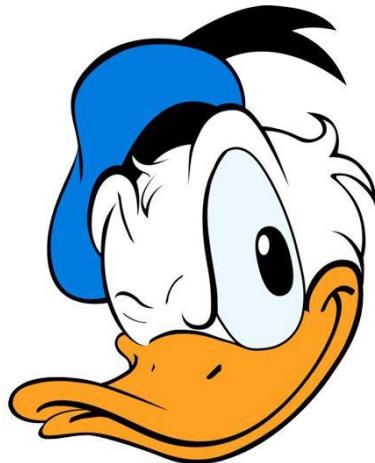


# DERMATOLOGY

## CME

*2018*





## *Index:*

1. Alopecia areata
2. Practical management of acne for Clinicians
3. Cutaneous squamous cell carcinoma
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## Alopecia areata



### Disease characteristics, clinical evaluation, and new perspectives on pathogenesis

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#### Learning objectives

After completing this learning activity, participants should be able to describe the novel trichoscopic clinical features of alopecia areata as well as the more recent findings in global epidemiology and risk factors; define the new histopathologic features of the disease and how these characteristics relate to the underlying disease mechanisms; explain the new discoveries of the immunobiology of the hair follicle that is affected with alopecia areata; and identify new exciting evidence implicating the specific aspects of the immune system involved in the pathogenesis of alopecia areata.

#### Disclosures

##### Editors

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Alopecia areata (AA) is a common, inflammatory, nonscarring type of hair loss. Significant variations in the clinical presentation of AA have been observed, ranging from small, well-circumscribed patches of hair loss to a complete absence of body and scalp hair. Patients affected by AA encompass all age groups, sexes, and ethnicities, and may experience frustration with the unpredictable nature of their disease for which there is currently no definitive treatment. The cause of AA remains incompletely understood, though it is believed to result—at least in part—from a loss of immune privilege in the hair follicle, autoimmune-mediated hair follicle destruction, and the upregulation of inflammatory pathways. Patients with AA frequently experience marked impairment in psychological well-being, self-esteem, and may be more likely to suffer from psychiatric comorbidities. Part one of this two-part continuing medical education series describes the epidemiology, clinical evaluation, prognosis, and recent advancements in the understanding of the pathogenesis of AA. (J Am Acad Dermatol 2018;78:1-12.)

**Key words:** alopecia areata; alopecia totalis; alopecia universalis; pathogenesis; prognosis; subtype.

## EPIDEMIOLOGY

### Key point

- Alopecia areata affects both sexes equally, affects patients of all ages, and is found in

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Ms Strazzulla and Dr Wang contributed equally to this article.

### approximately 0.1% to 0.2% of the general population

Among the US population, the cumulative lifetime incidence of alopecia areata (AA) is estimated at 2%,

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**Abbreviations used:**

AA:	alopecia areata
AT:	alopecia totalis
AU:	alopecia universalis
CTL:	cytotoxic T lymphocyte
CTLA-4:	cytotoxic T lymphocyte-associated protein 4
GWAS:	genome-wide association study
HF:	hair follicle
HLA:	human leukocyte antigen
IFN:	interferon
IL:	interleukin
JAK:	Janus kinase
MCH:	melanin-concentrating hormone
MCHR2:	melanin-concentrating hormone factor 2
MCHR2-AS1:	MCHR2 antisense RNA 1
MHC:	major histocompatibility complex
NKG2D:	natural killer group 2D
PRDX5:	peroxiredoxin-5
SALT:	Severity of Alopecia Tool
STX17:	syntaxin-17
Treg:	T regulatory cell
ULBP:	UL16-binding protein

while the prevalence is approximately 0.1% to 0.2%.<sup>1,2</sup> While AA affects both sexes equally, data from the Rochester Epidemiology Project revealed that men tended to be diagnosed earlier compared with women (mean age at diagnosis, 31.5 vs 36.2 years).<sup>2</sup> While some have suggested that the prevalence of AA may be greatest among pediatric populations and declines with each subsequent decade,<sup>3,4</sup> others found the peak incidence to be in the second and third decades of life.<sup>5,6</sup>

## CLINICAL EVALUATION

### Key points

- Alopecia areata presents most commonly as well-demarcated patches of nonscarring, inflammatory hair loss that can progress to include all scalp or body hairs
- Exclamation point hairs, dystrophic hairs, and yellow dots are features of alopecia areata that can be identified with trichoscopy
- Nail abnormalities, such as regular pitting, brittleness, or striations, are seen in 10% to 20% of patients

AA most commonly presents as a sudden onset of focal well-circumscribed patches of hair loss on the scalp without signs of significant inflammation or scarring (Fig 1).<sup>7</sup> In patients with active disease, a pull test may be positive, especially at the periphery of the lesion.<sup>8</sup> Generally, patients are asymptomatic, though tingling, itching, and dysesthesia are occasionally reported prior to hair loss. In severely affected individuals, AA may progress to include all

scalp hairs (alopecia totalis [AT]), or all scalp and body hairs (alopecia universalis [AU]).<sup>9</sup> Men may be more likely to initially present with beard involvement as opposed to scalp alopecia (50.5% vs 39.3%; Fig 2).<sup>6</sup>

Evaluation of the patient should include trichoscopy to allow for closer evaluation of the follicle, hair shaft, and surrounding skin, and to help determine the best area from which to obtain a biopsy specimen.<sup>10</sup> Clinicians should look for exclamation point hairs, which are considered a common, pathognomonic indicator of AA and describe a broken hair that is thicker at the distal end relative to the base. Dystrophic, broken hairs are also frequently present, and although not specific to AA, occur when mitotic activity in anagen follicles is interrupted. Yellow dots may be observed on trichoscopy but do not correlate well with clinical disease type or severity, and can be seen in other types of hair loss, such as androgenetic alopecia.<sup>11</sup> A Severity of Alopecia Tool (SALT) score can be determined by visually assessing the amount of terminal hair loss in 4 views of the scalp, and can be used to track treatment response.<sup>12</sup> A more recent scoring system, the SALT II, is now also available and divides the scalp into smaller increments for estimating hair density.<sup>13</sup> Nail changes are found in approximately 10% to 20% of patients and may occur more commonly in those with severe disease. Regular pitting, longitudinal ridging, trachyonchia, and red lunula are among the changes that may be seen (Fig 3).<sup>14,15</sup>

## DIFFERENTIAL DIAGNOSIS

### Key point

- Trichotillomania, temporal triangular alopecia, and telogen effluvium are the most important alternative diagnoses to consider

Trichotillomania can be challenging to differentiate from AA, and in some cases the two conditions may coexist. However, in trichotillomania, incomplete hair loss and a significant number of broken hairs will be observed on trichoscopy.<sup>16</sup> Temporal triangular alopecia causes a circumscribed triangular-like area of nonscarring hair loss in the frontotemporal area. Patches are usually single, persistent, unilateral, do not enlarge in size like in AA, and tend to be unresponsive to treatment.<sup>17</sup> A biopsy specimen can also be used to distinguish this condition from AA, because temporal triangular alopecia tends to be noninflammatory, though chronic AA lesions may also lack significant inflammation.<sup>18,19</sup> Diffuse AA may be difficult to differentiate from telogen effluvium, and this distinction frequently requires obtaining a biopsy specimen or identifying a triggering



**Fig 1.** **A-D,** Well-demarcated patchy alopecia areata. No epidermal changes were observed in the affected areas.



**Fig 2.** **A** and **B,** Patchy alopecia areata of the beard.

factor in the patient's history. Other disorders to consider include an early scarring alopecia, secondary syphilis (which may look histologically identical to AA), and systemic lupus erythematosus.

## CLINICAL SUBTYPES

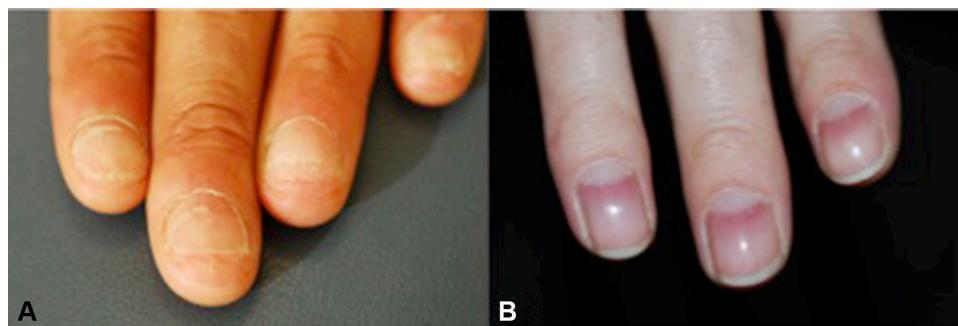
### Key point

- Several subtypes of alopecia areata have distinct presentations, including ophiasis, sisaiquo, sudden graying type, and diffuse forms

Patients with the ophiasis subtype of AA (Fig 4) have band-like alopecia usually at the occipital hairline extending toward the temples, or rarely at the frontal hairline, that can be confused with frontal fibrosing alopecia.<sup>9</sup> The sisaiquo subtype occurs in

the opposite distribution, causing hair loss centrally but sparing hairs at the margin of the scalp, and appearing similar to androgenetic alopecia.<sup>20</sup> In addition, a "sudden graying" or "white overnight" variant of AA results in loss of pigmented hairs.<sup>21</sup> Perinevoid AA refers to hair loss occurring around pigmented nevi, and of note removal of the nevi does not change the hair loss.<sup>22</sup>

Acute diffuse and total alopecia is a more recently described variant that presents as diffuse and sudden hair loss most commonly in women, and lasting approximately 3 months followed by rapid regrowth, though recurrence may occur.<sup>23</sup> AA incognita is also characterized by acute diffuse shedding of telogen hairs in the areas commonly affected by androgenetic alopecia and can be confused with



**Fig 3.** Characteristic nail findings in patients with alopecia areata. **A**, Brittle nails with splitting. **B**, Red lunula, the convex margin of the distal matrix.



**Fig 4.** Different clinical presentations of alopecia areata, including (**A** and **B**) the ophiasis subtype with hair loss at the occipital scalp, (**C**) hair loss in an androgenetic distribution, and (**D**) diffuse type.

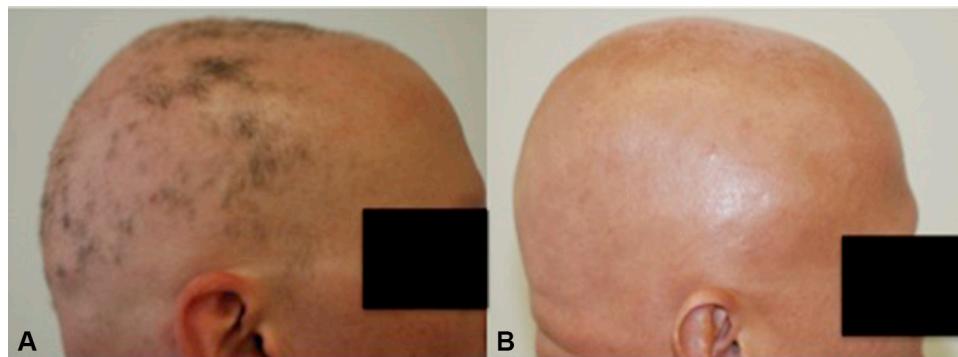
telogen effluvium; obtaining a biopsy specimen is often required for a definitive diagnosis.<sup>24</sup> Women are also more frequently affected by this subtype.<sup>10</sup>

## PROGNOSIS

### Key points

- Younger age at initial presentation and severity at onset are the most important prognostic indicators
- Risk of progression from limited alopecia areata to alopecia totalis or alopecia universalis is approximately 5%
- The ophiasis subtype has a poorer prognosis and the acute diffuse and total alopecia subtype has a more favorable prognosis

Factors that may contribute to prognosis include AA subtype, extent of hair loss, duration of hair loss, age at onset, and family history.<sup>14</sup> Approximately 5% of cases of patchy AA will progress to AT or AU (Fig 5).<sup>25</sup> Extensive involvement portends a more severe prognosis.<sup>4</sup> For example, Tosti et al<sup>26</sup> showed that among adult patients with mild disease (<25% of hair loss), 67% showed complete regrowth while those with more severe AT or AU forms of the disease tended to either remain stable or worsen overtime (mean follow-up time, 17.74 years). The patients from this study were treated with various therapies, including topical immunotherapy, which conferred a better overall prognosis to responders. Some patients in the study did not receive any treatment,



**Fig 5.** Progression of (A) patchy alopecia areata to (B) alopecia totalis.

and among those with 51% to 75% hair loss who were untreated 34.6% recovered or developed milder disease.<sup>26</sup> Younger age at onset is also regarded as a less favorable prognostic indicator.<sup>27,28</sup> The ophiasis subtype can have a poorer prognosis and may be less responsive to treatment, while the acute diffuse and total alopecia subtype generally has a favorable prognosis.<sup>23,29</sup>

## PATHOGENESIS

### Key points

- The anagen hair follicle is normally an immune privileged site, but this is disrupted in alopecia areata
- Inflammatory immune cells lead to dystrophic hair follicle cycling with premature entry into the telogen phase

The proximal portion of the anagen hair follicle (HF) constitutes an immune privileged site similar to the anterior chamber of the eyes, the pregnant uterus, and the testes.<sup>30,31</sup> This immune privilege appears to be disrupted in AA where an increase in major histocompatibility complex (MHC) I and II molecules, along with adhesion molecules, correlate with increased leukocyte trafficking into the dermis.<sup>32</sup> These changes enhance the presentation of antigens by HF cells and migration of T cells to close proximity of HFs in AA lesions.

Normally, the HF cycles between 3 distinct stages; active growth (anagen), followed by apoptosis of epithelial cells (catagen), and finally a resting phase (telogen).<sup>33</sup> In AA, this cycling becomes disrupted, leading to a dystrophic anagen phase. Also, during the catagen phase there is an infiltration of immune cells, leading to the hypothesis that the controlled apoptosis that occurs during catagen might expose the immune cells to more antigens from HF cells.<sup>34,35</sup> Eventually, with increased inflammation, the anagen phase follicles prematurely enter the telogen phase;

this is likely in response to an immune-mediated stimulus.<sup>36</sup>

### Autoimmune hypothesis

#### Key points

- Autoreactive T cells infiltrate the hair follicle, sparing the stem cell compartment
- CD8<sup>+</sup> T cell density and disease severity correlate
- Hair follicle–derived autoantigens may be involved

The first evidence of autoimmunity in AA against hair follicles involved the observation of a “swarm of bees” clustering of inflammatory cells (mostly T cells) toward the bulb region of hair follicles.<sup>37</sup> CD8<sup>+</sup> (cytotoxic T lymphocytes [CTLs]) and CD4<sup>+</sup> T cells comprise a significant portion of the infiltrate, along with an increased presence of antigen-presenting cells, such as Langerhans cells.<sup>38,39</sup> Of note, the lymphocyte attack in AA spares the stem cell compartment, preventing permanent organ destruction and allowing future regrowth to remain possible in most cases.<sup>40</sup> The clinical importance of lymphocytes in AA is highlighted by the observation that CD8<sup>+</sup> T cell density and disease severity appear to correlate.<sup>41</sup> Recently, the presence of mast cells in AA lesions in close association with CTLs has been identified in both AA-affected C3H/HeJ mice and humans, suggesting potential cross-communication between mast cells and CTLs during AA pathogenesis.<sup>42,43</sup>

The involvement of autoreactive T cells gave rise to the hypothesis of HF-derived autoantigens. The identity of the exact antigen is still being debated, but melanogenesis-associated antigens are likely involved, and this may account for the clinical observation that pigmented hairs tend to be preferentially affected by AA, and after resolution of an episode of AA, the nonpigmented hairs are typically the first to demonstrate regrowth.<sup>9</sup> HF

keratinocyte-derived antigens, such as trichohyalin, have also been identified as possible autoantigens for T cells<sup>44</sup> and autoantibodies.<sup>37,45</sup>

### Animal models

#### Key points

- The C3H/HeJ mouse model is widely used for alopecia areata research
- Studies in animal models support the role of autoreactive T cells in alopecia areata and the upregulation of inflammatory pathways

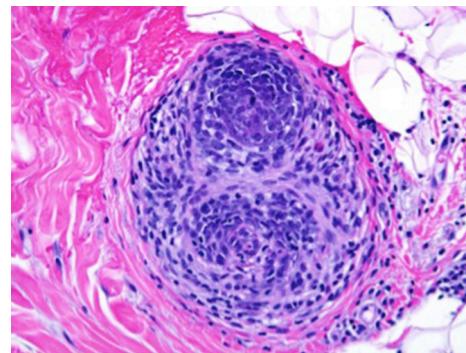
While animal models cannot represent human disease completely, the C3H/HeJ mouse model is one of the most well defined and widely used for AA research, along with DEBR rats and humanized severe combined immunodeficiency mice.<sup>46-49</sup> The high mechanistic similarities between C3H/HeJ mice and human AA have made it an attractive model for preclinical drug testing. Evidence from these models strongly supports the hypothesis that T cells drive the pathogenesis of AA, consistent with changes in the interferon-gamma and inflammatory gene expression signatures in AA. For example, transfer of T cells (but not B cells) can cause AA in C3H/HeJ mice,<sup>50</sup> while depletion of CD4<sup>+</sup> and CD8<sup>+</sup> T cell subsets using monoclonal antibodies in AA-affected mice causes hair regrowth.<sup>51,52</sup> Upregulation of interleukin-6 (IL-6), tumor necrosis factor-alpha, IL-12, and interferon-gamma is observed among mice that develop localized or multiple patches of AA. Similar changes in interferon and inflammatory signatures were also observed in humans with AA.<sup>41,50</sup> These observations led to rational development of experimental therapies either via targeting specific cytokines or cell populations.<sup>53,54</sup>

### Histologic findings

#### Key points

- In active phase alopecia areata there is peribulbar lymphocytic inflammation comprised of CD8<sup>+</sup> and CD4<sup>+</sup> T cells, a shift to catagen and telogen follicles, and miniaturization
- In the chronic phase, the majority of follicles are miniaturized, and in catagen or telogen there is minimal to sometimes no peribulbar inflammation

The histologic features of AA vary according to the disease stage. In acute, active disease there is peribulbar infiltration of CD8<sup>+</sup> and CD4<sup>+</sup> T lymphocytes surrounding anagen follicles, with extension into the hair matrix keratinocytes (Fig 6).<sup>55</sup> These lymphocytes cause disorganization and apoptosis of hair matrix cells. Degeneration results in melanin



