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Renal Involvement in Inflammatory Bowel Disease: Pathogenesis, Clinical Spectrum, and Management Strategies

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ABSTRACT

***Background*:** Renal involvement in inflammatory bowel disease (IBD) is an underrecognized yet clinically relevant extraintestinal manifestation. Affecting both Crohn's disease (CD) and ulcerative colitis (UC), renal complications encompass glomerular disorders, tubulointerstitial nephritis, nephrolithiasis, amyloidosis, and drug-induced injury. The mechanisms underlying renal involvement are multifactorial, including immune dysregulation, systemic inflammation, metabolic disturbances, surgical consequences, and adverse drug effects. Increasing evidence also supports the role of the gut–kidney axis, in which alterations in intestinal permeability and microbiota influence renal immune responses.

Although the prevalence of renal manifestations in IBD varies, ranging from 4% to 23% depending on the population studied, their clinical impact is substantial. Some complications, such as drug-induced nephritis, are reversible if recognized early, whereas others, such as amyloidosis, are associated with progressive renal impairment and poor prognosis. Nephrolithiasis remains one of the most frequent complications, particularly in Crohn's disease, while IgA nephropathy is the most common glomerular pathology associated with IBD. This review explores the pathogenesis of renal involvement in IBD, the clinical spectrum of renal manifestations, and management strategies. We highlight the importance of early recognition, routine screening, and a multidisciplinary approach integrating gastroenterologists, nephrologists, and dietitians. Understanding these renal complications is essential for improving outcomes, reducing morbidity, and preserving long-term kidney function in patients with IBD.

Keywords: Renal Involvement, Inflammatory Bowel Disease, Management Strategies

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic relapsing-remitting inflammatory condition of the gastrointestinal tract. Its systemic nature is increasingly recognized, with extraintestinal manifestations (EIMs) affecting up to 40% of patients [1]. Among these, renal involvement is less frequently discussed compared with musculoskeletal, dermatological, or hepatobiliary complications, yet it represents a significant source of morbidity and long-term disability [2].

Renal complications in IBD are diverse, ranging from glomerulonephritis and tubulointerstitial nephritis to metabolic disorders leading to nephrolithiasis, and, in rare cases, systemic amyloidosis. These manifestations may occur as a direct consequence of chronic inflammation, immune dysregulation, metabolic alterations, or drug-related toxicity [3]. They may develop independently of intestinal disease activity, adding complexity to diagnosis and management.

Despite their clinical relevance, renal manifestations in IBD remain under-researched. Most evidence is derived from case series or retrospective studies, with few large-scale prospective cohorts [4]. This knowledge gap contributes to delayed recognition and suboptimal management in routine practice. The aim of this review is therefore to provide an updated synthesis of current evidence regarding the pathogenesis, clinical spectrum, and management strategies of renal involvement in IBD, with a particular focus on mechanisms and therapeutic implications.

Epidemiology of Renal Involvement in IBD

Renal involvement in IBD has been reported in 4–23% of patients, although prevalence varies widely depending on the population, diagnostic methods, and duration of follow-up [5]. The most frequent manifestations are nephrolithiasis, drug-induced nephrotoxicity, and glomerulonephritis. Chronic kidney disease (CKD) appears to be more prevalent among IBD patients than in the general population, with large epidemiological studies confirming an increased risk independent of traditional risk factors such as hypertension or diabetes [6].

The type of IBD may influence the nature of renal complications. Crohn's disease is strongly associated with nephrolithiasis due to malabsorption, bile salt metabolism disturbances, and small bowel resections [7]. Ulcerative colitis, on the other hand, is more frequently linked with drug-induced nephrotoxicity, particularly from prolonged exposure to 5-aminosalicylates [8]. Glomerular diseases, including IgA nephropathy, can occur in both CD and UC, with some studies suggesting a slightly higher prevalence in CD [9].

Geographic variation has also been described. Studies from Europe and North America highlight nephrolithiasis as the predominant renal complication, whereas Asian cohorts report higher rates of glomerulonephritis, especially IgA nephropathy [10]. These differences likely reflect genetic predisposition, dietary factors, environmental exposures, and therapeutic practices. The true burden of renal involvement may, however, be underestimated due to the lack of systematic renal screening in many IBD cohorts [11].

Overall, epidemiological evidence underscores that renal involvement is not a rare complication of IBD but one that requires proactive surveillance. Patients with longstanding disease, prior intestinal resections, chronic diarrhea, or exposure to nephrotoxic therapies represent particularly high-risk groups who should undergo routine renal monitoring [12].

Pathogenesis of Renal Involvement in IBD

Immune Dysregulation and Systemic Inflammation

Renal complications in IBD largely reflect the systemic immune dysregulation that underlies the disease. Aberrant T-cell activation, impaired regulatory immune responses, and increased production of proinflammatory cytokines contribute to widespread inflammation beyond the gastrointestinal tract [13]. Circulating immune complexes can deposit in the renal glomeruli, triggering complement activation and mesangial proliferation, a hallmark of IgA nephropathy in IBD [14]. Chronic systemic inflammation further amplifies oxidative stress and endothelial dysfunction, predisposing to both glomerular and interstitial renal injury [15].

Cytokine Pathways and Inflammatory Mediators

Proinflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-17 (IL-17), play central roles in both intestinal and renal inflammation [16]. Elevated TNF-α levels contribute to glomerular endothelial

injury, while IL-6 promotes mesangial proliferation and deposition of acute-phase proteins, including serum amyloid A, predisposing to secondary amyloidosis [17]. IL-17, secreted by Th17 cells, has been implicated in autoimmune-mediated renal inflammation, highlighting shared immunopathogenic pathways between IBD and renal involvement [18].

