19ème Journée d'automne
Suivi des maladies digestives et hépatobiliaires : collaboration médecins généralistes et spécialistes - qui fait quoi ?

Tests hépatiques perturbés

Andrea De Gottardi
Service de Gastroentérologie et Hépatologie, Ente Ospedaliero Cantonale,
Faculté de Médecine, Università della Svizzera Italiana, Lugano

---

Tests hépatiques

SYSTEM/FUNCTION	MARKER	LOCALISATION
Integrity of hepatocytes	AST	Liver, **Muscle, Heart**, Kidney, Pancreas, Lung
	ALT	**Liver**, Muscle, Heart, Kidney, Pancreas, Lung
Cholestasis	Alcaline phosphatase	Liver, Bone, Placenta
	GGT	With AP: Cholestasis Without AP: non hepatic origin

modif. Giannini, CMAJ, 2005

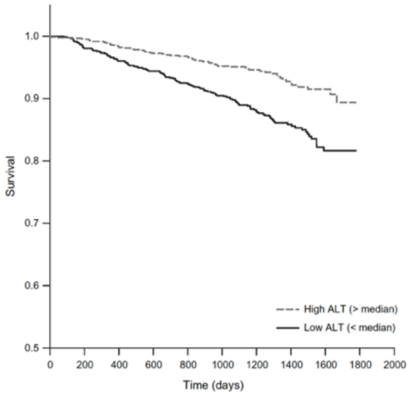
Transaminases, survie et mortalité

Transaminases élevées

ALT/AST level for increased mortality	Comments
AST>18	3X increase in all cause mortality
ALT 30–39	RR of liver mortality 2.9 (2.4–3.5) and 9.5 (7.9–11.5) in men, 3.8 (1.9–7.7) and 6.6 (1.5–25.6) in women
ALT 45–90 M 29–58 for F	SMR risk 1.32 for 1–2X ULN, and 1.78 for >2X ULN
ALT>30 for M ALT >19 for F	Increased liver related mortality