**Fig 6.** Hair matrical epithelial cells show disorganization and lymphocytic inflammation. (Original magnification:  $\times 400$ .)

incontinence and pigment deposition within the follicular epithelium, the dermal papilla, and the follicular stela (fibrovascular tracts).<sup>56</sup> The inflammatory infiltrate causes anagen arrest and abrupt cessation of hair shaft formation, causing a tapered and weakened hair shaft, manifesting clinically as the so-called “pencil/exclamation point hair.” As the disease progresses, anagen follicles shift to catagen and telogen and also miniaturize, although the total number follicles remains the same (Fig 7).<sup>55</sup> Peribulbar inflammation subsides as the number of anagen follicles is reduced. Residual inflammatory cells, including lymphocytes and eosinophils, may be present in follicular stelae (Fig 8). In chronic disease, the majority of follicles are in telogen phase and there is marked miniaturization (Figs 9 and 10). The recovery stage is characterized by a reduction in the inflammation, an increase in the proportion of anagen hairs, and a decrease in telogen hairs.<sup>57</sup>

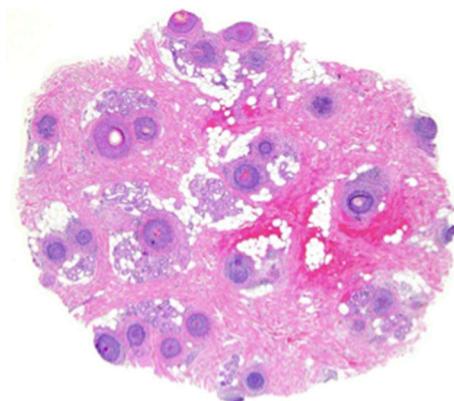
While a vertical section may be sufficient to diagnose AA in the active phase, in chronic disease, when inflammation may be less prominent, horizontal sectioning technique aids in accurate diagnosis by allowing the pathologist to visualize every follicle in the specimen, at different levels, from the subcutaneous fat to the epidermis, thereby assessing hair follicle density, diameters, and the distribution of follicles in different phases of the hair cycle.<sup>57</sup>

### Genetic studies

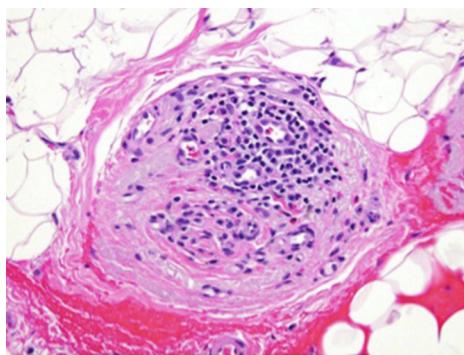
#### Key point

- Human leukocyte antigen I and II loci, genes involved in innate and adaptive immune pathways, and oxidative stress are implicated in AA

Initial candidate gene studies revealed the involvement of human leukocyte antigen (HLA)



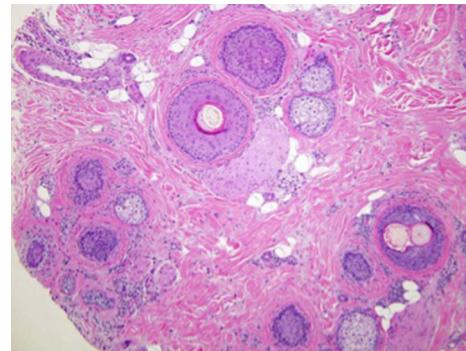
**Fig 7.** Peribulbar lymphocytic inflammation involving terminal and miniaturized follicles with marked shift to catagen and telogen. (Original magnification:  $\times 40$ .)



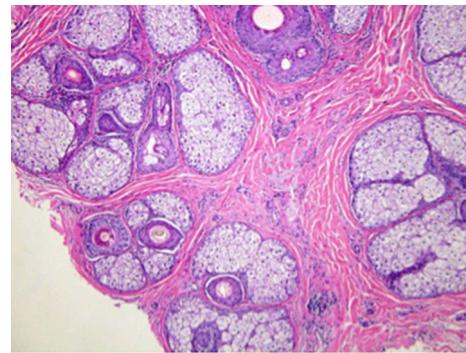
**Fig 8.** Lymphocytes, a few eosinophils, and melanin in a follicular stela. (Original magnification:  $\times 400$ .)

genes, which are important for antigen presentation in the pathogenesis of AA, as reviewed by Gilhar et al.<sup>40</sup> With the establishment of the National Alopecia Areata Foundation Registry, an extensive patient cohort became available for large-scale family-based genomewide linkage studies which further confirmed the involvement of HLA genes in 20 families with AA.<sup>58</sup>

Genome-wide association studies (GWASs) have greatly facilitated our understanding of the immune pathways involved in AA. The first GWAS for AA compared allele frequencies from 1054 unrelated patients with AA from the National Alopecia Areata Foundation Registry to 3278 control subjects.<sup>59</sup> The results from this study implicated both innate and adaptive arms of the immune system, including genes encoding the natural killer cell receptor (NKG2D, [natural-killer group 2, member D]) ligands UL16-binding proteins (ULBP) 3/6, cytotoxic T lymphocyte-associated protein 4 (CTLA-4), IL-2/IL-21 locus, IL-2 receptor A, and Eos in addition to previously identified HLA class II loci. The latest metaanalysis of GWASs for AA (now with 3253 cases



**Fig 9.** Horizontal sections showing a marked increase in the number of catagen and telogen follicles. (Original magnification:  $\times 100$ .)



**Fig 10.** Miniaturized follicles in chronic disease. (Original magnification:  $\times 100$ .)

and 7543 controls) further strengthened the initial GWAS findings and increased the number of risk loci from 8 to 16.<sup>60</sup> This study revealed the association of *ACOXL/BCL2L11*, *GARP*, and *SH2B3(LNK)/ATXN2*. These genes are related to autophagy/apoptosis, regulatory T cells (Tregs), and Janus kinase (JAK) signaling.<sup>60</sup>

An association was also demonstrated in the GWAS for the *ULBP* gene cluster on chromosome 6q25.1 that encodes activating ligands of NKG2D and notably ULBP3/6, which are novel risk genes that have not been identified in other autoimmune diseases.<sup>59</sup> These NKG2D ligands are stress-induced molecules that function as danger signals to alert immune cells via interaction with the NKG2D receptor. The majority of NKG2D<sup>+</sup> cells are CD8<sup>+</sup> T cells, which supports a role for CD8<sup>+</sup>NKG2D<sup>+</sup> cytotoxic T cells in AA.<sup>59</sup> Additional insight from C3H/HeJ mice suggests that CD8<sup>+</sup>NKG2D<sup>+</sup> T cells are in fact the dominant cell type in AA.<sup>61</sup>

Several of the genes identified in the GWASs are involved in directing Tregs, which exert immunoregulatory capacity on a broad range of effector cell types including T-helper 1, T-helper 2, and antigen-presenting cells to prevent immune

response against self-antigens.<sup>62</sup> Treg differentiation is dependent on IL-2 receptor A (CD25), IL-2, and a lineage determining factor Foxp3 that is regulated by Eos, a zinc finger transcription factor,<sup>63</sup> while CTLA-4 is a major determinant of Treg-suppressible capability.<sup>64</sup> Finally, IL-21 is a proinflammatory mediator that promotes the differentiation of T<sub>H</sub>17 effector cells while limiting Treg differentiation.<sup>65</sup>

Genome-wide analysis of copy number variants of candidate genes have also identified duplications in melanin-concentrating hormone receptor 2 (MCHR2) and MCHR2 antisense RNA 1 (MCHR2-AS1), which are both implicated in MCH signaling and further supports the hypothesis that genes affecting pigmentation are involved in AA.<sup>54</sup> Variants in syntaxin-17 (STX17), a SNARE protein, which plays a role both in autophagy and possibly pigmentation have been implicated in AA as well.<sup>59,66</sup> This gene is expressed in the follicle itself along with another gene, which also may be involved in AA, peroxiredoxin-5 (PRDX5). Dysregulation of PRDX5 may allow aberrant cells (potentially in response to oxidative stress) to survive which could result in the presentation of damaged self-antigens to the immune system promoting autoimmunity.<sup>67</sup> Identification of STX17 and PRDX5 suggested abnormalities other than immune response pathways and potential involvement of oxidative stress in the pathogenesis of AA.

### The Janus kinase/signal transducers and activators of transcription signaling pathway

#### Key point

- The Janus kinase/signal transducers and activators of transcription pathway is upregulated in alopecia areata but not in normal hair follicles

Human skin biopsy specimens from patients with AA show the overexpression of JAK3 and, to a lesser extent, JAK1 and JAK2 signaling.<sup>68</sup> Interferon-gamma (IFN- $\gamma$ ) signals through JAK1/2 while IL-15 signals via JAK1/3 (Fig 11). Several studies have shown that IFN- $\gamma$  is prominently expressed in lesional skin from patients with AA and is believed to contribute to the collapse of immune privilege through increased follicular expression of MHC class I and II molecules.<sup>46,50,69-72</sup> Blocking IFN- $\gamma$  with neutralizing antibodies at the time of grafting prevents AA development in mice, while reducing MHC upregulation and infiltration of CD8<sup>+</sup>NKG2D cells.<sup>61</sup> The IL-15 pathway is also upregulated in AA.<sup>61</sup> Both the IFN- $\gamma$  and IL-15 pathways are targeted by JAK inhibitors, including tofacitinib, ruxolitinib, and baricitinib (see the second article in this series for

more information). In addition, blockade of CXCR3 inhibits the downstream signaling of IFN- $\gamma$  and was found to prevent the development of AA in C3H/HeJ mice via inhibiting the recruitment of pathogenic T cells.<sup>73</sup> Blockade of CXCR3 may be a potential target of future therapeutics.

### Comorbidities

#### Key point

- Patients with atopy (including atopic dermatitis, asthma, and allergic rhinitis) and other autoimmune conditions may be more likely to develop alopecia areata

Increased risk of AA development in patients with atopy, including atopic dermatitis, asthma, and allergic rhinitis has been reported in various epidemiologic studies.<sup>74,75</sup> Multiple autoimmune diseases (including thyroid disease, psoriasis, and vitiligo) have been shown to have a high association with AA.<sup>76</sup> Co-occurrence of these diseases may be a result of shared genetic risk loci, immune cell populations, and cytokine profiles as identified by the GWASs.<sup>59,60</sup> Of note, GWASs have also revealed shared risk loci between AA and rheumatoid arthritis, celiac disease, and type I diabetes.

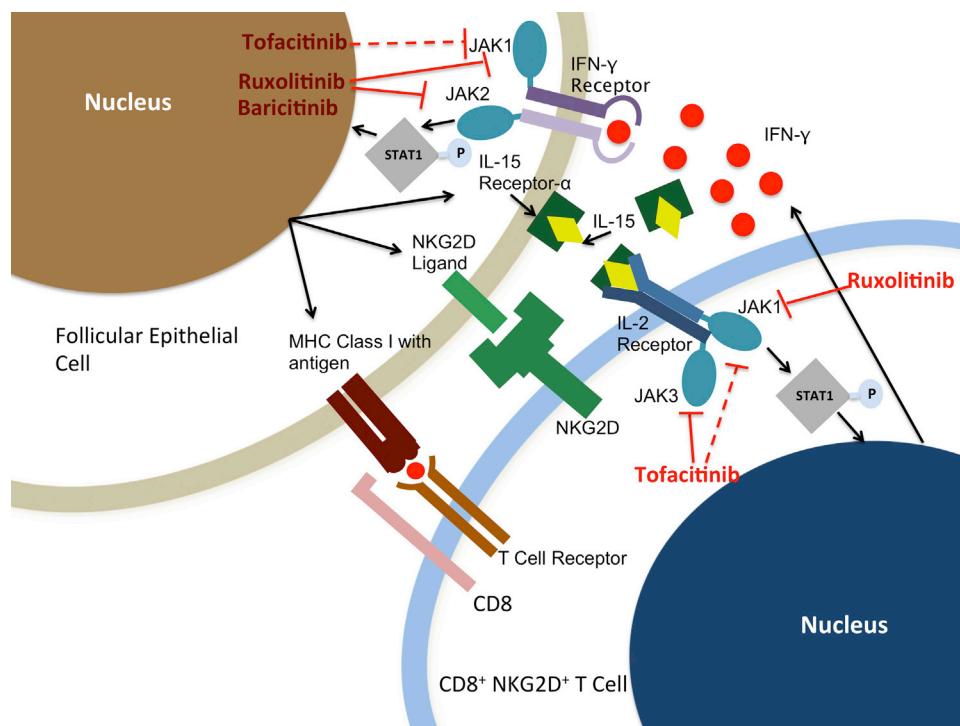
The development of AA could also have systemic effects on the body other than the skin. Cardiac hypertrophy has been identified in C3H/HeJ mice with AA in conjunction with higher levels of the serum heart disease marker cardiac troponin I.<sup>77</sup> While no differences in cardiovascular risk in human patients with AA have been found,<sup>78</sup> subclinical forms of heart damage may occur in patients with AA. Although not currently substantiated in AA, the circulating inflammatory cytokines certainly have the potential to adversely affect other organs, as seen in other autoimmune diseases like psoriasis, systemic lupus erythematosus, and rheumatoid arthritis.<sup>79-81</sup>

### OTHER FACTORS CONTRIBUTING TO ALOPECIA AREATA

#### Key points

- Epigenetic mechanisms may affect susceptibility to alopecia areata
- Stress and diet may contribute to the development of alopecia areata

**Epigenetics.** While there is a strong genetic component in AA with a 10-fold increased risk in first-degree relatives, there is only a 55% concordance rate in monozygotic twins, highlighting that there is missing heritability in AA.<sup>82</sup> Epigenetic mechanisms may therefore contribute to the susceptibility and rate of onset for AA. Many



**Fig 11.** In alopecia areata, CD8<sup>+</sup> T cells produce interferon-gamma (IFN- $\gamma$ ), which signals via Janus kinases 1 (JAK1) and JAK2 to enhance production of interleukin-15 (IL-15). In combination with the IL-15 receptor- $\alpha$  (chaperone protein), IL-15 binds to the surface of CD8<sup>+</sup> T cells leading to signaling through JAK1 and JAK3 to produce more IFN- $\gamma$ . The effect of the JAK inhibitors—tofacitinib, ruxolitinib, and baricitinib—are noted on this pathway. (Adapted with permission from Macmillan Publishers Ltd from Divito SJ, Kupper TS. Inhibiting Janus kinases to treat alopecia areata. Nat Med 2014;20:989-90. Copyright 2014.)

epigenetic mechanisms, such as histone modification, and microRNAs have recently been studied in AA, and increased methylation of genomic DNA and histone acetylation have been described in AA peripheral blood mononuclear cells.<sup>83,84</sup>

**Stress and psychiatric problems.** Stress and psychological disorders are among the most commonly cited causes of AA by patients, but the exact association is still debatable. A recent study reported a high prevalence of anxiety and depression among patients with AA.<sup>74</sup> However, the involvement of stress is likely at the molecular level with the secretion of stress hormones that may facilitate inflammation rather than as a direct cause.<sup>85</sup> In animal studies, dysregulation of hypothalamic-pituitary-adrenal activity was observed.<sup>86</sup> AA-affected mice displayed a delayed response to chronic psychological stress and blunted hypothalamic-pituitary-adrenal response to acute physiological stress; the expression of genes related to stress was also different in the brains of these mice.

**Diet.** Food with high dietary soy oil content seems to increase resistance to AA in C3H/HeJ mice.<sup>87</sup> Mice that received a high soy oil-containing diet showed hair regrowth after AA induction via

skin graft compared to those fed with a normal diet. A high soy diet may modulate estrogen-dependent mechanisms or inflammatory activity and prevent AA. In addition, soy oil may modulate the microbiome niche in mice, which has been shown to modulate autoimmune disease susceptibility.<sup>88,89</sup>

In conclusion, AA affects approximately 2% of the population and has many different clinical presentations, ranging from well-circumscribed patches of hair loss to diffuse alopecia. The main factors affecting prognosis include age at onset and disease extent. Recent evidence further supports an autoimmune etiology and upregulation of inflammatory pathways in AA. GWASs have helped to characterize the pathways involved in AA, including genes involved in innate and adaptive immunity, oxidative stress, and the Janus kinase/signal transducers and activators of transcription signaling pathway.

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# Alopecia areata



## An appraisal of new treatment approaches and overview of current therapies

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### Learning Objectives

After completing this learning activity, participants should be able to identify different classes of treatment options including injections, topical therapy, systemic medications, and phototherapy; explain the evidence supporting the use of each treatment, and list potential adverse effects; categorize the expected treatment outcomes for each therapy; and describe how new basic science research and insights into immune mechanisms of alopecia areata contribute to the development of new therapies. JAK inhibitors and phosphodiesterase 4 inhibitors represent important new options for severe alopecia areata. A new algorithmic approach will be presented integrating these new treatment modalities.

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Many therapies are available for the treatment of alopecia areata, including topical, systemic, and injectable modalities. However, these treatment methods produce variable clinical outcomes and there are no currently available treatments that induce and sustain remission. When making management decisions, clinicians must first stratify patients into pediatric versus adult populations. Disease severity should then be determined (limited vs extensive) before deciding the final course of therapy. The second article in this continuing medical education series describes the evidence supporting new treatment methods, among them Janus kinase inhibitors. We evaluate the evidence concerning the efficacy, side effects, and durability of these medications. An overview of conventional therapy is also provided with new insights gleaned from recent studies. Finally, future promising therapeutic options that have not yet been fully evaluated will also be presented. (J Am Acad Dermatol 2018;78:15-24.)

**Key words:** alopecia areata; alopecia totalis; alopecia universalis; corticosteroids; JAK inhibitors; minoxidil; topical immunotherapy.