The Gut–Kidney Axis and Microbiota Alterations

Emerging evidence supports the concept of a gut–kidney axis in IBD-related renal disease. Disruption of intestinal barrier integrity leads to increased translocation of bacterial antigens and metabolites, which may trigger systemic immune responses affecting the kidney [19]. Dysbiosis of gut microbiota has been linked to altered production of short-chain fatty acids, uremic toxins, and secondary bile acids that impact renal immunity and metabolism [20]. Experimental studies suggest that gut microbial imbalance in IBD may predispose to both glomerular inflammation and nephrolithiasis, reinforcing the need to consider microbial modulation as part of future therapeutic strategies [21].

Metabolic and Nutritional Contributions

Metabolic factors also play a pivotal role in renal pathogenesis among IBD patients. Malabsorption of bile salts and fatty acids in Crohn's disease increases colonic oxalate absorption, predisposing to hyperoxaluria and calcium oxalate nephrolithiasis [22]. Chronic diarrhea contributes to metabolic acidosis, hypocitraturia, and hypomagnesuria, all of which reduce urinary protective factors against stone formation [23]. In addition, vitamin D deficiency, prevalent in IBD due to malabsorption and inflammation, exacerbates secondary hyperparathyroidism and abnormal calcium metabolism, with indirect effects on renal stone risk and bone–kidney axis homeostasis [24].

Drug-Induced Mechanisms

Finally, treatment-related factors contribute significantly to renal pathogenesis. 5-aminosalicylates (5-ASA) can induce immune-mediated interstitial nephritis through hypersensitivity reactions, with infiltration of lymphocytes and eosinophils into renal tissue [25]. Calcineurin inhibitors such as cyclosporine cause dose-dependent vasoconstriction and tubular toxicity, while biologics, especially anti-TNF agents, have been linked to rare cases of immune complex glomerulonephritis [26]. Thus, the pathogenesis of renal involvement in IBD reflects a complex interplay of intrinsic disease mechanisms and iatrogenic factors, requiring careful diagnostic differentiation.

Drug-Induced Renal Injury in IBD

5-Aminosalicylates (5-ASA) and Interstitial Nephritis

5-aminosalicylates, including mesalamine, sulfasalazine, and olsalazine, are widely used in the management of ulcerative colitis and sometimes Crohn's disease. Although generally safe, 5-ASA can cause idiosyncratic, immune-mediated tubulointerstitial nephritis [27]. This adverse reaction may develop insidiously, even after years of therapy, presenting as asymptomatic renal impairment or mild proteinuria. Histology typically reveals lymphocytic and eosinophilic infiltration of the interstitium, with varying degrees of fibrosis. Importantly, early withdrawal of the offending agent often leads to recovery, whereas delayed recognition may result in irreversible chronic kidney disease [28].

Sulfasalazine and Mesalamine Toxicity

Among the 5-ASA formulations, sulfasalazine appears to have a higher incidence of nephrotoxicity, likely due to its metabolism into sulfapyridine, which can act as a hapten triggering immune-mediated injury [29]. Mesalamine, while considered safer, is also associated with interstitial nephritis, particularly in genetically predisposed individuals. Recent pharmacogenetic studies have suggested links between HLA polymorphisms and susceptibility to 5-ASA nephrotoxicity, although further validation is needed [30]. Because nephrotoxicity can occur in both dose-dependent and idiosyncratic forms, clinicians are advised to perform baseline renal function testing and periodic monitoring throughout therapy [31].

Biologic Therapies and Glomerular Disease

Biologic agents, particularly anti-TNF therapies such as infliximab and adalimumab, have revolutionized IBD management but are not without renal risks. Rare cases of biologic-induced glomerulonephritis have been reported, including membranous nephropathy, minimal change disease, and lupus-like nephritis [32]. These complications are thought to result from immune complex formation or autoimmune dysregulation triggered by biologics. Although uncommon, such cases highlight the need for vigilance in patients who develop new-onset proteinuria or hematuria during biologic therapy [33].

Calcineurin Inhibitors and Dose-Dependent Nephrotoxicity

Cyclosporine and tacrolimus are occasionally used as rescue therapies in severe, steroid-refractory ulcerative colitis. Both drugs are associated with dose-dependent nephrotoxicity mediated by afferent arteriolar vasoconstriction, leading to reduced renal perfusion and chronic interstitial fibrosis [34]. Monitoring trough drug levels and renal function is essential during therapy to balance efficacy against toxicity. In most cases, nephrotoxicity is reversible with dose reduction or discontinuation, but prolonged use may result in chronic damage [35].

Thiopurines and Other Agents

Azathioprine and 6-mercaptopurine, cornerstone immunosuppressants in IBD, rarely cause direct renal toxicity but may predispose to opportunistic infections and nephrotoxic drug interactions [36]. Methotrexate, though seldom used in IBD compared with rheumatology, has been associated with renal impairment in high doses due to crystalluria and tubular precipitation. With the growing use of newer biologics and small-molecule therapies, post-marketing surveillance will be essential to detect rare renal adverse effects. Ultimately, drug-induced nephrotoxicity remains a preventable complication if routine monitoring and early recognition are emphasized in clinical practice [37].

Glomerular Manifestations in IBD

Overview

Glomerular involvement in IBD is heterogeneous, encompassing both immune complex-mediated and podocytopathies. These manifestations are typically detected through urinary abnormalities such as hematuria and proteinuria, sometimes progressing to nephrotic syndrome or chronic kidney disease [38]. Although glomerular diseases represent a minority of renal complications in IBD compared with nephrolithiasis or drug-induced nephritis, they are clinically significant due to their potential for irreversible renal damage [39].

