GASTROINTESTINAL AUTOIMMUNE DISORDERS

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DISCLOSURES

- None

OBJECTIVES

- Become familiar with 5 of commonly seen autoimmune diseases of the GI tract
- Understand the role of antibodies or markers for the prediction of the disease
- Determine the signs and symptoms that would prompt a consideration for these diseases

Celiac Disease

BACKGROUND

- **Definition:**
  - A chronic, immune-mediated **enteropathy** triggered by the ingestion of **gluten**
  - Characterized by **villous atrophy**, **crypt hyperplasia**, and **intraepithelial lymphocytosis** in the small intestinal mucosa.
- **Pathophysiology:**
  - Gluten peptides are deamidated by **tissue transglutaminase (tTG)**, leading to an immune response mediated by **HLA-DQ2** or **HLA-DQ8** restricted **CD4+ T cells**.
  - This results in **cytokine release** (e.g., IFN-γ, IL-21), mucosal inflammation, and tissue damage.
- **Epidemiology:**
  - Prevalence: ~1% globally
  - **Seroprevalence** exceeds clinical diagnosis, highlighting under recognition.

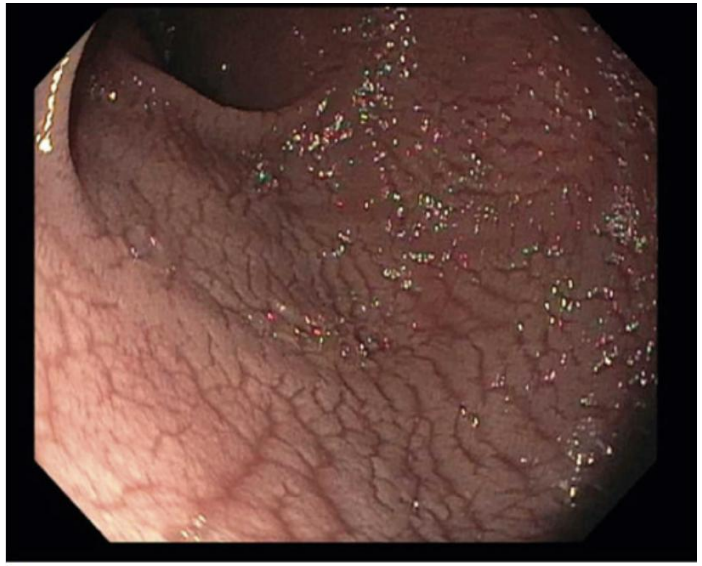
Rubio-Tapia et. Al. AJG 2023

CLINICAL PRESENTATION

- **Classic Symptoms:**
  - Chronic diarrhea, weight loss, abdominal pain, and bloating.
  - Malabsorption leading to deficiencies (iron, folate, vitamin D).
- **Atypical Symptoms:**
  - Fatigue, anemia, osteoporosis, neurological symptoms (e.g., peripheral neuropathy), elevated transaminases, and dermatitis herpetiformis.
- **Asymptomatic (Silent Celiac Disease):**
  - Detected incidentally during screening or evaluation for associated conditions.

DIAGNOSIS

- **Serologic Testing**
  - Tissue transglutaminase IgA antibody (tTG-IgA).
  - **If IgA deficient:** Use IgG-based tests (e.g., deamidated gliadin peptide IgG or tTG-IgG).
- **Confirmatory Testing:**
  - **Upper endoscopy with duodenal biopsies:**
    - Histologic findings include villous atrophy, crypt hyperplasia,
- Patients must be on a gluten-containing diet at the time of testing to avoid false negatives.
- HLA-DQ2 and HLA-DQ8 can be useful in the exclusion of CD in certain clinical situations



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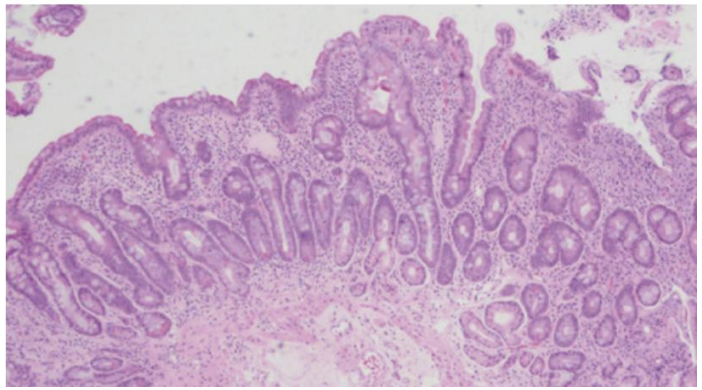

