

AA Amyloidosis in Africa: Epidemiology, Etiologies, Diagnostic Gaps, and Therapeutic Perspectives

Running title: AA Amyloidosis in Africa Etiologies and Management

Authors :

Ghalia Khellaf^{1,2}, Hamza Boucenna^{1,3}, Ali Benziane^{1,2}

Affiliations :

¹University Health of sciences Dr Youcef ElKhattib, Faculty of Medicine, Algiers, Algeria.

²Nephrology Department, Babeloued University Hospital Center, Algiers, Algeria.

³Pediatrics Department, Beni Messous University Hospital Center, Algiers, Algeria.

Corresponding Author:

Ghalia Khellaf MD, PhD -Orcid number : [0000-0002-5041-9243](https://orcid.org/0000-0002-5041-9243)

Department of Nephrology, Hemodialysis, Apheresis, and Renal Transplantation, Mohamed Lamine Debaghine

University Hospital Center (CHU Bab El Oued), Algiers 16000, Algeria.

Faculty of Medicine, University of Health Sciences, Ziania Campus, Algiers, Algeria.

Email : g.khellaf@yahoo.fr

DOI: <https://doi.org/10.5281/zenodo.21052887>

Received: 04 June 2026, Accepted: 23 June 2026, Online First: 01 July 2026

ABSTRACT

This review synthesizes epidemiological data from Algeria (378 cases), Tunisia (310 cases), Morocco (30 cases), Egypt (40 cases) and sub-Saharan Africa (autopsy incidence 0.28-0.57%). Tuberculosis remains the leading cause in all Maghreb countries, while Algeria shows a documented increase in autoinflammatory diseases; familial Mediterranean fever (FMF) predominates as the leading cause in Egypt. Diagnostic gaps include the absence of mass spectrometry in all African countries, limited anti-AA immunohistochemistry in sub-Saharan Africa, and no routine SAP scintigraphy. Therapeutic access is highly contrasted: adalimumab is available in several Maghreb countries, anakinra in Algeria (TRAPS approval 2025), and canakinumab is virtually absent. We propose national registries (based on the Egyptian FMF registry and the Armenian NAREG model), South-North telepathology, and expanded access to biotherapies through biosimilars.

Keywords: AA amyloidosis, Africa, diagnosis, SAP scintigraphy, Congo red, tuberculosis, FMF, autoinflammatory diseases, biotherapies.

1. INTRODUCTION

Amyloidosis is a heterogeneous group of disorders characterized by the extracellular deposition of misfolded proteins as insoluble fibrils, leading to progressive organ dysfunction ¹. Secondary AA amyloidosis results from the accumulation of fibrils derived from serum amyloid A protein (SAA), an acute-phase protein produced by the liver in response to chronic inflammation². Persistent elevation of SAA, particularly in the context of chronic inflammatory and infectious diseases, promotes misfolding and tissue deposition ³.

In Africa, AA amyloidosis represents a significant public health concern, but epidemiological data remain fragmentary. The autopsy incidence in sub-Saharan Africa is estimated between 0.28% and 0.57%, with AA amyloidosis being the most frequent (42-66% of cases)⁴

. The main etiologies are chronic infections, especially tuberculosis⁵. Renal involvement is the most frequent and severe manifestation, classically presenting with proteinuria, nephrotic syndrome, and progressive chronic kidney disease ⁶.

This review aims to:

- (i) summarize available epidemiological data from North and sub-Saharan Africa;
- (ii) highlight diagnostic challenges and therapeutic gaps;
- (iii) describe the emerging role of autoinflammatory diseases, especially FMF;
- (iv) discuss access to biotherapies; and (v) propose concrete perspectives to improve patient management.

However, no comprehensive review has summarized the epidemiology, diagnostic limitations and therapeutic challenges of AA amyloidosis across Africa.

This review provides the first continent-wide synthesis of AA amyloidosis in Africa by integrating epidemiological evidence, diagnostic infrastructure, genetic data, and therapeutic accessibility.

2. Epidemiology of AA Amyloidosis in Africa

2.1. North Africa

2.1.1. Algeria

The retrospective study by Khellaf et al.⁶ involving 378 patients over a 20-year period (1994–2014) demonstrated a major epidemiological transition. The results show an increase in inflammatory diseases from 42.8% to 54.6% ($p < 0.0011$) and a decrease in idiopathic causes from 29.7% to 19.7% ($p < 0.042$)⁶. This evolution reflects progress in antibiotic therapy and the national tuberculosis control program. Despite this increase in chronic and hereditary autoinflammatory diseases, tuberculosis remains the most frequent cause of AA amyloidosis in Algeria⁶. The resurgence of autoinflammatory diseases, particularly FMF, is due to better etiological identification through advances in genetic diagnosis. Genetic studies conducted between 2007 and 2015 on 183 Algerian patients suspected of FMF identified the

p.M694I mutation as the most prevalent, representing 63.2% of mutated alleles, followed by p.M694V (15.13%) and p.M680I (13.81%)⁷. The p.M694I mutation is specific to the Arab population of the Maghreb⁸[7]. Furthermore, a dedicated study on renal involvement in Algerian FMF patients confirmed that AA amyloidosis is the major long-term complication, with a high frequency of the M694I mutation⁹.

Genetic diagnosis delay in Algeria. While Egypt, Tunisia and Morocco had established local genetic testing for FMF from the 1990s-2000s, Algeria faced a long delay. In Algeria, Mrs. Ait-Idir, a biologist at Houari Boumediene University (Bab Ezzouar), was the first to perform *MEFV* exon 10 analysis locally. As demand increased and due to a shortage of reagents, some samples - particularly those requiring analysis of all exons of the *MEFV* gene - were sent to a private provider, the CERBA laboratory in France. This outsourcing was a temporary solution to cope with the growing number of requests, but it remained the only option for nearly two decades. Only in the last two years (2024–2025) have three Algerian university hospitals acquired a comprehensive panel for hereditary autoinflammatory diseases, ending the long-standing reliance on external testing. Figure 1 illustrates the wide disparity in genetic testing availability across Africa, with North African countries (except Algeria until recently) having established *MEFV* analysis for years, while most of sub-Saharan Africa has no routine access.