IgA Nephropathy

IgA nephropathy is the most common glomerular lesion associated with IBD, particularly Crohn's disease. It is characterized by mesangial deposition of IgA immune complexes, which likely originate from excessive mucosal immune stimulation in the gut [40]. Clinically, patients present with microscopic hematuria and proteinuria, sometimes accompanied by hypertension or progressive renal dysfunction. The course of IgA nephropathy often parallels IBD activity, with renal flares coinciding with intestinal relapses [41]. This association highlights shared pathogenic mechanisms and reinforces the need for integrated monitoring of gut and renal disease activity.

Minimal Change Disease (MCD)

Minimal change disease is rare in IBD but well documented in both adults and children. It typically presents as nephrotic syndrome, with edema, hypoalbuminemia, and heavy proteinuria [42]. The pathogenesis may involve T-cell dysfunction and cytokine-mediated podocyte injury, and in some cases, MCD has been temporally associated with anti-TNF therapy [43]. Corticosteroids remain the mainstay of treatment, and most patients achieve remission, though relapses can occur, especially if intestinal inflammation is uncontrolled. The rarity of MCD in IBD underscores the need for biopsy confirmation to avoid misclassification as other glomerulopathies.

Membranous Nephropathy

Membranous nephropathy is another glomerular pathology occasionally reported in IBD patients. It may arise spontaneously due to immune complex deposition or be triggered by medications such as 5-ASA or biologics [44]. Patients usually present with nephrotic-range proteinuria and, if untreated, may progress to chronic kidney disease. Case reports have linked membranous nephropathy with both infliximab and adalimumab exposure, suggesting a drug-related autoimmune mechanism [45]. Distinguishing idiopathic from secondary membranous nephropathy is essential for guiding management, as drug withdrawal may lead to resolution in secondary cases.

Rare Glomerular Entities

Other reported glomerular lesions in IBD include focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), and pauci-immune crescentic glomerulonephritis [46]. These conditions are uncommon but

clinically significant due to their association with progressive renal failure. Vasculitic syndromes, including ANCA-associated glomerulonephritis, have also been described in patients with ulcerative colitis, further reflecting the autoimmune overlap between IBD and systemic vasculitides [47]. Because these entities are rare, evidence comes primarily from case reports and small series, underscoring the importance of multicenter registries to clarify prevalence and outcomes.

Clinical Implications

The clinical implications of glomerular involvement in IBD are considerable. Unlike nephrolithiasis or drug-induced interstitial nephritis, glomerular diseases often necessitate long-term immunosuppression and careful renal follow-up. IgA nephropathy is the dominant entity, while minimal change disease and membranous nephropathy represent important but smaller subsets. Rare cases of FSGS, MPGN, or vasculitic glomerulonephritis remind clinicians of the systemic nature of IBD. Routine urinalysis, especially in patients with active disease or unexplained renal dysfunction, is essential for early detection and intervention [48].

Tubulointerstitial Manifestations in IBD

Overview of Tubulointerstitial Involvement

Tubulointerstitial nephritis is one of the most common renal manifestations of IBD, particularly linked to medications. It is characterized histologically by interstitial inflammation, tubular injury, and varying degrees of fibrosis [49]. Clinically, patients often present with mild renal impairment, sterile pyuria, or subnephrotic proteinuria, though many remain asymptomatic until advanced stages. Because the presentation is nonspecific, routine monitoring is crucial to avoid late diagnosis and irreversible damage.

Drug-Induced Interstitial Nephritis

The majority of tubulointerstitial nephritis in IBD arises from drug toxicity, particularly with 5-aminosalicylates (5-ASA). Mesalamine and sulfasalazine can trigger an idiosyncratic hypersensitivity reaction leading to interstitial nephritis, sometimes years after therapy initiation [50]. Risk appears independent of drug dose, and renal function may improve if the drug is withdrawn early. Biopsy often reveals interstitial lymphocytic infiltration with occasional eosinophils, consistent with drug-induced injury. Because of this, regular renal monitoring is recommended during prolonged 5-ASA therapy [51].

Biologics and Immunosuppressant-Related Tubular Damage

Biologic therapies, especially anti-TNF agents, have been associated with rare cases of acute interstitial nephritis and glomerular disease [52]. Calcineurin inhibitors such as cyclosporine and tacrolimus, used in severe refractory IBD, are nephrotoxic through vasoconstrictive effects on renal arterioles, causing dose-dependent tubular injury [53]. Prolonged use may lead to interstitial fibrosis and chronic kidney disease if not closely monitored. These observations highlight the delicate balance between controlling intestinal inflammation and avoiding iatrogenic renal harm.

Immune-Mediated Interstitial Nephritis

Not all interstitial nephritis in IBD is drug related. Cases of idiopathic immune-mediated interstitial nephritis have been described, often occurring in the absence of recent nephrotoxic drug exposure [54]. Histology may reveal lymphocytic infiltration, granulomas, or plasma cell predominance, suggesting a systemic autoimmune basis. Such cases are thought to reflect the broader inflammatory spectrum of IBD, with parallels to extraintestinal organ involvement. Corticosteroids remain the mainstay of treatment, although outcomes depend on the chronicity of renal injury at diagnosis [55].

