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Review Article - Clinical

Renal and Urological Disorders Associated With Inflammatory Bowel Disease

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Renal and urinary tract complications related to inflammatory bowel disease (IBD) have been relatively understudied in the literature compared with other extraintestinal manifestations. Presentation of these renal manifestations can be subtle, and their detection is complicated by a lack of clarity regarding the optimal screening and routine monitoring of renal function in IBD patients. Urolithiasis is the most common manifestation. Penetrating Crohn's disease involving the genitourinary system as an extraintestinal complication is rare but associated with considerable morbidity. Some biologic agents used to treat IBD have been implicated in progressive renal impairment, although differentiating between drug-related side effects and deteriorating kidney function due to extraintestinal manifestations can be challenging. The most common findings on renal biopsy of IBD patients with renal injury are tubulointerstitial nephritis and IgA nephropathy, the former also being associated with drug-induced nephrotoxicity related to IBD medication. Amyloidosis, albeit rare, must be diagnosed early to reduce the chance of progression to renal failure. In this review, we evaluate the key literature relating to renal and urological involvement in IBD and emphasize the high index of suspicion required for the prompt diagnosis and treatment of these manifestations and complications, considering the potential severity and implications of acute or chronic loss of renal function. We also provide suggestions for future research priorities.

Lay Summary

Renal and urinary tract complications related to inflammatory bowel disease (IBD) are important but have been neglected in the literature. We emphasize the high index of suspicion required for the prompt diagnosis, treatment, and prevention of these manifestations and complications.

Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, renal disease, extraintestinal manifestation

Introduction

Besides the gastrointestinal tract, inflammatory bowel disease (IBD) can also manifest in extraintestinal organs, contributing significantly to morbidity and mortality.[1,2] These extraintestinal symptoms of IBD are divided into extraintestinal complications and extraintestinal manifestations (EIMs). Extraintestinal complications refer to manifestations that are direct or indirect sequelae of intestinal inflammation.[1] In contradistinction, EIMs have been defined as "an inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is either dependent on extension/translocation of immune responses from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD."[3] They likely represent a composite of systemic inflammation, autoimmune susceptibility, and metabolic and nutritional derangement. Extraintestinal manifestations are due to an inflammatory process occurring outside the gut but are related to the underlying diagnosis of IBD; their clinical spectrum varies from mild, transient disease to severe, disabling complications. The reported frequencies of EIMs in IBD range from 6% to 47%; the heterogeneity in reported prevalence is likely due to the variability in definitions used for EIMs and because patients can be affected by multiple EIMs.[1] Almost any organ can be affected, but involvement of the joints, skin, eyes, liver, and biliary tract are the most commonly described EIMs.[1] Renal complications in IBD (Table 1) have received much less attention despite early studies reporting kidney involvement in nearly 25% of IBD patients.[4,5] In these early reports, nephrolithiasis, obstructive uropathy, and fistula formation between the bowel and urinary tract were the most common occurrences.

Renal parenchymal involvement in IBD has also been described in the form of glomerulonephritis, tubulointerstitial nephritis, and amyloidosis. However, its true prevalence is not clear because systematic analyses are lacking.[6] In recent years, the use of more potent drugs for treating IBD has increased the potential for nephrotoxicity, further highlighting the importance of this topic.[7] Parenchymal renal involvement can affect any or all of the glomerular, tubular, or interstitial compartments. It is the purpose of this review to report and evaluate the key data in the literature on renal involvement in IBD. We emphasize the high index of suspicion required for the prompt diagnosis, treatment, and ideally prevention of these manifestations and complications; we also highlight some practical considerations in clinical practice.

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Table 1. Renal and urological disorders associated with inflammatory bowel disease.

Nephrolithiasis
Calcium oxalate
Uric acid
Entero-vesical fistulae
Urinary tract malignancy
Kidney cancer
Urethral cancer
Bladder cancer
Drug-related nephrotoxicity
Glomerulonephritis
IgA nephropathy
Minimal change disease
IgM nephropathy
Membranous nephropathy
Membranoproliferative nephropathy
Focal and segmental glomerulosclerosis
Antiglomerular basement disease
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)
Tubulointerstitial disease
Acute tubular injury
Tubulointerstitial nephritis
Renal amyloidosis

Nephrolithiasis

Renal stone development in the context of IBD is a long-reported association dating back to the 1970s.[5, 8–10] Historical series report more than 5 times the prevalence of nephrolithiasis in IBD patients compared with the general population.[9, 11] It has been reported that up to 38% of IBD patients may develop asymptomatic nephrolithiasis.[12] Recently, in a prospective cohort of 2323 IBD patients from Switzerland, Fagagnini et al reported a prevalence of 4.6% and 3% for nephrolithiasis on imaging in those with Crohn's disease (CD) and ulcerative colitis (UC), respectively.[13] Multivariate analysis revealed that male sex, disease activity, history of bowel surgery, NSAID intake, and a lack of physical activity were all associated with the development of renal stones. Similarly, in a cohort of 3104 IBD patients from Mississippi, 6% and 6.7% of UC and CD patients developed urolithiasis, respectively.[14] It is typical to find either visible or invisible hematuria in renal stone disease; however, not all such hematuria is reliably stone mediated, as both gross and microscopic hematuria can be a manifestation of other kidney and ureteric pathologies.[15]

