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Autoimmune hepatitis in the liver transplant graft

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SYNOPSIS

Recurrent autoimmune hepatitis and *de novo* autoimmune hepatitis are two important causes of late graft failure after liver transplantation. Recurrent autoimmune hepatitis occurs in patients who undergo liver transplantation for autoimmune hepatitis. *De novo* autoimmune hepatitis occurs in patients who are transplanted for etiologies other than autoimmune hepatitis. Although typically treated with standard treatment for autoimmune hepatitis including corticosteroids and azathioprine, both recurrent and *de novo* autoimmune hepatitis may progress to end-stage liver disease requiring re-transplant.

Keywords

Autoimmune hepatitis; Recurrent autoimmune hepatitis; De novo autoimmune hepatitis

Recurrent and *de novo* Autoimmune Hepatitis after Liver Transplant

Autoimmune hepatitis (AIH) is a progressive inflammatory disease of the liver that can lead to acute liver failure and end-stage liver disease requiring liver transplantation (LT) first described by Waldenström in 1950.^{1,2} This condition, which affects mainly women, is characterized biochemically by increased aspartate and alanine aminotransferase (AST, ALT) levels, histologically by interface hepatitis and plasma cell infiltrates, and serologically by non-organ specific autoantibodies and increased immunoglobulin G (IgG).^{3,4}

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Approximately 2-3% of liver transplants performed on children and 4-6% of liver transplants performed on adults in Europe and the United States are for AIH.⁵

Recurrent AIH and *de novo* AIH are two important causes of late graft failure after liver transplantation. Recurrent AIH occurs in patients who undergo liver transplantation for AIH. *De novo* AIH occurs in patients who are transplanted for etiologies other than AIH.

Recurrent Autoimmune Hepatitis after Liver Transplant

Introduction

The first case report describing recurrent AIH, published in 1984, described the case of a 26-year old female who underwent liver transplant and developed recurrence of AIH at 18 months post-LT after corticosteroid reduction. She was treated with azathioprine, discontinuation of cyclosporine and an increase in corticosteroids and recovered.⁶

The International Autoimmune Hepatitis Group (IAHG) met and developed a set of diagnostic criteria and a scoring system to diagnose AIH.⁷ This criteria and scoring system has since been simplified and revised (Table 1)⁸ and although this scoring system was designed to diagnose AIH outside of the transplant setting, it is used to diagnose both recurrent and *de novo* AIH.^{9,10} A score of 6 or higher indicates probable AIH, while a score of 7 or higher indicates AIH.⁸

Incidence and Timing of Recurrent AIH

The incidence of recurrent AIH among adult patients undergoing LT reported in the literature is between 7% and 41%⁹⁻²³ and a recent systematic review reported a weighted recurrence rate of AIH of 22% (Table 2).²⁴ Timing of recurrence is also variable, but is usually reported to occur more than 12 months after LT.⁹⁻²³ The variability in recurrence rates and timing of recurrence reported in the literature may be partially accounted for by variability in study methodology, diagnostic criteria selection, follow-up period, timing of protocol and non-protocol biopsies, immunosuppression use and other factors.

The recurrence of AIH may be more common in children. In a small series of six children transplanted for AIH between 1985 and 1995 there were 5 recurrences (83.3%) in a mean of 11.4 months, with 3 requiring re-transplant.²⁵

Risk Factors/Pathogenesis Recurrent AIH

The pathogenesis of, and risk factors for, recurrent AIH are not clearly delineated. Risk factors for recurrent AIH that have been reported in the literature are outlined in Table 3.

HLA-DR3 and HLA-DR4 have been more commonly identified in patients with recurrent AIH than in patients without recurrence^{10,11,20,21}, although this finding is not consistent in all studies.^{9,16,19,23,26,27} Increased risk of recurrent AIH in HLA-DR3 recipients who are transplanted with a graft from an HLA-DR3 negative donor has also been demonstrated^{22,28}. Re-transplant for recurrent AIH has also been shown to be a risk factor for recurrent AIH²⁶, however this finding has also been refuted.^{19,23}

The association of occurrence of acute rejection and later development of recurrent AIH is also controversial with some studies demonstrating an association of episodes of acute rejection and recurrent AIH²⁹, while others demonstrate similar incidence and severity of episodes of acute rejection in patients with and without recurrent AIH.^{16,20,26}

Montano-Loza et al. completed a retrospective study of 46 patients transplanted for AIH with a focus on determining risk factors for AIH recurrence. On univariate analysis they found that pre-LT factors including concomitant autoimmune disease, high AST and ALT levels, high IgG levels, and moderate to severe inflammatory activity and plasma cell infiltrate on explant were significantly associated with recurrence of AIH. On multivariate analysis they found that IgG levels before LT greater than 2 times the upper limit of normal (HR 7.5, 95% CI: 1.45 – 38.45, P = 0.0) and moderate to severe inflammation on explant (HR 6.9, 95% CI: 1.76 – 26.96, P = 0.006) were associated with AIH recurrence. Of note, they also found that there was no difference in risk of AIH recurrence in patients who had and were treated for episodes of acute rejection. Additionally, they found no difference in pre-LT prednisone use or post-LT immunosuppression regimens. Their study failed to demonstrate a protective effect of prednisone against AIH recurrence. They also did not find an association between any of the donor factors they tested and AIH recurrence, and concluded that recurrence risk is limited to recipient factors.¹⁵ Ayata et al. confirm the finding that severe necroinflammatory activity at the time of LT predicts later recurrence.²⁹ Corticosteroid withdrawal has been reported to play an important role in AIH recurrence.^{19,21,30}

Diagnosis Recurrent AIH

In recurrent AIH, histologic changes may proceed clinical and biochemical evidence of recurrence.¹¹ Criteria used for diagnosis are the same as those used for patients with AIH who have not received a liver transplant.^{8,31} It is notable that these criteria have not been validated in the post-LT population. These criteria are outlined in Table 1.

