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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 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.

Abbreviation: GRWR, graft-recipient-weight ratio; SFSS, small for size syndrome; MELD, model for end stage liver disease; INR, international normalized ratio; PTLD, post-transplant lymphoproliferative disease; HCC, hepatocellular carcinoma; UCSF, University of California San Francisco; HBV, hepatitis B virus; HCV, Hepatitis C virus.

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Contents

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 with the emphasis primarily on the underlying rationale related to what they already know, bridging the knowledge gap instead of focusing on extensively detailed, specialized information [4]. When we prepared the teaching material for medical students and searched the literature, the available and suitable information for medical education is limited and not satisfactory. Therefore, the aim of this topic highlight is, with the hope for medical students, to gain enough insight of the general real-world picture of what the liver recipients look like and let them feel confident to approach these patients properly in the future. We also hope to inspire educators at medical schools to better address this issue.

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 upmost priority of multiple issues tangled each other in 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 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).

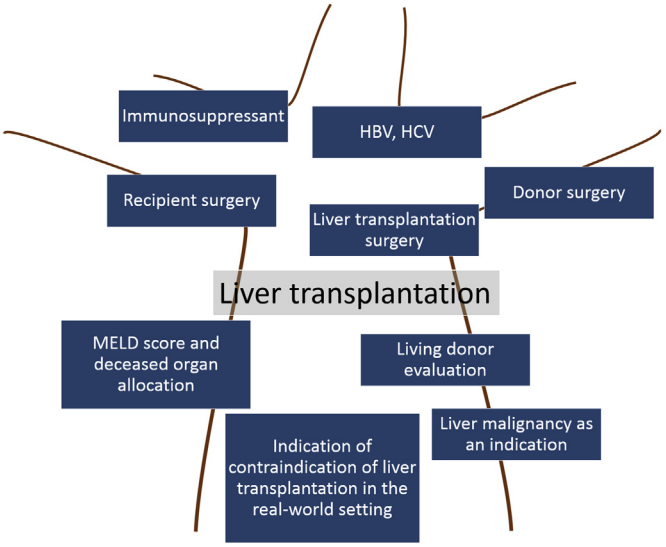

Fig. 1. Schematic of the knowledge tree of liver transplantation essential for medical student learning from tree root, trunk, to branch details of knowledge.

MELD: model for end-stage liver disease, an estimate of 3-month mortality due to liver disease. The score is calculated based on international normalized ratio (INR), bilirubin, and creatinine. It determines the prognosis and prioritizes liver transplant candidates [5].

Perfusion vs. reperfusion: ice-cold preservation solution with high potassium concentration is used to perfuse the liver graft to keep it at low metabolic rates and reduce the ischemic-reperfusion damage. Reperfusion means blood circulation is re-established in and out of the liver *in vivo* after reconstruction is finished.

PTLD: post-transplant lymphoproliferative disease, a B-cell related post-transplant malignancy. Usually due to over immunosuppression in recipients who carry Epstein-Barr virus.

Small for size syndrome (SFSS): GRWR below 0.6% is of high risk to develop SFSS. Typical signs of liver failure such as jaundice, ascites and coagulopathy will appear in this case. The underlying pathophysiology is portal hypertension due to flow overload and sinusoidal endothelial damage [6].

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 $= 3.78 \times \ln[\text{serum bilirubin (mg/dL)}] + 11.2 \times \ln[\text{INR}] + 9.57 \times \ln[\text{serum creatinine (mg/dL)}] + 6.43$. 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 standard technique presently used for hepatic vein reconstruction in most institutions; b. auxiliary liver transplant for acute liver failure provides native liver with an opportunity to regenerate and free of life-long immunosuppressants; c. reperfusion firstly though hepatic artery and hepatic vein.

Checking of Doppler flow of the reconstructed vessels is important to assess or differentiate the cause of abnormal liver function test quickly and non-invasively in the early post-operative period. Surgical complications such as biliary (bile leakage and biliary stenosis) and vascular (arterial, portal and hepatic venous stenosis and thrombosis) complications may occur in early post-operative period, especially in the setting of difficult and sometimes non-ergonomic (for surgeons) anastomosis of minute tubular structures. Table 1 summarizes main early and late post-operative complications after liver transplantation.

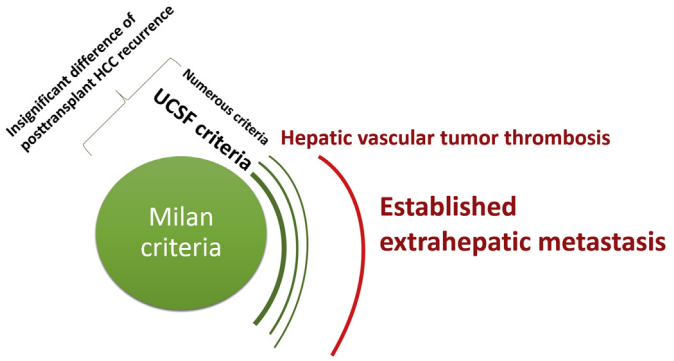

Fig. 2. Conceptual illustration of relationship between Milan criteria and others set for liver transplantation against hepatocellular carcinoma to complete en bloc removal of cancer and reduce the risk of post-transplant cancer recurrence.