Chronic Tubular Injury and Clinical Implications

Chronic tubulointerstitial injury is a major cause of irreversible renal impairment in IBD patients. Repeated subclinical drug-induced insults, ongoing systemic inflammation, and nutritional deficiencies may synergize to accelerate fibrosis and tubular atrophy [56]. Clinically, this presents as progressive chronic kidney disease with reduced concentrating ability and electrolyte disturbances. Preventive strategies, including regular renal monitoring, careful drug selection, and early withdrawal of nephrotoxic medications, are essential to preserve renal function in IBD patients [57].

Metabolic and Stone Disorders

Epidemiology and Clinical Burden

Nephrolithiasis is one of the most prevalent renal complications of IBD, with reported prevalence ranging from 4% to 23% [58].

Crohn's disease patients, particularly those with ileal involvement or prior small bowel resections, are at greatest risk, while the incidence in ulcerative colitis is comparatively lower [59]. Stones not only cause acute morbidity through renal colic and obstruction but may also predispose to recurrent urinary tract infections and long-term kidney damage.

Enteric Hyperoxaluria and Calcium Oxalate Stones

The dominant mechanism of stone formation in IBD is enteric hyperoxaluria. Malabsorption of bile salts and fatty acids leads to saponification of calcium, reducing its availability to bind oxalate in the intestinal lumen [60]. This increases free oxalate absorption in the colon and raises urinary oxalate excretion, favoring calcium oxalate stone formation. The risk is particularly high after ileal resection, with studies demonstrating up to a fivefold increase in calcium oxalate stones among these patients [61].

Hypocitraturia and Hypomagnesuria

Other metabolic derangements also contribute significantly. Chronic diarrhea and metabolic acidosis reduce urinary citrate levels, eliminating a key inhibitor of calcium crystallization [62]. Similarly, hypomagnesuria decreases urinary oxalate binding, further predisposing to stone formation. These alterations, combined with low urine volume from dehydration, create a milieu that strongly favors recurrent stone disease in IBD [63].

Uric Acid Stones and Chronic Diarrhea

Uric acid stones are also observed in IBD, particularly in patients with chronic diarrhea and persistently acidic urine. Gastrointestinal bicarbonate loss lowers urinary pH, creating conditions favorable for uric acid precipitation [64]. Dehydration and reduced urine volume compound this risk. Unlike calcium oxalate stones, uric acid stones may be managed effectively with urine alkalinization therapy, underscoring the importance of metabolic evaluation in tailoring treatment [65].

Prevention and Clinical Management

Management of nephrolithiasis in IBD hinges on preventive strategies, including high fluid intake, calcium supplementation to bind intestinal oxalate, and potassium citrate to correct hypocitraturia [66]. Dietary counseling, particularly regarding oxalate-rich foods, is crucial in patients with ileal resections or malabsorption syndromes. Given the high recurrence risk, regular metabolic evaluation and early urological referral are essential. Addressing underlying bowel disease activity is equally important, as disease control can reduce metabolic disturbances and mitigate stone risk [67].

Amyloidosis and Rare Entities

Epidemiology and Clinical Relevance of Amyloidosis

Secondary (AA) amyloidosis is a rare but serious complication of IBD, typically associated with longstanding, poorly controlled Crohn's disease. The prevalence in IBD is estimated at 0.5%–3%, with regional variability reflecting differences in disease duration and therapeutic access [68]. Amyloidosis is significantly less common in ulcerative colitis but has been described in severe, refractory cases. Although uncommon, its clinical impact is disproportionate, often leading to progressive renal dysfunction and high morbidity.

Pathogenesis of AA Amyloidosis in IBD

The pathogenesis of AA amyloidosis in IBD is linked to chronic systemic inflammation. Persistent elevation of serum amyloid A (SAA), an acute-phase reactant produced by the liver under cytokine stimulation (notably IL-1 and IL-6), leads to its deposition as insoluble fibrils in organs including the kidney [69]. In IBD, ongoing mucosal inflammation or inadequate therapeutic control accelerates SAA production. Glomerular deposition is most prominent, explaining why renal manifestations such as proteinuria and nephrotic syndrome are common presentations [70].

Clinical Course and Prognosis

Patients with IBD-associated amyloidosis often present with proteinuria, frequently in the nephrotic range, and progressive decline in renal function. Without effective control of intestinal inflammation, renal amyloidosis typically progresses to end-stage kidney disease within a few years [71]. Prognosis largely depends on the ability to suppress systemic inflammation. With modern biologic therapies, some reports describe stabilization or even regression of amyloid deposition when IBD is brought into remission [72].

Other Rare Renal Manifestations in IBD

Beyond amyloidosis, several rare renal complications have been described in IBD. Vasculitic processes, including ANCA-associated glomerulonephritis, have occasionally been linked with ulcerative colitis [73]. Similarly, case reports document hemolytic uremic syndrome and thrombotic microangiopathy in IBD patients, though causality remains uncertain. These rare manifestations highlight the systemic autoimmune overlap between IBD and renal disease. While uncommon, awareness is important, as many of these entities carry a risk of rapid progression and require aggressive immunosuppressive therapy [74].

Diagnostic Approaches

Importance of Early Detection

Renal involvement in IBD is often insidious, and many patients remain asymptomatic until advanced renal dysfunction develops. Early detection is therefore critical to prevent irreversible damage. Guidelines recommend baseline and periodic monitoring of serum creatinine and urinalysis in all IBD patients, particularly those on long-term 5-ASA or immunosuppressive therapy [75]. Early recognition of subtle abnormalities, such as microscopic hematuria or subnephrotic proteinuria, can facilitate timely intervention and improve outcomes.

