Strategies to Improve Outcome after Transplantation of Extended Criteria Donor Livers

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Abstract

**Purpose of Review:** The incidence, pathogenesis and management of the most common biliary complications are summarized with an emphasis on non-anastomotic biliary strictures (NAS) and potential strategies to prevent NAS after orthotopic liver transplantation (OLT).

**Recent findings:** NAS have variable presentations in time and localization, suggesting various underlying pathogeneses. Early-onset NAS (presentation within 1 year) has shown to be largely related to ischemia-induced injury, whereas late-onset NAS (> 1 year after OLT) has more immune-mediated causes. Cytotoxic hydrophobic bile salts and impaired biliary bicarbonate (HCO$_3^-$) secretion may also play a role in the occurrence of NAS. Recently, insufficient biliary epithelial regeneration capacity after transplantation has also been suggested to be important in the pathogenesis of NAS. A potential strategy to prevent NAS can come from machine perfusion instead of classical static cold storage (SCS). While machine perfusion has been shown to be a better preservation method for the liver parenchyma, efficacy in preventing ischemic injury of the biliary epithelium is largely unknown.

**Summary:** The potential advantages of machine perfusion are very promising as it may provide better protection of the vulnerable bile ducts against ischemia/reperfusion injury. Clinical trials will be needed to demonstrate the impact of machine perfusion in reducing the incidence of biliary complications, especially NAS, after OLT.
**Introduction**

Despite an increase in the number of donor livers obtained from donation after circulatory death (DCD) in some European countries and the US in recent years, donation after brain death (DBD) remains to be the major source of organs for orthotopic liver transplantation (OLT) in most western countries. In general, patient and graft survival rates after DBD liver transplantation are higher compared to DCD liver transplantation, mainly because of an increased rate of biliary complications after DCD liver transplantation (1,2). However, biliary complications are also the most frequent and troublesome complication after DBD OLTs.

Biliary complications occur in 10-40% of the patients after OLT and have an important impact on graft survival, hospital readmissions, the need for reinterventions and the overall costs of care (3-5). Among the variety of biliary complications occurring after OLT, bile leakage and bile duct strictures (anastomotic and non-anastomotic) are the most common. Relative minor (and infrequent) biliary complications, such as sphincter of Oddi dysfunction, external compression by peribiliary cysts, neuroma or lymphoma’s, have also been reported (6,7). An overview of the various types of biliary complications, their incidence and management is provided in Table 1.

**Table 1. Biliary Complications after Liver Transplantation**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile duct strictures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Anastomotic</td>
<td>9-12%</td>
<td>- Endoscopic/Percutaneous dilatation or stenting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Roux-en-Y hepatico-jejunostomy</td>
</tr>
<tr>
<td>- Non-anastomotic</td>
<td>1-30%</td>
<td>- Endoscopic dilatation/stenting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- PTC drainage/ dilatation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Surgical resection of extrahepatic bile duct + Roux-en-Y hepatico-jejunostomy</td>
</tr>
<tr>
<td>Bile Leakage</td>
<td>2-21%</td>
<td>- Conservative therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- PTC drainage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Endoscopic stenting/sphincterotomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Nasobiliary drainage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Hepatico-jejunostomy</td>
</tr>
<tr>
<td>Bacterial cholangitis</td>
<td>10%</td>
<td>- Antibiotic therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Treat strictures if present</td>
</tr>
<tr>
<td>Common bile duct filling defects</td>
<td>6%</td>
<td>- Endoscopic removal</td>
</tr>
<tr>
<td>- Stones/Casts/Sludge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sphincter of Oddi dysfunction</td>
<td>0-7%</td>
<td>- Endoscopic sphincterotomy/stenting</td>
</tr>
<tr>
<td>External compression of biliary tract</td>
<td>Rare</td>
<td>- Surgical excision of cystic duct remnant</td>
</tr>
<tr>
<td>- Cystic duct mucocele</td>
<td></td>
<td>- Treat underlying lymphoma + endoscopic stenting</td>
</tr>
<tr>
<td>- Periductal lymphoma</td>
<td></td>
<td>- Amputation neuroma</td>
</tr>
<tr>
<td>- Periductal neuroma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinking of redundant bile duct</td>
<td>Rare</td>
<td>- Surgical resection and re-anastomosing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Endoscopic stenting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Roux-en-Y hepatico-jejunostomy</td>
</tr>
</tbody>
</table>

