Autoimmune Hepatitis and Overlap Syndromes – East meets West

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Abstracts
Abstracts of Invited Lectures

Falk Workshop

AUTOIMMUNE HEPATITIS AND OVERLAP SYNDROMES – EAST MEETS WEST

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Session I
Definition and differential diagnosis of autoimmune hepatitis in West and East

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Autoimmune hepatitis (AIH) is a classical autoimmune liver disease characterized by marked elevation of ALT and AST, hyperglobulinemia/hypergammaglobulinemia and increased immunoglobulin G, positive for autoantibodies and lymphatic interface hepatitis (with plasma cell infiltration) hepatitis on histology. Together with primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC), AIH is increasingly reported in medical literature not only from the western but from the eastern countries, although it was generally regarded as a disease of the Caucasian. This may be explained by the increased awareness of this disease among Asian hepatologists and availability of autoantibody tests in that area. Indeed the report of AIH (mostly in Chinese language) has increased exponentially in China where chronic hepatitis B infection is still endemic but decreased dramatically due to universal vaccination among newborns. Except for some difference in HLA-DR frequency among patients, AIH manifest similarly in western and eastern peoples.

The diagnosis of AIH is not as straightforward as other liver diseases with well-defined etiology. Detailed history taking and rational use of laboratory tests are essential for the correct diagnosis of this disease. Methodological standardization and quality control of autoantibody detection (especially by immune fluorescence technique) is a pre-request. In 2002, a diagnostic criteria is published in a clinical practice guideline by AASLD, which emphasize the importance of excluding known etiology of liver diseases. According this guideline, several categories of liver diseases need to be excluded: viral hepatitis, drug, alcohol and other chemical injuries and inherited metabolic diseases. Actually, this “exclusion criteria” can be used as a guidance of differential diagnosis. Among the long list of need-to-rule out diseases, drug induced liver injury and inherited metabolic diseases are 2 major diagnostic challenges. This is especially true for idiosyncratic form of drug induced liver injury which is unexpecatable and the time interval from the administration of the medication and the onset of the liver injury varies greatly. An even more complex issue is the fact that drugs can induce autoimmune hepatitis-like liver diseases which mimics the clinical, biochemical, immunological and histopathological manifestation of AIH. While typical Wilson disease and inherited hemochromatosis can be easily to identified by clinical and biochemical investigations, alpha1-antitrypsin deficiency, especially for atypical cases in adults, is difficult to diagnose. Another disease needs to exclude is nonalcoholic steatohepatitis (NASH) which is becoming more and more common in the East as well as in the West. NASH some times causes remarkable elevation of ALT/AST and even some autoimmune phenomenon. Therefore, live histology is mandatory for the differential diagnosis.

For difficult cases, the score system formulated by the International Autoimmune Hepatitis Group (1999) on is of help. A simplified version of the score system (2008) was published recently and it may be more practical for day-to-day clinical use but its accuracy needs to be validated against the original system.
Autoantibodies and autoantigens: Nomenclature and diagnostic value

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Autoantibodies are crucial for the correct diagnosis and classification of autoimmune liver diseases, namely autoimmune hepatitis types 1 and 2 (AIH-1 and 2), primary biliary cirrhosis (PBC), and the sclerosing cholangitis variants in adults and children.

