Treatment of autoimmune cholangiopathy

Dr. hadi bagheri Hosseini

1402

Therapies to slow disease progression

Introduction

Ursodeoxycholic Acid (UDCA)

Drug	Year	Particiants	(mo)	Study Design	Conclusions	Reference
UDCA Monotherapy						
UDCA (13-15 mg/kg/day)	1992	14	12	Randomized, double blind, placebo controlled	Improved liver biochemistry, improved histologic score	Beuers et al.[212]
UDCA (13-15 mg/kg/day)	1997	105	24	Randomized, double blind, placebo controlled	No benefit in outcomes, despite improved liver biochemistry	Lindor[135]
UDCA (12-15 mg/kg/day)	1999	17	12	Open label	Improved liver biochemistry, no improvement in hepatic inflammation, fibrosis, or histologic stage	Van Milligen de Wit et al.[213]
UDCA (20 mg/kg/day)	2001	26	24	Randomized, double blind, placebo controlled	Improved liver biochemistry, reduced histologic and cholangiographic progression	Mitchell et al.[214]
UDCA (25-30 mg/kg/day)	2001	30	12	Open label	Improved liver biochemistry	Harnois et al.[138]
UDCA (17-23 mg/kg/day)	2005	219	60	Randomized, double blind, placebo controlled	No benefit	Olsson et al.[137]
UDCA (10 mg/kg/day vs 20 mg/kg/day vs 30 mg/kg/day)	2008	31	24	Randomized, double blind, placebo controlled	Improved liver biochemistry, improved Mayo risk score (high dosage)	Cullen et al.[136]
UDCA (28-30 mg/kg/day)	2009	150	60	Randomized, double blind, placebo controlled	No benefit, increased incidence of adverse events	Lindor et al.[139]
Immunomodulation						
Methotrexate (15 mg/wk)	1994	24	24	Randomized, double blind, placebo controlled	Mild improvement in ALP level only, poorly tolerated	Knox and Kaplan[215]
UDCA (500-75 mg/day); prednisone (1 mg/kg/day, tapered); azathioprine (1-1.5 mg/kg/day)	1999	15	41	Open label	Improved biochemistry, improved histologic stage in 6 of 10 patients	Schramm et al.[216]
UDCA plus budesonide (9 mg/day) or prednisone (10 mg/day)	2000	18	2	Randomized double blind	Decreased pruritus with prednisone, no improvement in liver biochemistry	Van Hoogstraten et al.[217]
Budesonide (9 mg/day)	2000	21	12	Open label	Marginal improvement in liver biochemistry, no change in histologic stage, worsened bone density	Angulo et al.[155]
Pentoxifylline (1200 mg/day)	2001	20	12	Open label	No benefit	Bharucha et al.[218]
UDCA (13-15 mg/kg/day) with or without mycophenolate mofetil (2 g/day)	2004	25	24	Randomized controlled trial	No benefit	Sterling et al.[219]
Mycophenolate mofetil (1-3 g/day)	2005	30	12	Open label	Mild improvement in liver biochemistry, no change in Mayo risk score	Talwalkar et al.[220]
Tacrolimus (0.1 mg/kg/day)	2007	16	12	Open label	Improved liver biochemistry	Talwalkar et al.[154]
Infliximab (5 mg/kg)	2008	10	6	Randomized, double blind, placebo controlled ($N = 10$)	No benefit	Hommes et al.[156]

Mechanisms of Action of UDCA in PBC

Hepatocytes:

- Stimulate biliary secretion of bile acids
- Inhibit apoptosis
- Activate glucocorticoid receptors
- Reverse aberrant expression of HLA Class I molecules

Cholangiocytes :

- Protect against cytotoxicity of hydrophobic bile acids
- Possible antiapoptotic effect (but not reduced risk of CCA)

Ileocytes :

- Inhibit bile acid carriers

Monocytes :

- Decrease cytokine secretion

Clinical Effects of UDCA in PBC

Laboratory Tests :

- Improves serum ALP, TB, GGT, AST, ALT, total cholesterol

Histology :

- Delays progression of fibrosis
- Improves portal inflammation
- Improves piecemeal necrosis

Symptoms :

- No clear effect on fatigue or pruritus

Complications of Primary Biliary Cholangitis :

- Delays development of esophageal varices
- Stabilizes or reduces portal vein gradient
- Does not improve bone disease

Survival :

- Extends survival free of transplantation

Ursodeoxycholic acid (ursodiol)

- UDCA reduces proliferation of colonic epithelial cells, and its long-term use in patients with PBC significantly reduces the probability that colorectal adenomas will recur following removal

- Adverse effects at **these doses** are generally uncommon, but include headache, GI disturbances, and nausea.