### APPROACH TO TREATMENT

#### Key points

- Alopecia areata is unpredictable, and therefore no treatment may be appropriate for a subgroup of patients as spontaneous

remission rates range from 8% to 68%, depending on disease severity

- Extent of hair loss and age of the patient are the most important factors to consider when determining management approaches

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**Abbreviations used:**

AA:	alopecia areata
AT:	alopecia totalis
AU:	alopecia universalis
DPCP:	diphenylcyclopropenone
JAK:	Janus kinase
SADBE:	squaric acid dibutylester
SALT:	Severity of Alopecia Tool
TAC:	triamcinolone acetonide

- **Patients should be educated about hairpieces and camouflage techniques**

Few treatment methods have been evaluated by randomized control trials to determine the most efficacious modalities to treat alopecia areata (AA), and therefore it is challenging for clinicians to guide patients regarding the best therapeutic options. However, extent of hair loss and patient age are the most important factors influencing the approach to treatment (Fig 1). Other factors to consider include cost, patient compliance, and the degree of psychosocial impact of hair loss on the patient.<sup>1</sup> Patients should be referred to the National Alopecia Areata Foundation ([www.naaf.org](http://www.naaf.org)), which provides advice, support, opportunities to participate in research including clinical trials, and options to purchase products, such as hairpieces, scarves, and hats.

It is important to note that in some instances it may be appropriate not to medically treat AA, if this is consistent with the patient's wishes; however, most that seek dermatologic care desire therapeutic intervention. Counseling patients regarding the likelihood of spontaneous remission can help them make an informed decision on treatment. Rates of spontaneous remission range from approximately 8% for extensive disease (>50% scalp involvement) to as high as 68% for limited alopecia (<25% scalp involvement).<sup>2</sup>

Patients should also be advised on the products available to conceal hair loss. Individuals with >50% hair loss may wish to have a scalp prosthesis made. These can be bought readymade or can be customized for an individual, which can take several weeks. Hairpieces range from offering partial to full scalp coverage and can be made from human or synthetic fibers. In general, wigs made from human hair are more expensive and less durable. Another approach to minimizing the appearance of hair loss involves semipermanent hair additions that may be bonded, glued, or sewed to existing hairs and are worn for up to 8 weeks at a time (Fig 2). Those with eyebrow loss may consider artificial eyebrows that are glued to the superior orbital ridge.<sup>3</sup> Alternatively,

patients may elect to undergo manual microblading, a semipermanent tattoo used to create the appearance of eyebrow hairs.

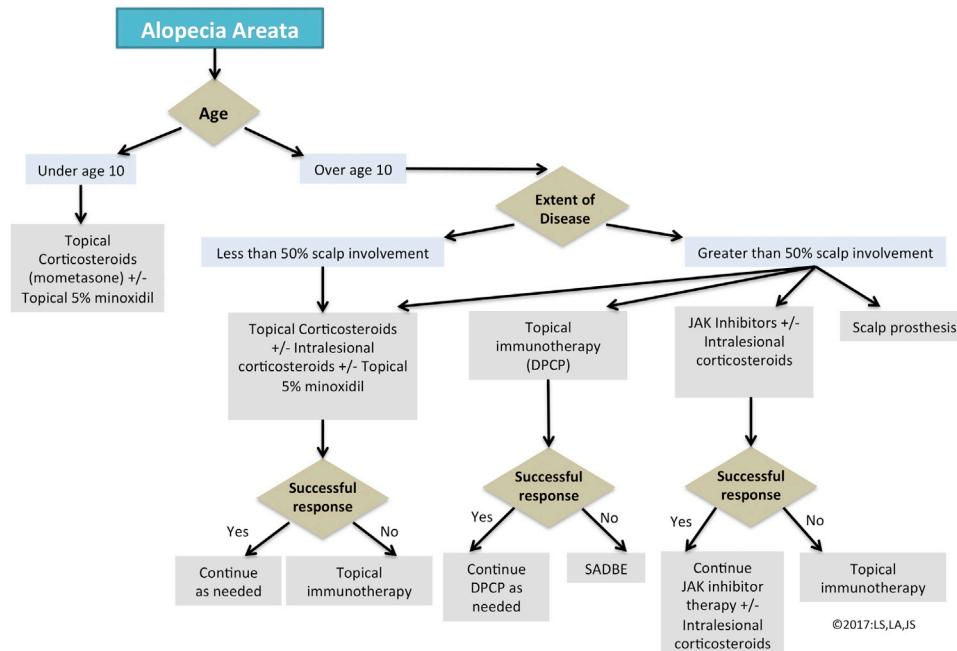
## INTRALESIONAL CORTICOSTEROIDS

### Key points

- **Intralesional corticosteroids are considered a first-line treatment method for limited disease, and can be used as adjunctive therapy in extensive disease**
- **Patients should be monitored for side effects, including skin atrophy, which may warrant dose modification or treatment discontinuation**

Intralesional corticosteroids, most commonly triamcinolone acetonide (TAC), are the criterion standard for treating patchy AA of limited extent and for cosmetically sensitive areas, such as the eyebrows. Tan et al<sup>4</sup> reported that 82.1% of 127 patients with limited AA showed >50% improvement with intralesional TAC injections for 12 weeks. Those with moderate to severe AA had poorer results, with 25% to 50% regrowth after 6 months.<sup>4</sup> Another retrospective review of 10 patients with >50% scalp involvement who were treated with TAC injections showed those with a better response tended to be younger (33 vs 53 years of age) and had AA for a shorter duration of time (2.5 vs 16.7 years). One interesting observation was that in the responder group 5 of 6 patients had a positive pull test, while 4 of 6 had exclamation point hairs on examination. In the nonresponder group, all had a negative pull test and only 1 had evidence of exclamation hairs. Because the pull test and exclamation point hairs may be regarded as indicators of inflammation, this suggests that patients with clinical evidence of active inflammation are better candidates for intralesional TAC.<sup>5</sup>

It has been recently reported that 2.5 mg/mL TAC confers the same benefit as either 5 or 10 mg/mL in patients with patchy AA.<sup>6</sup> Therefore, the authors recommend using low-dose TAC at a higher volume for the scalp (2.5 mg/mL, total volume 8 mL) and the same dose for the eyebrows with ≤0.5 mL volume into each eyebrow.<sup>6</sup> Discontinuation of therapy may be considered if the patient fails to respond within 3 to 6 months. Though intralesional steroids as monotherapy may be inadequate for extensive AA, in the experience of the authors, this treatment can be used as an adjunctive therapy to systemic treatment and may accelerate the effects of oral corticosteroids and response to Janus kinase (JAK) inhibitors.<sup>7</sup> Side effects include skin atrophy at the site of injection, which typically resolves after a few



**Fig 1.** Treatment algorithm for the management of alopecia areata. *DPCP*, Diphenylcyclopropane; *JAK*, Janus kinase; *SADBE*, squaric acid dibutylester.



**Fig 2. A and B.** This alopecia areata patient has hair extensions braided onto existing hairs.

months. This may be avoided if lower volumes of corticosteroids are injected at or below the dermoepidermal junction.<sup>8</sup> Caution should be exercised with injections near the eyes, such as into the eyebrows, because there is a small risk for increased intraocular pressure, glaucoma, and cataracts.<sup>9</sup>

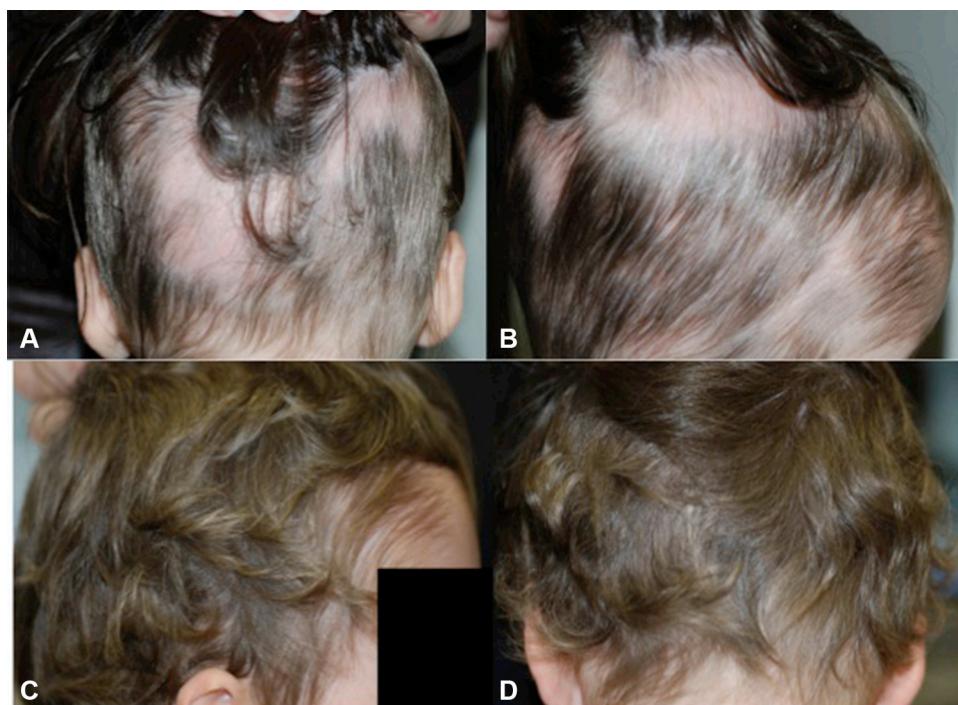
## TOPICAL CORTICOSTEROIDS

### Key points

- **Topical corticosteroids may be used alone or in conjunction with other treatments, including intraleisional corticosteroids**
- **Pediatric patients may prefer treatment with topical corticosteroids compared to injections**

Topically applied corticosteroids likely provide some benefit in AA, especially in patients with

limited disease, although the results may be inferior to intraleisional therapy. Evidence from split scalp studies has confirmed that regrowth results from local and not systemic effects of the medication.<sup>10</sup> In 54 patients with patchy AA who applied either 0.25% desoximetasone or placebo twice daily for 12 weeks, complete regrowth was higher among the corticosteroid-treated group (57.7% vs 39.3%); however, the difference between the groups was not statistically significant. Of the patients who did not achieve complete regrowth, 19 opted for treatment with intraleisional TAC, and while only 14 were available for follow-up, 13 of these patients achieved complete regrowth within 1 to 3 months. In fact, the response rate to intraleisional TAC in this study was significantly better than to desoximetasone cream ( $P = .03$ ).<sup>11</sup> Others have also shown approximately a 60%



**Fig 3.** **A** and **B**, This pediatric patient with alopecia areata was treated with 0.1% mometasone cream and 5% minoxidil solution twice daily, with (**C** and **D**) significant evidence of regrowth 2 months later. When the patient attempted to taper treatment, the alopecia returned.

response rate to topical corticosteroids.<sup>12</sup> Results from a study with a predominantly pediatric population (19/28) revealed that those <10 years of age and those with an AA duration of <1 year tended to respond more frequently to treatment with topical corticosteroids (0.2% fluocinolone acetonide cream).<sup>12</sup>

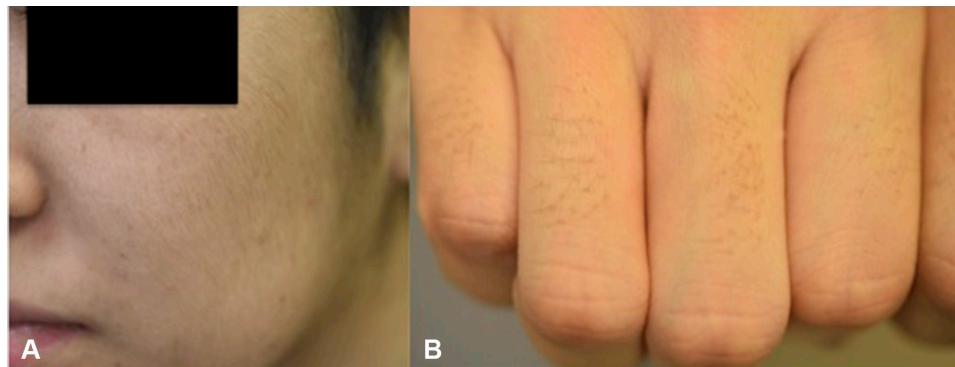
We typically recommend 0.05% clobetasol propionate foam, a superpotent steroid. However, in children <10 years of age, the less potent mometasone is more commonly used (Fig 3). In our clinic, we have noted that this treatment can be an effective monotherapy for patchy alopecia, especially among pediatric patients who are unable to tolerate injections. Clobetasol propionate foam without occlusion is considered more cosmetically acceptable and convenient for the patient compared to other formulations. This treatment method was evaluated in 34 patients with moderate to severe AA enrolled in a randomized, double-blind placebo controlled trial spanning 24 weeks. After 12 weeks, greater hair regrowth was noted on 89% of scalp sites treated with clobetasol foam versus 11% of sites treated with placebo.<sup>13</sup> Adverse effects of topical corticosteroids include mild itching, burning, acneiform eruption of the face (more common with ointment preparations than foam), striae, telangiectasia, and skin atrophy.<sup>14</sup>

## MINOXIDIL

### Key point

- **5% minoxidil foam or solution may be used as adjuvant therapy in alopecia areata**

As a monotherapy for AA, minoxidil may be insufficient to promote complete hair regrowth. Nonetheless, many studies have suggested that it does stimulate hair growth in patients with AA, though less commonly in severe forms of the disease. For example, a long-term study of 30 patients evaluated the efficacy of 3% minoxidil twice daily compared to placebo for 12 weeks followed by 52 weeks of minoxidil treatment. At 12 weeks, the treated group had slightly more growth compared to the placebo group, but these results failed to reach statistical significance. At 64 weeks, the results seemed to correlate with the degree of initial hair loss. Of the patients with complete scalp hair loss at baseline, all demonstrated no or slight hair growth, while of the 20 patients with less than full scalp involvement, 45% had cosmetically acceptable hair growth.<sup>15</sup> Another study evaluated 3% minoxidil solution in a double-blind placebo controlled protocol for 1 year that included 19 subjects with extensive AA (>50% scalp involvement). In the minoxidil group, 63.6% of patients had increased hair growth compared with 35.7% of those treated



**Fig 4. A and B,** This female patient with alopecia areata developed hypertrichosis on her hands and face after 8 weeks of twice daily 5% minoxidil foam application.

with placebo. This study found that in patients treated with minoxidil on one side of the scalp, hair increased on both sides but grew earlier and denser on the treated side.<sup>16</sup> Finally, minoxidil may help maintain hair growth stimulated by other treatments. Olsen et al<sup>17</sup> found that in patients treated with a prednisone taper, those who also used 2% topical minoxidil (3 times daily) for  $\geq 6$  weeks after maintained hair growth more frequently than those treated with placebo. The authors recommend 5% minoxidil as opposed to lower strengths because higher concentrations have been reported to be more effective, though there may be an increased likelihood of unwanted hair growth on other parts of the body compared to lower concentrations.<sup>18,19</sup>

Collectively, these results suggest that topical minoxidil may provide some benefit in patients with AA, though likely cannot alter the disease course or induce remission.<sup>15</sup> This medication is easy to use, and side effects are usually mild, including scalp itching and dermatitis.<sup>16</sup> Rarely, around 2% to 5% of patients may develop sparse vellus hairs on other parts of the body (Fig 4), and very infrequently some may experience tachycardia.<sup>20</sup>

## ORAL CORTICOSTEROIDS

### Key point

- Short courses (6 weeks) of oral corticosteroids are often sufficient to stimulate hair regrowth; however, the side effect profile precludes long-term use and the likelihood of relapse is significant

Systemic corticosteroids are widely used in autoimmune diseases and have demonstrated a significant benefit in most clinical variants of AA, with reduced efficacy in ophiasis and alopecia universalis (AU) types.<sup>21</sup> In a study of 32 patients who completed at least a 6-week course of

prednisone at a dose of  $<0.8$  mg/kg, 47% showed  $>25\%$  regrowth, while 25% of the patients had  $>75\%$  regrowth. Notably, 50% of these patients had alopecia totalis (AT) or AU.<sup>17</sup> This study shows that a short course of steroids is often sufficient to treat AA (Fig 5), though others have described patients treated with 3 to 5 months of therapy, and at a dose of 20 to 30 mg/day with similar results.<sup>4</sup> However, the response to pulse steroids may not be durable, and many patients will relapse within 4 to 9 weeks after discontinuing steroids.<sup>22</sup> The side effects of steroids generally preclude their long-term use. These include suppression of the pituitary–adrenal axis, effects on bone growth or integrity, ocular changes, and worsening of hypertension or diabetes.<sup>23</sup>

## METHOTREXATE

### Key point

- Methotrexate may be effective for patients who fail standard therapy

Successful treatment of AA with methotrexate has been reported in both adult and pediatric populations. Chartaux and Joly<sup>24</sup> described 33 patients with either AT or AU (mean disease duration, 7.7 years) who failed standard therapy and found that methotrexate (15–25 mg) alone or in combination with oral corticosteroids (prednisone 10–20 mg/day) resulted in complete hair regrowth in 63% of those on combined treatment and 57% of those treated with methotrexate alone. Another study by Royer et al<sup>25</sup> examined 14 children with severe AA who had failed to respond to conventional treatment. These patients were treated with a mean dose of 18.9 mg methotrexate (range, 15–25 mg), and 8 of 14 also received oral corticosteroids. Of the 13 children available for assessment, 5 had a successful response with  $>50\%$  regrowth (4 of these were also treated with short-term corticosteroids) and started responding after approximately 4.4 months.<sup>25</sup> These



**Fig 5.** A 28-year-old Asian female with acute diffuse and total alopecia areata at the initial visit (**A-C**) underwent treatment with 40 mg prednisone taper over 8 weeks combined with monthly intralesional corticosteroids, 5% minoxidil foam, and clobetasol solution twice daily. **D-F**, Significant regrowth was observed 8 weeks later.

results suggest that methotrexate may be a viable treatment option for refractory and severe AA.

