Review

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Liver transplantation and autoimmune hepatitis

Tomohiro Tanaka[1], Yasuhiko Sugawara[2,*], Norihiro Kokudo[2]

[1] *Organ Transplantation Service, The University of Tokyo Hospital, Tokyo, Japan;*
[2] *Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.*

Summary **Liver Transplantation (LT) is an effective treatment for patients with end-stage liver disease including autoimmune hepatitis (AIH). Indication for LT for AIH does not differ basically from other liver diseases including both acute and chronic types of disease progression, although it is reported to be an infrequent indication for LT worldwide due to the therapeutic advances of immunosuppression. The outcome following LT is feasible, with current patient and graft survival exceeding 75% at 5 years. Recurrent and *de-novo* AIH posttranslant has also been reported; and this seems to have important clinical implications because its management differs from the standard treatment for allograft rejection. In this review, we discuss the characteristics of AIH, focusing on the indication for LT and issues raised following LT.**

Keywords: Autoimmune hepatitis (AIH), liver transplantation, anti-nuclear antibody (ANA), rejection, *de-novo* AIH

1. Introduction

Autoimmune hepatitis (AIH) is a chronic or acute hepatitis which is characterized by hepatocyte injury by an autoimmune process (*1*). It generally includes the appearance of circulating autoantibodies such as anti-nuclear antibody (ANA) and anti-smooth muscle antibody (SMA), and high serum globulin concentrations mainly with elevation of IgG (*2*). AIH usually responds to immunosuppression (mainly corticosteroid with or without azathioprine), and its prognosis has been reported to be comparatively good (*2,3*). However, there are a group of patients which develop into decompensated liver cirrhosis or fulminant hepatic failure (FHF) despite aggressive medical treatment; liver transplantation (LT) is still a last resort for those with end-stage liver disease due to AIH for those refractory to such immunosuppressive therapy (*4-7*). Even though LT is considered to be the only therapeutic option for those with liver failure due to AIH, this disease can recur after LT, with the recurrence rate ranging from 17 to 41% (*8*). Posttransplant *de novo* autoimmune hepatitis has also been described, although it is still an unsolved question whether it is a true autoimmune disease or a type of rejection (*9*). The diagnosis of recurrent and *de novo* AIH is often challenging, and it is usually treated by increasing or re-introducing immunosuppressant (mainly corticosteroid) (*10*).

The scope of this review is to: (A) overview the indications and outcomes of patients with end-stage AIH; and (B) discuss the characteristics of its recurrence and *de novo* AIH in the allograft for better understanding of both improving liver transplantation in this setting and better understanding of the pathogenesis of the primary, recurrent and *de novo* AIH.

2. Indication of liver transplantation for chronic and acute liver failure due to autoimmune hepatitis

The majority of patients (more than 75%) with AIH are presented with chronic disease (*11-13*). Its diagnostic criteria have been standardized and validated by the International Autoimmune Hepatitis Group (IAIHG) and is widely used (*14*). On the other hand, although several useful prognostic models are proposed in other autoimmune liver diseases such as primary

**Address correspondence to:*
Dr. Yasuhiko Sugawara, Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
E-mail: yasusuga-tky@umin.ac.jp

biliary cirrhosis and primary sclerosing cholangitis (*15*), there are no useful prognostic tools available in AIH. Thus, the indication for LT based on the prognosis of the native liver in the AIH setting should be evaluated similarly as other non-autoimmune liver diseases; LT is usually indicated in patients with chronic decompensated liver disease with a Model for End-Stage Liver Disease (MELD) score of ≥ 15 (*16*). Complications of hepatopulmonary syndrome, portopulmonary hypertension and hepatocellular carcinoma with or without an elevated Child-Pugh score can be other factors in consideration for the timing of LT and a MELD exceptional point (*17-21*).

In contrast, fewer cases with AIH are presented with acute hepatitis, and a subset of these meet the criteria for acute liver failure (ALF). Because the number of "acute AIH" cases are few, it is usually difficult to propose optimal and simplified diagnostic criteria in this setting (*22,23*). Further studies are strongly warranted to find reliable biomarkers capable of defining AIH as the pathogenic process related to the development of ALF. Indeed, diagnosis of AIH in acute phase is based on serological markers such as autoantibodies, absence of viral/alcoholic/drug-induced etiology, physician's (clinical) experience, and when possible histopathological features (*23*). Especially severe coagulopathy induced by ALF often makes the decision to perform liver biopsies difficult, but finding the characteristics of central zonal perivenular hepatitis, a feature infrequently observed in chronic AIH is reported to be useful in acute hepatitis by AIH (*24*). However, in real clinical situations, the rapid and significant deterioration of patients with ALF forces physicians to decide whether the immunosuppressive therapy or urgent LT should be considered, before sufficient information for the diagnosis of AIH is obtained (*7,11*).

