Care Step Pathway - Arthralgias and Arthritis

Assessment

Look:
- Does the patient appear uncomfortable?
- Does the patient appear unwell?
- Is gait affected?
- Obvious swollen or deformed joint(s)?
- 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?
  - Fatigue (new or worsening)

Recognise:
- Is there a pre-existing autoimmune dysfunction?
- Is there a history of prior orthopedic injury, DJD, OA, RA?
- Other immune-related adverse effects
- Three subtypes of inflammatory arthritis associated with checkpoint inhibitors:
  1. Polyarthritis similar to RA
  2. True reactive arthritis with conjunctivitis, urethritis, and oligoarthritis
  3. Subtype similar to seronegative spondyloarthritis with inflammatory back pain and predominantly larger joint involvement

Grading Toxicity

Arthralgia

Definition: A disorder characterised 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 characterised 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
- Early intervention to maintain or improve physical function and impact on QOL; symptom control through the treatment of inflammation and pain is often achieved with NSAIDs, corticosteroids, and other adjunct therapies

Grade 1 (Mild)
- Anticipate immunotherapy to continue
- Encourage physical activity
  - 30 minutes of low-to-moderate–intensity physical activity 5 days per week can improve physical conditioning, sleep, and decreases pain perception
  - For physically inactive patients, advise supervised exercise, resistance training
  - Other: yoga, tai chi, Qigong, Pilates, aquatic exercise, focused dance program
- Anticipate use of analgesia
  - Low-dose NSAIDs
    - Topical: diclofenac (gel or patch). Best for localized, limited, superficial joint inflammation or for use in patients who cannot tolerate oral NSAIDs
    - Oral: ibuprofen, naproxen, celecoxib
      - ➢ Anticipatory guidance on proper administration
- Assess patient & family understanding of recommendations and rationale
  - Identify barriers to adherence

If symptoms do not improve in 4–6 weeks, escalate to next level of therapy

Grade 2 (Moderate)
- Ipilimumab to be withheld for any Grade 2 event (until Grade 0/1) and discontinued for events persisting ≥6 weeks or inability to reduce steroid dosage to 7.5 mg prednisone or equivalent per day
- Dose of pembrolizumab or nivolumab to be held as to not make symptoms worse
- Pembrolizumab or nivolumab to be discontinued for Grade 2 events persisting ≥12 weeks
- Continue to encourage physical activity
- Anticipate use of analgesia
  - NSAIDs
    - Oral: ibuprofen, naproxen, celecoxib
      - ➢ Anticipatory guidance on proper administration
- Anticipate referral to rheumatology for collaborative management and consideration of adjunct treatment
- Follow-up monitoring after diagnosis of arthritis/arthralgias (q 4–6 weeks after treatment initiation): CBC, ESR, CRP, BUN/Cr & aminotransferases, ANA, RF
- Intraarticular steroids to be used for significant symptomatic joint(s)
- Low-dose corticosteroids* (0.5 mg/kg/day) to be used
  - Anticipatory guidance on proper administration
  - Duration of corticosteroid* therapy is usually limited, lasting for about 4–6 weeks, with possible resolution of symptoms within weeks to months of treatment
- Assess patient & family understanding of toxicity, rationale for treatment hold (if applicable)
  - Identify barriers to adherence

If symptoms do not improve in 4–6 weeks, escalate to next level of therapy

Grades 3/4 (Severe or Life-Threatening)
- Pembrolizumab or nivolumab to be withheld for first-occurrence Grade 3/4 event and permanently discontinued if:
  - Grade 3/4 event recurs
  - Persists ≥12 weeks
- Ipilimumab to be permanently discontinued for any Grade 3/4 event
- High-dose steroids to be used (1 mg/kg) daily (rapid effect within days)
  - Anticipatory guidance on proper administration
  - Onset of action is rapid, typically within days
- If no improvement with corticosteroids in 2 weeks, consider infliximab or tocalizumab
- Anticipate referral to rheumatology for collaborative management and adjunct treatment
  - Nonbiologic agents (more likely to be recommended)
    - Conventional synthetic DMARDs (csDMARDs), which have a delayed effect and take weeks to work:
      - ➢ Methotrexate
      - ➢ Sulfasalazine†
      - ➢ Hydroxychloroquine
      - ➢ Leflunomide
  - Biologic agents (less likely to be recommended)
    - Biologic DMARDs (bDMARDs)
    - TNF inhibitors
      - ➢ Infliximab
      - ➢ Etanercept
      - ➢ Adalimumab
      - ➢ Golimumab
      - ➢ Certolizumab pegol
    - Anti B-cell agents (CD-20 blocking)
      - ➢ Rituximab
  - 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
  - Assess patient & family understanding of toxicity and rationale for treatment discontinuation
  - Identify barriers to adherence, specifically compliance with medication, physical activity

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

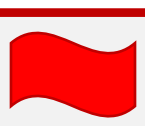
*Administering Corticosteroids:

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
- 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

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

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; 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; TNF = tumor necrosis factor