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Systematic review of immune checkpoint inhibitor-related gastrointestinal, hepatobiliary, and pancreatic adverse events

Malek Shatila [1], Hao Chi Zhang [1], Anusha Shirwaikar Thomas [1], Antonio Pizuorno Machado [2], Sidra Naz,[1] Nitish Mittal [2], Christine Catinis [2], Krishnavathana Varatharajalu,[1] Carolina Colli Cruz,[1] Eric Lu,[1] Deanna Wu,[1] Julie R Brahmer,[3] Franck Carbonnel,[4] Stephen B Hanauer,[5] Bret Lashner,[6] Bryan Schneider [7], John A Thompson [8], Michel Obeid [9], David P Farris [10], Yinghong Wang [1]

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ABSTRACT

Gastrointestinal immune-related adverse events (GI irAEs) are common manifestations of immune checkpoint inhibitor (ICI) toxicity. We present a comprehensive systematic review of the incidence, management, and clinical course of irAEs across the entire GI system, including the luminal GI tract, liver, and pancreas. MEDLINE, Embase, Web of Science Core Collection, and Cochrane Library were used to conduct this review. All studies pertaining to GI irAEs were included. Both abstracts and full manuscripts were eligible if they included human subjects and were written in the English language. Articles not available in English, animal studies, or research not specific to GI toxicity of immunotherapy were excluded. We excluded certain article types depending on whether stronger evidence was available in the literature for a specific toxicity, for example, if prospective studies were available on a topic, retrospective studies and case reports were excluded. We extracted a final 166 articles for our review and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for data reporting. Risk of bias tools were not used to evaluate the extracted studies given the narrative nature of this manuscript, but each study was critically appraised by the manuscript writer. We detail the incidence, presentation, evaluation, management, and outcomes of the various GI toxicities that may arise with ICI therapy. Specifically, we discuss the characteristics of upper GI toxicity (esophagitis and gastroenteritis), lower GI toxicity (colitis), hepatobiliary inflammation, pancreatitis, and rarer forms of GI toxicity. We hope this review serves as a useful and accessible clinical tool that helps physicians familiarize themselves with the nuances of gastrointestinal/hepatic/pancreatic ICI toxicity diagnosis and management.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have improved the field of cancer treatment and are used for an increasing number of malignancies.[1] By blocking inhibitory checkpoints of immune cell proliferation, ICIs stimulate the immune system and allow it to mount an enhanced antitumor response.[1] While this is effective at combatting malignancy, it can give rise to immune-mediated inflammatory responses, commonly referred to as immune-related adverse events (irAEs), in any organ system of the body.[2]

Gastrointestinal (GI) adverse events are the second most common irAEs after cutaneous toxicities and can have a spectrum of severity. They encompass a wide range of pathologies but most commonly involve inflammation of the colon, liver, and pancreas; less frequently affected is the upper GI tract including the stomach and esophagus. Mucositis, appendicitis, and diverticulitis have also been seen, and some toxicities such as immune-mediated celiac disease, bowel perforation, and gastroparesis, while exceedingly rare, have been reported. The precise mechanisms of such toxicities are yet to be fully elucidated.

Research into GI system adverse events has expanded in recent years as ICIs have become increasingly commonplace in the field of oncology. A plethora of studies ranging from case reports to meta-analyses explore specific outcomes among particular GI irAEs. However, there are very few comprehensive reviews of all GI irAEs. Only one systematic review has been published for hepatic irAEs.[3] However, it is unclear what search strategies or databases were used and whether it adhered to systematic review reporting guidelines. Three systematic reviews exist for pancreatic irAEs but focus on exploring the incidence of immune-mediated pancreatitis without describing the presentation, treatment, and

long-term outcomes of this disease.[4–6] Finally, immune-mediated colitis (IMC) is the best studied of all GI irAEs, and there are myriad systematic reviews on the subject.[7 8] Most of these reviews typically explore specific topics such as the utility of sigmoidoscopy in diagnosis,[9] the incidence and treatment of IMC,[10] histopathological and endoscopic findings of IMC,[11] and the role of surgery.[12] Given the rapid expansion of knowledge in the field of IMC, a more current review of the literature would be beneficial. To date, no systematic review encompasses all aspects of each individual GI irAE. The purpose of this systematic review, therefore, is to serve as an up-to-date and detailed reference on all possible GI, hepatobiliary, and pancreatic irAEs.

METHODS

This systematic review was conducted and written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

Inclusion/exclusion criteria

All studies pertaining to GI system irAEs were included, as were studies of neurological irAEs that presented as gastroparesis. Full manuscripts or conference abstracts of all study types were eligible if they included human subjects and were written in the English language.

We excluded any articles that were not available in English, animal studies, or research that did not involve or was not specific to GI toxicity of immunotherapy. We also excluded certain article types depending on the quality of literature available for a specific toxicity: case reports were excluded if multiple retrospective studies were available, retrospective studies were excluded if multiple prospective studies were published, and meta-analyses

were included whenever possible. Finally, narrative reviews were excluded unless found to be meaningful in full-text review.

