CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Diagnosis and Management of Immune Checkpoint Inhibitor Colitis and Hepatitis: Expert Review

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BACKGROUND & AIMS: Immune checkpoint inhibitors (ICIs) have transformed the treatment landscape for oncology, leading to durable remissions in a subset of patients, but also a broad range of potentially life-threatening inflammatory toxicities, many of which involve the gastrointestinal (GI) tract and liver. The purpose of this expert review was to update gastroenterologists on the gastrointestinal and hepatic toxicities of ICIs and provide best practice advice on their diagnosis and management. **METHODS:** The evidence reviewed in this work combines the expert clinical opinion of the authors with a comprehensive search of several English-language databases and a manual review of relevant publications.

Keywords: Immune Checkpoint Inhibitor; Toxicity; Adverse Event; Enterocolitis; Hepatitis.

BEST PRACTICE ADVICE STATEMENTS

Best Practice Advice 1: Infectious causes of diarrhea should be excluded before treatment of suspected ICI colitis.

Best Practice Advice 2: Early stool testing for inflammatory markers (lactoferrin and calprotectin) in patients with grade 2 or higher colitis/diarrhea (more than 4 bowel movements daily above baseline) according to the Common Terminology Criteria for Adverse Events, Version 5 (CTCAE) and selected patients with less-severe diarrhea may help stratify high-risk patients for endoscopic evaluation.

Best Practice Advice 3: Endoscopic confirmation of the diagnosis and severity of ICI colitis should be considered before initiation of high-dose systemic glucocorticoids.

Best Practice Advice 4: Abdominal imaging may be considered to exclude serious complications in patients with dominant symptoms of pain, fever, or bleeding, but should not be performed routinely in patients with diarrhea alone.

Best Practice Advice 5: Rapid progression of ICI colitis may occur within a period of days, particularly in patients treated with ipilimumab and, therefore, prompt diagnosis and treatment is required.

Best Practice Advice 6: ICI colitis typically responds to high-dose systemic glucocorticoids, given in doses of 0.5–2 mg/kg prednisone equivalent daily with a taper of 4–6 weeks; however, these doses and schedules have not been rigorously examined. Infliximab and vedolizumab are reasonable options for treatment of glucocorticoid refractory colitis.

Best Practice Advice 7: Budesonide is ineffective as prophylactic treatment for ICI colitis, but may be used for treatment of ICI-associated microscopic colitis.

Best Practice Advice 8: Patients who develop ICI colitis may be retreated with immunotherapy under select conditions.

Best Practice Advice 9: Patients with inflammatory bowel disease may have an increased risk of ICI-associated gastrointestinal adverse events, but may derive cancer treatment benefit from checkpoint blockade.

Best Practice Advice 10: All patients undergoing ICI therapy should undergo baseline evaluation of liver chemistries (total bilirubin, alkaline phosphatase, aspartate aminotransferase [AST], and alanine aminotransferase [ALT]), as well as pretreatment screening for hepatitis B virus serologies (hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody). Liver chemistries should be repeated before each ICI treatment cycle, with management based on CTCAE grade.

Best Practice Advice 11: For patients with CTCAE grade 1 hepatitis (AST/ALT 1–3× the upper limit of normal [ULN] or total bilirubin 1–1.5× ULN), liver monitoring should be repeated 1–2 times weekly. For patients with CTCAE grade 2 hepatitis (AST/ALT >3–5× ULN or total bilirubin >1.5–3× ULN), ICI therapy should be held until resolution to grade 1; for patients with clinical symptoms of liver toxicity, prednisone 0.5–1.0 mg/kg/d or equivalent may be administered.

Best Practice Advice 12: For patients with grade 3 hepatitis (AST/ALT >5–20× ULN or total bilirubin >3–10× ULN), ICI should be discontinued, urgent gastrointestinal/liver consultation is advised, and glucocorticoids should be initiated at a dose of 1–2 mg/kg methylprednisone or equivalent. Second-line immunomodulators, such as azathioprine or mycophenolate mofetil, may be considered in patients who fail to demonstrate improvement in clinical hepatitis within 3–5 days.

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Best Practice Advice 13: For patients with CTCAE grade 4 hepatitis (AST/ALT >20× ULN or total bilirubin >10× ULN or hepatic decompensation, such as ascites or encephalopathy) hospitalization is appropriate, preferably at a referral center with expertise in the care of patients with liver failure. ICI should be permanently discontinued, and patients started on 2 mg/kg/d methylprednisolone or equivalent.

Best Practice Advice 14: All patients who develop elevated liver chemistries on ICI therapy should undergo diagnostic evaluation for alternate etiologies of liver injury, including consideration of a liver biopsy.

Best Practice Advice 15: Patients who develop elevated alkaline phosphatase and/or bilirubin on ICI therapy should undergo biliary imaging to assess for biliary obstruction with hepatic ultrasound, magnetic resonance cholangiopancreatography, or endoscopic ultrasound.

