MACULOPAPULAR RASH (aka morbilliform rash)

Definition: A disorder characterized by the presence of macules (flat) and papules (elevated), frequently affecting the upper trunk, spreading towards the center and associated with pruritus

Grade 1 (Mild)
Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)

Grade 2 (Moderate)
Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness), having psychological effect and limiting instrumental ADLs (rash covering >30% BSA with or without mild symptoms)

Grade 3 (Severe)
Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADLs; skin sloughing covering <10% BSA

Grade 4 (Potentially Life-Threatening)
Papules/pustules covering any % BSA with or without symptoms and associated with superinfection requiring IV antibiotics; skin sloughing covering 30-50% BSA

Grade 5 (Death)

PRURITUS
Definition: A disorder characterized by an intense itching sensation

Grade 1 (Mild or localized; topical intervention indicated)

Grade 2 (Moderate)
Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriation, lichenification [blisters, leathery skin], oozing/ranus); limiting instrumental ADLs; oral intervention indicated

Grade 3 (Severe)
Widespread and constant; limited self-care ADLs or sleep; systemic corticosteroid or immunosuppressive therapy indicated

Grade 4 (Potentially Life-Threatening)

Overall Strategy
Assess for other etiology of rash: ask patient about new medications, herbs, supplements, alternative/complementary therapies, lotions, etc.

Management

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 skin changes?
- Xerosis (dry skin)
- Changes in skin pigment or color
- Is there oral involvement of the rash?
- Does the rash involve the genital-vaginal region?
- The scalp?

Listen:
- Does the patient have pruritus with or without rash?
- Is there a rash with or without pruritus?
- When did it start?
- Are symptoms interfering with ADLs?
- With sleep?
- Have symptoms worsened?

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

Grading Toxicity

Advising sun-protective measures
Advise gentle skin care:
Assess patient & family understanding of skin care recommendations and rationale
Identify barriers to adherence

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

Grade 1 (Mild)
Immunotherapy to continue
- Oral antihistamines will be used in some patients
- Moderate potency topical corticosteroids may be used in some patients (e.g., momethasone 0.1% to be applied TID)
- Advise vigilant skin care
  - Increase to twice daily applications of non-steroidal moisturizers or emollients applied to moist skin
  - Moisturizers with ceramides and lipids are advised. However, if cost is an issue, petroleum jelly is also effective
- Soothing methods
  - Cool cloth applications
  - Topicals with cooling agents such as menthol or camphor
- Refrigerating products prior to application
  - Avoid hot water; bath or shower with tepid water
  - Keep fingernail short
  - Cold temperature for sleep
  - Advise strict sun protection. SPF of at least 25 is recommended
- Monitor vigilantly. Instruct patient & family to call clinic with any sign of worsening rashes/symptoms. Attend office visit for evaluation
- Assess patient & family understanding of skin care recommendations and rationale
  - Identify barriers to adherence

Grade 2 (Moderate)
Consider holding pembrolizumab or nivolumab and monitor for improvement weekly. If no improvement, begin treatment with prednisone 1 mg/kg tapering over at least 4 weeks
- If prednisone is used, high potency topical corticosteroids can be considered for rash atoners
- Consider GABA agonist as needed
- Consider dermatology consult
- Patient education:
  - Proper administration of oral corticosteroids
  - Take with food
  - Take early in day
  - Concomitant medications may be prescribed
    - H2 blocker
    - Antibiotic prophylaxis
  - Advise vigilant skin care
    - Gentle skin care
    - Topical steroids for skin
    - If antihistamines not tolerated, try skin
  - Advise strict sun protection
  - Assess patient & family understanding of toxicity and rationale for treatment hold
  - Identify barriers to adherence

Grade 3 (Severe or Potentially Life-Threatening)
Nivolumab or pembrolizumab to be withheld for any Grade 3 event
- High-potency topical corticosteroids to be used; anticipate hospitalization and initiation of IV corticosteroids (0.1-1 mg/kg/day)
- Urgent dermatology consult +/- biopsy
- Concomitant medications may be prescribed
  - Orale: Rationale for hospitalization and treatment discontinuation
  - Rationale for prolonged steroid taper
  - Side effects of high-dose steroids
  - Risk of opportunistic infection and need for antibiotic prophylaxis
  - Effects on blood sugars, muscle atrophy, etc.
  - For Grade 3 pruritus
  - Nivolumab or pembrolizumab dose 0.5-1 mg/kg/day
  - Consider GABA agonist, aprepitant, or oralizumab
- Assess patient & family understanding of toxicity and rationale for treatment discontinuation
  - Identify barriers to adherence, specifically adherence with steroids when transitioned to oral corticosteroids

Grade 4 (Severe or Life-Threatening)
- Nivolumab or pembrolizumab to be withheld for any Grade 3 (severe) and discontinued for Grade 4 (life-threatening) skin conditions or confirmed SJS or TEN; pembrolizumab to be permanently discontinued for any Grade 3/4 event
  - High-potency topical corticosteroids to be used; anticipate hospitalization and initiation of IV corticosteroids (0.1-1 mg/kg/day)
  - Urgent dermatology consult +/- biopsy
  - Concomitant medications may be prescribed
  - Orale: Rationale for hospitalization and treatment discontinuation
  - Rationale for prolonged steroid taper
  - Rationale for pruritus
  - Side effects of high-dose steroids
  - Risk of opportunistic infection and need for antibiotic prophylaxis
  - Effects on blood sugars, muscle atrophy, etc.
  - For Grade 3 pruritus
    - Nivolumab or pembrolizumab dose 0.5-1 mg/kg/day
    - Consider GABA agonist, aprepitant, or oralizumab
- Assess patient & family understanding of toxicity and rationale for treatment discontinuation
  - Identify barriers to adherence, specifically adherence with steroids when transitioned to oral corticosteroids

Grade 5 (Death)

*Managing Corticosteroids:
Steroid taper: recommendation/protocol as a guide but not an absolute
- Taper steroid based on 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, hyperactive, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and report them (paper may need to be adjusted)

Long-term high-dose steroids:
- Consider anticholinergic prophylaxis (cimetidine/ranitidine/tacrine/ pepcid®) single dose if used daily or alternative if sulfa-allergic (e.g., atropine/ Mepron®) 1500 mg po daily
- Consider additional antihistaminic and antipruritic coverage
- Avoid alcohol/acetaminophen or other hepatotoxins
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

RED FLAGS:
- Extensive rash (>50% BSA), or rapidly progressive
- Anal, genitourinary, vaginal, or any mucous membrane involvement
- Concern for suprainfection

ADLs = activities of daily living; BSA = body surface area; po = by mouth; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis

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