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Considerations on liver transplantation. concise literature review and update

Abstract

Liver transplantation has gone through significant improvement since its start early last century. Which resulted in an increased demand unmatched by availability of donors, hence, several new approaches were devised to maintain an adequate supply of grafts, paralleled with tremendous efforts to minimize graft rejection in many aspects of the procedure, particularly, choice of patients to be transplanted, pre-operative preparation, intra-operative anesthetic as well as surgical management, the care of the transplanted patient in the intensive care unit, and finally long term follow up.The aim of this review was to update on the most recent approaches involves in different steps of the procedure. Several new modalities of management and interventions were recognized, pertaining to patient allocation, perioperative period, critical care management, and follow up.

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Introduction

It all started with the first successful liver transplantation (LT) back in 1963 by Thomas Starzl,[1] since then, the field of LT experienced a tremendous advancement and improvement, such that LT is now recognized worldwide as the only treatment modality for end-stage liver disease, acute fulminant hepatic failure, hepatocellular carcinoma, and a range of metabolic disorders,[2] as was ultimately declared by the National Institute of Health (NIH) in 1983.[3] This improvement resulted in increased success rates LT, and better patients' survival, as for example in Europe most transplanted patients have an eventless short Intensive Care Unit (ICU) stay, with mortality rate around 5%.[4] However; along with the improvement of LT procedures and increasing success rates arose the challenges and obstacles, outstanding among which is the organ shortage, along with surgical and anesthetic management, ICU postoperative period, to immunosuppression and its consequences.[5]

Aim of the review

To describe the multifactorial obstacles facing LT, at the different stages of the process, and enlighten about their progress till the current updated status.

Prioritization for liver transplantation

Early this century enrollment in LT waiting lists depended on the child-turcotte-pugh score (CTP), which suffered several limitations, such as the interpretation of subjective parameters, the likes of encephalopathy and ascites, furthermore, it was a subject of manipulation, which ultimately lead to misuse of available organs,[6] these shortcomings eventually lead to the development of a scoring system that depends largely on evaluating objective parameters, the MELD score,[7] and although it was originally validated to predict survival following the TIPS procedure (Transjugular intrahepatic portosystemic shunt), it has been widely used to prioritize the allocation of organs for LT in an objective manner, since it is a mathematical model based on measureable patient's parameters such as bilirubin concentration, international normalized ratio (INR), prothrombin time, and creatinine concentration. In fact, since its adoption by the United Network of Organ Sharing (UNOS) in 2002, percentages of death while awaiting allocation for LT dropped from 30% to 15%.[8]

Recently, the recommendation of the Austrian society of gastroenterology and hepatology (OGGH)[9] indicate that patients with acute or chronic liver failure should be assessed on individual basis, regardless of the etiology, with the understanding that a 1-year survival of less than 90% is the minimum requirement for enrollment on LT waiting lists. Other publications[10] detail indications for LT by causes, among which Acute Fulminant Liver Failure is on top of the list, mostly as a result of acetaminophen toxicity. Chronic liver failure with 1-year survival prognosis of 10% is an indication of LT, regardless of CTP or MELD scores. Patients with Alcoholic liver disease are indicated for LT under the condition of 3-6 month period of abstinence, psychiatric evaluation, and CTP score ≥ 7.[11] Viral hepatitis such as hepatitis B and C related chronic liver disease are also indicated for LT, although they are prone to recurrence in the new graft, still they constitute the majority of transplanted patients in the USA.[12] Other indications include cholestatic liver disease such as primary biliary cirrhosis, hepatic malignancies the likes of hepatocellular carcinoma, since it's associated with cirrhosis in up to 80% of cases, metabolic liver diseases causing decompensated irreversible damage such as Wilson's disease, and vascular diseases like Budd Chiari syndrome.[10, 13,14]

