**DIAGNOSIS WORKUP**

**ESSENTIAL:**
- Biopsy of suspicious skin sites
- Dermatopathology review of slides

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- IHC panel of skin biopsy
  - CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25, CD56, TIA1, granzyme B, βF1, TCR-CyM1
- Molecular analysis of skin biopsy: TCR gene rearrangements (assessment of clonality) by PCR methods
- Assessment of peripheral blood for Sezary cells (in cases where skin is not diagnostic, especially T4) including:
  - Sezary cell prep
  - Flow cytometry (CD3, CD4, CD7, CD8, CD26 to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype, including loss of CD7 or CD26) and PCR for TCR gene rearrangement
- Biopsy of suspicious lymph nodes (in absence of definitive skin diagnosis)
- Assessment of HTLV-1 serology in at-risk populations. HTLV-1 PCR if serology is indeterminate

**USEFUL IN SELECTED CASES:**
- Bone marrow biopsy (not required for staging but used to document visceral disease in those suspected to have marrow involvement including B2 blood involvement and in patients with unexplained hematologic abnormality)
- Biopsy of suspicious lymph nodes for identical clones (recommend assessment of clonality for all but particularly NCI LN 2-3) or suspected extracutaneous sites
- Rebiopsy if suspicious of large cell transformation
- Neck CT

**STAGE (MFSS-2 and MFSS-3)**

- **Stage IA** → See Primary Treatment (MFSS-4)
- **Stage IB-IIA** → See Primary Treatment (MFSS-5)
- **Stage IIB** → See Primary Treatment (MFSS-6)
- **Stage III** → See Primary Treatment (MFSS-7)
- **Stage IV** → See Primary Treatment (MFSS-8)

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# Mycosis Fungoides/Sezary Syndrome

## TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome

<table>
<thead>
<tr>
<th>TNMB</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td><strong>T1</strong> Limited patches, papules, and/or plaques covering &lt;10% of the skin surface</td>
</tr>
<tr>
<td></td>
<td><strong>T2</strong> Patches, papules, and/or plaques covering ≥10% of the skin surface</td>
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<tr>
<td></td>
<td><strong>T3</strong> One or more tumors (≥1 cm in diameter)</td>
</tr>
<tr>
<td></td>
<td><strong>T4</strong> Confluence of erythema ≥80% body surface area</td>
</tr>
<tr>
<td>Node</td>
<td><strong>N0</strong> No abnormal lymph nodes; biopsy not required</td>
</tr>
<tr>
<td></td>
<td><strong>N1</strong> Abnormal lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2</td>
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<tr>
<td></td>
<td><strong>N2</strong> Abnormal lymph nodes; histopathology Dutch Gr 2 or NCI LN 3</td>
</tr>
<tr>
<td></td>
<td><strong>N3</strong> Abnormal lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4</td>
</tr>
<tr>
<td></td>
<td><strong>NX</strong> Abnormal lymph nodes; no histologic confirmation</td>
</tr>
<tr>
<td>Visceral</td>
<td><strong>M0</strong> No visceral organ involvement</td>
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<tr>
<td></td>
<td><strong>M1</strong> Visceral involvement (must have pathology confirmation and organ involved should be specified)</td>
</tr>
<tr>
<td></td>
<td><strong>MX</strong> Abnormal visceral site; no histologic confirmation</td>
</tr>
<tr>
<td>Blood</td>
<td><strong>B0</strong> Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sezary) cells</td>
</tr>
<tr>
<td></td>
<td><strong>B1</strong> Low blood tumor burden: &gt;5% of peripheral blood lymphocytes are atypical (Sezary) cells but do not meet the criteria of B2</td>
</tr>
<tr>
<td></td>
<td><strong>B2</strong> High blood tumor burden: ≥1000/mcL Sezary cells or CD4/CD8 ≥10 or ≥40% CD4+/CD7- or ≥30% CD4+/CD26- cells</td>
</tr>
</tbody>
</table>

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Sezary syndrome (B2) is defined as a clonal rearrangement of the TCR in the blood (clones should be relevant to clone in the skin) and either ≥1000/mcL or increased CD4 or CD3 cells with CD4/CD8 of ≥10 or increase in CD4 cells with an abnormal phenotype (≥40% CD4+/CD7- or ≥30% CD4+/CD26- of the total lymphocyte count).

Patch = Any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.

Plaque = Any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting and/or poikiloderma should be noted. Histologic features such as folliculotropism or large cell transformation (≥25% large cells), CD30+ or CD30-, and clinical features such as ulceration are important to document.