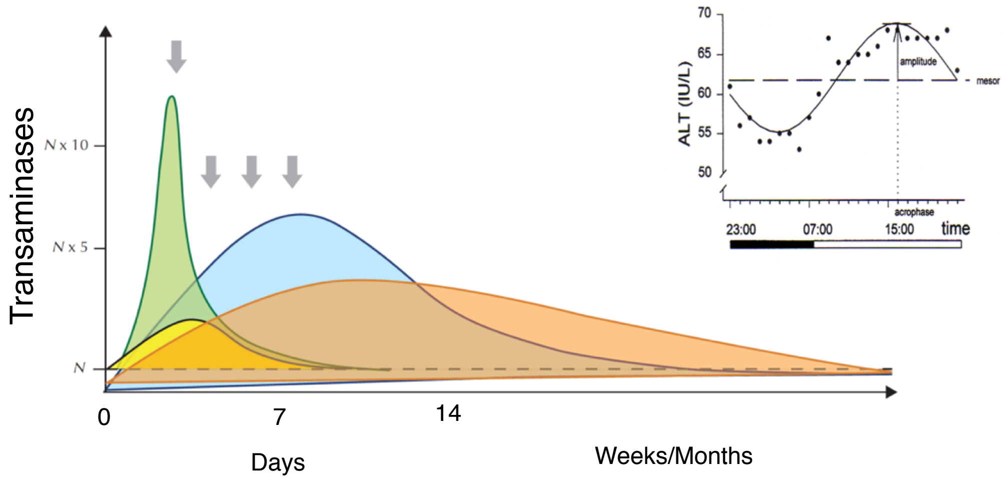
Kwo, Am J Gastro, 2017

Transaminases basses



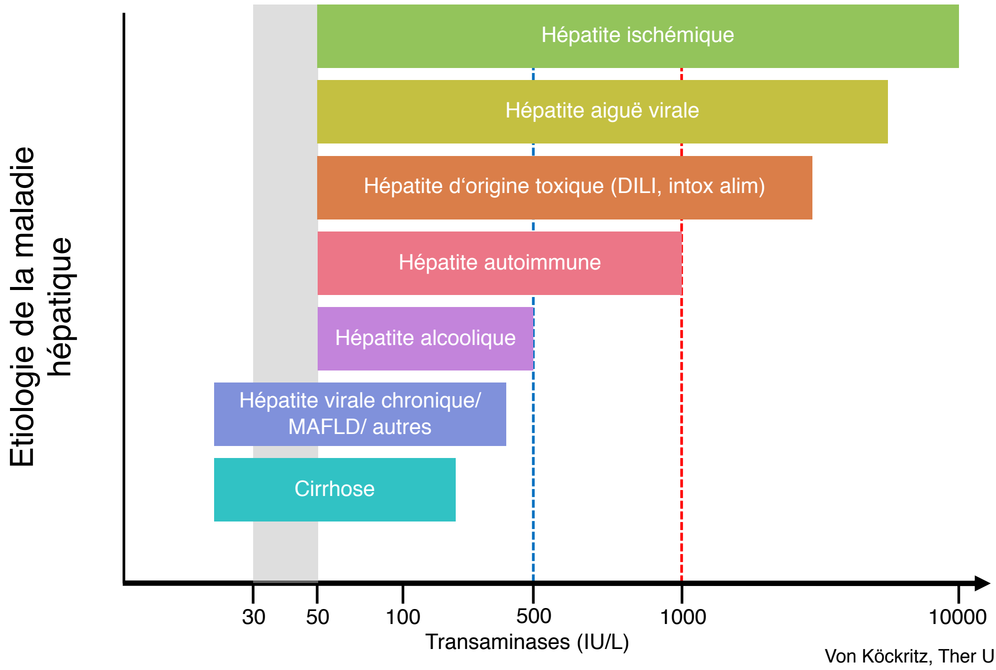
Le Couteur, J Gerontol, 2010

Transaminases: cinétique



modif. Giannini, CMAJ, 2005

Cordoba, Hepatology 1998



Von Köckritz, Ther Umschau, 2017

Causes d'une perturbation chronique des tests hépatiques

Infection virale HBV, HCV, (HDV, HEV)	anti-HBc, anti-HBs, HBs-Ag anti-HCV, anti-HDV, HEV-RNA
Cholangite biliaire primitive	anti-mitochondries, IgM
Hépatite autoimmune	IgG, ANA, anti-muscle lisse, anti-LKM, anti-SLA
Hémochromatose, maladie de Wilson	ferritine, saturation de la transferrine, coeruloplasmine
Déficit en alpha-1 antitrypsine	alpha-1-AT
Médicaments (par ex. méthotrexate, statines)	???
MAFLD	???
Maladie alcoolique	CDT, éthylglucuronide

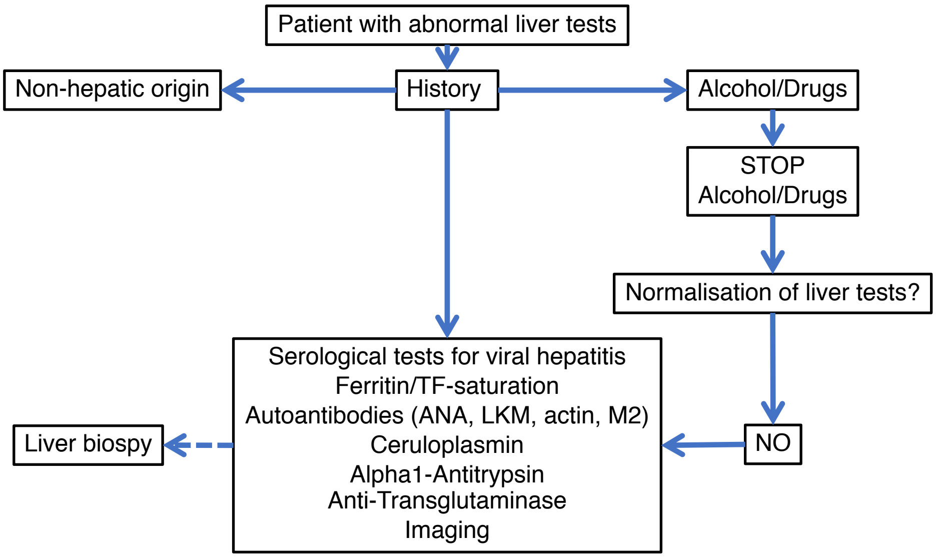
Phosphatase alcaline

Enzyme ubiquitaire, hautement exprimée dans le foie, dans les voies biliaires, le rein, l'os et le placenta.

Augmentation lors de cholestase suivant la GGT.

AUGMENTATION	**DIMINUTION**
Cholestase	Hypothyréose
Hépatopathie aiguë ou chronique	Anémie
Maladies osseuses, Paget	Maladie de Wilson
Hyperparathyroïdie	Contraceptifs oraux
Leucémie	
Lymphomes	
Sarcoïdose	

Comment procéder?