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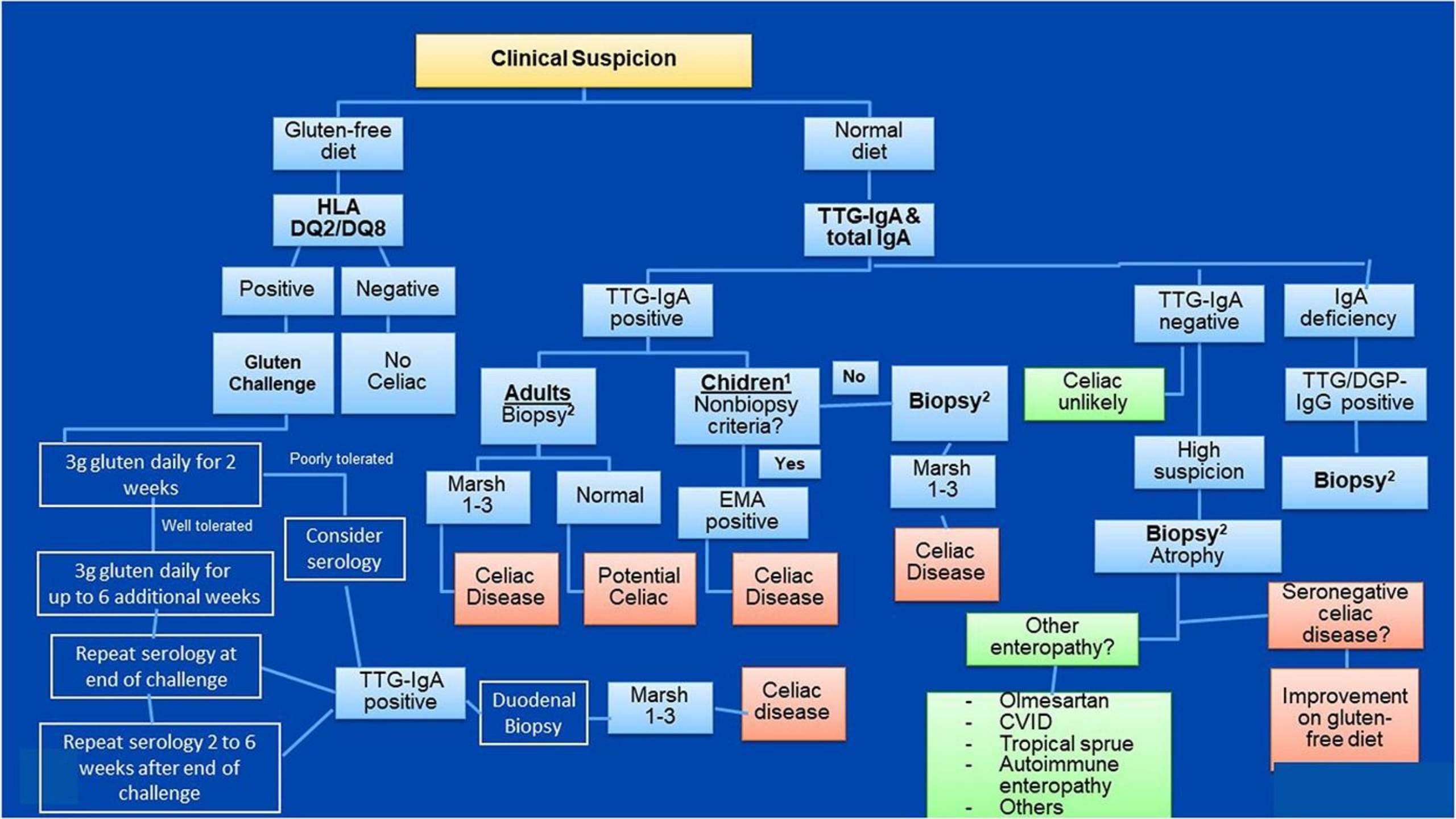

