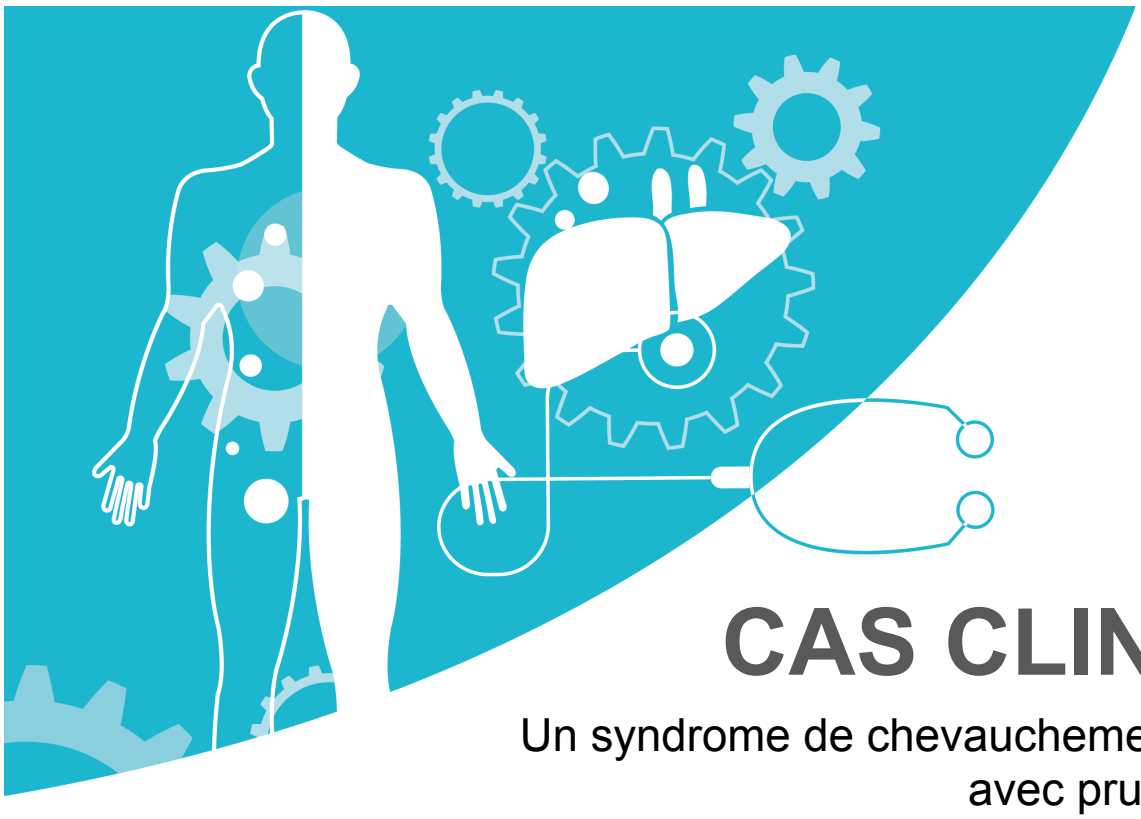


CAS CLINIQUE

Un syndrome de chevauchement CBP-HAI avec prurit invalidant

JEAN-CHARLES DUCLOS-VALLEE

CENTRE HÉPATO-BILIAIRE - DHU HÉPATINOV

CENTRE DE RÉFÉRENCE DES MALADIES INFLAMMATOIRES
DES VOIES BILIAIRES ET DES HÉPATITES AUTO-IMMUNES

Mme B… F… 55 ans

Poids 47 kg / Taille: 1m 52

- Pas d'antécédents
- Ne prenant pas de traitement
- Prurit inexpliqué depuis 3 ans

DEVANT UN BILAN HÉPATIQUE PERTURBÉ,
SON MÉDECIN TRAITANT
L'ADRESSE EN CONSULTATION D'HÉPATOLOGIE.

Bilan Biologique

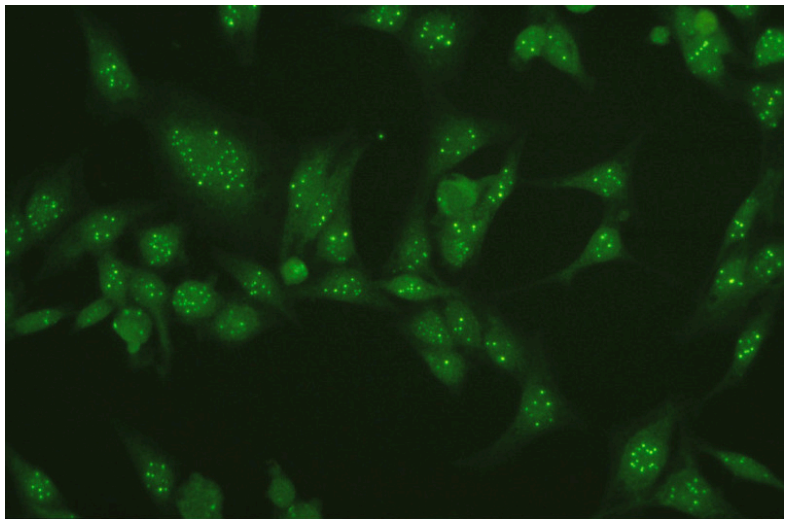
- Plaquettes 239 000/mm^3, TP 100%
- ASAT 131 UI/L (N:10-35), ALAT 169 UI/L (N:10-35)
- GGT 1006 UI/L (N:5-36), PAL 525 UI/L (N:35-105)
- Bilirubine totale 41 µmol/L,
- Bilirubine conjuguée 38 µmol/L
- Créatininémie 45 µmol/L, Albumine 40 g/L
- TSH normale

Bilan Immunologique

- Electrophorèse des protéines plasmatiques :
  Hyper-gammaglobulinémie 21,4 g/L
- IgG 19,2 g/L (N:7,7-15), IgM 6,8 g/L (N:1-2,2)
- Anti-nucléaires positifs 1/160 avec présence de dots nucléaires anti-sp100 positifs
- Anti-muscles lisses positifs 1/320
- Anti-LKM1 anti-LC1 anti SLA/LP négatifs
- Anti-mitochondries négatifs

Anti-sp100 positifs

- Immunofluorescence indirecte sur cellules Hep-2 montrant une fluorescence mouchetée avec présence de dots nucléaires