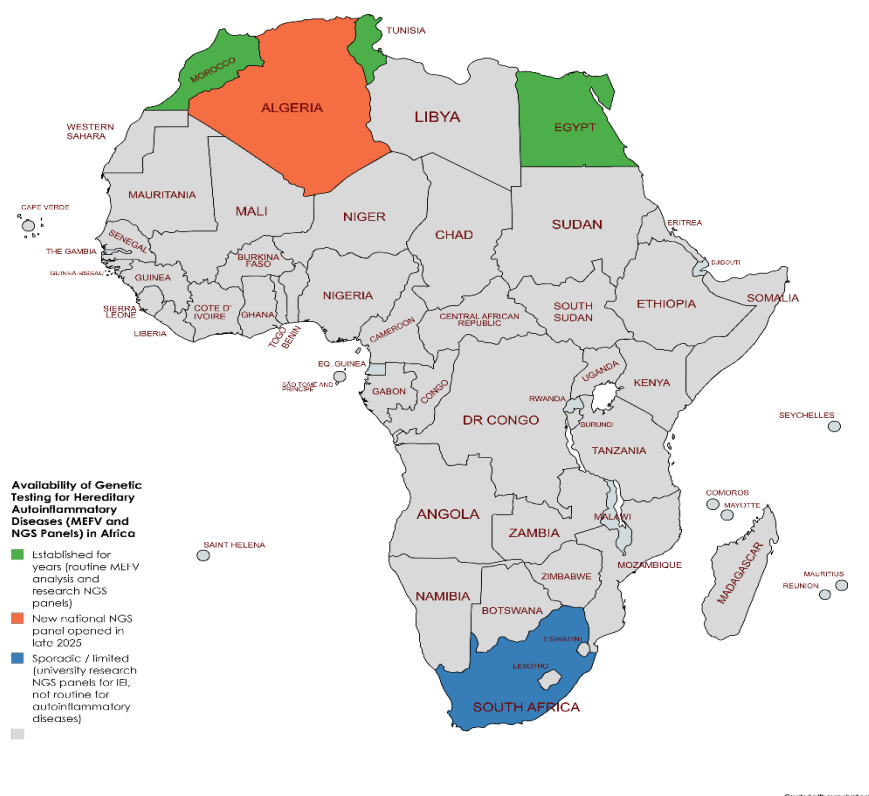


Figure 1 – Availability of genetic testing for hereditary autoinflammatory diseases (*MEFV* and NGS panels) in Africa

Green: established for years – Egypt, Tunisia, Morocco. Orange: new national NGS panel opened in late 2025 – Algeria. Light blue: advanced NGS capacity (clinical exome sequencing) – South Africa. Light grey: no access / no data – all other African countries. Data derived from [7, 8, 11, 19, 33, 42](#) and Algerian regulatory announcement (ANPP, 2025).

2.1.2. Tunisia

Kaaroud et al. ¹⁰ reported a series of 310 cases of renal amyloidosis over a 44-year period (1975–2019), of which 255 (82.3%) were AA type. Infections were the main cause, with tuberculosis being the most frequent etiology. The mean delay between the onset of the causative disease and the diagnosis of amyloidosis was 177 months, and 37.8% of patients were already at end-stage renal disease at diagnosis ⁹. FMF also exists in Tunisia, with M694V and M694I mutations representing 50% and 25% of cases, respectively ⁸.

2.1.3. Morocco

Bziz et al. [10] reported a series of 30 cases of renal AA amyloidosis, with a predominance of chronic infectious causes (60%), tuberculosis being the main etiology. Nephrotic syndrome was observed in 94% of patients. FMF exists in Morocco, with M694V (49%) and M694I (37%) mutations ⁸.

2.1.4. Egypt

Abdallah and Waked ¹¹ reported 40 cases of biopsy-proven renal amyloidosis (2003–2009), representing 2.5% of renal biopsies. AA amyloidosis

accounted for 80% of cases. FMF was the leading cause (30%), followed by pulmonary tuberculosis (20%)¹¹. This predominance of FMF as a cause of AA amyloidosis in Egypt is confirmed by other studies ^{12, 13}. The study by Beshlawy et al. ¹⁴ involving 500 pediatric FMF patients showed that 94.6% responded completely to colchicine, with an association between the M694V mutation and severe forms.

2.2. Summary for North Africa

Tuberculosis remains the most frequent cause of AA amyloidosis across North Africa (Algeria, Tunisia, Morocco). However, there is a significant increase in autoinflammatory diseases, particularly FMF, due to advances in genetic diagnosis. This trend is particularly marked in Algeria (documented epidemiological transition) and Egypt (where FMF has become the leading cause). Figure 2 provides a visual overview of the predominant etiologies across the continent, showing that tuberculosis still dominates most of Africa, while Egypt stands out with FMF as the primary cause and Algeria is in a transitional phase.