The association between nephrolithiasis and bowel surgery in IBD patients is well established and may occur in patients following ileostomy formation.[16] Torricelli et al evaluated the impact of extensive surgery (total proctocolectomy and either end-ileostomy or ileal pouch-anal anastomosis) on the urine profile, serum biochemistry, and stone composition in IBD patients.[17] In their case-control study, low urinary volume and hypocitraturia were risk factors associated with nephrolithiasis in IBD patients who underwent total proctocolectomy compared with kidney stone formers without IBD. Calcium oxalate and uric acid stones were most frequent. In the setting of fat malabsorption and subsequent steatorrhea caused by extensive active small bowel inflammation or bowel resection, luminal calcium binds free fatty acids, thereby decreasing the calcium that is available to bind and excrete oxalate in the stool. The resulting increase in intestinal absorption of oxalate leads to so-called "enteric hyperoxaluria" and calcium oxalate stone formation in the kidneys.[18]

Other mechanisms may be involved in oxalate stone formation. *Oxalobacter formigenes* degrades dietary oxalate, and its decolonization in the gut may lead to the hyperabsorption of oxalate. Oral administration of Oxalobacter decreases urinary oxalate concentration.[18] Low urinary levels of antilithogenic substances such as magnesium and citrate also play a role in renal calculi formation in IBD.[10] Magnesium and citrate replacement should ideally aim to correct urinary rather than serum levels towards normal.[10] Other preventative measures include a diet low in oxalate and fat, and pyridoxine supplementation.[19] Oral cholestyramine increases oxalate and decreases citrate excretion.[20] The toxic effects of oxalate on renal epithelial and tubular cells cause oxalate nephropathy with persistent hyperoxaluria and, together with stone formation, constitute a major but rare contributor to the development of chronic kidney disease (CKD).[19, 21]

Uric acid supersaturation of the urine, which promotes uric acid stone formation, is aided by low urinary pH resulting from loss of alkali in diarrheal stool and diminished urine volumes (especially after colonic resection) in IBD.[10, 18, 22, 23] Preventative measures include reduction in dietary purine intake, a high fluid intake to maintain a urine output of 2 to 3 litres, and alkalinization of the urine. Xanthine oxidase inhibitors such as allopurinol inhibit uric acid synthesis and uricosuria. Oral potassium citrate also helps prevent uric acid stone recurrence.[24]

Varda et al highlight the importance of prompt diagnosis to ensure appropriate treatment of IBD patients with renal stones.[25] Using data from the Nationwide Emergency Department Sample (2006-2009), they studied a cohort of over 3.5 million patients seeking care for urolithiasis at emergency departments in the United States, of whom 14 352 patients had concomitant IBD. Patients with IBD with urolithiasis were more likely to develop urinary tract infections, acute kidney injury, sepsis, end-organ failure, and to require hospital admission compared with those without IBD.

Unenhanced computed tomography of the kidneys, ureters, and bladder (CT KUB) is the diagnostic method of choice in the acute setting, benefitting from high sensitivity and specificity while also being a quick and safe examination to perform.[26] Low-dose CT conferring less than 3 millisieverts (mSv) of diagnostic medical radiation is now used universally, affording a sensitivity and specificity of 96% and 95%, respectively.[27] There is increasing interest in adopting ultra-low radiation techniques that may be particularly suitable in following up patients with urolithiasis.[28] This is pertinent in IBD where the cumulative exposure to diagnostic medical radiation is high.[29] Timely and accurate diagnosis is imperative to ensure that appropriate treatment is initiated. This may involve a conservative approach with lifestyle and dietary modifications, or extracorporeal shock wave lithotripsy (ESWL) and/or surgery for treating larger stones, where there is a heightened risk of significant urinary tract obstruction. The overarching aims are to decrease the risk of stone formation and associated complications,

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thereby reducing patient morbidity and preserving renal function.

Practical Considerations

Nephrolithiasis, comprising mainly oxalate and uric acid stones, is associated with IBD; although the wide reported range of prevalence is due to the lack of a consistent and robust reference standard in these studies (Table 2). A thorough clinical history and examination, in conjunction with urinalysis and a low threshold to perform imaging studies, should ensure that clinically relevant nephrolithiasis is diagnosed early (Figure 1). Low-dose unenhanced CT KUB is the modality of choice because of its excellent performance characteristics and low radiation burden. A multidisciplinary team approach that includes a urologist and nephrologist (if there is evidence of CKD) is essential.

Table 2. Unanswered clinical and research priorities to better understand the renal and urological complications and manifestations of IBD.

Determine the True Prevalence of Nephrolithiasis in IBD—Large Series or Population-Based Studies With Prolonged Follow-up and a Robust Reference Standard Are Needed
Studies to determine if monitoring certain IBD patients for nephrolithiasis is worthwhile
Dedicated studies to establish the association between IBD and urological malignancy
Development of biomarkers for tubular and glomerular pathology (valuable in all situations where GFR is at risk)
Devise an evidence-based strategy for the monitoring of renal function for IBD patients
Safety trials to understand the nephrotoxic effects of drugs used to treat IBD, focussing on biomarker or genetic clues to susceptibility
Standardised evidence-based approach for monitoring renal function in patients taking 5-ASAs

