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Review

French practical guidelines for the diagnosis and management of AA amyloidosis

Recommandations françaises de prise en charge de l'amylose AA

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ABSTRACT

AA amyloidosis is secondary to the deposit of excess insoluble Serum Amyloid A (SAA) protein fibrils. AA amyloidosis complicates chronic inflammatory diseases, especially chronic inflammatory rheumatisms such as rheumatoid arthritis and spondyloarthritis; chronic infections such as tuberculosis, bronchectasia, chronic inflammatory bowel diseases such as Crohn's disease; and auto-inflammatory diseases including familial Mediterranean fever. This work consists of the French guidelines for the diagnosis workup and treatment of AA amyloidosis. We estimate in France between 500 and 700 cases in the whole French population, affecting both men and women. The most frequent organ impaired is kidney which usually manifests by oedemas of the lower extremities, proteinuria, and/or renal failure. Patients are usually tired and can display digestive features anf thyroid goiter. The diagnosis of AA amyloidosis is based on detection of amyloid deposits on a biopsy using Congo Red staining with a characteristic green

Abbreviations:
ACE, Angiotensine converting enzyme
AID, Auto-Inflammatory Disease
AL, Light-chain amyloidosis
ANA, Antinuclear Antibodies
ANCA, Anti-Neutrophil Cytoplasmic Antibodies
ASCA, Anti-Saccharomyces Cerevisiae Antibodies
CAPS, Cryopyrin-associated periodic syndrome
CBC, Complete blood count
CeReMAIA, Referral Center for Auto-Inflammatory Diseases and Inflammatory Amyloidosis
CKD-Epi, Chronic Kidney Disease – Epidemiology Collaboration
CRP, C-reactive Protein
CVA, Cerebrovascular accident (stroke)
FMF, Familial Mediterranean Fever
GFR, Glomerular Filtration Rate
MDRD, Modification of Diet in Renal Disease
RF, Rheumatoid Factor
SAA, Serum Amyloid A
TNF, Tumor Necrosis Factor
TRAPS, Tumor necrosis factor Receptor-Associated Periodic Syndrome
TTR, Transthyretin
TSH, Thyroid-stimulating hormone
VEGF, Vascular Endothelial Growth Factor.

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birefringence in polarized light. Immunohistochemical analysis with an antibody directed against Serum Amyloid A protein is essential to confirm the diagnosis of AA amyloidosis. Peripheral inflammatory biomarkers can be measured such as C Reactive protein and SAA. We propose an algorithm to guide the etiological diagnosis of AA amyloidosis. The treatement relies on the etiologic treatment of the undelying chronic inflammatory disease to decrease and/or normalize Serum Amyloid A protein concentration in order to stabilize amyloidosis. In case of renal failure, dialysis or even a kidney transplant can be porposed. Nowadays, there is currently no specific treatment for AA amyloidosis deposits which constitutes a therapeutic challenge for the future.

Keywords :
AA amyloidosis
Inflammation
Kidney failure
Biopsy
Familial Mediterranean fever
Serum amyloid A protein (SAA)
Autoinflammatory diseases

RÉSUMÉ

L'amylose AA est secondaire au dépôt d'un excès de fibrilles insolubles de protéine sérique amyloïde A (SAA). L'amylose AA complique les maladies inflammatoires chroniques, notamment les rhumatismes inflammatoires chroniques tels que la polyarthrite rhumatoïde et les spondyloarthrites ; les infections chroniques telles que la tuberculose, les dilatations des bronches, les maladies inflammatoires chroniques intestinales telles que la maladie de Crohn ; et les maladies auto-inflammatoires, en particulier la fièvre méditerranéenne familiale. On estime la prévalence en France entre 500 et 700 cas, touchant aussi bien les hommes que les femmes. L'atteinte la plus fréquente est celle du rein qui se manifeste généralement par des œdèmes des membres inférieurs, une protéinurie et/ou une insuffisance rénale. Les patients sont le plus souvent fatigués et peuvent présenter des symptômes digestifs aspécifiques et un goitre thyroïdien. Le diagnostic d'amylose AA repose sur la détection de dépôts amyloïdes sur une biopsie utilisant une coloration au rouge Congo, avec une biréfringence verte caractéristique en lumière polarisée. Une analyse immunohistochimique avec un anticorps dirigé contre la protéine SAA est indispensable pour confirmer le diagnostic d'amylose AA. Des biomarqueurs d'inflammation périphériques peuvent être mesurés dans le sang comme la protéine C réactive et la SAA. Cet article propose les recommandations françaises actuelles pour le bilan diagnostique et le traitement de l'amylose AA qui comporte toujours la prise en charge de la maladie inflammatoire chronique sous-jacente pour diminuer et/ou normaliser la concentration sérique de SAA afin de stabiliser l'amylose. En cas d'insuffisance rénale, une dialyse ou même une greffe de rein peut être proposée.

Mots clés :
Amylose AA
Inflammation
Insuffisance rénale
Biopsie
Fièvre méditerranéenne familiale
Protéine amyloïde A sérique (SAA)
Maladies auto-inflammatoires

1. Summary for the family doctor

Inflammatory (AA) amyloidosis is a variety of amyloidosis secondary to the deposit of excess insoluble Serum Amyloid A (SAA) protein fibrils produced in chronic inflammatory situations. The deposits can affect numerous organs, but kidney function is impaired the most [1–4].

