Review

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A 2018 Reference Guide to the Banff Classification of Renal Allograft Pathology

Candice Roufosse, MD, PhD,[1,2] Naomi Simmonds, MD,[3] Marian Clahsen-van Groningen, MD, PhD,[4] Mark Haas, MD, PhD,[5] Kammi J. Henriksen, MD,[6] Catherine Horsfield, MD,[3] Alexandre Loupy, MD,[7] Michael Mengel, MD,[8] Agnieszka Perkowska-Ptasińska, MD,[9] Marion Rabant, MD, PhD,[10] Lorraine C. Racusen, MD,[11] Kim Solez, MD,[8] and Jan U. Becker, MD[12]

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Abstract: The Banff Classification of Allograft Pathology is an international consensus classification for the reporting of biopsies from solid organ transplants. Since its initial conception in 1991 for renal transplants, it has undergone review every 2 years, with attendant updated publications. The rapid expansion of knowledge in the field has led to numerous revisions of the classification. The resultant dispersal of relevant content makes it difficult for novices and experienced pathologists to faithfully apply the classification in routine diagnostic work and in clinical trials. This review shall provide a complete and simple illustrated reference guide of the Banff Classification of Kidney Allograft Pathology based on all publications including the 2017 update. It is intended as a concise desktop reference for pathologists and clinicians, providing definitions, Banff Lesion Scores and Banff Diagnostic Categories. An online website reference guide hosted by the Banff Foundation for Allograft Pathology (www.banfffoundation.org) is being developed, which will be updated with future refinement of the Banff Classification from 2019 onward.

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Since its first consensus meeting in 1991,[1] the Banff Classification of Allograft Pathology has provided a framework for the reporting of renal allograft biopsies. It was the first classification system of its kind and answered the need for an international consensus on renal transplant biopsy reporting, providing guidance for clinical diagnosis and enabling meaningful comparison between research studies and clinical trials investigating the diagnosis, treatment and outcome in kidney transplantation. The Banff Classification has since been further strengthened by evidence-informed biannual updates elaborated during open international expert meetings.[2] As a result, the Banff Classification of Allograft Pathology has become the predominant classification system used worldwide.[3]

A total of 14 meetings reported in 10 articles reflect the developments of the Banff Classification from the first consensus meeting in 1991 to the recently published consensus

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[1] *Department of Medicine, Imperial College, London, United Kingdom.*

[2] *North West London Pathology, London, United Kingdom.*

[3] *Department of Histopathology, Guy's and St. Thomas' National Health Service Foundation Trust, London, United Kingdom.*

[4] *Department of Pathology, Erasmus MC, Rotterdam, The Netherlands.*

[5] *Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, CA.*

[6] *Department of Pathology, University of Chicago, Chicago, IL.*

[7] *Paris Translational Research Center for Organ Transplantation, Paris, France.*

[8] *Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Canada.*

[9] *Department of Transplantology, Nephrology and Internal Diseases, Medical University of Warsaw, Warsaw, Poland.*

[10] *Department of Pathology, Necker Hospital University Paris Descartes, Paris, France.*

[11] *The Johns Hopkins University, Baltimore, MD.*

[12] *Institute of Pathology, University Hospital of Cologne, Cologne, Germany.*

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Correspondence: Jan U. Becker, MD, Institute of Pathology, University Hospital of Cologne, Kerpener Str. 62, 50937, Germany. (janbecker@gmx.com).

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after the 2017 meeting in Barcelona, Spain.[1,4-12] Each of these iterations provides a short summary of the meeting and contributes to the classification in a cumulative fashion. The dispersal of both relevant and outdated content over 10 articles could make access to the Banff Classification difficult for beginners and experts and has created ambiguities in the past.[3] Yet, accessibility and clarity are of utmost importance not only for clinical practice and research but also for the Banff Classification itself to evolve through accountability, critique, and change. To improve on these aspects, the Rules and Dissemination Banff Working Group was initiated at the last Banff meeting held in Barcelona, Spain in March 2017. With a scope beyond the helpful syllabus provided by the Banff group in the online supplement of the 2015 update[11] and incorporating the latest changes introduced in the 2017 update,[12] the aim of this Working Group is to collate all current content of the Banff Classification and improve its accessibility. A systematic inventory of the content is given in Figure 1. This practical guide is based on all content up to the 2017 update as the first output of our Working Group. It is divided in the following sections: a brief guide about the histopathological and serological work-up; a list of Banff Lesion Scores (previously known as components, eg, Banff *t* for tubulitis) with their current definitions, practical tips for their application and illustrative figures (see definitions below and thresholds in Table 2); and a list of Banff Diagnostic Categories in Table 1. Moreover, we provide a list of Additional Diagnostic Parameters, which need to be considered in addition to Banff Lesion Scores to reach a Banff Diagnostic Category (Table 3). Examples for these include "Severe Peritubular Capillary Basement Membrane Multilayering" which is among the criteria for antibody-mediated rejection (AMR) chronicity.[12] A glossary of terms is provided as Supplemental Digital Content (see **Glossary of Terms, SDC,** http://links.lww.com/TP/B604), explaining important concepts and terminology underlying the Banff Classification. Lastly, we provide a critical appraisal of areas of the Banff Classification that require clarification and provide an outlook for future developments. All terms from the Banff Classification will be given in capitals for clarity, all abbreviations for Banff lesion scores will be given in italic typeface.

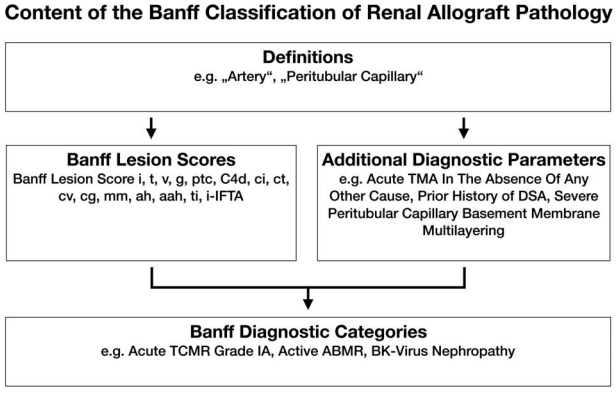

FIGURE 1. The content of the Banff Classification of Kidney Allograft Pathology can be inventoried as Banff Lesion Scores and Additional Diagnostic Parameters required by the algorithms behind the Banff Diagnostic Categories to reach a diagnosis. Moreover, overarching definitions are important and inform, for example, how one or even several Banff Lesion Scores are applied. TMA, thrombotic microangiopathy.

We hope this Banff 101 will serve as a handy reference for the clinicians and the pathologists, until the entire updated content appears online with the 2019 update of the Banff Classification of Renal Allograft Pathology, replacing this guide.

DIAGNOSTIC WORK-UP OF BIOPSIES

A kidney transplant biopsy should fulfill the criteria for specimen adequacy (see **Glossary of Terms, SDC,** http://links.lww.com/TP/B604) detailed in the Banff 1997 update.[5] C4d staining is considered indispensable, either as immunofluorescence (IF) on fresh frozen or immunohistochemistry (IHC) on paraffin-embedded tissue. The paraffin block should be cut in several numbered level sections examined with hematoxylin-eosin, periodic acid-Schiff (PAS), trichrome-elastic and Jones or methenamine silver stains. Immunohistochemistry staining for simian virus-40, cross-reacting with BK virus is highly recommended when indicated. Where available, minute portions of cortex should be embedded for transmission electron microscopy (EM).

Depending on clinical and histopathological findings a complete nephropathological work-up including staining for immunoglobulin heavy and light chains and complement split products might be necessary to rule out or confirm a diagnosis of glomerulonephritis. Other ancillary staining might be necessary as for native kidney biopsies to establish specific recurrent or de novo kidney diseases (eg, Congo red stain).

Serological testing for donor-specific antibodies (DSAs) should be performed as described in respective consensus documents.[13] Ancillary molecular tests, based on tissue and body fluids, are emerging.

Preimplantation biopsies should be obtained, processed, and reported as described by the Banff Working Group on Preimplantation Biopsies.[14]

BANFF LESION SCORES

Banff Lesion Scores assess the presence and the degree of histopathological changes in the different compartments of renal transplant biopsies, focusing primarily but not exclusively on the diagnostic features seen in rejection. These Banff Lesion Scores are not by themselves sufficient to reach the various Banff Diagnostic Categories in Table 1; the Additional Diagnostic Parameters—histopathological, molecular, serological and/or clinical—may be required to determine the diagnosis. For each Banff Lesion Score we give the current consensus definitions below. As new knowledge emerges, these might be refined for the forthcoming Banff 2019 update. A synopsis of their semiquantitative thresholds is given in Table 2. However, use of this threshold table without knowledge of the precise definitions and regulatory statutes underlying each Banff Lesion Score is strongly discouraged.

Banff Lesion Score *i* (Interstitial Inflammation)

This score evaluates the degree of inflammation in non-scarred areas of cortex, which is often a marker of Acute T Cell–Mediated Rejection (TCMR). As per the Banff update from 1997, areas that must not be considered for Banff Lesion Score *i* are "fibrotic areas, the immediate subcapsular cortex, and the adventitia around large veins and lymphatics".[5] As can indirectly be derived from the definition of Banff Lesion Score *ti* in the 2007 update of the Banff classification, nodular infiltrates, if in unscarred cortex, are also considered for Banff Lesion Score *i*.[8] An asterisk shall be

TABLE 1.

Banff Diagnostic Categories form the core of the Banff Classification of Renal Allograft Pathology

Category 1: Normal Biopsy Or Nonspecific Changes

Requires exclusion of any diagnosis from the Banff Diagnostic Categories 2-4, 6 below.

Category 2: Antibody-mediated changes

Use the Diagnostic Criteria Groups (right column) to reach 1 Diagnosis (left column)

Diagnoses	Diagnostic Criteria Groups
C4d Staining Without Evidence of Rejection Banff Lesion Score *C4d > 1* (IF on fresh frozen tissue) OR *C4d > 0* (IHC on paraffin-embedded tissue) AND Banff Lesion Scores *t0*, *v0*, no arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima, no criterion from group 1 (AMR activity), no criterion from group 4 (histologic features of AMR chronicity), no increased expression of thoroughly validated gene transcripts/classifiers in the biopsy tissue strongly associated with AMR	Criteria Group 1 AMR activity: – Banff Lesion Score *g > 0* in the absence of glomerulonephritis and/or Banff Lesion Score *ptc > 0* in the absence of TCMR or Borderline – Banff Lesion Score *v > 0* – Acute Thrombotic Microangiopathy In The Absence Of Any Other Cause (Figure 18) – Acute Tubular Injury In The Absence Of Any Other Apparent Cause
Active AMR No criterion of AMR chronicity (Criteria Group 4) AND At least 1 criterion from Criteria Group 1 (AMR activity) AND At least 1 criterion from Criteria Group 2 (antibody interaction with tissue) AND At least 1 criterion from Criteria Group 3 (DSA or equivalents)	Criteria Group 2 Antibody interaction with tissue: – Banff Lesion Score *C4d > 1* (IF on fresh frozen tissue) or *C4d > 0* (IHC on paraffin-embedded tissue) – At least moderate MVI (*g + ptc > 1*) in the absence of recurrent or de novo glomerulonephritis; Borderline (Diagnostic Category 3) or acute T cell-mediated rejection (TCMR; Diagnostic Category 4). If Borderline, acute TCMR, or infection are present, (Banff Lesion Scores *g + ptc) > 1* is not sufficient and Banff Lesion Score *g > 1* is required. – Increased Expression Of Thoroughly Validated Gene Transcripts/Classifiers In The Biopsy Tissue Strongly Associated With AMR
Chronic Active AMR At least 1 feature of AMR chronicity (Criteria Group 4) AND At least 1 criterion of antibody interaction with tissue (Criteria Group 2) AND At least 1 criterion of DSA or equivalents (Criteria Group 3)	Criteria Group 3 DSA or equivalents: – DSA (anti-HLA or other specificity) – Banff Lesion Score *C4d > 1* (IF on fresh frozen tissue) or *C4d > 0* (IHC on paraffin-embedded tissue) – Increased Expression Of Thoroughly Validated Gene Transcripts/Classifiers In The Biopsy Tissue Strongly Associated With AMR
Chronic AMR Banff 2017 permits the use of this term for biopsy specimens showing TG and/or peritubular capillary basement membrane multilayering in the absence of criterion of current/recent antibody interaction with the endothelium (Criteria Group 2) but with a prior documented diagnosis of Active or Chronic Active AMR or documented prior evidence of DSA	Criteria Group 4 Histologic features of AMR chronicity – Banff Lesion Score *cg > 0* (by LM or EM, if available), excluding biopsies with evidence of chronic thrombotic microangiopathy – 7 or more layers in 1 cortical peritubular capillary and 5 or more in 2 additional capillaries, avoiding portions cut tangentially by EM, if available (Severe Peritubular Capillary Basement Membrane Multilayering, see Figure 19) – Arterial Intimal Fibrosis Of New Onset, Excluding Other Causes; Leukocytes Within The Sclerotic Intima Favor Chronic AMR If There Is No Prior History Of Biopsy-Proven TCMR but are not required

Continued next page

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TABLE 1. (Continued)

Category 3: Suspicous (Borderline) For Acute TCMR

Foci of Banff Lesion Score *t > 0* AND Banff Lesions Score *i* ≤ *1* (retaining the Banff Lesion Score *i1* threshold from Banff 2005 is permitted but it must be made transparent in the methods section of reports and publications)
OR
Foci of Banff Lesion Score *t1* AND Banff Lesion Score *i* ≥ *2*

Category 4: TCMR

Acute TCMR IA
Banff Lesion Score *i* ≥ *2*
AND
Banff Lesion Score *t2*
Acute TCMR IB
Banff Lesion Score *i* ≥ *2*
AND
Banff Lesion Score *t3*
Acute TCMR IIA
Banff Lesion Score *v1* regardless of Banff Lesion Scores *i* or *t*
Acute TCMR IIB
Banff Lesion Score *v2* regardless of Banff Lesion Scores *i* or *t*
Acute TCMR III
Banff Lesion Score *v3* regardless of Banff Lesion Scores *i* or *t*
Chronic Active TCMR Grade IA
Banff Lesion Score *ti* ≥ *2*
AND
Banff Lesion Score *i-IFTA* ≥ *2*, other known causes of i-IFTA (eg, pyelonephritis, BK-virus nephritis etc.) ruled out
AND
Banff Lesion Score *t2*
Chronic Active TCMR Grade IB
Banff Lesion Score *ti* ≥ *2*
AND
Banff Lesion Score *i-IFTA* ≥ *2*, other known causes of i-IFTA ruled out
AND
Banff Lesion Score *t3*
Chronic Active TCMR Grade II
Arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima

Category 5: IFTA

Grade I (Mild)
Banff Lesion Score *ci1*
OR
Banff Lesion Score *ct1*

Grade II (Moderate)
Banff Lesion Score *ci2*
OR
Banff Lesion Score *ct2*
Grade III (Severe)
Banff Lesion Score *ci3*
OR
Banff Lesion Score *ct3*
Category 6: Other changes not considered to be caused by acute or chronic rejection (Figure 2D)
BK-Virus Nephropathy
Posttransplant Lymphoproliferative Disorder
Calcineurin Inhibitor Toxicity
Acute Tubular Injury
Recurrent Disease
De Novo Glomerulopathy (Other Than TG)
Pyelonephritis
Drug-Induced Interstitial Nephritis

We refer to the Banff Lesion Scores in the main body of this review as well as to the Additional Diagnostic Parameters listed in Table 3. Note that diagnoses from various Banff Diagnostic Categories can coexist in a given biopsy, for example, acute TCMR grade IB, chronic active AMR, moderate IFTA and calcineurin inhibitor toxicity. From each Banff Diagnostic Category except for 6, only 1 diagnosis must be made. Note that the Banff Diagnostic Categories suspicious for acute/active AMR, suspicious for chronic AMR, suspicious for chronic active AMR from the Banff 2015 update have been deleted.[12]

added to Banff Lesion Score *i* (eg, *i1**), "if there are more than 5% to 10% of eosinophils, neutrophils or plasma cells".[5] Exemplary lesions are shown in Figure 2.

i0—No inflammation or in less than 10% of unscarred cortical parenchyma.

i1—Inflammation in 10 to 25% of unscarred cortical parenchyma.

i2—Inflammation in 26 to 50% of unscarred cortical parenchyma.

i3—Inflammation in more than 50% of unscarred cortical parenchyma.[11]

Banff Lesion Score *t* (Tubulitis)

This Banff Lesion Score evaluates the degree of inflammation within the epithelium of the cortical tubules. As per the Banff 2003 update "Tubulitis—the presence of mononuclear cells in the basolateral aspect of the renal tubule epithelium" is one of the defining lesion of TCMR in kidney transplants.[6] According to Banff 1997, in tubules cut longitudinally, the score shall be determined as the number of mononuclear cells per 10 tubular epithelial cells, which is the average number of epithelial cells per tubular cross-section (Figure 3). Tubulitis must be present in at least 2 foci. We have emphasized this by rephrasing the criteria for Banff Lesion Score *t0* below; the most severely affected tubule determines the score.[5,11] Please note also that we have returned from the altered definition with "leukocytes" in the Banff 2015 update[11] to "mononuclear cells" as given in the 1997 update.[5] According to the most recent Banff update from 2017, for Acute TCMR Grade IA, IB and Chronic Active TCMR Grade IA and IB but not Borderline (Banff Diagnostic Category 3), tubulitis is considered in all but severely atrophic cortical tubules. Tubulitis in severely atrophic tubules does not count toward a diagnosis of either Borderline, Acute or Chronic Active TCMR, and severely atrophic tubules are defined by a diameter of less than 25% of that of unaffected or minimally affected tubules on the biopsy, often with an undifferentiated appearing, cuboidal or flattened epithelium (or in some cases even loss of epithelium with denudation of the tubular basement membrane), and pronounced wrinkling and/or thickening of the tubular basement membrane. This definition of severely atrophic tubules also includes very small, endocrine-like tubules with very narrow lumens, although the basement membranes of the latter may not be thickened.[12] An example of tubulitis in various stages of tubular atrophy is shown in Figure 4.

t0—No mononuclear cells in tubules or single focus of tubulitis only.

t1—Foci with 1 to 4 mononuclear cells/tubular cross section (or 10 tubular cells).

t2—Foci with 5 to 10 mononuclear cells/tubular cross section (or 10 tubular cells).

t3—Foci with >10 mononuclear cells/tubular cross section or the presence of ≥2 areas of tubular basement membrane destruction accompanied by *i2*/*i3* inflammation and *t2* elsewhere.[12]

Banff Lesion Score v (Intimal Arteritis)

This Banff Lesion Score evaluates the presence and the degree of inflammation within the arterial intima. Arteries are defined as having at least 2 layers of smooth muscle cells in the media (**Glossary of Terms, SDC**, http://links.lww.com/TP/B604). Note that intimal arteritis (also referred to as

TABLE 2.

This is a synopsis of the thresholds for all Banff Lesion Scores

Banff lesion score,	Abbreviation	0	1	2	3
Interstitial inflammation	*i*	<10%	10-25%	26-50%	>50
Tubulitis	*t*	None	1-4/tubular cross section or 10 tubular epithelial cells	5-10	>10 or foci of tubular basement membrane destruction with i ≥ 2 and t2 elsewhere
Intimal arteritis	*v*	None	<25% luminal area lost	≥25% luminal area lost	Transmural and/or fibrinoid change and medial smooth muscle necrosis
Glomerulitis	*g*	None	<25%	25-75%	>75%
Peritubular capillaritis	*ptc*	<3 leukocytes/ PTC	≥1 leukocyte in ≥10% of PTCs with max. of 3-4/PTC	≥1 leukocyte in ≥10% of PTCs with max. of 5-10/PTC	≥1 leukocyte in ≥10% of PTCs with max. of >10/PTC
C4d	*C4d*	None	<10%	10-50%	>50%
Interstitial fibrosis	*ci*	≤5%	6-25%	26-50%	>50%
Tubular atrophy	*ct*	None	≤25%	26-50%	>50%
Vascular fibrous Intimal thickening	*cv*	None	≤25%	26-50%	>50%
GBM double contours	*cg*	None	1a: only by EM 1b: ≤25% by LM	26-50%	>50%
Mesangial matrix expansion	*mm*	None	≤25%	26-50%	>50%
Arteriolar hyalinosis	*ah*	None	Mild to moderate in ≥1	Moderate to severe in >1	Severe in many
Hyaline arteriolar thickening	*aah*	None	1 without circumferential	≥1 without circumferential	circumferential
Total inflammation	*ti*	<10%	10-25%	26-50%	>50%
Inflammation in the area of IFTA	*i-IFTA*	<10%	10-25%	26-50%	>50%

The user of this table should be familiar with the exact definitions underlying each individual Banff Lesion Score. Reliance on these thresholds alone without consideration of the regulatory statutes behind these scores is strongly discouraged. max.:, maximum; PTC, peritubular capillary.

endothelialitis and endarteritis) is defined by the presence of inflammatory cells, mainly lymphocytes and monocytes, in the subendothelial space of 1 or more arteries.[10] One such cell suffices. Examples of this lesion are shown in Figure 5. Intimal arteritis is a feature seen in both Acute TCMR and Active AMR. For Banff Lesion Score *v*, the most severely affected artery dictates the score.[5] Similar lesions in arterioles are only coded as an asterisk behind the Banff Lesion Score *ah* and are disregarded for Banff Lesion Score *v*. Infiltrates buried deeper in the intima are not considered for the *v* Banff Lesion Score but have been recognized as Chronic Active TCMR since the 2005 update,[7] and graded in the 2017 update as Grade II.[12] In the presence of tubulointerstitial hemorrhage (see **Glossary of Terms, SDC,** http://links.lww.com/TP/B604) and/or and infarct (see **Glossary of Terms, SDC,** http://links.lww.com/TP/B604) an asterisk "*" is attached to the Banff Lesion Score *v* (eg, Banff *v0**, *v2**).[5]

v0—No arteritis.

v1—Mild to moderate intimal arteritis in at least 1 arterial cross section.

v2—Severe intimal arteritis with at least 25% luminal area lost in at least 1 arterial cross section.

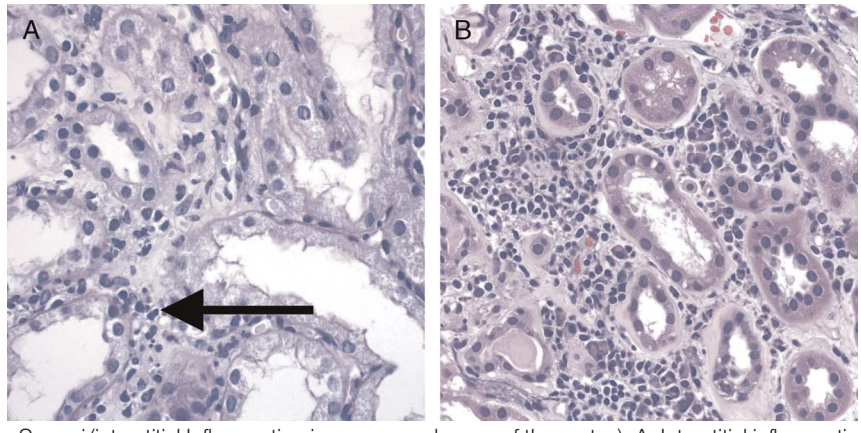

FIGURE 2. Banff Lesion Score *i* (interstitial Inflammation in nonscarred areas of the cortex). A, Interstitial inflammation in nonscarred areas of the cortex. This Banff Lesion Score, often a marker of TCMR, ranges from 0 to 3, based on the percentage of nonscarred cortex involved, and is usually dominated by mononuclear cells in the case of Acute TCMR. Note the contrast between the noninfiltrated interstitium in the right half of the micrograph and the infiltrate in the edema between the tubules on the left (long arrow). PAS, original magnification ×400. B, An example of plasma cell rich interstitial inflammation. If the infiltrate comprises more than 5% to 10% of either eosinophils, neutrophils or plasma cells an asterisk is added to the Banff Lesion Score i (eg, *i1**). H&E, hematoxylin and eosin, original magnification ×400.

