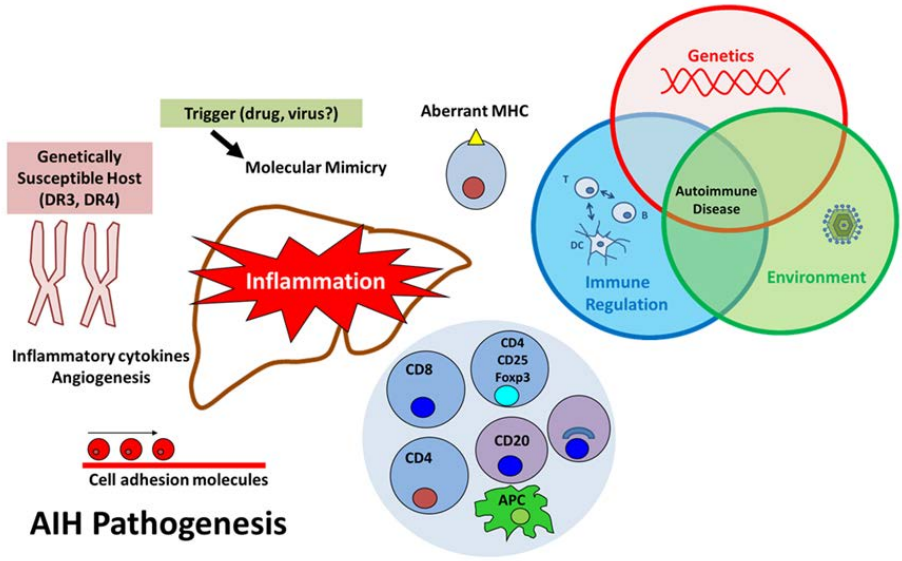
Chapter 9. Autoimmune & Drug Induced Hepatitis

9.1 Autoimmune Hepatitis (AIH)

Epidemiology & Pathophysiology

- **Epidemiology**
  - More common in women (4:1)
  - Occurs in all ethnic groups and across all ages
  - In Scandinavia
    - Incidence 10-20 per million
    - Prevalence 110-170 per million (1:6000)
- **Pathophysiology**
  - Complex interaction of a **dysregulated immune response** in response to an **environmental trigger** (e.g. drug or virus) in a **genetically susceptible host** which leads to autoantibody production and injury to hepatocytes

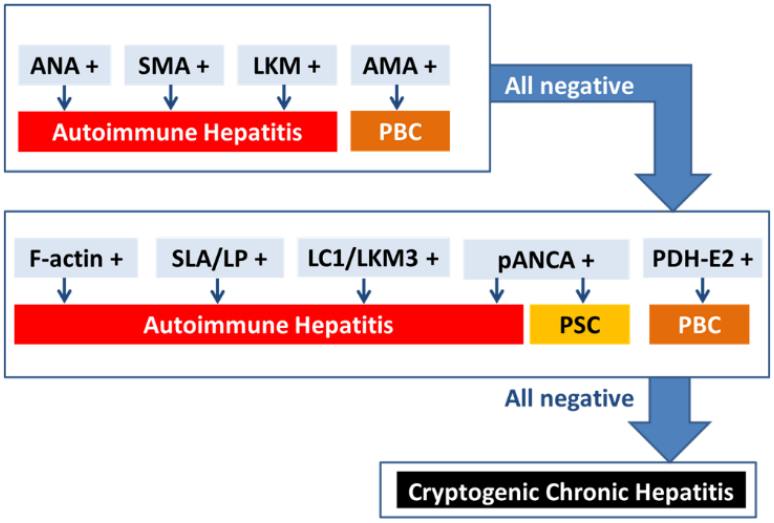


- **Drug-induced AIH**
  - Some drugs can induce an AIH-like picture *[see Chapter 9.2]*
  - Drugs associated with AIH include:
    - Minocycline
    - Nitrofurantoin
    - Phenytoin
    - Trazodone
    - Propylthiouracil
    - Isoniazid
    - Sulfonamides
    - α-methyldopa