Literature search and selection

A medical research librarian searched MEDLINE (Ovid), Embase (Ovid), Web of Science Core Collection (Clarivate), and Cochrane Library (Wiley) from inception to January 9, 2023. After consultation with the research team, the librarian developed and tailored the search strategy to each database and selected controlled vocabulary (MeSH and Emtree) and natural language terms for the concepts of cancer, ICIs, GI tract, liver, pancreas, and adverse events. No other limiters or published search filters were used. The search strategy can be found in online supplemental appendix A. Search results were uploaded to the Covidence online tool for systematic reviews.

In the initial phase, two independent and blinded reviewers screened the title and abstract of each article on Covidence and voted whether to include or exclude the article based on the criteria outlined above. Any conflicts were settled by an independent third reviewer. In the second phase, a fourth reviewer—the manuscript writer—conducted the full-text review of all articles selected in the first phase and included/excluded articles at their discretion. This last reviewer then divided the articles into three categories: luminal GI, pancreatic, and hepatobiliary.

The manuscript writer simultaneously reviewed the literature to identify any articles missed by the search strategy or published after completion of the initial article pull. A PRISMA flow diagram[14] can be found in figure 1, with a breakdown by specific organ toxicity in online supplemental figure 1.
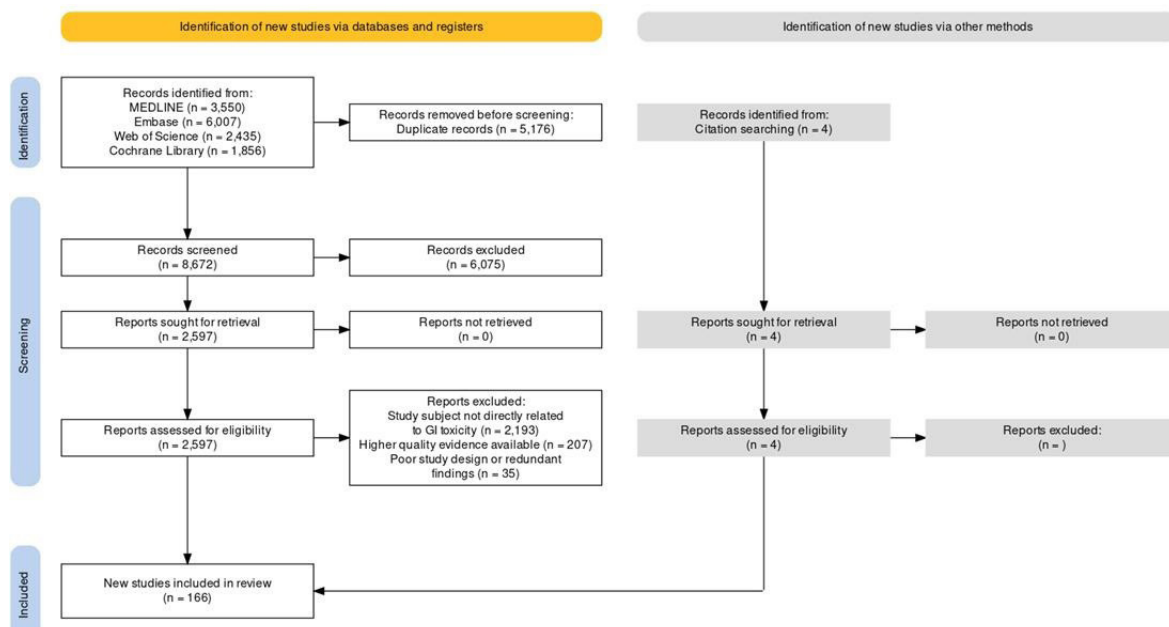

Figure 1 PRISMA article selection flow diagram. GI, gastrointestinal; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Risk of bias assessment

Since this is a narrative account with no statistical analyses conducted, and most studies on the topic are retrospective in nature, risk of bias was not assessed.

Figure 1 and online supplemental figure 1 show the overall article selection flow chart as well as a breakdown by organ toxicity, respectively. A total of 8672 articles were included in the initial screening, with 166 articles included in the final review.

Luminal GI adverse events

Upper GI toxicity (esophagitis, gastroenteritis)