Penetrating Crohn's Disease Involving the Renal Tract

Transmural inflammation in CD predisposes to bowel perforation and fistula formation, which occurs in about 10% of patients during long-term follow-up.[30] Adherence of inflamed intestine to the bladder wall may cause erosion and fistulization in the form of colo- and entero-vesical fistulae in 2% to 4% of Crohn's patients.[31, 32] Fistula formation may be preceded by subacute small bowel obstruction if there is coexistent intestinal stricturing.[33] Entero-vesical fistulae are often associated with intrapelvic abscess development. Presenting clinical features may be pneumaturia, urinary tract infection, and fecaluria—or a combination thereof.[34, 35]

Comprehensive evaluation of suspected entero-vesical fistula typically requires the utilization of several imaging modalities to precisely define the fistulous connection, the presence of an abscess, and the exclusion of coexistent bowel stricturing. Historically, plain abdominal x-ray, barium enema, and intravenous urography were used, but these have been superseded by cross-sectional imaging.[36, 37] Cystoscopy helps identify a possible fistulous tract, but the findings are often nonspecific, failing to identify a fistula in up to 65% of cases.[36] Ultrasound, which is safe and well-tolerated, is

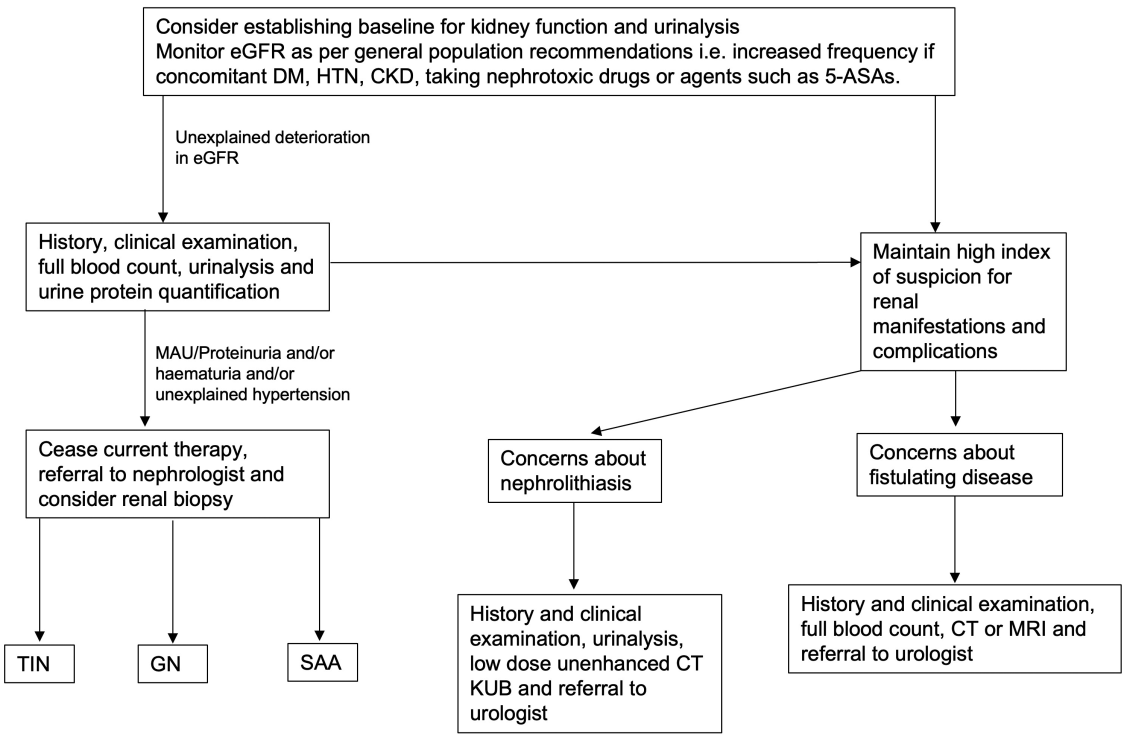

Figure 1. A proposed clinical strategy to consider the renal manifestations and complications related to IBD. Abbreviations: CKD, chronic kidney disease; CT KUB, computed tomography of kidneys, ureters and bladder; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis, HTN, hypertension; MAU, microalbuminuria; SAA, secondary amyloidosis; TIN, tubulointerstitial nephritis

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useful in the diagnosis of colo-vesical fistulae,[38] and its yield may be improved by the administration of oral contrast before performing the study.[39–41] However, it is highly operator-dependent and may not offer the anatomical detail afforded by other modalities.[29] Computed tomography (CT) and magnetic resonance imaging (MRI), which are now considered the gold standard, benefit from providing a multiplanar 3D representation of the fistula. This is invaluable in planning appropriate management and offers a preoperative road map for surgical intervention.

Computed tomography findings of colo-vesical fistulae include intravesical air in the absence of recent instrumentation (eg, urinary bladder catheterization), focal bladder wall thickening, and the presence of contrast in the urinary bladder that was administered either orally or via the rectum (Figure 2). Contrast-enhanced CT is highly sensitive in detecting fistulae, is fast to perform, and is the first-line investigation in many centers. However, a major drawback is that it confers exposure to diagnostic medical radiation, an important consideration in patients with IBD who often present at a young age and require repeated abdomino-pelvic imaging over many years, exposing them to high cumulative levels of radiation.[29]

Magnetic resonance imaging allows the accurate depiction of fistulous tracts with the advantage of being radiation-free. It offers superior soft-tissue resolution compared with CT and has similarly high sensitivity and specificity.[42] T2-weighted imaging demonstrates high signal fluid within the fistulous tract and detects associated fluid collections and inflammation within the bladder wall. T1-weighted imaging provides anatomical detail about the adjacent viscera that is useful when a surgical approach is contemplated. Some centers utilize MRI as their first-line investigation for colo-vesical fistulae, although its high cost and lack of widespread availability are limiting factors.[31,42] Endoscopy has a very low sensitivity for detecting a fistulous tract but is used perioperatively if there is concern for a malignant etiology.