Abbreviations used: PTC: percutaneous transhepatic cholangiography.
In this review the most common biliary complications will be discussed with an emphasis on the pathogenesis of non-anastomotic biliary strictures (NAS) and on the potential preventive role of oxygenated machine perfusion, as a potential strategy to reduce the incidence of NAS after OLT. In this review we have used the term NAS for biliary strictures that can be found in the intra- or extrahepatic bile ducts of the donor liver in the presence of a patent (open) hepatic artery. The terms ischemic-type biliary lesions (ITBL) and ischemic cholangiopathy are also used in the literature for this type of injury.

**Bile leakage**

Bile leakage has been reported in 2-21% of the patients after OLT. It can be categorized as early and late events and may be anastomotic or non-anastomotic in site, i.e. occurring at the T-tube tract exit site or the cut surface of the graft in case of living donor or partial liver graft transplantation (5,6). Bile leakage can later result in biloma due to extravasation of bile into the hepatic parenchyma or the abdominal cavity. Depending on the size of the leakage and the patient being asymptomatic or symptomatic, bile leaks can be managed conservatively, non-surgically or surgically (8,9).

**Bile duct strictures (anastomotic and non-anastomotic)**

Bile duct strictures can be categorized into anastomotic strictures (AS) and non-anastomotic strictures (NAS). A combined presentation of both AS and NAS is not uncommon. Solitary strictures at the site of biliary anastomosis have been reported in 9-12% of patients after OLT (4,10,11), with the majority occurring within the first 12 months after OLT (4,5,10,11). Major predictive risk factors for development of AS include donor age, prior anastomotic bile leak, duct to duct anastomosis, and sex mismatch with a female donor/male recipient (4,5). Local ischemia caused by surgical techniques is believed to be the main underlying mechanism, leading to fibrotic scarring of anastomosis. To minimize the risk of local ischemia at the end of donor choledochal duct, the bile duct should remain surrounded by sufficient amount of tissue (3). Uncomplicated anastomotic strictures can generally be successfully treated with endoscopic or percutaneous dilatation/stenting (12,13). Resection of the stenotic anastomosis and construction of a Roux-en-Y hepatico-jejunostomy is indicated if non-surgical treatment fails (4,14). Recurrent AS, which occurs in approximately 20% of the cases, can still be treated effectively with dilatation/stenting (15).

In contrast to anastomotic strictures, NAS may occur at any location of the biliary tree (extrahepatic as well as intrahepatic), but is usually limited to the large bile ducts in a multifocal pattern. The reported incidence of NAS in patients receiving a DBD liver graft varies between 1 and 20% (10,16,17). Non-surgical treatments for NAS
are endoscopic dilatation/stenting, percutaneous transhepatic cholangiography with drainage and/or dilatation. In case of extrahepatic NAS, surgical resection of the diseased part and construction with a hepatico-jejunostomy can be successful (4,6). In up to 50% of the patients with NAS, retransplantation may be the only treatment option (4). Therefore, NAS is the most troublesome complication and is associated with high rates of morbidity, mortality and overall costs of care (18). In the current shortage of available donor livers for OLT, a better understanding of pathogenesis and better strategies to prevent NAS after transplantation are needed.

**Variable presentations of NAS**

Presentations of NAS vary extensively in anatomical localization and severity as well as in time of occurrence. Fifty percent of the cases of NAS present within the first year after OLT, constituting early-onset versus late-onset (>1 year after OLT) NAS (19). Early-onset NAS have shown to mostly occur around the hepatic bifurcation and common bile duct. In contrast to early-onset NAS, late-onset NAS is more frequently identified in the periphery of the liver, affecting small bile ducts in a more diffuse pattern (19). It seems that early-onset and late-onset NAS not only develop at different anatomical locations but that they are also associated with different risk factors. Retrospective studies have suggested that early-onset NAS is prominently associated with ischemia related injury whereas late-onset NAS have been more frequently associated immunological factors (19,20).