Esophagitis/gastroenteritis

Gastric and esophageal inflammation due to ICIs are relatively rare toxicities that occur in around 3%–5.4% of patients on immunotherapy.[15–18] The inflammation can extend to neighboring structures, with up to 45% of patients having duodenal involvement and up to 70% of cases having concurrent enterocolitis.[16 19] This is more common in the presence of risk factors such as previous non-steroidal anti-inflammatory drug use (the impact of dose and temporality of which have yet to be studied) and concurrent chemotherapy or radiotherapy.[16] Esophageal inflammation typically presents with relatively mild symptoms such as nausea and vomiting that may be accompanied by dysphagia or odynophagia, hematemesis, dyspepsia, and melena. Symptoms of gastric and enteric inflammation include anorexia with weight loss, dyspepsia, nausea and vomiting, early satiety, bloating, melena, and rarely, iron-deficiency anemia. Abdominal pain and bloody diarrhea may be present in cases with concurrent colitis. Clinical symptom severity can be gaged via the Common Terminology Criteria for Adverse Events (CTCAE) grading of the overall esophagitis or gastritis. Alternatively, the CTCAE severity of individual symptoms can also be used. In patients with gastric malignancy (be it a primary or metastatic lesion), the antitumor response induced by ICIs may mimic gastroenteritis symptoms or even cause gastric perforation.[20]

Endoscopy is necessary to assess the severity and extent of inflammation to guide the need for steroid therapy. While all reported cases of esophagitis have demonstrated gross signs of inflammation, normal macroscopic findings in gastritis may belie underlying histological inflammation.[17] Biopsies are, therefore, essential (although often non-specific). Samples should be obtained from multiple locations, as there can be contrasting pathology at different sites.[17] Endoscopic evaluation also allows the identification and treatment of pathological conditions that may not be initially obvious, such as esophageal stenosis,[21 22] fistulization,[23] gastric hemorrhage,[24] or necrosis,[25] that may require surgical or endoscopic management. In most cases, esophageal inflammation is patchy and presents macroscopically as erosions and ulcerations of the esophageal mucosa, involving multiple locations along the organ in up to 50% of such cases.[15] Additional reported findings have included peelable whitish mucosa characteristic of esophagitis dissecans

superficialis[26] or outright necrosis.[27] For both conditions, there is a predominantly lymphocytic infiltrate on histology with signs of acute and chronic active inflammation, but neutrophilic[15] and eosinophilic[28 29] infiltration have both been noted.[16 30] Histological features of gastroenteritis include periglandular gastric inflammation[31] and high numbers of apoptotic events[32] that often distinguish immune-mediated gastritis from other causes, especially in the absence of features such as endocrine cell hyperplasia and intestinal metaplasia.[30] Involvement of the small intestine is reflected by the presence of villous blunting, expansion of the lamina propria, and increased neutrophils, with occasional surface erosions.[33] Cytomegalovirus coinfection has been seen in a few cases of upper GI toxicity so immunostaining for this pathogen may be beneficial in difficult-to-treat cases.[34 35] More recently, intestinal ultrasonography in one case demonstrated mild, diffuse submucosal gastric wall thickening as well as a decrease in echogenicity throughout the gastric wall with increased vascularity on color Doppler imaging.[36]

Supportive therapy using acid suppression therapy with proton pump inhibitors and histamine blockers is the mainstay of empiric treatment for these upper GI conditions, followed by immunosuppression with steroids (0.5–2.0 mg/kg per day for different CTCAE grade levels of toxicities with a taper over 4–6 weeks).[37 38] Biological therapy with either infliximab or vedolizumab has been shown to be effective for steroid-refractory cases. Mycophenolate had little success for ICI-related gastritis,[39] and tocilizumab was successful in treating one case of immunotherapy-induced esophageal stenosis.[40] Complications of esophageal and gastroenteric toxicity may need to be treated endoscopically—for example, esophageal stenosis has been managed with mechanical dilation[22] or esophageal stenting[21]—and surgical intervention may be necessary for esophageal fistulae. Bleeding and feeding difficulties requiring nutrition support have also been reported,[15] and patients undergoing esophageal stenting may be at risk for esophageal rupture and death.[21] For patients with complications such as hemorrhagic gastritis, endoscopic intervention with coagulation or hemostatic spray may be needed.[39] Around 15% of patients have recurrence of their symptoms after an initial resolution.[16] That said, up to 80% are symptom free within 3 months of irAE onset and remain so up to 1 year after their initial diagnosis, even among those resuming immunotherapy.[41] Long-term complications after symptom resolution have yet to be seen for either toxicity.

Lower GI toxicity

Colitis

IMC is the second most common of all irAEs and often the most severe.[42] It is also the most common irAE identified in the emergency department.[43 44] Diarrhea is the primary symptom, affecting 13%–37% of patients on immunotherapy.[10 11] Up to 9% of patients on ICIs may also develop colitis symptoms, including abdominal pain, fever, blood or mucus in stool, and rectal bleeding. The incidence of

lower GI toxicity among ICI recipients is lowest among patients receiving anti-PD-1/L1 therapy and highest among patients receiving combination immunotherapy of CTLA-4 and PD-1/L1. Concurrent tyrosine kinase inhibition may also increase the risk of IMC.[45] Infrequently, patients may present with complications of colitis such as bowel obstruction,[46 47] perforation,[48] toxic megacolon,[12] or severe electrolyte derangements.[49] Risk factors for the development of colitis include proton pump inhibitor use (hypothesized to be due to modulation of the gut microbiome),[50] non-steroidal anti-inflammatory drug use,[51] specific intestinal microbiome signals,[52 53] obesity,[54] and previous inflammatory bowel disease.[55 56]