## TOPICAL IMMUNOTHERAPY

### Key points

- Diphenylcyclopropenone has a success rate of approximately 60% to 70%, and is an option for the treatment of patients with extensive disease (>50% scalp involvement)
- Patients who do not respond to diphenylcyclopropenone may be treated with squaric acid dibutylester

Topical immunotherapy, including squaric acid dibutylester (SADBE) and diphenylcyclopropenone (DPCP), causes an allergic contact dermatitis and through an incompletely understood mechanism may cause antigenic competition, changing the milieu of immune cells surrounding hair follicles.<sup>26</sup> There is evidence to support its use in extensive AA, even for pediatric patients >10 years of age (Fig 6).<sup>1,27-30</sup> Patients who will undergo treatment with DPCP should first be sensitized using 2% DPCP to a circular area 4 cm in diameter. DPCP should be obtained from a pharmacy familiar with compounding it in acetone. Next, 0.001% DPCP is applied unilaterally beginning 1 week later with an increase in the concentration during each subsequent week until the patient develops a desired

mild tolerable dermatitis (with pruritus and erythema) that lasts 36 hours. Once the concentration that is effective for the patient is determined, this should be applied by the physician or nurse on a weekly basis. During the 48 hours after treatment, DPCP should remain on the scalp and should be covered to prevent exposure to light, which degrades the molecule. Once there is a trichogenic response on one side, then both sides are treated.<sup>31,32</sup> A greater risk for relapse after discontinuation of DPCP may be observed if the dose is not tapered, and therefore patients should be advised that treatment should not be interrupted suddenly.<sup>33</sup> A recent study reviewed 20 years of experience using DPCP for AA and found an overall response rate of 72.2%.<sup>34</sup> Durdu et al<sup>35</sup> reported that the efficacy of DPCP may be enhanced by combination therapy with anthralin (0.5-1.0%), which causes an irritant dermatitis. This study included 74 treatment-resistant patients, 47 of whom were treated with combination DPCP and anthralin. Combination therapy was shown to be more effective (88% of patients had >50% regrowth vs 54.5% for DPCP alone), elicited faster hair growth (regrowth duration was 4 weeks shorter), and importantly regrowth of eyelashes, eyebrows, and beard was also significantly better among the combination group. No significant differences in relapse rates between the 2 groups were identified.<sup>35</sup>



**Fig 6. A-D,** A 12-year-old female with alopecia areata who was noted on the initial examination to have sparse hairs only on the top of her scalp and who was treated with 1.5% diphenylcyclopropenone.

For patients who fail to respond successfully to DPCP, therapy with SADBE may be tried, with a similar efficacy as DPCP.<sup>28,33,36</sup> Of note, a recent study on SADBE reported that, unlike DPCP, an initial eczematous reaction to sensitization is not required for successful treatment. These investigators reported that of the 4 patients who chose not to undergo sensitization or who did not exhibit a response, all had regrowth.<sup>37</sup> Regarding efficacy, in a study of 54 patients with different clinical subtypes of AA treated with SADBE (3%) therapy, 79.6% of patients experienced complete regrowth compared to 50% regrowth in controls. Patients with more severe disease required significantly greater treatment times on average (AU, 45 weeks; AT, 32 weeks; patchy AA, 29 weeks). Over a follow-up period of 2 to 8 years, those treated with SADBE had reduced severity of relapse compared to the control group.<sup>38</sup> Topical sensitizers should not be used in pregnant women because the teratogenic effects and degree of systemic absorption of these compounds are unknown. Side effects from topical sensitizers include severe eczema and cervical and occipital lymphadenopathy, among others.<sup>34</sup>

## NOVEL THERAPEUTIC METHOD USING JANUS KINASE INHIBITORS

### Key points

- Oral Janus kinase inhibitors, including tofacitinib, ruxolitinib, and baricitinib, have

### been shown to be efficacious in alopecia areata

- The durability of response to these medications is variable, and most patients experience recurrence of hair loss after discontinuation
- Topical Janus kinase inhibitors may also be effective but have not been fully evaluated

JAK inhibitors have already demonstrated efficacy in multiple inflammatory diseases, such as psoriasis, rheumatoid arthritis, and vitiligo, with further new successful reports in treating  $T_{H}2$ -driven diseases, such as atopic dermatitis.<sup>39-43</sup> Dramatic hair regrowth was observed in preclinical studies using JAK inhibitors in C3H/HeJ mice, and this provided a strong rationale to test these medications in humans.<sup>44</sup> The first reports demonstrating efficacy of a JAK inhibitor in AA were a patient with AU treated with tofacitinib who experienced extensive hair regrowth, and 3 patients treated with ruxolitinib who had changes in biomarkers to resemble healthy controls.<sup>44,45</sup>

These early case reports were then corroborated by 2 open-label studies. One study was an open-label trial of ruxolitinib in patients with moderate to severe AA. Of the 12 patients in this study (treated with 20 mg twice daily for 3-6 months), the results were impressive, with 75% of patients responding successfully and an average regrowth of 92% at the end of treatment

among responders. However, during a 3-month, treatment-free follow-up period, 3 of 9 responders had marked shedding, while 6 had some shedding. Baseline scalp biopsies from these AA patients revealed gene expression profiles with elevated immune pathways that normalized after ruxolitinib treatment. In addition, responders appeared to demonstrate high interferon and cytotoxic T lymphocyte scores at baseline, while those who were nonresponders were noted to have lower interferon and cytotoxic T lymphocyte scores at baseline. The investigators speculated that nonresponder patients may therefore have an alternative etiology for their hair loss separate from the interferon-driven mechanism targeted by JAK inhibitors.<sup>46</sup>

The second open-label study evaluated oral tofacitinib (5 mg twice daily) in 66 patients with various forms of AA. This study found that overall 64% of patients responded to treatment and 32% achieved an improvement in the Severity of Alopecia Tool (SALT) score of >50% after 3 months of therapy. These findings were also corroborated by normalization of gene expression biomarkers in scalp biopsy specimens after treatment. To assess durability of response, patients were reevaluated during a 3-month treatment-free follow-up period. However, only 20 patients were available for follow-up, and all experienced hair loss (median 8.5 weeks after stopping treatment). Neither age nor sex appeared to correlate with change in SALT score, though subtype did affect mean percentage change in SALT; those with patchy AA showed a 34% greater change compared to AU ( $P = .0005$ ), while ophiasis had a 48% greater change compared to AU ( $P = .006$ ). Each additional year of disease resulted in a decrease in percentage change of SALT score by 0.78 ( $P = .0247$ ).<sup>47</sup> A third larger retrospective analysis of 90 patients with AA (the majority with AU or AT) treated with tofacitinib revealed an overall response rate of 77% (moderate, intermediate, or complete response). While this study failed to find a significant correlation between patient age and change in SALT score, a reduced likelihood of response to treatment in those with a >10-year duration of AA was identified.<sup>48</sup> Finally, the use of tofacitinib among adolescents was recently reported in a retrospective study that demonstrated regrowth in 9 of 13 patients with AA between 12 and 17 years of age. Tofacitinib given at 10 to 15 mg daily was well tolerated among these patients and no serious adverse events reported; however, the potential side effects should be carefully weighed in pediatric patients.<sup>49</sup>

Baricitinib has been reported in a patient with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome with concomitant ophiasis type AA. Though the ophiasis pattern of AA tends to be recalcitrant to treatment, improvement was noted shortly after initiating baricitinib, with complete regrowth after 9 months of treatment.<sup>50</sup> The use of ruxolitinib is also supported by a case report of a patient with AU being treated for essential thrombocytopenia (15 mg twice daily) who showed near complete regrowth after 10 months of treatment, and in a patient treated for AA along with chronic mucocutaneous candidiasis.<sup>51,52</sup> Finally, 2 cases of successful treatment of AU with tofacitinib have been reported.<sup>53</sup>

In general, side effects of JAK inhibitors include (potentially serious) infections, viral reactivation, bone marrow disruption, transaminase changes, and a theoretical—though unproven—risk for malignancy.<sup>46,54,55</sup> Given the serious adverse effects that could potentially result from long-term systemic JAK inhibitor therapy, some have considered the use of topical JAK inhibitors in place of systemic agents. However, this treatment modality has not yet been evaluated in large studies. One case reported a patient with AU who had previously failed most available treatment methods (including oral prednisone, intralesional corticosteroids, sulfasalazine, and topical immunotherapy) and was then treated with topical ruxolitinib 0.6% cream twice daily to the scalp and eyebrows. After 12 weeks, the eyebrows were improved and there was regrowth of 10% of the scalp hairs.<sup>56</sup> These encouraging results suggest that topical JAK inhibitors warrant additional study and could be improved by more sophisticated formulations targeting the hair follicle and reticular dermis.

## FUTURE DIRECTIONS

### Key point

- Existing medications are being evaluated for their utility in AA

Statins may have antiinflammatory properties,<sup>57</sup> and recently 40 mg/10 mg daily simvastatin/ezetimibe for 24 weeks was investigated in patients with AA (40–70% scalp involvement). Of the 19 patients who completed the study, 14 were considered responders, suggesting that this treatment method should be explored in future studies.<sup>58</sup> Apremilast, an oral phosphodiesterase-4 inhibitor, has been shown to prevent AA development in human scalp skin grafts in mice and is currently under investigation in a clinical

trial.<sup>59</sup> A topical phosphodiesterase-4 inhibitor, crisaborole, is now commercially available for the treatment of mild to moderate atopic dermatitis and could also be useful in AA.<sup>60</sup> Overall, there may be new treatment options on the horizon for patients with AA.

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# Practical management of acne for clinicians: An international consensus from the Global Alliance to Improve Outcomes in Acne



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Scientific advances are continually improving the knowledge of acne and contributing to the refinement of treatment options; it is important for clinicians to regularly update their practice patterns to reflect current standards. The Global Alliance to Improve Outcomes in Acne is an international group of dermatologists with an interest in acne research and education that has been meeting regularly since 2001. As a group, we have continuously evaluated the literature on acne. This supplement focuses on

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providing relevant clinical guidance to health care practitioners managing patients with acne, with an emphasis on areas where the evidence base may be sparse or need interpretation for daily practice. (J Am Acad Dermatol 2018;78:S1-23.)

**Key words:** acne vulgaris; adult acne; scar; post-inflammatory hyperpigmentation.

## INTRODUCTION

Acne is a chronic inflammatory skin disease that is estimated to affect approximately 85% of the population at some point in their lives.<sup>1</sup> Generally straightforward to recognize clinically, acne has a variable presentation with a constellation of lesion types including open and closed comedones, papules, pustules, nodules, and cysts.<sup>1,2</sup> The face is involved in most cases, and the trunk is affected in up to 61% of patients.<sup>3-6</sup> Acne lesions can progress to scars, postinflammatory hyperpigmentation (PIH), or both, which can be bothersome to patients.<sup>3,7,8</sup> The pathogenesis is multifactorial, involving the hormonal influence of androgens along with excess sebum production, disturbed keratinization, inflammation, and stimulation of the innate immune system by several pathways including hypercolonization by *Propionibacterium acnes*.<sup>9-11</sup>

Although acne is a very common disease, little time is spent on it in medical curricula, even within dermatology modules.<sup>12</sup> In fact, dermatology education as a whole is lacking in medicine in some countries; 33 US medical schools have no undergraduate dermatology programs, and more than half of American medical schools teach <10 hours of dermatology.<sup>12,13</sup> In Europe, which is home to 25,000 dermatovenerologists, teaching hours vary between 18 to 60 hours during medical

undergraduate training; however, all medical schools teach dermatovenerology. Scientific advances are continually improving the knowledge of acne and contributing to the refinement of treatment options; it is important for clinicians to regularly update their practice patterns to reflect current standards. The Global Alliance to Improve Outcomes in Acne is an international group of dermatologists with an interest in acne research and education that has been meeting regularly since 2001. As a group, we have continuously evaluated the literature on acne. We created consensus recommendations about acne management based on our experience and available research, which were published in 2 previous supplements to the *Journal of the American Academy of Dermatology*.<sup>9,10</sup> Outside of the Global Alliance, we have also each been involved in creating evidence-based national and international guidelines for acne management, including those published by the European Dermatology Forum (EDF); the Colegio Ibero-Latinoamericano de Dermatología; the Indian Society Dermatology, Venereology, and Leprosy; and the American Academy of Dermatology (AAD).<sup>3,14,15</sup> In our experience, evidence-based guidelines and clinical consensus recommendations can be quite different. Evidence-based guidelines rate the quality of evidence supporting available

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**Conflicts of interest:** All authors have served as advisory board members for Galderma and received honoraria. In addition, Dr Thiboutot has received fees and research funding for serving as a consultant and investigator for Allergan, Mimetica, Novan, and Sebacia and as a consultant for Dermira, Galderma, Photosonix, and Xenon. Dr Dreno has received honoraria serving as an advisory board member for Meda. Dr Alexis has received consulting fees from Roche, honoraria serving as an advisory board member for Allergan and Foamix and received grants paid to his institution for serving as an investigator for BioPharmix, Allergan, and Novan. Dr Araviiskaia has served as an advisory board member for L'Oréal and Vicy and received honoraria for speaking for La Roche Posay, Astellas Pharma, Pierre Fabre, Uriage, Jadran JGL, Glenmark, Meda, and Bayer Healthcare. Dr Costa has received honoraria and grants serving as an advisory board member for Hypermarcas, L'Oréal, and Avon and as an investigator for Galderma and Hypermarcas. Dr Hayashi received fees and honoraria serving as a speaker and consultant for Maruho and Glaxo SmithKline and as a speaker for Pola Pharma. Dr Herane has received honoraria serving as an advisory board member for Galderma. Dr Layton has received grants, fees, research funding, and honoraria for serving as an advisory board member, speaker, and

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investigator for Galderma, a consultant for Glaxo SmithKline, and an investigator and speaker for Meda. Dr Leyden has received honoraria serving as an advisory board member for Allergan and a consultant for BioPharmX, Uniliver, Cutanea, and Foamix. Dr See has received honoraria serving as an advisory board member for Allergan and Meda. Dr Tan has received honoraria and grants serving as an advisory board member for Allergan, Bayer, Cipher, Valeant, and Roche; a speaker for Cipher, Valeant, and Pierre Fabre; an investigator for Dermira, Galderma, and Xenon; and a consultant for Galderma, Xenon, and Boots/Walgreens. Dr Torres has received honoraria servinh as an advisory board member for Galderma. Dr Troielli has received honoraria serving as a speaker for La Roche Posay and a speaker and investigator for Galderma.

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*Abbreviations used:*

AAD:	American Academy of Dermatology
A/BPO:	adapalene/benzoyl peroxide
EDF:	European Dermatology Forum
FASET:	Facial Acne Severity Evaluation Tool
FDA:	Food and Drug Administration
IGA:	Investigator Global Assessment
OC:	oral contraceptive
OG:	olumacostat glasaretil
PIH:	postinflammatory hyperpigmentation

treatment options, but do not strongly advise the clinician about creating a practical treatment approach. Clinical consensus recommendations use expert opinion and experience and focus more on the philosophy of treatment, the individual patient, as well as clinical experience of what options work well in particular situations.

In this supplement, we aimed to identify the core principles of an effective acne management strategy using the Delphi method to reach consensus. The goal was to help guide clinicians to understand efficient acne therapeutic strategies that could be readily implemented in the office. We particularly focused on areas where the existing evidence base is less robust and expert opinion could have a role in refining practice patterns.

## DELPHI METHODOLOGY

A live meeting of the Steering Committee of the Global Alliance group was held to identify areas of acne management that could be useful to clinicians but that were not well defined in existing evidence-based guidelines. Topics discussed included acne grading, recent data with topical therapies, combination regimens for acne, and special topics of interest (acne in women, postinflammatory hyperpigmentation, and scarring). It was agreed that the Delphi methodology could be used to help create a strategic approach to acne.

A Delphi panel and questionnaire method was used to provide a systematic framework for arriving at consensus. This methodology incorporates expertise into a collective judgment via a panel of experts who respond to a set of questionnaires.<sup>16</sup> The panel comprised 36 internationally recognized dermatologists from 27 countries (Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Colombia, France, Germany, India, Italy, Japan, Mexico, Malaysia, Morocco, Philippines, Russia, Saudi Arabia, Singapore, South Korea, Spain, Sweden, Thailand, United States, United Kingdom, Venezuela). All were members of the Global Alliance international and regional groups.

An online questionnaire was developed by a selected subgroup of the Global Alliance Steering Committee and then distributed to panel members. Participants were asked to rate agreement with each statement on a 5-point Likert scale (strongly agree, agree, disagree, strongly disagree, unable to answer). Those who selected disagree, strongly disagree, or unable to answer were prompted to provide a written explanation of what they disagreed with. Responses from the first survey were classified as round 1, analyzed, and a summary of all areas of consensus and individual statements of disagreement was prepared. The results, along with modified survey questions (round 2), were sent to respondents. Again, results were collected and analyzed to arrive at the final results, which are presented here. The final statements and document were edited and reviewed by the panel. Consensus was defined as agreement among  $\geq 75\%$  of the dermatologists who participated in the panel. The statements and voting results are presented as *Supplemental Table I* (available at <http://www.jaad.org>).

## CONSENSUS RECOMMENDATIONS

### Assessing acne severity: impact of new topical medications

There is no standardized acne grading or classification system; however, acne is often categorized by an overall gestalt as mild, moderate, and severe in guidelines and recommendations as well as by clinicians treating patients.<sup>2,3,14</sup> These categories are useful to help guide selection of therapy but are chosen on the basis of the subjective opinion of the physician. As a more objective measure of severity, lesion counts or estimates may be used to help define acne severity.<sup>3,17</sup> For example, acne research trials typically associate a range of lesion counts to objectively classify acne severity, along with an Investigator Global Assessment (IGA).<sup>3,17,18</sup> But one problem in defining objective assessments is that lesion counts alone do not accurately convey subjective aspects of acne, such as variations in lesion size and visibility (Fig 1).<sup>18</sup> Furthermore, clinical studies in the past did not differentiate between small nodules  $>0.5-1$  cm and those  $>1$  cm, which is of clinical importance regarding selection of treatments and response rate. Therefore, comparison of evidenced-based clinical studies in moderate-to-severe acne is often not possible.<sup>3</sup>

Another problem in categorizing acne severity has emerged with the development of new, highly efficacious topical acne medications: how to denote acne severity in patients who might be good candidates for strong topical medications versus those who are best suited by early institution of



**Fig 1.** Illustration of differences in lesions of acne vulgaris that could affect overall assessment of acne severity but not lesion counts. Photos courtesy of DermQuest.com. Copyright © 2006 Galderma S.A. All rights reserved.