The important issues in management of ALF by AIH are: (A) establishing an appropriate diagnosis; (B) evaluation of risks and potential benefits of immunosuppressive therapy; and (C) urgent consideration for LT (*25*). As per the currently available data, universal application of imunosupressant (mainly corticosteroids) in ALF by AIH should be cautiously considered or even avoided, because of the risk of active infection/sepsis that might deprive a chance for LT which often could be the only curative treatment for this population (*11*). The critical issues in this decision are the selection of candidates for steroid therapy and the timing of withdrawal of steroids in viewing the possibility for LT. There are reports mentioning that a higher MELD score (such as greater than 24 or 28 points) was associated with poor response to steroid therapy (*11,12*). In addition, those receiving but not responding to steroids immediately (within 3 days) following its initiation showed a poor outcome (*25*). Thus, it can be argued that patients with ALF caused by AIH and severe deterioration should not receive steroids, and that immunosuppression should be discontinued and urgent LT becomes crucial if responses to such immunosuppressants are not confirmed promptly after introduction (*7,25)*.

3. Incidence of liver transplantation and its outcome

AIH is a relatively rare indication for LT; around 4-6% of transplantations in United States have been for AIH (*26*). European Liver Transplant Registry (ELTR) reported that 991 cases (3%) of all the 39,196 liver transplants performed in Europe from 1988 to 2001 were for those with AIH (*27*). Sixty of 5,510 (1%) living-donor liver transplantations (LDLT) were performed for patients with AIH between 1989 and 2009 in Japan (*28*).

The outcome following LT has been reported to be successful, since the development of the modern regimen of immunosuppressants which consists of the combination of corticosteroid and tacrolimus/cyclosporine A with or without mycophenolate mofetil (MMF), with 1- and 5-year graft survival rates of 84% and 75%, respectively, and 5- and 10-year patient survival rates of 80-90% and 75%, respectively (*2,29*). Especially as an important prognostic factor, recurrent AIH following LT and *de novo* autoimmune hepatitis, which are further discussed below, should be paid attention to (*8,9*).

In recipients who received LT with decompensated cirrhosis, there should be awareness for the development of osteoporosis. As AIH is predominantly in postmenopausal women with long-term use of corticosteroids, its risk is considered to be enormously high. The measurement of bone mineral density as well as the early initiation of medications such as vitamin D, calcium preparations or bisphosphonate, even before LT, is essential (*30,31*).

4. Diagnosis of recurrent autoimmune hepatitis, its risk factors and management

Despite receiving successful LT, several LT centers

Table 1. Diagnostic criteria of recurrent autoimmune hepatitis (*34-36*)

- Liver transplantation for confirmed diagnosis of autoimmune hepatitis
- Elevated transaminases
- Hyper-gammaglobulinemia (elevation of IgG)
- Presence of autoantibodies (ANA, SMA and/or Anti-LKM1)
- Compatible histopathology(interface hepatitis, portal inflammation and/or lymphoplasmacytic inflammatory infiltrates)
- Response to corticosteroid
- Exclusion of differential diagnostic considerations

have reported recurrent AIH posttransplantation (*8,32*), since the first report by Neuberger *et al.* in 1984 (*33*). However, there are no specific biomarkers to diagnose recurrent AIH. Currently proposed diagnostic criteria for recurrent AIH are shown as Table 1; it is essential to distinguish from other etiologies causing liver damage such as rejection, drug induced liver injury, biliary problems and viral hepatitis (*34-36*).

Recurrence rate of AIH posttransplant has been reported to be 17-41% (Table 2) (*5,34,37-46*), but they might have been influenced by diagnostic criteria, immunosupressants, follow up period, and the timing of liver biopsy especially between biopsy per protocol versus when clinically indicated.

