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Addressing challenges in diagnosis and treatment of IgG4-related gastrointestinal disease

Practice aid for IgG4-related gastrointestinal disease

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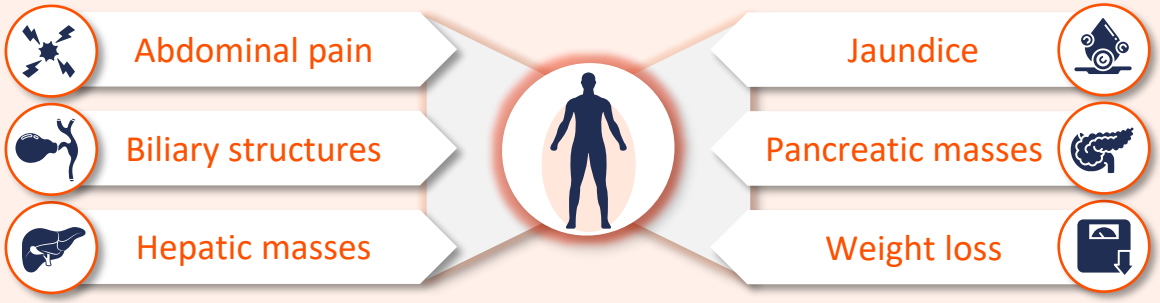
IgG4-RD often affects the pancreaticobiliary tract[1]

Clinical presentation of IgG4-related pancreaticobiliary disease[2]



Cholangitis is the most common hepatobiliary manifestation of IgG4-RD[2]

AIP-1 is a common pancreaticobiliary manifestation of IgG4-RD[3]

AIP-1 presents in acute and chronic forms:[2]

Acute

- Obstructive jaundice and/or
- Pancreatic mass

Chronic

- Pancreatic atrophy
- Calcifications

Pancreaticobiliary tumours may mimic AIP due to similar clinical presentation[2,4]

HISORt diagnostic groups: Patients meeting criteria for ≥1 group have AIP-1[5,6]

H Histology

I Imaging (pancreatic)

S Serology

O Other organ involvement

Rt Response to steroid therapy*

GROUP A — Pancreatic histology

Full spectrum of LPSP changes

- Periductal lymphoplasmacytic infiltrate
- Obliterative phlebitis
- Storiform fibrosis

and/or

IgG4 IHC

- ≥10 IgG4-positive cells per HPF of pancreatic lymphoplasmacytic infiltrate

GROUP B — Imaging + serology

CT or MRI

- Diffusely enlarged pancreas with delayed and 'rim' enhancement

and

Pancreatogram

- Diffusely irregular pancreatic duct

and

Serum IgG4

- Elevated serum IgG4 levels (≥135 mg/dL)[7]

GROUP C — Response to steroids

Pancreatic disease

- Clinical suspicion of AIP without definitive features on imaging or histology, and no evidence of pancreatic cancer

and

Response to steroids*

- Resolution/marked improvement in manifestations with steroid treatment

and

IgG4 levels

- Elevated serum IgG4 levels and/or other organ involvement (IgG4-positive cells)

*Steroid therapy should only be given to patients with negative workup for known aetiologies for pancreatic disease and only to patients in whom response can be objectively assessed. Steroid therapy should not be used as a substitute for a thorough investigation for aetiology.

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AIP-1 and AIP-2 are distinct disease entities[8]

	AIP-1[9] IgG4-related pancreatitis	AIP-2[9] IDCP or AIP with GELs
Male : Female	3:1	1:1
Mean age	65 years	40 years
Geography	Asia > Europe and US	Asia < Europe and US
Clinical presentation*	Jaundice 60–80% Weight loss 65% Acute pancreatitis 15%	Acute pancreatitis 80% Jaundice 30%
Biological presentation*	>80% Cholestasis 65% Diabetes 20% Insulin-dependent diabetes 40% Exocrine pancreatic insufficiency <3 × N Lipase	Rare Endocrine and exocrine pancreatic insufficiency >3 × N Lipase
IgG4 profile	>135 mg/dL (70% sensitivity; 93% specificity) >270 mg/dL (53% sensitivity; 99% specificity)	Not associated with elevated IgG4 levels in serum or tissue[10]

AIP-2 has no relationship to IgG4-RD[8]

*% of cases.

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IgG4-RD is a highly treatment-responsive disease[9]

Induction

GCs are the cornerstone of treatment[11]

- **40 mg/day prednisolone, for 4 weeks[12]**
- If response achieved after 1 month, **taper dose** at a rate of **5 mg every 1–2 weeks[3,12]**

Relapses are common following steroid tapering and are treated as per induction regimen[11]

Maintenance

Long courses of low-dose GCs[3,11,13]

- **2.5–10 mg/day prednisolone**

Long-term GC treatment is associated with adverse effects;[14] alternative treatments:

- GCs and immunosuppressants (limited evidence)[14]
- Off-label targeted therapy, including B-cell depletion[14]

Monitoring

Clinical monitoring for early detection of flares[3,13–17]

- Sequential assessment of **clinical, biochemical** and **radiological parameters[3,13–17]**
- **Biomarkers,** e.g. serum IgG4 levels[15]

Life-long follow-up is advisable[7]

Emerging treatments for IgG4-RD[18,19]

Phase I/II	Phase II				Phase III		Phase IV
Rituximab	Rilzabrutinib	Zanubrutinib	Abatacept	Elotuzumab	Obexelimab	Inebilizumab	Belimumab
NCT01584388 **Completed**	NCT04520451 **Active**	NCT04602598 **Recruiting**	NCT03669861 **Completed**	NCT04918147 **Recruiting**	NCT05662241 **Recruiting**	NCT04540497 **Active**	NCT04660565 **Unknown**
Anti-CD20 antibody	**BTK inhibitors**		**CTLA4-Ig fusion protein**	**Anti-SLAMF7 antibody**	**Anti-CD19 antibodies**		**Anti-BAFF antibody**

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Abbreviations and references

Abbreviations

AIP, autoimmune pancreatitis; AIP-1, AIP type 1; AIP-2, AIP type 2; BAFF, B-cell activating factor; BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; CT, computerized tomography; CTLA4, cytotoxic T-lymphocyte associated protein 4; GC, glucocorticoid; GEL, granulocyte epithelial lesion; HPF, high-power field; IDCP, idiopathic duct-centric pancreatitis; Ig, immunoglobulin; IgG4-RD, IgG4-related disease; IHC, immunohistochemistry; LPSP, lymphoplasmacytic sclerosing pancreatitis; MRI, magnetic resonance imaging; N, normal; SLAMF7, surface antigen CD319.

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