**Variable pathogenesis of NAS**

NAS is thought to have a multifactorial etiology, which can be grouped based on three relevant types of biliary injury; ischemia-related injury; immune-mediated injury; and cytotoxic injury caused by hydrophobic bile salts (3,21).

**Ischemia-Related Injury**

Prolonged ischemia time (>13 hours) during static cold storage has been identified as a main risk factor for the development of NAS (16,22). However, to reduce the detrimental impact of cold ischemia, the period of static cold storage has nowadays become shorter with an average of 8-10 hours (19). Oxygenation of biliary epithelial cells (cholangiocytes) is fully dependent on the hepatic artery, in contrast to the hepatocytes, which are oxygenated via both the hepatic artery and the portal vein. Hepatic artery thrombosis and stenosis may result in the development of massive bile duct necrosis after OLT (23). Moreover, injury of the peribiliary microvasculature has also been shown to have an important role in the occurrence of NAS after OLT (24). Thus, adequate flush out of the graft and the peribiliary vasculature with preservation fluid is crucial for effective preservation of the microvasculature and subsequently the bile duct. Some studies have suggested
that liver preservation with high-viscosity preservation fluids may lead to higher rates of biliary strictures, because of an insufficient flush out and preservation of the peribiliary microvasculature (25). However, it seems that perfusion with low-viscosity preservation fluid such as HTK solution is also not sufficient enough for an effective perfusion of the peribiliary microvasculature (26). Additional arterial back-table pressure perfusion may therefore be necessary for ample perfusion of the peribiliary microvasculature (27).

Another well-known risk factor for development of NAS is warm ischemia during organ procurement, especially during the period between cardiac arrest and cold perfusion in case of a DCD procedure. The incidence of NAS after OLT of livers from DCD donors is as high as 30%, which is much higher than the incidence of NAS after DBD OLT (1-20%) (17,28,29). The method of graft reperfusion during implantation has also been shown to have an impact on the occurrence of NAS. Retrograde reperfusion via the inferior vena cava while constructing the portal vein anastomosis has been associated with an increased risk of developing NAS, probably because of the relative warm ischemia of the bile ducts during implantation (30). Some investigators have advocated arterial reperfusion instead of portal vein reperfusion or simultaneous reperfusion via the portal vein and hepatic artery instead of sequential reperfusion; however, there is no strong evidence supporting any of these strategies. Initial reperfusion via the portal vein is mostly preferred because of its technical simplicity (31).

**Immune-Mediated Injury**

Many studies have suggested a role for immunological factors in development of NAS. For example, transplantation of ABO incompatible donor livers has shown to be associated with higher incidence of NAS (32). The reason for this immune-mediated biliary injury is thought to be the result of the existence of blood type antigens on the biliary epithelium of the donor bile ducts. As a result, ABO antibodies target these biliary epithelium cells (32,33). Moreover, pre-existing autoimmune diseases such as primary sclerosing cholangitis (PSC) are associated with a higher incidence of NAS (34). In addition, it has also been reported that a loss-of-function mutation in the chemokine receptor CCR5 (CCR5-Δ32) is related to the development of NAS (35,36). The CCR5 mutation has been associated with impaired attraction of regulatory T cells to the site of injury. Regulatory T cells reduce inflammation and suppress activation of potential harmful, self-reactive lymphocytes. The strong association between the CCR5 mutation and NAS could be explained by an increased inflammatory response of the host towards the biliary epithelium of the liver graft (35,36). The risk of developing NAS is even higher in patients transplanted for PSC who also have a CCR5-Δ32 mutation (36).
Cytotoxic Hydrophobic Bile Salts
In contrast to hydrophilic bile salts, which are cytoprotective, hydrophobic bile salts may cause injury to hepatocytes and cholangiocytes due to their detergent properties. The role of hydrophobic bile salts in the occurrence of NAS after transplantation can be explained by a couple of mechanisms; 1) insufficient flush out of bile from the bile ducts during organ procurement; 2) altered bile composition after OLT, leading to a relatively high biliary bile salt to phospholipid ratio; 3) intracellular accumulation of hydrophobic bile salts due to a disturbed cholehepatic shunt after OLT; and 4) an impaired biliary $\text{HCO}_3^-$ secretion after OLT. Studies have shown that early after transplantation, the composition of bile changes to a higher concentration of hydrophobic bile salts compared to phospholipids (37). This higher bile salt to phospholipid ratio may be explained by a different expression and function of the bile salt export pump (BSEP) and multidrug resistance protein 3 (MDR3) transporters (37). Disturbed protective micelle formation by a lower concentration of phospholipids allows injury of the cholangiocytes by hydrophobic bile salts, resulting in an increased incidence of NAS (38).

