



ISSUE HIGHLIGHTS

Indian Journal of Gastroenterology—January–February 2024 issue highlights

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Inflammatory bowel disease (IBD) is on the rise in several Asian countries, including India [1]. Most of the patients are in the second to fourth decade of life at the onset of disease and, if not managed properly, IBD can lead to significant morbidity and reduction in the quality of life [1]. In spite of growing volume of research, the exact pathogenesis of the disease remains unknown and medical cure is still elusive. There is relatively lesser information on epidemiology, long-term clinical course and therapeutic outcomes from developing nations compared to the developed countries. The current special issue on IBD contains several original research articles covering different aspects of this disease. In addition, there are review articles by experts from across the globe on a spectrum of topics related to IBD.

Review articles

The current issue of the *Journal* contains review articles on several important aspects of IBD. Gut microbiota has emerged as a key player in the pathogenesis of IBD. A narrative review provides current status of evidence on the role of bacterial population in IBD [2]. It presents a list of bacteria showing positive and negative association with both ulcerative colitis (UC) and Crohn's disease (CD) based on the available literature. Further, it also describes how certain selected bacterial species may play a role in the pathogenesis of IBD. Gut bacteria have been the main focus of investigation and there is less information on the role of virus and fungi. A narrative review on mycobiome in IBD provides an in-depth information on the methodology to study fungi

in gut, fungal dysbiosis in IBD and their implications in pathogenesis and the potential therapeutic options [3].

Crohn's disease may affect the perianal region in up to one-third of patients. Their management generally requires a multi-disciplinary team approach and can be challenging. The article by Devi and colleagues reviews the current status of diagnosis and therapy of perianal CD, including surgical interventions [4]. It then goes on to discuss the emerging therapies and challenges in managing perianal CD in the South Asian context. Aggressive disease behavior in CD is characterized by the formation of strictures and fistula. Elford et al., in their review article, discuss the pathogenesis, clinical features and investigations, including various imaging modalities and management of stricturing CD [5]. The medical, endoscopic and surgical management is discussed separately and a treatment algorithm has been provided. Intestinal ultrasound (IUS) has emerged as a useful test to assess disease activity in IBD. Despite being convenient and cost-effective, its utilization in clinical practice is sub-optimal. Another review article discusses in detail the various aspects of IUS in IBD, including the techniques and indications, to highlight the utility of this technique to the readers [6].

This special issue also includes several review articles on therapy of IBD. Fecal microbiota transplantation (FMT) has emerged as a promising therapy in IBD, especially UC. It aims to restore the gut microbial composition to a healthy state. The review article by Singh et al. discusses the current status of FMT in IBD [7]. It covers various aspects of FMT for IBD, including indications, safety and efficacy, areas of uncertainty and future directions. An alternative way to modulate bacterial population in the gut is by using antibiotics. However, they are beneficial for therapy in only selected situations. The review by Jha et al. provides a comprehensive evidence-based information on the situations, where antibiotics may be indicated in therapy of IBD [8]. Another narrative review provides an in-depth information on the management of acute severe colitis, including recognition of the condition, risk stratification,

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initial management and rescue therapy [9]. Thiopurines are effective and frequently used drugs for the management of IBD in countries such as India, where many patients cannot afford biological therapy. However, they have a narrow therapeutic window and need close monitoring of therapy to recognize the side effects and modify/discontinue the drug as required. Bayoumy et al., in their narrative review, discuss potential innovations in thiopurine therapy to reduce the adverse effects and improve efficacy [10]. Patients with IBD generally require prolonged therapy and the safety and efficacy of treatment are important considerations when following up these patients. In patients with lack of response to therapy, therapeutic drug monitoring (TDM) may help in making better decisions with regard to change of dose or switching to an alternative drug. The narrative review by Desai provides evidence-based and useful practical information on TDM for thiopurines and biologicals for patients with IBD [11].