The CTCAE grading system is the main severity index used to evaluate IMC symptoms and is based on clinical presentation. Further evaluation including stool infectious workup and fecal lactoferrin and calprotectin is indicated for moderate to severe cases. Infectious workup is necessary to identify possible coinfection with other pathogens such as *Clostridioides difficiles*,[57] *Giardia duodenalis*,[58] Epstein-Barr virus,[59] and cytomegalovirus,[60] which lead to a more severe disease course.[61] It is equally important to exclude infectious causes to avoid empiric antibiotic treatment as these medications have been associated with worse IMC outcomes.[62] Lactoferrin and calprotectin are both markers of inflammation and help stratify patients for further assessment: all patients with diarrhea at grade 2 and above and positive stool inflammatory markers or colitis-related symptoms are recommended to undergo endoscopic evaluation as well.

Current guidelines rely on CTCAE gradings to guide IMC evaluation and management.[37 63 64] Despite this, multiple studies have shown that the clinical grade of IMC symptoms does not correlate well with the severity of inflammation found on endoscopy or histology,[64] highlighting the importance of endoscopic evaluation. High-risk findings on endoscopy and biopsy have been associated with more frequent hospitalization, higher rates of recurrence, and the need for selective immunosuppressive therapy (SIT). Moreover, timely endoscopic evaluation in these patients can lead to earlier SIT introduction, and thus has been associated with shorter durations of symptoms and steroid therapy as well as less recurrence, highlighting the importance of this procedure.[65] Flexible sigmoidoscopy has been shown to be a suitable alternative to colonoscopy since as many as 98% of cases have left colon involvement.[9] To date, no endoscopic scoring systems have been validated for IMC, but those adopted from inflammatory bowel disease such as the Ulcerative Colitis Endoscopic Index of Severity, Mayo score, and Nancy histological index have shown some prognostic value.[66] Other markers such as C reactive protein levels have been shown to be useful for initial severity assessment. That said, they are not specific for IMC and have limited value for disease monitoring after treatment; they are, therefore, largely outdone by the more specific fecal calprotectin.[67 68] Finally, the role of CT imaging in the diagnosis is unclear, with studies showing a high positive predictive value[69] but a low negative predictive value.[70]

Grade 1 IMC is managed conservatively with supportive care and antidiarrheal agents such as loperamide and diphenoxylate/atropine. For cases grade 2 and above, corticosteroids are recommended if the diarrhea is not transient, with a taper over 4–6 weeks once symptoms improve to grade 1. Budesonide has been suggested as an effective alternative to systemic steroids in one study.[71] Patients with an inadequate response to steroids after 72 hours or with high-risk endoscopic features, such as ulcers >2 mm in depth and >1 cm in size and extensive inflammation, are recommended to start SIT with infliximab or vedolizumab. Both agents have comparable IMC response rates, but vedolizumab is associated with shorter steroid treatment durations and fewer hospitalizations, although with a longer time to clinical response.[72] Cases that are refractory to one agent could either be switched to another biologic or considered for fecal microbiota transplantation (FMT), which has shown great promise as both first-line[73] and salvage therapy[74] for IMC. Alternative agents used include tofacitinib,[75] tocilizumab,[76] tacrolimus,[77] mycophenolate,[78] and ustekinumab.[79] Extracorporeal photopheresis has been successfully used in one instance.[80] Surgical management with a subtotal colectomy is indicated in cases with bowel perforation, and a diverting ileostomy may be considered to control the symptoms of severe colitis in the acute setting.[12] Patients with symptoms grade 3 or above should be considered for inpatient management following the above guidelines, and gastroenterology consultation regardless of grade can help reduce symptom duration, hospital readmission, and recurrence rates.[81] Earlier GI consultation has been associated with better outcomes.[81 82] Factors associated with worse outcomes include findings of colitis on CT imaging,[83] non-collagenous or lymphocytic patterns of inflammation on biopsy,[84] increased integrin expression,[85] and specific endoscopic findings as described above.

Most patients eventually achieve clinical remission of their IMC, with around 90% of steroid-refractory cases improving after administration of infliximab, vedolizumab, or a combination of both.[72 86] For those whose symptoms do not respond to treatment with biological agents, FMT has been shown to improve symptoms in roughly 85% of patients with refractory disease.[74] Approximately half of patients can resume ICI therapy after resolution of their colitis,[10] but this comes with the risk of recurrence in 17%–36% of patients.[87] Usually, ICI resumption of anti-CTLA-4 agents is less favored given their higher risk for colitis and its recurrence compared with that of anti-PD-1/L1. Notably, maintenance therapy with infliximab or vedolizumab even after remission of the initial toxicity among these patients on ICI rechallenge is effective at mitigating this risk.[88 89] Independent of ICI resumption, IMC is associated with better cancer response and overall survival among these patients.[90–92] However, it may also be associated with later development of colonic adenoma.[93]

Currently, regular endoscopic follow-up can be considered to monitor treatment response and colitis activity.[63 64] This can be done after induction doses of SIT[64] to confirm endoscopic healing or in case symptoms are refractory to immunosuppression.[63] Calprotectin is an excellent and easy-to-obtain marker that can be used in both the initial assessment and long-term follow-up of IMC. Other modalities such as ultrasonography have also been used in a handful of cases for monitoring purposes.[94 95] There may be some benefit to continued endoscopic surveillance after disease resolution to monitor for the development of adenomatous polyps.[93] A summary of upper and lower GI toxicity features can be found in online supplemental table 1.