Diagnosis & Natural History

- **Clinical Presentations**
  - Asymptomatic rise in liver tests (mild, moderate, or severe ALT elevation)
    - Often have other autoimmune diseases
    - Frequently have subclinical cirrhosis at time of diagnosis
  - Symptomatic
    - Fatigue, arthralgias, jaundice are common
    - Severe acute hepatitis (40%) with ALT > 1000, jaundice, coagulopathy and acute liver failure (ALF) presentation *[see Chapter 10]* but may have established cirrhosis
- **Autoantibodies**
  - anti-nuclear antibody (ANA) in 67%
  - anti-smooth muscle antibody (ASMA) in 87%
  - anti-liver kidney microsomal (anti-LKM)
    - They are not specific for AIH, and are not pathogenic or predictive of the natural history, but rather are an epiphenomena of liver damage & immune activation

- Classification
  - **Type 1** = relatively common, young/middle-age, ANA & ASMA positive, no viral trigger
  - **Type 2** = rare, usually children, anti-LKM positive, HCV association
- Other autoantibodies can be done if ANA, ASMA and anti-LKM are negative (see below)
  - F-actin, soluble liver antigen (SLA) / liver pancreas (LP), liver cytosol 1 (LC1)/ liver kidney microsomal 3 (LKM3), and peripheral antinuclear cytoplasmic antibody (pANCA) which is also often elevated in PSC *[see Chapter 5.3]*
  - Antibodies to pyruvate dehydrogenase complex – E2 subunit (PDC-E2) are more specific than the anti-mitochondrial antibody (AMA) for PBC *[see Chapter 5.2]*



Adapted from Manns MP, et al. Hepatology 2010; 51(6): 2193-213.

- **Diagnosis**
  - Need to rule out drugs and alcohol by history and viral hepatitis and other liver diseases by testing *[see Chapter 3.5]*

- Patients will usually have an elevated immunoglobulin G (IgG) or gammaglobulin levels
- Autoantibodies are non-specific and can be elevated in other autoimmune conditions or other liver diseases (e.g. HCV, PBC, PSC)
- Therefore, a **liver biopsy** is needed to establish the diagnosis
  - Key findings on the liver biopsy are **lymphocytic infiltrate** with an abundance of **plasma cells** (yellow arrows), which make immunoglobulins, and **interface hepatitis** (blue arrows) with inflammatory cells spilling across the limiting plate into the lobule
  - There should be a lack of biliary findings unless there is an overlap with PBC or PSC *[see Chapter 5.2 and 5.3]*