- The most cost-effective dose of UDCA in patients with PBC is 13 to 15 mg/kg/day
- Can be given in 1 or 2 divided doses
- Taken with meals
- In patients also taking cholestyramine, UDCA should be taken at least 2 hours before or after cholestyramine to ensure intestinal absorption

PBC

General measures

Immunizations :

- Vaccinations for hepatitis A virus and hepatitis B virus
- Other (Pneumococcal vaccination)→ general population

Abstain from alcohol :

- Avoid heavy alcohol use (>14 drinks per week or >4 drinks on a given day for men and >7 drinks per week or >3 drinks on a given day for women)

Pretreatment testing

- ALT
- AST
- ALP
- Bil T
- Gamma-glutamyl transpeptidase
- Platelet count

Initial therapy

Initial therapy UDCA 13 to 15 mg/kg

3 month

↓ALP

Symptoms such as fatigue often do not improve

12 month

Responder (NL ALP)

Long term

Continue UDCA (ALP q 3-6month)

Obeticholic acid

- A derivative of the primary human bile acid chenodeoxycholic acid (CDCA) and is a ligand for the farnesoid X receptor, which plays a role in bile acid homeostasis.
- Obeticholic acid is a more potent agonist of the receptor (approximately 100-fold higher potency) than CDCA

Adverse Reactions

- Pruritus, Decreased HDL cholesterol,, abdominal pain,Fatigue ,Palpitations, peripheral edema ,Eczema, Thyroid dysfunction , Constipation, hepatic encephalopathy

Contraindications

- Decompensated cirrhosis (Child-Pugh class B or C) , complete biliary obstruction.

Caution in compensated cirrhosis with gastroesophageal varices, or persistent thrombocytopenia

Fibrates:

Fenofibrate and bezafibrate

- Regulate bile acid synthesis
- Safe and well tolerated in PBC patients.
- The most commonly reported side effects were gastrointestinal and musculoskeletal abnormalities.
- Can lead to the elevation of transaminases and serum creatinine
- Contraindicated for patients with decompensated cirrhosis.

Fenofibrate vs bezafibrate

- Fenofibrate (200mg/day) and bezafibrate (400mg/day) induced significant biochemical improvement
- Fenofibrate could better reduce the low-density lipoprotein cholesterol and uric acid
- Fenofibrate treatment was associated higher rates of side effects and withdrawal events than bezafibrate

Bezafibrat

- Antilipemic Agent

Adverse Reactions

- ↑AST, ↑CPK, Eczema, pruritus ,Decreased appetite, diarrhea, dyspepsia, flatulence, gastritis, Anemia,Dizziness, headache, ,Alopecia, erythema multiforme, skin photosensitivity, skin rash, urticarial,abdominal pain, cholelithiasis, cholestasis, constipation, nausea

Bezafibrat

Contraindications

- Hypersensitivity to bezafibrate,
- Photoallergic or phototoxic reactions to fibrates
- Renal impairment (serum creatinine >1.5 mg/dL, CrCl <60 mL/minute, or patients undergoing dialysis);
- Pre-existing gallbladder disease
- Concomitant use with HMG CoA reductase inhibitors
- Severe infection
- Trauma, surgery
- Pregnancy or breast-feeding

Non responder after 12 month

Add to UDCA:

Obeticholic acid or **Bezafibrat**

6 M **6 M**

(ALP < 1.67 ULN) ALP<1.5 ULN

Yes **No** **No** **Yes**

Continue Tx (ALP q 3-6 M) Liver Tx or investigational Tx Continue Tx (ALP q 3-6 M)

Investigational treatment of PBC

Prednisolone and Prednisone

- Prednisolone and prednisone may improve serum alkaline phosphatase and aminotransferase levels and liver histologic features in patients with PBC, at least in **the short term**
- Development of side effects with glucocorticoids, particularly a reduction in bone mass, precludes their use in the treatment of PBC

Budesonide

- **Noncirrhotic** PBC with oral budesonide (6-9 mg daily) in combination with UDCA (15 mg/kg/day) after 3 years of treatment had better histologic improvement than UDCA alone.
- The addition of budesonide to treatment with UDCA was associated with improvement in serum liver enzyme levels, without affecting other important prognostic markers such as the bilirubin level
- Budesonide may be of potential benefit for patients with early-stage PBC
- Budesonide is associated with important systemic glucocorticoid-related adverse events in patients with more advanced-stage disease

Methotrexate

- In a placebo-controlled trial of methotrexate for PBC, methotrexate in a dose of 7.5 mg a week for up to 6 years was not only of no benefit, but also was associated with more unfavorable outcomes than was observed with placebo.
- Methotrexate **should not be recommended** routinely as monotherapy or as an adjuvant to UDCA.