AIH-1 is characterised by anti-nuclear antibody (ANA) and smooth muscle antibody (SMA), the targets of ANA being multiple and non disease-specific, and those of SMA micro and intermediate filaments. AIH-2 is characterised by antibody to liver kidney microsomal antigen type-1 (anti-LKM1), whose target is cytochrome P4502D6, and anti-liver cytosol type 1 (anti-LC1) targeting formiminotransferase cyclodeaminase. Anti-soluble liver antigen (anti-SLA), targeting tRNP(Ser)Sec, is a more recently described reactivity, highly specific for autoimmune liver disease, which is associated with a particularly severe clinical course and, in contrast to the other autoantibodies, is not detectable by immunofluorescence, but only by molecular based assays. PBC is characterised by antimitochondrial antibodies (AMA) reacting with enzymes of the 2-oxo-acid dehydrogenase complexes (especially pyruvate dehydrogenase complex E2 subunit) and PBC-specific ANA mainly reacting with nuclear pore gp210 and nuclear body sp100. In classical primary sclerosing cholangitis (PSC) that affects mostly adult men, the main (and non-specific) reactivity is atypical perinuclear antineutrophil cytoplasmic antibody (p-ANCA). In the childhood disease called autoimmune sclerosing cholangitis (ASC) serological features resemble those of type 1 AIH, though pANCA is also present in 2/3 of the patients. Liver diagnostic serology is a fast-expanding area of investigation as new purified and recombinant autoantigens, and observer independent technologies such as ELISA, bead and radioligand assays, become available to complement (or even compete with) traditional immunofluorescence procedures. It is noteworthy, however, that immunofluorescence on a freshly removed rodent multi-organ substrate panel, including kidney, liver and stomach, remains the mainstay of liver diagnostic autoimmune serology, allowing for the simultaneous detection of ANA, SMA, anti-LKM1 as well as AMA and anti-LC1. A recent development is the possibility of using tetramer technology to detect epitope-specific cellular autoimmune responses, as it has been shown in anti-LKM1 and anti-SLA positive AIH.
Therapy of autoimmune hepatitis – Present and future

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Autoimmune hepatitis is a disease of unknown etiology. However, a loss of tolerance against the patients’ own liver is regarded as the main pathogenetic mechanism. Immunosuppressive therapy prolongs survival in patients with severe autoimmune hepatitis. Two phases of therapy have to be distinguished. In newly diagnosed autoimmune hepatitis induction of remission is the main goal. Here prednisolone alone or in combination with azathioprine was shown to induce remission in the majority of patients. In the past reduction of aminotransferase levels below two times the upper limit of normal was the aim of therapy. Nowadays normalisation of aminotransferase levels should be achieved. 60–80% of patients respond to therapy usually within six to twelve months. Usually a significant reduction of aminotransferase levels is achieved within a few weeks of therapy. Improvement in clinical symptoms is followed by improvement in biochemical parameters of disease activity and then by significant improvement in histological activity in liver biopsy. Around 20% of patients do not achieve remission. In these patients alternative therapies should be evaluated for the individual patient. Prospective controlled trials with a larger number of patients are missing in this population. At the moment mofetil/mycophenolate (MMF) at a dose of 2 x 1 g daily is able to achieve remission in a significant proportion of patients, either given alone or in combination with prednisolone. However, again prospective trials are missing. Alternative drugs include cyclophosphamide, cyclosporin A, tacrolimus. In particular women suffer from steroid specific side effects including weight gain, moon face, diabetes, glaucoma and bone disease. Recently a topical, budesonide, was shown to induce disease remission in combination with azathioprine. The second phase of therapy is maintenance of remission with the lowest possible dose in order to maintain remission while preventing significant side effects. Careful evaluation of the individual patients should lead to the decision whether budesonide, azathioprine or a combination of both is used to maintain remission of autoimmune hepatitis. Recently, a study has shown that after six months of induction therapy with prednisone plus azathioprine a switch to budesonide in combination with azathioprine reduced steroid specific side effects while maintaining remission of liver disease. Therefore the application of the topical steroids may be helpful in maintaining remission while reducing steroid specific side effects. Patients treated with budesonide should not have liver cirrhosis since the benefit of budesonide with its 90% pass effect in the liver is lost if the patient has already developed portal hypertension with significant porto-systemic shunting. Furthermore there are safety concerns for budesonide in cirrhotic patients derived from studies in primary biliary cirrhosis. If the diagnosis is correct and the appropriate therapy is chosen liver transplantation should be avoidable in patients with autoimmune hepatitis.
Session II
Primary sclerosing cholangitis – Pathogenesis, malignancy and therapy

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Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease that is characterized by an inflammatory and fibrotic process affecting intra- and extrahepatic bile ducts. The disease leads to irregular bile duct obliteration with formation of multifocal bile duct strictures and eventually develops into liver cirrhosis and liver failure.