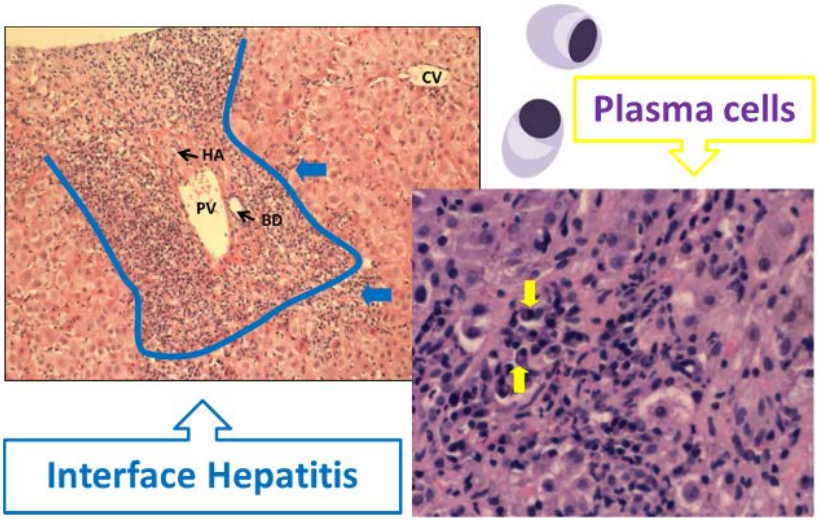


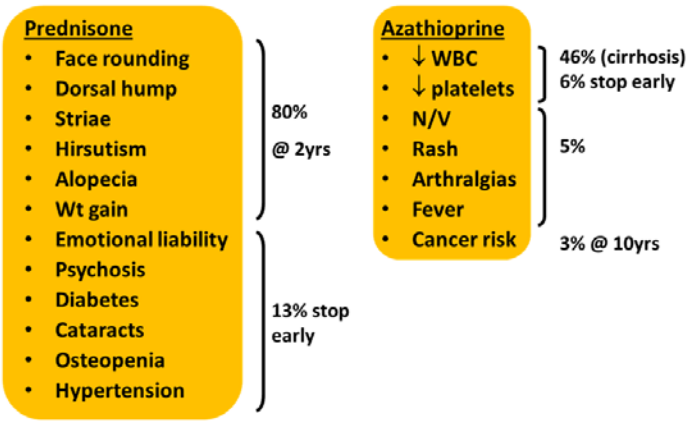
Image Source: http://www.aasld.org/practiceguidelines/Documents/AIH2010.pdf

- **Natural History**
  - Without treatment
    - 40% with severe disease die within 6 months
    - Cirrhosis develops in 40% and half will develop varices within 2 years

- **Treatment saves lives**
  - 20 year survival is > 80% and similar to age matched controls
  - However, AIH is controllable, not curable and it typically goes through cycles of remissions and flares, with treatment being “an art, more than a science”

Treatment

- **Absolute indications**
  - ALT or AST ≥10x ULN
  - ALT or AST ≥5x ULN with gammaglobulin or IgG ≥2x ULN
  - Interface hepatitis (bridging necrosis) on biopsy
  - Severe symptoms
- There are two options for initial treatment, but both treatments have side-effects
  - **Prednisone alone**
    - 60mg daily x 1 week → 40mg daily x 1 week → 30mg daily x 2 weeks → 20mg daily until remission
  - **Prednisone with azathioprine (AZA)**
    - Half the doses of prednisone above with azathioprine 50mg daily
    - This is preferred to reduce steroid related **side-effects**



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- **Remission**
  - **Biochemical remission** = normal ALT and IgG
  - **Histologic remission** = no or minimal inflammation on liver biopsy
  - Remission rates
    - 90% some response within 2 weeks, 65% remit within 18 months, 80% within 3 years
    - Median duration therapy before remission is approximately 2 years
  - Histologic improvement typically lags behind biochemical remission by 3-6 months
- Management upon remission
  - Withdraw prednisone over 4-8 weeks
  - Later attempt withdrawal of AZA
  - Regular monitoring for relapse
- Predicting Relapse
  - Liver biopsy done prior to stopping medications
    - 55% with normal ALT will still have interface hepatitis on biopsy

- Normal biopsy → 20% relapse in the future
- Portal inflammation → 50% relapse in next 6 months

- **Refractory AIH**
  - Worsening clinical, biochemical & histological features despite compliance
  - First line therapy
    - Prednisone 60mg or prednisone 30mg with AZA 150mg daily
    - Monthly dose reduction if improvement
  - Second line therapies
    - **Mycophenolate mofetil** (most evidence and preferred choice)
    - Budesonide (can also be used first line – fewer steroid related side-effects)
    - Methotrexate
    - Cyclosporine (also used in transplantation)
    - Tacrolimus (also used in transplantation)
    - Cyclophosphamide
    - Rituximab (monoclonal antibody to CD20 positive B cells)