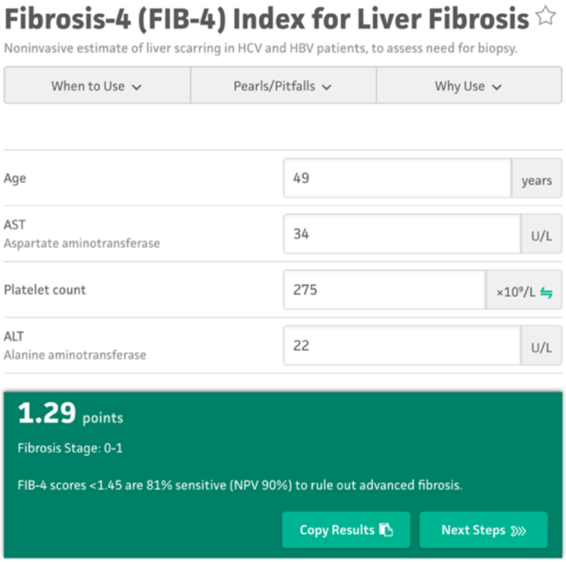

Patient with abnormal liver tests
Non-hepatic origin
History
Alcohol/Drugs
STOP Alcohol/Drugs
Normalisation of liver tests?
NO
Serological tests for viral hepatitis
Ferritin/TF-saturation
Autoantibodies (ANA, LKM, actin, M2)
Ceruloplasmin
Alpha1-Antitrypsin
Anti-Transglutaminase
Imaging
Liver biospy

Von Köckritz, Ther Umschau, 2017 & Modif. nach Giannini, CMAJ, 2005

Que faire quant tout est négatif?

- Revenir à l'histoire du patient: produits de phytothérapie, régime alimentaire, médicaments, hobbies, alcool...
- Refaire quelques tests: alpha1-antitrypsine, coeruloplasmine
- Considérer d'autres maladies: insuffisance cardiaque (droite), dysfonction thyroidienne
- Chercher des maladies musculaires (CK, aldolase)
- Repeter l'imagerie
- Attendre....mais pas trop longtemps!

Que faire quant tout est négatif?



Fibrosis-4 (FIB-4) Index for Liver Fibrosis ☆

Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy.

Age	49	years
AST Aspartate aminotransferase	34	U/L
Platelet count	275	$\times 10^9$/L
ALT Alanine aminotransferase	22	U/L

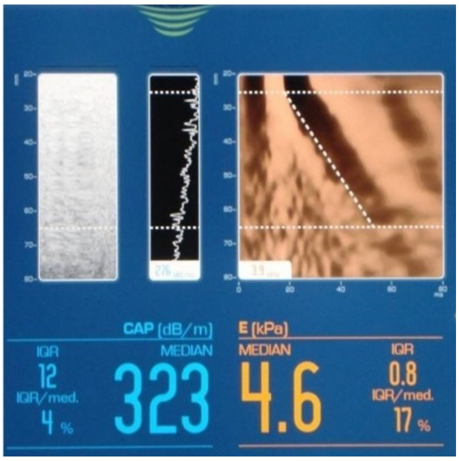
1.29 points

Fibrosis Stage: 0-1

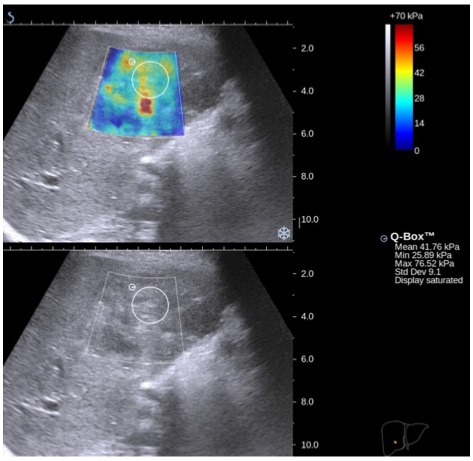
FIB-4 scores <1.45 are 81% sensitive (NPV 90%) to rule out advanced fibrosis.

