Where, (when and how) to take a biopsy for inflammatory skin diseases?

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Disclosures

I do not have any relevant relationships with industry.
Skin Biopsy

- **Quick and easy to perform**
  - Leaving the smallest possible tissue defect
  - Good cosmetic result

- **Specimens of high quality and adequate size**
  - Punch, shave, incisional or excisional elliptical biopsy are possible

- **How to get the ideal pathology result?**
  - This depends on many different parameters
  - Errors can occur in any step of the ‘skin biopsy pathway’
# The skin biopsy pathway

(adapted from JAAD 2016, 74: 19-25)

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Decision to perform a biopsy</td>
<td></td>
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<tr>
<td>2. Reasons for biopsy and risks are discussed (IC if necessary)</td>
<td></td>
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<tr>
<td>3. Biopsy details are determined: type and size, number of biopsies, body site(s) and location within lesion(s), transport medium</td>
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<tr>
<td>4. Labeling of transport media/container and completion of the requisition form</td>
<td></td>
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<tr>
<td>5. Biopsy specimen is obtained and placed in the correctly labeled container</td>
<td></td>
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<tr>
<td>6. Transportation of biopsy specimen and requisition form to dermatopathology lab</td>
<td></td>
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<tr>
<td>7. Accurate processing of the specimen (including lesion-directed cutting using derm dotting and in vivo/ex vivo dermoscopy)</td>
<td></td>
</tr>
<tr>
<td>8. A pathology report is generated and transmitted to the clinician</td>
<td></td>
</tr>
<tr>
<td>9. The clinician determines the mode of action/therapy</td>
<td></td>
</tr>
<tr>
<td>10. Communication of the result and mode of action/therapy to the patient (and other clinicians of necessary)</td>
<td></td>
</tr>
<tr>
<td>11. Treatment of disease based on the pathology report</td>
<td></td>
</tr>
</tbody>
</table>
The interface between clinician and pathologist

The physician's role in aiding the pathologist to reach an accurate diagnosis starts from the moment the decision for a biopsy/excision is made.
The interface between clinician and pathologist

What can go wrong (before the biopsy reaches the pathology lab)?

- Choosing inappropriate biopsy site or technique
- Biopsy specimen too small
- Artefacts due to electrocoagulation or inappropriate use of forceps
- Orientation of biopsy/excision
- Biopsy left to dry before being put in formalin fixation
- Provide no or minimal clinical information
The interface between clinician and pathologist

What can go wrong?
- Choosing inappropriate biopsy site or technique
- Biopsy specimen too small
- Artefacts due to electrocoagulation or inappropriate use of forceps
- Orientation of biopsy/excision
- Biopsy left to dry before being put in formalin fixation
- Provide no or minimal clinical information
The importance of clinicopathological correlation

The histological picture should be evaluated together with:

- Clinical information
  - Patient’s age and sex
  - Biopsy site
  - Clinical presentation and time course
  - Local and systemic treatments
  - Laboratory findings
  - Clinical pictures if possible

- Previous histology
The importance of clinicopathological correlation

*Influence of evaluation of clinical pictures on the histopathologic diagnosis of inflammatory skin disorders.*

**RESULTS:** After evaluation of the clinical images, the number of dermatopathologists making a correct diagnosis was increased in 70 cases, unchanged in 25 cases, and decreased in 5 cases. The total number of correct diagnoses increased from 332 (diagnoses before evaluation of clinical pictures) to 481 (diagnoses after evaluation of clinical pictures), with a 16.6% increase in the total.

**CONCLUSION:** Our study clearly shows that clinical pictures should be added to biopsy request slips of inflammatory skin disorders whenever possible, as they allow a better interpretation of histopathologic findings.
The choice of the lesion

1. For inflammatory skin disease a punch biopsy of min 3,5-4mm is in most cases the preferred technique

2. Biopsy a representative lesion

3. Biopsy center of a lesion (maximal induration or elevation)

4. If possible: avoid a biopsy of the lower legs

5. Deep dermatitis: perform an elliptical biopsy

6. Avoid biopsy over bony prominences

7. General considerations in bullous diseases
The choice of the lesion:
2. Biopsy a representative lesion

- Not too early (non specific histology) - not too late
  - Exception: blister or pustule: biopsy a fresh lesion (<1 day old)

- Select an untreated lesion (or else discontinue therapy for at least 1-2 weeks)

- Avoid lesions that have been manipulated, excoriated or secondarily infected
The choice of the lesion:
3. Biopsy the center of the lesion

- **Exception**: in annular lesions:
  - biopsy active border (granuloma annulare, dermatomycosis, erythema chronicum migrans, erythema annulare centrifugum, cutaneous lupus, porokeratosis, ...)

