

Management of Biliary Complications Following Orthotopic Liver Transplantation

Andrew E. Scanga, MD, and Kris V. Kowdley, MD

Corresponding author

Kris V. Kowdley, MD

Division of Gastroenterology, Department of Medicine, University of Washington Medical Center, Box 356174, 1959 NE Pacific Street, Seattle, WA 98195-6174, USA.

E-mail: kkowdley@u.washington.edu

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Biliary complications are a major cause of morbidity following orthotopic liver transplantation with an overall incidence between 11% and 25%. The most common complications are biliary leaks, strictures, and stones. These complications have an impact on graft survival, length of hospital stay, recovery, and overall cost of care. Therefore, knowledge of these complications and their management is important to the practicing gastroenterologist. Historically, biliary complications after liver transplantation have been managed surgically. However, with the growth of therapeutic endoscopic and percutaneous radiologic methods, most of these complications can now be managed less invasively. This article focuses on the incidence, timing, mechanism, and endoscopic management of biliary leak, strictures, stones, sludge, casts, and sphincter of Oddi dysfunction following liver transplantation.

Introduction

Complications involving the biliary tract are a major source of morbidity in liver transplant recipients. The overall incidence of biliary complications after orthotopic liver transplantation (OLT) has been reported to be between 11% and 25%, with lower rates reported in more recent years [1–4]. Complications are generally categorized as “early” or “late” based on whether they occur within 3 months or more than 3 months after OLT. In general, bile leaks tend to occur in the early post-OLT period, whereas strictures tend to occur later. Although biliary complications may develop at any time following OLT, two thirds occur within the first 3 months (Table 1)

[3]. Biliary complications can be classified as bile leaks, biliary strictures, biliary stones or debris, or sphincter of Oddi dysfunction (SOD). Strictures may be further subdivided as anastomotic or nonanastomotic. In the following sections, we review the different biliary complications, their causes, and management options, with an emphasis on recent data.

The type of biliary reconstruction used to reconstitute the biliary tract has an impact on the type and frequency of biliary complications. Two common methods exist for reconstructing the biliary system. One is through a choledochocholedochostomy (CC) with or without placement of an indwelling T-tube. In this method, the native common bile duct is joined to the graft duct, usually end to end. The other type of biliary anastomosis is a Roux-en-Y choledochojejunostomy (CJ), in which the donor duct is connected to a limb of small bowel. The presumed benefit of a CC reconstruction is that the normal anatomy is preserved, leaving an intact sphincter of Oddi, which is thought to decrease the risk of cholangitis; furthermore, noninvasive access to the biliary tract is possible through endoscopic retrograde cholangiopancreatography (ERCP). CJ is usually performed in cases of pre-existing biliary tract disease (such as primary sclerosing cholangitis [PSC]), prior biliary surgery, size discrepancies between donor and recipient ducts, or occasionally to revise complications of a CC reconstruction [5]. CC can be performed side to side or end to end with or without a T-tube. The benefits of T-tube placement include the ability to monitor bile flow and perform cholangiograms easily and be able to decompress the biliary tract quickly in cases of downstream obstruction. A theoretical benefit of this method is that it prevents anastomotic strictures. The routine use of T-tubes has decreased significantly over the past two decades because of their lack of clear benefit. The specific types of biliary complications, natural history, and current management are described in the following sections.

Bile Leaks

Bile leaks are a relatively common complication following OLT, with an incidence ranging from 2% to 21%. The

Table 1. Post-OLT biliary complications

Type of complication	Incidence (OLTs performed, %)	Average time to presentation following OLT, mo
Bile leak	2–21	<3
Biliary stricture	4–16	5–8
Anastomotic stricture	3.4–12.6	5–8
Nonanastomotic stricture	0.5–9.6	3.3–5.9
Biliary stones, sludge, and casts	3.3–12.3	19.2
SOD	2–3.5	3

mo—months; OLT—orthostatic liver transplantation; SOD—sphincter of Oddi dysfunction.
(Data from [2–4,6–11,24,28,29,45].)

