

# A Review of Inflammatory Bowel Disease in the Setting of Liver Transplantation

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## Keywords

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**Abstract:** Although inflammatory bowel disease (IBD) rarely arises in the setting of solid organ transplantation, IBD has a higher incidence in this setting than in the general population and poses challenging management issues. The most common association is hepatic orthotopic transplant for primary sclerosing cholangitis. This article discusses IBD in the setting of liver transplantation, including both the development of de novo IBD and the evolution of preexisting IBD posttransplant, as well as management considerations in addressing colorectal cancer risk in this patient population.

Inflammatory bowel disease (IBD) in the setting of liver transplantation is a clinical challenge because of the overlapping diagnostic possibilities and the paradoxical nature of an inflamed bowel despite significant immunosuppression for the prevention of organ rejection. This paradox suggests that de novo IBD after liver transplant or worsening of preexisting IBD after liver transplant may arise via a different disease process or may have a different pathogenic etiology than traditional IBD would in the non-organ transplant patient. This paper discusses IBD in the setting of liver transplantation, including de novo IBD and the evolution of preexisting IBD posttransplant, in addition to management considerations in addressing colorectal cancer (CRC) risk in this patient population.

IBD is a chronic relapsing and remitting condition that may arise after liver transplant despite postoperative immunosuppression. The course of patients with preexisting IBD who receive an organ transplant is variable and enigmatic. Most reported cases of IBD that arise after solid organ transplant (SOT) are discovered in the setting of hepatic orthotopic transplantation for end-stage primary sclerosing cholangitis (PSC). PSC is a progressively destructive immune disease that primarily affects the hepatobiliary system, occurs in the young and middle aged, and is often associated with IBD, especially ulcerative colitis.<sup>1</sup> IBD is diagnosed in approximately 70% to 80% of patients with PSC, while 1.4% to 7.5% of patients with IBD are at risk for development of PSC during their lifetime.<sup>2</sup> Extensive ulcerative colitis without rectal involvement frequently develops in

patients with IBD and PSC. These patients also tend to have backwash ileitis, carry an increased risk of CRC, are at greater risk for pouchitis after J-pouch creation, and have diminished survival compared with IBD patients without PSC.<sup>1-3</sup> Therefore, IBD/PSC patients could represent a specific phenotypic entity that is distinct from that of individuals with chronic colitis.<sup>4</sup> A liver transplant is the treatment of choice in patients with advanced PSC with evidence of hepatic failure. Of all liver transplant cases, 6% to 10% are performed in the setting of PSC, and transplant provides these patients an excellent chance of survival at 5 years.<sup>1</sup> However, the impact of transplant on coexisting IBD is poorly studied.<sup>5</sup>

### Development of De Novo IBD and Worsening of Preexisting IBD After Liver Transplant

In some patients, IBD develops posttransplant.<sup>6-16</sup> Such de novo IBD may be either ulcerative colitis or Crohn's disease. The incidence of de novo IBD after SOT is approximately 206 cases per 100,000 patients per year, which is higher than that found in the general population.<sup>8</sup> De novo posttransplant IBD also has been demonstrated in children.<sup>12</sup> Although the incidence of IBD is higher posttransplant in patients who received a liver transplant for PSC, it has been described following renal, cardiac, and hematopoietic stem cell transplants as well as after a liver transplant performed for autoimmune hepatitis, primary biliary cirrhosis, and hepatitis B virus infection.<sup>13,15</sup>

The rate of exacerbation of preexisting bowel disease after transplant in patients who are not placed on immunosuppressive therapy posttransplant ranges widely, from 0% to 86%. Studies show that most of these patients require corticosteroid treatment or colectomy for medically refractory bowel disease.<sup>17-20</sup> Other researchers report that IBD may regress posttransplant.<sup>17,18,21-33</sup> Moncrief and colleagues found that only 26.5% of their population cohort had worsening of preexisting bowel disease posttransplant.<sup>27</sup> Six patients (19%) underwent colectomy, and no predictors were identified for this outcome. Navaneethan and colleagues recently reported that among 86 patients with IBD and PSC requiring liver transplant, IBD severity was lower posttransplant, and the patients had an even lower rate of colectomy.<sup>32</sup>

