



Treatment of Autoimmune Hepatitis

EASL Clinical Practise Guideline

Autoimmune Hepatitis

Clinical Practice Guidelines



EASL Clinical Practice Guidelines: Autoimmune hepatitis[☆]

European Association for the Study of the Liver^{*}

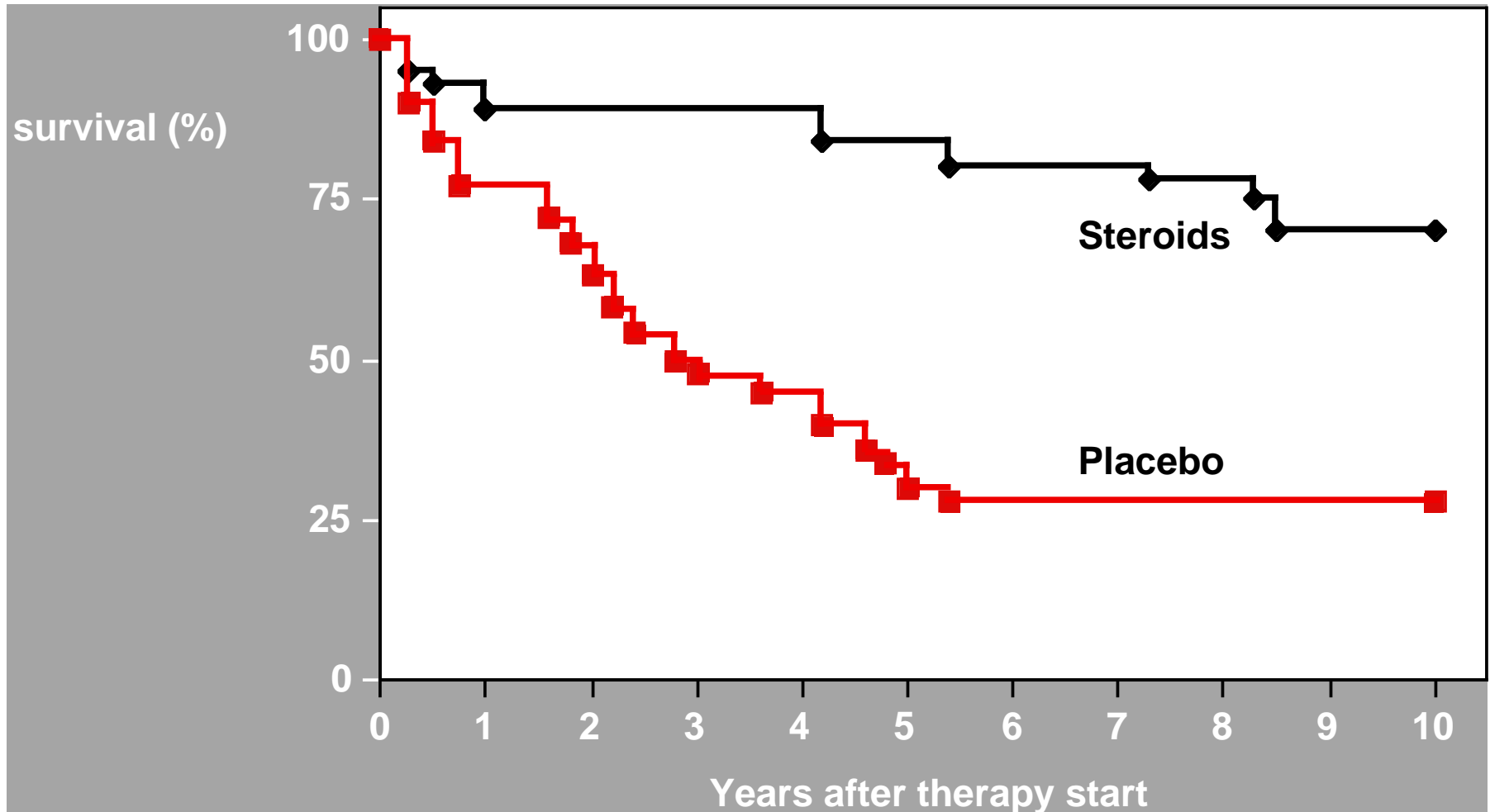
**Ansgar W. Lohse, Olivier Chazouillères,
George Dalekos, Joost Drenth,
Michael Heneghan, Harald Hofer,
Frank Lammert, Marco Lenzi**

**Journal of Hepatology
2015;63:971–1004**

Treatment of Autoimmune Hepatitis

- **Prednisolone 0.5 – 1 mg / kg initial dose, weekly reduction, for remission induction**
- **Azathioprine 1–2 mg / kg for maintenance therapy**
- **Treatment aim normal transaminases and IgG**

Autoimmune Hepatitis: Treatment is life-saving!



Royal Free Hospital Trial:

AP Kirk, S Jain, S Pocock, HC Thomas, and S Sherlock: Gut 1980; 21: 78-83

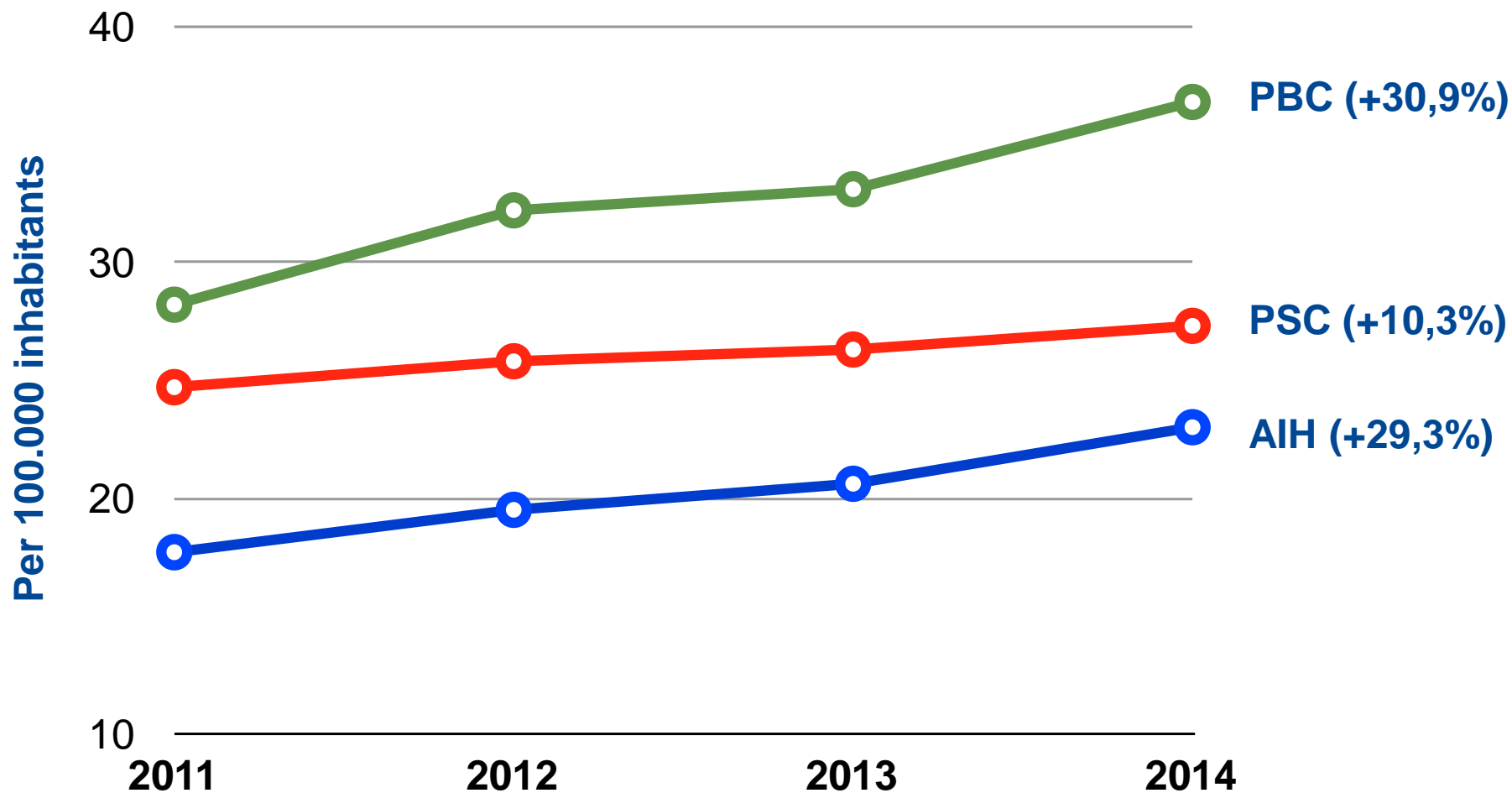
Autoimmune Hepatitis: Clinical need

- **Increasing incidence and prevalence**
- **Underdiagnosed (20 – 40% cirrhosis at diagnosis)**
- **Undertreated (<50% receive appropriate therapy)**
- **>80% of patients require life-long treatment**
 - **Side-effects**
 - **Non-compliance common problem**
- **3 - 5% of all liver transplants for AIH**

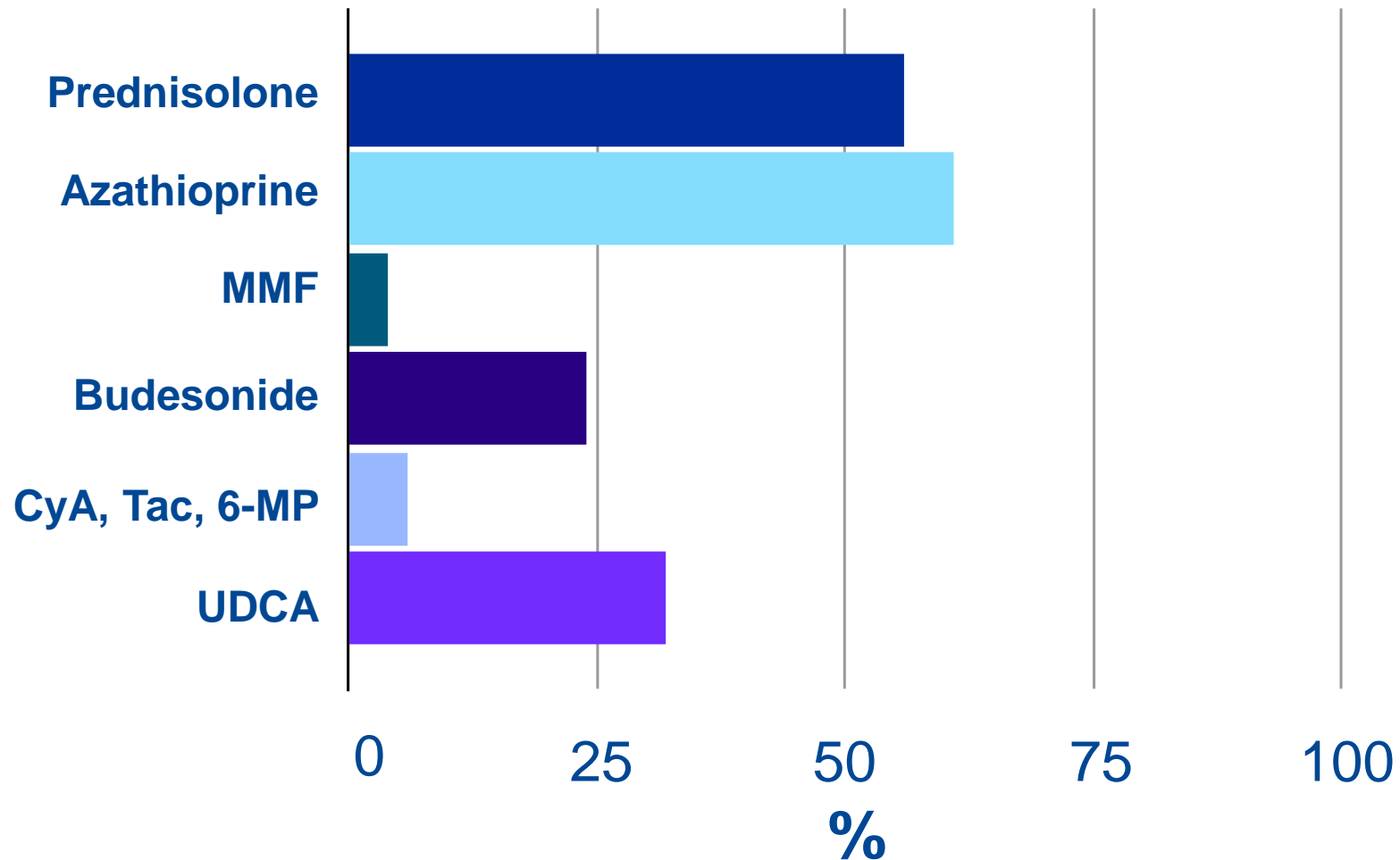
AIH incidence increasing Denmark 1994-2012



