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Meeting Report

2016 Comprehensive Update of the Banff Working Group on Liver Allograft Pathology: Introduction of Antibody-Mediated Rejection

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The Banff Working Group on Liver Allograft Pathology reviewed and discussed literature evidence regarding antibody-mediated liver allograft rejection at the 11th (Paris, France, June 5–10, 2011), 12th (Comandatuba, Brazil, August 19–23, 2013), and 13th (Vancouver, British Columbia, Canada, October 5–10, 2015) meetings of the Banff Conference on Allograft Pathology. Discussion continued online. The primary goal was to introduce guidelines and consensus criteria for the diagnosis of liver allograft antibody-mediated rejection and provide a comprehensive update of all Banff Schema recommendations. Included are new recommendations for complement component 4d tissue staining and interpretation, staging liver allograft fibrosis, and findings related to immunosuppression minimization. In an effort to create a single reference document, previous unchanged criteria are also included.

Abbreviations: AIH, autoimmune hepatitis; AMR, antibody-mediated rejection; C4d, complement component 4d; CDC, complement-dependent cytotoxicity; DSA, donor-specific antibodies; FFPE, formalin-fixed paraffin-embedded; HCV, hepatitis C virus; MFI, mean fluorescence intensity; OLTx, orthotopic liver transplantation; TCMR, T cell–mediated rejection

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Introduction

Except for liver (1–3) and lung (4), consensus criteria for kidney (5,6), heart (4,7), and pancreas (8) recognize two mechanistically distinct, but overlapping, rejection presentations: (1) T cell–mediated (TCMR) and (2) antibody-mediated rejection (AMR). TCMR manifests as CD4+/CD3+ and CD8+/CD3+ lymphocytic infiltrates accompanied by fewer CD20+ B cells, monocytes/macrophages, natural killer (NK) cells, eosinophils, plasma cells, neutrophils, and mast cells (9). TCMR severity is based on the following: (1) inflammation intensity and distribution; (2) tissue damage extent; and (3) direct or indirect signs of vascular/ischemic injury. Qualifying descriptors include "early" or "acute" and "late" or "chronic."

Early and late TCMR are not strictly time delineated: considerable overlap exists, so strict separation can be problematic (1,10). However, early (<6 months) acute TCMR is likely attributable to direct alloantigen presentation, while late (>6 months) or chronic TCMR likely depends on indirect alloantigen presentation. In liver allografts, the former shows more prevalent inflammatory bile duct damage, pleomorphic portal inflammation (lymphocytes, macrophages, eosinophils, etc.), and paucity of necro-inflammatory-type interface activity compared to "late" TCMR (1,10), which shows more homogeneous lymphoplasmacytic and histiocytic infiltrates, less lymphocytic cholangitis, and low-grade interface and perivenular necro-inflammatory-type activity (1,10). Thus, most idiopathic posttransplant hepatitis cases are now categorized as late TCMR and/or chronic AMR (see chronic AMR histopathology) in donor-specific antibody-positive (DSA+) patients (11).

Acute AMR manifests consistently across kidney, heart, and pancreas allografts as organ dysfunction and microvascular pathology (12,13), recognized as intraluminal pooling and/or margination of various leukocyte subsets (monocytes, macrophages, lymphocytes, neutrophils, and eosinophils) in dilated/irregularly shaped capillaries (14–19). Liver allografts exhibit a well-documented AMR resistance (reviewed in (20–22)), accounting for the low incidence of acute AMR.

The goals of this article include (1) standardized AMR criteria; (2) recommendations for tissue complement component 4d (C4d) staining and interpretation; and (3) a comprehensive update.

Terminology Updates

Older (discouraged) terminology	Newer (preferred) terminology
Humoral rejection	Antibody-mediated rejection (AMR)
(Acute) cellular rejection	T cell–mediated rejection (TCMR)
De novo auto-immune hepatitis	Plasma cell rich–rejection
Plasma cell hepatitis	

TCMR, chronic rejection, and fibrosis staging

Widespread Banff classification adoption (23–27), treatment responsiveness (1,2,10,24), and rarity of allograft failure from TCMR or chronic rejection (23–27) provide

Table 1: Typical T cell–mediated rejection

Grading criteria (global assessment):

- Indeterminate: Portal and/or perivenular inflammatory infiltrate that is related to an alloreaction, but shows insufficient tissue damage to meet criteria for a diagnosis of mild acute rejection,
- Mild: Rejection-type infiltrate in a minority of the triads or perivenular areas, that is generally mild, and mostly confined within the portal spaces for portal-based rejection and an absence of confluent necrosis/hepatocyte dropout for those presenting with isolated perivenular infiltrates.
- Moderate: Rejection-type infiltrate, expanding most or all of portal tracts and/or perivenular areas with confluent necrosis/hepatocyte dropout limited to a minority of perivenular areas.
- Severe: As above for moderate, with spillover into periportal areas and/or moderate-to-severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis involving a majority of perivenular areas.

Quantitative scoring (rejection activity index [RAI]):

Score	Criteria
	Portal inflammation:
1	Mostly lymphocytic inflammation involving, but not noticeably expanding, a minority of the triads.
2	Expansion of most or all of the triads, by a mixed infiltrate containing lymphocytes with occasional blasts, neutrophils, and eosinophils. If eosinophils are conspicuous and accompanied by edema and microvascular endothelial cell hypertrophy is prominent, acute antibody-mediated rejection (AMR) should be considered.
3	Marked expansion of most or all of the triads by a mixed infiltrate containing blasts and eosinophils with inflammatory spillover into the periportal parenchyma
	Bile duct inflammation damage:
1	A minority of the ducts are cuffed and infiltrated by inflammatory cells and show only mild reactive changes such as increased nuclear:cytoplasmic ratio of the epithelial cells.
2	Most or all of the ducts infiltrated by inflammatory cells. More than an occasional duct shows degenerative changes such as nuclear pleomorphism, disordered polarity, and cytoplasmic vacuolization of the epithelium.
3	As above for 2, with most or all of the ducts showing degenerative changes or focal luminal disruption
	Venous endothelial inflammation:
1	Subendothelial lymphocytic infiltration involving some, but not a majority of the portal and/or hepatic venules
2	Subendothelial infiltration involving most or all of the portal and/or hepatic venules with or without confluent hepatocyte necrosis/dropout involving a minority of perivenular regions.
3	As above for 2, with moderate or severe perivenular inflammation that extends into the perivenular parenchyma and is associated with perivenular hepatocyte necrosis involving a majority of perivenular regions.

little impetus for change (Tables 1 and 2). However, since atypical fibrosis patterns without preceding TCMR might represent chronic antibody-mediated injury or mixed TCMR and chronic AMR (28–31), staging fibrosis in three distinct compartments (32) is recommended (Table 2).

Atypical presentations

Plasma cell–rich rejection (*de novo* autoimmune/plasma cell hepatitis) is a poorly understood and uncommon (≈3–5% of recipients) cause of late (>6 months) dysfunction that resembles native liver autoimmune hepatitis (AIH) that often arises in interferon-treated hepatitis C virus positive (HCV+) recipients (33–38). Mixed TCMR/AMR etiology overlapping with autoimmunity (33,34,37–41) supports designation as "plasma cell–rich rejection" in patients without an AIH original disease diagnosis (Table 3). Compared to typical AIH, plasma cell–rich rejection shows the following characteristics:

- more prevalent and severe lymphocytic cholangitis (34);
- IgG4+ plasma cell over-representation (34) (>50% [34] vs. ≈3% [42]);
- more aggressive plasma cell–rich central perivenulitis (33,34,43–45);
- DSA+ (~60%; [41]);
- portal microvascular C4d deposition (46,47);
- atypical liver/kidney microsomal mismatching (44,47,48);
- prior γ-interferon treatment;
- more TCMR risk factors and steroid dependence (36,49);
- antibody-dependent effector mechanism (50–52);
- co-existent typical TCMR or chronic rejection features in 18–24% of cases (36,45).

