2018 11th Paris Hepatology Conference

Monday 15th January 2018

# Optimal management of auto-immune

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# Mister F, 32 year old

**October 2014 : admitted to the hospital for acute severe hepatitis**

Since 1 month: jaundice, fatigue

Laboratory tests at admission

| | | | | | |
|---|---|---|---|---|---|
| AST IU/L | 498 | Tot bili µmol/L | 334 | GB G/L | 9 |
| ALT IU/L | 602 | PT % | 20 | Hb g/L | 15 |
| GGT IU/L | 80 | INR | 5.22 | Plts G/L | 125 |
| Creatinine | 86 | FV % | 21 | MELD | 37 |

# Who is Mister F ?

**Lifestyle:**

- lives in a camping car
- wife, 1 child
- Unemployed
- Alcohol consumption > 150 g/d
- Tobacco 1 p/d
- Regular cannabis consumption

**Past medical or surgical history:**

Uneventful

No recent travel, no IV drugs, no medications

# Diagnostic work-up

## Virology

Ab HAV, Ag HBs, Ab HBs, Ab HBc, Ab HCV, HIV, HTLV 1-2, PCR CMV, EBV, HSV, HHV6, HHV8, HEV → Negatives

## Immunology

Anti-tissue Ab: ANA + 1:80 homogeneous and speckled, AMA, ASMA, anti-LKM1, anti-LC1 → negatives

IgG 13.90 (N<12.5), IgA 5.32 (N<3.07), IgM 2.31 (N<1.53)

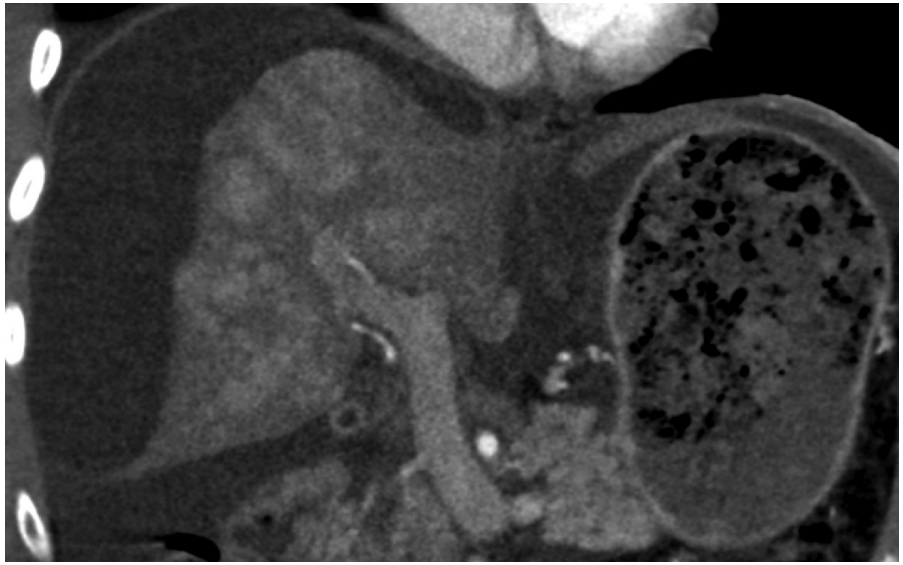
## Infection

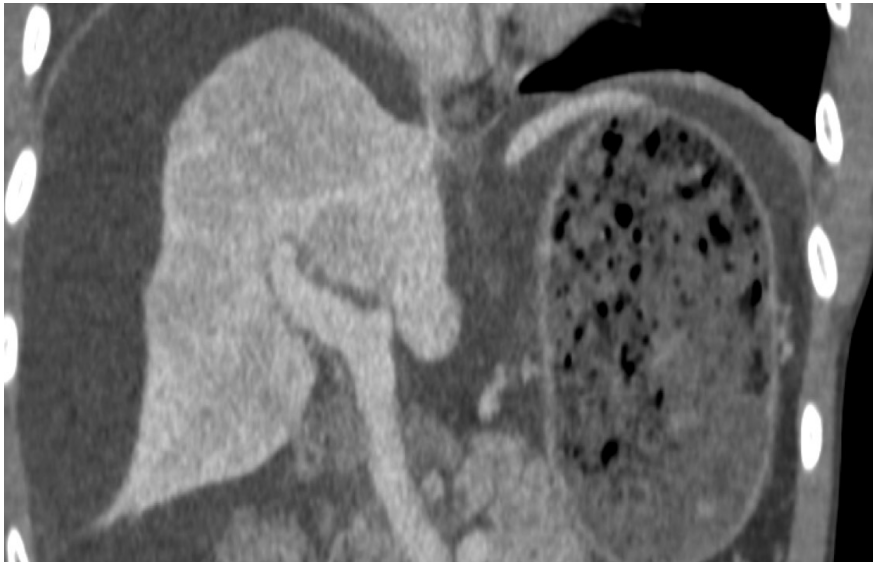
Urinary test - , blood test -, ascites -