Pathogenesis
Primary sclerosing cholangitis (PSC) is regarded as an immune-mediated liver disease. The pathogenesis of primary sclerosing cholangitis (PSC) is unclear. Genetic susceptibility factors are involved. The coincidence of PSC and inflammatory bowel disease in 70–90% of patients led to the assumption that intestinal bacterial products, after leakage into the portal circulation, may induce a chronic fibrosing inflammation in portal fields of genetically susceptible subjects. A novel pathogenetic concept that recruitment of long-lived intestinal mucosal T-cells in response to aberrantly expressed endothelial cell-adhesion molecules and chemokines that are normally restricted to the gut may induce biliary changes in genetically susceptible individuals is attractive, but requires further experimental evidence. A biochemical hallmark of PSC is the presence of atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA). Atypical pANCA are not specific for PSC, but are also observed in inflammatory bowel disease (IBD) or in autoimmune hepatitis (AIH). It is unclear whether they have any pathophysiological relevance.

Malignancy
Patients with PSC often (> 70%) suffer from inflammatory bowel disease, mainly ulcerative colitis (UC), and have an increased risk of developing hepatobiliary (> 160-fold), pancreatic (14-fold) and colon (10-fold) malignancies. Among these malignancies, colon carcinoma is probably the most frequent carcinoma – up to 30–50% colorectal dysplasia/carcinoma after 25 years in patients with PSC and ulcerative colitis (UC). UC itself is a risk factor for development of colorectal neoplasia. The presence of UC alone, however, does not explain the high risk of colon carcinoma in patients with PSC as patients with PSC/UC have a significantly higher risk to develop colon carcinoma than patients with UC only (Odds ratio > 4). Interestingly, the right colon is often affected in patients with PSC/UC, a finding less commonly described in UC only or the general population leaving room for speculation on pathophysiological mechanisms. Annual total colonoscopy with routine biopsies is now recommended in this group of patients for early detection of severe dysplasia and carcinoma and total colectomy when severe dysplasia or carcinoma is detected.

Malignancies of the biliary tree are a key concern in PSC. Cholangiocarcinoma has been described to develop in about 7–13% of PSC patients during follow-up in various cohorts independent of disease stage with an annual risk of up to 1–1.5% and a dismal prognosis. Gallbladder carcinoma has been observed in about 2% of PSC patients from Northern Europe and the United States. Cholecystectomy is recommended in all PSC patients with a gallbladder mass irrespective of its size as even polyps < 1 cm carry a considerable risk of malignancy in PSC.
Hepatocellular carcinoma was described in 2% of a cohort of PSC patients waiting for liver transplantation.

**Treatment**

*Medical treatment* with ursodeoxycholic acid (UDCA, 15–20 mg/kg/d) has been shown to improve serum liver tests consistently in patients with PSC. Effects of UDCA on histological and endoscopic features are less clear. Beneficial effects of UDCA on long-term prognosis have not yet been proven\(^9\) whereas malignancies in colon and bile ducts of PSC patients have been reported to be diminished in some cohorts of PSC patients\(^6\).

No other medical treatment (e.g., corticosteroids, cyclosporine, colchicine, methotrexate) have convincingly been shown to be of any benefit in PSC. Their use cannot be recommended in PSC. (In contrast, two other forms of sclerosing cholangitis, PSC-AIH overlap syndrome and IgG4-associated cholangitis (IAC), are well responsive to corticosteroids and other immunosuppressive drugs).

*Endoscopic treatment* of dominant bile duct strictures by balloon dilatation and/or short-term stenting has been shown to beneficially affect the course of patients with PSC.