Although there are no standard, validated criteria for diagnosis of recurrent AIH, the following are often used: elevated serum levels of transaminases, hypergammaglobulinemia or elevated immunoglobulin G levels, presence of autoantibodies, consistent histologic features such as lobular and/or periportal interface hepatitis with lymphoplasmacytic infiltrate predominance and steroid responsiveness, in the absence of viral infection or rejection.^{32,33}

Recipients with recurrent AIH present with features in common with most other post-LT complications including symptoms such as fever, fatigue, jaundice, abdominal pain, abnormal skin rash, joint pain and back pain.⁴ Biochemical signs of recurrence include elevated ALT and AST.⁴ Most patients with recurrent AIH have positive autoantibodies, although several studies have demonstrated that patients who undergo LT for AIH have persistent autoantibodies, but at lower titers than prior to LT.²⁶

Histologic signs of recurrence include interface hepatitis, plasma cell infiltration, acute lobular hepatitis with focal hepatocyte necrosis, acidophil bodies with lymphoplasmacytic cells and pseudo-rosettes of hepatocytes.^{34,35} There may be some differences in histology in recurrent

AIH versus AIH in the native liver including more common presentation with features of acute lobular necrosis in patients with recurrent AIH.²⁹ Some histological features of recurrent AIH may overlap with other conditions but distinctions can be made (Table 4).³⁶ Common histologic features of recurrent AIH can be seen in Figure 1.³³

Monitoring for Recurrence

Duclos-Vallee et al. performed a long-term study of 17 women who were transplanted for AIH and performed protocol liver biopsies at 1, 2, 5 and 10 years and as clinically indicated. Four of seven patients that recurred demonstrated histological evidence of recurrence on protocol biopsies including moderate to dense lymphoplasmacytic infiltrate, lobular activity and interface hepatitis. The mean interval between evidence of histological recurrence and the onset of other signs of recurrence was 9 (Range 6 – 14) years. They demonstrated that histologic recurrence proceeds biochemical recurrence and advocated for protocol biopsies after LT for AIH.¹¹ Sakai et al. advocate the use of the carboxyfluorescein diacetate succinimidyl ester-mixed lymphocyte reaction (CFSE-MLR) assay to monitor the immune status of AIH patients post-LT in order to optimize immunosuppression and monitor for recurrence.³⁷ Neither protocol biopsies nor the use of CFSE-MLR assay are currently standard practice.

Management Recurrent AIH

Treatment of recurrent AIH follows standard treatment for AIH including increased corticosteroid doses. Cyclosporine-based regimens are often modified to be tacrolimus-based. Mycophenolate mofetil can be added in non-responders.³⁶ Liver function tests, IgG levels, autoantibody levels and liver histology should serve as a guide for treatment.³⁶ Some patients may progress to graft failure and require re-transplant.²⁶

Corticosteroid withdrawal for patients who underwent LT for AIH is controversial. Krishnamoorthy et al. recently reported on 73 patients transplanted for AIH who were continued on long-term low-dose corticosteroid therapy with median follow-up of 94 months. Overall 1-, 3-, 5- and 10-year patient survival was 92%, 90%, 86% and 73%. Five patients developed AIH recurrence (7%). The authors concluded that use of low-dose corticosteroid treatment in the long-term reduced AIH recurrence without negatively impacting overall patient and graft survival.¹⁴

Trouillot et al. reported on 21 patients who underwent LT for AIH who were stable on maintenance immunosuppression. 68% of these patients were successfully withdrawn from corticosteroids with a mean follow-up period of 22 months (range 1 – 34 months). Patients successfully withdrawn from corticosteroids had reduction in serum cholesterol levels, decreased use of anti-hypertensive medications and reduced use of medications for glucose control.³⁸ Criticisms of this study include that while mean follow-up was 22 months, it was as short as 1 month in some patients.³⁰ Failure rates of corticosteroid withdrawal reported by other groups are much higher – between 50 and 64%.^{19,20} Additional investigation in this area is needed.

Outcomes Recurrent AIH

Few studies report on outcomes of AIH patients who undergo LT and recur versus those who do not recur. In a study of 46 patients who underwent LT for AIH in which 11 (24%) recurred in a mean of 48 +/- 16 months it was noted that there was no difference between 5- or 10-year survival in patients who did or did not recur (5-year: 82% versus 76%, $P=0.9$; 10-year: 77% versus 76%).¹⁵ A study of 41 patients transplanted for type 1 AIH in which 7 (17%) patients recurred, noted that there was no difference in 5-year patient and graft survival between patients who recurred and those who did not (86% versus 82%, $P=0.9$; 86% versus 67%, $P=0.5$).¹⁰ These studies may have been underpowered to detect a difference in outcomes between these two groups.