**Table I.** Investigator Global Assessment scale recommended by the US Food and Drug Administration<sup>17</sup>

Grade	Clinical description
0	Clear skin with no inflammatory or noninflammatory lesions
1	Almost clear; rare noninflammatory lesions with more than one small inflammatory lesion
2	Mild severity; greater than grade 1; some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than grade 2; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4	Severe; greater than grade 3; up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions

Scale not intended to cover candidates for oral isotretinoin therapy.

oral isotretinoin.<sup>19,20</sup> Many practicing dermatologists perceive the term severe to refer primarily to nodular/conglobate acne, which is appropriately treated with oral isotretinoin.<sup>2</sup> Now, however, there might be a need for a more refined system of classifying moderately severe, severe, and very severe that aligns with additional potential first-line treatment options. The 2016 European S3 Acne Guideline has used the following 4-point classification system that might help to approach these issues in a practical fashion<sup>3</sup>: 1) comedonal acne, 2) mild-moderate papulopustular acne; 3) severe papulopustular acne, moderate nodular acne; and 4) severe nodular acne, conglobate acne. Similarly, the IGA scale recommended by the US Food and Drug Administration (FDA) considers quality of lesions and quantity (Table I).<sup>17</sup> This scale also includes a grade of severe acne that is separate from nodular/conglobate acne. We propose that the designation very severe be reserved for cystic and conglobate acne, which are illustrated in Fig 2.

**Single-agent topical therapy for severe inflammatory acne.** Recently, there have been several studies of topical combination therapy that included patients that would be categorized as severe inflammatory acne (grade 3 on the European Union scale or grade 4 on the US FDA

scale). In 2016, Stein Gold et al reported that the fixed combination adapalene 0.3%/benzoyl peroxide 2.5% (A/BPO 0.3%) was the “first topical fixed-combination agent therapy developed for severe inflammatory acne.”<sup>20</sup> A/BPO 0.3% was evaluated in a 50%-50% population of subjects with moderate and severe acne (defined as moderate [IGA score of 3] or severe [IGA score of 4] with 20-100 inflammatory lesions, 30-150 noninflammatory lesions, and  $\leq 2$  nodules on the face).<sup>20</sup> A/BPO 0.3% was efficacious across the population and well tolerated (Fig 3); further, in the severe population A/BPO 0.3% showed significantly greater efficacy in achieving success (clear or almost clear or a 3-grade improvement) and reductions in lesion counts versus vehicle ( $P = .029$  for success and  $P < .001$  for lesion counts).<sup>20</sup> Stein Gold et al concluded that A/BPO 0.3% could have an important systemic antibiotic-sparing role for patients with moderate and severe inflammatory acne, particularly because it targets the microcomedone.<sup>20</sup> These investigators also suggested A/BPO 0.3% could be used alone or in combination with other therapies before moving to oral isotretinoin or while gaining access to oral isotretinoin therapy.<sup>20</sup>

Phase 2 studies with novel agents have also been published recently for moderate-to-severe acne. A

**Severe (can include some nodules)**



A

**Very Severe (Cystic/conglobate)**

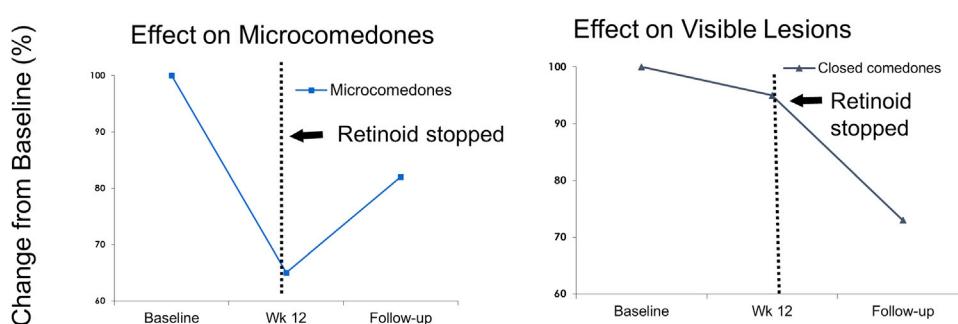


B

**Fig 2.** Illustrative photos of severe inflammatory acne vulgaris, largely without nodules (A). B, Very severe acne with cysts. Photos courtesy of [DermQuest.com](http://DermQuest.com). Copyright © 2006 Galderma S.A. All rights reserved.



**Fig 3.** Patient with severe acne vulgaris treated with adapalene/benzoyl peroxide at baseline and week 12.



**Fig 4.** Action of retinoids on microcomedones (acne vulgaris precursor lesions) and visible lesions. Note the lag time after cessation of retinoid therapy before visible lesions begin to reappear. Reprinted with permission from Thielitz et al.<sup>30</sup>

new topical agent, olumacostat glasaretil (OG) 7.5% (an inhibitor of acetyl coenzyme-A carboxylase with putative action as a topical sebum inhibitor), has shown promise for treating moderate-to-severe acne.<sup>21</sup> A phase 2 study of 108 patients treated with OG twice daily for 12 weeks showed that OG was significantly superior to vehicle in reducing inflammatory lesions ( $-63.9\%$  vs  $-45.9\%$ ,  $P = .0006$ ) and noninflammatory lesions ( $-48.1\%$  vs  $-28.8\%$ ,  $P = .0025$ ); in addition, more patients had improvement of at least 2 grades in IGA ( $24.5\%$  vs  $7.3\%$ ,  $P = .007$ ). OG was well tolerated, with mild-to-moderate application-site adverse events.<sup>21</sup> A topical foam formulation of minocycline 4% was evaluated in subjects with a mean of 33.5 inflammatory lesions at baseline. In a phase 2 study, minocycline foam was superior to vehicle in reducing both inflammatory and noninflammatory lesions ( $-71.7\%$  vs  $-50.6\%$ ,  $P = .0001$ ;  $-72.7\%$  vs  $-56.5\%$ ,  $P = .0197$ , respectively), as well as in improving IGA

score.<sup>22</sup> Two phase 3 studies were completed with the minocycline foam, with one reporting statistically significantly superior results to vehicle but the other failing to demonstrate a significant difference in IGA (1 of 2 co-primary endpoints). An additional phase 3 study is planned.<sup>23</sup> However, it should be noted that monotherapy with a topical antibiotic is advised against in current guidelines and recommendations because of the potential for antimicrobial resistance.<sup>2,3,14</sup> For additional details, see Zouboulis et al.<sup>24</sup>

Gold et al reported a post-hoc subgroup analysis of a phase 3 study of clindamycin 1.2%/BPO 3.75% in moderate-to-severe acne ( $n = 498$ ) that specifically compared results in participants with severe acne ( $n = 86$ ) with those in participants with moderate acne ( $n = 412$ ).<sup>25,26</sup> An improvement in global severity of at least 2 grades was achieved in 55.1% of patients with severe acne compared with 31.3% of those with moderate acne. The proportion of

**Table II.** Strategies to minimize the likelihood of tolerability problems associated with induction of topical retinoid therapy

- Take a detailed patient history
  - Have there been tolerability problems in the past?
- Educate patient
  - Mild irritation can be part of the treatment process, but usually subsides within 1-2 weeks and can be managed with appropriate steps
  - A small dose of retinoid (demonstrate fingertip or pea-sized dose) should be applied in a thin layer to the entire affected area
  - Patient should use a gentle cleansing regimen and avoid overcleansing
- Select most tolerable retinoid formulation for climate and season
  - Creams and lotions might be best for dry or sensitive skin and gels or foam for more oily skin (although newer aqueous gels might also be suitable for sensitive skin)
- Titrate retinoid dose at initiation
  - Apply retinoid every other day for first 2-4 weeks (based on clinical trial evidence that this is when irritation is most likely to occur)
  - Apply gentle, noncomedogenic moisturizer
  - Use a short contact method for first 2-4 weeks (apply retinoid to full face for 30-60 minutes then wash off)

Adapted with permission from Leyden et al.<sup>32</sup>

participants rated clear or almost clear at study endpoint was 30.6% in the severe group and 35.7% in the moderate group. The authors commented that “topical therapy may indeed be more valuable than often assumed in patients with severe acne vulgaris.” Gold et al also note that in their study persons with severe acne were more likely to be female and younger compared with the moderate group, which might have affected the results.<sup>25</sup>

**Combination regimens for severe acne.** Combination regimens with newer agents might also provide alternatives to oral isotretinoin or serve as an intermediate treatment step before isotretinoin. In a comparative study, Tan et al reported that A/BPO 0.1% plus doxycycline 200 mg/day was a noninferior alternative to oral isotretinoin.<sup>19</sup> The combination regimen compared with isotretinoin had a significantly earlier onset of action in reducing acne lesions at week 2. Overall, isotretinoin was superior to A/BPO 0.1% plus doxycycline in reducing nodules (95.6% vs 88.7%), inflammatory lesions (95.2% vs 79.6%), and total lesions (92.9% vs 78.2%; all  $P < .001$ ) at week 20. However, treatment-related, medically relevant adverse events were less frequent in the combination treatment arm versus isotretinoin arm (33 events in 18% of subjects vs 73 events in 33.8%, respectively). The investigators concluded “D-A/BPO showed a favourable composite efficacy/safety profile compared to ISO [isotretinoin].” Further, they indicated A/BPO 0.1% plus doxycycline is an acceptable alternative to isotretinoin for treatment of acne in patients who are unable or unwilling to have isotretinoin prescribed.<sup>19</sup> In a

noncomparative study, Gold et al had shown that the combination of A/BPO 0.1% plus doxycycline 100 mg was significantly more effective than vehicle plus doxycycline 100 mg in potential candidates for oral isotretinoin.<sup>27</sup> In a similar European study, Dreno et al studied A/BPO 0.1% plus lymecycline 300 mg in patients with moderate-to-severe acne, and reported statistically significantly superior improvements in acne with the combined regimen versus lymecycline alone.<sup>28</sup> Zaenglein et al reported results from a phase 4, open-label study of a population with a large proportion (77%) of patients with acne severe enough to warrant isotretinoin as judged by independent review of digital photographs.<sup>29</sup> In this study, a triple combination regimen of oral minocycline, BPO 6%, and clindamycin phosphate 1.2%/tretinoin 0.025% gel significantly improved acne, reducing lesion counts and improving IGA scores.<sup>29</sup> By the end of study at week twelve, 84% of those patients who were potential candidates for isotretinoin at baseline had experienced enough improvement that isotretinoin was no longer a necessary treatment approach.<sup>29</sup>

### Delphi results: strategic approach to acne therapy

**Consensus recommendation 1: retinoids have an essential role in treatment of acne.<sup>3,14</sup>** **For most patients with inflammatory acne, comedonal acne, or both, a topical retinoid plus BPO is first-line therapy.<sup>2</sup>** Together, these agents target multiple aspects of acne pathophysiology, working to normalize keratinization, reduce inflammation, and kill *P. acnes*.<sup>9,10</sup> Further, retinoids

have a unique class action reducing formation of acne precursor lesions (microcomedones) and limiting development of new lesions (Fig 4).<sup>10,30</sup> Using cyanoacrylate strips, Thielitz et al demonstrated that microcomedones rebound almost immediately after treatment is discontinued, whereas reductions in visible lesions continue for several weeks because of normal skin turnover.<sup>30</sup> This finding is why the AAD guidelines state topical retinoids "allow for maintenance of clearance."<sup>14</sup> Thielitz et al also showed the efficacy of azelaic acid in maintenance therapy was equivalent to that of adapalene as mentioned in the S3 EDF guideline.<sup>3,31</sup>

Generally, retinoids are similar in efficacy, and the efficacy improves with higher concentrations.<sup>32</sup> Dose-dependent effects were first shown with tretinoin in animal models and ultra-structural studies.<sup>30,33</sup> After 2 weeks of treatment, tretinoin 0.1% reduced microcomedones by 80% and tretinoin 0.025% achieved a 35% reduction.<sup>30,34</sup> Studies have shown that adapalene has a dose-dependent effect on down-regulating expression of molecules important in the innate immune response, including toll-like receptor 2, B-defensin 4, and interleukin-8, and increases expression of CD1d.<sup>35,36</sup> This helps to explain the greater clinical effect in patients with more severe acne reported with A/BPO 0.3% by Stein Gold et al.<sup>20</sup> Similarly, the pivotal trials of adapalene gel 0.3% found efficacy superior to adapalene 0.1% across all measures, and both dosages were similarly tolerated.<sup>37,38</sup> In the phase 3 study of adapalene gel 0.3%, the greatest improvements were achieved in patients who had higher lesion counts at baseline.<sup>37</sup> Thus, there are now more treatment options for patients with severe inflammatory acne.<sup>20</sup> For these patients, higher concentration retinoid therapy may be used as an option before adding systemic therapy. A once-daily topical agent can readily be added to the patient's existing skin care habits and may be preferred by some patients who do not wish to use an oral therapy. A simple regimen is also beneficial for patient adherence.<sup>39,40</sup>

Although there is a solid rationale and strong recommendations for use of topical retinoids in both the EDF and AAD guidelines,<sup>3,14</sup> a study of prescribing practices during 2012-2014 reported that dermatologists prescribed retinoids for just 58.8% of almost 75,000 acne patients and nondermatologists prescribed them for only 32.4% of cases.<sup>41</sup> Clinician perceptions of the irritation potential of topical retinoids can limit their use in practice.<sup>2,42</sup> However, when present, most topical retinoid side effects resolve within 2-3 weeks and can be managed by use of moisturizers.<sup>2</sup> Table II presents strategies that can be employed to minimize the likelihood of irritation.<sup>2,32,43,44</sup>

**Consensus recommendation 2: the role of antibiotics in acne therapy has changed. Neither topical nor systemic antibiotics should be used as monotherapy for acne treatment.**<sup>2,45,46</sup> Antibiotic resistance is a worldwide problem and should be an essential consideration when selecting therapy for acne.<sup>45-47</sup> Resistant microbial organisms are increasing throughout the world's populations, and worldwide health authorities have called upon the medical community to limit antibiotic use in situations where other management approaches may be used.<sup>48-50</sup> Use of antibiotics in acne affects a large number of people, considering that resistance can occur in both treated individuals and their close household contacts.<sup>51</sup> In addition, antibiotics are often prescribed for a much longer duration in acne than for typical infections (eg, months rather than days).<sup>52</sup> Thus, antibiotic use in acne exerts considerable selective pressure on microbes, including pathogenic and nonpathogenic organisms. However, some studies could not confirm the resistance problem following topical antibiotic treatment.<sup>53</sup> There are currently multiple nonantibiotic therapies for acne with proven efficacy, and it is reasonable for clinicians to develop antibiotic-sparing approaches for this disease.<sup>45</sup> Subantimicrobial-dose doxycycline is used in the treatment of acne due to anti-inflammatory properties but this treatment has not been studied in detail regarding the possible implications for antibiotic resistance.<sup>54</sup>

BPO is the preferred topical antimicrobial agent due to the current climate of antimicrobial stewardship.<sup>2,3,14,45,47</sup> BPO is a potent bactericidal agent, with strong oxidative activity. In a review article discussing management of acne in the era of antimicrobial resistance, Tzellos et al state "overall, BPO combined with topical or oral antibiotics or topical retinoids is the most efficacious evidence-based treatment option to prevent the development of antibiotic resistance in patients with acne and to confer significant clinical improvement on patients who have already developed antibiotic-resistant acne."<sup>55,56</sup> However, there is an urgent need for an antimicrobial agent with better tolerability than BPO in monotherapy and fixed combination therapies.

Systemic antibiotics are useful for moderate-to-moderately severe acne, but efforts should be made to limit the duration of therapy to 3-4 months.<sup>2,45-47</sup> In our clinical experience, the top 3 factors to consider when determining duration of antibiotic therapy include the severity of acne, the potential for bacterial resistance, and the response to treatment. Factors that make it difficult to limit the duration of systemic antibiotic therapy include acne recurrence and patient preference.

### Reducing antibiotic use in acne: Real-world strategies

#### Topical therapy<sup>2,10,14</sup>

- First-line acne therapy = topical retinoids and BPO
- Topical antibiotics should not be used as monotherapy
  - Rapid development of resistance
- BPO ± a topical retinoid should be added if topical antibiotic is prescribed
  - Speeds response and achieves superior clearing
- All strains of *P acnes* are sensitive to BPO
- Topical retinoids (with or without BPO) or azelaic acid are treatment of choice for maintenance

#### Systemic therapy

- Assessing risk-benefit analysis for systemic antibiotics should balance individual need versus public interest in preserving antibiotic effectiveness
  - Antibiotics should be avoided when effective alternatives are available
- Oral antibiotics are indicated when inflammatory acne is not responding well to topical treatments and acne involving trunk or multiple bodily areas
  - Response to therapy should be evaluated at 6-8 weeks
  - Target duration of therapy less than 3-4 months
  - A topical retinoid and BPO or azelaic acid can be used at discontinuation of antibiotic
- Avoid systemic antibiotic monotherapy
- Sub antimicrobial dose antibiotics, which have anti-inflammatory actions, can be useful to minimize potential for resistance

**Consensus recommendation 3: oral isotretinoin should be first-line therapy for very severe (cystic and conglobate) acne.<sup>2</sup>** Isotretinoin is a highly efficacious acne treatment, proven to clear acne lesions, including nodules and cysts, and achieve a prolonged remission period.<sup>57,58</sup> It usually has been recommended at a dose of 0.5-1.0 mg/kg administered over a period of ~4-6 months to reach a cumulative dose of 120-150 mg/kg—a target that has been recommended to reduce relapse and improve remission rates.<sup>59,60</sup> However, more modern thinking is reflected in core principle 4.<sup>61</sup> Systemic corticosteroids may be used at initiation of therapy to help speed lesion clearing. Many experts and researchers in the field think that isotretinoin use should not be restricted to cases with demonstrated failure to conventional therapy.<sup>62</sup>

**Consensus recommendation 4: oral isotretinoin therapy should proceed until full clearance of acne. Additional studies are needed to define a total cumulative dose that maintains remission.** After the introduction of oral isotretinoin, a threshold dose of 120-150 mg/kg over a

period of 4-6 months has been recommended to reduce relapse and improve remission rates. Tan et al performed a systematic literature search to evaluate evidence supporting cumulative dosing for isotretinoin.<sup>61</sup> Tan reported that the cumulative dose is based on data from studies that were not designed to evaluate the role of cumulative dose in relapse rates.<sup>61,63</sup> Further, a retrospective chart review of 1453 patients treated with oral isotretinoin showed that 22.4% required a second course of isotretinoin (follow-up ≥12 months, range 12 months-5 years) and that daily and cumulative doses did not influence relapse as long as treatment was continued for ≥2 months after complete resolution of acne.<sup>63</sup> The authors suggest proceeding with treatment until full clearance, independent of the cumulative dose.<sup>63</sup> We agree this is a reasonable and effective strategy for patients with severe acne. For those with moderate acne, full clearance can be achieved with lower cumulative doses. A rule of thumb may be to treat until full clearance plus an additional month.