Several risk factors of recurrent AIH have been proposed, but the clinical validity is still controversial (*47*). Although this is still controversial, the status of human leukocyte antigen DR3 (HLA-DR3) or HLA-DR4 were associated with a risk of recurrence in some research (*33,40,48,49*). It has been reported that the incident rate of rejection following LT is higher in AIH patients than non-autoimmune disease, although the impact of rejection for recurrent AIH is not certain (*5,32*). Interestingly it is suggested that acute (fulminant) AIH is less likely to recur than chronic presentation following LT (*5*). Primarily the immunosuppressive regimen does not seem to have great impact on recurrence rate (*50*). However, caution should be exercised when tapering patients off immunosuppression, especially corticosteroids, because recurrence has been associated with its discontinuation (*29,30,51*).

For recurrent AIH, mostly a re-introduction or an increase in the dose of corticosteroids and azathioprine is applied, and the response to this treatment is usually reasonable (*40,52*). For those refractory to the treatment, an alternative attempt, such as conversion to cyclosporine from tacrolimus (*53*), conversion to sirolimus from cyclosporine (*54*) or the addition of MMF (*35*), should be applied. However, there have been cases that required re-transplantation due to recurrence of AIH (*38,39*).

Table 2. Published series of recurrent autoimmune hepatitis following liver transplantation

Authors	Year	Cases (*n*)	Recurrence rate (%)	Time to recurrence (median, mo)
Prados *et al.*(*37*)	1998	27	33	30
Milkiewicz *et al.*(*38*)	1999	47	28	29
Ratziu *et al.*(*39*)	1999	25	20	24
Reich *et al.*(*5*)	2000	32	25	15
Gonzales-Koch *et al.*(*40*)	2001	41	24	52
Yusoff *et al.*(*41*)	2002	12	17	n/a
Heffron *et al.*(*42*)	2002	52	17	39
Molmenti *et al.*(*34*)	2002	55	20	n/a
Renz *et al.*(*43*)	2002	37	32	24
Duclos-Vallee *et al.*(*44*)	2003	17	41	30
Vogel *et al.*(*45*)	2004	28	32	12
Montano-Loza *et al.*(*46*)	2009	46	24	30

Table 3. Published series of *de novo* autoimmune hepatitis following liver transplantation

Authors	Year	Cases (*n*)	Frequency (%)	Median time to *de novo* AIH (mo)
Kerkar *et al.*(*55*)	1998	180	4	24
Gupta *et al.*(*56*)	2001	115	5	102
Hernandez *et al.*(*57*)	2001	155	2.5	61
Miyagawa-Hayashino *et al.*(*58*)	2004	633	2.1	37
Venick *et al.*(*59*)	2007	619	6.6	84
Eguchi *et al.*(*60*)	2008	72	5.6	18 (mean)
Cho *et al.*(*61*)	2011	149	2.7	78 (mean)

5. *De-novo* autoimmune hepatitis

A clinical entity with clinical, serologic, and histologic features resembling AIH may develop in adults and children undergoing LT for end-stage liver disease other than AIH, which is called *de novo* AIH (*9*). *De novo* AIH was first reported in pediatric cases in 1998 (*55*), followed by several adult cases shown in table 3, with frequencies ranging 2.1-6.6% (*55-61*). Clinical manifestations of *de novo* AIH are usually similar to those of recurrent AIH, namely characterized by an infiltrate rich in plasma cells with interface hepatitis and perivenular necro-inflammation as well as elevated serum gammaglobulin (high IgG) and positive autoantibodies (*62*). In 2006, Banff working group proposed the diagnostic criteria for *de novo* AIH (Table 4) (*36*). However in some cases, serum IgG or autoantibodies can be normal (*61*), and such variations make the understanding and the diagnosis of *de novo* hepatitis challenging.

As a risk factor developing *de novo* AIH, the appearance of autoantibodies post-LT (*63*), repeated cellular rejection (*58,59*), positive HLA DRB1*03 (*64*), positive anti-GSTT1 (*65*), and cyclosporine compared to tacrolimus (*66*) have been reported. Importantly, there have been several publications regarding *de novo* hepatitis during or after interferon-based anti-HCV treatment for recurrent hepatitis C posttransplantation (*67-69*). However, its pathophysiology is still uncertain, and it is still controversial whether *de novo* AIH represents a specific type of rejection or a form of

Table 4. Diagnostic criteria of *de novo* autoimmune hepatitis by Banff Working Group (*36*)

- Interface hepatitis with portal lymphocytic infiltrates
- Significant titers (> 1:160) of ANA, SMA, or Anti-LKM1
- Hyper-gammaglobulinemia
- Exclusion of virus-induced or drug-related hepatitis and late acute or chronic rejection

hepatitis related to auto- or allo-immunity (*9*).

