

## DILI - AASLD

### The 3 Mechanisms of Injury

Mechanism	How It Works	Key for the Clinician	Example
1. Direct (Intrinsic)	The drug or its metabolite directly poisons liver cells.	Dose-dependent. Predictable. High incidence. Short latency.	Acetaminophen (APAP)
2. Idiosyncratic	An unpredictable, often immune-mediated reaction to a drug in a susceptible individual.	Not dose-dependent. Unpredictable. Low incidence. Variable latency.	Amoxicillin-clavulanate
3. Indirect	The drug's intended biological effect indirectly causes liver injury (e.g., altering immunity).	Unpredictable. Latency depends on the drug's effect.	Immune Checkpoint Inhibitors (ICIs)

### Framework for Managing a Suspected DILI Case: The "**REMEDIES**" Approach

1. **Recognize the Pattern:** Identify biochemical injury (ALT >5x ULN, etc.) and calculate the R-value  $[(ALT/ULN) / (ALP/ULN)]$  to classify as Hepatocellular ( $R \geq 5$ ), Cholestatic ( $R \leq 2$ ), or Mixed.
2. **Exclude Alternatives:** Rule out other causes (Viral hepatitis, AIH, Biliary obstruction, Ischemia).
3. **Medication History:** Take a history of ALL prescription, OTC, and herbal products used in the last 6 months.
4. **Eliminate the Offender:** Immediately discontinue the most likely suspect drug(s).  
This is the most critical step.
5. **Database Check:** Consult LiverTox.org to see if the clinical picture (latency, pattern) matches reported cases for that drug.
6. **Investigate Severity:** Assess for signs of acute liver failure: Coagulopathy (INR >1.5) and Encephalopathy.  
Urgently refer ALF patients to a transplant center.
7. **Empirical Support:** Provide supportive care (antiemetics, antipruritics, hydration).
8. **Specific Therapy (if indicated):** Consider specific treatments like N-acetylcysteine for ALF or corticosteroids for immune-mediated features.

### The 4M Approach to Any Drug

1. **Mechanism:** Is this drug a direct toxin, an idiosyncratic offender, or an indirect agent?
2. **Monitor:** Does its profile warrant proactive lab monitoring or just patient education on symptoms to report?
3. **Manage:** Upon injury, the first step is always drug cessation. Then provide supportive care.
4. **Mitigate:** Use specific antidotes (NAC) or immunosuppression (steroids) where evidence supports it.

Drug (Class)	Mechanism of Injury	Clinical Presentation	Management Solution
Amoxicillin-Clavulanate	Non-dose-related, immune-mediated. Associated with HLA alleles (e.g., DRB1*15:01).	Pattern: Mixed or Cholestatic. Latency: 2-6 weeks (can occur after stopping). Key Feature: A leading cause of DILI-related transplant. Prolonged cholestasis possible.	1. Immediate discontinuation. 2. Supportive care (antipruritics). 3. Consider Ursodeoxycholic Acid for severe pruritus. 4. Monitor for vanishing bile duct syndrome.
Isoniazid	Accumulation of toxic metabolite. "Slow acetylators" are at higher risk.	Pattern: Hepatocellular. Latency: Variable, typically within first 2 months. Key Feature: Can present with acute hepatitis. A common cause of DILI globally.	1. Immediate discontinuation. 2. Patient education on symptoms is crucial; routine lab monitoring is less effective. 3. Rechallenge is risky and only for active, drug-resistant TB.
Nitrofurantoin	Oxidative-free radicals may damage hepatocytes, often with autoimmune features.	Pattern: Hepatocellular or Mixed (can mimic Autoimmune Hepatitis). Latency: Can be very long (months to years). Key Feature: May present as chronic hepatitis with autoantibodies.	1. Permanent discontinuation. 2. Check ANA, ASMA, IgG. 3. Corticosteroids may be needed if autoimmune features are prominent.
Methotrexate	Direct, dose-dependent accumulation leading to stellate cell activation and fibrosis.	Pattern: Insidious, cholestatic ( $\uparrow$ ALP/GGT). Latency: Chronic use (years). Key Feature: Risk of silent progression to cirrhosis. Not an acute hepatitis pattern.	1. Dose reduction or hold. 2. Regular LFT monitoring (q4-12wks). 3. Annual non-invasive fibrosis assessment (FibroScan, FIB-4) is key. 4. Manage risk factors (alcohol, obesity).
Immune Checkpoint Inhibitors (e.g., Pembrolizumab, Ipilimumab)	Indirect. Immune-mediated hepatitis (IMH) from unchecked T-cell activity.	Pattern: Hepatocellular. Latency: 6-12 weeks after initiation. Key Feature: Rule out liver mets/infection first with imaging.	Grade-Based: • G1 (ALT<3xULN): Continue, monitor. • G2 (ALT 3-5xULN): Hold dose; start Prednisone 0.5-1 mg/kg. • G3+ (ALT>5xULN): Permanently d/c; IV Methylprednisolone 1-2 mg/kg.
Acetaminophen (APAP)	Direct hepatotoxin. Toxic metabolite (NAPQI) depletes glutathione, causing zone 3 necrosis.	Pattern: Acute Hepatocellular. Latency: 24-48h post-overdose. Key Feature: AST/ALT >1000 U/L, low initial bilirubin. Can be unintentional (therapeutic misadventure).	1. N-Acetylcysteine (NAC) is the antidote. Start immediately. 2. Activated charcoal if within 4h of ingestion. 3. Transfer to liver transplant center if ALF develops.
Green Tea Extract (HDS)	Associated with HLA-B*35:01 allele. High catechin concentration may be toxic.	Pattern: Hepatocellular. Latency: Variable (1-6 months). Key Feature: Can be severe, leading to ALF and death.	1. Discontinue all HDS products. 2. Supportive care. 3. High vigilance due to severe potential outcome.
Anabolic Steroids (Bodybuilding HDS)	Likely direct toxicity to bile canaliculi, causing cholestasis.	Pattern: Bland Cholestasis (severe jaundice & itching, but minimal inflammation). Latency: Weeks to months. Key Feature: Profound jaundice, but often self-limiting.	1. Discontinue product. 2. Supportive care for pruritus (cholestyramine, UDCA). 3. Recovery is slow (months).
Azathioprine / 6-Mercaptopurine (Immuno-suppressant)	Vascular endothelial injury.	Pattern: Nodular Regenerative Hyperplasia (NRH), Sinusoidal Obstruction Syndrome (SOS). Key Feature: Can lead to non-cirrhotic portal hypertension.	1. Discontinue drug. 2. Manage complications of portal hypertension. 3. Diagnosis often requires liver biopsy.
Sodium Valproate (Antiepileptic)	Direct mitochondrial toxicity.	Pattern: Microvesicular Steatosis. Key Feature: Hyperammonemia, especially in children. Can be fatal.	1. Immediate discontinuation. 2. L-Carnitine supplementation is a specific treatment for valproate-induced toxicity.
Allopurinol (Uricosuric)	Severe hypersensitivity. Associated with HLA-B*58:01 allele.	Pattern: Mixed or Hepatocellular, often with severe systemic features (DRESS syndrome). Key Feature: Rash, eosinophilia, organ failure.	1. Immediate permanent discontinuation. 2. High-dose corticosteroids for DRESS syndrome. 3. Screen for HLA-B*58:01 in high-risk populations before initiation.