Laboratory Investigations

Laboratory testing is central to diagnostic evaluation. Basic renal function tests (serum creatinine, eGFR) should be complemented by urinalysis for hematuria, proteinuria, and pyuria [76]. Quantification of proteinuria, preferably by urine protein-to-creatinine ratio or 24-hour collection, is necessary when glomerular disease is suspected. Metabolic evaluation is essential in patients with nephrolithiasis, including measurement of urinary oxalate, citrate, uric acid, calcium, and magnesium [77]. Serological testing for autoantibodies such as ANA, ANCA, and anti-GBM may be helpful in distinguishing primary autoimmune nephritis from IBD-related renal disease [78].

Imaging Modalities

Imaging plays a supportive role, particularly in patients with suspected nephrolithiasis or obstructive uropathy. Ultrasound is the first-line modality due to its safety and accessibility, allowing detection of stones, hydronephrosis, and chronic parenchymal changes [79]. Non-contrast CT scanning offers higher sensitivity for nephrolithiasis, especially in recurrent stone formers. In complex cases, MRI can provide additional information while avoiding radiation, though it is less commonly required. Imaging results should always be integrated with laboratory and clinical findings.

Role of Renal Biopsy

Renal biopsy remains the gold standard for diagnosing glomerular and interstitial pathologies. It is indicated in patients with unexplained proteinuria, hematuria, or progressive renal dysfunction despite drug withdrawal [80]. Biopsy findings not only distinguish between IgA nephropathy, minimal change disease, and drug-induced interstitial nephritis but also guide therapeutic decisions regarding immunosuppression. In the context of amyloidosis, Congo red staining provides definitive diagnosis and prognostic information. Thus, biopsy is invaluable in clarifying the etiology of renal involvement in IBD [81].

Multidisciplinary Evaluation

Given the overlapping etiologies—autoimmune, metabolic, and drug-induced—a multidisciplinary approach is essential. Gastroenterologists, nephrologists, radiologists, and dietitians should collaborate in the diagnostic process [82]. Integrating renal monitoring into standard IBD management protocols ensures early recognition of renal complications. Such collaborative care improves not only renal outcomes but also overall quality of life, as many renal complications parallel intestinal activity and influence therapeutic decision-making.

Management Strategies

Control of Intestinal Inflammation

Effective control of intestinal inflammation is central to the management of renal complications in IBD. Persistent systemic inflammation contributes to glomerular diseases and amyloidosis, while bowel dysfunction promotes metabolic derangements leading to nephrolithiasis [83]. Corticosteroids, immunomodulators, and biologics not only improve intestinal outcomes but can

also stabilize renal disease by reducing inflammatory mediators such as TNF-α and IL-6. In amyloidosis, suppression of inflammation with anti-TNF therapy has been associated with reduced proteinuria and delayed progression to end-stage kidney disease [84].

Drug Withdrawal and Pharmacovigilance

When renal dysfunction is linked to drug toxicity, prompt withdrawal of the offending agent is critical. Interstitial nephritis caused by 5-ASA often improves after discontinuation, especially if recognized early [85]. In some cases, corticosteroids accelerate recovery. For calcineurin inhibitor nephrotoxicity, dose reduction or substitution with alternative therapy may restore renal function [86]. Clinicians should practice careful pharmacovigilance, particularly when prescribing long-term 5-ASA or immunosuppressants, and integrate renal monitoring into follow-up protocols.

Supportive Nephrology Care

Supportive therapy remains essential across all forms of renal involvement. Renin-angiotensin-aldosterone system (RAAS) inhibitors are recommended for patients with proteinuric glomerular disease to reduce proteinuria and slow chronic kidney disease progression [87]. In cases of nephrolithiasis, interventions include hydration protocols, calcium supplementation to bind oxalate in the gut, and potassium citrate to correct hypocitraturia [88]. Patients with advanced renal dysfunction require nephrology referral for timely planning of renal replacement therapy, including dialysis or transplantation.

Preventive Strategies for Nephrolithiasis

Stone prevention is a cornerstone of renal management in IBD, especially among Crohn's disease patients with ileal resections. Preventive measures include high fluid intake to maintain dilute urine, dietary adjustments to limit oxalate-rich foods, and supplementation with calcium to reduce oxalate absorption [89]. Potassium citrate supplementation corrects hypocitraturia and alkalinizes urine, providing dual protection against both calcium oxalate and uric acid stones. Such preventive strategies are particularly important given the high recurrence risk of stones in this patient population.

Multidisciplinary Collaboration

The complexity of renal manifestations in IBD necessitates a multidisciplinary approach. Gastroenterologists, nephrologists, urologists, and dietitians should collaborate in patient management to ensure optimal outcomes [90]. For instance, nephrologists provide expertise in managing proteinuria and CKD, while dietitians play a key role in preventing nephrolithiasis through dietary interventions. Close collaboration also facilitates balancing intestinal control with renal preservation when considering potentially nephrotoxic medications.

Long-Term Monitoring and Prognosis

Long-term monitoring is essential, as renal complications may evolve insidiously. Regular assessment of serum creatinine, eGFR, and urinalysis should be standard for all IBD patients, especially those at high risk [91]. The prognosis varies depending on the type of renal involvement: drug-induced nephritis often improves with early recognition, while amyloidosis remains associated with poor outcomes despite modern therapies. Nonetheless, proactive surveillance and integrated care significantly improve the likelihood of preserving renal function and overall patient quality of life.

Conclusion

Renal involvement in inflammatory bowel disease represents an underrecognized yet clinically significant spectrum of extraintestinal manifestations. The patterns of renal disease are diverse, encompassing glomerular disorders such as IgA nephropathy, interstitial nephritis often linked to 5-ASA therapy, nephrolithiasis driven by enteric hyperoxaluria, and rare but severe complications like secondary amyloidosis [92]. These manifestations may occur independently of intestinal activity, complicating both diagnosis and management.