## Toxic

Plasma and urine : THC +

# At CT scan





# How would you manage this patient ?

A. Perform a transjugular liver biopsy

B. Administer corticosteroids

C. List the patient for liver transplantation

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# Simplified diagnostic criteria of the International Autoimmune Hepatitis Group

| Feature/parameter | Discriminator | Score |
|---|---|---|
| ANA or SMA+ | ≥1:40 | +1* |
| ANA or SMA+ | ≥1:80 | +2* |
| or LKM+ | ≥1:40 | +2* |
| or SLA/LP+ | Any titer | +2* |
| IgG or γ-globulins level | >upper limit of normal<br>>1.1x upper limit | +1<br>+2 |
| Liver histology (evidence of hepatitis is a necessary condition) | Compatible with AIH<br>Typical of AIH<br>Atypical | +1<br>+2<br>0 |
| Absence of viral hepatitis | No<br>Yes | 0<br>+2 |

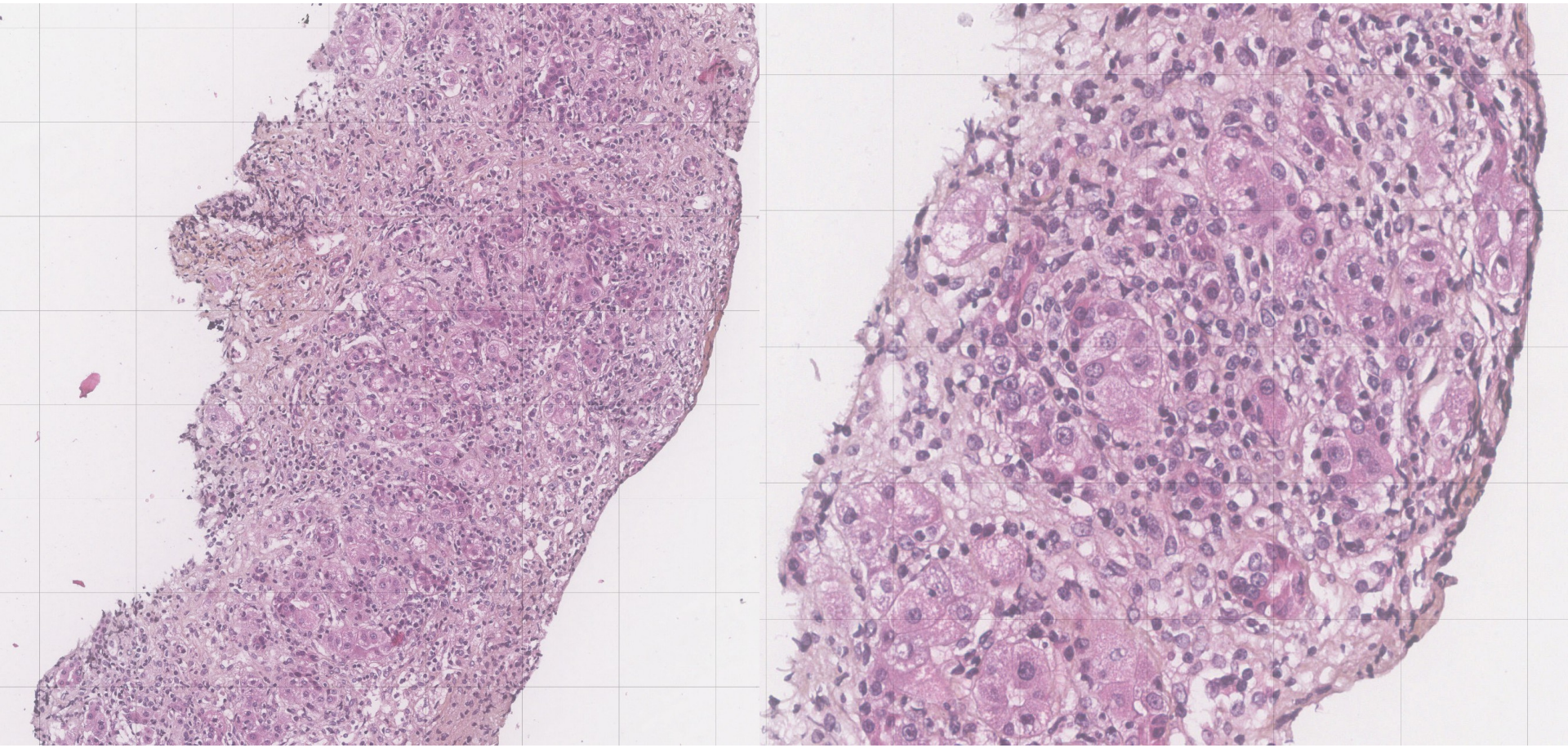
?

