11th Banff Conference on Allograft Pathology - An Update

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Enghien les Bains
Hôtel du Lac

The Banff Conferences on Allograft Pathology

Date	Venue	Comments
1991	Banff	Kidney only
1993	Banff	Kidney only
1995	Banff	First liver session. Acute rejection - diagnosis & grading. **Banff consensus paper – Hepatology 1997.**
1997	Banff	Chronic rejection – diagnosis & staging.
1999	Banff	Chronic rejection – diagnosis & staging. **Banff consensus paper – Hepatology 2001.**
2001	Banff	Late biopsies – role in identifying graft dysfunction
2003	Aberdeen	Late biopsies - role in identifying graft dysfunction
2005	Edmonton	Late biopsies - role in identifying graft dysfunction **Banff consensus paper – Hepatology 2006.**
2007	La Coruna	Late biopsies – role in identifying tolerance.
2009	Banff	Late biopsies – role in identifying tolerance.
2011	Paris	Late biopsies – role in identifying tolerance. **Banff consensus paper – in preparation**

Importance of Liver Biopsy Findings in Immunosuppression Management

Biopsy Monitoring and Working Criteria for patients with Spontaneous Operational Tolerance (SOT)

by

The Banff Working Group on Liver Allograft Pathology

(first draft produced in July 2009)

Liver Allograft Tolerance
(Demetris 2009, Sanchez-Fueyo 2010)

1. **True tolerance**
   - Immune non-reactivity maintained indefinitely without immunosuppression
   - Confined to experimental models

2. **Operational tolerance**
   - Maintenance of stable graft function without features of rejection and without need for continued immunosuppression
   - Aim of immunosuppression withdrawal studies:
     - Patients with stable graft function (>2 years post-transplant)
     - Overall success rate approximately 10-20%, better results in children

3. **Prope tolerance**
   - Maintenance of stable graft function with minimal immunosuppression

11th Banff Conference on Allograft Pathology
Liver Sessions

- 11 speakers, 2 afternoons
- 35 minutes per talk

End of 2nd afternoon

- 4:00 - 6:00 : Discussion of Consensus Paper

Banff 2011 - Liver Sessions

1. Histological and clinical studies of late post-transplant biopsies
   - 5 talks

2. Antibody-mediated rejection
   - 4 talks

3. Molecular studies
   - 2 talks (+ further talks in plenary sessions)

Studies of Late Post-Transplant Biopsies
Questions to be Addressed:

1. What are “acceptable changes” in late biopsies from patients with stable graft function?
2. Can these changes be used to guide immunosuppression, including identifying patients in whom immunosuppression can be withdrawn to achieve “operational tolerance”?
3. What is the role of liver biopsy in monitoring graft function after immunosuppression withdrawal?
4. How should biopsies be studied
   - Conventional histology
   - Multiplex immune imaging - simultaneous detection of multiple lymphoid subsets
   - Molecular techniques

Histopathology of long-surviving adult liver allograft recipients from a Protocol Biopsy Center

Mylene Sebagh, Paul Brousse Hospital, Paris, France

Role of Protocol 20 Year biopsies

- 91/544 patients transplanted 1984-1990 had a 20 year biopsy (protocol biopsies also at 1,2,5,10,15 years)
  - Main indications for transplantation were HBV and HCV
- 82/91 (90%) biopsies were abnormal
- Increased frequency of abnormal graft histology with time
  - 65% at 10 years, 80% at 15 years, 90% at 20 years

Histological Findings in 20 year Biopsies

Diagnosis	Number	Comments
Chronic viral hepatitis	42	Fibrosis stage : F1 - 9, F2-17, F3 – 6, F4 – 10 Inflammatory activity mostly mild
Chronic rejection	21	Mean ductopenia 37%
"Structural abnormalities"	18	NRH - 9, plate disarray – 6, peliosis -1, VOD -1
Fatty liver disease	10	Steatosis – 1, steatohepatitis/fibrosis - 9
"Idiopathic" post-transplant hepatitis	8	
Recurrent disease	7	PBC -3, PSC – 2, AIH -1
"AIH-like" hepatitis	4	