Where technically feasible, radiological intervention with percutaneous drainage is usually favored over surgery in the first instance to mitigate the requirement for stoma formation when the definitive operation to repair the fistula is undertaken.[32] In a retrospective cohort, a study of 97 CD patients with entero-vesical fistula reported that over a median follow-up time of almost 3 years, only antitumour necrosis factor alpha (anti-TNFα) agents were associated with remission without the subsequent requirement for surgery.[31] Overall, around 66% of IBD patients with an entero-vesical fistula ultimately proceed to surgery despite medical therapy.[32]

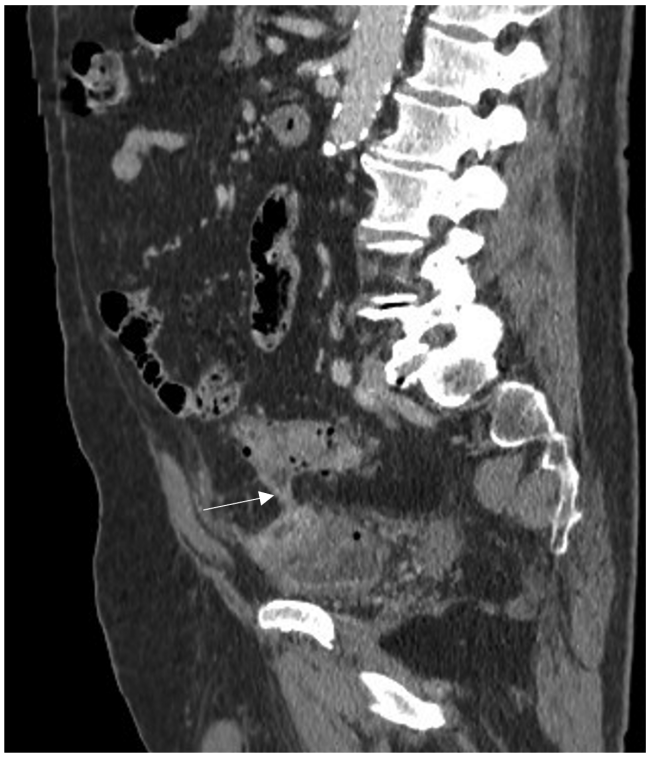

Figure 2. Portal venous sagittal computed tomography (CT) scan demonstrates a fistulous tract between the sigmoid colon and bladder wall (white arrow). There is a locule of intravesical air posteriorly, bladder wall thickening, and enhancement reflecting inflammation. Incidental, noninflamed sigmoid diverticular disease.

Practical Considerations

Diagnosis of entero-vesical fistulae can be challenging, as the onset can be insidious and nonspecific. Therefore, having a high index of suspicion is important. Presentation may only be with fever and abdominal pain, without the classical features such as pneumaturia and fecaluria. Early multispeciality discussion involving a gastroenterologist, surgeon, radiologist, and pathologist is recommended to devise an optimal, individualized management plan. Multimodality imaging is often required, and management may necessitate both medical and surgical approaches including anti-TNF treatment (Figure 2).

Cancer

Malignancy originating in the kidneys and urinary tract is over-represented in IBD patients, with a 5-fold increase in the relative risk compared with the general population.[43,44] A strong link has been established between cigarette smoking and urological malignancy in CD patients but not in those with UC.[45] Interestingly, in a recent meta-analysis, IBD was not associated with an increased risk for bladder cancer; but in the CD subgroup, there was a trend towards an increased bladder cancer risk, indicating marginal significance.[46] In a study of nearly 19 500 patients with IBD, 16 patients developed urological malignancy. In a multivariate analysis, thiopurine use was associated with a 3-fold increased risk of urinary tract cancers.[47] In a Chinese cohort of 1609 IBD patients, the risk of developing malignancy, including renal and urinary bladder carcinoma, was higher in patients suffering from elderly-onset IBD (60 years and older).[48] This is an area where there remains many unanswered questions, and further research is needed to better understand the association between IBD and urinary tract malignancy (Table 2).

Drug-related Nephrotoxicity

Tacrolimus, 5-aminosalicylate (5-ASA), and TNF-α inhibitor use have been implicated in progressive renal impairment. Although differentiating between drug-related side effects

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and deteriorating kidney function due to EIMs can be difficult (Table 3).

