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

### Assessment

**Look:**
- Does the patient appear fatigued or listless?
- Does the patient appear jaundiced?
- Does the patient appear icthyic?
- Do the patient's eyes appear diaphoretic?
- Does the patient have any ascites?

**Listen:**
- Change in energy level?
- Change in skin color? Yellowing?
- Change in urine color (darker/tea colored)?
- Abdominal pain: specifically, right upper quadrant pain?
- Fever?
- Increased itching?
- Change in mental status?
- Increased sweating?

### 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:</td>
<td>&gt;ULN – 3.0× ULN</td>
<td>&gt;3.0× – 5.0× ULN</td>
<td>&gt;5.0× – 20.0× ULN</td>
<td>&gt;20× ULN</td>
</tr>
<tr>
<td>AST or ALT Abn. Baseline:</td>
<td>&gt;1.5× – 3.0× ULN</td>
<td>&gt;1.5× – 3.0× ULN</td>
<td>&gt;3.0× – 10.0× ULN</td>
<td>&gt;10× ULN</td>
</tr>
<tr>
<td>Bilirubin:</td>
<td>&gt;ULN – 1.5× ULN</td>
<td>&gt;1.5× – 3.0× ULN</td>
<td>&gt;3.0× – 10.0× ULN</td>
<td>&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 (hepatitis A, hepatitis B, hepatitis C, hepatitis E), medications (acetaminophen, statins, and other hepatotoxic meds, or supplements/herbals), recreational substances (alcohol); consider disease progression

#### Infliximab 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

### Red Flags:
- Severe abdominal pain, ascites/peripheral oedema, somnolence, jaundice, mental status changes

### Administration of Corticosteroids:

**Steroid taper instructions/calendar 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 antacid 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, hyperactive, 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 (sulfamethoxazole/trimethoprim double dose M/W/F; single dose if used daily) or alternative if sulfas-allergic (e.g., atovaquone (Mepron®) 1500 mg po daily)
- 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

**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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