Investigations chez le spécialiste

Fibroscan


CAP (dB/m)
IQR
12
IQR/med.
4 %
MEDIAN
323
E (kPa)
MEDIAN
4.6
IQR
0.8
IQR/med.
17 %

Shear wave elastography


+70 kPa
56
42
28
14
0
2.0
4.0
6.0
8.0
10.0
Q-Box™
Mean 41.76 kPa
Min 25.89 kPa
Max 76.52 kPa
Std Dev 9.1
Display saturated

Revenons à notre patiente

Ferritine sg	☐	(15 - 150) µg/l	1119 △H
Transferrine sg	☐	(24.7 - 44.4) µmol/l	17 △L
Coef. Sat. Transf. sg	☐	(0.15 - 0.35)	0.84 △H
CK sg	☐	(25 - 140) U/l	
LDH sg	☐	(135 - 214) U/l	388 △H
ASAT (GOT) sg	☐	(9 - 32) U/l	137 △H
ALAT (GPT) sg	☐	(9 - 36) U/l	34 △
Phosphatase alcaline sg	☐	(36 - 108) U/l	24 △L
Gamma-GT sg	☐	(6 - 42) U/l	191 △H
Bilirubine totale sg	☐	(0 - 21) µmol/l	99 △H
Bilirubine directe sg	☐	(0 - 10) µmol/l	55 △H

Low Serum Alkaline Phosphatase Activity in Wilson's Disease

WILLIAM A. SHAVER,† HARSHIKA BHATT AND BURTON COMBES

The Liver Unit, Department of Internal Medicine, The University of Texas Health Science Center at Dallas, Southwestern Medical School, Dallas, Texas 75235

Hepatology, 1986

Low serum alkaline phosphatase activity associated with severe Wilson's disease. Is the breakdown of alkaline phosphatase molecules caused by reactive oxygen species?

Tadashi Hoshino*[a], Kazunari Kumasaka[a], Kinya Kawano[a], Fujio Yamagishi[b], Iwao Koyama[c], Yohko Fujimori-Arai[c], Takanori Nakajima[c], Tsugikazu Komoda*[c]

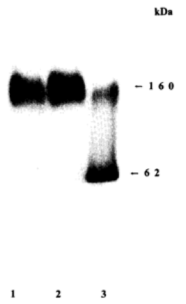
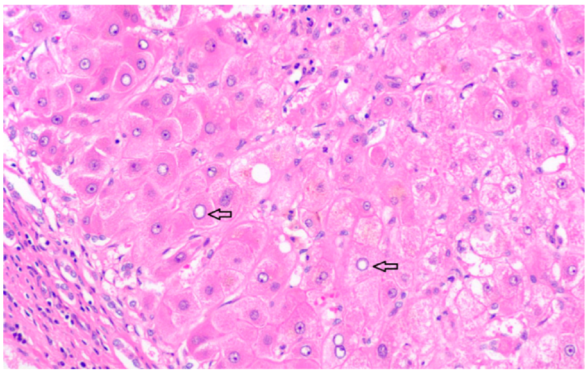


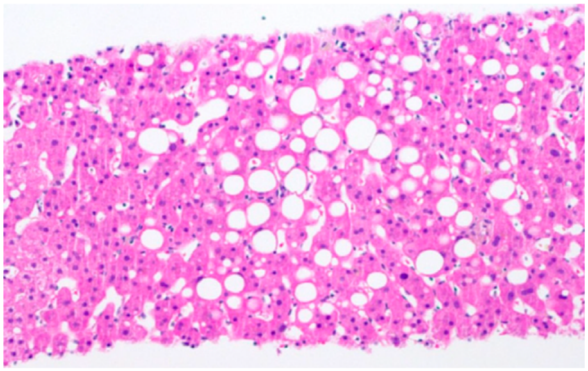
Fig. 2. Relative molecular size of the patient ALP by Western blotting using anti-bone ALP serum. Lane 1, healthy child (ALP activity: 339 units/l); lane 2, healthy child (468 units/l); lane 3, the patient (9 units/l); kDa, kilodalton. The Western blotting conditions are described in Methods.