I mmune checkpoint inhibitors (ICIs) have transformed the treatment landscape for oncology, replacing the prior standard of care for numerous malignancies and producing durable remissions, but also leading to a wide spectrum of inflammatory toxicities, collectively referred to as immune-related adverse events (irAEs).[1] Current ICIs target 2 immune regulatory pathways—cytotoxic T lymphocyte antigen (CTLA)-4 and programmed death (PD)-1 or its ligand (PD-L1)—both pathways have key roles in regulating autoimmunity.[1] Gastrointestinal toxicities are among the most commonly encountered severe toxicities from current ICI therapy, and are a frequent cause of morbidity, treatment interruption, and discontinuation, although mortality from gastrointestinal (GI) irAEs is rare.[1–3] With the expanded use of ICIs across multiple malignancies, GI irAEs are being increasingly recognized. Like most irAEs, GI irAEs typically respond to systemic immune suppression; however, refractory cases do occur, and systemic immune suppression is not without risks, for example, opportunistic infection and the potential for a deleterious effect on antitumor immunity.[1,4]

Colitis, with or without accompanying enteritis, which typically presents as diarrhea, is the single most common GI toxicity from ICIs, affecting up to 40% of patients, depending on the pathway targeted (ie, PD-1/PD-L1 vs CTLA-4).[1,4] Severe enterocolitis—requiring anti-inflammatory treatment and ICI delay or discontinuation—is less common, affecting 2%–5% of patients on PD-1/PD-L1 inhibitors and closer to 10% of patients on CTLA-4 inhibitors.[2,4] Although ICI-related gastritis has also been reported, isolated severe gastritis in the absence of small bowel or colonic inflammation is rare.[5,6] ICIs can also lead to inflammation outside of the GI tract, including hepatitis, which is common, as well as less common cholangitis, pancreatitis, and potentially cholecystitis.[7–9]

Many patients who developed GI toxicities from ICIs are managed by their oncology teams; however, gastroenterologists and hepatologists have important roles in the management of these patients, including ensuring proper diagnosis, risk assessment, and treatment of atypical or refractory cases. In addition, gastroenterologists should play an essential role in the management of patients at high risk

for developing GI complications on ICIs, such as those with underlying inflammatory bowel disease (IBD). Hepatologists should generally be involved in the care of patients with hepatocellular carcinoma treated with ICIs, as well as patients who have cirrhosis or other severe underlying liver disease. This expert review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of *Gastroenterology*.

Clinical Presentations and Diagnosis of Immune Checkpoint Inhibitor Enterocolitis

Validated severity indices for ICI colitis have not been established, and symptoms typically correlate poorly with endoscopic severity, radiologic findings, and response to treatment. Most current literature on enterocolitis uses a grading system established for oncology clinical trials called the Common Terminology Criteria for Adverse Events, Version 5 (CTCAE),[10] which grades toxicities on a scale from grade 1 (mild) to grade 5 (death), although the clinical utility of this grading system has not been established for irAEs (Table 1). Mild ICI enterocolitis presents with more frequent loose stools, which can be accompanied by symptoms of upper GI inflammation, including nausea, vomiting, decreased appetite, and reflux. In more severe disease, cramping, urgency, and watery diarrhea are common, and bloody diarrhea can be seen, although fevers are less typical. Rapid clinical changes generally associated with a recent ICI infusion are a hallmark of ICI enterocolitis, with symptoms escalating over a period of days, particularly when ipilimumab (anti–CTLA-4) is part of the ICI regimen. This rapidly evolving clinical presentation is more reminiscent of a colonic infection than of IBD (although infections are rarely identified), and is an important reason for expedited diagnostic testing and treatment.

Mild diarrhea is common on ICIs, and is typically managed with empiric, symptom-directed treatment. In general, diagnostic testing should be considered for any patient who has new-onset diarrhea on ICIs that is significant enough to interfere with their activities of daily living, or that is accompanied by abdominal pain, incontinence, bleeding, fever, nausea, vomiting, or inability to take in adequate nutrition. Treatments can then be tailored to the results of testing as discussed below, rather than selected empirically. The gastroenterologist has several important roles in the management of suspected ICI enterocolitis. These include providing endoscopic confirmation of the diagnosis, as well as assessment of the endoscopic severity of inflammation. Endoscopy with biopsy should be considered before initiation of high-dose systemic glucocorticoids. The gastroenterologist also has a key role in managing patients who have severe enterocolitis, or who do not respond to initial treatment, as we will discuss in the next section.

Table 1. Common Terminology Criteria for Adverse Events, Version 5[10] Grading for Gastrointestinal Toxicity

Variable		CTCAE		
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of <4 stools/d over baseline; mild increase in ostomy output compared with baseline	Increase of 4–6 stools/d over baseline; moderate increase in ostomy output compared with baseline; limiting instrumental ADL	Increase of ≥7 stools/d over baseline; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death

ADL, activities of daily living.

The differential diagnosis for patients with suspected ICI enterocolitis is broad. Although no large-scale analyses of the causes of diarrhea in patients on ICIs have been undertaken, ICI enterocolitis is confirmed in most suspected cases.[11] Although we have observed that infectious causes of diarrhea account for <5% of cases of diarrhea on ICIs, it is important to exclude these causes in all patients before initiation of immunosuppressive treatment. These tests should include *Clostrioides difficile* testing and stool cultures in all patients (Figure 1). Stool pathogen testing panels are a reasonable alternative to stool cultures where available. The decision to perform stool ova and parasite testing should be based on patient risk factors and local prevalence. Immune-mediated pancreatic insufficiency is an uncommon but important cause of diarrhea in this population, and fecal elastase testing with adjunctive spot or qualitative fecal fat testing should be considered in patients who do not respond to typical treatments or who present with steatorrhea.[12] New-onset celiac disease is another rare but important cause of diarrhea in these patients.[13]

Laboratory blood tests are rarely informative in patients with suspected ICI colitis, although stool tests for evidence of inflammation can be valuable, as discussed below. Patients may have an elevated white blood cell count and increased inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate; however, the specificity of these tests is low, given the prevalence of concurrent inflammatory toxicities outside of the GI tract from ICIs, as well as the ongoing antitumor responses that may be occurring. Newly symptomatic celiac disease is a rare complication of ICI therapy. Given both the high sensitivity and specificity of tissue transglutaminase IgA for celiac disease, testing for tissue transglutaminase IgA and total IgA is reasonable to consider in patients on ICI therapy with new diarrhea.[13] Because biologic immune suppression, such as infliximab, is used to treat a substantial fraction of patients with ICI enterocolitis, testing for hepatitis B (ie, surface antigen, surface antibody, and core antibody), and for latent tuberculosis should be considered in any patient with suspected ICI enterocolitis if these tests were not sent before ICI initiation. We also suggest testing for human immunodeficiency virus and hepatitis C virus.