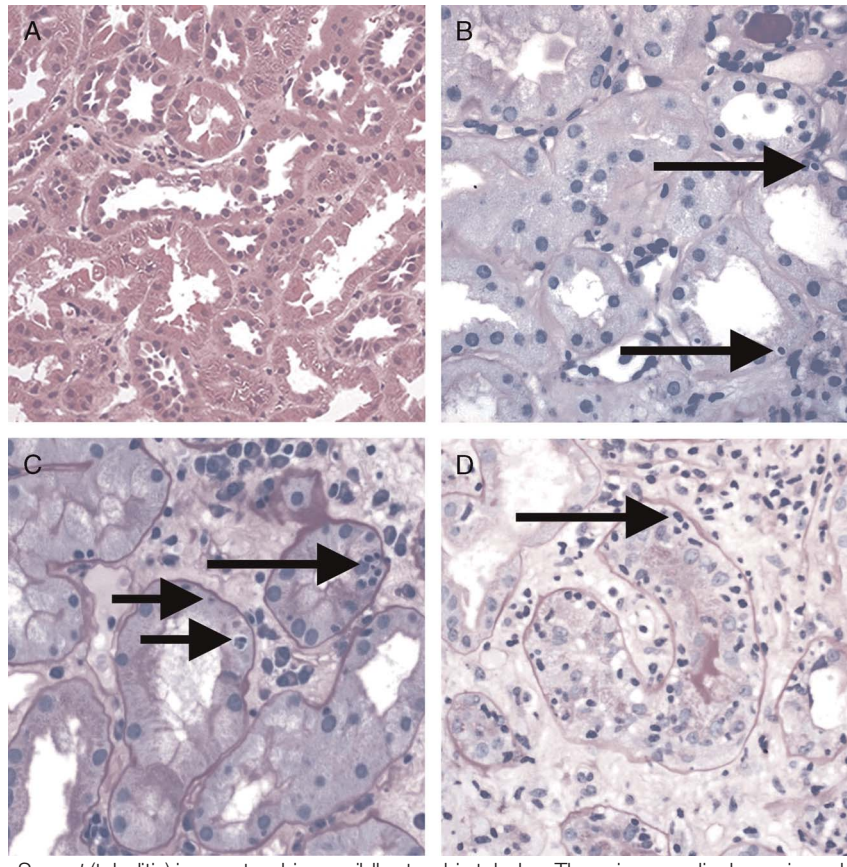

FIGURE 3. Banff Lesion Score *t* (tubulitis) in nonatrophic or mildly atrophic tubules. These images display various degrees of tubulitis which is characterized by the presence of mononuclear cells on the basolateral aspect of the tubular epithelial cells, within the confines of the basement membrane. Mononuclear cells (long and short arrows) are noticeable by their characteristic halo and smaller nucleus and more condensed chromatin compared to tubular epithelial cells. A, Banff Lesion Score *t0*—Cortical tubules without tubulitis which would be scored as *t0*. H&E, original magnification ×200. B, Banff Lesion Score *t1*—defined as foci of 1-4 mononuclear cells (arrows) per tubular cross section or per 10 tubular epithelial cells. PAS, original magnification ×400. C, Banff Lesion Score *t2*—defined as 5 to 10 mononuclear cells per tubular cross section or per 10 epithelial cells (long arrows). Note that the tubule to the left displays mild tubulitis (short arrows), but the most severely affected tubule dictates the score. PAS, original magnification ×400. D, Banff Lesion Score *t3*—defined as foci with >10 mononuclear cells/tubular cross section. Note that for this particular tubule the denominator is per 10 tubular epithelial cells as this tubule is sectioned longitudinally. PAS, original magnification ×400.

v3—Transmural arteritis and/or arterial fibrinoid change and medial smooth muscle necrosis with lymphocytic infiltrate in vessel.[11]

Banff Lesion Score *g* (Glomerulitis)

This Banff Lesion Score evaluates the degree of inflammation within glomeruli (Figure 6). Glomerulitis is a form of microvascular inflammation (MVI) and is a feature of activity and antibody interaction with tissue in AMR. It can also be seen in recurrent or de novo glomerulonephritis which must be excluded by appropriate immunostains and EM.

Banff Lesion Score *g* is determined by the proportion of glomeruli showing glomerulitis defined as "complete or partial occlusion of 1 or more glomerular capillary by leukocyte infiltration and endothelial cell enlargement."[10] Leukocytes include polymorphonuclear cells and mononuclear cells. Both endothelial cell enlargement and leukocyte(s) must contribute to the complete or partial occlusion. The denominator in this proportion is the number of nonsclerosed glomeruli in the biopsy.

g0—No glomerulitis.

g1—Segmental or global glomerulitis in less than 25% of glomeruli.

g2—Segmental or global glomerulitis in 25 to 75% of glomeruli.

g3—Segmental or global glomerulitis in more than 75% of glomeruli.[11]

Banff Lesion Score *ptc* (Peritubular Capillaritis)

This Banff Lesion Score evaluates the degree of inflammation within peritubular capillaries (PTCs). Together with glomerulitis, peritubular capillaritis constitutes MVI as a feature of Active AMR or Chronic Active AMR. Peritubular capillaritis can be observed with pure Acute TCMR or Borderline as well.

According to the Banff 2005 update, the Banff Lesion Score *ptc* is determined by the most severely involved PTC (Figure 7). Peritubular capillaries are by definition found in the cortex, their medullary equivalent are medullary vasa recta. The number of luminal inflammatory cells includes polymorphonuclear and mononuclear leukocytes, with an asterisk "*" used to indicate only mononuclear cells and absence of neutrophils. The extent of the PTC inflammation in the biopsy should be documented, either as focal (10-50% of cortical area) or diffuse (>50% of cortical area), but this does not contribute to the score. The presence of associated PTC dilatation may also be noted. Areas affected by acute

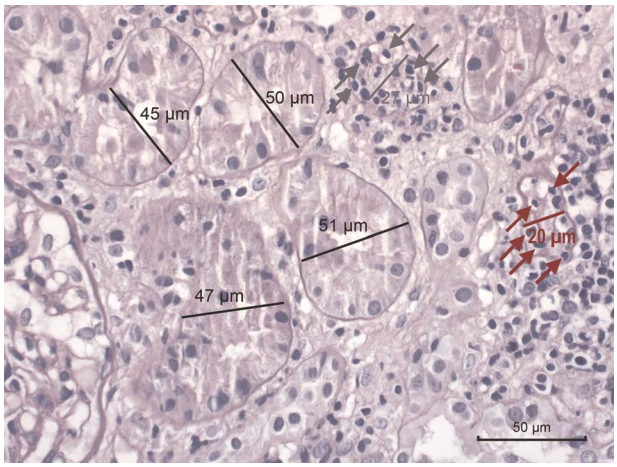

FIGURE 4. Banff Lesion Score *t* (tubulitis) in moderately atrophic tubules. In biopsies with Banff Lesion Scores *i*, *ti* and *i-IFTA* sufficient for a diagnosis of Acute TCMR Grade IA, IB or Chronic Active TCMR Grade IA and IB, Banff Lesion Score *t* must also be scored in moderately atrophic cortical tubules. Moderately atrophic tubules are defined as having less than 50% down to 25% of the diameter of the surrounding "unaffected or minimally affected [cortical] tubules in the biopsy".[12] This example shows such unaffected or minimally affected tubules with their diameter marked in black. Their mean diameter in this image would be around 48 µm. The tubule with the diameter marked in gray has a diameter of 27 µm which is more than 50% of 48 µm. Thus, this tubule would still qualify as mildly atrophic. It is heavily infiltrated with mononuclear cells (gray arrows). In contrast, the tubule with the diameter of 20 µm marked in red is moderately atrophic. The mononuclear tubulitis in this particular tubule must be scored toward Banff Lesion Score *t* in this biopsy which was diagnosed as Acute TCMR Grade IB. PAS, original magnification ×400.

pyelonephritis or necrosis and subcapsular cortex with nonspecific inflammation should not be scored. Inflammatory cells within PTCs must be distinguished from interstitial inflammation by careful examination of basement membrane stains (PAS, silver). Inflammatory cells within veins and medullary capillaries (*vasa recta*) should not be scored.[7] Consequently, peritubular capillaritis and Banff Lesion Score *ptc* can only be assessed in the cortex after exclusion of areas of pyelonephritis and infarcted areas and exclusion of areas close to lymphoid aggregates to avoid confusion with lymphatic vessels. Banff Lesion Score *ptc* should not be based on longitudinally cut PTCs.[8] Peritubular capillaries in areas affected by tubular atrophy and interstitial fibrosis must explicitly be considered for this Banff Lesion Score. Note that we have simplified the definition of *ptc0* from the original version in the Banff 2017 update.[12]

ptc0—Maximum number of leukocytes <3.

ptc1—At least 1 leukocyte cell in ≥10% of cortical PTCs with 3-4 leukocytes in most severely involved PTC.

ptc2—At least 1 leukocyte in ≥10% of cortical PTC with 5-10 leukocytes in most severely involved PTC.

ptc3—At least 1 leukocyte in ≥10% of cortical PTC with >10 leukocytes in most severely involved PTC.[11]

Banff Lesion Score *C4d*

This score evaluates the extent of staining for C4d on endothelial cells of PTCs and medullary *vasa recta* by IF on snap frozen sections of fresh tissue or IHC on formalin-fixated and paraffin-embedded tissue. Although Banff 2007 states that areas of tubular atrophy and interstitial fibrosis have reduced PTC density that could affect the extent of staining,[15] scoring of C4d in such cortical areas is not excluded.[8] Scoring of C4d staining is based on the percentage of peritubular capillaries and vasa recta that has a linear, circumferential staining pattern (Figure 8). The minimal sample for evaluation is 5 high-power fields of cortex and/or medulla without scarring or infarction. *C4d* must not be scored in areas of infarction. On IF, staining should be at least 1+ in intensity.[8] Strong staining is not required for a positive reading for IHC.[11] In terms of extent of staining, with IF, Banff Lesion Score $C4d \geq 2$ is considered positive and a criterion for antibody interaction with tissue and as equivalent to DSA (see Table 1 and **SDC, Glossary of Terms,** http://links.lww.com/TP/B604), whereas with IHC, Banff Lesion Score $C4d \geq 1$ is counted as positive already.[11] Note that the definition below deviates from the one provided in the Banff 2015 update,[11] in that it explicitly allows scoring in medullary vasa recta as originally intended, not only PTCs. The thresholds remain unchanged.

C4d0—No staining of PTC and medullary vasa recta (0%).

C4d1—Minimal C4d staining (>0 but <10% of PTC and medullary vasa recta).

C4d2—Focal C4d staining (10-50% of PTC and medullary vasa recta).

C4d3—Diffuse C4d staining (>50% of PTC and medullary vasa recta).

Banff Lesion Score *ci* (Interstitial Fibrosis)

This lesion score evaluates the extent of cortical fibrosis. The Banff Classification has never given a precise definition for individual areas of interstitial fibrosis (Figure 9). The reason for this is that Banff Lesion Score *ci* was meant to purely reflect the cortex composed of fibrous tissue, which does not necessarily correspond to areas that a pathologist would pick up as a patch of pathological tubulointerstitial fibrosis. The fraction of fibrous tissue in the cortex was considered as up to 5% for normal kidneys, hence the difference in cut-offs between *ci1* and *ct1*. A Working Group on this topic has produced useful reference guides (Figures 10 and 11).[17]

ci0—Interstitial fibrosis in up to 5% of cortical area.

ci1—Interstitial fibrosis in 6 to 25% of cortical area (mild interstitial fibrosis).

ci2—Interstitial fibrosis in 26 to 50% of cortical area (moderate interstitial fibrosis).

ci3—Interstitial fibrosis in >50% of cortical area (severe interstitial fibrosis).[11]

Banff Lesion Score *ct* (Tubular Atrophy)

This Banff Lesion Score evaluates the extent of cortical tubular atrophy which is usually tightly associated with the areas affected with interstitial fibrosis (Figure 9). Both correlate with time posttransplantation in the setting of progressive disease of any cause. Accordingly, neither Banff Lesion Scores *ct* nor *ci* have diagnostic specificity, but both have significant correlation with allograft function and prognosis.

Historically, the Banff classification has defined tubular atrophy as reflected in the Banff Lesion Score *ct* in the 1995 update[4] as tubules with a thickened basement membrane or a reduction of greater than 50% in tubular diameter. Banff Lesion Score *ct* is still based on this definition of tubular atrophy. The definitions of moderate and severe atrophy from the Banff 2017 update are irrelevant for Banff Lesion Score *ct*. In the following definition, we have omitted the designation as

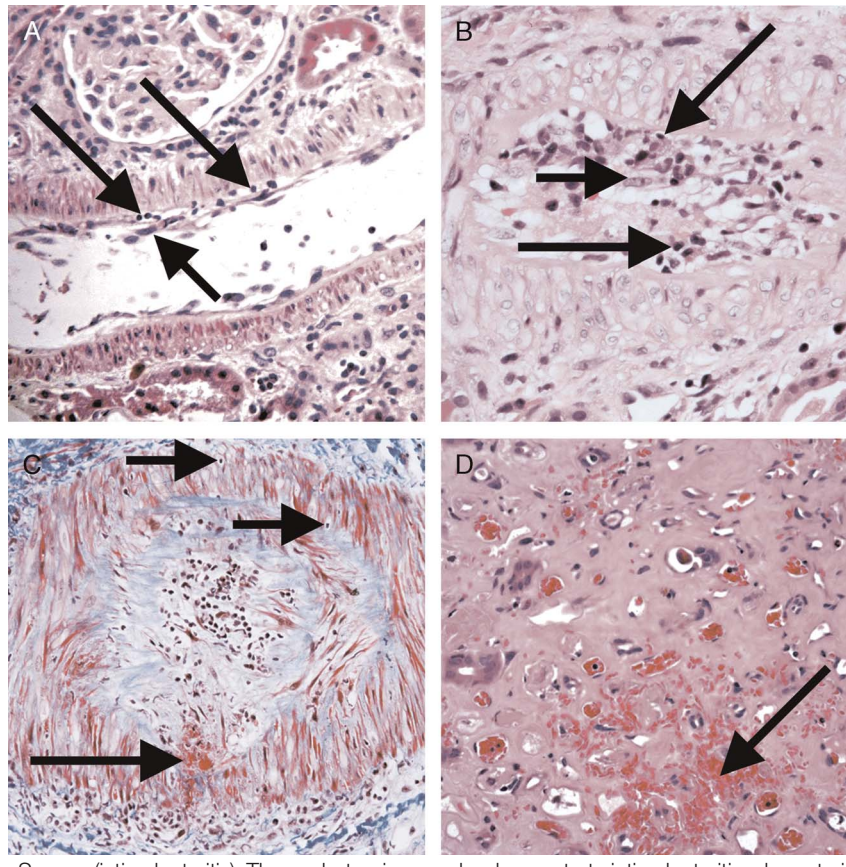

FIGURE 5. Banff Lesion Score *v* (intimal arteritis). These photomicrographs demonstrate intimal arteritis, characterized by the presence of inflammatory cells beneath the lining endothelial cells. A, Banff Lesion Score *v1*—mild to moderate arteritis with mononuclear cells (long arrows) immediately beneath lifted endothelial cells (short arrow). H&E, original magnification ×200. B, Banff Lesion Score *v2*—severe intimal arteritis involving over 25% of the arterial lumen with mononuclear cells (long arrows) immediately beneath lifted endothelial cells (short arrow). H&E, original magnification ×200; C, Banff Lesion Score *v3* -Transmural arteritis with fibrinoid necrosis in the media (long arrow) and mononuclear infiltrate in the arterial wall (short arrows). Intimal arteritis can be seen in both Acute TCMR Grade II and III and Active AMR. The most severely affected artery determines the score. Masson trichrome, original magnification ×100. D, This image demonstrates an area of interstitial hemorrhage characterized by extravasation of red blood cells into the surrounding interstitium (arrow). Although there is not a specific Banff Lesion Score for this feature, it can be recorded by attaching an asterisk to the v score (eg, *v**). Note that this asterisk attached to Banff Lesion Score *v* is not specific for interstitial hemorrhage as an area of cortical infarct (not shown) would also be coded like this. H&E, original magnification ×400.

"mild" for *ct1*, "moderate" for *ct2* and "severe" for *ct3* which was still included in the Banff 2015 update to avoid confusion between the definition of atrophy for an individual tubule as described above and the extent of tubular atrophy reflected in the Banff Lesion Score *ct*.

ct0—No tubular atrophy.

ct1—Tubular atrophy involving up to 25% of the area of cortical tubules.

ct2—Tubular atrophy involving 26 to 50% of the area of cortical tubules.

ct3—Tubular atrophy involving in >50% of the area of cortical tubules.[11]

Banff Lesion Score *cv* (Vascular Fibrous Intimal Thickening)

This Banff Lesion Score reflects the extent of arterial intimal thickening in the most severely affected artery (see **Definition of Terms, SDC,** http://links.lww.com/TP/B604), not the average of all arteries.[5] It does not discriminate between bland arterial intimal fibrosis and fibrosis containing leukocytes (Figure 12), although the latter is more likely to reflect chronic rejection (AMR and/or Chronic Active TCMR Grade II).[12] A visual analog scale for application in daily practice is provided in Figure 13.

cv0—No chronic vascular changes.

cv1—Vascular narrowing of up to 25% luminal area by fibrointimal thickening.

cv2—Vascular narrowing of 26 to 50% luminal area by fibrointimal thickening.

cv3—Vascular narrowing of more than 50% luminal area by fibrointimal thickening.[11]

Banff *cg* Score (Glomerular Basement Membrane Double Contours)

Banff Lesion Score *cg* is based on the presence and extent of glomerular basement membrane (GBM) double contours or multilamination in the most severely affected glomerulus (Figure 14). Scoring should be carried out on PAS or silver stains; a designation as *cg1a* requires transmission EM to exclude *cg0*. With Banff Lesion Score *cg* > *0* (including both *cg1a* and *cg1b*), a diagnosis of transplant glomerulopathy (TG) (see **Glossary of Terms, SDC,** http://links.lww.com/TP/B604) can be made, if other causes can be excluded. Banff Lesion Score *cg* > *0* can be a feature of Chronic AMR or

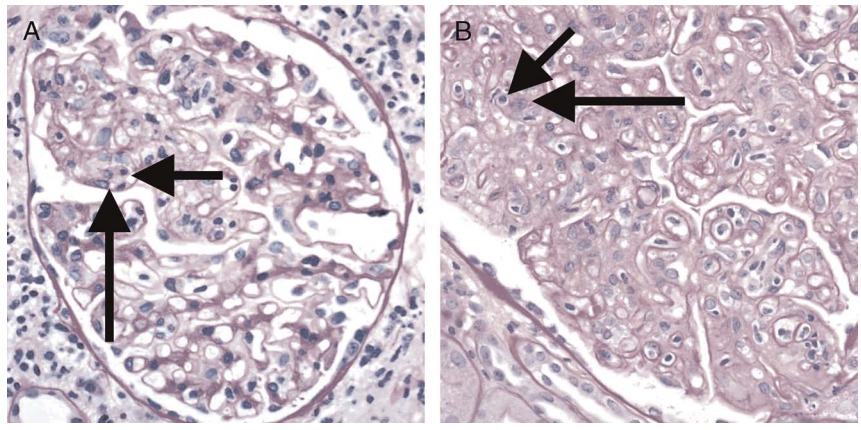

FIGURE 6. Banff Lesion Score *g* (glomerulitis). Glomerulitis is a form of MVI and a feature of AMR activity. A, Segmental glomerulitis; PAS, original magnification ×400. B, Global glomerulitis. Note the characteristic complete or partial occlusion of capillary loops by leukocytes (short arrows) and endothelial cell swelling (long arrows). The score of *g0* to *g3* is determined by the percentage of glomeruli involved with either segmental or global glomerulitis. Complete or partial occlusion of a single capillary loop suffices to mark the respective glomerulus as involved by the glomerulitis. PAS, original magnification ×400.

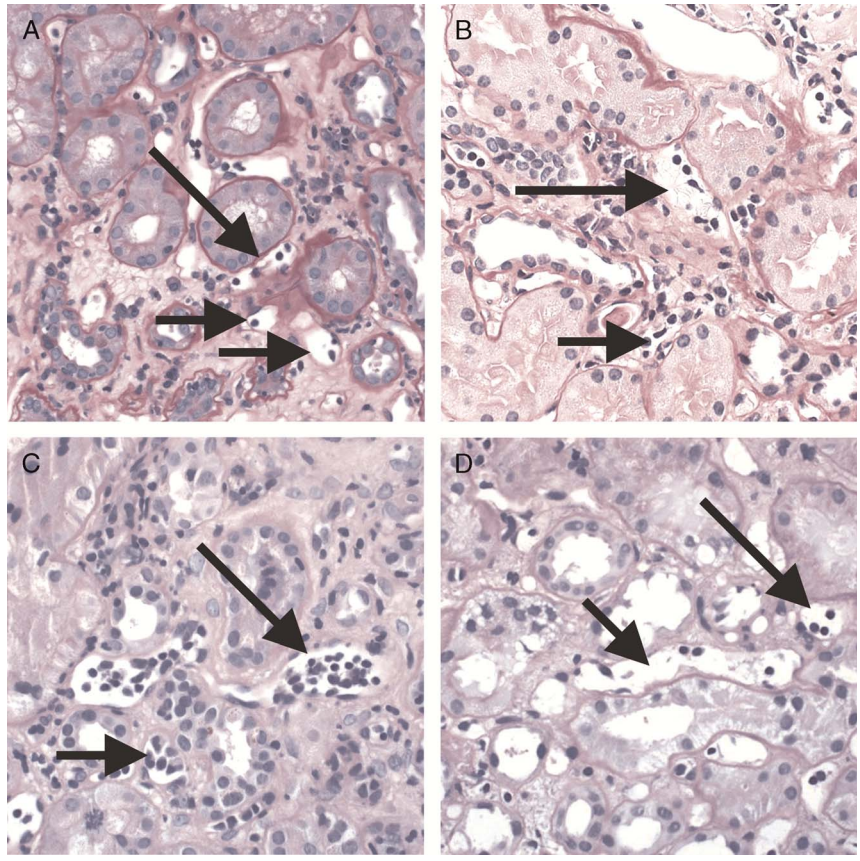

FIGURE 7. Banff Lesion Score *ptc* (peritubular capillaritis). Peritubular capillaritis is a form of MVI and a feature of AMR activity. Each image demonstrates the various *ptc* Scores which are in themselves determined by the number of inflammatory cells present within capillary lumina. A, Banff Lesion Score *ptc1*—Mild peritubular capillaritis defined as at least 1 cell in ≥10% of cortical PTCs (short arrows) with 3 to 4 in the most severely involved PTC (long arrow). Please note the slightly distended, open appearance of the capillary which can be a helpful feature; PAS, original magnification ×400. B, Banff Lesion Score *ptc2*—Moderate peritubular capillaritis defined as at least 1 cell in ≥10% of cortical PTCs (short arrows) with 5-10 in most severely involved PTC (long arrow); PAS, original magnification ×400. C, Banff Lesion Score *ptc3*—severe peritubular capillaritis defined as at least 1 cell in ≥10% of cortical PTCs (short arrows) with >10 in most severely involved PTC (long arrow). PAS, original magnification ×400. D, This peritubular capillary is cut longitudinally (short arrow) and although containing 4 mononuclear cells is to be disregarded for scoring. However, the neighboring peritubular capillary (long arrow) is cut orthogonally and would qualify for Banff Lesion Score *ptc1* provided that at least 10% of all PTCs contain at least 1 leukocyte. PAS, original magnification ×400.

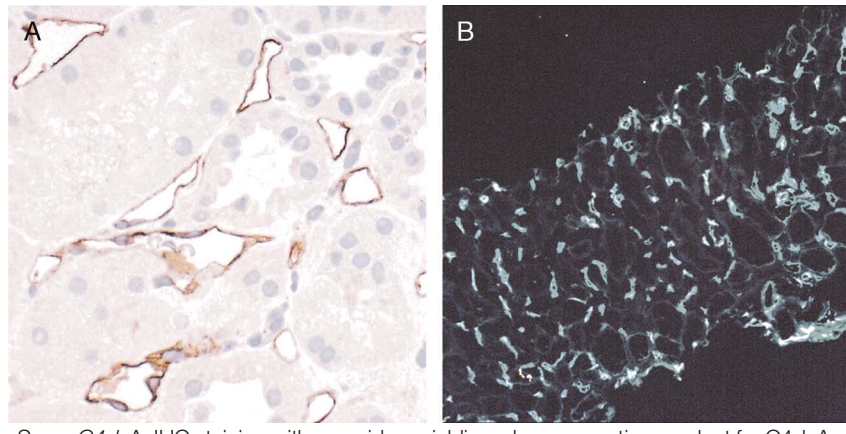

FIGURE 8. Banff Lesion Score *C4d*. A, IHC staining with peroxidase yielding a brown reaction product for C4d. An example of *C4d3*, this image demonstrates linear and circumferential staining of endothelial cells in virtually all peritubular capillaries. The staining was similar in all areas of the cortex and the medulla. The proportion of stained peritubular capillaries and medullary vasa recta informs the score. B, IF staining for *C4d*. This image shows an example of a Banff Lesion Score of *C4d3*; using IF, a minimum score of *C4d* ≥ *2* is considered positive. In addition to this, the staining intensity for an individual capillary or medullary vas rectum must be at least 1+ on the usual scale from negative, trace, 1+, 2+ to 3+. Indirect IF, mouse antihuman C4d followed by fluorescein isothiocyanate-conjugated anti-mouse IgG, original magnification ×100.