Clinica Chimica Acta, 1995

Rôle de la biopsie hépatique



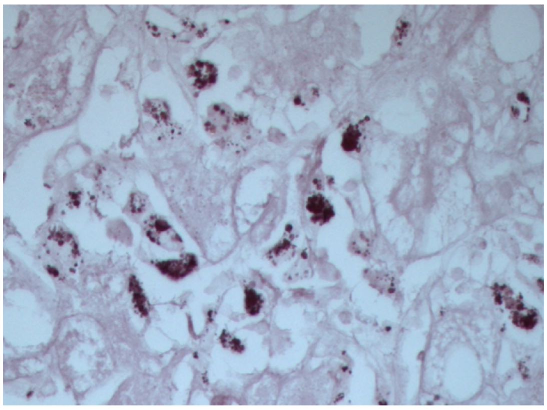
H&E: noyaux avec glycogène



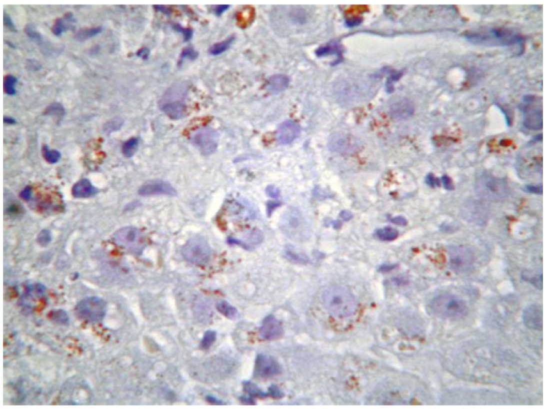
H&E: stéatose

Guindi, Semin Diagn Pathol, 2019

Rôle de la biopsie hépatique

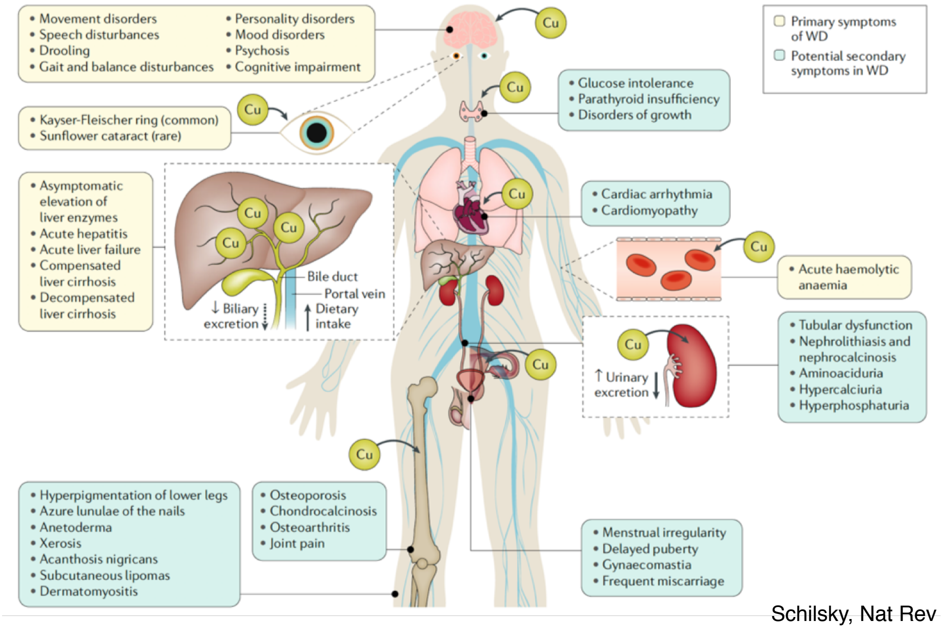


Orcéine



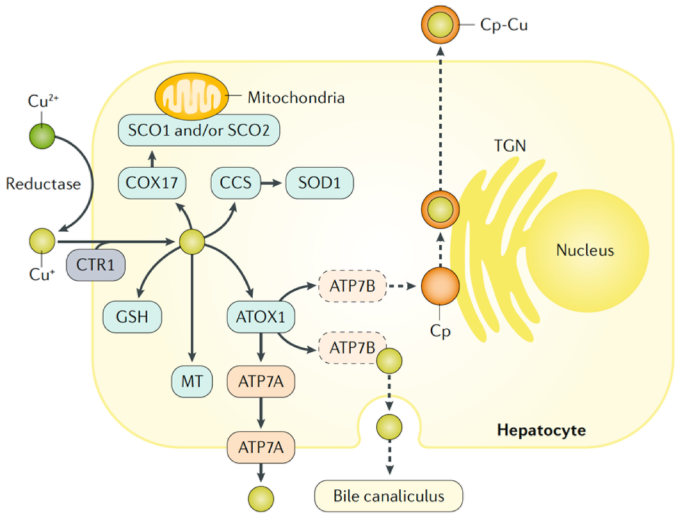
Rhodanine

Guindi, Semin Diagn Pathol, 2019; Schilsky, Nat Rev Dis Prim, 2018


• Movement disorders
• Speech disturbances
• Drooling
• Gait and balance disturbances
• Personality disorders
• Mood disorders
• Psychosis
• Cognitive impairment
Cu
☐ Primary symptoms of WD
☐ Potential secondary symptoms in WD
Cu
• Glucose intolerance
• Parathyroid insufficiency
• Disorders of growth
Cu
• Kayser-Fleischer ring (common)
• Sunflower cataract (rare)
• Asymptomatic elevation of liver enzymes
• Acute hepatitis
• Acute liver failure
• Compensated liver cirrhosis
• Decompensated liver cirrhosis
Cu
Cu
Cu
Bile duct
Portal vein
↓ Biliary excretion
↑ Dietary intake
Cu
• Cardiac arrhythmia
• Cardiomyopathy
Cu
• Acute haemolytic anaemia
Cu
↑ Urinary excretion
Cu
• Tubular dysfunction
• Nephrolithiasis and nephrocalcinosis
• Aminoaciduria
• Hypercalciuria
