**SUPPLEMENTAL TABLE 1** US Food and Drug Administration Warnings and Recommendations of selected drugs in the United States

|  |  |  |
| --- | --- | --- |
| **Drug** | **Warning/precaution** | **Actions to be taken** |
| Azathioprine | ↑ Enzymes and/or symptoms | Monitor periodically |
| Amoxicillin/clavulanate | Hepatitis | Monitor for hepatic impairment |
| Nitrofurantoin | Hepatitis | Monitor periodically |
| Minocycline | Hepatitis | Monitor monthly |
| Cefazolin | Hepatitis | Discontinue if symptoms/signs present |
| Azithromycin | Hepatitis | Discontinue if symptoms/signs present |
| Ciprofloxacin | Hepatitis | Discontinue if symptoms/signs present |
| Trimethoprim/sulfamethoxazole | Fatalities | Discontinue if symptoms/signs persist |
| Diclofenac | Fatalities | Measure ALT at baseline/periodically |
| Phenytoin | Fatalities | Discontinue if symptoms/signs present |
| Methyldopa | Fatalities | Monitor periodically for first 6–12 months |
| Isoniazid | Black box fatalities\* | Monitor symptoms monthly if age >35, monthly ALT |

Abbreviation: ALT, alanine aminotransferase.

\* In the United States, a “black box warning” on the [package insert](https://en.wikipedia.org/wiki/Package_insert) indicates a significant risk of serious or even life-threatening [adverse effects](https://en.wikipedia.org/wiki/Adverse_effect_%28medicine%29). See reference Chen et al.[171] for a full list of 192 drugs of most concern for causing liver injury that carry warnings and/or precautions.

**SUPPLEMENTAL TABLE 2** Liver injury, mechanistic, diagnostic, and prognostic DILI biomarkers in development

|  |  |  |
| --- | --- | --- |
| **Biomarker** | **Clinical context** | **Issues/limitations** |
| Liver injury markers |  |  |
|  Sorbitol dehydrogenase | Hepatocyte injury | Early marker of ALI |
|  Glutathione S-transferase alpha | Centrilobular liver injury and renal injury | Early serum marker of ALI. Early urine marker of AKI |
|  Bile acids | Elevated endogenous bile acids from impaired hepatocyte excretion | More liver specific than bilirubin. Not DILI specific |
|  Glutamate dehydrogenase | Reflect mitochondrial dysfunction | Elevated in other chronic liver diseases. More specific than ALT for liver |
|  Micro-RNAs: miR-122, mIR-192 | Noncoding, liver specific RNAs released in liver injury | Elevated in other acute and chronic liver diseases. Analytical methods need validation |
| Mechanistic biomarkers |  |  |
|  HMGB1 | Marker of tissue necrosis | Not liver specific |
|  Acetylated HMGB1 | Marker of innate immunity activation | Not liver specific. Requires mass spectroscopy |
|  Cytokeratin 18 fragments |  |  |
|   M-30 | Apoptosis marker | Not liver specific |
|   M-65 | Apoptosis and necrosis marker | Analytical validation ongoing |
| Diagnostic biomarkers |  |  |
|  Serum Cys-APAP adducts | Sensitivity and specificity for APAP hepatotoxicity | Point of care test in development |
|  Lymphocyte transformation test | Used in Japan | Not reproducible by other groups using other methods |
|  MetaHeps | Need to know suspect drugs | Derived from peripheral blood |
|  Liver organoids | Derived from hepatocytes or induced pluripotent stem cells | Allow for testing drugs in liver chip systems from individual patients |
| Prognostic biomarkers |  |  |
|  Macrophage colony stimulating factor receptor | Recruitment of inflammatory cells to the liver | Higher levels associated with poorer prognosis |
|  Osteopontin | Liver derived and involved in liver regeneration | Higher levels associated with poorer prognosis |

Abbreviations: AKI, acute kidney injury; ALI, acute liver injury; APAP, acetaminophen; DILI, drug-induced liver injury; Cys, cysteine ; HMGB1, high- mobility group box 1.