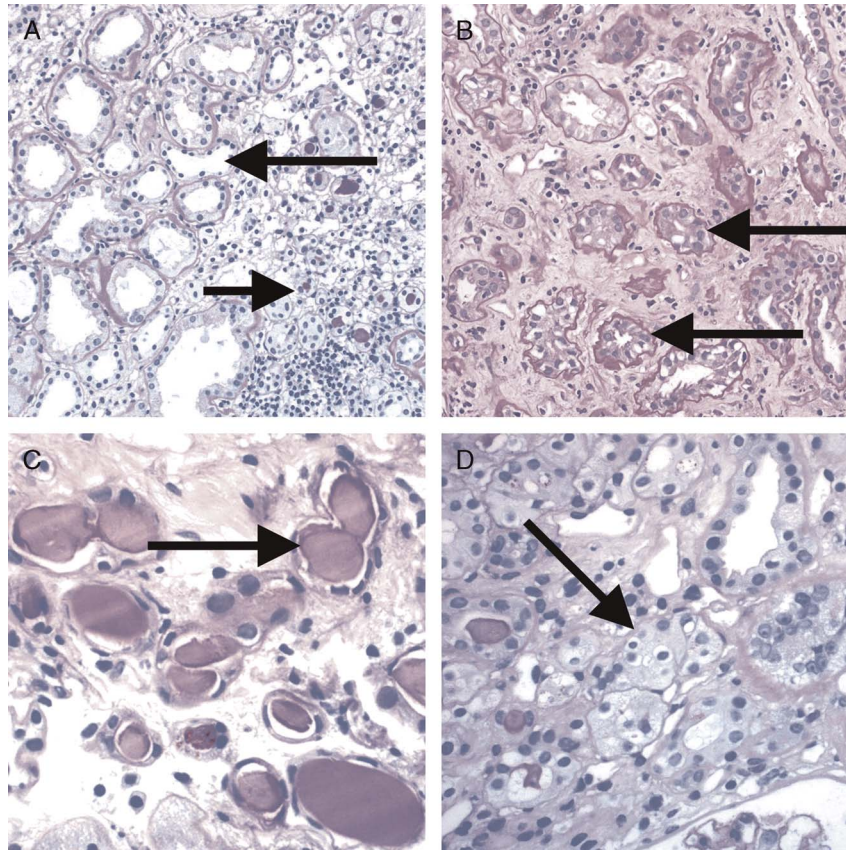

FIGURE 9. Banff Lesion Scores for *ct* (tubular atrophy) and *ci* (interstitial fibrosis). The *ci* and *ct* Scores are both based on calculating the total percentage of cortex involved and require a diligent assessment of all foci of *ct* and *ci* as this process is often multifocal; *ct* and *ci* scores may not always be equally advanced. A, This image demonstrates an area of nonatrophic tubules (long arrow), compared to an area of tubular atrophy (short arrow) without an obvious increase in interstitial fibrosis. PAS, original magnification ×200. There are different morphological types of tubular atrophy with differing histological appearances, including conventional, thyroidization, and endocrine-like types. B, Tubular atrophy of conventional type with interstitial fibrosis. Tubular areas are separated by areas of interstitial fibrosis and tubules show thickened basement membranes and > 50% reduction in tubular diameter (long arrows). PAS, original magnification ×200. C, Thyroidization type atrophy. Here, tubules appear dilated, have flattened epithelial cells, and contain eosinophilic and brightly periodic-acid-Schiff-positive uromodulin casts (long arrow). PAS, original magnification ×200. D, endocrine-like type, characterized by shrunken tubules with cuboidal epithelium and "tubular simplification" (long arrow). Compared with the other types of tubular atrophy, endocrine-like type does not have thickened basement membranes but still counts toward the ct score. PAS, original magnification ×400.

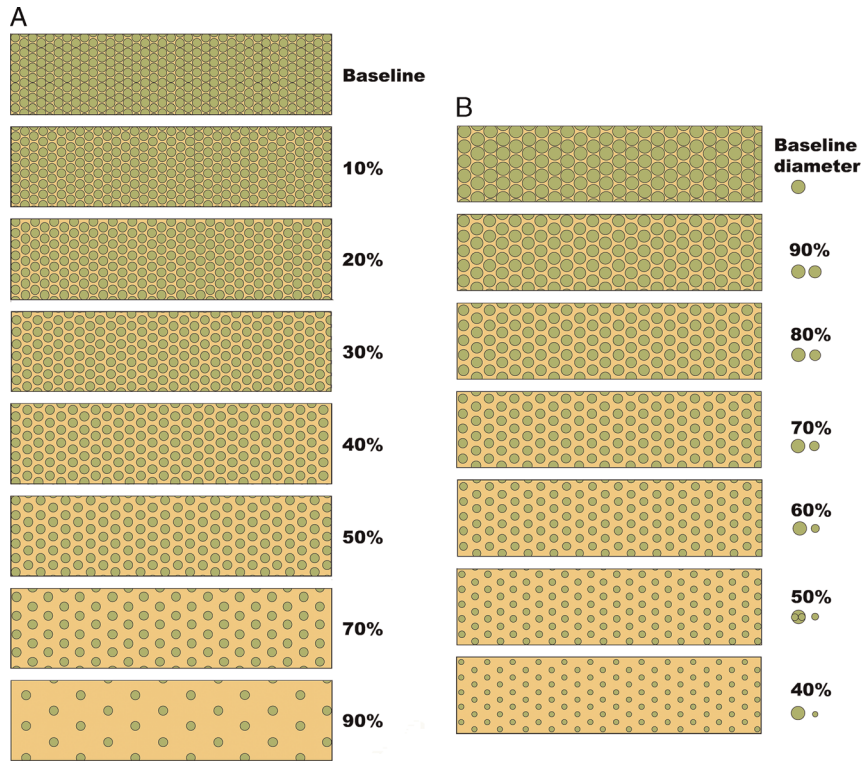

FIGURE 10. Visual analog scales provided by the Banff Working Group on Fibrosis. This working group developed schematic diagrams to facilitate and standardize scoring of Banff Lesion Scores *ci* and *ct*. A, Scale for the assessment of interstitial fibrosis without tubular atrophy. B, Scale for the assessment of diffuse tubular atrophy with "replacement fibrosis."[16] Reproduced with kind permission from American Journal of Transplantation.

Chronic Active AMR, but can also be seen in association with thrombotic microangiopathy of other causes than AMR, e.g., hepatitis C virus infection,[18] hypertensive glomerulopathy,[19] and glomerulonephritis. In analogy to Banff Lesion Score *g*, even in the presence of an explanation other than rejection for GBM double contours, Banff Lesion Score *cg* shall still be applied. Banff Lesion Score *cg* is not scored in ischemic or segmentally sclerosed glomeruli.[1,11] Late ischemic glomerulopathy is defined as "thickening, wrinkling and collapse of glomerular capillary walls associated with

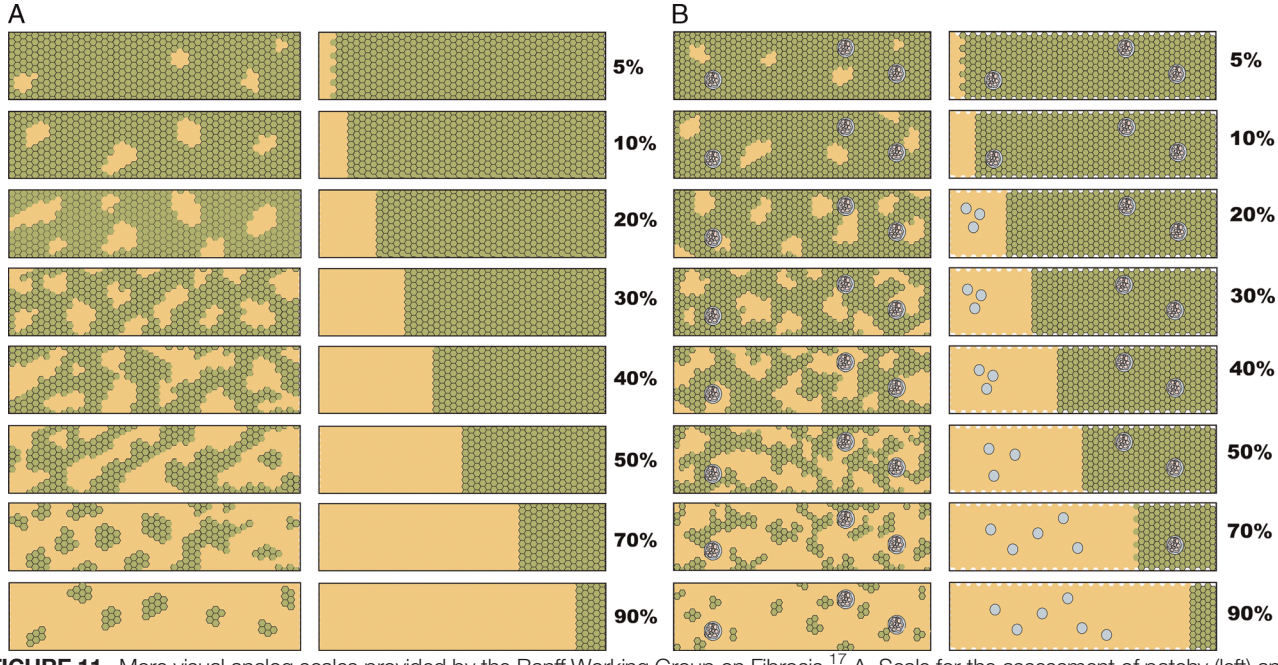

FIGURE 11. More visual analog scales provided by the Banff Working Group on Fibrosis.[17] A, Scale for the assessment of patchy (left) and confluent (right) interstitial fibrosis without glomeruli. B, Scale for patchy (left) and confluent (right) fibrosis with glomeruli.[16] Reproduced with kind permission from American Journal of Transplantation.

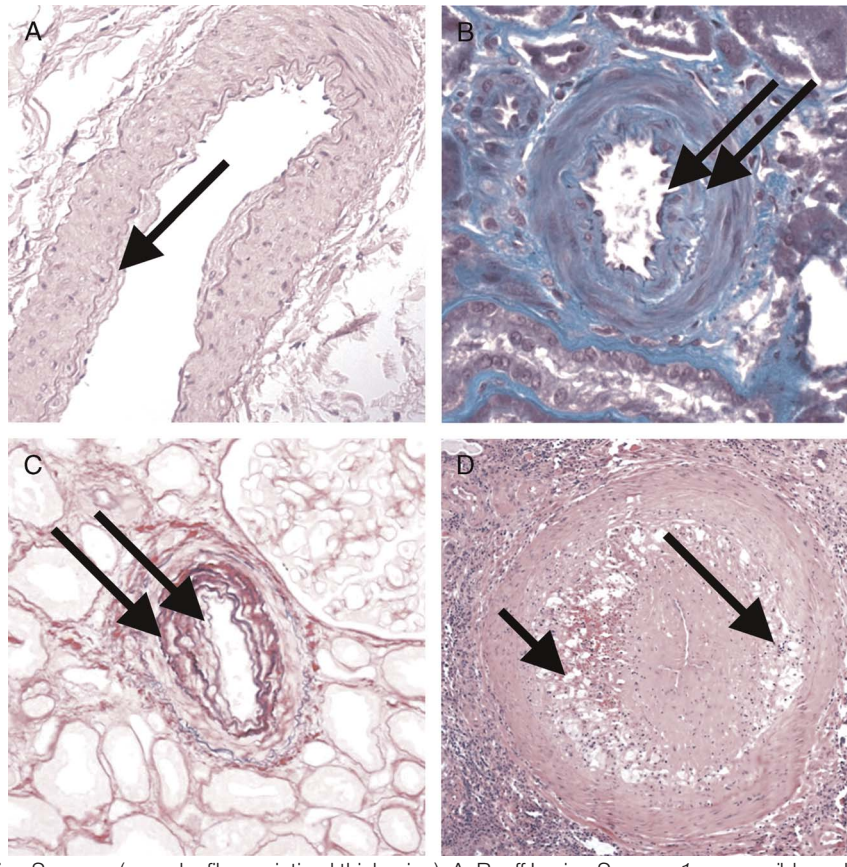

FIGURE 12. Banff Lesion Score *cv* (vascular fibrous intimal thickening). A, Banff Lesion Score *cv1*—very mild purely fibrous thickening of the arterial intima (arrow). PAS, original magnification ×200. B, Purely fibrous intimal thickening is depicted here in between the arrows in a trichrome stain. Note that this type of fibrous intimal thickening can also represent chronic damage in AMR. Masson trichrome, original magnification ×400. C, Arterial fibrous intimal thickening in between the arrows. Note the multiplication of the internal elastic lamina. Trichrome-elastica, original magnification ×400. D, Severe fibrointimal thickening *cv3*, with mononuclear infiltrates (long arrow) and foam cells (short arrow) in the fibrotic intima which can be a feature of both Chronic Active TCMR and Chronic Active AMR. Both types of lesion qualify for Banff Lesion Score *cv*, the score is determined by the loss of luminal area as shown in Figure 13 below. H&E, original magnification ×100.

extracapillary fibrotic material".[1] As stated above, the earliest lesion of TG (*cg1a*) requires transmission EM for diagnosis. To detect such lesions, it is recommended that at centers with EM capability, "ultrastructural studies should be performed in all biopsies from patients who are sensitized, have documented DSA at any time posttransplantation and/or who have had a prior biopsy showing C4d staining, glomerulitis and/or peritubular capillaritis". It is also advised that EM be considered in all biopsies performed from 6 months posttransplantation onward and in for-cause biopsies done from 3 months posttransplantation onward to determine if early changes of TG are present, prompting testing for DSA.[10] Electron microscopy is also recommended for any biopsy done for the indication of increasing or new onset proteinuria.

cg0—No GBM double contours by light microscopy (LM) or EM.

cg1a—No GBM double contours by LM but GBM double contours (incomplete or circumferential) in at least 3 glomerular capillaries by EM, with associated endothelial swelling and/or subendothelial electron-lucent widening.

cg1b—Double contours of the GBM in 1-25% of capillary loops in the most affected nonsclerotic glomerulus by LM; EM confirmation is recommended if EM is available.

cg2—Double contours affecting 26 to 50% of peripheral capillary loops in the most affected—glomerulus.

cg3—Double contours affecting more than 50% of peripheral capillary loops in the most affected-glomerulus.[11]

Banff Lesion Score *mm* (Mesangial Matrix Expansion)

This score evaluates the percentage of glomeruli with "moderate mesangial matrix expansion" in relation to all nonsclerosed glomeruli. Banff 1997 defines moderate mesangial matrix increase as "expansion of the matrix in the mesangial interspace to exceed the width of 2 mesangial cells in the average in at least 2 glomerular lobules".[5] An example is shown in Figure 15. Banff Lesion Score *mm* is currently not used to reach a Diagnostic Category and is purely descriptive.

mm0—No more than mild mesangial matrix increase in any glomerulus.

mm1—At least moderate mesangial matrix increase in up to 25% of nonsclerotic glomeruli.

mm2—At least moderate mesangial matrix increase in 26% to 50% of nonsclerotic glomeruli.

mm3—At least moderate mesangial matrix increase in >50% of nonsclerotic glomeruli.[11]

Banff Lesion Score *ah* (Arteriolar Hyalinosis)

This score evaluates the extent of arteriolar hyalinosis (Figure 16). The first edition of the Banff Classification defined *ah* as "nodular hyaline afferent arteriolar thickening

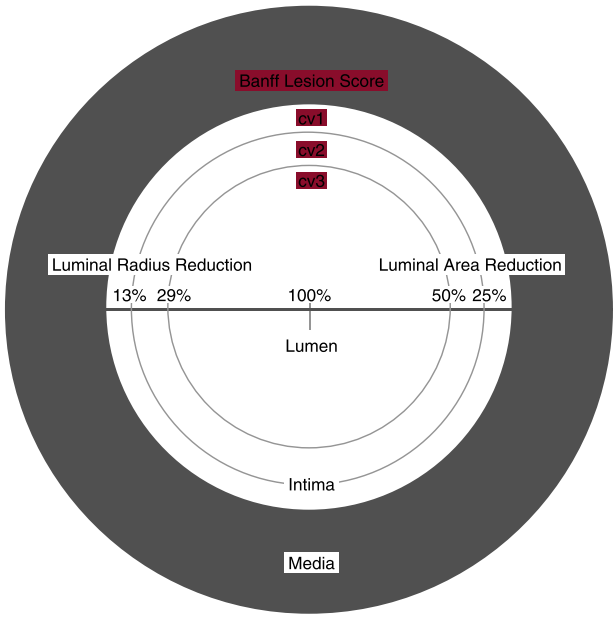

FIGURE 13. Visual analog scale for the determination of Banff Lesion Score *cv* (arterial fibrous intimal thickening). The remaining luminal area is related to the square of the remaining luminal radius. Thus, relatively modest decreases in luminal radius of 13% or 29% translate into relatively large reductions in luminal area of 25% or 50%, reflecting the thresholds for Banff Lesion Score *cv*.

suggestive of cyclosporine toxicity"; however, in Banff 1997 and later updates, Banff Lesion Score *ah* is defined simply as PAS-positive arteriolar hyaline thickening, as a finding of "uncertain significance". An asterisk "*" is added to the *ah* score when arteriolitis is present (eg, *ah0**, *ah2**).[5] Banff Lesion Score *ah* is currently not used to reach a diagnostic category and is purely descriptive.

ah0—No PAS (PAS)-positive hyaline arteriolar thickening.

ah1—Mild to moderate PAS-positive hyaline thickening in at least 1 arteriole.

ah2—Moderate to severe PAS-positive hyaline thickening in more than 1 arteriole.

ah3—Severe PAS-positive hyaline thickening in many arterioles.[11]

Banff Lesion Score *aah* (Hyaline Arteriolar Thickening)

This Banff Lesion Score provides an alternative way of quantifying arteriolar hyalinosis. It was proposed in the 2007 update, because of the insufficient reproducibility of the Banff Lesion Score *ah*.[8] This alternative tries to reach better reproducibility by focusing on circumferential or noncircumferential hyalinosis and the number of involved arterioles. Still, this lesion cannot be considered specific, that is, diagnostic for calcineurin inhibitor-related arteriolopathy. The use of this Banff Lesion Score *aah* has been left as optional since its introduction in 2007, no final decision has been reached whether it shall replace Banff Lesion Score *ah*. Banff Lesion Score *aah* is currently not used to reach a diagnostic category and is purely descriptive.

aah0—No typical lesions of calcineurin inhibitor-related arteriolopathy.

aah1—Replacement of degenerated smooth muscle cells by hyaline deposits in only 1 arteriole, without circumferential involvement.

aah2—Replacement of degenerated smooth muscle cells by hyaline deposits in more than 1 arteriole, without circumferential involvement.

aah3—Replacement of degenerated smooth muscle cells by hyaline deposits with circumferential involvement, independent of the number of arterioles involved.[11]

Banff Lesion Score *ti* (Total Inflammation)

This lesion score evaluates the extent of total cortical inflammation. According to the Banff 2007 update and in contrast to the Banff Lesion Score *i*, all of the cortical parenchyma, including areas of interstitial fibrosis and tubular atrophy (IFTA), subcapsular cortex and perivascular cortex including nodular infiltrates are considered for *ti* scoring.[8] Mengel et al found Banff Lesion Score *ti* to be better predictive of poor graft outcomes than the Banff Lesion Score *i* in cases where at least mild IFTA was present.[20] The association between interstitial inflammation in areas of IFTA as reflected in Banff Lesion Score *i-IFTA* and decreased graft survival was noted by Mannon et al[21] and subsequently confirmed by others.[22,23] As a consequence, Banff Lesion Score *ti* became part of the criteria for a diagnosis of Chronic Active TCMR Grade IA and IB;[12] both Banff Lesion Scores *ti* and *i-IFTA* must be at least 2 to consider a diagnosis of Chronic Active TCMR Grade IA or IB.[12]

ti0— No or trivial interstitial inflammation (<10% of total cortical parenchyma).

ti1— 10-25% of total cortical parenchyma inflamed.

ti2— 26-50% of total cortical parenchyma inflamed.

ti3— >50% of total cortical parenchyma inflamed.[11]

Banff Lesion Score *i-IFTA* (Inflammation in Area of IFTA)

This score evaluates the extent of inflammation in scarred cortex, ie, areas that qualify for Banff Lesion Scores *ci* and *ct* (Figure 17). The Banff Lesion Score *i-IFTA* was first introduced to the Banff Classification in 2015.[11] Both Banff Lesion Scores *ti* and *i-IFTA* must be at least 2 to consider a diagnosis of Chronic Active TCMR Grade IA or IB.[12]

i-IFTA0—No inflammation or less than 10% of scarred cortical parenchyma.

i-IFTA1—Inflammation in 10% to 25% of scarred cortical parenchyma.

i-IFTA2—Inflammation in 26% to 50% of scarred cortical parenchyma.

i-IFTA3—Inflammation in >50% of scarred cortical parenchyma.[11]

BANFF DIAGNOSTIC CATEGORIES

Table 1 presents the Banff Diagnostic Categories and is based on the original table of the most recent Banff update from 2017.[12] Readers should stay alert to future updates on the Banff Foundation website (www.banfffoundation.org) informed by updates to the Banff Classification from 2019 onward.

CRITICAL APPRAISAL

Since 1991, the Banff classification has undergone several amendments, reflecting the growing body of knowledge in transplant pathology. These amendments have been based on a consensus reached at the biannual Banff meetings. This constant refinement based on emerging data is a strength of the Banff process and has led to the worldwide dominance

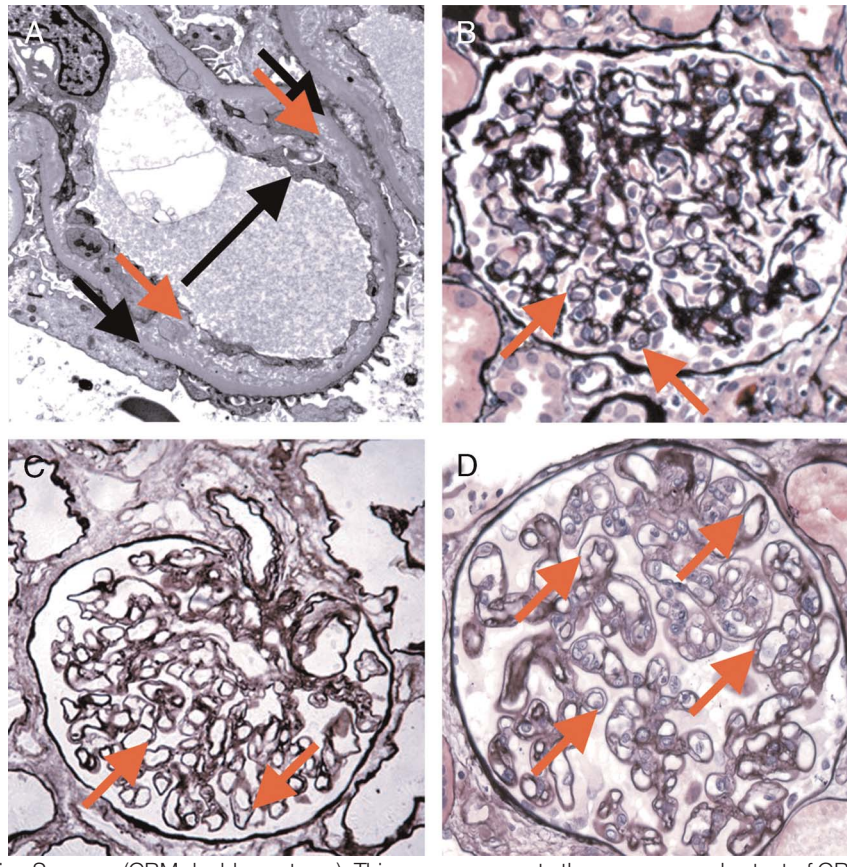

FIGURE 14. Banff Lesion Score *cg* (GBM double contours). This score represents the presence and extent of GBM double contours, a criterion for Chronic Active AMR. The score ranges from 0 to 3 and is based on the percentage of capillary loops with double contours as evident on EM (Banff Lesion Score *cg1a*) or LM (*cg1b* to *cg3*) in the most severely affected glomerulus. A, *cg1a*—GBM with double contours (short black arrows point to areas of original basement membrane and red arrows point to areas of new basement membrane formation), visible by EM only. Double contours, such as those noted in this image must be accompanied by endothelial cell swelling (long black arrow) and/or subendothelial widening and must involve at least 3 glomerular capillaries by EM for a Score of *cg1a*. Scores of greater than *cg1a* are based on light microscopic appearance which can best be examined by silver stains. Transmission EM, original magnification ×8000. B, Banff Lesion Score *cg1b*—double contours (arrow) identified on LM which involve up to 25% of the capillary loops of this most affected glomerulus. Jones silver stain, original magnification ×400. C, Banff Lesion Score *cg2*—double contours (arrows) present in 26-50% of this most affected glomerulus; Jones silver stain, original magnification ×400. D, Banff Lesion Score *cg3*—double contours (arrows) present in >50% of this most affected glomerulus. Jones silver stain, original magnification ×400.

of the Banff Classification for diagnostic practice, research and clinical trials. However, the iterative fashion in which the definitions and rules were published has dispersed the relevant content and created ambiguities. This has led to the creation of the Banff Rules and Dissemination Working Group in the aftermath of the Banff Meeting in Barcelona in March 2017. The aim of the Working group is not to alter the content of the Banff Classification. Rather, it shall collate all relevant Banff content in a central repository under the auspices of the Banff Foundation for Allograft Pathology, with a single updatable content, similar to the Union for International Cancer Control's TNM Classification. Changes in the content of the Banff Classification must only be made through review of evidence and expert consensus at the Banff meetings or within the relevant other Working Groups. Like the collation of content above, the following critical appraisal is based on this mission and does not touch on the content of the Banff Classification itself.

Although the Banff Lesion Scores required for a diagnosis of AMR have recently undergone a partial overhaul[10] and although a dedicated Working Group is reexamining the Banff Lesion Scores for TCMR, no or little effort has been devoted to the Additional Diagnostic Parameters in Table 3. For example, "Acute Tubular Injury In The Absence Of Any Other Cause" as a criterion for active AMR is as important as Banff Lesion Scores *v*, *g* or *ptc*,[12] yet this feature is still imperfectly defined, the last definition dating back to the 1995 update.[4] Another example is "infection," which precludes the use of Banff Lesion Score *ptc* alone as a criterion for AMR.[11] Use of the isolated term "infection" is ambiguous in the context of whether inflammation in the transplant should be considered as evidence for rejection or not. We would recommend treating these Additional Diagnostic Parameters like the Banff Lesion Scores, presenting them in clear and consistent wording, and, whenever necessary, by providing guidance through meaningful definitions elaborated over time through Working Groups and in alignment with the respective diagnostic criteria applied.

