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# Insulin Autoimmune Syndrome: A Chinese Expert Consensus Statement

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## ABSTRACT

Insulin autoimmune syndrome (IAS) is a rare autoimmune disorder characterized by spontaneous hypoglycemia. The incidence of IAS is higher in East Asian populations compared to other populations. Delayed diagnosis and treatment can lead to recurrent hypoglycemia, significant glucose fluctuations, and adverse clinical outcomes, including life-threatening situations. Currently, no standardized guidelines exist for the diagnosis and treatment of IAS. This consensus aims to provide a systematic summary of the epidemiology, triggers, pathogenesis, clinical manifestations, diagnosis, differential diagnosis, treatment, and prognosis of IAS, with the objective of standardizing its clinical management.

Insulin autoimmune syndrome (IAS) is characterized by hyperinsulinemic hypoglycemia or significant glucose fluctuations resulting from the presence of high titers of insulin autoantibodies (IAAs) in the absence of exogenous insulin [1]. IAS was first reported by Hirata in 1970 [2] and is thus also referred to as Hirata disease. The first case of IAS in China was reported in 1985 [3]. Exogenous insulin antibody syndrome (EIAS), in contrast, is induced by the use of exogenous insulin, triggering the production of autoantibodies against insulin, leading to insulin resistance, hyperglycemia, recurrent hypoglycemia, and allergic reactions. EIAS shares the same pathophysiological and clinical features as IAS and can thus be broadly categorized under IAS. Currently, there are no definitive epidemiological data on IAS, which are predominantly reported in Asian populations but seldom in Caucasian and African populations. A nationwide survey in Japan from 2017 to 2018 estimated the incidence of IAS to be 0.017 per 100,000 [4]. From the initial report until 2009, Japan documented at least 380 cases of IAS [5], making it the third most common cause of spontaneous hypoglycemia in Japan, while only 58 cases were reported in 16 non-Asian countries during the same period [6]. A recent literature review documented 795 cases of IAS reported across 26 countries since 1970, including Japan, China, and South Korea. Of these three countries, Japan accounted for 350 cases, China for 330 cases, and South Korea for 13 cases [7]. The incidence of IAS is similar between males and females, more common in individuals over 40 years of age, and rare in children [8].

IAS is characterized by recurrent hypoglycemia and significant glucose fluctuations. Delayed diagnosis and treatment can lead to adverse clinical outcomes that are potentially life-threatening. Currently, no standardized guidelines exist for the diagnosis and treatment of IAS. Thus, this consensus aims to systematically summarize both domestic and international evidence and clinical experiences, comprehensively review the epidemiology, triggers, pathogenesis, clinical manifestations,

diagnosis, differential diagnosis, treatment, and prognosis of IAS and EIAS, and provide a reference for the clinical management of IAS and EIAs.

## 1 | Methodology for Consensus Development

This consensus working group was composed of renowned clinical experts, researchers, and professionals from relevant fields in China. In May 2023, the IAS Consensus Workshop was convened, during which the overall framework of the consensus was established and specific tasks were assigned. The consensus focused on the diagnosis and treatment of IAS, covering epidemiology, triggers and risk factors, pathophysiologic mechanisms, clinical manifestations, diagnosis, differential diagnosis, treatment, prognosis, and recommendations for the diagnosis and treatment of EIAS. The IAS Consensus Workship aimed to provide a standardized clinical approach for managing IAS, grounded in current clinical practice and research evidence.

To ensure a scientific basis for developing the consensus, the working group conducted an extensive literature search across major domestic and international databases, including PubMed, Cochrane Library, Embase, and CNKI. The included literature comprised randomized controlled trials, systematic reviews, meta-analyses, high quality observational studies, and case reports. The working group classified the included evidence into six levels of evidence (Table 1) and three grades of recommendation strength (Table 2) following the Oxford Centre for Evidence-based Medicine levels of evidence [9].

## 2 | Pathogenesis of IAS

**Recommendations**

1. IAS is a genetically predisposed disorder most commonly associated with human leukocyte antigen (HLA)-DRB1*0406. IAS is more prevalent in Asian populations and rare in Caucasian populations (Level of evidence: 4; Recommendation strength: C).
2. IAS is frequently observed in patients with autoimmune diseases or blood disorders and occasionally in those with autoimmune polyendocrine syndrome (Level of evidence: 4; Recommendation strength: C).
3. Medications are significant triggers for IAS, with thiol-containing drugs being the most common, particularly methimazole, which is the most frequently reported (Level of evidence: 3; Recommendation strength: B) additionally, viral infections represent another major trigger for IAS (Level of evidence: 4; Recommendation strength: C).
4. The primary cause of hypoglycemia in IAS patients is the presence of IAAs with low affinity but high binding capacity (Level of evidence: 4; Recommendation strength: C).

### 2.1 | Etiology

The precise pathophysiologic mechanism underlying IAS remains undefined. IAS is believed to arise from genetic susceptibility combined with autoimmune abnormalities and external triggers, such as medications, which lead to the production of high levels of IAAs that bind to insulin, disrupting insulin action and metabolism.

1. Genetic Background

IAS is strongly associated with HLA, with identified susceptibility loci including HLA-DRB1*0406, DRB1*0403, DQB1*0302, DQA1*0301, DRB1*0415, and DRB1*1301 [10, 11]. Of these HLA loci, HLA-DRB1*0406 is the most prevalent. HLA-DRB1*0406 is more prevalent in Asian populations, particularly among the Japanese, whereas Caucasians primarily express DRB1*0403 and other rare HLA genotypes, such as DRB1*0406. Additionally, in

**TABLE 1** | Definition of evidence levels in this consensus.

| Level of evidence | Definition |
|---|---|
| 1a | Meta-analysis of multiple randomized controlled trials |
| 1b | At least one randomized controlled trial |
| 2a | At least one well-designed controlled study, but not randomized |
| 2b | At least one well-designed quasi-experimental study of other types |
| 3 | Well-designed descriptive studies of a non-experimental nature, such as comparative studies, correlation studies, case reports, etc. |
| 4 | Reports or opinions from expert committees, and clinical experience of authoritative experts |

**TABLE 2** | Definition of recommendation strength in this consensus.

| Recommendation strength | Definition | Level of evidence |
|---|---|---|
| A (strong) | One or more high quality randomized controlled trials addressing the clinical question | 1a, 1b |
| B (moderate) | Well-designed clinical studies but without randomization | 2a, 2b, 3 |
| C (weak) | Reports or opinions from expert committees, and clinical experience of authoritative experts, indicating a need for high-quality clinical research in the field | 4 |

the Chinese population, the primary susceptibility genes are DRB1*0406 and DRB1*0403 [12]. Differences in HLA susceptibility genotypes may account for the higher incidence of IAS in Asian populations compared to Western populations.