Patient symptoms do not correlate with endoscopic findings or predict the response of enterocolitis to treatment.[11,14] In contrast, endoscopic findings do predict response of enterocolitis to treatment, and endoscopic examination with biopsies is the reference standard for diagnosis of ICI enterocolitis.[11,14,15] Early endoscopy is correlated with improved outcomes in retrospective analyses, although the importance of a tissue diagnosis in ICI enterocolitis management has not been rigorously evaluated.[16] Although important in many situations, endoscopy may not be necessary in all patients who develop diarrhea on ICIs; initial screening of stool inflammatory markers (lactoferrin or calprotectin) can help to stratify patients with CTCAE grade 2 or higher diarrhea and select patients with grade 1 diarrhea to prompt endoscopic evaluation. Retrospective studies have shown the sensitivity of stool lactoferrin can be 90% for histologic inflammation.[16] Based
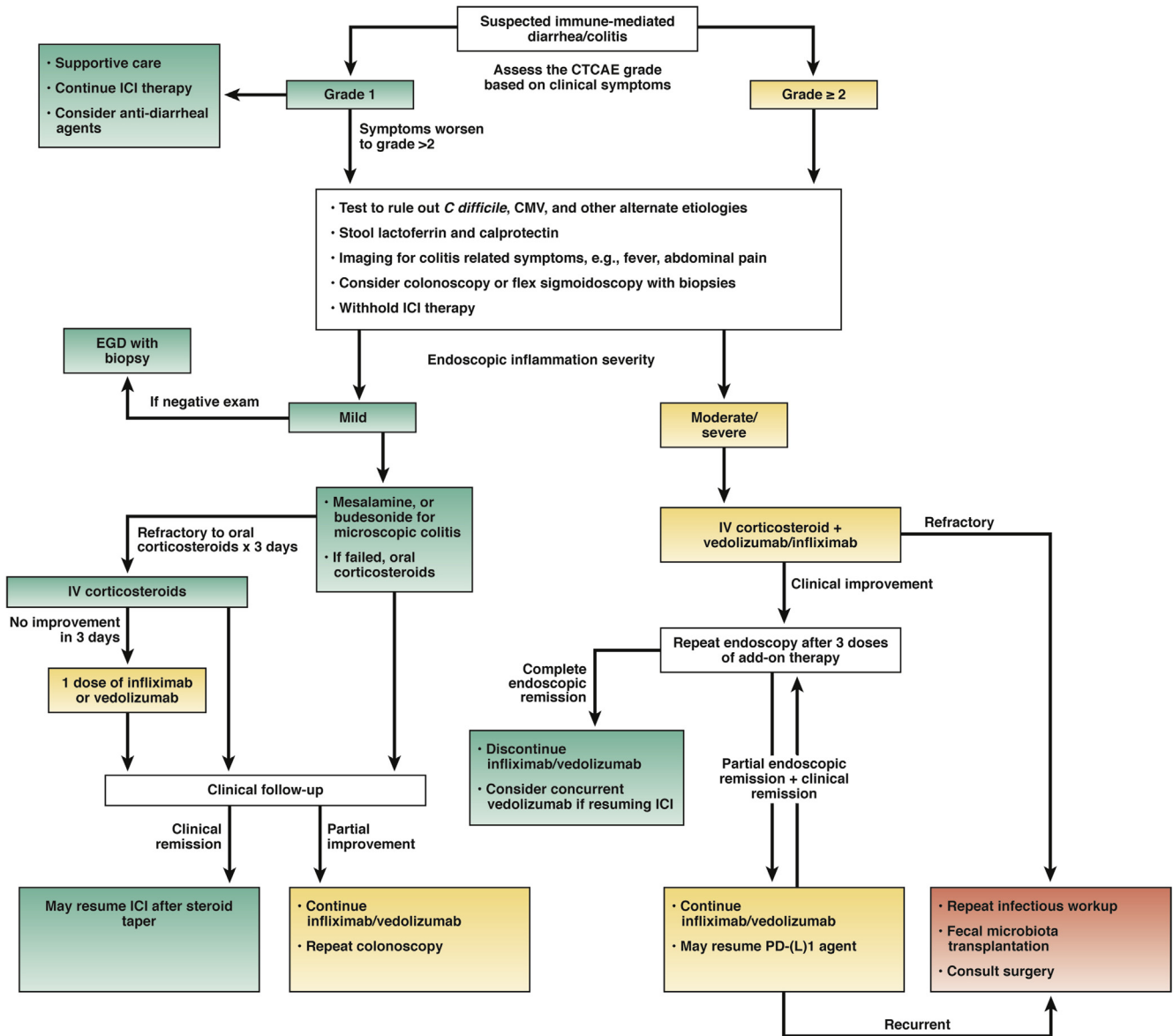
Figure 1. ICI colitis management algorithm. *Alternate etiologies include stool infectious workup for common and uncommon pathogens, pancreatic insufficiency, celiac disease, and thyroid dysfunction.

on existing literature, no mucosal inflammation is found in as many as 20%–30% of patients with suspected ICI enterocolitis, although this number may be smaller in patients treated with ipilimumab.[11] Colonic ulceration identified by endoscopy is the only established factor that predicts how ICI enterocolitis will respond to treatment (available endoscopic inflammation severity measuring tools are provided in Tables 2 and 3); in addition, endoscopy with biopsies is currently the only way to diagnosis ICI-related microscopic colitis, which has a distinct treatment response.[11,14,15] Endoscopic features are illustrated in Figure 2.