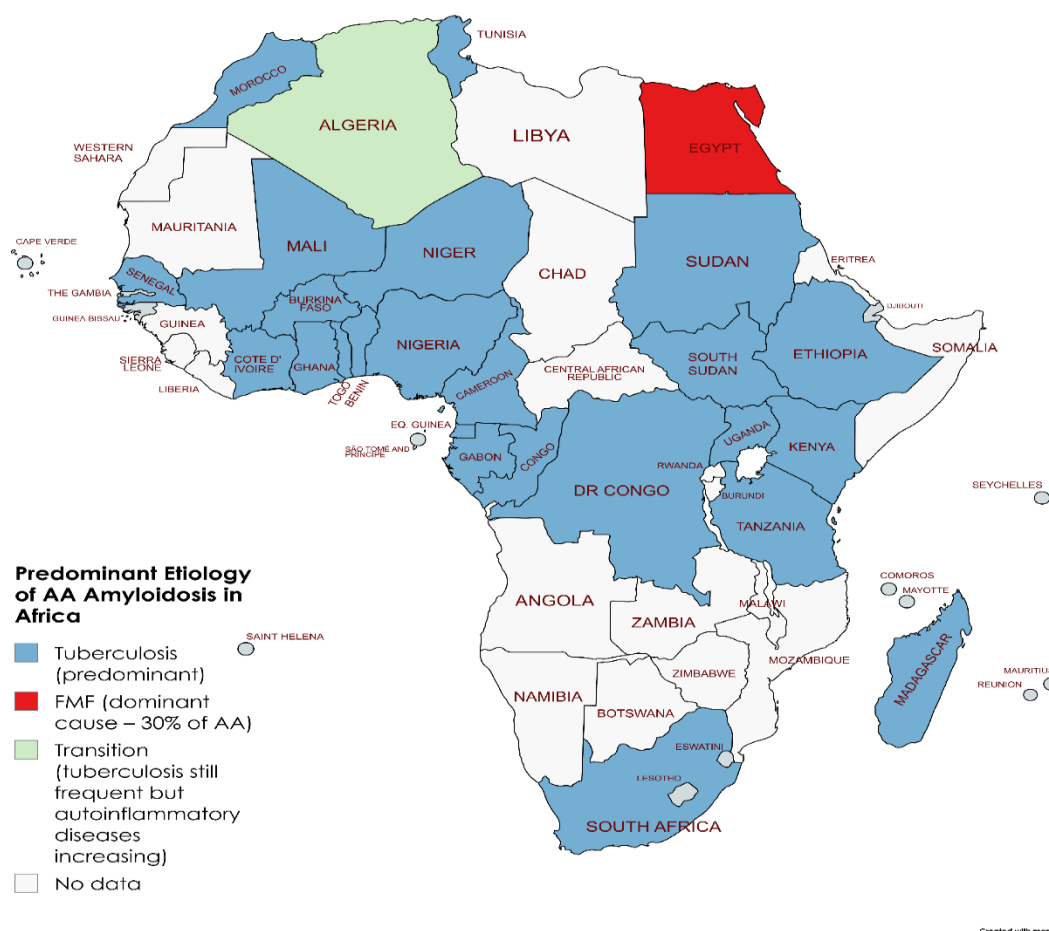


Figure 2 – Predominant etiology of AA amyloidosis in Africa

Dark blue: tuberculosis dominant – Tunisia, Morocco, Senegal, South Africa, most other countries. Red: FMF dominant (30% of AA) – Egypt. Orange: transitional phase – Algeria. Light grey: no data – most of sub-Saharan Africa. Data derived from ^{6, 10, 11, 17}.

2.3. Sub-Saharan Africa

Lekpa et al. ⁴ published a literature review on amyloidosis in sub-Saharan Africa. The autopsy incidence varies from 0.28% to 0.57%. Secondary AA amyloidosis is the most frequent, representing 42-66% of amyloidoses. Chronic infections, particularly tuberculosis, are the main cause, while autoinflammatory diseases such as FMF are exceptionally reported ⁴.

2.3.1. Senegal

Diallo et al. ¹⁵ reported a case of AA amyloidosis complicating lepromatous leprosy. Diouf et al. ¹⁶ reported 10 cases of systemic amyloidosis out of 3,602 systemic pathologies (0.28%). Autoinflammatory diseases are not documented.

2.3.2. South Africa

Hassen et al. ¹⁷ reported 46 cases of amyloidosis diagnosed on renal biopsy between 1985 and 2016, of which 20 (43%) were AA type and 26 (57%) were AL type. Among the AA cases, 60% were associated with tuberculosis, while HIV infection was documented in only two cases (10%). The median survival after

diagnosis was only 2 months, and no cases of FMF were reported.

Despite this, South Africa has emerged as a regional leader in genetic testing for rare diseases, including autoinflammatory conditions. However, a retrospective file review by Wiener et al. ¹⁸ revealed that 92% of patients with suspected genetic disorders remained undiagnosed after conventional first-tier tests, highlighting the urgent need for exome sequencing as a first-line diagnostic tool in resource-constrained settings. Importantly, Campbell et al. ¹⁹ provided tangible evidence that clinical exome sequencing can be successfully implemented in the state healthcare system, achieving a significant diagnostic yield in a cohort of South African infants with suspected genetic disorders.

Together, these studies demonstrate that while South Africa possesses the most advanced genomic infrastructure in sub-Saharan Africa, access to next-generation sequencing (NGS) panels for hereditary autoinflammatory diseases (including FMF) remains limited and should be scaled up. Currently, nationwide epidemiological data on FMF in the local population are still lacking, and the condition is likely underdiagnosed (see Table 1).

Table 1 – Epidemiological data by region

Region	Incidence/Prevalence	% AA	Main causes
Algeria	378 cases (20 years)	Predominant	Tuberculosis (remains most frequent); increasing autoinflammatory diseases (FMF)
Tunisia	310 cases (44 years)	82.3%	Tuberculosis; FMF present (M694V 50%, M694I 25%)
Morocco	30 cases (2 years)	Predominant	Tuberculosis (60%); FMF present (M694V 49%, M694I 37%)
Egypt	40 cases (6 years)	80%	FMF (30%) > tuberculosis (20%)
Sub-Saharan Africa	Autopsy 0.28-0.57%	42-66%	Tuberculosis, chronic infections; FMF exceptional
South Africa	1.38/100 biopsies	43% (57% AL)	Tuberculosis (60% of AA)

3. Diagnosis of AA Amyloidosis: From Congo Red to Mass Spectrometry

3.1. General principles

The diagnosis of AA amyloidosis relies on a multi-step histopathological approach: first, demonstration of amyloid deposits in a tissue sample (kidney, accessory salivary gland, abdominal fat, rectum); second, typing of deposits to distinguish AA from other forms (AL, ATTR, ALECT2, etc.). In specialized centers, advanced techniques allow precise typing and complete characterization ^{2, 20}.

