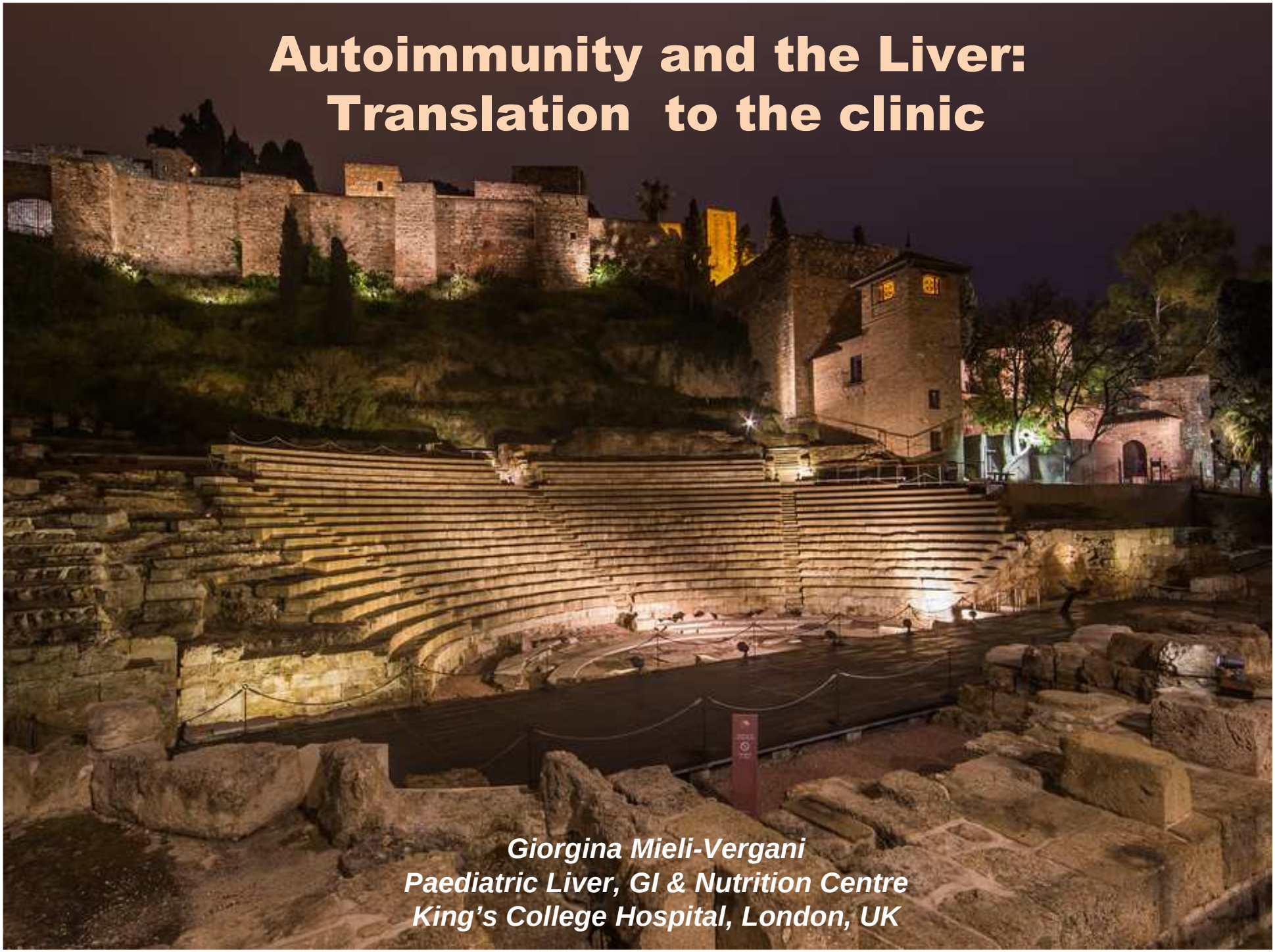
Autoimmunity and the Liver: Translation to the clinic



