Journal of Translational Gastroenterology **2026** | Epub
DOI: 10.14218/JTG.2026.00015

Guideline

Chinese Guidelines for the Diagnosis and Treatment of Autoimmune Pancreatitis (Shanghai, 2023)

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Received: April 14, 2026 | **Revised:** May 19, 2026 | **Accepted:** May 25, 2026 | **Published online:** June 23, 2026

Abstract

Autoimmune pancreatitis (AIP) is a rare immune-mediated form of chronic pancreatitis. It may affect multiple organs, and its heterogeneous clinical manifestations complicate diagnosis and management. Based on the *Chinese Guidelines for the Diagnosis and Management of Autoimmune Pancreatitis (Shanghai 2012 Draft)*, together with the latest domestic and international guidelines and research advances, the present guideline provides 20 recommendations covering four aspects: diagnosis, treatment, follow-up, and prognosis. The aim is to improve the diagnosis and management of AIP in China and ultimately improve patient outcomes.

Introduction

Autoimmune pancreatitis (AIP) is a distinct form of chronic pancreatitis that typically presents with obstructive jaundice, abdominal discomfort, and other clinical manifestations. It is immune-mediated and marked by lymphocytic and plasmacytic infiltration, pancreatic fibrosis, pancreatic dysfunction, and possible extrapancreatic organ involvement, and it generally responds well to glucocorticoid therapy. In 2012, the Chinese Journal of Pancreatology organized the development of the *Chinese Guidelines for the Diagnosis and Management of Autoimmune Pancreatitis (Shanghai, 2012 Draft)*. After 10 years of application in clinical practice, these guidelines have played an important role in improving the diagnosis and management of AIP in China. In recent years, substantial progress has been made in AIP research both in China and internationally, with a deeper understanding of the disease and increasingly standardized clinical practice, although some issues remain controversial. To better guide the clinical diagnosis and management of AIP, the National Clinical Research Center for Digestive Diseases (Shanghai), the National Key Laboratory of Immunity and Inflammation, the Professional Committee of Pancreatic Disease of the Chinese Medical Doctor Association, the Pancreas Study Group of the Chinese Society of Gastroenterology of the Chinese Medical Association, and the Editorial Board of the Chinese Journal of Pancreatology jointly established a multidisciplinary working group. This group included experts in gastroenterology, rheumatology, surgery, radiology, pathology, laboratory medicine, and evidence-based medicine, and revised the previous guidelines to form the present document. The present guidelines were registered on the Practice Guideline Registration for Transparency platform (PREPARE-2022CN812). The design and development followed the WHO Handbook for Guideline Development issued by the World Health Organization in 2014 and the Chinese guiding principles for the development/revision

Keywords: Autoimmune pancreatitis; IgG4-related disease; IgG4-related cholangitis; Guidelines; Glucocorticoid therapy; Multidisciplinary management.

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How to cite this article: Xin L, Cai Y, Hu L, Li H, Wu D, Li Z, *et al*. Chinese Guidelines for the Diagnosis and Treatment of Autoimmune Pancreatitis (Shanghai, 2023). *J Transl Gastroenterol*. Published online: June 23, 2026.

of clinical practice guidelines issued by the Chinese Medical Association in 2022,[1] with reference to the Appraisal of Guidelines for Research & Evaluation II and the Reporting Items for Practice Guidelines in Healthcare Statement.[2,3] Through a systematic review of the published literature and interviews with selected experts, 20 recommendations were formulated regarding diagnosis, treatment, follow-up, and prognosis. After evidence retrieval and methodological quality assessment, the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) was used to rate the quality of evidence (high, moderate, low, or very low) and the strength of recommendations (strong or weak).[4] Recommendations are presented as declarative statements (Table 1). Three rounds of Delphi surveys were conducted, and after further refinement based on expert feedback, consensus was reached for all recommendations (all consensus rates > 96.7%).

Diagnosis

I. Clinical manifestations

Recommendation 1. Patients with AIP commonly present with non-specific symptoms such as obstructive jaundice and abdominal discomfort, and some patients are asymptomatic. Clinical manifestations of extrapancreatic organ involvement should be carefully assessed. (Quality of evidence: High; Strength of recommendation: Strong; Level of consensus: 100%)

The mean age at diagnosis of type 1 AIP is approximately 60 years, and the incidence in men is about three times that in women.[5] The clinical manifestations of type 1 AIP can be divided into pancreatic and extrapancreatic manifestations. Pancreatic manifestations are non-specific, and common symptoms include obstructive jaundice (51.9–75.0%), abdominal discomfort or abdominal pain (41.0–65.4%), and weight loss (40.0–45.1%). Some patients present with polydipsia, polyuria, or fatigue, whereas others have no clinical manifestations and seek medical attention only after pancreatic enlargement is detected during a health examination.[6–10] These clinical manifestations resemble those of pancreatic cancer and may therefore lead to misdiagnosis.

A substantial proportion of patients with type 1 AIP have extrapancreatic manifestations, which essentially represent organ involvement in IgG4-related disease (IgG4-RD) affecting different organs. Such involvement does not necessarily parallel the severity of pancreatic lesions and may occur before, concurrently with, or after pancreatic manifestations. Some patients have corresponding physical signs, which should be carefully assessed on examination. Common extrapancreatic organ involvement includes sclerosing cholangitis, Mikulicz disease (dacryoadenitis and sialadenitis), retroperitoneal fibrosis, interstitial nephritis, superficial and deep lymphadenopathy (hilar, mediastinal, and abdominal), and interstitial pneumonia.[11] One study including 100 Chinese patients with AIP found that 77 patients (77.0%) had 81 extrapancreatic lesions,[12] with biliary lesions being the most common (64 lesions), including 42 strictures of the distal common bile duct and 22 strictures of the common hepatic duct or intrahepatic bile ducts. In addition, approximately 51.5% of patients with type 1 AIP had peripancreatic vascular involvement.[13]

The mean age at diagnosis of type 2 AIP is lower than that of type 1 AIP. One study reported a mean age of 43 years, and the disease generally occurs between 30 and 50 years of age, with no statistically significant sex difference in incidence.[14,15] Patients with type 2 AIP often present with abdominal pain resembling acute pancreatitis.[16] In addition, compared with type 1 AIP, type 2 AIP is more likely to be associated with inflammatory bowel disease (IBD).[17] In recent years, increasing attention has been paid to the relationship between AIP and IBD, and 6–27% of patients with AIP are reported to have concomitant IBD.[18,19]

II. Imaging examinations

Recommendation 2. Contrast-enhanced computed tomography (CT) is recommended as the first-line imaging modality for the diagnosis of AIP. (Quality of evidence: Moderate; Strength of recommendation: Strong; Level of consensus: 100%)