Original articles

Trends of inflammatory bowel disease from the Global Burden of Disease study (1990–2019)

Inflammatory bowel disease (IBD) is transitioning into a global disease from being a disease of the western developed nations in the past. A rising trend has been observed in several developing nations, including India, although epidemiological data is relatively limited. The Global Burden of Disease study synthesizes information from a large number of data sources across the world to provide comprehensive information on health indicators and outcomes on a number of diseases [12]. The inflammatory bowel disease collaborators of GBD 2017 reported an increasing prevalence of IBD globally [13]. The estimated number of patients with IBD in 2017 was 6.8 million [13]. GBD 2019 includes more data sources along with refinement in methodology and Dharni et al. report the trends in IBD from 1990 to 2019 based on this data set [14]. The authors have provided key information on the trend and current status of several parameters such as incidence, prevalence, mortality and disability-adjusted life years among IBD subjects. A striking observation was the lower number of estimated cases of IBD in 2019 (4.9 million) compared to 2017 and the declining incidence and prevalence of IBD compared to 1990. However, a rising incidence and prevalence was noted in countries with middle and low socio-demographic index. With regard to India, the estimated number of patients with IBD increased from 0.13 million in 1990 to 0.27 million in 2019.

Estimates of disease burden from heterogenous data sources and variations in measurement techniques have their limitations as reflected in the differences estimated between

GBD 2017 and GBD 2019. The trends for ulcerative colitis (UC) and Crohn's disease (CD) may not be similar and the GBD study does not provide separate information on these two conditions. Notwithstanding these limitations, the GBD study provides one of the most comprehensive estimates on disease characteristics/outcomes based on currently available information. It highlights the growing burden of IBD in countries such as India and the need to improve awareness and create necessary facilities to diagnose and manage a growing number of cases.

Role of adjuvant Crohn's disease exclusion diet plus enteral nutrition in asymptomatic pediatric Crohn's disease having biochemical activity: A randomized, pilot study

The goals of therapy in IBD have changed over the years with focus shifting from clinical remission to biochemical, endoscopic and histological remission [15]. The number of treatment options available has also increased, which includes immunomodulators, a host of biological agents, microbiota-based therapy and dietary therapy. Dietary therapy in the form of exclusive enteral nutrition (EEN) has been shown to be beneficial in the treatment of Crohn's disease, especially in pediatric patients [16]. However, EEN is not very palatable and this affects compliance with therapy. A combination of Crohn's disease exclusion diet (CDED) with partial enteral nutrition (PEN) has shown a better compliance rate without reduction in efficacy compared to EEN [16].

Patients in clinical remission, but elevated inflammatory markers have a higher risk of relapse in the next few months and may need escalation of therapy [17]. In the first study on pediatric IBD published in the current issue, Arcucci et al. from Argentina have evaluated the role of adding CDED with PEN in children (< 18 years of age) with CD who have no clinical symptoms, but elevated fecal calprotectin (FC > 250 µg/g) level [18]. In this randomized, open-label study, 12 children received dietary intervention along with continuation of biological therapy, while 10 patients in the control arm continued biological therapy with regular diet. At the end of 12 weeks, there was a 50% reduction in FC levels in 81.8% of cases who completed dietary therapy compared to only 20% in the control group ($p = 0.005$). However, reduction of FC to < 250 µg/g was noted in only five cases. Four of the control subjects had a relapse of disease compared to one case. Only one subject in the intervention arm stopped dietary therapy due to intolerance. This study highlights the role dietary intervention can play as an add-on therapy in achieving reduction of inflammatory marker without the need for changing the ongoing biological therapy. The small number of subjects and lack of data on long-term sustainability of response are some of the limitations, but this

data provides the groundwork for further larger studies with extended follow-up.

Spectrum and trend of pediatric inflammatory bowel disease: A two-decade experience from northern India

Data on IBD in pediatric population is quite limited from India. In the second original article on pediatric IBD in this special issue, Mohan et al. have reported the profile of pediatric (< 18 years) IBD cases seen at their center over the past 20 years [19]. Of the 126 patients with IBD, 76 had ulcerative colitis (UC) and 44 had Crohn's disease (CD). The mean age at diagnosis was about 11 years and the disease was more frequent in males (1.6:1). Abdominal pain and diarrhea were the main symptoms in CD, while rectal bleeding was the dominant symptom in UC. Very-early-onset IBD (age < 6 years) was noted in 12.6% of cases. A majority of patients with UC had pancolitis (77%) and 27.6% had severe disease. The commonest location for CD was in the ileocolonic region and aggressive disease behavior was noted in 33%. The authors compared their observations with the western data and a notable difference was the higher rate of aggressive CD (stricturing and/or penetrating disease) in Indian patients (33% vs. 18%). The induction of remission was commonly achieved with steroids and azathioprine was the agent most commonly used to maintain remission for both CD and UC. Use of biological agents for therapy was mainly limited by cost constraints.