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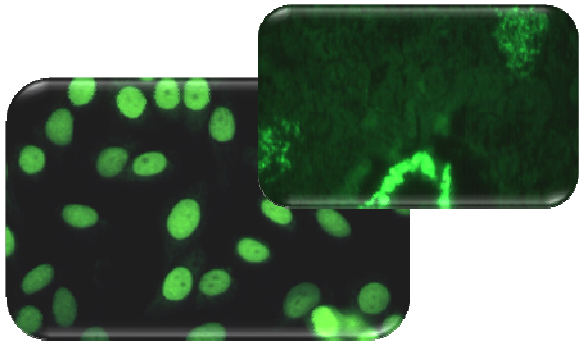
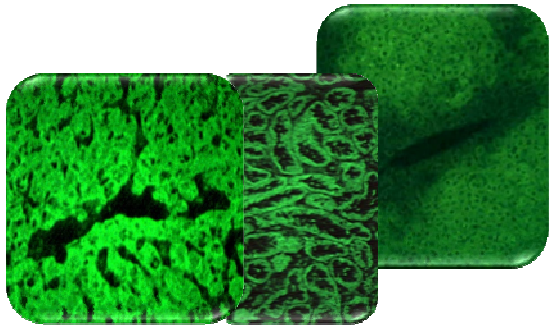
26 Jjanuary 2016

Autoimmune Hepatitis



type 1: adults and children



type 2: mainly children

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Autoimmune Hepatitis

Presentation

- adults: often chronic, mild/moderate severity

- children/young adults: often acute, aggressive

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Juvenile Autoimmune Hepatitis

- **type 1 (ANA/SMA positive): 2/3**
- **type 2 (LKM1 positive): 1/3**

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Juvenile Autoimmune Hepatitis

Similarities between Type 1 and Type 2 AIH

- females: *75%*
- associated AI disorders: *20%*
- family history of AI disease: *40%*
- high IgG: *80%*

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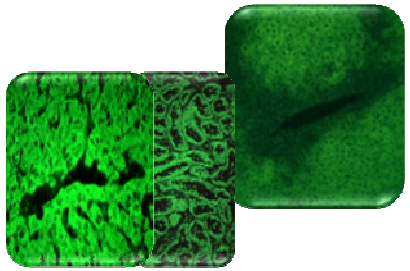
Juvenile Autoimmune Hepatitis

Differences between Type 1 and Type 2 AIH



LKM1 positive AIH presents:

- **at a younger age**
- **with partial IgA deficiency**
- **less frequently with cirrhosis**
- **more frequently with acute hepatic failure**

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Juvenile Autoimmune Hepatitis

~ 50% of children/adolescents with AIH-1 serology have an overlap syndrome with sclerosing cholangitis

Autoimmune Sclerosing Cholangitis

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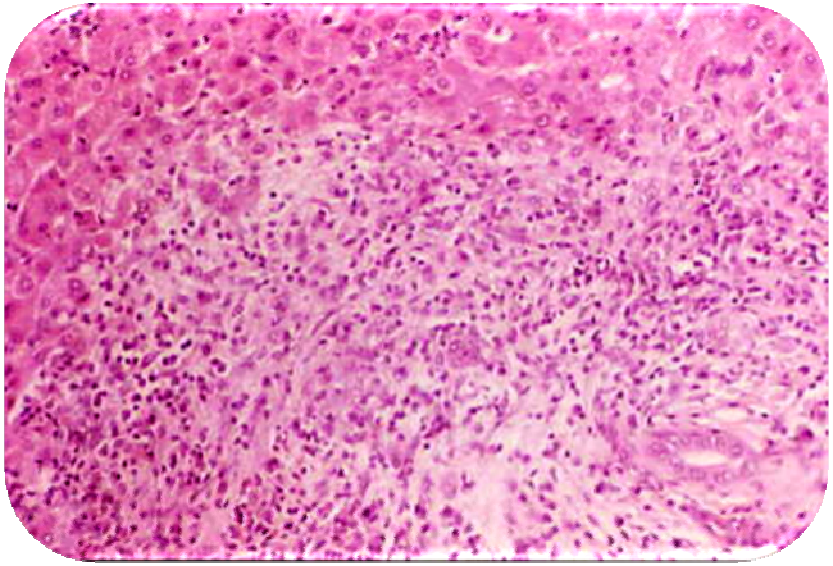
Autoimmune sclerosing cholangitis

Diagnostic Criteria



- interface hepatitis

- high IgG
- autoantibodies **(ANA/SMA)**

- abnormal cholangiogram

Gregorio et al, Hepatology 2001;33:544-553

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Autoimmune sclerosing cholangitis

- affects equally males and females
- GGT and AP often normal at presentation
- particularly high IgG levels
- frequent positivity for ANCA
- frequently associated with IBD (sometimes asymptomatic)

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Juvenile Autoimmune Liver Disease