Clinical Suspicion
Gluten-free diet
Normal diet
HLA DQ2/DQ8
TTG-IgA & total IgA
Positive
Negative
Gluten Challenge
No Celiac
TTG-IgA positive
TTG-IgA negative
IgA deficiency
Adults Biopsy²
Chidren¹ Nonbiopsy criteria?
No
Biopsy²
Celiac unlikely
TTG/DGP-IgG positive
3g gluten daily for 2 weeks
Poorly tolerated
Yes
Marsh 1-3
Normal
EMA positive
Marsh 1-3
High suspicion
Biopsy²
Well tolerated
Consider serology
Celiac Disease
Potential Celiac
Celiac Disease
Celiac Disease
Biopsy² Atrophy
3g gluten daily for up to 6 additional weeks
Seronegative celiac disease?
Repeat serology at end of challenge
TTG-IgA positive
Duodenal Biopsy
Marsh 1-3
Celiac disease
Other enteropathy?
Improvement on gluten-free diet
Repeat serology 2 to 6 weeks after end of challenge
- Olmesartan
- CVID
- Tropical sprue
- Autoimmune enteropathy
- Others

WHO SHOULD BE TESTED?

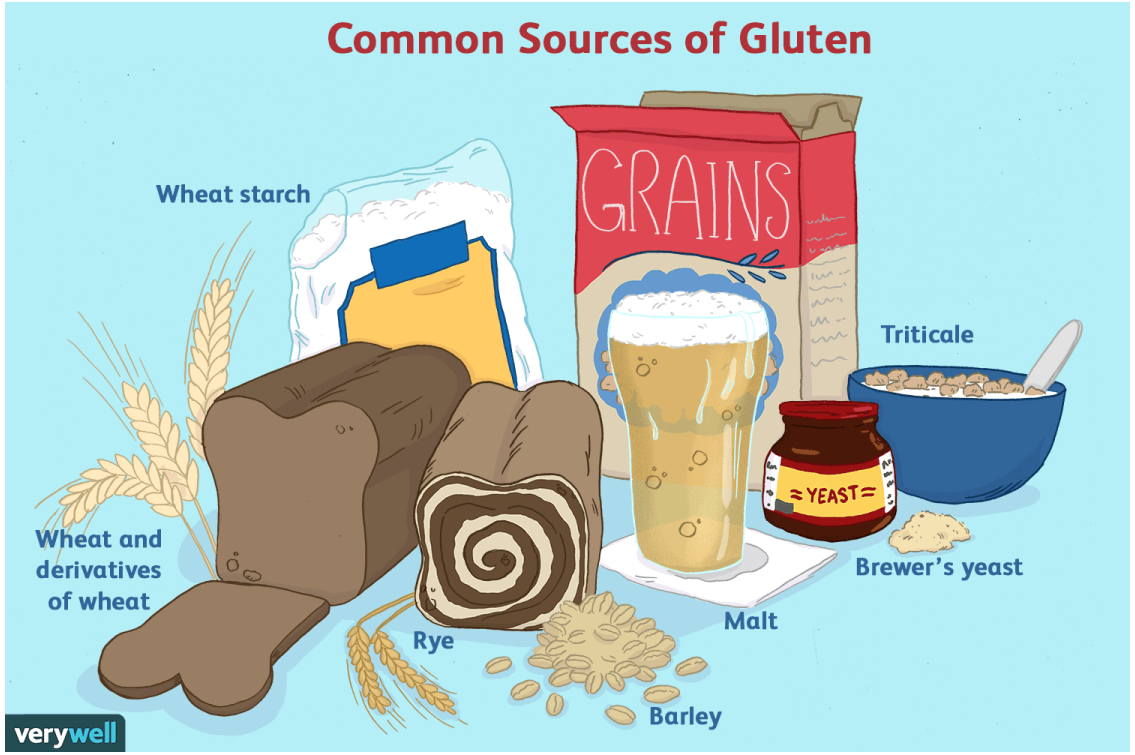
- Patients with classic or atypical symptoms.
- First-degree relatives of individuals with celiac disease.
- Conditions associated with celiac disease:
  - Type 1 diabetes, autoimmune thyroiditis, Down syndrome, and IgA deficiency.
- Unexplained elevated aminotransferases or iron deficiency anemia.
- Screen patients with irritable bowel syndrome (IBS)-like symptoms or functional dyspepsia who do not respond to standard therapies.

COMPLICATIONS

- **Short-Term:**
  - Nutritional deficiencies (iron, calcium, vitamins).
  - Growth failure in children.
- **Long-Term:**
  - Osteoporosis, anemia, infertility, and increased risk of malignancies (e.g., enteropathy-associated T-cell lymphoma).

