
بسم الله الرحمن الرحیم

شرح حال

- بیمار خانم 21ساله مورد liver transplantدر تاریخ ۹۶/۶/۲ در زمینه بیماری ویلسون می باشد اخرین آزمایش بیمار پس از پیوند (درمان با سل سپت و پروگرافت) به شرح زیربوده است:

- AST: 10
- ALT: 12
- ALK:118
- WBC :2830
- HB: 11.7

PLT:130000

Bili:0 .1 , total 0.5

بیماردر مرداد ماه سال ۱۴۰۳ با ضعف و بی حالی و زردی و افزایش انزیم های کبدی مراجعه کرده اند: RR: 18 PR: 90 T:37 BP:100/80

AST:260

ALT: 290

ALK:490

WBC: 2.4

HB:10.5

PLT:102

TOTAL BILI: 5.2

DBILI :3.2

تشخیص احتمالی و ارزیابی مناسب کدام است ؟

ارزیابی های اولیه

- **Color doppler Sono porta hepatic**: normal
- **Sono Abd**: liver is lower limit of normal size with **coarse parenchymal** (chronic parenchymal damage)
- **MRCP**: Intrahepatic bile ducts are almost collapsed with some irregularities without dilatation. intrahepatic bile ducts are normal to small caliber ongoing to collapse with minimal irregular outline, lab data and medical history correlation is recommended to rule out PSC recurrence / rejection.
- **BIOPSY: acute** t- cell mediated rejection
- **Fk level: 7/3**

CMV	**NEG**	**Hbc IGM**	**NEG**
EBV	**NEG**	**HBS Ag**	**NEG**
B/C	**NEG**	**Anti Hcv**	**NEG**
Hsv pcr	**NEG**		

بهترین اقدام و درمانی کدام است ؟

- بیمار تحت درمان با پالس متیل پردنیزولون ۱ گرم سه دوز متوالی برای دو دوره قرار گرفت.
,همچنین درمان با سیرولیموس ۱ میلی گرم شروع شد و دوز پرو گرافت افزایش یافت :
- جواب ازمایشات به شرح زیر است :

- **Fk level : 8**
- **Sirolimus : 8.3**

- **AST: 130**
- **ALT: 251**
- **ALK:319**
- **WBC :3500**
- **HB: 11.7**

PLT:109000

Bili:1.17 , total 2.02

CR :0.5

با توجه به آزمایشات بیمار بهترین توصیه کدام است ؟

- **CMV PCR: Negative**
- **C4d:Positive in 10-50% of portal tracts**

بهترین توصیه کدام است ؟

- بیمار تحت درمان با پلاسما فرز و IVIG به صورت یک روز درمیان برای ۵ جلسه قرار گرفت.
- نتایج ازمایشات پس از درمان :

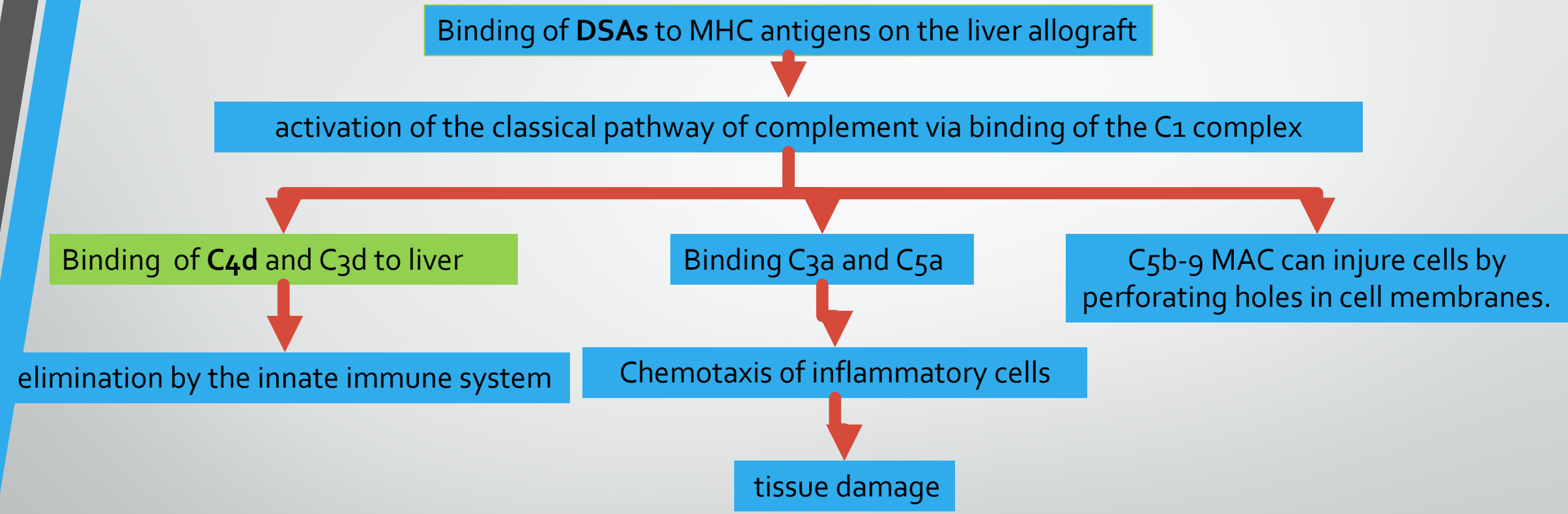
- **AST: 64**
- **ALT: 73**
- **ALK : 142**
- **BILI T:0.9 D:0.4**
- **WBC :3.3**
- **HB :8.7**
- **PLT : 88000**