De Novo Autoimmune Hepatitis after Liver Transplant

Introduction

Over the past two decades a body of literature has developed regarding LT patients transplanted for non-AIH etiologies who develop increased transaminases, histological features of plasma-cell infiltrate and typical autoimmune serology after LT. This condition, first described as *de novo* autoimmune hepatitis², has also gone by many other names including post-LT AIH-like hepatitis³⁹, graft dysfunction mimicking AIH⁴⁰, posttransplant immune hepatitis⁴¹, plasma cell hepatitis⁴²⁻⁴⁴ and *de novo* immune hepatitis.⁴⁵ The presentation is consistent with recurrent autoimmune hepatitis, however, this condition occurs in patients who were transplanted for other etiologies.

De novo AIH was first reported in children by Kerkar et al., in 1998. In this case series it was noted that 4% of pediatric (7/180) LT recipients presented with *de novo* AIH. Liver biopsies demonstrated findings consistent with AIH including dense lymphocytic portal-tract infiltrate with plasma cells, periportal hepatitis, and bridging collapse. They also had high titers of IgG, the presence of autoantibodies and met criteria for the diagnosis of autoimmune hepatitis.² The earliest report in adults was in 1999 when 2 patients transplanted for primary biliary cirrhosis developed an autoimmune-like hepatitis.⁴⁶

Incidence of De Novo Autoimmune Hepatitis

De novo autoimmune hepatitis may occur more commonly in children³⁶ and the incidence of *de novo* AIH in children has been reported to be variable, between 0.5% and 11%.^{2,41,47-55} Time to development of *de novo* AIH in children is also variable with median time to development ranging from 1.2 to 6.9 years.^{52,55} Characteristics of children with *de novo* AIH are detailed in Table 5. *De novo* AIH has an incidence between 0.5 and 3.4% in adults with reported time to development ranging from 0.3 and 7 years post-LT.^{40,56-58}

Histology

As its name implies, *de novo* AIH shares biochemical, serologic and histologic features with AIH and the criteria used to diagnose *de novo* AIH are very similar to those used to diagnose AIH. These include the International Autoimmune Hepatitis Group (IAHG) scoring systems – revised³¹ and simplified.⁸ The simplified scoring system is presented in Table 1. Other sets of diagnostic criteria have also been set forth, including the one from a review by

Edmunds et al. which is demonstrated in Table 6.⁵⁹ Criteria for diagnosis have also been outlined by the Banff working group and include at a minimum: interface hepatitis, significant titers of antibodies, hypergammaglobulinemia, and the exclusion of virus-induced or drug-related hepatitis.³⁴

Sebagh et al. contend that histology assumes a central role in the diagnosis of *de novo* AIH because upon biopsy recognition of plasma cell-rich hepatitis with aggressive necroinflammatory activity full serologic evaluations are not completed.⁶⁰ Although studies in both native livers and in *de novo* AIH suggest plasma cells comprising more than 30% of the infiltrate are diagnostic for AIH and rarely seen in other conditions, precise cutoffs for plasma cell infiltrates have not been clearly defined.^{60,61}

Cases of *de novo* AIH after cadaveric LT with IgG4-positivity have been reported to be associated with more severe histologic activity (Figure 2), however, these have been shown to respond to treatment with increased immunosuppression.^{44,62} It has been suggested that IgG4 positive *de novo* AIH and IgG4 negative *de novo* AIH are in fact separate clinical entities.⁴⁴ In contrast, Eguchi et al. reported that IgG4 did not play a causal role in *de novo* AIH after living donor LT in their series, which included 72 living donor LT patients and 4 (5.6%) with *de novo* AIH.⁶³

While some authors point out the necessity of obtaining a biopsy in a patient with positive autoantibodies prior to diagnosing *de novo* AIH, as some patients develop autoantibodies in the absence of histological changes, other demonstrate that classic histological features are not always present.⁵⁵

Presence of Antibodies in De Novo Autoimmune Hepatitis

Patients transplanted for non-AIH etiologies can develop autoantibodies after LT. The development of autoantibodies has been reported to be associated with the development of chronic hepatitis, chronic rejection, graft dysfunction, graft loss and death⁶⁴⁻⁶⁷. It has also been demonstrated that adults and children can develop autoantibodies in the absence of *de novo* AIH^{64,66,68,69}.

