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# Auto-inflammatory Diseases and Renal Involvement in Pediatric Rheumatology: A Review

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***Abstract***

Auto-inflammatory diseases (AIDs) are a diverse group of disorders characterized by inappropriate activation of the innate immune system, leading to chronic inflammation. In children, these conditions can significantly impact multiple organs, including the kidneys. This review article is based on the most recent studies published after 2020, focusing on various auto-inflammatory diseases and their impact on kidney function. The review aims to provide a comprehensive overview of auto-inflammatory diseases and their renal involvement in pediatric patients, focusing on advancements in understanding the molecular mechanisms, diagnostic strategies, and treatment options. By examining the latest research, this article aims to enhance clinical awareness of renal manifestations and improve management strategies for pediatric rheumatologists.

***Key Words:*** Amyloidosis, Auto-inflammatory diseases, Glomerulonephritis, Kidneys.

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## 1- INTRODUCTION

Auto-inflammatory diseases (AIDs) represent a group of disorders driven by aberrant activation of the innate immune system, leading to unregulated inflammation. While AIDs can affect various organs, the kidneys are particularly vulnerable, with renal involvement being a key feature in some of these diseases (Table 1). Pediatric rheumatologists play a crucial role in diagnosing and managing these conditions, especially when kidney function is compromised. The complexity of managing AIDs with renal involvement necessitates a deeper understanding of pathophysiological mechanisms and emerging treatment strategies. The underlying mechanisms of disease are highly diverse, ranging from amyloid deposition to non-amyloid kidney damage driven by inflammasome activation. Renal involvement in both monogenic and polygenic AIDs can manifest in various ways, including renal amyloidosis, IgA nephropathy, and, less commonly, different types of glomerulonephritis such as focal segmental glomerulosclerosis, collapsing glomerulopathy, fibrillary glomerulonephritis, or membranoproliferative glomerulonephritis. Vascular complications, including thrombosis, renal aneurysms, or pseudoaneurysms, may also occur, particularly in conditions like Behçet's disease. Therefore, regular monitoring of kidney function is essential in patients with AIDs to detect and manage renal involvement early.This review explores the pathogenesis, clinical features, diagnostic tools, and current treatment approaches for auto-inflammatory diseases with renal involvement in pediatric patients, with a focus on studies published after 2020.Auto-inflammatory diseases are primarily characterized by recurrent, self-limited episodes of systemic inflammation, often involving the skin, joints, and internal organs, including the kidneys. Kidney involvement in AIDs can range from mild proteinuria to severe nephropathy, including nephritis and end-stage kidney disease (1-4).

**Tables-1.**Renal Manifestation of auto-inflammatory diseases.

| Auto-inflammatory diseases | Renal Manifestation | Description |
|---|---|---|
| **Systemic Juvenile Idiopathic Arthritis (SJIA)** | Glomerulonephritis, Renal Amyloidosis | Renal complications in SJIA include glomerulonephritis and amyloidosis, especially in long-standing or severe cases. |
| **Familial Mediterranean Fever (FMF)** | Renal Amyloidosis | Chronic inflammation in FMF can lead to amyloid deposition in the kidneys, causing renal dysfunction over time. |
| **Cryopyrin-Associated Periodic Syndromes (cAPS)** | Renal Amyloidosis | cAPS can lead to renal amyloidosis due to persistent systemic inflammation, resulting in progressive kidney impairment. |
| **Muckle-Wells Syndrome (MWS)** | Renal Amyloidosis | Similar to other CAPS-related conditions, MWS may lead to kidney amyloidosis, resulting in renal dysfunction. |
| **Hyper-IgD Syndrome (HIDS)** | Renal Amyloidosis | In severe cases, HIDS can cause amyloidosis, leading to renal impairment. |
| **TNF Receptor-Associated Periodic Syndrome (TRAPS)** | Glomerulonephritis, Renal Amyloidosis | TRAPS may cause glomerulonephritis and renal amyloidosis due to prolonged inflammation. |

## 2- MATERIALS AND METHODS

This study is a narrative review based on a selected body of peer-reviewed literature and clinically relevant data on kidney involvement in autoinflammatory diseases. The review article synthesizes the most up-to-date research published after 2020, focusing on a wide range of autoimmune diseases and their effects on kidney function. It highlights the latest findings on how these conditions can lead to renal involvement, examining both the mechanisms behind kidney damage and the therapeutic approaches being explored to manage these complications.

