Review Article

Clinical Management of Gastrointestinal and Liver Toxicities of Immune Checkpoint Inhibitors

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Abstract

Immune checkpoint inhibitors have transformed the treatment paradigm for various types of cancer. Nonetheless, with the utilization of these groundbreaking treatments, immune-related adverse events (irAEs) are increasingly encountered. Colonic and hepatic involvement are among the most frequently encountered irAEs. Drug-induced side effects, infectious causes, and tumor-related symptoms are the key differentials for irAE complications. Potential risk factors for the development of irAEs include combination use of immune checkpoint inhibitors, past development of irAEs with other immunotherapy treatments, certain concomitant drugs, and a pre-existing personal or family history of autoimmune illness such as inflammatory bowel disease. The importance of early recognition, timely and proper management cannot be understated, as there are profound clinical implications on the overall cancer treatment plan and prognosis once these adverse events occur. Herein, we cover the clinical management of the well-established gastrointestinal irAEs of enterocolitis and hepatitis, and also provide an overview of several other emerging entities.

Clinical Colorectal Cancer, Vol. 23, No. 1, 4–13
Keywords: ICI, Immune checkpoint inhibitors, Immune-related adverse events, Immunotherapy, irAE, Toxicity

Introduction

Immune checkpoint inhibitors (ICIs) have transformed the treatment paradigm for various types of cancer. Nonetheless, with the utilization of these groundbreaking treatments, immune-related adverse events (irAEs) are increasingly encountered. Colonic and hepatic involvements are among the most frequently encountered irAEs. Drug-induced side effects, infectious causes, and tumor-related symptoms are the key differentials for ICI-induced complications. Potential risk factors for the development of irAEs include combination use of ICIs, past development of irAEs with other immunotherapy treatments, certain concomitant drugs, and a pre-existing personal or family history of autoimmune diseases such as inflammatory bowel disease.

The importance of early recognition, timely and proper management cannot be understated, as there are profound clinical implications on the overall cancer treatment plan and prognosis once these adverse events occur. Herein, we cover the clinical management of the well-established gastrointestinal-irAEs of enterocolitis and hepatitis, and also provide an overview of several other emerging entities.

General Concepts

The 2 main classes of ICI most commonly used in clinical practice are the antiprogrammed cell death protein 1 (anti-PD1)/programmed cell death ligand-1 and anti-cytotoxic T lymphocyte antigen-4 (anti-CTLA4) antibodies. CTLA-4 is a receptor that is constitutively found in regulatory T cells but is also found in other T cells or tumor cells. By binding with greater affinity than cluster of differentiation 28 (CD28) to CD80/CD86 that is expressed on antigen presenting cells, CTLA-4 is involved in T cell inactivation. PD-1 is found in a variety of immune cells, including T cells, B cells, dendritic cells and myeloid cells in the tumor microenvironment. It binds to PDL-1 or PDL-2, which are found in antigen-presenting and tumor cells. Binding of PDL-1 to PD-1 leads to inhibition of downstream signaling resulting from the interactions between T cell receptor/major histocompatibility (MHC) complexes and between CD28 and CD80/86. These immune checkpoints are involved in the normal physiological regulation of immune tolerance and can be upregulated in chronic inflammation. The inhibition of CTLA-4 or PD-1/PDL-1 thus reinvigorates inactivated T cells and restores their antitumor function.[1]

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Submitted: Nov 2, 2023; Revised: Dec 11, 2023; Accepted: Dec 12, 2023; Epub: 16 December 2023

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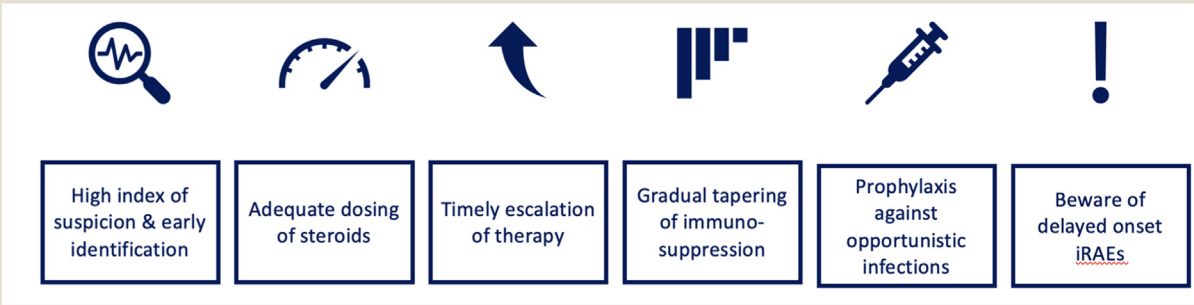
1533-0028/$ - see front matter
https://doi.org/10.1016/j.clcc.2023.12.003

Table 1 General Management of Immune Checkpoint Inhibitor Toxicities According to Severity

Grade of Toxicity	Management
1.	- Close monitoring (except for some neurologic, hematologic and cardiac toxicities)
2.	- Withhold ± corticosteroids
3.	- Withhold - High dose corticosteroids - Specialty consultation
4.	- Same as 3 - Usually permanent discontinuation (except some endocrinopathies with adequate hormone replacement) - For selected organ involvement, consider treatment escalation if no improvement

Adapted from Brahmer et al.[6]

Figure 1 Key principles in the management of immune checkpoint inhibitor-induced complications.