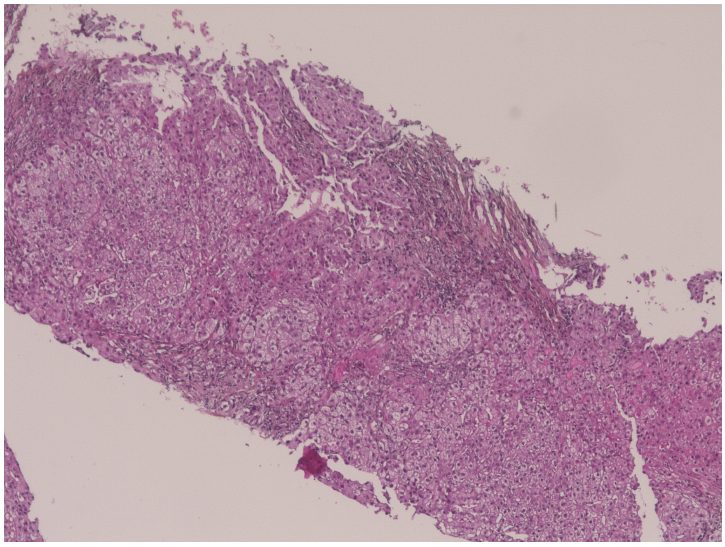
Anti-SP 100 sont présents dans 50 % des CBP sans anti-mitochondries.

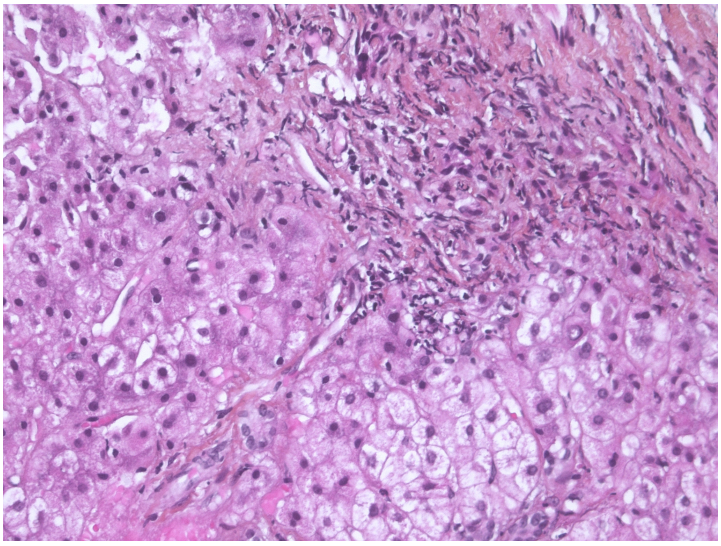
Endoscopie / Imagerie

- **FOGD:** pas de varices oesophagiennes
- **AFP** normale
- **Echographie hépatique :** hépatomégalie dysmorphique sans nodule suspect
- **FS**: 10.3 kPa
- **Cholangio-IRM :** foie dysmorphique sans dilatation des voies biliaires intra- ou extra-hépatiques

Histologie

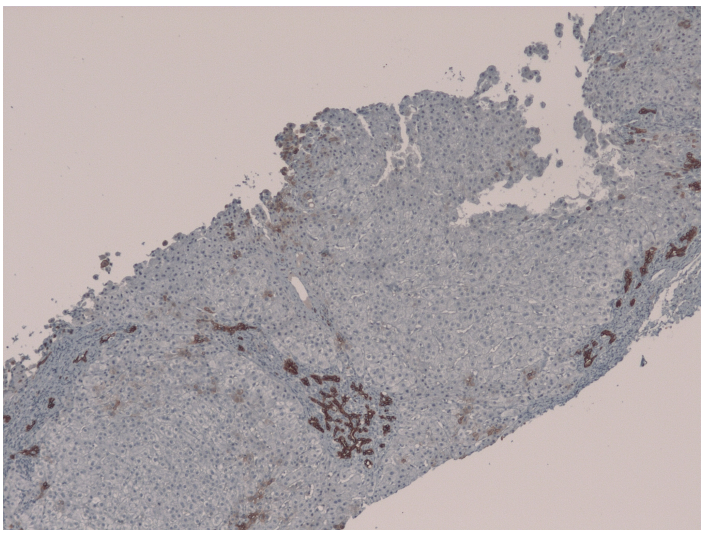
- Ponction biospie hépatique montrant des lésions d'hépatite chronique active avec piecemeal nécrosis modérée et cirrhose constituée (Classification METAVIR A2F4 - Stade 4 de Scheuer)

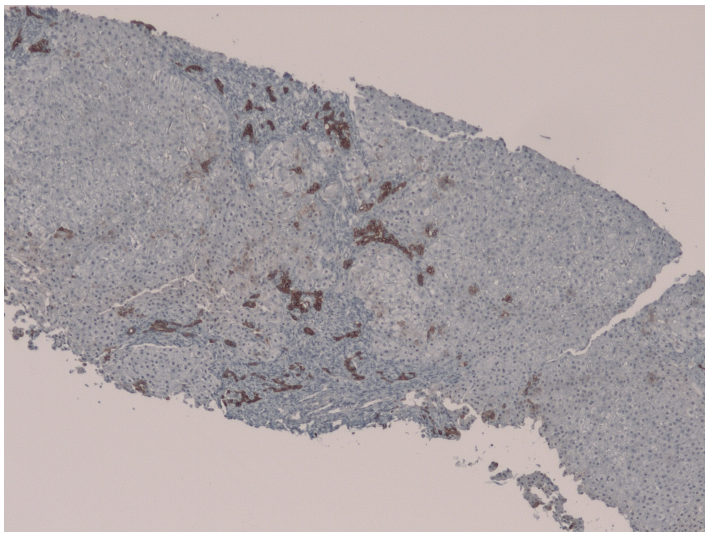




Histologie

- Cholangite destructrice lymphocytaire et Immuno-marquage des canaux biliaires par la Cytokératine 7 montrant une ductopénie et une prolifération ductulaire





Diagnostic de syndrome de chevauchement CBP-HAI au stade de cirrhose

- Au moins 2 des 3 critères pour la CBP et l'HAI, avec présence obligatoire d'une hépatite d'interface

Critères de CBP	Critères d'HAI
PAL > 2xN ou GGT > 5xN ✔	ALAT > 5xN
Anti-mitochondries ≥ 1/40 ✔	IgG > 2xN ou anti-muscles lisses positifs ✔
Biopsie hépatique montrant une lésion floride des canaux biliaires ✔	Biopsie hépatique montrant une hépatite d'interface modérée ou sévère ✔

N : limite supérieure de la normale

Chazouillères *et al.* Hepatology 1998(28):296-301.