2. Susceptible Populations and Triggers

IAS is frequently observed in patients with autoimmune diseases or blood disorders and occasionally in those with autoimmune polyendocrine syndrome [13]. Reported cases of IAS predominantly occur in patients with autoimmune diseases, with Graves' disease being the most common [14, 15], followed by Hashimoto's thyroiditis [15], systemic lupus erythematosus [16], rheumatoid arthritis, and chronic hepatitis. Relatively rare associated diseases include ankylosing spondylitis [17], psoriasis [18], and hematologic conditions, such as multiple myeloma [19, 20] and monoclonal gammopathy [21].

The two primary triggers for IAS are medications and infections/re-infections (Table 3). Medications are the primary trigger of IAS. Approximately one-half of IAS patients have a history of drug use prior to disease onset. The most common drugs are those containing thiol groups or thiol metabolites (> 90%) [22], with methimazole being the most frequently reported [23–28]. Other drugs include α-lipoic acid [29–32], clopidogrel [33, 34], tiopronin [35, 36], proton pump inhibitors (pantoprazole [37] and omeprazole [38]), carbimazole [39–43], nutritional supplements (coenzyme Q10 [44], pyrithione [45, 46], glutathione [35], and methionine [47]), antituberculosis medications (isoniazid [48]), glimepiride [49], antihypertensives (captopril [36, 50], hydralazine [51, 52], and diltiazem [36]), loxoprofen sodium [53], penicillamine [54, 55], antibiotics (imipenem [56] and penicillin G [57]), and α-interferon. Studies have shown that thiols bind to and break the disulfide bonds connecting the insulin A and B chains, increasing the immunogenicity of endogenous insulin. Infections are common, including those caused by measles virus, mumps virus, rubella virus, varicella-zoster virus, coxsackievirus B, and hepatitis C virus [50]. Additionally, several reports suggest that COVID-19 may also trigger IAS. Viral infections may act as superantigens, triggering IAA production and leading to IAS [58]. Recent studies suggest that the increase in autoimmune diseases associated with COVID-19 may contribute to a rise in IAS incidence, as viral infections may promote the abnormal recognition and binding of antibodies to endogenous insulin [52]. However, in patients without a history of taking medications that induce IAS or concurrent infections, IAS is classified as idiopathic or primary [59], meaning the cause remains unknown.

## 2.2 | Pathogenesis

The mechanism underlying blood glucose fluctuations in IAS patients may be involve the formation of insulin–autoantibody complexes through the binding of IAAs with endogenous insulin. During fasting, insulin levels are relatively low, leaving most autoantibodies unoccupied. When food is ingested and blood glucose levels rise, pancreatic β-cells are stimulated to produce insulin. Endogenous insulin binds to available sites on IAAs, forming insulin–autoantibody complexes. The accumulation of antibody-bound insulin in the blood impairs insulin clearance and action, resulting in hyperglycemia.

After several hours, blood glucose levels normalize, and insulin secretion decreases. Due to the low affinity of the antibodies, a reduction in free insulin may destabilize the insulin bound to autoantibodies. This complex dissociates releases a significant amount of insulin into the bloodstream, leading to severe hypoglycemia. Therefore, patients with IAS exhibit alternating episodes of hyperglycemia and hypoglycemia, characterized by recurrent hypoglycemic events, which may also be accompanied by impaired glucose tolerance or diabetes [62, 63].

In IAS, the binding of insulin to autoantibodies occurs independently of blood glucose levels. The severity and duration of hypoglycemia, as well as the transition from hyperglycemia to hypoglycemia, depend on the dissociation rate constant, titer, and intrinsic affinity of IAAs for insulin [62]. IAAs in IAS patients exhibit low affinity but high binding capacity for insulin, facilitating effective binding. IAAs include IgG, IgM, and IgA types, with IgG being the most common [23, 64–66]. In Japan, most IAS patients possess polyclonal IgG autoantibodies [67], whereas more than half of non-Asian patients exhibit monoclonal IAAs [6]. Although IgG is the most prevalent IAA serotype, IAS cases caused by IgA and IgM serotypes have also been reported [64, 68].

## 3 | Clinical Manifestations of IAS

**Recommendations**

1. The primary clinical feature of IAS is recurrent spontaneous hypoglycemia with or without alternating episodes of hyperglycemia (Evidence level: 3; Strength of recommendation: B).
2. Hypoglycemia in IAS typically manifests as adrenergic (autonomic) and neuroglycopenic symptoms (Evidence level: 3; Strength of recommendation: B).

A hallmark clinical feature of IAS is recurrent, irregular hypoglycemic episodes occurring without the use of antidiabetic medications or exogenous insulin [24] with or without alternating hyperglycemia and hypoglycemia. The clinical presentation of IAS varies significantly in terms of severity, duration, and remission rates [62, 69].

1. Hypoglycemia
   a. Adrenergic (autonomic) symptoms: Adrenergic symptoms encompass palpitations, tremors, sweating, and hunger. Evidence suggests that hypoglycemia may elevate all-cause mortality in patients with cardiovascular disease [70].
   b. Neuroglycopenic symptoms: Neuroglycopenic symptoms encompass fatigue, dizziness, confusion, blurred vision, diplopia, and dysarthria. Some patients may develop anxiety, paraphasia, seizures, or even progress to coma [26, 48, 52, 71, 72]. Persistent and severe hypoglycemia may lead to brain death [73].
   c. Characteristics of hypoglycemic episodes:

