Manejo endoscópico de las complicaciones biliare
post- trasplante hepático

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Barcelona, Spain
Introduction

• Despite important advances in liver transplantation, biliary complications are considered the *Achilles’ heel* of this operation.

• Biliary complications occur in 10 – 30 % of recipients and are a serious source of morbidity / mortality in 8-15% of patients.

• They not only affect *graft survival* but also have a major impact on the *quality of life* of patients.

Orthotopic Liver Transplantation
1/3
Right Hepatic art.

2/3
Retroduodenal & Retroperitoneal art.

Surgical techniques

Duct to duct

Roux en Y / PSC, other
Living-Donor Liver Transplantation
Biliary tract complications

- Occur in 30%
  - 5-20% DDLT
  - 40% of LDLT
- Wide range of reported incidence –
  - Type of anastomosis (duct to duct vs Roux)
  - Use of T-Tubes (bile leaks)
  - Deceased donor
  - Surgical experience/technique

Krok K, Cárdenas A, Thuluvath PJ. Clin Liv Dis 2010
Biliary complications

- Anastomotic strictures
- Bile leaks / biloma
- Non-anastomostic strictures
- Casts
- Bile duct stones
- Sphincter of oddi dysfunction
- Mucocele
- Hemobilia
Timeline

- Early < 4-6 weeks / Late > 6 weeks

Diagram:
- Frequency vs. Months
- Early complications:
  - leaks - several sources
  - anastomotic strictures
- Late complications:
  - sequelae of "early" complications
  - strictures and obstruction
    - anastomotic
    - hilar
    - intrahepatic
  - stones, sludge
  - mucocoele, ampullary stenosis
- Technical issues
- Ischemia/other
Risk factors

- Acute hepatic artery thrombosis
- Ischemia/reperfusion injury (ischemic-type biliary lesions)
- Technical factors during surgery
- Use of T-tubes
- Redundant bile duct
- Prolonged cold and warm ischemia
- Infections (CMV)
- ABO mismatched grafts
- Non heart-beating donors
- Primary sclerosing cholangitis
- Old age of donor

Krok K, Cárdenas A, Thuluvath PJ. Clin Liv Dis 2010
Sharma S, Gurakar A, Jabbour N. Liver Transplant 2008
Clinical features

- Nonspecific symptoms (fever and anorexia)

- Right upper quadrant abdominal pain (especially with bile leaks), pruritus, jaundice or ascites.

- Many cases: asymptomatic patients elevations of serum bili, alk phos, GGT or AST/ALT.

- Differential diagnosis: acute or chronic rejection, recurrence of the primary disease, fibrosing cholestatic hepatitis C or drug-induced cholestasis.
Abnormal liver enzymes and/or fever, RUQ pain, jaundice

Liver US and Doppler of hepatic vessels

Suspect HA stenosis or obstruction

Hepatic angiography

Biliary dilation and/or stones

¿Clinical suspicion of biliary obstruction?

Normal

High

Biliary obstruction

Low

Consider Liver Biopsy

Bile duct proliferation

MRCP

Rejection or ischemia

Normal

Treat

Investigate other causes

Endoscopic Retrograde Cholangiography

Before the ERCP... perform MRCP

The endoscopist's GPS

Sensitivity 96%, Specificity 94%
Diagnostic ERCP appears to be an acceptable clinical strategy in OLT recipients because of the high likelihood of a high-yield study and the low rate of serious complications.
Complications of ERCP in LT recipients

**TABLE 3.** Post-ERCP complications in 243 ERCP performed in 121 liver transplant patients

<table>
<thead>
<tr>
<th>Complications</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>9</td>
<td>3.7</td>
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<tr>
<td>Mild</td>
<td>5</td>
<td>2.05</td>
</tr>
<tr>
<td>Moderate</td>
<td>4</td>
<td>1.65</td>
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<tr>
<td>Cholangitis</td>
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<tr>
<td>Mild</td>
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<td>Moderate</td>
<td>3</td>
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<tr>
<td>Post-sphincterotomy bleeding</td>
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<tr>
<td>Mild</td>
<td>2</td>
<td>0.82</td>
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<tr>
<td>Moderate</td>
<td>2</td>
<td>0.82</td>
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<tr>
<td>Subcapsular hematoma</td>
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<td>0.41</td>
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<tr>
<td>Perforations</td>
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<td>0</td>
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<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Total complications</td>
<td>22</td>
<td>9.05</td>
</tr>
</tbody>
</table>