This variety of amyloidosis is becoming increasingly rare in western countries and constitutes about 10% of all amyloidosis cases outside of wild-type transthyretin (TTR) amyloidosis (= senile cardiac amyloidosis cases) [5]. It affects both men and women, and the number of cases in France is estimated at between 500 and 700 cases in 2019 in the whole French population (no prevalence study is yet available).

AA amyloidosis complicates diseases accompanied by a chronic inflammatory syndrome, primarily represented in France by: chronic inflammatory rheumatisms such as rheumatoid arthritis, spondyloarthritis, chronic infections such as tuberculosis, bronchectasis, chronic inflammatory bowel diseases such as Crohn's disease, and auto-inflammatory diseases including familial Mediterranean fever [1,2].

There are few suggestive signs signs of AA amyloidosis, which makes its consideration difficult in the context of a chronic illness; patients are usually tired [2,4]. Renal impairment is the most common organ impairment in AA amyloidosis; it usually manifests through oedemas of the lower extremities, proteinuria and/or renal failure; digestive impairment is almost always present, but not necessarily symptomatic: it can cause episodes of diarrhea, weight loss and anorexia; other afflictions include: hepatosplenomegaly, sometimes goiter but it is important to note that cardiac impairement is very rare [1–4].

The diagnosis of AA amyloidosis is based on the detection of amyloid deposits by means of an pathological analysis of a tissue biopsy [2,4,6]. These deposits are stained using Congo Red with a characteristic green birefringence in polarized light. Immunohistochemical analysis with an antibody directed against Serum Amyloid A protein is mandatory to confirm the diagnosis of AA amyloidosis. The preferred biopsy sites are: accessory salivary gland biopsy, periumbilical subcutaneous fat biopsy, renal biopsy [6]. Blood is also drawn to evaluate the biological inflammation markers (C reactive protein and serum amyloid A protein (SAA)) [2].

The treatment of the causative disease responsible for the chronic inflammation may permit stabilization and even regression of the amyloidosis; in the event of renal failure, treatment may include dialysis or even a kidney transplant but there is currently no specific treatment for AA amyloidosis [2,3]. More and more monogenic etiologies are being discovered; thus, the diagnosis and therapeutic strategies can be discussed in a national multidisciplinary coordination meeting [7].

2. Objectives of the French practical guidelines for diagnosis and management of AA amyloidosis.

The objective of this French practical guidelines is to explain to the professionals concerned the diagnostic, care and current optimal therapy and the course of care of a patient affected by AA amyloidosis. Its goal is to optimize and harmonize the management and the follow-up of this rare disease over the entire territory. It also identifies drugs used in an indication not provided for in the marketing authorization, as well as the specialties, products or services

necessary for the management of patients but not usually paid for or reimbursed.

These guidelines can be used as a reference for the attending physician (a doctor indicated by the patient to the Primary Health Insurance Fund) in consultation with the specialist doctor, especially when establishing the care protocol jointly with the consulting doctor and the patient, in the case of a request for exemption from the copayment due to an off-list condition.

However, these guidelines cannot consider all the specific cases, all the comorbidities or complications, all the therapeutic peculiarities, all the hospital care protocols, etc. It cannot claim to be exhaustive regarding the possible management approaches, nor can it replace the individual responsibility of the physician vis-à-vis his patient. The protocol does, however, describe the reference treatment for a patient with AA amyloidosis. It will need to be updated based on new validated data. It considers certain diagnostic elements common to all varieties of amyloidosis, but it does not address the care for other forms of multi-systemic amyloidosis: familial amyloid neuropathies (2018), cardiac amyloidosis (2021) and AL amyloidosis (upcoming).

The present recommandations were drafted in accordance with the "Method for Drafting a National Diagnostic and Care Protocol for Rare Diseases" published by the French Supreme Health Authority in 2012 (methodological guide available on the HAS site: www.has-sante.fr).

3. Initial diagnosis and evaluation

3.1. Objectives

The principal objective is to diagnose AA amyloidosis at an early stage, so that therapeutic care can be implemented rapidly, which affects the prognosis [8]. Indeed, AA amyloidosis diagnosis is most often made at an advanced renal disease stage characterized by abundant proteinuria and renal failure [1].

The clinical diagnosis of AA amyloidosis is therefore probably inadequately suspected, and the importance of screening for the disease by routinely measuring creatininemia and proteinuria in every patient with a chronic inflammatory syndrome should be reiterated [2].

3.2. Professionals involved

The appearance of AA amyloidosis may be part of the progress of diverse and varied (inflammatory, infectious, and tumoral) chronic diseases but manifests essentially as a clinical-biological picture suggestive of glomerular nephropathy [1,2]. Monitoring nephropathy markers is recommended in any chronic inflammatory disease, in order to spot either a renal complication of the disease or a complication related to the specific treatments for that disease. AA amyloidosis is a non-specific complication that must be added to the other complications of these chronic diseases; it should be suspected when there is renal impairment in these very different contexts that involve doctors in a variety of specializations, including (but not limited to): rheumatologists, internists, infectologists, gastroenterologists, nutritionists, and the attending physician [2,4,7].