**= 6**

Definite AIH ≥ 7 and Probable AIH ≥ 6

**Hennes, Hepatol 2008**

# At histology



Pour courtoisie du Dr M Sebagh

**« Hepatitis with sub acute evolution, sub-massive necrosis. The presence of plasma cells is evocative of AIH»**

# AIH histological features

## Typical

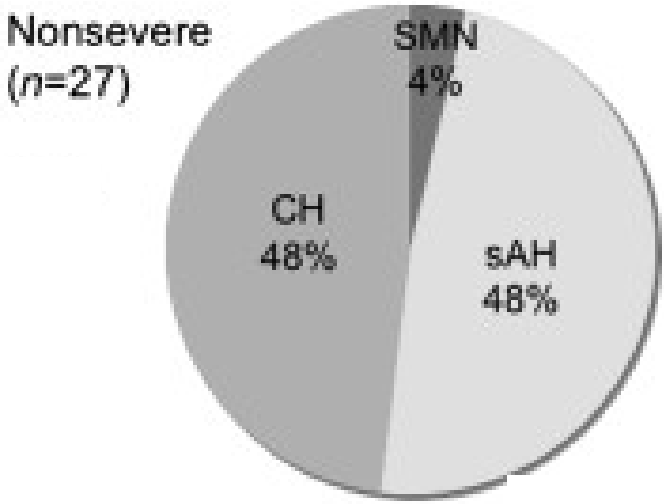
- Interface hepatitis
- Lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule
- Emperipolesis
- Hepatic rosette

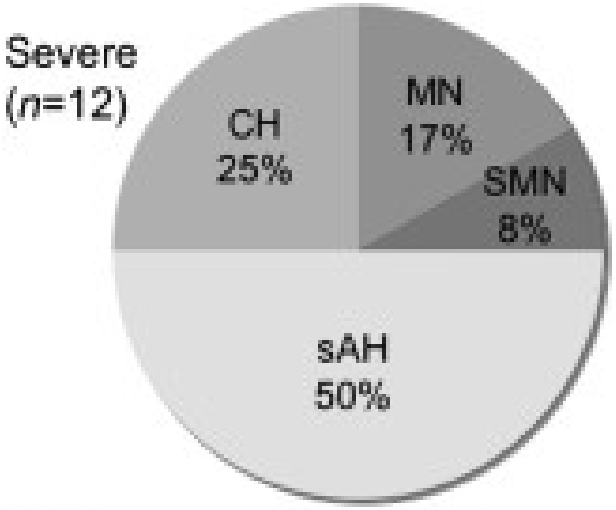
## Compatible

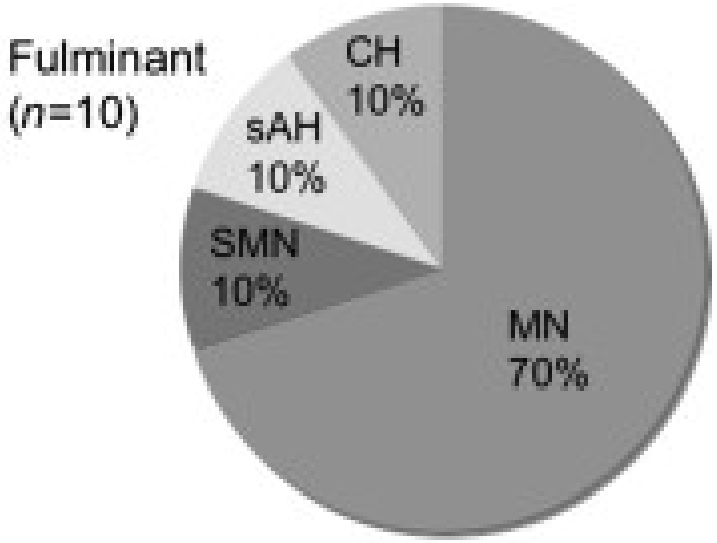
- Chronic hepatitis with lymphocytic infiltration without all the features considered typical

**EASL Guidelines, Journal of Hepatol 2015**

# Histology in acute onset of AIH: challenging




**CH**: chronic hepatitis
**MN**: massive necrosis
**SMN**: submassive necrosis
**sAH**: severe acute hepatitis

**Fujiwara, Liver International 20**

# Centrilobular inflammatory infiltration

## Infiltration of Plasma Cells into Liver Tissue

| | Portal areas (frequency per portal area)[a] | | | | Central areas (no. of specimens containing plasma cells) |
|---|---|---|---|---|---|
| | <1% | 1%–5% | 5%–10% | >10% | |
| Acute AIH (n = 15) | 1 | 6 | 5 | 3 | 5 (33%) |
| AH-HAV (n = 15) | 13 | 2 | 0 | 0 | 0 |
| AH-HBV (n = 25) | 22 | 3 | 0 | 0 | 0 |
| AH-HCV (n = 15) | 12 | 2 | 1 | 0 | 0 |
| AH-drug (n = 10) | 9 | 1 | 0 | 0 | 0 |

**Abe, Clinical Gstroenterol and Hepatol 2007**

# Characteristic histological features in AIH-ALF

72 patients from the ALF Study.
The diagnosis of probable AIH-ALF was based on 4 features:

1. Massive hepatic necrosis
2. Lymphoid follicles
3. Plasma-cell infiltration
4. Central perivenulitis

**Histological features of AIH-ALF predominate in the centrilobular zone**

**Stravitz, Hepatology**

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| ANA or SMA+ | ≥1:40 | +1* |
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| or SLA/LP+ | Any titer | +2* |
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| Liver histology (evidence of hepatitis is a necessary condition) | Compatible with AIH<br>Typical of AIH<br>Atypical | +1<br>+2<br>0 |
| Absence of viral hepatitis | No<br>Yes | 0<br>+2 |
| | | **= 8** |