**TABLE 4.** Multivariate analysis (forward stepwise logistic regression) of risk factors for post-ERCP complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
<th>Bootstrapping logistic regression analysis in 500 samples, %</th>
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<tbody>
<tr>
<td>mTOR inhibitor therapy</td>
<td>4.65</td>
<td>1.01-21.81</td>
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<tr>
<td>Serum creatinine &gt;2 mg/dL</td>
<td>4.17</td>
<td>1.07-16.26</td>
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<td>Biliary sphincterotomy</td>
<td>3.03</td>
<td>1.07-8.53</td>
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<td>67</td>
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<td>&gt;2 pancreatic duct contrast injections</td>
<td>2.95</td>
<td>1.10-7.91</td>
<td>.032</td>
<td>71</td>
</tr>
<tr>
<td>Prednisone therapy</td>
<td>0.23</td>
<td>0.08-0.63</td>
<td>.004</td>
<td>87</td>
</tr>
</tbody>
</table>

OR, Odds ratio; CI, confidence interval; mTOR, mammalian target of rapamycin.
Management

Diagnosis
• Noninvasive

Treatment
1. Non-operative
2. ERCP / most accepted 1st line treatment
3. PTC / radiology
4. Surgery for failed cases
Strictures

- 80% are anastomotic
  - 5-15% DDLT / 30% LDLT
  - Account for 60% of all biliary complications after LT.

- Appear first 12 months after LT

- Bile leak is an independent risk factor

- By definition, they are single and short in length, making them suitable for endoscopic intervention

Anastomotic strictures - DDLT

- Most common
- Present with cholestasis, pruritus or cholangitis
- Risk of rejection
- Favor HCV progression
- Risk of graft loss
Therapy of strictures

- ERCP with balloon dilation with diameters of 4 - 8 mm
- Placement of 7 - 12 Fr plastic stents
- Stents exchanged at 3-month intervals to avoid occlusion.
- 3-5 procedures: long-term success rates 70 - 92%
- Early strictures / may just dilate
- Hospital Clinic 2003-2016:
  - Overall resolution rate: 88%
  - Max stent therapy: 95%

Dumonceau JM et al Endoscopy. 2012
Anastomotic Stenosis
Incremental Dilation & Stenting

First ERCP session

Sphincterotomy

Balloon Dilate to 4 mm

Insert Largest Diameter Stent Possible (10Fr)

At 3 months

Re-dilate (6 mm)

Insert 2 stents

Repeat x 3
Dilate to 8 mm
3-4 stents

Maximal Stent Therapy / Multiple Plastic Stents (MPS)