The pathogenesis of renal complications in IBD is multifactorial, reflecting the interplay of systemic immune dysregulation, chronic inflammation, metabolic derangements, and drug-induced toxicity. Increasing evidence supports the role of the gut–kidney axis and microbiota in shaping renal outcomes, suggesting new avenues for therapeutic intervention [93]. Early recognition through systematic screening, including urinalysis and renal function monitoring, is essential, especially in high-risk patients such as those with long disease duration, prior bowel resections, or prolonged exposure to nephrotoxic therapies [94].

Optimal management requires a multidisciplinary approach integrating gastroenterologists, nephrologists, urologists, and dietitians. Strategies include controlling intestinal inflammation to prevent systemic complications, withdrawing or adjusting nephrotoxic medications, implementing preventive measures for nephrolithiasis, and providing supportive nephrology care. Despite advances in biologic therapies and improved recognition, important research gaps remain, particularly regarding prospective studies, biomarkers for early detection, and personalized treatment approaches. By addressing these gaps and integrating renal surveillance into standard IBD care, clinicians can reduce morbidity, preserve renal function, and improve overall outcomes in this vulnerable patient population [95].

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REFERENCES

1. Vavricka SR, Rogler G, Gantenbein C, Spoerri M, Prinz Vavricka BM, Navarini AA, French LE. Extraintestinal manifestations of inflammatory bowel disease. *Inflamm Bowel Dis*. 2015;21(8):1982-1992.
2. Said SM, Nasr SH. Renal manifestations of inflammatory bowel disease. *Semin Nephrol*. 2015;35(5):436-446.
3. Weng MT, Chiu YT, Wei SC. Mechanisms of inflammatory bowel disease-related extra-intestinal manifestations. *J Gastroenterol Hepatol*. 2016;31(3):389-394.
4. Magro F, Dias CC, Coelho R, et al. Extra-intestinal manifestations in a population-based cohort of inflammatory bowel disease patients: prevalence and risk factors. *Dig Liver Dis*. 2017;49(10):1327-1334.
5. Corrigan G, Stevens PE. Renal manifestations of inflammatory bowel disease. *Nephrol Dial Transplant*. 2000;15(7):1049-1056.
6. Kristensen SL, Ahlehoff O, Lindhardsen J, et al. Inflammatory bowel disease is associated with increased risk of chronic kidney disease: a nationwide cohort study. *Gut*. 2013;62(6):861-867.
7. Cury DB, Moss AC, Schor N. Nephrolithiasis in patients with inflammatory bowel disease in the community. *Int J Nephrol Renovasc Dis*. 2013;6:139-142.
8. Heap GA, So K, Weedon M, et al. Clinical features and HLA association of 5-aminosalicylate-induced nephrotoxicity in IBD. *Nephrol Dial Transplant*. 2016;31(10):1610-1618.
9. Ambruzs JM, Walker PD, Larsen CP. The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. *Clin J Am Soc Nephrol*. 2014;9(2):265-270.
10. Watanabe T, Matsui T, Kitani A, et al. Renal and urologic complications of inflammatory bowel disease in Japan. *Intern Med*. 1998;37(7):537-542.
11. Greuter T, Navarini A, Vavricka SR. Extraintestinal manifestations in inflammatory bowel disease – epidemiology, genetics, and pathogenesis. *Expert Rev Gastroenterol Hepatol*. 2017;11(8):709-720.
12. Rollino C, Vischini G, Coppo R. Kidney involvement in inflammatory bowel diseases. *J Nephrol*. 2016;29(6):761-769.
13. Strober W, Fuss IJ. Proinflammatory cytokines in the pathogenesis of IBD. *Gastroenterology*. 2011;140(6):1756-1767.
14. Ambruzs JM, Walker PD, Larsen CP. The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. *Clin J Am Soc Nephrol*. 2014;9(2):265-270.
15. Neurath MF. Cytokines in inflammatory bowel disease. *Nat Rev Immunol*. 2014;14(5):329-342.
16. Danese S, Fiocchi C. Ulcerative colitis. *N Engl J Med*. 2011;365(18):1713-1725.