majority of published articles report rates of 12% or less [2–4,6–10]. Bile leaks are most common in the early postoperative phase (within 3 months) [3,4,6,11]. The explanation for the early occurrence may be that most leaks appear to be related to perfusion abnormalities. Roughly the lower two thirds of the common bile duct receives its blood supply from the vasculature around the duodenum, whereas the upper third receives its blood supply from the right hepatic artery. Transection of the donor duct at harvest eliminates the lower blood supply, thus leaving the distal end of the transplanted duct vulnerable to ischemia, which can lead to necrosis and leaks early in the postoperative course [5]. This complication generally occurs at either the anastomotic site or higher up in the donor duct. Most leaks occur at the anastomosis, from the cystic duct remnant or, when T-tubes are used, from the T-tube exit site. Late bile leaks appear to be almost exclusively related to elective T-tube removal [3]. The presence of ischemia in the biliary tract is an important factor that influences outcomes in patients with biliary leaks and other biliary complications. In our experience, biliary leaks due to ischemia can be more difficult to treat than those due to technical issues or T-tube removal because the underlying cause is not resolved with endoscopic or percutaneous measures.

The risk of bile leak is not related to the method of biliary reconstruction except with the use of T-tubes, which are generally employed in the setting of a CC. The risk of bile leak is also unrelated to use of side-side or end-side anastomosis [2,3]. A prospective randomized trial and a retrospective study showed no significant difference between these two methods [12,13].

T-tube use with a CC, however, is associated with an increased risk of bile leak. Bile leaks related to T-tube removal occur at the exit site from the duct created for the percutaneous limb of the tube. Four randomized studies and several retrospective studies have examined the risks and complications of T-tube use in OLT recipients. The largest trial, from France, randomized 180 patients to CC anastomosis with or without a T-tube. The overall rate of complications was higher in the T-tube group (33.3% vs 15.5%, $P < 0.005$). The estimated hazard ratio was 1.96 (95% CI, 1.22–3.17). Cholangitis was the next

most common complication, with an overall incidence of 11.1%; the rate was higher in the T-tube group compared with the group without a T-tube (10% vs 2.2%, respectively). Seventy-eight percent of these biliary fistulae were located at the T-tube exit site. A trend toward increased overall patient survival was noted in the group without a T-tube (80.1% vs 72.8%), although the difference was not statistically significant [14]. In a second study, comprised of 60 patients in England who were randomized to CC with T-tube versus CC without T-tube placement, no overall difference was observed in the rate of biliary complications (five vs six patients, respectively). One bile leak occurred in the T-tube group, which resulted from accidental T-tube dislodgement. The rest of the complications in the T-tube group were due to bile duct stricture or cholangitis. All of the six complications in the no T-tube group were related to stricture [15]. In a more recent randomized trial of 84 patients who received a CC with T-tube versus without T-tube placement, an overall high incidence of biliary complications was observed in the T-tube group of 75% (21 of 28) and only 14.8% (4 of 27) in the non-T-tube group ($P < 0.0001$). Ten of the T-tube patients developed leaks following T-tube removal. A cost analysis was also performed, showing that the cost of treating the complications in the T-tube group was double that of the no T-tube group [16••]. A fourth retrospective study included a subset of patients who were randomized to either CC with T-tube or without T-tube placement. The authors discontinued the study after enrolling only 21 patients because four bile leaks occurred in nine patients with a T-tube versus none in the group without a T-tube. In the retrospective portion of the study of 90 patients, more complications were reported in cases with a T-tube than in those without (24% vs 12%), with leaks being more common in the T-tube group and strictures in the other group. These differences again did not achieve statistical significance [17]. Several other retrospective studies have described an increased risk of biliary complications with the use of T-tubes, with bile leakage reported as the most common complication [13,18–20]. Although most of these studies lacked sufficient statistical power, the combined data suggest that T-tubes should not be used routinely. By

contrast, investigators from one study asserted that CC without T-tube use had a higher incidence of conversion to CJ due to stricture formation [13].