Diagnostic criteria

- elevated transaminases
- exclusion of viral hepatitis, Wilson disease, NASH
- **positive autoantibodies**: ANA/SMA (titre ≥ 1:20) = **AIH-1** or **ASC**
  anti-LKM1 (titre ≥ 1:10), anti-LC1 = **AIH-2**
- elevated IgG
- **liver biopsy**: interface hepatitis/multilobular collapse
- **cholangiogram** (MRCP, ERCP): normal = **AIH**; abnormal = **ASC**

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Autoimmune Hepatitis

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treatment

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AIH – Definition of remission

- normal transaminase levels
- normal IgG levels

} adults

+

- negative/<1:20 ANA/SMA
  negative anti-LKM1

} children/ adolescents

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AIH – All presentations*
(excluding fulminant liver failure)

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standard treatment:

- **prednisolone**
- **azathioprine**

* *including acute liver failure with no or < grade 2 encephalopathy*

fulminant liver failure ► transplant

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Adulthood AIH

AASLD Guidelines

- **30 mg prednisone + 1–2 mg/Kg azathioprine/day**

or

- **prednisone monotherapy 40-60 mg/day**

AASLD Guidelines, Hepatology 2010; 51:2193-213

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AIH - Azathioprine (steroid-sparing agent)

Azathioprine can be *hepatotoxic*:

not advisable as first line Rx in ill, jaundiced patients

particularly if cirrhotic

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Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY
2015 vol. 63 | 971–1004

EASL Clinical Practice Guidelines: Autoimmune hepatitis☆

Adulthood AIH

Table 7. Treatment proposal for adult patients with AIH (e.g. 60 kg).

Week	Prednisolone (mg/day)	Azathioprine (mg/day)
1	60 (= 1 mg/kg body weight)	-
2	50	-
3	40	50
4	30	50
5	25	100*
6	20	100*
7 + 8	15	100*
8 + 9	12.5	100*
From week 10	10	100*

Reduction of prednisolone to 7.5 mg/day if aminotransferases reach normal levels and after three-months to 5 mg/day, tapering out at three-four months intervals depending on patient's risk factors and response. *Azathioprine dose of 1–2 mg/kg according to body weight.

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Juvenile AIH

Prednisolone

- 2 mg/Kg/day (maximum 60 mg/day)
- gradually decreased over **4-8 weeks** to **2.5-5 mg/day** depending on age

+ UDCA if ASC

(15 mg/Kg/day)

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Juvenile AIH

Azathioprine

- ***hepatotoxic*: never first line Rx in ill, jaundiced patients**
- **add if high steroid dose required to maintain normal or nearly normal AST or in the presence of serious steroid side effects**
- ***myelosuppressive*: start at low dose (0.5 mg/Kg/day) and increase gradually to 2 mg/Kg/day**

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Juvenile AIH

Rx schedule at King's

'Fine tuning' **to avoid severe side effects:**

- **weekly LFTs, INR, FBC**
- **aim to 80% AST decrease within 6 weeks**

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Juvenile AIH

80% ultimately require azathioprine

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AIH - Maintenance of remission

In adults:

- **sustained remission on azathioprine monotherapy** ***(Johnson et al, New Engl J Med 1995;333:958)***

In children:

- **successful in ANA/SMA+ AIH**
- **less successful in LKM1+ AIH**

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Juvenile AIH

*King's criteria for stopping treatment**

- **daily** treatment for at least **three years**
- at least one further year of **normal LFTs** & **IgG**, **negative** or **low titre autoantibodies** *(checked 3 monthly)*
- **no inflammation** on **liver biopsy** performed at the end of the year
- **gradual** discontinuation of azathioprine, then prednisolone

