Causes and consequences of ischemic-type biliary lesions after liver transplantation

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Abstract
Biliary complications are a major source of morbidity, graft loss, and even mortality after liver transplantation. The most troublesome are the so-called ischemic-type biliary lesions (ITBL), with an incidence varying between 5% and 15%. ITBL is a radiological diagnosis, characterized by intrahepatic strictures and dilatations on a cholangiogram, in the absence of hepatic artery thrombosis. Several risk factors for ITBL have been identified, strongly suggesting a multifactorial origin. The main categories of risk factors for ITBL include ischemia-related injury; immunologically induced injury; and cytotoxic injury, induced by bile salts. However, in many cases no specific risk factor can be identified. Ischemia-related injury comprises prolonged ischemic times and disturbance in blood flow through the peribiliary vascular plexus. Immunological injury is assumed to be a risk factor based on the relationship of ITBL with ABO incompatibility, polymorphism in genes coding for chemokines, and pre-existing immunologically mediated diseases such as primary sclerosing cholangitis and autoimmune hepatitis. The clinical presentation of patients with ITBL is often not specific; symptoms may include fever, abdominal complaints, and increased cholestasis on liver function tests. Diagnosis is made by imaging studies of the bile ducts. Treatment starts with relieving the symptoms of cholestasis and dilatation by endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiodrainage (PTCD), followed by stenting if possible. Eventually up to 50% of the patients with ITBL will require a retransplantation or may die. In selected patients, a retransplantation can be avoided or delayed by resection of the extra-hepatic bile ducts and construction of a hepaticojejunosotomy. More research on the pathogenesis of ITBL is needed before more specific preventive or therapeutic strategies can be developed.

Introduction
Biliary complications have long been recognized as a major cause of morbidity and graft failure in patients after orthotopic liver transplantation (OLT).1-3 Bile leakage and bile duct strictures are the most common complications. According to their localization, strictures can be classified as anastomotic or nonanastomotic. Nonanastomotic intrahepatic strictures (NAS) are considered to be the most troublesome biliary complication. NAS were first described in OLT associated with hepatic artery thrombosis, where the biliary tree becomes ischemic and eventually necrotic, resulting in a typical cholangiographic picture of biliary strictures, dilatations, and intraductal cast formation.4 However, these cholangiographic abnormalities of strictures and dilatations can also be seen in patients who do not have hepatic artery thrombosis,5,6 so the term “ischemic-type” biliary lesions (ITBL) emerged (Fig. 1).

The reported incidence of ITBL differs greatly between different series, ranging from 1% to 19%.7,8 Variations in the definitions of ITBL used in different studies, as well as the reporting of only symptomatic patients, can at least partly explain these differences. In the majority of series, an incidence of 5% to 15% is reported.9-16

Etiology and risk factors
The exact pathophysiological mechanism of ITBL is still unknown. However, several risk factors of this often cumbersome complication have been identified, strongly suggesting a multifactorial origin (Table 1). In general, risk factors for ITBL can be divided into three

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different categories: ischemia-related injury to the biliary epithelium; immunologically mediated injury; and cytotoxic injury, induced by bile salts. These categories may point towards different etiological mechanisms of ITBL, as will be described below.

**Ischemic injury**

The similarities between the radiological abnormalities of ITBL and the bile duct lesions seen in the presence of hepatic artery thrombosis strongly suggest an ischemic factor in the origin of ITBL. The quest for pathogenic mechanisms, therefore, started with factors associated with ischemia.

**Cold ischemic and reperfusion injury**

Multiple studies have indicated that prolonged cold ischemia time (CIT) predisposes the graft to the development of ITBL. In 1992, Sanchez-Urdazpal et al. reported an incidence of ITBL of 2% in livers with a CIT of less than 11.5 h, rising to 35% in livers with a CIT between 11.5 h and less than 13 h, and even up to 52% in grafts with a CIT of more than 13 h. Nowadays many centers therefore try to keep the CIT below 10 h. However, even with a CIT shorter than 10 h, Guichelaar et al. have shown that the duration of cold storage is still a risk factor for the development of ITBL. The strong positive correlation between CIT and ITBL can be explained by either direct ischemic injury of the biliary epithelium; increased susceptibility of the biliary epithelium to a second factor, such as reoxygenation injury; or secondary ischemia of the biliary epithelium, due to damage to the peribiliary arterial plexus.

The hypothesis that reperfusion injury during OLT contributes to bile duct injury is supported by data provided by the experimental work of Noack et al. Using cell cultures, Noack has shown that biliary epithelial cells are more susceptible to reperfusion/reoxygenation injury than hepatocytes. In an anoxic environment, bile duct epithelial cells and hepatocytes showed equally reduced levels of ATP. However, the rate of cell death after reoxygenation was significantly higher in the bile duct epithelial cells, compared to hepatocytes. Increased production of reactive oxygen species by bile duct epithelial cells, as well as a lower intracellular concentration of glutathione as antioxidant, may explain this difference. Clinical evidence for a contributing role of preservation injury is provided in a clinical study by Li et al. These investigators have shown that the incidence of ITBL is significantly increased in livers with increased preservation injury, as reflected by post-operative peaks in serum aspartate aminotransferase and alanine aminotransferase.

**Injury of the peribiliary vascular plexus**

Preservation injury results in increased arterial resistance and may cause circulatory disturbances in small capillaries, such as the biliary plexus. Because the blood supply to the biliary tract is solely dependent on

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**Table 1. Risk factors for the development of ITBL**

<table>
<thead>
<tr>
<th>Ischemic injury</th>
<th>Immunological injury</th>
<th>Bile salt-induced injury</th>
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</thead>
<tbody>
<tr>
<td>Warm ischemia in the donor</td>
<td>ABO incompatibility</td>
<td>Hydrophilic bile salts are cytoprotective</td>
</tr>
<tr>
<td>Prolonged cold ischemia</td>
<td>Pre-existing disease with autoimmune component</td>
<td>Hydrophobic bile salts are cytotoxic</td>
</tr>
<tr>
<td>Reperfusion injury</td>
<td>Primary sclerosing cholangitis</td>
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<tr>
<td>Warm ischemia during implantation</td>
<td>Cytomegalovirus infection</td>
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<td>Disturbed blood flow in the peribiliary plexus</td>
<td>Chronic rejection</td>
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</tbody>
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**Fig. 1a,b. Cholangiograms 4 months after orthotopic liver transplantation (OLT). a Normal; b ischemic-type biliary lesions (ITBL)**