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 itchy?
- Does the patient appear diaphoretic?
- Does the patient have any ascites?

Listen:
- Change in energy level?
- Change in skin color? Yellowing?
- Change in stool color (paler)?
- Change in urine color (darker/tea colored)?
- Abdominal pain: specifically, right upper quadrant pain?
- Bruising or bleeding more easily?
- Fevers?
- Increased itching?
- Change in mental status?
- Increased sweating?

Recognize:
- Elevation in LFTs
  - AST/SGOT
  - ALT/SGPT
  - Bilirubin (total/direct), reduction in platelet count
- Alteration in GI function
- Symptoms such as abdominal pain, ascites, somnolence, and jaundice
- Other potential causes (viral, drug toxicity, disease progression)

Grading Toxicity: ULN

Grade 1 (Mild)		Grade 2 (Moderate)		Grade 3 (Severe)		Grade 4 (Potentially Life-Threatening)		Grade 5 (Death)
AST or ALT:	>ULN – 3.0× ULN	AST or ALT:	>3.0× – 5.0× ULN	AST or ALT:	>5.0× – 20.0× ULN	AST or ALT:	>20× ULN	
AST or ALT Abn. Baseline:	>1.5× – 3.0× ULN	Bilirubin:	>1.5× – 3.0× ULN	Bilirubin:	>3.0× – 10.0× ULN	Bilirubin:	>10× ULN	
Bilirubin:	>ULN – 1.5× ULN							

Management of Transaminitis (without elevated bilirubin)

Management of Grade 2 or worse transaminitis with bilirubin >1.5x 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 <u>are not</u> recommended due to potential hepatotoxic effects

Grade 1 (Mild)
- Immunotherapy may be withheld if LFTs are trending upward; recheck LFTs within ~ 1 week, but exclude liver mets with underlying tumour

Grade 2 (Moderate)
- Immunotherapy to be withheld; recheck LFTs daily x 3 days or every 3 days; to be resumed when complete/partial resolution of adverse reaction (Grade 0/1)
- Immunotherapy to be discontinued for Grade 2 events lasting ≥6 (ipilimumab) or ≥12 weeks (pembrolizumab, nivolumab), or for inability to reduce steroid* dosage to 7.5 mg prednisone or equivalent per day
- Consider starting steroids* 0.5 mg – 1 mg/kg/day prednisone or equivalent daily (IV methylprednisolone 125 mg total daily dosage)
- Consider hospital admission for IV steroids*
- If LFTs normalized and symptoms resolved, steroids* to be tapered over ≥4 weeks when function recovers
- Once patient returns to baseline or Grade 0-1, consider resuming treatment

Grade 3 (Severe)
- Steroids* to be initiated at 1-2 mg/kg/day prednisone or equivalent daily oral
- Nivolumab to be permanently discontinued for Grade 3 events. Ipilimumab to be discontinued for any Grade 3 event, or pembrolizumab for any recurrent Grade 3 event or Grade 3 event persisting ≥12 weeks
- Admission for IV steroids*
- R/O hepatitis infection (acute infection or reactivation)
- LFTs every 1-2 days
- If sustained elevation is significant and/or refractory to steroids* potential for ADDING to steroid* regimen immunosuppressive agent:
  - CellCept® (mycophenolate mofetil) 500 mg - 1000 mg po q 12 hours OR
  - Antithymocyte globulin infusion
- Hepatology/gastroenterology consult
- Consider liver biopsy
- If LFTs stable/declining daily for 5 consecutive days: decrease LFT checks to q 3 days, then weekly
- If LFTs normalized and symptoms resolved, steroids* to be tapered over ≥4 weeks

Grade 4 (Life-Threatening)
- Immunotherapy to be permanently discontinued
- Hospital admission
- Steroids* to be initiated at 2 mg/kg/day prednisone or equivalent daily intravenous
- R/O hepatitis infection
- Daily LFTs
- If sustained elevation and refractory to steroids* potential for ADDING to steroid regimen:
  - CellCept® (mycophenolate mofetil) 500 mg - 1000 mg po or IV q 12 hours OR
  - Antithymocyte globulin infusion
- Hepatology/gastroenterology consult
- Consider liver biopsy
- If LFTs stable/declining daily for 5 consecutive days: decrease LFT checks to q 3 days, then weekly
- If LFTs normalized and symptoms resolved, steroids* to be tapered slowly over ≥4 weeks

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:

<u>Steroid taper instructions/calendar as a guide but not an absolute</u>
- 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)

<u>Long-term high-dose steroids</u>:
- 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 hepatoxins
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

RED FLAGS:
- **Severe abdominal pain, ascites/peripheral oedema, 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