# Care Step Pathway – Hepatotoxicity (immunotherapy-induced inflammation of liver tissue)

## Assessment

<table>
<thead>
<tr>
<th>Look:</th>
<th>Listen:</th>
<th>Recognize:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Does the patient appear fatigued or listless?</td>
<td>- Change in energy level?</td>
<td>- Elevation in LFTs</td>
</tr>
<tr>
<td>- Does the patient appear jaundiced?</td>
<td>- Change in skin color? Yellowing?</td>
<td>- AST/SGOT</td>
</tr>
<tr>
<td>- Does the patient have yellowing of eyes?</td>
<td>- Change in stool color (pale)?</td>
<td>- ALT/SGPT</td>
</tr>
<tr>
<td>- Does the patient appear lichy?</td>
<td>- Change in urine color (darken/tea colored)?</td>
<td>- Bilirubin (total/direct)</td>
</tr>
<tr>
<td>- Does the patient appear diaphoretic?</td>
<td>- Abdominal pain: specifically, right upper quadrant pain?</td>
<td>- Alteration in GI function</td>
</tr>
<tr>
<td>- Does the patient have any ascites?</td>
<td>- Bruising or bleeding more easily?</td>
<td>- Symptoms such as abdominal pain, ascites, somnolence, and jaundice</td>
</tr>
</tbody>
</table>

## Grading Toxicity: ULN

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST or ALT: &gt;1.0× – 3.0× ULN</td>
<td>AST or ALT: &gt;3.0× – 5.0× ULN</td>
<td>AST or ALT: &gt;5.0× – 20.0× ULN</td>
<td>AST or ALT: &gt;20× ULN</td>
<td>AST or ALT: &gt;20× ULN</td>
</tr>
<tr>
<td>Bilirubin: &gt;1.0× – 1.5× ULN</td>
<td>Bilirubin: &gt;1.5× – 3.0× ULN</td>
<td>Bilirubin: &gt;3.0× – 10.0× ULN</td>
<td>Bilirubin: &gt;10× ULN</td>
<td>Bilirubin: &gt;10× ULN</td>
</tr>
</tbody>
</table>

## Management of Transaminitis (without elevated bilirubin)

Management of Grade 2 or worse transaminitis with bilirubin >1.5× ULN: follow Grade 4 recommendations

### Overall Strategy:
- LFTs should be checked and results reviewed prior to each dose of immunotherapy
- Rule out infectious, non-infectious, and malignant causes. Consider assessing for new onset or re-activation of viral hepatitis, medications (acetaminophen, statins, and other hepatotoxic meds, or supplements/herbals), recreational substances (alcohol); consider disease progression

### Influnixim infusions are not recommended due to potential hepatotoxic effects

### Implementation:
- Check hepatitis labs in any patient with a history of hepatitis
- Institute early identification and evaluation of patient symptoms
- Institute early intervention with lab work and office visit if hepatotoxicity is suspected
- Grade LFTs and any other accompanying symptoms
- As noted in overall strategy, do not use infliximab because of hepatotoxic effects
- Assess patient & family understanding of recommendations and rationale
- Identify barriers to adherence

### *Administering Corticosteroids:*

Steroid taper instructions/calendared as a guide but not an absolute
- Taper should consider patient’s current symptom profile
- Close follow-up in person or by phone, based on individual need & symptomatology
- Steroids cause indigestion; provide antioxidant therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down & report them (taper may need to be adjusted)

### Long-term high-dose steroids:
- Consider antimicrobial prophylaxis
- Consider additional antiviral and antifungal coverage
- Avoid alcohol/acetaminophen or other hepatotoxins
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

### RED FLAGS:
- Severe abdominal pain, ascites, somnolence, jaundice, mental status changes

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GI = gastrointestinal; LFT = liver function test; po = by mouth; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal.

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