For patients who are evaluated endoscopically, the optimal choice of endoscopic examination for obtaining diagnostic biopsies and evaluating mucosal severity has not been established. Pancolitis is the most common presentation of luminal inflammation.[17] Approximately 95% of patients have inflammation in the left colon on biopsy, with the majority visible macroscopically; although regional variability in the severity of inflammation does occur, a flexible sigmoidoscopy is often adequate for making a diagnosis.[17] Isolated upper GI inflammation (gastritis, gastroenteritis, or enteritis) can also occur on ICIs with a frequency likely in excess of 10%.[11] Esophagogastroduodenoscopy is reasonable to consider in patients with negative flexible sigmoidoscopies, and may be higher yield than proceeding to a full colonoscopy.

Cross-sectional abdominal imaging by computed tomography (CT) or magnetic resonance imaging has a limited role in diagnosing ICI enterocolitis. Small retrospective analyses (both with 30–40 patients) have examined the diagnostic utility of CT in suspected ICI enterocolitis, finding

Table 2. MD Anderson Cancer Center Endoscopic Inflammation Grading

Severity	Endoscopic Features
Mild	Normal endoscopy and normal histology
Moderate	Normal colon appearance with pathology showing inflammation; small ulcer <1 cm, shallow ulcer <2 mm, and/or number of ulcers <3; inflammation limited to the left colon only, nonulcer inflammation
High	Large ulcer ≥1 cm, deep ulcer ≥2 mm, and/or number of ulcers ≥3; extensive inflammation beyond left colon

sensitivities ranging from 53% to 85% and specificities of 75% to 78%, leading to a relatively low negative predictive value.[14,18] In addition, the pattern of ICI enterocolitis on CT is indistinguishable from other forms of colitis (ie, infectious and ischemic).[18] For these reasons, CT and magnetic resonance imaging are typically helpful only for cases of suspected ICI enterocolitis with dominant symptoms of pain, fever, or bleeding as a means for ruling out serious complications. Diarrhea alone should not warrant abdominal imaging.

Treatment of Immune Checkpoint Inhibitors Enterocolitis

At present, we have minimal prospective data on the management of ICI enterocolitis, most of which were derived from clinical trials that were not designed to evaluate this entity. Consequently, management guidelines are based on retrospective analyses and expert opinion and uniformly recommend systemic glucocorticoids as first-line therapy.[19–21] Although ICI enterocolitis typically responds to high-dose systemic glucocorticoids, which are often given in doses of 0.5–2 mg/kg prednisone equivalent daily (either oral or intravenous) with a taper of 4–6 weeks, these doses and schedules have not been rigorously examined.[4] Lower doses of glucocorticoids or glucocorticoid-sparing treatments may have clinical benefit, as evidence from mice and humans suggests that systemic glucocorticoids may dampen antitumor responses.[1]

Table 3. Mayo Clinic Endoscopic Scoring

Disease activity	Score	Endoscopic features
Normal or inactive	0	None
Mild	1	Erythema, decreased vascular pattern, mild friability
Moderate	2	Marked erythema, absent vascular pattern, friability, erosions
Severe	3	Spontaneous bleeding, ulceration

Approximately one-third of patients with ICI enterocolitis have an inadequate response to first-line glucocorticoid treatment and may require a second-line immunosuppressant.[4] Patients who do not respond to high-dose glucocorticoids within 72 hours of initiation or do not have a complete response within a week should be considered for second-line immunosuppression. In addition, patients who have recurrent symptoms during the steroid taper or after completing a steroid course should also be considered for second-line immunosuppression. Colonic ulceration is the only currently identified predictive factor associated with the need for secondary immune suppression, and CTCAE grading is not predictive.[14] Identifying patients with colonic ulceration is one of the important roles of endoscopic evaluation of patients with suspected ICI enterocolitis.

The optimal choice for second-line immune suppression is currently unknown, but both infliximab and vedolizumab appear to be highly effective using doses and scheduling adapted from the treatment of IBD.[22,23] Infliximab is typically dosed at 5 mg/kg given intravenously and vedolizumab is given intravenously at a 300-mg dose. Both infusions are typically given at weeks 0, 2, and 6, with a minority of patients receiving longer-term treatment.[22,23] Responses to treatment are typically rapid, generally occurring in less than 1 week, which is an important contrast with IBD.[22,23] Although most cases of ICI enterocolitis will not recur unless the patient receives further ICI therapy, many patients require the full loading dose for infliximab or vedolizumab, and maintenance therapy may still be required for certain cases.