*Liver transplantation* is the treatment of choice for late stage PSC patients.

**References:**


Primary biliary cirrhosis – Latest developments in pathogenesis and therapies

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PBC is a chronic inflammatory autoimmune disease that affects mainly the biliary cells lining the small bile ducts of the liver. From a clinical standpoint, PBC is defined empirically as a syndrome characterized by chronic cholestasis and autoantibodies directed against specific epitopes in the multienzymatic complex of oxoglutarate dehydrogenase of the mitochondria. There are 3 major forms of the disease. The typical form is represented by the slowly progressive decline of patent small bile ducts and progressive parallel increase in liver fibrosis culminating in biliary cirrhosis over a period of 10–15 years. A second form that affects about 15–20% of the patients with cholestasis and mitochondrial antibodies is characterized by the fluctuating presence of the features of autoimmune hepatitis. As a result these patients have a more severe course with early development of liver fibrosis and liver failure if not appropriately diagnosed and treated. A third form which affects about 5–10% of the patients is represented by the so-called premature ductopenic variant. Its hallmark is a very rapid onset of ductopenia without cirrhosis at presentation but progressing very quickly towards cirrhosis and very severe cholestasis.

PBC like other autoimmune disorders is a complex disease. As opposed to single Mendelian traits PBC is caused by a combination of genetic, environmental factors and stochastic effects. Each of these factors can affect one or more components of the immune system and one or more components of the tissue which is targeted by the disease. Although a unified theory of PBC pathogenesis may not be possible currently, a conceptual multistage model that considers pathobiological events contributing to initiation and progression could be presented. The initiation process is marked by autoimmunity and/or an altered cholangiocyte homeostasis. This initiation phase is followed by a clinical phase characterized by chronic inflammation and cholestasis leading slowly and progressively to ductopenia, fibrosis culminating in cirrhosis and liver failure. All these steps are triggered or modulated by the host-genetic background and environmental factors.

All PBC patients with abnormal liver biochemistry should be considered for specific therapy.

UDCA, at the dose of 13–15 mg/kg/day, is currently considered the mainstay of therapy for PBC. The aim of UDCA therapy is to provide the normalization of the serum bilirubin, alkaline phosphatase and ALT or AST levels at the end of the first year of therapy. In many patients this could not be achieved. We define the optimal response to UDCA when serum bilirubin is less than 1 mg/dl and AST less than 2 times the upper limit of normal, and alkaline phosphatase less than 3 times the upper limit of normal at the end of the first year of therapy. Indeed the patients with these criteria have a normal life expectancy without liver transplantation (15%) a trial with daily doses up to 20 mg/kg/day is proposed to achieve a better response. About 40% of our patients have
a suboptimal response to UDCA. These patients need an adjuvant therapy. Patients with features of autoimmune hepatitis, severe interface hepatitis, abnormal serum bilirubin level or suboptimal response to UDCA – as defined above – deserve trials with adjuvant therapies. Currently glucocorticoids (prednisone or budesonide) and methotrexate could be considered for these patients.

Liver transplantation has greatly improved survival in patients with PBC. It is the only effective treatment for those with decompensated cirrhosis or liver failure. The patients who present with the features of the premature ductopenic variant of PBC do not respond to any medical therapy and despite the absence of any decompensation draws a major benefit from liver transplantation. PBC recurs in about 25% of patients at 5 years. Recurrence is more frequent in patients without a glucocorticoid and ciclosporin regimen. The beneficial long-term effect of UDCA in this setting remains unknown.
Overlap syndromes – Definitions and Therapy

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**Synonyms:** overlapping autoimmune disease, autoimmune cholangiopathy, antibody negative primary biliary cirrhosis, variant syndromes