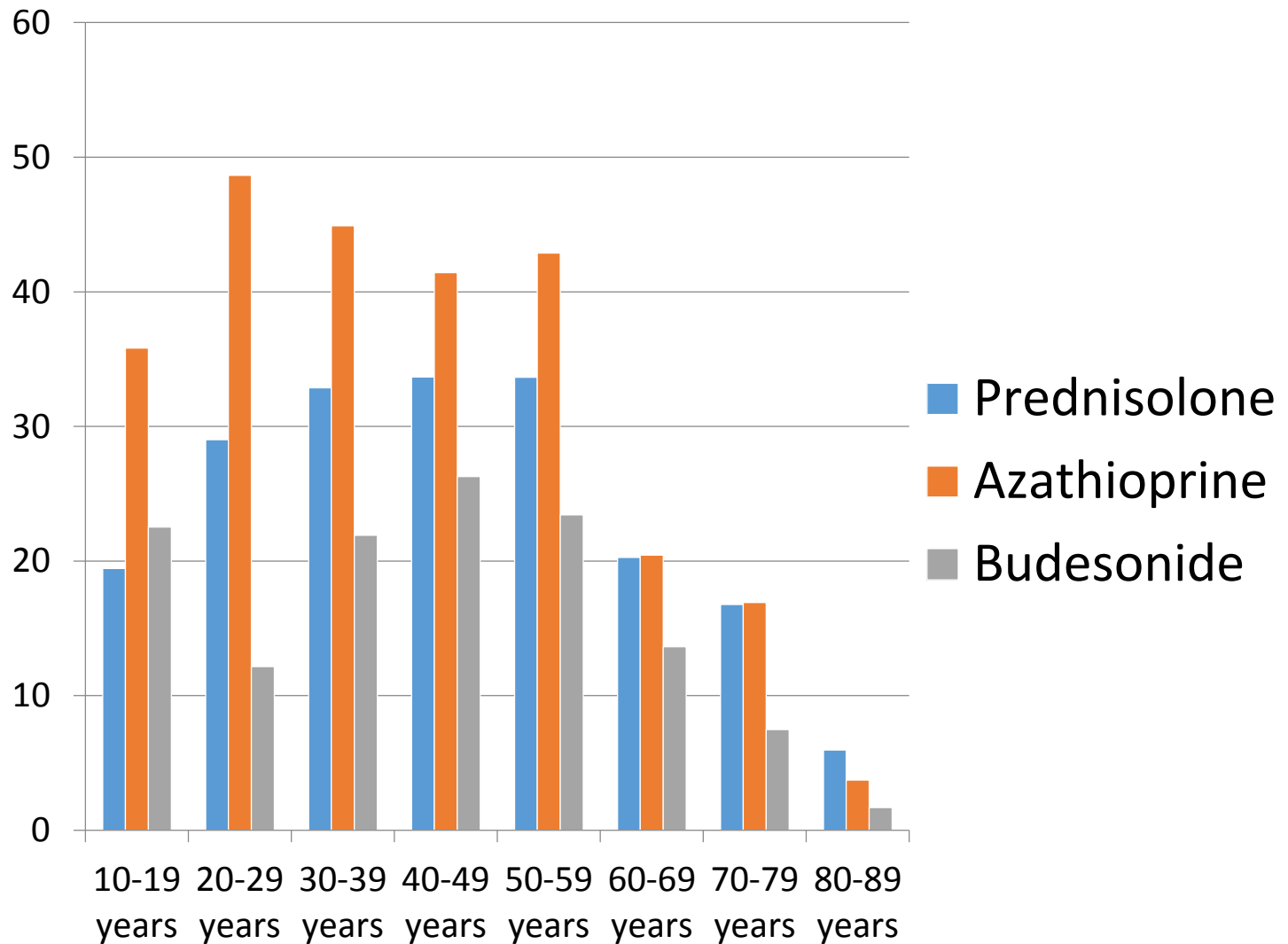
Prevalence of autoimmune liver diseases in Germany



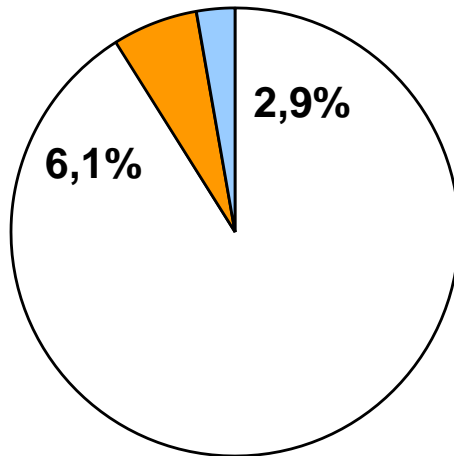
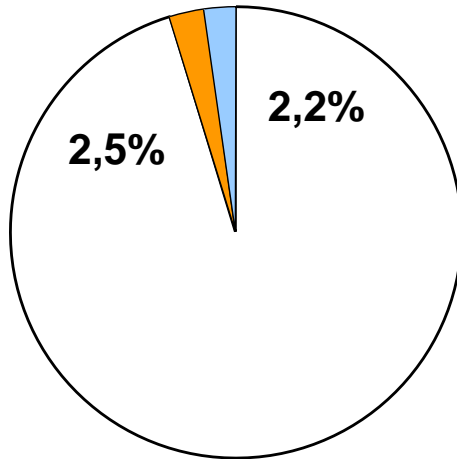
“Real-life” treatment of AIH patients in Germany



“Real-life” treatment of AIH patients in Germany

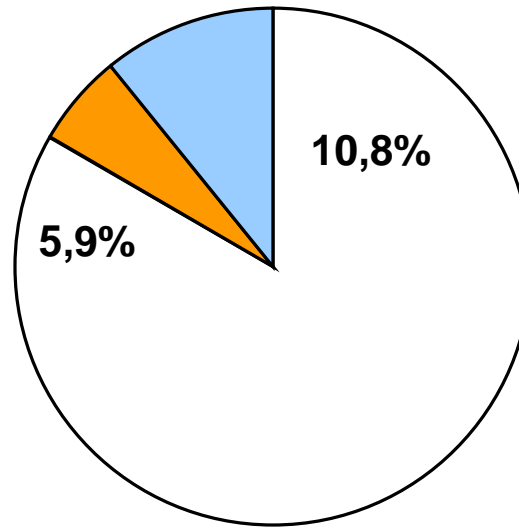


General population



Cancer

Autoimmune hepatitis



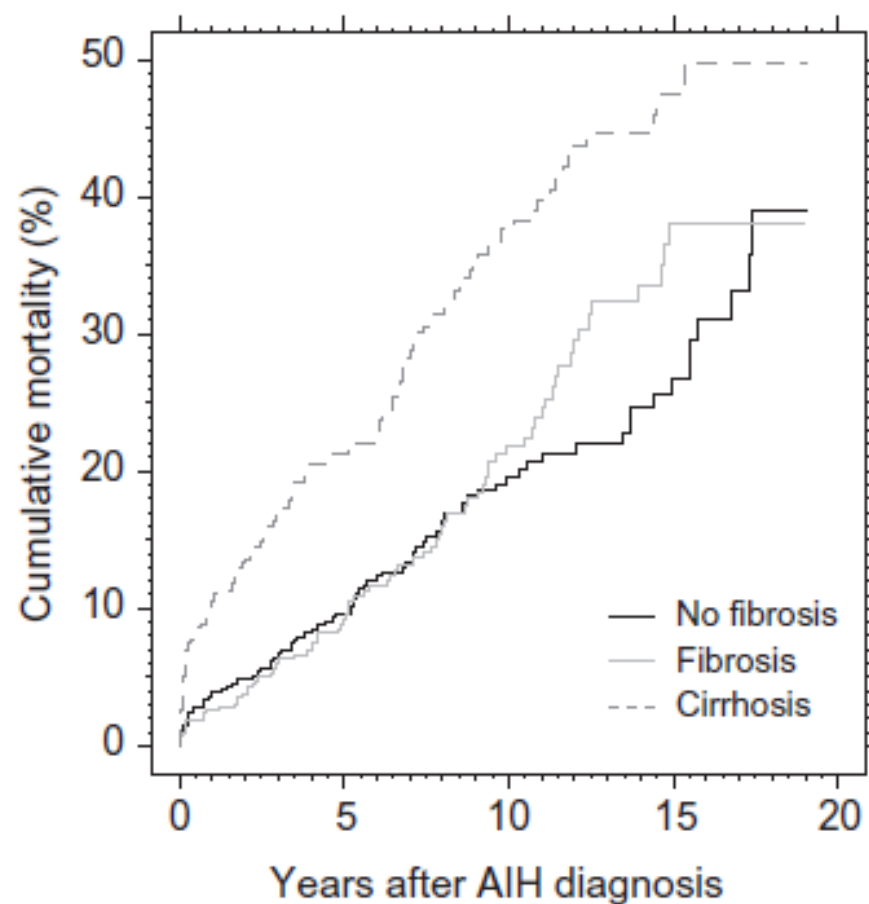
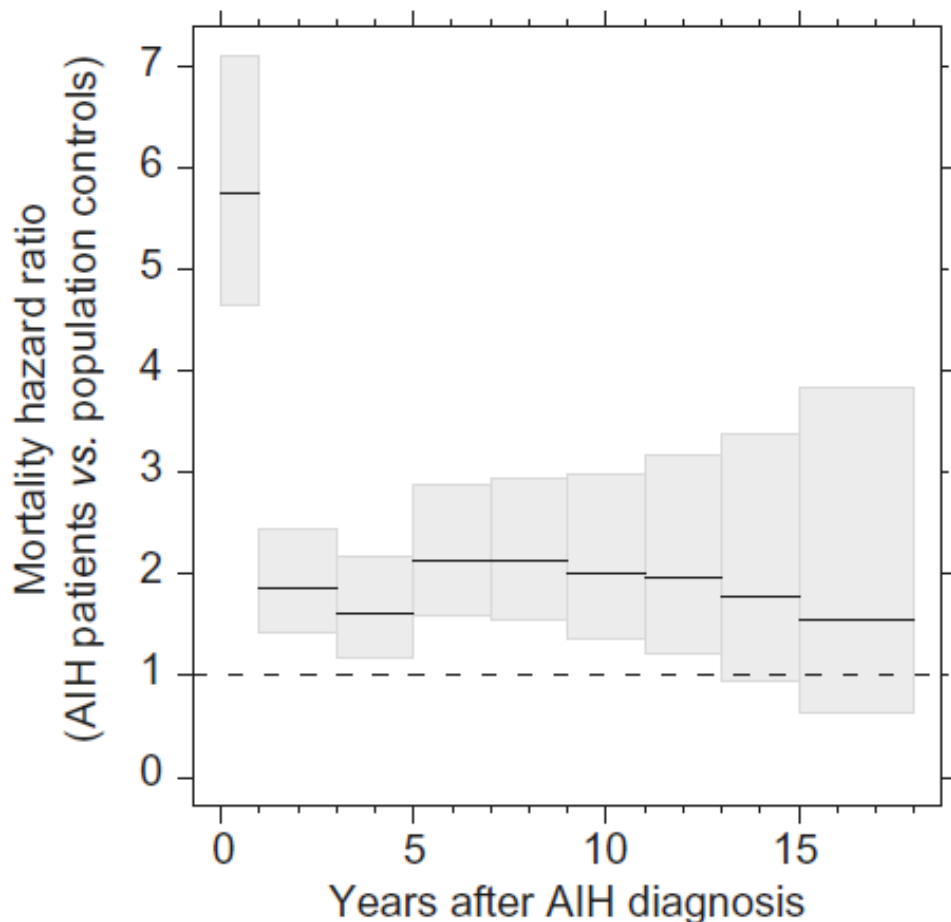
- ☐ No depressive disorder
- ☐ Depressive disorder
- ☐ Major depressive disorder

Autoimmune Hepatitis: Quality of Life (UK-AIH study)

- **Markedly decreased compared to general population**
- **5.5% depressed, additional 9.9% borderline**
- **15.3% high anxiety, additional 18.7% borderline**
- **Correlates closely with corticosteroid-use**

Increased mortality rate in AIH

Danish national registry study



Problems and Questions 1

Remission induction

- **Does everybody need treatment?**
- **Which steroid?**
- **Starting dose?**
- **How and when to assess response?**
- **What to do in poor response / non-response?**
- **When to start azathioprine, what dose?**
- **What to do in azathioprine intolerance?**

Problems and Questions 2

Maintenance of Remission

- **Monotherapy or combination therapy?**
- **Dose?**
- **Treatment aim?**
- **Monitoring strategy?**
- **Tapering strategy?**
- **Maintaining compliance?**
- **Managing (real and presumed) side-effects**

Problems and Questions 3

Special populations

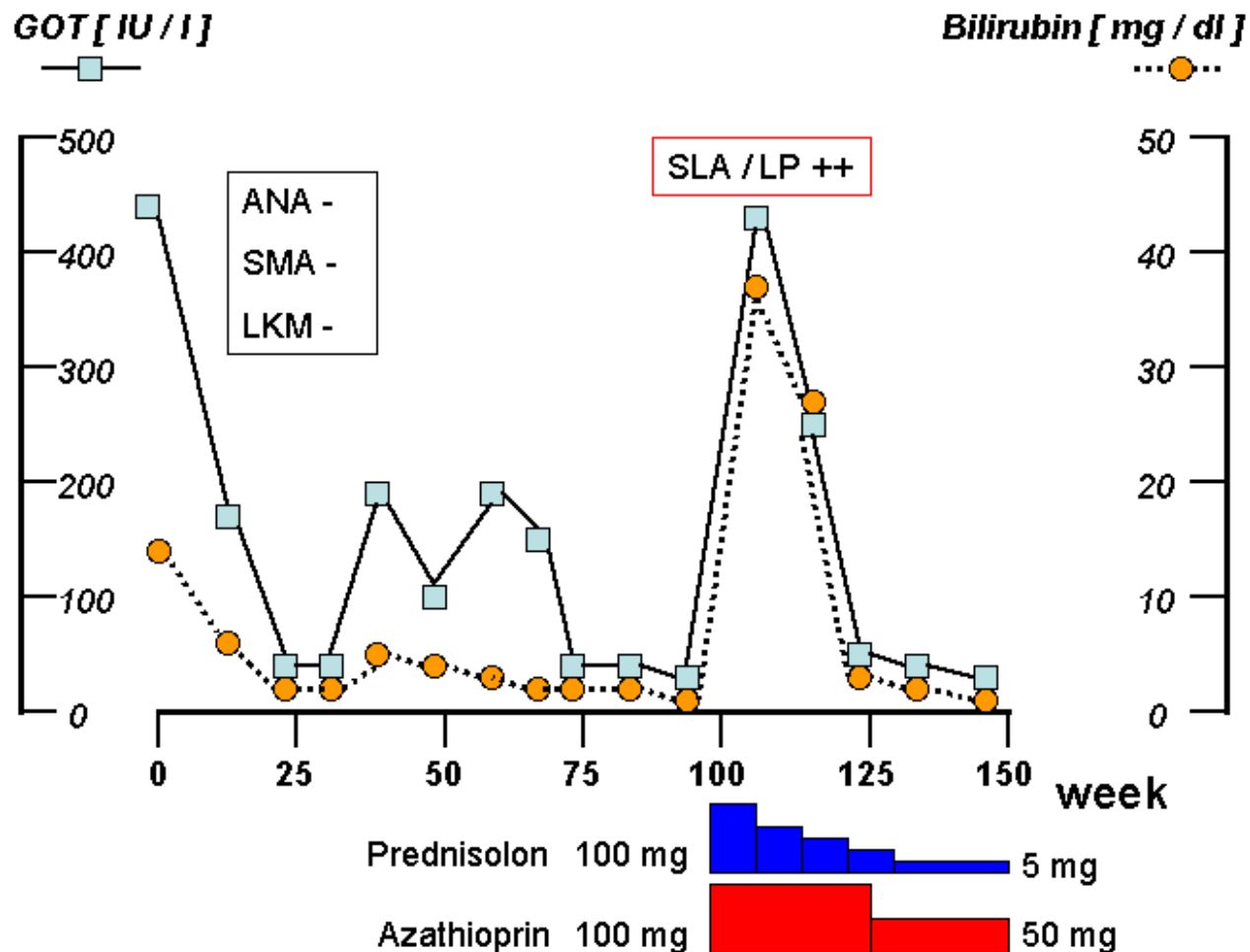
- **Advanced cirrhosis**
- **Fulminant AIH**
- **AIH in PBC (or PBC variant syndrome?)**
- **AIH in PSC (or PSC variant syndrome?)**
- **Puberty**
- **Pregnancy**
- **AIH in the elderly**
- **Severe comorbidity**

