Care Step Pathway – Inflammatory Arthritis (formerly Arthralgia/Arthritis)

Assessment

Look:
- Does the patient appear uncomfortable?
- Does the patient appear unwell?
- Does the patient have a skin rash?
- Is gait affected?
- Are there obvious swollen or deformed joint(s)?
- Does the patient have redness or warmth at the joint (r/o septic joint)?
- Is the patient having trouble getting up and down stairs?

Listen:
- Have symptoms worsened?
- Are symptoms limiting ADLs?
- Are symptoms increasing the patient's risk for fall? Other safety issues?
- Associated symptoms?
  - o Fatigue (new or worsening)

Recognize:
- Is there a pre-existing autoimmune dysfunction?
- Is there a history of prior orthopedic injury, DJD, OA, RA?
- Other immune-related adverse effects
- Family history of autoimmune disease?
- Various clinical presentations with different patterns of joint involvement
  1. Small joint polyarthritis similar to RA
  2. Larger joint, oligoarthritis with or without inflammatory back pain: including a pattern similar to reactive arthritis with conjunctivitis and sterile urethritis
  3. New-onset psoriatic arthritis

Grading Toxicity

Arthralgia

Definition: A disorder characterized by a sensation of marked discomfort in a joint

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL		

Arthritis

Definition: A disorder characterized by inflammation involving a joint

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
Mild pain with inflammation, erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL		

Management

Overall Strategy:
- Assess for other etiologies, such as lytic or osseous metastasis
- Symptom control through the treatment of inflammation and pain is often achieved with NSAIDs, corticosteroids, and other adjunct therapies. NSAIDs should not be used concurrently with corticosteroids because of the risk of GI side effects
- Early intervention to maintain or improve physical function and impact on QOL. ICI arthritis symptoms generally persist. Even if symptoms are not severe, early referral to rheumatology for consideration of adjunct medications such as DMARDs is advised in order to spare patients long-term treatment with corticosteroids

Grade 1 (Mild)
- Continue ICI therapy
- Symptom directed therapies
- Analgesia provided
  - o Topical NSAID: diclofenac (gel or patch). Best for localized, limited, superficial joint inflammation
  - o Oral NSAIDs: ibuprofen (600-800 mg 3 times daily), naproxen 375-500 mg twice daily),
    - § For patients with 1-3 joints involved, consider intraarticular steroid injection(s); may reduce need for additional treatment
    - § Prednisone 5-10 mg daily (or equivalent) for those who cannot tolerate oral NSAIDs or have relative contraindications to NSAID use.
    - § Taper upon symptom improvement
      - Ø Anticipatory guidance on proper administration
    - § If unable to taper steroids with 3-4 weeks, consider rheumatology for consideration of initiating a mild DMARD (HCQ or SSZ)
- Assess patient and family understanding of recommendations and rationale
  - o Identify barriers to adherence

Grade 2 (Moderate)
- Consider holding ICI therapy
- Consider joint imaging to evaluate for early erosions (will also rule out metastasis) Anticipate referral to rheumatology for collaborative management and consideration of adjunct treatment
- Analgesia provided
  - o Topical NSAID: diclofenac (gel or patch). Best for localized, limited, superficial joint inflammation
  - o Oral NSAIDs ibuprofen (e.g., 600-800 mg 3 times daily), naproxen (375-500 mg twice daily)
  - o Intraarticular steroids injection(s)
  - o For those who do not improve with NSAIDs and/or intraarticular steroid injections or for those who do not tolerate oral NSAIDs or have relative contraindications to NSAID use, prednisone 10-30 mg daily (or equivalent)
    - § Anticipatory guidance on proper administration
  - o If unable to taper steroids to 10 mg within 2-3 weeks, anticipate starting DMARDs
    - § Conventional synthetic DMARDs (csDMARDs), which have a delayed effect and take weeks to work. They can be continued as maintenance therapy to acquire and maintain symptoms control
      - Ø Methotrexate
      - Ø Sulfasalazine†
      - Ø Hydroxychloroquine
      - Ø Leflunomide
      - Ø Tofacitinib
- Assess patient and family understanding of toxicity, rationale for treatment hold (if applicable)
  - o Identify barriers to adherence

†Sulfasalazine is associated with rash; do not use in patients with history of or current treatment-related dermatitis

Grades 3/4 (Severe or Life-Threatening)
- Hold ICI therapy
- Anticipate rheumatology referral for collaborative management and consideration of adjunct treatment
- High-dose steroids to be used (1 mg/kg) daily (rapid effect within days)
  - o Anticipatory guidance on proper administration
- If symptoms are not easily controlled within 1-2 weeks, anticipate starting biologic DMARDs (bDMARDs), due to the rapid onset of action
  - o TNF inhibitors (TNFi)
    - § Infliximab
    - § Etanercept
    - § Adalimumab
    - § Golimumab
    - § Certolizumab pegol
- If refractory to TNFi, or contraindication to use, consider starting interleukin (IL)-6 inhibitor, tocilizumab, or sarilumab
  - o Agents NOT advised
    - § JAK inhibitors (tofacitinib) due to risk of colonic perforation
    - § T-cell co-stimulation inhibitor (abatacept) as it directly opposes the mechanism of checkpoint blockade agents
  - o Anticipatory guidance on proper administration
  - o Assess patient & family understanding of toxicity and rationale for treatment hold and or discontinuation
  - o 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 and those with underlying autoimmune dysfunction
- Educate patients that arthralgias and arthritis are the most commonly reported rheumatic and musculoskeletal irAEs with checkpoint inhibitors
- Arthritis-like symptoms can range from mild (managed well with NSAIDs and low-dose corticosteroids) to severe and erosive (requiring multiple immunosuppressant medications)
- Anticipate that the steroid requirements to manage arthralgias can be much higher (i.e., up to 1.5 mg/kg/day) than typically required to manage "classic" inflammatory arthritis
- Educate patients that symptoms can persist beyond treatment completion or discontinuation
- Ensure screening labs for hepatitis and TB testing have been performed in case biologic treatment is required

RED FLAGS:
- **Risk of fall due to mobility issue**

ADLs = activities of daily living; ANA = antinuclear antibody; BUN = blood urea nitrogen; CBC = complete blood count; CR = creatinine; CRP = C-reactive protein; DJD = degenerative joint disease; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; HCQ = hydroxychloroquine; ICI = immune checkpoint inhibitor; irAE = immune-related adverse event; JAK = Janus kinase; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; po = by mouth; QOL = quality of life; RA = rheumatoid arthritis; RF = rheumatoid factor; SSZ = sulfasalazine; TB = tuberculosis; TNF = tumor necrosis factor