17. Obici L, Merlini G. AA amyloidosis: basic knowledge, unmet needs and future treatments. *Swiss Med Wkly*. 2012;142:w13580.
18. Kitching AR, Holdsworth SR. The emergence of Th17 cells as effectors of renal injury. *J Am Soc Nephrol*. 2011;22(2):235-238.
19. Anders HJ, Andersen K, Stecher B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. *Kidney Int*. 2013;83(6):1010-1016.
20. Meijers BKI, Evenepoel P. The gut–kidney axis: indoxyl sulfate, p-cresyl sulfate and CKD progression. *Nephrol Dial Transplant*. 2011;26(3):759-761.
21. Vaziri ND, Zhao YY, Pahl MV. Altered intestinal microbial flora and impaired epithelial barrier structure and function in CKD: the nature, mechanisms, consequences, and potential therapies. *Nephrol Dial Transplant*. 2016;31(5):737-746.
22. Hylander E, Ladefoged K, Jarnum S. Enteric hyperoxaluria: dependence on small bowel resection, ileal disease and steatorrhoea in chronic inflammatory bowel disease. *Scand J Gastroenterol*. 1978;13(5):577-588.
23. Asplin JR. The management of patients with enteric hyperoxaluria. *Urolithiasis*. 2016;44(1):33-43.
24. Lim WC, Hanauer SB, Li YC. Mechanisms of disease: vitamin D and inflammatory bowel disease. *Nat Clin Pract Gastroenterol Hepatol*. 2005;2(7):308-315.
25. Gisbert JP, González-Lama Y, Maté J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis*. 2007;13(5):629-638.
26. Stokes MB, Foster K, Markowitz GS, et al. Development of glomerulonephritis during anti-TNF-α therapy for Crohn's disease. *Kidney Int*. 2005;67(6):2368-2372.
27. Ransford RA, Langman MJ. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut*. 2002;51(4):536-539.
28. Gisbert JP, González-Lama Y, Maté J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis*. 2007;13(5):629-638.
29. Christensen B, Rubin DT. 5-Aminosalicylates for the treatment of inflammatory bowel disease. *World J Gastroenterol*. 2016;22(43):9157-9162.
30. Heap GA, So K, Weedon M, et al. Clinical features and HLA association of 5-aminosalicylate-induced nephrotoxicity in IBD. *Nephrol Dial Transplant*. 2016;31(10):1610-1618.
31. Van Assche G, Vermeire S, Rutgeerts P. Medical management of Crohn's disease. *Gastroenterology*. 2010;138(5):2026-2038.
32. Stokes MB, Foster K, Markowitz GS, et al. Development of glomerulonephritis during anti-TNF-α therapy for Crohn's disease. *Kidney Int*. 2005;67(6):2368-2372.
33. Clajus C, Spiegel J, Bramlage C, et al. Membranous nephropathy during anti-TNF-α therapy. *Clin Nephrol*. 2009;72(2):144-148.
34. Feagan BG, Sandborn WJ, D'Haens G, et al. The role of cyclosporine and tacrolimus in the management of inflammatory bowel disease. *Gastroenterology*. 2016;150(2):324-333.
35. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc Nephrol*. 2009;4(2):481-508.
36. Choi JY, Jung HY, Kim YS, et al. Renal adverse effects of azathioprine in patients with inflammatory bowel disease. *Clin Nephrol*. 2012;77(1):27-32.
37. Rollino C, Vischini G, Coppo R. Kidney involvement in inflammatory bowel diseases. *J Nephrol*. 2016;29(6):761-769.
38. Said SM, Nasr SH. Renal manifestations of inflammatory bowel disease. *Semin Nephrol*. 2015;35(5):436-446.
39. Rollino C, Vischini G, Coppo R. Kidney involvement in inflammatory bowel diseases. *J Nephrol*. 2016;29(6):761-769.
40. Ambruzs JM, Walker PD, Larsen CP. The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. *Clin J Am Soc Nephrol*. 2014;9(2):265-270.
41. Churg J, Sobin LH. Renal disease in Crohn's disease and ulcerative colitis. *N Engl J Med*. 1968;278(15):738-741.
42. Beck LH Jr. Minimal change disease and other causes of nephrotic syndrome in children and adults. *UpToDate*. 2021.
43. Aigner C, Kain R, Winkler S, et al. Minimal change nephrotic syndrome associated with infliximab therapy. *Clin Nephrol*. 2008;69(6):451-454.
44. Said SM, Nasr SH. Membranous nephropathy associated with inflammatory bowel disease. *Kidney Int Rep*. 2016;1(2):130-135.
45. Clajus C, Spiegel J, Bramlage C, et al. Membranous nephropathy during anti-TNF-α therapy. *Clin Nephrol*. 2009;72(2):144-148.
46. Santos-Antunes J, Lopes S, Macedo G. Kidney and urological manifestations of inflammatory bowel disease. *World J Gastroenterol*. 2017;23(35):6507-6515.
47. Rollino C, Beltrame G, Ferro M, et al. Renal manifestations in inflammatory bowel disease: a multicenter study. *Nephrol Dial Transplant*. 2013;28(2):400-406.
48. Corrigan G, Stevens PE. Renal manifestations of inflammatory bowel disease. *Nephrol Dial Transplant*. 2000;15(7):1049-1056.
49. Said SM, Nasr SH. Renal manifestations of inflammatory bowel disease. *Semin Nephrol*. 2015;35(5):436-446.