Once diagnosed as *de novo* AIH, treatment with corticosteroids alone or in combination with azathioprine or MMF should be considered in addition to the basic immunosuppressive regimen (*55,64,70*). Development of cirrhosis and either death or requirement for retransplantation have been observed without successful immunosuppressive treatment for *de novo* AIH; however, well treated patients seem to be spared from progressive disease (*56,64,70*).

6. Conclusion

The indication for LT in patients with end-stage liver disease due to AIH is similar to those other than AIH, and its outcome seems reasonable. However, recurrent and *de novo* AIH have been a growing concern; further studies are strongly awaited to reveal their clinical characteristics and pathophysiology.

References

1. Manns MP, Vogel A. Autoimmune hepatitis, from mechanisms to therapy. Hepatology. 2006; 43:S132-144.
2. Krawitt EL. Autoimmune hepatitis. N Engl J Med. 2006; 354:54-66.
3. Roberts SK, Therneau TM, Czaja AJ. Prognosis of histological cirrhosis in type 1 autoimmune hepatitis. Gastroenterology. 1996; 110:848-857.
4. Mottershead M, Neuberger J. Transplantation in autoimmune liver diseases. World J Gastroenterol. 2008; 14:3388-3395.
5. Reich DJ, Fiel, Guarrera JV, Emre S, Guy SR, Schwartz ME, Miller CM, Sheiner PA. Liver transplantation for autoimmune hepatitis. Hepatology. 2000; 32:693-700.
6. Sanchez-Urdazpal L, Czaja AJ, van Hoek B, Krom RA, Wiesner RH. Prognostic features and role of liver transplantation in severe corticosteroid-treated autoimmune chronic active hepatitis. Hepatology. 1992; 15:215-221.
7. Czaja AJ, Freese DK; American Association for the Study of Liver D. Diagnosis and treatment of autoimmune hepatitis. Hepatology. 2002; 36:479-497.
8. El-Masry M, Puig CA, Saab S. Recurrence of non-viral liver disease after orthotopic liver transplantation. Liver Int. 2011; 31:291-302.
9. Guido M, Burra P. *De novo* autoimmune hepatitis after liver transplantation. Semin Liver Dis. 2011; 31:71-81.
10. Schreuder TC, Hubscher SG, Neuberger J. Autoimmune liver diseases and recurrence after orthotopic liver transplantation: What have we learned so far? Transpl Int. 2009; 22:144-152.
11. Ichai P, Duclos-Vallée JC, Guettier C, Hamida SB, Antonini T, Delvart V, Saliba F, Azoulay D, Castaing D, Samuel D. Usefulness of corticosteroids for the treatment of severe and fulminant forms of autoimmune hepatitis. Liver Transpl. 2007; 13:996-1003.
12. Verma S, Maheshwari A, Thuluvath P. Liver failure as initial presentation of autoimmune hepatitis: Clinical characteristics, predictors of response to steroid therapy, and outcomes. Hepatology. 2009; 49:1396-1397.
13. Ferrari R, Pappas G, Agostinelli D, Muratori P, Muratori L, Lenzi M, Verucchi G, Cassani F, Chiodo F, Bianchi FB. Type 1 autoimmune hepatitis: Patterns of clinical presentation and differential diagnosis of the 'acute' type. QJM. 2004; 97:407-12.
14. Alvarez F, Berg PA, Bianchi FB, *et al*. International Autoimmune Hepatitis Group Report: Review of criteria for diagnosis of autoimmune hepatitis. J Hepatol. 1999; 31:929-938.
15. Tamura S, Sugawara Y, Kaneko J, Togashi J, Matsui Y, Yamashiki N, Kokudo N, Makuuchi M. Recurrence of cholestatic liver disease after living donor liver transplantation. World J Gastroenterol. 2008; 14:5105-5109.
16. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant. 2005; 5:307-313.
17. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: Asystematic review of 118 studies. J Hepatol. 2006; 44:217-231.
18. Freeman RB Jr, Gish RG, Harper A, Davis GL, Vierling J, Lieblein L, Klintmalm G, Blazek J, Hunter R, Punch J. Model for end-stage liver disease (MELD) exception guidelines: Results and recommendations from the MELD Exception Study Group and Conference (MESSAGE) for the approval of patients who need liver transplantation with diseases not considered by the standard MELD formula. Liver Transpl. 2006; 12:S128-136.
19. Planas R, Montoliu S, Ballesté B, Rivera M, Miquel M, Masnou H, Galeras JA, Giménez MD, Santos J, Cirera I, Morillas RM, Coll S, Solà R. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol. 2006; 4:1385-1394.
20. Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keefe EB, Kneteman NM, Lake JR, Martin P, Rakela J, Shiffman ML, So S, Wiesner RH. Minimal criteria for placement of adults on the liver transplant waiting list: A report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Transplantation. 1998; 66:956-962.
21. Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, Rodés J. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol. 1999; 30:890-895.
22. Hennes EM, Zeniya M, Czaja AJ, *et al*. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008; 48:169-176.
23. Potts JR, Verma S. Optimizing management in autoimmune hepatitis with liver failure at initial presentation. World J Gastroenterol. 2011; 17:2070-2075.
24. Hofer H, Oesterreicher C, Wrba F, Ferenci P, Penner E. Centrilobular necrosis in autoimmune hepatitis: A histological feature associated with acute clinical presentation. J Clin Pathol. 2006; 59:246-249.
25. Ilyas JA, O'Mahony CA, Vierling JM. Liver transplantation in autoimmune liver diseases. Best Pract Res Clin Gastroenterol. 2011; 25:765-782.
26. Seaberg EC, Belle SH, Beringer KC, Schivins JL, Detre KM. Liver transplantation in the United States from 1987-1998: Updated results from the Pitt-UNOS Liver Transplant Registry. Clin Transpl. 1998:17-37.
27. Adam R, McMaster P, O'Grady JG, *et al.* Evolution of liver transplantation in Europe: Report of the European Liver Transplant Registry. Liver Transpl. 2003; 9:1231-