Hepatobiliary toxicities

Immune-mediated hepatobiliary toxicities (IMH) encompass a spectrum of phenotypes from hepatitic or hepatocellular-predominant injury to more cholangitic patterns and are a form of indirect liver injury.[3]

IMH may occur in up to 10% and 12% of patients treated with anti-CTLA-4 and anti-PD-1/L1 agents, respectively. This incidence is increased to about 30% in patients receiving a combination of the two. High-grade IMH is less common, affecting 3% of patients on ICI monotherapy and up to 14% of those on combination treatment. Mortality from IMH alone is rare,[96 97] representing roughly 3% of all IMH cases.[98 99] Most IMH cases tend to occur 5–13 weeks after the initiation of ICI treatment but can occur after a single administration of ICI or many months after cessation of ICI.[3 100–102]

The degree of liver injury is categorized by the CTCAE version 5.0 grading system and relies on evaluation of serum levels of alanine aminotransferase (ALT), aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, bilirubin, and prothrombin time/international normalized ratio. Liver failure should be assessed for and includes the presence of any new-onset hepatic encephalopathy. A panel of serological tests for liver disease is performed early in the diagnostic evaluation to exclude viral infections (such as acute viral hepatitis A, B, C, and E) and determine if an alternative cause of acute liver injury is present. Abdominal imaging is important to assess for other causes of increasing levels of liver enzymes, such as significant infiltrative liver lesions, liver metastases, or vascular obstruction but is non-specific for IMH.

Liver biopsy evaluation provides additional exclusion of other etiologies to demonstrate a drug-induced cause in difficult-to-identify cases of IMH, especially in the presence of abnormal autoimmune markers like the anti-nuclear antibody, the anti-smooth muscle antibody, and the anti-mitochondrial antibody.[100 103 104] Histological features of IMH include lobular and panlobular hepatitis, necroinflammation, fibrin ring granulomas, central vein endotheliitis, and sinusoidal lymphohistiocytic infiltrates. Cases of cholangiohepatitis are characterized by neutrophilic and eosinophilic infiltration, mild bile duct injury and/or ductular reaction; interface hepatitis could also be present but is predominantly lymphocytic, with a paucity of plasma cells.[100] About 10% of cases of suspected IMH are disproven by liver biopsy, with other causes including malignant biliary obstruction, tumor infiltration of the liver, autoimmune hepatitis, and non-ICI drug-induced liver injury.[104]

Treatment of grades 2–4 IMH generally involves holding of ICI treatment and initiation of corticosteroids, which are tapered over 4–6 weeks.[37 38 105] Around 33%–50% of IMH can resolve on their own without steroids despite still requiring the holding of ICI agents, with a similar timeline of resolution to steroid-treated cases.[99 100 106–108] Thus, immunosuppression may not be needed in all cases of IMH, and monitoring of liver enzymes may suffice. Until more robust data become available, the decision to initiate steroids is up to the clinician's judgment on a case-by-case basis, based on liver biopsy histology if available, trends in the liver biochemistry, and the presence of any hepatic synthetic dysfunction.

While multiple guidelines outline detailed treatment plans for IMH with a reliance on corticosteroids, a growing body of literature since their inception suggests that corticosteroid doses exceeding 1 mg/kg/day were not more beneficial than lower doses, and that doses of 60 mg/day ought to be sufficient.[3 104 106 109 110] A small case series also demonstrated a slightly faster time to improvement towards grade 1 ALT levels in patients induced with a combination of corticosteroids and azathioprine.[110] The role of oral budesonide was first reported as a secondary prophylactic measure in patients rechallenged with ICI but has been used in clinical practice for induction or initial treatment of IMH, with an advantage over prednisone in mitigating potential steroid-related adverse effects.[111–115] ALT improvement typically occurs within 13–29 days to improvement to grade 1 ALT values; complete resolution may take 2 weeks to 3 months. This variability may reflect different levels of steroid responsiveness.[101 104 110 116 117] Pilot studies exploring steroid responsiveness suggest evaluating ALT improvement after 7 days of corticosteroids. As many as 27% of cases are deemed steroid-refractory IMH, with a longer time to ALT normalization (57 days) than steroid-responsive cases (35 days).[104]

Steroid-resistant IMH, which has been defined by one group as an ALT level remaining 70% or higher after 1 week of steroid treatment,[104] warrants addition of adjunctive agents such as mycophenolate mofetil, tacrolimus, and azathioprine; other treatments include antithymocyte globulin, intravenous immunoglobulin, plasma exchange, and tocilizumab, an IL-6 receptor antagonist.[118–124] Tocilizumab has been used for difficult-to-treat IMH that did not resolve even with second-line and third-line treatments, helping to overcome resistant cases.[125–133] Infliximab is typically avoided for its risk of hepatoxicity. As steroid-resistant cases of IMH are not uncommon, steroid-sparing strategies remain an avenue of interest for ongoing research as an urgent unmet need.