3.2. Congo red staining and polarized light microscopy

Congo red staining is the gold standard for histologic detection of amyloid ^{2, 21}. Under polarized light, amyloid

produces characteristic apple-green birefringence ²¹. However, reliability depends on stain quality, section thickness, and pathologist's experience ²⁰. In resource-limited countries, the absence of polarizing microscopes or good-quality reagents limits access ⁴. Figure 3 illustrates the stark contrast in availability of Congo red staining across Africa: North African countries and South Africa have moderate to wide availability, while most of sub-Saharan Africa either lacks these techniques entirely or relies on non-specific stains such as Masson's trichrome, which cannot confirm amyloid.

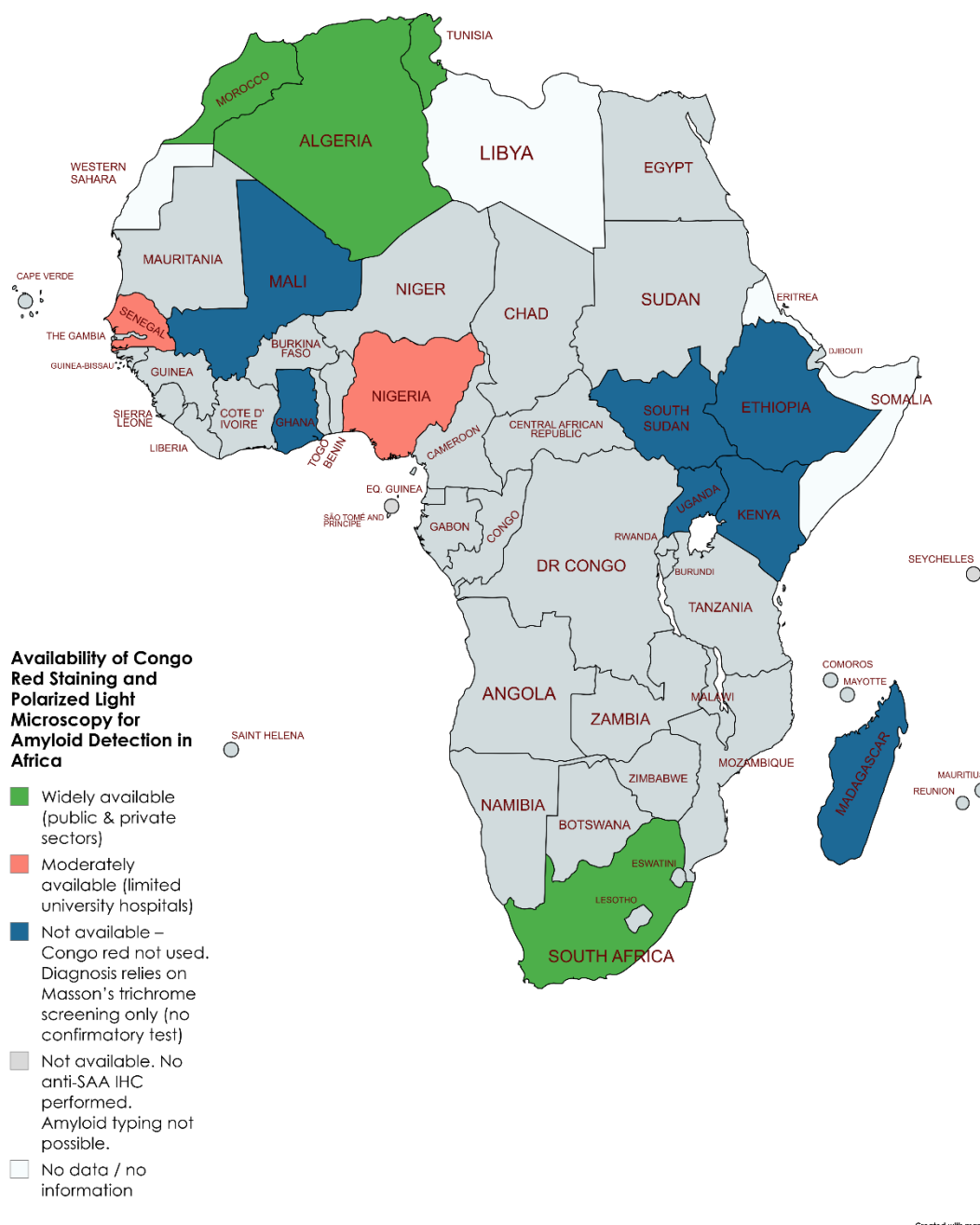


Figure 3 – Availability of Congo red staining and polarized light microscopy

Green: widely available – Algeria, Tunisia, Morocco, South Africa. Orange: moderately available – Egypt, Nigeria, Senegal. Light blue: sporadic – Ghana, Kenya, Ethiopia, Sudan, Mali. Light grey: not available / very limited – all other sub-Saharan African countries. Data derived from^{6, 10, 11, 17}.

3.3. Anti-SAA immunohistochemistry

Immunohistochemistry (IHC) using a monoclonal antibody against SAA is the most widely available routine method for typing². Strong positive staining with anti-SAA, combined with absence of staining with anti-immunoglobulin or anti-light-chain antibodies, confirms AA amyloidosis²⁰. This technique is crucial to differentiate AA from AL or ALECT2 amyloidosis. In Africa, anti-SAA IHC is available only in a few university hospitals in the Maghreb and South Africa; it is virtually absent elsewhere.

3.4. Mass spectrometry (proteomics)

In specialized centers, mass spectrometry is the gold standard for amyloid fibril typing²². It allows unambiguous identification of the precursor protein, even in mixed forms or when IHC is equivocal²⁰. This technique is expensive, requires heavy equipment, and is practically unavailable in sub-Saharan Africa and rarely available in the Maghreb⁴.

3.5. Immunofluorescence for light and heavy chains

Direct immunofluorescence can detect kappa or lambda light chains, and sometimes IgG, IgA, or IgM heavy chains. It is essential for diagnosing immunoglobulin-derived amyloidoses (AL, AHL, AH).