Pruritus

General recommendations for cholestasis-associated pruritus:

- Using emollients and oat meal extract to improve dry and inflamed skin
- Avoiding hot baths or showers (at night)
- Using cooling gels (menthol gels) for affected skin areas
- Keeping nails shortened
- Searching for added allergens, especially in patients with associated hypereosinophilia or IgE-mediated allergy
- Psychologic intervention for addictive scratching/scratch dependence

UDCA may alleviates pruritus, although on occasion pruritus may worsen with initiation of UDCA

In warm countries, exposure to ultraviolet light without sun block can alleviate pruritus, and not surprisingly, the pruritus of PBC subsides during the summer months

Pruritus in PBC

Cholestyramine is first-line therapy

- Starting dose is 4 g/day, which can be increased up to four times daily
- It should be administered at least 2 to 4 hours apart from UDCA and other medications to prevent loss of efficacy.

Rifampicin is second-line agent

- Starting with only 150 mg/day and titrating up to a maximum of 300 mg twice a day

Opioid antagonists as third-line

- Naltrexon 25 to 50 mg/day .This has been dampened by adverse side effects including an opioid withdrawal–like reaction, pain, and confusion
- Preloading the patient with escalating doses of intravenous naloxone has been advocated to prevent such a withdrawal-like syndrome.

Sertraline can be used instead of naltrexone as a third-line option.

- Start with 25 mg/day ,The optimum dose is 75 to 100 mg/day

Refractory Pruritus in PBC

- **Extracorporeal albumin dialysis, plasmapheresis have been reported as rescue therapy for refractory cases.**
- Anti-histamines sometimes have a non-specific anti-pruritic effect
- Phenobarbital at bedtime
- liver transplantation
- Novel ileal bile acid transport (IBAT) inhibitors
- Phototherapy with ultraviolet light (UV-B)
- Nasobiliary drainage
- Propofol
- Androgens (such as methyltestosterone) increase serum bile acids and worsen jaundice, yet they paradoxically relieve pruritus in some patients with cholestasis
- **The use of vagal nerve stimulation remains experimental.**

Fatigue

seeking and treating associated and alternate causes:

- Anaemia
- Hypothyroidism
- Adrenal insufficiency
- Depression
- Sleep disturbance
- Associated conditions or therapies: (type II diabetes,Pruritus at night, autonomic dysfunction, dehydration, restless legs and drug such as beta-blockers)

Fatigue

- Tab Modafinil 100 to 200 mg/day
- Vitamin E if deficiency
- **Avoidance of social isolation**
- Regular exercise
- Medications such as β-blockers and calcium channel blockers, which can exacerbate autonomic dysfunction, should be adjusted.

- **Not responsive to UDCA or OCA therapy**
- Fluoxetine, ondansetron, and fluvoxamine have all **failed** to improve fatigue in patients with PBC

Sicca complex

- Dry eyes and/or dry mouth
- Dysphagia
- Vaginal dryness

Management

- Artificial tears and saliva are often helpful
- Pilocarpine or cevimeline (muscarinic receptor agonists)
- Vaginal moisturisers and oestrogen creams
- Patients with severe xerostomia should be given oral hygiene advice

Oral candidiasis in patients with severe xerostomia

Extrahepatic Complications

- Bone Disease
- Fat-Soluble Vitamin Deficiency
- Hyperlipidemia
- Associated Autoimmune Diseases (dry eyes/dry mouth syndrome, thyroiditis, scleroderma/CREST syndrome, rheumatoid arthritis, celiac disease, systemic lupus erythematosus

Fat-Soluble Vitamin Deficiency

- Patients with early-stage PBC with T Bil>2 mg/dL should be checked **annually** Vitamin A and D levels and the prothrombin time.

- Patients with advanced-stage PBC should be tested annually for deficiencies of vitamins A, D, E, and K, and replacement should be prescribed as indicated, followed by a maintenance dose:

Vitamin	Recommend daily doses (adults) Repletion	Maintenance
Vitamin A	5000–100,000 IU daily × 2 weeks	1500–5000 IU daily
Vitamin D[d]	*Serum 25(OH)D < 12 ng/ml*	
	50,000 IU weekly × 8 weeks	800 IU daily
	Serum 25(OH)D 12–20 ng/ml	
	800–1000 IU daily	800–1000 IU daily
	Serum 25(OH)D 20–30 ng/ml	
	600–800 IU daily	600–800 IU daily
Vitamin E	200–2000 mg daily	15 mg daily
Vitamin K	2.5–10 mg daily	5–10 mg oral weekly to daily

Hyperlipidemia

- In the early stages of PBC: HDL levels elevated
- The disease progresses: ↓HDL and ↑LDL

