Review

Succinct guide to liver transplantation for medical students

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Highlights

- Recipient candidates may have reversible contraindications that halt the surgery temporarily and therefore, it warrants re-evaluation before transplant.
- Organ allocation policy is primarily based on disease severity instead of the waiting time period.
- Hepatocellular carcinoma can be cured by liver transplantation if certain criteria met to predict low risk of extrahepatic dissemination before transplant.
- Transplant surgery usually involves resection of the whole liver, in situ implantation with reconstruction of the hepatic vein, the portal vein, the hepatic artery and the biliary duct in sequence.
- The primary goal of artificial immunosuppression is to prevent graft rejection, and the secondary one is to reduce its complication or side effects.

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Abstract

Literature on liver transplantation for use in medical education is limited and as yet unsatisfactory. The aim of this article is to help medical students gain enough insight into the reality of being a liver transplant recipient. This is crucial so in the future they can feel confident in approaching these patients with adequate knowledge and confidence. The knowledge-tree based learning core topics are designed for a 2-h class including indication/contraindication in the real-world setting, model for end stage liver disease scoring and organ allocation policy, liver transplantation for hepatic malignancy, transplantation surgery, immunosuppression strategy in practical consideration, and management of viral hepatitis. The rationales of each topic are discussed comprehensively for better understanding by medical students. Recipient candidates may have reversible contraindications that halt the surgery temporarily and therefore, it warrants re-evaluation before transplant. Organ allocation policy is primarily based on disease severity instead of the waiting time. Transplant surgery usually involves resection of the whole liver, in situ implantation with reconstruction of the hepatic vein, the portal vein, the hepatic artery and the biliary duct in sequence. The primary goal of artificial immunosuppression is to prevent graft rejection, and the secondary one is to reduce its complication or side effects. Life-long oral nucleoside/nucleotide analogues against hepatitis virus B is needed while short course of direct acting agents against hepatitis viral C is enough to eradicate the virus. Basic understanding of the underlying rationales will help students prepare for advanced learning and cope with the recipients confidently in the future.

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1. Introduction

Liver transplantation is the gold-standard treatment in end stage liver disease of most etiologies [1] [2]. As recipients survive longer, medical personnel in all fields other than transplantation will be exposed to these patients requesting ordinary medical help [3]. To acquire basic understanding of liver transplantation is, therefore, important for medical students to develop future career. Medical students are expected to learn the professional knowledge that is essential for medical students to get acquainted with before they step into the clinical practice.

Before the learning journey of liver transplantation, one important notice is that liver transplantation is a science of multidisciplinary and integrated medicine, and oftentimes clinicians need to make compromised decisions and judge the utmost priority of multiple issues tangled each individualized patient care, eg, multiple liver disease diagnoses (cancer, cirrhosis, viral hepatitis); compromising graft size by striking balance between remaining liver of living donor and liver harvested for recipient; immunologic risk between recipient; immunologic risk between infection and rejection.

The knowledge-tree based learning core topics are designed for a 2-h class include indication/contraindication in the real-world setting, model for end stage liver disease (MELD) score and organ allocation policy, liver transplantation for hepatic malignancy, transplantation surgery, immunosuppression strategy in practical consideration, and management strategy of hepatitis viral infection (Fig. 1). We believe the topics highlighted here are essential for medical students to get acquainted with before they step into the clinical practice.

2. Terminology commonly used in liver transplantation

Firstly, common terms used in liver transplantation are listed below with each brief description.

**Acute rejection:** acute onset of graft injury due to allo-immunologic response. It is not referred to the timing occurred after liver transplantation although it occurs more frequently in the early postoperative period. If not mentioned specifically, it often means acute cellular rejection.

**Allocation:** to distribute deceased-donor liver grafts to recipient candidates on the waiting list.

**Graft vs explant:** new implanted liver vs. removed native liver.

**GRWR:** graft–recipient weight ratio, used to measure whether the amount of liver graft is enough to a particular recipient.