Nonetheless, around 40% of patients are able to resume immunotherapy after developing IMH, with a recurrence rate of around 25%.[99 134]

Pancreatic toxicity
Pancreatitis

Pancreatic injury occurs in an estimated 1.1%–3.7% of patients receiving ICIs.[5 135] This can take the form of isolated pancreatic enzyme elevations (1.3%–4.2% of patients),[4] diabetes mellitus following an autoimmune process targeting pancreatic islet cells (around 0.9% of patients),[136] or acute or chronic pancreatitis (0.9%–1.9% of patients).[4] Rarely, isolated exocrine pancreas insufficiency may be present without accompanying pancreatic inflammation.[137] ICI-mediated pancreatitis is an autoimmune injury of the exocrine pancreas resulting from ICI exposure.[138] It may be asymptomatic in up to two-thirds of patients, appearing only on radiological imaging.[139] When symptomatic, however, it presents similarly to classic pancreatitis, with abdominal and/or back pain, nausea and vomiting, fever, and diarrhea.[140] No risk factors have been identified except for a prior history of pancreatitis, which is associated with symptomatic ICI-mediated pancreatitis.[139] That said, the intestinal microbiota may be implicated in the pathogenesis and severity of this disease, particularly, the ratio of *Bacteroidetes* species to *Firmicutes*.[141]

Toxicity to the exocrine pancreas is the most common presentation of ICI-associated pancreatic injury and will be the focus of this section. Current guidelines for the diagnosis and management of immune-mediated exocrine pancreatic injury do not recommend the routine evaluation of amylase and lipase levels.[142] On discovery of moderate to severe amylase and lipase elevations (>3×upper limit of normal) or symptoms suspicious for pancreatitis, abdominal contrast CT is recommended. Most cases do not have any abnormal imaging findings,[139 143] but when present, typically constitute features of mild acute interstitial pancreatitis such as pancreatic enlargement (focal, diffuse, or mass-like), heterogeneous enhancement, and peripancreatic fat stranding.[144] Rarely, collections of necrosis or peripancreatic fluid[145] have been reported. In the largest study on the topic to date, parenchymal atrophy indicative of chronic injury has been described.[138] Occasionally, fluorodeoxyglucose-18 uptake mimicking pancreatic malignancy can be seen on positron emission tomography–CT.[146 147] In cases where initial radiographic findings are normal, MR cholangiopancreatography has been used to establish a diagnosis.[142] Endoscopic ultrasound-guided fine-needle aspiration has also been proposed to be a useful tool.[148]

Current guidelines for the management of pancreatic irAEs are primarily based on recommendations from expert opinion, given the paucity of research on the subject. Treatment involves aggressive hydration, pain control, holding diet, and hospitalization when warranted, alongside ICI cessation and glucocorticoids for moderate to severe cases.[142] The use of steroids in treating this entity is controversial, however. While National Comprehensive Cancer Network (NCCN) guidelines endorse this use, the largest study to date on ICI-mediated pancreatitis found that while intravenous hydration reduced the risk of long-term adverse outcomes from this disease, corticosteroids had no impact on shortening the acute phase of the disease, preventing long-term adverse outcomes, or improving overall survival.[139] In another study, corticosteroids also failed to meaningfully mitigate pancreatitis pain, prevent pancreatic volume loss, prevent pancreatitis recurrence, or expedite ICI resumption.[149] This same study found that steroid treatment may in fact contribute to long-term pancreatic atrophy. In light of these findings, corticosteroids ought to be used with caution in this disease.[138] Additionally, steroids are typically not recommended in the management of endocrine pancreas dysfunction related to ICI. The use of infliximab to treat steroid-refractory ICI-related pancreatitis is described by two anecdotal case reports.[150 151]

Around 15% of patients with ICI-related pancreatitis develop long-term adverse outcomes, including pancreatitis recurrence, chronic pancreatitis, and diabetes mellitus.[139] There is also a significant risk of pancreatic volume loss among those with pancreatic enzyme elevations, even if asymptomatic[152]; this is typically apparent within 1 year of pancreatic injury.[153] Finally, though infrequent, fistulization between the pancreas and neighboring organs has also been reported.[154] A summary of hepatobiliary and pancreatic toxicity features can be found in online supplemental table 2.