Tumor = at least one >1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of large cell transformation has occurred. Phenotyping for CD30 is encouraged.
Clinical Staging of MF and SS<sup>h</sup>

<table>
<thead>
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<th>T</th>
<th>N</th>
<th>M</th>
<th>B</th>
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<td>0</td>
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<td>1</td>
<td>0-2</td>
</tr>
</tbody>
</table>


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Stage IA

Skin-directed therapies (may be alone or in combination with other skin-directed therapies): See Suggested Treatment Regimens "Skin-Directed Therapies (Skin-Limited/Local)" (MFSS-A)

If B1 blood involvement, consider primary treatment for Stage III, B1 MFSS-7 (category 2B)

If histologic evidence of folliculotropic or large-cell transformed MF

CR/PR\(^o\) or inadequate response

Relapse with or persistent T1 skin disease

Refactory disease\(^p\) or progression to > stage IA on skin-directed therapies

Systemic therapy ± skin-directed therapy (see Stage IB on page MFSS-5) or

Total skin electron beam therapy (TSEBT) or

Clinical trial

Consider primary treatment for Stage IIB (See MFSS-6)

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### Stage IB-IIA

**Generalized skin treatment**
- See Suggested Treatment Regimens "Skin-Directed Therapies (Skin-Generalized)" (MFSS-A) ± adjuvant local skin treatment (see stage IA on MFSS-4)
- If blood B1 involvement, consider primary treatment for Stage III B1 (MFSS-7) (category 2B)
- If histologic evidence of folliculotropic or large-cell transformed MF

**Consider primary treatment for Stage IIB (See MFSS-6)**

**Relapse with or persistent T1-T2 disease:**
- T1 (see stage IA on MFSS-4)
- T2 (see generalized skin treatment (MFSS-A))

**CR/PR° or inadequate response**

**Refractory disease° or progression to > stage IB-IIA**

**See Suggested Treatment Regimens**
- Clinical trial
- Systemic Therapies (SYST-CAT A) (MFSS-A)
- Combination Therapies ± skin-directed therapy

**CR/PR° or inadequate response**

**Refractory disease° or progression**

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°It is preferred that treatment occur at centers with expertise in the management of the disease.

°°Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607).

°°°Patients achieving a response and/or a clinical benefit should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

°°°°Refractory or intolerant to multiple previous therapies.

°°°°°For patients with recalcitrant sites after generalized skin treatment, additional local treatment may be needed.
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The role of allogeneic HSCT is controversial. See Discussion for further details.

Generalized skin-directed therapies (other than topical steroids) may not be well-tolerated in stage III and should be used with caution. Phototherapy (PUVA or UVB) or TSEBT can be used successfully. Mid-potency topical steroids should be included (± occlusive modality) with any of the primary treatment modalities to reduce skin symptoms. Erythrodermic patients are at increased risk for secondary infection with skin pathogens and systemic antibiotic therapy should be considered.

Combination therapy options can be considered earlier (primary treatment) depending on treatment availability or symptom severity.

Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.

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STAGE
(MFSS-2 and MFSS-3)

Sezary syndrome
Stage IV
Non Sezary or Visceral disease (solid organ)

PRIMARY TREATMENT

CR/PR or inadequate response

M

See Suggested Treatment Regimens
- Systemic Therapies (SYST-CAT A) (MFSS-A)
- Combination Therapies

Relapse or persistent disease
- Consider allogeneic transplant, as appropriate

RESPONSE TO THERAPY

CR/PR or inadequate response

See Suggested Treatment Regimens - Systemic Therapies (SYST-CAT B) (MFSS-A)

Refactory disease or progression
- Alemtuzumab
- Clinical trial

See Suggested Treatment Regimens - Systemic Therapies (SYST-CAT C) (MFSS-A)

Refactory disease or progression
- Multi-agent chemotherapy ± RT for local control

CR/PR or inadequate response

See Supportive Care for MF/SS (MFSS-B)

Relapse or persistent disease
- Consider allogeneic transplant, as appropriate

See monoclonal antibody and viral reactivation (NHODG-B)

Clinical trial

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Refractory or intolerant to multiple previous therapies.
The role of allogeneic HSCT is controversial. See Discussion for further details.

Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.

Patients with stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. If there is no evidence of more aggressive growth, systemic therapies from SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

Consider adjuvant systemic biologic therapy (SYST-CAT A) after chemotherapy to improve response duration.
**SKIN-DIRECTED THERAPIES**

*For limited/localized skin involvement (Skin-Limited/Local)*
- Topical corticosteroids
- Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine)
- Local radiation (8-36 Gy)
- Topical retinoids (bexarotene, tazarotene)
- Phototherapy (UVB, nbUVB for patch/thin plaques; PUVA for thicker plaques)
- Topical imiquimod

*For generalized skin involvement (Skin-Generalized)*
- Topical corticosteroids
- Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine)
- Phototherapy (UVB, nbUVB, for patch/thin plaques; PUVA for thicker plaques)
- Total skin electron beam therapy (TSEBT) (12-36 Gy) (reserved for those with severe skin symptoms or generalized thick plaque or tumor disease, or poor response to other therapies)

**SYSTEMIC THERAPIES**

**Category A (SYST-CAT A)**
- Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin)
- Interferons (IFN-alpha, IFN-gamma)
- HDAC-inhibitors (vorinostat, romidepsin)
- Extracorporeal photopheresis
- Methotrexate (<100 mg q week)

**Category B (SYST-CAT B)**
- First-line therapies
  - Liposomal doxorubicin
  - Gemcitabine
- Second-line therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (>100 mg q week)
  - Low-dose pralatrexate