Prevalence of combined lesions & structural changes increases with time

Clinical Correlations

1. LFTs
   - Abnormal graft histology in 27/33 (82%) with normal LFTs
   - Abnormal graft histology in 55/58 (95%) with abnormal LFTs

2. Non-invasive methods for assessing graft fibrosis (Fibrotest, Fibroscan)
   - High discordance rate with METAVIR stage (80% for both)
   - Good predictive value for significant fibrosis

3. Changes in immunosuppression
   - 32/91 had change in immunosuppression (13 decrease, 10 increase, 9 switch)
   - ? Not influenced by LFTs or graft histology

Long-Term Biopsy Findings in Paediatric Liver Allograft Recipients

Similar findings but conflicting explanations from different centres

Stefan Hübscher, Birmingham, U.K.

http://cybernephrology.ualberta.ca/banff/2011/programme.htm

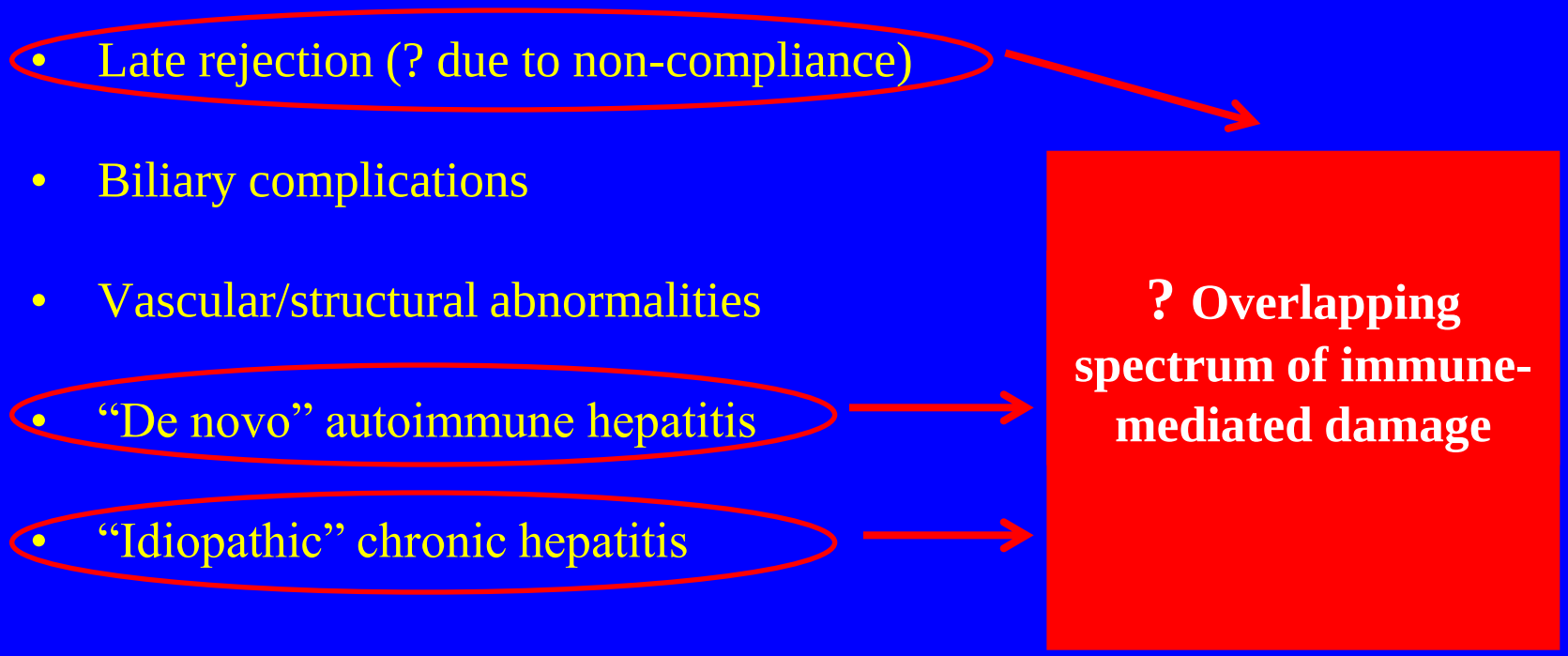
Late Post-Transplant Biopsies
Children versus Adults