Dumonceau JM et al Endoscopy. 2012
<table>
<thead>
<tr>
<th>Authors: (Number of patients who underwent ERC after LT) / [ref]</th>
<th>Nº patients with AS</th>
<th>Technical success rate (%)</th>
<th>Number of stents (mean)</th>
<th>No. ERC’s per patient (mean)</th>
<th>Follow-up in months (mean)</th>
<th>Resolution n (%)</th>
<th>AS recurrence</th>
<th>Recurrence treatment</th>
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</thead>
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<tr>
<td>Rerknimitr et al, 2002. U.S. (N=121) / [3]</td>
<td>43</td>
<td>43/43 (100)</td>
<td>3.6</td>
<td>3.7</td>
<td>39.6</td>
<td>43/43 (100)</td>
<td>0</td>
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<td>Alazmi et al, 2006. USA (N=148) / [61]</td>
<td>148</td>
<td>143/148 (97)</td>
<td>2-4</td>
<td>3</td>
<td>28</td>
<td>131/148 (89)</td>
<td>24/131 (18)</td>
<td>1-4 ERCP</td>
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<tr>
<td>Holt et al, 2007. UK (N=53) / [42]</td>
<td>53</td>
<td>49/53 (92)</td>
<td>3</td>
<td>3*</td>
<td>18*</td>
<td>34/53 (64)</td>
<td>1/34 (3)</td>
<td>1 ERCP</td>
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<tr>
<td>Morelli et al, 2008. U.S. (N=38) / [78]</td>
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<td>38/38 (100)</td>
<td>0.5</td>
<td>3.45</td>
<td>12</td>
<td>33/38 (89)</td>
<td>5/33 (15)</td>
<td>4 ERCP, 1 Surgery</td>
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<tr>
<td>Tabibian et al, 2010, U.S. (N=83) / [38]</td>
<td>69</td>
<td>69/69 (100)</td>
<td>3 max.</td>
<td>4.2 ± 2.8</td>
<td>11*</td>
<td>65/69 (94)</td>
<td>2/65 (3)</td>
<td>ERCP</td>
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<tr>
<td>Sanna et al, 2011, Italy (N=94) / [79]</td>
<td>45</td>
<td>34/34 (100)</td>
<td>-</td>
<td>2.5 ± 1.2</td>
<td>88.8*</td>
<td>22/34 (65)</td>
<td>6/34 (18)</td>
<td>Surgery</td>
</tr>
<tr>
<td>Hsieh et al, 2013, U.S. (N=38) / [72]</td>
<td>32</td>
<td>32/32 (100)</td>
<td>3</td>
<td>4</td>
<td>74.2</td>
<td>32/32 (100)</td>
<td>8 (21)</td>
<td>8 ERCP</td>
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<tr>
<td>Poley et al, 2013, Netherlands (NA) / [44]</td>
<td>63</td>
<td>31/31 (80.6)</td>
<td>4</td>
<td>5</td>
<td>28</td>
<td>25/31 (80.6)</td>
<td>6 (19.4)</td>
<td>1 ERCP (SEMS), 5 Surgery</td>
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<tr>
<td>Cárdenas et al, 2015. Spain (N=50) / [unpubl data]</td>
<td>42</td>
<td>42/42 (100)</td>
<td>3.12</td>
<td>3.12</td>
<td>41.48</td>
<td>37/42 (88)</td>
<td>3/37 (8.2)</td>
<td>3 ERCP</td>
</tr>
</tbody>
</table>
Anastomotic strictures - LDLT

- Up to 30-40% complications
- Small duct:
  - difficult anastomosis.
  - Higher chance of ischemic injury
- Therapy – ERC + dilation / stent
- Long term therapy

Fully covered SEMS in LT

- Controversial
- Long term resolution in 70% (removal in 2-5 months)
- Recurrence rates - 15-40%
- Stent migration in up to 30%
- Pancreatitis, cholangitis.
- Not well compared with plastic stents
- They seem to be less effective
- Not recommended outside clinical studies

Tarantino et al. Endoscopy 2012
Sauer et al. Endoscopy 2012
Poley et al Gastrointest Endosc 2012
Fully covered SEMS in LT
A Systematic Review...

• Similar resolution rates MPS vs SEMS
  - When using SEMS as primary treatment
  - When SEMS placed >3 months
• Similar complication rate
• High SEMS migration rate: 16%

• Limitations
  - No controlled studies, no randomized studies...
  - 12/21 retrospective studies
  - Heterogeneous designs

Fully covered SEMS in LT
Non-randomized prospective Trial

- Per protocol resolution rate: 88%
- ITT resolution rate: 68%
- Recurrence rates:

Serious Adverse Effects:

Effect of Covered Metallic Stents Compared With Plastic Stents on Benign Biliary Stricture Resolution: A Randomized Clinical Trial

Stricture resolution in patients with LT (n=73)
Multiple plastic stents versus covered metal stent for treatment of anastomotic biliary strictures after liver transplantation: a prospective, randomized, multicenter trial.