The mechanism of ICI toxicities can vary among different organs. For instance, ICI-colitis has been described to be related to the proliferation of effector cytotoxic T cells which are clonally related to tissue resident T cells that are found in abundance in colonic tissues.[2] On the other hand, ICI-hypophysitis from ipilimumab is mediated by CTLA-4 blockade of native cells in the pituitary gland, resulting in subsequent complement activation.[3] The distribution of organ involvement by ICI toxicities may also depend on the class of ICI used. For example, while ICI-colitis is more frequently encountered with CTLA-4 inhibitor treatment,[4] ICI-thyroiditis is more commonly seen with PDL-1/PDL-1 treatment.[5]

It is important to differentiate immunotherapy induced adverse events from other differential diagnoses such as tumor-related complications, infective and other drug-related side effects. In general, close monitoring is warranted for lower grades of toxicity, while more serious toxicities require the withholding of ICIs, prescribing systemic corticosteroids, and consultations to appropriate specialties; usually permanent discontinuation of immunotherapy is likely required for grade 4 toxicity (Table 1). The management of these patients require a high index of suspicion for irAEs, adequate dosing of steroids, timely escalation of therapy when suboptimal clinical responses are encountered, gradual tapering of immunosuppression if improving, low threshold to initiate prophylaxis against opportunistic infections, and awareness of the possibility of delayed onset of irAEs (Figure 1).[7]

Immune Checkpoint Inhibitor Enterocolitis

Immune checkpoint inhibitor-colitis or diarrhea is a commonly encountered immune-related gastrointestinal (GI) toxicity. The frequency depends on the type of ICI used, with PD-1/PDL-1 inhibitors (10% diarrhea, 2% colitis) generally having less diarrhea/colitis than CTLA-4 inhibitor monotherapy (33% diarrhea, 7% colitis) or combined PD-1/CTLA-4 (21%-37% diarrhea, 4%-8% colitis). ICI combined with chemotherapy or tyrosine kinase inhibitors (TKI) is also associated with a high frequency of diarrhea (17%-56%), though severe colitis is not commonly encountered (0.5%). Diagnosis is challenging sometimes as TKI or chemotherapy itself may be a cause of diarrhea.[4] The dosage of ipilimumab may also increase the frequency of developing colitis.[8] The intestinal microbiome[9] and Vitamin D levels[10] have been linked with the severity of ICI colitis. Importantly, around one-third of patients with inflammatory bowel disease or microscopic colitis on ICIs experience a flare up of colitis.[11] Thus, caution should be exercised with this risk clearly stated when consenting these patients to immunotherapy.

The composition of gut microbiome can predispose to the development of ICI-colitis. In 1 study, the presence of *Firmicutes* and reduced microbiome diversity was associated with CTLA-4 inhibitor related ICI-colitis.[12] On the other hand, the abundance of *Bacteroidetes*, and microbiome genes related to polyamine transport

Table 2 CTCAE v 5.0 Grading of Diarrhea and Colitis[23]

	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily living	Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; peritoneal signs	Life-threatening consequences; urgent intervention indicated

systems and certain types of vitamin B have demonstrated protective effects against ICI-colitis.[13] Different gut microbiome constitutions have been reported in various ICI toxicities and cancer types.[14] Antibiotic use may also disrupt the gut microbiome, and indeed a recent study showed that recent antibiotic use prior to ICI treatment is associated with inferior survival and the development of ICI-colitis.[15] Another study showed that antibiotics with anaerobic coverage in particular was associated with ICI-colitis.[16]

The median onset of ICI colitis is 6 to 8 weeks, but is variable as it can occur well after treatment discontinuation.[17] Strictly speaking, ICI colitis and diarrhea can be graded separately based on the Common Terminology for Adverse Events (CTCAE) version 5.0 (Table 2). The American Society of Clinical Oncology (ASCO) grades diarrhea only as it is more commonly used, while the European Society for Medical Oncology (ESMO) and the American Gastroenterological Association (AGA) use a combination of both in their treatment algorithm.[18-20] In reality, both represent different spectrums of the same disease and should be considered together. Caveats include the often observed discordance between the severity of symptoms and severity of endoscopic inflammation,[21] with the latter being a better indicator for subsequent need for immunosuppressants.[22] In addition, grading of the severity of abdominal pain is subjective and yet this has been used to segregate grade 2 from grade 3 colitis. It is therefore crucial to integrate all relevant clinical information into decision-making, rather than solely relying on grading systems and treatment algorithms.