Because no current data exist to distinguish infliximab from vedolizumab as initial biologic therapy for glucocorticoid unresponsive ICI enterocolitis, the decision to choose one biologic therapy over the other should be based on other risk factors. These should include the underlying malignancy and comorbidities, risk of infection, expected duration of treatment, and other concurrent immune-related adverse events. In particular, infliximab should be avoided in patients with underlying hematologic malignancies because tumor necrosis factor–α inhibitors are associated with the development of rare lymphomas, and should be used with caution in patients with underlying severe congestive heart failure. Infliximab may also be associated with worse cancer outcomes based on a recent report, although this finding should be interpreted with caution, as the confounding factors (eg, steroid dose and duration) were not adequately addressed in the analysis.[24] The use of infliximab in patients with both ICI hepatitis and enterocolitis should be decided on a case by case basis because infliximab can induce a rare form of hepatitis.[25] Vedolizumab may interfere with ongoing antitumor responses in the GI mucosa in patients receiving immunotherapy for primary GI malignancies or for tumors with GI metastases. At present, neither therapy has been shown to have a substantial influence on antitumor responses more generally, although use of these agents is highly correlated with use of high-dose systemic glucocorticoids, creating substantial bias in retrospective analyses.
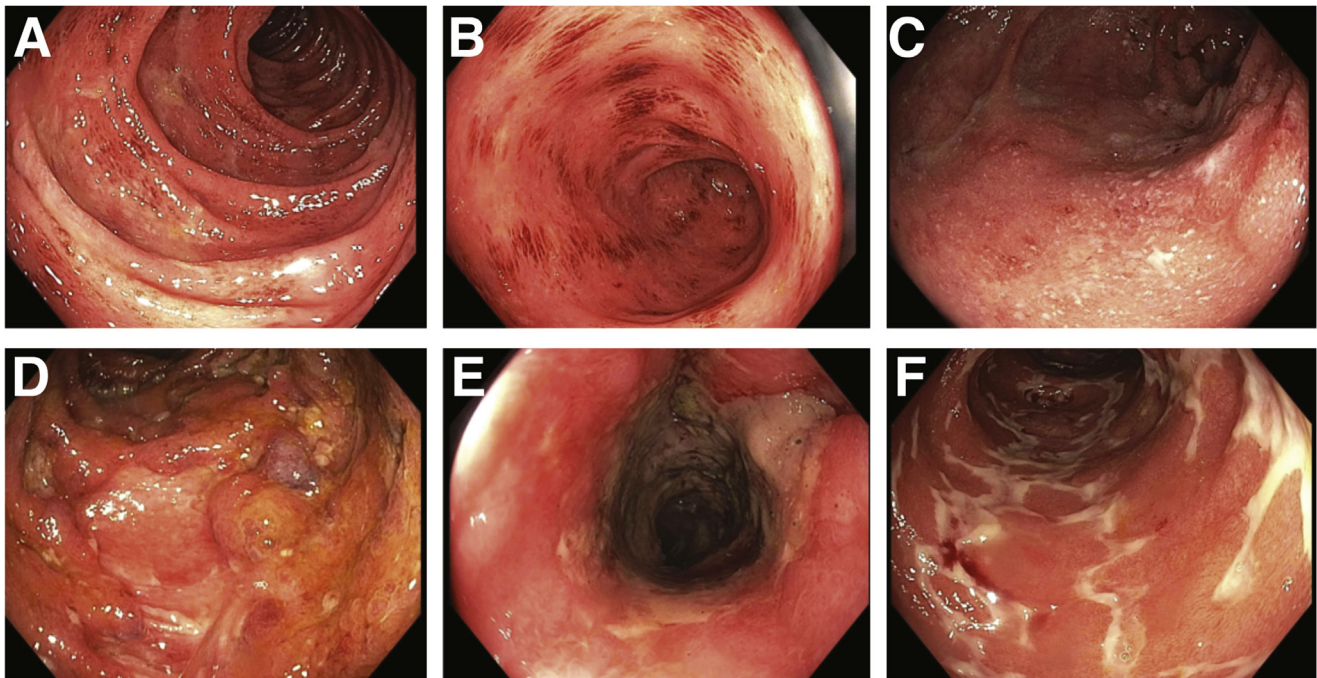
Figure 2. Endoscopic features of ICI colitis. (*A–C*) Ulcerative colitis pattern with diffuse and patchy erythema, loss of vasculature, edema, friability, and exudate. (*D–F*) Crohn's colitis pattern with edema, friability, cobblestoning, serpiginous, and multiple large deep ulcerations.

Patients who do not respond to the initial choice of biologic therapy should switch treatment class from infliximab to vedolizumab or vice versa.[23] Given the severity of these cases, waiting for a standard washout period is not recommended, and patients should be treated within a few weeks of their last infusion of the prior medication as soon as it is evident that they are not responding. Treatment approaches for patients who fail both vedolizumab and infliximab are not well established. Fecal microbiota transplantation has been reported in 2 such patients.[26] Alternative medications, such as the p40 inhibitor ustekinumab, the JAK inhibitor tofacitinib, and CTLA-4-Ig (abatacept), can be considered in life-threatening cases, but each has a substantial risk of interfering in antitumor responses based on their mechanisms of action.

A single randomized controlled trial evaluated prophylactic therapy with colonically formulated budesonide in the prevention of enterocolitis from ipilimumab.[27] This trial showed no therapeutic benefit to budesonide as prophylactic treatment for ICI enterocolitis; however, retrospective analyses suggest that budesonide may have a role in the management of patients with microscopic colitis from checkpoint inhibitors.[11] In this study, patients with ICI-associated microscopic colitis, defined as histologic lymphocytic inflammation in the colon in the absence of macroscopic signs of inflammation or small bowel involvement, were highly responsive to colonic budesonide.[11] Many of these patients were also able to continue on their ICI using budesonide as concurrent treatment.[11] An ICI colitis management algorithm is shown in Figure 1.[16,22,23,28]