In addition to the elevated bile salt to phospholipid ratio, reuptake of bile acids by cholangiocytes as part of the cholehepatic shunt may be disturbed after OLT, causing accumulation of toxic bile salts inside cholangiocytes. This phenomenon has been explained by misbalance in function and/or expression of transporter responsible for reuptake of bile salts by cholangiocytes from the apical side (apical sodium-dependent bile acid transporter or ASBT) and the basolateral transporters responsible for secretion of bile salts into the peribiliary vascular plexus (organic solute and steroid transporters OSTα and OSTβ). This could lead to cellular accumulation of the hydrophobic bile salts and subsequently the development of intracellular injury (3).

Experimental studies have shown that biliary $\text{HCO}_3^-$ secretion prevents bile salt-induced cholangiocyte injury. By alkalizing the bile close to the apical membrane of the cholangiocytes, most of the hydrophobic bile salts become deprotonated and neutralized. Neutralizing of the hydrophobic bile salts protects the cholangiocytes against penetration of toxic bile salts (39,40). The main transporters in biliary bicarbonate secretion are the cholangiocyte Cl⁻/$\text{HCO}_3^-$ exchanger AE₂ and transporter cystic fibrosis transmembrane conductance regulator (CFTR), which are all adenosine triphosphate (ATP) dependent. Not only ATP levels but also the expression of these transporters is disturbed due to ischemia, which may lead to a diminished function of the biliary “$\text{HCO}_3^-$ umbrella” after transplantation (41).
Lack of regeneration: a new concept of pathogenesis of NAS

Recent retrospective studies on histological examinations of biopsies taken from the distal end of extrahepatic bile duct at the time of OLT have shown signs of severe injury characterized by biliary epithelial loss, mural stroma necrosis, and injury of the peribiliary vasculature (24,42). Despite the universal biliary epithelial injury of large bile ducts of donor livers (about 90%), only a minority of recipients develop NAS after OLT. This has brought up a new concept of pathogenesis of NAS based on insufficient regeneration and repair capacity of the biliary epithelium after OLT (43). More studies will be needed to investigate better the true relevance of this new finding and examine whether stimulation of the regenerative capacity of the biliary epithelium may result in a reduction of NAS.

Oxygenated machine perfusion: a strategy to reduce NAS?

As described before, NAS is associated with high rates of morbidity, mortality, and subsequently higher overall costs of care after OLT. It is therefore necessary to develop new strategies to reduce the occurrence of NAS. The potential strategies can be defined as reduction of biliary epithelial cell injury by; 1) reduction of ischemia induced injury; 2) reduction of cold induced injury; 3) enhancement of endogenous protective mechanisms (e.g. stimulation of the “HCO₃⁻ umbrella”) and 4) stimulation of regenerative strategies.