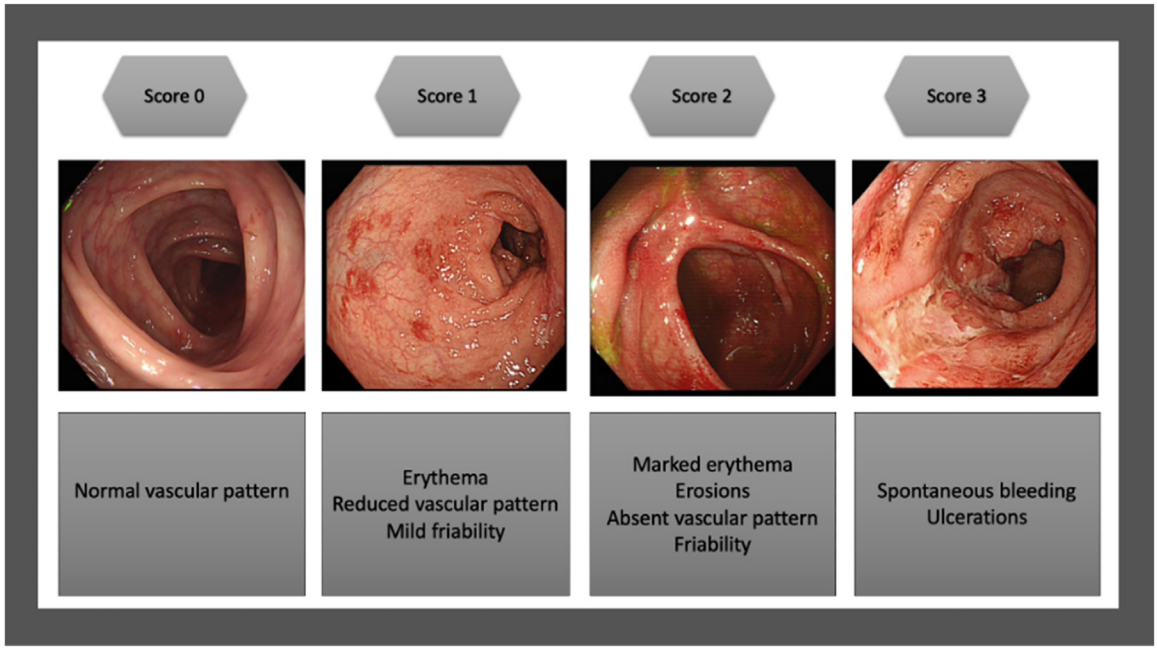
In addition, it is important to exclude causes other than ICI-related toxicity when patients present with gastrointestinal symptoms during treatment with these agents. Drug, metabolic infection and cancer progression need to be ruled out and managed accordingly. Stool should be obtained for cultures, virological testing, and other relevant endemic pathogens, microscopy for ova and parasites as well as detection of *Clostridioides difficile* toxin should also be performed. Blood tests such as C-reactive protein, albumin and hemoglobin are not specific enough to predict the severity of colitis.[22] Imaging similarly lacks specificity but is used primarily to rule out surgical complications in patients who present with fever, abdominal pain or GI bleeding.[24] Radiologic findings may include mesenteric hyperemia, bowel wall thickening, pericolonic stranding, fluid filled dilated bowels, or even frank visceral perforation.

Stool testing for calprotectin and lactoferrin can serve as a noninvasive tool to assess for bowel inflammation[25] and monitor for colitis remission.[26] The AGA guidelines suggest using stool inflammatory markers to triage patients with selected grade 1, or grade 2 or above colitis or diarrhea for colonoscopy. Studies have shown that stool lactoferrin has a 90% sensitivity in detecting histologic inflammation[20] ESMO further suggests using a stool calprotectin cutoff of 400 μg/mg for grade 3 or above colitis as a surrogate when colonoscopy is not readily available for deciding treatment intensification with biologics.[19] ASCO recommends using stool calprotectin as one of the markers of colitis remission and to determine when to rechallenge ICI.[18]