• Hyperphosphaturia
Cu
• Hyperpigmentation of lower legs
• Azure lunulae of the nails
• Anetoderma
• Xerosis
• Acanthosis nigricans
• Subcutaneous lipomas
• Dermatomyositis
• Osteoporosis
• Chondrocalcinosis
• Osteoarthritis
• Joint pain
• Menstrual irregularity
• Delayed puberty
• Gynaecomastia
• Frequent miscarriage

Schilsky, Nat Rev Dis Prim, 2018

Mécanismes


Cp-Cu
Cu^{2+}
Mitochondria
SCO1 and/or SCO2
Reductase
COX17
CCS
SOD1
TGN
Cu^{+}
CTR1
Nucleus
GSH
ATOX1
ATP7B
Cp
ATP7B
MT
ATP7A
ATP7A
Hepatocyte
Bile canaliculus

Mutations dans le gène ATP7B (> 700 connues)

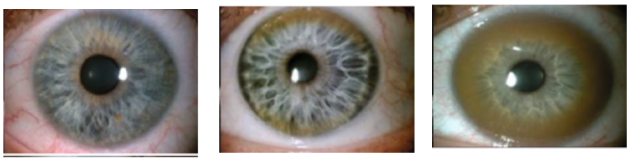
Inactivation de ATP7B, protéine responsable de

1) l'excrétion de cuivre dans la bile et
2) son incorporation dans l'apo-coeruloplasmine

Incidence 1: 30'000 (Sardaigne 1: 7000)

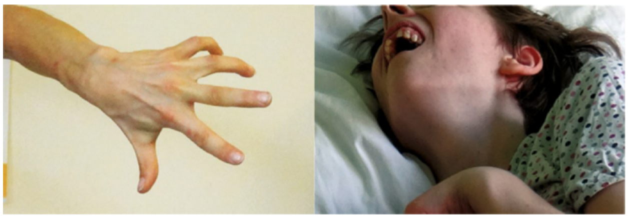
Schilsky, Nat Rev Dis Prim, 2018

Manifestations cliniques



Anneau de Kayser-Fleischer: 95% des patients avec symptomes neurologiques

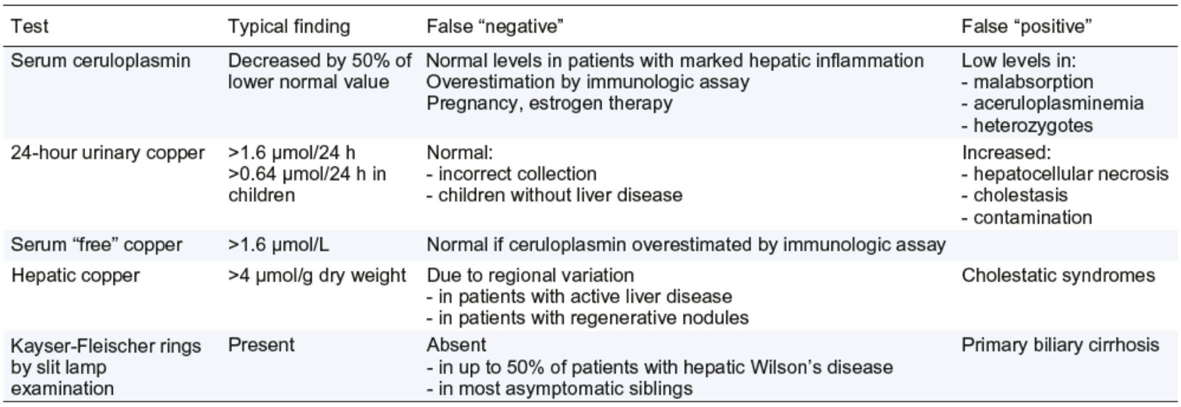
>50% des patients sans symptomes neurologiques



Akinetic-rigid syndrome
Dystonie
Tremblements
Dysphagie
Dysarthrie
Dépression, instabilité émotionnelle
Psychoses