Among the Banff Lesion Scores, the Banff Lesion Score *cv* has a confusing array of terminologies, appearances and diagnostic implications. "Arterial fibrointimal thickening" or "vascular fibrous intimal thickening" imply a chronic fibrous change, whereas arterial intimal thickening can be cellular and nonfibrous in "transplant vasculopathy" or "chronic

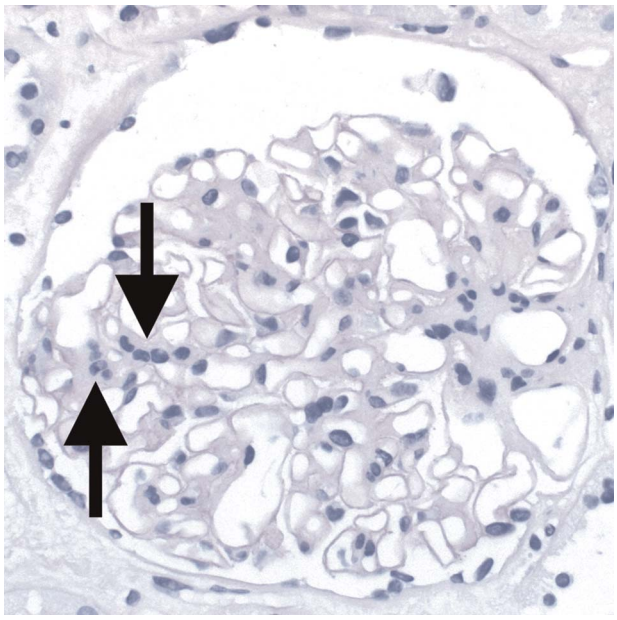

FIGURE 15. Banff Lesion Score *mm* (mesangial matrix expansion). This glomerulus fulfils the criteria for moderate mesangial matrix expansion with more than 2 mesangial cells in these 2 adjacent glomerular lobules (arrows). The proportion of glomeruli with such mesangial matrix expansion among all nonsclerosed glomeruli informs the score. The underlying reason for the mesangial matrix expansion in this biopsy was recurrent IgA glomerulonephritis revealed by IHC and EM. PAS, original magnification ×400.

allograft arteriopathy". As a manifestation of chronic TCMR, it is defined as "arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neointima[12] whereas, as a criterion for AMR chronicity, it is defined as "arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor chronic AMR if there is no prior history of biopsy-proven TCMR with arterial involvement but are not required".[12] In clinical practice, it might not always be possible to exclude prior TCMR or to precisely diagnose "Arterial intimal fibrosis of new onset" as a criterion for AMR chronicity.[12] A related problem is attached to Banff Lesion Score *cg*: "evidence of chronic thrombotic microangiopathy (TMA)" excludes the use of Banff Lesion Score *cg* > *0* as a criterion for AMR chronicity, whereas Active AMR can be diagnosed with TMA, as long as it is "in the absence of any other cause [than AMR]". Because Active AMR causing TMA can lead to glomerular lesion qualifying as TG, it would make sense to change the *cg* criterion to only exclude chronic TMA of any other cause than AMR.

The use of asterisks ("*") attached to Banff Lesion Scores *v*, *i*, *ah* and *ptc*[5,7] is problematic and widely neglected. Their reproducibility and diagnostic value are unknown, and they are ambiguous: an asterisk behind the Banff Lesion Score *ptc* signifies only mononuclear cells and absence of neutrophils, whereas the asterisk behind Banff Lesion Score *i* denotes a significant neutrophilic, eosinophilic or plasmacellular component in the infiltrate, and these different cell types can have widely differing implications. We suggest the Banff community should reassess these modifiers, either by improving their definitions and assigning them a significance or by abandoning them.

Inevitably, the Banff Classification has focused mainly on features of rejection, but with Banff Lesion Scores developed for other features with little or no guidance on their contribution to diagnosis. An example for this is Banff Lesion Score *aah*, originally intended to replace the poorly reproducible Banff lesion score *ah*.[7] However, its use is still optional, and it has neither been widely adopted nor used in any of the Banff Diagnostic Categories. The Banff community should reassess arteriolar hyalinosis lesion scores, and clarify grading and diagnostic implications.

Regarding the Banff Diagnostic Categories, a clear diagnostic pathway should be recommended when dealing with Borderline or Acute TCMR (Banff Diagnostic Categories 3 and 4) in the presence of BK Virus Nephropathy, Pyelonephritis or other infectious diseases of the transplant, as well as AMR with glomerulitis in the presence of recurrent or de novo glomerulonephritis. These issues could be referred to the Banff TCMR and Glomerulonephritis Working Group respectively. The definition of Banff Borderline with regards to the Banff Lesion Score *i* threshold (*i0* or *i1*) is still ambiguous[11] but should be resolved by the TCMR Working Group.

There are uncertainties around the application of transmission EM in the diagnosis of AMR which are currently being addressed by the Electron Microscopy Working Group. These issues include precise guidelines for indications and methods for application of EM in transplant biopsies; perhaps also the introduction of a new Banff Lesion Score for multilamination of the basement membranes of peritubular capillaries which we have covered as an Additional Diagnostic Parameter for now.

Another critical issue is related to the molecular diagnostics of AMR and TCMR. Although the current Banff classification endorses the use of molecular diagnostics in the definition of AMR, there is limited guidance regarding methods and diagnostic cut-offs, which could be elaborated by the Molecular Working Group.

Lastly, the introduction of the new diagnostic categories of Chronic Active TCMR is likely to undergo changes informed by the TCMR Working Group. Before Banff 2017, there were no specific criteria for Chronic Active TCMR outside of arteries, and tubulitis was only scored in nonatrophic and mildly atrophic tubules, effectively excluding moderately and severely atrophic tubules. To avoid having 2 separate criteria for Banff Lesion Score *t* in Acute versus Chronic Active TCMR, it was decided that for both diagnoses tubulitis would be scored in all tubules except severely atrophic tubules. The difference between Banff 2017 and previous versions of the classification with respect to Acute TCMR is that tubulitis in moderately atrophic tubules is now counted toward Banff Lesion Score *t*. Because the latter was done for clarity and to avoid confusion rather than on the basis of specific evidence, it would be beneficial that future studies be done to address the most clinically relevant threshold for the level of atrophy permitted in scoreable tubules, especially for diagnosis of Acute TCMR. In addition, the 2017 changes to the TCMR criteria also suggest future work be aimed at examining the response of Chronic Active TCMR to steroids and other anti–T cell therapies (eg, thymoglobulin), determining if there are differences in this response between: (1) Grade IA versus Grade IB Chronic Active TCMR and (2) biopsies with Chronic Active TCMR that would otherwise meet

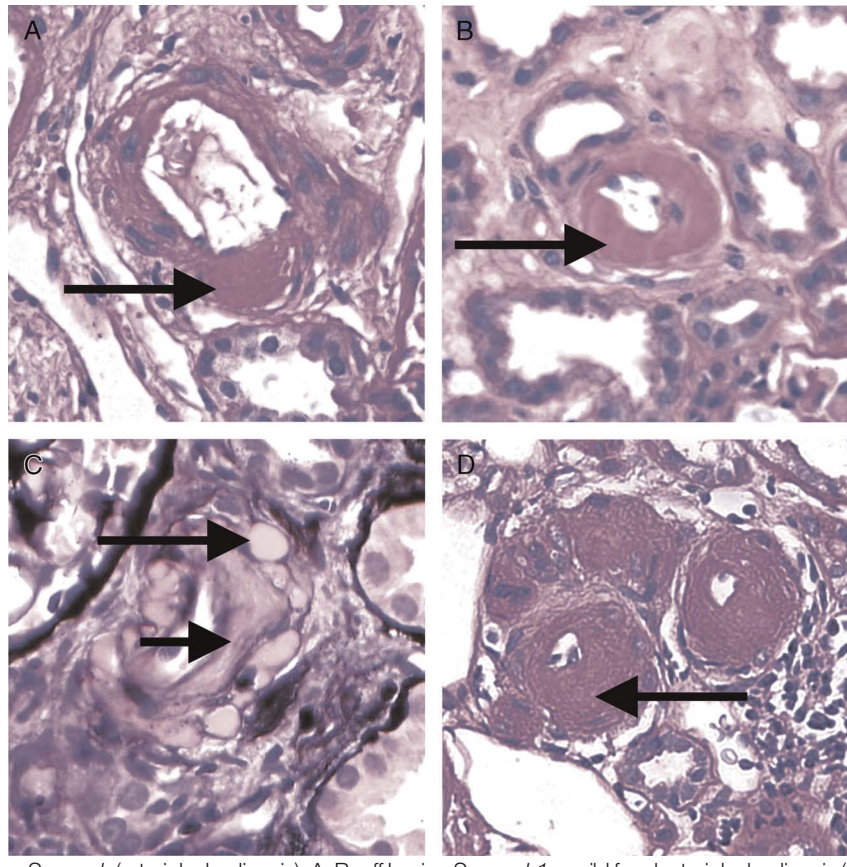

FIGURE 16. Banff Lesion Score *ah* (arteriolar hyalinosis). A, Banff Lesion Score *ah1*—mild focal arteriolar hyalinosis (arrow). PAS, original magnification ×630. B, *ah2*—Moderate arteriolar hyalinosis (arrow). PAS, original magnification ×630. C, Banff Lesion Score *ah2*—Note in this image there is both linear (short arrow) and nodular hyalinosis (long arrow). For a score of *ah2*, more than 1 arteriole displaying moderate to severe is required. Jones silver stain, original magnification ×630. D, Banff Lesion Score *ah3*—severe circumferential arteriolar hyalinosis with luminal occlusion. For Banff Lesion Score *ah3*, hyalinosis of this severity (arrow) must be present in many arterioles as depicted here. PAS, original magnification ×630.

criteria for acute TCMR (ie, with Banff Lesion Score $i \geq 2$) and those that would not (with Banff Lesion Score $i \leq 1$). The alignment of diagnoses from the spectrum of Acute TCMR with those from the spectrum of Chronic Active TCMR of different compartments could be problematic. For example, a biopsy with Banff Lesion Score *v1* fulfilling also the criteria for chronic active TCMR grade IB would be diagnosed as the latter only,[12] as according to Banff 2017, a diagnosis of Chronic Active TCMR precludes the diagnosis even of higher grade Acute TCMR. In such cases, however, the use of modifying text independent from Banff diagnostic categories should be considered (eg, Acute TCMR

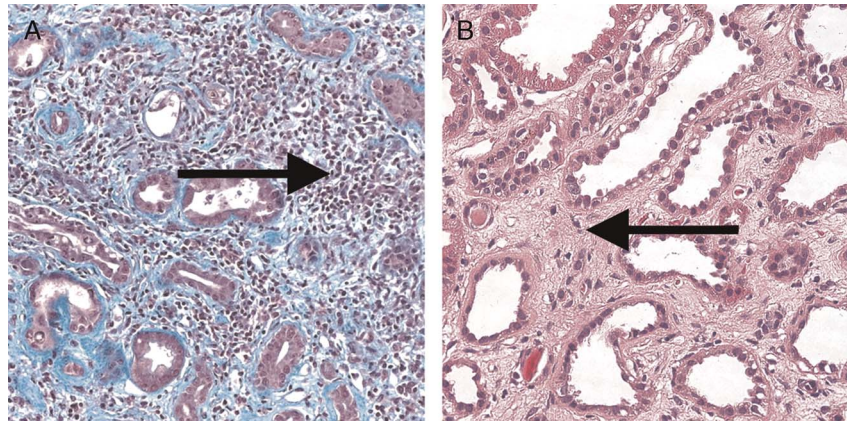

FIGURE 17. Banff Lesions Score *i-IFTA* (Inflammation in areas of IFTA). Image A shows Inflammation in areas of IFTA (arrow). This Lesion Score ranges from 0 to 3, based on the percentage of scarred areas of the cortex (ie, areas qualifying for *ci* and *ct*) involved by inflammation. It is one of the criteria necessary for a diagnosis of Chronic Active TCMR Grade IA or IB. Masson trichrome, original magnification ×200. B, In contrast shows interstitial fibrosis without significant infiltrate (arrow). H&E, original magnification ×400.

TABLE 3.

These additional diagnostic parameters, some histopathologic, some clinical, are derived from the diagnostic algorithms in Table 1

Parameters	Required for diagnostic category
Acute Thrombotic Microangiopathy In The Absence Of Any Other Cause (Figure 18)	Active and Chronic Active AMR
Acute Tubular Injury In The Absence Of Any Other Apparent Cause	Active AMR
Absence Of Recurrent Or De Novo Glomerulonephritis	Active and Chronic Active AMR
Infection	Active and Chronic Active AMR
Arterial Intimal Fibrosis Of New Onset, Excluding Other Causes	Chronic AMR and Chronic Active AMR
Leukocytes Within The Sclerotic [Arterial] Intima Favor Chronic AMR	Chronic Active AMR and Chronic AMR
Increased Expression Of Thoroughly Validated Gene Transcripts/Classifiers In The Biopsy Tissue Strongly Associated With AMR	Active AMR, Chronic Active AMR, Chronic AMR
Severe Peritubular Capillary Basement Membrane Multilayering (Figure 19)	Chronic AMR and Chronic Active AMR, Chronic Active TCMR Grade IA and IB
Arterial Intimal Fibrosis With Mononuclear Cell Inflammation In Fibrosis And Formation Of Neointima	Chronic Active TCMR Grade II
Prior Evidence Of DSA	Chronic AMR
Serologic Evidence Of DSAs (DSA To HLA Or Other Antigens)	Active AMR, Chronic Active AMR, Chronic AMR
Prior Documented Diagnosis Of Active Or Chronic Active AMR	Chronic AMR
Prior History Of TCMR	Chronic Active AMR and Chronic AMR
Evidence Of Chronic TMA	Chronic Active AMR and Chronic AMR
C4d Staining On Fresh-Frozen Or Paraffin-Embedded Tissue	C4d Staining Without Evidence Of Rejection, Active AMR, Chronic Active AMR, Chronic AMR
BK-Virus Nephropathy	Other Changes Not Considered To Be Caused By Acute Or Chronic Rejection
Posttransplant Lymphoproliferative Disorder	
Calcineurin Inhibitor Toxicity	
Acute Tubular Injury	
Recurrent Disease	
De Novo Glomerulopathy (Other Than TG)	
Pyelonephritis	
Drug-Induced Interstitial Nephritis	

Depending on the constellation of findings they may be required in addition to the Banff Lesion Scores to determine the Banff Diagnostic Categories.

Grade II with a chronic active tubulointerstitial component; Acute TCMR Grade II with isolated intimal arteritis [isolated v]).

PROSPECTS

Although this article is intended to provide a comprehensive and convenient desk-top reference, it is destined to expire with the publication of the 2019 Banff update. After this update, a Web resource will serve as the continuously updated go-to resource for the relevant Banff content. Depending on the progress in the definitions and diagnostic rule sets we are aiming to develop web-based resources such as diagnostic algorithms to further strengthen standardization and reproducibility of the Banff Classification for clinical practice and

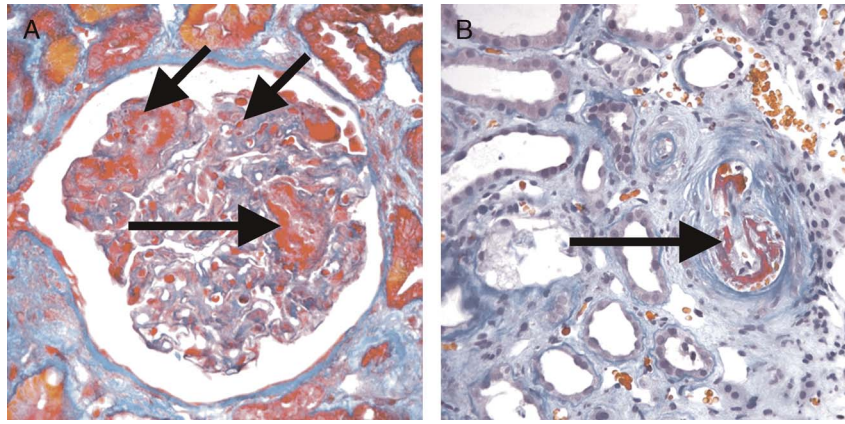

FIGURE 18. Acute TMA. A, An acute TMA affecting a glomerulus with fibrin thrombi (long arrows) and fragmented red blood cells (short arrow) in capillary loops. Trichrome, original magnification ×400. B, An acute TMA affecting a small arteriole (arrow). Acute TMA is one of the histological features used as histological evidence of acute tissue injury in Active AMR. However, TMA is not specific for AMR and can be seen in, for example, recurrent disease or calcineurin inhibitor toxicity. Trichrome, original magnification ×400.

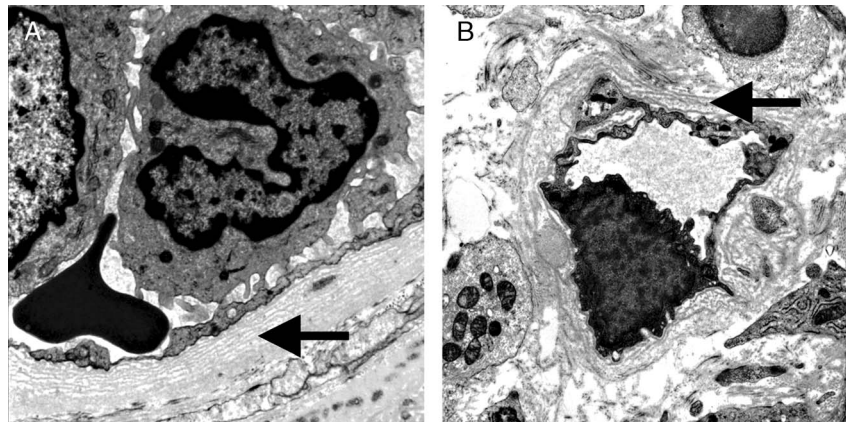

FIGURE 19. Severe Peritubular Capillary Basement Membrane Multilayering (PTCML) as demonstrated by EM. A, This Additional Diagnostic Parameter is a criterion for AMR chronicity. It is defined as 7 or more layers of basement membrane in at least a single cortical peritubular capillary and 5 or more in at least 2 additional capillaries. This particular capillary shows 8 layers (arrow). Transmission EM, original magnification ×14000. B, This image demonstrates a peritubular capillary with 5 layers of basement membrane (arrow). Transmission EM, original magnification ×10000.

research. It should be emphasized that the Banff Classification of Kidney Allograft Pathology does not cover all relevant aspects of transplantation medicine. Allograft transplantation only reaches 10% of patients needing new organs. Through regenerative medicine and tissue engineering and other optimizing initiatives we will eventually be able to provide organs to everyone in need. For this, we will need a new Banff Classification of Tissue Engineering Pathology[24,25]

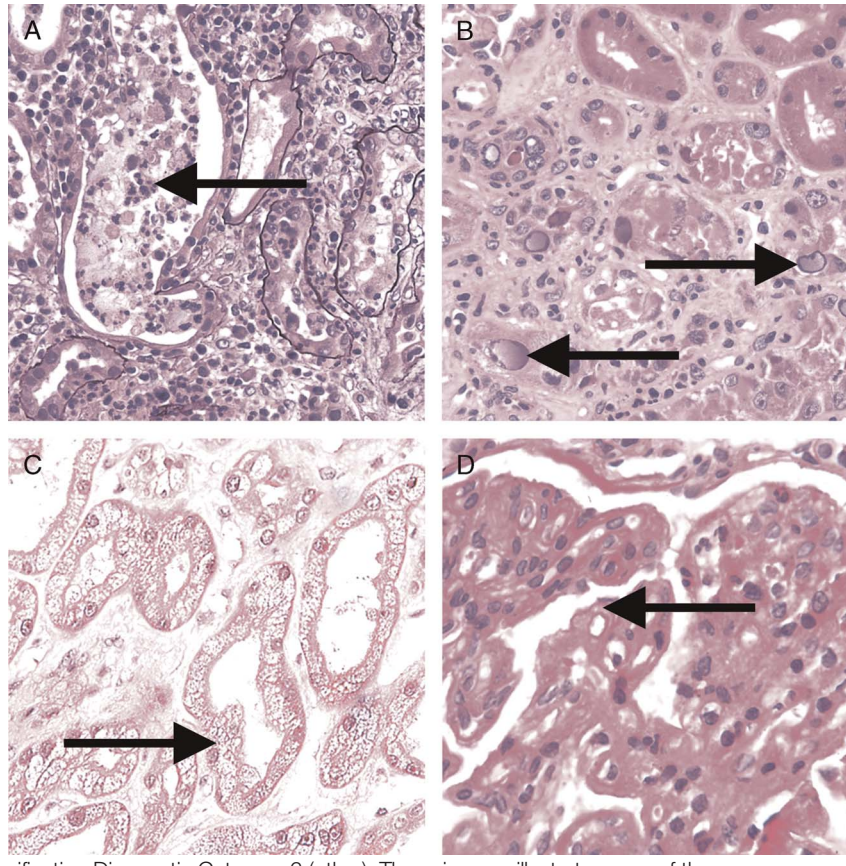

FIGURE 20. Banff Classification Diagnostic Category 6 (other). These images illustrate some of the more common examples of key lesions specified under category 6. A, Pyelonephritis with neutrophilic casts (arrow) and neutrophilic infiltrates with tubulitis. H&E, original magnification ×200. B, BK virus nephropathy with typical ground glass intranuclear inclusions as seen on hematoxylin and eosin stain (arrows). H&E, original magnification ×400. C, Acute tubular injury with widespread isometric vacuolization of tubular epithelial cells (arrow) associated with acute Calcineurin Inhibitor Toxicity and other forms of injury. H&E, original magnification ×200. D, Recurrent glomerulonephritis (membranoproliferative immune complex glomerulonephritis type I in this case) with split GBMs (arrow). The diagnosis was confirmed and TG excluded by positive IF for immunoglobulin heavy-, light-chains and complement slit products as well as abundant subendothelial electron dense immune complex deposits on EM. PAS, original magnification ×400.

reflecting the new challenges of delivering the right cells to the right places in a bioengineered organ and having them function normally. Rejection will no longer be the primary threat in bioengineered organs. For a decade or more the new Banff Classification of Tissue Engineering Pathology will be used concurrently with the existing Banff Classification of Allograft Pathology.

Getting the right cells in the right places sounds simple, but in fact, we have poor knowledge of what all the normal cell types in transplanted organs are. For instance, in the kidney, we have traditionally taught that there are 26 cell types,[26] but in fact, high throughput single cell analysis in the Human Cell Atlas Project[27-29] shows many more than that and can determine not only cell identity but also lineage and activation state. The transplantation and transplantation pathology community need to embrace Human Cell Atlas technology, so we are not blindsided by this new technology. The scale of the likely impact of the Human Cell Atlas Project on nephrology and transplantation is currently being analyzed (Moghe I, Magor B, and Solez K, article in preparation, 2018).

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International Liver Transplantation Society Consensus Statement on Immunosuppression in Liver Transplant Recipients

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International Liver Transplantation Society Consensus Statement on Immunosuppression in Liver Transplant Recipients

Michael Charlton, MD,[1] Josh Levitsky, MD,[2] Bashar Aqel, MD,[3] John O'Grady, MD,[4] Julie Hemibach, MD,[5] Mary Rinella, MD,[2] John Fung, MD,[1] Marwan Ghabril, MD,[6] Ray Thomason, MD,[7] Patrizia Burra, MD,[8] Ester Coelho Little, MD,[9] Marina Berenguer, MD,[10] Abraham Shaked, MD,[11] James Trotter, MD,[12] John Roberts, MD,[13] Manuel Rodriguez-Davalos, MD,[14] Mohamed Rela, MBBS,[4] Elizabeth Pomfret, MD,[15] Caroline Heyrend, PharmD,[14] Juan Gallegos-Orozco, MD,[7] and Faouzi Saliba, MD[16]

Abstract: Effective immunosupression management is central to achieving optimal outcomes in liver transplant recipients. Current immunosuppression regimens and agents are highly effective in minimizing graft loss due to acute and chronic rejection but can also produce a substantial array of toxicities. The utilization of immunosuppression varies widely, contributing to the wide disparities in posttransplant outcomes reported between transplant centers. The International Liver Transplantation Society (ILTS) convened a consensus conference, comprised of a global panel of expert hepatologists, transplant surgeons, nephrologists, and pharmacologists to review the literature and experience pertaining to immunosuppression management to develop guidelines on key aspects of immunosuppression. The consensus findings and recommendations of the ILTS Consensus guidelines on immunosuppression in liver transplant recipients are presented in this article.

(*Transplantation* 2018;102: 727–743)

The steady improvement in patient and graft survival rates after liver transplantation (LT) has been related to many factors, including improved efficacy of immunosuppression (IS). Effective IS management is central to achieving optimal outcomes in liver transplant recipients. The advent of more specific, potent IS agents has, while greatly reducing graft losses through acute and chronic rejection, been associated with an increasing burden of toxicities. Although dosing

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[1] *Transplant Institute, University of Chicago, Chicago, IL.*

[2] *Kovler Transplant Institute, Northwestern Memorial Hospital, Chicago, IL.*

[3] *Transplant Center, Mayo Clinic Arizona, Phoenix, AZ.*

[4] *Liver Transplant Unit, King's College Hospital, London, England, UK.*

[5] *Transplant Center, Mayo Clinic, Rochester, MN.*

[6] *Division of Gastroenterology and Hepatology, Indiana University, Indianapolis, IN.*

[7] *Division of Gastroenterology and Hepatology, University of Utah, Salt Lake City, UT.*

[8] *Multivisceral Transplant Unit, Padova University, Padova, Italy.*

[9] *Banner University Medical Center, Phoenix, AZ.*

[10] *Liver Unit, Hospital Universitario y Politécnico La Fe, Valencia, Spain.*

[11] *Transplant Institute, Pennsylvania University Hospital, Philadelphia, PN.*

[12] *Simmons Transplant Institute, Baylor University Medical Center, Dallas, TX.*

[13] *Department of Surgery, University of California San Francisco, San Francisco, CA.*

[14] *Intermountain Transplant Center, Primary Children's Hospital, Salt Lake City, UT.*

[15] *Transplant Center, University of Colorado Medical Center, Denver, CO.*

[16] *Center Hépato-Biliaire, Hospital Paul-Brousse, Paris, France.*

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guidelines are available for individual IS agents, the overall approach to IS varies widely between transplant centers. The ILTS convened a consensus conference, comprised of a global panel of expert hepatologists, transplant surgeons, nephrologists, and pharmacologists to develop guidelines on key aspects of IS management. Summaries of the evidence were presented to the entire group of panelists. Six broad areas of IS were addressed by the consensus panel. These topics were addressed through a critical review of the literature, followed by working group proposals and subsequent consensus, which was reviewed by the whole group. As for other ILTS guidelines, the Grading of Recommendations Assessment Development and Evaluation approach was used to determine the grade of the evidence and the strength of the recommednations.[1] Quality of evidence, benefits to risk ratio, resource use, and cost-effectiveness were all considered in developing guidelines. Recommendations were rated according to quality of the evidence (rated as very low, low, moderate, or high) and strength (rated as strong or conditional [weak]) and reflect perceived probability of benefit likely to be gained by adherence to guidance.

