INTRODUCTION

Liver transplantation (LT) is currently regarded as a standard treatment option for end-stage liver diseases (ESLD). However, due to the continued shortage of donor organs, only a minority of the patients in need will finally receive a timely liver transplantation. In this triage situation, the need for an urgent transplantation has to be balanced with the probability of a good long-term posttransplantation survival of the recipient ***(Weismuller et al., 2013).***

To optimize the outcome after transplantation in this high-risk patient collective, the careful selection of appropriate transplant candidates is based on an extensive evaluation including cardiac, pulmonary, and renal testing and different imaging methods to exclude an infective focus or malignancies, which would exclude the patient from transplantation ***(Weismuller et al., 2013).***

Although current guidelines recommend regular upper gastrointestinal (GI) endoscopies for every cirrhotic patient ***(Garcia-Tsao et al., 2007),*** there is no clear consensus whether colonoscopy should be mandatory in this situation. While some centers recommend only screening sigmoidoscopies ***(Zaman et al., 1999),*** other institutions perform screening colonoscopies in patients older than 45 yr or 50 yr, according to the local colorectal cancer screening programs ***(Gravante et al., 2008).***

Colonoscopy is performed as part of the evaluation to assess eligibility for orthotopic liver transplantation (OLT) to rule out malignancies that would exclude patients from receiving a graft ***(Jeschek et al., 2015).***

Furthermore, the detection and treatment of premalignant abnormalities (high-grade adenomas) might be of clinical relevance, because the required immunosuppression after transplantation increases the risk of progression to frank malignancy ***(Engels et al., 2011).***

Although there are indications that immunosuppression may shorten the interval of progression from premalignant lesions to colorectal cancer (CRC) ***(Nicolaas et al., 2010),*** there is evidence that CRC risk after OLT is increased only in patients with concomitant primary sclerosing cholangitis because of the strong association with inflammatory bowel disease ***(Singh et al., 2013).***

Etiology of the liver disease may be linked to the colonoscopic findings, such as chronic hepatitis HCV and colorectal adenoma ***(Rustagi et al., 2014)***.

Also Because of shared risk factors such as (obesity, diabetes, and metabolic syndrome), patients with nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are at higher risk of colorectal neoplasia, both adenomas and carcinomas, which remained after adjustment for risk factors ***(Stadlmayr et al., 2011)***.

AIM OF THE WORK

1- To evaluate the importance and the role of pretansplant screening colonoscopy in Egyptian potential liver transplant candidates.

2- To identify predictors of patients who should be screened by colonoscopy pre-transplantation.

Chapter 1
LIVER TRANSPLANTATION

Introduction

Liver Transplantation (LT) has evolved rapidly, becoming the standard therapy for acute and chronic liver failure of all etiologies ***(EASL Guidelines, 2016)*** Survival rates have improved significantly in the last 25 years, achieving rates of 96% and 71% at 1 and 10 years after LT respectively ***(Adam et al., 2012).***

This great success is mostly attributable to several advances such as the introduction of new immunosuppressive agents and preservation solutions, to the improvements in surgical techniques and to the early diagnosis and management of complications after LT ***(Dutkowski et al., 2010).***

As a consequence of these achievements, indications for LT have been expanded resulting in a growing demand for transplantable grafts and in a dramatic organ shortage. Therefore, one of the main ongoing challenges the transplant community is facing is to expand the donor pool in order to minimize the rate of patient death on the waiting list ***(Dutkowski et al., 2015).*** On the other hand, liver transplanted patients are surviving longer after the operation and long-term outcomes are becoming the main concern for clinicians, who

have to deal with direct and indirect side effects of immunosuppressive therapy ***(EASL Guidelines, 2016).***

Indications to liver transplantation (Table 1)