## 3- DISCUSSION

### *Prevalence of Kidney Involvement in Autoinflammatory Diseases*

Kidney involvement in AIDs is not uniformly observed across all conditions within this category; however, it remains a significant clinical concern in several of these disorders, particularly when left chronic or inadequately treated. The prevalence and severity of renal involvement vary greatly depending on the specific autoinflammatory disease in question and the associated complications, such as amyloidosis or glomerulonephritis (3, 4).

While kidney manifestations are relatively frequent in certain AIDs, such as Familial Mediterranean Fever (FMF), they are less common in others like Muckle-Wells Syndrome (MWS), TNF Receptor-Associated Periodic Syndrome (TRAPS), and Hyper IgD Syndrome (HIDS). Regardless of prevalence, early recognition and prompt intervention—often with agents like colchicine, IL-1 inhibitors, and TNF inhibitors—remain paramount in mitigating renal involvement and preserving kidney function (4-6).

### *Familial Mediterranean Fever*

In FMF, kidney involvement is particularly prominent, with amyloidosis emerging as the most frequent and debilitating renal complication. Amyloid deposits, predominantly in the form of AA amyloid, gradually accumulate in various tissues, including the kidneys. These deposits are responsible for the development of nephrotic syndrome, with the potential to progress to renal failure if left unchecked.

In untreated or poorly managed FMF, the prevalence of renal amyloidosis can reach 20-30% of patients, marking it as the primary cause of kidney-related morbidity in this condition. The long-term consequences of amyloid deposition can be severe, leading to irreversible kidney damage and, ultimately, end-stage renal disease (ESRD) if not appropriately managed with colchicine or other anti-inflammatory agents. Therefore, early diagnosis and continuous management are essential in preventing renal complications in FMF (3, 7).

### *TNF Receptor-Associated Periodic Syndrome*

Kidney involvement in TRAPS is less frequent compared to FMF but still warrants attention, primarily due to the systemic inflammation characteristic of the disease. Chronic inflammation in TRAPS can compromise vascular integrity, leading to glomerulonephritis or tubulointerstitial nephritis, conditions that can cause progressive renal dysfunction. It is estimated that 5-10% of patients with TRAPS will develop renal complications over the course of their disease (2, 8).

The renal damage in TRAPS is largely driven by sustained, untreated inflammation, which underscores the importance of early initiation of targeted therapies, such as TNF inhibitors, to curb the inflammatory response and prevent the onset of renal pathology. With adequate intervention, renal involvement can often be minimized or prevented (2, 3).

### *Hyper IgD Syndrome*

Though kidney involvement is rarer in HIDS, it remains a potential complication, particularly during severe inflammatory flares. The renal manifestations in HIDS are typically the result of interstitial nephritis or glomerulonephritis, which occur as a direct consequence of heightened systemic inflammation. Kidney involvement is estimated to affect 2-5% of HIDS patients, with the incidence being more pronounced during recurrent inflammatory episodes. Given the episodic nature of the disease, careful monitoring of kidney function and early intervention with IL-1 inhibitors can help mitigate the risk of renal complications and long-term damage (4, 9).

### *Muckle-Wells Syndrome*

In MWS, kidney involvement is primarily a result of secondary amyloidosis. As with FMF, the chronic inflammation that characterizes MWS leads to the deposition of amyloid fibrils in kidney tissues, resulting in nephrotic syndrome and a potential decline in renal function. It is estimated that 10-20% of MWS patients will develop kidney involvement, particularly in the absence of adequate anti-inflammatory treatment (1, 2).