Heneghan et al. reported two distinct presentations of *de novo* AIH. Of 7 patients identified, 3 had detectable LKM-1 at high titer in association with mean AST of 895 IU/L and 4 had positive ANA or ASM antibodies at low titer and in association with a mean AST level of 209 IU/L. Histology findings included presence of moderate to severe hepatitis with interface hepatitis, predominantly lymphocyte and plasma cell infiltrate, perivenular cell dropout, bridging necrosis and collapse. Due to their failure to recognize the condition originally they were able to observe the natural history of the disease, which was that histology on serial biopsy progressed from parenchymal bridging collapse to cirrhosis.⁴⁰

Although elevated IgG and autoantibody titers are typically considered to be part of the diagnostic criteria for *de novo* AIH, there are centers that have reported cases of *de novo* AIH in patients with low IgG levels and absent autoantibodies.⁶⁹ Autoantibodies can be present after LT in the absence of *de novo* AIH and a biopsy must therefore be performed to

confirm the diagnosis.^{59,66,67,69} Similarly, *de novo* AIH can be diagnosed in patients without autoantibodies or hypergammaglobulinemia.^{69,70}

Risk Factors for Development of *De Novo* Autoimmune Hepatitis

Early authors speculated that *de novo* AIH might be a form of rejection or the consequence of drug- or viral infection-triggered autoimmune injury.² While the pathogenesis of *de novo* AIH remains unclear, several risk factors have been identified and their roles supported and refuted over the years. These are summarized in Table 7.

The development of *de novo* AIH has been commonly reported in patients who develop hepatitis C virus (HCV) recurrence after LT and who have been treated with pegylated interferon and ribavirin, suggesting that either HCV recurrence or treatment for HCV recurrence increase risk of developing this condition.^{43,71-77} It will be interesting to see if we continue to see similar incidences of *de novo* AIH after HCV treatment in our current era of interferon free regimens.

Early studies suggested that *de novo* AIH is a true autoimmune process after patients with HLA type 1 matches developed the condition.⁴⁶ Later studies, however, reported that the condition did not occur more often in patients receiving grafts from living related donors where there is increased haplotype matching.⁵¹ It has also been demonstrated that increased matches or mismatches at the HLA A, B and DR loci are not associated with the development of *de novo* AIH.⁵¹ Heneghan et al. examined extended HLA haplotypes of donors and recipients and found a mean mismatch score of 5.3 across class I and II alleles, and concluded that increased matching did not lead to an increased risk.⁴⁰

Of the 7 children who developed *de novo* AIH in the first published study, 5 (71.4%) of them had donors who were HLA-DR3 or HLA-DR4 positive.² Heneghan et al. report HLA-DR3 or HLA-DR4 positivity in all donors or recipients.⁴⁰ In comparing *de novo* AIH patients to healthy blood donors, Salcedo et al, note that *de novo* AIH patients showed a higher prevalence of HLA-DR3.⁵⁷ Other studies fail to show an association between HLA-DR3 and *de novo* AIH.^{40,78} As noted previously, some authors report an increased risk of recurrent AIH in HLA-DR3 recipients who are transplanted with a graft from an HLA-DR3 negative donor.²²

In a single center study of 788 grafts received by 619 children over a 20-year period, 41 children (6.6%) developed *de novo* AIH and were compared with a control group. Age, gender, race, initial diagnosis, ischemia time, graft type, EBV infection, CMV infection, HLA haplotype and immunosuppressive regimens were not different between groups. Single immunosuppressive therapy, corticosteroid discontinuation and episodes of allograft rejection were all higher in the *de novo* AIH group.⁵⁴ Miyagawa-Hayashino et al. also report that among patients who later developed *de novo* AIH, 69% had episodes of acute rejection.⁵¹

The pathogenesis of *de novo* AIH is unclear, but may be related to molecular or structural mimicry, uncovering of hidden epitopes, or epitope spreading.⁷⁹ Molecular mimicry is an immune response to a non-self antigen that becomes directed at a similar self-antigen.^{80,81}

It has also been suggested that *de novo* AIH is a form of late cellular rejection. This hypothesis is supported in several ways. First, antibodies are directed against graft-antigens (non-self) rather than self-antigens. Second, autoantibodies arise in patients after episodes of acute rejection. Third, acute rejection is a risk factor for development of *de novo* AIH.³⁶ Also supporting the *de novo* AIH as a rejection hypothesis, it has been demonstrated that patients who are Glutathione S-Transferase T1 negative (GSTT1-negative) develop antibodies 80% of the time when transplanted with GSTT1-positive donors. This is true in all patients who develop AIH.³⁶

There is some evidence that *de novo* AIH is an alloimmune reaction, as opposed to a true autoimmune response. Glutathione S-transferase T1 (GSTT1) is an enzyme involved in detoxification of electrophilic compounds including reactive oxygen species and its role in *de novo* AIH has been an area of significant interest since when it was first explored.^{56,82} The proposed role of GSTT1 is related to a donor/recipient mismatch at this locus.⁵⁶ 20% of Caucasians and 11-58% of other ethnic groups possess a genetic deletion at the GSTT1 locus⁸³ and immune sensitization results from a GSTT1 negative recipient receiving a graft from a GSTT1 expressing donor.^{45,84} In a study of 35 LT recipients there was a higher incidence of *de novo* AIH and of anti-GSTT1 antibodies among those who received tacrolimus (plus/minus MMF) than those who received cyclosporine.⁸⁵ However, not all patients with GSTT1 donor/recipient mismatch develop anti-GSTT1 antibodies and not all patients with anti-GSTT1 antibodies have clinically evident *de novo* AIH. In the population of GSTT1-mismatch patients, male donor gender and non-alcohol related pre-LT disease were found to be predictive of the development of *de novo* AIH.⁷⁸