MANAGEMENT

- **Gluten-Free Diet (GFD):**
  - Strict, lifelong avoidance of gluten (wheat, barley, rye).
  - Referral to a dietitian with expertise in celiac disease.
  - Education on hidden sources of gluten (e.g., processed foods, medications).
- **Monitoring and Follow-Up:**
  - Repeat serologic testing (tTG-IgA) to assess dietary adherence.
  - Resolution of symptoms and normalization of serology indicate response to GFD.
  - Repeat upper endoscopy at 2 years
- **Management of Refractory Disease:**
  - Rare cases may require immunosuppressive therapy (e.g., corticosteroids, azathioprine).



Autoimmune Hepatitis

BACKGROUND

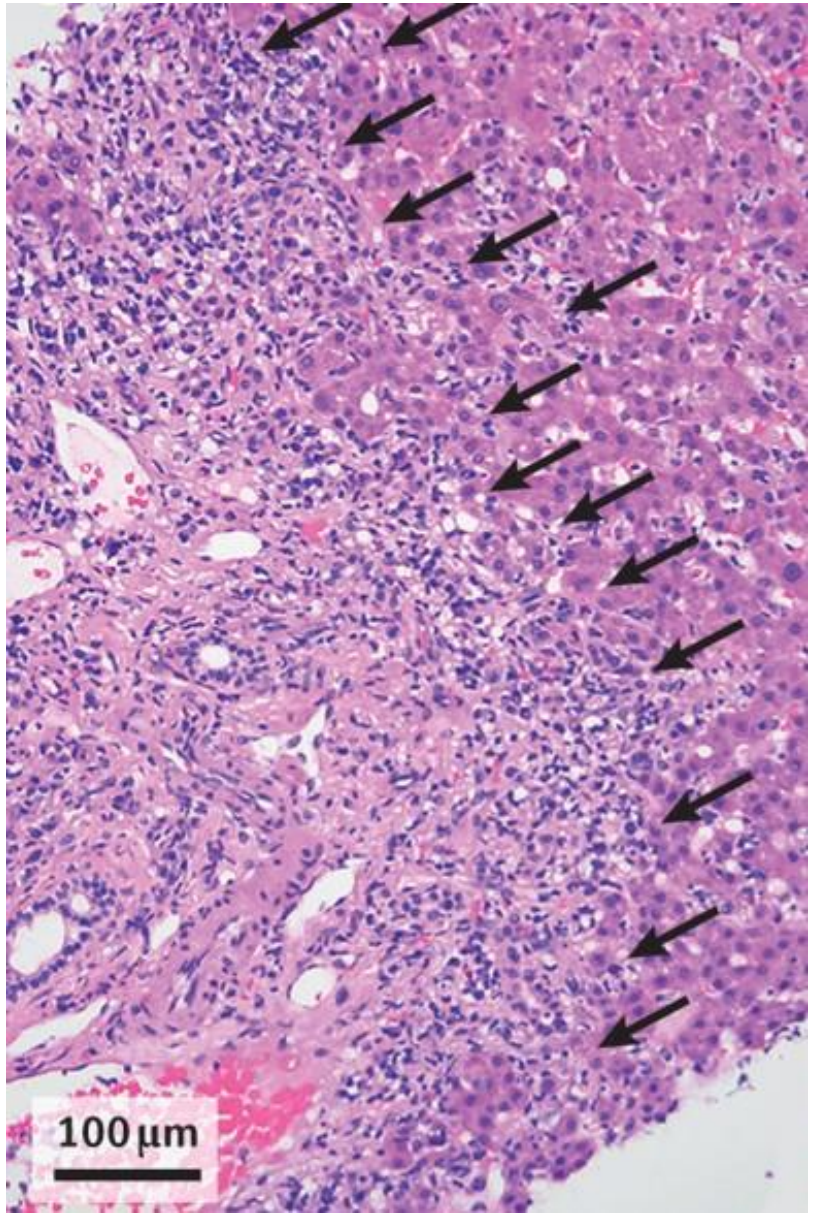
- **Definition:**
  - A chronic, immune-mediated liver disease characterized by **hepatocellular inflammation**, **elevated transaminases**, and **hypergammaglobulinemia**.
  - Can lead to **fibrosis**, **cirrhosis**, and **liver failure** if untreated.
- **Epidemiology:**
  - Prevalence: ~16-18 cases per 100,000
  - Female predominance (3:1 female-to-male ratio).
  - Bimodal age distribution: peaks in adolescence and middle age.
- **Pathophysiology:**
  - Loss of immune tolerance to hepatocytes.
  - **CD4+ T-cell-mediated** damage
  - Associated with **HLA-DR3** and **HLA-DR4**.