In addition to the need for treatment to remission (dosage will vary by individual), there is also a goal of maintaining remission. For maintaining remission, specific dosing has not been established by high-quality clinical trials. Factors that have been implicated as higher risk for relapse include severe seborrhea, young age, family history of acne, prepubertal acne, and truncal acne.<sup>63-66</sup>

Similarly, although it has been suggested that higher cumulative doses of oral isotretinoin may be needed for severe truncal acne, in our clinical experience severe truncal acne can usually be treated with the same dose as that for severe facial acne. There are no clear statistical data supporting a different dose.

**Consensus recommendation 5: acne flare with oral isotretinoin can be minimized by initiating therapy at a low dose.** Acne flare occurs in a small proportion of patients (up to 15%) at the initiation of oral isotretinoin therapy.<sup>67</sup> The group reached consensus that starting with a low dose (0.5 mg/kg in the United States and ≤0.2 mg/kg in some countries as reported by Borghi et al)<sup>67</sup> reduces the likelihood of flare, although several panelists felt that sometimes the propensity for inflammatory flare is independent of dose.

**Consensus recommendation 6: most patients with acne should receive maintenance therapy with a topical retinoid with or without BPO. Topical antibiotics should not be used as acne maintenance therapy.** Topical retinoid monotherapy may be sufficient in some cases, with BPO or an oral antibiotic added as needed.<sup>68-72</sup>

Thielitz et al were able to demonstrate that maintenance therapy with a topical retinoid achieved sustained reductions in microcomedones, which in turn translated to fewer active acne lesions.<sup>71</sup> Clinical trials with adapalene, A/BPO, and tazarotene have shown significant superiority over their respective vehicles when used as maintenance therapy after successful acute phase therapy.<sup>69,70,72-74</sup> Thielitz et al showed that good results could be achieved with retinoid therapy applied every other day, which might be appealing for patients.<sup>71</sup> Azelaic acid may be a maintenance option for women with acne.<sup>31</sup>

**Consensus recommendation 7: azelaic acid cream 20% or gel 15% is a useful acne treatment in pregnant women and patients with acne and PIH.** The group reached consensus that azelaic acid should be recommended as a second-line therapy<sup>3,14</sup>; however, dissenting panelists commented that it has a relatively high potential to cause irritation and aggravate already inflamed skin. Further, it was noted that azelaic acid is not available in all regions of the world and is a risk category B drug in pregnancy. Although there was a consensus that azelaic acid is useful in patients with acne and PIH, data supporting its use in this setting are sparse.<sup>75</sup> Kircik et al reported that azelaic acid gel 15% twice daily improved both mild-moderate acne and PIH in 20 adults with Fitzpatrick skin type V and VI. At study conclusion (week 16), PIH was cleared in 31% of subjects and slight or mild improvement was noted in 69% of subjects.<sup>75</sup>

**Consensus recommendation 8: at present, devices, including laser, intense pulsed light, and photodynamic therapy should not be considered first-line treatment for inflammatory acne.** Although laser and light devices have some benefit in the setting of acne, well-designed studies evaluating their effectiveness versus standard medical therapies are lacking.<sup>76</sup> In addition, standardized regimens have not been agreed upon; multiple treatments are generally necessary (and costly), and the results are temporary.<sup>14</sup> A recent Cochrane database systematic review of light therapies in acne found “high-quality evidence on the use of light therapies for people with acne is lacking.”<sup>76</sup> In the AAD guidelines, Zaenglein et al report that photodynamic therapy with a photosensitizer has the best supporting evidence and shows great promise, but that more studies are needed to optimize the treatment regimen, including the optimal sensitizer, incubation time, and light source.<sup>14</sup>

**Consensus recommendation 9: a minority of women ≥25 years of age have acne lesions localized only to the lower face. Topical retinoids with or without BPO are important components in therapy of adult acne.** There is a clinical impression that women with acne have a subtype of acne that is difficult to treat and primarily driven by hormonal abnormalities. However, a large-scale international study showed that 89% of women have a facial distribution of acne lesions that is similar to adolescent acne (Fig 5).<sup>77</sup> Further, analysis of clinical registration data for adapalene and A/BPO have both shown good efficacy in the adult female population.<sup>78,79</sup> Adding skin care regimens, such as moisturizers and pH-balanced cleansers, has been shown to improve both efficacy and tolerability for women.<sup>80</sup> Long-term maintenance is particularly important in the adult female population because frequent recurrences are common. In addition, dry and sensitive skin is more common in this group, supporting use of strategies to minimize irritation from topical treatments (application every other day initiation; short-contact therapies; use of moisturizers and gentle, nonsoap cleansers).<sup>81,82</sup>

Oral therapies, including limited-duration antibiotics, isotretinoin, and hormonal treatments, can be useful for adult female acne.<sup>81,82</sup> A discussion on the use of oral contraceptives and hormonal therapy is provided later in this supplement.

**Consensus recommendation 10: early and effective treatment is important to minimize potential risk for acne scarring.** Acne lesions can evolve into more permanent scars, which can be either atrophic or hypertrophic. It is challenging to identify which patients will scar, but early administration of effective therapy can reduce one modifiable risk factor for scarring: prolonged uncontrolled acne.<sup>8,83-85</sup> There are a number of risk factors that have been linked to the development of atrophic acne scars, including severe acne (although scars can occur even with mild acne), family history, extent and duration of inflammation, and (perhaps most important) the time to effective treatment of acne.<sup>8,83,84</sup> Additional risk factors might include manipulation of lesions, onset of acne at a young age, frequent relapses, localization to the trunk, and ethnicity.<sup>8</sup> Histologic data suggest that an early strong inflammatory response in the skin appears to be associated with less scarring than milder forms of acne that demonstrate delayed inflammatory response.<sup>86</sup> A tool to assess risk of acne scarring was recently developed after a review of the literature and clinical trials and a modified Delphi

## Mandibular



## Non-Mandibular



**Fig 5.** Examples of adult female acne vulgaris. Photos courtesy of Dr Araviiskaia of the Department of Dermatology and Venereal Diseases First Pavlov Medical University of St. Petersburg, St. Petersburg, Russia; Dr Castinahan; Dr Kemeny of the Department of Dermatology and Allergology, University of Szeged; and Dr Troielli.

process involving an expert panel (Fig 6).<sup>87</sup> The tool is a short, simple, self-administered questionnaire that can readily be used both to educate patients and to help assess risk for acne scarring and raise awareness. The outcome is dichotomous, ranking patient risk as either low or high. The creators found the tool correctly categorized nearly two thirds of the population and had a sensitivity of 82% and specificity of 43%.<sup>87</sup>

In a split-face, randomized controlled trial, Dreno et al showed that A/BPO 0.1% reduced the risk for atrophic scar formation in subjects with moderate inflammatory acne.<sup>88</sup> Over a period of 6 months, scar counts remained stable with A/BPO treatment but increased by 25% with vehicle treatment ( $P = .036$ ).<sup>88</sup> To the best of our knowledge, this is the first study to confirm the clinical impression that effective treatment of acne minimizes risk of scarring.

In our clinical experience, a higher concentration of topical retinoid with BPO may be useful for patients at high risk of scarring. However, higher

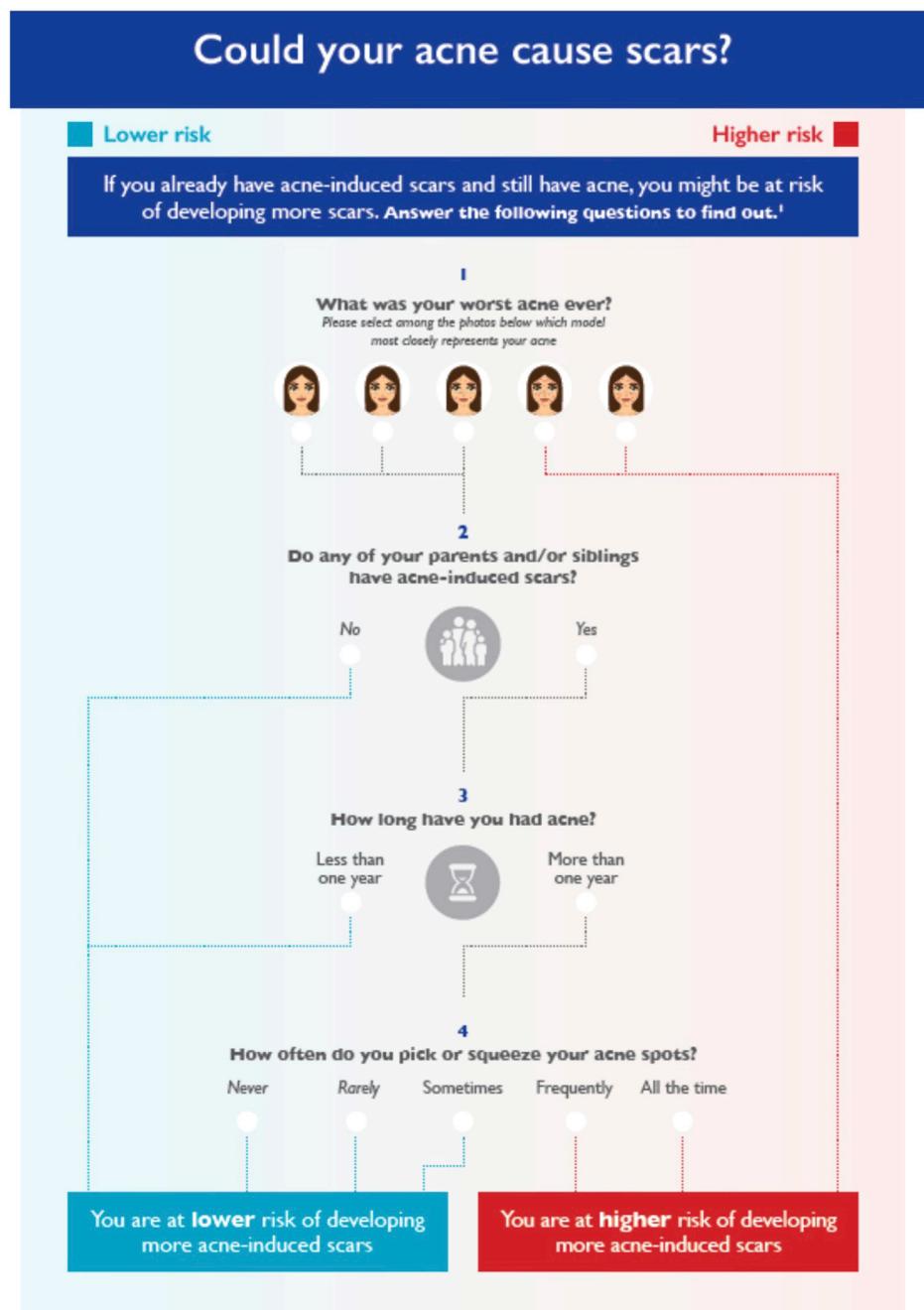
concentrations might be less well tolerated, so selection of retinoid concentration should be individualized. Recent publications have shown that scars continuously form during the course of acne and some resolve<sup>8,89</sup>; in addition to having greater efficacy in treating existing lesions, a higher concentration of retinoid might have a greater impact on skin healing and, thereby, reduce formation of scars. Further studies are needed to elucidate the dose-dependent differences in topical retinoid formulations.

### Summary: acne management algorithm

Fig 7 shows an algorithm that summarizes a treatment approach on the basis of the consensus recommendations described above.

### PRACTICAL APPROACH TO TREATMENT IN VARIOUS SETTINGS

A literature review was performed to address what is known about acne and PIH, acne and scarring, and acne in women. In addition, because there are some aspects of these topics that are not

**Fig 6.** Atrophic acne scar risk assessment tool.<sup>87</sup>

well explored in the literature, a secondary online questionnaire was provided to the Delphi panel members. This questionnaire did not follow the Delphi process but rather asked a series of open-ended questions to allow the panel members to share their clinical pearls and practice tips. These are incorporated below.

#### Acne and PIH

Human skin has a wide variety of hues, including pinks, yellows, and browns that arise

from the individual contributions of melanin, bluish-white connective tissue, and hemoglobin. Generally, darker skin reacts to injury or insult with localized melanin deposition, resulting in uneven skin tones, but even pale skin can have long-lasting dark or red spots after resolution of an acne lesion (Fig 8). PIH is a common occurrence in patients with acne, particularly in those with darker skin and those who excoriate their lesions.<sup>7</sup> Patients and clinicians both report that PIH often has a prolonged duration and can be more

## Managing Acne

MILD	MODERATE	SEVERE
Comedonal Topical Retinoid or Fixed combination with retinoid > BPO or Azelaic Acid Salicylic Acid	Papular/pustular Fixed Combination or BPO or Topical Retinoid or Azelaic Acid	Papular/pustular Fixed Combination Preferred ± Hormonal therapy and/or Oral Antibiotic*
		Moderately Severe - Severe Fixed Combination + Oral Antibiotic Preferred Or + Oral Isotretinoin Or + Oral Hormonal Therapy

If patient responds, treat until clear or almost clear

### Maintenance Therapy: Topical Retinoid or Retinoid/BPO Combination

\* Particularly if the trunk is involved

#### Actions if Response is Poor

- ✓ Check non-drug related reasons (seborrhea, stress and diet, Malassezia furfur, G- bacteria, comedogenic skin care products, endocrine profile)
- ✓ Check drug-related reasons (adapt vehicle to skin type and environmental conditions, change topical agent, mechanically remove comedones, change from monotherapy to fixed-combination, change to higher concentration of topical). For females, check type of contraception.
- ✓ Probe patient's adherence (application technique, missed doses, tolerability)
- ✓ Ask about adverse events

## Managing Very Severe Acne

NODULAR and/or CONGLOBATE ACNE	
<b>Males</b>	<b>Females</b>
Oral Isotretinoin or Fixed Combination + Oral Antibiotics	Oral Isotretinoin + anti-androgenic hormonal therapy or Fixed Combination + Oral Antibiotics (consider high dose) and/or oral anti-androgenic hormonal therapy

If patient responds, treat until clear or almost clear

### Maintenance Therapy: Topical Retinoid or Retinoid/BPO Combination

#### If Response is Poor

- ✓ Check non-drug related reasons (seborrhea, stress and diet, Malassezia furfur, G- bacteria, comedogenic skin care products, endocrine profile) and exclude hidradenitis suppurativa/acne inversa
- ✓ Check drug-related reasons (type/dose antibiotic, microbial resistance, spot treatment, consider adding prednisone, for females check use of anti-androgenic agents)
- ✓ Consider intralesional injections of steroids or mechanical removal of macrocomedones
- ✓ Probe patient's adherence (application technique, missed doses, tolerability)
- ✓ Ask about adverse events

**Fig 7.** Practical approach to acne management.

bothersome than active acne lesions for the patient.<sup>7,90</sup> In a study of Middle Eastern acne patients, more than half (56.4%) were primarily concerned with uneven skin tone, and 49.4% had acne lesions as their top concern.<sup>91</sup>

There are few published epidemiologic data, but what does exist suggests that half or more

acne patients with dark skin tones also have PIH.<sup>92</sup> In an Asian population (324 persons from 7 countries), Abad-Casintahan et al found PIH in 60% of acne patients evaluated sequentially.<sup>7</sup> PIH typically has a long duration, and in the same study 65.2% of patients reported having PIH for  $\geq 1$  year.<sup>7</sup>



**Fig 8.** Spectrum of postinflammatory hyperpigmentation. BPO, Benzoyl peroxide. Photos courtesy of DermQuest.com, Dr C. L. Goh, and Dr R. Kubba. Copyright © 2006 Galderma S.A. All rights reserved.

PIH affects individuals of all genders and ages.<sup>93</sup> Clinically, PIH might present as localized or diffuse colored macules at the sites of former acne lesions.<sup>93</sup> Dyspigmentation often becomes more apparent after acne lesions and associated erythema have resolved.<sup>93</sup> PIH ranges in color from light brown to grey or black; dark purple lesions may be an early form of PIH.<sup>93</sup>

PIH is a hypermelanotic reaction to skin inflammation.<sup>94</sup> Conversion of tyrosine in melanocytes creates melanin, which can be packaged into melanosomes and transferred to keratinocytes. When acne is present, melanocytes are stimulated by inflammatory mediators, cytokines, and arachidonic acid metabolites to increase melanin synthesis and deposition of pigment to nearby keratinocytes. Excess melanin production or an abnormal distribution of melanin pigment deposited in skin produces visible PIH.<sup>96</sup> Mechanical insults to skin such as excoriation can exacerbate PIH.

**Treating acne patients prone to PIH.** A variety of methods may be used to determine which patients to treat, including assessment of overall clinical severity (eg, visibility from a distance and with and without makeup), patient preferences, stated impact on quality of life, and known excoriation. Prevention (including sun protection)

and treatment of underlying acne-associated inflammation early and effectively is a primary approach to PIH management.<sup>97</sup> Table III reviews pathways that are targets of medical intervention in pigmentation disorders.<sup>98,99</sup> Chemical peels, lasers, and other light therapies may also be used for PIH; however, these methods can also cause pigmentation problems so should be used with care.<sup>99</sup> In addition, it is important to weigh the cost-benefit of a procedural approach because the reduction in time to resolution might be relatively small.