Organ shortage and preservation

With the undoubted improvement in LT and increasing success rates, comes the burden of locating donors as the demand for grafts increases, a demand that is not parallel to availability of grafts, resulting in 18% of patients on LT lists die or become too sick to operate before a graft is allocated.[4] Several approaches have been suggested to overcome this issue of unbalanced demand and availability, one approach is to utilize grafts from donors with high risks, after a well thought balancing of inevitable death against grafting from a high risk donor, risks from donors may be in the form of transmission of infection (such as HIV) or malignancy,[4,15] but has also been reported for autoimmune diseases such as idiopathic thrombocytopenia and metabolic conditions like porphyria.[16,17] Living donors provide and increasing source of organs particularly in the Far East, with different regulatory frameworks and supporting systems among different countries in order to mitigate issues such as transplant tourism,[5] this is not the case, however; in western countries as the numbers of living donors has not increased over 10 years.[18] Outcomes of recipients are similar to if not better than those transplanted from a deceased donor, at least in terms of shorter waiting periods, as for the donors mortalities range from 1/250 to 1/500 donors.[19]

Many centers worldwide try to overcome the issue of organ shortage by widening the range of possible graft donors, such as the use of (in addition to high risk donors) auxiliary transplantation, which was performed early in the years of LT but became unpopular in view of the development of cancer in the original liver, and is now being replaced by auxiliary partial transplantation particularly for patients with acute liver failure.[20] The majority of transplanted livers remains from deceased donors, in different stages of end of life, such as donors after determination of circulatory death, this category constitutes up to 33% of deceased donor grafts in UK,[21] and initially showed discouraging results due to prolonged perfusion ischemia of the graft, however; more recently several studies provided evidence of their beneficial impact such as the relatively young age of donors, less than 30 minutes donor warm ischemia time, and less than 10 minutes donor cold ischemia time.[22,23] Splitting livers has become an attractive solution to scarcity of organs, whereby a donated liver is shared between an adult and a pediatric patient, and despite greater technical difficulties associated with such technique compared to whole liver transplantation, results from studies show 82% 10-year survival and 62% 10-year survival in pediatric and adult patients respectively.[6, 24]

As previously outlined the majority of organ grafts are from deceased donors, which automatically raises the importance of preserving the vitality and viability of the organ till it is transplanted. The main well studied solutions to preserve a liver graft are: The university of Wisconsin solution (UW), the Institute George Lopez solution-1 (IGL-1), Celsior solution, and histidine-tryptophan ketoglutarate preservation solution (HTK),[25] and the UW solution is the standard of care in multiple countries including USA. A report of the European Liver Transplant Registry showed comparable results with IGL-1,[26] and a meta-analysis recently showed similar outcomes using those four solutions.[27] In addition to the different preservation solutions, static cold storage used to be the most popular method used for graft preservation all over the world,[25] not only for liver grafts but also for lung, heart, and kidney grafts. But as the process of LT advanced, dynamic techniques of preservation started to gain popularity and utilization. Of which, three main categories can be identified, namely: Normothermic machine perfusion (NMP), Subnormothermic machine perfusion (SNMP), and Hypothermic machine perfusion (HMP).[28,29] Machine perfusion (whether hypo or normothermic) is usually done ex situ, and the commercially available machines allow not only for the perfusion of the graft, but also performs several physiologic assessments, like lactate clearance, and bile production, which greatly aid surgeons in making the decision whether or not to use the graft, on the other hand, such machines are quite expensive, and consume resources, which renders their routine use a debatable issue.[5] The concept of hypothermic perfusion is that hypothermia slows down metabolism of cells, and prolongs the period an organ may remain viable despite deprivation of oxygen.[18] The clinical significance of the concept was shown as studies[30,31] revealed better graft function, lower transaminases, and duration of hospital stay using this method. On the contrary to HMP where the concept is to lower cellular metabolism, NMP aims at continuing cell metabolism at close to normal rates, as result it is more demanding, since it requires a continuous supply of oxygen and nutrients, thus minimizing ischemia of the graft, and theoretically improving its function.[18] The benefits of NMP were demonstrated on discarded livers of deceased patients in the work by Dries et al.[32] as after 6 hours of NMP at 37 degrees Celsius histological examination of the cells revealed no cellular damage or ischemia, and bile production was maintained. In a recent randomized controlled trial comparing NMP to static cold preservation, NMP was associated with 50% lower graft injury and discard, while no difference in patient or graft survival was observed between the two groups.[33] The third technique used for liver preservation is SNMP, which is usually performed at 20 C, and carries the advantages of avoiding ischemia – reperfusion injury, continuation of liver cell metabolism, and the ability to monitor the graft's function, in order to make an informed decision of whether to discard the graft or not, monitoring which is reflected in serum urea, albumin, and production of bile.[34] Identified literature indicate that NMP is the most extensively studied method of hepatic graft preservation. Yet, recently a modification of HMP was evaluated in two trials by the same author, the modification entails Hypothermic Oxygenated Perfusion (hence the name HOPE).[35,36] Initially, after a follow up period of 8 and a half months there were no signs of intrahepatic biliary complications, later on they were able to demonstrate an improvement of 1-year survival as compared to static cold preservation, 11% reduction of graft dysfunction, and 30% reduction of biliary complications.