The consensus findings and recommendations of the International Liver Transplant Society Consensus guidelines on IS in liver transplant recipients are presented in this document. The guidance, which will be updated to reflect new evidence as it becomes available, is intended for healthcare providers caring for patients before and after LT. This guidance is also intended to assist third parties in decision making regarding access to IS regimens.

General Aspects of Liver Transplant IS

Immunosuppression after LT can be divided into the induction and maintenance phases, as well as general resumption of these phases in managing a rejection episode. Induction therapy usually consists of intravenous corticosteroids immediately posttransplant for several days until oral corticosteroids can be initiated. Use of other induction agents, such as IL-2 receptor antibodies or more lymphodepleting therapy (antithymocyte globulin), is increasing because these are often used to delay the introduction of calcineurin inhibitor (CNI) therapy in patients with kidney dysfunction. Other uses of induction therapy are for those at higher immunological risk (retransplantation for rejection, immune-mediated liver disease, simultaneous liver-kidney; highly sensitized) compared with essentially all other recipients who are considered lower immunological risk. The mainstay of maintenance IS therapy are the CNIs, with tacrolimus (TAC) being preferred over cyclosporine for initial therapy. Antiproliferative agents, such as mycophenolic acid and azathioprine, and mTORis can be used to lower the toxicity of CNI therapy or for those at higher risk of rejection, usually in combination with lower-dose CNI therapy. The specific nuances of induction and maintenance therapy decision making are further discussed in the sections below, after the initial review of liver transplant rejection.

Acute and Chronic T Cell-mediated and Antibody-mediated Rejections

Hepatic allograft rejection remains an important cause of morbidity and can lead to graft loss in patients undergoing LT. Major advances in immunosuppressive therapy have significantly lowered the incidence of rejection, and for the most part, the IS required to treat rejection is often more impactful on outcomes than the rejection itself, with the exception being late acute or chronic rejection.[2-5] Liver biopsy is mandatory for all types of rejection discussed below and may need to be repeated if biochemical responses are not achieved or other etiologies implicated. Based on the Banff Working Group, T cell–mediated rejection (TCMR) should replace the older terminology of acute cellular rejection, and antibody-mediated rejection (AMR) should replace the older terminology of humoral rejection.[6]

TCMR

T cell–mediated rejection is characterized by T-cell infiltrates with fewer populations of other inflammatory cells. Tacrolimus-based IS is more effective at reducing the incidence and severity of TCMR compared with cyclosporine-based therapy and remains the mainstay for initial and maintenance IS therapy. T cell–mediated rejection 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.[6,7] Histological grading should be standardized based on the Banff working group on liver allograft pathology[6-8]: global assessment of the overall rejection grade and a semiquantitative assessment of the 3 main histological characters: portal inflammation, bile duct inflammation/damage, and venous endothelial inflammation. The individual scores are added to produce the overall rejection activity index (RAI): mild (RAI, < 4), moderate (RAI, 4-6), and severe (RAI, > 7-9).

Early TCMR is typically within 90 days of transplant and characterized by inflammatory bile duct damage and pleomorphic portal inflammation, with paucity of interface activity. Incidence is between 10% and 30%, and most studies reveal little impact on graft and patient survival, depending on the era analyzed.[2,5] Mild TCMR should be treated by an increase in CNIs with or without addition of other agents (antimetabolites or mTORi); pulse steroid therapy may not be required. Moderate and moderate to severe TCMR should be treated with pulse steroid therapy (typically 500-1000 mg given daily or every other day for 3 doses) with an increase in maintenance CNI and/or other agents if appropriate. Patients who fail to respond, generally on repeat biopsy, or select patients with severe cholestatic TCMR should be treated with lymphodepletional antibody therapy (eg, antithymocyte globulin). T-cell and B-cell subset monitoring can be considered when using thymoglobulin and dose can be increased in absence of adequate response. IL-2 receptor blockers have no role in treatment and there is limited evidence to support the use of alemtuzumab. On balance, most would advocate for resuming opportunistic infection prophylaxis (antiviral, antifungal, pneumocystis carinii pneumonia) for a period similar to after the transplant procedure - 3 to 6 months - in patients given lymphodepleting antibodies or several courses of pulse steroids.

Early TCMR

Recommendation 1.1

Diagnosis of TCMR (early and late) should be based on histological findings. Repeat liver biopsy after treatment is not required in patients with appropriate biochemical response. However,

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repeat liver biopsy should be considered in patients with suboptimal biochemical response to guide further treatment escalation.

Recommendation 1.2

Treatment of TCMR should be determined by degree of liver injury and histological activity.

Mild TCMR should be treated by an increase in CNI and may not require steroid therapy.

Moderate and moderate-severe TCMR should be treated by an increase in CNI with pulse intravenous steroid therapy followed by a slow oral steroid taper. In selected patients with severe TCMR associated with significant graft injury and cholestasis, antibody-depleting therapy can be considered as a first-line therapy.

Steroid-resistant TCMR should be treated with antibody depleting therapy (anti-thymocyte globulin).

Quality/Certainty of Evidence: High
Strength of Recommendation: Strong

Late TCMR occurs greater than 90 days in 7.5%-23% of liver recipients.[2,4] Several studies showed that late TCMR is associated with reduced graft survival.[2-4,9] Risk factors include younger age, female gender, autoimmune etiology of liver disease, nonbiologically related donor, prior episode of early TCMR, and noncompliance. Histology can be different than classic TCMR, for example, interface hepatitis, plasma cell infiltrates, and perivenulitis.[10,11] Although there may be a correlation between plasma cell hepatitis and the development of alloantibodies, it is unclear if hepatic injury is inflammation or antibody-mediated. Treatment is generally based on the same algorithm used to treat early TCMR (see above). Steroid resistance can be seen in a small percentage, with up to 25% progressing to chronic rejection.[2-4,9]

Chronic rejection usually evolves from severe or persistent acute rejection and results in potentially irreversible bile duct and/or vascular injury.[8] The incidence of chronic rejection is approximately 1% to 5% in adults, but as high as 16% in the pediatric population.[12] Risk factors include autoimmune etiology of liver disease, donor/recipient sex mismatch, cyclosporine-based IS, noncompliance, number and severity of TCMR episodes, and retransplantation for rejection.[13,14] The minimal diagnostic criteria include: 1. Bile duct loss affecting greater than 50% of the portal tracts or 2. Bile duct atrophy/pyknosis affecting the majority of the bile ducts with or without duct loss or 3. Foam cell obliterative arteriopathy.[8] Although there is limited evidence to support a specific immunosuppressive regimen for chronic rejection, a cyclosporine-based regimen should be switched to a TAC-based one.[13]

Chronic TCMR

Recommendation 1.3

Diagnosis of Chronic TCMR should be suspected in patients with prior history of TCMR, who develop progressive cholestasis that is unresponsive to modifications in the *IS* regimen. Diagnosis should always be confirmed by liver biopsy.

Treatment of chronic TCMR is difficult. Patients with chronic TCMR who are receiving cyclosporine should be switched to TAC.

Quality/certainly of evidence: Moderate
Strength of recommendation: Strong

AMR

Although donor-specific antibodies may be seen in nearly 25% of liver transplant candidates and recipients, biopsy-proven AMR is rare (<1% of all and <5% of sensitized patients).[15-20] In patients with TCMR not responding to the standard therapy, AMR should be considered.

Utilizing the Banff criteria, a diagnosis of acute AMR requires classic histologic features, C4d (+) vascular staining, circulating DSA, exclusion of other causes and classified as definite, suspicious, or indeterminate.[6] Mild acute AMR likely responds to steroid boluses or lymphodepletion therapy used to treat moderate to severe TCMR, which can be coexisting. Moderate to severe AMR should be treated with DSA-depleting strategies, despite a lack of evidence and consensus. The only available data are based on case reports or inferred from the strategies used in nonhepatic transplants, such as plasmapheresis, intravenous immunoglobulin, and anti-B cell or plasma cell agents (ie, rituximab, bortezomib).[21-23] Treatment, such as eculizumab aimed at blocking complement, has been described in kidney AMR.[24-26]

The diagnosis of chronic AMR requires mild-moderate inflammation with low-grade interface activity and fibrosis, (+) C4d staining (may be negative, and this is "possible" chronic AMR), and circulating DSA present in last 3 months.[6] However, there is a lack of certainty regarding the diagnosis of chronic AMR given that many of the findings have been noted in biopsies of stable patients with normal liver tests. Evidence on incidence is limited, and there is currently no defined treatment strategy.

AMR

Recommendation 1.4

Diagnosis of AMR requires a liver biopsy demonstrating classic histology, C4d (+), circulating DSA, and exclusion of other causes.

Initial treatment of mild, acute AMR should be with steroid boluses.

Treatment of moderate to severe AMR can include plasmapheresis and IVIG with or without anti-B cell agents, such as rituximab, bortezemib, or eculizumab

Chronic AMR has no defined treatment strategy.

Quality/Certainty of Evidence: Moderate
Strength of Recommendation: Conditional

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TABLE 1.

The impact of IS on metabolic syndrome

	Hyperlipidemia	Hypertension	Obesity	Diabetes mellitus
CNIs	+ Population studied: Liver transplant	++ Population studied: Liver transplant	+ Population studied: Liver transplant	++ Population studied: Liver transplant Caveats: (Tac > CsA)
Mycophenolate/azathioprine	–	–	–	–
Corticosteroids	+ Population studied: Liver transplant	+ Population studied: Liver transplant	+ Population studied: Liver transplant	+++ Population studied: Liver transplant
mTOR inhibitors	++ Population studied: Liver transplant	+ Population studied: Renal transplant	–	–
Thymoglobulin	–	–	–	–
IL2-receptor antibodies	–	–	–	–

IS in Patients With Metabolic Syndrome

The metabolic syndrome (MetS), widely defined by the modified National Cholesterol Education Program Adult Treatment Panel III,[27] is characterized by the presence of central obesity, hyperlipidemia, insulin resistance and hypertension. Metabolic syndrome can worsen or develop de novo after LT. The International Diabetes Federation definition should be considered in Asian patients.[28] The risk of developing de novo MetS after LT has been reported to be 33%, 27%, and 40% at 3, 6, and 12 months, respectively.[29]

The Impact of IS on Metabolic Syndrome

Choice of IS can influence the development of various aspects of the MetS (**Table** 1). Calcineurin inhibitors are associated with hyperlipidemia, hypertension, and diabetes mellitus, steroids are associated with these conditions as well as obesity and mTORis are associated with hyperlipidemia (**strong evidence**).

Posttransplant MetS and IS

Recommendation 2.1

Corticosteroids carry significant risk for all components of MetS and should be minimized where possible.

Calcineurin inhibitors, in addition to independently causing renal insufficiency, contribute to post-LT hypertension and dyslipidemia.

Antiproliferatives, (azathioprine and mycophenolate) and **antibody-based therapies** (basiliximab and thymoglobulin) are neutral with regard to impact on features of post-LT MetS.

Mammalian target of rapamycin inhibitors (mTORi) (eg, everolimus [EVL]) are associated with diminished weight gain, a lower frequency of cardiac events but also with dyslipidemia post-LT. They are neutral with regard to diabetes mellitus (DM) and hypertension (HTN).

Quality/certainly of evidence: Limited-Moderate
Strength of recommendation: Conditional

Considerations in the Management of Obesity

Liver transplant recipients gain 10% to 20% of their weight in the first 6 to 12 months post,[30,31] and pre-LT obesity predicts post-LT diabetes mellitus.[32] There are limited data on the efficacy of general diet and exercise recommendations or weight loss medications on the prevalence or outcomes of MetS post-LT.[33] Sleeve gastrectomy during or after LT, and gastric bypass post-LT appear to be effective in selected patients.[34-38] Among bariatric surgery techniques, sleeve gastrectomy has the comparative advantage of not altering IS absorption.

The impact of steroid avoidance or minimization on weight gain post-LT is likely favorable, though evidence has

TABLE 2.

Important DDI between IS and common medications to treat metabolic conditions

	HMG-CoA reductase inhibitors (Statins)	Angiotensin converting enzyme inhibitors (ACEi)	Angiotensin receptor antagonists (ARB)	Calcium channel blockers (CCB)
CNIs (TAC, cyclosporine)	↑ in statin concentrations	↑ risk of AKI	↑ risk of AKI	↑ in CNI concentration
mTORi (SRL, EVL)	No DDI	↑ Risk of angioedema	No DDI	↑ in mTORi concentration
Antiproliferative agents (mycophenolate)	No DDI	No DDI	No DDI	No DDI

DDI, drug-drug interactions.

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been mixed.[39-42] The use of mTORi for CNI minimization or elimination is associated with less weight gain post-LT than standard-dose CNI regimens.[43,44]

Obesity

Recommendation 2.2

Exercise and nutritional modifications are cornerstones of managing weight gain after LT.

Specific medical or surgical interventions for post-LT obesity can be considered on an individual basis. Weight loss surgery can be considered in patients with medically complicated obesity resistant to behavioral modification.

Minimizing exposure CNIs and corticosteroids is recommended to mitigate posttransplant weight gain.

Quality/certainly of evidence: Moderate
Strength of recommendation: Strong

Considerations in Management of Hyperlipidemia

Dyslipidemia is present in 40% to 66% of post-LT patients. Immunosuppressants (CNI, mTORi, and corticosteroids) can contribute to post-LT hyperlipidemia.[45-47] Therefore, yearly fasting lipid panel is recommended in LT recipients. It is important to consider the interaction between HMGCoA reductase inhibitors (statin) and CNIs, as both are metabolized by cytochrome P450-3A4, resulting in increased statin concentrations that may increase the risk of rhabdomyolysis. Statins should be started at a lower dose and gradually titrated. Hydrophilic statins such as fluvastatin and pravastatin are preferred as they are not metabolized by cytochrome P450-3A4 (Table 2).

The American Cardiology Association/American Heart Association atherosclerotic cardiovascular disease (ASCVD) risk calculator is recommended to assess risk of ASCVD[48] (http://tools.acc.org/ASCVD-Risk-estimator/) followed by selection of appropriate therapy according to risk category.[49] Recommendations for managing dyslipidemia post-LT are summarized in Figure 1.[45]

Dyslipidemia

Recommendation 2.3

Screening: Fasting lipid panel should be obtained at 3-6 months, 1 year and annually thereafter post LT. Recommended target LDL-C is <100 mg/dL. Recommended triglyceride levels <250 mg/dL.

Management: All patients with post-LT dyslipidemia should attempt dietary/lifestyle measures. If no improvement within six months, a statin should be added.

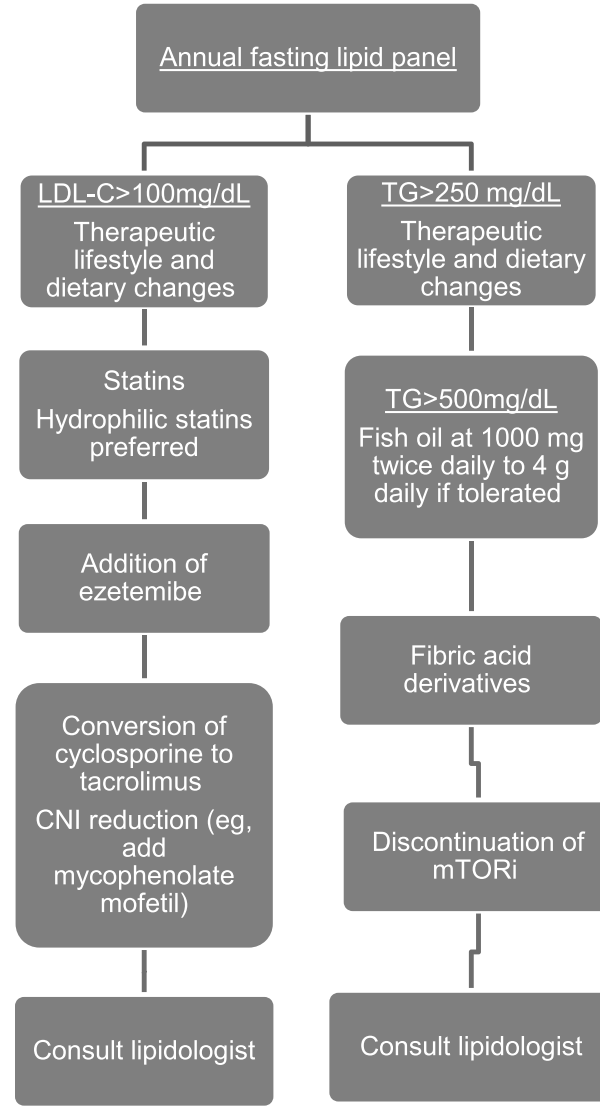

FIGURE 1. A stepwise approach to the treatment of dyslipidemia post liver transplantation.

Pravastatin is preferred for initial statin therapy due to less interactions with calcineurin inhibitors. Other statins should be started at 50% of recommended dose in patients on CNI and avoided in conjunction with cyclosporine A.

If dyslipidemia develops on cyclosporine A, consider switching to tacrolimus due to decreased severity of drug-drug interactions with statins.

If dyslipidemia develops while receiving mTORi, initially treat with lipid lowering agent. If unable to reach triglyceride goal, then consider mTORi dose-reduction or switching to alternative immunosuppressive agent.

Quality/certainly of evidence: Limited-Moderate
Strength of recommendation: Conditional

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Considerations in Management of Diabetes Mellitus

The prevalence of DM pre-LT is approximately 33% 1 year post-LT, with the prevalence of new-onset DM after transplant occurring in up to 26% of patients.[50,51] Diabetes mellitus is a major predictor of adverse events, including hepatic artery thrombosis, rejection and mortality.[46,52]

Pretransplant DM almost always persists and may become more severe after LT. Contributing factors include IS, weight gain and denervation of the liver at transplantation.[51] The goals of post-LT DM management are similar to the nontransplant setting, with the exception of HgbA1c target goal of less than 7.0%.[51] Lifestyle modifications, such as American Diabetes Association Diet and exercise, are cornerstones of managing DM post-LT.

Tacrolimus and cyclosporine impair insulin synthesis and secretion by beta cells. Corticosteroids can promote insulin resistance via an increase in gluconeogenesis, decreased beta-cell insulin production and peripheral glucose utilization. mTORi can decrease beta-cell proliferation and increase glucose transporter-4 signaling. Early posttransplant hyperglycemia can often be improved by addressing modifiable factors, such as minimization of maintenance IS agents (corticosteroids and CNI). Transplant specific and general facets of medical therapy of DM are presented in Table 3. When high-dose corticosteroids are administered, insulin therapy is the safest and most effective agent for hyperglycemia control. As TAC is more diabetogenic than cyclosporine, conversion might improve glucose control.

Diabetes Mellitus (DM)

Recommendation 2.4

Screening and Monitoring: Glucose intolerance is very common post-LT. All LT recipients should undergo fasting glucose and HgbA1c measurement, at a minimum, at 3 to 6 months, 1 year and annually thereafter. HgbA1c target goal should be <7.0%, Screening for retinopathy and proteinuria should be performed annually.

Management: A combination of lifestyle modifications and IS minimization, especially corticosteroids, aligned with program protocols is the most important modifiable factors in limiting the impact of post-LT DM. Medical therapy of post-LT DM should be according to standard guidelines (eg, American Diabetes Association guidelines).
Conversion from TAC to cyclosporine-based IS may improve control of diabetes and glucose intolerance.

Quality/certainly of evidence: Moderate
Strength of recommendation: Strong

Considerations in Management of Hypertension

Hypertension increases cardiovascular disease, chronic kidney disease (CKD), and the risk of overall death more than 1-year post-LT.[46] The prevalence of post-LT hypertension approaches 70%, with blood pressure being particularly abile in the early posttransplant period[46,53-55] primarily related to the effects of the CNI through renal vasoconstriction.

The ILTS recommendations on the management of HTN are guided primarily by the presumed mechanism, concomitant diseases, and the recommendations from national joint taskforces for the general population. Table 4 displays the considerations of anti-hypertensive agents in the liver transplant population.

Hypertension

Recommendation 2.5

Screening and Monitoring: Hypertension

TABLE 3.

Considerations in treatment of diabetes mellitus post-LT

Drug	Available evidence in transplant patients	Considerations
Metformin	Safe in kidney transplant	Preferred with normal renal function due to decreased weight gain. Caution in AKI/CKI (lactic acidosis). Hold for significant infection. Consider in pre-DM.
Sulfonylureas	Efficacy not proven. Small study kidney transplant. No ΔCSA kinetics	More hypoglycemia with AKI/CKI DDI with CSA. Glipizide or glimepiride preferred in renal dysfunction.
Thiazoledinediones	Safe and effective in small studies KTx	Weight gain, CHF, bone loss Efficacy in pre-LT NASH, CVD protection
Repaglinide	Safe, effective, no DDI c CNI, sm study KTx c PTDM	Risk of hypoglycemia with ↓ GFR vs. sulfonylureas
DPP4 inhibitors	Vildagliptin safe, effective kidney transplant RCT Sitagliptin:(CCS and retrospective data)	Dose reduce all but linagliptin with ↓GFR
GLP-1 agonists	Liraglutide: 5 kidney transplant patients treated, no effect on IS Exenatide: no data	Nausea, impacts gastric emptying, gut motility. No if GFR < 40 mL/min
SGLT-2 inhibitors	No data	Volume depletion, increased risk of GU infection, DKA. **Avoid.**
α-glucosidase inhibitors	No data	Avoid with low GFR

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TABLE 4.

Considerations in the pharmacologic management of hypertension in liver transplant recipient

Agent class	Clinical considerations
Calcium channel blockers	Amlodipine, and nifedipine are preferred due to their inhibition of CNI's renal vasoconstriction. The non-dihydropyridine calcium channel blockers—diltiazem and verapamil are not recommended due to their propensity to drug-drug interactions that increase bioavailabilty of CNI's levels.
Beta-blockers	Nonspecific Beta-blockers are second line agents without the same physiologic basis as CCB, but are as effective as CCB in LT patients
ACEs, ARBs, and direct renin inhibitors	These agents are recommended as first line in LT patients with CKD(with or without proteinuria), and DM.
Diuretics	Thiazides and loop diuretics may be used to address volume overload associated with CNIs and MTOR inhibitors in LT patients. Note of caution: CNIs and MTORs with diuretics require electrolyte monitoring due to potential electrolyte disturbances.

is common post-LT. All LT recipients should undergo measurement of resting blood pressure at a minimum, daily for the first month, at 3 to 6 months, 1 year and annually thereafter. The blood pressure goal after LT (not adjusting for age) is less than 130/80 mm Hg.

Quality/certainly of evidence: High
Strength of recommendation: Strong

Management: A combination of lifestyle modifications and IS minimization, especially corticosteroids and CNIs, are the important modifiable factors in limiting the impact of post-LT HTN. Lifestyle measures should include sodium restriction, weight loss and exercise. Medical therapy (see Table 4) is often initiated in conjunction with lifestyle and IS modifications.

Quality/certainly of evidence: Moderate
Strength of recommendation: Strong

IS Minimization

Long-term IS management should be aimed at identifying the appropriate drug type(s) and dose that suppresses alloimmune responses while minimizing adverse consequences of IS. The identification of the ideal IS regimen for each individual patient begins at the time of transplantation and is based primarily on the clinical presentation at the time of transplant and the etiology of liver failure. Personalizing IS can be viewed as adjustment of IS protocols that take into consideration recipient characteristics, etiology of primary liver disease and magnitude of alloimmune activation. Immunosuppression minimization strategies are safest when initiated after the first third postoperative month and should, in general, be considered in the context of liver chemistry tests that have been stable for at least 4 weeks preceding the protocol initiation. There is no need for a liver biopsy before starting the IS minimization protocol. If liver chemistry tests become elevated during the protocol, the first step is to return to the previous dose of/or regimen of IS. If the liver chemistry tests remain elevated, liver biopsy is performed to evaluate for late rejection.[2,4,56] Overall, clinically guided minimization is possible and safe, whereas the development of biomarkers of immune activation is still in its early stages.