1243.
28. Yamashiki N, Sugawara Y, Tamura S, Kaneko J, Takazawa Y, Aoki T, Hasegawa K, Sakamoto Y, Koike K, Kokudo N. Living-donor liver transplantation for autoimmune hepatitis and autoimmune hepatitis-primary biliary cirrhosis overlap syndrome. Hepatol Res. 2012; 42:1016-1023.
29. Futagawa Y, Terasaki PI. An analysis of the OPTN/UNOS Liver Transplant Registry. Clin Transpl. 2004:315-329.
30. Neuberger J. Transplantation for autoimmune hepatitis. Semin Liver Dis. 2002; 22:379-386.
31. Haga H, Miyagawa-Hayashino A, Taira K, Morioka D, Egawa H, Takada Y, Manabe T, Uemoto S. Histological recurrence of autoimmune liver diseases after living-donor liver transplantation. Hepatol Res. 2007; 37(Suppl) 3:S463-469.
32. Carbone M, Neuberger JM. Autoimmune liver disease, autoimmunity and liver transplantation. J Hepatol. 2014; 60:210-223.
33. Neuberger J, Portmann B, Calne R, Williams R. Recurrence of autoimmune chronic active hepatitis following orthotopic liver grafting. Transplantation. 1984; 37:363-365.
34. Molmenti EP, Netto GJ, Murray NG, *et al*. Incidence and recurrence of autoimmune/alloimmune hepatitis in liver transplant recipients. Liver Transpl. 2002; 8:519-26.
35. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM; American Association for the Study of Liver Diseases. Diagnosis and management of autoimmune hepatitis. Hepatology. 2010; 51:2193-2213.
36. Banff Working G, Demetris AJ, Adeyi O, *et al*. Liver biopsy interpretation for causes of late liver allograft dysfunction. Hepatology. 2006; 44:489-501.
37. Prados E, Cuervas-Mons V, de la Mata M, Fraga E, Rimola A, Prieto M, Clemente G, Vicente E, Casanovas T, Fabrega E. Outcome of autoimmune hepatitis after liver transplantation. Transplantation. 1998; 66:1645-1650.
38. Milkiewicz P, Hubscher SG, Skiba G, Hathaway M, Elias E. Recurrence of autoimmune hepatitis after liver transplantation. Transplantation. 1999; 68:253-256.
39. Ratziu V, Samuel D, Sebagh M, Farges O, Saliba F, Ichai P, Farahmand H, Gigou M, Féray C, Reynès M, Bismuth H. Long-term follow-up after liver transplantation for autoimmune hepatitis: Evidence of recurrence of primary disease. J Hepatol. 1999; 30:131-141.
40. González-Koch A, Czaja AJ, Carpenter HA, Roberts SK, Charlton MR, Porayko MK, Rosen CB, Wiesner RH. Recurrent autoimmune hepatitis after orthotopic liver transplantation. Liver Transpl. 2001; 7:302-310.
41. Yusoff IF, House AK, De Boer WB, Ferguson J, Garas G, Heath D, Mitchell A, Jeffrey GP. Disease recurrence after liver transplantation in Western Australia. J Gastroenterol Hepatol. 2002; 17:203-207.
42. Heffron TG1, Smallwood GA, Oakley B, Pillen T, Welch D, Martinez E, Romero R, Stieber AC. Autoimmune hepatitis following liver transplantation: Relationship to recurrent disease and steroid weaning. Transplant Proc. 2002; 34:3311-3312.
43. Renz JF, Ascher NL. Liver transplantation for nonviral, nonmalignant diseases: Problem of recurrence. World J Surg. 2002; 26:247-256.