Treatment of High-Risk Populations

Patients who develop ICI colitis may be retreated with immunotherapy under some conditions, particularly when alternative effective cancer therapies are not available. The risk of reintroduction of ICIs is incompletely understood and based entirely on retrospective analyses of patients who were re-treated as part of standard of care cancer therapy, a population that may underestimate the risk in unselected patients because retrospective data likely include predominantly patients whose initial presentation was less severe, justifying the risk of re-treatment. Patients who switch ICI classes still have risk for recurrent irAEs, but generally lower risk if they switch from ipilimumab to PD-1/PD-L1 blocking therapy. In a multicenter retrospective study of patients who were re-treated after a diagnosis of ICI enterocolitis, the risk of recurrent ICI colitis was approximately 30% for most regimens, but appeared to be higher in patients who developed enterocolitis on PD-1/PD-L1 inhibitors and then switched to CTLA-4 inhibitors.[29] Maintenance therapy with a biologic such as infliximab or vedolizumab may also be effective at reducing the risk of ICI enterocolitis recurrence in patients who remain on their immunotherapy, as was reported in a small case series.[30] Yet the safety of long-term use of immunosuppressants and the effect on tumor response to ICI in this setting remains to be determined. Even in the setting of recurrent ICI enterocolitis, standard therapies typically remain effective. Enterocolitis before ICI initiation should not be considered an absolute contraindication for future immunotherapy if ICIs are the only available options.
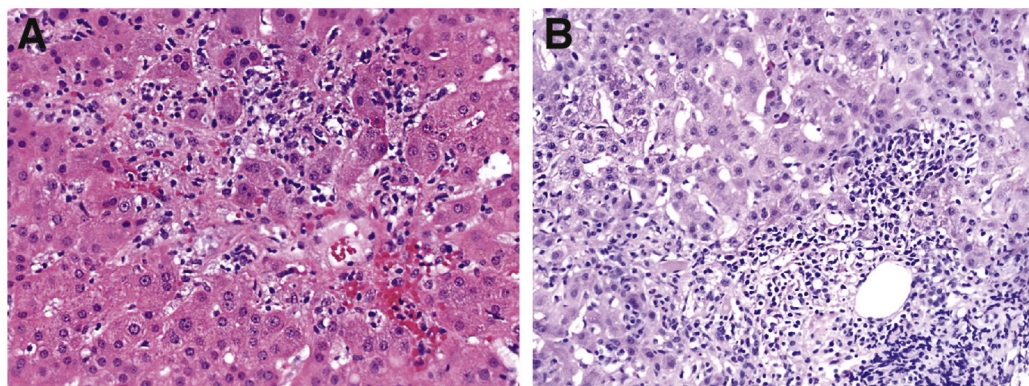
Figure 3. Liver pathology of ICI hepatitis with lymphocytic centralobular inflammation (*A*), and autoimmune hepatitis with plasma cell–rich portal inflammation (*B*). Images courtesy of Dr Joseph Misdraji, Massachusetts General Hospital.

Patients with autoimmune disease, including IBD, have been excluded from clinical trials of ICIs. Consequently, we have no prospective data on outcomes of ICI therapy in patients with ulcerative colitis and Crohn's disease, although a large multicenter, retrospective analysis that included more than 100 patients with IBD was published in 2020.[31] The population in this study was split evenly between ulcerative colitis and Crohn's disease. Nearly all patients had quiescent disease and 50% were not on IBD-directed therapy, likely reflecting a treatment bias, with patients who had severe IBD unlikely to be recommended for treatment. Most patients received PD-1/PD-L1 inhibitors. In this study, the GI irAE rate was 41%, with 21% developing severe GI irAEs, including some patients who presented with perforations.[31] A multicenter control cohort had an 11% GI irAE rate.[31] Nevertheless, ICI responses in the tumors were similar to those expected for the general population, and no patients died from GI irAEs. These data indicate that patients with IBD have an increased risk of GI irAEs on ICI compared with control populations, but may derive cancer treatment benefit from checkpoint blockade. Therefore, IBD patients can still be evaluated cautiously and treated with ICI on an individual case basis. Treatment success for patients with IBD and cancer will require close collaboration between oncology and gastroenterology. A prospective clinical trial is now enrolling patients with IBD who have an indication for ICI, as part of a wider study of patients with cancer and underlying autoimmunity (AIM-NIVO, ClinicalTrials.gov ID NCT03816345). This will provide the first prospective data on ICI treatment of patients with IBD, critical information for assessing risk and developing evidence-based treatment protocols.

Checkpoint Inhibitor Hepatitis

Abnormal liver enzymes are less commonly observed with ICI therapy than enterocolitis, with an incidence of <5% in clinical trials of ICI monotherapy, and severe hepatitis is rare. Consequently, far less is known about the etiology, diagnosis, and treatment of ICI hepatitis than for ICI enterocolitis. Although rare with monotherapy, the incidence of ICI hepatitis rises substantially in the setting of combination treatments, with approximately one-quarter of patients on ipilimumab and nivolumab combination therapy developing hepatitis.[32] Similarly, hepatitis is more common in the setting of both chemotherapy and targeted therapy combinations with ICIs.[33] This amplification of hepatitis in the setting of combination regimens suggests that ICIs may sensitize the liver to other forms of drug injury.

The typical histologic patterns of liver injury from ICIs have been described in small case series.[34–36] Although diverse pathology is seen, the majority of ICI hepatitis cases are associated with either a lymphocytic or granulomatous pattern of hepatocellular injury, whereas hepatitis with fibrin ring granulomas represents a specific subset of liver injury from PD-1 blockade.[34–36] Of note, the plasma cell infiltration commonly observed in autoimmune hepatitis appears to be less common in ICI hepatitis, suggesting a distinct immune etiology (Figure 3). The relationship between these pathologic subtypes of ICI hepatitis and both clinical outcome and response to treatment remains uncertain.