Traitement

- Acide ursodésoxycholique (AUDC)
  15 mg/kg/jour
- Cholestyramine 2 sachets par jour

Peu d'efficacité sur le prurit, pas de réponse biochimique.

- Ajout de Prednisone 30 mg/jour et Azathioprine
  50 mg/jour

Disparition de l'ictère mais prurit invalidant persistant. Amélioration de la cytolyse et normalisation du taux d'IgG et de bilirubine. Persistance d'un taux de PAL à 4N.

Traitement

- Acide ursodésoxycholique (AUDC) et Azathioprine poursuivis
- Introduction de Bézafibrate 400 mg/jour[1] rapidement interrompu en raison de myalgies invalidantes.[2]
- Prurit évalué à 7/10 (échelle visuelle analogique)
- Patiente réticente à l'introduction d'un traitement potentiellement prurigineux.

1. Usage hors AMM
2. Effet indésirable connu de fréquence comprise entre ≥ 1/1000 et <1/100 (RCP Befizal)

Quelle prise en charge du prurit proposeriez vous ?

Quelle prise en charge du prurit proposeriez vous ?

1) Cholestyramine 4 à 16 g/j
   (2 à 4 h avant ou après d'autres prises médicamenteuses)

2) Rifampicine 150 à 600 mg/jour

3) Antagonistes des opiacés
   (Naltrexone jusqu'à 50 mg/j)

4) Sertraline 75-100 mg/jour

5) Photothérapie

6) Système MARS™

7) Transplantation hépatique

EASL Clinical Practice Guidelines 2017 on PBC: Journal of Hepatology 2017 vol. 67 j 145–172

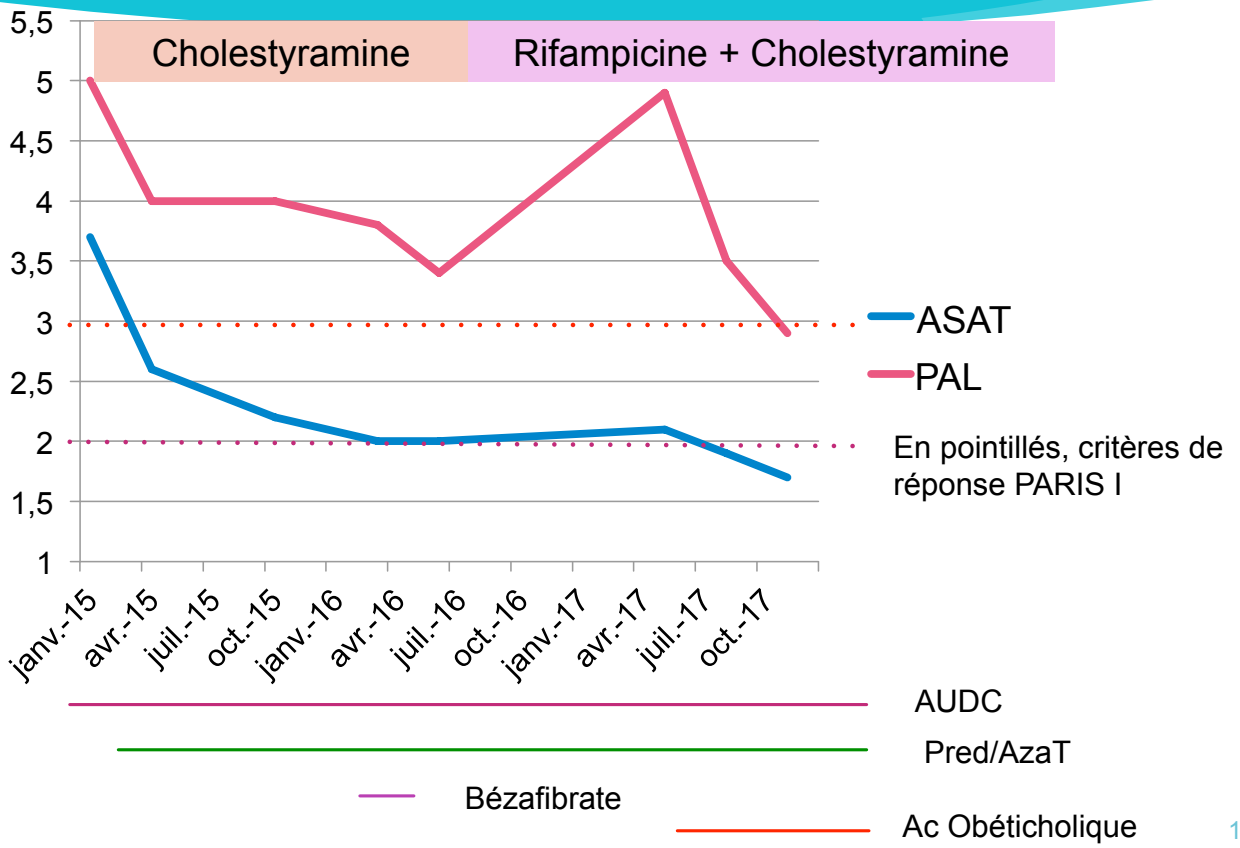
Traitement mis en place chez cette patiente

- Poursuite de Cholestyramine à 2 sachets par jour, mal toléré
- Introduction de Rifampicine 150 puis 300 mg/jour

A 3 mois : Prurit évalué à 2/10 (échelle visuelle analogique)

- Acide ursodésoxycholique (AUDC) poursuivi
- Introduction d'acide obéticholique à 5 mg/jour
- Pas de majoration du prurit

A 6 mois, réponse biochimique selon les critères de Paris I


Cholestyramine
Rifampicine + Cholestyramine
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
janv.-15
avr.-15
juil.-15
oct.-15
janv.-16
avr.-16
juil.-16
oct.-16
janv.-17
avr.-17
juil.-17
oct.-17
ASAT
PAL
En pointillés, critères de réponse PARIS I
AUDC
Pred/AzaT
Bézafibrate
Ac Obéticholique

Conclusions

- **Le traitement du syndrome de chevauchement CBP-HAI repose sur l'association AUDC-Corticoïdes-Immunosuppresseurs.[1]**