Autoimmunity evidence includes histopathological similarities to native liver AIH and detection of classical (35,36) and other autoantibodies (53–55). Distinguishing recurrent AIH from plasma cell–rich rejection needs work.

Corticosteroids with or without azathioprine constitute the essential therapy (56), but high doses of steroids are often required; when immunosuppression is tapered, biopsy findings can recur.

Table 2: A. Typical chronic rejection evaluation. B. Adapted from Venturi et al (32)

(A) Structure	Early chronic rejection (at least two findings should be present)	Late chronic rejection (at least two findings should be present)
Small bile ducts (<60 μm)	Senescence-related changes involving a majority of ducts (see text); bile duct loss <50% of portal tracts	Loss in ≥50% of portal tracts; degenerative changes in remaining bile ducts
Portal tract hepatic arterioles	Occasional loss involving <25% of portal tracts	Loss involving >25% of portal tracts
Terminal hepatic venules and zone 3 hepatocytes	Perivenular mononuclear inflammation; lytic zone 3 necrosis and inflammation; and mild perivenular fibrosis (see below)	Variable inflammation; focal obliteration; moderate-to severe-(bridging) fibrosis (see below).[1]
Large perihilar hepatic artery branches	Intimal inflammation, focal foam cell deposition without luminal compromise	Luminal narrowing by intimal foam cells; fibrointimal hyperplasia
Large perihilar bile ducts	Inflammation damage and focal foam cell deposition	Mural fibrosis
Other	So-called "transition" hepatitis with spotty necrosis of hepatocytes	Sinusoidal foam cell accumulation; cholestasis

(B)

Suggested Fibrosis Scoring: Fibrosis should be scored in three separate compartments: (1) portal/periportal; (2) sinusoidal/subsinusoidal; and (3) perivenular in a semiquantitative fashion on a scale from 0 (none) to severe (bridging), described in more detail, below. The final score is achieved by adding the three components together for a total possible score of "9." However, retaining the granular scores for each compartment should be helpful in uncovering pathogenic mechanisms of injury.

Portal/Periportal: 0 (none)—3 (portal-to-portal or portal-to-central bridging)
Subsinusoidal: 0 (none)—3 (thick; marked and diffuse)
Perivenular: 0 (none)—3 (central-to-central or central-to-portal bridging)

AMR, antibody-mediated rejection; DSA, donor-specific antibody.
[1]Chronic AMR might be contributing to the development of perivenular fibrosis; C4d stains and DSA determinations should be considered.

Antibody-Mediated Rejection (AMR)

General considerations

Susceptibility and resistance mechanisms: AMR susceptibility is dependent on antibody class, titer, specificity and timing, and density and target antigen distribution (20). Liver AMR was first recognized with ABO-incompatible (ABO-I) allografts (57–61) and later with lymphocytotoxic/DSA antibodies (62–66). Banff Schema AMR inclusion was delayed because (1) ABO-I grafting is not widespread; (2) ABO-C grafts are less sensitive than kidney allografts to acute AMR (67); and (3) livers can protect subsequent syngeneic kidney and heart allografts from AMR in sensitized experimental animals (68,69) and to some extent in humans (70,71). However, syngeneic partial auxiliary liver allografts failed to protect kidney allografts from AMR in two of seven broadly sensitized recipients (72). As noted below, livers protect kidney allografts from class I more than class II DSA.

Mechanisms for liver allograft AMR-resistance include (20,21,73) the following:

(1) Kupffer cell DSA clearance of activated complement, platelet aggregates (74), and immune complexes formed between soluble donor HLA class I and anti-class I DSA (68,69,75–77). Supporting evidence includes (i) *increased* AMR susceptibility and *decreased* protection of sequentially placed extrahepatic allografts in Kupffer cell–depleted liver allografts (68,69,75–77); and (ii) amelioration of acute heart allograft AMR in sensitized recipients by donor class I gene transfection that produces soluble HLA antigens (78).
(2) Variable hepatic (79) versus constitutive kidney (80) and heart (81) microvascular class II expression providing fewer class II DSA targets, possibly explaining preferential clearance of class I versus class II DSA (82,83).
(3) Large liver size dilutes antibody-binding across a larger endothelial cell surface, potentially explaining increased AMR susceptibility in reduced-size allografts (77).
(4) Kupffer and liver sinusoidal endothelial cells Fc receptor expression and phagocytic activity (84–86).
(5) Hepatic regenerative capacity and ability to heal either without fibrosis or reverse fibrosis (87).

Table 3: Criteria for the diagnosis of plasma cell–rich rejection[1,2]

Must fulfill criteria 1 and 3; criterion 2 is desirable, but not absolutely required:

(1) Portal and/or perivenular plasma cell–rich (estimated >30%) infiltrates with easily recognizable periportal/interface and/or perivenular necro-inflammatory activity usually involving a majority of portal tracts and/or central veins. Most of these cases are graded at least "moderate" with a total RAI score ≥5 because "V score" is usually "3" because of aggressive perivenular activity, whereas "Portal Inflammation" score is usually ≥2.
(2) Lymphocytic cholangitis is usually present and a desirable feature, but not absolutely required (inflammatory bile duct damage might be a relatively minor component, but Banff component score for bile duct injury is usually ≥1).
(3) Original disease other than autoimmune hepatitis.

RAI, rejection activity index.
[1]C4d stains are recommended on all biopsies diagnosed as plasma cell–rich rejection; IgG and IgG4 stains might also be considered to better understand the underlying pathophysiology in some recipients.
[2]Other contributory, but nonessential features include antibodies to GSTT1 in null recipients of GSTT1-positive donor livers and the *de novo* appearance of donor-specific HLA antibodies (DSA).

Target antigen expression: ABH blood group antigens are ubiquitously expressed on all hepatic endothelial cells (reviewed in [79]). HLA class I and II expression has been studied in formalin-fixed, paraffin-embedded (FFPE) and frozen "normal" human livers (e.g. organ donors, biopsies obtained from patients with nonhepatic diseases, uninvolved liver resected for tumors) using immunostaining (88–95). All studies reported diffuse and strong class I HLA expression on all cell types, except hepatocytes where expression is weaker. HLA-DR class II expression is strongest on portal, perivenular, and subcapsular dendritic cells, and Kupffer cells with DQ weaker than DR. Portal vein branch endothelia class II expression was consistently negative, but portal capillary, septal venule, sinusoidal, and central vein endothelia vary from negative to focally positive (88–95). More work is needed because few studies address class II expression in specific endothelial compartments (e.g. portal capillary/peribiliary plexus, lymphatic capillaries, inlet venules, septal venules, and large duct peribiliary plexus). Co-existent disorders (e.g. HCV, TCMR) can upregulate microvascular and other cell HLA II expression, thereby increasing DSA target antigen density and potentially AMR-related pathology (21,22,101).

Specimen adequacy, C4d staining methods, and interpretation

Guidelines (1,102) include two passes with a 16-gauge needle for adequate fibrosis assessment; shorter (<20 mm) and thinner needles systematically underestimate fibrosis (103) and <11 portal tracts might not be representative (reviewed in [102]).