Clinical aspects of liver transplantation

Since the early 1960s outcomes of liver transplantation surgeries have significantly improved, this is mainly due to the improvement and advancement of all the clinical aspects of the procedure, starting at preoperative assessment, to the anesthesia management and surgical techniques, followed by the critical care period, and finally the long run follow up including immunosuppression. We will cover in this section the updates of these clinical aspects.

Preoperative assessment

Assessment of the end stage liver disease patient before LT procedure is mandatory, as this is a high risk patient, ongoing a high risk procedure.[37] Among the most important evaluations is the cardiac, as coronary artery disease has been linked to end stage liver disease in studies[38] with an increased incidence of up to 27%. Perfusion imaging of the myocardium with dobutamine stress echocardiography and single photon emission tomography are usually performed,[6] furthermore, cirrhotic patients may suffer cirrhotic cardiomyopathy, that is characterized by baseline increased cardiac output, and impaired reserve of contractile functions in response to stress, diastolyic dysfunction particularly in the presence of ascites, along with prolongation of QT interval.[39]

Portopulmonary hypertension (PPH) is a pulmonary hypertension syndrome coexisting with portal hypertension as a result of vascular obstruction. All patients for LT should be screened for PPh as it is detrimental in the postoperative period. PPH could be detected by and electrocardiograph or an echocardiography study, but accurate values of pulmonary hypertension are obtained by right heart catheterization, and severity of the syndrome may classified according to mean pulmonary artery pressure into: mild (PAPm 25–34 mmHg), moderate (PAPm 35–44 mmHg) and severe (PAPm>45 mmHg).[37] Pleural effusion is not uncommon in cirrhotic patients, usually alongside ascites, and it may be needed to be drained prior to surgery.[40] An evaluation of renal functions is also required, since renal dysfunction is associated with cirrhotic liver as a result of decreased blood volume due to vasodilatation. The most commonly associated renal dysfunction with cirrhotic liver are Hepato-renal syndrome types 1 and II.[37,41] The coagulation status of an end stage liver disease patient is usually deranged, and the guidelines of European society of Anesthesia don't recommend correction of INR between 1.5 and 5.[42] A neurologic assessment is also required, as many cirrhotic patients suffer encephalopathy presumably due to high levels of ammonia gaining access to the systemic circulation through the dysfunctional liver, cognitive functions and level of consciousness may be evaluated in those patients using the West Haven criteria,[43] which range from 1: trivial lack of awareness, to 4: Coma.

Anesthetic management

Despite advances in all aspects of anesthesia, managing a patient for LT remains a challenge for the anesthesiologist, as the patient is subject to major hemodynamic instabilities that differ according to the stage of surgery.[37] Initially the LT patient should be extensively monitored using routine as well as invasive monitoring of the different body systems and functions. Routine monitoring include 5-lead ECG, pulse oximetry, non-invasive blood pressure, temperature, and capnography. Invasive monitoring may include an arterial line with invasive blood pressure monitor, a central venous catheter, or less commonly a right sided cardiac catheter, Trans-esophageal echocardiography, in addition to Bispectral index monitoring.[44] More recently, newer techniques (other than Swan Ganz) have been implemented in the measurement of cardiac output, methods such as Pulse-induced Contour Cardiac Output, utilizing a catheter inserted in femoral artery, and thoracic bio-impedance which estimates cardiac output and numerous other hemodynamic parameters based on electric properties of the chest as a result of blood movement.[45,46] As for neurological monitoring transcranial Doppler echography is used to diagnose vasospasm and intracranial hypertension, while Jugular bulb oxygen saturation (SjvO2) is used to detect ischemia with values < 50%, or hypremia with values > 75%.[37]

Anesthetic management of hemodynamic changes during the phases of surgery

LT procedure is well known to be associated with bleeding and loss of significant volumes of blood, and consequently, transfusion of blood products, although over the years, this has greatly declined[47]. Clamping of the inferior vena cava during the procedure reduces venous return and cardiac preload, resulting in drop of blood pressure, which is not compensated for by right and left ventricular responses in the next stage as a result of the substances secreted by the liver. All these effects mandate specific management for each stage of the procedure[37, 44]:

Pre-anhepatic phase: During this phase and before clamping of the inferior vena cava the anesthetist should try to reach normovolemia, and compensate for fluids lost in ascetic fluid. Albumin 5% to 20% can be used in this phase.