Chronic kidney disease (CKD) is a significant concern for these patients, and the risk of progression to ESRD is heightened in those with untreated or inadequately treated disease. Early detection and treatment with IL-1 inhibitors or other anti-inflammatory agents are crucial to preventing irreversible renal damage (10).

### *Cryopyrin-Associated Periodic Syndromes (CAPS)*

In Cryopyrin-Associated Periodic Syndromes (CAPS), which include conditions such as CINCA/NOMID, familial cold autoinflammatory syndrome, and MWS, kidney involvement is primarily attributed to the development of amyloidosis or, in rarer instances, glomerulonephritis. The prevalence of renal involvement in CAPS is estimated to be around 10-15%, often manifesting as amyloid-related renal damage due to chronic systemic inflammation (2, 4).

Given the significant renal risks associated with CAPS, early intervention with IL-1 inhibitors is critical to controlling disease activity and preventing long-term kidney damage (11).

### *Other Rare Autoinflammatory Diseases*

Some less common autoinflammatory disorders, such as PAPA syndrome (Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne) and DIRA syndrome (Deficiency of IL-1 Receptor Antagonist), may occasionally present with kidney involvement. However, such cases are rare and kidney manifestations are typically secondary to systemic inflammation or immune complex deposition. Renal complications in these conditions are generally seen in more severe or untreated cases (4, 12).

The kidney is a vital organ that can be profoundly impacted by chronic or poorly controlled autoinflammatory diseases. Conditions like FMF, MWS, and TRAPS can lead to significant renal morbidity, ranging from nephrotic syndrome to progressive kidney failure. Early and accurate diagnosis, coupled with targeted therapies such as colchicine, IL-1 inhibitors, and TNF inhibitors, are essential to preventing kidney involvement and preserving renal function. In the context of these conditions, timely intervention is crucial to minimize the risk of long-term renal damage and optimize patient outcomes (9, 13, 14).

### *Pathophysiological Mechanisms of Renal Involvement*

- *Inflammatory Pathways and Cytokine Mediators:*

The underlying pathophysiology of renal involvement in auto-inflammatory diseases is primarily driven by dysregulated immune responses. Key cytokines such as IL-1, TNF-α, IL-6, and IL-18 play central roles in the initiation and propagation of inflammation within the kidneys. These cytokines promote the recruitment of inflammatory cells to renal tissue, leading to glomerular and tubular damage. Activation of IL-1 triggers systemic inflammation and can cause glomerulonephritis. TNF-α promotes endothelial dysfunction and renal fibrosis through increased vascular permeability and glomerular damage. IL-6 and IL-17 contribute to both acute and chronic kidney injury by driving inflammation and fibrosis (11, 13).

- *Immune Cell Involvement in Renal Damage:*

T cells, B cells, and macrophages are critical players in the renal inflammation observed in these diseases. The activation of these immune cells leads to the release of additional inflammatory mediators, further exacerbating kidney damage. Macrophage infiltration and T-cell-mediated responses have been implicated in conditions such as lupus nephritis and vasculitis, contributing to both acute and chronic renal injury (4, 11).

In addition to genetic predisposition, several environmental factors may influence disease onset and severity. Early-life infections, frequent use of antibiotics during infancy, and nutritional factors such as lack of breastfeeding or early exposure to allergenic foods have been hypothesized to modulate immune development and potentially trigger autoinflammatory responses. Further research is warranted to elucidate these associations (6,9).

### *Diagnostic Approaches to Renal Involvement in AIDs*

Early diagnosis and prevention of renal involvement in autoinflammatory diseases require a multifaceted approach. Family history screening, regular monitoring of inflammatory markers (such as serum amyloid A), and close surveillance during disease flares can significantly improve outcomes. Educational programs targeting primary care and pediatric providers may also facilitate earlier recognition and referral of suspected cases (2,4).