**TABLE 3** | Common triggers of insulin autoimmune syndrome.

| Trigger | | Evidence level | Recommendation strength |
|---|---|---|---|
| Drugs | | | |
| Antithyroid medications | Methimazole [23–28] | 3 | B |
| | Carbimazole [39–43] | 3 | C |
| | Propylthiouracil [14, 60] | 4 | C |
| Supplements | α-lipoic acid [29–32] | 4 | C |
| | Glutathione [35] | 4 | C |
| | Methionine [47] | 4 | C |
| | Pyrithione [45, 46] | 4 | C |
| Cardiovascular medications | Clopidogrel [33, 34] | 4 | C |
| | Captopril [36, 50] | 4 | C |
| | Hydralazine [51, 52] | 4 | C |
| | Procainamide [51] | 4 | C |
| | Diltiazem [36] | 4 | C |
| Anti-inflammatory drugs | Loxoprofen sodium [53] | 4 | C |
| | Corticosteroids [36] | 4 | C |
| Antibiotics | Imipenem [56] | 4 | C |
| Proton pump inhibitors | Pantoprazole [37] | 4 | C |
| | Omeprazole [38] | 4 | C |
| Antituberculosis medications | Isoniazid [48] | 4 | C |
| Antidiabetic drugs | Glimepiride [49] | 4 | C |
| Others | Tofacitinib [36] | 4 | C |
| | Albumin preparations [61] | 4 | C |
| | Penicillamine [54, 55] | 4 | C |
| | α-interferon | 4 | C |
| Viral infections | | | |
| Mumps virus [50] | | 4 | C |
| Rubella virus [50] | | 4 | C |
| Coxsackie B virus [50] | | 4 | C |
| Hepatitis C virus [50] | | 4 | C |
| Varicella-zoster virus [50] | | 4 | C |
| Measles virus [50] | | 4 | C |
| COVID-19 virus | | 4 | C |

i. Timing: In IAS patients, hypoglycemia may occur at any time but is often mealtime-related, typically occurring 3–5 h postprandially [6]. Some patients experience fasting hypoglycemia or unpredictable episodes.
ii. Frequency: The frequency of IAS-induced hypoglycemia is variable, ranging from occasional to frequent episodes, sometimes reaching multiple occurrences per day.

2. Alternating hyperglycemia and hypoglycemia: Postprandial hyperglycemia followed by hypoglycemia is another characteristic feature of IAS patients. Glycated hemoglobin levels may vary depending on the frequency and severity of hypoglycemic episodes and blood glucose fluctuations and can be normal or elevated in certain patients [50, 74].
3. Order of occurrence of hypoglycemia and comorbidities: In IAS patients with systemic autoimmune diseases,

hypoglycemia may precede, follow, or coincide with other autoimmune manifestations, potentially involving endocrine glands or other organ systems [13].

## 4 | Diagnosis of IAS

**Recommendations**

1. The diagnostic criteria for hypoglycemia include symptoms or signs of adrenergic (autonomic) and/or neuroglycopenic symptoms, venous plasma glucose ≤ 2.8 mmol/L, and resolution of symptoms after food intake or intravenous glucose administration. A 72-h fast should be considered for patients without spontaneous hypoglycemia within a specific period. In patients with confirmed hypoglycemia, insulin, C-peptide, proinsulin, blood and urine ketones, serum cortisol, and growth hormone should be measured alongside glucose to preliminarily assess the cause of hypoglycemia (Evidence level: 3; Strength of recommendation: B).

2. IAS is a form of endogenous hyperinsulinemic hypoglycemia, characterized by the following blood biochemistry panel criteria: insulin ≥ 3 μIU/mL (18 pmol/L), C-peptide ≥ 0.6 ng/mL (0.2 nmol/L), proinsulin ≥ 5 pmol/L, and negative urine ketones or blood β-hydroxybutyrate ≤ 2.7 mmol/L, with venous plasma glucose ≤ 2.8 mmol/L. Insulin ≥ 3 μIU/mL (18 pmol/L) but C-peptide < 0.6 ng/mL (0.2 nmol/L) and proinsulin < 5 pmol/L is suggestive of hypoglycemia related to insulin overdose (EIAS due to exogenous insulin injections is an exception) (Evidence level: 3; Strength of recommendation: B).

3. Patients with IAS typically exhibit significantly elevated insulin levels, often exceeding 100 μIU/mL, along with elevated C-peptide and proinsulin levels. Additionally, most patients demonstrate a discrepancy between C-peptide or proinsulin levels and insulin levels, with an inverse molar ratio of insulin to C-peptide or proinsulin > 1. However, this phenomenon may not be observed in all cases (Evidence level: 4; Strength of recommendation: C).

4. For patients with suspected IAS, IAA testing is recommended, with both positive and negative results requiring confirmation by polyethylene glycol (PEG) precipitation and/or gel chromatography in accredited laboratories to detect insulin-insulin antibody complexes in serum (Evidence level: 4; Strength of recommendation: C).

5. In suspected IAS cases, a comprehensive history of medication use (e.g., sulfhydryl-containing drugs), autoimmune diseases, and viral infections should be collected. Screens for autoantibodies, M proteins, and viral markers are also recommended to identify potential triggers of IAS (Evidence level: 4; Strength of recommendation: C).

6. The clinical diagnostic criteria for IAS are (1) confirmed hypoglycemia, particularly spontaneous or alternating hypoglycemia and hyperglycemia; (2) a blood biochemistry profile indicative of endogenous hyperinsulinemic hypoglycemia, with significantly elevated insulin levels (often > 100 μIU/mL), and insulin-to-C-peptide or insulin-to-proinsulin ratios > 1 in most patients; (3) circulating insulin–insulin antibody immune complexes (high-titer IAAs confirmed by PEG precipitation or gel chromatography); and (4) no history of exogenous insulin use (see Section 7 for EIAS details).

The etiology of hypoglycemia is complex, and IAS is one of its rare causes. Proper diagnosis and differential diagnosis require a thorough evaluation of the patient's medical history, symptoms, and examination results, as illustrated in Figure 1.

1. Levels of insulin, C-peptide, proinsulin, and ketones: Venous plasma glucose measured using the glucose oxidase method typically suppresses insulin, C-peptide, and proinsulin secretion to ≤ 3 μIU/mL (18 pmol/L), ≤ 0.6 ng/mL (0.2 nmol/L), and < 5 pmol/L, respectively. Insulin ≥ 3 μIU/mL (18 pmol/L) with plasma glucose ≤ 2.8 mmol/L suggests endogenous or exogenous hyperinsulinemic hypoglycemia. A C-peptide ≥ 0.6 ng/mL (0.2 nmol/L) with proinsulin ≥ 5 pmol/L indicates endogenous hyperinsulinemic hypoglycemia, commonly caused by insulin secretagogues, insulinoma, or IAS. Conversely, non-hyperinsulinemic hypoglycemia, indicated by plasma glucose ≤ 2.8 mmol/L, insulin < 3 μIU/mL (18 pmol/L), C-peptide < 0.6 ng/mL (0.2 nmol/L), and proinsulin < 5 pmol/L, may result from severe liver disease, hormone insufficiency (e.g., adrenal insufficiency, pituitary cachexia, and severe hypothyroidism), or insulin-like growth factor 2 (IGF2)-secreting tumors. Elevated ketones (e.g., blood β-hydroxybutyrate > 2.7 mmol/L) suggest non-hyperinsulinemic hypoglycemia, whereas levels ≤ 2.7 mmol/L are indicative of hyperinsulinemic hypoglycemia.