3.3. Discovery circumstances and diagnostic suspicion

Detection of proteinuria and later a nephrotic syndrome, with or without renal failure, in a patient being monitored for a known inflammatory or chronic infectious disease represents the most frequent method of discovering AA amyloidosis [2,3]. More rarely, it can occur that, inversely, the unexpected discovery of AA amyloidosis through a renal biopsy permits the diagnosis of a previously unidentified chronic inflammatory disease. Proteinuria is of glomerular origin, composed primarily of albumin; typically, this nephropathy is not accompanied by hematuria or leukocyturia. It is not associated with high blood pressure; in fact, low blood pressure is common; this presentation therefore differs from other glomerulopathies where high blood pressure is usually severe. Normal or even increased kidney size is another particularity of amyloid nephropathy. The renal impairment may be isolated, but the association with impairment of other organs represents another characteristic suggestive of amyloidosis, although the panorama of extra-renal symptoms is more restricted in AA amyloidosis than in AL amyloidosis [1–3]. Other potentially affected organs are the digestive tract, spleen, liver, thyroid gland, and adrenal gland. Digestive manifestations are varied: abdominal pain, diarrhea, vomiting, malabsorption, endoscopic anomalies. Adrenal failure is possible.

3.4. Diagnosis confirmation

The diagnosis of AA amyloidosis must be documented histologically: the anatomopathology diagnosis is based on detection of amyloid deposits in a biopsy sample [2,6]. By definition, these deposits are stained using Congo Red with a characteristic green birefringence in polarized light. Immunohistochemical study is thus the most commonly used technique for demonstrating that deposits consist of SAA protein; the use of antibodies directed against light chains of immunoglobulins (ideally by immunofluorescence technique) is necessary in parallel to rule out AL amyloidosis.

Since AA amyloidosis involves essentially renal signs, it can be diagnosed by analyzing a renal biopsy; however, due to the multi-systemic histological distribution of AA amyloidosis, less invasive sampling (accessory salivary gland biopsy, peri-umbilical fat biopsy, digestive biopsies) should be preferred initially and the renal biopsy used only if the other methods do not permit detection of amyloid deposits [2,6]. It can be valuable to consider looking for amyloid deposits in prior biopsies through the retrospective use of Congo Red staining.

Typing is sometimes difficult, and it is important not to miss the diagnosis of AL amyloidosis, given the severity of this form of amyloidosis. It is necessary to be attentive in heart disease cases, which are rare in AA amyloidosis, or when there is impairment of other organs not usually affected by AA amyloidosis. Etiologic studies should include looking for monoclonal protein in blood and urine (Table 1). The existence of a monoclonal gammopathy of undetermined significance (MGUS) is common in elderly people and often of no clinical consequence, but the presence of a monoclonal gammopathy, especially if accompanied by an excess of monoclonal free serum light chain, should suggest the AL amyloidosis diagnosis [2,6].

3.5. Etiological research

The search for the cause of AA amyloidosis can in large part be superimposed over the search for the cause of a chronic inflammatory syndrome, itself arising from the question of an unexplained prolonged fever (Fever of Unknown Origin – FUO). There is no validated diagnostic algorithm for these questions, which encompass a very broad section of medicine, and the approach must be reasoned, oriented by clinical data and accomplished in successive steps (see our proposed algorithm, Fig. 1).

The search for the cause of AA amyloidosis must be guided by the patient's history, including his/her personal and family backgrounds, a complete physical exam, and access, if possible, to prior biological test results including a complete blood count and inflammation markers (CRP, fibrinogen, Sedimentation rate). Table 1 lists

Table 1
Important elements to compile for the etiologic profile of an AA amyloidosis case.

	Elements to be compiled	Etiology to consider
Family histories	AA amyloidosis	Monogenic AID
	Dialysis	
	Kidney transplant	
	Inflammatory disease	
	Mediterranean descent	(Familial Mediterranean fever)
	Inbreeding	
	Dominant AA Amyloidosis with normal CRP	SAA1 promoter mutation
Personal histories	Recurring fever	Monogenic autoinflammatory diseases
	High CRP in the past	
	Cutaneous, digestive, musculoskeletal symptoms	
	Pseudo-erysipelas of the ankles	(Familial Mediterranean fever)
	Hearing loss, hives	(Cryopyrinopathy)
	Livedo, cutaneous vascularitis, stroke	(ADA2 deficiency)
	Elderly man with macrocytic anemia	(VEXAS syndrome)
	Chronic diarrhea	Inflammatory bowel disease
	Buccal aphthae	Rare monogenic autoinflammatory diseases
	Inflammatory arthralgias	Inflammatory rheumatism
	Arthritis	
	Lumbagos	
	Overweight (weight curve and body mass index)	Obesity
	Repeated ORL, broncho-pulmonary infections	Immune deficiency
	Change in general condition	Tuberculosis
	Chronic cough	
	Dyspnea	
	Repeated secondary bronchial infections	Bronchiectasis

the important clinical elements to be compiled in the etiology of an AA amyloidosis case. Paraclinical exams should be guided by the clinical symptoms and history and will not be the same for all patients. Table 2 lists the exams to be proposed based on the suspected causes [2,7]. In general, we feel that it is important to measure serum SAA protein (see Box 1) together with CRP at least once in the diagnostic process. In fact, a dissociation between normal CRP and elevated SAA is possible; in these rare cases, the inflammation should be monitored by measuring SAA. Importantly, a recent cause of AA amyloidosis linked to mutation in the *SAA1* promoter in a large dominant family was reported, meaning that this etiology should be searched in case of elevated SAA but normal CRP [9]. Another very valuable exam, in patients of Mediterranean origin, is exon 10 sequencing for the *MEFV* gene associated with FMF (since this exon includes most of the pathogenic mutations associated with this disease) to diagnose a form of FMF in which the inflammatory attacks are rare or have not been identified [8,10].