For AA amyloidosis, it is not routinely needed but helps rule out an incidentally associated AL amyloidosis. In Africa, this technique is exceptionally available⁴.

3.6. SAP scintigraphy: an unavailable tool in Africa
Serum amyloid P component (SAP) scintigraphy is the only non-invasive technique able to demonstrate whole-body amyloid burden^{23, 24}. It is particularly useful for confirming systemic AA amyloidosis, quantifying organ involvement, and monitoring response to treatment²⁵. However, due to the short half-life of ¹²³I (requiring a local cyclotron), high production cost, and need for specialized nuclear medicine expertise, SAP scintigraphy is currently unavailable in all African countries, including South Africa and the Maghreb. Consequently, histopathological confirmation with Congo red staining and anti-SAA IHC remains the diagnostic gold standard in Africa.

3.7. African data on AA amyloidosis diagnosis
Available data indicate that the diagnosis of AA amyloidosis in Africa relies almost exclusively on renal or accessory biopsy with Congo red staining⁴. In North

Africa, hospital series have published histological results from renal biopsies^{10, 11}. In South Africa, a series of 46 renal amyloidosis cases reported 43% as AA type¹⁷. In Senegal, a case was confirmed by renal biopsy and Congo red staining¹⁵. Anti-SAA IHC is rarely mentioned, and mass spectrometry is not available in routine practice⁴. Therefore, there is an urgent need to strengthen diagnostic capacities to improve patient management^{4, 20}.

4. Etiologies: Focus on Autoinflammatory Diseases

In Algeria, the study by Khellaf et al.⁶ shows a resurgence of chronic and hereditary autoinflammatory diseases due to advances in genetic diagnosis, but tuberculosis remains the most frequent cause. In Egypt, FMF has become the leading cause of AA amyloidosis¹¹ [11], with a high prevalence of p.M694I (36.7%) and p.M694V (7.94%) mutations²⁶. The p.M694I mutation is specific to the Arab population of the Maghreb⁸. A summary of etiological features by country is provided in Table 2 and illustrated in Figure 2.

Table 2 – Etiologies of AA amyloidosis in Africa

Country	Tuberculosis	FMF	Other inflammatory diseases	Genetic specificities
Algeria	+++ (remains most frequent)	++ (increasing)	IBD, RA, hidradenitis suppurativa	Documented transition; p.M694I predominant (63.2%)
Tunisia	+++	+	RA, IBD	p.M694V (50%), p.M694I (25%)
Morocco	+++	+	RA, IBD	p.M694V (49%), p.M694I (37%)
Egypt	++	+++ (30% of AA)	RA	p.M694I (36.7%), p.M694V (7.94%); M694V associated with amyloidosis
Sub-Saharan Africa	+++	Exceptional	Rare	Not documented
South Africa	+++	Not reported (likely underdiagnosed)	Rare	Advanced genetic infrastructure but limited FMF data

5. Diagnostic and Therapeutic Challenges in North Africa

5.1. Access to Diagnostic Biopsy Services
Access to confirmatory biopsy services for AA amyloidosis diagnosis remains uneven across Africa. In North Africa, university hospitals have moderate availability of Congo red staining, the gold standard histologic stain for amyloid detection^{2, 21}, but this is largely restricted to major academic centers, limiting access for patients in peripheral regions. Anti-SAA immunohistochemistry (IHC) is not universally available, further delaying or preventing proper AA typing²⁰. In Algeria, diagnosis relies on a rigorous histopathological approach, but immunohistochemical

typing remains limited to anti-AA antibodies without extended panels, exposing patients to diagnostic errors^{26, 27}. In contrast, most of sub-Saharan Africa lacks specialized staining and polarized light microscopy entirely, relying on non-specific histology⁴. A pilot study identified granuloma as a potential site for SAA-derived amyloid deposition in tuberculosis patients³, but such early detection strategies are not routine.

5.2. Availability of Disease-modifying Therapies
The cornerstone of AA amyloidosis management is suppressing the underlying inflammatory or infectious trigger²⁸. In resource-rich settings, biologic agents

Access to these therapies is highly unequal. Colchicine is widely available and inexpensive³¹. In contrast, adalimumab is available in several North African countries and South Africa, but access is restricted by high cost and lack of universal reimbursement³³. Anakinra has been approved only in Algeria (for TRAPS, 2025)³⁰. Canakinumab remains virtually absent across the continent^{33, 34}. Thus, expanding access to biologic agents and ensuring their affordability are urgent priorities for North Africa.



Green: widely available – South Africa. Orange: adalimumab (biosimilar) + anakinra – Algeria. Light blue: adalimumab available (limited) – Morocco, Tunisia, Egypt. Yellow: very limited – rituximab available but very expensive; anti-TNF in only 4% of centers – Senegal, Burkina Faso, Niger, Guinea, Togo, Côte d'Ivoire, Cameroon, Mali, Benin, Chad, Mauritania, Tanzania (Zanzibar). Light grey: not available / no data – all other African countries. Data derived from [33](#), [38](#) and national regulatory approvals.

³¹. For tuberculosis-associated AA, effective anti-tuberculous treatment can halt disease progression⁶. For chronic inflammatory diseases such as rheumatoid arthritis and hidradenitis suppurativa, anti-TNF agents (e.g., adalimumab) have been used successfully^{29, 30}.

However, across most of Africa, therapy remains limited to traditional DMARDs, which are often insufficient for severe cases. Therefore, early etiologic diagnosis and targeted treatment are critical to prevent irreversible renal damage.

6. Public Health Implications and Recommendations

6.1. Surveillance and Registry Opportunities

Robust epidemiological surveillance through national registries is indispensable for understanding the AA amyloidosis burden and guiding health policy, but remains largely absent across Africa³⁵. Only Egypt has an established FMF registry¹². Based on the Armenian NAREG model³⁶, implementing similar registries in Morocco, Tunisia, and Algeria is crucial for

documenting disease incidence, prevalence, etiologies, and treatment outcomes.