Eligibility for IS Minimization

Recommendation 3.1

Patients may be considered for IS minimization protocols, except:

(1) those with biopsy proven steroid-resistant rejection,
(2) those who are transplanted for immune mediated diseases (initial or re-transplant) and
(3) those who had a definitive episode of AMR

Quality/certainly of evidence: Moderate
Strength of recommendation: Conditional

Steroid Discontinuation

By 3 months after liver transplant, most patients should be off corticosteroids. The recommendation is to decrease the dose of corticosteroids slowly with a goal of discontinuation. As mentioned above, in patients at higher immunological risk (eg, immune-mediated diseases), consideration should be given to either maintaining low dose steroids long term or adding AZA, mycophenolate mofetil (MMF) or MPA to facilitate steroid weaning.[57]

CNI Monotherapy

Patients who had an uneventful first 3 months post-transplant and remain stable are candidates for CNI monotherapy after 3 months.[58] In countries where sustained release TAC formulation is not available, compressing the standard dose of TAC and administering the equivalent dose once a day can be considered with the goal of improving compliance. For transplant centers that favor the IS with TAC, the trough TAC level at 3 months should be 6 to 10 ng/mL.[59] If cyclosporine is the CNI of choice, the expected level at 3 months is between 150 and 200 ng/mL. From months 3 to 12, the dose of CNI can be decreased slowly while monitoring levels. At the end of the first year, TAC trough levels should be no higher than 5 ng/mL and cyclosporine trough levels no higher than 100 ng/mL. From year 1 onward, the TAC trough levels can be dropped to 3 ng/mL. After year 5,

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drug levels are less *important,* and if there is good graft function as evidenced by stable and normal liver chemistry tests, trough levels of TAC just above the lower limit of detection are acceptable. However, complete IS withdrawal should be limited to clinical trials. In patients with posttransplant lymphoproliferative disorder and those with other malignancies postliver transplant, the rate of IS minimization can be accelerated with a goal of using very low doses of IS (see malignancy section below).

Dual to Monotherapy Conversion

A patient on dual therapy should be evaluated for possible switch to monotherapy at any time point post-LT (usually >1 year), assuming low immunological risk and likelihood of benefit from monotherapy. Monotherapy can be with TAC, with a trough level around 5 ng/mL; EVL with a trough level between 3 and 8 ng/mL[60]; MMF at a dose of 1 g every 12 hours.[61,62] The switch to EVL monotherapy, for example, for renal sparing effect, may be done earlier than at 1 to 2 years, keeping in mind the substantial risk of rejection seen in EVL monotherapy conversion studies. It may be preferable to utilize a second maintenance agent, for example, MMF or low dose corticosteroids. In such cases, close monitoring for rejection is recommended. The ILTS recognizes that some centers use sirolimus (SRL) in posttransplant patients. Nevertheless, the consensus group did not make any recommendations for SRL use, given that it is not FDA-approved, and there are other alternatives (EVL) available.

Strategies for Minimization of IS

Recommendation 3.2

Corticosteroids: By 3 months after liver transplant most patients should be tapered off of corticosteroids; those at higher immunological risk (eg, immune-mediated diseases, history of steroid-resistant rejection) should be considered for long-term low-dose steroids or replacement with antiproliferative agents.

Calcineurin Inhibitor monotherapy: All patients who are eligible for minimization of IS are potential candidates for CNI monotherapy after 3 months.

Dual to monotherapy conversion: Patients who are intolerant of CNI monotherapy or at higher immunological risk should be considered for dual therapy with a combination of 2 of the following: CNI, MMF, or EVL. Generally after 1 year, non-CNI monotherapy may be considered in patients at low immunological risk.

Quality/certainly of evidence: Moderate
Strength of recommendation: Conditional

Malignancy and IS

Malignancy is one of the most important complications in liver transplant recipients. The most common cancers are nonmelanoma skin cancer and recurrent hepatocellular carcinoma (HCC), followed by non-Hodgkins lymphoma, lung and renal cell cancer (RCC).[63] Patients transplanted for alcoholic liver disease and primary sclerosing cholangitis are particularly at risk.[64] There are convincing data in animal and human studies that IS promotes malignancy.[65-67] Modulation of IS may alter the development of specific malignancies and the most widely recognized immunosuppressive agents in this category are mTORis which have anti-neoplastic effects.[68] In fact, mTOR inhibitors are approved for the treatment of several malignancies including neuroendocrine tumor (NET), advanced RCC, astrocytoma, pancreatic cancer and certain breast cancers. Because of their recognized anti-neoplastic effects, mTOR inhibitors have been extensively studied in the prevention of malignancies common in transplant recipients, namely skin cancer and HCC.

IS and HCC

There is some evidence suggesting that high levels of IS may be associated with higher rates of HCC recurrence. Longer courses of corticosteroids and higher levels of CNIs are associated with an increased risk of recurrence.[69,70] Results from retrospective studies suggest that mTOR inhibitors, primarily SRL, reduce HCC recurrence by approximately 50%[71-75] and several meta-analyses reiterate these findings.[76-78] However, these studies may have been biased by the selection of historical controls whose rate of recurrence was up to twofold higher. Based on these initial promising findings, a randomized controlled trial (RCT) was undertaken to study the effect of SRL on HCC recurrence.[79] Five hundred twenty-five liver transplant recipients with HCC were randomized at 4 to 8 weeks after transplant to SRL or non-SRL containing immunosuppressive regimens. Although there was no difference in recurrence-free or overall survival with SRL at study end (year 8), patients within Milan criteria at transplant (lower risk) had higher recurrence-free and overall survival at five years. Whether the same findings would be observed with EVL, which is approved in LT as opposed to SRL, is unknown. Currently, there is an ongoing RCT evaluating the effect of EVR on HCC recurrence in patients whose disease is over Milan criteria on explant.[44]

IS and Skin Cancer

Early observations reported significantly less squamous cell skin cancer in kidney transplant recipients on SRL. These observations led to 4 RCTs which reported an approximately 50 % reduction in the recurrence of nonmelanoma skin cancer in patients with previous skin lesions, mostly prior SCCa.[80-83] These results have been confirmed in meta-analyses.[84,85]

IS and Other Malignancies

Because posttransplant malignances are so problematic, pretransplant candidates are actively screened for malignancies and affected patients are often disqualified from transplantation. As a result, studies measuring the impact of IS on these other cancers require large cohorts of patients primarily drawn from registry analyses and meta-analyses of large registration trials.[63,84,86] These reports have shown no overall benefit of mTOR inhibitors in preventing other malignancies. Although there is a higher rate of prostate cancer in recipients on mTOR inhibitors, the clinical significance and

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explanation for this observation are not clear. Because EVR has demonstrated efficacy against NET and RCC, recipients with either of these tumors may benefit from EVR-based IS.[87,88]

IS and Malignancies

Recommendation 4.1

HCC: Beyond generally minimizing overall IS, the optimal IS strategy for minimizing the frequency and severity of recurrence of HCC, including the use of mTOR inhibitors, has not been determined

Skin cancers (SCCa): There is evidence that SRL reduces the risk of nonmelanoma skin cancer recurrence in kidney transplant patients. Whether the same effects occur with EVL, which is approved in LT, is not known but seems likely.

Non-HCC, non-SCCa malignancies: There is no direct evidence that mTOR inhibitors prevent other (nonskin, non-HCC) malignancies in liver transplant recipients, although patients with NET or RCC may benefit from EVL-based IS.

Quality/certainly of evidence: Moderate

Strength of recommendation: Conditional

IS in Pediatric Liver Transplant Recipients

Management of IS in the pediatric liver transplant (PLT) population presents several unique challenges compared to adults due to variations in growth and development, disease states, adherence, and risks of long-term exposure to IS. Differences in pediatric pharmacokinetics, route of administration, medication formulation, and sensitivity to medication toxicities further complicate management. Despite the lack of robust studies, consensus guidelines on the management of IS are needed for this population.[89,90]

Initial IS in PLT Recipients

Review of the centers enrolled in the Studies for Pediatric Liver Transplantation revealed that more than 90% use TAC, a CNI, as primary IS.[91] Tacrolimus is generally preferred over cyclosporine as the latter has increased nephrotoxicity, can cause hirsutism and gingival hyperplasia and may have less bioavailability related to the bilio-enteric anastomosis commonly used in children.[92,93] Most high-volume pediatric LT programs will start TAC on postoperative days 0 to 1 in combination with intravenous steroids. A third of international centers utilize induction therapy with either IL-2 receptor antagonists or antithymocyte globulin.[94] With induction therapy, TAC administration can be delayed until postoperative days 3 to 5, particularly if renal sparing is required due to perioperative renal dysfunction.[95] The use of induction has also been shown in small randomized European studies to reduce exposure to corticosteroids, which are associated with growth retardation, osteoporosis, hypertension, and diabetes.[96,97]

Maintenance IS in PLT Recipients

Calcineurin inhibitors provide highly effective maintenance IS after LT. Optimal TAC trough concentrations, based on international centers surveyed, are 10 to 12 ng/mL at 0 to 3 months, 6 to 8 ng/mL at 3 to 6 months, and approximately 5 ng/mL after 6 months.[98,99] Corticosteroids should be weaned within the first 12 months if appropriate.[97,100] Studies have shown that bone density is not always affected by the use of low doses.[101] Data on low-dose chronic prednisone for prevention of graft fibrosis is controversial. The goal of most centers is to reach TAC monotherapy at 1 year after pediatric LT.[58] Most centers surveyed have set strict goals and monitoring if IS is even more aggressively minimized.[97,102]

Therapeutic Drug Monitoring in Pediatric LT

Multiple factors affect trough concentrations in children including age, route of administration, medication formulation, graft function, medication interactions, and intestinal motility.[103] The current standard of care for therapeutic drug monitoring (TDM) of CNI therapy is to obtain trough concentrations at steady state (approximately 3-4 doses or 2-3 days). mTOR inhibitor TDM should also include trough concentrations at steady state, 5 to 7 days for SRL and 2 to 3 days for EVL. Weight-based doses of mycophenolate without TDM have produced excellent safety and efficacy. When TDM of MPA is performed, MPA-AUC is much more reliable than MPA troughs although difficult to perform in clinical practice.[98] Research in pharmacogenomics and immune assays will likely play an important role in the future of pediatric drug dosing and monitoring.[97]

Modification of IS Based on Primary Disease

More aggressive induction regimens after transplant may be warranted for patients at higher immunological risk, for example, ABO-incompatible organs, retransplantation for rejection, or positive crossmatch if even performed. In contrast, centers often avoid aggressive induction for patients who currently or previously had malignancy or those in acute liver failure.[104,105] Antiproliferative agents, such as mycophenolate or azathioprine in combination with a CNI, are used in some centers for patients with autoimmune liver disease or multi-visceral organ transplants. These agents may also facilitate more aggressive steroid or CNI reduction.[106] The use of mTOR inhibitors as putative antineoplastic agents has been described for patients with posttransplant lymphoproliferative disorders and other malignancies, such as hepatoblastoma.[107,108]

Optimization of Adherence

Adherence to IS regimens is always an issue of central importance in pediatric transplantation, requiring the child's and caregiver's cooperation and commitment.[109] Deliberate or unintentional nonadherence to medications can include errors in frequency, dose, or timing required. Adherence can be assessed by patient/family report, refill and pill count assessment, and the medication level variability index, an assessment of deviation from standard trough levels. Depression, posttraumatic stress disorder, child abuse, impulsivity and inattention, poor family functioning, and lack of social support may contribute to nonadherence and are best addressed by mental health and social service professionals.[110] Mode of delivery, palatability, cost, frequency, and timing of medication

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administration, male sex, nonwhite race/ethnicity, and the adolescent period can also play a role in nonadherence.[111,112]

Adherence should be continuously addressed with open communication encouraged. Physicians should ask patients in a nonjudgmental way about how often they miss doses, whether they experience side effects, and whether they understand the benefits of taking the medications. Awareness of modifiable psychosocial and financial risk factors might guide earlier interventions.[113-115] Instructions to maximize adherence should be coherent and practical. Simple dosing and cues to remind patients to refill and take medications can improve adherence. Other interventions including a token reinforcement system, incentives, teacher or nurse reminders, organized pillboxes, the use of Disease Management Assistance System, and personalized cell phone alarms/text messages has been shown to improve medication adherence and the incidence of rejection.[116,117]

IS in Pediatric Recipients

Recommendation 5.1

TAC is the CNI of choice for initial and maintenance IS after pediatric LT.

Antibody induction therapy: If antibody induction therapy is used immediately after LT, initiation of CNI therapy can be delayed, typically for up to 5 days. Antibody induction therapy followed by immediate CNI and antiproliferative agents may be warranted for patients at high immunological risk.

mTOR inhibitors may have a role in patients with a history of prior or current malignancy.

Maintenance IS should, when possible, be with TAC monotherapy without corticosteroids after the first year, weighing the risk of rejection.

Adherence to immunosuppressant therapy should be discussed openly at all points of contact with the patient and caregivers, and the use of technology to provide reminders should be considered in clinical practice.

Quality/certainly of evidence: Moderate
Strength of recommendation: Strong

IS in Patients With Renal Insufficiency

Definition and Assessment of Kidney Function in Liver Transplant Candidates and Recipients

Diagnosis and staging of acute kidney injury (AKI) in patients with liver disease should be guided by Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine (Scr) criteria.[118-120] Chronic kidney disease is defined as abnormalities of kidney structure (albuminuria, abnormal urine sediment, renal histology and/or renal ultrasonography) or decreased glomerular filtration rate (GFR) present for ≥ 3 months.[121] CKD should be classified by severity according to the Kidney Disease Outcomes Quality Initiatives (K/DOQI) (Table 5). While SCr values are used for initial evaluation of kidney function, they should be interpreted with caution in patients with transplant patients due to their tendency to overestimate GFR, especially in patients with malnutrition and fluid overload. Future research is needed to develop estimated GFR (eGFR) equations and biomarkers of renal injury in pre- and post-LT patients.

Assessing Renal Function

Recommendation 6.1

Before transplantation the MDRD-6 equation should be used to derive an eGFR.

After the third postoperative month MDRD-4, 6 or CKD-EPI equation should be used to derive an eGFR.

GFR-derived equations should be used cautiously for assessment of kidney function in this patient population, since they tend to overestimate GFR. Additional tests, such as measured GFR, should be considered when eGFR equations based on Scr are less accurate.

Quality/certainly of evidence: High
Strength of recommendation: Strong

Frequency and Impact of Renal Insufficiency Before and After LT

Kidney dysfunction occurs in 50% of outpatients with decompensated cirrhosis and 20% to 25% of hospitalized patients.[122] The incidence of mortality, infections and cirrhosis-specific complications increases with severity of AKI.[123] At the time of transplantation, 20% to 25% have eGFR less than 30 mL/min per 1.73 m^2.[124,125] The incidence of AKI after LT ranges from 17% to 94%.[126] Severe AKI and the need for renal replacement therapy have been associated with increased mortality posttransplant.[126,127] Causes of AKI are related to perioperative events, such as hemodynamic instability, ischemia-reperfusion syndrome,[128] primary dysfunction of the graft, the use of nephrotoxic medications and vena cava clamping.[129] After LT, the cumulative incidence of CKD ≥ stage 3 ranges from 36% to 57%[129-132]

TABLE 5.

From KDIGO clinical practice guideline for the evaluation and management of CKD[4]

GFR categories in CKD	GFR (mL/min per 1.73 m^2)
1	≥90
2	60-89
3a	45-59
3b	30-44
4	15-29
5	<15

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and ≥ stage 4, 5% to 25%.[133,134] Subjects with CKD ≥ stage 4 have an increased risk of death parallel to their kidney function.[134-136] The cumulative incidence of post-LTx CKD at 5 years in patients with model for end-stage liver disease < 20 and in those with model for end-stage liver disease > 20 at LT was 17% and 37% respectively.[136]

Immunosuppressive therapy with CNIs has been the major cause of CKD post-LT. Other additional factors related to lesions preexisting before transplant (membranoproliferative glomerulonephritis, diabetes mellitus, IgA nephropathy, acute tubular necrosis) or acquired in the peri-operative period. Kidney biopsies are uncommonly performed after LT and generally show lesions such as focal segmental glomerulosclerosis, thrombotic microangiopathy, or related to diabetes mellitus and the use of CNI therapy and hydroxyethylstarch.[137]

Initial IS in Patients With Renal Insufficiency

Early Postoperative Period

CNI-based regimens are associated with a decrease of renal function ranging from 13% to 33% according to whether the CNI is administered alone or in combination with antimetabolite or induction therapy.[130,138-144] In the 2 largest RCTs (The Respect and the Diamond studies), induction therapy with an anti-interleukine-2 receptor (anti IL-2R) in combination to MMF, with either an initial low dose of prolonged-released TAC or delayed introduction of TAC or prolonged-released TAC until day 5, was associated with significant improvement of renal function at 6 to 12 months.[138,145]

In the absence of combination therapy with MMF/MPA, the trough levels generally used in RCT during the first month posttransplant range from 8 to 15 ng/mL. In more recent trials using an induction therapy and/or combination with MMF, TAC trough levels during the first month range from 6 to 8 ng/mL with a similar rate of rejection.[138,141] In one study, the use of intravenous MMF followed by switch to oral form was associated with a low risk of rejection.[146] A meta-analysis of 2 RCTs[138,141] for renal impairment (n = 712) showed that reduced TAC trough concentrations (<10 ng/mL) within the first month after LTx were associated with less renal impairment at 1 year (RR = 0.51 [0.38-0.69] compared with conventional TAC trough levels (>10 ng/mL).[99]

Early trials with SRL use in the immediate postoperative period were associated with high incidence of hepatic arterial thrombosis, graft loss, and death and this lead to an FDA "black box" warning for its use in de novo LTx recipients.[147] Similarly Belatacept, a selective costimulation blocker, has not been approved for liver transplant recipients for similar reasons.[142] Despite the use in few centers of low dose mTORis to facilitate TAC reduction during the first week posttransplant, the benefit/risk of a very early initiation of mTORis is still under investigation.

Is in the peri-operative period to optimize renal function

Recommendation 6.2

Induction therapy (interleukin-2 receptor antibodies or short-term of antilymphocyte/thymocyte antibody preparations) combined with cortiosteroids and MMF/MPA and reduced dose or delayed initiation of CNIs is associated with superior renal function and less need for renal replacement therapy than early initiation and standard dosing of CNIs.

mTORis should be avoided in the first postoperative month.

Quality/certainly of evidence: Moderate
Strength of recommendation: Strong

Medium and Long-term Postoperative Periods

There is no strict definition but when taking into consideration immunosuppressive medication changes in trials, the medium-term could be considered between 1 and 6 months posttransplant and the long term, 1 year or longer. No data are available on the impact of modification of immunosuppressive regimens between 6 and 12 months posttransplant. Cautious screening, monitoring and treatment of risk factors that could affect renal function should be taken into account in addition to modification of the immunosuppressive regimen following KDIGO clinical guidelines.[121]

Randomized controlled trials that have used mTOR inhibitors for CNI sparing are shown in Tables 6 and 7. De novo use of SRL was associated with increased risk of hepatic arterial thrombosis, graft loss and infection without clear benefit on renal function. In the H2304 pivotal trial, a CNI sparing regimen that used EVL (EVL) with target trough levels of 3 to 8 ng/mL, introduced at 28 days posttransplant, and low dose TAC (trough levels below 5 ng/mL) was compared to a TAC arm with standard exposure. EVL plus reduced TAC showed significant improvement of renal function out to 3 years posttransplant, with very low risk of rejection, despite a higher discontinuation rate in the EVL plus reduced TAC arm.[148-150] Similar data were shown in the PROTECT multicenter RCT.[151,152]

Two main mTOR inhibitor studies with renal function as a primary endpoint tested a CNI-free strategy beyond 1 month and compared SRL + MMF[153] and EVL + MPA[154] to a control group treated with TAC + MMF/MPA. The use of mTORis plus MMF/MPA groups was associated with a beneficial effect on renal function but a moderate increase risk of rejection rate (10-12%). In the H2304 study, EVL (monotherapy) arm with TAC withdrawal at month 4 was terminated early because of increased risk of rejection (~20%).

TABLE 6.

Renal function by stage of kidney disease at various timepoints in 1508 liver transplant patients from 15 centers[13]

Stage of kidney disease	GFR (mL/min per 1.73 m^2)	Before LTx, %(n)	After LT [%(n)]		
			1 Month	12 Months	60 Months
1	≥90	54.3 (819)	15.9 (240)	7.7 (117)	5.7 (86)
2	60-89	34.9 (526)	36.4 (549)	41.1 (619)	36.6 (552)
3	30-59	9.5 (143)	43.9 (662)	48.7 (734)	52.7 (795)
4	15-29	1.1 (17)	3.5 (53)	2.4 (36)	3.7 (56)
5	<15 and HD	0.2 (3)	0.3 (4)	0.13 (2)	1.3 (19)

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TABLE 7.

Main reported RCTs on the use of mTOR inhibitors after LT according to early or late conversion for EVL and sirolimus respectively

First author (year)	Study arms	N	Time of conversion	Follow-up, mo	Mean (SD) eGFR mL/min per 1.73 m2	*P*	Rejection N (%)
EVL early conversion							
Levy G[61]	EVL 0.5 mg BID + CsA	30	Day 0	12	67.3 ± 22		32.1
Phase II (2006)	EVL 1 mg BID + CsA	28			53.7 ± 15	0.15	26.7
	EVL 2 mg BID + CsA	30			59.1 ± 13		25.8
	Placebo + Cyp	31			59 ± 21		40.0
Levy G[61]	EVL 0.5 mg BID + CsA	11	Day 0	36	73.9 ± 23		39.3
Phase II (2006)	EVL 1 mg BID + CsA	11			61.5 ± 30	0.44	30.0
	EVL 2 mg BID + CsA	6			69.9 ± 7		29.0
Masetti M[62] (2010)	EVL + CSA	52	D10	12	87.7 ± 26.1	<0.001	5.7%
	CsA ± MMF	26			59.9 ± 12.6		7.7%
De Simone P[34]	EVR + low TAC	245	D30 ± 5	12	80.9 ± 27.3	<0.001	3.7
H2304 (2012)	TAC control	243			70.3 ± 23.1		10.7
	TAC elimination	231			80.8 ± 28.8		19.9
Saliba F[35]	EVR + low TAC	245	D30 ± 5	24	74.7 ± 26.1	0.007	6.1
H2304 (2013)	TAC control	184			67.8 ± 21.0		13.3
	TAC elimination	163			77.5 ± 26.2		26.4
Fischer L[36]	EVR + low TAC	106	D30 ± 5	36	78.7 ± 25.7	<0.005	7.3[a]
H2304 (2015)	TAC control	125			63.5 ± 18.3		17.7[a]
	TAC elimination	51			85.5 ± 28.1		26.8[a]
Fisher L[37]	EVL + Cs	101	W4-W12	12	80.3 ± 26.4	0.021	17.7
Protect (2012)	CNI + Cs	102			72.1 ± 24.5		15.3
Sterneck M[38]	EVL + Cs	41	W4-W12	36	77.5 ± 23.4	0.059	19.5
Protect (2014)	CNI + Cs	40			67.9 ± 21,.8		2.5
Sterneck M[63]	EVL + Cs	41	W4-W12	59	77.0 ± 26.0	0.029	17.7
Protect (2016)	CNI + Cs	40			65.3 ± 21.1		15.3
Saliba F[40]	EVL + MPA + Cs	93	W4	6	95.8 ± 27.7	<0.001	10.0
Simcer (2017)	TAC + MPA + Cs	95			76.0 ± 24.5		2.2
EVL late conversion							
De Simone P[45]	EVR	72	M12-60	12	53.8 ± 12.8[b]	0.463	4.1
Rescue (2009)	CNI control	73	CrCl ≤ 60 mL		52.5 ± 12.7[b]		1.4
Sirolimus early conversion							
Arsani SK[32]	SIR + low TAC	111	<48 h	24	85.6[b]	0.1	26.4
Phase II (2014)	Tac control	111			77.8[b]		12.5
Teperman L[39]	SIR + MMF	148	W4-W12	12	78.6 ± 27.61[b]	<0.001	12.2
Spare the nephron (2013)	CNI + MMF	145			64.7 ± 28.02[b]		4.1
Sirolimus late conversion							
Watson CJ[65] (2007)	SIR + AZA	13	≥11 M	12	46.3 ± 11.1	<0.001	0
	CNI + AZA	14			31.8 ± 9.3		0
Shenoy S[64] (2007)	SIR + AZA/MMF	20	6 M-8Y	12	72 ± 27[b]	0.09	5
	CNI + AZA/MMF	20			58 ± 22[b]		5
Abdelmalek MF[44] *(2012)*	SRL	393	M6-144	12	−4.45 ± 1.12[c]	0.34	11.7
	CNI control	214			−3.07 ± 1.36[c]		6.1

[a] ITT analysis.
[b] Creatinine clearance.
[c] Expressed as mean difference of increased creatinine clearance at study endpoint to baseline.
CsA, cyclosporine A; Cs, corticosteroids; AZA, azathioprine; MPA, mycophenolic acid; D, day; M, month; Y, year.

However, if performed, trough levels of mTOR inhibitors should be 5 ng/mL or higher in CNI-free regimen.[149,154,155]

Optimizing renal function in the early postoperative period

Recommendation 6.3

Early institution at one month of EVL in combination with low dose TAC (≤5 ng/mL) results in a significantly better renal function than is achieved with standard dosing of TAC. This strategy is particularly beneficial in patients with

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CKD >/= stage 3 (eGFR <60 mL/min per 1.73 m^2).

Quality/certainly of evidence: High
Strength of recommendation: Strong

Long-term IS in Recipients With CKD (>1 year)

Several RCTs and uncontrolled studies that aimed to introduce MMF and either reduce CNI by at least 50% or withdraw CNI completely have been recently summarized.[126,137] Introduction of MMF/MPA and reduction of CNI was associated with a modest renal improvement and low risk of rejection rate (3.5%).[126,156] Introduction of MMF/MPA and withdrawal of CNI was associated with significant renal improvement (increase of eGFR by a mean of 8.3 mL/mn) but also with an increased risk of acute rejection (3-30%).[157] Therefore MMF/MPA monotherapy should be initiated with caution and on a case by case basis.