Remission induction

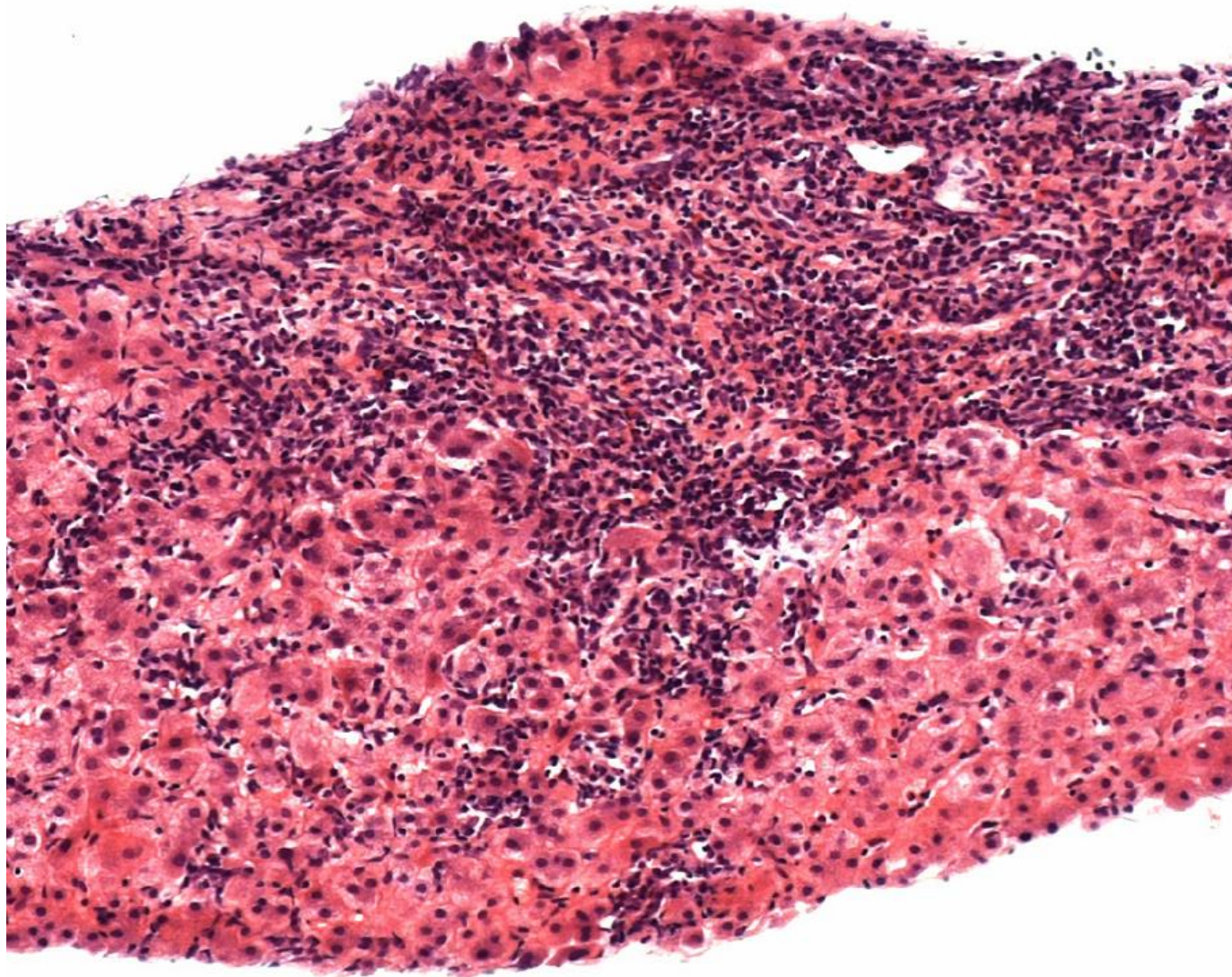
Problems and Questions

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Fluctuating course of AIH: Evidence for immune regulation / dysregulation



Autoimmune Hepatitis



AIH: treatment for everybody?

- **Yes, with very few exceptions**
 - **Because silent disease is often progressive**
 - **Biopsy may reveal high inflammation despite normal lab results**
 - **Flares can happen any time**
- **Exceptions can be**
 - **Serious co-morbidity; life-threatening other diseases**
 - **Old age, good liver function and mild disease**
 - **Stable remission**

Remission induction

Problems and Questions

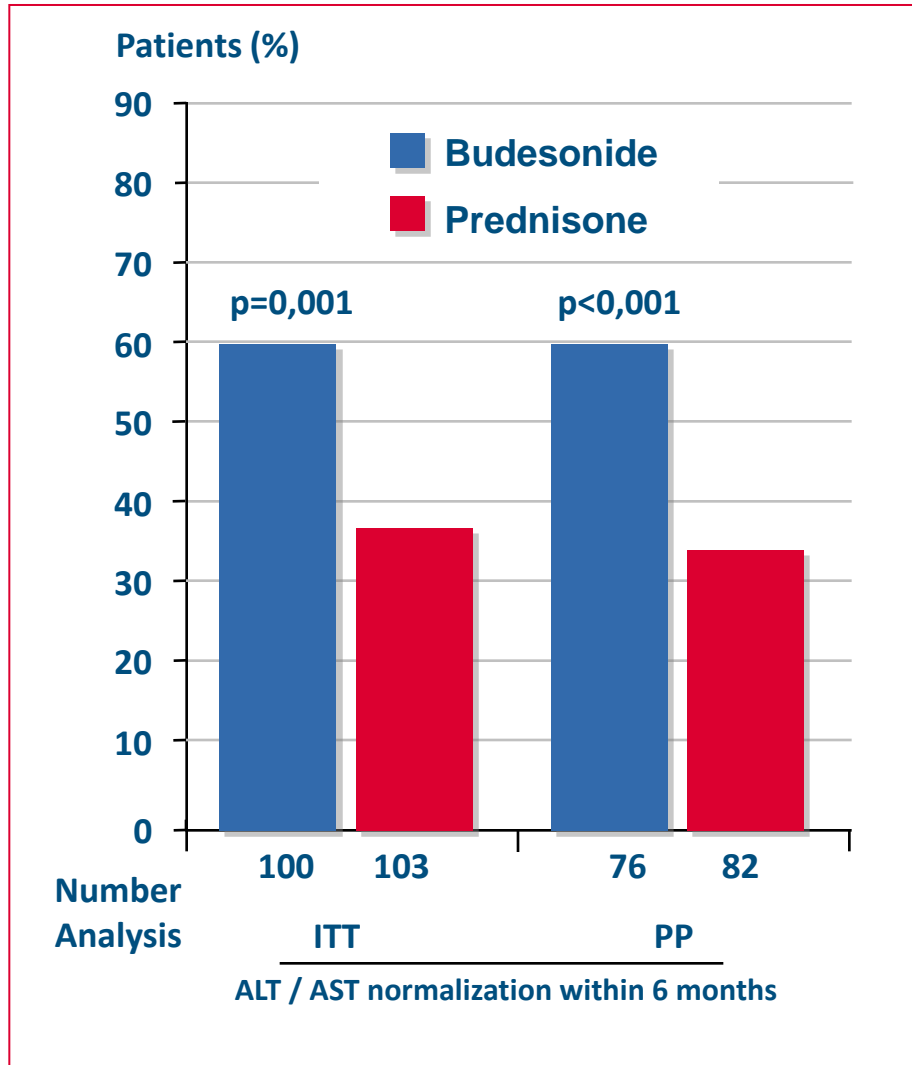
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- Which steroid?
- Starting dose?
- How and when to assess response?
- What to do in poor response / non-response?
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AIH treatment

Remission induction

Predniso(lo)ne (0.5 – 1mg / kg) as initial therapy followed by the addition of azathioprine after two weeks is the first line treatment of Autoimmune Hepatitis

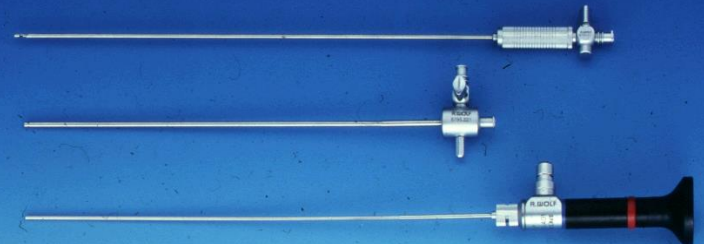
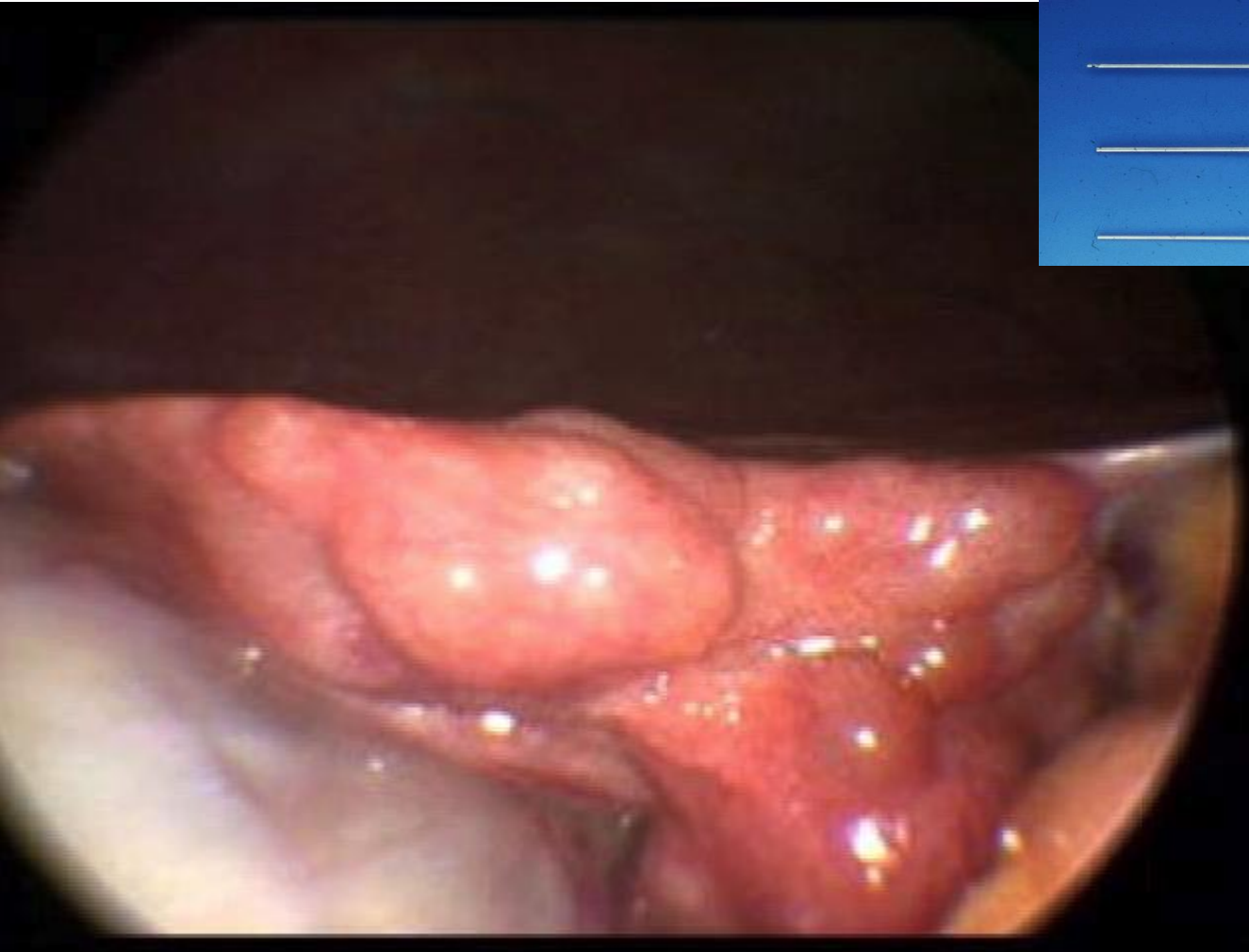
Budesonide as alternative to prednisone?