The diagnosis of a bile leak after OLT is usually made during the work-up of abnormal liver function tests, clinical evidence of peritonitis, or following identification of fluid collections seen on imaging studies. Cholangiogram either by percutaneous cholangiography (PTC) or endoscopic retrograde cholangiography (ERC) is considered the gold standard for the diagnosis of bile leaks. However, two studies have reported that ERC only detected 84% and 87% of bile duct leaks that were clinically suspected and/or found on hepato-iminodiacetic acid (HIDA) scan [8,10]. The lower sensitivity observed in these studies can be questioned because clinical suspicion is sometimes incorrect and HIDA scan results may be falsely positive. The main advantage of HIDA scan is that it is noninvasive compared with ERCP. More recently, magnetic resonance cholangiopancreatography (MRCP) has been studied as a mode of detecting biliary complications after OLT but has not been effective in diagnosing leaks [21–23]. PTC or ERC have an advantage in the evaluation of bile leaks in that therapeutic intervention can be performed at the time of diagnosis. ERC has the additional benefit in the treatment of bile leaks of eliminating downstream obstruction at the level of the biliary sphincter through biliary sphincterotomy.

CC bile leaks can usually be managed successfully without surgical intervention with endoscopic or interventional radiology. In several retrospective reviews nonoperative management has been reported to be successful 75% to 100% of the time [4,7–10,24–26]. On average, resolution of the defect requires 4 to 5 weeks [4,26]. Endoscopic management generally consists of stent placement with or without biliary sphincterotomy. Both nasobiliary drains and indwelling endobiliary stents have been used for treatment of bile leaks. Nasobiliary drains provide easy access to the biliary tract for cholangiography and can easily be removed without endoscopy but are inconvenient and uncomfortable to the patient. Two studies have examined the use of sphincterotomy alone and have reported success rates of 88% (22 of 25) and 100% (5 of 5) respectively [9,27]. For small leaks, sphincterotomy alone may be sufficient because a second ERCP would not be needed to remove the stent. However, stent placement is advocated for larger leaks and in strictures to determine if the stricture is a significant contributing factor to the leak [26]. Leaks with biliomas can be treated effectively with endoscopic stenting by facilitating flow into the duodenum. If a bilioma does not resolve or becomes infected, the addition of a percutaneous drain placed under CT guidance or by ultrasound may be indicated. In persistent leaks or large ductal defects, surgical revision is indicated. If possible, revision to the CC anastomosis or conversion to CJ can be performed.

Biliary Strictures

Strictures are the most common biliary complication following OLT, with an incidence between 4% and 16% [3,4,7,28,29]. In general, strictures can occur at any point in the postoperative course; the mean interval before development of strictures is approximately 5 to 8 months after OLT, with a range between 0.25 and 86 months [3,4,7,9,24,28,29]. Biliary strictures are commonly classified as anastomotic or nonanastomotic. Nonanastomotic strictures (NAS) are usually either intrahepatic or in the donor duct proximal to the anastomosis. NAS comprise 10% to 25% of all stricture complications, with an incidence between 0.5% and 9.6% of OLTs performed [3,4,7,29,30]. These strictures tend to occur earlier than anastomotic strictures, with a mean time to stricture development of 3.3 to 5.9 months reported in two studies [29,30]. The longest time interval between OLT and development of stricture was 86.7 months [29].

The method of biliary reconstruction may also affect the incidence of strictures. The majority of strictures have been associated with choledochojejunostomy or hepaticojejunostomy (50% vs 85%); therefore, these types of anastomosis have been considered risk factors for stricture formation [3,7,28]. However, these findings may have been due to selection bias because the overall range in incidence of strictures in patients with CJ reconstructions is only from 3.5% to 5.4% [3,4,28]. Placement of a T-tube does not appear to be associated with stricture formation. The four randomized studies of T-tube placement did not find a difference between the rate of stricture formation with or without a T-tube [14–17]. One retrospective study found a lower rate of anastomotic strictures among patients with T-tubes compared with those without T-tubes (7 of 124 [6%] vs 19 of 103 [18%]; $P < 0.05$) [13].

The first indication of biliary obstruction is frequently an asymptomatic elevation in serum liver biochemical test results in a cholestatic pattern. Ultrasonography is often the next step in the diagnostic evaluation because it is relatively low in cost, safe, rapid, and able to provide additional information about patency of the major vessels of the liver. Dilated bile ducts seen on ultrasound can support the diagnosis of an obstruction. However, a negative ultrasound may lack sensitivity to exclude biliary obstruction among OLT recipients. In one study of 144 patients, the sensitivity and specificity of ultrasound compared with cholangiography were 66% and 76%, respectively [31]. In another study, among 101 patients, the sensitivity and specificity of ultrasonography to identify biliary obstruction were 38% and 98%, respectively [32]. MRCP is an increasingly used noninvasive imaging modality for evaluation of strictures. In the setting of OLT, three small studies ($n=12-25$) found MRCP to be 87.5% to 100% sensitive and 92.3% to 100% specific for identification of strictures [21–23]. The disadvantages of MRCP are that it is expensive and that therapeutic intervention is not possible. Therefore, MRCP is often used as a screening test in patients with greater