  But the risk of myocardial infarction and stroke does not appear to be increased

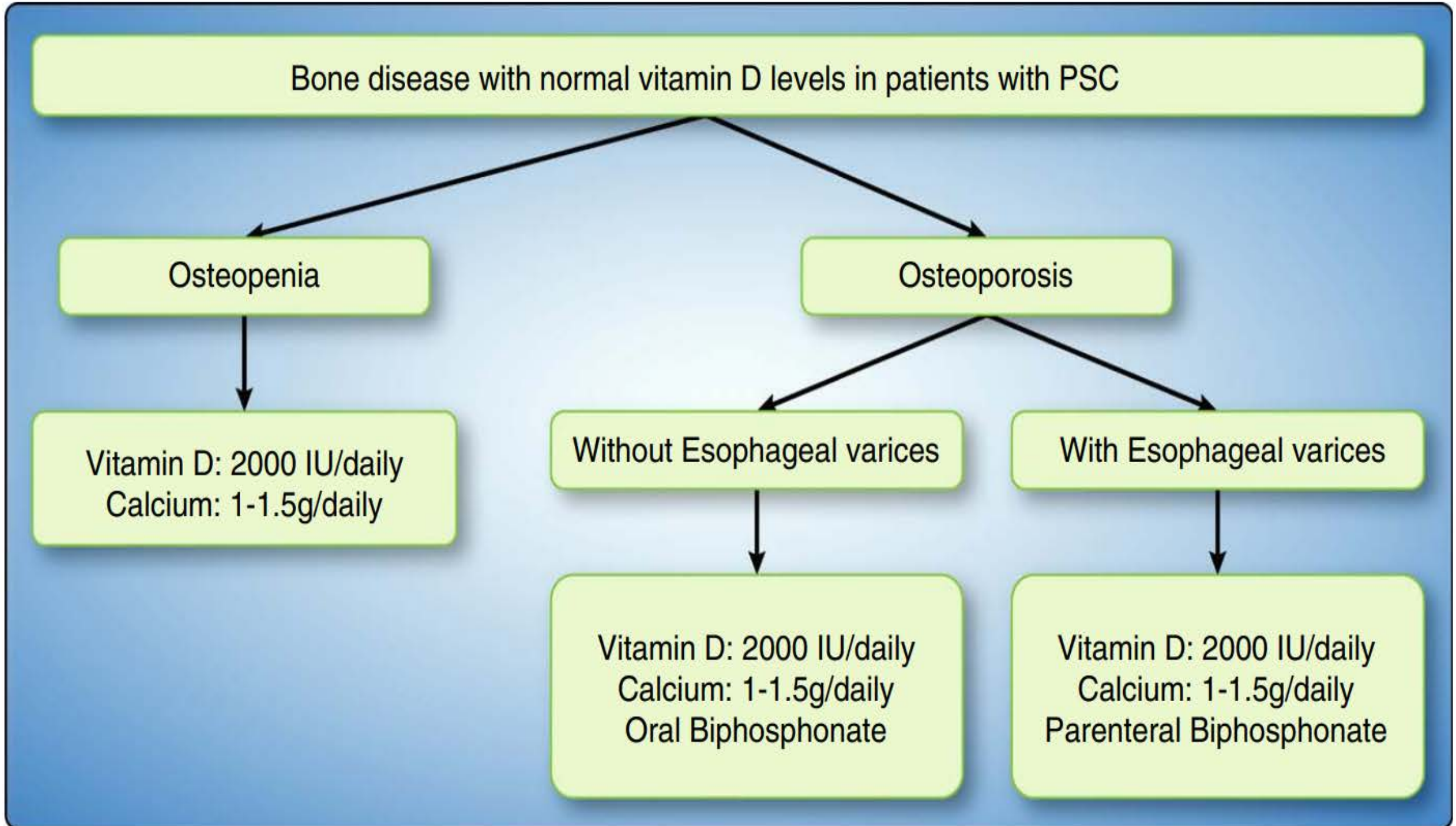
- Xanthelasmas (deposits of cholesterol in the skin) may develop
- Surgical removal of xanthelasmas is seldom successful, and such attempts should be avoided.
- Treatment is according to the patient's individual risk factors for cardiovascular disease.
- Statins have proven safe in small studies in this population

Metabolic Bone Disease

- BMD at baseline and then every 2 to 3 years
- Bisphosphonates in patients with PBC and osteoporosis (T score < −2.5)

- Because of the carcinogenic properties of estrogens and the risk of thromboembolism, they are not considered first-line agents.