Anhepatic phase: During this phase fluid restriction is advised, while maintaining adequate blood pressure through the use of vasoactive drugs, the recommended choice of which is Noradrenaline. Neohepatic phase: During this phase adequate fluid resuscitation should take place, guided by measured parameters of cardiac output, and special care should be given to gradual decrease of vasoactive medications.

Post-perfusion syndrome

This is one of the most challenging events in LT procedure, as it is the most unstable period of the procedure, characterized by 30% drop of arterial blood pressure just after unclamping of inferior vena cava. Though it is not clear why the syndrome takes place, several theories have been put forward to explain it, such as the cold preservation solution, release of nitric oxide, and proinflammatory cytokines.[48] Suggested strategies to handle this period of hemodynamic instability include: Attaining normovolemia ahead of unclamping, graft wash with 5% albumin prior to unclamping, correction of hyperkalemia and hypocalcemia, and administration of Adrenaline bolus 5 minutes prior to release of inferior vena cava clamp, to achieve a mean arterial pressure of 85-100 mmHg.[49]

Critical care management

Undoubtedly, the postoperative period after LT is quite unique, in view of the preoperative condition of the patient, the nature of the surgical procedure, and the hemodynamic targets and goals to be achieved in the ICU in order to preserve and maintain the graft, ensuring success of the whole procedure. Surprisingly, little is known about this period in the journey of LT patients, since they are usually excluded from clinical trials.[50]

General principles: Once a LT patient is admitted to ICU, general principles of monitoring are applied, similar to any other critically ill patients. Such principles include: intensive hemodynamic monitoring, including both non-invasive devices (blood pressure, oxygen saturation, temperature, cardiac monitoring, urine output…etc) as well as invasive techniques such as arterial lines, central venous pressure, and possibly pulmonary artery pressure monitoring.[51] Initiation of standard of care monitoring is followed by laboratory workup, which should include at least arterial blood gases, complete blood count including hemoglobin, complete coagulation profile, metabolic panel investigations including liver and renal functions, ammonia, and lactate), baseline electrolytes should be established, and all lab investigations to be repeated every 6-12 hours.[52]

*Hemodynamic maintenance:*The primary aim is to maintain adequate arterial pressure to ensure perfusion of the graft, and a mean arterial pressure of 70 mmHg is generally accepted, to counter act the expected hypotension that may occur due to several reasons including bleeding, hypothermia, and fluid shifts due to hypoalbuminemia. Fluid replacement can be established using crystalloids or albumin containing fluids, and hemodynamics may be augmented by vasopressors such as noradrenaline or adrenaline.[53]

Respiratory monitoring: In addition of the previously outlined monitoring, a chest radiograph should be obtained, and all parameters of respiratory functions closely monitored, as pulmonary oedema following LT is common in up to 50% of cases in the first 24 hours, and should be managed promptly, pulmonary oedemamay be caused by the already present cardiomyopathy, or the increased afterload.[54]

Renal complications: Renal impairment is reported to occur in up to 50% of LT patients, and up to 17% require renal replacement therapy, with certain indications that may be biochemical (refractory hyperkalemia, acidosis, hypo or hypernatremia), or clinical indications (oliguria, refractory hypervolemia, uremic encephalopathy).[55,56]

Nutrition: End stage liver disease patients usually suffer disturbances in lipid, carbohydrate, and protein metabolism, and frequently are malnourished prior to surgery. These disturbances have been linked to post-operative infection, respiratory complications, and prolonged ICU stay. Based on the level of stress to which the patient is exposed to (related to stability) it is generally accepted that a caloric requirement of 25 – 40 Kcal/kg/day is adequate, to be achieved gradually over 5-7 days, the energy sources should be divided between carbohydrates and lipid as 60%: 40%.[57]