**Definition and Characteristics:**
The term overlap syndrome describes a disease condition, which is only incompletely defined and is somewhat misleading. In general, most clinicians approach autoimmune liver diseases diagnostically when serological evidence of autoantibodies has been established. However, it is important to realize that serological autoimmunity in liver diseases is a common phenomenon not always indicative of true autoimmune disease. Circulating autoantibodies are detectable in the classical autoimmune diseases, in viral hepatitis B and C, but also in some drug-associated hepatic diseases such as hepatitis following the exposure with dihydralazine, halothane and other pharmaceuticals. In addition, autoantibodies are detected in the autoimmune polyendocrine syndrome type 1 (APS-1, syn. APECED), which combines endocrine diseases of the adrenals and parathyroid glands with mucocutaneous candidiasis, and in 10% leads to a form of autoimmune hepatitis. While the latter is a true overlap of different autoimmune components and is based on a genetic defect of the autoimmune regulator (AIRE) gene, the former examples of serological autoimmunity are epiphenomena and do not qualify as genuine autoimmune diseases or as an overlap of the same. True overlap syndromes are characterized by the coexistence of clinical, biochemical or serological features of autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and depending on the definition also viral hepatitis C. In this respect the term overlap is misleading because each of the overlapping disease entities has its own clinical description and diagnostic algorithm. Therefore, overlap syndromes result from the detection of criteria for more than one autoimmune disease of the liver. In adult patients an overlap of PBC and AIH is most frequently encountered although it is often unclear whether this is true co-existence of both diseases or an immunoserological overlap characterized by the presence of antinuclear (ANA) as well as antimitochondrial (AMA) antibodies. In AMA positive patients ANA can be present in as much as 50% without providing enough criteria for the existence of ANA-positive AIH. Frequently, these PBC-associated ANA show specific reactivities with sp100, Laminin B or gp210 antigen. In many AMA-negative patients with a cholestatic liver enzyme profile ANA are present as well. This has been termed autoimmune cholangiopathy or AMA-negative PBC. Apart from a clinical presentation of coexistence of 2 defined diseases such as AIH and PBC, autoimmune liver diseases can also develop into each other i.e. the sequential manifestation of PBC and autoimmune hepatitis or the other way around. The true coexistence of AIH and PSC has been conclusively shown in pediatric patients where it has been termed autoimmune sclerosing cholangitis. It can be hypothesized whether a general predisposition toward liver autoimmunity exists which has a cholestatic, a hepatitic and a bile duct facet, which may be variable depending upon unknown host factors.
Prevalence:
Reliable data on the prevalence of autoimmune overlap syndromes is not available. The overlap of AIH and PBC appears to be present in about 8% of AIH patients, AIH and PSC overlap in about 6% of AIH patients. In contrast AIH can be present in about 9% of PBC patients. In 10% of autoimmune diseases of the liver a syndrome of autoimmune cholangiopathy can be present. The prevalence of PBC alone is estimated at 65 per 100,000 in women and 12 per 100,000 in men with an incidence of 5 per 100,000 in women and 1 per 100,000 in men. The prevalence and incidence appear to vary regionally. An increase of PBC incidence in recent years may be the result of more specific testing of antimitochondrial antibody reactivity. Based on limited epidemiological data, the prevalence of AIH is estimated to range between 50 and 200 cases per 1 million in Western Europe and North America among the Caucasian population.

Immunogenetics:
There has been no report of a genetic predisposition for overlap syndromes. The genetics of AIH and PBC have been studied but differ from each other. AIH has been found to be associated with the HLA A1-B8-DR3/DR4 haplotype in Caucasians. There are a number of other minor associations and a great deal of geographical diversity. PBC is not associated with the human leukocyte antigen haplotype A1-B8-DR3/DR4 found in AIH and other autoimmune diseases. An association has been described with HLA DRw8, HLA DPB1*0301, C4AQ0, and C4B2 which is in linkage with DR8. HLA DR8 is the only convincing association but is characterized by great variability of frequency in different populations. PBC is clustered in families further indicating genetic factors.