CLINICAL PRESENTATION

- **Acute Presentation:**
  - Fatigue, jaundice, abdominal pain, and nausea.
  - May mimic acute viral hepatitis or drug-induced liver injury (DILI).
- **Chronic Presentation:**
  - Asymptomatic or nonspecific symptoms (fatigue, arthralgias, malaise).
  - Signs of chronic liver disease: Hepatomegaly, spider angiomata, palmar erythema.
- **Advanced Disease:**
  - Cirrhosis, portal hypertension, and complications (ascites, variceal bleeding, hepatic encephalopathy).
- **Associated Conditions:**
  - Other autoimmune diseases: Thyroiditis, rheumatoid arthritis, ulcerative colitis, and celiac disease.

DIAGNOSTIC WORKUP

- **Key Laboratory Findings:**
  - Elevated **ALT** and **AST** (typically >10x ULN in acute AIH).
  - Hypergammaglobulinemia (elevated IgG).
  - Positive autoantibodies: (next slide)
- **Exclusion of Other Causes:**
  - Rule out viral hepatitis (HBV, HCV), Wilson disease, alpha-1 antitrypsin deficiency, and DILI.
- **Liver Biopsy:**
  - Gold standard for diagnosis - biopsy strongly recommended in all suspected cases
  - Histologic features: **Interface hepatitis, lymphoplasmacytic infiltrate, and rosette formation.**



AIH ANTIBODIES

- **Type 1 Autoimmune Hepatitis - ~95% of adult presentations**
  - **ANA (Antinuclear Antibodies):**
    - Present in ~50-70% of cases.
    - Non-specific but highly sensitive for Type 1 AIH.
  - **SMA (Smooth Muscle Antibodies):**
    - Present in ~50-80% of cases.
    - Directed against actin, particularly **F-actin.**
  - **Additional Antibodies: Anti-SLA (Soluble Liver Antigen)**
    - Present in ~10-30% of cases.
    - Highly specific for AIH and associated with more severe disease.
- **Type 2 Autoimmune Hepatitis:**
  - **Anti-LKM1 (Liver-Kidney Microsomal Type 1 Antibodies):**
    - Present in ~90-100% of cases.
  - **Anti-LC1 (Liver Cytosol Type 1 Antibodies):**
    - Present in ~30-50% of cases.
    - Associated with more aggressive disease in children.
  - **Clinical Relevance:**
    - Type 2 AIH is more common in children and adolescents. (Average age 14)

Mack CL, et al. Hepatology 2020

DIAGNOSTIC SCORING SYSTEM

- **Simplified Criteria:**
  - Based on autoantibodies, IgG levels, histology, and exclusion of viral hepatitis.
  - Score ≥6: Probable AIH.
  - Score ≥7: Definite AIH.

Component	Result	Points
Autoantibodies		
-ANA or SMA	≥1/40	+1
-ANA or SMA	≥1/80 or	+2
-Anti LKM1	≥1/40 or	+2
-Anti SLA	≥Positive	+2
Immunoglobulin G level	≥UNL	+1
	≥1.1UNL	+2
Liver histology	Compatible	+1
	Typical	+2
Viral disease	No viral markers	+2
	Viral markers present	0
Pretreatement aggregate score	Definite diagnosis	≥7
	Probable diagnosis	6

Hennes EM, et al. Hepatology 2008

TREATMENT

- **First-line:**
  - **Prednisone** + **Azathioprine**.
  - Induction: Prednisone 40 mg/day, tapered over 4-8 weeks.
  - Maintenance: Low-dose prednisone (5-10 mg/day) + azathioprine (1-2 mg/kg/day).
- **Second-line:**
  - **Mycophenolate mofetil (MMF)** for non-responders or azathioprine-intolerant patients.
  - Calcineurin inhibitors (tacrolimus, cyclosporine) as alternative options.
- **Monitoring:**
  - Regular LFTs, IgG levels, and monitoring for side effects (e.g., bone loss, diabetes, cytopenias).
  - Monitor azathioprine metabolites (6-TGN) in non-responders.
  - May consider withdrawal of therapy after 1-2 years of remission. (50% relapse rate)
- **Liver Transplantation:**
  - Indicated for decompensated cirrhosis or acute liver failure.
  - Post-transplant recurrence occurs in ~20-30% of cases.