Definite AIH ≥ 7 and Probable AIH ≥ 6

**Hennes, Hepatol 2008**

# Mister F, 32 year old

**October 2014 : admitted to the hospital for acute severe hepatitis**

Clinical exam: jaundice, no hepatic encephalopathy

Laboratory tests at admission and 3 days later

| | | | |
|---|---|---|---|
| AST IU/L | 498 > 400 | **Tot bili µmol/L** | **334 > 349** |
| ALT IU/L | 602 > 559 | **PT %** | **20 > 14** |
| GGT IU/L | 80 > 97 | **INR** | **5.22 > 5.9** |
| Creatinine | 96 | **FV %** | **21 > 19** |

# Would you treat this patient ?

A. No. The patient is too severe. List the patient for liver transplantation

B. Yes. Treat with 1mg/kg/day of corticosteroids

C. Yes. Treat with 0.5mg/kg/day + azathioprine

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# Management of AS-AIH

29. Patients with acute severe AIH should be treated with high doses of intravenous corticosteroids (≥1 mg/kg) as early as possible. Lack of improvement within seven days should lead to listing for emergency liver transplantation **(III)**

**EASL Guidelines, J Hepatol 2**

# Management of Acute Liver Failure

## King's College criteria

**ALF not due to paracetamol**

- INR >6.5 or
- 3 out of 5 following criteria:
  - Aetiology: indeterminate aetiology hepatitis, drug-induced hepatitis
  - Age <10 years or >40 years
  - Interval jaundice-encephalopathy >7 days
  - Bilirubin >300 µmol/L
  - INR >3.5

**Beaujon-Paul Brousse criteria (Clichy)**

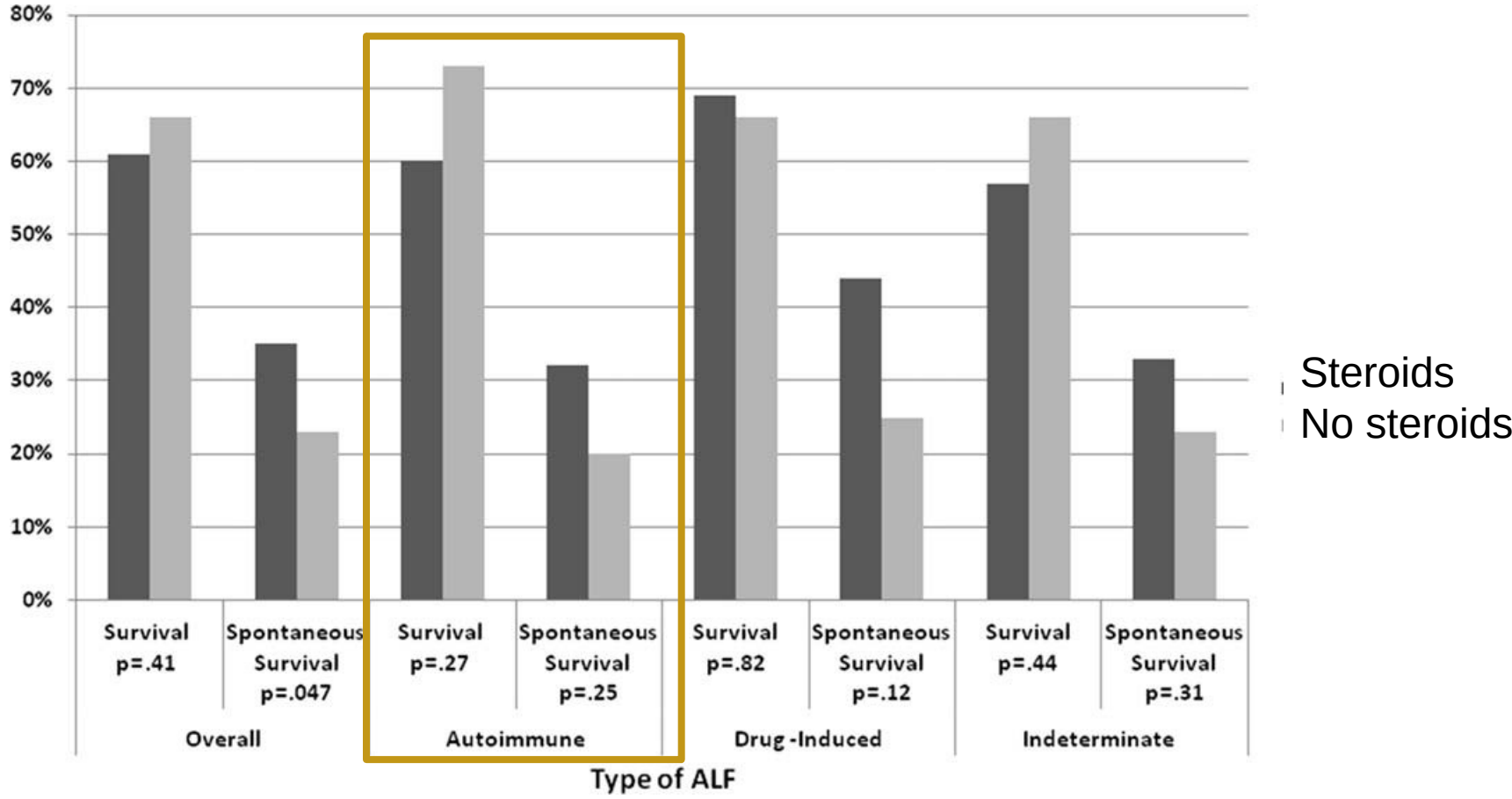
- Confusion or coma (hepatic encephalopathy stage 3 or 4)
- Factor V <20% of normal if age <30 year