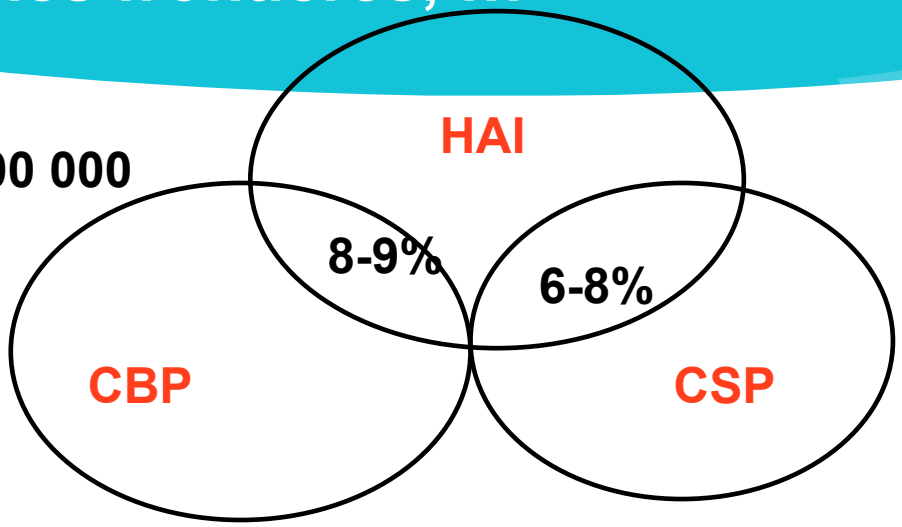
- **La prise en charge adéquate du prurit est indispensable au préalable de l'introduction du traitement par acide obéticholique.**

- **En cas de prurit sous acide obéticholique, la posologie peut être réduite transitoirement à 5 mg, 1 jour sur 2.[2]**

1. EASL Clinical Practice Guidelines 2017 on PBC: Journal of Hepatology 2017 vol. 67 j 145–172
2. RCP Ocaliva

Hépatites Auto-Immunes, CBP, CSP Formes frontières, …

HAI:
10 à 17/ 100 000



Formes frontières		Formes séquentielles
HAI-CBP	Cholangite Auto-Immune	AIH <=> PBC
HAI-CSP		
HAI-CSP		AIH <=> PSC

New scoring Classing for PBC-AIH overlap syndrome

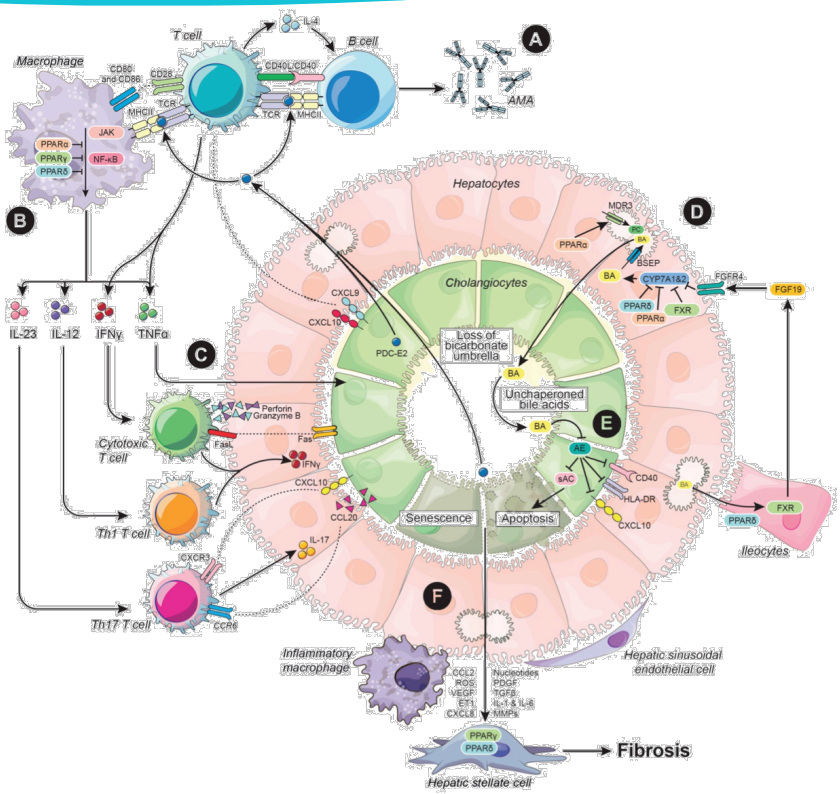
TABLE 1. PROPOSED SCORING CLASSIFICATION FOR OVERLAP SYNDROME

Component	Result	Score
Biochemical category		
AST or ALT above ULN	>2	+3
	1.5-2	+2
	1-1.5	+1
	<1	0
ALP above ULN	>1	+2
	0.75-1	+1
	<0.75	0
Serum globulin above ULN	>1.5	+2
	1-1.5	+1
	<1	0
Immunologic category		
ANA, ASMA, or LKM1	>1:80	+3
	1:80	+2
	1:40	+1
	<1:40	0
or		
Anti-SLA, pANCA	Positive	+2
AMA	Positive	+3
Histologic category		
	Interface hepatitis	+3
	Lymphoplasmacytic	+1
	Hepatic rosettes	+1
	Biliarydamage	
	Granulomas	+3
	Florid ductal lesion	+1
	Ductular proliferation	+1
	Bile duct loss	+1
Others category		
Viral markers	Positive	−3
	Negative	+3
Drugs	Yes	−4
	No	+1
Alcohol	<25 g/day	+2
	>60 g/day	−2
Interpretation of scores	Definitive	≥21
	Probable	19 or 20
	Rejected	<19