C4d staining facilitates an AMR diagnosis (104,105), but deposition does not necessarily trigger downstream effector mechanisms (14,106,107). Linear/granular microvascular endothelial cell C4d staining is accepted as evidence of tissue-based complement activation (15,106,108). Ideally, more sensitive frozen tissue immunofluorescence (IF) (109–114) C4d staining should be carried out if acute or chronic AMR is suspected. However, most centers rely on immunoperoxidase staining of FFPE tissue using rabbit polyclonal or monoclonal anti-C4d antibodies after antigen retrieval, and the sensitivity can be increased by pressure-cooker antigen retrieval (104,115–120).

An unpublished FFPE tissue microarray C4d staining study (D. Neil, personal communication) showed the following: (1) several "best" methods use different primary antibodies, with antigen retrieval performed at both high and low pH suggesting that there is no single best antibody or pH of antigen retrieval; and (2) "best C4d staining methods" in liver showed variable staining in kidney and heart AMR. A liver tissue positive control is ideal, but positive kidney or heart allograft tissue is acceptable. Each laboratory should validate its anti-C4d reactions against positive and negative controls to monitor the effect of fixation times, processing techniques, automation, and selection of antibodies.

Normal liver allograft biopsies are usually negative for endothelial cell C4d staining, but background/nonspecific C4d labeling can be seen in arterial elastic lamina; occasionally in portal and perivenular elastic fibers; necrotic and steatotic hepatocytes, and areas of sinusoidal fibrosis. Linear-to-granular endothelial cell staining of portal veins, portal capillaries, sinusoids, central veins, and arterial endothelium, lymphoid nodules, and periductal and portal stromal C4d staining has been described in native pediatric livers with hepatitis B (HBV) and C (HCV), and AIH (123) and in allografts when "no-rejection" insults are thought to be the primary cause of allograft dysfunction (e.g. biliary obstruction [104], recurrent HBV [115] or HCV [118], and plasma cell hepatitis [*de novo* AIH]) (47). However, these deposits are less widespread and intense than those associated with AMR (73,105,116,124–126). Moreover, recipients with nonrejection causes of allograft dysfunction are not protected from developing DSA and C4d tissue deposition, but in fact, these might be more common in these circumstances because of HLA upregulation (21,101,127).

Portal venous and capillary, arterial, and sinusoidal and central vein endothelial C4d staining has been significantly associated with DSA+ recipients (120), acute AMR (122,128), macrophage and plasma cell infiltrates (116), microvasculitis (129,130), and TCMR (104,115–120). In some studies, C4d deposits were directly proportional to Banff TCMR grade, suggesting that "severe" episodes might represent combined TCMR/AMR (104, 115–120). Portal vein and capillaries and sinusoidal endothelial cell C4d staining appears to be most specific for acute AMR (128,130,133,134), whereas portal C4d "stromal" staining seems to be more strongly associated with ABO-incompatible acute AMR (117), TCMR (120), and chronic rejection (131,135), including chronic AMR (101). Although the prevalence is unknown, C4d deposits are often less intense or negative in putative chronic AMR (101), similar to renal allografts (107, 136,137).

Since HLA class II target antigen density can affect antibody binding/C4d fixation, C4d staining/scoring (Table 4) can be contextual: TCMR manifesting primarily as central perivenulitis can locally upregulate HLA class II, leading to preferential venular and perivenular endothelial C4d deposition (101). HLA class II staining might help delineate DSA target antigen distribution. Liver allograft IF can be more difficult to interpret than FFPE staining because of difficulties with recognizing the underlying architecture.

We therefore recommend scoring of both IF and FFPE C4d deposition in the following compartments: portal veins, portal capillaries, portal stroma, sinusoidal, and central vein endothelial as negative, minimal (<10%); focal (10–50%), and diffuse (>50%) of structures.

Acute Antibody-Mediated Injury

Antibody characteristics

IgM and IgG isoagglutinins titer and complement-fixing ability influence pathogenic potential (57,117,138,139): recipients who develop >1:64 isoagglutinins often manifest graft dysfunction and histopathological damage (117,139). Reducing to titers <1:16 by plasmapheresis/exchange can largely avoid ABO-I AMR (138), but careful monitoring of titers post–orthotopic liver transplantation (OLTx) is essential to determine whether further intervention is required.

Cell-based DSA detection assays (CDC) show that 8–15% of recipients are DSA positive (>30–50% lysis) pretransplant (62,129,140), particularly female and autoimmune-prone individuals (126,132,141–143). Solid phase assays validate and extend these findings (22). Solid phase single antigen beads are more sensitive and detect DSA in ≈4% of CDC-negative recipients (83).

Table 4: Component lesion scoring for acute AMR

C4d-(immune)-score (formalin-fixed, paraffin-embedded[1,2]):

(0) No C4d deposition in portal microvasculature
(1) Minimal (<10% portal tracts) C4d deposition in >50% of the circumference of portal microvascular endothelia (portal veins and capillaries)
(2) Focal (10–50% portal tracts) C4d deposition in >50% of the circumference of portal microvascular endothelia (portal veins and capillaries)—usually without extension into periportal sinusoids
(3) Diffuse (>50% portal tracts) C4d deposition in >50% of the circumference of portal microvascular endothelia (portal veins and capillaries)—often with extension into inlet venules or periportal sinusoids

h-(histopathology)-score[3,4,5]

(1) Portal microvascular endothelial cell enlargement (portal veins, capillaries, and inlet venules) involving a majority of portal tracts with sparse microvasculitis defined as three to four marginated and/or intraluminal monocytes, neutrophils, or eosinophils in the maximally involved capillary with generally mild dilation (Figure 1).
(2) Monocytic, eosinophilic, or neutrophilic microvasculitis/capillaritis, defined as at least 5–10 leukocytes marginated and/or intraluminal in the maximally involved capillary prominent portal and/or sinusoidal microvascular endothelial cell enlargement involving a majority of portal tracts or sinusoids, with variable but noticeable portal capillary and inlet venule dilatation and variable portal edema (Figure 2).
(3) As above, with marked capillary dilatation, marked microvascular inflammation (10 or more marginated and/or intraluminal leukocytes in the most severely affected vessels), at least focal microvascular disruption with fibrin deposition, and extravasation of red blood cells into the portal stroma and/or space of Disse (subsinusoidal space) (Figure 3).

AMR, antibody-mediated rejection; PAS, periodic acid-Schiff; RBC, red blood cells.
[1]Formalin-fixed, paraffin-embedded tissues are known to show weaker staining than fresh-frozen tissues, but interpretation of frozen tissues can be more difficult because of background/nonspecific staining and poor preservation of morphology. Sinusoidal staining should be localized to sinusoidal endothelial cells; false positive staining of connective tissue fibers can occur in livers with subsinusoidal fibrosis.
[2]Ideally the C4d positive control should be a liver allograft, but peritubular capillary staining of a kidney allograft is an acceptable alternative.
[3]Special stains that help identify capillaries, such as CD31, CD34, and/or PAS are often needed to help identify involved portal-based capillaries.
[4]Other features commonly seen, but not necessarily associated with severity include ductular reaction and cholestasis.
[5]Fibrin deposition and RBC sludging occurs earlier and is more common and prominent in ABO-incompatible allografts.