  or
- Factor V <30% if age >30 year

**EASL Guidelines, J Hepatol 2**

# Steroid Use in Acute Liver Failure

Overall and spontaneous survival among different aetiologies of ALF




Mean INR 3.33

***Karkhanis, Hepatology 2014***

## The role of corticosteroids is still highly debatable in acute severe autoimmune hepatitis

### Uselessness of corticosteroids in severe and fulminant forms

*Ichai, Liver Transpl 2007*

12/16 (75%) treated patients

↓

10/12 (83%) liver transplantation

### The role of corticosteroids in modifying outcome

*Yeoman, J Hepatol 2015*

23/32 (75%) treated patients

↓

10/23 (43%) liver transplantation

*De Martin, J Hepatol 2015*

# Prognostic factors in AS-AIH patients treated with corticosteroids

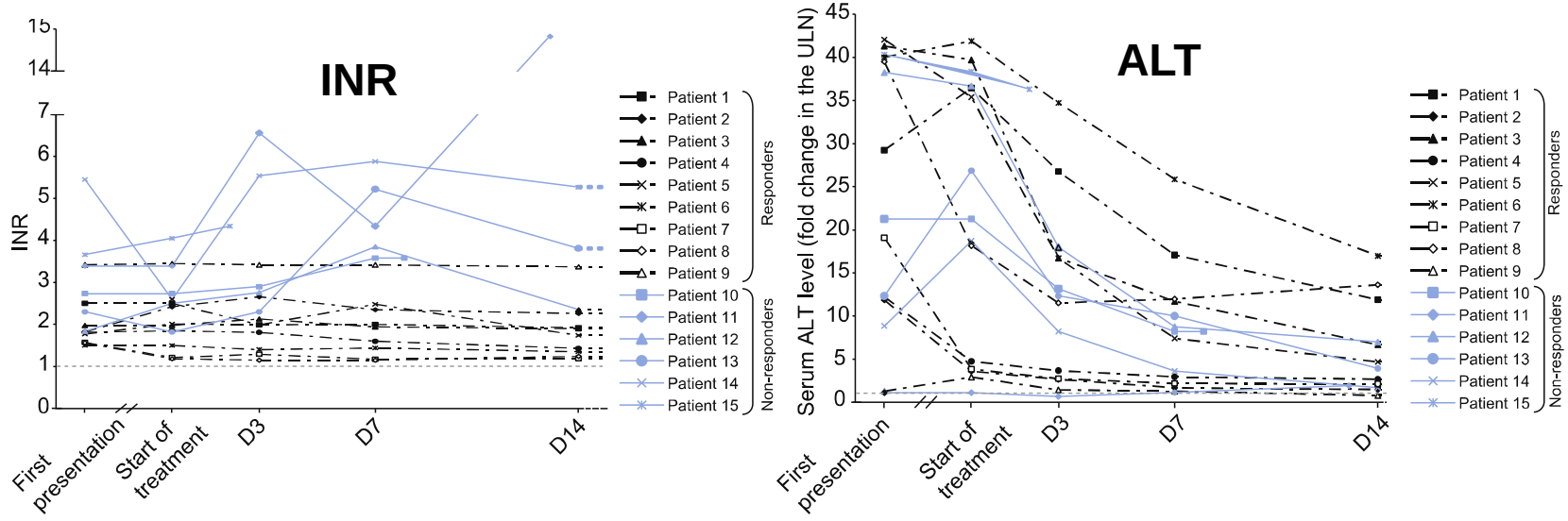
15/17 (88%) treated patients

↓

9/15 (60%) liver transplantation

Prognostic factors :

- Massive Hepatic Necrosis type 5
- INR at presentation : cut off 2.46
- MELD at presentation : cut off 28.5




*Moenne-Loccoz, J Hepatol 2016*

# Early predictors of treatment failure in icteric AIH..

**At diagnosis**

- Median bilirubin

(451 lmol/L vs 262 lmol/L, P

5 0.02)

- INR (1.62 vs 1.33, P 5

  0.005),

- MELD score (26 vs 20, P

  5 0.02)

**Analysis of area under the AUROC values at day 7**

- Delta bilirubin

  (AUROC 0.68)

- Delta creatinine

  (0.69)

- Delta MELD (0.79)