On contrast-enhanced CT, AIP commonly presents as diffuse enlargement of the pancreas. A hypoenhancing capsule-like rim may be seen during the pancreatic parenchymal phase, producing a "sausage-like" appearance; punctate enhancement may be present within the pancreatic parenchyma, followed by delayed enhancement on later-phase images. AIP may also present as a focal pancreatic mass, and a small number of cases show multifocal lesions.[20,21] The International Consensus Diagnostic Criteria (ICDC) for AIP classify pancreatic parenchymal CT findings into two levels: typical and indeterminate. Typical findings include diffuse pancreatic enlargement with delayed enhancement, whereas indeterminate findings include focal or multifocal enlargement with delayed enhancement.[16] A capsule-like rim around the pancreas is uncommon in other diseases and is therefore a relatively specific imaging sign of AIP. Delayed enhancement is also characteristic of AIP, although it is less common in cases with less marked fibrosis.[22]

CT can differentiate AIP from chronic pancreatitis. The features of typical chronic pancreatitis include pancreatic atrophy, parenchymal or intraductal calcification, irregular ductal dilatation with side-branch ectasia, and pseudocyst formation. However, recent studies have shown that mild pancreatic ductal dilatation is not rare in AIP. Approximately 10% of patients with a longer disease course may develop pancreatic atrophy, pancreatic duct stones, and related changes,[23] and cases complicated by pseudocysts have also been reported.[24]

CT is of major value in differentiating AIP from pancreatic cancer. A meta-analysis showed that the sensitivity and specificity of contrast-enhanced CT for distinguishing AIP from pancreatic cancer were 59% (95% confidence interval (CI), 0.410–0.750) and 99% (95% CI, 0.880–1.000), respectively.[25] The typical CT appearance of AIP is diffuse pancreatic enlargement, whereas pancreatic cancer typically appears as a hypovascular focal mass. It should be noted that pancreatic enlargement alone cannot accurately distinguish AIP from pancreatic cancer or other malignant tumors. In a study of 245 patients with diffuse pancreatic enlargement on contrast-enhanced CT, only 54.7% had AIP; other malignant lesions included pancreatic ductal adenocarcinoma (35.9%), pancreatic neuroendocrine tumor (4.5%), lymphoma (1.6%), metastasis (1.6%), solid pseudopapillary tumor (1.2%), and acinar cell carcinoma (0.4%). The presence of residual normal pancreatic parenchyma, a longer short-axis diameter (cutoff, 3.15 cm), and a lower delayed-phase lesion-to-aorta enhancement ratio (cutoff, 0.75) suggested a higher likelihood of malignancy.[21] In practice, multiple imaging signs should be integrated when differentiating these two diseases. CT features suggestive

DOI: 10.14218/JTG.2026.00015 | 2026

Table 1. Summary of recommendations, evidence quality, recommendation strength, and consensus level

No.	Recommendation	Evidence/Strength	Consensus
1	Patients with autoimmune pancreatitis (AIP) commonly present with non-specific symptoms such as obstructive jaundice and abdominal discomfort, and some patients are asymptomatic. Clinical manifestations of extrapancreatic organ involvement should be carefully assessed	High/Strong	100%
2	Contrast-enhanced computed tomography (CT) is recommended as the first-line imaging modality for the diagnosis of AIP	Moderate/Strong	100%
3	Contrast-enhanced magnetic resonance imaging (MRI) is suggested as an important imaging modality for the diagnosis of AIP. Magnetic resonance cholangiopancreatography is suggested for the assessment of pancreatic ductal and biliary changes in AIP	Low/Weak	100%
4	In patients with indeterminate CT or MRI findings, positron emission tomography-CT may be used as an adjunct for the diagnosis and differential diagnosis of AIP	Low/Weak	100%
5	Endoscopic ultrasound (EUS) can identify characteristic changes in the pancreatic parenchyma and the pancreaticobiliary ducts in AIP, and can also provide histologic or cytologic specimens for diagnosis and differential diagnosis. It is therefore recommended as an important diagnostic modality for AIP	Moderate/Strong	100%
6	Endoscopic retrograde cholangiopancreatography can identify characteristic pancreaticobiliary ductal changes in AIP; however, it is not recommended as a routine diagnostic modality because of its invasiveness	Low/Weak	100%
7	Serum IgG4 is suggested as the preferred laboratory test for the diagnosis of type 1 AIP, assessment of treatment response, and monitoring of disease activity	Low/Weak	96.7%
8	Characteristic pathological changes are important diagnostic evidence for AIP. Tissue acquisition and pathologic diagnosis should therefore be emphasized, and EUS-guided fine-needle biopsy is recommended as the preferred method	Moderate/Weak	100%
9	The diagnosis of AIP is recommended to be based on an integrated assessment of symptoms, signs, imaging, EUS findings, serum IgG4, pathological findings, and extrapancreatic organ involvement, with reference to the response to glucocorticoid therapy	Moderate/Strong	100%
10	In patients with suspected AIP, differential diagnosis from pancreatic cancer and other diseases should be emphasized	High/Strong	100%
11	In patients with established type 1 AIP, dynamic assessment of disease activity by imaging and serum IgG4 during the disease course is suggested	Low/Weak	96.7%
12	Induction therapy is suggested for patients with AIP who have symptoms or laboratory/imaging evidence of active disease	Moderate/Weak	100%
13	Oral glucocorticoids are recommended as the first-line induction therapy for AIP. Prednisone 30–40 mg/day, or approximately 0.6 $mg \cdot kg^{-1} \cdot day^{-1}$, may be used initially and tapered gradually after remission is achieved	Moderate/Strong	100%
14	In patients with diffuse pancreatic enlargement, slow radiologic remission after treatment, or serum IgG4 levels remaining more than twice the upper limit of normal, low-dose glucocorticoid maintenance therapy is recommended to reduce the risk of relapse	High/Strong	96.7%
15	Re-treatment with glucocorticoids is suggested for patients with relapsed AIP	Low/Weak	100%
16	In patients with AIP who are refractory to glucocorticoids or experience repeated relapses during tapering or after withdrawal, combination treatment with immunosuppressive agents or switching to biologic therapy is suggested	Moderate/Weak	100%
17	Pancreatic enzyme replacement therapy is suggested for patients with AIP who have pancreatic exocrine insufficiency	Low/Weak	100%
18	Routine biliary drainage is not recommended for patients with AIP complicated by obstructive jaundice	Moderate/Strong	100%
19	Because AIP may involve multiple organs, strengthening multidisciplinary collaboration is suggested during diagnosis and management	Low/Weak	100%
20	Long-term follow-up should be emphasized in patients with AIP, with attention to the risks of relapse, pancreatic endocrine and exocrine insufficiency, pancreatic duct stones, and malignancy	Low/Weak	100%

of pancreatic cancer include absence of diffuse pancreatic enlargement, a hypovascular mass, absence of renal involvement, invasion of the pancreatic or bile ducts, invasion of adjacent vessels, and enlarged lymph nodes.[26] In a radiomics study including 42 cases of focal AIP and 334 cases of pancreatic cancer, the radiomics model yielded a sensitivity of 95.24%, specificity of 92.73%, and accuracy of 94.00% for the diagnosis of focal AIP.[27] Similarly, the use of relative CT values of the adjacent pancreatic parenchyma has also shown high feasibility for differentiating focal AIP from pancreatic cancer.[28]