Pretransplant DSA positivity with potential clinical significance has been tentatively defined as mean fluorescence intensity (MFI) ≥ 5000, but positivity cutoff varies by laboratory and standardization is needed. MFI is not equivalent to traditional metrics of antibody titer or avidity. Empirically, high MFI for individual or aggregated

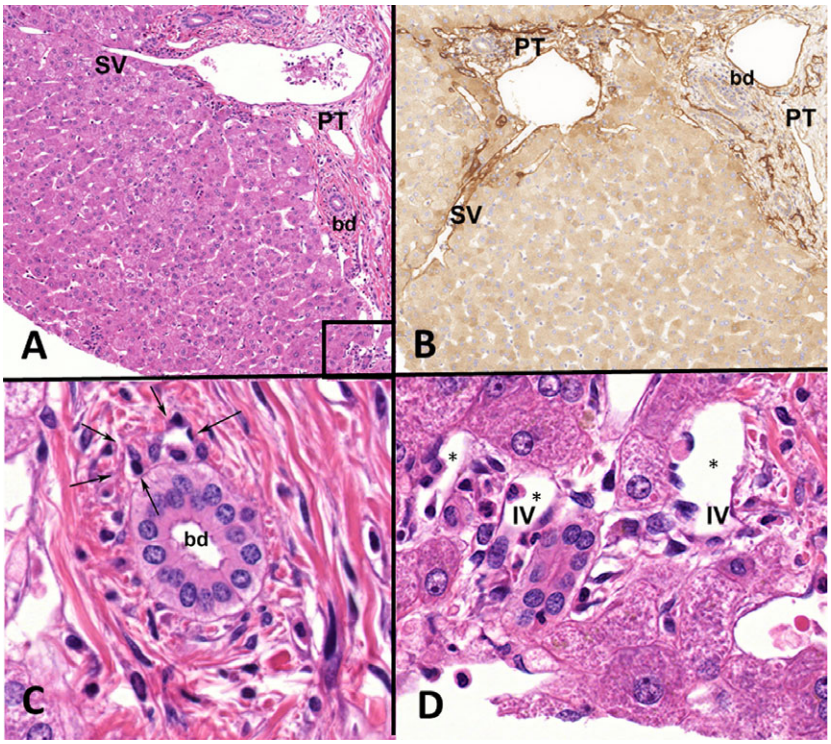

Figure 1: Composite of early acute AMR with mild portal microvascular endothelial cell enlargement (portal veins, capillaries, and inlet venules) with sparse microvasculitis (h1 score; see Table 4). (A) Low magnification hematoxylin and eosin overview. The lower right inset is shown at high magnification in (D). (B) C4d stain showing diffuse portal microvascular staining in the portal peribiliary plexus and inlet venules. This would score as C4d: "3." (C) High magnification of the peribiliary capillary plexus showing mild endothelial cell hypertrophy and dilatation and monocyte margination (arrows). (D) High magnification of inlet venules (IV) showing mild endothelial cell hypertrophy and dilatation and monocyte margination (*). The h-score for this area would be 1–2. bd, bile duct; AMR, antibody-mediated rejection; PT, portal tract; SV, septal venules.

anti-HLA DSA is a useful indicator of clinically significant DSA, but without additional testing (e.g. titration, C1q assay), an isolated MFI value can be misleading (144).

The vast majority of lower MFI class I DSA (<10 000 MFI) resolves shortly after transplantation, but C4d tissue deposits are detected in some highly sensitized recipients early after OLTx without apparent short-term or long-term consequences (126,141). Regardless, preformed DSA does not adversely influence short-term survival in the vast majority of low to moderately (<8000 MFI) sensitized recipients (126,132,134,141–143). High-MFI class II DSA (≥10 000) persist in approximately one third of recipients (141) associated with an increased risk of early TCMR, and perhaps, mixed TCMR and acute AMR (141). A tiny fraction (<5%) of highly sensitized (DSA+) recipients have sufficient DSA (usually multiple class I and II usually in high MFI/titers) to cause clinically significant acute AMR (130,132,134). Lower-level sensitization usually results in rapid DSA disappearance with either no injury or transient antibody-mediated damage often misrepresented as "preservation injury"(20,129,140).

Clinical manifestations

Acute AMR usually occurs within the first several weeks after transplantation in highly sensitized recipients (64,129) (polyspecific high titer/high MFI antibodies). Many also fix complement, but non-complement-fixing antibodies cannot be ignored. Acute AMR-mediated rapid allograft failure with microvascular injury, thrombosis, and hemorrhagic necrosis (145) can rarely occur, but less florid injury is more common, characterized by graft dysfunction/hyperbilirubinemia (129,134,140,146); thrombocytopenia (129,134,140,146); low serum complement levels (129,140); posttransplant DSA persistence (especially class II); circulating immune complexes (20,129, 140), disproportionate posttransplant transaminasemia in relationship to clinical assessment of donor liver quality; and histopathological microvascular injury.

Rapid DSA clearance accounts for protection of sequentially placed syngeneic allografts (70,147). "Protection," however, is occasionally only partial: syngeneic kidneys can experience AMR, more commonly with class II than class I DSA (82,141,148), possibly due to the lower density class II expression and DSA clearance related to the donor liver (discussed previously). Although uncommon,

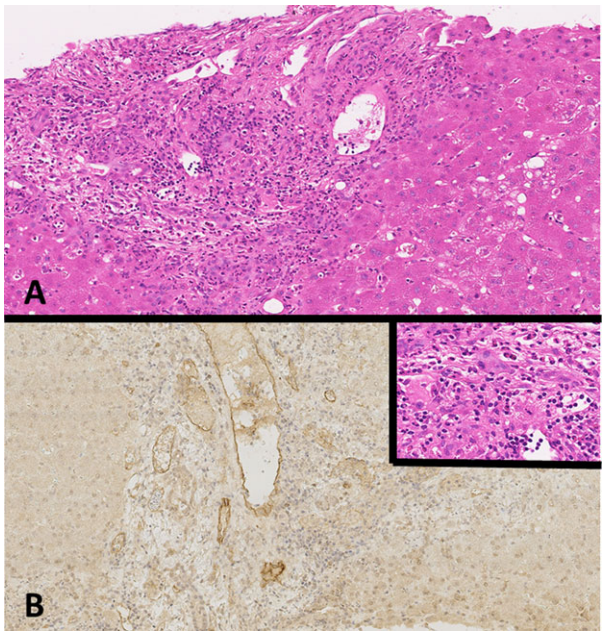

Figure 2: Composite of moderate acute AMR (h2 score; see Table 4) with (A) mild-to-moderate portal microvascular endothelial cell enlargement (portal veins, capillaries, inlet venules) with (B) diffuse C4d positivity and easily recognizable microvascular inflammation (inset). Portal lymphocytic inflammation is also seen, which likely represents a component of overlapping TCMR. AMR, antibody-mediated rejection; TCMR, T cell–mediated rejection.

late-onset acute AMR (>6 months) can occur with *de novo* DSA (149).

Acute AMR histopathology

The "signature" acute AMR microvascular pathology lesions include endothelial cell hypertrophy/enlargement, capillary dilatation, leukocyte sludging and/or leukocyte margination, and edema. In severe cases, microvascular disruption and interstitial hemorrhage occurs (5,7,12–17). Linear to granular, portal vein and capillary, inlet venule, and focal sinusoidal and central vein endothelial cell C4d deposition is usually present and required under current criteria.