Less Common In Children

- Recurrent Disease (< 1%)

More Common in Children

- Late rejection (? due to non-compliance)
- Biliary complications
- Vascular/structural abnormalities
- "De novo" autoimmune hepatitis
- "Idiopathic" chronic hepatitis



Histological Findings in Paediatric Allograft Biopsies > 1 year Post-Transplant (Protocol Biopsies, > 50% have normal LFTs)

Centre	Number biopsied	Time of biopsy	Abnormal histology	Main histological findings
Paris (Fouquet 2005)	67	>10 yrs	73%	Chronic rejection (42%), centrilobular fibrosis (22%), biliary cirrhosis (4%), other (4%)
Birmingham (Evans 2006)	113,135,64	1,5,10 yrs	69% (at 10 years)	Chronic hepatitis +/- fibrosis (64%), biliary fibrosis (2%), recurrent PSC (2%), other (2%) - at 10 year
London, KCH (Bachina 2008)	13	>10 yrs	91%	Fibrosis (92%), lymphocytic infiltration (54%)
Chicago (Ekong 2008)	63	> 3yrs	97%	Fibrosis (97%), inflammation (70%)
Groningen (Scheenstra 2009)	77,64, 66, 55	1,3,5,10 yrs	69% (at 10 years)	Fibrosis (69%) - at 10 years

- Birmingham, Groningen - prevalence & severity of abnormal histology increase with time
- Groningen – fibrosis progression unrelated to graft inflammation

Unexplained Portal Inflammation in Late Paediatric Allograft Biopsies

	Birmingham (n=158) (Evans 2006)	**Montreal (n=119)** (Herzog 2008)	**Chicago (n=63)** (Ekong 2008)
Terminology	Chronic Hepatitis	Interface Hepatitis	Graft Inflammation
Prevalence/time of presentation	22% at 1year 43 % at 5 years, 64 % at 10 years	24% (median 2 years)	28% (>3 years)
Association with fibrosis	37% -bridging fibrosis 15% - cirrhosis (at 10 years)	35% -bridging fibrosis 35% - cirrhosis (at 10 years)	22%-bridging fibrosis (> 3years)
Other findings	70-80% auto- antibodies (vs 10-13% in non-CH cases, always in low titre) Only 6% diagnosed as de novo AIH (AST < 2x normal)	No association with auto-antibodies 55% - chronic rejection (risk factors for CR in 100%) Abnormal LFTs	No auto-antibody data 10% - chronic rejection No correlation with abnormal LFTs

Chronic Hepatitis with "Auto-/Allo-Immune Features" Clinical Implications

Graft Monitoring

- Routine LFTs unreliable
- Role for protocol biopsies
- Autoantibody testing (particularly in children)

Treatment (immunosuppression to prevent disease progression?)

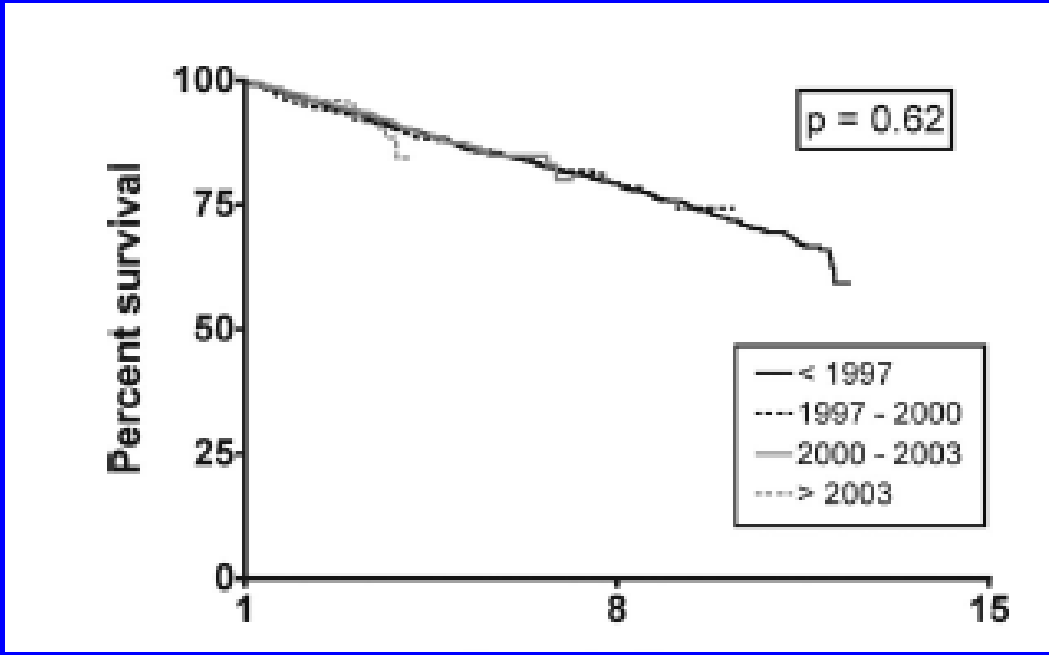
- Criteria for treatment and monitoring therapeutic responses not clearly defined
- Increase in immunosuppression may improve outcome in children
  - Reduced frequency of fibrosis at 5 years (34% vs 50%) after long-term corticosteroid therapy re-instated (Birmingham Childrens Hospital, Haller 2009)
  - Increased immunosuppression after IPTH diagnosed resulted in improved in fibrosis in 21/29 cases (Kyoto, Miyagawa-Hiyashino 2009)