44. Duclos-Vallée JC, Sebagh M, Rifai K, Johanet C, Ballot E, Guettier C, Karam V, Hurtova M, Feray C, Reynes M, Bismuth H, Samuel D. A 10 year follow up study of patients transplanted for autoimmune hepatitis: Histological recurrence precedes clinical and biochemical recurrence. Gut. 2003; 52:893-897.
45. Vogel A, Heinrich E, Bahr MJ, Rifai K, Flemming P, Melter M, Klempnauer J, Nashan B, Manns MP, Strassburg CP. Long-term outcome of liver transplantation for autoimmune hepatitis. Clin Transplant. 2004; 18:62-69.
46. Montano-Loza AJ, Mason AL, Ma M, Bastiampillai RJ, Bain VG, Tandon P. Risk factors for recurrence of autoimmune hepatitis after liver transplantation. Liver Transpl. 2009; 15:1254-1261.
47. Liberal R, Zen Y, Mieli-Vergani G, Vergani D. Liver transplantation and autoimmune liver diseases. Liver Transpl. 2013; 19:1065-1077.
48. Wright HL, Bou-Abboud CF, Hassanein T, Block GD, Demetris AJ, Starzl TE, Van Thiel DH. Disease recurrence and rejection following liver transplantation for autoimmune chronic active liver disease. Transplantation. 1992; 53:136-139.
49. Balan V, Ruppert K, Demetris AJ, Ledneva T, Duquesnoy RJ, Detre KM, Wei YL, Rakela J, Schafer DF, Roberts JP, Everhart JE, Wiesner RH. Long-term outcome of human leukocyte antigen mismatching in liver transplantation: Results of the National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database. Hepatology. 2008; 48:878-888.
50. Gautam M, Cheruvattath R, Balan V. Recurrence of autoimmune liver disease after liver transplantation: A systematic review. Liver Transpl. 2006; 12:1813-24.
51. Czaja AJ. The immunoreactive propensity of autoimmune hepatitis: Is it corticosteroid-dependent after liver transplantation? Liver Transpl Surg. 1999; 5:460-463.
52. Vergani D, Mieli-Vergani G. Autoimmunity after liver transplantation. Hepatology. 2002; 36:271-276.
53. Hurtova M, Duclos-Vallée JC, Johanet C, Emile JF, Roque-Afonso AM, Feray C, Bismuth H, Samuel D. Successful tacrolimus therapy for a severe recurrence of type 1 autoimmune hepatitis in a liver graft recipient. Liver Transpl. 2001; 7:556-558.
54. Kerkar N, Dugan C, Rumbo C, Morotti RA, Gondolesi G, Shneider BL, Emre S. Rapamycin successfully treats post-transplant autoimmune hepatitis. Am J Transplant. 2005; 5:1085-1089.
55. Kerkar N, Hadzić N, Davies ET, Portmann B, Donaldson PT, Rela M, Heaton ND, Vergani D, Mieli-Vergani G. *De-novo* autoimmune hepatitis after liver transplantation. Lancet. 1998; 351:409-413.
56. Gupta P, Hart J, Millis JM, Cronin D, Brady L. *De novo* hepatitis with autoimmune antibodies and atypical histology: A rare cause of late graft dysfunction after pediatric liver transplantation. Transplantation. 2001; 71:664-668.
57. Hernandez HM1, Kovarik P, Whitington PF, Alonso EM. Autoimmune hepatitis as a late complication of liver transplantation. J Pediatr Gastroenterol Nutr. 2001; 32:131-136.
58. Miyagawa-Hayashino A, Haga H, Egawa H, Hayashino Y, Sakurai T, Minamiguchi S, Tanaka K, Manabe T. Outcome and risk factors of *de novo* autoimmune hepatitis in living-donor liver transplantation. Transplantation. 2004; 78:128-135.
59. Venick RS, McDiarmid SV, Farmer DG, Gornbein J, Martin MG, Vargas JH, Ament ME, Busuttil RW.