ABO-incompatible liver allografts: Postreperfusion biopsies in recipients with moderate to high pretiter (>1:32) isoagglutinins often show sinusoidal and portal vein platelet-fibrin thrombi and red blood cell (RBC) and neutrophil sinusoidal sludging, focal Disse space and portal connective tissue hemorrhage, and hepatocellular cytoaggregation/apoptosis (57). First-week follow-up biopsies in at-risk recipients (50% with high titer [>1:64] isoagglutinins [139]) show portal microvascular endothelial cell enlargement/hypertrophy, focal fibrin deposition, portal edema, periportal hepatocyte clusters with coagulative necrosis, and RBC congestion and hemorrhage (57,139). Other portal tract changes include variable fibrinoid degeneration of portal artery branches, neutrophilic inflammation, focal cholangitis/cholangiolitis, a ductular reaction (57,139), and portal vein and capillary endothelia and portal stromal C4d deposition (152), which is characteristic of early acute ABO-I AMR (117).

In untreated recipients with high titers, progressive patchy geographic hemorrhagic infarction occurs; those who survive can later develop biliary strictures caused by ischemic cholangiopathy (20,153,154). Recipients harboring lower-titer isoagglutinins can develop endothelial cell C4d positivity without developing other acute AMR effector mechanisms (133), as in kidney ABO-I grafts.

ABO-compatible allografts: Postreperfusion biopsies from highly sensitized (high titer/high MFI, often multiple, anti-HLA) allografts often show platelet aggregates in portal and/or central veins (129,155), accompanied by diffuse portal microvasculature C4d staining (Figure 1) (126,134). Portal microvascular endothelial hypertrophy and cytoplasmic eosinophilia, occasionally resulting in variable "hobnailing," appear within days to weeks in those developing early acute AMR (129,130,134). Other features include capillary dilatation and leukocyte sludging/margination involving portal vein branches, portal and peribiliary plexus capillaries, and inlet venules, rarely extending into sinusoids and central veins (Figures 2 and 3).

Other changes include portal/periportal edema, ductular reaction, hepatocyte apoptosis, centrilobular hepatocellular swelling and hepatocanalicular cholestasis (129,130, 134,156), and in severe cases, focal perihilar bile duct necrosis and arterial vasospastic changes (129). Significant AMR components can produce biliary strictures (129,157,158) and veno-occlusive-type central vein lesions, as in ABO-I grafts. Superimposed TCMR is common (129,130,134,159–161). Standard criteria for AMR (Tables 4 and 5) and TCMR should be used in mixed AMR/TCMR episodes. Lymphocytic intimal inflammation and necrotizing arteritis are rare, but diagnostic of acute AMR when combined with diffuse C4d deposits and DSA, as in kidney allografts (6).

Microvascular dilatation, endothelial cell enlargement/hypertrophy, and "microvasculitis," especially involving central veins, distinguish acute AMR from preservation/reperfusion injury and obstructive cholangiopathy (21,73,116,128,130,134,162). Stringent acute AMR diagnostic criteria will help to prevent overdiagnosis (105,128,130–132,134,162) (Table 5).

Chronic Antibody-Mediated Injury

Chronic AMR general considerations

Antibody characteristics: Late-onset acute AMR, and mixed AMR/TCMR appear in suboptimally immuno-

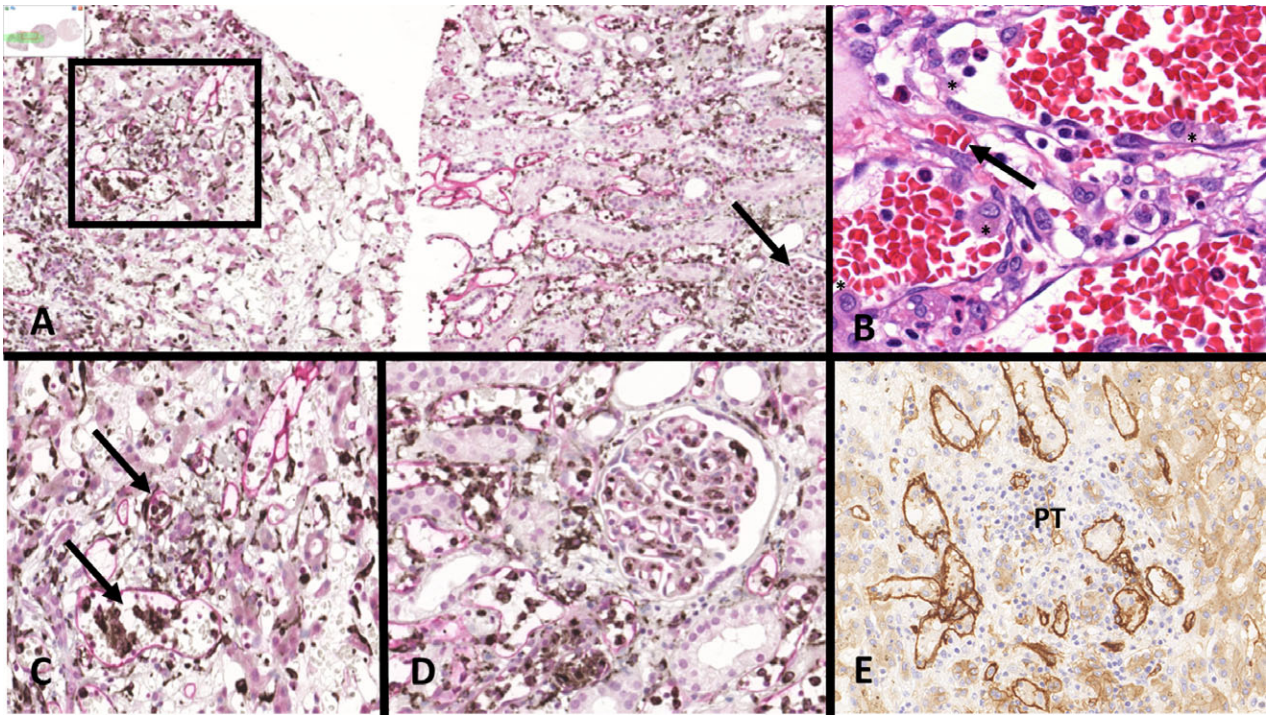

Figure 3: Composite of severe acute AMR (h3 score; see Table 4) with (A) comparison of severe acute AMR in liver (left side) versus kidney (right side) (C4d: red; CD68: black). Note the capillary dilatation in both organs. (B) High magnification of a portal tract showing dilated portal capillaries, focal interstitial hemorrhage (arrow), and marginated monocytes/macrophages (*). Higher magnification of the liver area outlined by the square in (A) is shown in (C); h-score: "3." Higher magnification of the kidney near the arrow in (A) is shown in (D). Note the margination of black-stained monocytes/macrophages in both organs with acute AMR. (E) Diffuse portal microvascular endothelial cell positivity. C4d score: "3." AMR, antibody-mediated rejection; PT, portal tract.