Recently, machine perfusion (MP) showed to be a more powerful preservation method than the current method static cold storage (SCS) (44). During MP, livers are perfused with an oxygenated (45) or non-oxygenated perfusion fluid (46), at either low temperature or normal body temperature. A relatively simple technique to “revitalize” grafts after the period of cold ischemia is end-ischemic hypothermic oxygenated machine perfusion (perfusion at 10-12° C) (47). A couple of studies have demonstrated that oxygenated machine perfusion can help organ recovery by improving cellular energy homeostasis. The restoration of mitochondrial function by oxygenated MP will result in increased intracellular concentration of ATP concentration and a reduction of the oxygen debt. This has been associated with less formation of reactive oxygen species after graft reperfusion and subsequent less cellular injury (47-49). Subnormothermic oxygenated machine perfusion (20° C) has also shown to have a beneficial role in recovery of the liver graft after transplantation (50). In all the above techniques the metabolism of the liver is limited due to low temperatures. Normothermic machine perfusion, on the other hand, allows the organ to have a full metabolism in a near physiological environment. In a recent study, the technical feasibility of normothermic machine perfusion was demonstrated in discarded human livers. In this study, a commercially available device (Liver Assist, Organ Assist,
Groningen, the Netherlands), was used for machine perfusion of the liver, using continuous portal perfusion and pulsatile arterial perfusion (45). Normothermic machine perfusion provides the opportunity to assess viability and function of liver grafts before OLT. So far, studies only have demonstrated that machine perfusion results in a better preservation of the liver parenchyma compared to SCS preservation. Although these results are very promising, it has yet to be established whether machine perfusion is also a superior preservation method for the vulnerable biliary epithelium compared to SCS. We postulate that during machine perfusion the status of the biliary epithelium could be investigated by measuring biomarkers of bile duct injury in perfusate and/or bile. For example, detection of gamma-glutamyl transferase (gamma-GT) and lactate dehydrogenase (LDH) in bile samples during machine perfusion can be correlated with the degree of biliary epithelial injury. In addition, a recent study reported that cholangiocyte microRNA's can be used as a specific marker to predict the development of NAS after OLT. MicroRNA's are stable and can be easily detected in perfusate, bile or tissue during machine perfusion prior to OLT (51).

Moreover, machine perfusion also provides an opportunity to improve organ viability. During machine perfusion, organs can be treated with therapeutic agents, such as hydrophilic bile salts (i.e. ursodeoxycholic acid and nor-ursodeoxycholic acid) to substitute hydrophobic bile salts and increase the "HCO₃⁻ umbrella" function (Figure 1, next page) (39,40). The benefits of such strategies, however, have to be proven in future studies.

Summary

Biliary complications remain to be a burden in liver transplantation. Biliary leakage and stricture formation are the most frequent types of biliary complications. While bile leakage and AS can usually be managed successfully with non-surgical or surgical approaches, NAS are frequently therapy resistant and leave long-term sequelae. NAS have variable presentations in time and localization, suggesting different underlying mechanisms and pathogeneses. Early-onset NAS has shown to be more ischemia-related in contrast to late-onset NAS. Late-onset NAS is more frequently immune-mediated. Cytotoxic hydrophobic bile salts play a critical role in biliary epithelial injury and occurrence of NAS. An adequate flush out of the liver, peribiliary microvasculature, and the bile ducts during organ procurement could reduce biliary epithelial injury to some extent. However, bile duct injury during subsequent cold ischemic storage of a liver graft may still be substantial and may contribute to a high incidence of biliary complications after OLT, especially in case of an extended criteria (pre-injured) liver graft. Two recent histopathology studies of bile duct biopsies taken from human DBD donor livers at the time of OLT have shown almost universal loss and injury of the biliary epithelial lining of the extrahepatic bile duct (up to 90% of all grafts). The degree of injury was strongly
associated with the occurrence of NAS after OLT. These studies have suggested that lack of complete and timely regeneration of the biliary epithelium rather than the amount of initial bile duct wall injury may be an important underlying cause of NAS. Machine perfusion has received increasing attention during the last years as an attractive alternative method of graft preservation prior to OLT. Although the most optimal method of machine perfusion still needs to be determined (temperature, duration, timing, etc.), most studies have shown an improved preservation of the liver parenchyma with this technique. Much less is known about the potentially beneficial effects of machine perfusion on the bile ducts of a donor liver. However, the capacities of machine perfusion are very promising (i.e. viability testing by biomarkers or administering therapeutic agents) and may provide a new tool to protect the vulnerable bile ducts against preservation-induced injury. Therefore, further studies regarding the role of machine perfusion in its ability to reduce bile duct injury are awaited with great interest.