Rare GI toxicities
Oral toxicity

Inflammation of the oral mucosa is a common side effect of many anticancer treatments that significantly impair the patient's quality of life. It has been reported in 1.5%–6.3% of patients treated with ICIs,[155] with roughly 0.2% of patients reporting severe disease.[155] This toxicity primarily develops following anti-PD-1/L1 inhibition but may be more severe after treatment with anti-CTLA-4 agents, as reflected by a more refractory disease course.[156] It usually presents with mucosal lesions closely resembling those found in lichen planus—symmetric, white reticulations with or without ulcerative or erythematous plaques[157 158]—though non-lichenoid disease has also been described.[159] These lesions may occasionally be accompanied by other cutaneous or esophageal mucosal findings.[157 158] Odynophagia and oral pain are characteristic symptoms, with bleeding and dysphagia also commonly reported. Many patients may experience nausea and vomiting as well, but this is a non-specific symptom.[156] Atypical presentations of oral involvement due to ICIs include xerostomia and dysgeusia (alone or with other manifestations of mucositis) in up to 5% of patients,[160] though the former may be a manifestation of ICI-induced sicca syndrome.[63] Biopsies for histological analysis, which show predominant CD8+ lymphocyte infiltration suggestive of immune-mediated pathology; swabs to assess for infectious causes; and blood

tests to rule out abnormal cell counts are all essential tools for evaluating newly developed mucosal lesions.[155] Management recommendations are mainly anecdotal, with no definitive guidelines on the subject.[37 38 161] Topical steroids as well as mouthwash containing topical steroids, nystatin, and viscous lidocaine with or without antibiotics, antihistamines, or antacids (also called magic mouthwash) have been used for mild cases, with systemic steroids reserved for more severe cases. There may be some utility for maintenance laser therapy for oral pain control,[157] colchicine mouthwash with metronomic cyclophosphamide[159] and infliximab for steroid-refractory disease.[162] Sialogogue therapy with muscarinic agonists is recommended for mouth dryness.[37 38 161] Although mucositis is generally low-grade and well tolerated, a subset of patients may require hospitalization and nutritional support via tubal feeding, and patients experiencing mouth dryness may be at risk for infection. Most cases of oral mucositis necessitate ICI discontinuation despite its high resolution rate of around 88%, likely due to its moderate recurrence rate (~33%).[156] Finally, the oral microbiome may be implicated in the pathogenesis of this condition, which may be a future avenue for study.[159] A summary of rare GI toxicity features can be found in online supplemental table 3.

Celiac disease

Little is known regarding immune-mediated celiac disease (ICI-celiac disease) and whether it is an unmasking of underlying disease. What information is available is limited to a handful of case studies in the literature. ICI-celiac disease presents with abdominal pain, diarrhea, steatorrhea, fatigue, nausea and vomiting, and vitamin and mineral deficiencies.[33 163] It is clinically and histologically similar to ICI duodenitis, with similar CD3, CD8, and γδ T cell subsets and with PD-L1 populations on histology that are distinct from the findings in classical celiac disease.[33] It can be differentiated from ICI-duodenitis by the presence of transglutaminase immunoglobulin A antibodies, which are specific to celiac disease and also found in its conventional version, though not all cases have positive serology.[33] Nonetheless, endoscopy and serology are important aspects of evaluation. The treatment of ICI-celiac disease differs from that of ICI-duodenitis by its responsiveness to gluten avoidance.[33] Other malabsorption syndromes such as ICI-induced protein-losing enteropathy are exceedingly rare and typically mimic their classic counterparts.[164]

Gastroparesis

Only one case series of three patients has been presented on ICI-gastroparesis.[165] It presents as non-specific symptoms, for example, nausea and vomiting, early satiety, weight loss, and possibly constipation. Endoscopy to evaluate other etiologies may reveal stasis of gastric contents, and gastric emptying scintigraphy is needed to confirm the diagnosis. It is unclear whether this condition arises from associated gastric inflammation or as an isolated autoimmune reaction in the enteric nervous system. A few other case reports have described gastric dysmotility as part of an overarching autonomic dysfunction secondary to a neurological irAE.[166] Treatment consisting of adherence to a gastroparesis diet (small, frequent meals, reduced fat intake, avoiding coffee, alcohol, or spicy foods) can be effective in managing this condition. Prokinetic agents such as metoclopramide may also be beneficial.[165]

Diverticulitis

ICI-induced diverticulitis is a rare entity that occurs in roughly 0.5% of patients receiving ICI therapy.[167] It typically presents 3–4 months after initiation of ICI with classical symptoms of abdominal pain, diarrhea, and fever and radiological findings such as colon wall thickening and pericolic fat stranding. Most patients improve after treatment with antibiotics, but a subset may need surgical/IR intervention. CT imaging can identify most cases of diverticulitis, and endoscopic evaluation is not recommended. Most cases require the discontinuation of ICI despite low recurrence rates, and mortality is worse among patients whose diverticulitis is complicated by perforation, fistulization, or abscess formation.