- Raloxifene is as an alternative to estrogen replacement therapy for postmenopausal osteoporosis


Bone disease with normal vitamin D levels in patients with PSC
Osteopenia
Osteoporosis
Vitamin D: 2000 IU/daily
Calcium: 1-1.5g/daily
Without Esophageal varices
With Esophageal varices
Vitamin D: 2000 IU/daily
Calcium: 1-1.5g/daily
Oral Biphosphonate
Vitamin D: 2000 IU/daily
Calcium: 1-1.5g/daily
Parenteral Biphosphonate

Steatorrhea

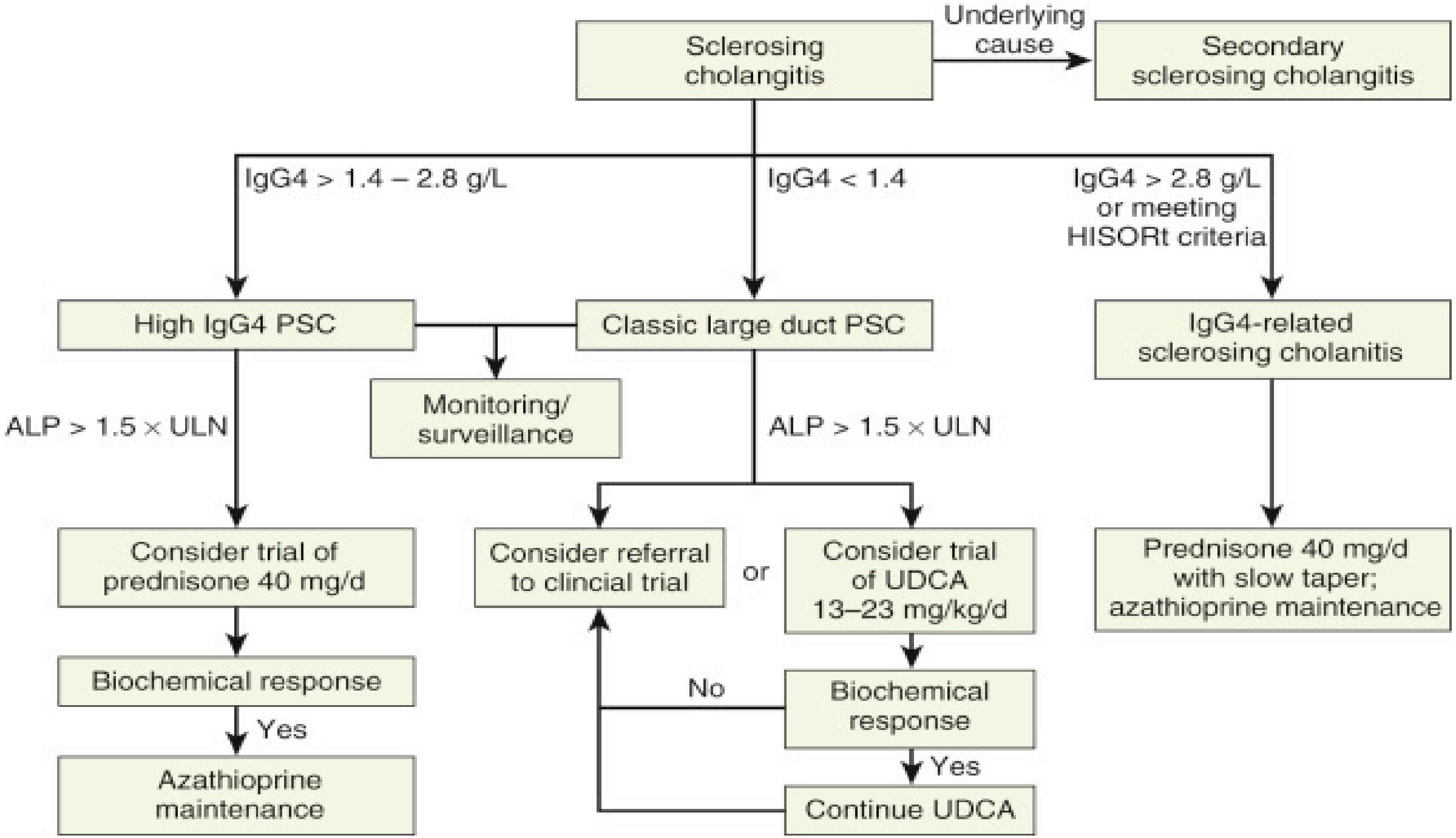
Steatorrhea can occur in patients with advanced PBC because:

- ↓bile acid delivery → ↓bile acids in the small intestine
- Exocrine pancreatic insufficiency
- Coexisting celiac disease
- SIBO

PBC in pregnancy

- Expert consultation for all pregnant patients
- Pregnancy is typically well tolerated in non-cirrhotic patients with PBC.
- Continued use of UDCA in pregnancy
- Pruritus management is important
- Rifampicin has been used by experts during the third trimester
- Pregnancy in patients with cirrhosis carries a higher risk of maternal and fetal complications
- Offering patients pre-conception counselling and relevant specialist monitoring