Endoscopy is routinely recommended for grade 2 or above symptoms by all major societies. At the very least, a flexible sigmoidoscopy with biopsy should be considered as the majority of colitis involves the left sided colon.[27] Clinicians must be prepared for arranging further endoscopic workup as isolated ileitis and upper GI presentations are possible.[28,29] The distribution of colitis is typically diffuse or patchy, though segmental or even negative findings are possible.[21] Endoscopic findings may also range from nonulcerative inflammation such as erythema to frank ulceration. Further stratification can be made according to the Mayo Endoscopic Subscore[30] (Figure 2) or through identification of high-risk endoscopic features such as 2 mm or deeper ulcers, greater than 1 cm ulcers, and features of extensive colitis,[25] which are associated with the need for immunosuppressants. A biopsy is usually warranted for establishing the diagnosis and ruling out other causes such as cytomegalovirus (CMV) infection, which is an important differential diagnosis in patients who are immunosuppressed. Histological findings may show features of acute (eg neutrophilic infiltration of lamina propria, crypt apoptosis, crypt microabscesses) and/or chronic inflammation (eg cryptic distortion, Paneth cell hyperplasia, basal lymphoplasmacytosis).[31] A distinct entity of ICI-microscopic colitis which presents similarly with the classical microscopic colitis and responds to budesonide therapy has also been reported.[32]

All major societies agree that for grade 1 diarrhea/colitis, treatment may be continued with supportive care measures. For grade 2 diarrhea/colitis or above, treatment should be withheld and steroids started promptly. Steroid refractory (> 72 hours), or high-risk cases with adverse endoscopic features should be evaluated for biologics.[18–20] Both infliximab and vedolizumab have been shown to be efficacious for the management of ICI colitis, but vedolizumab may take longer to achieve remission.[33] On the other hand, infliximab may be less preferred in patients with latent tuberculosis, congestive heart failure, demyelinating disease, or if they

Figure 2 Mayo endoscopic subscore adapted for the grading of immune checkpoint inhibitor-induced colitis.[30]



are at high risk for opportunistic infections.[34,35] A prospective study is underway comparing the 2 drugs in the management of ICI colitis (NCT04407247).[36] For recalcitrant cases, tofacitinib,[37] ustekinumab,[38] and fecal microbiota transplants[39] have all been used with varying degrees of success as reported in case reports and series.

Immune Checkpoint Inhibitor Hepatitis

The liver is the third most commonly involved organ, after the dermatological and GI systems, accounting for around 5% to 10% of irAEs.[40] ICI-hepatitis occurs at similar frequencies in anti-PD1/programmed cell death ligand-1 and anti-CTLA4 antibodies,[41] although there is a tendency towards more severe hepatic disease with anti-CTLA4 antibodies. Notably, combination therapy with other ICIs or targeted therapies and a history of autoimmune liver diseases are linked to an increased risk of developing hepatitis during ICI treatment.[42] A previous phase I trial in renal cell carcinoma patients showed that a higher dose of ipilimumab combined with nivolumab was associated with a higher risk of hepatotoxicity.[43] Some report that up to 25% to 30% of patients develop hepatotoxicity when given combined therapy, with around a 15% incidence rate for grade 3 ICI-related hepatitis.[44]

The PD-L1 and CTLA-4 receptors are normally expressed on liver cells to maintain an immune tolerant state to avoid triggering unwanted immunological responses to harmless antigens that regularly pass through the portal circulation. Immunotherapy disrupts this pathway and leads to immune activation, T cell upregulation, cytokine production, and the development of hepatitis.[45] ICI-hepatitis typically manifests within the first 6 to 12 weeks after treatment initiation.[46] Often times, it presents as an asymptomatic elevation in liver enzymes, with hepatocellular (38%) and cholestatic (36%) patterns seen at a similar frequency.[47] It may also present with nonspecific symptoms, including fatigue, anorexia, and abdominal discomfort. On the other side of the spectrum, some patients may present with acute symptomatic hepatitis and rarely fulminant hepatitis, exhibiting signs and symptoms such as jaundice, tea-colored urine, fever, coagulopathy and hepatic encephalopathy.[6] There are no specific markers or histological findings diagnostic for ICI-hepatitis and thus it is mainly a clinical diagnosis of exclusion. Workup for other underlying causes of deranged liver function by conducting a thorough drug and alcohol history, blood tests for viral hepatitis or autoimmune serology, abdominal imaging to rule out biliary or obstructive pathology are needed.[48] The role of a liver biopsy in this clinical context is mainly to exclude secondary liver pathologies, those with atypical presentations or in those who do not respond to conventional therapy. In general, the accessibility and risk of biopsy, higher grade toxicities, diagnostic uncertainty about the etiology, and whether the outcome of the biopsy would alter management are considerations when deciding whether it is necessary to proceed with a biopsy.[49] Typical histological features in liver biopsies can mimic those of autoimmune hepatitis with a mixed panlobular hepatitis, CD8+ T lymphocyte infiltration, and signs of focal to confluent necrosis. Portal mononuclear infiltrates can also be seen with ipilimumab treatment.[50] Other reported features associated with anti-CTLA4 treatment include granulomatous

