

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 have yellowing of eyes?
- Does the patient have a rash or appear itchy?
- Does the patient appear diaphoretic?
- Does the patient have any ascites?

Listen:

- Change in energy level and/or increasing fatigue?
- Change in skin color? Yellowing?
- Loss of appetite?
- Change in stool color (paler)?
- Change in urine color (darker/tea colored)?
- Nausea and/or vomiting?
- Abdominal pain: specifically, right upper quadrant pain?
- Bruising or bleeding more easily?
- Fevers?
- New or increased itching?
- Change in mental status?

Recognize:

- Generally asymptomatic; abnormal labs noted on routine blood work
- Three patterns of liver injury:
 - o Hepatocellular pattern: asymptomatic elevation in AST (SGOT) and ALT (SGPT)
 - o Cholestatic pattern: elevated ALP and/or T bilirubin
 - o Mixed pattern
- Alteration in GI function
- Symptoms such as abdominal pain, jaundice, and pruritus may indicate biliary obstruction
- Other potential causes: viral infection (Hepatitis A/B/C, CMV, EBV, HSV), medications, alcohol, tumor-related (obstruction, progression)
- Patients with underlying chronic liver disease (NAFLD, alcoholic liver disease) have higher risk

Grading Toxicity: ULN

Grade 1 (Mild)

ALT > 3.0 x ULN if baseline is normal;
> 1.5–3.0 x baseline if baseline was abnormal **or**

AST > 3.0 x ULN if baseline is normal;
> 1.5–3.0 x baseline if baseline was abnormal **or**

ALP > 2.5 x ULN if baseline is normal;
> 2.0–2.5 x baseline if baseline was abnormal **or**

TBil > 1.5 x ULN if baseline is normal;
> 1.0–1.5 x baseline if baseline was abnormal

Grade 2 (Moderate)

ALT > 3.0–5.0 x ULN if baseline is normal;
> 3.0–5.0 x baseline if baseline was abnormal **or**

AST > 3.0–5.0 x ULN if baseline is normal;
> 3.0–5.0 x baseline if baseline was abnormal **or**

ALP > 2.5–5.0 x ULN if baseline is normal;
> 2.5–5.0 x baseline if baseline was abnormal **or**

TBil > 1.5–3.0 x ULN if baseline is normal;
> 1.5–3.0 x baseline if baseline was abnormal

Grade 3 (Severe)

ALT > 5.0–20.0 x ULN if baseline is normal;
> 5.0–20.0 x baseline if baseline was abnormal **or**

AST > 5.0–20.0 x ULN if baseline is normal;
> 5.0–20.0 x baseline if baseline was abnormal **or**

ALP > 5.0–20.0 x ULN if baseline is normal;
> 5.0–20.0 x baseline if baseline was abnormal **or**

TBil > 3.0–10.0 x ULN if baseline is normal;
> 3.0–10.0 x baseline if baseline was abnormal

Grade 4 (Potentially Life-Threatening)

ALT > 20.0 x ULN if baseline is normal; > 20.0 x baseline if baseline was abnormal **or**

AST > 20.0 x ULN if baseline is normal; > 20.0 x baseline if baseline was abnormal **or**

ALP > 20.0 x ULN if baseline is normal; > 20.0 x baseline if baseline was abnormal **or**

TBil > 10.0 x ULN if baseline is normal; > 10.0 x baseline if baseline was abnormal

Management by Grade

Overall Strategy:

- LFTs should be checked and results reviewed prior to each dose of immunotherapy
- **Avoid infliximab. It is not recommended due to potential hepatotoxic effects.**

Grade 1 (Mild)

- ICI therapy can be continued with close monitoring of LFTs with at least weekly labs
- Temporarily hold hepatotoxic medications if possible and avoid alcohol
- Consider holding ICI therapy for concerning laboratory value trends

Grade 2 (Moderate)

- ICI therapy to be withheld
- Temporarily hold hepatotoxic medications and avoid alcohol
- Consider hepatology/gastroenterology consult
- Consider liver biopsy
- If no other cause is identified, and LFTs remain elevated or are increasing, corticosteroids* to be initiated at 0.5 mg – 1 mg/kg/day oral prednisone or equivalent
- Monitor LFTs q 3-5 days
- Consider hospital admission for IV steroids if refractory to oral prednisone. If no improvement in 3-5 days, add 2nd line agent
 - o Mycophenolate mofetil (CellCept) 500-1000 mg q 12 hours
- If LFTs normalize and symptoms (if applicable) resolve, convert to oral prednisone (if applicable) and taper over ≥4 weeks. Corticosteroids can be re-escalated if LFTs worsen while tapering
- Once LFTs improve to baseline or Grade 0-1, and prednisone dose is ≤10 mg/day, consider resuming treatment with ongoing close monitoring of liver enzymes

Grade 3 (Severe) and 4 (Life-threatening)

- ICI therapy to be withheld
- Hold hepatotoxic medications and avoid alcohol
- Hepatology/gastroenterology consult; consider liver biopsy if no contraindications
- Corticosteroids* to be initiated: 1-2 mg/kg/day IV methylprednisolone or equivalent)
- Admission for IV corticosteroids* if needed
- Monitor LFTs, metabolic panel (with glucose) every 1-2 days
- Once LFTs improve to baseline or Grade 0-1, convert IV corticosteroid to oral equivalent, and taper over at least 4-6 weeks (generally 10 mg/week). Steroid can be re-escalated if LFTs worsen while tapering. If steroid refractory (little or no improvement in LFTs in 3-5 days), add 2nd agent (based on expert guidance/management)
 - o Mycophenolate mofetil 500-1000 mg q 12 hours OR tacrolimus 1-2 mg q 12 hours (max dose trough level of 8-10 ng/mL)
 - o A 3rd agent may be necessary if refractory to above or with fulminant hepatitis: azathioprine (AZA), tocilizumab, antithymocyte globulin, (ATG) or plasmapheresis
 - o For Grade 3 patients, once LFTs improve to baseline or Grade 0-1, convert IV corticosteroid to oral equivalent and taper over at least 6-8 weeks (generally 5-10mg/day). Re-escalate dose as necessary if LFTs increase while tapering. Once corticosteroid taper is completed, begin to taper other immunosuppressive agents, one at a time
 - o For Grade 4, LFTs should be checked daily
- Generally, ICI to be permanently discontinued following high-grade toxicity, however, retreatment may be considered on a case-by-case basis and in collaboration with expert guidance in conjunction with hepatology/gastroenterology

Implementation:

- Check hepatitis serologies 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
- Evaluate for myocarditis/myositis if AST appears out of proportion to ALT or in the absence of ALP or bilirubin elevation
- 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/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, 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 (sulfamethoxazole/trimethoprim double dose M/W/F; single dose if used daily) or alternative if sulfa-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

RED FLAGS:

- Severe abdominal pain, ascites, somnolence, jaundice, mental status changes



ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; CMV = cytomegalovirus; EBV = Epstein Barr Virus; GGT = gamma-glutamyltransferase; GI = gastrointestinal; HSV = Herpes simplex virus; ICI = immune checkpoint inhibitor; LFT = liver function test; po = by mouth; NAFLD= non-alcoholic fatty liver disease; PT/INR = prothrombin time/international normalized ratio; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TB = tuberculosis; TBil = total bilirubin; ULN = upper limit of normal