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EDITORIAL

Editorial commentary on the Indian Journal of Gastroenterology March–April 2020 issue

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Etiology and short-term outcome of diarrhea in kidney transplant recipients

Diarrhea is one of the most common gastrointestinal complaints following renal transplantation, which is associated with significant morbidity from the impaired quality of life, hospitalization, and serious consequences on graft survival and death [1]. Post-transplant immunosuppression with antecedent risks of infection and polypharmacy are recognized risk factors for diarrhea; however, these are mostly based on data from the West, where infection-related adverse outcomes may be less pronounced [1].

Sonambekar and colleagues report a single-center prospective observational study on 47 renal transplant recipients [2]. The etiology of diarrhea was infective in 33/64 (51.5%). Non-infective diarrhea was mainly related to immunosuppressants, urosepsis, and antibiotics. In both the groups, diarrhea occurred more commonly >6-months after transplantation. Graft dysfunction occurred in 53 (82%) episodes with graft function normalizing in 3 months in 27/28 infective and 19/25 non-infective episodes. The high prevalence of non-infectious diarrhea in an Indian cohort and its detrimental impact on graft function are novel findings. Large cohort studies assessing risk factors and outcomes using validated algorithms are urgently needed.

Functional constipation or redundancy of the colon?

Functional constipation is the most common cause of constipation in children. Noviello and colleagues describe a retrospective experience on children with chronic refractory constipation [3]. Assessments involved contrast enema, anorectal manometry, and rectal suction biopsy as necessary. Of 69 children, two each had anal stenosis and colonic aganglionosis. Fifty-seven children were diagnosed having functional constipation in whom colonic diameter was assessed (rectum, sigmoid, descending, transverse and ascending colon) along with the rectosigmoid length and the ratio compared to the width of the second lumbar vertebra using previously described techniques in children without constipation [4]. The mean ratio of rectosigmoid length and width of second lumbar vertebra was significantly different (19.03 vs. 9.75 in normal 1-year-old children and 19.46 vs. 9.59 in older children), leading the investigators to hypothesize that the dysfunctional segment may be immediately above the rectum and suggest maintenance of colonic fluid equilibrium and avoidance of long periods without defecation. The study also emphasizes the importance of systematic assessment of constipation to characterize etiology accurately.

Reversal of anti-drug antibodies against tumor necrosis factor inhibitors with the addition of immunomodulators: A systematic review and meta-analysis

Anti-TNF therapies have transformed the care of patients with inflammatory bowel disease. These are immunogenic, with up to 30% of patients demonstrating primary non-response and up to 50% developing secondary loss of response (LOR) from low/undetectable drug concentrations due to immune (anti-drug antibodies, [ADA]) and non-immune clearance [5]. Following LOR, successive therapies may be less effective,

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emphasizing the need to optimize anti-TNF treatment [5]. This meta-analysis of 4 retrospective studies, demonstrates that the addition of an immunomodulator (thiopurines in 61.2% and methotrexate in 38.8%) after development of ADAs resulted in the reappearance of clinical response in 73.86% of patients with reduction or elimination of ADAs [6]. Larger prospective studies assessing the effect of the addition of an immunomodulator and outcomes such as longevity of response and potential complications are needed. Meanwhile, in patients with LOR to anti-TNF and low ADA titers, the judicious addition of an immunomodulator may be a useful strategy to "recapture" response and continue therapy.

Blood transfusion is unlikely to be a source for hepatitis E virus transmission in India

Hepatitis E is a common cause of acute viral hepatitis (HEV) in the developing world, from the consumption of contaminated food and drink. Transfusion-associated HEV has been reported from countries with genotype 3 predominance, with 43% of recipients in a UK study developing HEV infection, leading to the introduction of screening of blood/blood products for HEV RNA [7]. Data on transfusion-related HEV transmission, where genotype 1 is endemic, are lacking. Halkurike and colleagues report a prospective observational study on 335 patients admitted for cardiac surgery, with no transfusions in the preceding 12-months [8]. Data were available for 191 patients, of whom 88 were HEV IgG negative at baseline and had liver enzymes and anti-HEV testing 2–3 monthly for 6 months. Encouragingly, none of these patients developed jaundice or anti-HEV (IgM/IgG) antibodies. Longitudinal data from large multicentre prospective cohorts are needed to settle this critical issue of public health importance.

Role of esophageal manometry and 24-h pH testing in refractory reflux symptoms

Gastrooesophageal reflux disease (GERD) is the most common gastrointestinal diagnosis recorded in out-patient visits. Diagnostic testing is typically invoked to evaluate empirical treatment failures, avert misdiagnosis, and identify reflux-related complications. The Indian Society of Gastroenterology (ISG) Task Force recommends investigation of patients not responding to conventional 4-week proton pump inhibitor (PPI) therapy [9]. Dr's Jain and Agrawal report a retrospective experience of high-resolution esophageal manometry (HREM) and 24-h pH recording in 96 patients with GERD refractory to 8-weeks PPI therapy [10]. A third of patients (31.7%) with typical GERD symptoms were diagnosed having non-GERD pathology that included eosinophilic esophagitis, supra-gastric belching, rumination syndrome, achalasia, hypersensitive esophagus, and functional heartburn. The study highlights the need to identify alternative diagnoses that masquerade as GERD and for which management strategies differ. The timely and judicious use of HREM and esophageal pH testing has an important role in modern diagnostic evaluation of "reflux".