Table 3 CTCAE v5.0 Grading of Hepatitis[23]

	Grade 1	Grade 2	Grade 3	Grade 4
Alanine aminotransferase increased	> ULN[a] - 3 x ULN if baseline was normal; 1.5 - 3 x baseline if baseline was abnormal	> 3 - 5 x ULN if baseline was normal; > 3 - 5 x baseline if baseline was abnormal	> 5 - 20 x ULN if baseline was normal; > 5 - 20 x baseline if baseline abnormal	> 20 x ULN if baseline was normal; > 20 x baseline if baseline was abnormal
Alkaline phosphatase increased	> ULN - 2.5 x ULN if baseline was normal; 2 - 2.5 x baseline if baseline was abnormal	> 2.5 - 5 x ULN if baseline was normal; > 2.5 - 5 x baseline if baseline was abnormal	> 5 - 20 x ULN if baseline was normal; > 5 - 20x baseline if baseline abnormal	> 20 x ULN if baseline was normal; > 20 x baseline if baseline was abnormal
Aspartate aminotransferase increased	> ULN - 3 x ULN if baseline was normal; 1.5 - 3 x baseline if baseline was abnormal	> 3 - 5 x ULN if baseline was normal; > 3 - 5 x baseline if baseline was abnormal	> 5 - 20 x ULN if baseline was normal; > 5.0 - 20.0 x baseline if baseline was abnormal	> 20 x ULN if baseline was normal; > 20 x baseline if baseline was abnormal

[a] ULN: upper limit of normal

hepatitis with the presence of fibrin ring granulomas and central vein endotheliitis.[51]

As with other irAEs, prompt discontinuation of ICI therapy is crucial in preventing disease progression and fulminant liver failure. For grade 2 or above hepatitis (Table 3), corticosteroids are often the first line therapy.[52] Oral prednisolone at 0.5 to 1 mg/kg/day with slow tapering and close monitoring of liver function is recommended. With grade 3 or above toxicity, intravenous methylprednisolone may be warranted. A dose higher than 1 mg/kg/day of methylprednisolone was found to have no difference in alanine aminotransferase (ALT) normalization but was associated with a significantly higher rate of steroid-related adverse events such as infection, reactivation of current or past chronic hepatitis B or hyperglycaemia.[53,54] Budesonide maybe a good alternative in this scenario given its extensive first-pass metabolism, allowing the drug to exert its effect mainly on the intestine and liver with fewer systemic side effects.[55] In steroid refractory cases, other immunosuppressive agents such as mycophenolate mofetil can be used. Agents targeting T-cells such as calcineurin inhibitors as well as antithymocyte globulin have also been reported to be effective. Interleukin-6 blockade has been reported to be efficacious. However, in general high quality data on the efficacy and safety of many of these therapeutic agents are lacking.[56,57] We seldom use azathioprine due to its slow onset of action, and the possibility of liver side effects that may lead to further rises in liver enzymes which may complicate the clinical picture.[7] Of note, tumor necrosis factor (TNF)-alpha inhibitors are not recommended in the setting of ICI-hepatitis due to its association with de novo autoimmune hepatitis.[58]

Immune Checkpoint Inhibitor Cholangiopathy

There is limited data on ICI-cholangiopathy as it is thought to be a rare condition. It can be divided into small-duct, large-duct or mixed variants[59] which is analogous with the subtypes of primary sclerosing cholangitis (PSC). Small-duct variants affecting intrahepatic bile ducts are often underdiagnosed due to the fact that this requires a histological diagnosis with liver biopsy, or they may have been mislabeled as ICI-hepatitis with a cholestatic pattern of liver enzyme derangement. The incidence of large-duct variants has been reported to be around 0.05% to 0.7%. In a postmarketing surveillance of patients on nivolumab in Japan from 2014 to 2017, the incidence rate of sclerosing cholangitis was reported to be 0.05%.[60] Large-duct changes have been more commonly reported with pembrolizumab and nivolumab use.[59,61]

Common presentations of ICI-cholangiopathy include a cholestatic pattern of deranged liver enzymes. Abdominal pain, jaundice and fever may be observed.[62] It is important to differentiate ICI-cholangiopathy from other causes of intrahepatic cholestasis or extrahepatic biliary obstruction as this will alter the overall management of these patients. Differential diagnoses are broad, including malignant biliary obstruction, metastatic infiltration, periductal infiltrating cholangiocarcinoma, autoimmune causes such as primary biliary cholangitis, PSC, IgG4-related cholangiopathy, and drug-induced liver injury.[63]

Although there may not be any specific radiological changes associated with small-duct toxicity, cross-sectional imaging is important in diagnosing large-duct disease. Diffuse intra- and extra hepatic biliary strictures, upstream dilatation, or focal bile duct thickening may be seen on magnetic resonance cholangiopancreatography (MRCP).[64] Imaging is important to help exclude other biliary pathologies such as stone disease or tumor. Computed tomography may also be helpful in evaluating the bile duct walls, the presence of extrinsic compression or hepatic and pancreatic parenchymal disease. Endoscopic retrograde cholangiography(ERCP)[65] with or without cholangioscopy can be helpful in selected cases which allows for the direct visualization of bile duct lesions and obtaining biopsies for histological diagnosis.