58 patients: MPS (n = 24) required 4 ERCP vs cSEMS (n=24) required 2 ERCP. cSEMS migration 33.3%.

Treatment duration did not differ significantly.

Initial treatment success (95.8%) in the MPS group and (100%) for cSEMSs.

Tal OA. Et al GIE 2017 Dec;86(6):1038-1045
Cholangioscopy
Liver transplant strictures

- Conventional ERCP may fail to traverse severe strictures in 15-20%
- Cholangioscopy is useful and time-sparing in such cases
- Allows direct visualization for biopsy and also for placement of guidewire

Prospective Evaluation of Single-Operator Peroral Cholangioscopy in Liver Transplant Recipients Requiring an Evaluation of the Biliary Tract

Anastomotic biliary stricture on single-operator cholangioscopy

**Pattern A**
- Mild erythema and scarring
  - Continue ERCP sessions until AS resolution

**Pattern B**
- Severe edema, erythema and ulceration with sloughing
  - Complete current ERCP session and consider surgical therapy

Normal Bile Duct

CBD stone

Balderramo D. Liver Transpl 2013
Digital cholangioscopy

First Generation SpyGlass System

SpyGlass DS System

Stricture

Biopsy

First Generation SpyGlass System

SpyGlass DS System

Stone

Normal Ducts
Bile leak

- Incidence 2-25 %
- Diagnosis- clinical
- MRC/HIDA
- Occurs at the
  - Anastomosis,
  - cystic duct,
  - T-tube tract
  - Cut surface of the liver

Thuluvath PJ, Liver Int 2004
Morelli, Gastrointest Endosc 2001
Oh, Gut Liver. 2015
Treatment of Bile leak

• Small ascites (t-tube in place? → open)
• Large ascites (JP drain)
• ERCP + sphicterotomy
• Stent placement (10F)
• Leave stent for 4-8 weeks
• Success in 90% of cases
• Failure –
  - Covered metal stent?
  - surgery

Thuluvath PJ, Endoscopy 2005
Londoño MC, Cardenas A, WJG 2007
Endoscopic management of bile leaks after liver transplantation: An analysis of two high-volume transplant centers

- Retrospective study
- 2 centers
  - Hospital Clínic, Barcelona
  - Mayo Clinic, Rochester

- N = 80
  - Sphincterotomy 33 (41%)
  - Sphincterotomy + stent 47 (59%)

<table>
<thead>
<tr>
<th></th>
<th>Stent group (n = 47)</th>
<th>Sphincterotomy alone group (n = 33)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RESOLUTION</strong> [n (%)]</td>
<td>44 (93,6%)</td>
<td>19 (57,6%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>NEED FOR PTBD</strong> [n (%)]</td>
<td>2 (4,3%)</td>
<td>4 (12,1%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>NEED FOR SURGERY</strong> [n (%)]</td>
<td>3 (6,4%)</td>
<td>14 (42,4%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>SURVIVAL (3 months)</strong> [n (%)]</td>
<td>44 (93,6%)</td>
<td>30 (90,9%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Sendino et al. United European Gastroenterol J. 2018 Feb;6(1):89-96
Non-anastomotic strictures
Non-anastomotic strictures

- Hepatic artery thrombosis
- Increased cold ischemia time or ABO-blood type incompatibility.
- Peribiliary arteriolar endothelial injury resulting in irreversible microvascular thrombosis
- Early NAS – ischemia
- Late NAS – immunological factors

NAS occur > 0.5 cm proximal to the anastomosis and often involve the hilum and multiple separate obstructions at the level of the sectoral or segmental branch ducts.
Non-anastomotic strictures

• Treatment similar to AS (dilation + stent)
• Time to response is more prolonged.
• Only half of patients have a long-term response with endoscopic therapy
• 30 to 50% of patients undergo retransplantation or die as a consequence of this complication despite endoscopic therapy
Sphincter of Oddi dysfunction