Recommendation 3. Contrast-enhanced magnetic resonance imaging (MRI) is suggested as an important imaging modality for the diagnosis of AIP. Magnetic resonance cholangiopancreatography (MRCP) is suggested for the assessment of pancreatic ductal and biliary changes in AIP. (Quality of evidence: Low; Strength of recommendation: Weak; Level of consensus: 100%)

Typical MRI findings of AIP include diffuse pancreatic enlargement or a focal mass accompanied by abnormal signal intensity, usually with slightly low signal on T1-weighted imaging and slightly high signal on T2-weighted imaging; a capsule-like rim around the pancreas may be seen on both T1- and T2-weighted images.[29,30] Compared with contrast-enhanced CT, MRI provides better soft-tissue contrast, although its cost and technical requirements are higher; therefore, it may serve as an adjunct to CT. The main MRI features used to distinguish AIP from pancreatic cancer include multiple strictures of the main pancreatic duct, absence of marked upstream main pancreatic duct dilatation, a capsule-like rim around the pancreas, and the duct-penetrating sign. Among these, the absence of significant upstream ductal dilatation has the highest sensitivity, whereas the capsule-like rim has the highest specificity.[31] In addition, MR elastography may be useful for differentiating AIP from pancreatic cancer and holds promise as a quantitative imaging modality for both differential diagnosis and treatment monitoring.[32]

Typical MRCP findings in AIP are long-segment and multiple pancreatic duct strictures. The ICDC for AIP also classify main pancreatic duct abnormalities as typical or indeterminate.[16] Typical findings include long strictures involving more than one-third of the main pancreatic duct or multiple strictures without significant upstream dilatation, whereas indeterminate findings include focal or multifocal strictures without significant upstream dilatation (pancreatic duct diameter < 5 mm). After glucocorticoid therapy, the pancreatic duct diameter may return to normal; therefore, MRCP may also be used to assess treatment response in AIP.[33] With continued progress in recent years, MRCP has gradually become the preferred imaging modality for evaluating the pancreatic duct.[34]

MRI and MRCP are also useful for differentiating AIP from ordinary chronic pancreatitis. On MRI, ordinary chronic pancreatitis typically presents with pancreatic atrophy or irregular pancreatic contours, heterogeneous parenchymal signal intensity, parenchymal or intraductal stones appearing as signal voids, pseudocysts, and irregular dilatation of the main pancreatic duct with side-branch ectasia. On MRCP, long-segment or multiple strictures of the main pancreatic duct without significant upstream ductal dilatation are indicative of AIP, whereas irregular ductal dilatation, ductal obstruction by stones, side-branch ectasia, and pseudocyst formation are more suggestive of ordinary chronic pancreatitis.

Recommendation 4. In patients with indeterminate CT or MRI findings, positron emission tomography-computed tomography (PET-CT) may be used as an adjunct for the diagnosis and differential diagnosis of AIP. (Quality of evidence: Low; Strength of recommendation: Weak; Level of consensus: 100%)

Typical PET-CT findings in AIP include diffusely increased fluorodeoxyglucose (FDG) uptake in the pancreas with heterogeneous intensity. Similar uptake patterns may also be seen in involved extrapancreatic organs,[35,36] which can facilitate differentiation from pancreatic cancer.[37] A study comparing PET-CT findings between AIP and pancreatic cancer found that a maximum standardized uptake value (SUVmax) >7.08 and focal or multifocal homogeneous FDG uptake were independent predictors of pancreatic cancer ($P < 0.05$).[38] FDG uptake decreases after glucocorticoid therapy in patients with AIP; therefore, PET-CT may also be used to evaluate treatment response, although its cost should be taken into account. In addition, dual-time-point PET-CT and quantitative radiomics prediction models may also be helpful in differentiating AIP from pancreatic cancer.[39,40]

III. Digestive endoscopy

Recommendation 5. Endoscopic ultrasound (EUS) can identify characteristic changes in the pancreatic parenchyma and pancreaticobiliary ducts in AIP and can also provide histologic or cytologic specimens for diagnosis and differential diagnosis. It is therefore recommended as an important diagnostic modality for AIP. (Quality of evidence: Moderate; Strength of recommendation: Strong; Level of consensus: 100%)

Typical EUS findings in AIP include diffuse pancreatic enlargement or a localized mass, with predominantly hypoechoic pancreatic parenchyma containing internal hyperechoic foci (linear, patchy, or heterogeneous changes), wavy margins, and irregular narrowing of the main pancreatic duct accompanied by ductal wall thickening.[41,42] In patients with biliary involvement, thickening and hypoechogenicity of the bile duct wall may be seen. The outer and inner layers of the bile duct wall may show hyperechoic bands, resulting in a “sandwich-like” or “onion-skin-like” appearance, whereas cholangiocarcinoma usually appears as a heterogeneously hypoechoic mass.[43]

Enhanced EUS imaging techniques may facilitate the diagnosis of AIP. On contrast-enhanced EUS, AIP shows a hypervascular pattern relative to the surrounding normal pancreatic parenchyma, which differs from the hypovascular appearance of pancreatic cancer; in addition, arborizing vessels are characteristic of AIP.[44,45] On contrast-enhanced harmonic EUS, AIP shows isoenhancement with a homogeneous echo distribution of the contrast agent, whereas pancreatic cancer shows hypoenhancement with heterogeneous echo distribution.[46] However, studies of these techniques have generally included small sample sizes and non-randomized designs, and further research is needed to confirm the diagnostic value of EUS.

Studies of artificial intelligence-assisted EUS diagnosis may further improve diagnostic accuracy for AIP. In one study, EUS images from 81 patients with AIP and 100 patients with chronic pancreatitis were analyzed, and 14 of 115 textural parameters

in the region of interest were selected for discrimination, yielding a sensitivity of 84.1%, specificity of 92.5%, and accuracy of 89.3%.[47] Another study based on a convolutional neural network model using both static EUS images and dynamic videos reported a sensitivity of 94% and specificity of 71% for differentiating AIP from chronic pancreatitis, and a sensitivity of 90% and specificity of 93% for differentiating AIP from pancreatic cancer.[48]