Timely and accurate diagnosis of renal involvement is crucial for managing auto-inflammatory diseases. Pediatric rheumatologists utilize a combination of clinical findings, laboratory tests, and imaging modalities to assess renal function and identify early signs of kidney damage. Measurement of serum creatinine, urea, and electrolytes to assess renal function. Proteinuria and hematuria are also indicative of renal involvement. Urinary biomarkers such as protein-to-creatinine ratio, red blood cell casts, and the presence of leukocytes can suggest glomerular or tubular injury. In cases where diagnosis is uncertain or the disease is advanced, kidney biopsy provides critical information on the extent of renal damage and the underlying pathological process. Techniques such as ultrasound, CT, and MRI are useful for assessing renal size, structure, and the presence of complications like cysts or fibrosis (3, 10, 14).

### *Diagnostic Challenges*

Differentiating between the various causes of renal involvement in pediatric auto-inflammatory diseases can be challenging. The overlap of clinical symptoms with other conditions, such as infections or malignancies, may delay the diagnosis. Additionally, the lack of

specific renal biomarkers in some diseases adds complexity to the diagnostic process.

### *Current and Emerging Treatment Strategies*

Recent advances in biologic therapies have revolutionized the management of auto-inflammatory diseases with renal involvement. Recent advances in targeted therapies, including IL-1 inhibitors (anakinra, canakinumab) and TNF inhibitors (etanercept), have demonstrated considerable efficacy in reducing systemic inflammation and preventing secondary amyloidosis in high-risk patients. These therapies not only improve quality of life but also play a key role in preserving long-term kidney function (3,9).

Medications targeting specific inflammatory pathways are increasingly being used to treat these conditions, particularly in cases resistant to conventional therapy. IL-1 inhibitors (e.g., anakinra, canakinumab) are effective in treating conditions like CAPS and FMF, where IL-1 is a major driver of inflammation. TNF-α inhibitors (e.g., etanercept, infliximab) are particularly beneficial in managing diseases like SJIA and other autoinflammatory syndromes, where TNF-α plays a key role in disease pathogenesis. IL-6 inhibitors (e.g., tocilizumab) have proven successful in treating systemic juvenile idiopathic arthritis (SJIA), a condition where IL-6 is a central mediator of inflammation. These biologics target specific inflammatory pathways to reduce systemic inflammation and improve patient outcomes. The targeted inhibition of these cytokines represents a critical therapeutic approach in autoinflammatory diseases (9-14).

### *Renal Replacement Therapy and Kidney Transplantation*

In cases of severe kidney damage, such as those seen in lupus nephritis or vasculitis, renal replacement therapies (dialysis) may be required. For patients who develop end-stage renal disease (ESRD), kidney transplantation is considered, although this comes with its own set of challenges, particularly in immunosuppressive therapy management (7, 11).

### *Ongoing Research and Therapeutic Development*

Despite advances in treatment, many challenges remain in the management of auto-inflammatory diseases with renal involvement. Research is ongoing into novel therapies that can better target specific inflammatory pathways without the side effects of current treatments. Furthermore, biomarker discovery to predict renal involvement early in the disease course could significantly improve outcomes. Establishing national and international registries for autoinflammatory diseases, particularly those with renal complications, is critical for better epidemiological understanding and patient care. Developing standardized diagnostic and therapeutic care algorithms, especially for pediatric populations in endemic regions, could enhance early intervention and reduce disease burden (4,6).

### *Challenges in Pediatric Populations*

One of the key challenges in managing AIDs in children is the lack of pediatric-specific data, as most clinical trials focus on adult populations. Additionally, the long-term effects of biologic therapies on growth and development in children remain largely unknown.

## 4- CONCLUSION

Auto-inflammatory diseases with renal involvement pose a significant challenge in pediatric rheumatology. Advances in understanding the underlying inflammatory mechanisms and the development of targeted therapies have

greatly improved outcomes for many children. However, early diagnosis and individualized treatment are crucial. Ongoing research into the pathogenesis and management of these diseases is necessary to further refine treatment strategies and improve the prognosis for affected children.