- The biopsy should include maximal lesional skin and minimal normal skin
  - Lesions between 1-4mm: biopsy center or excision biopsy of the entire lesion
  - Larger lesions: thickest portion, area most abnormal in color
The choice of the lesion:
4. Avoid biopsy of the lower legs

Disturbing background of stasis dermatitis

From: Dermatopathology 1st Edition, N.K. Brinster, Ph. McKee et al
The choice of the lesion:
4. Avoid biopsy of the lower legs

- Biopsy wounds heal more slowly
- Lower extremities show the lowest incidence of positive direct immunofluorescence in bullous pemphigoid!
The choice of the lesion
5. Deep dermatitis

- Panniculitis, necrobirosis lipoidica, vasculitis of medium sized vessels
  - incisional (elliptical) deep biopsy including subcutaneous fat
The choice of the lesion
6. Avoid biopsy over bony prominences

- More painful
- More difficult wound healing
- Non-specific lymphohistiocytic infiltrate
- Overlying epidermal hyperplasia
7. Choice of the lesion: Bullous diseases: direct immunofluorescence

- Take non-bullous lesional skin or uninvolved perilesional skin (<1cm from the blister)
  - Bullous skin and uninvolved skin farther from bullae $\rightarrow$ ↑ false negative results
  - Mucosal surface: take normal appearing mucosa 3-5mm away from erosion

- Lower extremity skin should be avoided $\rightarrow$ ↑ false negative results
  - Biopsy above the waist (trunk!)
7. Choice of the lesion: Bullous diseases: light microscopy

- **Intact vesicle or bulla (bullous pemphigoid, PCT,...)**
  - If small vesicle: punch out completely
  - If larger bulla: biopsy edge of blister + intact skin (inflammatory infiltrate)

- **Epidermolysis bullosa:**
  - Blister <12 hours old
    - Epidermal necrosis, proteolytic antigen degradation or reepithelialization: false negative results!
  - Induce a blister (not palms or soles) by pressing down and turning 180° is produced:
    - biopsy after 5 minutes
    - Take border of erythematous and non-erythematous skin
  - Perform a blister producing activity
From: McKee’s Pathology of the Skin
Annular lesions: 1. Granuloma annulare

From: McKee’s Pathology of the Skin, 4th Edition

- **Time**: well developed lesion
- **Location**: active border
- **Type**: punch
Annular lesions: 1. Granuloma annulare

From: McKee’s Pathology of the Skin, 4th Edition
Annular lesions: 2. Erythema annulare centrifugum

Time: well developed lesion
Location: active border
Type: punch
Annular lesions: 3. Erythema chronicum migrans

Time: well developed lesion
Location: active border
Type: punch

From: Dermatopathology, N.K. Brinster, Ph. McKee et al
Annular lesions: 4. Porokeratosis

From: Dermatopathology, N.K. Brinster, Ph. McKee et al
From: McKee’s Pathology of the Skin, 4th Edition
Annular lesions: 5. Tinea

From: McKee's Pathology of the Skin, 4th Edition
Annular lesions: 6. Lupus

- Cutaneous lupus requires a punch biopsy ≥4mm of an active lesion
- Lupus panniculitis: deep biopsy!
- DIF: lupusband test
  - lesional skin!
    - 50-94% + in SLE
    - 60-80% + in CDLE
    - 60% + in SCLE
- CDLE: chronic lesion >6 months old
- SLE: 67% lupusband in normal sun protected skin
  - 20% of sun exposed skin of normal healthy individuals has a positive lupusband
Annular lesions: 6. Lupus

From: McKee’s Pathology of the Skin, 4th Edition
Annular lesions: 6. Lupus

From: McKee’s Pathology of the Skin, 4th Edition
Targetoid lesions: Erythema multiforme