Pathophysiology:
The pathophysiological mechanisms leading to the clinical, biochemical, immuno-serological and histological overlap remain unidentified. The pathophysiological concepts of the individual diseases are discussed in the respective chapters.

Diagnostic principles:
The diagnosis of an overlap syndrome relies on the biochemical profile (either cholestatic with elevated alkaline phosphatase, gamma glutamyltransferase and bilirubin, or hepatitic with elevated aspartate aminotransferase and alanine aminotransferase levels in addition to elevated gamma globulins), the histology showing portal inflammation with or without the involvement of bile ducts, and the autoantibody profile showing AMA or autoanbibodies associated primarily with AIH such as liver kidney microsomal antibodies (LKM), soluble liver antigen antibodies (SLA/LP) or ANA. In cholestatic cases cholangioagraphy detects sclerosing cholangitis. In an overlap syndrome the classical appearance of the individual disease component is mixed with features of another autoimmune liver disease, immunoglobulins are elevated in all autoimmune liver diseases. The coexistence of PSC requires a biopsy and a cholangiogram (ERC or MRCP). From a practical point of view the failure of a previously effective therapeutic management of a compliant patient should lead to the suspicion of a consecutive overlapping syndrome.

Therapeutic principles:
In general, the leading disease component is treated. In an overlap syndrome presenting as hepatitis, immunosuppression with prednisone (or combination therapy with azathioprine) is initiated. In cholestatic disease ursodeoxycholic acid is administered.
Both treatments can be combined when biochemistry and histology suggest a relevant additional disease component. Validated therapeutic guidelines for overlap syndromes are not available. The most important consideration is the realization that the prognosis of the patient is mainly defined by the course of AIH and the development of cirrhosis. Several studies have documented that cirrhosis development and mortality is associated with the AIH component of an overlap. This should therefore be therapeutically controlled until remission is reached. Recent data suggests that those patients suffering from an overlap between AIH and PSC suffer the most severe course of disease.

**Suggested literature for the topic:**


Liver transplantation for autoimmune liver diseases: The challenge of recurrent disease

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Three autoimmune liver diseases (AILD), autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC), are indications for orthotopic liver transplantation (OLT). Currently, the frequency of OLT is approximately 5–6% for AIH, 12% for PBC and 8% for PSC.

Recurrence of primary disease after orthotopic liver transplantation: Specific diagnostic criteria have been proposed for the recurrence of each AILD. All require exclusion of alternative explanations for liver dysfunction and histopathology (Table).

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<th>PBC</th>
<th>PSC</th>
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<td>Viral hepatitis</td>
<td>Ischemic strictures</td>
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<td>Biliary obstruction</td>
<td>Cholangitis with strictures</td>
<td>Acute rejection</td>
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<td>Chronic rejection</td>
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<td>GVH disease</td>
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Autoimmune hepatitis: For AIH the criteria include: 1) elevation of ALT/AST; 2) persistent autoantibodies; 3) hypergammaglobulinemia and/or increased IgG; 4) characteristic histopathology (lymphoplasmacytic portal inflammation and interface hepatitis); and 5) response to corticosteroids. No validated scoring system exists for the diagnosis. The differential diagnosis includes viral hepatitis, acute cellular rejection, biliary obstruction and drug-induced liver injury (DILI). Recurrent AIH in the allograft occurred in an unadjusted average of 26%, while the calculated weighted recurrence rate in a systematic review was 22%, and significant publication bias was identified. Risk factors for recurrent AIH include low dose immunosuppression (especially discontinuation of corticosteroids), type 1 vs. type 2 AIH (34% vs. 5%) and possibly the magnitude of necroinflammatory activity at the time of OLT. Coincidental matching between donor and recipient HLA in HLA-DR3/DR4 positive recipients has been proposed but remains controversial. Risk of recurrence is unaffected by choice of cyclosporine or tacrolimus for immunosuppression. Reintroduction or increased doses of steroid are usually effective therapies. Some reports advocate addition of azathioprine, substitution of tacrolimus for cyclosporine or conversion to sirolimus. The prognosis of recurrent AIH is excellent in the mid-term, but 10% graft loss occurs after 13.7 years. AIH can also recur again after retransplantation. De novo AIH in allografts has been reported in both children and adults. Therapy with intensified immunosuppression can be beneficial, but graft loss has been reported in a minority of patients.
**Primary biliary cirrhosis:** A diagnostic scoring system for recurrent PBC has been devised that includes the basic criteria of: 1) OLT for PBC; 2) persistence of AMA (and/or ANA or SMA if original disease was AMA-negative); and 3) assigning one point for each of the following histopathological features: mononuclear inflammation of portal tracts, formation of lymphoid aggregates, epithelioid granulomas and non-suppurative destructive cholangitis. When the basic criteria are present along with 3 or more of the 4 histopathological criteria, the diagnosis of recurrent PBC is definite. When only 2 of the 4 histopathological criteria are present, diagnosis is probable. Recurrent PBC occurs in an unadjusted average of 26% of patients, but the calculated weighted recurrence rate was 18%. In contrast to AIH, no publication bias was observed. Risk factors for PBC recurrence include: tacrolimus as primary immunosuppression, early discontinuation of steroids, donor age, warm ischemia time and live donor transplantation. The rate of retransplantation for recurrent PBC was 4% in a UNOS database analysis; thus, recurrence has an adverse long-term impact only in a minority.