Histological findings of the small-duct variant of ICI-cholangiopathy are nonspecific and are similar to that of drug-induced bile duct injury. Portal inflammation with mixed inflammatory cell infiltration and predominance of CD8+ T cell infiltration can be seen. CD8 to CD4+ T cell ratio was found to be much higher in the ICI-cholangiopathy group when compared to the autoimmune hepatitis and drug-induced liver injury groups.[66] Other findings similar to PBC including florid duct sign and periductal fibrosis can also be seen. With large-duct variant ICI-cholangiopathy, inflammatory infiltration with diffuse fibrosis of the extrahepatic bile ducts has been reported.[67]

Current guidelines for the management of ICI-cholangitis recommend prompt discontinuation of offending drugs and close monitoring. Initiation of corticosteroids is recommended in high-grade toxicity.[57] ICI-cholangitis tends to respond less well to corticosteroids alone, usually with a longer recuperation time before complete recovery. Some studies have found that serum alkaline

Table 4 CTCAE v5.0 Grading of Pancreatitis and Increased Amylase/Lipase[23]

	Grade 1	Grade 2	Grade 3	Grade 4
Pancreatitis	-	Enzyme elevation; radiologic findings only	Severe pain, vomiting; medical intervention indicated (eg. analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated
Amylase/ Lipase increase	> ULN[a] - 1.5 x ULN	> 1.5 - 2 x ULN; > 2 - 5 x ULN and asymptomatic	> 2 - 5 x ULN with signs or symptoms; > 5 x ULN and asymptomatic	> 5 x ULN and with signs or symptoms

[a] ULN: Upper limit of normal

phosphatase may take more than 18 months to normalize. This may be due to the slow improvements in cholestasis.[68] Unfortunately, because of the prolonged period of liver derangement, patients with ICI-cholangitis usually have limited options for further chemo- or immunotherapy, leading to cancer progression and therefore confers a poor prognosis. Ursodeoxycholic acid has emerged as a promising treatment option in steroid-refractory disease. It protects cholangiocytes from the cytotoxicity of hydrophobic bile acids and has immunomodulatory properties by inhibiting cytokine release. Small studies have shown that Ursodeoxycholic acid is a safe and effective option as a single agent or in combination with steroids and it is worth exploring in future clinical trials.[63]

Immune Checkpoint Inhibitor Pancreatitis

This entity is relatively uncommon, with reported incidence rates estimated to be around 1% to 2% in patients receiving ICIs for various malignancies with the majority being asymptomatic biochemical elevations in pancreatic enzymes. Grade ≥ 3 pancreatitis has been reported to have an incidence of 0.68% only in a recently published meta-analysis. However, the prevalence may vary depending on the specific ICI used and whether combination therapies are employed. A prior history of pancreatitis or presence of concomitant irAEs may lead to an increased risk of ICI-pancreatitis for patients. Pembrolizumab was found to be most strongly associated with the incidence of ICI-pancreatitis. These patients present with symptoms relating to exocrine and endocrine deficiency. Endocrine presentations include hyperglycaemia, new onset diabetes, and in severe cases even diabetic ketoacidosis.[69] Exocrine impairment leads to pancreatic enzyme insufficiency, malabsorptive symptoms and steatorrhea. Acute pancreatitis may present with typical features of epigastric pain, nausea, vomiting, and fever, along with raised serum lipase or amylase levels. According to the CTCAE grading (Table 4), ICI-pancreatitis is divided into grades 2 to 4. Grade 2 is defined as lipase or amylase enzyme elevation and radiological findings only, whereas grade 3 are those who present with severe pain, vomiting requiring medical interventions, and grade 4 are those with life-threatening consequences requiring urgent interventions. Long term sequelae of ICI-pancreatitis may include the development of pseudocysts or chronic pancreatitis. Isolated asymptomatic lipase elevation (with its own CTCAE grading) is sometimes observed in some patients treated with ICIs, but its relationship to the development of pancreatitis is not entirely clear. Those with clinical features of pancreatitis usually have a higher peak serum lipase level than those who are asymptomatic.[70] In patients with persistent lipase elevations, subclinical pancreatitis needs to be excluded. Distinguishing ICI-pancreatitis from other etiologies, such as gallstones or alcohol-induced pancreatitis, is crucial. Thorough clinical evaluation, imaging studies, and laboratory tests are all essential in making an accurate diagnosis to initiate the appropriate treatment.