Follow up and immunosuppression

LT outcomes are improving, yet, survival is reduced in terms of quantity as well as quality, many patients particularly children continue to suffer psychological problems,[58] a great part of the success rate increase in LT is due to the large arsenal of immunosuppressive drugs, with variable mechanisms of action, such as T-cell depleting antibodies (alemtuzumab), interleukin 2 receptor blocking antibodies, antimetabolites, and corticosteroids.[58] Newer agents have been subject of trials, particularly after their promising results in renal transplantation, such as Belatacept (selective blocker of co-stimulation Anti CD28).[59] However, despite all these improvements in LT, an estimate of up to one third of grafts are lost due to non-compliance, particularly in pediatric and adolescent patients, with psychological factors probably intermediating, in addition to financial and logistic factors. One possible solution is the use of tacrolimus preparations that are given once daily, as this may help stabilize serum levels, and bring about better compliance among transplanted patients.[60,61]

Conclusion

LT is a challenging procedure for all medical personnel involved, it has experienced great improvements and advancements since its early days in the 60s, and continues to investigate and research novel approaches, techniques, and medications, with the aim of overcoming a major healthcare issue, the imposes a great burden on the community and health systems.

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References

1. Starzl TE, Marchioro TL, Vonkaulla KN, et al. Homotransplantation ofthe liver in humans. Surg Gynecol Obstet. 1963;117: 659–676.
2. Jadlowiec CC, Taner T. Liver transplantation: Current status and challenges. *World J Gastroenterol*. 2016;22(18):4438–4445.
3. National institutes of health consensus development conference statement: liver transplantation--June 20-23, 1983. *Hepatology*. 1984;4 (1 suppl):S107–S110.
4. Baganate F, Beal EW, Tumin D, et al. Early mortality after liver transplantation: defining the course and the cause. *Surgery*. 2018;164:694–704.
5. Neuberger J. An update on liver transplantation: A critical review. *J Autoimmun*. 2016;66:51–59.
6. Serkan D, Ahmet G. Liver transplantation update: 2014. *Euroasian J Hepato-Gastroenterol*. 2015;5(2):98–106.
7. Freeman RB Jr, Wiesner RH, Harper A, et al. UNOS/OPTN Liver Disease Severity Score, UNOS/OPTN Liver and Intestine, and UNOS/OPTN Pediatric Transplantation Committees. The new liver allocation system: moving toward evidence-based transplantation policy. *Liver Transpl*. 2002;8(9):851–858.
8. Kamath PS, Kim WR, Advanced liver disease study group. The model for end-stage liver disease (MELD). *Hepatol*. 2007;45(3):797–805.
9. Graziadei I, Zoller H, Fickert P, et al. Indications for liver transplantation in adults: Recommendations of the Austrian Society for Gastroenterology and Hepatology (ÖGGH) in cooperation with the Austrian Society for Transplantation, Transfusion and Genetics (ATX). *Wien Klin Wochenschr*. 2016;128(19-20):679–690.
10. Vibha V, Naimish M, Vinay K, et al. Indications and Contraindications for Liver Transplantation. *International Journal of Hepatology*. 2011.
11. Neuberger J, Schulz KH, Day C, et al. Transplantation for alcoholic liver disease. *Journal of Hepatology*. 2002;36(1):130–137.
12. Curry MP. Hepatitis B and hepatitis C viruses in liver transplantation. *Transplantation*. 2004;78(7):955–963.
13. UNOS Policy 3 Appendix 3B, 2011.
14. Sherman M. Hepatocellular carcinoma: epidemiology, risk factors, and screening. *Seminars in Liver Disease*. 2005;25(2):143–154.
15. Desai R, Neuberger J. Donor transmitted and de novo cancer after liver transplantation. *World J Gastroentrol*. 2014;20:6170e6179.
16. Pereboom IT, de Boer MT, Haagsma EB, et al. Transmission of idiopathic thrombocytopenic purpura during orthotopic liver transplantation. *Transpl Int*. 2010;23:236e238.
17. Popescu I, Dima SO. Domino liver transplantation Low far can we push the paradigm? *Liver Transpl*. 2012;18:22e28.
18. Caroline C Jadlowiec, Timucin Taner. Liver transplantation: Current status and challenges. *World J Gastroenterol*. 2016;22(18):4438–4445.
19. Ladner DP, Dew MA, Forney S, et al. Long-term quality of life after liver donation in the adult-to-adult living liver transplantation cohort study (A2ALL). *J Hepatol*. 2015;62:346e353.
20. Shawcross DL, O'Grady J. The 6-month abstinence rule in liver transplantation. *Lancet*. 2010;376:216e221.
21. Manara AR, Murphy PG, O'Callaghan G. Donation after circulatory death. *Br J Anaesth*. 2012;108 (Suppl 1):i108e121.
22. Mateo R, Cho Y, Singh G, et al. Risk factors for graft survival after liver transplantation from donation after cardiac death donors: an analysis of OPTN/UNOS data. *Am J Transplant*. 2006;6:791–796.
23. Taner CB, Bulatao IG, Willingham DL, et al. Events in procurement as risk factors for ischemic cholangiopathy in liver transplantation using donation after cardiac death donors. *Liver Transpl*. 2012;18:100–111.
24. Oniscu GC, Diaz G, Levitsky J. Meeting report of the 19th Annual International congress of the International liver transplantation society (sydney convention and exhibition centre, Sydney, Australia, June 12-15, 2013). *Liver Transpl*. 2014;20(1):7–14.
25. Marcio F Chedid, Marcelo A Pinto, Jose Felipe G Juchem, et al. Liver preservation prior to transplantation: Past, present, and future. *World J Gastrointest Surg*. 2019;11(3):122–125.
26. Adam R, Delvart V, Karam V, et al. ELTR contributing centres, the European Liver, Intestine Transplant Association (ELITA). Compared efficacy of preservation solutions in liver transplantation: a long-term graft outcome study from the European liver transplant registry. *Am J Transplant*. 2015;15:395–406.