This is the largest single center data on pediatric IBD from India and provides valuable insight into the characteristics of this disease in children. Globally, pediatric onset IBD is on the rise and in this study as well, there was a rising trend in the number of cases seen over time [20]. The median delay in diagnosis of CD was over four years, while the situation was better for UC. More than half the patients with CD had body weight < 3rd centile and one-third had height < 3rd centile. These observations highlight some of the issues in pediatric IBD, including diagnostic delays and its detrimental effect on growth of the child and call for improving awareness among pediatricians for early recognition and referral.

Transition from intravenous to subcutaneous biological therapies in inflammatory bowel disease: An online survey of patients

Biological therapies have been effective in the control of symptoms and inflammation in IBD. These agents need to be administered parenterally (intravenous or subcutaneous). Intravenous administration generally requires hospital visit, while subcutaneous injection may be self-administered. This makes subcutaneous injection potentially convenient, as it avoids hospital visit and absence from work. While the benefit may be obvious, it is

crucial to know the opinion of patients themselves on transition to subcutaneous therapy to get a better insight.

Napolitano et al. conducted an online survey of adult patients with IBD from Italy who were on maintenance therapy with intravenous biological agents (infliximab or vedolizumab) [21]. The questionnaire had 31 items and explored various domains of transition to subcutaneous therapy. Among the 311 patients surveyed, almost half of them perceived the transition favorably. Patients who had to travel longer distance to hospital or those with commitments to work/family were more likely to favor subcutaneous therapy. Interestingly, a majority of patients were unaware about the availability of subcutaneous injections. Although the questionnaire used in this study was not validated, the results support switching to subcutaneous therapy after communicating to the patients about the safety/efficacy and obtaining their approval.

Depression and active disease are the major risk factors for fatigue and sleep disturbance in inflammatory bowel disease with consequent poor quality of life: Analysis of the interplay between psychosocial factors from the developing world

Fatigue is a frequent symptom in patients with IBD and affects the quality of life. A recent meta-analysis of 20 studies showed the pooled prevalence of fatigue to be 47% (95% CI, 41–54) in patients with IBD [22]. Except for one report from China, the data sources for this meta-analysis were from studies conducted in developed nations outside Asia indicating the limited information on this issue from Asian countries and developing world. Pal et al. have addressed this knowledge gap by assessing the frequency of anxiety, depression, fatigue and sleep disturbance in adult patients with IBD from India [23]. Two hundred and two patients (123 CD and 79 UC) were recruited among whom 73.8% had active disease. The participants completed the following questionnaires: IBD fatigue score, hospital anxiety and depression score, Pittsburgh sleep quality index and short inflammatory bowel disease questionnaire. Fatigue was noted in 55.9%, poor sleep quality in 53.5%, anxiety in 44.5% and depression in 34.1% of the subjects. Subsequently, the risk factors for fatigue and sleep disturbance were assessed using logistic regression. A majority of patients with fatigue (95.6%) and sleep disturbance (93.5%) had active disease. Accordingly, active disease was the key predictor for both fatigue and disturbed sleep. Presence of depression was also associated with fatigue and poor sleep. The high frequency of fatigue among active cases was also noted in the meta-analysis cited above, although a key difference was the presence of fatigue in 47% of patients with disease in remission as well [22].

Lack of validation of questionnaire translated in regional language is a limitation considering the sociocultural

differences between different regions and the authors have mentioned this in the discussion. Since approximately nine out of every 10 patients with fatigue or poor sleep quality had active disease, appropriate treatment to induce remission may be the most effective strategy to counter these symptoms.

Upfront tofacitinib in patients with biological-naïve ulcerative colitis—An Indian multicentric experience

The usual treatment options for steroid-dependent or refractory UC include immunomodulators (e.g. azathioprine, 6-mercaptopurine), biological agents or fecal microbiota transplantation. Biological agents are expensive and FMT needs endoscopy for administration. The availability of oral small molecule Janus kinase inhibitors has provided a useful alternative to the above agents. Clinical trials have confirmed the efficacy of tofacitinib for the induction and maintenance of remission in moderate to severely active UC and long-term safety data has also become recently available [24].