Clinical perspective on the use of biopsy findings in immunosuppression management in conjunction with recent monitoring studies

Graeme Alexander, Cambridge, UK

Current Problem

- No improvement in graft survival after 1 year
  - Deaths after 1 year mostly due to extrahepatic complications (e.g. cardiovascular diease, malignancy, infection)
  - These events related to effects of immunosuppression which results in "immune senescence" (e.g. telomere shortening in T lymphocytes)



(from Gelson Transplantation 2011;91: 1240–1244)

Aim

- Identify “functionally tolerant” individuals who might benefit from immunosuppression
  - Stable graft function > 3 years post-transplant
  - Normal liver tests
  - Prepared to undergo liver biopsy
    (many who refused did so because worried about reducing immunosuppression)

Protocol Biopsies (> 3 years post-LT) from Patients with normal LFTs Histological Findings

(Gelson. Transplantation. 2010 Mar 27;89(6):739-48)

Diagnosis	Number	Comments
Normal	8	
Acute rejection	2	
Recurrent disease	19	PBC- 7, HCV - 4, PSC -2
Mild non-specific hepatitis	25	
Steatosis	6	
Siderosis	4	
Alpha-1-AT globules	1	
Total	**55**	

Individual histological features (inflammation, fibrosis , steatosis, ductular reaction, duct loss) assessed and scored semi-quantitatively

Correlations between Histology and Other Features
Principle Component Analysis

Three main groups identified

1. Minimal inflammation
2. Biliary injury with portal inflammation (all PBC or PSC)
3. Steatosis

- Group 1 (minimal inflammation) had lowest ALT levels
- Groups 1 & 3
  - More likely to be older
  - More likely to be transplanted for ALD/NAFLD
  - Less likely to be transplanted for autoimmune liver disease
- Group 1 (and maybe 3) may be most amenable to immunosuppression

Study Plan

- Prospective randomised trial
- Halving immunosuppression
- Approximately 40% suitable
- Select according to ALT
- Protocol biopsies (entry, then 3,4 & 5 years)
- Exclude those with fibrosis and/or inflammation

http://cybernephrology.ualberta.ca/banff/2011/programme.htm

Immunosuppression Withdrawal in Adult and Pediatric Liver Transplant Recipients

What do we know?

What do we not know?

Where should we go?

Sandy Feng, MD, PhD
University of California San Francisco
11th Banff Meeting on Allograft Pathology

Tolerance Induction Trials

Alemtuzumab / Tacrolimus

Thymoglobulin / Sirolimus

Thymoglobulin / Tacrolimus

- Drug combinations given from time of transplant
- High frequency of acute rejection and “serious adverse events”

Spontaneous Operational Tolerance

ITN029: Immunosuppression Withdrawal for Pediatric Parental Living Donor Liver Transplant Recipients

Single arm, three center pilot trial of 20 patients

UCSF Children's Hospital

Sandy Feng, M.D., Ph.D.
Phil Rosenthal, M.D.
John Roberts, M.D.