In patients whose diagnosis of AIP cannot be established by typical imaging and laboratory findings, EUS-guided acquisition of pancreatic histologic or cytologic specimens may be used either to diagnose AIP or to exclude malignancy. It was previously thought that specimens obtained by EUS-guided fine-needle aspiration (EUS-FNA) were limited in quantity and had relatively low sensitivity but high specificity for the diagnosis of AIP and were therefore mainly used for differential diagnosis from pancreatic cancer. In recent years, with improvements in needle design, increasing numbers of studies have reported histologic diagnosis of AIP using EUS-FNA or EUS-guided fine-needle biopsy (EUS-FNB). A Chinese study including 27 patients with AIP who underwent EUS-FNA using a 22G needle found that samples from 63% of patients met the histologic criteria proposed in the ICDC for AIP (grade 1 in 5 cases and grade 2 in 12 cases).[49] A meta-analysis including nine studies of EUS-FNA in 309 patients with AIP and seven studies of EUS-FNB in 131 patients with AIP,[50] using grade 1 and grade 2 histologic diagnostic evidence as endpoints, showed that the pooled diagnostic yield was 55.8% (95% CI 0.370–0.739) for FNA and 87.2% (95% CI 0.688–0.981) for FNB, with a statistically significant difference (P = 0.030). The histologic acquisition rate and adverse event rate were similar between FNA and FNB, and 19G needles had a higher diagnostic yield than 22G needles. For the use of EUS-FNA/FNB-obtained tissue in the diagnosis of AIP, the Japanese guidelines for the histological diagnosis of AIP may be referenced.[51]

Recommendation 6. Endoscopic retrograde cholangiopancreatography (ERCP) can identify characteristic pancreaticobiliary ductal changes in AIP; however, it is not recommended as a routine diagnostic modality because of its invasiveness. (Quality of evidence: Low; Strength of recommendation: Weak; Level of consensus: 100%)

Typical ERCP findings of AIP include (i) long (>1/3 the length of the pancreatic duct) stricture; (ii) lack of upstream dilatation from the stricture (<5 mm); (iii) multiple strictures; and (iv) side branches arising from a strictured segment.[52] In contrast, pancreatic cancer more commonly presents with focal ductal stenosis and upstream dilatation.

In some patients with AIP, ERCP cholangiography may show bile duct stricture or features of sclerosing cholangitis. Brush cytology and bile cytology at the site of biliary stricture can aid differential diagnosis.[53] Intraductal ultrasonography is useful for differentiating IgG4-related sclerosing cholangitis (IgG4-SC), primary sclerosing cholangitis (PSC), and cholangiocarcinoma. Typical intraductal ultrasonography findings in IgG4-SC include preservation of the three-layer structure of the bile duct wall and uniform, symmetric wall thickening, which may also be seen in non-stenotic segments. PSC often shows destruction of the three-layer bile duct wall structure, asymmetric wall thickening, irregular inner margins, interruption of the outer margin, and diverticulum-like outpouchings. Cholangiocarcinoma typically presents as asymmetric wall thickening or intraluminal protrusion, with irregular inner margins and interruption of the outer margin, without wall thickening in non-stenotic segments.[9] With the development of peroral cholangioscopy-assisted ERCP techniques, biopsy performed under direct vision can diagnose IgG4-SC,[54] although no reports are yet available on pancreatoscopy-guided biopsy via ERCP for the diagnosis of AIP.

In some patients with AIP, the duodenal papilla may also be involved; therefore, concurrent biopsy during ERCP may provide additional diagnostic evidence.[55,56]

The ICDC for AIP and the Japanese Clinical Diagnostic Criteria (2011) for AIP regarded pancreatography as important diagnostic evidence for AIP, whereas MRCP was not included among the diagnostic criteria. With advances in MRCP, the 2018 Japanese diagnostic criteria for AIP placed MRCP alongside ERCP as the preferred imaging modality for assessing the pancreatic duct.[34] Considering the invasiveness and medical costs of ERCP, the present guidelines do not recommend its use as a routine diagnostic method for AIP.

IV. Laboratory tests

Recommendation 7. Serum IgG4 is suggested as the preferred laboratory test for the diagnosis of type 1 AIP, assessment of treatment response, and monitoring of disease activity. (Quality of evidence: Low; Strength of recommendation: Weak; Level of consensus: 96.7%)

Serum IgG4 levels are elevated in 60–90% of patients with type 1 AIP but are also elevated in 7–10% of patients with pancreatic cancer. Using an IgG4 level greater than twice the upper limit of normal as a diagnostic criterion can significantly improve specificity.[57,58] Some patients with AIP also have hypergammaglobulinemia, elevated IgG and IgE, increased erythrocyte sedimentation rate, elevated C-reactive protein, or positive autoantibodies such as antinuclear antibodies and rheumatoid factor; however, these markers are only suggestive.[59] In type 2 AIP, serum IgG4 is generally not elevated and autoantibodies are usually negative.

A meta-analysis including 11 studies, 594 patients with AIP, and 958 patients with pancreatic cancer found that elevated serum IgG4 had a sensitivity of 72% (95% CI, 0.680–0.750) and a specificity of 93% (95% CI, 0.920–0.950) for distinguishing AIP from pancreatic cancer.[60] When serum IgG4 levels greater than twice the upper limit of normal were used to differentiate AIP from pancreatic cancer, the sensitivity was 43% (95% CI, 0.380–0.490) and the specificity was 98% (95% CI, 0.970–0.990).

Some studies have suggested that a decrease in serum IgG4 after treatment for type 1 AIP reflects control of inflammation, whereas persistent elevation above the normal range after treatment predicts relapse. A systematic review including 10 studies and 850 patients with AIP found that the baseline serum IgG4 level at diagnosis was a risk factor for relapse after glucocorticoid induction therapy (β = −0.001, P = 0.009).[61] In addition, both a high baseline serum IgG4 level and re-elevation of serum IgG4 during follow-up are risk factors for relapse.[62] A nationwide survey in Japan found no statistically significant difference in serum IgG4 levels at diagnosis between patients who relapsed and those who did not, but the lowest post-treatment IgG4 level was higher in patients who relapsed.[11]

V. Pathological findings

Recommendation 8. Characteristic pathological changes are important diagnostic evidence for AIP. Tissue acquisition

and pathologic diagnosis should therefore be emphasized, and EUS-FNB is recommended as the preferred method. (Quality of evidence: Moderate; Strength of recommendation: Weak; Level of consensus: 100%)

Both type 1 and type 2 AIP show lymphocytic and plasmacytic infiltration around pancreatic ducts and inflammatory changes in the pancreatic stroma, whereas the pathological features of ordinary chronic pancreatitis, such as intraductal protein plugs, stones, and calcification, are less common.