Differences between T-cell mediated rejection and antibody mediated rejection.

Differentiating factors	TCMR	AMR
Onset	In the initial weeks to months after liver transplantation.	AMR can occur at any time post-liver transplantation, including both early and late phases.
Immune Players	Both CD4+ and CD8+ *T*-cells play a salient role.	Donor-specific antibodies (DSAs).
Target	Hepatocytes, bile duct epithelial cells, and endothelial cells in the liver.	DSAs target antigens on the surface of donor cells.
Histological features	Lymphocytic infiltration in the portal and periportal areas. Interface Hepatitis where the inflammatory cells invade the interface between hepatocytes and bile duct. Bile duct damage	Bile duct injury, endothelialitis, microvascular injury and in some cases, central vein involvement.
Diagnosis	Histopathological evaluation, elevated serum transaminases, response to standard immunosuppression, liver biopsy	Elevated liver enzymes, high cholestatic enzymes, signs of liver dysfunction, C4d staining, Donor specific antibodies (DSA), plasma exchange response, biomarkers like P-selectin, E-selectin, VCAM-1,ICAM-1, vWF etc.

Differentiating factors	TCMR	AMR
Response to therapy	Often responds well to standard immunosuppressive therapy, such as corticosteroids.	Strategies like plasma exchange, intravenous immunoglobulin (IVIG), targeted immunosuppression and complement inhibitor agents in severe cases.