Liver transplantation should be considered in any patient with end-stage liver disease, in whom the LT would extend life expectancy beyond what the natural history of underlying liver disease would predict or in whom LT is likely to improve the quality of life (QoL). Patients should be selected if expected survival in the absence of transplantation is one year or less, or if the patient had an unacceptable QoL because of liver disease. A detailed medical evaluation is performed to ensure the feasibility of LT ***(EASL Guidelines, 2016).***

Liver transplantation is indicated for severe acute or advanced chronic liver disease when the limits of medical therapy have been reached **(Table 1).** Recognition of cirrhosis per se does not imply a need for LT. Many patients with cirrhosis in the absence of an index complication such as ascites or variceal hemorrhage will not develop hepatic decompensation, although patients with cirrhosis have diminished survival compared to the population as whole ***(Fleming et al., 2012).***

Occurrence of a major complication is an important predictor of decreased survival and should prompt discussion about a possible role for LT ***(Martin et al., 2014).***

Patients should be referred to transplant centres when major complications of cirrhosis, such as variceal haemorrhage, ascites, hepatorenal syndrome and encephalopathy occur ***(EASL Guidelines, 2016).***

Conversely, acute liver failure represents an urgent indication to LT ***(Lee et al., 2008)***. Viruses (especially hepatitis viruses A and B), drugs (acetaminophen), and toxic agents are the most common causes of acute liver failure, with the proportions varying between countries. Seronegative hepatitis is also an important cause of LT for acute liver failure. Prognosis is essentially determined by neurological status, but is also rapidly affected by damage to other organs. LT has revolutionized the prognosis of acute liver failure, causing survival to increase from 10–20% (all causes combined) to 75–80% at 1 year and 70% at 5 years ***(EASL Guidelines, 2016).***

Table (1): Indications to liver Transplantation ***(Martin et al., 2014)***

Acute Liver Failure
Complications of cirrhosis:
Ascites
Chronic gastrointestinal blood loss due to portal hypertensive gastropathy
Encephalopathy
Liver cancer
Refractory variceal hemorrhage
Synthetic dysfunction
Liver-based metabolic conditions with systemic manifestations:
α_1-Antitrypsin deficiency
Familial amyloidosis
Glycogen storage disease
Hemochromatosis
Primary oxaluria
Wilson disease
Systemic complications of chronic liver disease:
Hepatopulmonary syndrome
Portopulmonary hypertension

The timing of LT is crucial since patients who should be transplanted for end-stage liver disease need to undergo surgery before life-threatening systemic complications occur. They should not be transplanted too early since the advantage of transplant might be unbalanced by the risk of surgery and immunosuppression for life ***(EASL Guidelines, 2016).***

Priority on the waiting list was based in the past by the waiting time, and severity of liver disease. The Child-Pugh-Turcotte classification and since 2002 also the model of end-

stage liver disease (MELD) score had been used to assess for patients priority ***(Wiesner et al., 2003).***

The MELD was developed to determine the short-term prognosis for patients undergoing TIPS after gastrointestinal bleeding ***(Malinchoc et al., 2000),*** and then proposed for predicting 3-month mortality in patients with end-stage liver disease. In patients with MELD ≤ 14, 1-year survival was lower with rather than without transplantation ***(Merion et al., 2005).*** Consequently, a MELD score ≥ 15 is recommended to list patients with end-stage liver disease. However, it does not provide a prediction of mortality following LT except for those patients with very high MELD scores over 35 ***(Habib et al., 2006).***

In very sick patients with MELD >30, the risk of mortality and morbidity after transplantation should be addressed. MELD does not reflect the impact of complications such as refractory ascites and recurrent encephalopathy in the risk of mortality without transplantation ***(EASL Guidelines, 2016).***

There are several exceptions to MELD, including pulmonary complications of cirrhosis, hepatic encephalopathy, amiloidosis, primary hyperoxaluria, etc. **(Table 2).** In these cases, extra points could be attributed to patients in order to give them priority to transplantation ***(Freeman et al., 2006).***