5-aminosalicylates

Often, 5-ASAs are used to treat active disease and help maintain remission in UC; even though there is a lack of evidence for their efficacy, they continue to be prescribed widely in CD.[49] There has been considerable debate around the entity of 5-ASA nephrotoxicity, with many contradictory series in the literature.[50–53] A recent retrospective cohort and nested case-control study using primary care data from the United Kingdom that included 35 601 patients with either UC or CD found that exposure to 5-ASAs was not associated with a risk of nephrotoxicity.[54] Rather, the study found that active inflammatory disease, duration of disease, coexisting cardiovascular disease, and the use of established nephrotoxic drugs were independently associated with the development of nephrotoxicity. Nephrotoxicity related to 5-ASA in IBD patients is rare and occurs in an idiosyncratic manner independent of 5-ASA dose, making proof of causality difficult.[51] A large international study identified patients with likely 5-ASA-induced nephrotoxicity from 89 centers.[51] Five cases were categorized as definite 5-ASA-induced nephrotoxicity, having had a second episode of acute kidney injury when rechallenged with the drug. A further 146 probable cases were also identified following a rigorous case adjudication process. The authors performed a genome-wide association study that revealed a human leukocyte antigen (HLA) association, notably HLA-DRB1*03:01, was related to 5-ASA-induced nephrotoxicity. They reported that 5-ASA-induced nephrotoxicity is more common in males and can present at any age; and the most common histological finding is chronic tubulointerstitial nephritis. Nephrotoxicity occurred after a median treatment duration of 3 years. Of particular concern, only 30% fully recovered renal function, with 10% requiring permanent renal replacement therapy. Although very rare, annual monitoring of renal function is recommended to detect 5-ASA related nephrotoxicity early.[7]

Practical Considerations

There is currently no evidence to support a specific kidney monitoring strategy to prevent 5-ASA-related nephrotoxicity and no consensus within international guidelines (Table 4).[7,55–58] There is a lack of clarity about the optimal approach to monitoring renal function, as this has not been addressed systematically in the literature. Until further data are available and there is agreement on an optimal monitoring strategy, we offer a suggested approach (Figure 3).

Tacrolimus and Ciclosporin

Tacrolimus and ciclosporin are calcineurin inhibitors that have many roles in medicine, especially in the prevention of solid-organ transplantation rejection episodes.[59] Their use mandates careful attention to dosing and monitoring of trough serum concentrations of the drugs to avoid the risk of acute kidney injury. During prolonged use, careful attention is required to minimize the risk of chronic tubulointerstitial fibrosis, atrophy, and loss of kidney function.

These agents have an established role in treating acute severe UC, but the evidence for their use in CD is less clear.[60–63] Multiple contradictory studies in the literature have raised the possibility of nephrotoxicity associated with tacrolimus, leading to safety concerns.[64–66] However, a recent large series has provided some reassurance. In a retrospective 22-center study from Spain comprising 143 patients with CD or UC receiving tacrolimus, 7% developed acute kidney injury. In

Table 3. Potential drug-associated nephrotoxic effects in IBD.

Drug	Potential Nephrotoxic Manifestation	Renal Manifestation
5-ASA	Tubulointerstitial nephritis	• Microscopic hematuria, microalbuminuria, sterile pyuria (± eosinophiluria) • Decrease in eGFR • Very rare e.g 0.3% per annum[114]
Calcineurin inhibitors	Acute kidney injury due to tubulointerstitial damage evident as electrolyte disturbances. Chronic kidney disease due to vasoconstriction/ischaemia leads to interstitial fibrosis	• Hyperkalemia, hypomagnesemia, hyperchloremic metabolic acidosis, hyperuricemia, hyperglycemia • Microalbuminuria • Hypertension • Decrease in eGFR • Increasing risk with continuous temporal exposure, especially over 5 or more years[59]
TNF-α inhibitors	Acute kidney injury Glomerulonephritis	• Microalbuminuria/proteinuria • New onset hypertension • Decrease in eGFR • Very rare (but vigilance is prudent)
Vedolizumab	Acute interstitial nephritis	• Dipstick hematuria, microalbuminuria, sterile pyuria (± eosinophiluria) • Decrease in eGFR • Very rare (but vigilance is prudent)
Tofacitinib	Acute kidney injury	• Decrease in eGFR • Very rare (but vigilance is prudent)
Filgotinib	Increased drug concentration in renal impairment so reduce dose	• Monitor eGFR looking for early evidence of loss of renal function

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Table 4. Current Gastroenterology guidelines available and their suggested monitoring frequency interval of renal function for patients on 5-ASA therapy.

Guidelines (Ref.)	Monitoring Regimen
ACG (57)	Every 3–6 months in the first year, annually thereafter
AGA (55)	"Periodically"
AOCC/APAG (56)	Not stated
BSG (7)	Baseline evaluation, repeat at 2-3 months and then annually
ECCO (58)	Every 3-6 months

Abbreviations: ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; AOCC/APAG, Asian Organization for Crohn's and Colitis/Asia Pacific Association of Gastroenterology; ECCO, European Crohn's and Colitis Organization. Interested readers are directed towards nephrology guidance such as that provided by the UK Kidney Association.[126]

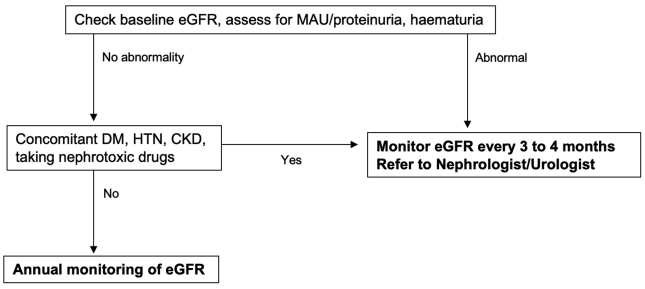

Figure 3. A suggested approach for monitoring kidney function in patients commencing 5-ASA or calcineurin inhibitor therapy.

