failure is one of the severe complications in these patients. Patients with heart failure usually have concomitant multiple organ failure, as well as renal failure, in the later phase of the RA disease course. To improve the outcome of these patients, frequent examinations for infection and acute inflammatory reactants such as CRP and SAA are necessary.

## 8. Conclusion

The best approach to treatment of amyloidosis is to prevent progression by controlling the serum level of SAA. In AA amyloidosis, proteinuria, renal dysfunction and GI symptoms are diagnostically informative. It is important not to overlook these symptoms, and to confirm the presence of amyloidosis by organ biopsy. Treatment with biologic agents plays a key role, especially for decreasing the production of SAA, along with prophylactic administration of anti-tuberculosis and anti-fungal agents. Monitoring of adverse events such as infection is an important part of the standard strategy associated with biologics treatment and checks for chronic inflammatory disorders should be conducted routinely. Physicians should make consideration to use biologics out of difficulties such as hepatitis B. These efforts should help to improve the outcome of patients with AA amyloidosis, achieve stabilization or regression of amyloid deposits, and prolong survival.

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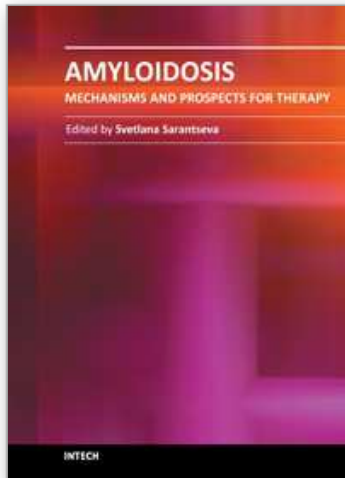
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## **Amyloidosis - Mechanisms and Prospects for Therapy**

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Amyloidoses are a heterogeneous group of diverse etiology diseases. They are characterized by an endogenous production of abnormal proteins called amyloid proteins, which are not hydrosoluble, form depots in various organs and tissue of animals and humans and cause dysfunctions. Despite many decades of research, the origin of the pathogenesis and the molecular determinants involved in amyloid diseases has remained elusive. At present, there is not an effective treatment to prevent protein misfolding in these amyloid diseases. The aim of this book is to present an overview of different aspects of amyloidoses from basic mechanisms and diagnosis to latest advancements in treatment.

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