The pathophysiology behind ICI-pancreatitis is thought to be due to CD3+ T lymphocytes infiltration into pancreatic islets, increasing the ratio of CD8+/ CD4+ T lymphocytes in peritumoral areas. There may also be associated pancreatic fatty infiltration and pancreatic lipoatrophy.[71] This leads to destruction of pancreatic tissue and the subsequent impairment of its associated endocrine and exocrine pancreatic function.[72]

Given the rarity of irAEs affecting the pancreas, the current management on ICI-pancreatitis is based on scanty published data. In general, asymptomatic elevations of pancreatic enzymes do not require the discontinuation of ICI. Routine monitoring of pancreatic enzymes in asymptomatic patients is also not recommended. They may be checked in patients who develop symptoms or with incidental imaging findings suggestive of pancreatitis.[18] The cornerstone of managing ICI-pancreatitis is the immediate discontinuation of ICI therapy. Early recognition and prompt diagnosis are key to an improved prognosis. Supportive care such as those usually practiced in acute pancreatitis, including intravenous fluids, pain control, and bowel rest, may be initiated.[73] Although corticosteroids have generally been used in an attempt to suppress the immune-mediated inflammatory response, it has not been found to be effective in preventing short or long-term adverse outcomes or improving overall survival in ICI-pancreatitis according to a retrospective study of more than 2000 patients.[74] Late endocrine sequelae such as diabetes or exocrine dysfunction may occur, and joint input from endocrinologists should be sought. For patients with severe complications such as diabetic ketoacidosis, ICIs may need to be withheld.[75] Subsequent resumption of ICI may increase the risk of relapse of ICI-pancreatitis, however this is generally associated with better outcomes and longer overall survival when compared to those who discontinue ICIs permanently.[74]

Immune Checkpoint Inhibitor Upper GI Toxicity

ICI related upper GI inflammation is an emerging entity that has been increasingly described in recent literature. ICI-gastritis can occur in isolation or more frequently, with concomitant ICI-enteritis and/or colitis. The most reported symptoms for isolated upper GI involvement are abdominal bloating and dyspepsia. Those

Table 5 Incidence of Gastrointestinal irAE by ICI Drug Targets

	Colitis[4]	Hepatitis[48]	Cholangitis[82,83]	Pancreatitis[84]
PD-1/ PD-L1	2%	1%-6%	0.05%-0.7%[a]	0.94%
CTLA-4	7%	2%-15%		3.98%
Combined PD-1/PDL1 + CTLA-4	4-8%	13%–30%		10.60%

[a] No data for different types of immunotherapy available due to rarity of condition

with concomitant enteritis/colitis may present with predominantly abdominal pain or diarrhea, which may mask any suspicion for gastritis, thus possibly leading to an under-reporting of ICI-gastritis in the past. Around 20% of patients may have normal endoscopic findings, and the rest may have variable severity from erythema to ulcerations.[76] Some irAEs are severe, with 1 retrospective, multicenter cohort study reporting cases with pneumomediastinum, ulcerated pyloric stricture, and even mortality. Of note, endoscopic lesions were reported to persist in up to two thirds of patients.[77] Conversely, some patients may be asymptomatic and the decision of whether continuing immunotherapy with concomitant ulcer healing medications must be individualized.[78]

Histologically, there are similarities between ICI-gastritis and *Helicobacter pylori* gastritis, and between ICI-enteritis and celiac disease. However, important differences have been noted, such as more intraepithelial lymphocytes, specifically CD8+ cells, and less lamina propria inflammation in ICI-gastritis when compared to *Helicobacter pylori* associated gastritis. Though villous blunting and intraepithelial lymphocytes were seen in both celiac disease and ICI-enteritis, ICI enteritis had more neutrophilic infiltration and a higher distribution of CD3+ and CD8+ cells. These histological differences further substantiate the hypothesis that ICI-gastritis and ICI-enteritis are in fact separate entities.[79] Treatment such as proton pump inhibitors (PPIs), steroids, or biologics have been used in the past. Patients with isolated gastritis typically have a lesser need for commencing immunosuppressants.[28,76]

ICI-esophagitis is a rare entity that has been described which usually occurs in the context of concomitant stomach or duodenal inflammation. In a small retrospective study, the diagnosis was made based on exclusion of other etiologies such as gastroesophageal reflux disease, eosinophilic esophagitis, and esophageal infections, and supported by histological findings of inflammation. Most cases were mild and resolved quickly with nonimmunosuppressants such as H2 blockers, PPIs, and sucralfate.[80]

ICI-mucositis has been investigated in a retrospective analysis of 152 patients, mostly presenting with aphthous ulcers. The majority of cases were mild and resolved expectantly, and only 24% received topical or systemic steroids. The study is limited by possible important confounders such as concomitant chemotherapy in 57% of patients, as well as the lack of histological evaluation.[81] In addition, whether this is a mucosal manifestation of a more systemic irAEs, as in the case of IBD or Behcet's disease, is unknown.