all these cases, reversibility was achieved after dose reduction (40%) or discontinuation of the drug (60%).[60] In this patient cohort, the median serum creatinine during the tacrolimus treatment was 186 µmol/L (interquartile range, 159-230; maximum value, 451 µmol/L). It can be difficult to optimize the dose of tacrolimus and maintain safety; in attaining the target blood concentration to maximize efficacy, there can be large individual differences in dosage for a target range of 10 to 15 ng/mL.[67] Yamamoto et al found that the tacrolimus dose to maintain equivalent blood concentrations was lower in patients carrying the cytochrome (CYP) 3A5*3/*3 than in those carrying the CYP3A5*1 genotype, and the concentration/dose ratio was significantly higher in the latter.[68]

Ciclosporin is an option for treating acute severe UC, but it has a significant toxicity profile, with nephrotoxicity occurring in 6.3%.[7, 69] Rat models have revealed that acute renal damage secondary to ciclosporin is due to vasoconstriction of the afferent arterioles, leading to diminished renal blood flow and glomerular filtration, with a consequent rise in serum creatinine.[70, 71] The histopathological changes seen in ciclosporin-induced chronic renal damage are interstitial fibrosis and arteriolar disruption.[72]

Practical Considerations

In the context of solid-organ transplantation, there is abundant evidence of progressive kidney damage with chronic exposure to calcineurin inhibitors and the importance of adjusting drug dose in response to pharmacokinetic profiling of blood drug concentrations.[73] At present, aside from recommendations for target drug concentrations, the international consensus guidelines do not offer specific advice on how frequently to monitor the renal function of patients taking calcineurin inhibitors; we offer a suggested approach in Figure 3.

TNF-α Inhibitors

Anti-tumour necrosis factor (TNF)-α medications, including infliximab, adalimumab, certolizumab pegol, and golimumab, are increasingly used in the treatment of both CD and UC.[74] Infliximab, adalimumab, and etanercept have been associated with glomerulonephritis in systemic lupus erythematosus; although causality remains unproven. Most cases have been reported in other autoimmune conditions such as rheumatoid arthritis and psoriasis rather than IBD.[70, 75] A possible case of infliximab-induced focal segmental glomerulosclerosis presenting as a severe nephrotic syndrome in a patient with UC has been described,[76] and a similar case in the setting of ankylosing spondylitis.[77] More data related to the possible renal side effects of anti-TNF therapy are needed, but available data suggest that renal complications are uncommon.[74]

Emerging Therapies

An increasing number of novel agents are available to the clinician for treating IBD, but their potential to adversely affect kidney function is poorly understood (Table 3). Vedolizumab, a biologic used to treat moderate to severe UC and CD, has been associated with acute tubulointerstitial nephritis in a case report, although this was reversed following the administration of glucocorticoids.[78] Furthermore, it was successfully reintroduced without further kidney injury.[78] Ustekinumab, an anti-interleukin (anti-IL)-23 biologic is another option for moderate to severe UC and CD, but may be associated with nephrotic syndrome secondary to focal segmental glomerulosclerosis.[79] However, a recent real-world study was reassuring, with no renal complications described.[80] Tofacitinib was the first oral Janus kinase (JAK) inhibitor approved for the treatment of UC. It has been linked with rising serum creatinine, although the specific clinical relevance of this remains undetermined.[81] Other JAK inhibitors like upadacitinib do not appear to have any nephrotoxic effects.[82] Filgotinib, another JAK inhibitor, is an emerging option currently licensed for the treatment of UC in the EU and UK, but not in the United States. Although there is limited clinical experience regarding filgotinib in patients with renal impairment, no specific complications have been reported to date. However in pharmacokinetic studies, an increased drug concentration was observed in patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m²; thus dose reduction in these patients is suggested.[83] More data pertaining to the effects on the kidneys of therapeutic agents used for managing IBD are needed (Table 2).

IBD-related Glomerulonephritis

Glomerular disease as an EIM of IBD was first proposed 4 decades ago.[84, 85] However, infrequent reports brought into question whether there was a causal link. Nevertheless in most cases, not only did the onset of glomerulonephritis coincide with acute exacerbation of intestinal inflammation but renal function improved in parallel with the treatment

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of the gastrointestinal disorder.[86–88] Although not often practiced, repeat kidney biopsy has shown histological resolution of the inflammatory response following treatment of the acute flare.[85] A wide spectrum of histological patterns of the glomerulonephritides has been described in patients with IBD, including IgA nephropathy,[87,89–94] minimal change disease,[92,94] Immunoglobulin M (IgM) nephropathy,[93,95] membranous nephropathy,[88,92–94] membranoproliferative nephropathy,[96] focal and segmental glomerulosclerosis,[92–94] and antibasement glomerular disease.[97] Proving true causation (as opposed to association) can be difficult to establish with certainty, so aiming for close monitoring to ensure that there is a treatment-related change in the trajectory of renal functional decline is important. Seeking continued nephrological input (more than "whether to biopsy") is ideal in these cases.