• Occurs in 2 to 7%
• Denervation of CBD in the ampullary region
• Hypertonic sphincter causing dilated ducts and cholestasis.
• Suspect:
  - Cholestasis and a uniformly dilated bile duct without filling defects.
  - Abdominal pain may not be present.
• Therapy- ERC + sphincterotomy
Summary

• Biliary complications are common after LT
• Always suspect in those with cholestasis and abnormal liver tests
• Early diagnosis and intervention will reduce morbidity and outcome of post-liver transplant biliary complications
• ERCP is the preferred 1st line therapy
• Patients need surveillance after treated
• Surgery needs to be considered when ERC and PTC fails
Thanks for your attention!
795 LT patients (2003-2013)

201 LT patients underwent ERC
(460 ERCP procedures)

49/201
Indication of ERCP: cholestasis + dilated bile ducts

23/201
Initial criteria of SOD

Sphincterotomy 23/23

Definite SOD 13

No SOD 10
(alternative diagnosis)

BAS 1
Lithiasis 3
Graft rejection 4
HCV recurrence 1
Pancreatitis 1
Anastomotic Stenosis

Maximal Stent Therapy Vs. Dilation only

LT Patients with AS
n =  50

Max Stent Therapy
n =  42
Completed Treatment
n =  39 (93%)
  Resolution
n =  37 (95%)
  Recurrence
n =  3 (8.2%)
    100% re-treated endoscopically

Failed Procedure
n =  3 (7%)
  No Response
n =  2 (5%)

Dilation Only
n =  8
  Resolution
n =  5 (62.5%)
  Recurrence
n =  3 (37.5%)
  Surgery

Cardenas A. Unpublished data.
SOD in LT

1036 LT patients (2003-2015)

227 LT patients underwent ERC
(560 ERCP procedures)

54/227 Indication cholestasis + dilation

23/227 Initial criteria of SOD

Sphincterotomy 23/23

13/23 56.52%

13/1036 1.2%

23/1036 2.2%

31/54 Alternative explanation on ERC or No biliary duct dilation

Definite SOD 13

No SOD 10 (alternative diagnosis)

- BAS 1
- Lithiasis 3
- Graft rejection 4
- HCV recurrence 1
- Pancreatitis 1

12 months
SOD in LT

Retrospective Study...

- 2003-2015: 1036 LT’s
- 225 LT recipients underwent 561 ERCP’s during the study period.
- 23 patients with suspected SOD in ERCP
  - N = 13 (56%) had SOD diagnosis confirmed.
    - Overall rate 1.6%
- 100% confirmed SOD patients responded to sphincterotomy

### Alternative diagnosis

<table>
<thead>
<tr>
<th>n</th>
<th>Lab enzymes</th>
<th>Pre Sphx Mean</th>
<th>Pre Sphx SD</th>
<th>Post Sphx Mean</th>
<th>Post Sphx SD</th>
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<tbody>
<tr>
<td>13</td>
<td>Bilirubin</td>
<td>2,0</td>
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<td>.701</td>
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<td>93,3</td>
<td>48,3</td>
<td>.074</td>
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Fernandez-Simon A, Cardenas A. United European Gastroenterology Journal October 2016 vol. 4 no. 5 suppl P0736.
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<td>AST</td>
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<td>127,8</td>
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</table>

Fernandez-Simon A, Cardenas A. United European Gastroenterology Journal October 2016 vol. 4 no. 5 suppl P0736.
Common bile duct filling defects

Uncommon 5-10%

- Stones
- Sludge
- Casts
- Debris
- Blood clots
- Migrated stents
**Common bile duct stones/sludge**

**Stones / Sludge - 70% of CBD defects**
- Seen in association with strictures
- Appear late after LT

**Therapy**
- Rx stricture + stones
- Endoscopic treatment if stricture is extrahepatic
- Percutaneous preferred for intrahepatic strictures
Bile duct casts

- 18% of LT recipients
- Casts often associated with diffuse ischemic strictures
- Associated with acute cellular rejection, ischemia, hepatic artery stenosis and biliary obstruction
- ERC and or PTC can clear casts in 60-70%
- Can be difficult to treat

Liver Int. 2013 Sep;33(8):1287-92