Routine monitoring of liver blood tests (ie, total bilirubin, alkaline phosphatase, AST, and ALT) is standard of care for patients treated with immunotherapy, generally at the time of ICI initiation and each treatment cycle. In addition, patients should have pretreatment testing for hepatitis B virus infection with measurement of surface antigen, surface antibody, and core antibody, given the possibility that undetected hepatitis B could complicate ICI therapy or the management of other irAEs, such as enterocolitis, with immune suppression, which increases the risk for reactivation and fulminant liver failure.

Hepatitis is often detected incidentally in asymptomatic patients through routine liver testing, but can present with jaundice, fevers, and malaise. Many of these patients are managed by oncology teams according to CTCAE-based management guidelines that use ALT/AST thresholds to direct diagnostic testing and treatment recommendations.[19–21] These guidelines provide a useful framework for management; however, the primary role of the gastroenterologist or hepatologist in managing patients with suspected ICI hepatitis is to ensure that competing
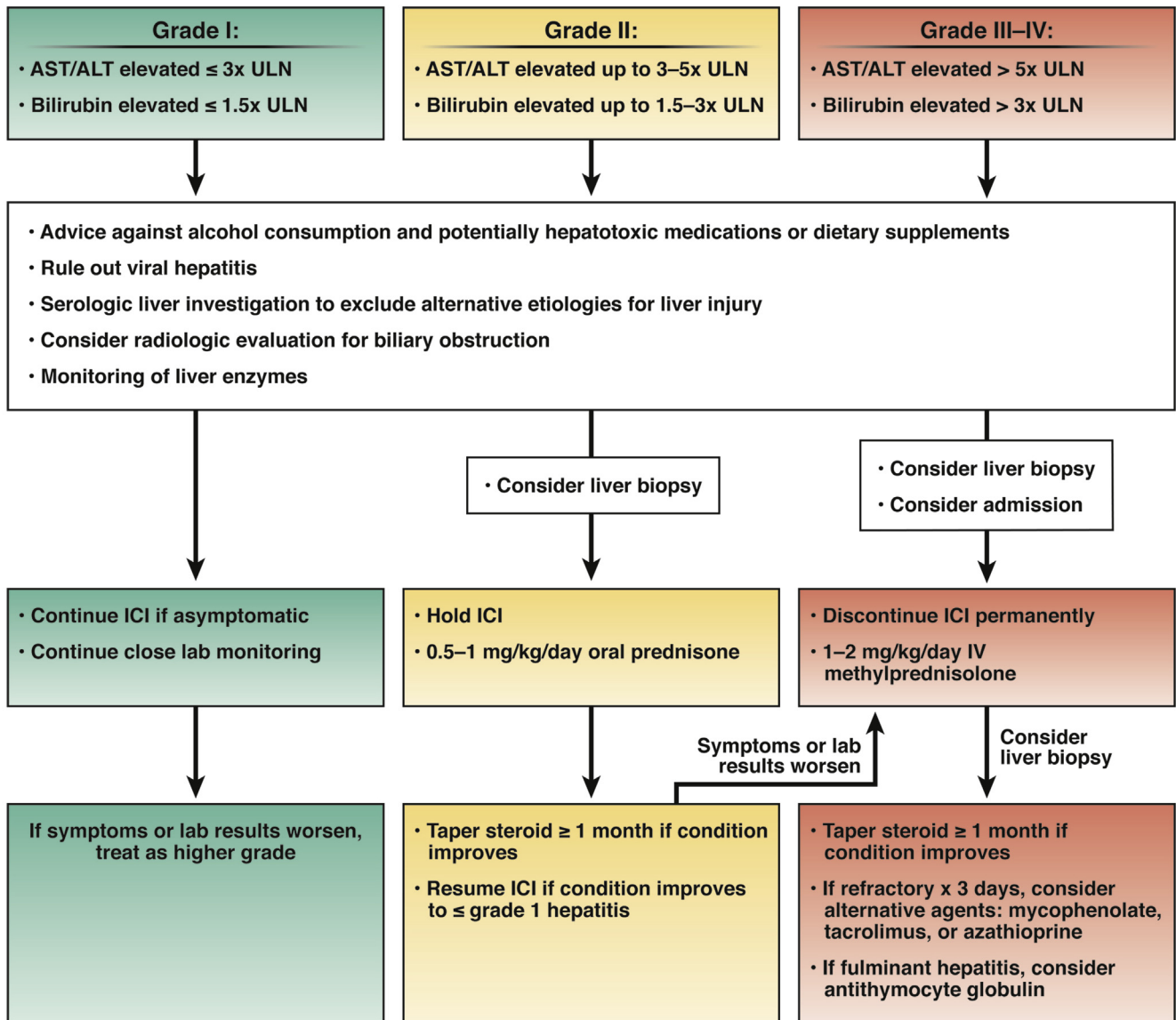
Grade I:	Grade II:	Grade III–IV:
• AST/ALT elevated ≤ 3x ULN	• AST/ALT elevated up to 3–5x ULN	• AST/ALT elevated > 5x ULN
• Bilirubin elevated ≤ 1.5x ULN	• Bilirubin elevated up to 1.5–3x ULN	• Bilirubin elevated > 3x ULN

• Advice against alcohol consumption and potentially hepatotoxic medications or dietary supplements

• Rule out viral hepatitis

• Serologic liver investigation to exclude alternative etiologies for liver injury