This retrospective study provides data from six centers across India on the safety and efficacy of tofacitinib in patients with UC who were biological-naïve [25]. Clinical response and remission were assessed by calculating partial Mayo scores at baseline, eight weeks, 16 weeks and 24 weeks. Forty-seven patients were included for the final data analysis and their median age was 32 (18–56) years. The indications for starting tofacitinib were steroid-dependent disease in 27, immunomodulator refractory/intolerant state in 11 and steroid refractory disease in nine patients. At week eight, 33 (70.2%) patients achieved clinical remission and another four patients achieved remission over the next eight weeks. The remission was sustained in a majority of them at 24 weeks. Adverse effects occurred in 21.2% of cases, including two cases of tuberculosis. The authors did not report on the improvement in markers of inflammation on follow-up, which is a limitation. Overall, this study showed good efficacy of tofacitinib in the improvement of clinical symptoms in patients with UC. At the same time, it also emphasizes on careful screening for infection before starting therapy as is done for biological therapy. The appropriate position of tofacitinib in the therapeutic algorithm of UC is still evolving, but they may be used in patients who are immunomodulator-naïve/treated or biological-naïve/treated. Their lower price compared to biological agents makes them an attractive option in patients not able to afford more expensive therapy.

Post-traumatic stress disorder symptoms are frequent among inflammatory bowel disease patients of South Asian descent—A case-control study

Patients with IBD have an increased risk of psychiatric disorders [25]. Symptoms of anxiety and depression have been noted in about one-third of them [26]. Yet, mental health of the patients is perhaps not given as much attention as the physical health. Psychiatric symptoms negatively impact patient's quality of life and are also associated with disease activity and flare ups [26]. A case-control study published in this issue of the journal evaluated the frequency and severity of post-traumatic stress disorders (PTSD) among South/South-East (S/SE) Asians ($n=51$) and its association with disease activity and health-related quality of life [27]. White, non-Hispanic subjects with IBD served as controls ($n=110$). Patients were recruited via social media and patient support group and were asked to complete a self-administered questionnaire related to clinical and disease activity profile, post-traumatic stress disorder checklist 5 (PCL-5) and health-related quality of life using an online platform.

PTSD was noted in 47% of the cases compared to 13.6% controls. In addition, the mean global score for PTSD was three times higher in cases than in controls. All IBD-PTS symptoms, including hyperarousal, negative mood, avoidance behaviors and intrusion, were more frequent in S/SE Asians compared to controls. The presence of PTS was associated with a poor quality of life and was more severe in those with active disease. This study highlights the importance of evaluating mental health in patients with IBD and the effect of race/ethnicity on symptoms. Assessment of disease activity as well as psychiatric symptoms by oneself may not be very accurate and this is a limitation of this study along with the small sample size. The frequency/severity of symptoms in the migrant population may not be similar to the situation in their home country. Nonetheless, this study throws important insight into an important and under-recognized aspect of care for IBD patients.

Comprehensive assessment of nutritional and functional status of patients with ulcerative colitis and their impact on quality of life

Nutritional deficiencies are prevalent in patients with IBD and recognition and appropriate management are important components of therapy. Poor nutritional status is associated with sub-optimal response to therapy, higher risk of infection and higher cost of care.

In this study from northern India, Sachan et al. report their observations on the nutritional status in patients with

UC ($n = 126$) compared to controls ($n = 57$) [28]. They performed a comprehensive assessment of nutritional status by anthropometry, functional assessment, clinical features and laboratory test. A short IBD questionnaire was used to assess the quality of life in UC. The presence of low body weight, functional impairment and macronutrient and several micronutrient deficiencies were more common in UC subjects compared to controls. About two-third of UC patients had a poor quality of life. Histologically active disease and vitamin D deficiency were identified as risk factors for poor quality of life. Data on nutritional status and quality of life in UC patients are limited from India and the results from this study reflect the significant impact IBD can have on both of them.

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Data availability Not applicable.

Declarations

Conflict of interest AKD declare no competing interests.

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