Pathways of antibody-mediated rejection



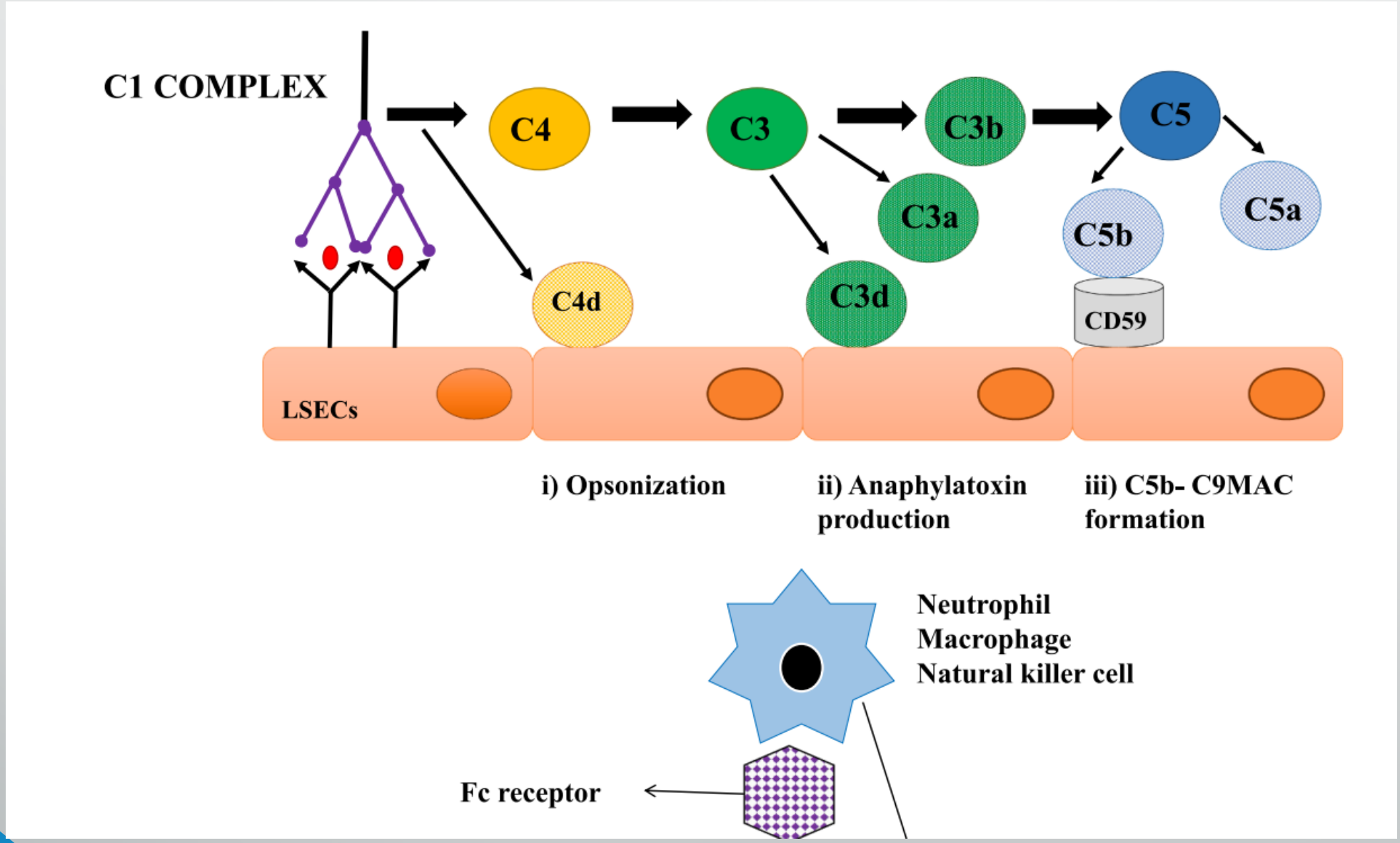
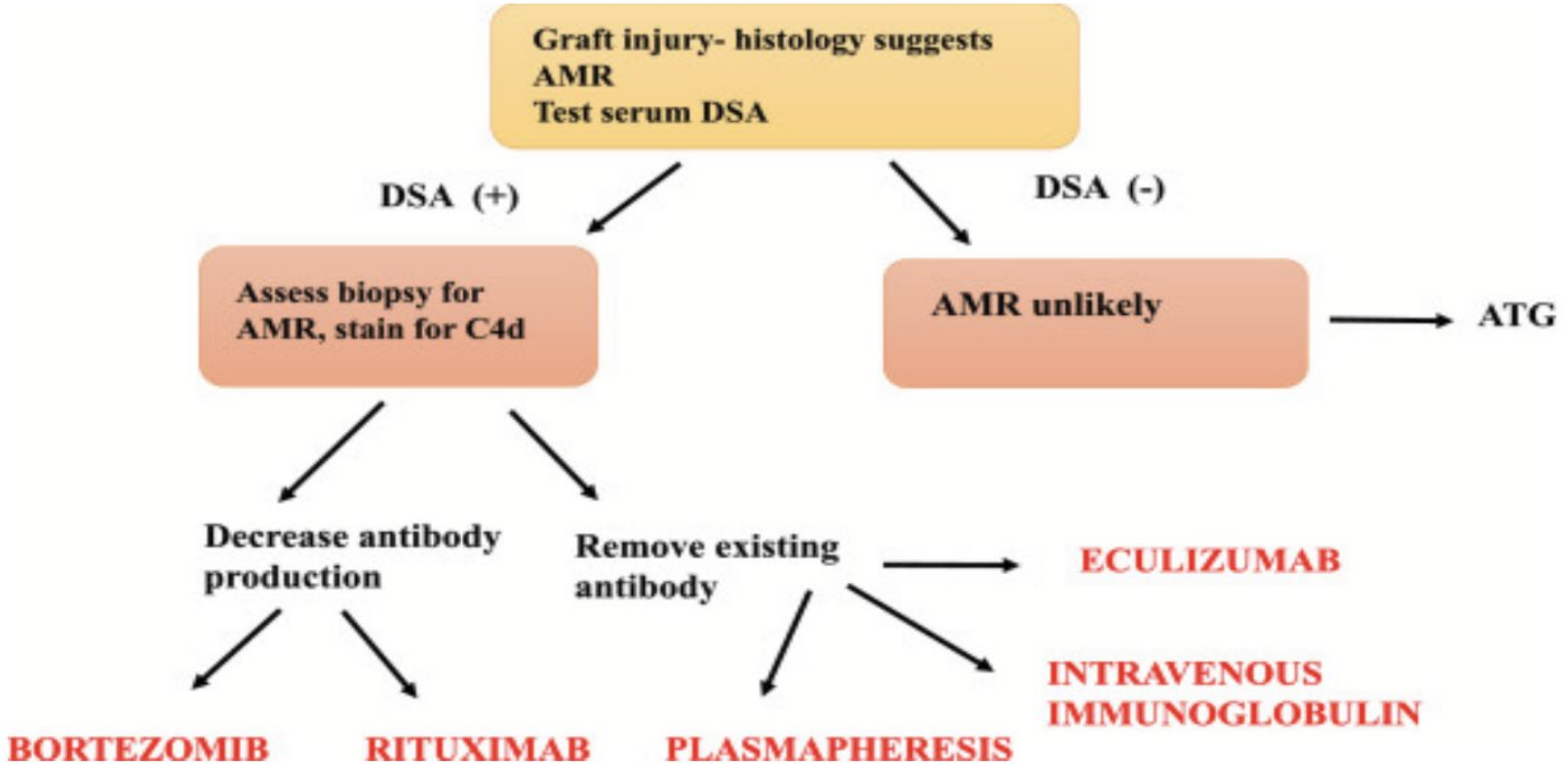