2. Magnitude of insulin elevation, insulin: C-peptide molar ratios and proinsulin: Under normal physiological conditions, insulin and C-peptide are cleaved equimolarly from proinsulin, which is secreted by pancreatic β-cells, and remain equimolar. Insulin is rapidly metabolized by the liver, while that of C-peptide is cleared more slowly by the kidneys. The half-life of insulin is 5–10 min, while that of C-peptide is 30–35 min. Thus, under normal circumstances, the plasma insulin: C-peptide molar ratio is typically < 1. IAA binding to insulin significantly prolongs the half-life of IAAs in IAS, extending it from approximately 5 min to several hours, while the half-life of C-peptide remains unchanged at 30–35 min. Consequently, patients with IAS often present with a high serum insulin level (typically > 100 μIU/mL) but normal or slightly elevated C-peptide and proinsulin levels, resulting in reversed insulin: C-peptide and insulin: proinsulin ratios exceeding 1. However, it is important to note that while IAAs primarily affect insulin, they may also bind to endogenous proinsulin and C-peptide in rare cases, leading to a molar ratio < 1. The occurrence and extent of this effect may also be influenced by the proinsulin and C-peptide quantification method employed in the laboratory, as well as by variations in immunoassay interference from IAAs. In the examination of 16 IAS cases admitted to Peking Union Medical College Hospital, approximately half of the patients exhibited

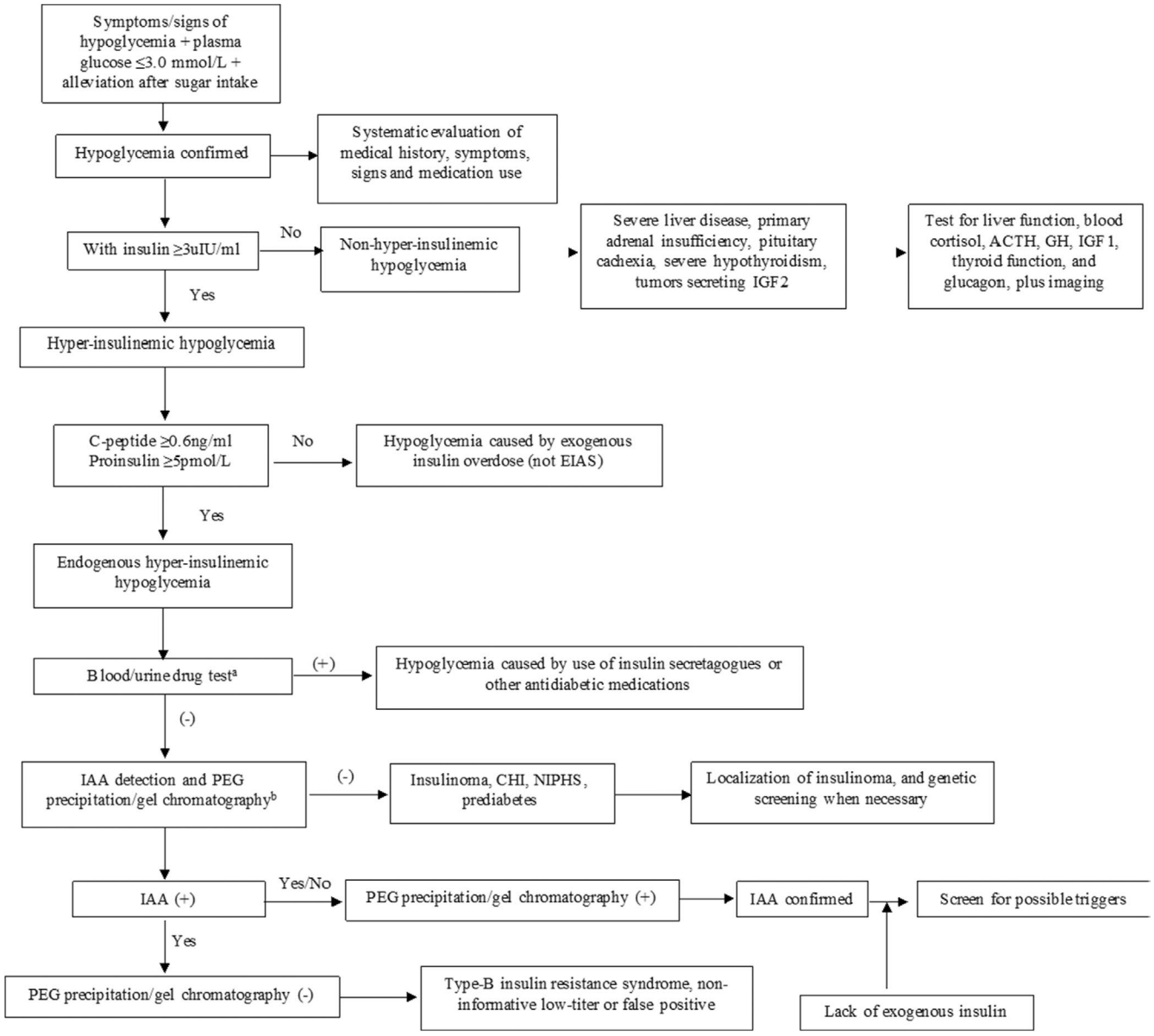


**FIGURE 1** | Flowchart of diagnosis and differential diagnosis of IAS. [a]Recommended at eligible laboratories only, may be omitted otherwise; [b]Recommended at eligible laboratories only, may be omitted otherwise. ACTH, adrenocorticotropic hormone; Blood F, blood cortisol; CHI, congenital hyperinsulinism; EIAS, exogenous insulin antibody syndrome; GH, growth hormone; IAA, insulin autoantibody; IAS, insulin autoimmune syndrome; IGF2, insulin-like growth factor 2; NIPHS, non-islet pancreatic insulin syndrome.

inverse insulin: C-peptide molar ratios. Consequently, when evaluating insulin metabolism in IAS patients, unexpected assay interferences and limitations should be taken into account.