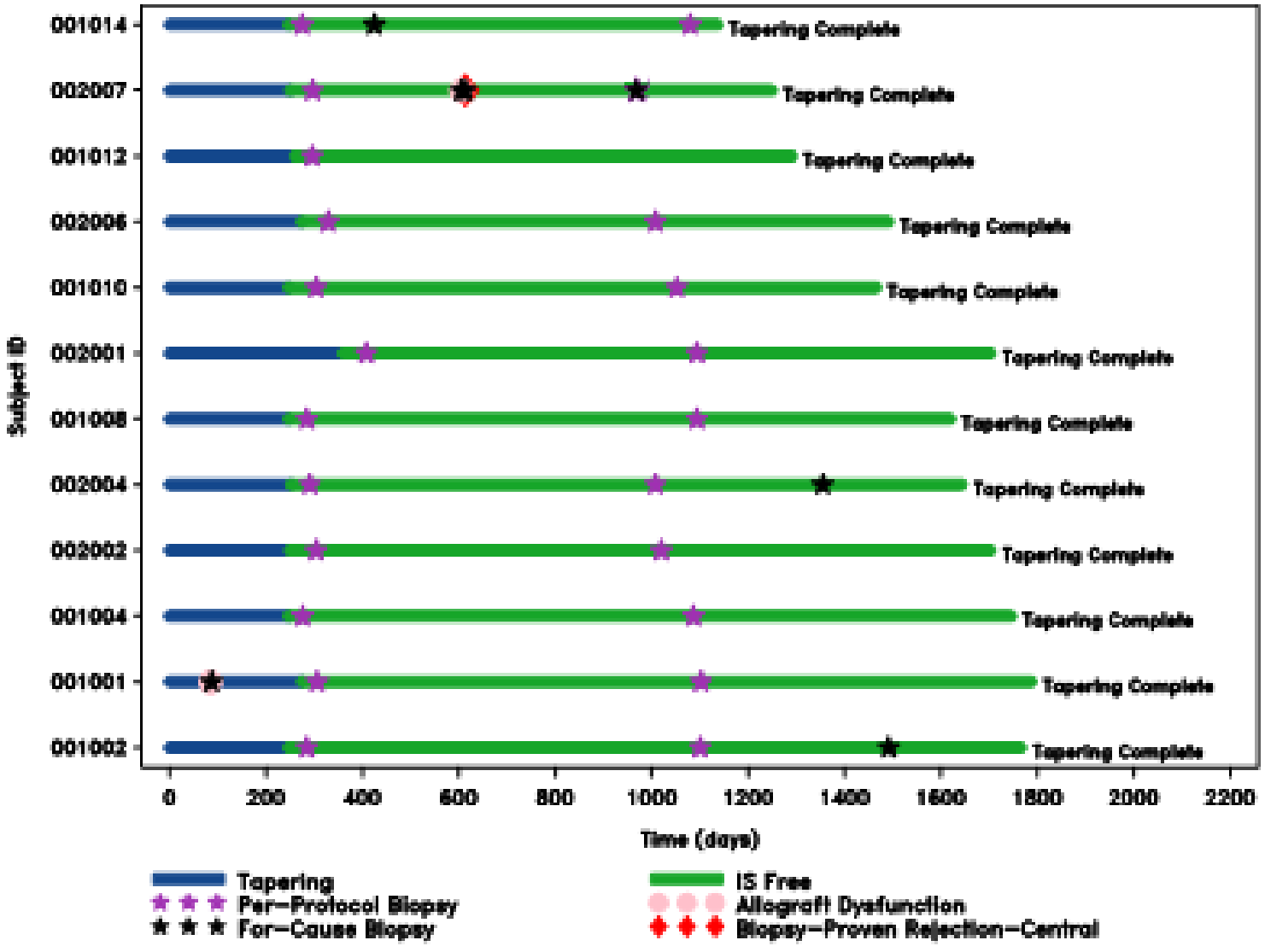
Children's Memorial Hospital
Where kids come first.

Udeme Ekong, M.D., Ph.D.
Estella Alonso, M.D.
Peter Whitington, M.D.