Complement component 4d is generated and deposited during activation of the classical complement pathway. Retrospective analysis of liver biopsies identified C4d-positivity localization in the portal tracts of *de novo* AIH specimens, while in two control groups C4d-positivity was present in only 4/7 biopsies from patients who experienced rejection and none of the patients who experienced HCV recurrence.⁸⁴ The authors, whose significant work in the area of GSTT1 has already provided evidence of donor specific antibody production posit that this supports the hypothesis that *de novo* AIH is a type of rejection.⁸⁴ They also demonstrated that IgG1 and IgG4 were the most common IgG subclasses present and noted that IgG4 related diseases are autoimmune diseases, but that the role of anti-GSTT1-IgG4 is currently unknown.⁸⁶

Granulocyte colony stimulating factor (G-CSF) given for neutropenia has been reported to be a protective factor against development of *de novo* AIH.^{72,75}

Outcomes

Pongpaibul et al. report 70 patients of 685 pediatric LTs who developed *de novo* AIH. The majority of patients who developed *de novo* AIH showed resolution of laboratory studies after treatment with mean follow-up time after diagnosis of *de novo* AIH of 6.7 years and 1-, 5- and 10-year graft survival in this group was 96%, 89%, 76%, and patient survival 98%, 94%, 81%.⁵⁵

Treatment

Standard therapy for AIH is corticosteroids and azathioprine in combination. These are effective in approximately 80% of patients. Additional therapies have been tried, including mycophenolate mofetil, d-penicillamine, sirolimus and anti-T cell therapies in patients who do not respond to standard therapy.⁵ Treatment for *de novo* AIH is similar to standard treatment for recurrent AIH after LT.

Heneghen et al. report in an early study that patients presenting with this condition not currently on corticosteroids were given prednisolone 40 mg/d and then tapered to a maintenance dose of 10 mg/d over 2 months. Patients who had remained on low doses of steroids were increased to 20 mg/d and then tapered to 10 mg/d maintenance dose. There were no further attempts at corticosteroid withdrawal in this patient population.⁴⁰

Liberal et al., in a comprehensive review, report recommendations for treatment for *de novo* AIH and these are summarized in Table 8.¹² Most cases can be treated effectively, but others may progress to graft failure and require retransplantation.⁸⁷

Summary/Discussion

Recurrent autoimmune hepatitis and *de novo* autoimmune hepatitis are important causes of late graft failure after liver transplantation and should be included in the differential diagnosis. Recurrent autoimmune hepatitis occurs in patients who undergo liver transplantation for autoimmune hepatitis. *De novo* autoimmune hepatitis occurs in patients who are transplanted for etiologies other than autoimmune hepatitis. Although typically treated with standard treatment for autoimmune hepatitis including corticosteroids and any further adjustments in a patient's immunosuppression, both recurrent and *de novo* autoimmune hepatitis may progress to end-stage liver disease requiring re-transplantation.

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KEY POINTS

- Recurrent autoimmune hepatitis and *de novo* autoimmune hepatitis are two important causes of late graft failure after liver transplantation.
- Recurrent autoimmune hepatitis occurs in patients who undergo liver transplantation for autoimmune hepatitis.
- *De novo* autoimmune hepatitis occurs in patients who are transplanted for etiologies other than autoimmune hepatitis

Figure 1.

Recurrent AIH (A) Liver parenchyma with septal fibrosis and a prominent inflammatory infiltrate (H&E, original magnification $\times 100$). (B) Septal and interface inflammation. Note a bile duct adjacent to the artery and vein (H&E, original magnification $\times 200$). (C) Lymphoplasmacytic infiltrate (H&E, original magnification $\times 600$). (D) Bridging fibrosis confirmed by trichrome stain (original magnification $\times 100$). (Courtesy of Dr Monica Garcia, Department of Pathology, University of Miami Miller School of Medicine.) From: *Mendes F, Couto CA, Levy C. Recurrent and de novo autoimmune liver diseases. Clin Liver Dis. 2011 Nov;15(4):859-78. PubMed PMID: 22032533. eng.*

Figure 2.

Pathological findings of immunoglobulin G4-associated *de novo* AIH after LT for chronic hepatitis B and C-related cirrhosis and hepatocellular carcinoma. A. Hematoxylin and eosin. Portal tracts are enlarged by lymphocytes aggregation with mild centrilobular necrosis. B. Immunologic stain for plasma cells (CD138) shows a cluster of positive plasma cells at the margin of interface hepatitis. At this time there are no immunoglobulin G4 (IgG4)-bearing plasma cells. C. This biopsy with CD138 staining shows more severe plasma cell infiltrates at the margin of interface hepatitis. D. Immunologic stain for IgG4 shows abundant IgG4-bearing plasma cells in a portal tract. From Zhao XY, Rakhda MI, Wang TI, Jia JD.

Immunoglobulin G4-associated de novo autoimmune hepatitis after liver transplantation for chronic hepatitis B- and C-related cirrhosis and hepatocellular carcinoma: a case report with literature review. Transplant Proc. 2013 Mar;45(2):824-7. PubMed PMID: 23498828. eng.