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

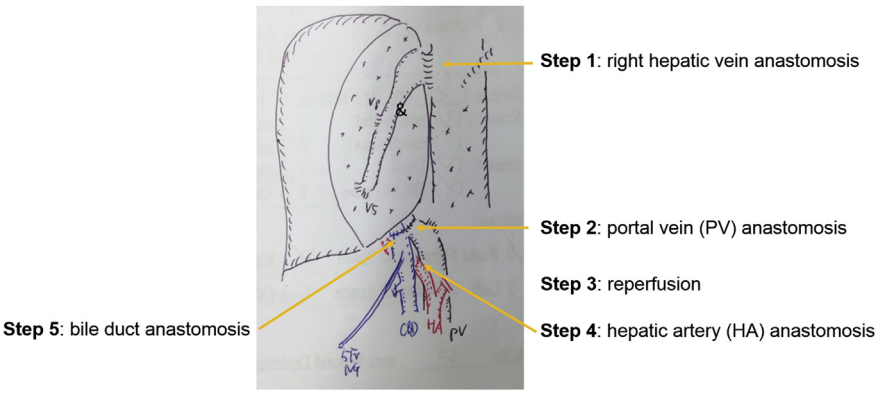

Fig. 3. An illustrative example of the principal steps of the right lobe implantation in a living donor liver transplantation. Reperfusion of the liver circulation is established by releasing the clamping of hepatic vein and portal vein after these anastomoses are completed. Hepatic artery anastomosis is usually performed under microscopic field. No.5 French nasogastric tube (NG) is used as an external stenting in this case. CBD, common bile duct. & bridging vein graft connecting cutting surface hepatic veins draining segment 5 (V5) and 8 (V8).

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 risk	+	+
Metabolic syndrome	–	+
Malignancy	–	+

(up to 60% in 4 years). 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

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[a]	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]
	Treatment	Pulse	Steroid[a]	Solumedrol, solucortef	Surges in blood sugar
Antibody-mediated rejection	Prophylaxis in ABO incompatible transplantation	Induction (2 weeks before transplantation)	Anti-CD20[a]	Rituximab	Allergy, infection
			Calcineurin inhibitor	Tacrolimus, cyclosporin	Metabolic syndrome, renal injury
			Antimetabolite	Mycophenolate mofetil, mycophenolic acid	GI upset, bone marrow suppression
			IVIG[a]	–	Allergy
			Plasmapheresis	–	Allergy, infection
	Treatment	Course	Anti-CD20[v]	Rituximab	Allergy, infection
			Proteasome inhibitor[a]	Bortezomib	Allergy, infection
			IVIG[a]	–	Allergy
			Plasmapheresis	–	Allergy, infection

[a] Intravenous; IVIG, intravenous immunoglobulin.

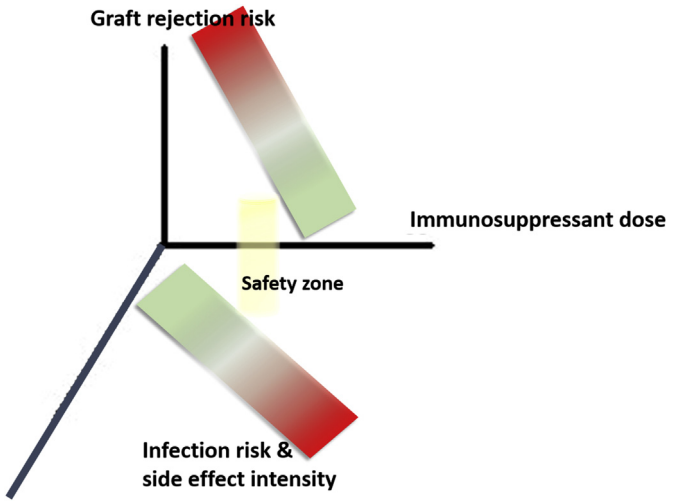

Fig. 4. Conceptual illustration of impact of immunosuppressant dosage on graft rejection, infection and side effects. Note that the narrow safety zone of immunosuppressant dosing in yellow. Safety zone varies between individuals and changes with time following transplantation. Dose titration is necessary.

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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Author contribution

study concept and design: HCM, LPH; acquisition of data: HCM, LPH; analysis and interpretation of data: HCM, LPH; drafting of the manuscript: Critical language and grammar revision: TCW; HCM; critical revision of the manuscript for important intellectual content: all; technical, or material support: HCM, LPH; study supervision: HRH, HMC, WYM.

Conflicts of interest

Nothing to disclose.

Guarantor

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Po-Huang Lee.

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