Outcomes after conversion to mTOR inhibitors beyond 1 year in patients with established CKD have been associated with variable outcomes (Table 6). The 2 main RCTs that compared either SRL beyond 6 months[158] or EVL beyond 1 year[159] to a CNI regimen failed to demonstrate significant improvement in renal function. Retrospective studies have reported a modest improvement with a low risk of rejection.[160,161] Overall, the likelihood of prolonged renal function stabilization or improvement after mTOR conversion has not been demonstrated. Therefore, mTOR inhibitors are not generally recommended after 1 to 2 years.

Optimizing renal function in the late (>1 year) postoperative period
Recommendation 6.4

CNI minimization should attempted in patients with CKD in the late postoperative period.
Late (≥1 yr) conversion to mTORis is of unclear effect on renal function, particularly in patients with CKD ≥ 3.

Quality/certainly of evidence: Moderate
Strength of recommendation: Conditional

Simultaneous Liver and Kidney Transplantation

In patients with simultaneous liver kidney transplantation (SLK), acute cellular rejection and AMR rates are reasonably low.[162-164] However, liver allografts may not be fully protective of the renal allograft, especially with preexisting MHC class II DSA.[165] In a series of 140 SLK recipients with long-term follow-up, borderline cellular, acute cellular, antibody-mediated, and chronic kidney rejection occurred in 11.4%, 6.4%, 1.4% and 0.7% patients, respectively.[162] Acute cellular and chronic liver rejections were diagnosed in 11.4% and 2.9% patients respectively. Taner et al also reported that SLK, when compared to kidney transplantation alone, is associated with reduced chronic cellular (OR : 0.13, 95%CI 0.06-0.27) and antibody-mediated alloimmune injury (OR : 0.11, 95% CI 0.03-0.32) in the kidney allograft.[166] In 56 SLK patients, Leca et al[167] analyzed positive flow cytometry crossmatches and/or the presence of high levels of donor-specific antibodies and found that sensitization did not have a significant negative impact on the survival.

Analysis of the Scientific Registry of Transplant Recipients database showed that less than 20% of patients undergoing SLK received lymphocyte-depleting agents as induction, even among sensitized recipients.[168] In other reports, high-risk recipients with panel-reactive antibody greater than 10% against HLA class I and class II or patients with a positive crossmatch received induction with either an anti IL-2 receptor antagonist or antithymoglobulin. Induction allowed avoidance of steroids and delayed introduction and minimization of CNI therapy.[169]

In a meta-analysis of RCT, the use of MMF was superior to AZA for improvement of graft survival and prevention of acute rejection after kidney transplantation.[170] The benefit of MMF in SLK transplantation is not known but likely extrapolated from the kidney alone literature. The use of mTORs to reduce the risk of reduction of cytomegalovirus (CMV) disease and de novo malignancies is common in kidney alone transplantation. No data are available on the use of mTORs in patients with SLK transplantation.[171-173]

Combined liver and kidney transplant recipients

Recommendation 6.5

Induction therapy, for example, with antithymocyte globulin, can be considered in highly sensitized patients (positive crossmatch, high DSA MFI levels) who undergo SLK to reduce the risk of acute rejection. Induction therapy may also be recommended in patients with delayed renal graft function to delay and/or minimize CNI use.
CNIs, ideally TAC, in combination with corticosteroids and mycophenolate, is recommended for maintenance IS in SLK recipients.
Quality/certainly of evidence: Moderate
Strength of recommendation: Conditional

Future Directions

Unfortunately, several classes of other agents that have had some success and development in non-LT, for example, costimulatory blockade agents, janus-activated kinase inhibitors, protein kinase C inhibitors, have failed to prove both safe and effective in early trials in liver recipients. Thus, the current and near future of IS in liver transplant recipients still relies on better optimization of current therapies that are effective but need to be personalized further, as described in this document. The real future may be in cell therapies, such as regulatory T cells and mesenchymal stem cells, that may allow for minimization or withdrawal of our existing agents, rather than develop and test new ones. This tolerogenic aspect of LT supports the further development of personalized therapies to ensure protection against both immune injury and IS toxicity.

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HAUTE AUTORITÉ DE SANTÉ

SYNTHESE DES RECOMMANDATIONS PROFESSIONNELLES

Suivi ambulatoire de l'adulte transplanté rénal au-delà de 3 mois après transplantation

Novembre 2007

OBJECTIF

Assurer une qualité optimale du suivi et de la prise en charge de l'adulte transplanté rénal dans le cadre du suivi partagé entre l'équipe de transplantation et le médecin et les autres professionnels de la santé correspondants amenés à suivre le patient au-delà du troisième mois après la transplantation rénale.

Définir dans ce but :

- l'organisation du suivi partagé en termes de consultations, d'éléments et d'outils de suivi
- les modalités de suivi

ORGANISATION DU SUIVI PARTAGE D'UN PATIENT TRANSPLANTE RENAL

Le projet thérapeutique individuel est à partager par l'ensemble des professionnels de la santé impliqués dans le suivi du patient. Le centre de transplantation a la responsabilité de l'organisation du suivi partagé. Il identifie en son sein pour chaque patient le médecin référent auquel les professionnels en charge du suivi ambulatoire pourront s'adresser. Il assume l'évaluation des activités de transplantation, en relation avec l'Agence de la biomédecine.

Au début du suivi partagé, il est recommandé que le centre de transplantation transmette au médecin correspondant (néphrologue, médecin traitant, etc.) les éléments suivants :

- les antécédents du patient, en particulier néphrologiques
- les caractéristiques de la transplantation
- les données du suivi des trois premiers mois
- les éléments cliniques et biologiques post-transplantation du patient au moment du début du suivi partagé
- les modalités de suivi du patient, les traitements en cours et, avant tout, le type et les modalités d'immunosuppression
- les coordonnées des personnes à contacter dans le centre de transplantation

Ultérieurement, le suivi partagé nécessite un échange des informations (cahier de suivi ou tout autre support) entre les différents intervenants, dont les modalités sont définies par le centre de transplantation.

CIRCONSTANCES JUSTIFIANT UN CONTACT AVEC LE CENTRE DE TRANSPLANTATION OU UN RECOURS A CELUI-CI

Il est recommandé au médecin correspondant de prendre contact avec le médecin référent du centre de transplantation, voire d'adresser le patient à ce centre, dans les circonstances ci-dessous.

Signes cliniques	• Fièvre non expliquée par une pathologie infectieuse banale ou non rapidement résolutive (48-72 h) • Tension ou douleur du transplant • Hématurie macroscopique • Oligurie, anurie
Signes biologiques	• Élévation de la créatininémie ≥ 20 % par rapport à sa valeur la plus basse après transplantation • Anémie, leucopénie ou thrombopénie significatives • Augmentation significative de la protéinurie
Changements thérapeutiques	• Événement justifiant une modification majeure du traitement immunosuppresseur (vomissements empêchant la prise, suspicion d'événement indésirable grave…) • Reprise d'un traitement par épuration extrarénale ou proposition de réinscription en liste d'attente • Inclusion du patient dans un essai thérapeutique
Autres circonstances	• Patient non observant (traitement, consultations) • Indication d'une ponction-biopsie rénale • Hospitalisation quelle qu'en soit la cause • Projet de grossesse ou grossesse • Diabète • Toute pathologie sévère, notamment cancéreuse • Décès du patient

CALENDRIER DE SUIVI

La répartition de ces consultations est à définir entre le centre de transplantation et le(s) médecin(s) correspondant(s) qui assure(nt) le suivi partagé.

Une consultation annuelle au minimum doit avoir lieu systématiquement dans le centre de transplantation.

Suivi	4 à 6 mois	7 à 12 mois	Au-delà de 1 an
Examen clinique / Anamnèse	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
Ionogramme sanguin : Na, K, Cl, HCO_3^-, protides	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
Bilan hépatique : ALAT, ASAT, gamma-GT	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
Surveillance de la fonction rénale et du transplant			
- Créatinémie et estimation du débit de filtration glomérulaire	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
- Protéinurie des 24 heures ou rapport protéinurie/créatininurie	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
- Bandelette urinaire, et ECBU si bandelette positive	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
- Ponction-biopsie rénale	En cas d'altération inexpliquée de la fonction rénale, ou d'apparition ou d'aggravation d'une protéinurie		
Suivi immunologique			
- Recherche d'anticorps anti-HLA (classes I et II)	1 x / an et en cas de rejet, de diminution de l'immunosuppression ou d'événement immunisant		
Surveillance des immunosuppresseurs			
- Effets indésirables des immunosuppresseurs	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
- Suivi pharmacologique :			
- Immunosuppresseurs à index thérapeutique étroit (ciclosporine, tacrolimus, sirolimus, évérolimus) : concentration sanguine	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
- Pour tout immunosuppresseur : concentration sanguine ou plasmatique	En cas d'adaptation posologique ou de risque d'interaction médicamenteuse		
- Observance thérapeutique	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
Prévention du risque cardio-vasculaire			
- Pression artérielle	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
- Anomalies glucidiques : glycémie (à jeun)	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
- Anomalies lipidiques : bilan lipidique	Tous les 6 mois		
- Obésité : indice de masse corporelle (IMC)	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
- Suivi cardiologique (ECG, échocardiographie)	1 x / an		
- *Homocystéinémie*	*Dosage non recommandé*		
- Fistule artério-veineuse : surveillance de la fonction ventriculaire par échocardiographie	1 x / an en cas de fistule artério-veineuse à débit élevé		
Suivi de la polyglobulie ou de l'anémie			
- Hémogramme	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
Autres suivis biologiques			
- Uricémie	1 x / an		
- Magnésémie	En cas de symptômes cliniques ou biologiques évocateurs		
Suivi carcinologique			
- Lymphomes :			
- Chez les patients à risque : signes cliniques	Au moins 1 x / 3 mois		1 x / an
- Chez les patients EBV séronégatifs receveurs d'un transplant EBV séropositif : réplication virale par PCR	Au moins 1 x / 3 mois ou en cas de signes cliniques		En cas de signes cliniques
- Cancers cutanés : examen cutanéo-muqueux complet :			
- Chez tous les patients	Avant la transplantation, sinon dans les 6 mois après	1 x / an	

Suivi	4 à 6 mois	7 à 12 mois	Au-delà de 1 an
- En cas d'antécédent de carcinome spinocellulaire ou de kératoacanthome	1 x / 3 mois		
- En présence d'autres lésions prémalignes ou malignes	1 x / 3 à 6 mois		
- Biopsie de lésion verruqueuse cutanée ou muqueuse	En cas de lésion à caractère inflammatoire		
- Cancers urologiques :			
- Tumeur rénale ou urothéliale : échographie du haut et bas appareil urinaire, tomodensitométrie, cystoscopie si examens précédents négatifs	En cas d'hématurie macroscopique isolée		
- Tumeur rénale : échographie des reins natifs	1 x / an		
- Cancers des autres organes solides (prostate, côlon, seins, col de l'utérus)	Mêmes règles que pour la population générale		
Suivi osseux			
- Ostéopénie et ostéoporose :			
- Mesure de la taille	1 x / an		
- Interrogatoire : recherche des facteurs de risque de fracture	1 x / an		
- Calcémie et phosphatémie	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
- Dosage sérique de vitamine 25(OH)D3 et parathormone	À 3 mois	À 12 mois	1 x / an
- Examen densitométrique osseux	Avant la transplantation et 6 mois après ; si ce dernier est normal, l'examen densitométrique est répété tous les 2 ans, sinon, ou en cas de corticothérapie à fortes doses, il est répété tous les ans		
- Ostéonécrose : IRM du bassin	Au moindre doute clinique		
Suivi infectieux			
- Infection et maladie à cytomégalovirus (CMV) :			
- Réplication virale	En cas de signes cliniques et biologiques (fièvre, atteinte d'organe, leucopénie, cytolyse hépatique, hypoxie, zona ou herpès extensif)		
- Statut sérologique du patient et réplication virale	En fonction des habitudes et selon les modalités définies par le centre de transplantation		
- *Infection à parvovirus B19*	*Pas de sérodiagnostic systématique*		
- Infection à papillomavirus : examen cutanéo-muqueux	1 x / an		
- Infection à herpes virus humain 8 (HHV8) : examen cutanéo-muqueux à la recherche d'une maladie de Kaposi chez les patients transplantés HHV8 séropositif	1 x / an		
- Infections à virus Herpes simplex (HSV) et virus varicelle zona (VZV) : traitement et prophylaxie idem population générale, sauf :			
- En cas de lésion extensive ou de localisation méningée d'une infection à HSV ou VZV	Traitement parentéral par aciclovir en urgence		
- Pour les patients transplantés séronégatifs pour le VZV et potentiellement à risque d'un contage	Prophylaxie par valaciclovir *per os* (hors AMM)		
- Pneumocystose : prophylaxie	Prophylaxie par cotrimoxazole, ou en cas d'intolérance, par aérosols de pentamidine, pendant au moins 6 mois		
- Toxoplasmose	Diagnostic à évoquer devant une fièvre inexpliquée ou des symptômes neurologiques centraux chez les patients séronégatifs pour le toxoplasme		
- Infection à BK virus (BKV) : recherche dans le sang ; si test positif : à confirmer dans les 4 semaines et/ou suivi d'un test quantitatif dans le sang	- Dépistage systématique pendant les deux premières années post-transplantation (modalités précises non définies) - En cas de lésions évocatrices sur biopsie rénale		

Suivi	4 à 6 mois	7 à 12 mois	Au-delà de 1 an
- Hépatite B (VHB) : - Dosage plasmatique des anticorps anti-HBs	1 x / 12 mois (rappel ou revaccination si Ac-anti-HBs < 10 mUI/ml)		
- Recherche des marqueurs de cirrhose ou de carcinome hépatocellulaire	En cas d'hépatite chronique liée au VHB		
- Hépatite C (VHC) : recherche d'une évolution vers une cirrhose ou un cancer, ainsi que les signes d'atteinte rénale et systémique liée au VHC	1 x / 12 mois		
- Infection par le VIH : - Recherche d'infection ano-génitale à papillomavirus	1 x / 6 mois		
- Tuberculose : - Radiographie du thorax - Test tuberculinique cutané, ou intradermoréaction à la tuberculine (IDR)	Post-transplantation si non fait avant la transplantation : - Test positif si lésion > 5 mm à la 48-72e heure - Si test négatif, refaire 2 semaines après		
- Bilan hépatique	En cas de prophylaxie par isoniazide (traitement de 6 ou 9 mois) : au moins 1 x / 2 semaines pendant les 2 premiers mois, puis 1 x / mois		
- Infections à pneumocoque	Vaccination antipneumococcique tous les 3 ans		
- Vaccinations	- Vaccins vivants atténués (polio oral, BCG, varicelle) contre-indiqués - Vaccins inactivés autorisés		
Suivi urologique et chirurgical			
- Bandelette urinaire, et ECBU si bandelette positive	1 x / 2 semaines	1 x / mois	1 x / 1 à 4 mois
- Recherche d'un obstacle de la voie urinaire ou d'une tumeur du transplant : échographie du transplant	1 x / an		
- Recherche d'une sténose de l'artère rénale ou d'une obstruction de la voie urinaire : échographie Doppler du transplant	En cas de dégradation de la fonction rénale ou d'apparition d'une hypertension artérielle		
- Recherche d'un reflux vésico-urétéral	En présence de pyélonéphrites aiguës récidivantes		
Suivi de la fonction sexuelle			
- Évaluation et prise en charge adaptées	À la demande du patient		
Contraception et grossesse			
- Contraception : - Contraception progestative	La plus souvent proposée		
- Contraception œstroprogestative	Peut être utilisée (mais rechercher systématiquement les facteurs de risque thromboembolique artériel et veineux)		
- Dispositifs intra-utérins	Généralement contre-indiqués		
- Grossesse : information et prise en charge adaptée	Suivi obstétrical effectué en collaboration avec le médecin en charge du suivi de la transplantation		
Suivi de la qualité de vie	Éducation thérapeutique avec suivi multidisciplinaire		

(Les examens surlignés sont pratiqués lors de chaque consultation du suivi systématique)

Ce document présente les points essentiels des recommandations professionnelles « Suivi ambulatoire de l'adulte transplanté rénal au-delà de 3 mois après transplantation » – Recommandations pour la pratique clinique – novembre 2007.

Ces recommandations et l'argumentaire scientifique sont consultables dans leur intégralité sur **www.has-sante.fr**

HAUTE AUTORITÉ DE SANTÉ

(Conférence de consensus organisée avec la participation de l'Anaes)

Conférence de consensus

Indications de la transplantation hépatique

19 et 20 janvier 2005
Lyon (Palais des congrès)

TEXTE DES RECOMMANDATIONS
(version courte)

PROMOTEURS

Association française de chirurgie hépato-biliaire et de transplantation hépatique
Association française pour l'étude du foie

COPROMOTEUR

Établissement français des greffes

ASSOCIÉS

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Académie de médecine
Association française de chirurgie
Association nationale de prévention en alcoologie et addictologie
Collège national universitaire des enseignants en addictologie
Société de pathologie infectieuse de langue française
Société de réanimation de langue française
Société française d'alcoologie
Société française d'anesthésie et de réanimation
Société française de chirurgie digestive
Société française de pathologie
Société francophone de transplantation
Société nationale française de gastro-entérologie
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D. SAMUEL, secrétaire : hépatologue, Villejuif

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H. BISMUTH : chirurgien, Villejuif
Y. CALMUS : hépatologue, Paris
O. CHAZOUILLÈRES : hépatologue, Paris
D. CHERQUI : chirurgien, Créteil
L. CHICHE : chirurgien, Caen
S. COHEN : médecin au département médical et scientifique, Établissement français des greffes, Paris
P. DOSQUET : méthodologie Anaes, Saint-Denis La Plaine
C. DUVOUX : hépatologue, Créteil
C. JACQUELINET : médecin au département médical et scientifique, Établissement français des greffes, Paris
B. LAUNOIS : chirurgien, Rennes
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M. MESSNER : hépatologue, Rennes
GP. PAGEAUX : hépatologue, Montpellier
C. PAINDAVOINE : méthodologie Anaes, Saint-Denis La Plaine
C. PARTENSKY : chirurgien, Lyon
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JURY

D. SICARD, président : médecin interniste, Paris

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A. BIOSSE DUPLAN : chargé de mission santé, UFC Que Choisir, Paris
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G. LE LOUP : médecin généraliste, Amiens
JL. NANCY : philosophe, Strasbourg
EA. PARIENTE : hépato-gastro-entérologue, Pau
C. PETITNICOLAS : journaliste, Paris
H. ROUSSET : médecin interniste, Pierre-Bénite
B. TIREL : directeur d'hôpital, professeur à l'École nationale de la santé publique, Rennes
G. TORPIER : association Transhépate, Lille

EXPERTS

R. ADAM : chirurgien, Villejuif
D. AZOULAY : chirurgien, Villejuif
M. BERENGUER : hépatologue, Valencia
H. BISMUTH : chirurgien, Villejuif
O. BOILLOT : chirurgien, Lyon
K. BOUDJEMA : chirurgien, Rennes
Y. CALMUS : hépatologue, Paris
C. CAMBY : directrice générale, Établissement français des greffes, Paris
L. CHICHE : chirurgien, Caen
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A. SAUVANET : chirurgien, Clichy
O. SOUBRANE : chirurgien, Paris
C. TRÉPO : hépatologue, Lyon
P. VINCENEUX : médecin interniste, Colombes

GROUPE BIBLIOGRAPHIQUE

T. ASSELAH : hépatologue, Clichy
PH. BERNARD : hépatologue, Bordeaux
M. BISMUTH : hépatologue, Montpellier
P. COMPAGNON : chirurgien, Rennes
T. DECAËNS : hépatologue, Paris
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QUESTIONS POSÉES

Question 1. Comment optimiser la prise en charge des patients transplantés pour hépatite virale ?

Question 2. Dans quels cas la cirrhose alcoolique est-elle une indication de transplantation hépatique ?

Question 3. Quels cancers du foie peut-on traiter par la transplantation hépatique ?

Question 4. Quelle est la place du donneur vivant en transplantation hépatique ?

Question 5. Quelles sont les extensions à l'indication de transplantation hépatique ?

ABRÉVIATIONS

CHC	carcinome hépato-cellulaire
HAART	*highly active anti-retroviral therapy*
IFN	interféron
IFNp	interféron pégylé
Ig anti-HBs	immunoglobulines anti-HBs
TH	transplantation hépatique
THDC	transplantation hépatique par donneur cadavérique
THDV	transplantation hépatique par donneur vivant
VHB	virus de l'hépatite B
VHC	virus de l'hépatite C
VIH	virus de l'immunodéficience humaine

Pour l'organisation de cette conférence de consensus, l'Association française de chirurgie hépato-biliaire et de transplantation hépatique et l'Association française pour l'étude du foie ont reçu une subvention éducationnelle de :

Établissement français des greffes, Fujisawa, Novartis, Roche, Ferring, Genzyme, GlaxoSmithKline, Johnsson & Johnsson, Schering-Plough

AVANT-PROPOS

Cette conférence a été organisée et s'est déroulée conformément aux règles méthodologiques préconisées par l'Agence nationale d'accréditation et d'évaluation en santé (Anaes).

Les conclusions et recommandations présentées dans ce document ont été rédigées par le jury de la conférence, en toute indépendance. Leur teneur n'engage en aucune manière la responsabilité de la Haute Autorité de santé.

Introduction

Après les phases de maturation de la décennie 84/93 et de perfectionnement de la décennie 93/03, cette conférence de consensus s'intéresse à l'élargissement des indications de la transplantation hépatique (TH), impliquant une réflexion sur son organisation générale et sur la place du donneur vivant.

Expansion et/ou optimisation des ressources existantes ?

Le contraste est fort en effet entre :

- la rareté persistante de l'offre d'organes prélevés et la demande croissante, favorisée par les progrès des dépistages, de l'imagerie et l'augmentation de la prévalence des maladies chroniques virales et/ou tumorales du foie ;
- l'approche thérapeutique selon des programmes prédéfinis et l'approche individuelle d'une personne malade ;
- la tentation constante d'élargissement des indications et la nécessité de se fonder sur des preuves de niveau élevé.

Face à la rareté des dons, le recours de plus en plus banalisé à cette thérapeutique justifie que les indications soient fondées sur :

- des connaissances épidémiologiques plus précises : le nombre de patients à transplanter et les besoins réels de greffons ne sont pas connus ;
- une meilleure expression des résultats de la TH, qui devrait permettre de mieux comparer les différentes indications et stratégies thérapeutiques quant à l'efficacité et aux données économiques ;
- une meilleure coordination des centres français entre eux et avec les centres européens, les difficultés actuelles d'utilisation des foies partagés (*split*) en étant l'illustration frappante ;
- une meilleure organisation afin de réduire les hétérogénéités de l'accès aux soins et les délais sur liste d'attente trop disparates ;
- un renforcement dans toutes les régions françaises d'une politique dynamique de prélèvements sur les personnes en état de mort encéphalique, qui devrait pallier les disparités régionales actuelles. Cette politique doit se fonder sur une motivation des équipes de prélèvement, une amélioration de l'information et l'éducation de la population générale vis-à-vis du don d'organes.

La réflexion sur les indications de la TH ne peut ignorer :

- l'incidence croissante attendue des hépatites C et des carcinomes hépato-cellulaires (CHC), essentiellement liée aux progrès des dépistages et des outils diagnostiques ;
- les effets néfastes attendus de la diminution nette des vaccinations contre l'hépatite B des enfants et nourrissons en France ;
- l'indifférence sociale et médicale vis-à-vis de la dépendance à l'alcool, ainsi que les carences de sa prise en charge psychologique, sociale et médicale encore trop connotée de jugements moralisateurs ;

- l'insuffisance des politiques de prévention primaire des risques infectieux liés à l'usage parentéral de drogues ;
- l'augmentation des besoins de TH liés au vieillissement de la population ;
- l'augmentation des hépatites B et C observées chez des personnes immigrées.

La prise en charge des maladies chroniques du foie liées à l'alcool ou aux hépatites, d'évolution longue et souvent fluctuante, nécessite une collaboration précoce entre médecins généralistes et hépatologues, de façon à mieux connaître les besoins et coordonner une prise en charge adaptée bien avant la discussion éventuelle du recours à la TH. Cette démarche conjointe autour du patient doit permettre une amélioration et une homogénéisation des résultats thérapeutiques.

Les conférences de consensus de 1983 et 1993, qui abordaient déjà ces questions, recommandaient aussi une évaluation des soins et des pratiques, en privilégiant l'existence de centres de TH peu nombreux et à activité importante, source d'amélioration de la compétence des équipes. Ces recommandations ont été peu suivies d'effet, en particulier en France où le nombre des centres, dont certains ont une activité faible, a augmenté.

Question 1.
Comment optimiser la prise en charge des patients transplantés pour hépatite virale ?

En cas d'hépatite virale, la TH doit être envisagée en cas d'hépatite fulminante, de cirrhose décompensée et/ou de CHC.

Les hépatites virales représentent actuellement 20 % des indications de TH en France, soit environ 200 à 250 TH par an (sans compter les TH pour CHC ; cf. *question 3*). En l'absence de données épidémiologiques précises, on ne sait cependant pas quel pourcentage des malades atteignant l'insuffisance hépatique terminale et/ou le CHC sont actuellement proposés à la TH.

Les progrès et limites de la TH pour hépatite virale dépendent aujourd'hui principalement de ceux des traitements antiviraux dans le contrôle de la virémie.