Table 1

Diagnostic Criteria for Autoimmune Hepatitis

Variable	Cutoff	Points
ANA or SMA	1:40	1
ANA or SMA or LKM or SLA	1:80	*2
IgG	> ULN	1
	>1.1 *ULN	2
Liver Histology (evidence of hepatitis required)	Compatible	1
	Typical	2
Absence of viral hepatitis	Yes	2

Adapted from Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology*. 2008 Jul;48(1):169-76. PubMed PMID: 18537184. eng.

6; probable AIH

7; definite AIH

* Addition of 2 points for all autoantibodies (maximum 2 points)

Table 2

Recurrent AIH in Adults

Author	Year of Publication	Time Period of Study	N Transplanted	N Recurred	Time to Recurrence
Krishnamoorthy, et al. ¹⁴	2016	1999-2014	73	5 (7%)	18, 19, 48, 60, 88 months
Montano-Loza, et al. ¹⁵	2009	NR	46	11 (24%)	Mean 48 +/- 16 months (Range 9 - 144, Median 30)
Gonzalez-Koch, et al. ¹⁰	2009	1985-1998	41	7 (17%)	Mean 4.6 +/- 1 year
Vogel, et al. ¹⁶	2004	1987-1999	28	9 (32%)	Median 12 months
Duclos-Vallee, et al. ¹¹	2003	1985-1990	17	7 (41%)	Mean 2.5 years (Range 0.6 - 3)
Molmenti, et al. ⁹	2002	1984-1998	55	11 (20%)	5/11 (45%) within first year
Yusoff, et al. ¹⁷	2002	1985-1999	12	2 (17%)	NR
Renz, et al. ¹⁸	2002	1988-1997	37	12 (32%)	Median 24 months, Mean 25 +/- 22 months
Reich, et al. ²⁶	2000	1988-1995	32	6/24 (25%)	Mean 15 +/- 2 months
Milkiewicz, et al. ¹⁹	1999	NR	47	13 (28%)	Mean 29 months (Range 6-63)
Narumi, et al. ²⁰	1999	1988-1997	40	8 (20%)	Mean 17.5 +/- 12.6 months
Prados, et al. ²¹	1998	1984-1996	27	9 (33%)	Mean 2.6 +/- 1.5 years
Wright, et al. ²²	1992	1981-1989	43	11 (26%)	NR
Ratzl, et al. ²³	1999	1985-1992	25	3/15 (20%)	Mean 24 +/- 12 months (Range 12-36)

Table 3**Risk Factors for Recurrent AIH**

Risk Factors for Recurrent AIH
HLA-DR3 positive recipient, HLA-DR3 negative donor ^{22,28}
HLA-DR3 positive ^{11,20}
HLA-DR3/HLA-DR4 positive recipient ¹⁰
Retransplantation for recurrent AIH ²⁶
Transplanted for chronic AIH versus fulminant hepatic failure ²⁶
Concomitant autoimmune disease ¹⁵
Pre-LT high AST ¹⁵
Pre-LT high ALT ¹⁵
Pre-LT high IgG ¹⁵
Explant moderate to severe inflammatory activity ¹⁵
Explant plasma cell infiltrate ¹⁵
Episodes of Acute Rejection ²⁹

Table 4

Acute Rejection, Recurrent Hepatitis C Viral Infection, Recurrent Autoimmune Hepatitis.

Acute Rejection	Predominantly mixed inflammatory infiltrate, bile duct damage, endothelialitis. Can have small numbers of plasma cells. ⁸⁸
Recurrent Hepatitis C Viral Infection	Predominantly lymphocytic portal infiltrate and lobular activity including parenchymal necrosis and apoptotic hepatocytes. Can have small numbers of plasma cells. ^{89,90}
Recurrent Autoimmune Hepatitis	Presence of interface hepatitis and significantly increased plasma cells. ¹¹