9.2 Drug Induced Liver Injury (DILI)

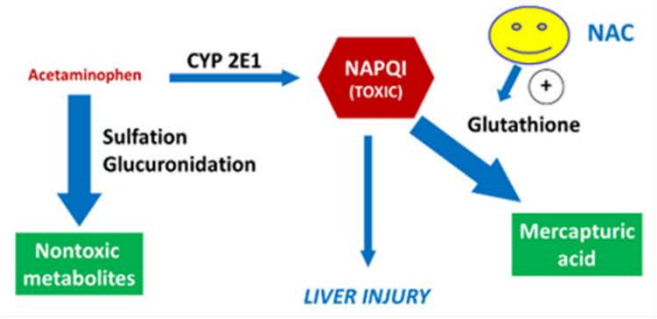
Epidemiology & Pathophysiology

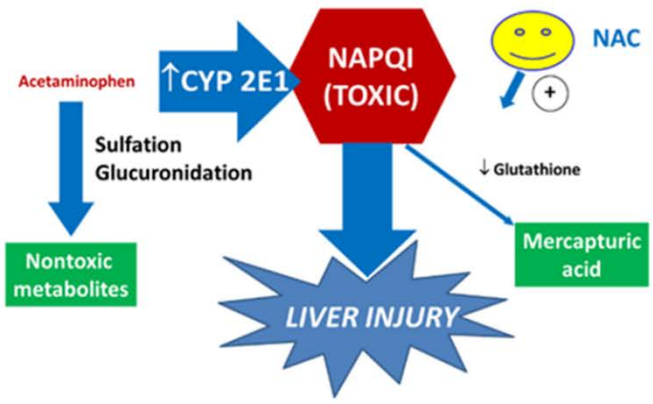
- Liver most important organ for drug metabolism and converts lipid soluble compounds to water soluble compounds for excretion into:
  - Plasma for renal excretion
  - Bile for hepatic excretion

- Factors affecting drug metabolism and risks for hepatotoxicity
  - Age – more common in elderly
  - Sex – 75% occur in women
  - Diet – micronutrients, caffeine, ETOH
  - Pregnancy
  - Diabetes
  - Liver & renal disease
  - Enzyme polymorphism
  - Drug-drug interaction
  - Enzyme induction – e.g. ETOH and acetaminophen (see below)
- **Types of hepatotoxicity**
  - **Dose-dependent** = predictable injury, very small list of drugs / toxins
    - Ethanol → steatohepatitis
    - Amiodarone → steatohepatitis
    - Cocaine → ischemic necrosis
    - Cyclosporine → cholestasis
    - Methotrexate → fibrogenesis
    - Birth control pills → adenomas
    - Acetaminophen → hepatocyte necrosis
  - **Idiosyncratic** = unpredictable, dose-independent, very long list (any drug)
    - See website for further information **http://www.livertox.nih.gov/**

- Acetaminophen (Tylenol®)
  - **Toxic dose is >10 grams** and is usually safe if <4 grams ingested per day
  - However, 2 – 4 grams is sufficient for injury in alcoholics
  - Untreated overdose (OD) results in severe liver injury in 10-20%
    - Leading cause of **acute liver failure (ALF)** in North America *[see Chapter 10]*
    - 20% mortality with severe liver injury
    - However, survival possible even if >50 grams are ingested
  - Patients present with nausea and vomiting due to hepatocyte necrosis
  - Often feel better within 48 hours
  - ALT (usually >1000) peaks at 72-96 hours
    - Dose dependent hepatotoxicity causing hepatocyte necrosis (starting in zone 3)
  - Elevated INR and encephalopathy (confusion) = **ALF**
  - Renal dysfunction (high creatinine) is common
  - Overdoses are treated with **N-acetylcysteine (NAC)** which donates cysteine to replenish glutathione (anti-oxidant)
- **Why are alcoholics more susceptible to acetaminophen toxicity?**
  - **Acetaminophen** has two metabolism pathways
    - Sulfation and glucuronidation (similar to bilirubin) metabolize it to non-toxic metabolites
    - CYP2E1 metabolizes it to NAPQI (toxic metabolite = direct hepatic injury)
    - Glutathione helps change NAPQI to mercapturic acid which is non-toxic

- **Alcohol** is metabolized by two pathways *[see Chapter 7.1]* and with chronic ingestion more is metabolized by MEOS (specifically CYP2E1)
  - If alcoholics ingest acetaminophen, more NAPQI is produced because of the upregulation of CYP2E1
  - Also, they often are glutathione depleted because of poor nutrition
  - This leads to increased risk of liver injury
- Individuals who actively abuse alcohol should avoid acetaminophen
- However, the risk of hepatotoxicity is NOT increased in patients with other pre-existing liver disease (if dose kept to <2 grams per day maximum)
- Acetaminophen is much safer than NSAIDs in cirrhosis, which can cause bleeding from ulcers and hepatorenal syndrome *[see Chapter 14.3]*
- THEREFORE, TYLENOL IS SAFE IN PATIENTS WITH LIVER DISEASE (with the exception of those actively abusing alcohol)