I. Quels traitements proposer pour réduire le risque de récidive de la maladie virale B sur le greffon ?

Le bien-fondé de l'indication de TH pour hépatite B n'est aujourd'hui plus discuté, et la survie à moyen et long terme est parmi les meilleures (75 % à 5 ans, 63 % à 10 ans dans le registre européen) (grade[1] C). Le principal problème est la prévention de la récidive sur le greffon, dont le risque (de l'ordre de 80 % avant l'instauration de mesures préventives) croît avec la charge virale prétransplantation.

I.1. Avant la transplantation

Il faut essayer de réduire la virémie au moins au-dessous de 10^5 copies/ml, en utilisant la lamivudine ou l'adéfovir (l'interféron est contre-indiqué en cas de cirrhose décompensée) chez tous les malades ayant une virémie détectable (avis d'experts). Si la virémie est = 10^5 copies/ml, la TH est à discuter.

La lamivudine ou l'adéfovir peuvent améliorer la fonction hépatique et faire revenir certains malades en dehors des indications de TH, mais avec un risque d'échappement par induction de résistance virale, plus important avec la lamivudine qu'avec l'adéfovir (grade C).

Le traitement antiviral B doit être discuté avant son institution avec une équipe de TH chez tout malade cirrhotique potentiellement transplantable. L'utilisation trop précoce de

[1] Voir *annexe 1*.

traitements antiviraux au long cours, et notamment de l'adéfovir, doit être limitée chez des malades ayant des lésions hépatiques peu sévères pour ne pas induire de résistance virale avant la TH.

I.2. Pendant et après la transplantation

L'administration systématique de fortes doses d'immunoglobulines anti-HBs (Ig anti-HBs) diminue le risque de récidive (définie par la réapparition de l'antigène HBs) (grade C). Ce risque reste cependant élevé chez les malades ayant une virémie $>10^5$ copies/ml avant la TH. Il justifie l'adjonction d'un antiviral ; cette prophylaxie est indiscutable en cas de réplication virale et à discuter en l'absence de réplication (grade C).

La thérapeutique par Ig anti-HBs et antiviraux ne doit pas être interrompue tout au long de la vie, sauf lorsqu'une séroconversion spontanée anti-HBs peut être suspectée quand le titre des anticorps anti-HBs ne diminue pas entre 2 injections d'Ig anti-HBs.

L'arrêt ou la diminution des Ig anti-HBs sous couvert de la poursuite d'un antiviral ne devrait pas être proposé en dehors d'essais randomisés de taille et de durée suffisantes, dont le jury recommande la mise en œuvre rapide en raison du coût très élevé du traitement à vie par les Ig anti-HBs.

II. Quels traitements proposer pour réduire le risque de récidive de la maladie virale C sur le greffon ?

Le bien-fondé de l'indication de la TH pour hépatite C n'est pas remis en cause par la dégradation aujourd'hui certaine des résultats à moyen et long terme, par rapport à un passé récent plus favorable à la TH dans cette indication. Ces résultats sont liés à :

- la réinfection plus ou moins précoce du greffon par le VHC ;
- l'évolution accélérée vers la cirrhose (10 à 40 % à 5 ans), avec ensuite un risque de décompensation très important (40 % 1 an après le diagnostic), avec une augmentation de la mortalité de 10 à 20 % après 5-10 ans de suivi par rapport aux autres indications de la TH. La survie à 5 ans dans le registre européen est de 62 % en cas de cirrhose et de 89 % en l'absence de cirrhose ;
- l'âge croissant des patients et des donneurs.

II.1. Avant la transplantation hépatique

L'éradication du VHC doit être recherchée, notamment chez les malades qui n'ont pas reçu antérieurement un traitement antiviral optimal.

La TH est indiquée même chez les sujets qui restent virémiques après antiviraux. Il n'y a pas de limite maximale du nombre de copies accepté pour faire une TH. Mais, les malades qui ont une charge virale $> 10^6$ copies/ml ont une survie du greffon et une survie propre inférieures comparativement à ceux qui ont une charge virale $< 10^6$ copies/ml. Il n'y a pas de limitation des indications de TH en fonction du génotype viral.

II.2. Après la transplantation hépatique

Une évaluation histologique régulière du foie est indispensable.

La période optimale du traitement de la récidive virale C semble se situer après 1 an (avis d'experts), lorsque apparaissent des lésions au moins égales à A1F1, prédictives d'un risque élevé d'évolution vers la cirrhose (grade C). Bien qu'une augmentation du risque de rejet n'ait pas été observée avec le traitement antiviral, il est prudent de ne pas trop diminuer l'immunosuppression pendant le traitement de la récidive virale C (avis d'experts).

Avec l'association d'interféron pégylée (IFNp) et de ribavirine (à posologie optimale tout en s'aidant de facteurs de croissance), une réponse virologique (virémie nulle par PCR) durable est observée chez environ un tiers des malades (grade C). Le traitement antiviral doit être poursuivi si possible au moins 6 mois après la négativation de la recherche du VHC par

PCR. S'il n'y a pas de négativation, le traitement est arrêté. Le bénéfice éventuel de l'adjonction d'amantadine n'a pas été évalué après la TH.

Une dégradation progressive des résultats de la TH pour hépatite virale C a été observés au cours des 3 dernières décennies, sans que la cause en soit connue avec certitude. Il est possible qu'elle soit liée à l'âge plus élevé des donneurs, à l'utilisation des donneurs vivants et au renforcement des traitements immunosuppresseurs. Il est actuellement recommandé d'éviter les bolus de corticoïdes, l'anti-OKT3, de ne diminuer que lentement la corticothérapie et d'utiliser un traitement immunosuppresseur limité à un anticalcineurine (avis d'experts).

La réduction des cofacteurs aggravant l'évolution cirrhogène (consommation d'alcool, de tabac, syndrome métabolique) est toujours nécessaire (avis d'experts).

III. Peut-on proposer la transplantation hépatique chez les malades co-infectés par le VIH ?

Les maladies virales B et C du foie sont devenues la première cause de décès chez les malades infectés par le VIH. La prévention, le dépistage et le traitement des hépatites virales B et C sont impératifs chez tous ces malades.

III.1. Traitement des co-infections

L'évolution lésionnelle de l'hépatite B peut être ralentie par des antiviraux anti-VHB (interféron, lamivudine, adéfovir, ténofovir), avec des chances d'obtenir une réponse virale durable plus faibles que chez les malades non co-infectés. L'utilisation des antiviraux anti-VHB doit être raisonnée et discutée entre infectiologues et hépatologues, pour ne pas, en fonction des stades d'évolution des 2 infections, hypothéquer leur avenir.

La guérison de l'hépatite C peut être obtenue avec une bithérapie associant INFp et ribavirine chez environ 1/3 des malades traités (grade B). L'épidémiologie actuelle comme l'évolution cirrhogène des hépatites virales, nettement plus rapide chez les malades infectés par le VIH (grade C), font du recours éventuel à la TH une question majeure chez le sujet co-infecté.

III.2. Transplantation hépatique chez les malades co-infectés

On ne dispose actuellement que de courtes séries de TH totalisant environ 200 malades. Les TH ont été essentiellement réalisées pour cirrhose décompensée, chez des malades très sélectionnés, dont l'infection VIH était contrôlée par la HAART. Le recul est faible, généralement 2-3 ans.

En cas d'hépatite B ou C, la survie à court terme en cas de co-infection n'apparaît pas être plus mauvaise qu'en d'absence de co-infection VIH (grade C).

En cas de co-infection VIH-VHC, la charge virale C et surtout la vitesse de progression de la fibrose sont très supérieures à celles observées chez les malades non co-infectés. Le traitement de l'hépatite C est plus difficile et a une efficacité plus limitée qu'en l'absence de co-infection. Des complications spécifiques (cytopathies mitochondriales notamment) doivent être prévenues et dépistées. Le traitement immunosuppresseur doit être très rigoureusement adapté en raison d'interactions médicamenteuses majeures avec les antiprotéases.

En résumé, la TH chez des malades infectés par le VIH apparaît faisable (grade C) chez des malades hautement sélectionnés ayant notamment une infection VIH stable, dans les mêmes indications que chez les malades indemnes d'infection VIH, aux conditions d'une organisation particulière des services transplanteurs, d'un accompagnement renforcé et d'une évaluation prospective rigoureuse (avis d'experts). La lourdeur particulière du traitement, impliquant une observance plus difficile, et du suivi laisse présager une réinsertion sociale encore plus difficile que chez les malades non co-infectés.

Question 2.
Dans quels cas la cirrhose alcoolique est-elle une indication de transplantation hépatique ?

La cirrhose alcoolique est en France la première cause de TH (270 sur 850 TH réalisées en 2003). La survie selon le registre européen est de 83 % à 1 an, 72 % à 5 ans, 59 % à 10 ans.

Malgré ces résultats, une controverse persiste sur l'indication de la TH dans la cirrhose alcoolique du fait du risque de récidive de l'intoxication alcoolique après la greffe et à propos de la durée d'abstinence avant la greffe. Cependant, les recommandations existantes vont toutes dans le même sens :

- la cirrhose alcoolique est une indication de la TH au même titre que les autres cirrhoses ;
- la prise en charge de la maladie alcoolique doit être assurée par une équipe pluridisciplinaire.

En dehors du CHC, l'indication de la TH reste limitée aux cirrhoses compliquées (classe C de Child-Pugh) (grade B). Elle n'est pas recommandée en cas de classe B de Child-Pugh.

L'inscription des malades en liste d'attente de TH est possible à 2 conditions :

- un bilan prégreffe particulièrement attentif à la recherche des lésions liées à une toxicité alcoolique, voire alcoolo-tabagique, extra-hépatique, tels les cancers et états pré-cancéreux ORL, bronchiques, œsophagiens, une pathologie cardiovasculaire et respiratoire ;
- une prise en charge alcoologique aussi précoce que possible par une équipe spécialisée. Celle-ci peut aider au sevrage alcoolique, qui peut permettre une amélioration fonctionnelle hépatique suffisante pour faire sortir le malade des critères d'indication d'une TH.

Le sevrage est indispensable et la période prégreffe doit être utilisée pour forger la motivation à l'arrêt de l'alcool. Cet arrêt engage le patient dans une démarche de soins alcoologiques susceptible de le protéger de la rechute en post-greffe. La durée de 6 mois d'abstinence avant TH (grade B) ne doit plus être une règle intangible et ne doit pas être considérée comme une condition à elle seule de l'accès à la TH.

La prévention de la rechute de l'alcoolisme avant et après la TH doit être une préoccupation constante pluridisciplinaire, qui a été trop longtemps négligée. Il existe des éléments d'orientation prédictifs d'une rechute comme la précocité du début de l'intoxication, des antécédents familiaux et des conditions socio-économiques difficiles (grade B). Un épisode de réalcoolisation ne préjuge pas d'une rechute : l'intervention d'un psychiatre, d'un psychologue ou d'un addictologue est recommandée pour évaluer cet événement et éviter la rechute.

La comorbidité hépatite C-alcool (30-40 % des malades alcooliques) ne constitue pas une contre-indication de la TH. La TH associe alors les contraintes de soins et de suivi liées à la fois au VHC et à l'intoxication alcoolique. Une prise en charge alcoologique est recommandée, d'autant plus que l'alcool est un facteur reconnu d'évolution cirrhogène des hépatites C.

La consommation concomitante d'alcool et de tabac nécessite une attention particulière car les patients abstinents en matière d'alcool peuvent majorer leur consommation tabagique. Il est alors recommandé de proposer une substitution nicotinique.

En résumé :

- la cirrhose alcoolique est une bonne indication de TH ;

- un encadrement alcoologique systématique est fortement recommandé, car la période avant la greffe doit permettre la mise en place d'un projet de soins alcoologique ;
- la période post-greffe de cirrhose alcoolique doit, dans le cadre d'une alliance thérapeutique, mobiliser l'attention de l'ensemble de l'équipe de suivi au même titre que les autres formes de cirrhoses. La participation à cette période d'une équipe alcoologique est fortement recommandée ;
- le regard de la société et des professionnels de santé sur la cirrhose alcoolique doit changer. Le patient cirrhotique alcoolique candidat à la TH doit être considéré comme souffrant d'une double pathologie, à la fois alcoolique et hépatique, et devrait en conséquence bénéficier systématiquement d'une double prise en charge spécialisée.

Question 3.
Quels cancers du foie peut-on traiter par transplantation hépatique ?

I. Le carcinome hépatocellulaire

Le CHC représente 15 % des indications de TH en Europe. La TH est contre-indiquée en cas de métastases, d'adénopathies, d'envahissement vasculaire.

La réalisation d'une biopsie hépatique n'est pas contre-indiquée chez les candidats à la TH sous réserve de protection du trajet pariétal et d'une sélection attentive des indications (avis d'experts) :

- tumeur unique de petite taille : sous réserve de difficulté d'interprétation liée à la taille de l'échantillon tumoral et aux variations inter-observateurs, elle peut préciser la nature d'un petit nodule isolé et diminuer ainsi les faux positifs ;
- tumeur plus volumineuse : elle permet de rechercher des critères (mauvaise différenciation, invasion microvasculaire) qui pourraient être de mauvais pronostic. Ils n'ont de valeur que s'ils sont présents et amènent alors certaines équipes à discuter l'indication de la TH, mais cette attitude est controversée. Le jury suggère des études spécifiques sur cette question.

Les CHC formés d'une tumeur unique de moins de 5 centimètres ou de 2 à 3 nodules de moins de 3 cm (« critères de Milan ») représentent l'indication la mieux validée de TH (grade B).

Bien que la TH soit le traitement le plus efficace à long terme, le CHC unique de moins de 2 cm (TNM1) ne doit plus être considéré comme une indication systématique de TH en dehors de la cirrhose Child-Pugh C (avis d'experts). Les raisons sont l'existence d'alternatives thérapeutiques (notamment la TH de rattrapage immédiat), le risque de faux positifs, la rareté des greffons contrastant avec l'augmentation prévisible de cette situation.

En France, 28 % des CHC transplantés dépassent les « critères de Milan ». Les tumeurs définies par les critères UCSF (un nodule < 6,5 cm de diamètre, ou plusieurs nodules dont le plus volumineux est < 4,5 cm et dont la somme des diamètres n'excède pas 8 cm) auraient une survie de 50 % à 5 ans. Le jury recommande une évaluation pour confirmer cette survie et préciser les facteurs pronostiques, notamment histologiques et biologiques. Il est essentiel, compte tenu de la pénurie actuelle de greffons, de faire de telles TH uniquement dans le cadre d'études.

Bien qu'un traitement d'attente soit habituellement prescrit, aucun n'a fait la preuve de son efficacité réelle. Il est indispensable de les évaluer.

II. Autres cancers

La place de la TH dans la prise en charge des tumeurs malignes autres que le CHC est incertaine en raison de la multiplicité des étiologies, de l'hétérogénéité des stades de prise en charge et de l'insuffisance méthodologique des données de la littérature.

Une survie d'au moins 50 % à 5 ans autorise la TH de rares patients porteurs d'hépatoblastome, d'hémangio-endothéliome épithélioïde ou de métastases de tumeur carcinoïde (grade C).

Les mauvais résultats des TH pour métastases de cancer colorectal, tumeur endocrine pancréatique, cholangiocarcinome périphérique contre-indiquent ces indications. Soit ces tumeurs sont résécables et ne relèvent pas de la TH, soit elles sont inextirpables par hépatéctomie partielle, donc évoluées, et la TH a de mauvais résultats.

Le cholangiocarcinome hilaire semble faire parti de ce dernier groupe : le taux élevé de récidive et la fréquence des complications septiques, associé à la pénurie de greffons a contre-indiqué cette indication pour la majorité des équipes. Une publication récente de la Mayo Clinic repose la question ; mais elle a concerné un groupe hypersélectionné (2 % des patients), a associé un traitement adjuvant lourd et n'a porté que sur 28 cas.

Question 4.
Quelle est la place du donneur vivant en transplantation hépatique ?

I. La transplantation hépatique à partir d'un donneur vivant

La TH à partir d'un donneur vivant (THDV) s'est développée ces dernières années pour répondre à des exigences culturelles (impossibilité de prélèvement dans certains pays liée à l'image du corps) ou à des exigences contextuelles (rareté et délai prolongé d'accès aux greffons incompatible avec la survie de certains patients).

?En Europe, les THDV représentaient 2,7 % des greffes et en France 5 % en 2003. Globalement, un centre sur 2 est concerné et en France 12 sur 24, avec ces 3 dernières années, 40 greffes annuelles en moyenne au plan national.

Du fait de l'hétérogénéité des situations, de l'amélioration des techniques et de la progression des expériences, il n'est pas possible d'avoir un avis définitif sur les résultats de la THDV, mais l'intérêt de cette procédure est acquis avec des survies qui semblent comparables aux TH à partir de donneurs cadavériques (THDC) chez l'adulte et probablement meilleures chez l'enfant.

Il n'y a pas d'indications spécifiques à la THDV et le jury, préoccupé par une mortalité du donneur de 0,27 % en Europe (0,46 % en cas de prélèvement de foie droit qui est celui utilisé pour la TH chez l'adulte) et une morbidité élevée (27 %), suggère que cette activité soit limitée à certains centres ayant une expérience suffisante et régulière.

?Les contre-indications, en dehors de celles communes à la THDC, sont représentées essentiellement par un volume hépatique fonctionnel inadéquat, à la fois pour le donneur et le receveur, et par certaines particularités anatomiques.

Chez le donneur, on doit s'assurer de l'intégrité hépatique (absence de fibrose et de stéatose), de l'absence de comorbidités, de fragilité psychologique et de troubles psychiatriques invalidants. Ceci impose un bilan très rigoureux sur le plan médical et des entretiens successifs permettant une information complète et bien comprise, de façon à obtenir un consentement éclairé et en toute liberté, dans le respect des dispositions prévues par la loi relative à la bioéthique du 6 août 2004.

?Le jury insiste sur l'obligation absolue de prévoir pour le donneur un suivi médical, psychologique et social à long terme. La tenue d'un registre par l'Établissement français des greffes, prévue par la loi, est conforme à ce souhait et permettra une estimation à long terme des risques encourus, information qui n'est pas disponible à ce jour. Pour des cas exceptionnels de complications chez le donneur, la solidarité nationale doit être mobilisée.

?La THDV est une solution de recours qui ne doit pas conduire, dans l'état actuel des connaissances, à un élargissement des indications, même si le jury a bien perçu l'extension souhaitée par certains dans le cadre du CHC.

?La THDV est une procédure qui devrait se stabiliser, si l'on se donne les moyens en personnel et en matériel de faire appel à d'autres techniques à développer ou à initier.

Ainsi, deux modalités (*split* et domino), pour lesquelles le jury regrette que l'on ne puisse à ce jour avoir une évaluation suffisante, nécessitent une meilleure coordination et coopération entre les centres avec une rationalisation des moyens et devraient être étendues. La technique de prélèvement sur cœur arrêté, à l'instar d'autres pays européens, doit être rapidement initiée en France.

Enfin, le jury souhaite insister sur le point le plus important de sa réflexion, à savoir la nécessité de se donner les moyens d'une information et d'une éducation du public et des médecins, ciblées sur l'utilisation optimale des possibilités de prélèvements cadavériques, qui restent manifestement sous-exploitées.

II. Quels sont les moyens chirurgicaux autres que le donneur vivant pour pallier le manque de greffons hépatiques ?

?La *bipartition du foie (split)* nécessite des équipes chirurgicales très entraînées et maîtrisant parfaitement cette technique. Elle nécessite encore plus une organisation sophistiquée autour de l'acte opératoire et la collaboration de plusieurs équipes habituées à travailler ensemble. Le receveur du foie gauche, quand il ne s'agit pas d'un enfant, doit être soigneusement sélectionné, particulièrement en fonction du poids.

?La transpl*antation séquentielle (*ou *domino)* est représentée actuellement par la polyneuropathie amyloïde familiale, où la TH est devenue le traitement de choix, et pour laquelle le foie explanté ne provoque pas de symptomatologie pendant au moins 10 ans. Une surveillance attentive est requise, car le recul à moyen et long terme est insuffisant.

?L'utilisation de *foies marginaux* ne peut être acceptée en routine, mais peut rendre des services chez des receveurs en danger immédiat.

?Le *prélèvement sur donneur à cœur arrêté* n'est pas autorisé actuellement en France. Il nécessite des procédures contraignantes et des équipements importants rapidement mobilisables. Malgré ces difficultés, le jury recommande que cette procédure soit initiée rapidement en France.

Question 5.
Quelles sont les extensions à l'indication de transplantation hépatique ?

I. Comment tenir compte de l'âge en transplantation hépatique ?

Donneurs et receveurs ont vieilli. Ainsi en 2003, 15 % des malades greffés avaient plus de 60 ans, 4 % plus de 65 ans et ils étaient principalement transplantés pour cirrhose (69 %) et cancer (20 %). L'âge des malades arrivés au stade de la TH pour hépatite C est en augmentation constante.

?L'utilisation de greffons provenant de donneurs de plus de 60 ans ne semble pas délétère, sauf peut-être en cas de TH pour hépatite C.

?En l'absence de comorbidité affirmée après un bilan particulièrement développé (notamment aux plans cardiovasculaire et oncologique), il est légitime d'accepter de transplanter jusqu'à l'âge de 70 ans (à l'exception des malades hospitalisés en unité de soins intensifs). L'augmentation de la morbidité post-greffe, liée principalement au traitement immunosuppresseur, explique probablement la surmortalité d'environ 10 % par rapport aux malades de moins de 60 ans observée dans la décennie suivant la TH.

?Les indications ne doivent pas différer de celles admises pour les malades plus jeunes.

II. Retransplantation hépatique

Dix pour cent des TH en France sont de retransplantations.

?Celles-ci s'imposent en cas de non-fonctionnement ou de dysfonctionnement du greffon en super urgence ou en urgence. Globalement le résultat est inférieur de 20 % à celui d'une TH primaire.

? Les TH tardives ou « électives », généralement pour récidive de la maladie initiale, imposent aux équipes un choix entre transplantation primaire et retransplantation, ce qui justifie de définir, de manière souple, les contre-indications à la retransplantation.

La décision de retransplantation repose d'abord sur l'analyse détaillée des souhaits du patient lui-même et doit intégrer l'âge et les possibilités thérapeutiques sur le ou les facteurs étiologiques. C'est particulièrement le cas pour l'infection du greffon par le virus de l'hépatite C, où les résultats des retransplantations sont incomplètement connus et où les indications doivent être analysées au cas par cas.

III. Indications des greffes multi-organes

Elles représentent 5% des THDC, essentiellement greffes foie-rein, et font l'objet d'une priorité régionale attribuée aux greffes multiples.

La question de l'effet protecteur de la TH sur la greffe rénale sur le plan immunitaire reste une constatation dont l'explication n'est pas claire.

Si l'indication de greffe foie-rein est incontestable dans une affection comme l'hyperoxalurie primitive de type I ou la polykystose hépato-rénale, la question se pose des doubles greffes dans les cirrhoses. L'indication dans le cas de la cirrhose alcoolique associée à une néphropathie chronique pré-terminale n'est pas clairement définie. Dans le cadre des cirrhoses virales, la survie globale, lorsqu'elle est comparée à la THDC isolée, ne semble pas différente.

Le syndrome hépato-rénal n'est pas une indication du fait de la réversibilité de l'atteinte rénale après TH isolée.

La question a été débattue du caractère prioritaire accordé aux receveurs des doubles greffes. Son caractère systématique a été critiqué au profit d'une discussion au cas par cas.

Quant aux greffes foie-cœur, foie-poumon ou foie-intestin, le manque de données nécessaires pour évaluer correctement leurs indications nécessite une collaboration internationale et leur soumission systématique à un registre exhaustif avant de proposer des recommandations.

Conclusion

La rareté des dons d'organes et la croissance des indications ne doivent pas orienter exclusivement la recherche vers les solutions qui substituent à la THDC des techniques toujours plus complexes ou contraignantes.

L'humanité constitue désormais, grâce aux (ou à cause) des propositions médico-chirurgicales de plus en plus audacieuses, un réseau interactif permanent ; celui-ci doit encourager l'inscription des dons provenant de personnes en état de mort cérébrale dans l'univers culturel quotidien. Il ne s'agit pas seulement de générosité et de compassion, mais d'un véritable enjeu de solidarité écologique interhumaine.

La pénurie, mieux nommée rareté des organes transplantables, n'est pas une situation à laquelle on doive se résigner. Des exemples français et européens montrent l'efficacité d'initiatives régionales ou nationales pour maximiser les dons.

À ce prix seulement l'élargissement des indications pourra être discuté. Le recours au donneur vivant, au donneur à cœur arrêté, au partage des foies pourra certes améliorer la situation, mais ne remplacera jamais le pool des greffons disponibles non exploités. Un effort majeur doit être déployé dans ce domaine, sans hésiter à affronter les obstacles culturels contemporains, au premier rang desquels figure ce paradoxe d'une société individualiste simultanément demandeuse de réparation et hostile au prélèvement du corps.

Annexe 1. Échelle de gradation des recommandations utilisées par l'Anaes pour les études thérapeutiques.

Tableau. Grade des recommandations.

Niveau de preuve scientifique fourni par la littérature (études thérapeutiques)	Grade des recommandations
Niveau 1 - Essais comparatifs randomisés de forte puissance - Méta-analyse d'essais comparatifs randomisés - Analyse de décision basée sur des études bien menées	**A** Preuve scientifique établie
Niveau 2 - Essais comparatifs randomisés de faible puissance - Études comparatives non randomisées bien menées - Études de cohorte	**B** Présomption scientifique
Niveau 3 - Études cas-témoins	**C**
Niveau 4 - Études comparatives comportant des biais importants - Études rétrospectives - Séries de cas	Faible niveau de preuve

Les versions longue et courte des recommandations sont disponibles sur demande écrite auprès de :
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