Topical retinoids effectively manage acne and can also improve pigmentation by inhibiting melanosome transfer to keratinocytes and increasing epidermal turnover and lessening pigmentation.<sup>9,93,97,100,101</sup> Combination acne therapy can improve the speed and degree of lesion resolution.<sup>10,97</sup>

Variations of the classic Kligman's formula of a retinoid + hydroquinone + corticosteroid are also used for skin lightening or brightening.<sup>100</sup> These products may be used during acne therapy but are more commonly prescribed after resolution of acne lesions.<sup>100</sup> Cosmeceuticals with skin-lightening ingredients may be a cost-effective approach, and azelaic acid may also be helpful.<sup>102</sup> Results can be

**Table III.** Actions of agents used to treat postinflammatory hyperpigmentation

Agent	Mechanism
Retinoids	Increase keratinocyte turnover and remove pigmentation, inhibit tyrosinase, and reduce pigment transfer
Hydroquinone	Inhibition of melanogenesis via reduction in active tyrosinase
Kojic acid	Inactivates tyrosinase by chelating copper atoms
Azelaic acid	Selectively influences hyperactive and abnormal melanocytes, prevents tyrosine-tyrosinase binding
Flavonoids (aloesin from aloe vera plants, stilbene derivatives such as resveratrol, licorice extracts)	Inhibit tyrosinase activity at distal portions of the melanogenic pathway
Antioxidants/Redox agents (beta carotene and vitamin C and E)	Prevent oxidative damage to skin, scavenge reactive oxygen species, inhibit second messengers that stimulate melanogenesis, interact with copper at active site of tyrosinase
Niacinamide	Interrupts melanosome transfer from melanocyte to keratinocyte
Alpha hydroxy acids, salicylic acid, linoleic acid	Accelerate skin turnover, dispersing melanin; linoleic acid also reduces tyrosinase activity
Arbutin	Structural homolog for tyrosinase (competitive inhibitor), inhibits melanosome maturation

Reprinted with permission from Gollnick et al.<sup>99</sup>

improved by combining modalities; for example, in a study of 45 patients, salicylic acid peel plus a topical retinoid improved PIH more than either treatment alone, with good tolerability and a low recurrence rate.<sup>103</sup>

Education for patients is a key aspect of management. It is important for the patient to be aware that many PIH lesions resolve spontaneously, but slowly. They should also know that adhering with acne therapy and preventing new acne lesions will minimize the potential for PIH. Avoidance of sun exposure plus sun protection should be recommended, along with avoidance of excoriation of any skin lesions. Improving insulin resistance through diet and lifestyle can have a positive impact on both acne and the propensity for PIH. Table IV presents additional recommendations for patient counseling, which might be more or less relevant, depending on the individual being treated.<sup>99</sup>

Medical colleagues should be aware that early acne therapy has a vital role in minimizing PIH, and that PIH is a very bothersome problem for some patients and should not be trivialized. Maintenance therapy can be useful in limiting development of PIH. In some cases, ephelides, lentigines, and melasma-like pigmentation can be mistaken for PIH. Clues that the skin lesion is not caused by PIH include a localization to the temple area, zygomas, and accompanying dermal elastolysis.

#### Clinical pearls for acne and PIH

- Oftentimes, identifying the patient who requires PIH management involves discussing how bothersome the problem is for the individual person, but the presence of visible PIH merits a discussion with the patient
  - A score of  $\geq 4$  on the Visual Analog Scale of 1-10 may be an indicator of need for treatment
- Most patients want to know how long it will take before dark spots resolve
  - For these patients, it is important to emphasize the need for effective treatment of acne, regular use of photoprotection, and avoidance of lesion excoriation
- Cosmeceuticals including antioxidants or exfoliants, chemical peels, intense pulsed light, lasers, and iontophoresis with tranexamic gel may be useful although there is a lack of evidence-based studies on these approaches, particularly among dark skin types
- Treating hormonal pathologies can help mitigate underlying factors
- Early treatment with retinoids can diminish the risk of PIH by inhibiting tyrosinase and blocking pigment transfer from melanocytes to keratinocytes

**Table IV.** Patient counseling for postinflammatory hyperpigmentation

Physician action	Counseling/Recommendation
Evaluate use of cosmetic products to lighten skin tone	<ul style="list-style-type: none"> <li>Cocoa butter should be avoided due to potential to exacerbate acne</li> <li>Recommend alternatives such as prescription topical retinoids, azelaic acid, or hydroquinone</li> <li>Avoid oil-based, heavy pomades</li> <li>Select silicone-based products</li> <li>Avoid</li> </ul>
Review hair care product use	<ul style="list-style-type: none"> <li>Use sunscreen</li> <li>Goals are to minimize and prevent new acne lesions and sequelae such as PIH and scarring</li> <li>While PIH can resolve spontaneously, it is often long-lasting</li> </ul>
Discuss use of exfoliants, witch hazel, and potentially irritating treatments	
Educate about role of sun in pigmentation	
Review goals of acne therapy and potential duration of PIH	

Reprinted with permission from Gollnick et al.<sup>99</sup>

PIH, Postinflammatory hyperpigmentation.

### Acne and scarring

In a recent study of 1942 subjects with acne, 43% had acne scarring.<sup>8</sup> Further, 69% of all patients with scars had mild-to-moderate acne at the time of evaluation.<sup>8</sup> These data agree with older published studies by Layton et al and Tan et al, and highlight the importance of this acne sequela.<sup>83,85</sup> Acne-associated scarring often includes an emotional toll, with depression, anxiety, poor self-esteem, and social impairment all reported.<sup>104,105</sup> The day-to-day impact of emotional problems from scarring can include lowered academic performance and underemployment.<sup>106</sup> This underscores the need for dermatologists and other clinicians to evaluate and address scarring as well as counsel patients about treatment.<sup>106</sup>

Acne scars have very diverse presentations, with widely varying shapes and sizes. A popular method for classifying atrophic scarring uses scar shapes. This method is appealing, but very subjective and poorly reproducible even among acne researchers.<sup>107</sup> Kang et al reported that classifying atrophic scars based on size (<2 mm, 2–4 mm, and >4 mm) is reproducible both for sequential ratings by the same individual and for agreement between raters.<sup>108</sup> A size-based classification was the basis for a validated tool to assess severity of scars (Facial Acne Severity Evaluation Tool or FASET).<sup>109</sup> This tool incorporates 3 domains: scar counts, overall global assessment of severity, and estimation of involved skin area.<sup>109</sup> It can be used for patients with acne scarring with or without active acne lesions and might have utility assessing the performance of interventions for atrophic acne scars.<sup>109</sup>

**Managing acne in scar-prone and scarred patients.** Scar treatment is determined by scar type and severity as well as the size of the involved area.<sup>106,110</sup> Management considerations encompass cost, patient expectations and physician goals, and the psychologic effect of the scars.<sup>106</sup> Fife recently

suggested practical questions for an acne scar history (Table V).<sup>106</sup> During physical examination, it is useful to shine light on the skin to highlight atrophic areas, use a mirror to help the patient identify areas of concern, assess physical characteristics of the scar (color, depth, width, size), and stretch skin to see if the scar disappears.<sup>106</sup>

A variety of scar treatments are available (Table VI),<sup>106</sup> and often a combination of modalities is superior to a single approach.<sup>110,111</sup> Unfortunately, a rapid, permanent solution that fully eliminates atrophic scars is rarely available.<sup>106</sup> Procedures can be grouped by function into resurfacing, lifting, excisional, and other. Resurfacing approaches depend on injuring the epidermis and superficial dermis and, thereby, stimulating neocollagenesis and epidermal repair. Lifting techniques attempt to match the scar base with the surrounding skin surface, and excisions remove deep, sclerotic, or hypopigmented scars. Many techniques have risks, such as infection, hyperpigmentation, prolonged erythema, or poor healing; these may be exacerbated in darker skin patients.<sup>106</sup>

### Clinical pearls for atrophic acne scars

- Mild-to-moderate acne can lead to atrophic scars in a surprising proportion of patients, and it is important to implement effective treatment as quickly as possible
- Inflammation is present in all acne lesions
- Combining treatment modalities can achieve best results
- Pigmentary changes (red or brown) are not scarring
- Treating acne is easier than treating scarring
- It is useful to have a baseline idea of which patients might be more prone to scars

**Keloids and hypertrophic scars.** Keloids and hypertrophic scars form when abnormal wound healing leads to excess tissue, usually in dark-skinned individuals.<sup>112</sup> There is sustained and intense localized inflammation at the site, with recruitment of inflammatory cells and fibroblasts, formation of new blood vessels, and deposition of collagen, which collectively create the scar. Keloids and hypertrophic scars occur in both sexes and across age groups (although rarely in very young or old individuals).<sup>112</sup> They most often first appear during adolescence or pregnancy and tend to affect the lateral face, jawline and neck, and upper torso.<sup>106</sup> Treatment for hypertrophic scars may include intralesional injection of 5-fluorouracil or triamcinolone acetonide, cryotherapy, silicone gel sheeting, pulsed dye laser, fractional laser, surgical excision plus radiation, or triamcinolone acetonide injections.<sup>106</sup> Currently, the best practice known includes cryotherapy followed by tissue injection of triamcinolone in edematous tissue.

#### Clinical pearls for hypertrophic or keloidal scars

- Adding pulsed dye laser to intralesional steroid injections helps reduce erythema associated with hypertrophic scars and reduces steroid-induced telangiectasias on the face
- Use a silicone sheet after intralesional steroids
- Intralesional bleomycin might be useful
- For disseminated lesions, off-label use of oral pentoxifylline and topical piroxicam plus steroid injection may be considered
- Avoid trauma and surgical intervention
- There is rarely a quick fix; successful treatment might take multiple treatments and modalities

#### Acne in women

**Efficacy of topical therapy.** There is a growing population of women consulting physicians for treatment of acne. There is a clinical perception that acne in women requires systemic treatment, but recent analyses of clinical trials have shown that topical therapy can be efficacious in this group.<sup>31,78,80,113,114</sup> In addition, a recent large-scale study of acne in adults has shown that most patients have an acne presentation that is similar to adolescent acne, with mixed inflammatory and noninflammatory lesions on multiple facial areas (not limited to the mandibular area).<sup>77</sup>

There are data supporting use of retinoids in adult acne, including A/BPO in both 0.1% and 0.3% concentrations,<sup>78</sup> tretinoin 0.04%,<sup>113</sup> and

**Table V.** Acne scar history

#### Current acne assessment

- Are you using an acne treatment now?

#### Patient-specific questions

- What aspect of your skin is most bothersome? (dark spots, acne, wrinkles, other)
- Please identify scars or areas of your face that bother you the most
- How do the scars affect your lifestyle?
- Do you have time constraints due to work or travel?

#### Questions that could affect the therapeutic regimen

- Have you done anything in the past to treat your scars?
  - If yes, how many sessions, what was the associated down time, how well did the treatment work, and were there any problems healing?
- What do you want to achieve with treatment?
- Did you need isotretinoin to treat your acne? If yes, when was your last dose?
- Does your skin have a tendency to darken after acne lesions, surgery, or other injury?
- Do you have any painful, thick, or itchy scars?

Adapted with permission from Fife.<sup>106</sup>

retinaldehyde 0.1%/glycolic acid 6% cream.<sup>115</sup> Among antimicrobial agents, both dapsona and clindamycin/BPO have shown efficacy for acne in women in subgroup analyses and studies.<sup>114,116</sup> These products are not recommended as monotherapy; a topical retinoid should be added to expand pathophysiologic features targeted and achieve best results.<sup>78</sup> Finally, azelaic acid 15% gel has also shown good results in a small study ( $n = 55$ ) of women with acne.<sup>31</sup> In our judgment, topical therapy with a retinoid and antimicrobial can be a good option for adult female patients and should be given trial. This patient population might also appreciate the beneficial effects of topical retinoids on photoaging.<sup>78</sup>

**Hormonal therapy: the secret weapon.** Hormonal therapy, including oral contraceptives (OCs), can play an important role in management of acne in women. It is typically used in combination with topical acne therapy, in part because onset of action is relatively slow and results might not be apparent for at least 3 months. OCs for acne include both estrogen and progestin. These agents are as effective as oral antibiotics in reducing acne lesions at 6 months of treatment, and the AAD guidelines assign OCs a grade A recommendation for use.<sup>14,117,118</sup> Female patients with acne who desire contraception or do not intend to become pregnant may be candidates for hormonal therapy. **Table VII**

**Table VI.** Interventions for treating facial atrophic acne scars

Resurfacing procedures
<ul style="list-style-type: none"> <li>• Chemical peels           <ul style="list-style-type: none"> <li>◦ Full face</li> <li>◦ CROSS technique</li> </ul> </li> <li>• Dermabrasion</li> <li>• Laser resurfacing           <ul style="list-style-type: none"> <li>◦ Ablative</li> <li>◦ Nonablative</li> <li>◦ Fractional (ablative vs nonablative)</li> </ul> </li> </ul>
Lifting procedures
<ul style="list-style-type: none"> <li>• Subcision</li> <li>• Fillers           <ul style="list-style-type: none"> <li>◦ Directly under scars</li> <li>◦ Volumizing</li> <li>◦ Autologous fat transfer</li> </ul> </li> <li>• Punch elevation</li> </ul>
Excisional techniques
<ul style="list-style-type: none"> <li>• Punch excision</li> <li>• Elliptical excision</li> <li>• Punch grafting</li> </ul>
Other
<ul style="list-style-type: none"> <li>• Microneedling</li> <li>• Facelift</li> <li>• Combination techniques</li> </ul>

Reprinted with permission from Fife.<sup>106</sup>

CROSS, Chemical reconstruction of skin scars.

shows contraindications and situations where OCs may be used with caution or special monitoring.<sup>14,119</sup>

OCs vary in formulation, although all combine an estrogen (usually ethinyl estradiol) and a progestin. There are 4 generations of OCs (Table VIII) and efficacy for treating acne seems to be comparable among those studied.<sup>120</sup> Table IX shows the OCs approved by the US FDA for treatment of acne, and Table X shows the AAD recommendations for hormonal agents.<sup>14</sup> Cyproterone acetate and spironolactone are additional agents that might be available, depending on country availability.

It is important for dermatologists to formulate an approach to prescribing OCs for acne. Many women have knowledge, experience, or perceptions about OCs that the dermatologist should know. When counseling, ask the patient about her knowledge of and expectations. For patients new to OC therapy, discuss that acne requires long-term treatment.

**Contraceptives other than OCs.** The birth control patch (ethinyl estradiol plus norelgestromin) uses a hormonal combination that is similar to OCs and has a beneficial effect on the skin. Compliance is

better because of once-weekly administration. The pharmacokinetic profile is different from OCs, and the patch delivers higher steady state concentrations but lower peak concentrations. It is not known whether the increased estrogen exposure increases risk of adverse events. However, the patch is linked to higher failure rates (unintended pregnancies) in patients >198 lb (98 kg) and caution is advised with use in this setting. The patch can be applied to a variety of body sites (abdomen, upper outer arm, upper torso, buttock) on the first day of the patient's menstrual period and once per week for the next 2 weeks (3 total) followed by one patch-free week.<sup>120</sup>

Injectable contraception (medroxyprogesterone acetate) delivers only progestin; this drug might not improve acne but rather exacerbate it. Some implanted birth control methods (intrauterine devices) also do not include estrogen. Some include progestin and might trigger hormone-induced acne flares, which usually diminish after a few months. The intravaginal ring (etonogestrel/ethynodiol dienoate) is similar to a combined oral contraceptive and should have similar effects on acne.

Although hormonal therapy can be effective against acne in women, side effects related to the proportion of estrogen and progestin can lead to discontinuation of the therapy (Table XI).<sup>120</sup> For example, women who have nausea, vomiting, bloating, or decreased libido might benefit from a contraceptive with a lower estrogen dose, while those experiencing acne or hirsutism might have too much progestin and would benefit from reducing the progestin content.<sup>120</sup> It is important for clinicians to be aware that many progestins also have an androgenic effect; hormonal therapies involving these agents should be avoided in acne when androgenic clinical effects appear.

Serious adverse effects can occur with systemic hormonal therapy, although they are generally quite safe. OCs are linked to higher incidence of breast cancer; cervical cancer; and cardiovascular problems, including myocardial infarction, stroke, venous thromboembolism (including deep venous thrombosis), and pulmonary embolism. Overall, risks are small and usually can be anticipated by assessment of the woman's health status (presence of cardiovascular risk factors) and estrogen dose. Greater risk is associated with smoking; obesity; family history of coronary artery disease; age ≥35 years; and comorbidities, such as hypertension, diabetes, and hyperlipidemia. These risk factors should be assessed during history taking.<sup>120</sup> Acne flare can occur after discontinuation of OCs or hormonal therapy.

**Table VII.** World Health Organization recommendations for selecting patients for oral contraceptives therapy

Not recommended	Use with caution or requires special monitoring
✓ Pregnancy	✓ Breastfeeding (6 weeks-6 months postpartum)
✓ Current breast cancer	✓ Postpartum (<21 days)
✓ Breastfeeding <6 weeks postpartum	✓ Age ≥35 years and light smoker (<15 cigarettes per week)
✓ Age ≥35 years and heavy smoker (≥15 cigarettes/day)	✓ History of hypertension (including pregnancy) or if monitoring is not feasible
✓ Hypertension: systolic ≥160 mm Hg or diastolic ≥100 mg Hg	✓ Hypertension: systolic 140-159 mm Hg or diastolic 90-99 mm Hg or controlled and monitored
✓ Diabetes with end organ damage	✓ Headaches: migraine without focal neurologic symptoms <35 years
✓ Diabetes >20 years duration	✓ Known hyperlipidemia should be assessed (eg, type and severity)
✓ History of or current deep vein thrombosis or pulmonary embolism	✓ History of breast cancer ≥5 years of no disease
✓ Major surgery with prolonged immobilization	✓ Biliary tract disease
✓ Ischemic heart disease (history or current); valvular heart disease with complications	✓ Mild compensated cirrhosis
✓ History of cerebrovascular accident	✓ History of cholestasis related to oral contraceptive use
✓ Headaches (eg, migraine with focal neurologic symptoms at any age, or without aura if ≥35 years)	✓ Concurrent use of drugs that affect liver enzymes
✓ Active viral hepatitis	
✓ Severe decompensated cirrhosis	
✓ Liver tumor (benign or malignant)	

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**Table VIII.** Generations of oral contraceptives

Generation	Progestin	Estrogenic	Progestational	Androgenic
First	Norethindrone	++	++	++
	Ethynodiol diacetate	++	+++	+
	Norgestrel	--	+++	+++
	Norethindrone acetate	++	++	++
Second	Levonorgestrel	--	++++	++++
Third	Norgestimate	--	++	++
	Desogestrel	+/-	++++	++
Fourth	Drospirenone	--	+/-	--

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+ indicates low activity, -- indicates no activity.

#### Clinical pearls for acne in women

- When taking history, ask about prior experience with any hormonal or birth control therapies; women often have preformed opinions that should be taken into account when designing a regimen
- Work with the patient to evaluate existing skin care and makeup regimen, substituting products as needed to minimize potential negative impact on acne and maximize positive impact
- When possible, use simple regimens that dovetail with the patient's existing daily routines
- Be willing to consider a management approach for women that is similar to what is used for adolescents, but also be alert that hormonal approaches can add significant benefit

**Table IX.** Overview chart of oral contraceptives approved for treatment of acne in women

Generic drug name	Brand
Norgestimate-ethynodiol estradiol	Ortho Tri-Cyclen
Norethindrone acetate-ethynodiol estradiol	Estrostep Fe
Drospirenone-ethynodiol estradiol	Yaz

Many more contraceptives exist, and there is variability among countries.