In the absence of an obvious etiologic orientation element, we propose getting a specialized opinion, through discussion with the national multidisciplinary consensus meeting, or through the AA amyloidosis expert referral center.

Box 1
SAA protein

Serum Amyloid A protein is a protein from the acute inflammation phase whose kinetic evolution is comparable to that of CRP but with an augmentation amplitude that can be higher than that of CRP [15]. Therefore, the initial concentration of SAA can be multiplied by 1000 during the acute inflammation phase. Its plasma half-life is about 10 hours, a little shorter than that of CRP (≈19 hours), and as with CRP, its concentration is low in healthy subjects.

The SAA level is determined through the use of immuno-precipitation techniques in liquid: nephelemetry or turbidimetry. It is currently being done in several hospitals in France such as Poitiers, Lyon, Tenon and Mondor in Paris, as well as on private platforms such as CERBA or BIOMNIS, for example. Levels are determined in serum, and the results are generally available in one week.

In customary clinical practice, the information provided by the SAA level is similar to that of CRP. These two inflammation markers are therefore not measured simultaneously, particularly in acute disease cases. In the presence of diagnosed AA amyloidosis or a potentially amyloidogenic disease, this proposal may be nuanced, since SAA protein is the direct precursor of amyloid fibrils and its serum concentration may better reflect the amylogenic risk. However, the prevalence of dissociation between the serum concentrations of these proteins is not known precisely in chronic inflammatory diseases, and the literature may show discordant results.

In practice, it is important to remember that:

- SAA is just an inflammation marker; its elevation is not synonymous with AA amyloidosis.
- Normal CRP/SAA levels do not rule out the AA amyloidosis diagnosis, because the inflammation could have been marked in the past and then normalized.
- The important factor in terms of amylogenic risk is to show evidence of a prolonged inflammatory syndrome and quantify it.
- We recommend verifying at least once, if possible, that when CRP is normal, SAA is also normal.
- In case of elevated SAA but normal CRP, consider *SAA1* promoter mutation.

3.6. Evaluation of disease severity/extent; search for comorbidities and evaluation of the prognosis

AA amyloidosis has a more limited clinical extent than AL amyloidosis; it affects essentially the kidneys in almost all patients, then the digestive tract, liver, and spleen [1–3,16].

Assessing the extent of the disease therefore requires few additional exams (Table 3).

Cardiac involvement in AA amyloidosis is rare. It is therefore necessary to rule out other types of amyloidosis (in particular AL and transthyretin amyloidosis) in the event of cardiac amyloidosis presentation [1].

Detection of a cardiac pathology in a patient with AA amyloidosis who is in end-stage renal failure and on hemodialysis can sometimes suggest an amyloid cardiopathy. However, confirming the AA amyloid nature of the cardiac involvement in this context is particularly difficult, since there is often complex cardiopathy secondary to the chronic dialysis and because numerous associated cardiovascular risk factors can lead to heart disease. In case of doubt or in complex situations, an expert cardiac amyloidosis opinion is needed.

AA amyloid neuropathy is also rare; in the presence of peripheral neuropathy, another cause should therefore be sought (such as malnutrition or renal failure).