Mack CL, et al. Hepatology 2020

PROGNOSIS

- **Untreated AIH:**
  - High risk of progression to cirrhosis and liver failure.
- **Treated AIH:**
  - 80-90% achieve remission with immunosuppression.
  - Relapse is common (~50%) after treatment withdrawal.
- **Long-term Complications:**
  - Cirrhosis, hepatocellular carcinoma (HCC), and drug-related side effects.

Autoimmune Pancreatitis

BACKGROUND

- **Definition**: Rare form of chronic pancreatitis driven by autoimmune mechanisms, characterized by inflammation and fibrosis of the pancreas.
- **Types**:
  - **Type 1 (IgG4-related AIP)**: Associated with systemic manifestations and elevated IgG4 levels.
  - **Type 2 (Idiopathic duct-centric AIP)**: Characterized by a localized pancreatic involvement without systemic features.
- **Epidemiology**:
  - **Age**: Typically affects middle-aged or older adults.
  - **Gender**: More common in men, particularly Type 1 AIP.

CLINICAL PRESENTATION

- **Symptoms:**
  - Obstructive jaundice (most common).
  - Abdominal pain (less severe than in acute pancreatitis).
  - Weight loss, fatigue, and steatorrhea.
- **Mimics:** Often misdiagnosed as pancreatic cancer due to similar imaging findings presenting as a mass

DIAGNOSIS

- Diagnosis relies on a combination of clinical, imaging, serologic, and histologic findings.
- **Imaging:** CT/MRI showing diffuse pancreatic enlargement or focal mass with a "sausage-shaped" pancreas.
- **Serology:** Elevated IgG4 levels (more specific for Type 1 AIP).
- **Histology:** Lymphoplasmacytic infiltrate with IgG4-positive cells (if biopsy is performed).
- **Response to steroids:** Rapid improvement with steroid therapy supports the diagnosis.

TREATMENT

- **First-line Therapy:**
  - **Corticosteroids:** Prednisone 40 mg/day for 4 weeks, followed by a gradual taper over 2-3 months
- **Relapse Management:**
  - Relapse is common, especially in Type 1 AIP.
  - Maintenance therapy with low-dose steroids or immunomodulators (e.g., azathioprine) may be considered.

PROGNOSIS

- **Type 1 AIP:** Higher risk of relapse and extra-pancreatic involvement.
- **Type 2 AIP:** Lower relapse rates and better long-term outcomes.
- **Monitoring:** Regular follow-up with imaging and IgG4 levels to detect relapse.

Primary Sclerosing Cholangitis

BACKGROUND

- **Definition**: Chronic, progressive, and immune-mediated disorder of the bile ducts leading to stricturing, fibrosis, and cholestasis.
- **Prevalence**: Rare, affects approximately 6-16 per 100,000 people, more common in men, typically diagnosed between 30-50 years.
- **Association**: Strongly associated with inflammatory bowel disease, specifically UC
  - ~ 70% of PSC patients have UC.

PATHOPHYSIOLOGY

- Primarily affects the intrahepatic and extrahepatic bile ducts, leading to fibrosis and strictures.
- **Genetic Factors**: Associations with genetic markers such as **HLA-B8** and **DR3**, as well as mutations in **IRF5** and **STAT3**.
- **Progression**: Chronic inflammation causes progressive liver damage, leading to cirrhosis, liver failure, and increased risk of cholangiocarcinoma.

DIAGNOSIS

- **Clinical Presentation**
  - Symptoms: Fatigue, pruritus, jaundice, right upper quadrant pain.
  - Associated with UC or Crohn's disease.
- **Laboratory Tests**
  - **Elevated alkaline phosphatase (ALP)**, **gamma-glutamyl transferase (GGT)**, and **bilirubin**
- **Autoantibodies**: Positive **pANCA** (perinuclear anti-neutrophil cytoplasmic antibodies) in some cases.
  - Check IgG4 to rule out IgG-4 RD (responds to steroids)
- **Imaging**
  - **Magnetic Resonance Cholangiopancreatography (MRCP)**
  - “beading,” ”tree-in-bud appearance”
- **Liver Biopsy**
  - A liver biopsy is **not required** for diagnosis but may be useful in cases with unclear imaging or in cases of suspected overlap syndrome.