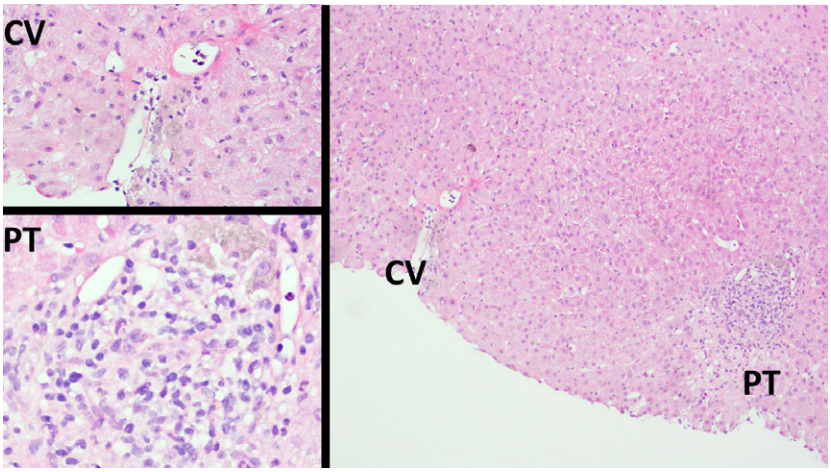

Figure 4: Changes commonly associated with chronic AMR include portal and perivenular inflammation. The portal tract (PT) and central vein (CV) shown in the right panel are illustrated at higher magnification in the left panels. AMR, antibody-mediated rejection.

suppressed recipients with persistent, often *de novo,* DSA+ (149). Putative chronic liver AMR occurs in an unknown percentage of the ≈8–15% of recipients who keep or develop *de novo* DSA (149,163) directed at HLA class II, especially DQ (149,163). *De novo* DSA risk factors include cyclosporine versus tacrolimus use, low immunosuppression and Model for End-Stage Liver Disease score (163), young age, and previous transplants

Table 5: Criteria for establishing the diagnosis of acute AMR in liver allografts

Definite for acute/active[1] AMR (all four criteria required):

(1) Histopathological pattern of injury consistent with acute AMR, usually including the following: portal microvascular endothelial cell hypertrophy, portal capillary and inlet venule dilatation, monocytic, eosinophilic, and neutrophilic portal microvasculitis, portal edema, ductular reaction; cholestasis is usually present, but variable; edema and periportal hepatocyte necrosis are more common/prominent in ABO-incompatible allografts (57,117,139); variable active lymphocytic and/or necrotizing arteritis
(2) Positive serum DSA
(3) Diffuse (C4d score = 3) microvascular C4d deposition[1] on frozen or formalin-fixed, paraffin-embedded tissue in ABO-compatible tissues or portal stromal C4d deposition in ABO-incompatible allografts.
(4) Reasonable exclusion of other insults[2] that might cause a similar pattern of injury (see text). Most cases will score (C4d-score: 3+ h-score = 5 or 6; see below).

Suspicious for AMR (both criteria required):

(1) DSA is positive (see definitions).
Non-zero h-score with: C4d-score + h-score of 3 or 4.

Indeterminate for AMR (requires 1+2 and 3 or 4):

(1) C4d-score + h-score is ≥ 2.
(2) DSA not available, equivocal, or negative.
(3) C4d staining not available, equivocal, or negative.
(4) Co-existing insult might be contributing to the injury.

AMR, antibody-mediated rejection; DSA, donor-specific antibody.
[1]Optimized C4d staining including positive control is critical for proper evaluation.
[2]Thrombocytopenia, low serum complement levels, persistence of DSA early after transplantation, and elevated liver injury tests are usually present, but might not be prominent in mild cases.

(149). Multivariate analyses show *de novo* DSA is associated with decreased patient survival (163) and allograft fibrosis (149), with IgG3 and C1q+ DSA giving the highest risk (41,164–166).

Pathophysiologically linking DSA to tissue pathology has been more difficult than for acute AMR (21,22). DSA+ recipients more often experience progressive fibrosis and architectural distortion (22,31,141,164,165,167,168), but others who are operationally tolerant show little change over a 7-year follow-up period (166,169). Similar difficulties are encountered in chronic renal allograft AMR (21,22,107): Alloantibodies clearly cause acute AMR, and evidence supporting their pathogenic etiology in chronic alloantibody-mediated rejection is complicated by several confounding factors such as slow evolution, immunosuppression, DSA titer, and antigenic target variations.

Evidence supporting a pathogenic role for antibodies in chronic kidney injury (106) include the following: (1) Four stages exist in nonhuman primate renal allografts models: alloantibody production, peritubular capillary and glomeruli C4d deposition, chronic histopathological changes, and graft loss. (2) Prospective studies show circulating anti-HLA are associated with late graft failure. (3) Histological changes associated with late graft loss are spatially associated with peritubular C4d deposition. Chronic renal allograft AMR criteria (2007) include the following: (1) histological evidence of chronic injury; (2) C4d deposition; and (3) DSA (170).

Liver allografts, by comparison, lack large nonhuman primate data where the effect of antibodies on allograft structural integrity is studied, but small-animal models are emerging (171,172). In addition, only rare prospective liver allograft studies exist that include paired serum and biopsy samples (101). However, candidate histopathological lesions are being linked (portal and perivenular inflammation, interface activity, and fibrosis) with C4d deposits (31,41,131,133,167,173,174). Some aspects of disease "activity," however, might be defined differently in liver than in kidneys (e.g. direct stellate cell activation by DSA).

Chronic liver allograft AMR suffers from a lack of specific/typical clinical or biochemical features: many histopathological features potentially associated with chronic AMR are observed in protocol biopsies from clinically well recipients with normal liver injury tests.

Chronic AMR histopathology

Candidate chronic AMR histopathological lesions are emerging from (1) long-term follow-up of pediatric recipients (31,41,55,167,176,177,179); (2) suboptimally immunosuppressed recipients (22,41,167,179); (3) immunosuppression weaning studies (167,180,181); and (4) protocol simultaneous serum and biopsy samplings (22,127,130,134). Pediatric populations are informative since most original diseases do not recur, making putative chronic AMR recognition easier, especially when candidate lesions differ substantially from typical TCMR, viral hepatitis, and vascular or biliary complications. Persistent/recurrent kidney allograft AMR eventually leads to peritubular capillary basement membrane lamination; capillary rarefaction and replacement fibrosis occur in kidney and heart allografts (12,13,15–17,150,182).

De novo DSA signals tolerance loss in kidney allografts (183) and often develops in pediatric OLTx recipients weaned from immunosuppression (166,167) and with chronic suboptimal immunosuppression (21,55,167,183), but are not inevitably associated with graft loss. Protocol follow-up biopsies obtained after sustained lowering or withdrawal of IS are limited (1,10,184,185). Some study endpoints consider *de novo* DSA development a failure, regardless of histopathology, but after weaning not all

DSA+ patients experience TCMR, fibrosis, architectural deterioration, or sinusoidal endothelial (CD34- to CD34+) or stellate cell phenotypic changes (SMA− to SMA+) within 5 years (166).

Lesions most strongly associated with persistent DSA include low-grade portal, periportal, and perivenular lymphoplasmacytic inflammation with low-grade interface and perivenular necro-inflammatory activity and noninflammatory fibrosis (Figures 4 and 5; Table 6). Portal capillary dilatation, endothelial cell hypertrophy, and leukocyte margination are less common and/or noticeable with chronic AMR compared to acute AMR and, if present, can be difficult to interpret in the context of coexistent portal inflammation perhaps related to mixed chronic AMR/TCMR. Biliary strictures (129,157,158), nodular regenerative hyperplasia, and obliterative arteriopathy are suspected (21,22,101).

Putative chronic AMR lesions are also associated with microvascular endothelial C4d deposition in most studies, but diffuse intense microvascular inflammation is less common than in acute AMR (21,31,47,73,101,133, 135,167,168,186). This might be related to lower antibody production because of activated B cell deletion via a PD-L1-mediated mechanism (187) or others.

Most candidate lesions, except for obliterative arteriopathy, are also caused by other complications (1,10,52). However, DSA could worsen lesions of coexistent disorders, such as recurrent HCV and TCMR, via upregulation of microvascular HLA Class II (21,22,101). Potential pathogenic mechanisms linking DSA to tissue inflammation and fibrosis include microvascular destruction, non-microvascular antibody-dependent cellular cytotoxicity, phenotypic modulation/activation of endothelial and stellate cells and portal myofibroblasts, and complement-mediated chemotaxis with or without coexistent TCMR.