3. Fasting test: The fasting test is recommended for inducing hypoglycemia in patients without spontaneous hypoglycemia within a specific period. The extended 72-h fasting test is currently the most commonly used protocol. The specific steps are as follows: first, record the time of the last meal at the start of the test, after which food intake should be avoided, but water (non-caloric and caffeine-free) is permitted. During the fast, the patient should remain active during waking hours. Blood samples are collected every 6 h to measure glucose, insulin, C-peptide, and proinsulin; and when the blood glucose levels ≤ 3.3 mmol/L, insulin and C-peptide levels should be monitored every 1–2 h. The fast is terminated when blood glucose is ≤ 3.0 mmol/L, or when symptoms or signs of hypoglycemia develop. At the end of the test, collect blood samples to measure glucose, insulin, C-peptide, proinsulin and either β-hydroxybutyrate or urinary ketone, followed by intravenous administration of 1 mg of glucagon. Blood samples are then collected 10, 20, and 30 min post-injection to measure glucose levels (Note: as glucagon is currently unavailable in China, this step cannot be performed), and the patient may resume eating thereafter. If a deficiency in hyperglycemic hormones is suspected, cortisol, growth hormone, or glucagon should be measured at both the start and end of the test. Caution should be exercised in elderly patients,

those at high risk for cardiovascular or cerebrovascular diseases, and those with a history of epilepsy.

4. Presence of IAAs: It is recommended that all patients with hyperinsulinemic hypoglycemia undergo IAA detection. A positive test result or elevated IAA titers indicate the presence of IAAs. The tests can yield false negatives, so negative results do not rule out IAS. IAA detection methods include immunoblotting, enzyme-linked immunosorbent assay (ELISA), and radioimmunoassay (RIA). Immunoblotting is a qualitative test with low sensitivity and high specificity. Both ELISA and RIA are quantitative tests. RIA is currently recommended by the International Organization for Standardization due to its high sensitivity and specificity. Therefore, if IAS is highly suspected despite negative IAA results, repeat testing using an alternative method is advised. Furthermore, it should be noted that false positives or ambiguous results are also possible. IAA positivity alone is insufficient to establish an IAS diagnosis.

5. PEG precipitation and gel chromatography for IAA detection: It is recommended that these experiments be conducted in certified laboratories, particularly when IAA testing does not confirm a diagnosis of IAS. Both methods indirectly confirm the presence of insulin-insulin antibody immune complexes in the bloodstream. PEG precipitates large IgG molecules but does not affect insulin. Therefore, if insulin-IgG antibody immune complexes are present, PEG will precipitate these complexes, resulting in a lower level of free insulin compared to the total level measured prior to precipitation. A decrease of more than 40% in the free insulin level after precipitation is generally considered indicative of the formation of insulin-IgG antibody immune complexes. The PEG precipitation method is relatively simple to perform and can serve as an initial screening test. Gel chromatography separates proteins based on their molecular weight. Because the molecular weight of IgG is significantly greater than that of insulin, insulin-IgG antibody immune complexes will elute faster than free insulin when passing through the column, resulting in higher insulin levels in the high molecular weight fraction of the eluent. Gel chromatography requires more technical expertise to perform and serves as a confirmatory test. Patients with negative IAAs but positive PEG precipitation or gel chromatography results, along with clinical and biochemical findings consistent with IAS, may be diagnosed with IAS. Caution is advised for patients with positive IAAs (especially low titer IAAs) but negative PEG precipitation or gel chromatography tests in the diagnosis of IAS. In some patients with hypoglycemia due to type-B insulin resistance syndrome, a positive low-titer IAA may be observed, and the differential diagnosis should be based on clinical presentation and other laboratory findings.

6. Screening for IAS triggers: Screening for precipitating factors is a crucial step in the diagnosis and differential diagnosis of IAS, as well as in providing guidance for its prevention and treatment. Many IAS patients experience spontaneous remission once the triggering factor is removed. Detailed information on factors that induce IAS can be found in the "Section 2". A detailed medical history focusing on medications, autoimmune diseases, and viral infections is necessary, along with screening for autoantibodies, M-proteins, and viral infection markers.

## 5 | Differential Diagnosis of IAS

**Recommendation**

IAS must be differentiated from all conditions that can lead to spontaneous hypoglycemic episodes, particularly hyperinsulinemic hypoglycemia, including insulinomas, drugs, non-insulinoma pancreatogenous hypoglycemic syndrome, B-type insulin resistance, and congenital hyperinsulinemia (Evidence level: 3; Recommended strength: B).

1. Insulinoma

An insulinoma is one of the most common diseases that should be differentiated from IAS due to its relatively high prevalence and similarity to the clinical presentation of IAS [75]. The primary criteria for identification are as follows: (1) An insulinoma is typically detectable as a space-occupying lesion within the pancreas, and, in rare cases, outside the pancreas, by imaging methods such as pancreatic perfusion CT and high-resolution pancreatic MRI. Increased radioactivity uptake of the lesion is suggested by nuclide imaging techniques, including octreotide imaging and $^{68}$Ga-Exendin4-PET/CT. (2) In patients with insulinomas who have no prior exposure to exogenous insulin, the IAA assay is typically negative. (3) In patients with insulinomas, the increase in insulin concentration is synchronized with the increase in C-peptide levels during hypoglycemia episodes, whereas in IAS patients, serum insulin levels are more markedly elevated, often exceeding 100 μIU/mL [39, 76].

2. Non-Insulinoma Pancreatogenous Hypoglycemia Syndrome

Non-insulinoma pancreatogenous hypoglycemia syndrome is another cause of endogenous hyper-insulinemic hypoglycemia, typically occurring postprandially and more prevalent in males [77, 78]. It has a lower incidence than insulinomas, and IAA negativity remains a crucial consideration in the differential diagnosis [79].

3. Hypoglycemia due to Exogenous Insulin Administration

Hyperinsulinemia occurs during hypoglycemic episodes, but both C-peptide and proinsulin concentrations are low [79, 80], and IAAs remain negative [81].

4. Hypoglycemia Caused by Other Drugs

The differential diagnosis of drug-induced hypoglycemia, such as that caused by oral sulfonylurea hypoglycemic agents, can be made by obtaining detailed information about the patient's medication history. If distinguishing the medications is challenging, drug concentrations should be measured in blood or urine samples [79].