Table 5

De Novo AIH in Children

Author	Year	Incidence	Gender	Median Age	Median Duration After Surgery	Indications for Transplant	Immunosuppression	Histology	Autoantibodies	Median IgG Titer	Treatment
Pongpaibul et al. ⁵⁵	2012	70/685 (10.2%)	19 M, 32 F	4.1 +/- 4.2 Yr	6.9 +/- 4.7 Yr	Primary biliary atresia (53%), fulminant hepatic failure (18%), metabolic liver disease (18%)	Median tacrolimus trough 5.8 ng/mL, median cyclosporine trough 96 ng/mL	Hepatitis (36/51, 71%), variable necroinflammatory activity - lobular hepatitis most common when present, plasma rich infiltrates (16/51, 31%), uncommon central vein endothelitis	61% ANA (median titer 1:640), 59% ds-DNA antibodies (median titer = 545 IU/mL), 27% SMA (median titer 1:40), 2% LKM (median titer = 1:80).	NR	Continuation of calcineurin inhibitor; addition of mycophenolate mofetil and prednisone (31, 61%), continuation of calcineurin inhibitor and increased in or addition of prednisone (10, 20%), continuation of calcineurin inhibitor and addition of mycophenolate mofetil (9, 18%), other (5, 10%)
Venick, et al. ⁵⁴	2007	619 (6.6%)	NR	Mean 3.6 +/- 0.9 Yr	Mean 7.0 +/- 2 Yr	cholestatic liver disease (23), fulminant hepatic failure (13), metabolic liver disease (5)	Pre-1987: cyclosporine, prednisone, 1987: AZA added, 1994: Tacrolimus and prednisone, 1995: Weaning prednisone	Portal tract infiltrate, periportal hepatitis involving lymphocytes and plasma cells	24 - ANA, 25, anti-dsDNA, 10 - SMA, 1 - LKM	NR	21 - Mycophenolate mofetil (25 mg/kg/day) and prednisone (1-2 mg/kg/day) tapered over 6 weeks, 8 - increased dose of prednisone alone, 7 - Mycophenolate mofetil alone, 3 - Mycophenolate mofetil and change from cyclosporine to tacrolimus
Gibelli, et al. ⁴⁸	2006	1/205 (0.5%)	1 F	9 Yr	4 Years	alpha 1-antitrypsin	cyclosporine and prednisolone	active chronic hepatitis progressing to cirrhosis, portal lymphocyte aggregates, large number of plasma cells	gastric parietal cell antibody, liver-kidney microsomal antibody, anti-hepatic cytosol antibody	4447 mg/dL	Reduced dose of cyclosporine, increased corticosteroid dose to 1 mg/kg/day tapered to 20 mg every other day, added mycophenolate mofetil 1 g/day and increased to 2 g/day
Petz, et al. ⁵⁰	2002	18/155 (11%)		1 Yr	30 Mo	biliary atresia (16), Alagille's syndrome (1), alpha 1-antitrypsin (1)	9 - cyclosporine and steroids, 9 - tacrolimus and steroids	16 - chronic hepatitis with portal mononuclear infiltrate, interface hepatitis, 1 - nonspecific changes, biliary ductule proliferation	53% ANA, 58% SMA, 2 LKM	1400 (600 - 2170)	11 - steroids (1.5 mg/kg) and AZA (1.5 mg/kg), 5 - no therapy due to rapid normalization of LFTs, 2 - no therapy started yet
Gupta, et al. ⁵³	2001	115 (5%)	2 M, 4 F	2.2 Yr (0.8-6.0)	8.5 Yr (3-11)	biliary atresia (5), propyl thiouracil toxicity (1)	Cyclosporine, AZA, prednisone. AZA discontinued 6 months post-LT. Prednisone tapered off. All on single-drug at time of graft dysfunction.	Mononuclear infiltrates in portal areas with foci of periportal spillover, portal fibrosis and mild bile ductular proliferation. No infiltration of biliary	5 ANA + (Mean 1226, Range 320 - 2560), all dsDNA -, 2 SMA, all LKM -	NR	Prednisone (1-2 mg/kg/day) and AZA (1-2 mg/kg/day). Improvement in liver enzymes. Repeat biopsies in 4 showed progression of fibrosis. 2 developed end-stage liver disease. 1 died

Author	Year	Incidence	Gender	Median Age	Median Duration After Surgery	Indications for Transplant	Immunosuppression	Histology	Autoantibodies	Median IgG Titer	Treatment
								epithelium, duct damage or loss or endothelialitis. Viral studies all normal.			awaiting retransplant. 1 underwent successful retransplant.
Spada, et al. ⁵²	2001	5/116 (4.3%)	3 M, 2 F	NR	1.2 Yr (0.6 - 18)	biliary atresia (4), alpha-1 antitrypsin (1)	3 - Cyclosporin and prednisone, 2 - Tacrolimus and prednisone	Portal infiltrate, interface hepatitis, lobular necrosis, parenchymal fibrosis	NR	1800 mg/dL	Azathioprine 1.5 -2 mg/kg/day. Prednisone 2 mg/kg/day. Steroids tapered within 6 - 8 weeks down to 5 mg/kg in responders.
Andries, et al. ⁴¹	2001	11/471 (2.4%)	6 M, 5 F	10.5 Yr (7 - 13)	115 Mo (6.9 - 182)	biliary atresia (7), progression familial intrahepatic cholestasis (1), fulminant hepatitis (2)	Pre-1993: cyclosporin A, AZA (stopped 1 Mo- 1 Yr), steroids (tapered to 0.25 mg/kg), Post-1993: Tacrolimus as primary	Variable degree of portal and lobular inflammation, piecemeal necrosis, and bridging collapse	9 - ANA (titer 1/80 up to 1/10,000), 1 - SMA (1/320), 2 LKM-1 (1/1280)	1365 mg/dL	Did not respond to increasing doses of cyclosporine (n=10) or tacrolimus (n=1). 11 received steroids (Prednisolone 2 mg/kg/day, then tapered) and AZA (1.5-2.5 mg/kg/day).
Hernandez, et al. ⁴⁹	1999	5/155 (2.5%)	2 M, 3 F	3.5 Yr (0.5-14)	5.1 Yr (1.5-9)	biliary atresia (4), primary sclerosing cholangitis (1)	Primary immunosuppression with cyclosporine	Pt 1: portal inflammation, plasma cell predominance, Pt. 2: lobular infiltrate, plasma cells, interface hepatitis, Pt. 3: consistent with AIH. Pt. 4: portal infiltrate, plasma cells, portal fibrosis, Pt. 5: interface hepatitis, plasma cells, fibrosis	4 - ANA titers 1:160-1:640, 1- also SMA 1:80, 1- elevated total serum protein level	NR	Standard therapy for autoimmune hepatitis - daily steroids and azathioprine. Cyclosporine doses eliminated in two and reduced in three.
Kerkar, et al. ²	1998	7/180 (4%)	5 M, 2 F	10.3 Yr (2.0-19.4)	24 Mo (6-45)	biliary atresia (4), Alagille's syndrome (1), drug-induced acute liver failure (1), alpha-1 antitrypsin deficiency (1)	Four on triple with cyclosporine, AZA, prednisolone, and three on tacrolimus	Portal and periportal hepatitis with lymphocytes and plasma cells, bridging collapse, perivenular-cell necrosis without changes typical of acute or chronic rejection	1 ANA, 2 ANA and SMA, 3 atypical LKM, 1 GPC	22 g/L (17.2-34.4)	All but one responded to prednisolone 2 mg/kg/day and an increase or addition of AZA (1.5 mg/kg/day) within a median of 32 days (7-316)
Miyagawa-Hayashino, et al. ⁵¹	2004	13/633 (2.1%)	2 M, 11 F	10 (8 Mo - 26 Yr)	3.1 Yr (0.7-9.5)	NR	NR	9 - Definite AIH, 4 - Probable AIH	NR	NR	11 patients who underwent follow-up histologic evaluation: 3 - retransplant, 8 -similar findings on subsequent biopsies, fluctuations in amount of necroinflammatory activity, increase in fibrosis despite treatment