Rejection and steroid dependence: Unique risk factors in the development of pediatric posttransplant *de novo* autoimmune hepatitis. Am J Transplant. 2007; 7:955-963.
60. Eguchi S, Takatsuki M, Hidaka M, Tajima Y, Zen Y, Nakanuma Y, Kanematsu T. *De novo* autoimmune hepatitis after living donor liver transplantation is unlikely to be related to immunoglobulin subtype 4-related immune disease. J Gastroenterol Hepatol. 2008; 23:e165-169.
61. Cho JM, Kim KM, Oh SH, Lee YJ, Rhee KW, Yu E. *De novo* autoimmune hepatitis in Korean children after liver transplantation: A single institution's experience. Transplant Proc. 2011; 43:2394-2396.
62. Richter A, Grabhorn E, Helmke K, Manns MP, Ganschow R, Burdelski M. Clinical relevance of autoantibodies after pediatric liver transplantation. Clin Transplant. 2007; 21:427-432.
63. Czaja AJ. Diagnosis, pathogenesis, and treatment of autoimmune hepatitis after liver transplantation. Dig Dis Sci. 2012; 57:2248-2266.
64. Salcedo M, Vaquero J, Bañares R, Rodríguez-Mahou M, Alvarez E, Vicario JL, Hernández-Albújar A, Tíscar JL, Rincón D, Alonso S, De Diego A, Clemente G. Response to steroids in *de novo* autoimmune hepatitis after liver transplantation. Hepatology. 2002; 35:349-356.
65. Aguilera I, Wichmann I, Sousa JM, Bernardos A, Franco E, García-Lozano JR, Núñez-Roldán A. Antibodies against glutathione S-transferase T1 (GSTT1) in patients with *de novo* immune hepatitis following liver transplantation. Clin Exp Immunol. 2001; 126:535-39.
66. Aguilera I, Sousa JM, Praena JM, Gómez-Bravo MA, Núñez-Roldan A. Choice of calcineurin inhibitor may influence the development of *de novo* immune hepatitis associated with anti-GSTT1 antibodies after liver transplantation. Clin Transplant. 2011; 25:207-212.
67. Berardi S, Lodato F, Gramenzi A, *et al*. High incidence of allograft dysfunction in liver transplanted patients treated with pegylated-interferon alpha-2b and ribavirin for hepatitis C recurrence: Possible *de novo* autoimmune hepatitis? Gut. 2007; 56:237-242.
68. Ueda Y, Yoshizawa A, Ogura Y, Miyagawa-Hayashino A, Haga H, Chiba T, Uemoto S. Plasma cell hepatitis induced by the termination of antiviral therapy for recurrent hepatitis C after living donor liver transplantation. Hepatol Res. 2014; 44:E279-283.
69. Ikegami T, Yoshizumi T, Shirabe K, Maehara Y. Frequent plasma cell hepatitis during telaprevir-based triple therapy for hepatitis C after liver transplantation. J Hepatol. 2014; 60:894-896.
70. Heneghan MA, Portmann BC, Norris SM, Williams R, Muiesan P, Rela M, Heaton ND, O'Grady JG. Graft dysfunction mimicking autoimmune hepatitis following liver transplantation in adults. Hepatology. 2001; 34:464-470.

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