From: McKee’s Pathology of the Skin, 4th Edition
Targetoid lesions: Erythema multiforme

From: McKee’s Pathology of the Skin, 4th Edition
Vasculitis

- DIF biopsy: lesion <24h old otherwise fibrinogen and Ig deposits might be difficult to detect.
  - IgA often remains in established lesions

- H&E biopsy: fully evolved (purpuric) lesion >72h old

- Biopsy should be taken from the center of the lesion
  - Livedo racemosa: from the pale center of erythematous ring

- If medium sized vessel vasculitis is suspected: deep biopsy!
Panniculitis

- A deep incisional biopsy is necessary

From: McKee’s Pathology of the Skin, 4th Edition
Time: active lesion, first week
Location: center
Type: deep biopsy

From: McKee's Pathology of the Skin, 4th Edition
Atopic or contact dermatitis: life of lesions

From: Dermatopathology, N.K. Brinster, Ph. McKee et al
Atopic or contact dermatitis: life of lesions

From: Dermatopathology, N.K. Brinster, Ph. McKee et al
Psoriasis

- Life of lesions

- Specific anatomic localisations
  - Palmoplantar
  - Mucosal/ Genital
  - Nail
Psoriasis: Life of lesions
Psoriasiform epidermal hyperplasia

Thinning of suprapapillary plates

Spongiform pustule of Kogoj

Munro microabsces

Hypogranulosis

Dilated and tortuous papillary blood vessels
Psoriasis: Life of lesions
Mounds of parakeratosis with neutrophils

Hypogranulosis

Slight epidermal hyperplasia

Dilated papillary blood vessels
Psoriasis: palmoplantar
DD palmoplantar psoriasis-eczematous dermatitis

Table 1. The histologic features of palmoplantar psoriasis and eczematous dermatitis

<table>
<thead>
<tr>
<th>Histologic features</th>
<th>Palmoplantar psoriasis (n = 17, n (%))</th>
<th>Eczematous dermatitis (n = 25, n (%))</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple foci of parakeratosis</td>
<td>12 (70.6)</td>
<td>11 (44)</td>
<td>0.089</td>
</tr>
<tr>
<td>Confluent parakeratosis</td>
<td>5 (28.4)</td>
<td>11 (44)</td>
<td>0.333</td>
</tr>
<tr>
<td>PNL* at the summits of parakeratosis</td>
<td>1 (5.9)</td>
<td>1 (4)</td>
<td>0.652</td>
</tr>
<tr>
<td>Only plasma in the parakeratotic foci</td>
<td>2 (11.8)</td>
<td>1 (4)</td>
<td>0.556</td>
</tr>
<tr>
<td>Plasma and PNL in the parakeratotic foci</td>
<td>16 (94.1)</td>
<td>20 (80)</td>
<td>0.374</td>
</tr>
<tr>
<td>Vertical alternation of parakeratosis and orthokeratosis</td>
<td>13 (76.5)</td>
<td>8 (32)</td>
<td>0.005</td>
</tr>
<tr>
<td>Loss of granular layer</td>
<td>7 (41.2)</td>
<td>9 (36)</td>
<td>0.735</td>
</tr>
<tr>
<td>Psoriasiform epidermal hyperplasia</td>
<td>15 (88.2)</td>
<td>20 (80)</td>
<td>0.681</td>
</tr>
<tr>
<td>Irregular epidermal hyperplasia</td>
<td>2 (11.8)</td>
<td>5 (20)</td>
<td>0.681</td>
</tr>
<tr>
<td>Thinning of rete ridges</td>
<td>9 (52.9)</td>
<td>13 (52)</td>
<td>0.952</td>
</tr>
<tr>
<td>Clubbing and anastomosing of the rete ridges</td>
<td>14 (82.4)</td>
<td>22 (88)</td>
<td>0.672</td>
</tr>
<tr>
<td>Full-thickness spongiosis</td>
<td>8 (47.1)</td>
<td>12 (48)</td>
<td>0.952</td>
</tr>
<tr>
<td>Spongiosis at the lower part of the epidermis</td>
<td>8 (47.1)</td>
<td>9 (36)</td>
<td>0.474</td>
</tr>
<tr>
<td>Spongiotic vesicle</td>
<td>13 (76.5)</td>
<td>15 (60)</td>
<td>0.226</td>
</tr>
<tr>
<td>Dyskeratotic cells</td>
<td>14 (82.4)</td>
<td>15 (60)</td>
<td>0.124</td>
</tr>
<tr>
<td>Thinning of the suprapapillary plates</td>
<td>10 (58.8)</td>
<td>10 (40)</td>
<td>0.231</td>
</tr>
<tr>
<td>Edema of the papillary dermis</td>
<td>5 (29.4)</td>
<td>3 (12)</td>
<td>0.235</td>
</tr>
<tr>
<td>Tortuous capillaries in the papillary dermis</td>
<td>9 (52.9)</td>
<td>11 (44)</td>
<td>0.569</td>
</tr>
<tr>
<td>Capillaries touching the undersurface of epidermis</td>
<td>15 (88.2)</td>
<td>24 (96)</td>
<td>0.556</td>
</tr>
<tr>
<td>Dilated capillaries in the papillary dermis</td>
<td>13 (76.5)</td>
<td>18 (72)</td>
<td>0.518</td>
</tr>
<tr>
<td>Extravasated erythrocytes</td>
<td>5 (29.4)</td>
<td>5 (20)</td>
<td>0.714</td>
</tr>
<tr>
<td>Collagen fibers parallel to rete ridges</td>
<td>15 (88.2)</td>
<td>23 (92)</td>
<td>0.538</td>
</tr>
<tr>
<td>Eosinophils in the upper dermis</td>
<td>2 (11.8)</td>
<td>3 (12)</td>
<td>0.693</td>
</tr>
</tbody>
</table>