* M = male, F = female, NR = not reported, ANA = anti-nuclear antibody, SMA = smooth muscle antibody, LKM = liver kidney microsomal antibody, GPC = gastric parietal-cell antibody, AZA = azathioprine

Table 6Diagnostic Criteria for *De Novo* AIH post-LT

Diagnostic Criteria For <i>De Novo</i> Autoimmune Hepatitis after LT	
Liver transplant recipient without history of AIH	
Presents with unknown etiology of late graft dysfunction	
Elevated aminotransferases	
Usually occurs greater than 2 years after transplantation	
Graft Dysfunction is not due to:	
Acute rejection	
Chronic rejection	
Hepatitis B or C virus	
Epstein Barr virus	
Cytomegalovirus infection	
Vascular problems	
Biliary complications	
Drug toxicity	
Sepsis	
Recurrence of primary disease	
Posttransplant lymphoproliferative disorder	
Elevated serum IgG	
Positive autoantibody titers:	
ANA	
ASMA	
anti-LKM	
Characteristic biopsy findings:	
Dense lymphocytic portal-tract infiltrate	
Plasma cells	
Interface hepatitis	

Adapted From: *Edmunds C, Ekong UD. Autoimmune Liver Disease Post-Liver Transplantation: A Summary and Proposed Areas for Future Research. Transplantation. 2016 Mar;100(3):515-24. PubMed PMID: 26447505. PMCID: PMC4764021. eng.*

Table 7Risk Factors for *De Novo* AIH

Risk Factors
Antiviral therapy for HCV infection with pegylated interferon and ribavarin ^{43,65,71-77}
Use of Antilymphocyte Antibodies ⁷²
Donor and/or Recipient HLA-DR3 and/or HLA-DR4 and/or Donor/Recipient Mismatch ^{2,65,78}
Episodes of Acute Rejection ^{51,54,65}
GSTT1 Donor/Recipient Mismatch ^{56,59}
Type 1 AIH ^{2,35}
Severe Necroinflammatory Activity in the Explant ⁴
Withdrawal of Corticosteroids or Early Withdrawal of Corticosteroids ⁴
Inadequate immunosuppression secondary to non-adherence ⁴
Co-existing autoimmune disorders ⁴
Higher titers of autoantibodies at the time of LT ⁴
Prolonged course of the underlying AIH associated with prolonged immunosuppression pre-LT ⁴
Single Immunosuppressive Therapy ⁵⁴
Protective Factors
Administration of Granulocyte Colony Stimulating Factor (GCSF) ^{72,75}

Table 8

Treatment Recommendations for De Novo AIH

Treatment Recommendations for Children	
1	Give 1-2 mg/kg prednisone or prednisolone (not to exceed 60 mg) AND 1-2 mg/kg azathioprine daily
2	Reduce dose of prednisone or prednisolone in weeks 4-8 to 5-10 mg/day
3	In absence of response replace azathioprine with up to 40 mg/kg/day of mycophenolate mofetil in up to two divided doses
Treatment Recommendations for Adults	
1	Give 30 mg of prednisone or prednisolone AND 1-2 mg/kg of azathioprine daily
2	Reduce dose of prednisone or prednisolone to 5-10 mg/day
3	In absence of response replace azathioprine with 1 gram twice daily of mycophenolate mofetil

Adapted from: Liberal R, Longhi MS, Grant CR, Mieli-Vergani G, Vergani D. Autoimmune hepatitis after liver transplantation. Clin Gastroenterol Hepatol. 2012 Apr;10(4):346-53. PubMed PMID: 22056300. eng.