Zhang et al; Hepatology commun. 2018

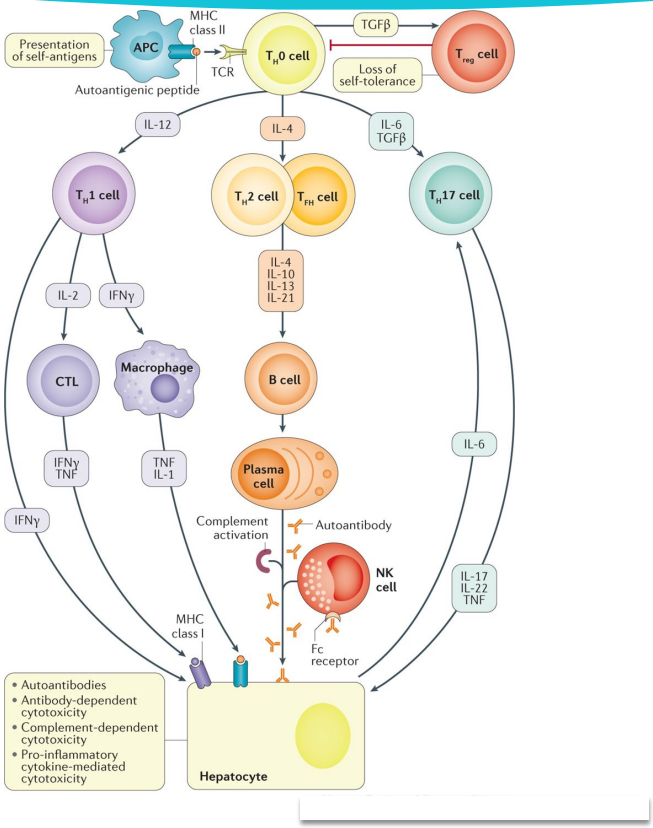
Pathogenesis of Primary Biliary Cholangitis

- Effective biliary secretion is essential for adequate hepatic detoxification and is integral to digestive function
- **PBC** reflects the consequences of immune and cellular injury to biliary epithelial cells, resulting in cholestasis and progressive liver fibrosis



EASL CPG PBC. J Hepatol 2017;67:145–72

Pathogenesis of Auto-Immune Hepatitis



Vergani GM et al. Nature Reviews Disease Primers 2018

Diagnostic approach to cholestasis

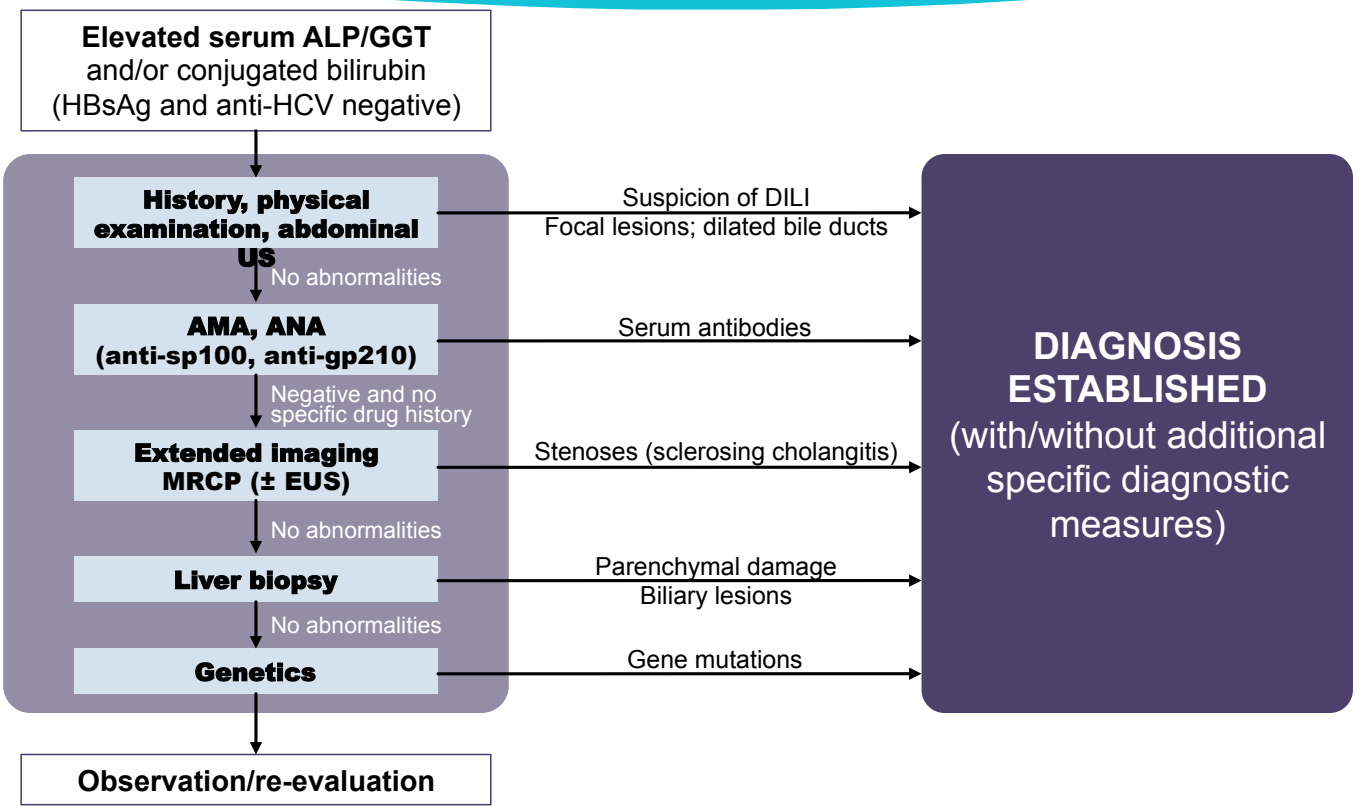
- A systematic approach to diagnosis of PBC is recommended

Recommendations*	Grade of evidence	Grade of recommendation
Take detailed **history** and **physical examination** when evaluating patients with biochemical tests that suggest cholestatic liver disease	III	1
Ultrasound should be the first-line non-invasive imaging procedure to differentiate intra- from extrahepatic cholestasis	III	1
Perform serological screening for **AMA** and **PBC-specific ANA** by immunofluorescence in all patients with unexplained cholestasis	III	1
Image using **MRCP** in patients with unexplained cholestasis. **EUS** can be an alternative to MRCP to evaluate distal biliary disease	III	1
Consider **liver biopsy** after serological screening and extended imaging in patients with ongoing unexplained intrahepatic cholestasis	III	1
Consider **genetic tests** for inherited cholestatic syndromes in patients where clinically appropriate	III	1