**Primary sclerosing cholangitis:** The most widely accepted criteria for the diagnosis of recurrent PSC include: 1) OLT for confirmed PSC; 2) cholangiography showing strictures of the intra- and/or extra-hepatic biliary tract, beading and irregularities > 90 days post-OLT; and 3) histopathology showing fibrous cholangitis and/or fibroobliterative with or without ductopenia, fibrosis or cirrhosis. Key exclusion criteria are: 1) absence of hepatic artery thrombosis or stenosis; 2) chronic ductopenic rejection; 3) biliary anastomotic stricture ≤ 90 days post-OLT; 4) bacterial or fungal cholangitis; and 5) ABO incompatibility between donor and recipient. The frequency of PSC recurrence varies widely in published reports from < 2–40%, and the calculated weighted recurrence rate was 11% in a systematic review that also identified publication bias. Predictors of recurrent PSC include: 1) CMV infection; 2) intact colon and male gender; 3) steroid-resistant rejection; 4) OKT3 treatment for steroid-resistant rejection; and 5) HLA mismatch between donor and recipient. However, one of the larger reported series failed to identify any risk factors. In patients with PSC and IBD, pre-OLT colectomy was associated with a lower rate of PSC recurrence. UDCA has been widely used in patients with recurrent PSC without proof of efficacy. The intermediate prognosis of recurrent PSC is good, but long-term there is a higher risk of biliary cirrhosis and need for retransplantation (7.5% in a recent UNOS database analysis). The post-OLT prognosis for patients with PSC and CCA is poor, but incidental, nodular CCA of ≤ 1 cm diameter have a favorable prognosis. The Mayo protocol for hilar CCA (external beam radiation → brachytherapy → staging laparotomy → capecitabine → OLT) has resulted in a > 70% 5 year survival for those who completed the sequential protocol.

**Inflammatory bowel disease after orthotopic liver transplantation:** Both PSA and AIH are associated with inflammatory bowel disease (IBD; ulcerative colitis >> Crohn’s colitis). IBD recurs in 70% of patients transplanted for PSC and AIH, and de novo IBD may develop in up to 30% after 10 years. Risk factors for IBD after OLT include: 1) presence of IBD before OLT; and 2) tacrolimus immunosuppression. In patients without prior IBD, the risk of post-OLT IBD is increased in CMV-negative recipients of CMV-positive donor livers. Empiric use of 5-aminosalicylate after OLT significantly reduced the risk of recurrent IBD.
Selected references:


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