PSC


Sclerosing cholangitis
Underlying cause
Secondary sclerosing cholangitis
IgG4 > 1.4 – 2.8 g/L
IgG4 < 1.4
IgG4 > 2.8 g/L or meeting HISORt criteria
High IgG4 PSC
Classic large duct PSC
IgG4-related sclerosing cholanitis
Monitoring/ surveillance
ALP > 1.5 × ULN
ALP > 1.5 × ULN
Consider trial of prednisone 40 mg/d
Consider referral to clincial trial
or
Consider trial of UDCA 13–23 mg/kg/d
Prednisone 40 mg/d with slow taper; azathioprine maintenance
Biochemical response
No
Biochemical response
Yes
Yes
Azathioprine maintenance
Continue UDCA

Medical Therapy for PSC

No Proved Benefit	Possible Benefit
Antibiotics	Ursodeoxycholic acid [192193194195196197199200201202203204205]
Cholestyramine	
Glucocorticoids [206207]	
Azathioprine	
Methotrexate [208]	
Cyclosporine	
Tacrolimus [209]	
Pentoxifylline [210]	
Colchicine [212]	
d -penicillamine [213]	
Nicotine [215216]	
Perfenidone [217]	

- UDCA at doses of 15-20 mg/kg/d can be given since it may improve serum liver tests and surrogate markers of prognosis.

Antibiotics

- Gut dysbiosis → biliary injury→ PSC

- The most studied antibiotic is oral vancomycin
- Oral vancomycin 125 mg four times daily→ ↓PSC Mayo risk score

- Long-term use of antibiotics is not recommended for treatment of PSC in the absence of recurrent bacterial cholangitis

Acute bacterial cholangitis in PSC

1. First presentation of the disease (6%)
2. Post ERCP

- Bacterial cholangitis → antibiotics→ recurrence →rotating antibiotics
- Initial episode of bacterial cholangitis →MRCP → stricture→ ERCP
- Acute bacterial cholangitis→inadequate response →ERCP

Pruritus in PSC

- General recommendations for patients suffering from cholestasis-associated pruritus include using emollients to prevent dryness of skin, avoiding hot baths or showers, using cooling gels (e.g., menthol gels) for affected skin areas, or keeping nails shortened.

Pruritus in PSC

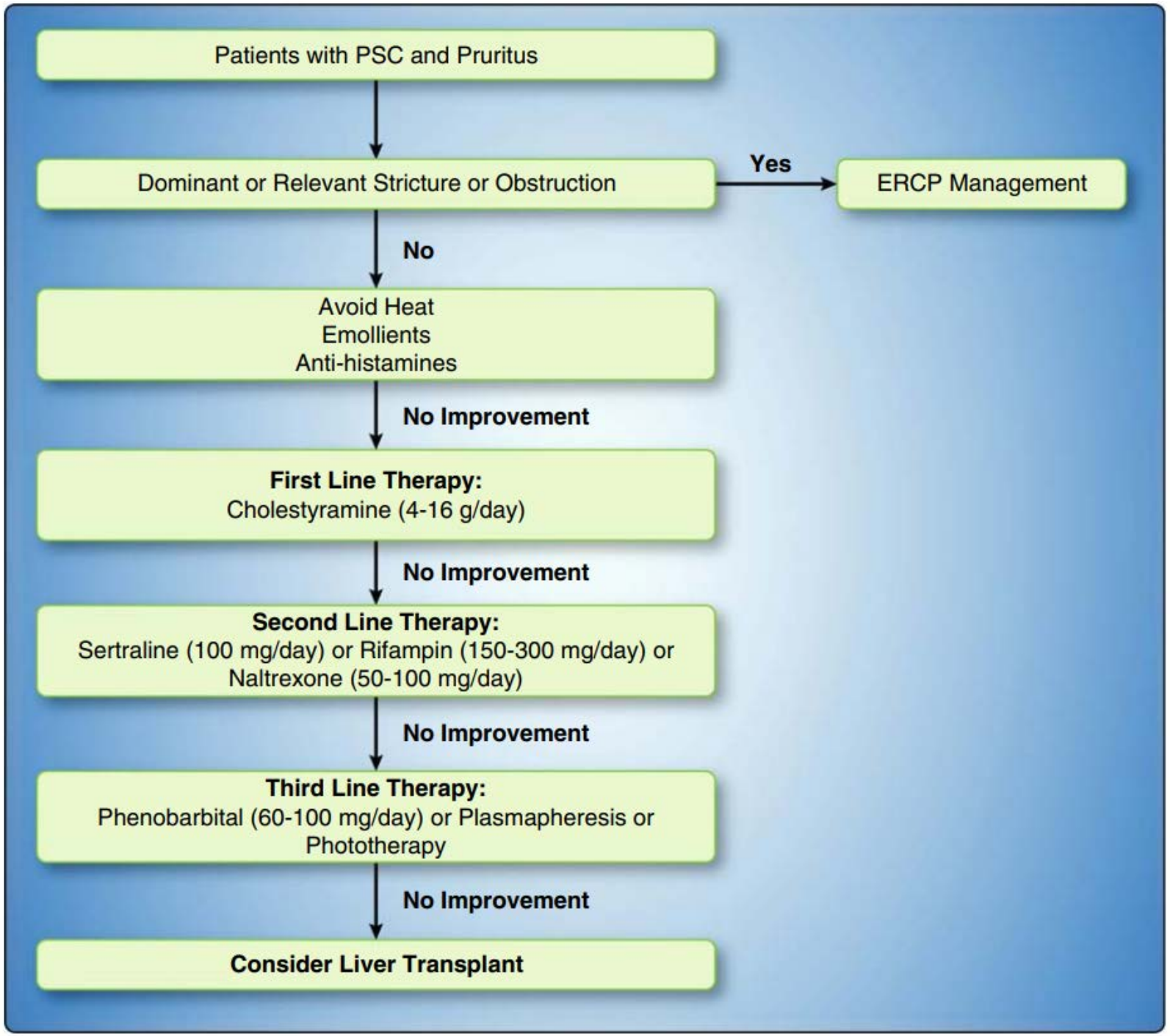
- It is recommended to exclude relevant bile duct strictures in large duct sclerosing cholangitis as the cause of progressive pruritus.
- If present and reachable, relevant strictures should be treated by endoscopic balloon dilatation (or stenting, if balloon dilatation alone is insufficient) after brushing
- Pharmacological treatment of moderate to severe pruritus in sclerosing cholangitis with bezafibrate or rifampicin is recommende
- New-onset or worsening pruritus → MRCP → ERCP