A kidney biopsy series has established the association between IgA glomerulonephritis and IBD.[92] IgA nephropathy was found in 24% of a total of 83 biopsies performed in IBD patients with acute and chronic kidney disease. Moreover, the prevalence of IgA nephropathy was significantly higher in patients with IBD than in patients without IBD. This suggests a shared pathophysiology between intestinal and kidney disease. Plasma cells in gut mucosa produce large quantities of IgA that plays an important role in regulating the composition of the gut microbiota and in defense against environmental and pathogenic bacterial antigenic exposure.[98] Mucosal inflammation promotes enteric permeability, which leads to loss of systemic antigenic exclusion and stimulates abnormal IgA production. A frequent observation is of mucosal infection triggering episodes of IgA glomerulonephritis, alongside an increase in local mucosal IgA generation.[99] Furthermore, specific bacteria and proteins found at the interface between the intestinal mucosa and lumen can be used to differentiate and classify IBD and healthy human subjects.[100] Dysregulation of IgA production results in increased serum levels of IgA and IgA-containing immune complexes.[101] The circulating level of immune complexes containing IgA correlates directly with clinical activity and extent of glomerular crescent formation.[102] T cells are implicated in the pathogenesis of this disorder, but their precise role is unclear, as few T cells can be identified in the glomerular mesangium. Joher et al studied a case series of 24 patients with IBD-associated IgA glomerulonephritis relative to a cohort of 134 patients with primary IgA nephropathy in the absence of IBD.[103] They found that IBD-associated IgA glomerulonephritis has frequent inflammatory lesions at onset and variable long-term outcomes. They reported no association between IBD activity and IgA glomerulonephritis outcome. Larger series with longer follow-up (such as in idiopathic IgA nephropathy, which has no specific therapy, and can take decades potentially to lead to severe loss of renal function) will help to better define the aetiopathological link between IBD and the development of IgA glomerulonephritis.

The link between a dysregulated gut-associated lymphoid tissue and IgA nephropathy was postulated in the 1980s following the observation of the increased association of IgA nephropathy with celiac disease.[104] Data have demonstrated a role for alimentary antigens, particularly gliadin in developing IgA nephropathy in BALB/c mice. A reduction in IgA antigliadin antibodies and proteinuria was reported after gluten free-diet in patients with IgA nephropathy.[105] A genome-wide association study demonstrated that the majority of loci associated with IgA nephropathy are also associated with immune-mediated inflammatory bowel diseases, maintenance of the intestinal barrier, and response to gut pathogens.[106] Transgenic mice that overexpress the B cell-activating factor develop IgA nephropathy modulated by alimentary components and intestinal microbiota. Mice expressing human IgA1 and a soluble form of the IgA receptor (sCD89) develop IgA nephropathy, which is regulated by dietary gluten. Recent data have established gut-associated lymphoid tissue hyperreactivity in IgA nephropathy patients with IgA against various alimentary components.[107] The NEFIGAN randomised controlled trial utilised an enteric controlled-release formulation of budesonide that was targeted specifically to Peyer's patches.[108] A reduction in proteinuria was seen after 9 months of treatment, as well as normalising of renal function with few reported safety concerns. This promising approach is now being tested more rigorously in the NefIgArd trial.[109,110] The gut-renal connection is an emerging and promising avenue for novel treatment approaches for patients with IgA nephropathy.[107,109,110]

Genome-wide association studies of IgA nephropathy have advanced the notion of genetic cross-susceptibility of IBD and glomerular disease.[106] For instance, HLA-DR1 confers increased risk for IgA nephropathy and HLA-DR1/DQw5 for CD; this might explain why these 2 diseases co-occur more often than expected by chance.[92] Conversely, HLA-Cw*1202-B*5201-DRB1*1502 haplotype increases the risk for UC but reduces that for CD. Among non-HLA loci, an increasing number of IgA nephropathy loci are implicated with risk of IBD (eg, CARD9, HORMAD2) or encode proteins involved in maintaining the intestinal mucosal barrier or regulating mucosal immune response (eg, DEFA, TNFSF13, VAV3, ITGAM-ITGAX, PSMB8).[106]

Acute Tubular Injury and Tubulointerstitial Nephritis

Acute Tubular Injury

In nephrology, early diagnosis and prompt intervention for acute tubular injury, which has many causations, is encouraged. In the context of IBD, acute-on-chronic loss of circulating volume (salt and water depletion) and disease-modifying drugs can both lead to acute—and even chronic—loss of kidney function, which is not always reversible. A full exposition on this important topic is beyond the scope of this article, but interested readers are directed to a review article by Kellum et al.[111]

Tubulointerstitial Nephritis

Tubulointerstitial nephritis (TIN) has many potential etiological associations. The diagnosis of TIN can be challenging and usually warrants a kidney biopsy as part of the diagnostic workup. Frequently, the urinalysis findings may be modest or minimal, but the diagnosis should always be considered in IBD patients for whom loss of kidney function, often but not invariably, takes place over time and without an obvious causative factor.[112,113] Continued close follow-up with nephrological input is key.

Tubulointerstitial nephritis has been reported in patients with IBD, but it is often difficult to determine whether this should be considered as an EIM or as an extraintestinal

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complication secondary to medical treatment from drugs such as 5-ASA, ciclosporin, and TNF-α inhibitors (Figure 4).[93,114,115] For example, in a Finnish series of 819 patients undergoing kidney biopsy, 35 patients (4.3%) proved to have IBD but in those with TIN, the prevalence of IBD was 13.3%.[93] In this cohort, all patients with TIN had an ongoing or previous history of 5-ASA exposure, so the authors were unable to conclude whether this observation was an EIM or medication-related. Nevertheless, multiple studies have demonstrated a link between tubulointerstitial damage and IBD activity by assessing the levels of various proteins excreted in the urine, which are considered to be specific markers of tubular damage in both adult [116,117] and pediatric patients.[118] In health, low molecular weight proteins such as alpha-1-microglobulin (α-1-MG) and cystatin C are filtered by the glomerulus and reabsorbed in the proximal tubule.[119] Their presence in the urine implies diminished reabsorption and are considered sensitive markers of tubular damage. In some cases, the presence of a predominantly lymphocytic infiltrate with non-necrotising granulomata has been observed on renal biopsy, lending further support that the diagnosis of TIN is an EIM rather than secondary to medication.[118,120–123] Once again, continued close follow-up with nephrological input is key.