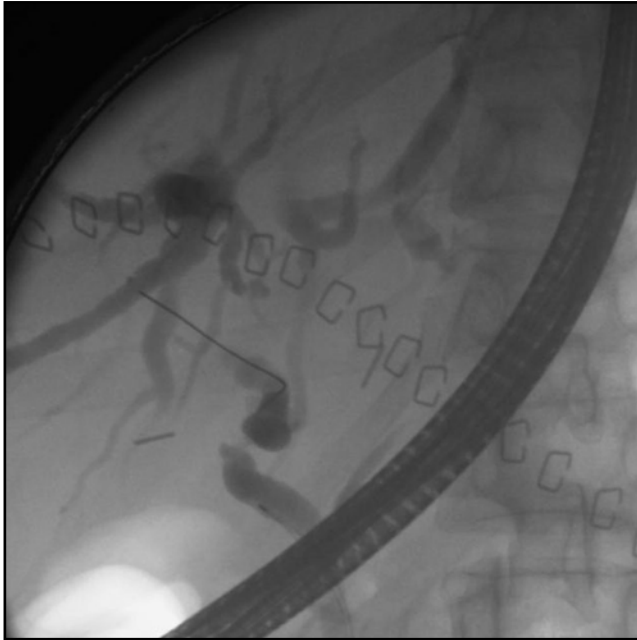


Figure 1. Radiographic image of anastomotic stricture.

risk of procedural complications. Direct cholangiography is usually the modality of choice to evaluate suspected biliary strictures as intervention can also be provided at the same time as confirmation of diagnosis. ERC is preferable to PTC as the first-line test because it is less invasive and allows for internal drainage. Cholangiography may occasionally falsely lead to suspicion of a biliary stricture if a large size discrepancy exists between the donor and native ducts; clinical experience and functional assessment of possible stricture (eg, via assessment of resistance to passage of a stone-extraction balloon and drainage of contrast during fluoroscopy) are necessary prior to stent placement or balloon dilation in such situations. Historically, management of strictures has predominantly been surgical, using either revision of the primary anastomosis or conversion to a CJ. Over the past decade and a half, endoscopic and percutaneous methods have become the primary modes of management, with surgery as second-line therapy when other measures have failed. Endoscopic therapy usually includes balloon dilation followed by stent placement. The commonly used stents are plastic and removable and exchanged every 3 months until stricture resolution. Self-expandable metal stents have been used on occasion but should be employed only in unusual circumstances because their long-term efficacy and safety have not been definitively established in benign strictures. One study reviewed the outcomes after placement of self-expandable stents in 12 patients with strictures (6 were nonanastomotic). The authors reported that eight patients had patent stents at the end of a 60-month follow-up period; however, three patients died during the study period and four others needed additional procedures to maintain stent patency. Seven of the 12 patients had complications of obstruction

from recurrent strictures within the stents due to mucosal hyperplasia and stone formation [33].

Anastomotic strictures

Anastomotic strictures generally result from scar formation after healing of the anastomosis, local ischemia, or suboptimal surgical technique (Fig. 1) [5]. CC anastomotic strictures are usually managed by endoscopy with an overall success rate between 74% and 100% reported in the majority of studies and sample sizes ranging from 18 to 143 subjects [7,9,10,24,29,34–38]. In most studies a combination of balloon dilation and stenting or stenting alone has been used either with single or up to three 7-Fr to 11.5-Fr plastic endoprostheses. The stents were generally exchanged every 3 months for an average of 1 year with a range of 3 months to up to 2 years [9]. In the largest study, risk factors for recurrence after stent removal included late initial presentation, presence of a bile leak, and T-tube use [38].