**HLA:** human leukocyte antigen, a gene complex encoding the major histocompatibility complex proteins in humans and responsible for the self/non-self immune recognition and signaling. HLA typing is a method to determine how closely the tissues/organs matched between two persons.

**Living donor vs. deceased donor:** living donors always donate partial liver graft to the corresponding recipients. Deceased donors can donate their livers to one or more recipients (split liver into partial livers for transplant in the latter case).

![Fig. 1. Schematic of the knowledge tree of liver transplantation essential for medical student learning from tree root, trunk, to branch details of knowledge.](image-url)
3. Indications and contraindications for liver transplantation in the real-world setting: you are indicated but ...

Evaluating whether a patient needs a transplant or not is based on assessing whether their irreversible liver disease can be reversed by total liver replacement [7]. Transplantation is required for those with end-stage liver disease. In adults, this can be cirrhosis with or without hepatocellular carcinoma (HCC). In children this can be due to biliary atresia, following Kasai procedures with prolonged jaundice, repeated biliary tract infections as well as failure to thrive. Advanced cirrhosis will have a variety of complications and is detailed elsewhere [8]. Specific frequency of these etiologies depends on the geographic variation. In addition, as the growing number of morbid obesity and new treatment options for hepatitis C, nonalcoholic steatohepatitis will be one of the main reasons for liver transplantation in the near future [9]. MELD score may be used as a screening tool (eg. score >10) but it might include patients without liver disease at all if only MELD score is considered (such as heart disease and congestive liver under medication of coumadin, or chronic renal insufficiency with highly elevated creatinine level). Acute liver failure is another uncommon but usually urgent indication for liver transplantation [10]. King's college criteria is applied in this situation and patients can be triaged into two groups, depending on whether the underlying etiology is acetaminophen-induced or not. Nonetheless, INR is the key prognostic factor in acute liver failure. Contraindications could co-exist and therefore, against liver transplantation either temporarily or permanently, such as uncontrolled sepsis, active psychosis, active alcohol abuse, irreversible brain stem dysfunction, or active extrahepatic malignancy [7] [10]. The evaluation process is dynamic until a patient finally receives a liver transplant or drops out. For example, candidates can still receive liver transplantation if control of infection, HCC downstaging (explained later) or alcohol abstinence can be achieved. However, candidates can also be rejected due to different reasons, eg: HCC exceeding Milan/University of California San Francisco (UCSF) criteria (explained later), medically unfit or poor cardiopulmonary function. All these reasons make surgery very risky and futile. Multi-organ transplantation may provide a solution in the latter case. Of note is that the indication/contraindication profile may evolve over time with the advance of medicine. For example, hepatitis B virus (HBV) carriers used to be rejected for liver transplantation decades back before because of the high mortality rate of frequent post-transplant HBV recurrence until the introduction of lamivudine [11].

4. MELD score and organ allocation: how it works?

The truth behind the graft allocation policy is that resource of organ supply is limited worldwide and not enough for every recipient candidate. The system bases primarily on severity and emergency of patient condition under ABO compatibility, and then follows allocation policies (in order to decide and to prioritize who can get the deceased liver) established by some allocation organizations in different geographic regions, e.g. eurotransplant [12,13].

MELD was originally developed statistically for predicting death of patients with end-stage liver disease for the use of transjugular intrahepatic portosystemic shunts [5]. The calculation of MELD score = \(3.78 \times \ln([\text{serum bilirubin (mg/dL)}) + 11.2 \times \ln \left([\text{INR}\right] + 9.57 \times \ln([\text{serum creatinine (mg/dL)}) + 6.43\)

Nowadays it is widely applied in prioritizing the recipient candidates on the waiting list since Child-Turcotte-Pugh score classification system is not differentiable (range 5–15) enough for triage than MELD score (range 0–40). Patients with HCCs usually have extra points added because the malignancy may grow beyond the criteria limit and then the candidates may be forced to drop out [14].