Renal Amyloidosis

Serum amyloid A protein (SAA) amyloidosis, also known as secondary amyloidosis, involves the extracellular deposition of insoluble amyloid fibrils in any organ, derived from the acute-phase reactant; SAA and its production occurs in some chronic inflammatory states such as IBD. A systematic review comprising nearly 10 000 patients found that IBD-related amyloidosis is a rare entity with an estimated overall prevalence of 0.53%. Crohn's disease is complicated by amyloidosis in 1.05% of cases compared with just 0.08% in UC.[124] The most common presentation of SAA amyloidosis is renal involvement presenting with renal impairment in the setting of nephrotic syndrome. In about 15% of cases, neither proteinuria nor elevated serum creatinine is found, and so a high index of suspicion is required to make the diagnosis.[124] The diagnostic gold standard is a biopsy of the target organ (Figure 1). Serum amyloid A protein is associated with an increased incidence of acute tubular necrosis and faster progression to advanced chronic kidney disease and end-stage renal disease; thus, it is likely to be associated with amyloid- and kidney-related pathologies leading to reduced patient survival.[125] Treatment is targeted at the underlying IBD disease activity to reduce the new formation and deposition of SAA protein and address renal amyloidosis. Curative therapies for renal amyloidosis are not yet available, but one approach to contain the disease is a combination of anti-TNF agents and colchicine.[124]

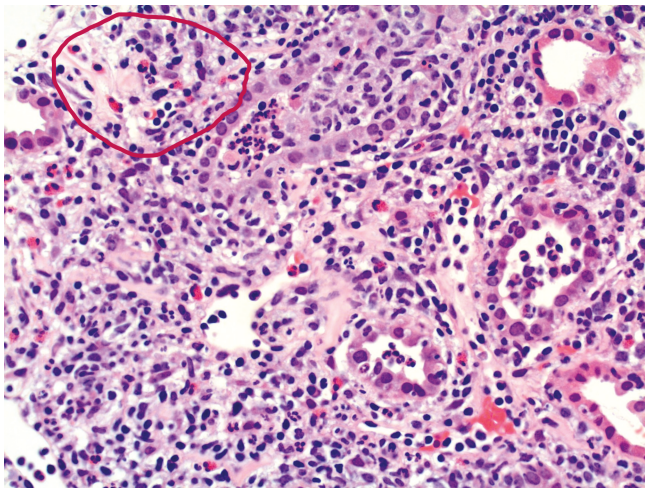

Figure 4. A high-power (100x magnification) haematoxylin and eosin (H&E) stain, derived from a biopsy of the interstitial compartment of the renal parenchyma from a patient with Crohn's disease. There is an intense eosinophil-rich interstitial infiltrate (example encircled in red) comprising polymorphonuclear leucocytes and lymphocytes, in some places exhibiting "tubilitis" (infiltration and blockage of the renal tubular lumina by cells) (See online version for color figure).

Conclusions

The presentation of renal and urinary complications related to IBD can be subtle and requires continued vigilance to ensure prompt diagnosis and treatment. Involvement of a multidisciplinary approach (urology, nephrology) seems both prudent and valuable. We have identified a number of clinical and research priorities in this field (Table 2) that highlight the compelling need for detailed combined phenotypic and genotypic characterization of large cohorts followed for at least 10, preferably 20 years. The detection of early renal impairment (loss of excretory function) is of paramount importance because once significant renal functional loss has occurred, this may be both irreversible and progressive (eg, recurrent episodes of acute kidney injury or overexposure to potential disease-modifying drugs with their own toxicities). The management of all aspects of IBD is considerably more complex if patients become dialysis-dependent, so avoiding this degree of loss of renal function is of paramount importance. The cornerstone of preventive nephrology still depends on repeated measurement of plasma creatinine concentrations over time that are then converted to an estimated GFR.[126] As repeated episodes of acute kidney injury are linked to progressive loss of kidney function, patients should receive appropriate monitoring of eGFR at their follow-up visits, following nationally approved and endorsed standards of care. Control of blood pressure using renin-angiotensin-aldosterone system inhibitors (RAASi) and, increasingly, sodium/glucose co-transporter-2 inhibitors (SGLT-2i) are cornerstone management tools to arrest progressive loss of renal function, although SGLT-2i have not been much studied in the context of IBD. Timely referral for nephrological advice around diagnosis and management is also important.[126]

Until dedicated, high-quality clinical and investigational studies with large cohorts and long-term follow-up are undertaken to discover the true nature of the relationships between IBD and chronic kidney disease. The most effective strategy for prevention of kidney and urological involvement in IBD is to achieve rapid diagnosis, treatment, and remission of the primary bowel pathology. Increased awareness of the renal manifestations and complications associated with IBD should reduce the risk of both acute and chronic kidney injury, leading to better patient outcomes.

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Conflicts of Interest

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