- **Drug Reactions** (some of the more common offending agents)
  - Severe Hepatocellular Reactions
    - Severe elevation ALT due to immune-allergic or drug-induced AIH
    - Immuno-allergenic reactions
      - Isoniazid (INH), halothane, ketoconazole, NSAIDs
      - Ecstasy
      - Herbals – kava-kava, germander, chaparral leaf, comfrey, jin bu haun
      - Weight loss agents containing usnic acid
    - Drug induced AIH
      - minocycline, nitrofurantoin, INH, sulfonamides, phenytoin, trazodone, propylthiouracil, α-methyldopa
  - Steatohepatitis
    - Macrovesicular steatohepatitis (amiodarone)
    - Microvesicular steatohepatitis (tetracycline, valproate, didanosine (ddI), ASA in children which can cause Reye's syndrome)

      NOTE: statins (cholesterol lowering drugs) are associated with very small risk of hepatotoxicity but may actually help patients with NAFLD and may have additional benefits in cirrhosis (lower risk of HCC and decrease portal pressure)
  - Cholestasis
    - Canalicular mechanism to cholestasis (amoxicillin + clavulanic acid, erythromycin, trimethoprim/sulfamethoxazole, chlorpromazine, androgens, estrogens)

- Fibrosis
  - Methotrexate (MTX) has toxic metabolite of microsomal origin and is more common when used to treat psoriasis (↑ risk if they abuse alcohol, have diabetes or obesity) than when used to treat rheumatoid arthritis or inflammatory bowel disease
  - Vitamin A causes toxicity by activating Ito cells to become hepatic stellate cells and typically at doses of 25,000 IU/d for 6 years or 50,000 IU/d for 2 years (↑ toxicity if alcohol abuse)
- Vascular changes
  - Sinusoidal dilation (androgens, estrogens)
  - Peliosis or dilated vascular channels (estrogens, tamoxifen, androgens)
  - Veno-occlusive disease presents with weight gain, ascites, RUQ pain, jaundice (azathioprine, cytotoxic chemotherapy)
- Nodules / tumours
  - Adenoma (anabolic steroids, estrogens) *[see Chapter 12.4]*
  - Focal Nodular Hyperplasia (estrogens) *[see Chapter 12.4]*
  - Angiosarcoma (vinyl chloride)

Diagnosis & Natural History

- **Diagnosis**
  - History is most important and you should suspect any new drug started in last 3-6 months
  - In addition to prescription medications, remember to ask about over-the-counter (OTC) medications, complementary and alternative medications (CAM) including

herbals, supplements and weight loss agents, as well as, illicit drugs (cocaine or ecstasy)

- **Natural history**
  - Typically will improve with withdrawal of offending agent
  - Acute liver failure *[see Chapter 10]*
    - Acetaminophen overdose has good prognosis
    - Idiosyncratic drug reactions have poor prognosis

Treatment

- Withdrawal of offending drug followed by careful observation
  - Follow ALT, ALP, bilirubin, INR (for prognosis) and watch for ALF (↑INR and encephalopathy)
- Specific therapies
  - NAC for acetaminophen overdose
  - Steroids for hypersensitivity
  - Ursodeoxycholic acid (UDCA) may be used for cholestasis
- Prevention
  - Monitor ALT monthly after starting drugs with known hepatotoxicity
  - Recommended for isoniazid (INH), methotrexate
  - No longer recommended for statins
  - PRO argument = can stop drugs at first sign of hepatotoxicity
  - CON argument = not likely to prevent severe adverse reactions, which can develop abruptly

Abbreviations

Anti-LKM – anti-liver kidney microsomal antibody

ASA – -acetylsalicylic acid

AZA – azathioprine

ddI – didanosine

IgG – immunoglobulin G

INH – isoniazid

LC1 – liver cytosol 1

LKM3 – liver kidney microsomal 3

LP – liver pancreas

MTX – methotrexate

NAC – N-acetylcysteine

NSAID – non-steroidal anti-inflammatory drug

OD – overdose

PDC-E2 – pyruvate dehydrogenase complex-E2

SLA – soluble liver antigen

Figure citations

AIH Diagnosis, AIH Treatment Side Effects, AIH Pathology. Adapted from Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010; 51(6):2193-213.

References

1. Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010; 51(6):2193-2213.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. *J Hepatol* 2015; 63(4):971-1004.
3. Chalasani NP, Hayashi PH, Bonkovsky HL, et al. Diagnosis and management of idiosyncratic drug-induce liver injury. *Am J Gastroenterol* 2014; 109(7):950-966.