27. Szilágyi ÁL, Mátrai P, Hegyi P, et al. Compared efficacy of preservation solutions on the outcome of liver transplantation: Meta-analysis. *World J Gastroenterol*. 2018;24:1812–1824.

28. Quillin RC, Guarrera JV. Hypothermic machine perfusion in liver transplantation. *Liver Transpl*. 2018;24:276–281.

29. Ravikumar R, Jassem W, Mergental H, et al. Liver transplantation after ex vivo normothermic machine preservation: a phase 1 (First-in-Man) clinical trial. *Am J Transplant*. 2016;16:1779–1787.

30. Guarrera JV, Estevez J, Boykin J, et al. Hypothermic machine perfusion of liver grafts for transplantation: technical development in human discard and miniature swine models. *Transplant Proc*. 2005;37:323–325.

31. Guarrera JV, Henry SD, Samstein B, et al. Hypothermic machine preservation facilitates successful transplantation of "orphan" extended criteria donor livers. *Am J Transplant*. 2015;15(1):161–169.

32. S op den Dries S, Karimian N, Sutton ME, et al. Ex vivo normothermic machine perfusion and viability testing of discarded human donor livers. *Am J Transplant*. 2013;13(5):1327–1335.

33. Nasralla D, Coussios CC, Mergental H, et al. Consortium for organ preservation in europe. a randomized trial of normothermic preservation in liver transplantation. *Nature*. 2018;557:50–56.

34. Boteon YL, Boteon AP, Attard J, et al. Impact of machine perfusion of the liver on post-transplant biliary complications: A systematic review. *World J Transplant*. 2018;8(6):220–231.

35. Dutkowski P, Schlegel A, de Oliveira M, et al. HOPE for human liver grafts obtained from donors after cardiac death. *J Hepatol*. 2014;60:765–772.

36. Dutkowski P, Polak WG, Muiesan P, et al. First comparison of hypothermic oxygenated perfusion versus static cold storage of human donation after cardiac death liver transplants: an international-matched case analysis. *Ann Surg*. 2015;262(5):764–770.

37. Gabriela Droc and Lavinia Jipa. Anesthesia for liver transplantation, organ donation and transplantation - current status and future challenges, Georgios Tsoulfas, IntechOpen, DOI: 10.5772/intechopen.75167.

38. Safadi A, Homsi M, Maskoun W, et al. Perioperative risk predictors of cardiac outcomes in patients undergoing liver transplantation surgery. *Circulation*. 2009;120(13):1189–1194.