Typical pathological findings of type 1 AIP include dense lymphoplasmacytic infiltration around pancreatic ducts, storiform fibrosis of the parenchyma, obliterative phlebitis, and abundant IgG4-positive plasma cells. Inflammatory cell infiltration within the pancreatic lobules is often prominent, frequently causing acinar atrophy, and fibrosis in the interlobular septa or around the pancreas is more obvious.[63] The ICDC statement on the pathology of IgG4-RD recommends that, for diagnosing pancreatic lesions of IgG4-RD, biopsy specimens should contain >10 IgG4-positive plasma cells per high-power field (40×, 0.2 mm^2), and surgical resection specimens should contain >50 IgG4-positive plasma cells per high-power field. An IgG4-positive/IgG-positive plasma cell ratio >40% is also an important diagnostic criterion for IgG4-RD. However, it should be noted that the number of IgG4-positive plasma cells or the IgG4/IgG ratio alone cannot directly establish the diagnosis of AIP, because both pancreatic ductal adenocarcinoma tissue and peritumoral tissue may also show varying degrees of IgG4-positive plasma cell infiltration.[64]

Typical pathological findings of type 2 AIP include marked neutrophilic infiltration within the lumen and epithelium of interlobular ducts, resulting in granulocytic epithelial lesions, whereas storiform fibrosis, obliterative phlebitis, and IgG4-positive plasma cell infiltration are uncommon.[65]

As a minimally invasive diagnostic method, EUS-FNB has a clearly higher diagnostic yield for AIP than EUS-FNA.[50] In patients with suspected AIP based on imaging and laboratory findings, EUS-FNB should be considered first for obtaining histopathologic specimens to confirm the diagnosis.

VI. Diagnosis and differential diagnosis

Recommendation 9. The diagnosis of AIP is recommended to be based on an integrated assessment of symptoms, signs, imaging, EUS findings, serum IgG4, pathological findings, and extrapancreatic organ involvement, with reference to the response to glucocorticoid therapy. (Quality of evidence: Moderate; Strength of recommendation: Strong; Level of consensus: 100%)

At present, several clinical diagnostic criteria for AIP have been proposed by experts in China and abroad. The most widely used are the ICDC for AIP and the Japanese Clinical Diagnostic Criteria for AIP.[9,16] In addition, because type 1 AIP is a form of IgG4-RD, diagnosis may also refer to the Japanese criteria and American/European classification criteria for IgG4-RD.[66,67]

The *Chinese Guidelines for the Diagnosis and Management of Autoimmune Pancreatitis (Shanghai, 2012 Draft)* proposed practical diagnostic criteria for AIP tailored to Chinese clinical practice. Based on subsequent research advances in China and abroad, the preliminary diagnostic criteria for AIP in current clinical practice are adjusted as follows:

1. Imaging: CT or MRI shows typical findings such as diffuse or focal enlargement of the pancreas and a capsule-like rim; MRCP shows irregular narrowing of the main pancreatic duct.
2. Laboratory tests: serum IgG4 is significantly elevated.
3. Histopathology:
   a. the pancreas shows marked lymphocytic and plasmacytic infiltration with storiform fibrosis and obliterative phlebitis, and immunohistochemistry demonstrates >10 IgG4-positive plasma cells per high-power field;
   b. there is abundant neutrophilic infiltration around the pancreatic ducts causing ductal epithelial injury;
   c. EUS-guided cytology or histology excludes pancreatic and biliary malignancies.
4. Extrapancreatic organ involvement: hilar or intrahepatic bile duct strictures, enlargement of the salivary or lacrimal glands, retroperitoneal fibrosis, renal involvement, and related lesions.
5. Response to glucocorticoids: after diagnostic glucocorticoid therapy, pancreatic and/or extrapancreatic manifestations improve significantly.

A preliminary diagnosis of AIP may be made if any one of the following groups is met:

- Group A: 1 + (2 and/or 4);
- Group B: 3a (type 1 AIP) or 3b (type 2 AIP);
- Group C: (1 or 2 or 4) + 3c + 5.

In clinical practice, patients suspected of AIP should first undergo imaging examinations. If typical imaging findings are present and are supported by laboratory findings and/or extrapancreatic organ involvement, a preliminary diagnosis of AIP may be made (Group A). If only one of the following is present—typical imaging findings, laboratory findings, or extrapancreatic organ involvement—EUS-FNB/FNA is recommended to obtain tissue samples for diagnosing AIP (Group B); alternatively, after pancreatic malignancy has been excluded, diagnostic glucocorticoid therapy may be given, and a marked response supports the diagnosis of AIP (Group C). The duration of diagnostic glucocorticoid therapy should not exceed 2 weeks,[68] after which imaging should be repeated to assess improvement in pancreatic or extrapancreatic lesions. In patients who undergo surgery, a diagnosis of AIP may also be established if postoperative pathology shows typical features of AIP (Group B).

Recommendation 10. In patients with suspected AIP, differential diagnosis from pancreatic cancer and other diseases should be emphasized. (Quality of evidence: High; Strength of recommendation: Strong; Level of consensus: 100%)

AIP can easily be confused with pancreatic malignancy, and cases complicated by sclerosing cholangitis are readily misdiagnosed as cholangiocarcinoma. Differentiation between AIP and pancreaticobiliary malignancy requires integration of imaging examinations, digestive endoscopy, laboratory testing, extrapancreatic manifestations, pathology, and response to glucocorticoid therapy. The key points for differentiation are detailed in the foregoing recommendations. It should be noted that CA19-9, a tumor marker commonly used in the diagnosis of pancreatic cancer, may also be elevated in some patients with AIP.[8] In addition, although histopathology is the gold standard for the diagnosis and differentiation of AIP and pancreatic cancer, a case report has suggested that AIP may occur as a peritumoral manifestation of pancreatic cancer,[69] and this possibility should be kept in mind in clinical

practice.

AIP should also be distinguished from chronic pancreatitis, particularly in patients with a long-standing or relapsing disease course. Imaging features favoring AIP include pancreatic enlargement, a capsule-like rim, delayed enhancement, and long or multiple ductal strictures without marked upstream dilatation, whereas chronic pancreatitis more often shows pancreatic atrophy, parenchymal or intraductal calcification, irregular ductal dilatation with side-branch ectasia, and pseudocyst formation. Given that imaging findings in certain advanced-stage AIP may overlap with those of chronic pancreatitis, the diagnosis should be based on a comprehensive clinicopathologic evaluation rather than imaging alone.

AIP is often accompanied by IgG4-SC. When pancreatic lesions are not prominent, it must also be differentiated from PSC and related conditions. In general, patients with PSC are younger, have a higher rate of coexisting IBD, respond poorly to glucocorticoid therapy, and show a "pruned-tree" appearance of the intrahepatic bile ducts or pseudodiverticulum-like changes of the bile ducts on imaging. Korean investigators proposed a scoring system to distinguish IgG4-SC from PSC, which includes three aspects: age (<30 years, 0 points; 30–40 years, 1 point; 40–50 years, 2 points; 50–60 years, 3 points; ≥60 years, 4 points), other organ involvement (present, 3 points; absent, 0 points), and beaded changes on cholangiography (present, 2 points; absent, 0 points). A total score of 0–4 suggests PSC, 5–6 suggests a diagnostic trial of glucocorticoid therapy, and 7–9 suggests IgG4-SC.[70]

Recommendation 11. In patients with established type 1 AIP, dynamic assessment of disease activity by imaging and serum IgG4 during the disease course is suggested. (Quality of evidence: Low; Strength of recommendation: Weak; Level of consensus: 96.7%)