*Statements 1–6

EASL CPG PBC. J Hepatol 2017;67:145–72

Structured algorithm to diagnose chronic* cholestasis



*Lasting for >6 months

EASL CPG PBC. J Hepatol 2017;67:145–72

Overview of utility of investigations in PBC

▶ Elevated ALP is typical of PBC

Test	Finding	Notes
ALP	↑	Values associated with disease progression
AST/ALT	↑	↑↑ May be suggestive of PBC with features of AIH
GGT	↑	Reflects cholestatic liver injury
IgM	↑	Elevated values associated with disease
AMA (>1/40)	+	Diagnostic in >90% of cases in correct clinical context
Specific ANA	+	Specific immunofluorescence patterns* present in 30%
Anti-gp210	+	Specific immunoassays available
Anti-sp100	+	Specific immunoassays available
Anti-centromere	+	Associated with portal hypertensive phenotype
Bilirubin	↑	Elevation at late stages frequently indicative of cirrhosis†
Platelets	↓	Indicative of cirrhosis
INR	↑	Indicative of cirrhosis
Albumin	↓	Indicative of cirrhosis

***Perinuclear rims, nuclear dot, centromere;**
† Except in patients with ductopenic non-cirrhotic variant
EASL CPG PBC. J Hepatol 2017;67:145–72

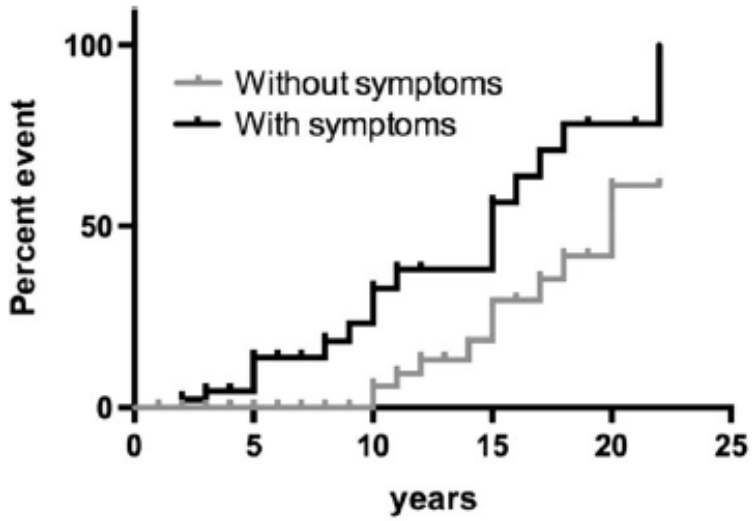
Stratification of risk in PBC

Recommendations*	Grade of evidence	Grade of recommendation
Recognize that patients at greatest risk of complications from PBC have **inadequate biochemical response to therapy**, and **cirrhosis**	II-2	1
Actively recognize that the strongest risk factors for inadequate biochemical response to therapy are **early age at diagnosis** (e.g. <45), and **advanced stage at presentation**	III	1
Evaluate all patients for **stage of disease** using a combination of non-invasive tests (bilirubin, alkaline phosphatase, AST, albumin, platelet count and elastography) at baseline, and during follow-up	III	1
Elevated serum bilirubin and ALP can be used as **surrogate markers of outcome** for patients with PBC • Routine biochemistry and haematology indices should underpin clinical approaches to stratify individual risk of disease progression	II-2	1
Recognize that **transplant-free survival** for early-stage patients with ALP <1.5x ULN and a normal bilirubin after 1 year of therapy with UDCA, is not significantly different to a control healthy population	II-2	1
Use **elastography** and **risk scores** (eg, GLOBE and UK-PBC score) for patients with PBC, to help better define individual risk of developing **complications** of advanced liver disease in the future	III	1

*Statements 13–18

EASL CPG PBC. J Hepatol 2017;67:145–72

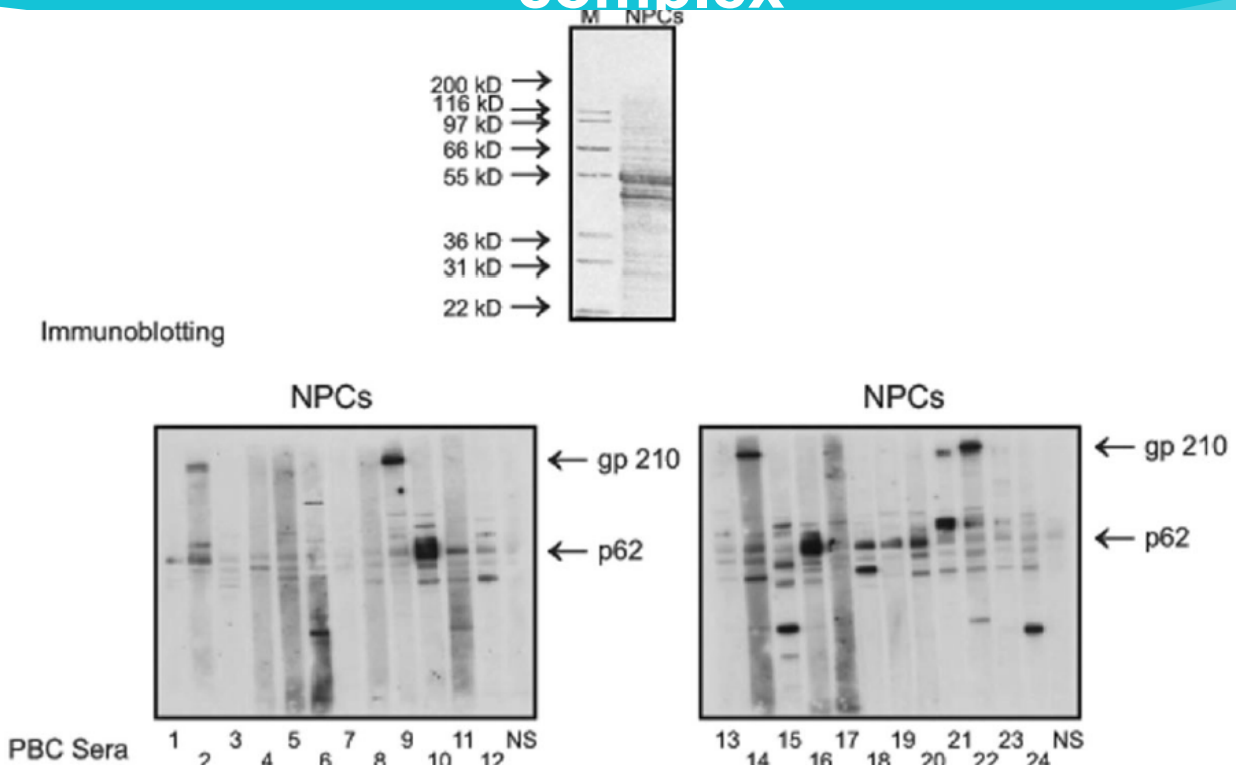
PBC patients presenting with symptoms such as fatigue and pruritus present a severe evolution