5. Type B Insulin Resistance Syndrome

Type B insulin resistance syndrome is another form of autoimmune-related hypoglycemia [6, 82]. Patients may have both positive IAAs and insulin receptor antibodies. IAAs bind to insulin, preventing it from exerting its normal glucose-lowering effect. Alternatively, insulin receptor antibodies bind to the insulin receptor, which can be bidirectionally regulated or the downstream signaling pathway of insulin may be activated, exerting a glucose-lowering effect in an insulin-like manner, potentially leading to spontaneous hypoglycemia or causing antagonistic effects, resulting in insulin resistance and hyperglycemia [8, 83–85]. Most patients with type B insulin resistance also exhibit insulin-C-peptide dissociation [86]. However, they typically present with features of severe insulin resistance, such as hyperglycemia and acanthosis nigricans, due to a poor response to insulin [87], which are not typically present in IAS patients [86].

6. Congenital Hyperinsulinemia

Congenital hyperinsulinemia is the most common cause of hypoglycemia in children. It typically manifests in infancy or early childhood and is often characterized by persistent hypoglycemia. More than 12 causative genes have been identified, and genetic testing is required for diagnosis confirmation. Unlike IAS, the IAA test is typically negative in these patients. The degree of elevation of insulin levels during hypoglycemic episodes is less pronounced, and biochemical findings are often similar to those of an insulinoma [88].

7. Multiple Other Etiologies of Non-hyperinsulinemic Hypoglycemia

Hepatic and renal insufficiency, severe consumptive diseases, hypoglycemia due to tumor secretion of IGF2, adrenocortical insufficiency, and severe hypothyroidism are also causes of hypoglycemia. These disorders are characterized by synchronous insulin $<3\,\mu$IU/mL (18 pmol/L) and C-peptide $<0.6$ ng/mL (0.2 nmol/L) at a glucose $<3.0$ mmol/L, distinguishing them from IAS.

## 6 | Treatment and Prognosis of IAS

Despite the high spontaneous remission rate in IAS, the necessity of drug intervention treatment remains controversial. The treatment goal for IAS patients is the elimination of IAAs, as well as the correction and prevention of hypoglycemia. The treatment methods currently available in clinical practice are based on case reports and lack comprehensive analyses or randomized controlled trials. The selection of clinical interventions and treatments primarily depends on the severity of patient symptoms. Different treatment plans may be adopted depending on the specific IAS symptoms [69].

### 6.1 | Symptomatic Treatment

**Recommendations**

1. IAS patients with hypoglycemia are advised to consume smaller, more frequent meals, incorporating low glycemic index foods into their diet (Evidence level: 3; Recommended strength: B).
2. Patients experiencing hypoglycemic episodes are advised to engage in low-intensity aerobic exercise, avoiding high-intensity exercise or exercise on an empty stomach.
3. Patients with recurrent severe hypoglycemic episodes should use oral raw cornstarch, continuous intravenous glucose infusion, and alpha-glucosidase inhibitors to prevent and treat hypoglycemic. If these treatments prove ineffective, glucagon therapy should be considered (Evidence level: 3; Recommended strength: B).
4. IAS patients with recurrent hypoglycemic episodes may use continuous glucose monitoring systems (CGMs) combined with self-monitoring of blood glucose (SMBG) to assess blood glucose levels, taking into account the accuracy and compliance of glucose monitoring. Additionally, the accuracy of different CGM brands and SMBG at lower blood glucose levels should be considered.

Symptomatic treatment is primarily aimed at patients with recurrent hypoglycemic episodes, with the goal of maintaining blood glucose stability and preventing hypoglycemia. Symptomatic treatment primarily focuses on dietary adjustments and physical activity. Dietary treatment should include the following: (1) adjusting the frequency of meals by consuming smaller, more frequent meals (5–6 meals per day is appropriate) [89]; (2) low glycemic index foods are recommended to inhibit early postprandial insulin secretion [89]; and (3) further intensive supportive treatment is required for patients with recurrent hypoglycemia episodes, including the consumption of raw cornstarch [80] and continuous intravenous glucose infusion, which may reduce or even prevent hypoglycemia [69]. Since exercise can aggravate hypoglycemia, IAS patients are advised to avoid strenuous exercise or exercising while fasting and instead engage in a small amount of low-intensity exercise after meals [89]. The combination of CGM and SMBG accounts for the accuracy and compliance of blood glucose monitoring, thereby reducing the risk of severe hypoglycemia [50, 90]. Additionally, α-glucosidase inhibitors slow carbohydrate absorption and prevent postprandial hyperglycemia, providing varying degrees of benefit in reducing glycemic fluctuations in patients with IAS [91, 92]. If the above symptomatic treatments fail to alleviate recurrent episodes of severe hypoglycemia, glucagon may be considered to elevate the glucose levels [27].

### 6.2 | Antagonistic Treatment

**Recommendations**

1. Drugs that may induce IAS should be discontinued (Evidence level: 3; Recommended strength: B).
2. Immunosuppression therapy should be considered for patients whose symptoms do not resolve spontaneously after the discontinuation of causative drugs or for those who are unable to discontinue these drugs, such as patients with type 1 diabetes due to exogenous insulin-induced IAS (Evidence level: 4; Recommended strength: C).
3. Half- to full-dose glucocorticoid therapy, such as prednisone (0.5–1 mg/kg/day) and methylprednisolone

(0.4–0.8 mg/kg/day), is preferred for immunosuppressive therapy. If glucocorticoid therapy fails to alleviate symptoms, alternative treatments, including azathioprine, mycophenolate mofetil, and rituximab, either alone or in combination, for a duration of 1–2 months, may be considered (Evidence level: 4; Recommended strength: C).

4. If drug treatment is ineffective, plasma exchange can be attempted to reduce the serum IAA concentration (Evidence level: 4; Recommended strength: C).

Most patients with IAS may experience spontaneous remission within 2–3 months [36]. Although no studies have compared the effects of discontinuing versus maintaining causative medications on IAS remission rates, existing literature indicates that drug-induced IAS cases were typically managed by discontinuing medications at early-onset IAS, with remission of hypoglycemia occurring several weeks to months after discontinuation. However, there are few studies comparing IAS remission rates following drug discontinuation versus the continuation of induced drug therapy.