Type 1 AIP is a multiorgan disease; therefore, once the diagnosis is established, patients should undergo comprehensive assessment including clinical manifestations, extrapancreatic organ involvement, laboratory tests, and imaging examinations. Laboratory evaluation mainly includes complete blood count, urinalysis, liver and renal function, blood glucose, blood lipids, electrolytes, erythrocyte sedimentation rate, C-reactive protein, immunoglobulins, and IgG subclasses. In addition to evaluating the severity of pancreatic lesions, imaging should also assess the extent of involved extrapancreatic organs. Disease assessment may refer to the IgG4-RD Responder Index.[71] This index evaluates disease status over the previous 28 days and assigns 0–3 points according to the degree of involvement in each organ, with the total score being the sum of organ-specific scores. When an involved vital organ is affected urgently and requires active treatment, the score for that organ is doubled. During treatment, patients should also be assessed regularly for disease remission and drug-related adverse effects. An IgG4-RD Responder Index ≥9 is an independent risk factor for relapse of AIP.[72]

Treatment

Treatment of AIP should be individualized. The goals are to reduce inflammation, maintain remission, preserve organ function, and minimize treatment-related adverse effects. Treatment of AIP includes induction therapy, maintenance therapy, and management after relapse.

I. Glucocorticoid therapy

Recommendation 12. Induction therapy is suggested for patients with AIP who have symptoms or laboratory/imaging evidence of active disease. (Quality of evidence: Moderate; Strength of recommendation: Weak; Level of consensus: 100%)

AIP is an autoimmune disease, and 10–25% of patients may undergo spontaneous remission. However, active drug therapy is generally considered appropriate to prevent progression of inflammation and fibrosis and to delay or avoid irreversible organ damage. Several international guidelines are broadly consistent regarding indications for induction therapy[9,73,74]: symptomatic patients with AIP, such as those with obstructive jaundice, abdominal pain, or back pain, should be actively considered for induction therapy; asymptomatic patients should also be treated if they have abnormal liver function or imaging evidence of active lesions. No clinical studies have supported treatment of asymptomatic AIP solely to delay pancreatic endocrine or exocrine insufficiency, and clinical evidence on the long-term prognosis of untreated asymptomatic patients remains limited.

Recommendation 13. Oral glucocorticoids are recommended as first-line induction therapy for AIP. Prednisone 30–40 mg/day, or approximately 0.6 $mg \cdot kg^{-1} \cdot day^{-1}$, may be used initially and tapered gradually after remission is achieved. (Quality of evidence: Moderate; Strength of recommendation: Strong; Level of consensus: 100%)

Oral glucocorticoids are the cornerstone of induction therapy for AIP, with the goal of rapidly controlling active disease. Both type 1 and type 2 AIP generally respond well to glucocorticoids. A Chinese systematic review including 26 studies showed that 78.4% of patients received glucocorticoid therapy, with a pooled remission rate of 96.2%.[8] Before glucocorticoid treatment, pancreaticobiliary tumors should be carefully excluded; if the response to glucocorticoids is poor, the diagnosis should be reconsidered.

An initial dose of prednisone 30–40 mg/day or 0.6–1.0 $mg \cdot kg^{-1} \cdot day^{-1}$ is generally recommended. A nationwide Japanese survey of 1,474 patients with AIP showed that 84.4% received initial glucocorticoid therapy, most commonly prednisolone 30 mg/day (63.9%) or 40 mg/day (21.0%); when the initial dose was converted to 0.45 mg/kg, the induction remission rate remained high (202/205, 98.5%).[11] A Dutch study including 65 patients categorized into low-dose (prednisone 10–20 mg/day, n = 14),[75] medium-dose (30 mg/day, n = 15), and high-dose (40–60 mg/day, n = 36) groups found broadly similar baseline characteristics and, after 6 months of follow-up, similar clinical, biochemical, and imaging remission across groups; complete remission rates were 71%, 40%, and 72%, respectively. In addition, intravenous methylprednisolone (initial dose 500 mg/day for 3 days per week for 2 consecutive weeks), followed by oral prednisolone (20 mg/day) maintenance, may be more beneficial in patients with concomitant common bile duct involvement.[76] The glucocorticoid dose should be individualized. Higher doses may be considered in critically ill patients, whereas lower doses may be appropriate in elderly patients or those with mild symptoms. Tapering should also be individualized. Assessment is generally performed after 2–4 weeks of initial therapy; if clinical symptoms, laboratory findings, and

imaging signs have improved significantly, tapering may begin, usually by reducing the dose by 5 mg every 1–2 weeks.

Recommendation 14. In patients with diffuse pancreatic enlargement, slow radiologic remission after treatment, or serum IgG4 levels remaining more than twice the upper limit of normal, low-dose glucocorticoid maintenance therapy is recommended to reduce the risk of relapse. (Quality of evidence: High; Strength of recommendation: Strong; Level of consensus: 96.7%)

The 2017 International Consensus for the Treatment of Autoimmune Pancreatitis by the International Association of Pancreatology recommended low-dose glucocorticoid maintenance therapy for patients with type 1 AIP who have diffuse pancreatic enlargement,[74] delayed radiologic remission, persistently elevated serum IgG4 after treatment, two or more extrapancreatic lesions, or proximal bile duct involvement. The optimal dose and duration of maintenance therapy have not yet been established, but many Chinese and international reports have used prednisone 5–10 mg/day for 6 months to 3 years.

Multiple studies have shown that low-dose glucocorticoid maintenance therapy can reduce the risk of relapse in AIP. In a Japanese multicenter randomized controlled study including 49 patients with AIP,[77] the 3-year relapse rate was significantly lower in the maintenance group (prednisolone 5–7.5 mg/day for 3 years, n = 30) than in the withdrawal group (prednisolone 5–7.5 mg/day for 12 weeks, n = 19; 23.3% vs. 57.9%, $P = 0.011$), and relapse-free survival was significantly longer in the maintenance group ($P = 0.007$). Another Japanese study involving 22 centers and 510 patients with type 1 AIP found that the 7-year relapse rate in the prednisolone 5 mg/day maintenance group was 26.1%,[78] significantly lower than that in the withdrawal group (45.2%) and the prednisolone 2.5 mg/day maintenance group (43.4%). Compared with maintenance therapy for less than 1 year, maintenance therapy for more than 1 year was associated with a lower pooled relapse rate,[61] and lack of maintenance therapy is a risk factor for relapse.[79]

During glucocorticoid maintenance therapy, the patient's clinical status and disease course should be dynamically assessed, and the dose and duration should be adjusted individually, with close monitoring for possible adverse events.[80,81]

Recommendation 15. Re-treatment with glucocorticoids is suggested for patients with relapsed AIP. (Quality of evidence: Low; Strength of recommendation: Weak; Level of consensus: 100%)

Most patients with relapse can achieve remission again with the initial glucocorticoid dose. When necessary, the glucocorticoid dose may be increased or the treatment course extended to improve disease control. A Chinese systematic review showed that among patients who relapsed after discontinuation of glucocorticoid therapy,[8] re-treatment with glucocorticoids achieved a remission rate of 94.8% (95% CI 0.882–0.988). If patients develop significant glucocorticoid-related adverse effects, the addition of immunosuppressive agents or switching to biologic therapy is recommended.