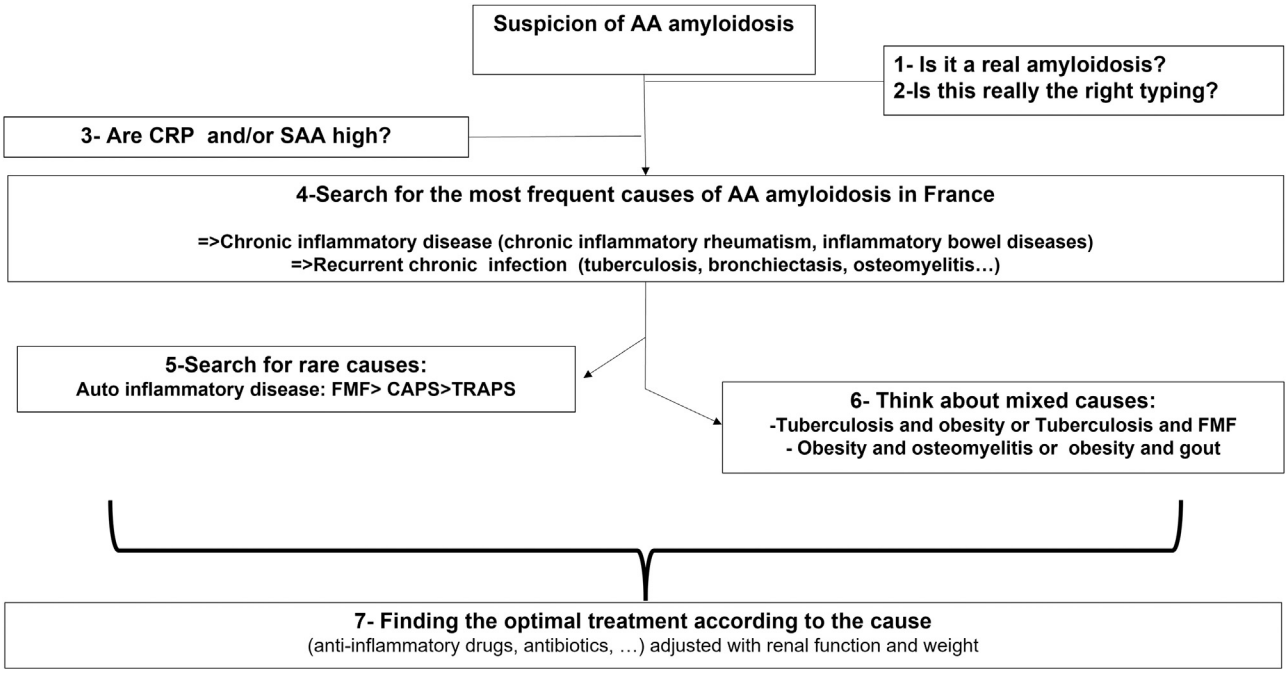

Fig. 1. Proposed etiologic diagnosis algorithm for AA amyloidosis. If AA amyloidosis is suspected, one should always ask whether it is really amyloidosis (1) and then confirm the amyloidosis typing (2). When the AA amyloidosis typing is confirmed, the inflammation parameters are measured to see whether CRP and SAA are elevated (3). The cause of the chronic inflammation is then investigated, always starting with the most common causes (4). If no frequent cause is found, a rare disease such as autoinflammatory diseases is evoked, bearing in mind that familial Mediterranean fever should be evoked first, especially if the patient has Mediterranean origins (5). Mixed causes with one or more associated causes of inflammation should be considered (6). Finally, the treatment should be tailored to the cause(s) identified as the source of inflammation with the aim of normalizing the SAA protein level (7).

Table 2
Explorations to be proposed for AA amyloidosis based on suspected causes.

Suspected cause	Biological tests	Morphologic tests
Inflammatory rheumatism (rheumatoid arthritis, spondylarthritis, psoriatic rheumatism)	RF, ANA, anti-CCP antibodies anti-CCP antibodies, HLA B27	Standard radiography - hands, feet (RA) - frontal pelvic, dorso-lumbar spine (SPA), painful joints MRI of spine and sacroiliacs if clinical suspicion of SPA
Chronic inflammatory bowel diseases	Fecal calprotectin ANCA and ASCA autoantibodies	Digestive endoscopies with biopsies
Monogenic AID	Genetic research if history suggests an autoinflammatory disease (in particular FMF, CAPS, VEXAS and TRAPS) Strategy to be discussed with the geneticist depending on the number of genes to be studied	Depending on the clinical situation Not mandatory for the first line
Immune deficiency	*First line: Serum protein electrophoresis, IgG, A, and M levels; Diphtheria and tetanus vaccine serologies (pneumococcus before/after vaccination); Phenotyping of T, B (naive and memory), and NK lymphocytes. Second line: IgG subclasses	CT scan of sinuses Thoracic CT scan
Tuberculosis	Search for Mycobacterium tuberculosis bacillus Mycobacteriologic cultures Biopsy of a lymph node	Thoracic ± abdominal-pelvic CT scan Bronchial fibroscopy Positron Emission Tomography (PET) scan
Bronchiectasis	See *First line (Immune deficiency, above)	Thoracic CT scan
Hemopathy	Electrophoresis of serum proteins ± Blood and urine immunofixation ± Free light chains in blood If possible hemopathy, bone marow aspiration ± biopsy	Imaging searching for a tumoral syndrome (echography, CT scan, PET scan)
Castleman disease	Lymph node or suspected tumoral lesion biopsy	Thoracic-abdominal-pelvic CT scan PET scan
Obesity	Diagnosis of exclusion	Diagnosis of exclusion

Table 3
Proposed explorations for the AA amyloidosis extent profile.

Organ	Required tests	Optional tests
Kidney	Proteinuria/creatininuria on a urine sample or 24-hour proteinuria Urinary sediment Blood ionogram, urea, creatinine Protidemia, albuminemia Renal echography	Renal biopsy puncture
Digestive tract	Albuminemia	Digestive endoscopy Stool examination
Spleen	Echography or tomodensitometry	
Liver	Liver tests Echography or tomodensitometry	
Adrenal gland		8-hour blood cortisol, ACTH stimulation test
Thyroid		Echography, TSH
Heart	Electrocardiogramm Troponin and BNP/NT-proBNP Holter ECG/24-hr Cardiac echography	Cardiac MRI
Peripheral nerve		Electromyogram
Skin		Biopsy of a lesion
Chest	Chest X-ray	Tomodensitometry

The usual comorbidities should be looked for: diabetes and atherosclerosis to start with.

The prognosis involves several factors [17]:

- Related to amyloidosis. As with most renal diseases, the presence of renal failure when diagnosed is a major prognosis factor for progression toward end-stage renal failure, even if the disease causing the inflammation is controlled by the specific treatment.
- The presence of digestive symptoms related to amyloidosis (diarrhea, malabsorption, bleeding, perforation) is a high-severity element that is modified little by current treatments.
- Nature of the underlying disease. Infectious diseases that are complicated by AA amyloidosis are usually poorly accessible to radical treatment, especially if a primary or secondary immune deficiency is participating in the recurrence of the infections.
- For inflammatory diseases, the prognostic element is the ability of anti-inflammatory treatments to reduce the inflammation.
- Comorbidities and in particular atherosclerosis promoted by chronic inflammation and accelerated in hemodialysis patients.

3.7. Announcing the diagnosis and informing the patient

The diagnosis is based on the histologic proof of amyloidosis and its typing.