### Risk Factors for Development of De Novo IBD and Worsening of Preexisting IBD After Liver Transplant

Risk factors associated with the development of de novo IBD and worsening or reactivation of preexisting IBD after SOT are summarized in Table 1. De novo IBD

**Table 1.** Associated Risk Factors for the Development of De Novo IBD and Worsening or Reactivation of Preexisting IBD After SOT

De Novo IBD	Preexisting IBD
Autoimmune process; alterations to DAMPs or PAMPs	Cigarette smoking
Presence of CMV (positive donor and negative recipient of SOT)	Active IBD at the time of SOT
Use of tacrolimus post-SOT	Short interval between diagnosis of IBD and SOT
	Use of tacrolimus post-SOT
	Infectious colitis (ie, <i>Clostridium difficile</i> infection)

CMV, cytomegalovirus; DAMPs, damage-associated molecular patterns; IBD, inflammatory bowel disease; PAMPs, pathogen-associated molecular patterns; SOT, solid organ transplantation.

appears to be related to an autoimmune process. Alterations to damage-associated molecular patterns or pathogen-associated molecular patterns have been implicated in the development of this clinical entity.<sup>10</sup> Some studies have also suggested that the presence of cytomegalovirus (CMV) in the donor organ could be involved in the development of de novo IBD posttransplant.<sup>14,16</sup> CMV also could affect epithelial barrier function as well as the mucosal immune system, both of which are factors in the development of IBD.<sup>16</sup> Tacrolimus therapy may be associated with de novo IBD. In a study of 14 patients in whom new-onset IBD developed after surgery, 71% were receiving tacrolimus therapy at the time of diagnosis.<sup>8</sup> Other researchers have also suggested that tacrolimus can increase IBD activity post-liver transplant, presumably because of its effect in reducing interleukin-2-dependent generation of regulatory T cells.<sup>23,31</sup>

Studies suggest that advanced PSC requiring liver transplant is associated with relatively mild inflammation of the bowel pretransplant,<sup>32,34</sup> but it is unclear whether the evolution of IBD is modified posttransplant. Active bowel inflammation at the time of organ transplant and a short interval between diagnosis of IBD and liver transplant have been considered risk factors for worsening bowel disease in the posttransplant period.<sup>17,31</sup> In addition, although there is evidence that cigarette smoking may have a protective effect in ulcerative colitis, active cigarette use at the time of liver transplant may be associated with reactivation of bowel disease posttransplant.<sup>19</sup> Despite these findings, other studies have shown that neither IBD activity nor immunosuppressant or corticosteroid use prior to liver transplant predicts posttransplant evolution of IBD.<sup>19,25,27</sup> Compromised humoral and cellular immunity, associated with liver cirrhosis, as well as incarceration of lymphocytes in the cirrhotic liver may explain why patients with severe PSC have milder colitis.<sup>34,35</sup> Furthermore, posttransplant,

the better health of the new liver may be, in part, due to a shift of an immune system burden to the bowel.

### Differential Diagnosis of Diarrhea After Liver Transplant

Approximately 43% of patients present with diarrhea after liver transplant or hematopoietic stem cell transplant.<sup>36,37</sup> Management includes studying stool samples to evaluate for infectious colitis and performing colonoscopy with biopsies to rule out graft vs host disease, CMV, neoplasia, and medication effect. Both immunosuppressive agents and antibiotics can lead to drug-induced diarrhea. Mycophenolate mofetil has been more commonly associated with diarrhea when compared with other immunosuppressants in several studies. A study by Arslan and colleagues found that 11.6% of cases were associated with mycophenolate mofetil.<sup>38</sup> In addition, antibiotics commonly used in the posttransplant period alter the gut flora and lead to diarrhea. It is also important to assess for *Clostridium difficile* infection, which is a common cause of exacerbation of IBD during the pre- and posttransplant periods.<sup>39</sup>