C1 COMPLEX
C4
C3
C3b
C5
C4d
C3a
C3d
C5b
C5a
CD59
LSECs
i) Opsonization
ii) Anaphylatoxin production
iii) C5b- C9MAC formation
Neutrophil
Macrophage
Natural killer cell
Fc receptor

Fig.4 summarizes the treatment of antibody-mediated rejection after liver transplantation. [70], [71], [72], [73], [74], [75]

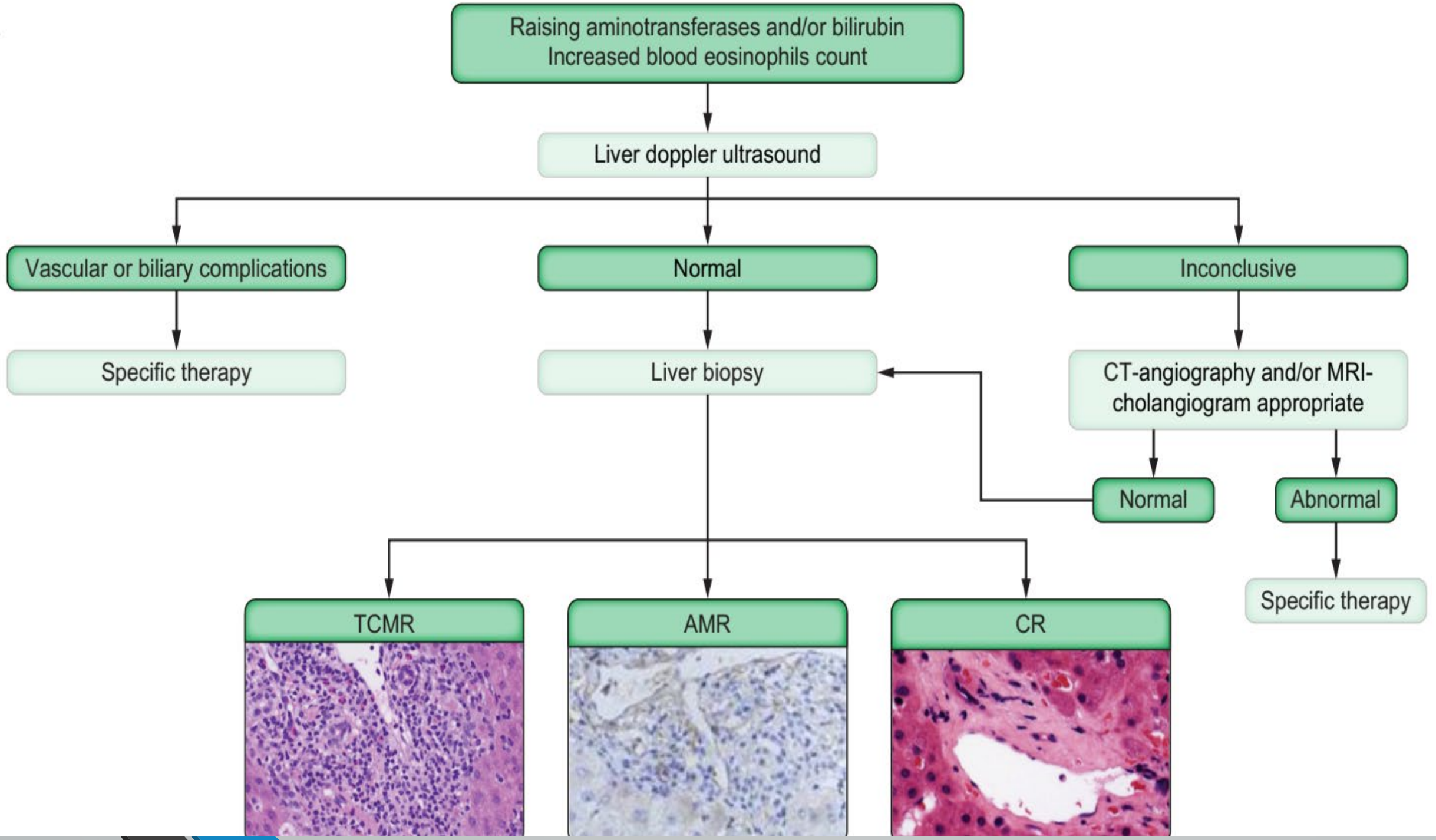


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Fig. 4. Treatment of antibody mediated rejection in liver transplant.

A


Raising aminotransferases and/or bilirubin
Increased blood eosinophils count
Liver doppler ultrasound
Vascular or biliary complications
Normal
Inconclusive
Specific therapy
Liver biopsy
CT-angiography and/or MRI-cholangiogram appropriate
Normal
Abnormal
Specific therapy
TCMR
AMR
CR