** never just before or during puberty*

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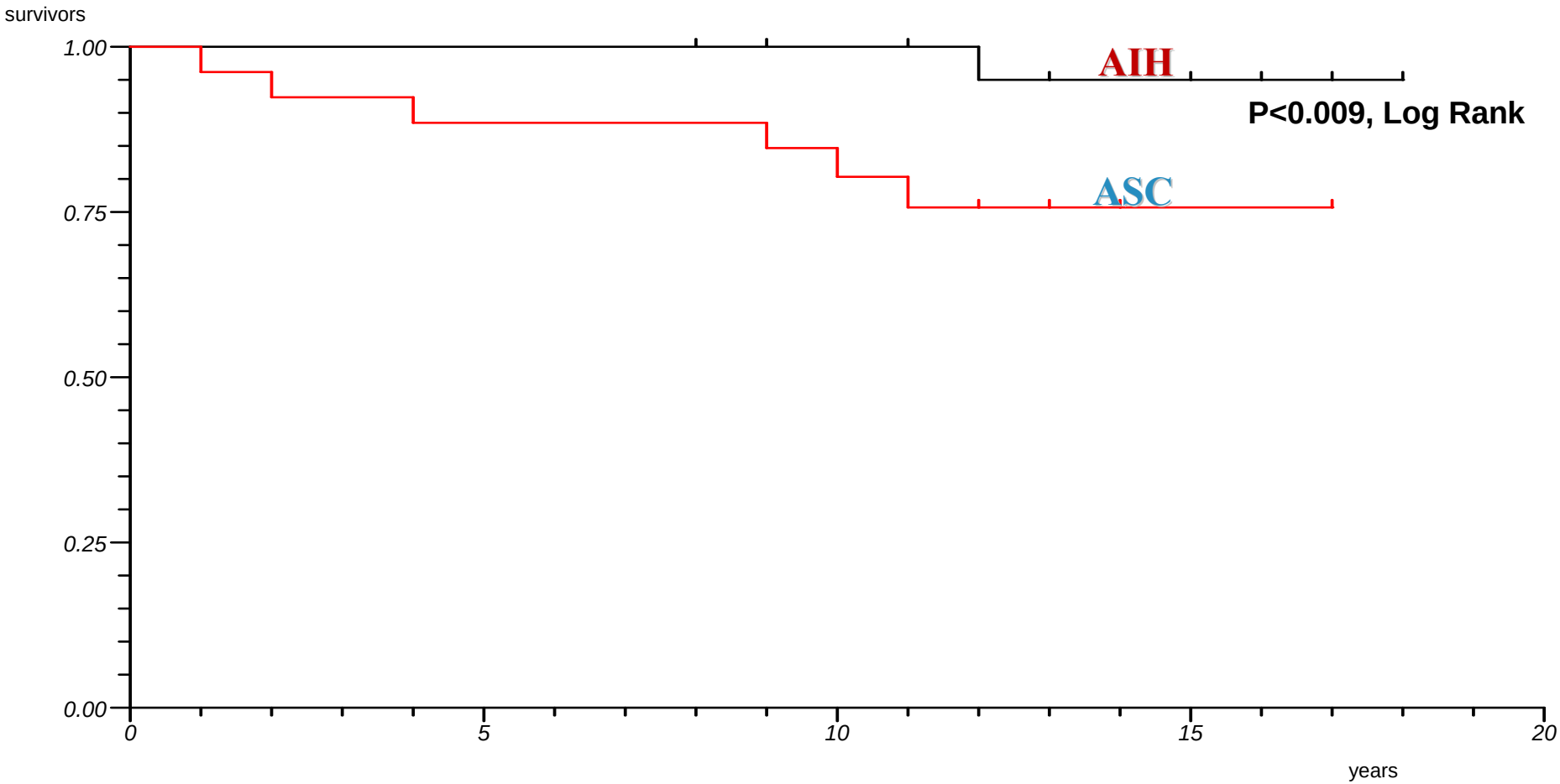
AIH vs ASC

13-year (8-29) follow up – *Transplant-free survival*



Scalori et al, Hepatology 2007;46 Suppl 1:555A

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AIH vs *ASC*

Outcome (King's prospective study)

	AIH-1	AIH-2	ASC
LT rate	6%	14%	27%
recurrence post LT	0%	0%	71%

Gregorio et al, Hepatology 2001;33:544-553
Scalori et al, Hepatology 2007;46 Suppl 1:555A

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Autoimmune sclerosing cholangitis

King's prospective study

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progression of liver disease and recurrence post transplant are associated to

active inflammatory bowel disease

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Autoimmune Hepatitis

Alternative treatments

- for induction of remission
- for difficult-to-treat patients

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Induction of remission

- 6-month CyA priming in AIH-1 followed by pred + aza:

  uncontrolled study, benefits unclear

- budesonide 3mg/tds + aza vs prednisone 40mg/od + aza

Alvarez et al, J Hepatol 1999;30:222

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Budesonide - AIH

Multicentre European Study - Study design

azathioprine 1-2 mg/Kg +

- **budesonide 3 mg tds, decreased upon response**

versus

- **prednisone 40 mg once daily reduced per protocol irrespective of response**

- **for 6 months, then budesonide to all for further 6 months**

Manns et al. Gastroenterology 2010;39:1198-206
Woynarowski et al. J Pediatr;163:1347-1353