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## 6- DECLARATIONS

### 6-1. Ethics Approval

This article was written in compliance with the principles stated in the Declaration of Helsinki.

### 6-2. Consent for Publication

All authors have reviewed and agreed to submit this manuscript for publication.

### 6-3. Availability of Data and Materials

The datasets utilized and/or analyzed during the current study can be obtained from the corresponding author upon reasonable request.

### 6-4.Competing Interests

We have no competing interests to declare.

## 7- FUNDING

Not applicable.

## 8- REFERENCES

1. Karabulut Y, Gezer HH, Duruöz MT. Canakinumab is effective in patients with familial Mediterranean fever resistant and intolerant to the colchicine and/or anakinra treatment. Rheumatology International. 2022 Jan;42(1):81-6.

2. Grevich S, Shenoi S. Update on the management of systemic juvenile idiopathic arthritis and role of IL-1 and IL-6 inhibition. Adolescent health, medicine and therapeutics. 2017 Nov 9:125-35.

3. Brunner HI, Ruperto N, Zuber Z, Cuttica R, Keltsev V, Xavier RM, et al. Efficacy and safety of tocilizumab for polyarticular-course juvenile idiopathic arthritis in the open-label two-year extension of a phase III trial. Arthritis & Rheumatology. 2021 Mar;73(3):530-41.

4. Lopetuso LR, Cuomo C, Mignini I, Gasbarrini A, Papa A. Focus on anti-tumour necrosis factor (TNF)-α-related autoimmune diseases. International Journal of Molecular Sciences. 2023 May 3;24(9):8187.

5. Del Giudice E, Sota J, Orlando F, Picciano L, Cimaz R, Cantarini L, et al. Off-label use of canakinumab in pediatric rheumatology and rare diseases. Frontiers in Medicine. 2022 Oct 18;9:998281.

6. Horneff G, Minden K, Rolland C, Daly AC, Borlenghi C, Ruperto N. Efficacy and safety of TNF inhibitors in the treatment of juvenile idiopathic arthritis: a systematic literature review. Pediatric Rheumatology. 2023 Feb 24;21(1):20.

7. Lavalle S, Caruso S, Foti R, Gagliano C, Cocuzza S, La Via L, et al. Behçet's disease, pathogenesis, clinical features, and treatment approaches: A comprehensive review. Medicina. 2024 Mar 29;60(4):562.

8. Yokota S, Imagawa T, Mori M, Miyamae T, Takei S, Iwata N, et al. Longterm safety and effectiveness of the anti-interleukin 6 receptor monoclonal antibody tocilizumab in patients with systemic juvenile idiopathic arthritis in Japan. The Journal of rheumatology. 2014 Apr 1;41(4):759-67.

9. Andronesi AG, Ismail G, Gherghiceanu M, Mitroi G, Hârza MC. Familial Mediterranean fever-associated renal amyloidosis: case report and review of the literature. Rom J Morphol Embryol. 2019 Jan 1;60(4):1299-303.

10. Arnold DD, Yalamanoglu A, Boyman O. Systematic review of safety and efficacy of IL-1-targeted biologics in treating immune-mediated disorders. Frontiers in immunology. 2022 Jul 6;13:888392.

11. Hegazy MT, Fayed A, Nuzzolese R, Sota J, Ragab G. Autoinflammatory diseases and the kidney. Immunologic Research. 2023 Aug;71(4):578-87.

12. Koga T, Kawakami A. Interleukin-6 inhibition in the treatment of autoinflammatory diseases. Frontiers in Immunology. 2022 Jul 26;13:956795.

13. Broderick L, Hoffman HM. IL-1 and autoinflammatory disease: biology, pathogenesis and therapeutic targeting. Nature Reviews Rheumatology. 2022 Aug;18(8):448-63.

14. Jung SM, Kim WU. Targeted immunotherapy for autoimmune disease. Immune network. 2022 Feb 17;22(1):e9.