6.2. Health System Strengthening and Resource Allocation

Strengthening laboratory and pathology infrastructure is critical for improving AA amyloidosis diagnosis across the continent. Expanding Congo red staining and polarized light microscopy services to district hospitals, enhancing training for pathologists on proper Congo red staining and birefringence interpretation²⁰, and supporting capacity for anti-SAA IHC to enable accurate typing are essential. National tuberculosis control programs have already reduced infectious causes of AA amyloidosis in Algeria⁶, but similar structured approaches are needed for other chronic inflammatory conditions.

Table 3 – Availability of diagnostic tools, treatments and registries for AA amyloidosis in African countries

Country	Congo red & biopsy	Anti-AA IHC	Mass spectrometry	Colchicine	Adalimumab	Anakinra	Canakinumab	Registry
Algeria	Yes (univ. hospitals)	Yes (limited)	No	Yes	Yes	Limited (TRAPS approval)	No	No
Tunisia	Yes (univ. hospitals)	Yes	No	Yes	Limited	No	No	No
Morocco	Yes (univ. hospitals)	Yes	No	Yes	Limited	No	No	No
Egypt	Yes	Yes	No (research only)	Yes	Limited	No	No	Yes (FMF)
Senegal	Limited (Dantec Hospital)	No	No	Yes	No	No	No	No
South Africa	Yes	Yes	No	Yes	Yes (private sector)	Very limited	Very limited	No
Rest of Africa	No (except rare hospitals)	No	No	Variable	No	No	No	No

Legend for Table 3:

Yes = Available

No = Not available

Limited = Available but with restrictions (access, cost, or limited centers)

Very limited = Exceptionally rare, only in specific research or compassionate use

Variable = Availability differs across countries (mostly available but not universal)

6.3. Education and Awareness Campaigns

Educational initiatives targeting clinicians who manage chronic inflammatory diseases are paramount, as many cases of AA amyloidosis are likely underdiagnosed⁴. Integrating AA amyloidosis awareness into medical school curricula and specialist training (rheumatology, nephrology, gastroenterology, internal medicine) is necessary. Raising public awareness about the link between chronic inflammation and kidney disease is

also critical for early detection and improving outcomes.

6.4. Research Gaps and Future Directions

Major research gaps need to be addressed. Comprehensive multi-center cohort studies are lacking across Africa to better define true incidence, risk factors, and clinical outcomes^{4, 37}. Developing and validating point-of-care tests for AA detection could greatly improve early diagnosis. Health economic and

implementation studies should explore the cost-effectiveness of screening programs, registry development, and diagnostic scale-up. Finally, rigorous trials and collaborative efforts are needed to make biologic agents accessible and affordable to patients on the continent^{38, 39}.

7. Limitations

- Most available studies were retrospective.
- Few multicenter studies exist.
- Limited genetic databases.
- Publication bias cannot be excluded.

8. DISCUSSION

This review highlights important regional differences in the epidemiology, diagnosis, and management of AA amyloidosis across Africa. Tuberculosis remains the predominant underlying cause in most African countries, particularly in North Africa and sub-Saharan Africa, reflecting the continued burden of chronic infectious diseases. However, a significant epidemiological transition is emerging in some North African countries, especially Algeria and Egypt, where hereditary autoinflammatory diseases, particularly familial Mediterranean fever (FMF), are increasingly recognized because of improved genetic testing and greater clinical awareness.

The findings also reveal substantial disparities in diagnostic capacity across the continent. While renal biopsy with Congo red staining is available in most university hospitals in North Africa and South Africa, advanced diagnostic techniques such as anti-SAA immunohistochemistry, laser microdissection, and mass spectrometry remain unavailable or extremely limited in routine clinical practice. The complete absence of SAP scintigraphy throughout Africa further restricts disease assessment and therapeutic monitoring. These limitations may contribute to delayed diagnosis, inappropriate amyloid typing, and underestimation of the true disease burden.

Access to disease-modifying therapies is similarly heterogeneous. Colchicine is widely available for FMF-associated AA amyloidosis; however, access to biologic agents targeting TNF- α , IL-1, and IL-6 remains limited because of high costs, restricted reimbursement policies, and insufficient healthcare infrastructure. Although adalimumab is available in several North African countries and South Africa, anakinra has only recently become available in Algeria, whereas canakinumab remains largely inaccessible across the continent. Expanding access to biosimilars may represent a practical strategy for improving treatment availability in low- and middle-income African countries.

Compared with Europe and North America, where chronic inflammatory rheumatic diseases are the principal causes of AA amyloidosis, the African disease profile continues to be dominated by infectious diseases, particularly tuberculosis. Nevertheless, the

increasing recognition of FMF and other hereditary autoinflammatory disorders suggests that the epidemiology of AA amyloidosis in Africa is evolving. This transition emphasizes the need for wider implementation of molecular genetic testing and improved clinician awareness to facilitate earlier diagnosis.

The review also identifies several important knowledge gaps. Most published African studies are retrospective, single-center investigations with relatively small sample sizes, and comprehensive multicenter registries are largely absent. Consequently, reliable estimates of disease incidence, prevalence, long-term outcomes, and therapeutic effectiveness remain limited. Future collaborative research involving multiple African countries is essential to establish standardized epidemiological databases, evaluate diagnostic strategies, and optimize evidence-based management. Overall, strengthening pathology services, expanding access to advanced diagnostic technologies and biologic therapies, implementing national and regional disease registries, and promoting international research collaborations should be considered priority strategies to improve the diagnosis, treatment, and long-term outcomes of patients with AA amyloidosis across Africa.

9. CONCLUSION

AA amyloidosis in Africa is an underdiagnosed condition whose prevalence varies significantly by region. In sub-Saharan Africa, it remains dominated by tuberculosis and chronic infections, with an autopsy incidence estimated between 0.28% and 0.57%⁴. In North Africa, tuberculosis remains the most frequent cause, but there is a documented resurgence of chronic and hereditary autoinflammatory diseases, particularly FMF, thanks to advances in genetic diagnosis⁶. Egypt stands out with FMF predominance as the leading cause of AA amyloidosis¹¹. The p.M694I mutation is specific to the Maghreb population, while the Egyptian mutational spectrum also includes p.M694I and p.M694V, with M694V associated with more severe disease and amyloidosis risk^{11, 14, 26}.