### Management Considerations for De Novo IBD and Preexisting IBD After Liver Transplant

Management considerations for patients with preexisting IBD or de novo IBD after SOT are presented in Table 2. Systemic corticosteroid therapy, azathioprine, mesalamine (also known as mesalazine), and anti-tumor necrosis factor therapy such as infliximab (Remicade, Janssen) are possible treatment modalities in new-onset IBD after transplant surgery.<sup>16</sup> Although mycophenolate mofetil is efficacious as immunosuppressive therapy post-SOT, its role in IBD is unclear.<sup>40</sup> Budesonide has been shown to induce remission of terminal ileitis and inflammation of the colon with fewer systemic side effects than conventional corticosteroids in the nontransplant IBD patient and is an effective steroid-sparing agent. In the liver transplant patient already receiving systemic immunosuppression, budesonide can be considered first-line therapy for de novo posttransplant IBD as an approach to spare the use of systemic steroids. Although it has not been proven in large randomized, controlled trials, this approach has been effective in case series.<sup>11</sup> Of note, patients with de novo IBD have a better therapeutic response rate with lower colectomy rates than patients whose preexisting IBD flares after surgery.<sup>16</sup>

The most effective medical management strategy posttransplant in patients with PSC and preexisting IBD is unknown. The induction and maintenance of IBD remission postoperatively in patients with a known history of IBD preoperatively can often be challeng-

**Table 2.** Management Considerations for Patients With Active IBD and Immunosuppression for SOT

De Novo IBD	Preexisting IBD
Evaluation and treatment for <i>Clostridium difficile</i> infection	Evaluation and treatment for <i>C difficile</i> infection
Budesonide for cecal and ascending colon inflammation	Cyclosporine
Corticosteroids (after weighing the risks and benefits of prolonged use)	Corticosteroids (after weighing the risks and benefits of prolonged use)
Azathioprine (2-2.5 mg/kg per day)	Azathioprine (2-2.5 mg/kg per day)
Mesalamine	Consideration of preemptive use of oral mesalamine to prevent relapse of IBD
Anti-tumor necrosis factor- $\alpha$ therapy (infliximab)	Anti-tumor necrosis factor- $\alpha$ therapy (infliximab)
Proctocolectomy with or without restorative J pouch	Proctocolectomy with or without restorative J pouch

IBD, inflammatory bowel disease; SOT, solid organ transplantation.

ing.<sup>17,18,21-28,41,42</sup> Studies show that the majority of these patients may require colectomy for medically refractory bowel disease.<sup>17-20</sup> In 1 case report, a patient developed fulminant colitis that led to emergency colectomy despite treatment with 3 immunosuppressants (tacrolimus, mycophenolate mofetil, and prednisone).<sup>43</sup>

Immunosuppressive therapy, used in transplant medicine, may play a role in the evolution of IBD after surgery. Retrospective studies have found that tacrolimus utilized to prevent organ rejection posttransplant may be associated with IBD reactivation postoperatively.<sup>17,20,31</sup> Cyclosporine, however, does not appear to influence IBD evolution posttransplant and may be a preferred therapeutic option to prevent organ rejection.<sup>18,31</sup> The effect of tacrolimus could be due to its ability to suppress interleukin-2, thus generating T-regulatory lymphocytes and intestinal permeability alterations, which result in enhanced exposure of intestinal mucosa to the immune system.<sup>17,31,44</sup> Azathioprine appears to be associated with protection from IBD posttransplant.<sup>17,28</sup> Corticosteroid use posttransplant also may be associated with favorable effects on IBD evolution, including a decreased risk of colectomy.<sup>27,45</sup> However, the beneficial effects of corticosteroid therapy should be weighed against any adverse effects from prolonged use and its lack of efficacy as a maintenance regimen in patients with IBD. Preemptive therapy with oral mesalamine administered posttransplant has been shown to prevent IBD relapse.<sup>31</sup> No observational studies of patients with IBD who received SOT other than liver transplant are available, but it may be reasonable to extrapolate from findings of IBD outcomes

in liver transplant recipients and apply them to patients with IBD who received other SOT.