39. Garg A, Armstrong W. Echocardiography in liver transplant candidates. *JACC: Cardiovascular Imaging*. 2013;6(1):105–119.

40. Dalal A. Anesthesia for liver transplantation. *Transplantation Reviews*. 2016;30(1):51–60.

41. Martin P, DiMartini A, Feng S, et al. Evaluation for liver transplantation in adults: 2013 practice guideline by the AASLD and the American Society of Transplantation. *Hepatology*. 2014;59(3):1144–1165.

42. Kozek-Langenecker SA, Afshari A, Albaladejo P, et al. Management of severe perioperative bleeding: Guidelines from the European Society of Anaesthesiology. *European Journal of Anaesthesiology*. 2013; 30(6):270–382.

43. Wróblewski T, Kobryń K, Kozieł S, et al. Acetaminophen (Paracetamol) induced acute liver failure – A social problem in an era of increasing tendency to self-treatment. *Ann Agric Environ Med*. 2015;22(4):762–767.

44. S Kashimutt, A Kotzé. Anaesthesia for liver transplantation. *BJA Education*. 2017;17(1):35–40.

45. Alhashemi JA, Cecconi M, Hofer CK. Cardiac output monitoring: An integrative perspective. *Critical Care*. 2011;15(2):214.

46. De Pietri L, Mocchegiani F, Leuzzi C, et al. Transoesophageal echocardiography during liver transplantation. *World Journal of Hepatology*. 2015;7(23):2432–2448.

47. Starzl TE, Iwatuski S, VanThiel DH, et al. Evolution of liver transplantation. *Hepatology*.1982;2(5):614–636.

48. Paugam-Burtz C, Kavafyan J, Merckx P, et al. Postreperfusion syndrome during liver transplantation for cirrhosis: Outcome and predictors. *Liver Transplantation*. 2009;15(5):522–529.

49. Fayed NA, Murad WS. Goal directed preemptive ephedrine attenuates the reperfusion syndrome during adult living donor liver transplantation. *Egyptian Journal of Anaesthesia*. 2014;30(2):187–195.

50. Ian D. McGilvray, Paul D. Greig. Critical care of the liver transplant patient: an update. Current Opinion in Critical Care. 2002; 8(2):178–182.

51. Mert Akan. Intensive care management in adult liver transplantation. *Anaesthesia, Pain and Intensive Care*. 2016;20(1):92–110 ·

52. Akdur A, Sevmiş Ş, Karakayalı H. Erişkin karaciğer naklinde postoperatif bakım. Yoğun Bakım Dergisi. 2010;9:85–97.

53. Smyrniotis V, Kostopanagiotou G, Theodoraki K, et al. The role of central venous pressure and type of vascular control in blood loss during major liver resections. *Am J Surg*. 2004;187(3):398–402.

54. Feltracco P, Barbieri S, Galligioni H, et al. Intensive care management of liver transplanted patients. *World J Hepatol*. 2011;3(3):61–71.

55. Campbell MS, Kotlyar DS, Brensinger CM, et al. Renal function after orthotopic liver transplantation is predicted by duration of pretransplantation creatinine elevation. Liver Transplant. 2005;11(9):1048–1055.

56. Arroyo V, Fernandez J, Gines P. Pathogenesis and treatment of hepatorenal syndrome. *Semin Liver Dis*. 2008;28(1):81–95.

57. lauth M, Cabré E, Riggio O, ESPEN guidelines on enteral nutrition: liver disease. *Clinical Nutrition*. 2006;25(2):285–294.

58. A Huda, R Newcomer, C Harrington, et al. Employment after liver transplantation: a review. Transpl Proc. 2015;47(2):233–e239.

59. GB Klintmalm, S Feng, JR Lake, et al., Belatacept-based immunosuppression in de novo liver transplant recipients: 1-year experience from a phase II randomised study, *Am J Transpl*. 2014;14(8):1817–1827.

60. J Ferguson, JA Leithead, C Lloyd, et al. Pediatric liver transplant recipients who undergo transfer to the adult health care service have good long-term outcomes, *Am J Transpl*. 2015;15(7):1864–e1873.

61. Coilly A, Calmus Y, Chermak F, et al. Once-daily prolonged release tacrolimus in liver transplantation: expert's literature review and recommendations. *Liver Transpl*. 2015;21(10):1312–1321.