In one study, balloon dilation alone was used for anastomotic strictures in 29 patients. Nine patients did not need any further intervention; 10 needed a median of two repeat balloon dilations, and 10 subsequently needed stent placement. Of those who needed repeat dilation, the second procedure was performed at a median of 14 weeks [35]. Similar results were observed in another study, in which 71% of 65 anastomotic strictures originally treated with balloon dilation needed stent placement due to persistence or early recurrence. A median of two balloon dilations and one stent placement was required [29]. These data suggest that balloon dilation alone may not be sufficient for therapy of anastomotic strictures. In addition, earlier identification and treatment of strictures may increase the likelihood of successful response to endoscopic therapy [4].

Treatment of CJ anastomotic strictures requires a percutaneous approach because of the difficulty of access to the biliary tract via ERCP in this setting. However, with the advent of double balloon enteroscopy, endoscopic intervention may become possible, as noted in one case report [39]. In general, PTC has a success rate between 50% and 75% [7,40,41].

Nonanastomotic strictures

Nonanastomotic strictures (NAS) are those that form proximal to the anastomosis in the extra- and intrahepatic donor biliary tract (Fig. 2). The distinction between NAS and anastomotic strictures is important, as their pathology, response to treatment, and outcomes, are different. Known risk factors for NAS include hepatic artery thrombosis (HAT), chronic ductopenic rejection, and ABO incompatibility. The importance of graft ischemia time as a risk factor for NAS has been clarified over the past two decades. In one study, among 188 patients, 31 ischemic-type strictures were identified in the absence of HAT, ductopenic rejection, or ABO incompatibility. Grafts

preserved with University of Wisconsin solution and a cold ischemia time of less than 11.5 hours had an incidence of NAS of 2%. When cold ischemia time exceeded 11.5 hours, the incidence rose to 35%. With use of Euro-Collins solution, the incidence of NAS was 24%, with cold ischemia time greater than 6.5 hours, compared with 2% with shorter ischemia times. No relationship was seen between NAS and type of biliary reconstruction, cellular rejection, or CMV [42]. Another study identified 72 of 749 liver transplant recipients who developed NAS. An association was found between NAS and longer warm and cold ischemic times; grafts of patients with NAS had increased cold ischemia time (8.7 vs 7.7 hours) and increased warm ischemia time (1.4 vs 1.2 hours) compared with those without NAS ($P < 0.01$). Other risk factors included HAT, PSC, and autoimmune hepatitis. Although patient survival did not appear to be affected, graft survival was diminished among those with NAS (RR=2.78, 95% CI 1.77–4.37). Two years after OLT, graft survival was lower among patients with NAS (54% vs 80%) [30]. Another study described a higher rate of strictures among recipients who received organs from patients with cardiac death compared with those from patients with brain death (33% vs 10%, respectively, $P = 0.0001$) and a trend toward more NAS (13.8% vs 8.0%, respectively, $P = 0.007$) [43••].

In the setting of PSC, NAS may be due to disease recurrence or ischemia, although the cholangiographic features may be similar with either cause. In one study of 32 patients with PSC who underwent OLT, six had intrahepatic strictures and only one had PSC determined by histologic examination at his second transplant. The other five all had evidence of vascular compromise [44].

Endoscopic management of NAS has a lower success rate than in anastomotic strictures; only 50% to 75% of patients have a long-term response to endoscopic therapy [8–10,29,37]. In one study of 12 NAS compared with 10 anastomotic strictures, ERCP was successful for NAS in 73% of patients. Patients with NAS usually underwent 4- to 6-mm balloon dilation (compared with 6 to 8 mm for anastomotic strictures) followed by 10- to 11.5-Fr stent placement exchanged every 2 to 3 months. The median time of therapy was 185 days for the NAS group versus 67 days for the anastomotic group ($P = 0.02$) [37]. Investigators from another study comparing the two types of strictures also found that the NAS group required significantly more ERCPs, dilations, and stent placements than did the anastomotic stricture group [29]. Overall, the studies used some combination of balloon dilation, stent placement, and occasionally sphincterotomy, as described in the management of anastomotic strictures.