### Special Considerations

**Colorectal Cancer Risk** As management of patients with IBD and SOT with immunosuppressants continues to evolve, so too does CRC surveillance, with advancements in endoscopic techniques.<sup>46</sup> Patients with IBD and PSC who subsequently receive a liver transplant and have an intact colon at the time of transplant should be evaluated separately from those with IBD and PSC who had a previous partial colectomy at the time of transplant, and separately still from those patients with IBD who receive a liver transplant for reasons other than PSC.<sup>47,48</sup> The incidence of CRC in patients with IBD and PSC and also a liver transplant who have an intact colon varies from 0 to 43.5 per 1000 persons per year.<sup>5</sup> In patients with PSC and preexisting IBD who have had a liver transplant, as well as patients in whom de novo IBD developed after liver transplant, CRC is typically localized to the cecum and ascending colon.<sup>49</sup> The distribution of neoplasia in the right colon, which is similar before and after liver transplant, suggests a cytotoxic and hydrophobic effect of biliary acid on colonic mucosa.<sup>50</sup> Surgical management and chemotherapy can be safely recommended for treatment due to efficacy and favorable outcomes.<sup>51</sup>

Some evidence suggests that posttransplant immunosuppressive therapy may lead to an increased CRC risk in patients with liver transplant,<sup>52</sup> but other researchers have not demonstrated such an association.<sup>53</sup> Studies also suggest that the duration of IBD evolution, and not the liver transplant, is associated with an increased risk of CRC.<sup>20</sup> Both PSC and colitis can increase the risk of CRC development, suggesting the need for a strict surveillance regimen in the posttransplant period.<sup>54</sup> It has been reported that patients with PSC who require liver transplant generally have less histologic and endoscopic bowel inflammation, for which they require relatively less corticosteroid therapy or immunosuppression; proceed to colectomy less often than their counterparts with milder PSC; and have a lower incidence of CRC and dysplasia.<sup>32</sup>

Patients with IBD and PSC can present with minimal inflammatory response and a subclinical prolonged phase, which can lead to underestimation of their CRC risk.<sup>32</sup> High-grade dysplasia and colonic adenocarcinoma have been demonstrated even in clinical remission in patients with IBD and PSC who received a liver transplant.<sup>41</sup> A retrospective study conducted by Hanounch and colleagues found that CMV infection led to an increased risk for the development of posttransplant CRC in patients with IBD and PSC,<sup>53</sup> but this finding has not been confirmed in prospective studies. Loftus and colleagues found a 4.4 times higher rate of CRC in patients with a liver transplant compared with a historic cohort of patients with PSC

and IBD who did not undergo liver transplant.<sup>3,5</sup> The European Association for the Study of the Liver advises annual colonoscopy in IBD/PSC patients after liver transplant.<sup>20,55</sup>

**Venous Thrombosis** Thrombotic events are frequent in patients with IBD and PSC compared with patients who have PSC alone. Joshi and colleagues found a higher crude incidence of thrombotic events in an IBD/PSC group (19%) compared with a group of patients with PSC alone (2%).<sup>19</sup> The increased risk of thrombosis may be due to a hypercoagulable state caused by chronic inflammation of the bowel as opposed to the chronic inflammation caused by PSC.<sup>56</sup> This risk is of particular importance in patients with IBD and PSC who receive a liver transplant, in whom maintaining the integrity of vascular sutures and the patency of the vascular anastomosis is mandatory.

### Conclusions

IBD in association with SOT is infrequent and of unknown cause but is a challenge both to diagnose and to manage. The development of de novo IBD should be considered as a possible cause of diarrhea in post-SOT or hematopoietic stem cell transplant patients after appropriate workup is performed to rule out other causes. For patients with preexisting IBD who receive a liver transplant, the risk of proceeding to colectomy appears to be related to the severity of IBD prior to transplant. Patients with PSC and colitis who undergo liver transplant are at high risk for CRC and should be surveyed carefully.

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