Serum sodium (MELD-Na), serum sodium and age (integrated MELD) scores have been proposed to improve the predictive value of MELD ***(Kim et al., 2008).***

Delta MELD (DMELD), meaning the change MELD over time, might also be a better predictor of mortality ***(Huo et al., 2005).***

Another exception to MELD is HCC. Waiting list time dependent points can be added to laboratory MELD to give priority to patients with HCC. Additional points can be added depending on the type of tumour (size, number of nodules, alpha fetoprotein (AFP) level, waiting time, response to downstaging procedures) ***(EASL Guidlines, 2016).***

Table (2): Exceptions to MELD score ***(EASL Guidelines, 2016)***

Manifestations of cirrhosis
Refractory ascites
Recurrent gastrointestinal bleeding
Recurrent encephalopathy or chronic encephalopathy
Hepatopulmonary syndrome
Portopulmonary hypertension
Intractable pruritus resistant to medical therapies
Miscellaneous liver diseases
Budd-Chiari syndrome
Familial amyloidotic polyneuropathy
Cystic fibrosis
Hereditary haemorrhagic telangiectasia
Polycystic liver disease
Primary oxaluria
Recurrent cholangitis
Uncommon metabolic disease
Malignancy
Cholangiocarcinoma
Hepatocellular carcinoma
Uncommon liver tumours
Other

The management of a patient in the waiting list aims at eliminating not only contraindications of surgery, but also contraindications to taking long-term immunosuppressive treatment. This assessment is not uniform and should be discussed in each transplant centre ***(EASL Guidelines, 2016).***

LT may be deferred or even avoided if medical therapy is effective. Examples of specific therapies, which may markedly improve hepatocellular function, include oral antiviral agents for hepatitis B infection or corticosteroids for autoimmune hepatitis. However, even if there is a potentially reversible component to hepatic decompensation, LT evaluation should

not be deferred if otherwise indicated, as improvement is not invariable even with specific therapy ***(Martin et al., 2014).***

Disease specific indication for LT and management of patients on the waiting list

Hepatitis C virus induced liver disease: The most common indication for liver transplantation worldwide. In the era of lack of curative antiviral therapy prior to LT, nearly all grafts became reinfected immediately after transplant. After LT the tempo of HCV infection is accelerated, with high rates of graft dysfunction and progression to cirrhosis in 20-30% of patients with graft failure due to recurrent HCV in 10% of HCV-infected recipients within 5-10 years of LT, which is reflected in decreased survival compared to other LT indications ***(Rubin et al., 2011).***

Despite this, the outcomes for LT for HCV are acceptable. Indications for LT for HCV do not differ from that of other causes of liver disease and include decompensated cirrhosis and HCC. To reduce the risk of HCV recurrence LT candidates should be treated before transplantion whenever possible. The achievement of negative HCV viral load can improve liver function either before or after transplant. New IFN-free antiviral therapies are better tolerated and are a promising option for decompensated cirrhosis.

Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score <18-20 can be treated with one of the following combinations: sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, or paritaprevir, ombitasvir, retonavir (Qurevo) or sofosbuvir and daclatasvir, with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). Patients that could not be treated before LT need to be treated afterwards ***(EASL Guidelines, 2016).***

Hepatitis B virus (HBV)-related liver disease: The indication of decompensated HBV cirrhosis is declining probably due to the outcome of HBV vaccination and advent of oral antiviral agents. The indication for transplantation is similar to other causes of cirrhosis. In addition, it is essential to know the precise HBV status of the patient and in particular the existence of HBV replication. Whatever the level of HBV DNA, if detectable, antiviral treatment with entecavir or tenofovir should be started as soon as possible ***(EASL Guidelines, 2009).***

The need for an antiviral treatment with nucleot(s)ide analogues (NUCs) has two objectives: 1) the improvement of liver function; and 2) to decrease the risk of HBV recurrence after transplantation since viral replication level at the time of LT is correlated with the risk of HBV recurrence ***(EASL Guidlnes, 2016).***