Heterogeneous population including pediatric patients, severe and not severe AIH

*Yeoman, Hepatology 2011*

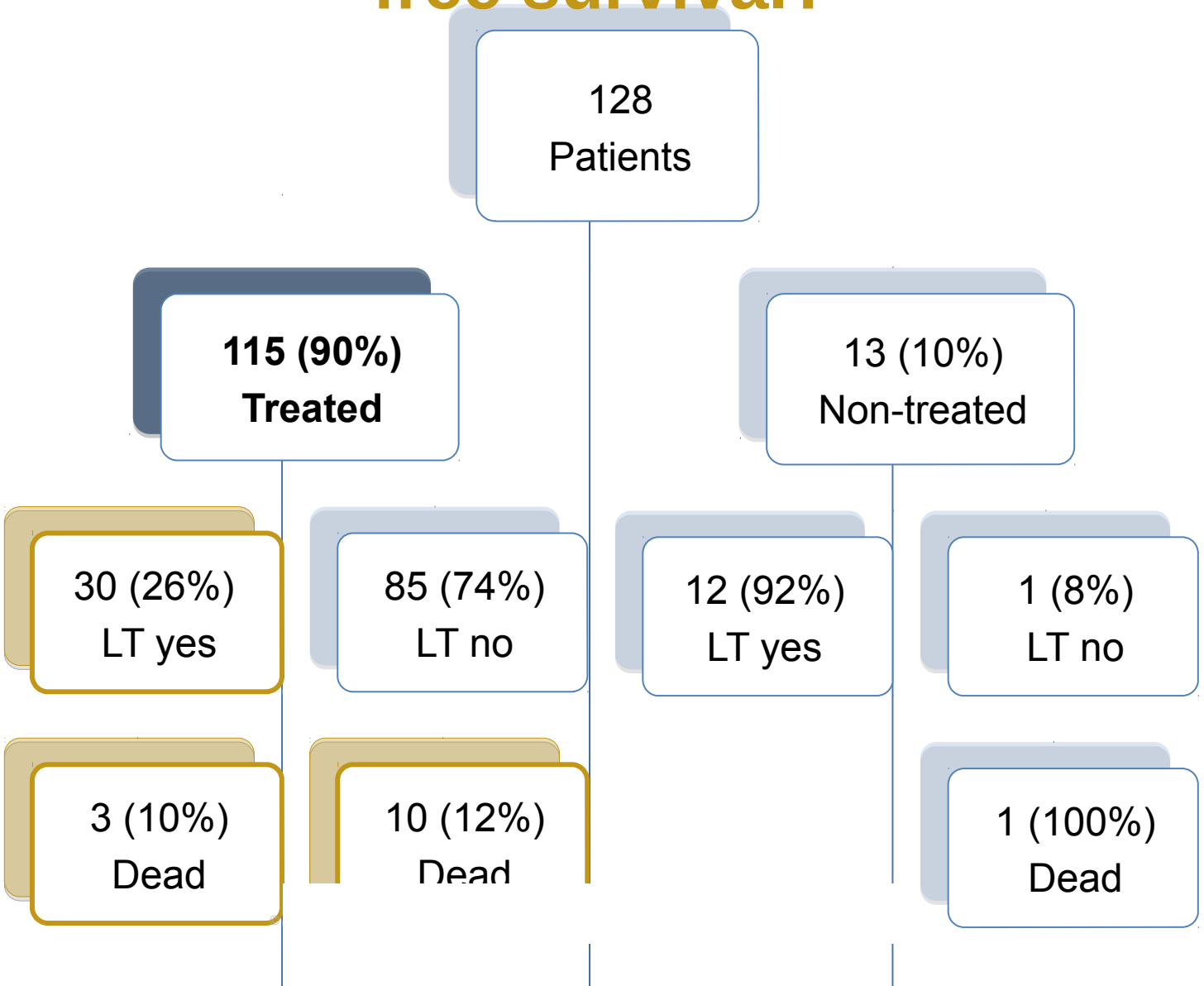
# Multicenter French study

FILFOIE
FILIÈRE DE SANTÉ MALADIES RARES DU FOIE DE L'ADULTE ET DE L'ENFANT

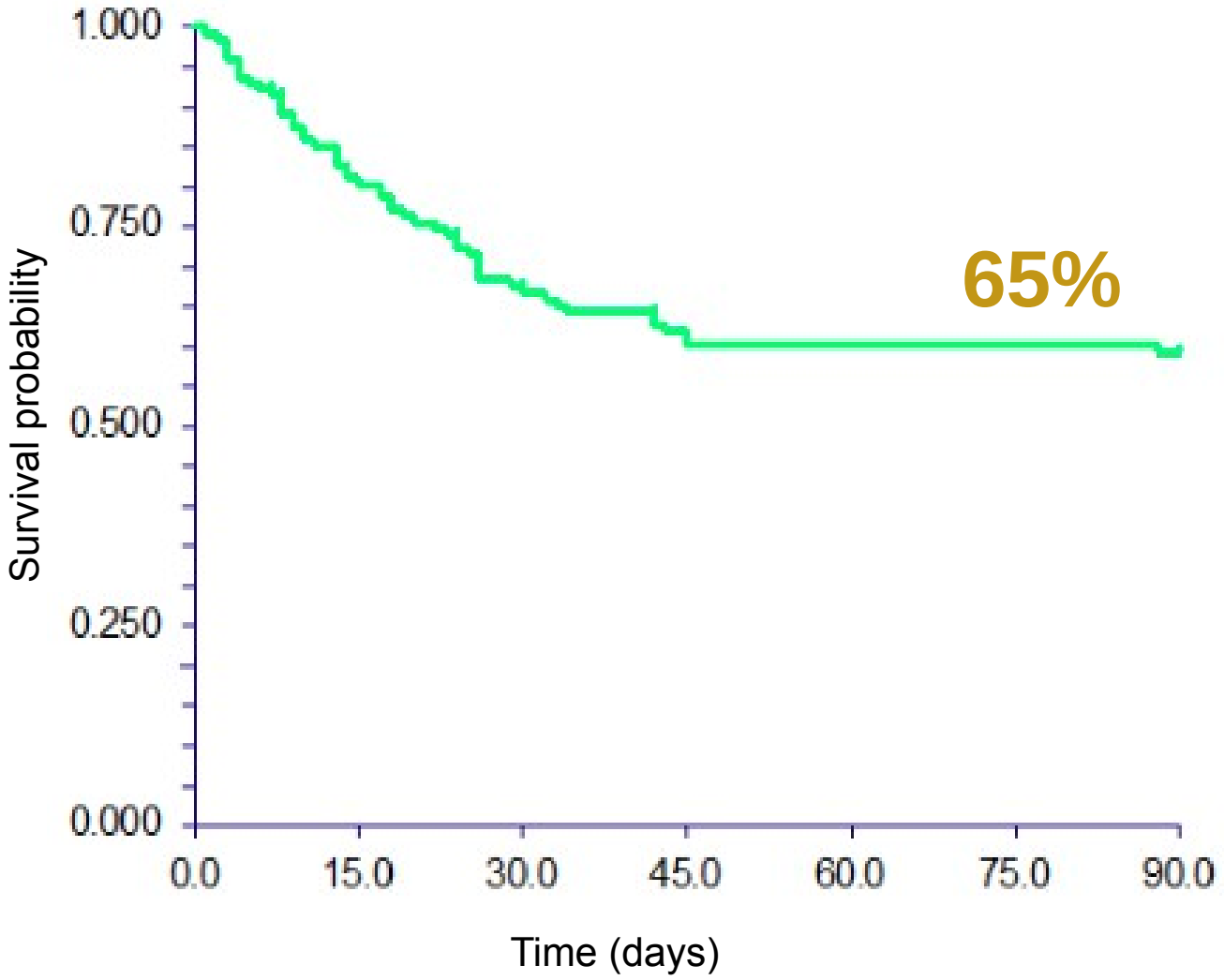
Hépatinov

HOPITAL PAUL BROUSSE
Centre Hépato-Biliaire

# Which are the predictive factors for corticosteroid response defined by the LT-free survival?



# Corticosteroid response at 90 days



# Predictive factors of corticosteroid response

| | Responders N= 75 | Non Responders* N= 38 | p |
|---|---|---|---|
| Age, years | 52 [39-63] | 54 [41-61] | 0.9803 |
| Gender, female | 58 (75) | 24 (67) | 0.3365 |
| **HE** | **1 (1)** | **5 (14)** | **0.0185** |
| ALT, IU/L | 784 [407-1120] | 699 [408-1124] | 0.9067 |
| Total bilirubin, µmol/L | 272 [207-386] | 346 [265-414] | 0.0803 |
| **INR** | **1.6 [1.4-2]** | **2.7 [2-3.6]** | **<.0001** |
| Creatinine, µmol/L | 59 [52-72] | 63 [50-71] | 0.9374 |
| **MELD** | **22 [21-24]** | **28 [26-32]** | **<.0001** |
| **Platelets, G/L** | **202 [145-275]** | **130 [81-196]** | **0.0007** |
| **Infection** | **13 (19)** | **13 (36)** | **0.0468** |
| Admission corticosteroids, days | 7 [3-10] | 4 [2-9] | 0.4058 |
| **Fibrosis stage 0-1/ 2-3/ 4** | **29(43)/27(40)/12(18)** | **14(56)/3(12)/8(32)** | **0.0333** |

2 patients were excluded, 1 dead and 1 LT before day 3 of corticosteroid therapy

*The continuous variables are expressed using median [range IQR 1st and 3rd]. The qualitative variables are expressed using number (%).*