- n=203 Patients
- Double blind, multicentre trial
- Prednisone 40 mg tapering versus Budesonide 3 x 3 mg (both + Azathioprine)

AIH Cirrhosis

Mini-laparoscopy



Why I do not like Budesonide for AIH

- **Cirrhosis contraindication**
- **Cirrhosis easily missed in diagnosis**
- **Very difficult to dose individually**
- **Difficult to taper out**
- **For maintenance treatment azathioprine better**
- **The worst Cushingoid side-effects I have seen in budesonide treated patients**



Oct. 2009
3 x 3 mg Budesonid
10 mg Prednisolon



Oct. 2010
5 mg Prednisolon
75 mg Azathioprin

Alternatives for insufficient response

- Intensify standard treatment, taper more slowly
 - Measure 6-TGN, optimize azathioprine dose
- Cyclophosphamide
 - Effective, but toxic side-effects
- Cyclosporine / Tacrolimus
 - Effective, long-term side-effects
- Anti-TNF
 - Effective, risk of infectious complications
- Rituximab
 - Variable response; little data

Maintenance of Remission Problems and Questions

- **Monotherapy or combination therapy?**
- **Dose?**
- **Treatment aim?**
- **Monitoring strategy?**
- **Tapering strategy?**
- **Maintaining compliance?**
- **Managing (real and presumed) side-effects**

Treatment Aim

Complete biochemical and histological remission, at minimum treatment side-effects, in order to prevent fibrosis progression

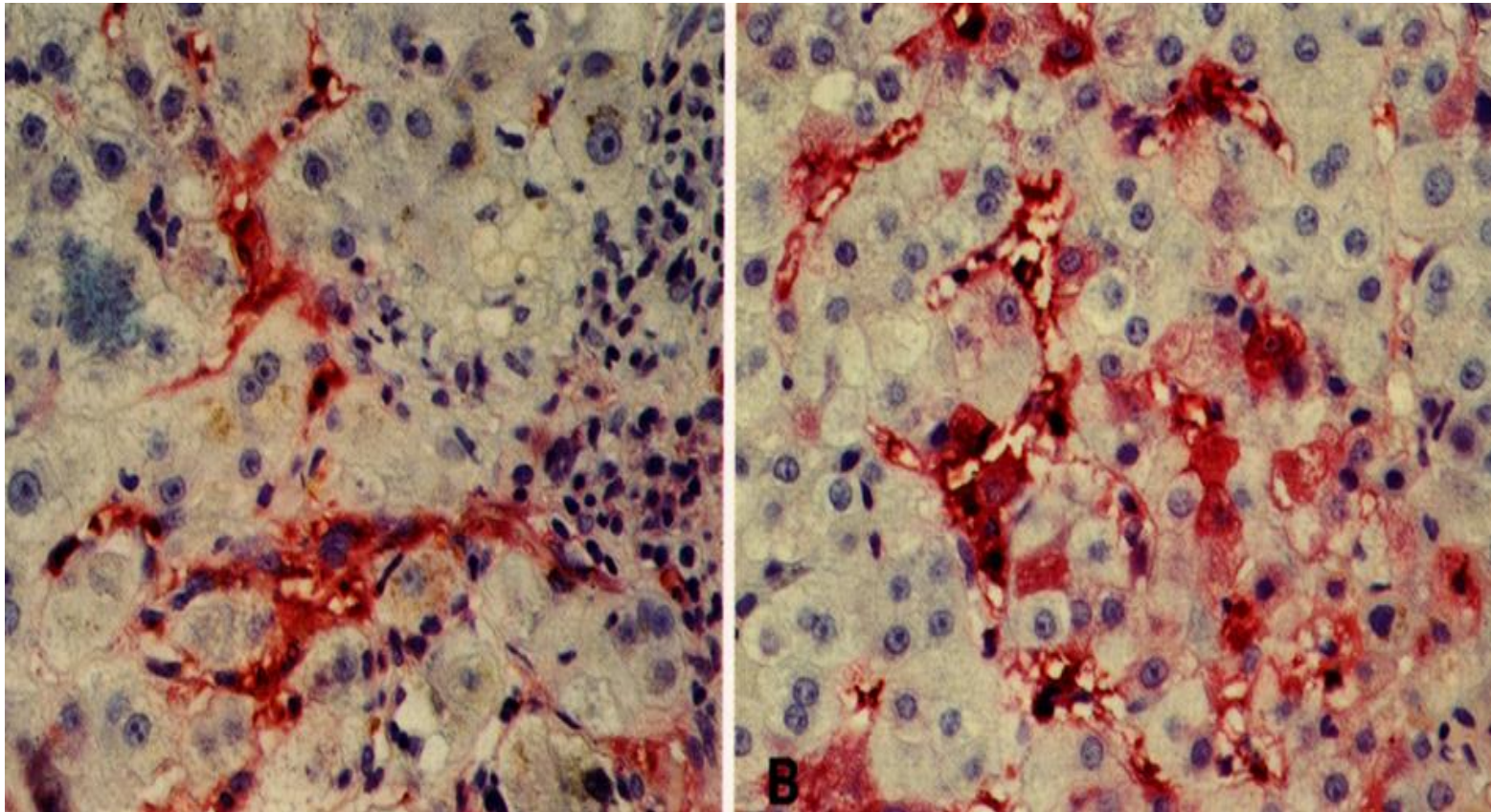
- **Biochemical remission:**

Transaminases and IgG normal

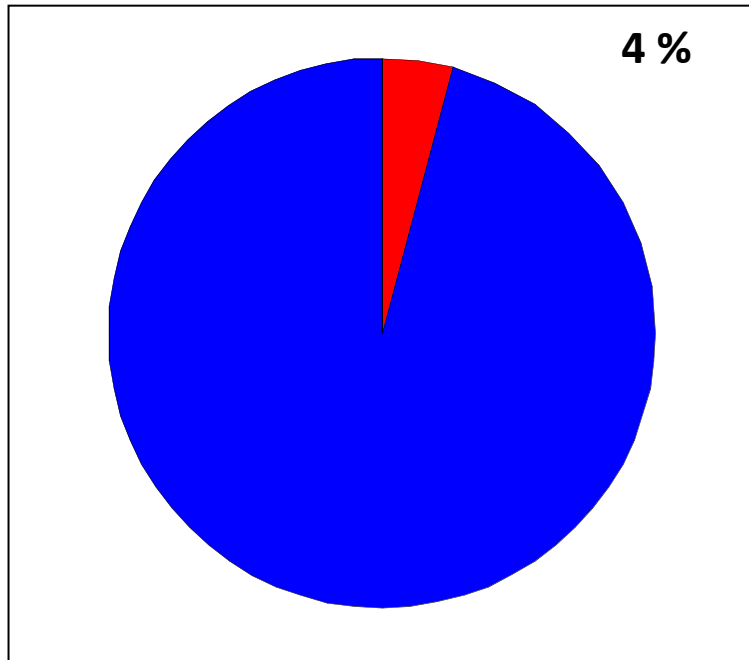
- **Histological remission:**

Normal histology or minimal hepatitis (HAI < 4 / 18)