5. Liver transplantation for hepatic malignancy

Generally speaking, solid organ transplantation is not applied to patients with malignancy because the immunosuppressants will also suppress their immunity against cancer which may cause it to progress rapidly after transplantation [15]. However, liver transplantation do apply to hepatic malignancies (such as HCC, neuroendocrine liver tumors, hemangioendothelioma, hepatoblastoma, or possibly, cholangiocarcinoma) in certain conditions [7]. The rationale behind is that total hepatectomy can remove the tumor en bloc and give patients chance to cure. Many primary liver malignancies involve chronic liver diseases such as hepatitis, fibrosis or cirrhosis. Liver transplantation also prevents the chronic diseased liver “soil” to develop de novo malignancy in the future. The most well-known and well established (although still in need of further breakthrough) cancer is HCC. Milan criteria set the stage and remains as the gold standard for liver transplantation of HCC with simple combination of tumor size and number in a cirrhotic background if there is no vascular tumor thrombosis [16]. HCC patients who fulfill the criteria will have much lower risk of tumor recurrence than those who do not. UCSF criteria (another combination of tumor size and number), little loose than Milan criteria, is developed later and applied to HCC patients planning for liver transplant as well [17]. Many other criteria were developed from regional experiences and data although none were superior to Milan criteria (Fig. 2). The survival models of these criteria predict the possibility of HCC cure after total hepatectomy. Biologically, patients who meet these criteria may have no extra-hepatic spread of HCC but currently no biomarkers could accurately predict whether malignant cells are all confined within the recipient's own liver (Fig. 2). The success of Milan criteria is based on the fact that HCC cancer cells mainly disseminate within the liver through the portal venous system and tumor thrombosis can be identified with ease in medical images. Cholangiocarcinoma, however, spreads outside of the liver earlier through biliary and lymphatic systems, and is thus more difficult to clearly identify. Aside from liver transplantation, liver resection of HCC (without removal of the whole liver) also provides a chance of cure in patients without liver cirrhosis, especially in regions of scarce deceased donors [18]. Therefore, the primary treatment choice between liver resection and liver transplantation for HCC varies geographically.
6. Surgeries for liver transplantation: you mean donor or recipient?

Detailed transplant surgical techniques are beyond the scope of this paper and many videos of liver transplant surgery or donor surgery can be accessed online for references. However, one needs to be specific when addressing the issue of surgery (donor or recipient, especially living donor surgery vs. living donor liver transplantation).

Donor graft quality can be assessed by several indexes such as age, liver fat percent, graft volume measurement, perioperative ischemic time. Donor livers of borderline quality are known as ‘marginal donors’ [19]. For living donors, common reasons of being rejected to donate are advanced fatty liver, or relative small liver size either for donation or for self-keeping. HLA mismatch does not render a living donor unsuitable. Size mismatch may occur between donor graft liver and recipient based on GRWR. It may cause complication, particularly in living-donor liver recipients, to both adult (SFSS, GRWR <0.6%) and children (large for size, GRWR > 4%). Large-for-size transplant may have problems such as inlet vessel compression, artery strangulation, or blood-sponge hypotensive effect [20].

Recipient operation involves total hepatectomy (removal) and graft implantation (reconstruction), in the order of division (hepatic artery/bile duct-portal vein-hepatic vein) and reconstruction (hepatic vein-portal vein-reperfusion-hepatic artery-bile duct) [21]. Fig. 3 illustrates the principal steps of the right lobe implantation in a living donor liver transplantation. There are variants of the liver transplantation surgery. Here are some examples: a. venovenous bypass is not routinely used in transplantation nowadays. Instead, the piggyback technique is the most used approach. b. auxiliary liver transplant for acute liver transplantation nowadays. Instead, the piggyback technique is the some examples: a. venovenous bypass is not routinely used in