Stringent chronic AMR criteria (Table 7) will help to avoid overdiagnosis until the entire spectrum of morphological manifestations is appreciated. Standard criteria should be used to grade each component and a diagnosis of mixed AMR/TCMR. Clearly more work is needed on this topic.

Acute and Chronic AMR Treatment

ABO-incompatible AMR can be prevented. Isoagglutinin titers are tested pretransplant and therapy with total plasma exchange and usually rituximab with or without other modalities (e.g. intravenous immunoglobulin [IVIg], cyclophosphamide, local infusion therapy, and splenectomy) is employed to achieve a pretransplant titer $\leq$1:8 (1). Following transplantation, isoagglutinin titers should be monitored prospectively and therapy instituted if they increase to >1:8–16 (188).

ABO-compatible AMR therapy has been limited to acute AMR in single-center retrospective case reports (1–9 patients; reviewed [189]). Further limitations include prior lack of severity differentiation, variation in diagnosis timing relative to disease onset, variable treatment algorithms, short-term biochemical follow-up usually devoid of liver pathology, absence of long-term follow-up, an emphasis on the use of living donor liver allografts with smaller liver mass than deceased donor livers, and inevitable publication bias.

TCMR early after transplant in DSA+ recipients without acute AMR features requires the standard approach to TCMR. This occurs more commonly with preformed class II DSA, likely because of Fc binding receptors present on some but not all alloantibodies (83,190,191). If clear acute AMR features are present before any therapy, or an episode is steroid resistant, serum DSA testing, tissue C4d staining, and exclusion of other causes of similar injury are needed to diagnose acute AMR (Table 5). The absence of literature-reported mild acute AMR cases suggests that most respond to standard TCMR treatment with a steroid recycle with or without steroid-resistant therapy (131). Moderate to severe AMR, however, necessitate early intervention, usually with plasmapheresis and IVIg with or without B cell–directed therapy depending on the severity and timing posttransplant of AMR and stability of the patient (128,156, 159,161,192–194).

Given the infrequency of acute AMR, the most important therapeutic target will inevitably be chronic AMR, although no published studies exist to date. It is clear, however, with experience from classical chronic rejection, that compliance with a tacrolimus (as opposed to cyclosporine) based immunosuppression regimen is critical to prevention (in the first year after transplant) and possibly treatment (197). Regardless, treatment of both acute and chronic AMR must commence in prospective multicenter studies, utilizing strict diagnostic criteria and unified protocols (189) that include severity grading, although prevention is always preferable (197).

Biopsy Findings in IS Management

Pre-weaning biopsy findings associated with unsuccessful immunosuppression weaning, such as microvascular C4d deposits (169), portal lymphocytic inflammation (169,198), and more lobular CD3+ and CD8+ lymphocytes (198) overlap with histopathological changes associated with class II DSA+ long-surviving pediatric (199) and adult (101) recipients with putative chronic AMR. Absent pathology before weaning might contribute to allograft stability after weaning despite DSA positivity because of "protective or tolerogenic mechanisms," discussed above, including less HLA II expression (101,166,169) (Tables 8 and 9).

Table 6: Histopathological changes with posttransplant DSA and AT1R antibodies

Study	No. pts	Age surv (months)	Association between DSA and LBx	Histopathological findings associated with DSA
Yamada et al (31)	28	Pediatric >12 months	Protocol and indication	↑ Portal and perivenular C4d associated with perivenular fibrosis ↑ Perivenular CD3+, CD20+ cells, and ↑ DR expression associated with perivenular fibrosis; DSA not assayed in this study.
Miyagawa-Hayashino et al (167)	79	Pediatric Median 11 years	Protocol	↑ Bridging fibrosis or cirrhosis; fibrosis likely to be perivenular; higher frequencies of diffuse/focal endothelial C4d staining; mild/indeterminate T cell–mediated rejection; 4 DSA− versus 0 DSA+ patients off immunosuppression.
Ohe et al (55)	81	Pediatric Median 16.3 years	Protocol LBxs	↑ Fibrosis with anti-class II DSA. All patients with both high-level DSA-DRB1 and high-level anti-angiotensin II receptor type I (AT1R) Ab showed advanced fibrosis. C4d staining not conducted
Del Bello et al (149)	267	Adults 6–220 months	Indication LBx	↑ Fibrosis, NOS 24% of patients with *de novo* DSA developed acute AMR: lymphocytic portal inflammation, lymphocytic cholangitis, PV C4d+, endotheliitis
Salah et al (133)	143	Pediatric and adult Generally > 30 days	Indication LBxs	C4d associated with anti-DR DSA, but not all DSA C4d associated with bridging fibrosis
Iacob et al (168)	174	Adults 67 months	Protocol: 1+3 years and indication	↑ Fibrosis, NOS DSA strongly correlated with portal capillary C4d (IPEX) Portal capillary C4d (IPEX) positivity significantly associated with more frequent and earlier graft failure
Grabhorn et al (176)	43	Pediatric > 5 years in well patients	Protocol LBxs from well patients versus indication LBxs from recipients with severe CR	DSA present more commonly in recipients with severe chronic rejection, but no specific pathological findings attributed to chronic AMR. C4d staining not conducted
Wozniak et al (41)	50	Pediatric ≈12 years	Indication LBXs Compared 3 groups: (1) Nontolerant (2) *de novo* AIH (3) Stable	DSA associated with late immune activity (T cell–mediated rejection, *de novo* AIH, and chronic rejection) C4d staining not conducted
Markiewicz-Kijewska et al (177)	33	Pediatric 99 days–11 years	Indication LBxs	Possible association between DSA and liver fibrosis. Recognized AMR by diffuse C4d and CD20+ or CD138+ predominant infiltrates
Feng et al (199)	157	Pediatric > 4 years	Protocol	Deceased donor and Class II DSA predicted assignment to patients with interface activity with/without fibrosis whereas only recipient age predicted assignment patients with fibrosis, alone.
O'Leary et al (101)	90	Adult > 5 years	Protocol	↑ Portal inflammation and interface activity ↑ lobular/perivenular inflammation and typical TCMR ↑ portal venopathy, portal "collagenization" and portal/periportal and sinusoidal fibrosis DSA strongly correlated with portal capillary and portal stromal C4d (IPEX)

AIH, autoimmune hepatitis; AMR, antibody-mediated rejection; CR, chronic rejection; DSA, donor-specific antibodies; IPEX, immunoperoxidase on formalin-fixed, paraffin-embedded tissue; LBx, liver biopsy; NOS, not otherwise specified; TCMR, T cell–mediated rejection.

Table 7: Criteria for chronic active liver allograft AMR

Probable chronic active AMR (all four criteria are required):
(1) Histopathological pattern of injury consistent with chronic AMR: both required:
(a) Otherwise unexplained and at least mild mononuclear portal and/or perivenular inflammation with interface and/or perivenular necro-inflammatory activity (Figures 4 and 5).[1]
(b) At least moderate portal/periportal, sinusoidal and/or perivenular fibrosis.[2]
(2) Recent (for example, measured within 3 months of biopsy) circulating HLA DSA in serum samples;
(3) At least focal C4d-positive (>10% portal tract microvascular endothelia) (Figure 5).
(4) Reasonable exclusion of other insults that might cause a similar pattern of injury (see text).
Possible chronic active AMR:
(1) As above, but C4d staining is minimal or absent

ADCC, antibody-dependent cellular cytotoxicity; AMR, antibody-mediated rejection; DSA, donor-specific antibodies; HLA, human leukocyte antigen; TCMR, T cell–mediated rejection.
[1]It is difficult, at this time, to determine whether the mononuclear infiltrates are related to AMR (e.g. ADCC with capillaritis) or TCMR (mostly T effectors cells) or mixed AMR and TCMR. More research is needed on this topic.
[2]CD34 and SMA stains might be considered to study sinusoidal capillarization and stellate cell activation.

