Care Step Pathway – Pneumonitis (inflammation of lung alveoli)

Assessment

Look:
- Does the patient appear uncomfortable?
- Did the patient have difficulty walking to the exam room? Or going up stairs?
- Does the patient appear short of breath?
- Is the patient tachypneic?
- Does the patient appear to be in respiratory distress?

Listen:
- Has the patient noted any change in breathing?
- Does the patient feel short of breath?
- Does the patient note new dyspnea on exertion?
- Does the patient notice a new cough? Or a change in an existing cough?
  - Is it a dry cough or a productive cough?
- Have symptoms worsened?
- Are symptoms limiting ADLs?
- Associated symptoms?
  - Fatigue
  - Wheezing

Recognize:
- Is the pulse oximetry low? Is it lower than baseline or compared with last visit? Is it low on ambulation?
- Is there a pre-existing pulmonary autoimmune condition (e.g., sarcoidosis)?
- Does patient have lung metastases?
- History of radiation to the lung?
- History of recent COVID-19 infection?
- Is there a history of prior respiratory compromise (e.g., asthma, COPD, congestive heart failure)?
- Has the patient experienced other immune-related adverse effects?

Grading Toxicity

Pneumonitis

Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma

Grade 1 (Mild)
Asymptomatic; confined to one lobe of lung; clinical or diagnostic observations only; intervention not indicated

Grade 2 (Moderate)
Symptomatic; involves more than one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only

Grade 3 (Severe)
Severe symptoms; hospitalization required; involves all lung lobes or >50% of lung parenchyma; limiting self-care ADLs; oxygen indicated

Grade 4 (Potentially Life-Threatening)
Life-threatening respiratory compromise; urgent intervention indicated (tracheostomy, intubation)

Grade 5 (Death)

Management

Overall Strategy:
- Assess for other etiologies such as infection (e.g., nasal swab for viral pathogens; sputum culture; blood and urine cultures and sensitivities), pulmonary embolism, progressive lung metastases, pleural effusion, or lung disease
- Early intervention to maintain or improve physical function and impact on QOL
- Assess pulse oximetry (resting and on exertion) at baseline and at each visit to assist in identifying a decrease at early onset
- Chest CT is preferred imaging modality for diagnosis of pneumonitis (with contrast if obtained to evaluate for other etiologies, such as pulmonary embolus)
- Assess patient and family understanding of recommendations and rationale
- Identify barriers to adherence, including adherence with medication, physical activity

Prevention
- Decrease or cease smoking; preventive vaccinations for flu, COVID-19, and pneumonia

Grade 1 (Mild)
- Consider holding ICI therapy or proceed with close monitoring
- Resume with radiographic evidence of improvement or resolution. If no improvement, treat as G2
- Anticipate weekly including pulse oximetry (both resting and with exertion). Chest CT if uncertain diagnosis and/or to follow progress. Repeat chest CT in 3-4 weeks, or sooner if patient becomes symptomatic. Review symptoms to watch for with patient and family, and remember to assess at every subsequent visit
- Identify barriers to adherence

Grade 2 (Moderate)
- Hold ICI therapy until clinical improvement to < Grade 1
- Monitor pulse oximetry (resting and with exertion) at least weekly
- Anticipate treatment with:
  - Corticosteroids* (e.g., prednisone 1–2 mg/kg/day or equivalent) until symptoms improve to baseline, and then taper over 4-6 weeks
  - If symptoms do not improve within 48-72 hours, treat as Grade 3
  - Additional supportive care medications may also be initiated
- Anticipate the use of empiric antibiotics until infection is excluded
- Consider pulmonary consult
- Anticipate bronchoscopy with BAL with or without transbronchial biopsy may be ordered on some patients

Grades 3/4 (Severe or Life-Threatening)
- Permanently discontinue ICI therapy
- Obtain pulmonary
- Patient will likely need to be admitted to the hospital for further management and supportive care
- Nasal swab for viral pathogens including COVID-19, sputum, etc
- Anticipate the use of empiric antibiotics until infection is excluded
- Anticipate the use of high-dose IV corticosteroids* (e.g., methylprednisolone 1–2 mg/kg/day or equivalent). Additional immunosuppressive may be necessary if no improvement in 48-72 hours (e.g., infliximab, mycophenolate, cyclophosphamide, IVIG)
- Bronchoscopy with BAL may be considered with or without transbronchial biopsy. Once symptoms have resolved to baseline or Grade 1, convert to equivalent oral corticosteroid dose and then taper slowly over at least 4-6 weeks
- Identify barriers to adherence, specifically compliance with medication, physical activity

*Administering Corticosteroids:
- Corticosteroid 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 and symptomatology
- Corticosteroids may cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on corticosteroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review corticosteroid 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 and report them (taper may need to be adjusted)

- Long-term high-dose corticosteroids:
- 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
- If extended corticosteroid use, risk for osteoporosis; initiate calcium and vitamin D supplements
- Patients with asthma or who smoke may have decreased sensitivity to corticosteroids

Implementation:
- Identify high-risk individuals (e.g., asthma, COPD, prior thoracic radiation therapy) and those with cardiopulmonary symptoms prior to initiating immunotherapy. Establish a thorough baseline, including pulse oximetry (resting and with ambulation)
- Educate patients that new or worsening/changing pulmonary symptoms should be reported immediately
- Anticipate that the steroid requirements to manage pneumonitis are high (1-2 mg/kg/day) and patient will be on corticosteroid therapy for at least 1 month
- Educate patients and family about the rationale for discontinuation of immunotherapy in patients who do develop moderate or severe pneumonitis
- For severe/life-threatening pneumonitis, treat patient as immunocompromised, so ID workup to include nasal swab (viral), sputum, blood, and urine cultures
- Patients with a history of asthma and/or smoking may be less responsive to corticosteroids, which can affect dosage requirements

RED FLAGS:
- **Risk of acute onset**
- **Risk of mortality if pneumonitis treatment is delayed**
- **Risk of pneumonitis is greater in patients receiving combination immunotherapy regimens**

ADLs = activities of daily living; COPD = chronic obstructive pulmonary disease; ICI = immune checkpoint inhibitor; IVIG = intravenous immunoglobulin; po = by mouth

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