II. Immunosuppressive agents and biologic therapy

Recommendation 16. In patients with AIP who are refractory to glucocorticoids or experience repeated relapses during tapering or after withdrawal, combination treatment with immunosuppressive agents or switching to biologic therapy is suggested. (Quality of evidence: Moderate; Strength of recommendation: Weak; Level of consensus: 100%)

If glucocorticoid monotherapy fails to control disease activity in AIP, if the disease recurs during glucocorticoid tapering, or if glucocorticoid-related adverse effects are prominent, combination therapy with immunosuppressive agents is suggested to help reduce glucocorticoid exposure.[82,83] Commonly used immunosuppressive agents include mycophenolate mofetil, azathioprine, cyclophosphamide, and leflunomide.

A Chinese randomized controlled trial included 69 treatment-naive patients with IgG4-RD (39 with pancreatic involvement) who received glucocorticoid monotherapy or glucocorticoids plus low-dose mycophenolate mofetil. Remission rates were not significantly different between groups, but the 12-month cumulative clinical relapse rate was lower in the combination group (11.76% vs. 34.29%).[82] Another Chinese randomized controlled trial involving 66 patients with IgG4-RD showed that the relapse rate was significantly lower in the leflunomide plus glucocorticoid group than in the glucocorticoid monotherapy group (18.2% vs. 42.4%, $P = 0.032$).[84] However, another cohort study including 277 patients with IgG4-RD who experienced re-elevation of serum IgG4 during treatment found that although 45.1% of patients receiving glucocorticoids combined with various immunosuppressive agents (cyclophosphamide, mycophenolate mofetil, azathioprine, methotrexate, or leflunomide) showed a trend toward reduced relapse,[85] the difference was not statistically significant. During treatment with conventional immunosuppressive agents, potential adverse reactions such as leukopenia, thrombocytopenia, and liver dysfunction should be closely monitored.

Regarding biologic therapy, multiple studies have shown that rituximab is effective in patients with AIP who are resistant to or dependent on glucocorticoids.[86–88] In patients with IgG4-RD-related pancreaticobiliary disease treated with rituximab, the complete remission rate at 6 months was 88.9% (95% CI 0.805–0.939), and the relapse rate was 21.9% (95% CI 0.105–0.403), although the relapse rate was higher in patients with multiorgan involvement (35.9%, 95% CI 0.173–0.601).[89] Before biologic therapy is initiated for AIP, patients should be fully evaluated, and adverse events should be closely monitored throughout treatment.

III. Pancreatic enzyme replacement therapy

Recommendation 17. Pancreatic enzyme replacement therapy is suggested for patients with AIP who have pancreatic exocrine insufficiency (PEI). (Quality of evidence: Low; Strength of recommendation: Weak; Level of consensus: 100%)

Patients with AIP may have PEI to varying degrees. A systematic review of 18 studies showed that the prevalence of PEI at the time of diagnosis of AIP was 45% (95% CI 0.329–0.574),[90] although this estimate showed substantial heterogeneity. A French study including 44 patients reported a PEI rate of 34% during a median follow-up of 41 (5–130) months, defined as fecal elastase-1 <200 μg/g.[91] A prospective Dutch cohort study including 68 patients with AIP reported a PEI rate of 82% during a

median follow-up of 75 (50–106) months, again defined as fecal elastase-1 <200 μg/g; however, a substantial proportion of patients in that study had undergone pancreatic resection, which may have contributed to the high PEI rate.[92] Because fecal elastase-1 is not widely used in routine practice, some studies have assessed PEI in AIP on the basis of symptoms. In a Chinese study, 4% (4/100) of patients with AIP initially presented with steatorrhea.[79] In a Korean study of 138 patients with type 1 AIP followed for a median of 60 (24–197) months, four patients (2.9%) developed marked steatorrhea, and all had relapsed during the disease course.[93] PEI is an important independent risk factor for mortality in chronic pancreatitis[94]; therefore, monitoring and treatment of PEI should be emphasized during follow-up of patients with AIP. Treatment of PEI mainly consists of exogenous pancreatic enzyme replacement therapy, such as high-lipase pancreatic enzyme preparations with enteric coating that permits release of active enzymes in the intestine; these should be taken during meals.[95]

IV. Endoscopic interventional therapy

Recommendation 18. Routine biliary drainage is not recommended for patients with AIP complicated by obstructive jaundice. (Quality of evidence: Moderate; Strength of recommendation: Strong; Level of consensus: 100%)

Some investigators have proposed that biliary drainage should be performed first in AIP patients with obstructive jaundice to reduce the risk of cholangitis induced after glucocorticoid therapy.[9,96] However, two recent Chinese studies showed that glucocorticoid monotherapy is safe and effective in AIP patients with obstructive jaundice and that combined biliary drainage is not necessary. One study included 48 patients with AIP and obstructive jaundice[97]; 25 underwent ERCP biliary stenting before glucocorticoid treatment, and 23 received glucocorticoid therapy alone. Baseline total and direct bilirubin levels were higher in the stent group, but after 4 weeks there were no significant differences in liver function indices between the two groups. In the glucocorticoid-alone group, liver function indices decreased by 53–81%, and no patient developed infection or required biliary stenting. Another study included 87 patients with type 1 AIP and marked obstructive jaundice (total bilirubin ≥ 51 μmol/L),[98] of whom 48 underwent ERCP biliary drainage before glucocorticoid therapy and 39 received glucocorticoid therapy alone. There was no significant difference in the risk of cholangitis after treatment, and after a median follow-up of 41 months, the remission and relapse rates also did not differ significantly between groups. Thus, in patients with AIP and obstructive jaundice but without acute cholangitis, glucocorticoid therapy may be initiated first, and routine biliary drainage is unnecessary.

V. Multidisciplinary diagnosis and management

Recommendation 19. Because AIP may involve multiple organs, strengthening multidisciplinary collaboration is suggested during diagnosis and management. (Quality of evidence: Low; Strength of recommendation: Weak; Level of consensus: 100%)

The clinical manifestations of AIP are complex and diverse. In particular, type 1 AIP often involves other organs, and multidisciplinary collaboration among relevant specialties is frequently required to complete diagnosis, evaluation, treatment, and follow-up. With increasing awareness of AIP, surgery is now considered only when malignancy cannot be excluded clinically. In recent years, both the misdiagnosis rate of AIP and the rate of unnecessary surgery in China have decreased significantly.[99]

Follow-up and prognosis

Recommendation 20. Long-term follow-up should be emphasized in patients with AIP, with attention to the risks of relapse, pancreatic endocrine and exocrine insufficiency, pancreatic duct stones, and malignancy. (Quality of evidence: Low; Strength of recommendation: Weak; Level of consensus: 100%)

AIP has a long disease course. A considerable proportion of patients relapse, and some develop pancreatic duct stones, pancreatic endocrine or exocrine insufficiency, and related clinical manifestations. The relationship between AIP and tumors of the pancreas or other organs remains unclear. In clinical practice, regular follow-up of patients with AIP is recommended, with attention to symptoms, imaging changes, drug-related adverse effects, and long-term outcomes.