50. Ransford RA, Langman MJ. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated. *Gut*. 2002;51(4):536-539.
51. Gisbert JP, González-Lama Y, Maté J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis*. 2007;13(5):629-638.
52. Stokes MB, Foster K, Markowitz GS, et al. Development of glomerulonephritis during anti-TNF-α therapy for Crohn's disease. *Kidney Int*. 2005;67(6):2368-2372.
53. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc Nephrol*. 2009;4(2):481-508.
54. Higenbottam TW, Bloom DS, Holdsworth CD. Idiopathic interstitial nephritis in association with ulcerative colitis. *Gut*. 1969;10(9):739-744.
55. González E, Gutiérrez E, Morales E, Hernández E, Andrés A, Praga M. Factors influencing the progression of renal damage in interstitial nephritis. *Clin J Am Soc Nephrol*. 2011;6(7):1607-1614.
56. Rollino C, Vischini G, Coppo R. Kidney involvement in inflammatory bowel diseases. *J Nephrol*. 2016;29(6):761-769.
57. Corrigan G, Stevens PE. Renal manifestations of inflammatory bowel disease. *Nephrol Dial Transplant*. 2000;15(7):1049-1056.
58. Cury DB, Moss AC, Schor N. Nephrolithiasis in patients with inflammatory bowel disease in the community. *Int J Nephrol Renovasc Dis*. 2013;6:139-142.
59. Hylander E, Jarnum S. Nephrolithiasis in patients with ileostomy. *Scand J Urol Nephrol*. 1978;12(3):233-236.
60. Worcester EM, Coe FL. Nephrolithiasis. *Prim Care*. 2008;35(2):369-391.
61. Lieske JC, Tremaine WJ, De Simone C, O'Connor HM, Li X, Bergstralh EJ. Diet, but not oral probiotics, effectively reduces urinary oxalate excretion and calcium oxalate supersaturation. *Kidney Int*. 2010;78(11):1178-1185.
62. Asplin JR. The management of patients with enteric hyperoxaluria. *Urolithiasis*. 2016;44(1):33-43.
63. Nouvenne A, Meschi T, Guerra A, Allegri F, Prati B, Borghi L. Diet to reduce the risk of kidney stones. *EMJ Urol*. 2014;1(2):79-84.
64. Sakhaee K. Uric acid nephrolithiasis: current concepts and controversies. *Rev Urol*. 2005;7(3):113-121.
65. Pak CY. Medical prevention of renal stone disease. *Nephron Clin Pract*. 2004;98(2):c49-c53.
66. Siener R, Hesse A. Current aspects of epidemiology and nutrition in urinary stone disease. *World J Urol*. 2020;38(1):165-172.
67. Rollino C, Vischini G, Coppo R. Kidney involvement in inflammatory bowel diseases. *J Nephrol*. 2016;29(6):761-769.
68. Greenstein AJ, Sachar DB, Panday AK, Dikman SH, Meyers S, Janowitz HD. Amyloidosis and inflammatory bowel disease: a 50-year experience with 25 patients. *Medicine (Baltimore)*. 1992;71(5):261-270.
69. Obici L, Merlini G. AA amyloidosis: basic knowledge, unmet needs and future treatments. *Swiss Med Wkly*. 2012;142:w13580.
70. Said SM, Sethi S, Valeri AM, et al. Renal amyloidosis: origin and clinicopathologic correlations of 474 recent cases. *Clin J Am Soc Nephrol*. 2013;8(9):1515-1523.
71. Gillmore JD, Lovat LB, Persey MR, Pepys MB, Hawkins PN. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. *Lancet*. 2001;358(9275):24-29.
72. Papa R, Lachmann HJ. Secondary, AA, amyloidosis. *Rheum Dis Clin North Am*. 2018;44(4):585-603.
73. Rollino C, Beltrame G, Ferro M, et al. Renal manifestations in inflammatory bowel disease: a multicenter study. *Nephrol Dial Transplant*. 2013;28(2):400-406.
74. Said SM, Nasr SH. Renal manifestations of inflammatory bowel disease. *Semin Nephrol*. 2015;35(5):436-446.
75. Gisbert JP, González-Lama Y, Maté J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis*. 2007;13(5):629-638.
76. Corrigan G, Stevens PE. Renal manifestations of inflammatory bowel disease. *Nephrol Dial Transplant*. 2000;15(7):1049-1056.
77. Asplin JR. The management of patients with enteric hyperoxaluria. *Urolithiasis*. 2016;44(1):33-43.
78. Said SM, Nasr SH. Renal manifestations of inflammatory bowel disease. *Semin Nephrol*. 2015;35(5):436-446.
79. Fulgham PF, Assimos DG, Pearle MS, Preminger GM. Clinical effectiveness protocols for imaging in the management of ureteral calculous disease: AUA technology assessment. *J Urol*. 2013;189(4):1203-1213.
80. Ambruzs JM, Walker PD, Larsen CP. The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. *Clin J Am Soc Nephrol*. 2014;9(2):265-270.
81. Gillmore JD, Lovat LB, Persey MR, Pepys MB, Hawkins PN. Amyloid load and clinical outcome in AA amyloidosis. *Lancet*. 2001;358(9275):24-29.
82. Casella G, Tontini GE, Bassotti G, Pastorelli L, Villanacci V, Vecchi M. Extraintestinal manifestations of inflammatory bowel disease. *Dig Liver Dis*. 2014;46(9):753-759.
83. Van Assche G, Vermeire S, Rutgeerts P. Medical management of Crohn's disease. *Gastroenterology*. 2010;138(5):2026-2038.
84. Papa R, Lachmann HJ. Secondary, AA, amyloidosis. *Rheum Dis Clin North Am*. 2018;44(4):585-603.

85. Gisbert JP, González-Lama Y, Maté J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis*. 2007;13(5):629-638.
86. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc Nephrol*. 2009;4(2):481-508.
87. Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int Suppl*. 2021;100(4S):S1-S276.
88. Siener R, Hesse A. Current aspects of epidemiology and nutrition in urinary stone disease. *World J Urol*. 2020;38(1):165-172.
89. Asplin JR. The management of patients with enteric hyperoxaluria. *Urolithiasis*. 2016;44(1):33-43.
90. Casella G, Tontini GE, Bassotti G, Pastorelli L, Villanacci V, Vecchi M. Extraintestinal manifestations of inflammatory bowel disease. *Dig Liver Dis*. 2014;46(9):753-759.
91. Rollino C, Vischini G, Coppo R. Kidney involvement in inflammatory bowel diseases. *J Nephrol*. 2016;29(6):761-769.
92. Said SM, Nasr SH. Renal manifestations of inflammatory bowel disease. *Semin Nephrol*. 2015;35(5):436-446.
93. Anders HJ, Andersen K, Stecher B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. *Kidney Int*. 2013;83(6):1010-1016.
94. Gisbert JP, González-Lama Y, Maté J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis*. 2007;13(5):629-638.
95. Rollino C, Vischini G, Coppo R. Kidney involvement in inflammatory bowel diseases. *J Nephrol*. 2016;29(6):761-769.