# of patients at risk	5 yrs	10 yrs	15 yrs	20 yrs	22 yrs
With symptoms (75 pts)	37	16	10	3	1
Without symptoms (141 pts)	67	34	15	6	1

Quarneti et al. Liver International 2015

Immunoreactivity of serum of patients with PBC with Nuclear pore complex



Wesierska-Gadek J et al. Hepatology 2006

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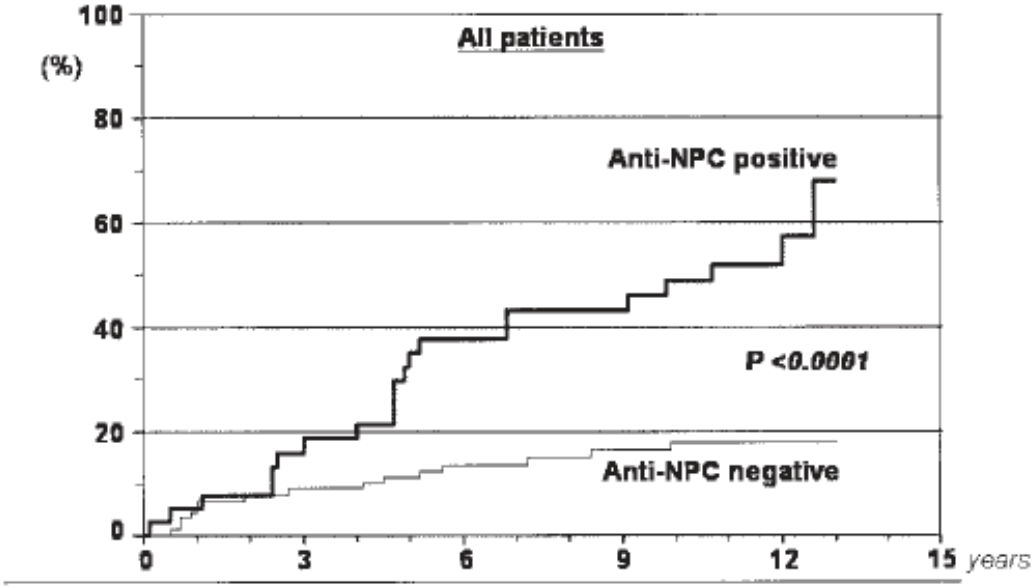


Anti-NPC						
positive	38	30	23	20	9	0
negative	89	81	71	58	22	0

Defining inadequate response to treatment

- **Treatment failure must be defined on validated surrogate endpoints**
  - To account for the slow progression of disease
- **Qualitative biochemical response to UDCA assessed using binary definitions or continuous scoring**

Binary definitions	Time (months)	Treatment failure
Rochester[1]	6	ALP ≥2 ULN or Mayo score ≥4.5
Barcelona[2]	12	Decrease in ALP ≤40% and ALP ≥1x ULN
Paris-I[3]	12	ALP ≥3x ULN or AST ≥2x ULN or bilirubin >1 mg/dl
Rotterdam[4]	12	Bilirubin ≥1x ULN and/or albumin <1x ULN
Toronto[5]	24	ALP >1.67x ULN
Paris-II[6]	12	ALP ≥1.5x ULN or AST ≥1.5x ULN or bilirubin >1 mg/dl
Ehime[7]	6	Decrease in GGT ≤70% and GGT ≥1 ULN
Continuous scoring	**Time (months)**	**Scoring parameters**
UK-PBC[8]	12	**12 months:** bilirubin, ALP and AST (or ALT); **Baseline:** albumin and platelets
GLOBE[9]	12	**12 months:** bilirubin, ALP, albumin, and platelet count; **Baseline:** age

See notes for full reference list
EASL CPG PBC. J Hepatol 2017;67:145–72

Treatment: therapies to slow disease progression

- **Ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) approved in PBC**
- **Heterogeneity of treatment efficacy in clinical trials may be due to:**

Recommendations*	Grade of evidence	Grade of recommendation
Oral UDCA: 13–15 mg/kg/day as the first-line pharmacotherapy for all patients with PBC. UDCA is usually continued for life	I	1
Oral OCA: Biochemical efficacy in patients with ALP >1.67x ULN and/or bilirubin elevated <2x ULN demonstrated in a Phase 3 study • Conditionally approved for patients with PBC in **combination with UDCA** for those with an inadequate response to UDCA, or as monotherapy in those intolerant to UDCA • Consider use in such patients (initial dose 5 mg; dose titration to 10 mg according to tolerability at 6 months)	I	2
Data from Phase 3 randomized trials for **budesonide** (in non-cirrhotic patients), and **bezafibrate**, both in **combination with UDCA**, not yet published; currently, a recommendation for therapy cannot be made	II-2	2

*Statements 19–21
EASL CPG PBC. J Hepatol 2017;67:145–72

Treatment: therapies to slow disease progression

- **Ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) approved in PBC**
- **Heterogeneity of treatment efficacy in clinical trials may be due to:**
  - Variable inclusion criteria without reference to disease risk or stage

Recommendations*	Grade of evidence	Grade of recommendation
Oral UDCA: 13–15 mg/kg/day as the first-line pharmacotherapy for all patients with PBC. UDCA is usually continued for life	I	1
Oral OCA: Biochemical efficacy in patients with ALP >1.67x ULN and/or bilirubin elevated <2x ULN demonstrated in a Phase 3 study • Conditionally approved for patients with PBC in **combination with UDCA** for those with an inadequate response to UDCA, or as monotherapy in those intolerant to UDCA • Consider use in such patients (initial dose 5 mg; dose titration to 10 mg according to tolerability at 6 months)	I	2
Data from Phase 3 randomized trials for **budesonide** (in non-cirrhotic patients), and **bezafibrate**, both in **combination with UDCA**, not yet published; currently, a recommendation for therapy cannot be made	II-2	2

*Statements 19–21 EASL CPG PBC. J Hepatol 2017;67:145–72

PBC with features of autoimmune hepatitis

- **~8–10% of patients with PBC have features characteristic of AIH**
  - 'AIH-PBC overlap syndrome', 'hepatitic form of PBC', or 'PBC with secondary AIH'
- **With non-response to UDCA after 6-12 months additional AIH features should be investigated**
  - Paris criteria used most commonly†