Cholecystitis

The incidence of cholecystitis due to ICIs is estimated at around 0.6%.[168] It is similar to classical cholecystitis in presentation and management. Abdominal pain, nausea and vomiting, and fever are the most common symptoms, often accompanied by an alkaline phosphatase enzyme elevation. Most patients require hospitalization and treatment with antibiotics, and around 20% of patients require percutaneous drainage or surgical cholecystectomy, which typically achieves complete resolution of symptoms. The role of steroids remains unclear. Up to half of patients are able to resume immunotherapy, and no cholecystitis-related deaths have been reported in the literature thus far.

Appendicitis

Immune-related appendicitis may occur in around 0.07% of patients receiving immunotherapy.[169] Abdominal pain and fever are the most common presenting symptoms, with CT findings of appendiceal dilation, wall thickening, inflammation, and fat stranding. Perforation and abscesses may also be identified on initial presentation. All patients with this condition in the literature required hospitalization and treatment with antibiotics, and around half required surgical or percutaneous intervention, even in the absence of complications. Almost all patients had complete resolution of their symptoms, and most were able to resume the cancer treatment.

Mesenteritis

Mesenteritis refers to a rare fibroinflammatory process in the intestinal mesentery. It is an extremely rare consequence of ICI treatment and is typically asymptomatic.[170] Patients may present with non-specific symptoms such

as abdominal pain, nausea and vomiting, diarrhea, and fever. Corticosteroids are an effective treatment for this condition, with almost all patients having clinical and radiological resolution after treatment. No surgical or percutaneous interventions were needed in the cohorts studied thus far, and there is no documented impact on overall mortality.

Pneumatosis intestinalis

Pneumatosis intestinalis designates the presence of free air in the extraluminal spaces of the intestines. For the most part, it is discovered incidentally on imaging for other indications.[171] Patients may occasionally be symptomatic with a similar presentation to mesenteritis (abdominal pain, fever). Antibiotics are the mainstay of treatment, and most cases thus far have been mild, so no surgical or percutaneous interventions have been needed. Most patients have complete resolution of their condition with no increased risk of death.

Pouchitis

Pouchitis following ICI treatment is an exceedingly rare toxicity with only two cases reported in the literature thus far.[172] It refers to an inflammation of the ileal pouch created after anastomotic surgery for inflammatory bowel disease and presents with non-bloody, watery diarrhea with or without abdominal pain. Endoscopic and laboratory findings echo those of IMC, with signs of non-ulcerative and ulcerative inflammation on pouchoscopy and elevation of stool biomarkers such as lactoferrin and calprotectin.[172] This toxicity can occur even if the patient underwent the surgery decades before immunotherapy initiation. The treatment of this entity is also similar to that of colitis, with steroids being the mainstay, with biological agents such as vedolizumab or ustekinumab options used for refractory cases, and it follows a similar disease course to IMC, in which most cases resolve but recurrent disease is possible.[172]

CONCLUSION

We describe here the incidence, presentation, and management of the full spectrum of observed GI toxicities arising from immune checkpoint inhibition. Much of the research into treatment of these pathologies is still in its early stages, and larger-scale studies are needed to identify risk factors and effective treatment options for these irAEs, as well as to better understand their clinical course. Finally, given the speed at which research has expanded in recent years, there could be merit to updating current guidelines frequently to reflect these new findings.

Author affiliations
[1]Department of Gastroenterology, Hepatology & Nutrition, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[2]Department of Internal Medicine, The University of Texas Health Science Center at Houston, Houston, Texas, USA
[3]Department of Thoracic Medical Oncology, Johns Hopkins University, Baltimore, Maryland, USA
[4]Department of Gastroenterology, Université Paris-Saclay, Le Kremlin-Bicêtre, France
[5]Department of Gastroenterology, Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois, USA
[6]Center for Inflammatory Bowel Disease, Cleveland Clinic, Cleveland, Ohio, USA
[7]Department of Thoracic Medical Oncology, University of Michigan, Ann Arbor, Michigan, UK
[8]Department of Medicine, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington, USA
[9]Department of Medicine, Service of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[10]Research Medical Library, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

X Malek Shatila @malekshatilaMD and Nitish Mittal @mittaln96

ORCID iDs
Malek Shatila http://orcid.org/0000-0001-8503-7811
Hao Chi Zhang http://orcid.org/0000-0003-0330-0167
Anusha Shirwaikar Thomas http://orcid.org/0000-0003-1878-4678
Antonio Pizuorno Machado http://orcid.org/0000-0002-4118-6310
Nitish Mittal http://orcid.org/0000-0002-7168-2550
Christine Catinis http://orcid.org/0009-0002-0002-6625
Bryan Schneider http://orcid.org/0000-0003-4189-3805
John A Thompson http://orcid.org/0000-0002-7877-1580
Michel Obeid http://orcid.org/0000-0003-2095-2677
David P Farris http://orcid.org/0000-0002-9224-9270
Yinghong Wang http://orcid.org/0000-0002-5148-6130

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