Morgan Stanley Children's Hospital of NewYork-Presbyterian
Columbia University Medical Center

Steven Lobritto, M.D.
Jean Emond, M.D.

12 of 20 Participants Met the Primary Endpoint:
Off Immunosuppression for 30.0 – 50.7 Months



Histological Assessments

- Protocol biopsies – pre-weaning, 1 year, 3 years, ?5 years
- Fibrosis assessments – portal, space of Disse, central
- C4d immunostaining

Factors associated with tolerance

- Longer time post-transplant (median 8 years vs 4 years in non-tolerant)
- Lower C4d scores
- Higher gamma-delta 1/gamma-delta 2 ratio in portal lymphoid cells

(fibrosis mild and fluctuating – not mentioned as being associated with tolerance)

Histopathological, immunological, and clinical aspects of immunosuppression free patients after pediatric living-donor liver transplantation
Update of Kyoto experience

Takaaki Koshiba, Kyoyto, Japan

Kyoto Experience with Immunosupression Weaning

- 600 paediatric LDLT (1990 -2008)

- 540 survived
-
- 200 weaning attempted
  - 84 group-tolerance
  - 50 group-intolerance (24 rejection, 26 fibrosis)
  - 66 in progress

Factors associated with tolerance

- Absence of early rejection
- Longer time post-transplant (median 10 years vs 4.3 years)
- Younger recipient age (median 1.0 vs 4.2 years)

Graft Tolerance is Associated with Fibrosis Progression

(Yoshitomi 2009, Ohe 2011)

	Baseline	Maintenance IS	Graft tolerance
Ishak Fibrosis Stage Mean (range)	0	1.0 (0-3)	1.7 (0-4)

Possible explanations for increased fibrosis in graft-tolerance group

- Longer time post-transplant
- Higher numbers of portal Tregs – may be pro-fibrogenic

BUT

1. For 21 patients with Ishak fibrosis stage $\geq$ 3 Tacrolimus monotherapy instigated on the basis that low-grade rejection could not be excluded
   - Fibrosis improved in 11, no change in 8, worse in 2

2. Fibrosis also associated with C4d deposits in portal capillaries

Immunological Changes in Operational Tolerance – Summary

1. The frequency of both conventional and naïve Tregs was high in OT.
2. Both Tregs exerted donor-specific suppressive activity in OT only.
3. OT in this population was non-deletional.
4. The number of naïve Tregs increased with time after cessation of immunosuppression, but not conventional Tregs

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Table 3. BASELINE OR PRE-WEANING BIOPSY FINDINGS CONDUCIVE TO MINIMIZATON OF IS

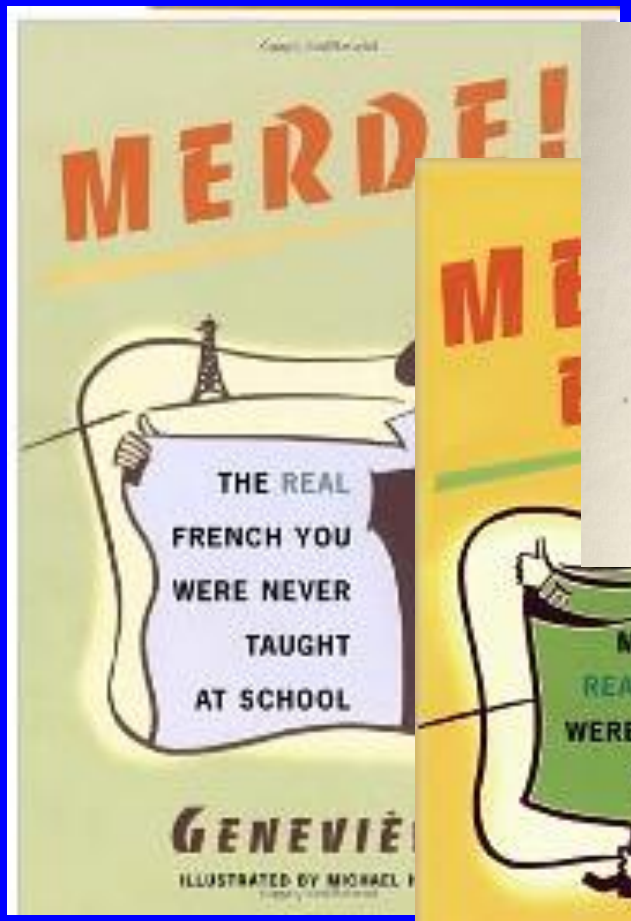
Excludes patients with underlying AIH, HCV, PBC or PSC (see text)