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Budesonide - AIH

Definition of response

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normal transaminase levels

without steroid side effects

Manns et al. Gastroenterology 2010;39:1198-206
Woynarowski et al. J Pediatr;163:1347-1353

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Budesonide - AIH

European multicentre study - 203 pts

- **budesonide:** **60% remission**
- **prednisone:** **39% remission**

Manns et al, Gastroenterology 2010;139:1198-206

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Budesonide – Juvenile AIH

Multicentre European Study
Paediatric cohort - 46 patients, 10-18 yr

complete response	budesonide	prednisone
6 months	16%	15%
12 months	50%*	42%*

** compared to ~90% with King's protocol*

Woynarowski et al. J Pediatr;163:1347-1353

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Difficult-to-treat patients: resistant or unresponsive

- **MMF**

  retrospective studies, more effective in AIH than in ASC [teratogenic!]

- **Calcineurin inhibitors**
- **Rituximab**
- **anti-TNFα**

} ***anecdotal experience***

Aw et al, J Hepatol 2009;51:156

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Thank you

Children's Liver Disease Foundation

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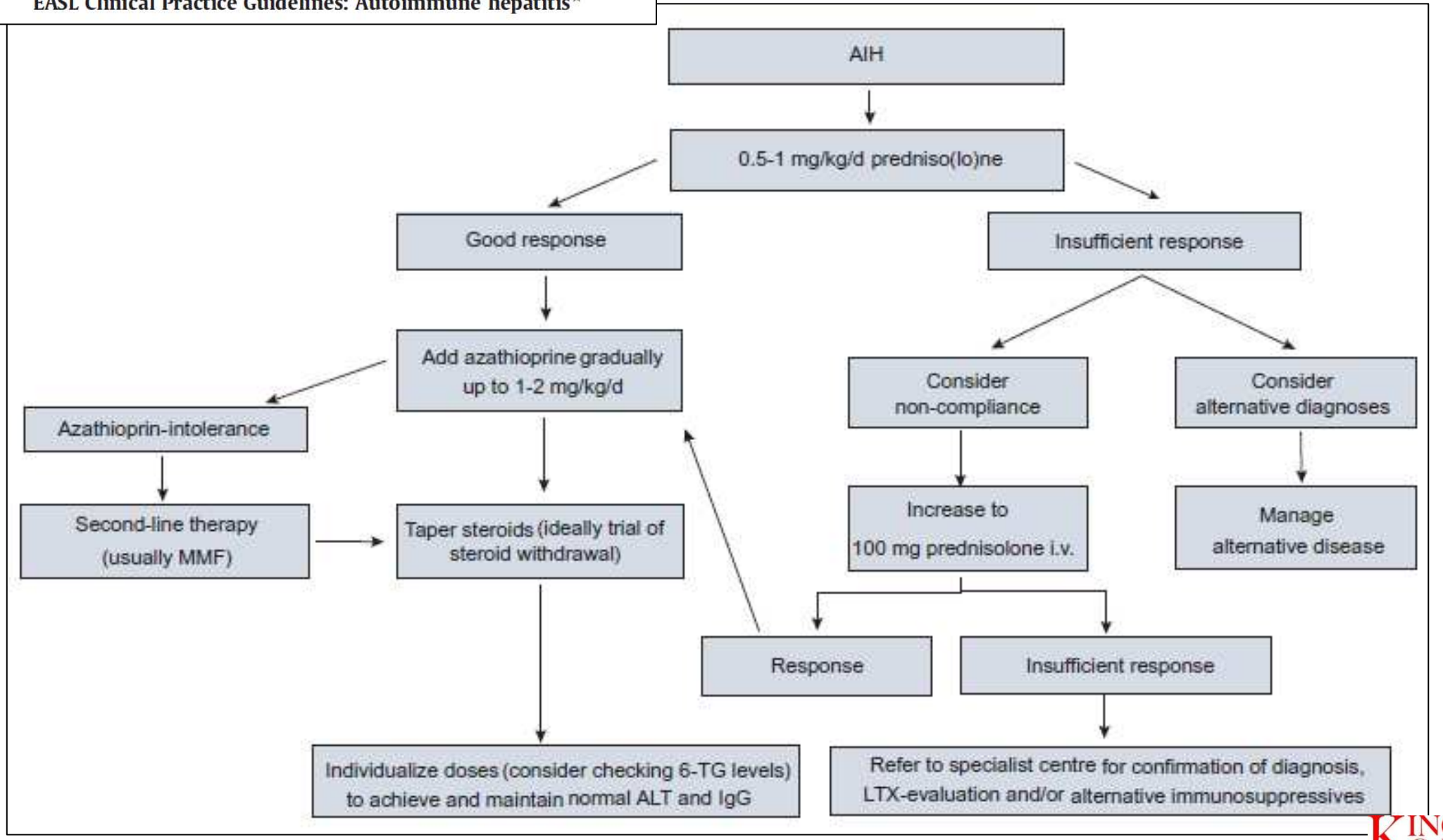