Significant diagnostic gaps persist across the continent: absence of mass spectrometry for amyloid typing in all African countries, limited access to immunohistochemistry in sub-Saharan Africa, and unavailability of SAP scintigraphy in routine practice. Figure 3 clearly shows that Congo red staining – the most basic confirmatory test for amyloid – is not available in most of sub-Saharan Africa. Therapeutic access is also highly unequal: adalimumab is available in several North African countries and South Africa; anakinra is available only in Algeria (TRAPS approval 2025); canakinumab is not available in North Africa and only very limited in South Africa (Figure 4).

AA amyloidosis is a preventable and treatable condition when the underlying inflammatory disease is properly managed³². In Africa, where tuberculosis remains

endemic ⁴⁰ and autoinflammatory diseases are increasingly recognized ⁴¹, improving diagnostic capacity and therapeutic access should become a public health priority. Concerted efforts are needed to establish national registries (modeled on Egypt's FMF registry and Armenia's NAREG), train local pathologists and clinicians, expand access to biotherapies through compassionate use programs and biosimilars, develop functional imaging techniques through South-North partnerships, and conduct cost-effectiveness studies to advocate for prevention-focused health policies. Future collaborative research, improved diagnostic infrastructure, and equitable access to biologic therapies are essential to reduce the burden of AA amyloidosis across Africa.

10. Funding

The authors received no external funding.

11. Data Availability

No new datasets were generated or analyzed during this review.

12. Ethical Approval

Not applicable because this study is a literature review.

13. Acknowledgements

The authors thank all researchers whose work contributed to this review.

14. Conflict of Interest

The authors declare no conflicts of interest. Ghalia Khellaf is the principal author and takes full responsibility for the integrity of the work.

15. REFERENCES

1. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med*. 2003;349(6):583–96.
2. Westermarck GT, Fändrich M, Westermarck P. AA amyloidosis: pathogenesis and targeted therapy. *Annu Rev Pathol*. 2015;10:321–44.
3. Said SS, Kühl MJ, Fevang BS, Nystad TW, Johansson KA. Treating rheumatoid arthritis in Zanzibar: a cost effectiveness study comparing conventional, biologic, and targeted-synthetic disease modifying anti-rheumatic drugs. *Front Med (Lausanne)*. 2025;12:1618493.
4. Lekpa FK, Ndongo S, Pouye A, Tiendrebeogo JW, Ndao AC, Ka MM, et al. [Amyloidosis in sub-Saharan Africa]. *Med Sante Trop*. 2012;22(3):275–8.
5. Banerjee S BJ, Daniel C, Pfeiffer PB, Hitzenberger M, Kuhn L, Wiese S, Bijzet J, Haupt C, Amann KU, Zacharias M, Hazenberg BPC, Westermarck GT, Schmidt M, Fändrich M. Amyloid fibril structure from the vascular variant of

systemic AA amyloidosis. *Nature Communications*. 2022;13(1):7265.

6. Khellaf G, Benziane A, Kaci L, Benabadji M. AA renal amyloidosis: Clinical observations over 20 years. *Clin Nephrol*. 2022;97(3):167–72.
7. Ait-Idir D, Djerdjouri B. Differential mutational profiles of familial Mediterranean fever in North Africa. *Ann Hum Genet*. 2020;84(6):423–30.
8. Belmahi L, Sefiani A, Fouveau C, Feingold J, Delpech M, Grateau G, et al. Prevalence and distribution of MEFV mutations among Arabs from the Maghreb patients suffering from familial Mediterranean fever. *C R Biol*. 2006;329(2):71–4.
9. Khellaf G, Benziane A, Kaci L, Ait-Idir D, Missoum S, Benabadji M. Renal involvement in familial Mediterranean fever in an Algerian population. *Clin Nephrol*. 2023;99(4):172–9.
10. Kaaroud H, Harzallah A, Hajji M, Chargui S, Barbouch S, Turki S, et al. Renal Amyloidosis: Epidemiological, Clinical, and Laboratory Profile in Adults from One Nephrology Center. *Int J Nephrol*. 2022;2022:8493479.
11. Abdallah E, Waked E. Incidence and clinical outcome of renal amyloidosis: a retrospective study. *Saudi J Kidney Dis Transpl*. 2013;24(5):950–8.
12. Al-Haggar MS, Yahia S, Abdel-Hady D, Al-Saied A, Al-Kenawy R, Abo-El-Kasem R. Phenotype-genotype updates from familial Mediterranean fever database registry of Mansoura University Children' Hospital, Mansoura, Egypt. *Indian J Hum Genet*. 2014;20(1):43–50.
13. el-Garf A, Salah S, Iskander I, Salah H, Amin SN. MEFV mutations in Egyptian patients suffering from familial Mediterranean fever: analysis of 12 gene mutations. *Rheumatol Int*. 2010;30(10):1293–8.
14. Beshlawy AE, Zekri AER, Ramadan MS, Selim YMM, Abdel-Salam A, Hegazy MT, et al. Genotype-phenotype associations in familial Mediterranean fever: a study of 500 Egyptian pediatric patients. *Clin Rheumatol*. 2022;41(5):1511–21.
15. Diallo S, Diouf B, Niang A, Ka F, Dieng MT, Pouye A, et al. [Renal amylosis AA complicating lepromatous leprosy in Senegal: case report and review of the literature]. *Med Trop (Mars)*. 2005;65(6):605–7.
16. Diallo S, Ndao AC, Diédhiou I, Niasse M, Adogblé LM, Diouck FS, et al. Pathologies systémiques : étude multicentrique de 3602 observations au Sénégal. *Revue du Rhumatisme*. 2023;90:A231–A2.