It is necessary first to explain the patient's disease (amyloidosis), the formation of amyloid fibrils in prolonged inflammation cases (AA amyloidosis), and the insoluble deposits in tissues that can cause renal impairment in particular, even leading to dialysis in end-stage renal failure cases. The amyloidosis booklet published by the association française contre l'amylose can be a useful written supplement to give to the patient, in printed or PDF form (https://amylose.asso.fr/).

Box 2
Recent evolution of AA amyloidosis causes

- The proportion of AA amyloidosis cases without a clearly identified cause is growing.
- In this group, obesity is emerging as a possible cause, or at least as an amyloidosis risk factor [11,12].
- In certain patients, several causes may be considered diachronically or synchronically.
- New monogenic causes where recently identified, especially *UBA1* mutation associated with VEXAS syndrome and *SAA1* promoter mutation associated with AA amyloidosis with normal CRP [9,13,14].

4. Therapeutic management

4.1. Objectives

The principal objective is to normalize the serum concentration of CRP/SAA (Box 2) to prevent the amylogenic process from continuing [18].

In order to do this, it is absolutely necessary to find the cause of the chronic inflammation and propose an adapted etiologic treatment if one exists.

Chronic renal failure should be treated, if necessary by extrarenal purification and, depending on the patient's age and condition and on the underlying causative disease, by renal transplant.

Finally, symptomatic treatment may be proposed in cases of pain, diarrhea, or goiter, for example.

4.2. Professionals involved

The professionals involved in managing these cases are a nephrologist, because there is almost always renal impairment, and specialized physicians who treat the underlying disease as well as any comorbidities. Table 4 below summarizes their possible roles and proposes follow-up frequency.

4.3. Therapeutic management (pharmacological and other)

Therapeutic management involves several aspects: the first concerns the inflammation and the second the kidneys, the main organ targeted by AA amyloidosis, which is itself divided into two parts (nephroprotection and treating renal failure).

4.3.1. Anti-inflammatory treatments

We will not discuss preventive treatment for AA amyloidosis, since the same treatment applies for all diseases involving chronic inflammation.

This section therefore focuses only on the "curative" treatment for existing AA amyloidosis, without delineating all of the too many possible situations, but designating the principal ones and addressing a few specific cases that are among the most common.

First we look at chronic inflammatory diseases.

The therapeutic strategy for a diagnosis of AA amyloidosis is divided schematically into two situations [2,3].

In the first, the AA amyloidosis diagnosis is made while the causative disease has not been diagnosed, or has been diagnosed but not treated. Treatment of the AA amyloidosis therefore is basically treatment of the underlying disease.

In the second situation, the amyloidosis diagnosis is made while the causative disease has been actively treated (with or without a precise diagnosis) for several years. The amyloidosis treatment issue in this case is that of intensifying the treatment for the causative disease. Only this latter issue is addressed here.

Table 4
Proposed follow-up by healthcare professionals for AA amyloidosis patients and how frequently they should be seen.

Healthcare professionals	Role	Follow-up frequency (suggestion)
Nephrologist	Diagnosis, follow-up, slow the progression of chronic renal disease and prepare the patient, if necessary, for a renal replacement technique (hemodialysis, peritoneal dialysis, kidney transplant), and dialysis if needed	Follow-up: at least twice a year (more often in case of renal failure with GFR < 30 ml/min)
Internist	Etiologic diagnosis Follow-up for an inflammatory or auto-inflammatory disease Care coordination	Follow-up: once or twice a year, alternating with the nephrologist
Rheumatologist	Diagnosis, follow-up for chronic inflammatory rheumatism	Follow-up: once or twice a year, alternating with the nephrologist, and more often if uncontrolled inflammatory rheumatism
Clinical hematologist/immunologist	Diagnosis, follow-up for hemopathy or immune deficiency	Follow-up: once or twice a year, alternating with the nephrologist
Nutritionist, diabetes specialist	Management and monitoring of obesity, diabetes	Follow-up: once or twice a year
Gastroenterologist	Management and monitoring of chronic inflammatory disease or diarrhea	Follow-up: once or twice a year
Dermatologist	Management and monitoring of dermatosis integrated into a systemic disease responsible for AA amyloidosis	As needed
Pneumologist	Management and monitoring of a pulmonary affliction	Based on the presence or absence of pulmonary impairment
Infectologist	Management and monitoring of a chronic infection	Follow-up: once or twice a year, alternating with the nephrologist
Cardiologist	Cardiac comorbidities	As needed
General practitioner	Management and monitoring. Care coordination. Screening for complications and adverse effects of treatments, management of associated comorbidities.	Follow-up: 2-4 times per year, alternating with the other specialists
Physical therapist	Management and monitoring of effects on joints	As needed for the joints
Psychologist	Management and monitoring of any psychological repercussions	Based on the patient's needs

In general, first-line therapy no longer includes the use of powerful immunosuppressant medications, with non-specific action and major short- and medium-term adverse effects (essentially cyclophosphamide and chloraminophene). Biologic therapies are now the most-used treatments: primarily anti-TNF, anti-IL-1, anti-IL-6R [2,3,5,19].

The rarity of AA amyloidosis explains the absence of solid clinical trials comparing the efficacy of these treatments, including for amyloidosis complicating the most common inflammatory diseases. Only case studies have been reported. Overall, variable clinical responses have been observed with anti-TNF and anti-IL-6, using renal impairment (proteinuria and renal failure) as the assessment criterion. Responses are most often assessed over the short or medium term; long-term responses are rarely known. Remission of the nephrotic syndrome is possible. The benefit is even more significant when treatment is early and permits the complete disappearance of the inflammatory syndrome [20–22].

