Care Step Pathway - Skin Toxicities (rash or inflammatory dermatoses [including pruritus], dermatoses, and severe cutaneous adverse reactions [SCAR])

Assessment

Look:
- Does the patient appear uncomfortable?
- Does the patient appear unwell?
- Is there an obvious rash?
- Is the patient scratching during the visit?
- Is skin integrity intact?
- Are there skin changes?
  - o Xerosis (dry skin)
  - o Changes in skin pigment or color
- Is there mucosal (nasal, oral, genital) involvement of the rash?
- Is the rash painful?
- Is there upper extremity edema, pustules, blisters, or erosions?

Listen:
- Does the patient have pruritus with or without rash?
- Is there a rash with or without pruritus?
- Are symptoms interfering with ADLs?
- With sleep?
- Have symptoms worsened?
- Are there systemic symptoms: fevers, malaise, muscle, or joint pain?

Recognize:
- Is there a history of dermatitis, pre-existing skin issues (psoriasis, eczema, wounds, prior radiation to region, etc.)?
- Are there laboratory abnormalities consistent with other etiologies (e.g., eosinophils on complete blood count, liver function abnormalities)?

Grading Toxicity

Rash or Inflammatory Dermatitis (including pruritus alone)

Grade 1 (Mild)
Involvement of <10% BSA with or without symptoms (e.g., pruritus, burning, tightness) OR pruritis alone that is mild or localized

Grade 2 (Moderate)
Involvement of 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); having psychological effect and limiting instrumental ADLs; involvement of >30% BSA with or without mild symptoms OR pruritus that is widespread and intermittent leading to skin changes from scratching (e.g. edema, lichenification, oozing, etc.) limiting instrumental ADLs

Grade 3 (Severe)
Involvement of >30% BSA with or without associated symptoms; limiting self-care ADLs; skin sloughing covering <10% BSA OR pruritus that is widespread and constant; limiting self-care ADLS or sleep

Grade 4 (Potentially Life-Threatening)
Severe consequences requiring hospitalization or urgent intervention (life-threatening consequences)

Bullous Dermatoses

Grade 1 (Mild)
Asymptomatic, or blisters covering <10% BSA with no erythema

Grade 2 (Moderate)
Blisters covering 10-30% BSA, symptoms limiting instrumental ADLs

Grade 3 (Severe)
Skin sloughing covering >30% BSA; pain limiting self-care ADLs;

Grade 4 (Potentially Life-Threatening)
Blisters covering >30% BSA with associated fluid or electrolyte abnormalities

Severe Cutaneous Adverse Events (SCAR)*

For all cases, refer urgently to dermatology and discontinue immune checkpoint inhibitor therapy. Monitor closely.

Grade 1 and 2 (Mild or Moderate)
Not applicable. Have a high suspicion for rapid evolvement in any patients with skin sloughing

Grade 3 (Severe)
Skin sloughing <10 BSA with mucosal involvement-associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)

Grade 4 (Potentially Life-Threatening)
Skin erythema and blistering or sloughing covering >=10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment) and/or systemic symptoms and concerning blood work abnormalities (e,g., LFT elevation in the setting of DRESS)

Management

Overall Strategy
- Assess for other etiology of rash: ask patient about new medications, herbals, supplements, alternative/complementary therapies, lotions, etc.
- Consider photographing involved areas (with patient permission)
- Assess patient and family understanding of prevention or management strategies and rationale
- Identify barriers to adherence, particularly related to step-down in corticosteroids

Intervention in At-Risk Patients
- Advise gentle skin care:
  - o Avoid soap. Instead, use non-soap cleansers that are fragrance- and dye-free (use mild soap on the axillae, genitalia, and feet)
  - o Daily applications of non-steroidal moisturizers or emollients containing humectants (urea, glycerin)
  - o Apply moisturizers and emollients in the direction of hair growth to minimize development of folliculitis
- Advise sun-protective measures
- Assess patient & family understanding of prevention strategies and rationale
  - o Identify barriers to adherence