If IAS does not resolve spontaneously after drug withdrawal, immunosuppressive agents should be introduced to reduce IAA production. Case analysis statistics revealed that most patients preferred glucocorticoid therapy, with methylprednisolone and prednisone being the most commonly used formulations. Some cases have reported using half-to-full doses (prednisone 0.5–1 mg/kg/day) [90, 93], which can be divided into two or three doses to minimize the risk of nocturnal hypoglycemia. Treatment typically lasts 1–2 months, with a gradual improvement in symptoms.

Existing IAS case reports have documented the use of mycophenolate mofetil, azathioprine, and rituximab, either alone or in combination, in conjunction with glucocorticoid therapy. No recurrence has been observed in patients treated with mycophenolate mofetil (1 g bid for 6 months) after drug withdrawal [94]. Several case reports have demonstrated that rituximab (375 mg/m$^2$ body surface area for 1 week, administered over 4 weeks) effectively reduces IAA concentrations, thereby improving IAS [90, 94, 95]. There are also cases of successful treatment with rituximab dose of 1 g/m$^2$ body surface area, administered twice at a 10-week interval [58].

If immunosuppressive therapy proves ineffective or if severe hypoglycemia recurs repeatedly, plasma exchange may be considered to reduce IAA concentrations [96–98] (Figure 2).

## 7 | EIAS

### Recommendations

1. EIAS should be considered in diabetic patients using exogenous insulin who exhibit severe blood glucose fluctuations

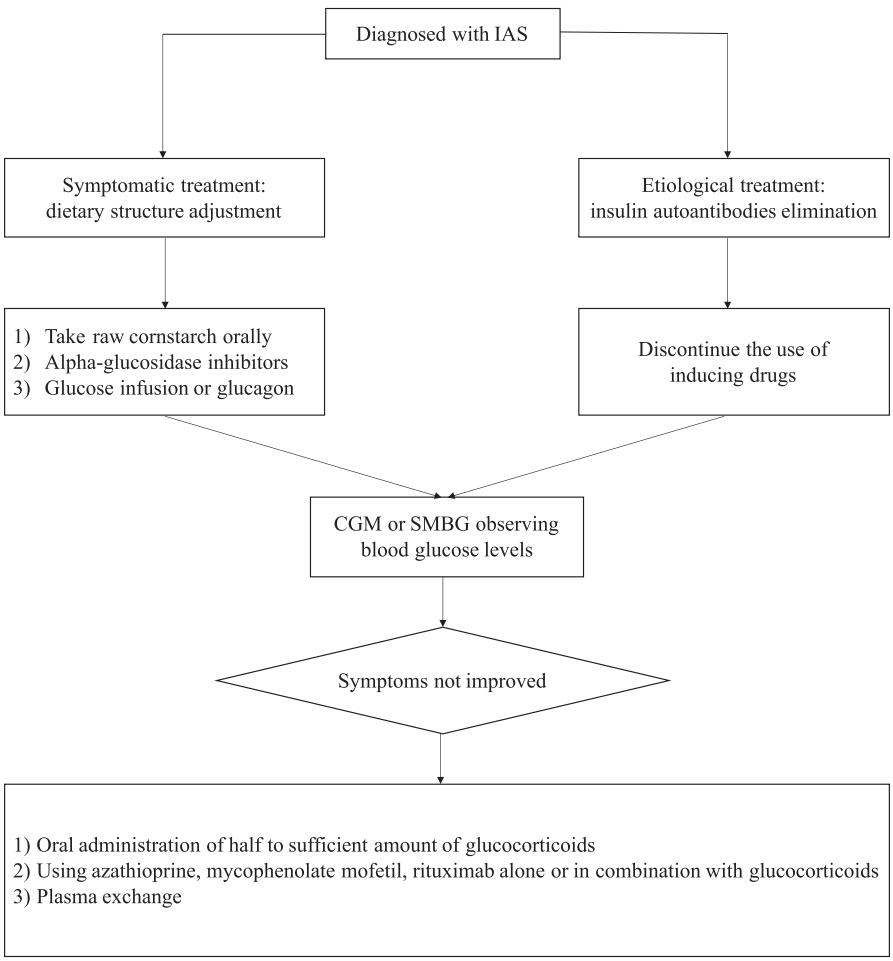


**FIGURE 2** | Flowchart of IAS treatment selection.

that exhibit explained solely by insulin dosage, such as severe insulin resistance and recurrent hypoglycemia (Evidence level: 4; Recommended strength: C).

2. The presence of any of these conditions in EIAS patients who cannot discontinue insulin, exhibit markedly elevated serum insulin levels measured during insulin use, and have undetectable C-peptide levels due to pancreatic β-cell failure, may lead to false-positive serum insulin: C-peptide ratios (mol/mol) in EIAS determination (Evidence level: 4; Recommended strength: C).
3. In patients with type 1 diabetes or other forms of diabetes involving pancreatic β-cell failure, if insulin cannot be discontinued and adjusting insulin dosage proves ineffective, immunosuppressive therapy that does not affect blood glucose levels should be considered to induce EIAS remission (Evidence level: 4; Recommended strength: C).

It is not uncommon for IAAs to be positive in patients receiving exogenous insulin. Studies have shown that the proportion can be as high as 40%, although most cases are asymptomatic [99]. In rare instances, high IAA titers may lead to clinical events, including insulin resistance, hyperglycemia, and recurrent hypoglycemia, which are classified as EIAS [100]. Currently, reports on EIAS are limited to a few case studies, making the exact incidence unclear. Similar to IAS, EIAS is more prevalent in Asian populations [101]. Hypoglycemia due to insulin overdose is more frequent in diabetic patients using exogenous insulin, particularly in those with pancreatic β-cell failure, where blood glucose fluctuations and hypoglycemia are more common during insulin use. As a result, hypoglycemia induced by EIAS may be overlooked in its early stages, leading to an underestimation of its incidence. There is a lack of systematic reviews on EIAS evidence in clinical practice, as well as a shortage of high-quality randomized controlled trials or cohort studies. Consequently, there is a lack of established experience and criteria for early identification and intervention of EIAS.

EIAS is currently considered to be similar to IAS, as both involve the production of high titers of IAAs, which are categorized into two types: low affinity/high volume and high affinity/low volume. The former dissociates easily from insulin, leading to recurrent hypoglycemic episodes, while the latter binds insulin in large amounts and dissociates less easily, resulting in insulin resistance and hyperglycemia. The former is more common in patients with IAS, while the latter is more frequently observed in patients with EIAS; however, both types can occur in either condition [100]. Patients with EIAS may experience severe persistent hyperglycemia due to insulin resistance and, in some cases, diabetic ketoacidosis, presenting a more complex glycemic profile than IAS.