*PNL, polymorphonuclear leukocytes.

### Table 1. Histopathologic features in 42 cutaneous biopsies from palms and soles (22 PSO cases and 20 ACD cases)

<table>
<thead>
<tr>
<th>Feature</th>
<th>PSO (%)</th>
<th>ACD (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of parakeratosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(focal)</td>
<td>2 (9.1)</td>
<td>5 (25.0)</td>
<td>NS</td>
</tr>
<tr>
<td>(moderate)</td>
<td>9 (40.9)</td>
<td>11 (55.0)</td>
<td>NS</td>
</tr>
<tr>
<td>(marked)</td>
<td>11 (50.0)</td>
<td>4 (20.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Regular epidermal hyperplasia</td>
<td>15 (68.5)</td>
<td>7 (35.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Irregular epidermal hyperplasia</td>
<td>7 (31.5)</td>
<td>13 (65.0)</td>
<td></td>
</tr>
<tr>
<td>Thinning of granular layer</td>
<td>20 (90.9)</td>
<td>16 (80.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Intracorneal neutrophils</td>
<td>10 (45.5)</td>
<td>7 (35.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Spongiosis</td>
<td>17 (77.3)</td>
<td>19 (95.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of serum</td>
<td>18 (81.8)</td>
<td>19 (95.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Vesicle formation</td>
<td>5 (22.7)</td>
<td>7 (35.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Lymphocytic exocytosis</td>
<td>19 (86.4)</td>
<td>16 (80.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Dermal eosinophils</td>
<td>19 (86.4)</td>
<td>18 (90.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Dilated capillaries</td>
<td>5 (22.7)</td>
<td>6 (30.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

PSO, psoriasis; ACD, allergic contact dermatitis; NS, not significant.

### Table 2. Number of S100 protein-positive DCs and Mib-1-positive keratinocytes in 10HPF of skin in 22 cases of PSO, 20 cases of ACD, and four cases of normal palmar skin