7. Strategy and clinical application of immunosuppressants in liver transplantation

An unique part of liver transplantation compared to other liver surgeries is artificial immunosuppression. The primary goal of the immunosuppression is to prevent (or reduce the risk of) graft rejection and treat it if it does occur. Graft loss occurs upon untreated rejection. It is estimated that up to 30% graft loss was due to non-adherence of immunosuppressants. Strategy and commonly used immunosuppressants are listed in Table 2 and also detailed elsewhere [22]. Interleukin 2 signaling pathway in T cell is the main target of immunosuppression in order to prevent acute cellular rejection [23]. Calcineurin inhibitor, such as tacrolimus or cyclosporin, is the current backbone of immunosuppressants. As they are metabolized by liver enzyme cytochrome P450 3A4, grapefruit consumption is not recommended. Similarly, some drugs may have obvious drug-drug interaction with calcineurin inhibitors, such as fluconazole. The immunosuppressants, however, are not without side-effects. Actually, the imaginary therapeutic safety window (without rejection, infection or other side effects) for the immunosuppressants is narrow and varies between individuals (Fig. 4). The safety window may change or fluctuate with time following transplantation. Compared to other solid organ transplants, dosage of immunosuppressants for liver transplant is generally lower probably because the liver is an immune-privileged site much like that of the cornea [24]. Clinicians need to estimate the rejection risk on a case by case basis to achieve adequate degree of immunosuppression at the lowest expense of immunosuppressants to minimize as many side effects as possible, such as renal impairment, neurotoxicity, metabolic syndrome (hypertension, hyperlipidemia, diabetes, hyperuricemia), infection, or malignancy (such as PTLD). We can use two or three kinds of immunosuppressants with different mechanisms together to reduce each side effect. Relevant laboratory tests are ordered based on the profiles of side effects (Table 2) and, many times, subsequent additional medications are prescribed if necessary. Acute rejection is often recognizable in cases of sudden unexplained surge of serum liver enzymes (with no other signs of anatomical reasons such as anastomotic vascular thrombosis). Onset of antibody-mediated rejection is usually insidious and is more difficult to confirm. Liver biopsy is needed to make the final diagnosis of rejection. The future prospective of immunosuppression therapy in liver transplantation community is aimed to: 1) find a “tailored immunosuppression therapy” for each recipient (due to the introduction of new drugs); 2) minimize immunosuppression regimen to reduce side effects; 3) to identify “tolerant” recipients (by clinical characteristics and tolerant blood biomarkers) who can benefit of total withdrawal of immunosuppression drugs after the first years from liver transplantation.

8. HBV and hepatitis C virus (HCV) in liver transplantation: how to deal with them clinically?

Liver transplantation is commonly applied as the management of the complication (such as cirrhosis or HCC) of viral hepatitis due to HBV or HCV. Dealing with these viruses is necessary in liver transplantation. Hepatitis B immunoglobulin (HBIG, anti-HBs antibody) is applied in the perioperative and the short-term post-operative period while nucleoside/nucleotide analogues are administered life-long as HBV prophylaxis after liver transplantation [26]. HBV flare up will occur after liver transplantation without oral nucleoside/nucleotide analogues, as discussed earlier. HBV recurrence under oral nucleoside/nucleotide analogues, although infrequently, may occur in several conditions. Lamivudine, the first introduced nucleoside analogue against HBV, is well-known to have high rate of recurrence due to drug resistance.
Newer analogue agents such as entecavir or tenofovir are of higher viral breakthrough barrier and lower resistance rates [26]. Drug compliance is another issue needed to be addressed when clinicians encounter HBV recurrence. Direct detection of pathogen (such as viral DNA/RNA) after liver transplantation is important because the indirect method (such as antibody detection) is often hampered by artificial immunosuppression.

Chronic hepatitis may occur in HCV (+) liver recipients and result in progressive fibrosis at a rate faster than that before transplantation. Management of HCV in liver transplantation has been rapidly revolutionized nowadays and guidelines are updated frequently as more and more evidence accumulated [27–29]. The trend of anti-HCV therapies has been shifted toward all oral direct acting agents that are free of interferon and ribavirin, and with pan-genotypic spectrum [30]. In contrast to anti-HBV life-long therapy after liver transplantation. Anti-HCV agents are often used on short-term basis because HCV viral genome is accommodated in cytosol without incorporating into host DNA. Three to six months are generally sufficient to achieve long-term sustained virologic response (suggesting total eradication) in recipients without severe fibrosis or cirrhosis. In fact, new treatment of chronic hepatitis C (up to 60% in 4 years).