Rechallenge of Immunotherapy

Whether ICI rechallenge can be contemplated needs to be an individualized decision, preferably made by a multidisciplinary team experienced in caring for patients with irAEs. In general, the decision would depend on the organ involvement of the irAE, the severity and whether patients have responded to treatment and symptoms have been ameliorated to grade 1 or less. In an observational study assessing the recurrence rate of irAE in cancer patients, the use of anti-CTLA4, and the initial development of ICI colitis and -hepatitis were associated with a higher rate of irAE recurrence.[85] Dual checkpoint blockades are also known to be associated with a higher likelihood for irAES with a more severe clinical course. In those who developed irAE whilst on combined therapy, the option to rechallenge with monotherapy (eg anti-PD1) may be considered based on a lower risk of irAE recurrence which is typically associated with a less severe toxicity profile.[86,87]

For grade 4 colitis, ASCO explicitly discourages any rechallenge. For lesser grade colitis, the timing of resumption may be guided by endoscopic resolution of inflammation and fecal calprotectin levels. A cutoff of 116 μg/mg has been proposed with 94% specificity for endoscopic remission.[26] Some patients may also rechallenge ICI while on maintenance biologics.[18] Oncologists should also be aware of the higher risk of rechallenging CTLA-4 inhibitors compared to PD-1/PDL-1 inhibitors.[88] It is not known whether switching therapeutic agents or classes is of any benefit in this particular clinical scenario. Other potential strategies being explored include the use of prophylactic treatment for preventing ICI-colitis, though at present no such treatments have been approved. Budesonide has failed to demonstrate any reduction of colitis among patients on ipilimumab.[89,90] Concomitant interleukin(IL)-6 blockade with tocilizumab as secondary prophylaxis may be an emerging strategy but more studies are needed.

For ICI-hepatitis, the decision on whether to resume or permanently discontinue ICI is similar to other irAEs and remains a clinical dilemma that should be individualized. Guidelines have suggested permanent drug discontinuation in grade 3 or 4 hepatotoxicity, whilst resumption of ICI with careful monitoring can be considered in mild (grade 1) hepatotoxicity.[20] Nevertheless, a small prospective trial has reported a 65% rate of successful drug rechallenge in grade 3 or 4 toxicity after improvement in liver function.[91] The coadministration of budesonide during rechallenge of ICI has been proposed to reduce the risk of recurrent toxicity. More prospective studies to investigate the optimal prophylactic strategies as well as appropriate timing and threshold for treatment rechallenge are urgently needed.[47]

Conclusion

ICIs have undoubtedly revolutionized the treatment landscape of cancer and greatly improved the survival rate of some cancer

patients. With the expanding indications of ICIs, the prevalence of ICI toxicities encountered in clinical practice will certainly rise (Table 5). While practical guidelines for the management of most ICI toxicities are readily available, many recommendations are not based on high level of evidence, thus a critical appraisal of the available literature is needed. There are still many gaps in our understanding of the pathophysiology and treatment of ICI-induced toxicities. By identifying certain patient characteristics or even biomarkers that predisposes to irAE in the future, it can be envisioned that we can pre-emptively treat or prevent these adverse outcomes. Furthermore, the question on ICI rechallenge after irAEs still remains to be answered, and more studies are needed to address this issue. Only by mitigating the toxicities of treatment can we truly reap its full benefits, and further research in this area is eagerly awaited. In the meantime, these patients should be under the care of a multidisciplinary team of oncologists, gastroenterologists, hepatologists and surgeons with expertise in the management of gastrointestinal and liver irAEs. Given the increasing complexity of cancer management, requirement of advanced endoscopic diagnostic modalities, nuances in the treatment of adverse events, and the decision of whether treatment rechallenge can be considered, the argument for development of gastrointestinal oncology as a formal specialty has never been stronger.[92]

CRediT authorship contribution statement

Kevin Mok: Writing – original draft, Writing – review & editing. **Claudia Wu:** Writing – original draft, Writing – review & editing. **Stephen Chan:** Writing – review & editing. **Grace Wong:** Writing – review & editing. **Vincent Wai-Sun Wong:** Writing – review & editing. **Brigette Ma:** Writing – review & editing. **Rashid Lui:** Conceptualization, Supervision.

Funding

No funding was involved for this manuscript.

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