# Predictive factors of corticosteroid response

| | Responders N= 75 | Non Responders* N= 38 | p | OR | 95%CI | p |
|---|---|---|---|---|---|---|
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| **INR** | **1.6 [1.4-2]** | **2.7 [2-3.6]** | **<.0001** | **8.533** | **3.270-22.26** | **<.0001** |
| Creatinine, µmol/L | 59 [52-72] | 63 [50-71] | 0.9374 | | | |
| **MELD** | **22 [21-24]** | **28 [26-32]** | **<.0001** | | | |
| **Platelets, G/L** | **202 [145-275]** | **130 [81-196]** | **0.0007** | | | |
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# Predictive factors of corticosteroid response

| | Responders N=75 | Non Responders* N=38 | p |
|---|---|---|---|
| Delta ALT d3-d0 | -132 [-391/-45] | -89 [-317/-13] | 0.3573 |
| **Delta Total bilirubin d3-d0** | **-51 [-85/-14]** | **17 [-19/64]** | **<.0001** |
| **Delta INR d3-d0** | **0 [-0.16/0.0]** | **0 [0.0/0.2]** | **0.0162** |
| **Delta MELD d3-d0** | **-0.9 [-2.2/0.07]** | **0.3 [-0.43-1.5]** | **0.0015** |
| Delta ALT d7-d0 | -278 [-577/-88] | -186[-482/-18] | 0.3841 |
| **Delta Total bilirubin d7-d0** | **-98 [-140/-22]** | **6.5 [-90/117]** | **0.0072** |
| **Delta INR d7-d0** | **-0.2 [-0.3/0.0]** | **0.2 [-0.2/0.4]** | **0.0004** |
| **Delta MELD d7-d0** | **-2.8 [-4.13/-1]** | **0.0 [-1.0/2.8]** | **0.0004** |

2 patients were excluded, 1 dead and 1 LT before day 3 of corticosteroid therapy

*The continuous variables are expressed using median [range IQR 1st and 3rd]. The qualitative variables are expressed using number (%).*

# Predictive factors of corticosteroid response

| | Responders N=75 | Non Responders* N=38 | p | OR | 95% CI | p |
|---|---|---|---|---|---|---|
| Delta ALT d3-d0 | -132 [-391/-45] | -89 [-317/-13] | 0.3573 | | | |
| **Delta Total bilirubin d3-d0** | **-51 [-85/-14]** | **17 [-19/64]** | **<.0001** | **1.017** | **1.001-1.034** | **0.0365** |
| **Delta INR d3-d0** | **0 [-0.16/0.0]** | **0 [0.0/0.2]** | **0.0162** | | | |
| **Delta MELD d3-d0** | **-0.9 [-2.2/0.07]** | **0.3 [-0.43-1.5]** | **0.0015** | | | |
| Delta ALT d7-d0 | -278 [-577/-88] | -186[-482/-18] | 0.3841 | | | |
| **Delta Total bilirubin d7-d0** | **-98 [-140/-22]** | **6.5 [-90/117]** | **0.0072** | **1.004** | **1.000-1.008** | **0.0485** |
| **Delta INR d7-d0** | **-0.2 [-0.3/0.0]** | **0.2 [-0.2/0.4]** | **0.0004** | | | |
| **Delta MELD d7-d0** | **-2.8 [-4.13/-1]** | **0.0 [-1.0/2.8]** | **0.0004** | | | |

2 patients were excluded, 1 dead and 1 LT before day 3 of corticosteroid therapy

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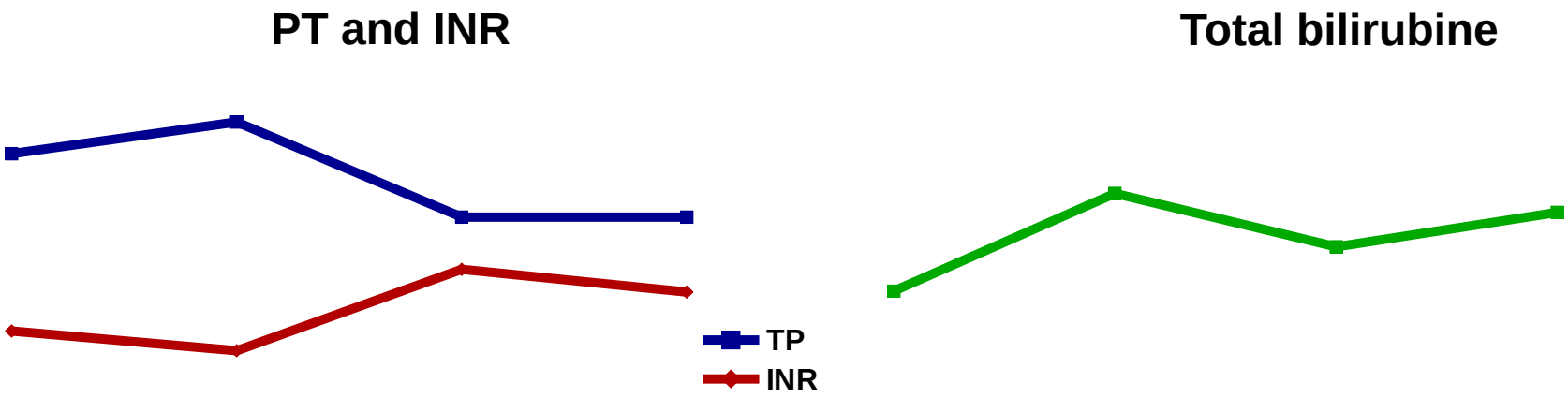
# Evolution of Mister F on corticosteroids

Corticosteroid initiation the 9th October (1mg/kg/day)




**At day 7 since corticosteroid administration MELD = 40 + grade 3 hepatic encephalopathy**

# 16.10.2014 Liver transplantation