I. Relapse

The relapse rate of AIP is relatively high, particularly in type 1 AIP. Approximately 20–40% of patients relapse after discontinuation of glucocorticoid induction therapy. A nationwide Japanese survey showed that 23.4% (344/1,471) of patients with AIP experienced relapse; 49.7% of relapses involved the pancreas, 30.5% were extrapancreatic relapses, and 19.8% involved both pancreatic and extrapancreatic sites. The cumulative relapse rates at 3, 5, and 10 years were 14%, 25%, and 40%, respectively.[11] Reported risk factors for relapse in type 1 AIP include extrapancreatic organ involvement (especially bile duct involvement), high pretreatment serum IgG4 levels, persistently elevated IgG4 after treatment, and diffuse pancreatic enlargement.[61,100] Type 2 AIP has a lower relapse rate. A systematic review including 107 patients with type 2 AIP reported a post-treatment relapse rate of 15.9%.[61]

II. Pancreatic endocrine and exocrine insufficiency

Pancreatic endocrine and exocrine insufficiency are typical long-term outcomes of chronic pancreatitis. Endocrine insufficiency commonly manifests as diabetes mellitus. A systematic review including 62 studies and 6,522 patients with AIP showed that the prevalence of diabetes at the time of AIP diagnosis was 37% (95% CI 0.320–0.420), while the prevalence of diabetes during follow-up among patients treated with glucocorticoids was 44% (95% CI 0.261–0.624). In AIP patients who have abnormal glucose metabolism at diagnosis, blood glucose levels often worsen during glucocorticoid therapy, but pancreatic endocrine function may partially improve as the disease remits and glucocorticoids are tapered. A nationwide Japanese survey showed that 66.5% of patients with AIP had diabetes at disease onset; after glucocorticoid therapy, diabetes improved in 47.2%, whereas 17.0% developed new-onset diabetes or experienced worsening diabetes after glucocorticoid treatment. The older the patient, the higher the proportion of new-onset or worsened diabetes.[101] In addition, although long-term glucocorticoid maintenance therapy improves serum C-peptide levels, it also increases the homeostasis model assessment index for insulin resistance.[102] Therefore, whether glucocorticoid maintenance

therapy is beneficial for preserving pancreatic endocrine function remains uncertain.

PEI often manifests as dyspepsia and weight loss, and severe cases may develop steatorrhea. For discussion of PEI, see Recommendation 17.

III. Pancreatic duct stone formation

Pancreatic duct stones are a characteristic pathological feature of chronic pancreatitis. It was once thought that AIP differs from typical chronic pancreatitis and rarely leads to pancreatic duct stones or pancreatic calcification. However, with increasing research, 5–41% of patients with AIP have been reported to develop new pancreatic duct stones or an increased stone burden during follow-up.[93,103–107] A long disease course and relapse are widely recognized risk factors for pancreatic duct stone formation.

IV. Risk of malignancy

Cases of pancreatic cancer and other malignancies occurring concurrently with or subsequent to AIP have been reported. However, because available studies are limited by sample size and study design, the association between AIP and malignancy remains inconclusive. A systematic review including 17 studies and 2,746 patients with AIP reported an overall prevalence of malignancy of 9.6% (95% CI 0.057–0.135), with prevalences of 3.7% before or concurrent with the diagnosis of AIP and 4.6% after the diagnosis of AIP. The most common malignancies were gastric cancer (1.3%, 95% CI 0.005–0.021) and colorectal cancer (1.2%, 95% CI 0.006–0.010). Thirty-five cases of pancreatic cancer were reported, but it remains uncertain whether AIP is a risk factor for these tumors or represents a paraneoplastic syndrome.[108] A Chinese multicenter retrospective study including 602 patients with IgG4-RD, with a median follow-up of 47.0 months, found that the overall prevalence of malignancy was significantly higher than that in the general population (standardized prevalence ratio, 8.66; 95% CI 5.84–12.31), and that AIP was an independent risk factor for malignancy in patients with IgG4-RD (odds ratio = 2.400, 95% CI 1.038–5.549, $P = 0.041$).[109] Therefore, attention should be paid during follow-up to the risk of pancreatic cancer and other malignancies in patients with AIP.

Compared with international guidance, including the 2011 International Consensus Diagnostic Criteria for AIP, the Japanese consensus guidelines, the European guideline on IgG4-related digestive disease, and the international treatment consensus for AIP,[9,16,73,74] the present Chinese guidelines have several distinctive features. First, they were developed using a formal guideline-development framework, including systematic literature review, GRADE assessment, and three rounds of Delphi consensus. Second, they incorporate Chinese evidence and expert experience and adapt recommendations to clinical practice in China. Third, while referring to the framework of the ICDC, they propose simplified and more clinically practical diagnostic criteria that are better suited to routine practice. Fourth, they specifically address the management of AIP with obstructive jaundice and, based on available evidence, do not recommend routine biliary drainage in the absence of specific indications.

These guidelines reflect the evidence and expert consensus that were available during their development. Because research on AIP and IgG4-RD continues to evolve, future updates should incorporate newly published evidence through systematic reviews and formal consensus procedures. In diagnostic technologies, emerging evidence suggests that tissue acquisition with newer EUS-FNB needles may improve histologic diagnosis, while radiomics and artificial intelligence-assisted imaging may provide additional support for differentiating AIP from pancreaticobiliary malignancies.[48,110,111] Novel biomarkers beyond serum IgG4, including circulating plasmablasts, cytokine profiles, and disease-related autoantibodies, may also contribute to diagnosis, disease-activity assessment, and relapse prediction.[112,113] In therapeutic aspects, B-cell-targeted strategies remain an important area of development. In addition to rituximab, newer approaches such as CD19-targeted therapy with inebilizumab and B-cell inhibition with obexelimab are under clinical investigation in IgG4-RD.[114–116] Cellular therapies, including CD19-directed CAR-T therapy, have shown proof-of-concept activity in refractory B-cell-mediated autoimmune diseases; however, their role in IgG4-RD and AIP remains to be elucidated.[117]

Acknowledgments

We thank the Guideline and Standard Research Center of the Institute of Health Data Science, Lanzhou University, for providing methodological guidance during the development of the present guidelines.

Funding

None.

Conflict of interest

ZLiao has been an Editorial Board Member of *Journal of Translational Gastroenterology* since 2023. The other authors have no conflict of interests related to this publication.

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