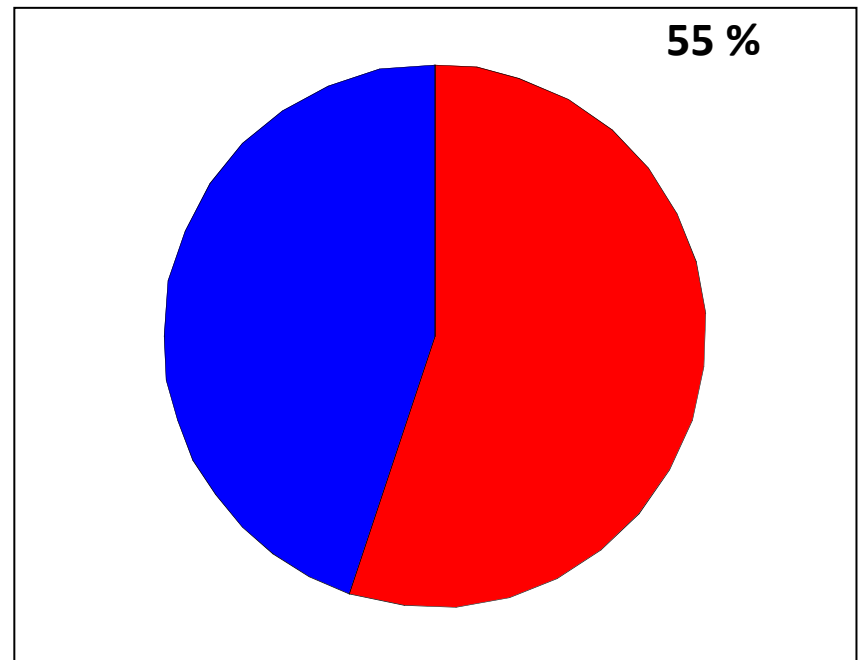
TGF β in the liver in AIH



Rate of fibrosis progression in treated ALH depends on completeness of remission

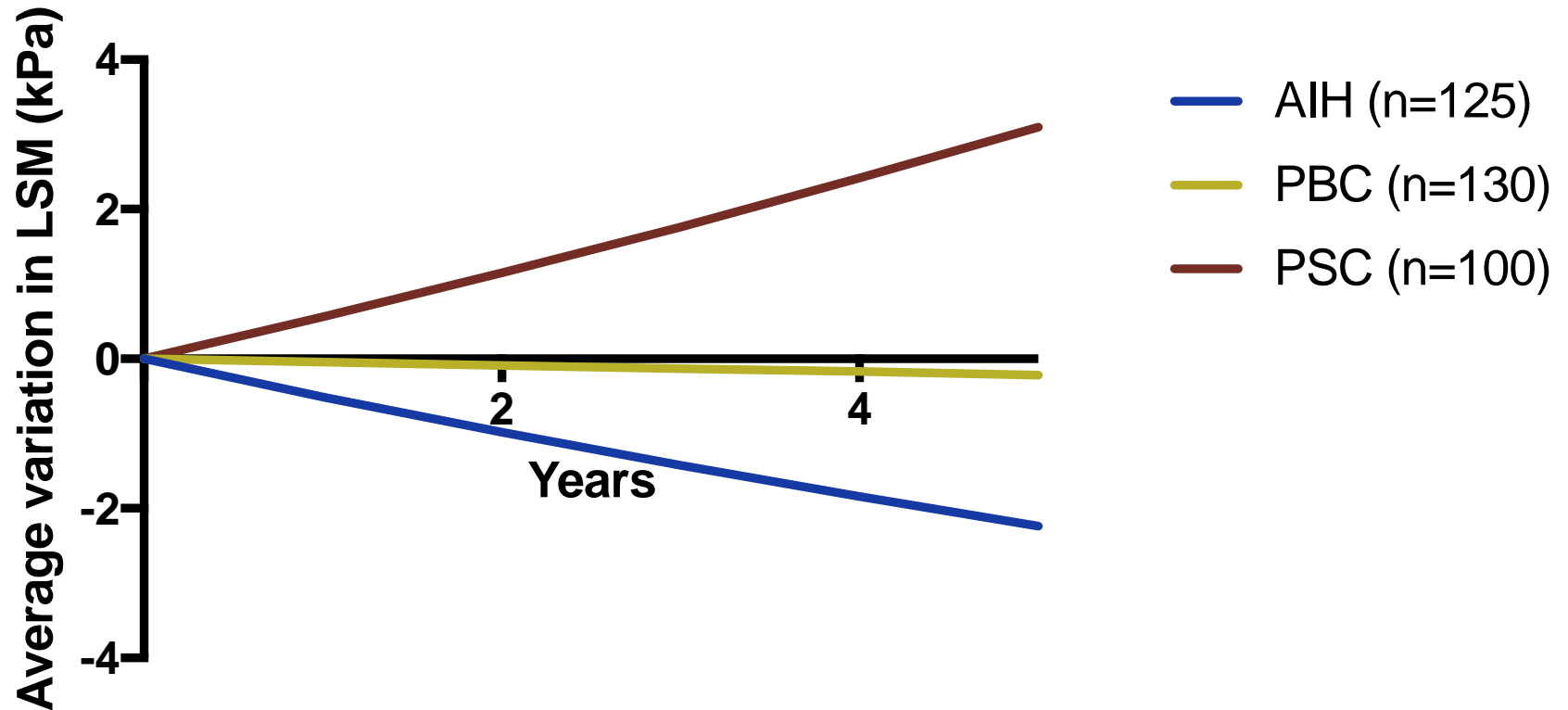


Complete Remission

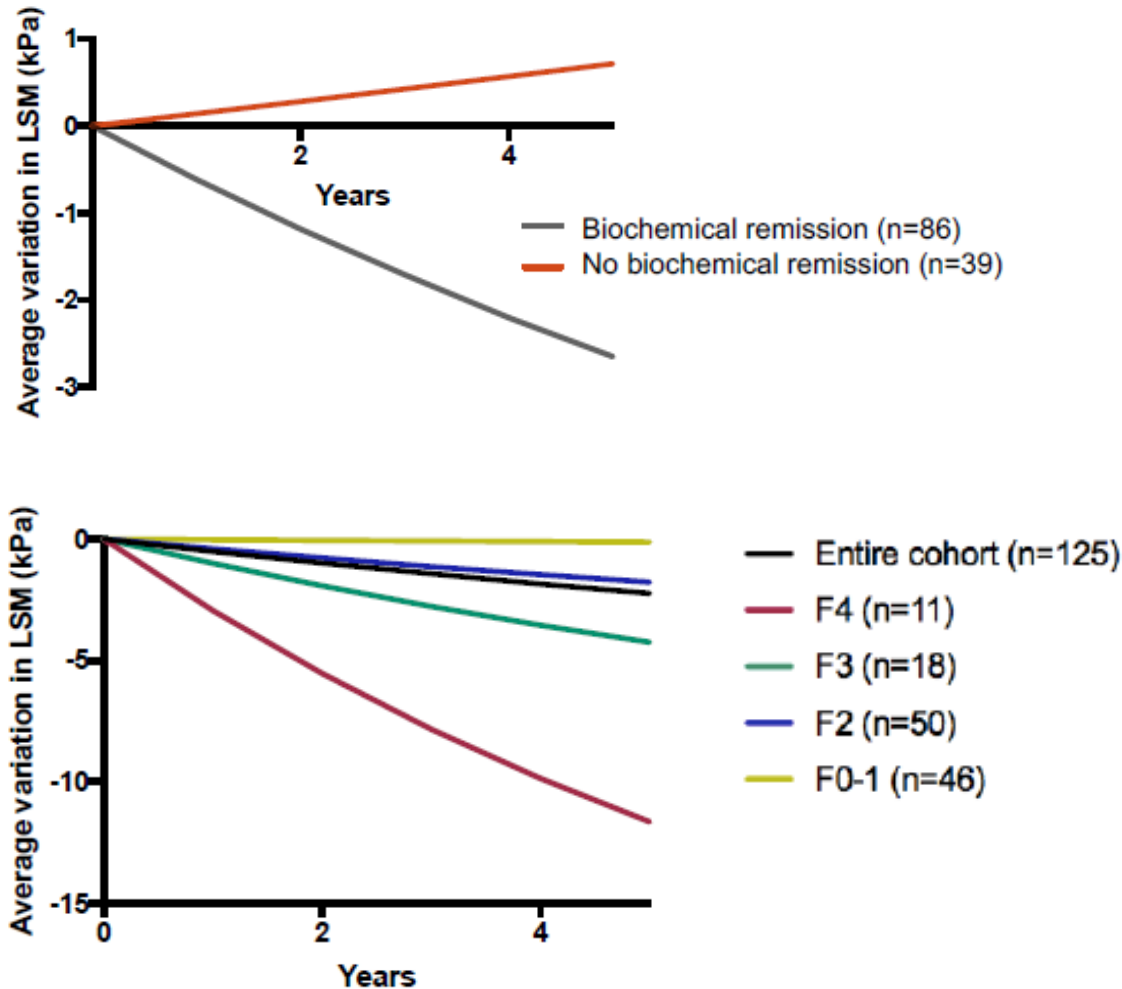


Incomplete Remission

Regression of fibrosis in AIH



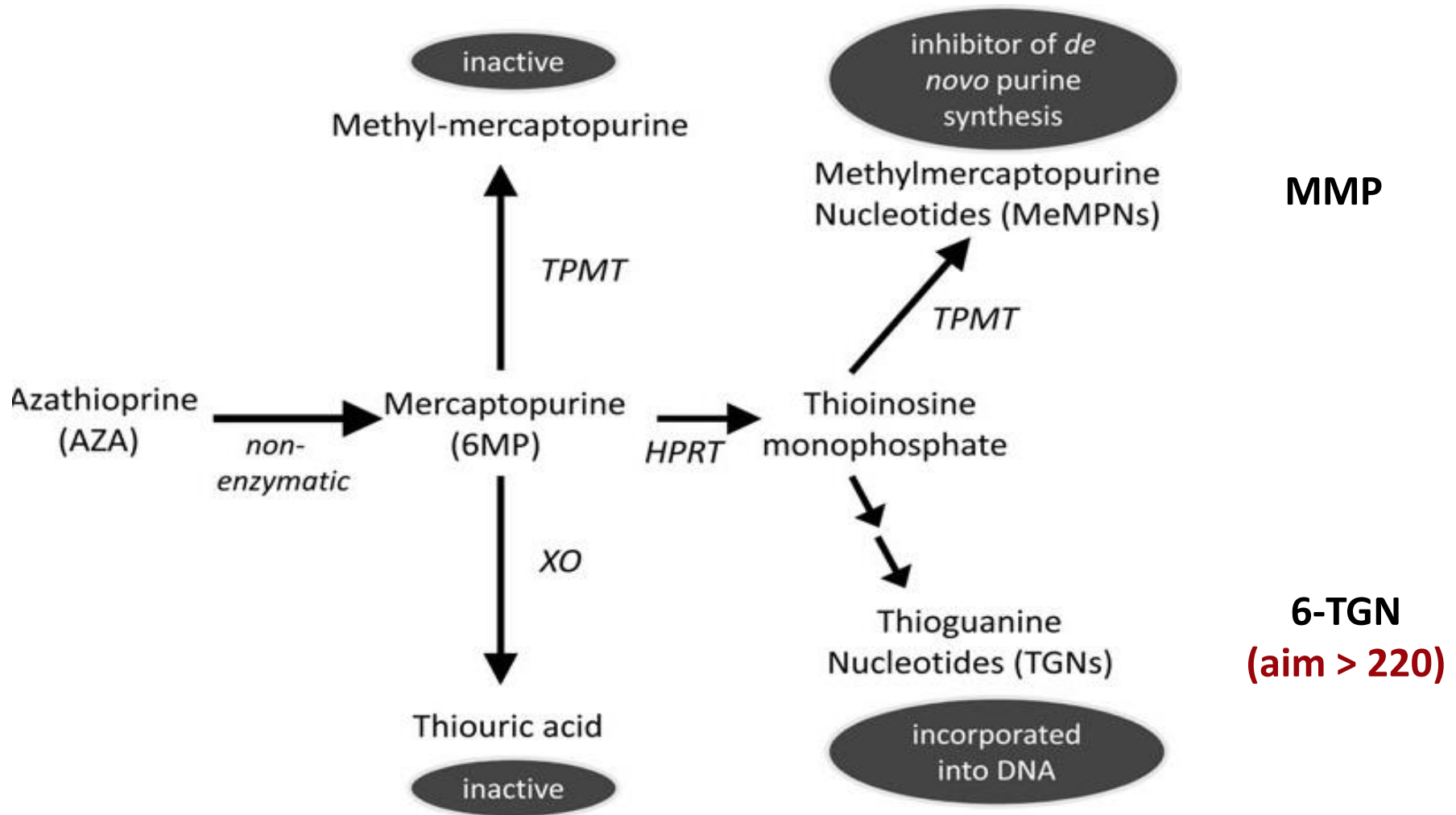
Complete Remission = Fibrosis Regression



Maintenance therapy: failure to maintain remission

- **Check compliance**
- **Check azathioprine metabolism**
- **Adapt dose**
- **Consider alternative immunosuppressants**

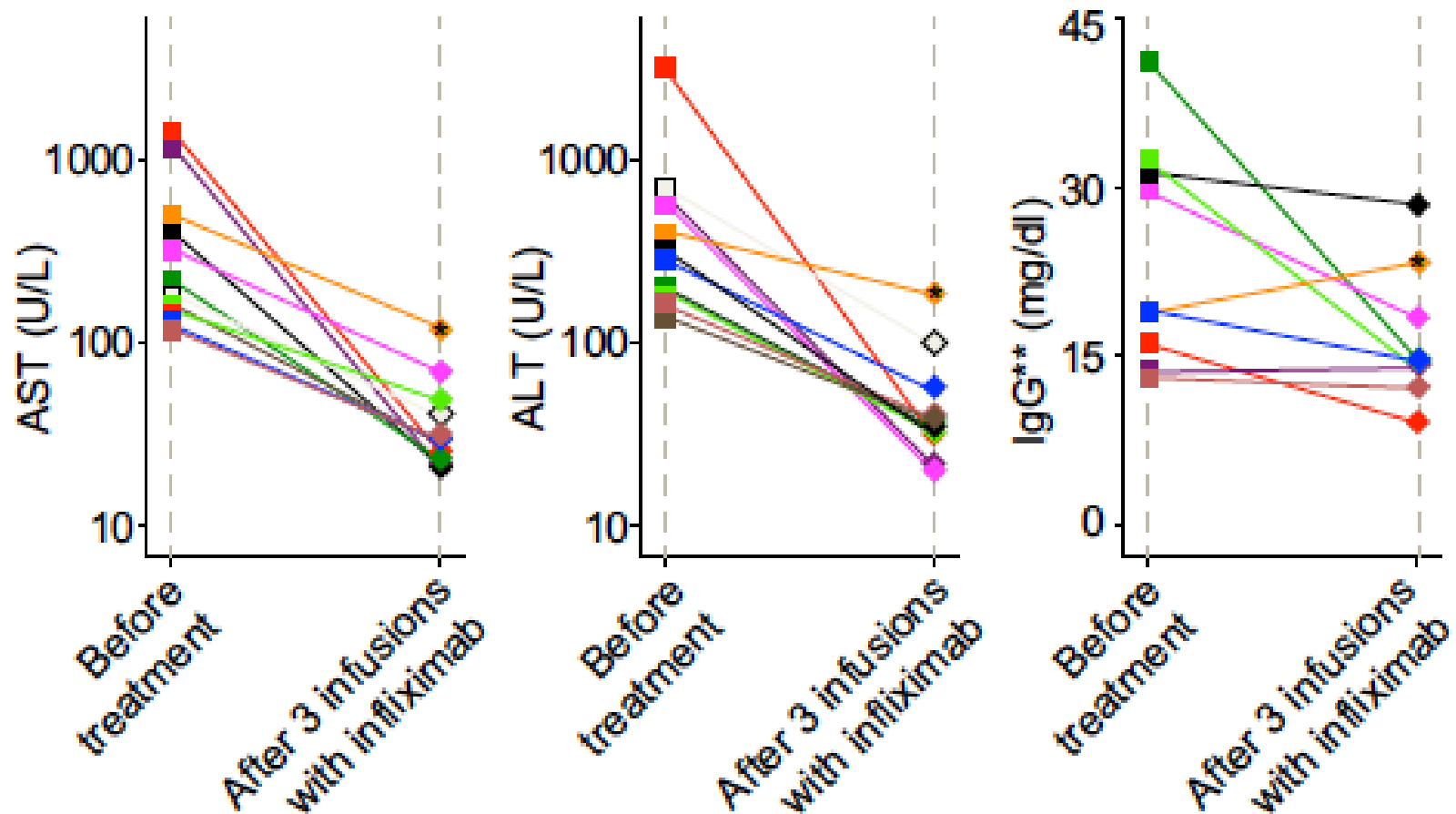
Azathioprine-metabolism



Maintenance therapy: azathioprine intolerance

- **Is it really azathioprine intolerance?**
- **6-MP may be tolerated in ca. 50% of aza-intolerant patients**
- **Try mycophenolate mofetil (works in 2 / 3 pts)**
- **Consider steroid monotherapy (if bone density is good and prednisolone dose of 5 - 10 mg / d sufficient)**
- **Alternative immunosuppressants?**