### Table 1
Main post-operative complications (early and late) after liver transplantation.

| Post-operative complications | Early | Late |
|------------------------------|-------|------|
| Hemorrhage                   | +     | –    |
| Graft function               |       |      |
| Primary nonfunction          | +     | –    |
| Graft dysfunction            | +     | +    |
| Rejection                    | +     | +    |
| Liver disease recurrence     | –     | +    |
| Vascular stenosis/thrombosis |       |      |
| Hepatic artery               | +     | –    |
| Portal vein                  | +     | –    |
| Hepatic vein                 | +     | –    |
| Bile duct                    | +     | –    |
| Bile leak                    | +     | –    |
| Biliary stricture            | +     | –    |
| Systemic infection           |       |      |
| Infection risk               | +     | +    |
| Metabolic syndrome           | –     | +    |
| Malignancy                   | –     | +    |

### Table 2
Management strategy and medications of immunosuppression commonly applied in liver transplantation.

| Immunologic risk of graft | Aim | Duration | Management | Drugs | Main side effect |
|---------------------------|-----|----------|------------|-------|-----------------|
| Cellular rejection        | Prophylaxis | Induction | Anti-CD25<sup>+</sup> | Basiliximab | Allergy |
|                           |      | Maintenance | Calcineurin inhibitor | Tacrolimus, cyclosporin | Metabolic syndrome, renal injury |
|                           |      |            | mTOR inhibitor | Everolimus, sirolimus | Hyperlipidemia, proteinuria, poor wound healing |
|                           |      |            | Antimetabolite | Mycophenolate mofetil, mycophenolic acid | GI upset, bone marrow suppression |
|                           |      |            | Steroid | Prednisolone | Numerous [25] |
|                           |      |            | Steroid<sup>+</sup> | Solumedrol, solucortef | Surges in blood sugar |
|                           |      |            | Anti-CD20<sup>+</sup> | Rituximab | Allergy, infection |
|                           |      |            | Calcineurin inhibitor | Tacrolium, cyclosporin | Metabolic syndrome, renal injury |
|                           |      |            | Antimetabolite | Mycophenolate mofetil, mycophenolic acid | GI upset, bone marrow suppression |
|                           |      |            | IVIG<sup>a</sup> | – | Allergy |
|                           |      | Pulse | Plasmapheresis | Rituximab | Allergy, infection |
|                           |      | Induction (2 weeks before transplantation) | Anti-CD20<sup>+</sup> | Bortezomib | Allergy, infection |
|                           |      | | Proteasome inhibitor<sup>+</sup> | – | Allergy, infection |
|                           |      | | IVIG<sup>a</sup> | – | Allergy |
|                           |      | | Plasmapheresis | – | Allergy, infection |

<sup>a</sup> Intravenous; IVIG, intravenous immunoglobulin.
like Sofosbuvir will, perhaps, lower the number of transplantations due to chronic hepatitis C.

9. Future perspective

The success of liver transplantation makes it gold-standard in the treatment of end-stage liver diseases. Future research directions such as individualizing immunosuppression using a phenotypic personalized medicine platform [31], mixed chimerism which could help reduce the need for immunosuppressive drugs [32], 3D printing of organs as attempts to address organ shortages [33], or cell replacement therapy [34] are of great potential and open for students who are going to intercalate mid-way through their medical education.

In conclusion, medical students are expected to see these long-lived recipients visiting all kinds of clinical practice in the future. Basic understanding of the essentials (and the underlying rationales) of liver transplantation will help students prepare for advanced learning and cope with the liver recipients without fear in the future.

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Conflicts of interest

Nothing to disclose.
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