Biliary Stones, Sludge, and Casts

Biliary stones and sludge are relatively common following OLT, with an incidence between 3.3% and 12.3% [7–10,24,45]. Sludge, stone, and cast formation have been



Figure 2. Radiographic image of nonanastomotic stricture above the bifurcation in the left hepatic duct.

postulated to be related to ischemia, bacterial infection, mucosal damage, and obstruction [1,5,46]. An association between ischemia and biliary strictures has been reported. Combined data from three studies indicate that stones, sludge, and casts were present in 33% to 45% of cases with strictures and that strictures were present in 53% to 90% of cases with stones or sludge [7,9,10]. In one study of 367 patients, stones were shown to occur at a median of 19.2 months following OLT and after documented clearance had a 17% recurrence rate at follow-up ERCP at a median of 5.9 months [9]. In this same study, ERCP was successful at clearing the debris during the first session in 59% of cases; two sessions were required in 24%, and three or more sessions were needed in the remaining 17%. In general, ERCP is very successful at clearing stones and sludge, with success rates between 90% and 100% [7,8,10,24]. Biliary sphincterotomy is usually performed in this setting to facilitate stone clearance and to maintain bile duct patency.

By contrast, definitive therapy for biliary casts is more difficult to achieve. Two studies reported endoscopic success rates of 25% and 60% in removing casts [8,46]. Various combinations of sphincterotomy, balloon and basket extraction, stent placement, and lithotripsy are often necessary. Bilirubin is generally the main component of casts (10%–50%) in addition to cholesterol, bacteria, and bile acids as well as cellular debris. The presence of cellular debris has led to the postulation that cellular rejection is a risk factor in addition to the risk factors for stones and sludge [46,47].

Sphincter of Oddi Dysfunction

In four studies, the prevalence of SOD was between 2% and 3.5% [3,8–10]. SOD following transplant is usually

defined as a cholestatic pattern of laboratory abnormalities and a dilated recipient common bile duct. A proposed mechanism for SOD is that transection of the common bile duct results in a hypertonic sphincter due to denervation. One study compared five patients with suspected SOD with elevated biliary sphincter pressures measured through the T-tube with the measurements of control subjects, who either had undergone OLT but were not suspected of having SOD or simply had undergone a cholecystectomy with bile duct exploration. Four of the five patients had elevated sphincter pressures and infrequent phasic activity. One patient had low basal pressures with absent phasic activity [48]. Results from this study support the notion of denervation as the mechanism of SOD in the liver transplant population. Treatment of SOD with sphincterotomy and occasional stent placement is generally successful in 80% to 100% of cases [8,10,48]. If endoscopic therapy fails, conversion to CJ anastomosis is the second-line option.

Complications of Endoscopic Therapy

Endoscopic therapy is generally safe after transplantation. The complication rate per patient in seven different studies ranges between 3.1% and 23%, with only two studies reporting rates greater than 13% [7–10,24,35,37]. The reported complication rate per procedure ranges from 1.5% to 6% [8–10,35,37]. The two most common complications reported with ERCP are pancreatitis and post-sphincterotomy bleeding; the latter complication can usually be controlled at the time of endoscopy with local injection of epinephrine. Only one procedure-related death has been reported in a patient with numerous comorbidities who underwent stent placement for a stricture and died ultimately from hepatic necrosis [10]. Other complications of ERCP include bile leak, cholangitis, perforation from sphincterotomy, and stent migration. Proximal stent migration usually results in an obstructive picture and can be relieved by stent replacement. Distal stent migration is not usually problematic because the stent passes through the digestive system without much difficulty. However, occasionally distal stent migration may cause bowel complications. In one study, five patients with stent migration were observed to have colonic perforation, entero-enteric fistula, biliocolic fistula, and small bowel obstruction [49]. Distal migration caused perforation of the duodenum in another patient [9]. Another complication reported after OLT is pancreatic fistula, which developed in two patients who underwent stent placement for biliary fistula without sphincterotomy. In both cases the fluid being drained externally changed from a bilious appearance to a clear fluid with a high amylase content. Neither patient had pancreatitis or a pancreatic fistula on ERCP. Downsizing of the endobiliary stent resolved the pancreatic duct leak, suggesting that pancreatic fluid was migrating up the duct and externally out the fistula tract [50].

Conclusions

Biliary complications are common following OLT, with strictures and bile leaks being the most common complications. Based on recent reports, we can conclude that endoscopic therapy for management of biliary complications is safe, relatively noninvasive, and effective and has emerged as the initial modality of choice for diagnosis and therapy for most biliary complications in patients with CC. PTC and surgery should be reserved as second-line approaches if endoscopic therapy is unsuccessful or not possible for technical reasons.

Acknowledgments

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