Endoscopic ultrasound-guided celiac plexus neurolysis improves pain in gallbladder cancer

Gallbladder cancer (GBC) is the most common biliary malignancy with only 10% to 30% patients eligible for curative resection at diagnosis and a median survival rate of 3–6 months for unresectable disease [11]. Narcotic agents are effective for analgesia but associated with side-effects. Endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) has been shown to be effective in pain-relief in chronic pancreatitis and pancreatic cancer [12]. In a novel prospective observational study, Rai and colleagues [11] describe EUS-CPN in alleviating pain (using a visual analog scale) from unresectable GBC, unresponsive to NSAID's and tramadol. Notably, stronger opioid analgesia was not administered. Technical success was achieved in 19/21 patients, with a statistically significant early improvement in pain scores at 2 and 4 weeks (95% and 63%, respectively) and a numerical (but not statistically significant) reduction in pain by week 8. No procedure-related complications were reported. Larger prospective and randomized studies against the current "standard of care" are needed to validate these observations further.

An Indian national survey of therapeutic drug monitoring with anti-TNF medications in inflammatory bowel disease

Therapeutic drug monitoring (TDM) has emerged as the new standard of care for optimizing anti-TNF therapy in patients with inflammatory bowel disease (IBD), but data on perceptions and barriers to the use of TDM are scarce [5, 13]. Patel and colleagues report the first Indian national survey of gastroenterologists aiming to understand attitudes, perceptions, and barriers to TDM in optimizing anti-TNF therapy [14]. Only 20% of gastroenterologists completing the survey used TDM with anti-TNF agents, 89.5% of which were to assess the secondary loss of response, and 14 clinicians (73.7%) used TDM pro-actively. The cost of TDM, lack of availability, and time-lag for results were the main barriers reported. Almost all respondents (97.5%) not using TDM would optimize anti-TNF therapy using TDM if all obstacles were removed.

Biosimilar agents have improved access to anti-TNF treatments. The judicious use of TDM can augment decision-making and optimize patient outcomes, making it a worthy consideration for all clinicians treating IBD.

Changes in the severity of gastric mucosal inflammation associated with *Helicobacter pylori* in humans co-infected by intestinal helminths

The variable biological effects of *Helicobacter pylori* (*H pyloti*), ranging from benign gastritis to malignancy has (among the other factors) led to speculation that immunomodulatory effects of co-existing intestinal helminth (IH) infection may influence *H pylori* pathogenesis. Fuenmayor-Boscan and colleagues studied the association between *H pylori* and IH and cytokine expression in 46 adults with endoscopic gastropathy in 3 groups: *H pylori*-negative and IH-negative; *H pylori*-positive and IH negative; *H pylori*-positive and IH-positive [15]. Pro-inflammatory cytokine expression (IL-1ß), degree of histological inflammation, and gastric cancer index risk (GCRI) were higher in the *H pylori*-positive and IH negative group compared with *H pylori*-negative and IH-negative patients. Conversely, increased IL-4 and decreased pro-inflammatory cytokine expression (Th2-dominant response), with a lower degree of histological inflammation and GCRI risk, were seen in the *H pylori*-positive and IH-positive group. The role of Th2-type immunomodulatory responses triggered by helminths in the biological expression of *H pylori* and their therapeutic and preventative potential is worthy of further exploration.

Chronic vomiting in children: a prospective study reveals rumination syndrome is an important etiology that is underdiagnosed and untreated

The differential diagnosis of chronic or recurrent vomiting in children is broad and hinges on systematic assessment to differentiate organic from functional etiologies [16]. Malik and colleagues describe a prospective evaluation of 50 consecutive children referred with ≥2 month history of chronic or recurrent vomiting [17]. Diagnostic testing included blood and urine tests, contrast radiology, ultrasound, upper gastrointestinal endoscopy with biopsy, pH and manometry testing, and gastric emptying studies. Using ROME III criteria to assess functional symptoms, 30 children were diagnosed having rumination syndrome, 29 of whom were previously diagnosed as malingering, gastroesophageal reflux, and others. Symptoms improved following counseling and diaphragmatic breathing techniques in 23% and 19/23, and 2/23, respectively had a complete and partial response in a median time of 10 days. Cyclical vomiting syndrome and functional vomiting were diagnosed in 8 and 6 children, respectively. A systematic approach that incorporates assessment of functional etiology can avoid misdiagnosis and improve outcomes.

The effect of TJ-28 (Eppikajutsuto) on the prevention of hand-foot syndrome using capecitabine for colorectal cancer: the Yokohama clinical oncology group study (YCOG1102)

Capecitabine is commonly used as adjuvant chemotherapy following curative colorectal cancer resection. Capecitabine-induced hand-foot syndrome (HFS), characterized by desquamation and blistering, is a common adverse event resulting in treatment discontinuation with limited data on HFS prevention. Watanabe and colleagues report a randomized, open-label trial on 22 patients following curative colorectal cancer resection, received Eppikajutsuto (TJ-28, a Japanese herbal medicine) 2500 mg or pyridoxine 20 mg three times daily and followed until the development of HFS grade ≥ 2 or until chemotherapy was completed [18]. The study failed to meet its primary endpoint with no statistically significant differences in the occurrence of grade ≥ 2 HFS (50.0% in the TJ-28 group and 40.0% in the pyridoxine group; $p = 0.658$) although chemotherapy treatment failure was significantly lower in the TJ-28 group (8.3%) than in the pyridoxine group (60.0%) (p 0.020). Larger randomized trials may further our understanding of the effect of TJ-28 on capecitabine-induced HFS.

Compliance with ethical standards

Conflict of interest JKL declares that he has no conflict of interest.

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