TREATMENT

- Currently, there is no cure for PSC. The main treatment is **symptomatic management**.
- **Endoscopic Therapy**: For patients with bile duct strictures or stones, **endoscopic retrograde cholangiopancreatography (ERCP)** with balloon dilation or stent placement can provide symptom relief.
- **Ursodeoxycholic acid (UDCA)**:Historically used but does not alter the disease progression or survival in PSC.
- **Liver Transplantation**: Indicated for cirrhosis/decompensated liver disease, or some cases of cholangiocarcinoma.
  - Only effective long-term treatment for PSC once cirrhosis develops.

DISEASE MONITORING

- **Cholangiocarcinoma and gallbladder carcinoma** surveillance annually
  - MRI/MRCP with or without serum CA 19-9
  - ERCP with tissue sampling for new concerning strictures
- **Cholecystectomy** should be considered in gallbladder polyps >8mm
  - Polyps <8mm should be monitored every 6 months with US
- In patients with IBD and PSC, colonoscopy should be repeated at 2 year intervals
- Colonoscopy every 5 years for patients with PSC and no IBD

Primary Biliary Cholangitis

BACKGROUND

- **Definition:**
  - A chronic, progressive **autoimmune liver disease** characterized by **destruction of intrahepatic bile ducts**, leading to **cholestasis**, **fibrosis**, and potentially **cirrhosis**.
- **Epidemiology:**
  - Prevalence: ~40 cases per 100,000 in the U.S.
  - Female predominance (9:1 female-to-male ratio).
  - Typically diagnosed in middle-aged women (40-60 years).

CLINICAL FEATURES

- **Symptoms:**
  - Fatigue (50-80% of patients).
  - Pruritus (20-70% of patients).
  - Asymptomatic in ~50% of cases (diagnosed incidentally).
- **Signs of Chronic Liver Disease:**
  - Jaundice, hepatomegaly, and xanthomas.
- **Advanced Disease:**
  - Complications of cirrhosis (e.g., portal hypertension, ascites, variceal bleeding).
- **Associated Conditions:**
  - Osteoporosis, hyperlipidemia, and fat-soluble vitamin deficiencies.
  - Other autoimmune diseases (e.g., Sjögren’s syndrome, autoimmune thyroiditis, rheumatoid arthritis).

DIAGNOSIS

- **Serologic Testing:**
  - **Anti-mitochondrial antibodies (AMA):**
    - Present in ~95% of cases.
    - Highly specific for PBC (≥1:40 titer).
  - **Anti-nuclear antibodies (ANA):**
    - Present in ~30-50% of cases.
    - Associated with more aggressive disease.
- **Liver Biochemistry:**
  - Elevated **alkaline phosphatase (ALP)** and **gamma-glutamyl transferase (GGT)**.
  - Mildly elevated **ALT** and **AST**.
- **Liver Biopsy:**
  - Not required for diagnosis if AMA-positive and cholestatic biochemistry.
  - Indicated for AMA-negative cases or to assess disease stage.
  - Histologic findings: Florid duct lesions, bile duct loss, and granulomas.

TREATMENT

- **First-line Therapy**: **Ursodeoxycholic acid (UDCA)**: The standard of care for slowing disease progression.
  - Improves liver function, delays progression to cirrhosis, and improves survival.
  - **Dosing**: 13-15 mg/kg/day divided in 2-3 daily doses.
  - **Side effects**: Generally well-tolerated but can worsen pruritis in some patients.
- **Second-line Therapy**:
  - **Obeticholic Acid (OCA)**
  - **Selaldepar** - peroxisome proliferator-activated receptor (PPAR)-delta agonist
  - Both approved for patients with inadequate response or intolerance to UDCA.
  - Not approved for decompensated cirrhosis
- **Pruritus management**: Cholestyramine, rifampin, fibrates, or sertraline.
- **Liver Transplantation**: Indicated for patients with cirrhosis and complications of portal hypertension, ALF, or cholangiocarcinoma.
- **Osteoporosis:** Increased risk for osteoporosis. Index DEXA should be obtained at time of diagnosis

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