<table>
<thead>
<tr>
<th>Feature</th>
<th>N.Sk. (mean ± SD)</th>
<th>PSO (mean ± SD)</th>
<th>ACD (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100+ DCs (epidermis)</td>
<td>8 ± 3</td>
<td>58.40 ± 28.67</td>
<td>90.75 ± 39.94</td>
</tr>
<tr>
<td>N.Sk. vs PSO (p = 0.001)</td>
<td></td>
<td>PSO vs ACD (p = 0.01)</td>
<td></td>
</tr>
<tr>
<td>N.Sk. vs ACD (p = 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S100+ DCs (dermis)</td>
<td>-</td>
<td>62.59 ± 33.99</td>
<td>99.70 ± 54.76</td>
</tr>
<tr>
<td>S100+ DCs (whole skin)</td>
<td>8 ± 3</td>
<td>121.00 ± 51.70</td>
<td>186.45 ± 81.90</td>
</tr>
<tr>
<td>N.Sk. vs PSO (p &lt; 0.001)</td>
<td></td>
<td>PSO vs ACD (p = 0.006)</td>
<td></td>
</tr>
<tr>
<td>N.Sk. vs ACD (p &lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mib1 + KCs</td>
<td>50 ± 10</td>
<td>322.95 ± 152.16</td>
<td>281.15 ± 167.89</td>
</tr>
<tr>
<td>N.Sk. vs PSO (p = 0.001)</td>
<td></td>
<td>PSO vs ACD (NS)</td>
<td></td>
</tr>
<tr>
<td>N.Sk. vs ACD (p = 0.006)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DC, dendritic cell; HPF, high power field; PSO, psoriasis; ACD, allergic contact dermatitis; N.Sk., normal skin; SD, standard deviation; KC, keratinocytes; NS, not significant.
Erythroderma

- Difficult!
- Several biopsies in different areas from different lesions

**Early skin biopsy is helpful for the diagnosis and management of neonatal and infantile erythrodermas.**

*Leclerc-Mercier S*, *Bodemer C*, *Bourdon-Lanoy E*, *Larousse F*, *Hovnanian A*, *Brousse N*, *Fraïtage S.*

**CONCLUSION:** Skin biopsy is helpful for etiologic diagnosis of early erythroderma of infancy, particularly in ID and NS, the most severe diseases. Consequently, these results justify an early systematic skin biopsy for a better and earlier management.
Psoriasis erythroderma

**Histology:**
- Can be non specific: multiple biopsies sometimes necessary!!
- Absent/reduced stratum corneum
- More prominent dilatation of papillary vessels-extravasation RBC
- Histological features of early psoriasis
- CAVE: psoriasiform features in non-psoriatic erythroderma
Stratum corneum thin

Spongiosis

Lymphocyte exocytosis

Prominent papillary blood vessels
Pityriasis lichenoides

From: McKee’s Pathology of the Skin, 4th Edition
Lichen planus

Time: any
Location: violaceous papule
Type: punch

From: McKee’s Pathology of the Skin, 4th Edition
Lichen Sclerosus

From: McKee’s Pathology of the Skin, 4th Edition
Lichen Sclerosus

From: McKee’s Pathology of the Skin, 4th Edition
Morphea

- Deep incisional biopsy (or deep punch)
- Lilac border: nodular lymphoplasmocytic infiltrate in superficial and deep vascular plexus
- Advanced morphea:
  - Hyalinizing collagen bundles and loss of periadnexial fat
  - Parallel sides in a punch biopsy
Morphea

From: McKee’s Pathology of the Skin, 4th Edition
From: McKee’s Pathology of the Skin, 4th Edition
Pyoderma gangrenosum

**Time**: small, early, non-ulcerated lesion (early pustule)

**Location**: entire lesion

**Type**: excision with tissue culture

From: McKee’s Pathology of the Skin, 4th Edition
Pyoderma gangrenosum

From: McKee’s Pathology of the Skin, 4th Edition
Parapsoriasis (small plaque, chronic superficial dermatitis)

- **Time**: established untreated lesion
- **Location**: center
- **Type**: punch

From: McKee’s Pathology of the Skin, 4th Edition
Mycosis fungoides

From: McKee’s Pathology of the Skin, 4th Edition

**Time**: patch stage: untreated lesion  
**Location**: center  
**Type**: 2 or more punch biopsies

**Time**: plaque stage, non-ulcerated  
**Location**: most infiltrated area  
**Type**: one or 2 punches

**Time**: tumor stage, non-ulcerated  
**Location**: indurated area  
**Type**: punch
Take home message

1. The physician’s role in aiding the pathologist to reach an accurate diagnosis starts from the moment the decision for a biopsy/excision is made

2. In inflammatory skin diseases clinicopathological correlation (clinical pictures) is essential!

3. As a general rule: biopsy the center (except annular lesions) of a representative untreated and unmanipulated lesion avoiding the lower legs if possible
Thank you!