Positive HBV DNA at the time of LT seems to influence the rate of death due to HBV recurrence in HBV/HCC patients. Patients with fulminant or severe hepatic disease may benefit from NUC treatment. Entecavir or tenofovir should be used in these patients. In patients with liver function deterioration in spite of anti-HBV therapy, active HDV infection should be ruled out. HDV replication is not a contraindication for LT ***(EASL Guidlines 2016).***

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH): In the setting of the metabolic or insulin resistance syndrome, NAFLD and NASH are becoming increasingly common medical problems in the developed world. Patients with histological necrotic-inflammatory changes and/or fibrosis may progress to end-stage liver disease and require LT.

NAFLD and NASH are increasingly recognised as an indication to LT at the stage of cirrhosis and liver failure ***(Charlton et al., 2011).*** Some patients may have both NAFLD linked to metabolic syndrome and chronic alcohol consumption acting as a cofactor for cirrhosis development. One specific point that should be carefully evaluated is the presence of comorbid factors linked to metabolic syndrome, which might increase the risk of complications during a surgical procedure ***(Charlton, 2013).***

In particular obesity, hypertension, diabetes and dyslipidemia required a specific work-up in the pre-transplant phase or screening and should be addressed in the post-transplant setting as they might exacerbate ***(Dare et al., 2014).*** It is likely that many potential LT candidates with NASH are excluded from LT due to comorbid conditions related to metabolic syndrome. In particular, morbid obesity might be a limiting factor to transplantation as it increases infection complications, as well as the length of stay in the intensive care unit (ICU) and hospital ***(Hakeem et al., 2013)***.

Indication to LT in obese patients with a body mass index (BMI) over 35 should be discussed within a multidisciplinary team including dietician, psychologist, hepatologist, anestethist and surgeon ***(EASL Guidelines, 2016).***

Primary biliary cirrhosis: In PBC patients, indication to LT should be given for decompensated liver disease, complicated portal hypertension and for uncontrolled and intolerable pruritus refractory to all medical therapies ***(EASL Guidelines, 2016).*** The Mayo risk score is an approved mathematical model predicting survival in non-transplanted patients suffering from PBC. However, the score did not predict the course of our liver transplanted patients in a long-term follow-up. ***Jacob et al.*** could not demonstrate a reduced patient survival at a median MRS of 9.4 and about 10.0. Therefore, it is, from the authers' view, questionable if the optimal time point for OLT is still 7.8 ***(Jacob et al., 2008).***

Primary sclerosing cholangitis: In PSC patients, indication to LT should be given for decompensated liver disease, complicated portal hypertension and repeated episodes of cholangitis. PSC is a risk factor for cholangiocarcinoma, thus cholangiocarcinoma should be excluded by radiological and biological markers before LT. Patients with PSC and ulcerative colitis should undergo colonoscopy annually before and after LT due to the higher risk of developing colon cancer ***(EASL Guidelines, 2016).***

Genetic diseases: represent a heterogeneous group of disorders, which affects 10 out of 1000 births. They could manifest as predominant liver parenchymal damage (genetic cholestatic disorders, Wilson's disease, hereditary haemochromatosis, tyrosinemia, alpha-1-antitrypsine deficiency) or they could be liver-based genetic disorders characterized by architecturally near-normal liver (urea cycle disorders, Crigler-Najjar syndrome, familial amyloid neuropathy, primary hyperoxaluria type 1, atypical haemolytic uremic syndrome-1). For the first group, hepatic complications are the main indications to LT while in the second, extrahepatic manifestations are the main cause of morbidity and mortality while liver function is preserved ***(Fagiuoli et al., 2013).***

The indication of LT in patients with Wilson's disease should be made in cases of acute liver failure or end-stage liver disease. LT can improve neurological symptoms but they can also worsen after the procedure. The neurological assessment before the transplant is mandatory ***(EASL Guidelines, 2016).***