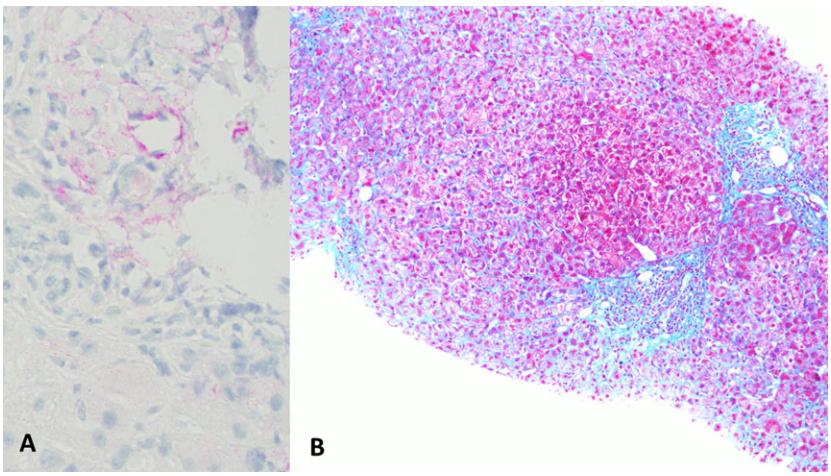

Figure 5: (A) C4d stain of a long-surviving OLTx recipient with a positive DSA showing portal capillary positivity. (B) Trichrome stain highlights the mild-to-moderate portal/periportal, sinusoidal, and perivenular fibrosis. DSA, donor-specific antibody; OLTx, orthotopic liver transplantation.

European multicenter adult trials (185,200) showed no DSA association with any histopathology or rejection after weaning, but limitations included (1) suboptimal DSA evaluation (enzyme-linked immunosorbent assay screening), which might miss class II DSAs; and (2) allowance of HCV fibrosis progression pre- and postweaning.

Japanese IS weaning trials in pediatric recipients showed (1) increased periportal and perivenular fibrosis after weaning with or without coexistent lymphocytic inflammation (167,180,186); (2) a direct or indirect relationship to IS minimization and *de novo* HLA class II DSA (167,180,186); (3) portal endothelial and stromal C4d deposition; and (4) CD20+ perivenular infiltrates (167). Peribiliary plexus capillary and sinusoidal endothelial cell HLA-DR upregulation was spatially linked with nearby TCMR-associated inflammation (31). Since increasing IS decreased C4d deposits and stabilized or reversed perivenular fibrosis (186), these changes likely represent subclinical combined chronic AMR/TCMR (1,79), but regulatory T cell infiltrates are also possible (201). Relaxed hepatitis-related fibrosis criteria are likely appropriate for HCV+ patients after therapeutic sustained virological response.

Future Directions

Routine donor and recipient HLA typing helps facilitate an AMR diagnosis and provides baseline data for DSA

Table 8: Baseline or pre-weaning biopsy findings conducive to minimization of IS[1]

Compartment	Findings
Portal inflammation and interface activity	Preferably absent, but minimal-to-focal mild portal mononuclear inflammation may be present. Interface necro-inflammatory activity is absent or equivocal/minimal and, if present, involves a minority of portal tracts.
Centrizonal/perivenular inflammation[2]	Current recommended criteria: Negative for perivenular inflammation Banff 2012 Criteria: Preferably absent, but minimal/mild perivenular mononuclear inflammation around a minority of central veins without hepatocyte necrosis without endothelitis.
Bile duct changes	Absence of lymphocytic bile duct damage, ductopenia and biliary epithelial senescence changes, unless there is an alternative, nonimmunologic explanation (e.g. biliary strictures).
Fibrosis[1]	Fibrosis, if present, should be mild overall and not more than rare portal-to-portal bridging. Perivenular fibrosis should not be more than mild according to Banff Criteria. Patients who achieved sustained virologic response to HCV treatment might have more substantial fibrosis and architectural distortion.
Arteries	Negative for isolated "v" lesions (lymphocytic arteritis)[3] obliterative or foam cell arteriopathy.

AIH, autoimmune hepatitis; HCV, hepatitis C virus; IS, immunosuppression; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.
[1]Excludes patients with underlying AIH, HCV, PBC, or PSC (see text). More substantial fibrosis and architectural distortion can be tolerated in patients who achieved sustained virologic response to HCV treatment.
[2]Modified from Banff 2012 recommendations (1) because of widespread recognition that the lesion represents a rejection reaction and has the potential to progress and cause perivenular fibrosis after weaning.
[3]"Isolated "v" lesions (lymphocytic arteritis) was added to the Banff 2012 because of evidence of similar lesions in renal allografts leading to a suboptimal outcome even in patients maintained on immunosuppression (205).

Table 9: Follow-up biopsy findings suggesting that the patient is unlikely to benefit from minimal or absent immunosuppression; proceed only with extreme caution (see Figure 2)[1,2]

Compartment	Finding(s)
Portal inflammation and interface activity	Increased portal inflammation compared to pre-weaning biopsy, especially when associated with histopathologic evidence of focally worsening or more prevalent lymphocytic bile duct damage, interface hepatitis, or appearance of venous endothelitis.
Centrizonal/perivenular inflammation	New-onset perivenular inflammation compared to pre-weaning biopsy associated with necro-inflammatory activity.
Bile duct changes	New-onset biliary epithelial cell senescence changes or ductopenia where sampling problems and/or an alternative, nonimmunologic explanation (e.g. biliary stricture) are reasonably excluded.
Fibrosis	Current recommended criteria: Greater than 1 grade increase in fibrosis in any one compartment: (a) portal/periportal; (b) perisinusoidal; or (c) perivenular fibrosis; or new-onset bridging fibrosis without an alternative explanation (e.g. biliary strictures) that involves more than one area and not readily explained by a sampling error. Banff 2012 criteria: Increase of fibrosis over consecutive biopsies (see text) without an alternative explanation (e.g. biliary strictures). New onset or increase of perivenular fibrosis.
Arteries	Any evidence of foam cell or obliterative arteriopathy.

AIH, autoimmune hepatitis; HCV, hepatitis C virus; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.
[1]Excludes patients with underlying AIH, HCV, PBC, or PSC (see text).
[2]Modified from Banff 2012 recommendations (1) to recognize the need to score liver allograft fibrosis according to compartments.

determinations; retrospective typing can be carried out on stored donor and recipients cells and/or nucleic acids. Routine DSA monitoring may help IS management, but work is needed to better define the following: (1) DSA-associated tissue injury patterns (33,55,202); (2) antibody characteristics (C1q, MFI, titer, IgG subclass, etc.); (3) specific effector mechanisms of antibody-mediated injury including involvement of NK cells, which play an important role in kidney and heart allografts and are possibly specifically amenable to therapeutic intervention (203); (4) relative contribution of AMR to "mixed" TCMR and AMR episodes; (5) cost-effective DSA and tissue screening protocols; (6) incorporation of "molecular signatures"(204); and (7) appropriate IS management.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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