Factors influencing the production of IAAs are as follows: (1) In terms of immunogenicity, it is generally accepted that animal insulin induces a higher immune response than recombinant human insulin and insulin analogs, although the immunogenicity of the latter two remains controversial [101]. Animal insulin is more likely to induce EIAS. Consequently, most case reports on EIAS were published in the last century, and since animal insulin is now rarely used, the incidence of EIAS has significantly declined, with fewer case reports available. In contrast, insulin analogs are now more commonly used in clinical practice than recombinant human insulin. As a result, EIAS is more As a result induced by insulin analogs [101]. (2) Studies have demonstrated that increasing the frequency of subcutaneous insulin injections or using continuous subcutaneous insulin infusion (e.g., insulin pumps) raises the risk of IAA production [102]. (3) Patient factors include (a) Similar to IAS, previous cases of EIAS have reported susceptibility to IAS-associated HLA loci, such as DRB1-0406 and DRB1-0403 [101]. (b) Published case reports indicate that patients with EIAS exhibit a range of autoimmunogenic features, including combinations of other autoimmune diseases (e.g., Hashimoto's thyroiditis, IgG4-related disorders, and drug hypersensitivity syndromes), positive antinuclear antibodies, a history of food and drug allergies, skin allergic reactions following insulin injections, and insulin injection site subcutaneous fat atrophy [101]. (c) Some studies have found that the likelihood of IAA production with exogenous insulin is inversely correlated with age, with a 3% reduction in the risk of IAA production for each additional year of age. The exact mechanism underlying this age-related reduction is unclear but may be associated with a decline in immune competence, resulting in a reduced ability to generate persistent memory cells, a diminished delayed hypersensitivity response, and a reduced ability to form IAAs [103].

The clinical manifestations of EIAS are often similar to IAS, primarily involving blood glucose fluctuations (e.g., alternating high and low blood glucose levels, recurrent hypoglycemia, and insulin resistance). Clear diagnostic criteria for EIAS are lacking. Based on evidence from previous studies and expert consensus, the following clinical diagnostic criteria for EIAS are proposed [101]: (1) Non-dose-related recurrent hypoglycemic episodes in diabetic patients applying exogenous insulin; (2) No improvement in hypoglycemia in diabetic patients after reducing or discontinuing insulin; (3) A significant increase in IAA titer and a marked decrease in serum insulin level measured after PEG precipitation in patients who are initially IAA-negative; and (4) Elevated serum insulin levels disproportionate to C-peptide, with an insulin: C-peptide ratio (mol/mol) is $>1$. Compared to IAS, the primary challenge in diagnosing EIAS lies in the interference of exogenous insulin with serum insulin measurements, or in patients with pancreatic β-cell failure, the inability to measure C-peptide, which complicates the evaluation of the insulin: C-peptide ratio. Typically, high serum insulin levels in patients receiving exogenous insulin or C-peptide levels near 0 ng/mL result in a high rate of false positives for the insulin: C-peptide ratio $>1$ criterion. There is no clear and reliable method to resolve this issue.

Treatment of EIAS is more complex and challenging than IAS due to the comorbidity of diabetes. Most patients experience spontaneous remission within an average of 1.5 months after dietary modification and the discontinuation or replacement of insulin preparations [101]. Patients with early postprandial hyperglycemia and late postprandial hypoglycemia may benefit from treatment with α-glucosidase inhibitors to slow carbohydrate absorption and reduce blood glucose fluctuations. The main difficulty in treatment arises in patients with type 1 diabetes or other types of diabetes with pancreatic β-cell failure, in whom insulin cessation is not feasible and switching insulin types may not be effective. If these patients fail to achieve

spontaneous remission or discontinue insulin, glucocorticoids (which may exacerbate hyperglycemia), immunosuppressive agents (e.g., azathioprine, mertiomaximab), biologics (e.g., rituximab), and intravenous immunoglobulin agents. If the response remains inadequate, plasma exchange may be attempted. The treatments specifics vary based on individual case reports, and there is no high-quality evidence, with most treatment protocols derived from IAS management (see above). The majority of patients achieve remission after immunosuppressive treatment, and a significant decrease in serum insulin levels and IAA titers during the treatment may indicate EIAS remission, serving as a reliable marker for monitoring efficacy [101]. Very few patients experience relapse after remission, and the risk factors for relapse remain unclear.

## 8 | Conclusion and Future Directions

IAS is a rare autoimmune hypoglycemic disorder with a low incidence, which can lead to poor clinical outcomes if not diagnosed and treated promptly. Patients may experience recurrent hypoglycemic episodes, along with fluctuations in blood glucose levels (both high and low). Early identification and diagnosis of IAS, through the detection of triggers, clinical features, and biochemical characteristics, combined with standardized interventions, can significantly improve prognosis. There remain numerous unresolved issues in the diagnosis and treatment of IAS that warrant further investigation. These include obtaining more comprehensive and precise epidemiological data of China and other countries, identifying genetic susceptibility factors of IAS, evaluating the efficacy and influencing factors of various treatments, conducting high-quality large-scale randomized controlled trials, and summarizing refractory cases to optimize therapeutic strategies.

### Author Contributions

Yuxiu Li, Qi Pan, Mingxia Yuan, and Huabing Zhang conceptualized and led the framework development, established the working group, and reviewed the final draft. Lingling Xu, Wei Li, and Fan Ping directed the literature review and the drafting of the initial manuscript. Yuxiu Li and Qi Pan organized the multidisciplinary experts, facilitated discussions, and finalized the consensus document. All members reviewed and provided critical revisions. Xiaoling Cai, Shihong Chen, Shuchun Chen, Xiaoping Chen, Jianling Du, Ling Gao, Yanping Gong, Haixia Guan, Yanying Guo, Guoxin Hou, Ji Hu, Hongyu Kuang, Jun Li, Ling Li, Xia Li, Yiming Li, Yuzhen Liang, Xiahong Lin, Ming Liu, Bin Lu, Jie Qin, Yingfen Qin, Jinxing Quan, Yunfeng Shen, Shaofang Tang, Haining Wang, Zhaoli Yan, Guoqing Yang, Mingxia Yuan, Jie Zhang, Dong Zhao, Fenping Zheng, Tianshu Zeng, Qiumei Zhang, and Xinli Zhou contributed to revising and proofreading the consensus content.


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### Conflicts of Interest

The authors declare no conflicts of interest.

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