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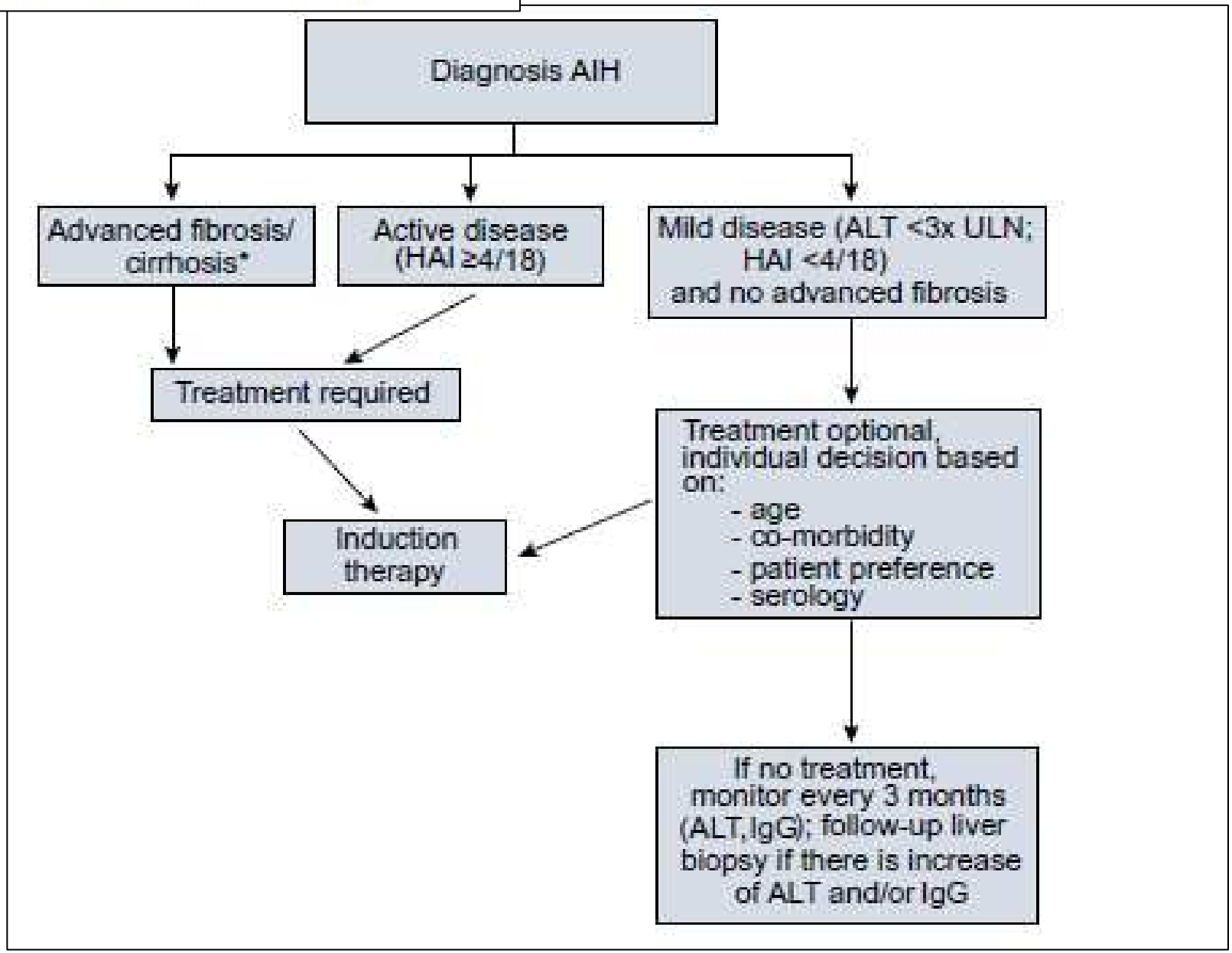

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