Some situations pose particular problems:

- Familial Mediterranean fever (FMF) amyloidosis: Colchicine is the only medication that has proven effective in preventing AA amyloidosis and remains the first-line treatment for this complication. Colchicine alone at the maximum dose (2.5–3 mg per day subject to renal function normality) can cause the regression and disappearance of a nephrotic syndrome. If the nephrotic syndrome is resistant to colchicine, anti-IL-1 biotherapy can be added while continuing with 1 mg of colchicine per day. In the event of advanced renal failure (GFR < 30 ml/min.), colchicine should be stopped and replaced by an IL-1 inhibitor, usually anakinra at the hemodialysis stage [23]. When a kidney transplantation is done, we recommend continuing the anakinra for several months after the transplant and resuming colchicine, usually at the 1 mg/day dose, as soon as renal function allows it while gradually discontinuing the anakinra.
- Amyloidosis where obesity is the only well-defined amyloidosis risk factor. The first-line treatment here is weight loss, accompanied by decreased blood inflammation. Dieting is usually insufficient, and bariatric surgery may be discussed. The risk of renal function degradation related to the surgical intervention is a major element in the treatment decision. Anti-IL-1 and anti-IL-6 biotherapies in this context has not been proven and should be discussed in National multidisciplinary meeting.
- AA amyloidosis with no identified inflammatory disease. In this situation, anakinra has been used with some success but also tocilizumab; indeed an expert opinion should be obtained for these patients [5,19].

4.3.2. Renal protection

Non-specific nephroprotection measures are proposed in the majority of nephropathies with renal failure and/or proteinuria, for long-term preservation of nephronic capital. These therapeutic interventions have never truly been evaluated in the specific context of AA amyloidosis, but they are also applied here by extension.

4.3.2.1. Anti-proteinuria treatment. The use of an anti-hypertensive treatment such as an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II AT1-receptor antagonist (ARA-II) is classically proposed for glomerular nephropathies accompanied by albuminemia > 300 mg/24 hr. This treatment's benefit to preserving renal function has been clearly demonstrated in diabetic nephropathy or in certain primitive glomerular nephropathies (IgA nephropathy, extra-membranous glomerulonephritis), but no trial has specifically studied its efficacy in amyloidosis. Two studies focusing on small populations showed that losartan was able to reduce pro-

teinuria and significantly improve albuminemia in patients with AA amyloidosis, but this drug's effect on preserving medium- or long-term renal function has not yet been proven. In addition, the clinician must be very cautious in prescribing these drugs for amyloidosis (whether the indication is renal or cardiac), because these are often hypotensive patients (independent neuropathy, adrenal failure, or hypovolemia due to capillary leakage), who can be made even more symptomatic by this treatment. Furthermore, it is necessary to inform a patient being treated with ACE inhibitors or ARA-II that this treatment must be stopped if an intercurrent event occurs, such as diarrhea or another cause of dehydration [24,25]. This is because the appearance of hypovolemia in a patient whose renin/angiotensin system is inhibited can involve the risk of severe acute renal failure, usually temporary but sometimes permanent, in particular if the patient is receiving a diuretic treatment for the oedematous syndrome induced by the nephrotic syndrome.

4.3.2.2. Anti-hypertensive treatment. When the patient remains hypertensive in spite of prescribed ACE inhibitors or ARA-II (which are often given as the first-line treatment), it is necessary to add other drug classes, such as a calcium inhibitor or diuretic. However, it must be emphasized that this situation is rare in amyloid nephropathy (unlike diabetic nephropathy or other types of glomerulonephritis), because patients with amyloidosis are usually hypotensive even before anti-hypertension drugs are introduced.

4.3.2.3. Adjustment to the dietary regime. The protein restriction normally proposed for chronic renal failure cases does not automatically apply to renal amyloidosis. This is because nephrotic patients present hypoprotidemia requiring that a dietary protein intake greater than 1.2 g/kg/day be maintained. As to sodium intake, it should be limited when there is significant edema, but should be adjusted for daily losses when there is chronic diarrhea or adrenal failure secondary to the amyloidosis. The fluid restriction should be imposed only if hyponatremia is present.

4.3.2.4. Elimination of nephrotoxic medications. To the extent possible, it is necessary to avoid giving any nephrotoxic medication (such as non-steroid anti-inflammatory drugs, aminoglycosides, nephrotoxic chemotherapies such as platinum salts, etc.) to a patient with chronic renal failure. In addition, radiologic studies with injection of iodized contrast agents should be proposed with caution and preceded by pre-hydration to limit tubulopathy secondary to these potentially nephrotoxic drugs when they are prescribed to a patient with renal failure or hypovolemia.

4.3.2.5. Control of other metabolic and cardiovascular risk factors. Controlling the glycemia balance in diabetes cases, smoking cessation, management of dyslipidemia (often aggravated by the nephrotic syndrome) are essential elements in slowing the progression of nephropathy, but also in limiting cardiovascular risk, the leading cause of death in renal failure patients.

4.3.3. Management of end-stage renal failure

Patients with end-stage renal failure can be treated with peritoneal dialysis or hemodialysis, but peritoneal dialysis runs the risk of aggravating hypoalbuminemia. The prognosis for dialyzed patients with AA amyloidosis is poor, with an average survival of 20-50 months depending on the type of population. One study reports the absence of any benefit from biotherapies on the survival of hemodialized patients. Renal transplantation improves overall patient prognosis and survival, but it is still lower than for patients receiving transplants due to end-stage chronic renal failure with a different cause. However, survival of the transplanted organs is at least similar to that with other causes of end-stage renal failure [26,27][3].