Recommendations*		
Liver biopsy is mandatory in confirming the features of AIH, and should be considered in patients with disproportionate elevations in ALT and/or IgG	III	1
Patients with PBC and typical features of AIH may benefit from **immunosuppressive treatment** in addition to **UDCA** • Use immunosuppressive treatment in patients with **severe interface hepatitis**, and consider in patients with moderate interface hepatitis • Counsel patients about immunosuppressive treatment side effects	III	2

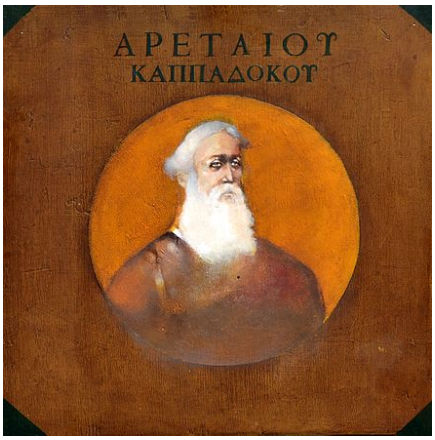
*Statements 24, 25;
†According to these criteria, a diagnosis can be made in a patient with PBC with at least two of the following: 1. ALP >2x ULN or GGT >5x ULN. 2. AMA >1:40. 3. Florid bile duct lesion on histology AND two of the following three features:1. ALT >5x ULN.
2. IgG serum levels >2x ULN or smooth muscle autoantibody positive. 3. Moderate or severe interface hepatitis on histology
EASL CPG PBC. J Hepatol 2017;67:145–72

Therapy of overlap – EASL guidelines – Autoimmune Hepatitis

50. In AIH patients with features of PBC ("AIH-PBC variant syndrome"), combined therapy with UDCA and immunosuppressants is recommended (III). In AIH patients with PSC features ("AIH-PSC variant syndrome") addition of UDCA to immunosuppressant can be considered **(III)**
In patients with dominant AIH features, an alternative approach is to start with immunosuppressants only and then add UDCA if response is insufficient **(III)**

« Le prurit est causée par des particules bilieuses épineuses »

Aretaeus le Cappadocien (2nd Century B.C.)



Current suggested pharmacological therapy for pruritis associated with jaundice

Treatment	Agent	Dosage
Initial	UDCA	10-15 mg/kg.d (PO)
First line	Cholestyramine	4-16 g/d (PO)
Second line	Rifampicin	300-600 mg/d (PO)
Third line	Naltrexone	50 mg/d (PO)
Fourth line	Sertraline	100 mg/d (PO)

UDCA: Ursodeoxycholic acid; PO: Oral administration.

GASTROENTEROLOGY 2010;139:1008–1018

Lysophosphatidic Acid Is a Potential Mediator of Cholestatic Pruritus

ANDREAS E. KREMER,[*] JOB J. W. W. MARTENS,[*] WIM KULIK,[‡] FRANZISKA RUËFF,[§] EDITH M. M. KUIPER,[‖] HENK R. VAN BUUREN,[‖] KAREL J. VAN ERPECUM,[¶] JURATE KONDRACKIENE,[#] JESUS PRIETO,[**] CHRISTIAN RUST,[‡‡] VICTORIA L. GEENES,[§§] CATHERINE WILLIAMSON,[§§] WOUTER H. MOOLENAAR,[‖‖] ULRICH BEUERS,[*] and RONALD P. J. OUDE ELFERINK[*]

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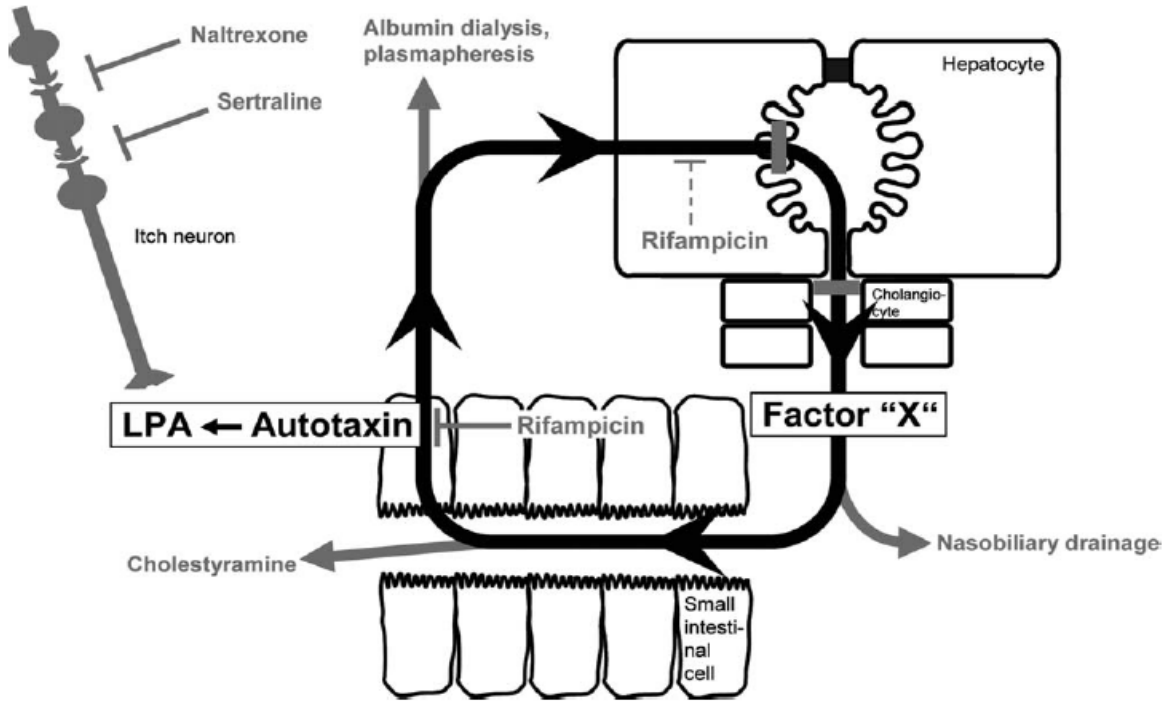
The itch neuron

Schematic representation of receptors and neurotrasmitters that may play a role in itch transmission



Beuers et al. Hepatology 2014

Merci pour votre attention