aga

Table 1. Current and Emerging Pharmacotherapy for Cholestatic Pruritus in PSC

Category	Agent	Dosing	Comment
Current therapies			
Nonpharmacologic	Emollients, heat avoidance	As needed	Sufficient for mild pruritus
Antihistamine	Hydroxyzine	25 mg q8h	Drowsiness
Bile acid sequestrants	Cholestyramine	4–6 g/taken 20 minutes before meals	Frequent GI intolerance
SSRI	Sertraline	100 mg/d	Limited efficacy
μ-opioid antagonist	Naltrexone	50–100 mg/d	Limited efficacy
PXR agonist	Rifampin	150–300 mg/d	May cause hepatotoxicity, A hemolytic anemia
PPAR agonists	Fenofibrate, Bezafibrate	160 mg/d 400 mg/d	Significant improvement in pruritus in FITCH study (bezafibrate)
Systemic therapies	Plasmapheresis, ultraviolet phototherapy	5–10 sessions or until effect	Variable efficacy
Potential future therapies			
G-protein–coupled–receptor 5	MAS-related GPR family member X4 EP547		NCT05525520
Ileal sodium–bile acid cotransporter inhibitor (ASBTi)	Frequent adverse effect: drug-induced diarrhea Volixibat Maralixibat (LUM001) Odevixibat (A4250) A3907	NCT04663308 NCT02061540 NCT05642468	

Approach to pruritus in PSC.
In a patient with PSC and new-onset pruritus



EASL

Table 6. Medical treatment of pruritus in sclerosing cholangitis.