**SYSTEMIC THERAPIES (continued)**

**Category C (SYST-CAT C)**
- Liposomal doxorubicin
- Gemcitabine
- Romidepsin
- Low- or standard-dose pralatrexate
- See regimens listed on TCEL-B

**COMBINATION THERAPIES**

**Skin-directed + Systemic**
- Phototherapy + retinoid
- Phototherapy + IFN
- Phototherapy + photopheresis
- Total skin electron beam + photopheresis

**Systemic + Systemic**
- Retinoid + IFN
- Photopheresis + retinoid
- Photopheresis + IFN
- Photopheresis + retinoid + IFN

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**Safety of combining TSEBT with systemic retinoids or HDAC inhibitors, such as vorinostat or romidepsin, or combining phototherapy with vorinostat or romidepsin is unknown.**

**Photopheresis may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).**

**Patients with large cell transformed (LCT) MF and stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. In general, agents listed in SYST-CAT C are preferred in these circumstances.**

**Combination regimens are generally reserved for patients with relapsed/refractory or extracutaneous disease.**

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*aSee references for regimens MFSS-A 2 of 4, MFSS-A 3 of 4, and MFSS-A 4 of 4.

*bLong-term use of topical steroid may be associated with skin atrophy and/or striae formation. This risk worsens with increased potency of the steroid. High-potency steroid used on large skin surfaces may lead to systemic absorption.

*cCumulative dose of UV is associated with increased risk of UV-associated skin neoplasms; thus, phototherapy may not be appropriate in patients with a history of extensive squamoproliferative skin neoplasms or basal cell carcinomas or who have had melanoma.

*dIt is common practice to follow TSEBT with systemic therapies such as interferon or bexarotene to maintain response.

*eSafety of combining TSEBT with systemic retinoids or HDAC inhibitors, such as vorinostat or romidepsin, or combining phototherapy with vorinostat or romidepsin is unknown.

*fPhotopheresis may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).

*gPatients with large cell transformed (LCT) MF and stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. In general, agents listed in SYST-CAT C are preferred in these circumstances.

*hCombination regimens are generally reserved for patients with relapsed/refractory or extracutaneous disease.*
SUGGESTED TREATMENT REGIMENS

References


Total skin electron beam therapy (TSEBT)


Systemic Therapies

Alemtuzumab for Sezary syndrome ± lymph node disease


Retinoids

Bexarotene Gel


Topical imiquimod


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Continued on next page

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Systemic Therapies Continued

**Vorinostat**

**Romidepsin**

**Extracorporeal photopheresis (ECP)**

**Methotrexate**

**Liposomal doxorubicin**

References

**Gemcitabine**

**Pentostatin**

**Temozolomide**

**Low-dose Pralatrexate**

**Pralatrexate**

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Continued on next page
Combination Therapies
Skin-directed + Systemic


Systemic + Systemic


Allogeneic stem cell transplant


SUPPORTIVE CARE FOR MF/SS

Pruritus

• Assessment
  ▶ Pruritus should be assessed at each visit using consistent measurements
  ▶ Generalized pruritus and localized pruritus should be distinguished
  ▶ Correlation between sites of disease and localization of pruritus should be noted
  ▶ Other potential causes for pruritus should be ruled out

• Treatment
  ▶ Moisturizers, emollients, and barrier protection
  ▶ Topical steroid (appropriate strength for body region) ± occlusion
  ▶ Optimize skin-directed and systemic therapy
  ▶ Topical preparations - camphor/menthol formulations, pramoxine formulations
  ▶ Systemic agents
    ◆ First-line
      - Antihistamines
      - Doxepin
      - Gabapentin
    ◆ Second-line
      - Aprepitant
      - Mirtazapine
      - Selective serotonin reuptake inhibitors
    ◆ Third-line
      - Naltrexone

Infections

• Active or Suspected Infections
  ▶ Erythroderma:
    ◆ Skin swab and nares cultures for Staphylococcus aureus (S. aureus) infection or colonization
    ◆ Intranasal mupirocin
    ◆ Oral dicloxacillin or cephalaxin
    ◆ Sulfamethoxazole/trimethoprim, doxycycline if suspect MRSA
    ◆ Vancomycin if no improvement or bacteremia
    ◆ Bleach baths or soaks (if limited area)
  ▶ Ulcerated and necrotic tumors:
    ◆ Gram-negative rods (GNR) common in necrotic tumors may lead to bacteremia and sepsis
    ◆ If high suspicion for infection, obtain blood cultures, start antibiotics even if fever absent
    ◆ Role of wound cultures not clear due to colonization
    ◆ Empirical therapy for both GNR and gram-positive coccal infections is necessary initially
  ▶ Prophylaxis
    ▶ Optimize skin barrier protection
    ▶ Mupirocin for S. aureus colonization
    ▶ Bleach baths or soaks (if limited area)
    ▶ Avoid central lines (especially in erythrodermic patients)
    ▶ For patients receiving alemtuzumab, see NHODG-B.

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