Effect of infliximab in refractory AIH



**Before
Infliximab**

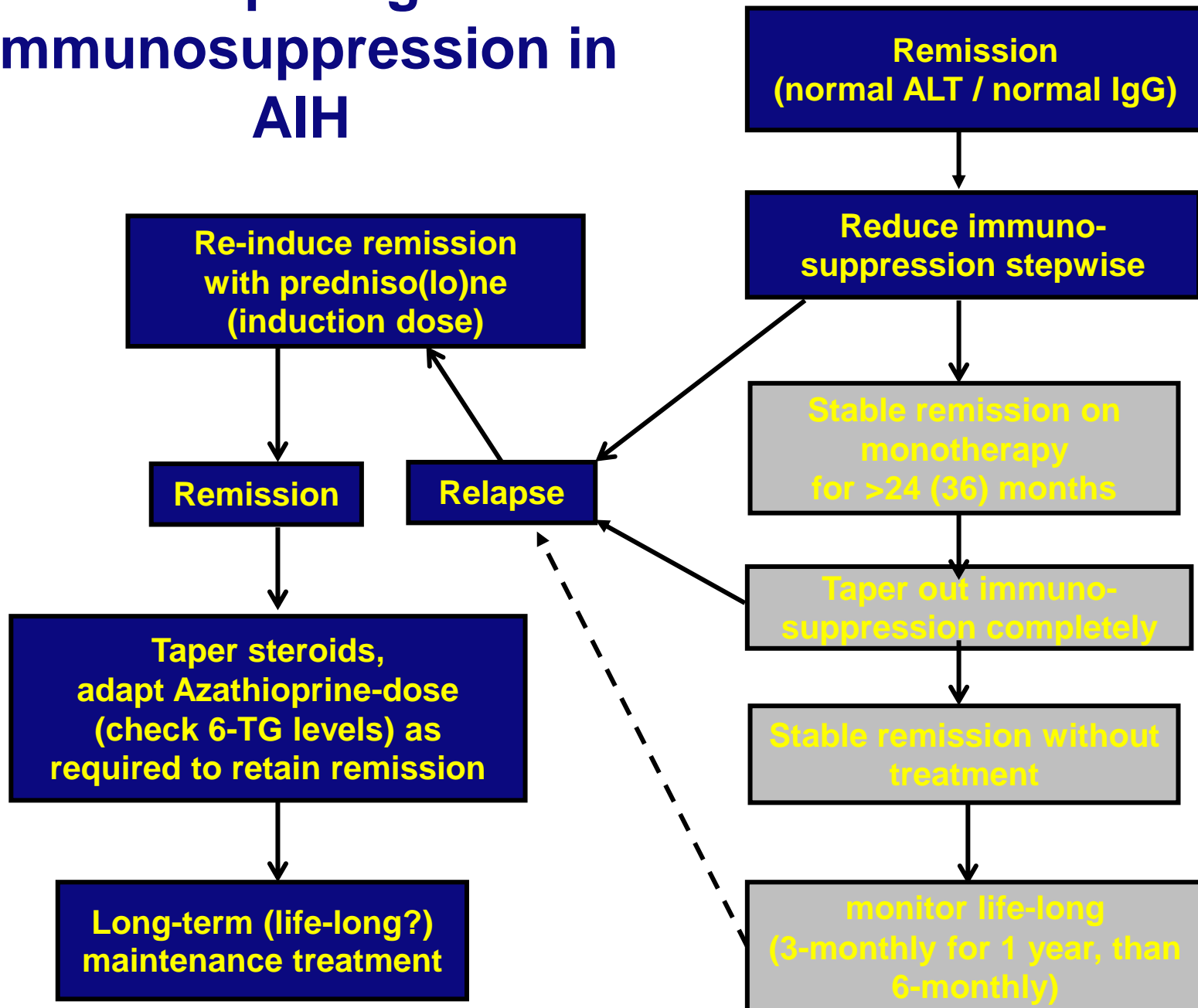


After 6 months infliximab

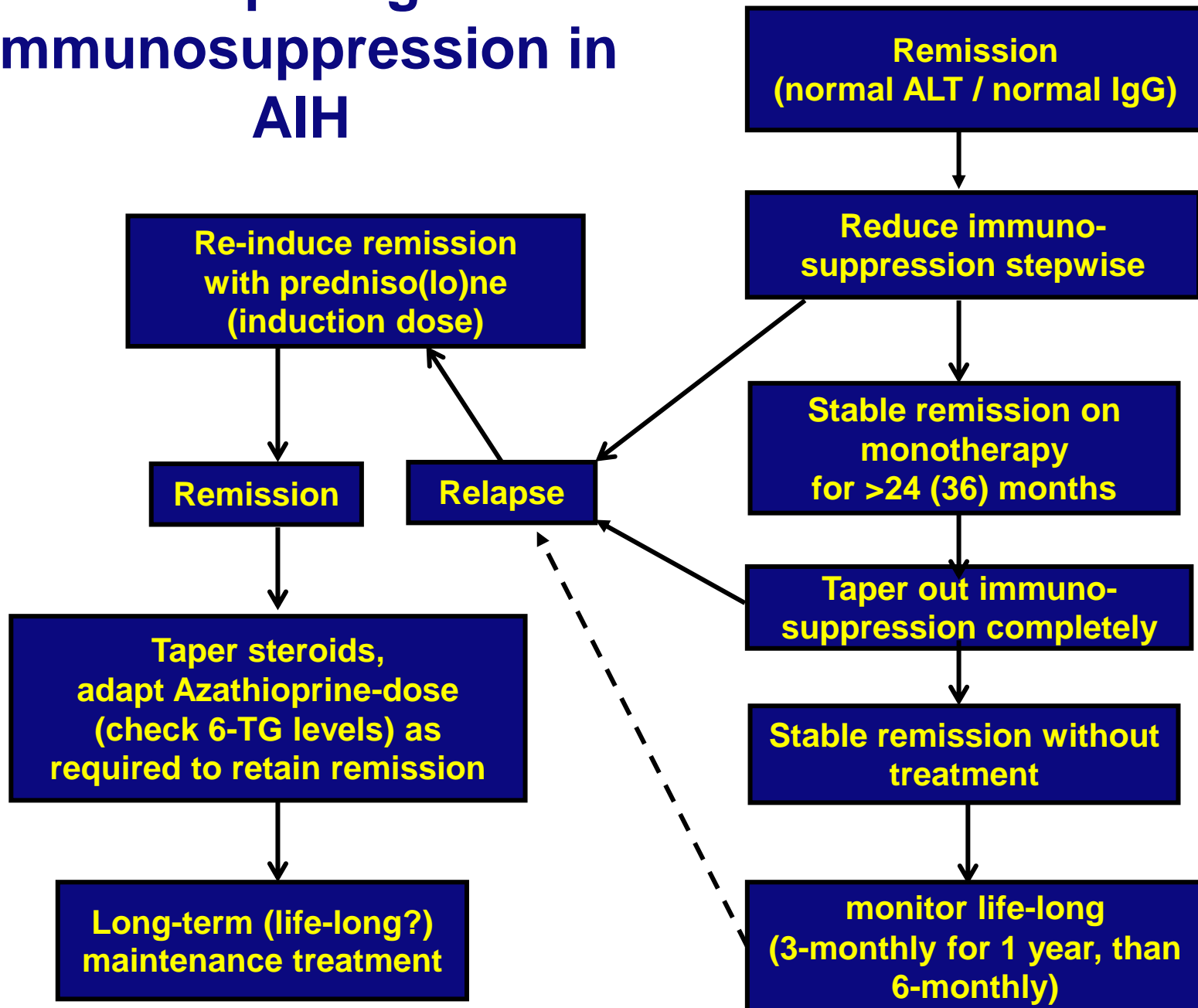
Maintenance of Remission Problems and Questions

- **Monotherapy or combination therapy?**
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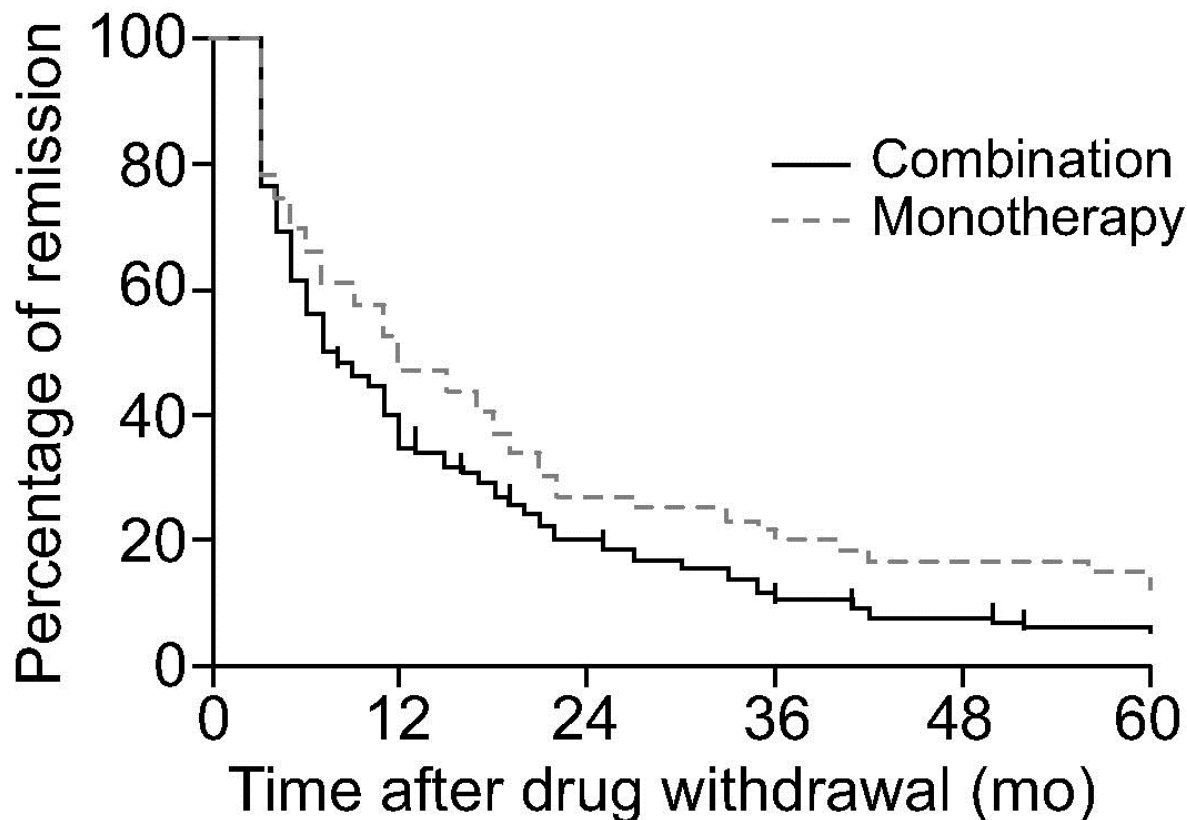
Tapering immunosuppression in AIH



Tapering immunosuppression in AIH



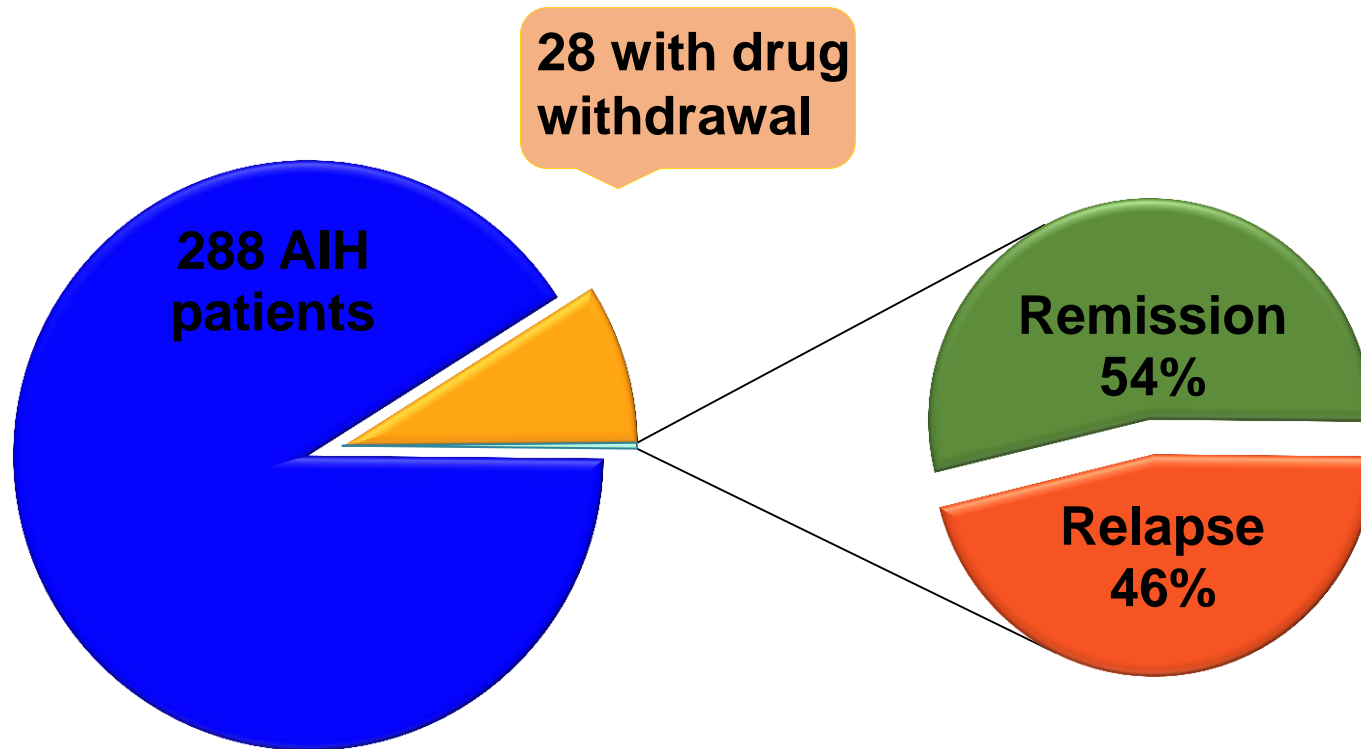
Relapse after treatment withdrawal



Number of patients in remission

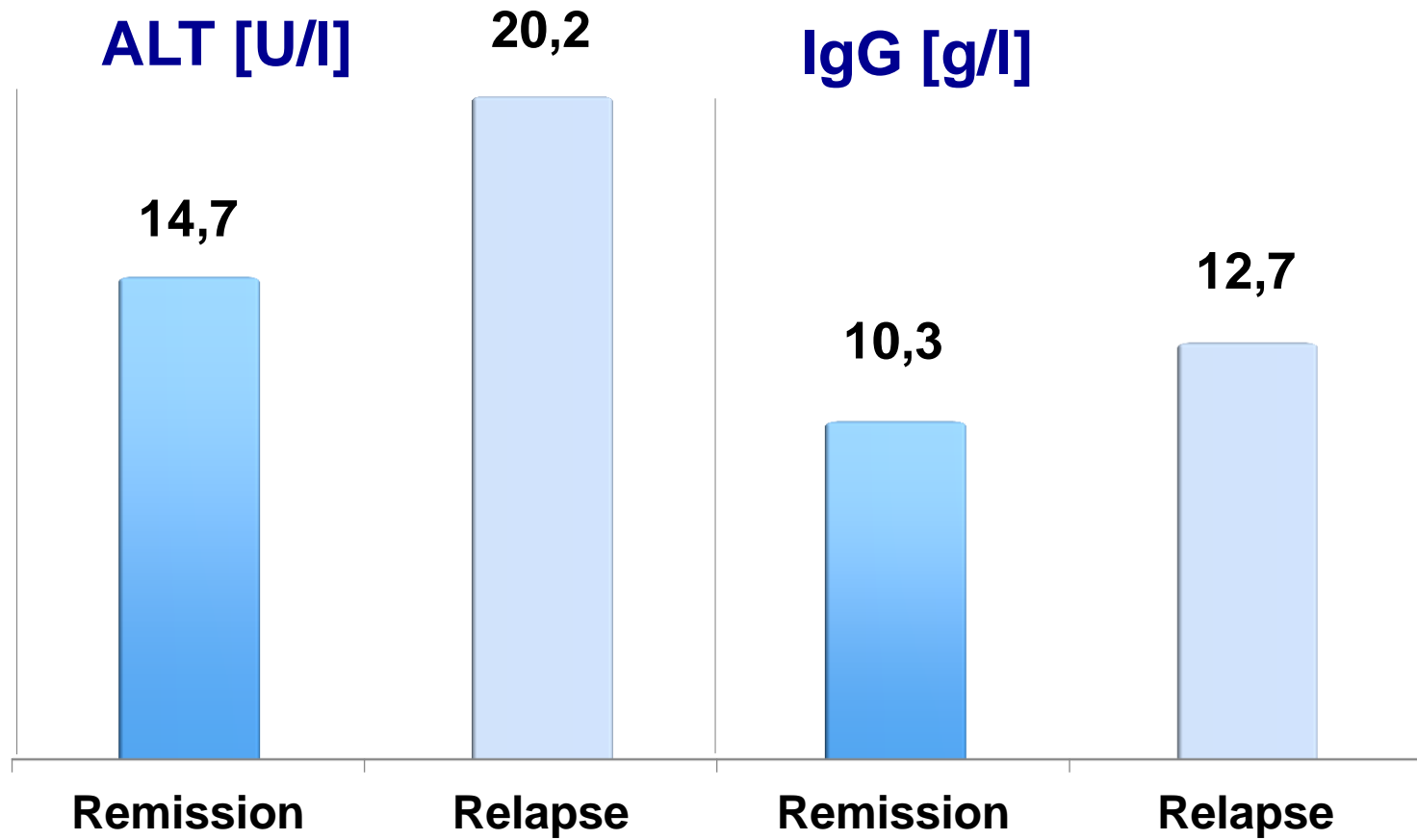
Time after drug withdrawal (mo)	Combination	Monotherapy
0	131	131
12	54	54
24	35	35
36	25	25
48	20	20
60	16	16

Drug withdrawal in autoimmune hepatitis



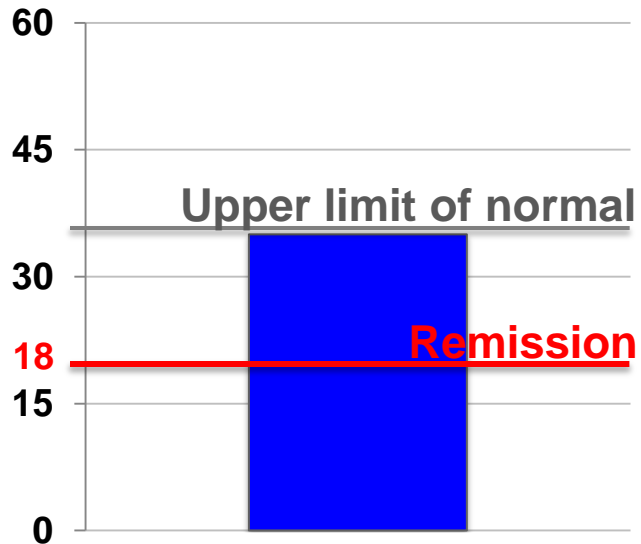
Drug withdrawal after complete biochemical remission under immunosuppressive monotherapy for a minimum of 2 years.