• Consider radiologic evaluation for biliary obstruction

• Monitoring of liver enzymes

• Consider liver biopsy

• Consider liver biopsy
• Consider admission

• Continue ICI if asymptomatic • Continue close lab monitoring	• Hold ICI • 0.5–1 mg/kg/day oral prednisone	• Discontinue ICI permanently • 1–2 mg/kg/day IV methylprednisolone

Symptoms or lab results worsen

Consider liver biopsy

If symptoms or lab results worsen, treat as higher grade	• Taper steroid ≥ 1 month if condition improves • Resume ICI if condition improves to ≤ grade 1 hepatitis	• Taper steroid ≥ 1 month if condition improves • If refractory x 3 days, consider alternative agents: mycophenolate, tacrolimus, or azathioprine • If fulminant hepatitis, consider antithymocyte globulin

Figure 4. ICI-related liver toxicity management.

diagnoses have been excluded, and to manage patients who do not respond to first-line treatments.

Patients with cancer are at elevated risk for liver injury from a variety of causes, including hepatic metastasis, thromboembolic disease, biliary compression, perfusion injury, opportunistic infections, and drug reactions. Due to these reasons, all patients on ICI therapy with elevated liver chemistries should be evaluated for alternative etiologies for their hepatitis, including a thorough history and review of their medications to exclude other causes of drug-induced liver injury. Specific testing should include serologies for hepatotrophic (eg, hepatitis A virus, hepatitis B virus, hepatitis C virus, and hepatitis E virus) and non-hepatotrophic viruses (eg, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus), and an evaluation of the hepatobiliary tree and hepatic vasculature with abdominal ultrasound. Elevated alkaline phosphatase and/or bilirubin should prompt cross-sectional hepatobiliary imaging, such as CT/

magnetic resonance imaging, and cross-sectional imaging may be valuable more broadly in any patient at risk for or with known hepatic metastases. For patients who have risk factors for biliary obstruction, such as hepatic or intra-abdominal metastases, and have a normal abdominal ultrasound, magnetic resonance cholangiopancreatography, or endoscopic ultrasound should be considered based on safety, availability, and local expertise. Endoscopic retrograde cholangiopancreatography may be necessary when anatomic obstruction or stricture is observed on imaging. When competing etiologies have been excluded, liver biopsy should be considered in patients with grade 2 hepatitis or higher, who may require systemic glucocorticoids or potential ICI discontinuation. Ideally, these biopsies should be performed before starting glucocorticoids to maximize the diagnostic utility of the biopsy.

Current treatment guidelines for ICI hepatitis are based largely on expert opinion and small cases series.[19–21]

Systemic glucocorticoids represent the primary treatment for patients whose liver chemistries do not resolve spontaneously and/or require a delay in ICI dosing. For patients with grade 1 hepatitis (AST/ALT 1–3× the upper limit of normal [ULN] or total bilirubin 1–1.5× ULN), more frequent monitoring of liver chemistries with once or twice weekly blood draws is suggested, with or without a delay in ICI dosing.

Patients with probable or confirmed grade 2 ICI hepatitis (AST/ALT >3–5× ULN or total bilirubin >1.5–3× ULN), holding ICI treatment is suggested. Consultation with a gastroenterologist or hepatologist with expertise in the management of ICI hepatitis should be considered for patients with grade 2 or higher disease, and potential hepatotoxins should be discontinued if medically feasible. For patients with clinical symptoms of liver toxicity, prednisone 0.5–1.0 mg/kg/d or equivalent may be administered, and ICI may be resumed if and when the patient recovers to grade 1 hepatitis with a steroid dose of ≤10 mg of prednisone or equivalent daily. For patients with confirmed or probable ICI hepatitis that fails to resolve after a 1- to 2-week delay in ICI dosing, systemic glucocorticoids should be administered.

For patients with probable or confirmed grade 3 ICI hepatitis (AST/ALT >5–20× ULN or total bilirubin >3–10× ULN), ICI therapy should be discontinued and urgent consultation with a gastroenterologist/hepatologist is appropriate. Liver biopsy to confirm the diagnosis and hospitalization for urgent management should be considered on a case by case basis. Glucocorticoids are generally initiated at a dose of 1–2 mg/kg methylprednisolone or equivalent with a planned 4- to 6-week taper, although these doses were empirically determined and have not been rigorously examined.[19–21] Minimal data are available on optimal management of patients who do not respond to glucocorticoids within 3–5 days, or who have hepatitis flare during steroid taper. Second-line immunomodulators, such as azathioprine, mycophenolate mofetil, or tacrolimus, may be considered in these patients. Infliximab should be used with caution in patients with suspected ICI hepatitis due to potential risk of idiosyncratic liver toxicity, and the absence of clinical benefit in this population.

Patients with confirmed or suspected grade 4 ICI hepatitis (AST/ALT >20× ULN or total bilirubin >10× ULN or hepatic decompensation, such as ascites or encephalopathy) should be hospitalized, preferably at a referral center with expertise in the care of patients with liver failure. ICI treatment should be permanently discontinued, and patients started on 2 mg/kg/d methylprednisolone or equivalent with a planned 4- to 6-week taper in patients who respond. Competing etiologies for hepatitis should be rigorously excluded in these patients. Patients who do not respond to glucocorticoids with a drop in transaminases of at least 50% in 3 days should be started on secondary immune suppression with azathioprine, mycophenolate mofetil, or tacrolimus.[32] Antithymocyte globulin has been reported as a treatment for fulminant ICI hepatitis, although its use should be reserved for refractory and severe cases, as it may interfere with optimal antitumor response.[37] An ICI hepatitis management algorithm is illustrated in Figure 4.

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