Schilsky, Nat Rev Dis Prim, 2018

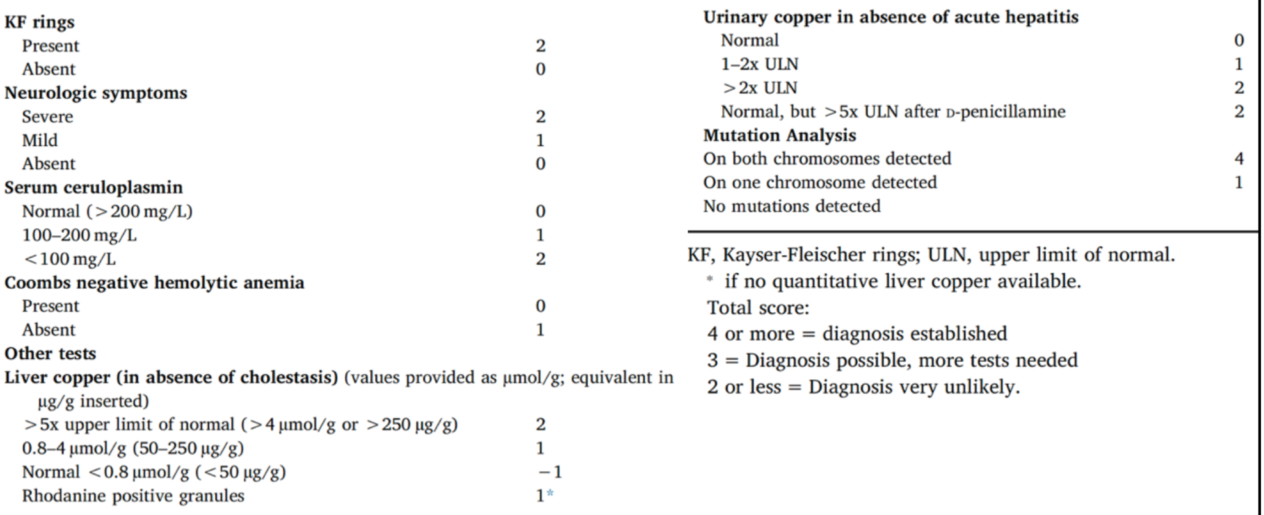
Diagnostic



Test	Typical finding	False "negative"	False "positive"
Serum ceruloplasmin	Decreased by 50% of lower normal value	Normal levels in patients with marked hepatic inflammation Overestimation by immunologic assay Pregnancy, estrogen therapy	Low levels in: - malabsorption - aceruloplasminemia - heterozygotes
24-hour urinary copper	>1.6 μmol/24 h >0.64 μmol/24 h in children	Normal: - incorrect collection - children without liver disease	Increased: - hepatocellular necrosis - cholestasis - contamination
Serum "free" copper	>1.6 μmol/L	Normal if ceruloplasmin overestimated by immunologic assay	
Hepatic copper	>4 μmol/g dry weight	Due to regional variation - in patients with active liver disease - in patients with regenerative nodules	Cholestatic syndromes
Kayser-Fleischer rings by slit lamp examination	Present	Absent - in up to 50% of patients with hepatic Wilson's disease - in most asymptomatic siblings	Primary biliary cirrhosis

EASL, CPG, 2012

Score de Leipzig



KF rings	
Present	2
Absent	0
Neurologic symptoms	
Severe	2
Mild	1
Absent	0
Serum ceruloplasmin	
Normal (>200 mg/L)	0
100–200 mg/L	1
<100 mg/L	2
Coombs negative hemolytic anemia	
Present	0
Absent	1
Other tests	
Liver copper (in absence of cholestasis) (values provided as μmol/g; equivalent in μg/g inserted)	
>5x upper limit of normal (>4 μmol/g or >250 μg/g)	2
0.8–4 μmol/g (50–250 μg/g)	1
Normal <0.8 μmol/g (<50 μg/g)	−1
Rhodanine positive granules	1*
Urinary copper in absence of acute hepatitis	
Normal	0
1–2x ULN	1
>2x ULN	2
Normal, but >5x ULN after D-penicillamine	2
Mutation Analysis	
On both chromosomes detected	4
On one chromosome detected	1
No mutations detected	