Biochemical markers at drug withdrawal

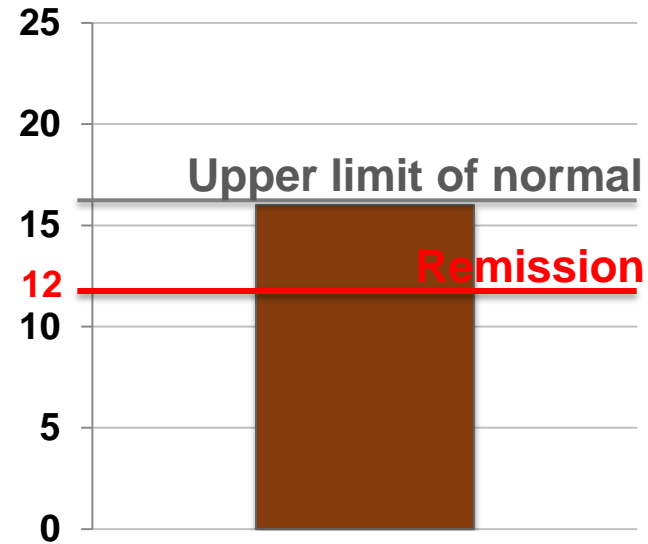


Biochemical markers at drug withdrawal

ALT [U/L]



IgG [U/L]



Predictors for long-term remission:

- ALT $\leq \frac{1}{2}$ ULN
- IgG ≤ 12 g/L

Problems and Questions: Special populations

- Advanced cirrhosis
- Fulminant AIH
- AIH in PBC (or PBC variant syndrome?)
- AIH in PSC (or PSC variant syndrome?)
- Puberty
- Pregnancy
- AIH in the elderly
- Severe comorbidity

Variant (Overlap) Syndromes of AIH

EASL-CPG

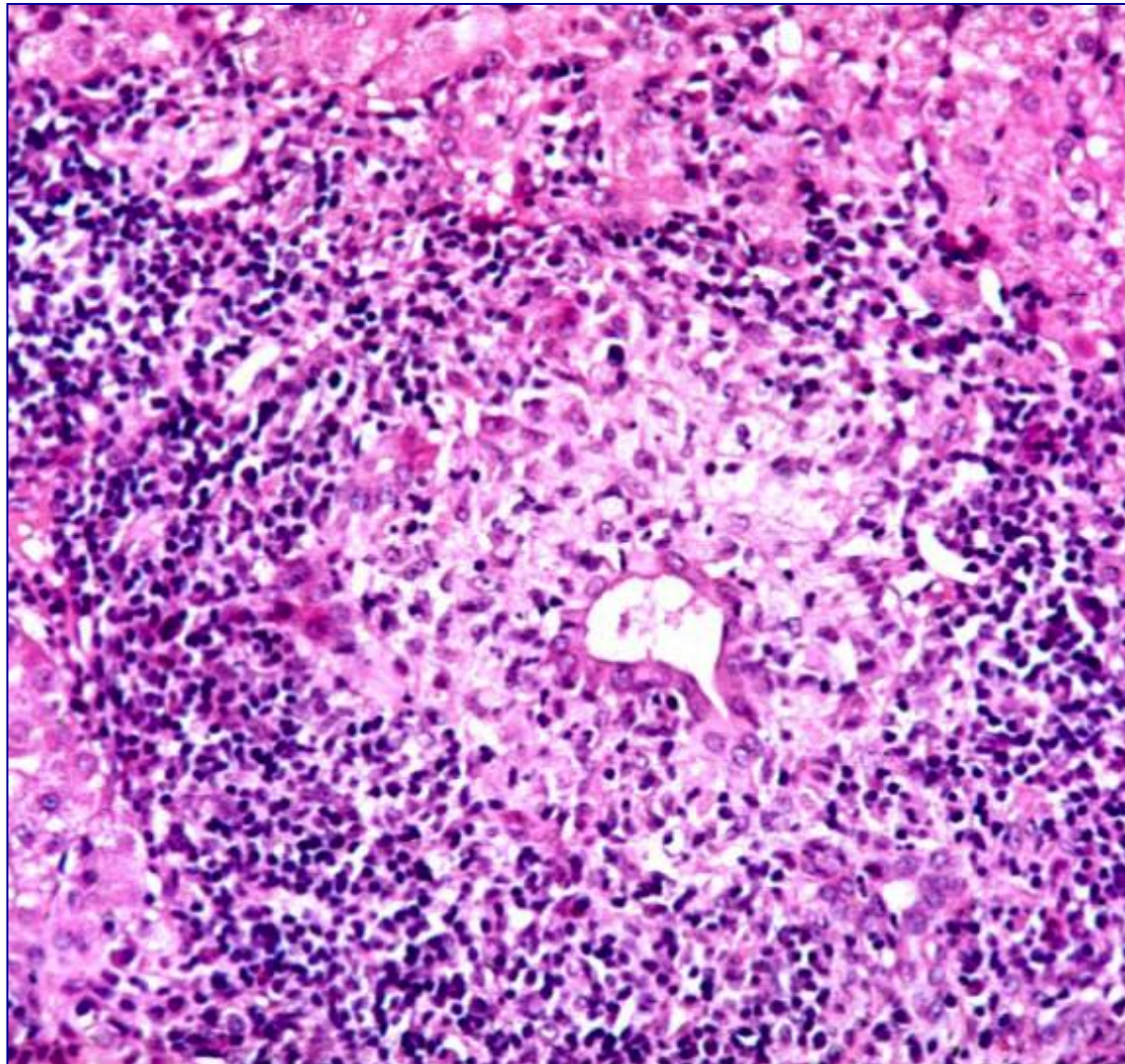
Recommendation 19:

- **Diagnostic tests for PBC and PSC should be performed in patients showing features of cholestasis**

Recommendation 39:

- **All children with a diagnosis of AIH should undergo (MR-)cholangiography to exclude autoimmune sclerosing cholangitis**

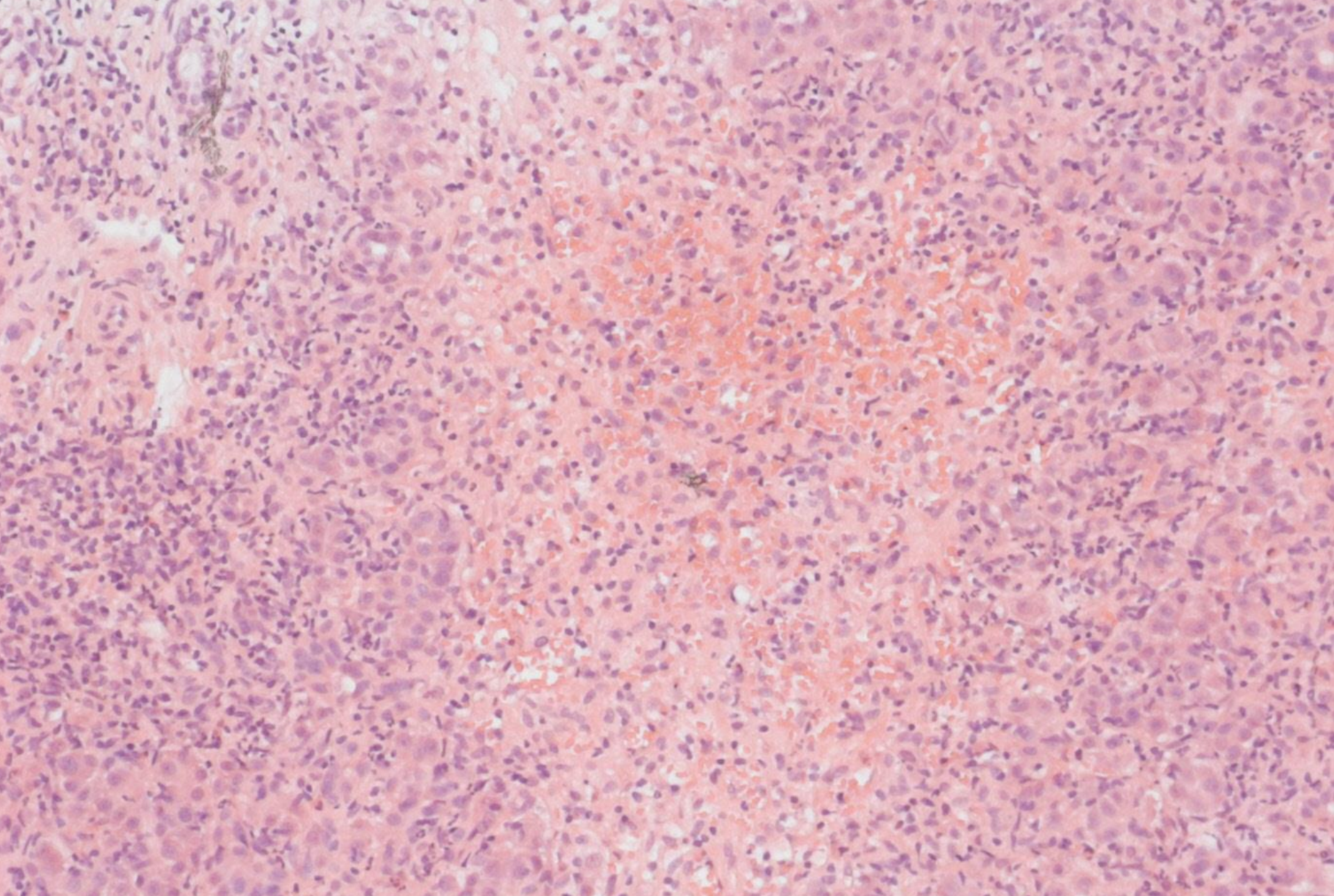
PBC with secondary AIH **(destructive cholangitis and interface hepatitis)**



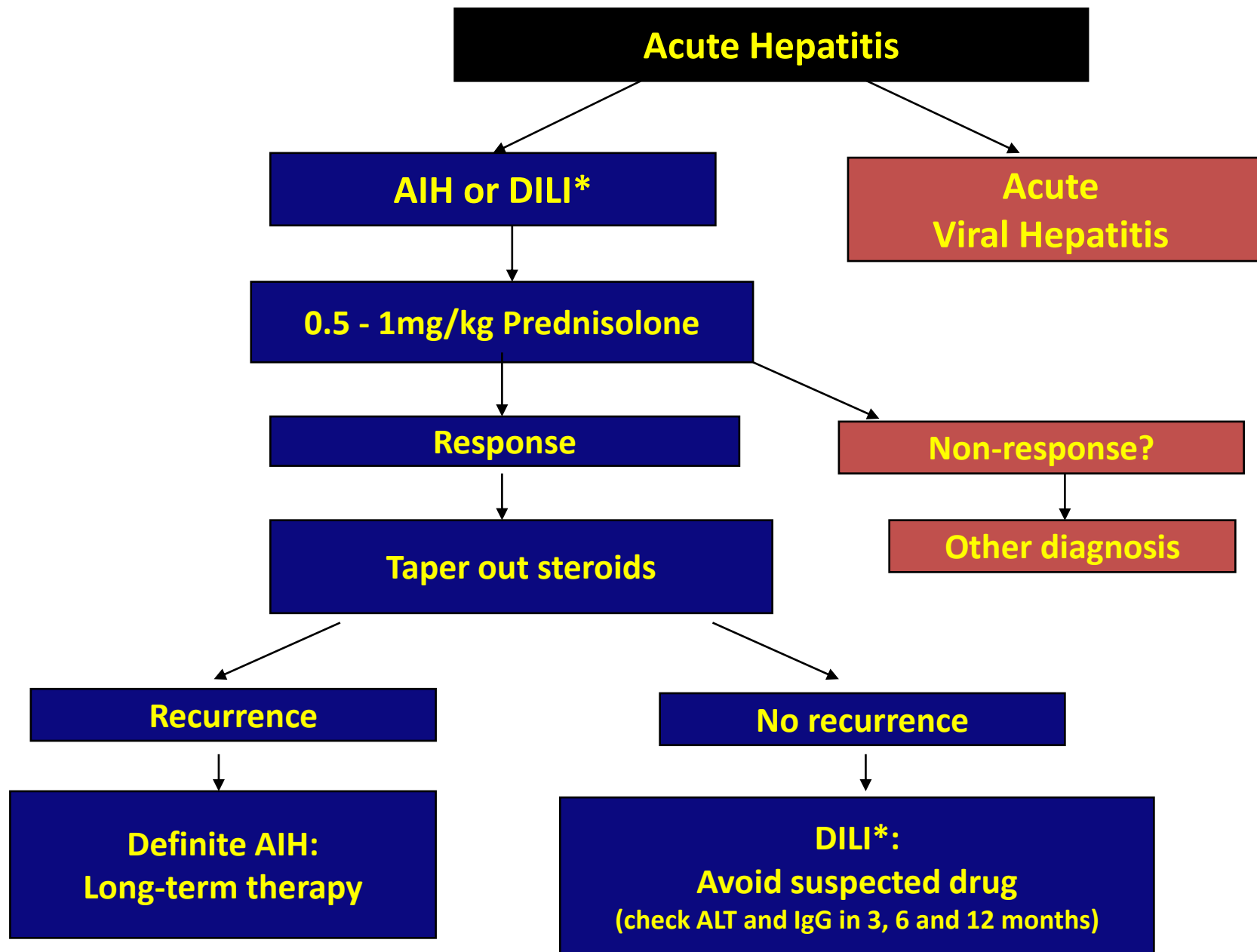
Variant (Overlap) Syndromes of AIH

AIH features in PBC or PSC should presumably be managed like AIH without PBC or PSC,

but usually needs lower doses



**Centrilobular necroses suggestive of drug-induced liver injury
(immunoallergic hepatitis)**



* DILI = Drug-induced liver injury

Remission induction

Problems and Questions

- Does everybody need treatment?
 - Yes, with very few exceptions
- Which steroid?
 - Prednisolone standard of care
- Starting dose?
 - Probably not important: risk and response guided
- How and when to assess response?
 - < 20% fall in ALT after two weeks at the latest
- What to do in poor response / non-response?
 - Check diagnosis; try prednisolone i.v.
- When to start azathioprine, what dose?
 - After clear initial response, and when bilirubin < 6mg / dl
- What to do in azathioprine intolerance?
 - MMF 2 – 1g / d