4.4. Therapeutic education and lifestyle modification

In 2022, an education program dedicated to AA amyloidosis was developped in collaboration with the patients association and the French nationale reference center for AA amyloidosis.

Quality of life especially is altered by dialysis, which can also impact professional life.

Some patients have significant asthenia, which impairs them in their daily activities.

4.5. Amyloidosis patient associations

There is a very dynamic and well-organized association for amyloidosis patients in France: the French Amyloidosis Association (Association Française contre l'Amylose – AFCA).

Website: http://www.amylose.asso.fr/

Exchanges between members afflicted with the disease are possible.

A booklet about the disease is available on the association's website.

A webcast on AA amyloidosis has been produced in collaboration with the patient association and is available on YouTube: https://www.youtube.com/watch?v=A4SdgZi2fMA

Referral to a psychologist is possible through the patient association.

A social worker can also counsel patents and families through the administrative processes.

Recently, an international patient's association was created: https://www.amyloidosisalliance.org/.

5. Follow-up

5.1. Objectives

The objectives of follow-up care, in addition to rapid and complete control of inflammation, are monitoring renal function and prognostic factors including albuminemia and serum SAA concentration (Box 2).

As for all patients with chronic renal disease, it is necessary to screen for and treat complications of chronic renal disease – anemia, hyperkalemia, metabolic acidosis, phosphorous-calcium, vitamin and bone disorders – and to decrease the cardiovascular risk.

At a later stage, and in the event of unfavorable progress, it will be necessary to adequately anticipate preparation for replacement treatments: dialysis and/or kidney transplant, including the creation of venous access ports because the development of a fistula can be difficult.

It is particularly important to keep vaccines (annual flu and pneumococcus) up to date and optimized in order to prevent infectious episodes in this fragile population, and even more so for patients treated with anti-cytokine antibodies (see the 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases).

Therapeutic tolerance and compliance will be systematically verified.

[3] For more information: https://www.has-sante.fr/plugins/ModuleXitiKLEE/types/FileDocument/doXiti.jsp?id=p_3289324

5.2. Frequency and content of consultations

Table 4 lists the visit frequency.

The severity of renal impairment is a determining factor for the frequency of visits to the nephrologist[4].

If there is no renal impairment, the patient can be followed by only an internist specializing in amyloidosis. Otherwise, 2 visits per year to the nephrologist should be alternated with 2 per year to the internist. In cases with a specific cause (infection, obesity, rheumatology, etc.), the specialist concerned should be seen once or twice a year. We propose that care be coordinated by the internist or nephrologist.

5.3. Additional examinations

General exams: 4 times a year: CRP, CBC, renal function (creatininemia measurement and estimate of GFR using the MDRD or CKD-EPI formulas), and proteinuria (part of the proteinuria/creatininuria report for a urine sample), associated with albuminemia levels in the event of glomerular proteinuria.

If SAA is correlated with CRP, it can be done just once a year.

A sheet containing these biological elements is welcome, correlated to the treatment received by the patient over time.

Specific exams: depending on the cause, imaging if the cause is rheumatologic, neoplastic, or tuberculosis.

5.4. Pregnancy, breastfeeding, and AA amyloidosis

The occurrence of a pregnancy in a patient being treated for AA amyloidosis is a rare situation but is usually at risk for complications. The reported cases concern essentially patients being treated for FMF [28–30]. Pregnancy in this context can be complicated by spontaneous miscarriage, pre-eclampsia with a risk of delayed intra-uterine growth, and even intra-uterine fetal death. There is a risk of renal function deterioration, depending on the initial renal failure stage and on proteinuria levels. Patients who experience a deterioration in renal function usually have renal failure and/or proteinuria $\geq$ 2 g/24 hr at the time of conception. In addition, controlling the inflammation with a treatment adapted to the causative disease is vital in order for the best conditions to be maintained. Some authors have hypothesized that pregnancy may be a precipitating factor for amyloidosis due to a moderately pro-inflammatory state resulting from the secretion of cytokines derived from the placenta or extra-placental membranes.

It is also necessary to ensure the absence of any drug-related contraindications to the progress of the pregnancy and to plan for an alternate treatment if needed. Treatment will be subject to the advice of experts and adapted to the data from the literature, updated when the pregnancy occurs.

The decision to authorize a pregnancy should therefore be made in consultation with colleagues, depending on the cause of the AA amyloidosis and based on the opinions of the referring physician and the nephrologist, and after having given clear, reliable, and comprehensible information to the patient so that she can make the decision with full understanding of the situation. In this case, the patient should be seen for monitoring at least every 2 months and have additional monthly inflammation, renal function, and proteinuria tests.

Breastfeeding is not an automatic contraindication, but will depend on the mother's treatments and the risks to the breastfed infant.

[4] Guide du parcours de soins – Maladie rénale chronique de l'adulte (MRC). https://www.has-sante.fr/plugins/ModuleXitiKLEE/types/FileDocument/doXiti.jsp?id=p_3289324

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SGL, GG, JJB, DB and LS wrote the first draft of the manuscript; SF, JPB and AK participated to writing. All authors participated to edition. All authors read and approved the final version of the manuscript.

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The French version is available free of charge on the following link: Haute Autorité de Santé - Amylose AA (has-sante.fr).

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