Grade 1 (Mild except SCAR)
- ICI therapy to continue
- Mild-to-moderate potency topical corticosteroid may be used in some patients
- For blisters that are asymptomatic and not deroofed, observe or provide local wound care
- Advise vigilant skincare
  - o Increase to twice daily applications of non-steroidal moisturizers or emollients applied to moist skin
  - o Moisturizers with ceramides and lipids are advised; however, if cost is an issue, petroleum jelly is also effective
  - o Soothing methods
    - § Cool cloth applications
    - § Topicals with refrigerated cooling agents such as menthol or camphor, pramoxine (for pruritus)
  - o Avoid hot water; bathe or shower with tepid water
  - o Keep fingernails short
  - o Cool temperature for sleep
- Advise strict sun protection
- Monitor vigilantly. Instruct patient and family to call clinic with any sign of worsening rash/symptoms. Anticipate office visit for evaluation

Grade 2 (Moderate except SCAR)
- Consider holding ICI therapy and monitor weekly for improvement, resume after symptoms have improved to Grade 1 (skin condition is mild/localized with only topical intervention indicated) If not improved after 4 weeks, toxicity is considered Grade 3
- Medium-to-high-potency topical corticosteroids may be used; if unresponsive to topical, consider prednisone (or equivalent) (0.5 - 1.0 mg/kg) and taper over 4 weeks
- For pruritus without rash, oral antihistamines, refrigerated topical antipruritics (e.g., menthol and pramoxine) can be used or GABA agonists (e.g., gabapentin, pregabalin) may be considered
- Consider dermatology consult for possible biopsy
- Advise vigilant skin care
  - o Gentle skin care
  - o Tepid baths; oatmeal baths
- Advise strict sun protection

Grades 3 (Severe)
- Hold ICI
- Dermatology consult advised: consideration of biopsy, determine appropriateness of rechallenge when improved to Grade 1 AND prednisone (or equivalent) is below 10 mg/day, and co-manage when appropriate
- High potency topical corticosteroids
- Prednisone (or equivalent) 1 mg/kg tapering over at least 4 weeks
- For pruritus without rash, oral antihistamines, gabapentin, pregabalin, aprepitant, or dupilumab, may be considered
- In certain instances, phototherapy may be considered (under management of dermatology provider)
- Provide anticipatory guidance:
  - o Rationale for hospitalization and treatment discontinuation
  - o Rationale for prolonged steroid taper
  - o Side effects of high-dose and or long-term use of corticosteroid
  - o Risk of opportunistic infection and need for antibiotic prophylaxis
  - o Effects on blood sugars, muscle atrophy, etc.
  - o For SCAR, appropriate multidisciplinary care to prevent sequelae from scarring

Grades 4 (Potentially Life-Threatening)
- Immediately hold ICI. Anticipate permanent discontinuation of ICI therapy.
- Patient to be admitted to the hospital immediately with urgent dermatology consult
- IV methylprednisolone (or equivalent) at 1-2 mg/kg and convert to oral steroids when appropriate. Anticipate slow taper over at least 4 weeks
- Provide anticipatory guidance:
  - o Rationale for hospitalization and treatment discontinuation
  - o For SCAR, multidisciplinary care to prevent sequelae from scarring

*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

RED FLAGS:
- **Extensive (>50% BSA) or rapidly progressive rash**
- **Any mucous membrane involvement**
- **Concern for suprainfection**
- **Fever accompanied by rash, skin pain, skin sloughing, facial or upper extremity edema, pustules, blisters, or erosions**

*Severe cutaneous adverse reactions (SCAR) include SJS, DRESS syndrome, and TEN.

ADLs = activities of daily living; BSA = body surface area; po = by mouth; ICI = immune checkpoint inhibitor; SCAR = severe cutaneous adverse events, also known as exfoliant dermatitis; SJS = Stevens-Johnson syndrome; DRESS syndrome = drug reaction with eosinophilia and systemic symptoms; TEN = toxic epidermal necrolysis