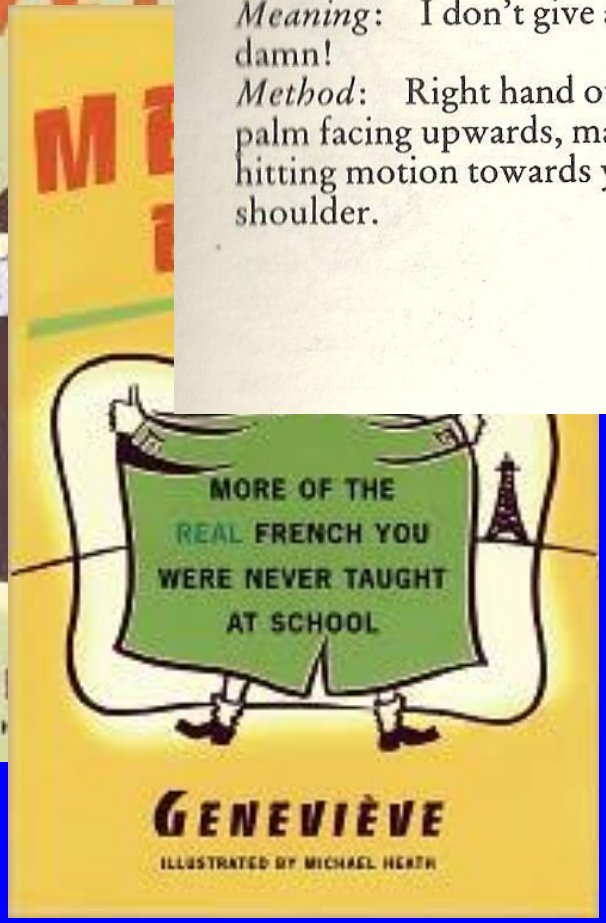
Portal inflammation and interface activity	Preferably absent, but minimal to focal mild portal mononuclear inflammation may be present. Interface necro-inflammatory activity is absent or equivocal/minimal and, if present, involves a minority of portal tracts.
Centrizonal/Perivenular inflammation	Preferably absent, but minimal/mild perivenular mononuclear inflammation around a minority of central veins without hepatocyte necrosis without endothelitis.
Bile duct changes	Absence of lymphocytic bile duct damage, ductopenia and biliary epithelial senescence changes, unless there is an alternative, non-immunologic explanation (e.g. biliary strictures).
Fibrosis	Fibrosis, if present, should be mild overall and not more than rare portal-to-portal bridging. Perivenular fibrosis should not be more than mild according to Banff Criteria.
Arteries	Negative for obliterative or foam cell arteriopathy.

Table 4. FOLLOW-UP BIOPSY FINDINGS THAT MERIT CONCERN AND CONSIDERATION OF CLOSE FOLLOW-UP DURING OR AFTER WEANING

Portal inflammation and interface activity	Increased portal inflammation compared to pre-weaning biopsy especially when associated with histopathologic evidence of focally worsening or more prevalent lymphocytic bile duct damage, interface hepatitis, or appearance of venous endothelitis.
Centrizonal/Perivenular inflammation	Increased perivenular inflammation compared to pre-weaning biopsy associated with necro-inflammatory activity.
Bile duct changes	New onset biliary epithelial cell senescence changes or ductopenia where sampling problems and/or an alternative, non-immunologic explanation (e.g. biliary stricture) are reasonably excluded.
Fibrosis	Increase of fibrosis over consecutive biopsies (see text) without an alternative explanation (e.g. biliary strictures). New onset or increase of perivenular fibrosis.
Arteries	Any evidence of foam cell or obliterative arteriopathy.


Et enfin, ……..





9 J'm'en fous!
Meaning: I don't give a damn!
Method: Right hand out, palm facing upwards, make a hitting motion towards your shoulder.

1 Va te faire foutre!
The king of gestures, known as "le bras d'honneur"