### Abbreviations used:
- BS: bile salts
- BS/PS ratio: bile salt to phospholipid ratio
- MDR3: multidrug resistance protein 3
- ATP: adenosine triphosphate
- HCO₃⁻: bicarbonate
- (nor-)UDCA: (nor)ursodeoxycholic acid
- TUDCA: tauroursodeoxycholic acid

### Figure 1: Schematic overview of the mechanisms of biliary injury during and after liver transplantation.
Machine perfusion is an attractive alternative method of organ preservation that could contribute to better preservation of the biliary tree and may subsequently result in a reduction of preservation induced biliary complications.

<table>
<thead>
<tr>
<th>Pathogenesis</th>
<th>Potential Treatment</th>
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</thead>
<tbody>
<tr>
<td><strong>Ischemia-related:</strong></td>
<td>• Oxygenated machine perfusion</td>
</tr>
<tr>
<td>• Cold ischemia</td>
<td>• Adequate back table flush out</td>
</tr>
<tr>
<td>• Preservation</td>
<td></td>
</tr>
<tr>
<td>• Warm ischemia</td>
<td></td>
</tr>
<tr>
<td><strong>Immune-mediated:</strong></td>
<td></td>
</tr>
<tr>
<td>• ABO incompatibility</td>
<td>• Oxygenation</td>
</tr>
<tr>
<td>• Preexisting autoimmune disease</td>
<td>• Increase ATP content</td>
</tr>
<tr>
<td>• CCR5Δ32 polymorphism</td>
<td>• Viability testing</td>
</tr>
<tr>
<td><strong>Bile salt toxicity:</strong></td>
<td></td>
</tr>
<tr>
<td>• High BS/PL ratio</td>
<td>• Administer hydrophilic bile salts (i.e. UDCA, nor-UDCA, TUDCA)</td>
</tr>
<tr>
<td>• Impaired BS re-uptake</td>
<td>• Induce MDR3 (statins, fibrates)</td>
</tr>
<tr>
<td>• Impaired HCO₃⁻ secretion</td>
<td>• Induce “HCO₃⁻ umbrella”</td>
</tr>
</tbody>
</table>

Non-Anastomotic Biliary Strictures

Pathogenesis | Potential Treatment
---|---
Ischemia-related:  | • Oxygenated machine perfusion  
• Cold ischemia  |   
• Preservation  | • Adequate back table flush out  
• Warm ischemia  |   
Immune-mediated:  |   
• ABO incompatibility  | • Oxygenation  
• Preexisting autoimmune disease  | • Increase ATP content  
• CCR5Δ32 polymorphism  | • Viability testing  
Bile salt toxicity:  |   
• High BS/PL ratio  | • Administer hydrophilic bile salts (i.e. UDCA, nor-UDCA, TUDCA)  
• Impaired BS re-uptake  | • Induce MDR3 (statins, fibrates)  
• Impaired HCO₃⁻ secretion  | • Induce “HCO₃⁻ umbrella”  

Figure 1. Schematic overview of the mechanisms of biliary injury during and after liver transplantation.
**Key points**

Biliary complications remain to be the major problem after liver transplantation.

Non-anastomotic biliary strictures are the most challenging complication after liver transplantation due to variability in pathogenesis and resistance to therapy.

The main mechanisms described for pathogenesis of NAS include ischemia/reperfusion injury, immune-mediated injury, cytotoxic hydrophobic bile salts, and impaired biliary bicarbonate secretion.

Insufficient regeneration capacity of biliary epithelium has recently been proposed as a new perspective to view the pathogenesis of NAS.

Machine perfusion has been proposed as a potential preservation strategy to reduce ischemia/reperfusion injury in donor livers; however, clinical trials are needed to demonstrate whether machine perfusion can reduce the incidence of NAS after liver transplantation.
References


