**Supplementary Table 3. Updated RUCAM for the cholestatic or mixed liver injury of DILI and HILI1**

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| --- | --- | --- |
| **Items for cholestatic or mixed liver injury** | **Score** | **Result** |
| 1. Time to onset from the beginning of the drug/herb |  |  |
| ●   5–90 days (rechallenge: 1–90 days) | +2 | □ |
| ●   <5 or > 90 days (rechallenge: > 90 days) | +1 | □ |
| Alternative: Time to onset from cessation of the drug/herb |  |  |
| ●   (except for slowly metabolized chemicals: ≤ 30 days) | +1 | □ |
| 2. Course of ALP after cessation of the drug/herb |  |  |
| Percentage difference between ALP peak and N |  |  |
| ●   Decrease ≥ 50% within 180 days | +2 | □ |
| ●   Decrease < 50% within 180 days | +1 | □ |
| ●   No information, persistence, increase, or continued drug/herb use | 0 | □ |
| 3. Risk factors |  |  |
| ●   Alcohol use current drinks/d: > 2 for women, > 3 for men) | +1 | □ |
| ●   Alcohol use (current drinks/d: ≤ 2 for women, ≤ 3 for men) | 0 | □ |
| ●   Pregnancy | +1 | □ |
| ●   Age ≥ 55 years | +1 | □ |
| ●   Age < 55 years | 0 | □ |
| 4. Concomitant use of drug(s)/herb(s) |  |  |
| ●   None or no information | 0 | □ |
| ●   Concomitant drug/herb with incompatible time to onset | 0 | □ |
| ●   Concomitant drug/herb with compatible or suggestive time to onset | −1 | □ |
| ●   Concomitant drug/herb known as hepatotoxin and with compatible or suggestive time to onset | −2 | □ |
| ●   Concomitant drug/herb with evidence for its role in this case (positive rechallenge or validated test) | −3 | □ |
| 5. Search for alternative causes | Tick if negative | Tick if not done |
| Group I (7 causes) |  |  |
| ●   HAV: Anti-HAV-IgM | □ | □ |
| ●   HBV: HBsAg, anti-HBc-IgM, HBV-DNA | □ | □ |
| ●   HCV: Anti-HCV, HCV-RNA | □ | □ |
| ●   HEV: Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA | □ | □ |
| ●   Hepatobiliary sonography/color Doppler sonography of liver vessels/endosonography/CT/MRC | □ | □ |
| ●   Alcoholism (AST/ ALT ≥ 2) | □ | □ |
| ●   Acute recent hypotension history (particularly if underlying heart disease) | □ | □ |
| Group II (5 causes) |  |  |
| ●   Complications of underlying disease(s) such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis, or sclerosing cholangitis, genetic liver diseases | □ | □ |
| ●  Infection suggested by PCR and titer change for |  |  |
| ●   CMV (anti-CMV-IgM, anti-CMV-IgG) | □ | □ |
| ●   EBV (anti-EBV-IgM, anti-EBV-IgG) | □ | □ |
| ●   HSV (anti-HSV-IgM, anti-HSV-IgG) | □ | □ |
| ●   VZV (anti-VZV-IgM, anti-VZV-IgG) | □ | □ |
| Evaluation of group I and II |  |  |
| ●   All causes—groups I and II—reasonably ruled out | +2 | □ |
| ●   The seven causes of group I ruled out | +1 | □ |
| ●   6 or 5 causes of group I ruled out | 0 | □ |
| ●   Less than five causes of group I ruled out | −2 | □ |
| ●   Alternative cause highly probable | −3 | □ |
| 6. Previous hepatotoxicity of the drug/herb |  |  |
| ●   Reaction labeled in the product characteristics | +2 | □ |
| ●   Reaction published but unlabeled | +1 | □ |
| ●   Reaction unknown | 0 | □ |
| 7. Response to unintentional re-exposure |  |  |
| ●   Doubling of ALP with the drug/herb alone, provided ALP below 2 N before re-exposure | +3 | □ |
| ●   Doubling of ALP with the drugs(s)/herbs(s) already given at the time of first reaction | +1 | □ |
| ●   Increase of ALP but less than N in the same conditions as for the first administration | −2 | □ |
| ●   Other situations | 0 | □ |
| Total score for the case | | □ |

Total score and resulting causality grading: ≤ 0, excluded; 1–2, unlikely; 3–5, possible; 6–8, probable; and ≥9, highly probable. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; CT, computed tomography; DILI, drug-induced liver injury; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAg, hepatitis B antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HILI, herb induced liver injury; HSV, herpes simplex virus; MRC, magnetic resonance cholangiography; N, upper limit of normal; RUCAM, Roussel Uclaf Causality Assessment Method; VZV, varicella zoster virus.

**Reference**

1. Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. Int J Mol Sci 2015;17(1):14. doi: 10.3390/ijms17010014, PMID: 26712744