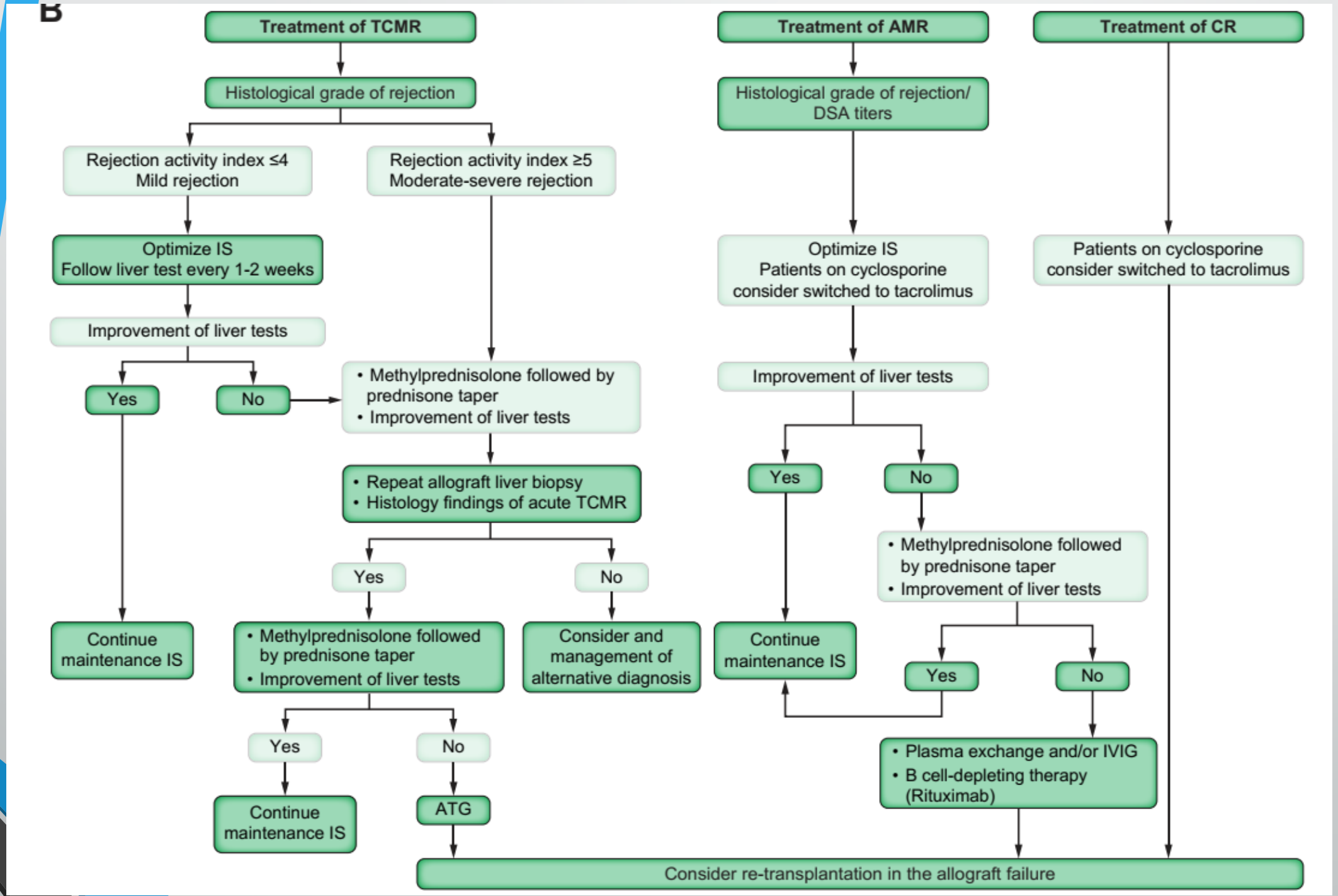

B
Treatment of TCMR
Histological grade of rejection
Rejection activity index ≤4
Mild rejection
Rejection activity index ≥5
Moderate-severe rejection
Optimize IS
Follow liver test every 1-2 weeks
Improvement of liver tests
Yes
No
• Methylprednisolone followed by prednisone taper
• Improvement of liver tests
• Repeat allograft liver biopsy
• Histology findings of acute TCMR
Yes
No
Continue maintenance IS
• Methylprednisolone followed by prednisone taper
• Improvement of liver tests
Consider and management of alternative diagnosis
Yes
No
Continue maintenance IS
ATG
Treatment of AMR
Histological grade of rejection/ DSA titers
Optimize IS
Patients on cyclosporine consider switched to tacrolimus
Improvement of liver tests
Yes
No
Continue maintenance IS
• Methylprednisolone followed by prednisone taper
• Improvement of liver tests
Yes
No
• Plasma exchange and/or IVIG
• B cell-depleting therapy (Rituximab)
Treatment of CR
Patients on cyclosporine consider switched to tacrolimus
Consider re-transplantation in the allograft failure

Table 1. Histologic criteria for diagnosis and grading of rejection in liver transplantation.

T cell–mediated rejection - Rejection activity index	
Category	**Score and criteria**
Mixed portal inflammatory infiltrate	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 3 Marked expansion of most or all of the triads by a mixed infiltrate containing numerous blasts and eosinophils with inflammatory spillover into the periportal parenchyma
Bile duct epithelial inflammation and 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 are 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
Mild if the score is <4, moderate if 4-6, and severe if ≥7. Early TCMR episodes (*i.e.* within 90 days of LT) are characterized by more intense inflammatory bile duct damage and pleomorphic portal inflammation, with a paucity of interface activity. Late TCMR episodes (i.e. from 90 days post-LT onwards) are characterized by fewer blastic lymphocytes, less venous subendothelial inflammation, and greater interface and lobular inflammatory activity. From Banff Working Group on Liver Allograft Pathology.[92]	

Chronic rejection		
Category	**Early chronic rejection***	**Late chronic rejection***
Small bile ducts	• Senescence-related changes (bile duct atrophy/pyknosis) involving a majority of ducts; 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	• Variable inflammation; focal obliteration; moderate-to severe-(bridging) fibrosis
Other features	• So-called "transition" hepatitis with spotty necrosis of hepatocytes	• Sinusoidal foam cell accumulation; cholestasis
*At least two findings should be present. 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)		

Antibody-mediated rejection	
Findings	• Portal microvascular endothelial cell hypertrophy, • Capillary dilation, • Mixed portal microvasculitis, • Portal oedema, ductular reaction, and typical microvascular component 4d deposition, either focal or diffuse.
Putative chronic AMR: Recently described entity characterised by mild mononuclear portal/perivenular inflammation with interface/perivenular necro-inflammatory activity together with a moderate portal, sinusoidal and/or perivenular fibrosis, and focal C4d-positive (>10% portal tracts)[139]	

AMR, antibody-mediated rejection; LT, liver transplantation; TCMR, T cell-mediated rejection.