17. Hassen M, Bates W, Moosa MR. Pattern of renal amyloidosis in South Africa. *BMC Nephrol.* 2019;20(1):406.
18. Wiener EK, Buchanan J, Krause A, Lombard Z. Retrospective file review shows limited genetic services fails most patients - an argument for the implementation of exome sequencing as a first-tier test in resource-constraint settings. *Orphanet J Rare Dis.* 2023;18(1):81.
19. Campbell L, Fredericks J, Mathivha K, Moshesh P, Coovadia A, Chirwa P, et al. The implementation and utility of clinical exome sequencing in a South African infant cohort. *Front Genet.* 2023;14:1277948.
20. Picken MM. Diagnosis of amyloid beyond Congo red. *Curr Opin Nephrol Hypertens.* 2021;30(3):303–9.
21. Puchtler H, Sweat F. Congo red as a stain for fluorescence microscopy of amyloid. *J Histochem Cytochem.* 1965;13(8):693–4.
22. Mattia Riefolo¹, Matteo Conti^{3,4}, Simone Longhi⁵, Benedetta Fabbri⁶ and Ornella Leone^{1*}. Amyloidosis: What does pathology offer? The evolving field of tissue biopsy. *Frontiers in Cardiovascular Medicine.* 2022;Volume 9 - 2022
23. Hawkins PN, Lavender JP, Pepys MB. Evaluation of systemic amyloidosis by scintigraphy with ¹²³I-labeled serum amyloid P component. *N Engl J Med.* 1990;323(8):508–13.
24. Hachulla E, Maulin L, Deveaux M, Facon T, Bl  try O, Vanhille P, et al. Prospective and serial study of primary amyloidosis with serum amyloid P component scintigraphy: from diagnosis to prognosis. *Am J Med.* 1996;101(1):77–87.
25. Richards DB, Cookson LM, Berges AC, Barton SV, Lane T, Ritter JM, et al. Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component. *N Engl J Med.* 2015;373(12):1106–14.
26. Trabzonlu L, Helland TL, Kwan MC, Kumiega N, Zhang ML, Chebib I, et al. Interobserver agreement and diagnostic challenges of Congo red staining for amyloid detection on fat pad aspiration biopsies. *J Am Soc Cytopathol.* 2024;13(5):359–66.
27. Buob D. [Amyloidosis - The pathologist's perspective]. *Ann Pathol.* 2024;44(6):414–22.
28. Ghosh S, Kala C, Garg A, Thakur AK. Amyloid deposition in granuloma of tuberculosis patients: A single-center pilot study. *Tuberculosis (Edinb).* 2022;136:102249.
29. Goldfinger SE. Colchicine for familial Mediterranean fever. *N Engl J Med.* 1972;287(25):1302.
30. Ghalia Khellaf SC, Houria Sahel, Rym Hadj Sahraoui, Nacima Djennane, Ali Benziane. Adalimumab for AA Amyloidosis Secondary to Severe Hidradenitis Suppurativa. *Case Reports in Nephrology.* 2026;2026(1 /5476216).
31. Alioua M TR, Djahdou Z, Arbaoui I, Mansouri K, editor Estimation of the Economic Burden of Renal Complications of Diabetes in Algeria Value in Health Info ISPOR Europe 2022; 2022 December 2022); Vienna, Austria.
32. Ahmet Gul Safak MOmer UOzge HGizem KIlay BStavros A DEleni F. AA Amyloidosis: A Contemporary View. *Curr Rheumatol Rep* 3 April 2024 26:248–59.
33. Missounga L, Iba Ba J, Nseng Nseng Ondo IR, Nziengui Madjinou MIC, Mwenpindi Malekou D, Mouendou Mouloungui EG, et al. Treatment of chronic inflammatory rheumatism by biotherapy in Gabon: eligibility and follow-up of the first 8 patients in sub-Saharan Africa. *Med Sante Trop.* 2018;28(2):197–200.
34. Bettiol A, Lopalco G, Emmi G, Cantarini L, Urban ML, Vitale A, et al. Unveiling the Efficacy, Safety, and Tolerability of Anti-Interleukin-1 Treatment in Monogenic and Multifactorial Autoinflammatory Diseases. *Int J Mol Sci.* 2019;20(8).
35. South Africa Amyloidosis Treatment Market Size & Outlook, 2033. In: Inc. GVR, editor. GVR-2-68038-443-72022,.
36. Group NS. National Armenian Registry of Autoimmune and Autoinflammatory Systemic Diseases (NAREG): A prospective longitudinal multicenter registry with biobanking. 2023.
37. Essouma M, Noubiap JJ. Lupus and other autoimmune diseases: Epidemiology in the population of African ancestry and diagnostic and management challenges in Africa. *J Allergy Clin Immunol Glob.* 2024;3(4):100288.
38. Ndour MAa b, Diedhiou Da, Dieng Ma, Ilboudo Ac, Diallo IMA, Djiba Ba, Champion Kb, Sarr Aa, Mouly Sb, S  ne Db. Biotherapy in sub-saharan Africa: status, challenges, limitations and future prospects: "biotheraf". *Revue Africaine de Medecine Interne.* 2023;10(01-01):19–27.
39. Kraus R, Yeung RSM, Persaud N. Biologic medicine inclusion in 138 national essential medicines lists. *Pediatr Rheumatol Online J.* 2021;19(1):140.

40. Otchere ID, Edem VF, Togun T, Yeboah-Manu D, Antonio M. Defying barriers to fight tuberculosis in West Africa: a model of equitable partnerships within a research capacity-strengthening network in the subregion. *Front Public Health*. 2025;13:1590282.
41. Jeffrey Hanover SBuchner R. The Incidence Rate of AL Amyloidosis: A Systematic Review and Meta-analysis. New Jersey Medical School. 2022–10–17
42. El-Bassyouni HT, Eldeen GN, Sokkar MF, Taher MB, Sayed-Ahmed MM, Salama II, et al. The relation of MEFV gene variants to clinical phenotype and selected laboratory markers in Egyptian patients with familial Mediterranean fever. *Journal of The Arab Society for Medical Research*. 2024;19(2):186–93.