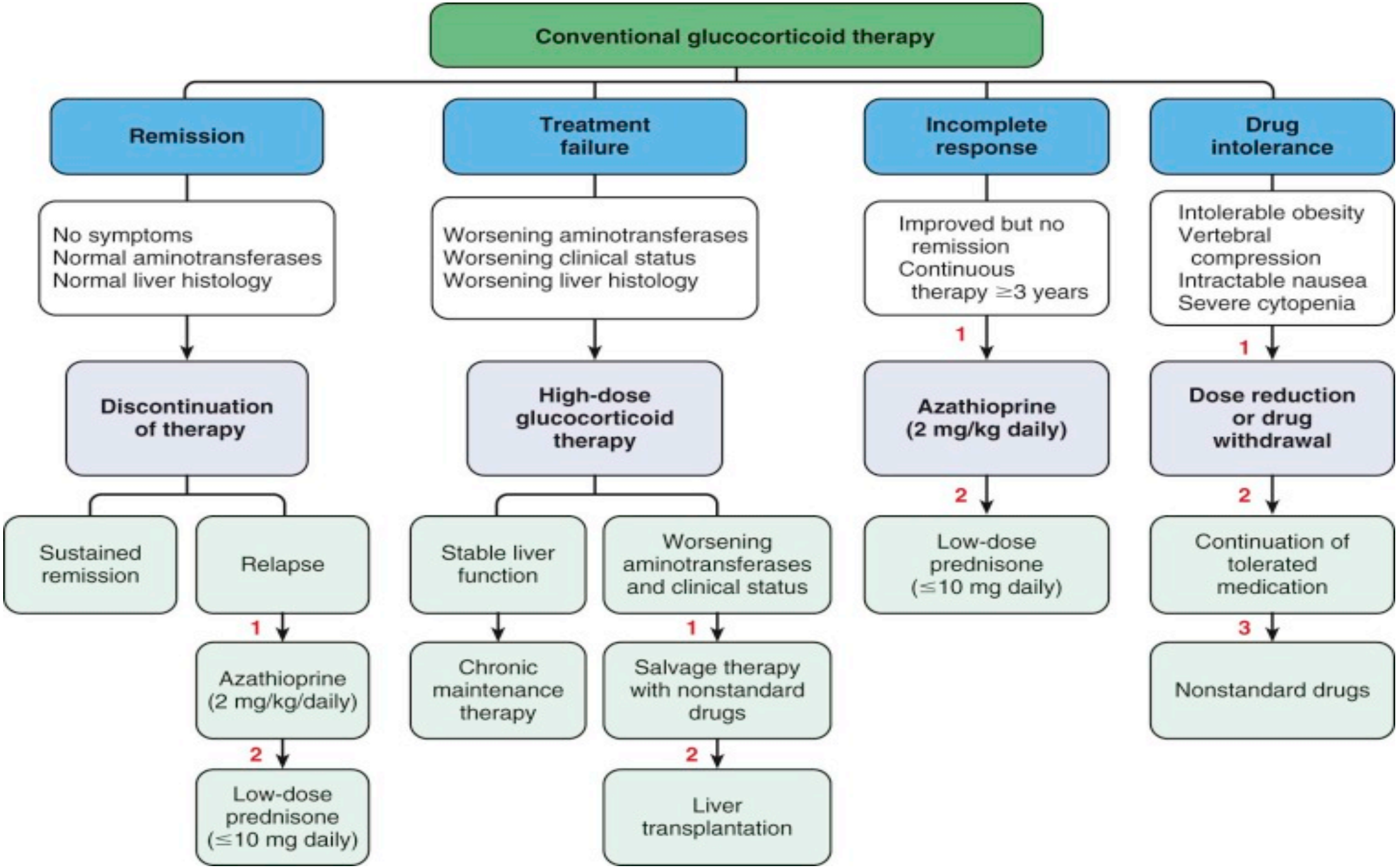
Evidence	Drug
1st line	Bezafibrate (400 mg daily)
2nd line	Rifampicin (150-300 mg/d)
3rd line	Naltrexone (12.5-50 mg/d)
No evidence for PSC	Anion exchange resins (cholestyramine [4 g once to four times daily], colesevelam [1,250-1,875 mg twice daily]; 4 hours separate from other medication)
No evidence for PSC	Sertraline (50-75 mg/d)
Experimental	ASBT inhibitors
Experimental	Selective PPARα and PPARδ agonists

Overlap

PBC	PSC	Cholestasis
Prednisone (10 mg daily) in combination with azathioprine (50 mg daily) if AP ≤ 2 × ULN	Prednisone (10 mg daily) in combination with azathioprine (50 mg daily) and low-dose UDCA (13-15 mg/kg daily)	Prednisone (10 mg daily) in combination with azathioprine (50 mg daily) and/or low-dose UDCA (13-15 mg/kg daily) depending on AP level and histologic features
Prednisone (10 mg daily) in combination with azathioprine (50 mg daily) and low-dose UDCA (13-15 mg/kg daily) if AP > 2 × ULN and/or **florid duct lesions**		

AIH add to PBC

- EASL recommend that a liver biopsy is mandatory in confirming the features of AIH, and should be considered in patients with disproportionate elevations in ALT and/or IgG


Conventional glucocorticoid therapy
Remission
No symptoms
Normal aminotransferases
Normal liver histology
Discontinuation of therapy
Sustained remission
Relapse
1
Azathioprine (2 mg/kg/daily)
2
Low-dose prednisone (≤10 mg daily)
Treatment failure
Worsening aminotransferases
Worsening clinical status
Worsening liver histology
High-dose glucocorticoid therapy
Stable liver function
Chronic maintenance therapy
Worsening aminotransferases and clinical status
1
Salvage therapy with nonstandard drugs
2
Liver transplantation
Incomplete response
Improved but no remission
Continuous therapy ≥3 years
1
Azathioprine (2 mg/kg daily)
2
Low-dose prednisone (≤10 mg daily)
Drug intolerance
Intolerable obesity
Vertebral compression
Intractable nausea
Severe cytopenia
1
Dose reduction or drug withdrawal
2
Continuation of tolerated medication
3
Nonstandard drugs