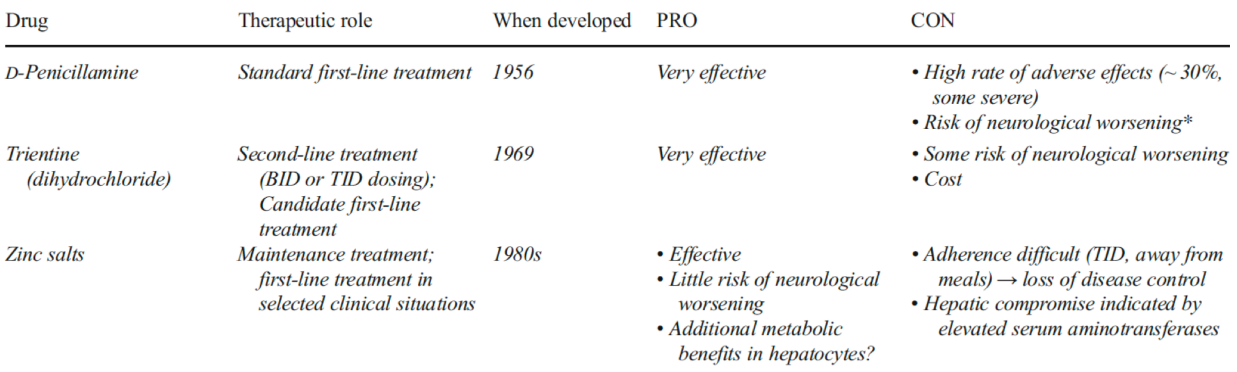
KF, Kayser-Fleischer rings; ULN, upper limit of normal.

* if no quantitative liver copper available.

Total score:
4 or more = diagnosis established
3 = Diagnosis possible, more tests needed
2 or less = Diagnosis very unlikely.

Ferenci, Liver Int, 2003

Principes du traitement



Drug	Therapeutic role	When developed	PRO	CON
D-Penicillamine	*Standard first-line treatment*	*1956*	*Very effective*	• *High rate of adverse effects (~ 30%, some severe)* • *Risk of neurological worsening**
Trientine (dihydrochloride)	*Second-line treatment (BID or TID dosing); Candidate first-line treatment*	*1969*	*Very effective*	• *Some risk of neurological worsening* • *Cost*
Zinc salts	*Maintenance treatment; first-line treatment in selected clinical situations*	*1980s*	• *Effective* • *Little risk of neurological worsening* • *Additional metabolic benefits in hepatocytes?*	• *Adherence difficult (TID, away from meals) → loss of disease control* • *Hepatic compromise indicated by elevated serum aminotransferases*

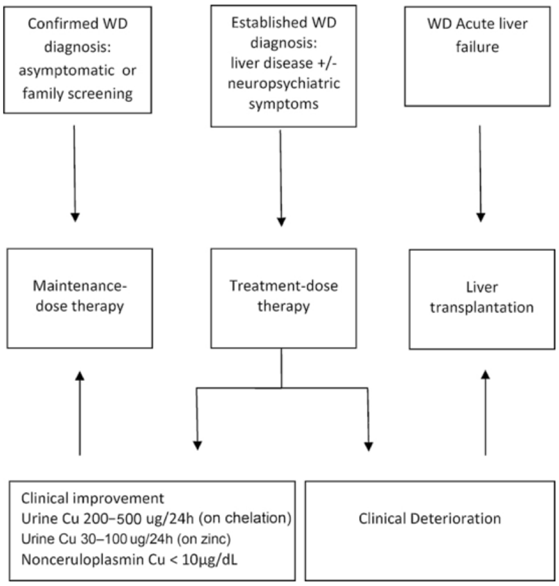
Roberts, Curr Gastroenterol Rep, 2018

Principes du traitement

D-pénicillamine (Metalcaptase, D)
250 mg/j – 1500 mg/j
Suppression médullaire
Syndrôme néphrotique
Effets cutanés
+ pyridoxine 25-50 mg/sem

Trientine (Triogen, CH)
250 mg/j – 1500 mg/j
Effets cutanés
Nausées
Anémie

Zinc (Burgerstein gluconate de zinc, CH)
30 mg/j
Effets digestifs
Augmentation amylase/lipase



Confirmed WD diagnosis: asymptomatic or family screening

Established WD diagnosis: liver disease +/- neuropsychiatric symptoms

WD Acute liver failure

Maintenance-dose therapy

Treatment-dose therapy

Liver transplantation

Clinical improvement
Urine Cu 200–500 ug/24h (on chelation)
Urine Cu 30–100 ug/24h (on zinc)
Nonceruloplasmin Cu < 10µg/dL

Clinical Deterioration

Pendant la grossesse:
continuer le traitement

Allaitement:
Ne pas allaiter et ne pas interrompre le tt pour allaiter!

Rosencrantz, Semin Liv Dis, 2011

Take home messages: tests hépatiques perturbés

Le médecin de famille peut faire beaucoup
(s'il veut!)

Durée prolongée = consultation avec un spécialiste

Phosphatase alcaline normale ou diminuée:
pensez à la maladie de Wilson