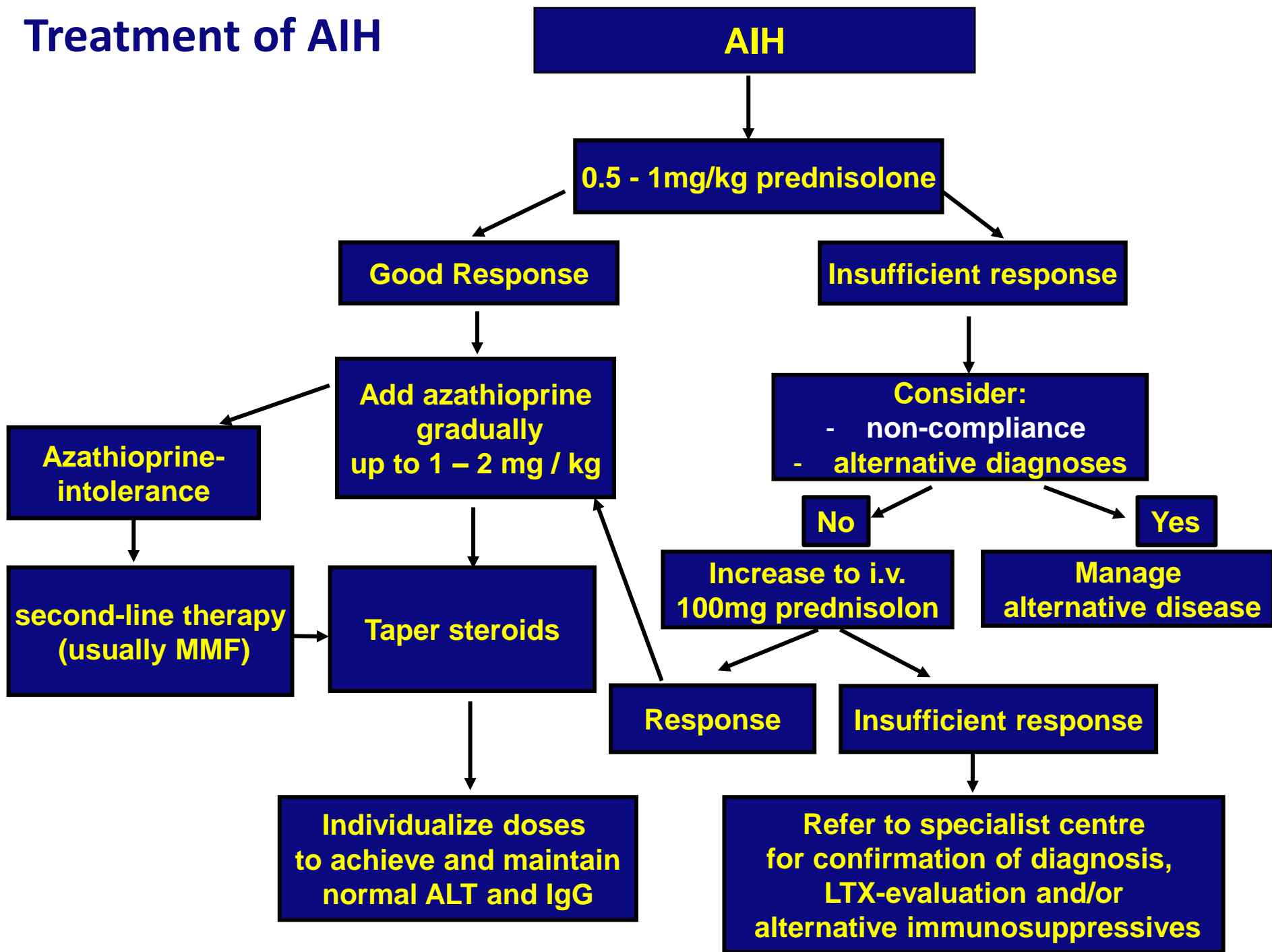
Maintenance of Remission Problems and Questions

- **Monotherapy or combination therapy?**
 - 6 – 12 months combination, than try azathioprine mono
- **Dose?**
 - Lowest dose to maintain remission, mostly 1 – 2 g aza
- **Treatment aim?**
 - Normal ALT and IgG (HAI < 4 / 18)
- **Monitoring strategy?**
 - ALT and IgG-levels every three months
- **Tapering strategy?**
 - Initially weekly, than monthly, than every three months
- **Maintaining compliance?**
 - Regular follow-up, trial of withdrawal, if requested
- **Managing (real and presumed) side-effects**
 - Individualized; good patient-doctor relationship

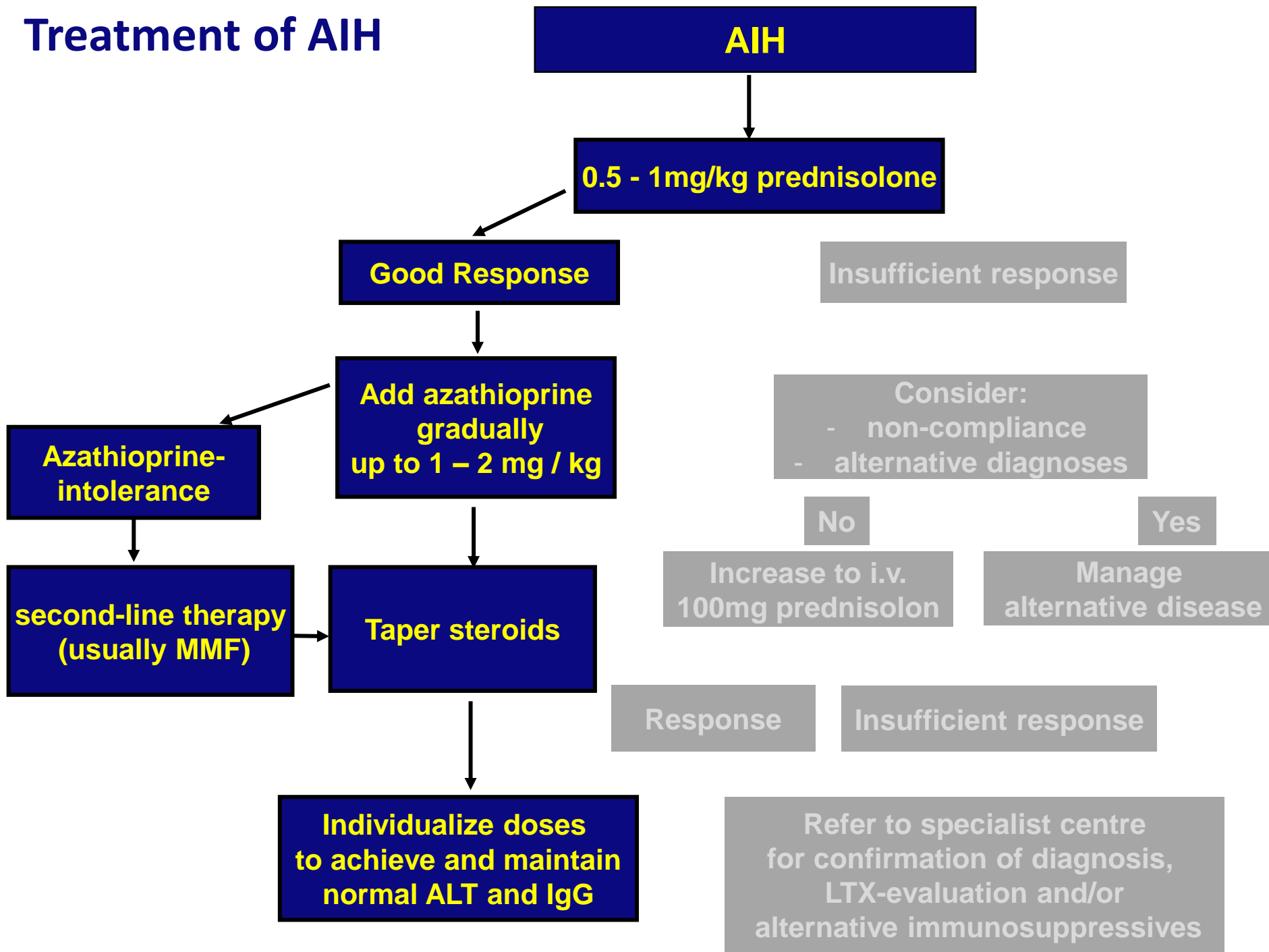
Problems and Questions: Special populations

- **Advanced cirrhosis**
 - **Yes, guided by histology; watch for side-effects**
- **Fulminant AIH**
 - **1 mg / kg prednisolone i.v. for 1 week, ?LTX**
- **AIH in PBC (or PBC variant syndrome?)**
 - **AIH is AIH (All AIH is equal); i.e. treat if HAI > 3 / 18**
- **AIH in PSC (or PSC variant syndrome?)**
 - **AIH is AIH (All AIH is equal); i.e. treat if HAI > 3 / 18**
- **Puberty**
 - **Be tolerant; involve nurse and psychologist**
- **Pregnancy**
 - **Continue therapy (lower dose?); increase after delivery**
- **AIH in the elderly and Severe comorbidity**
 - **Assess overall prognosis; individualize therapy and aims**

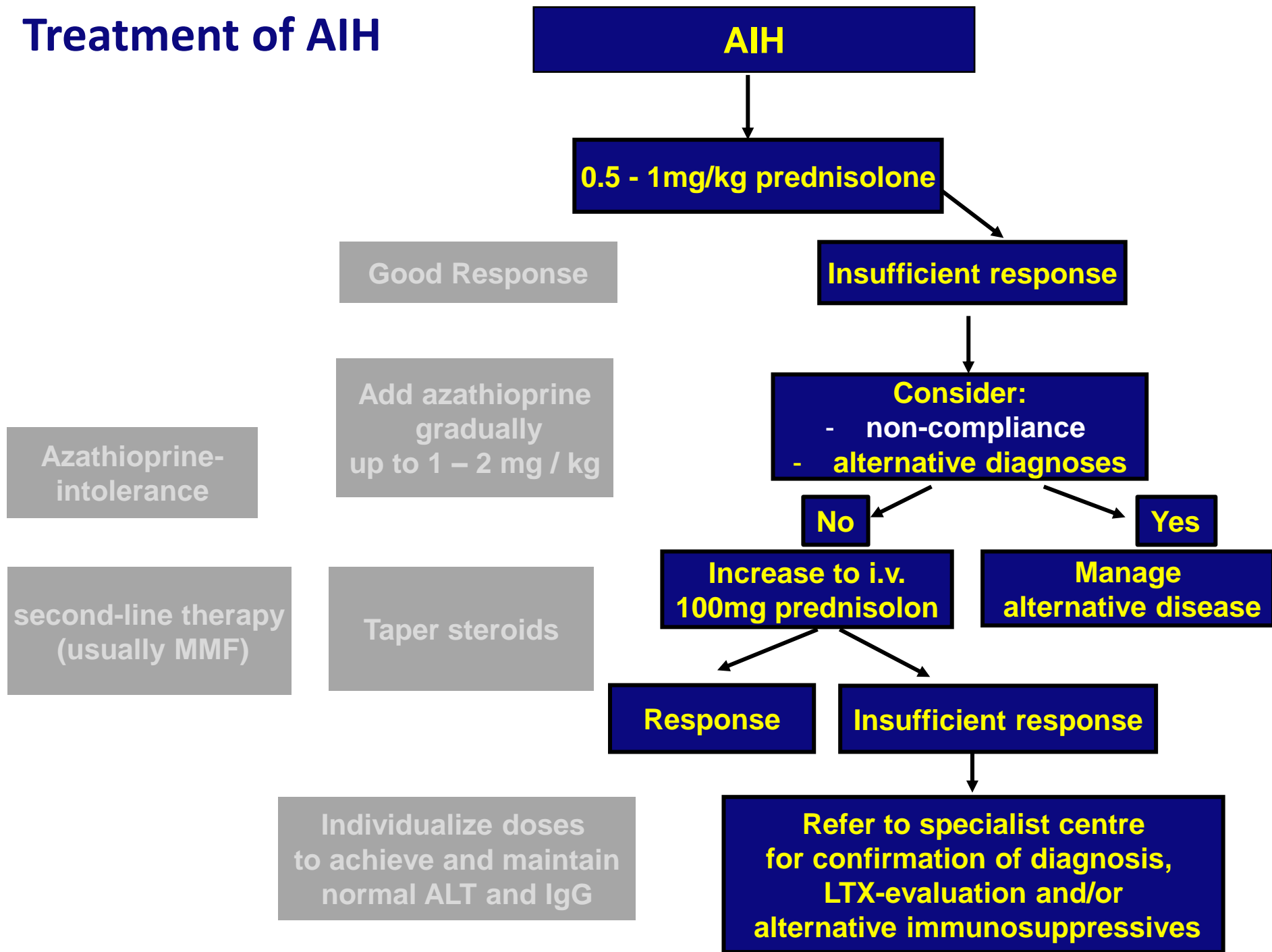
Treatment of AIH



Treatment of AIH



Treatment of AIH



Autoimmune Hepatitis