#### CONCLUSIONS

Acne is a widespread disease and dermatologists should take the lead in not only implementing best practices but also in educating other health care professionals about treatment strategies. New and improved treatments are continuously being developed, and the role of various agents is changing. In

**Table X.** American Academy of Dermatology recommendations for hormonal agents

Estrogen-containing combined oral contraceptives are effective and recommended in treatment of inflammatory acne in female patients.
Spironolactone is useful in treatment of acne in select females patients.
Oral corticosteroid therapy can be of temporary benefit in patients with severe inflammatory acne while starting standard acne treatment.
In patients who have well-documented adrenal hyperandrogenism, low-dose oral corticosteroids are recommended.

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**Table XI.** Estrogen and progestin dose-related adverse effects

Estrogen	Progestin
Excess	Excess
✓ Nausea, vomiting ✓ Bloating, edema ✓ Hypertension ✓ Migraine headache ✓ Breast tenderness ✓ Decreased libido ✓ Weight gain ✓ Heavy menstrual flow ✓ Leukorrhea	✓ Acne ✓ Increased appetite, weight gain ✓ Fatigue ✓ Hypertension ✓ Depression ✓ Hirsutism ✓ Vaginal yeast infections
Deficiency	Deficiency
✓ Early cycle spotting/breakthrough bleeding ✓ Amenorrhea ✓ Vaginal dryness	✓ Late breakthrough bleeding ✓ Amenorrhea ✓ Heavy menstrual flow

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the era of antimicrobial resistance, there should be diminished use of antibiotics. Because of their preventive action in acne by targeting microcomedones, retinoids should form the cornerstone of therapy. The variety of formulations and concentrations of available agents provides great flexibility for clinicians to individualize therapeutic regimens for patients, while achieving good results.

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**Supplemental Table I.** Results of Delphi voting and statements that reached consensus with round 1 and round 2

Statement	Strongly agree, %	Agree, %	Consensus	Disagree, %	Strongly disagree, %	Unable to answer, %
<b>Round 1</b>						
Topical antibiotics should no longer be used as monotherapy for acne treatment.	73.5	17.7	91.2%	5.9	2.9	0
BPO is the preferred topical antimicrobial agent due to the current climate of antimicrobial stewardship.	70.6	23.5	94.1%	2.9	2.9	0
Antibiotic resistance should be an essential consideration when selecting therapy for acne.	65.6	25.0	90.6%	9.4	0	0
Systemic antibiotics should be prescribed for a limited duration (up to 4 months) in moderate-to-severe acne.	51.5	39.4	90.9%	6.1	3.0	0
Systemic antibiotics should not be used as monotherapy.	70.6	17.7	88.3%	5.9	5.9	0
Topical retinoid plus benzoyl peroxide is first-line therapy for most patients with inflammatory or comedonal acne.	58.8	32.4	91.2%	5.9	0	2.9
Retinoids have a unique class action in reducing formation of acne precursor lesions and limiting development of new lesions.	72.7	27.3	100%	0	0	0
Topical retinoid side effects resolve within 2-3 weeks in most patients and can be managed by use of a gentle cleanser and moisturizers.	55.9	41.2	97.1%	2.9	0	0
Azelaic acid 20% cream or 15% gel is a second-line therapy for acne vulgaris.	24.2	45.5	No	18.2	6.1	6.1
Azelaic acid is a useful acne treatment in pregnant women.	32.4	50.0	82.4%	8.8	2.9	5.9
Azelaic acid is useful for acne patients who have PIH.	36.4	51.5	87.9%	9.1	3.0	0
Cumulative dose is an important consideration in determining duration of oral isotretinoin therapy.	26.5	23.5	No	41.2	5.9	2.9
Acne flares with oral isotretinoin can be minimized by initiating therapy with a low dose ( $\leq 0.5$ mg/kg).	50.0	37.5	87.5%	9.4	0	3.1
Higher cumulative doses of oral isotretinoin are needed for severe truncal acne.	33.3	33.3	No	27.3	0	6.1
Oral isotretinoin should be first-line therapy for severe nodulocystic acne.	75.0	21.9	96.9%	3.1	0	0
Most patients with acne should receive maintenance therapy with a topical retinoid $\pm$ BPO.	36.4	54.6	91.0%	9.1	0	0
Topical antibiotics should not be used as acne maintenance therapy.	84.9	9.1	95.0%	3.0	3.0	0
At present, laser, IPL, or PDT should not be considered as first-line treatment for inflammatory acne.	69.7	24.2	93.9%	6.1	0	0
A minority of women with acne have lesions localized only to the lower face.	15.2	69.7	84.9%	15.2	0	0
Topical retinoids $\pm$ BPO are important components in therapy of adult acne.	48.5	48.5	97.0%	3.0	0	0
Early and effective treatment is important to minimize potential risk for acne scarring.	81.8	18.2	100%	0	0	0
<b>Round 2</b>						
Azelaic acid 20% cream or 15% gel could be considered a second-line therapy for acne vulgaris.	15.2	69.7	84.9%	9.1	6.1	0
Cumulative dose should no longer be considered the primary consideration in determining duration of oral isotretinoin therapy in patients with severe acne.	28.1	31.3	No	28.1	9.4	3.1
Oral isotretinoin treatment should proceed until full clearance of acne. Additional studies are needed to define a total cumulative dose that maintains remission.	56.3	28.1	84.4%	12.5	0	3.1
Higher cumulative doses of oral isotretinoin are needed for severe truncal acne.	35.5	25.8	No	25.8	3.2	9.7
A higher concentration of topical retinoid (such as adapalene 0.3%) with BPO should be considered for patients with higher risk of scarring.	32.3	41.9	No	6.4	0	19.4

BPO, Benzoyl peroxide; *IPL*, intense pulsed laser; *PDT*, photodynamic therapy; PIH, postinflammatory hyperpigmentation.

# Cutaneous squamous cell carcinoma



## Incidence, risk factors, diagnosis, and staging

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*Boston, Massachusetts, and Washington, District of Columbia*

### Learning objectives

After completing this learning activity, participants should be able to describe the incidence of cSCC and define factors that are independently associated with poor outcomes on multivariate analysis of cSCC; outline the various staging systems for cSCC, the features that upstage a cSCC, and the rate of local recurrence, metastatic disease, and disease specific death at each stage; and identify aggressive cSCC that require further work-up and treatment.

### Disclosures

#### Editors

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Cutaneous squamous cell carcinoma (cSCC), a malignant proliferation of cutaneous epithelium, represents 20% to 50% of skin cancers. Although the majority of cSCCs are successfully eradicated by surgical excision, a subset of cSCC possesses features associated with a higher likelihood of recurrence, metastasis, and death. The proper identification of these aggressive cSCCs can guide additional work-up and management. In the first article in this continuing medical education series, we discuss the incidence, recurrence rates, mortality rates, and risk factors associated with cSCC and review the staging systems used to stratify patients into high- and low-risk groups. The second article in this series reviews the treatment options for cSCC, with focused attention on the management of high-stage tumors. (J Am Acad Dermatol 2018;78:237-47.)

**Key words:** 5-fluorouracil; imiquimod; ingenol mebutate; acitretin; American Joint Commission on Cancer; Brigham and Women's Hospital staging system; capecitabine; *CDKN2A*; cetuximab; chemotherapy; classification; cSCC; CT; cutaneous squamous cell carcinoma; familial cancer syndromes; high-risk; management; MRI; N1S3 staging; nicotinamide; nivolumab; *NOTCH1*; p53; PD-1; pembrolizumab; photodynamic therapy; radiation therapy; Ras; retinoids; risk factors; sentinel lymph node biopsy; sirolimus; staging.

## EPIDEMIOLOGY AND ESTIMATES OF INCIDENCE

### Key points

- Cutaneous squamous cell carcinoma is the second most common nonmelanoma skin

cancer after basal cell carcinoma, and in some studies approaches the incidence of basal cell carcinoma

- The incidence of cutaneous squamous cell carcinoma is increasing yearly in the United States

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**Abbreviations used:**

AJCC-8:	American Joint Committee on Cancer, 8th edition
BCC:	basal cell carcinoma
BWH:	Brigham and Women's Hospital
<i>CDKN2A</i> :	cyclin-dependent kinase inhibitor 2A
cSCC:	cutaneous squamous cell carcinoma
EGFR:	epidermal growth receptor factor
HPV:	human papillomavirus
MAPK:	mitogen-activated protein kinase
N1S3:	revised nodal staging system for head and neck cSCC
PD1:	programmed cell death protein 1
SOTR:	solid organ transplant recipient
<i>TP53</i> :	tumor protein p53

- **Estimates of mortality rates of cutaneous squamous cell carcinoma approximate that of renal and oropharyngeal carcinomas and melanoma in the southern and central United States**

Cutaneous squamous cell carcinoma (cSCC) is the second most common nonmelanoma skin cancer/keratinocyte carcinoma. While cSCC traditionally accounted for 20% of skin cancers, a recent study cited a 1:1 ratio between basal cell carcinoma (BCC) and SCC in the Medicare fee-for-service population.<sup>1</sup> Data from the Rochester Epidemiology Project, conducted by the Mayo Clinic, showed an overall 263% increase in the incidence of cSCC between the 1976 to 1984 and 2000 to 2010 periods.<sup>2</sup> Rates are likely increasing with the growing elderly population<sup>3</sup> and the increased focus on skin cancer screening.

Unfortunately, cSCC is not included in the US national tumor registries, making it difficult to know the exact incidence and mortality rates in our country. European data show that the age-standardized incidence of cSCC ranges from 9 to 96 per 100,000 male inhabitants and 5 to 68 per 100,000 female inhabitants (2002-2007 estimates).<sup>4-6</sup> In Australia, the incidence of cSCC was as high as 499 per 100,000 for men and 291 per 100,000 in women (2002 estimates).<sup>7</sup> In 2011, the cSCC mortality incidence in Australia was 2 per 100,000 individuals.<sup>8</sup> A study in Denmark estimated that 3% to 4% of cSCCs diagnosed in 1984 were associated with cSCC-specific mortality.<sup>9</sup>

In the United States, a 2012 estimate by Karia et al<sup>10</sup> suggested that 5604 to 12,572 people with cSCC developed nodal metastases and 3932 to 8791 people died from cSCC in the United States in that year. The incidence of cSCC was higher in the southern and central United States, where the estimated mortality rate approximates that of renal and oropharyngeal carcinomas and melanoma.

Given its increasing incidence and potential for poor outcomes, cSCC is emerging as a public health problem. Understanding the features of cSCC associated with poor prognosis can help dictate an appropriate work-up and management strategy.

## PATHOGENESIS AND ETIOLOGIC RISK FACTORS

### Key points

- **Genes commonly mutated in patients with cutaneous squamous cell carcinoma include *TP53*, *CDKN2A*, *Ras*, and *NOTCH1***
- **Risk factors that predispose to the development of cutaneous squamous cell carcinoma include light skin (Fitzpatrick skin types I-III), age, male sex, exposure to sunlight or other ultraviolet radiation, immunosuppression, human papillomavirus, chronic scarring conditions, familial cancer syndromes, and environmental exposures, such as arsenic**

### Molecular basis

cSCC carries more mutations than other common malignancies—5 times the mutation rates in lung cancer<sup>11</sup> and >4 times the mutation rates in melanoma.<sup>12</sup> Through the accumulation of these mutations and other cellular changes, an area of skin (usually in response to ultraviolet light damage) can progress through increasing levels of dysplasia and transform into a cSCC.

Tumor protein 53 (*TP53*) is the most commonly mutated tumor suppressor gene in patients with cSCC. Most of the *TP53* mutations in cSCC are C→T single-base transition mutations at dipyrimidine sites.<sup>13</sup> *TP53* mutations enable tumor cells to resist apoptosis and expand clonally at the expense of neighboring normal keratinocytes. Other mutations commonly involved are cyclin-dependent kinase inhibitor 2A mutations (*CDKN2A*), involved in cell cycle control proteins<sup>14</sup>; *Ras* mutations, involved in cellular signal transduction; and mutations of Notch homolog 1, a tumor suppressor gene that acts as a gatekeeper event in cSCC carcinogenesis.<sup>15</sup> Most cSCCs have a multitude of other mutations in addition to these 4. Also, mutations in *TP53* and *Ras* have been found in sun-damaged skin (actinic keratosis).<sup>16-19</sup> This suggests that mutations in *TP53*, *CDKN2A*, and *Ras* may be early events from ultraviolet light damage that set the stage for cSCC development, but other additional mutations are likely required for tumor formation and growth.

Understanding this molecular basis can help pave the way for targeted therapy in the future, although the sheer number of mutations in cSCC may make single-agent targeted therapy infeasible. At the

moment, there is no therapy designed specifically for cSCC. Therapies under investigation for the treatment of cSCC include epidermal growth receptor factor (EGFR) inhibitors, which impact the Ras–Raf–mitogen-activated protein kinase (MAPK) pathway, and programmed cell death protein 1 (PD1) inhibitors, which stimulate T cells to attack tumors.

Medications that target other skin cancers, such as melanoma and BCC, can paradoxically lead to the development of cSCCs. For example, patients exposed to vismodegib, a smoothened inhibitor used for advanced basal cell carcinoma, have 8 times the risk of cSCC compared to control patients.<sup>20</sup> The hypothesis is that targeted inhibition of smoothened by vismodegib selects for tumor cells that proliferate through the Ras–MAPK pathway. The use of a BRAF inhibitor for metastatic melanoma is associated with the eruption of squamoproliferative lesions, including keratoacanthomas, and is hypothesized to also activate the MAPK pathway.<sup>21,22</sup> More research is needed to understand how these therapies work and why cSCC develops.

### Risk factors

The most significant risk factors resulting in cSCC include sun exposure, age, fair skin, and immunosuppression. cSCC is most common in white individuals and is more common in men than women (3:1 ratio). The incidence increases with age, with an average age of onset in the mid-60s.<sup>23</sup> Though less common in Hispanic, black, and Asian patients, cSCC is the most common skin cancer in these populations.<sup>24</sup> In black patients, cSCC results in a high mortality rate (18%) because of delayed diagnosis and the occurrence of cSCCs on sites of previous trauma or scarring, which carries a worse prognosis.<sup>25</sup>

Immunosuppression can play a major role in cSCC, with solid organ transplant recipients (SOTRs) bearing 65 to 250 times the risk of cSCC compared with the general population.<sup>26–28</sup> The rate of cSCC formation is proportional to the number of immunosuppressive agents a SOTR is taking at any given time.<sup>26</sup> Heart and lung transplant recipients tend to have a higher risk of cSCC than renal transplant recipients because of the more intensive immunosuppression regimens and the older age of these patients.<sup>29</sup> The risk of cSCC development is greater for SOTRs in general than it is for hematopoietic stem cell transplant recipients.<sup>30</sup> Patients with chronic lymphocytic leukemia, who lack a competent cell-mediated and humoral immunity, also have an 8- to 10-fold increased risk for developing cSCC.<sup>31–33</sup> cSCC seems to be highly immunologically mediated, and therefore boosting T cell–mediated antitumor responses may be

particularly helpful in controlling advanced cSCC. A PD1 inhibitor is currently under investigation in a phase 2 trial dedicated to cSCC,<sup>34</sup> and this will be discussed further in the second article in this continuing medical education series.

Oncogenic human papillomavirus (HPV) can be associated with cSCC, particularly periungual and anogenital cSCC. HPV types 16 and 18 possess E6 and E7 proteins that prevent apoptosis and allow for continuous replication of viral DNA by regulating p53 and retinoblastoma, respectively.<sup>35</sup> cSCCs of SOTRs also commonly express HPV types 8, 9, and 15, suggesting a potential role for HPV in the development of cSCC among SOTRs.<sup>36</sup> However, HPV is not transcriptionally active in cSCC; if HPV is involved in pathogenesis, it is likely involved during the induction, not the maintenance, of cSCC.<sup>37</sup>

Environmental exposures associated with cSCC include arsenic<sup>38</sup> (sometimes present in well water and previously used in pesticides containing lead arsenate), polycyclic aromatic hydrocarbons (tar, pitch, and soot), nitrosamines, and alkylating agents.<sup>39</sup> In addition, any exposure to ionizing radiation is associated with more aggressive cSCC, with high rates of recurrence and a 10% to 30% rate of metastasis.<sup>40</sup>

The presence of rare familial syndromes associated with photosensitivity or defective DNA repair can predispose an individual to multiple cSCCs at a young age. For a more detailed discussion of these syndromes, we refer the reader to Jaju et al.<sup>41</sup>

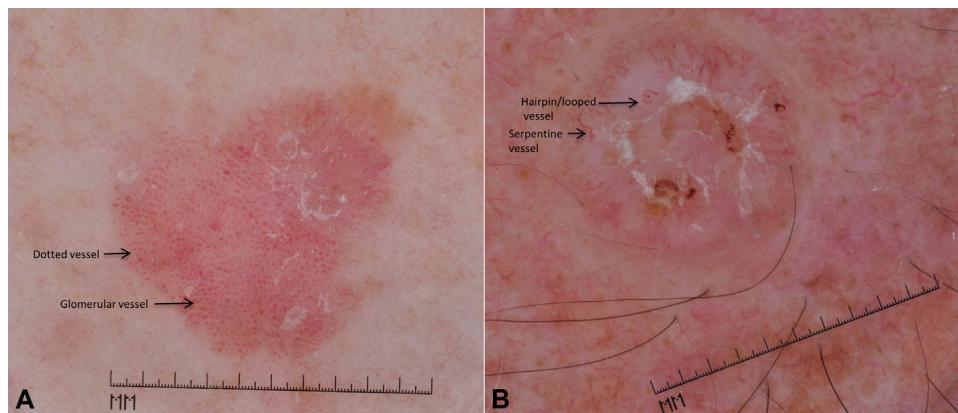
## CLINICAL AND HISTOPATHOLOGIC DIAGNOSIS

### Key points

- Histopathologic subtypes of cutaneous squamous cell carcinoma that are well-differentiated with low metastatic potential include keratoacanthoma and verrucous carcinoma
- This includes Buschke–Lowenstein tumors found in the genitalia and groin and epithelioma cuniculatum, which is found on the plantar surface of the foot
- Histopathologic subtypes of cutaneous squamous cell carcinoma with poor prognosis include desmoplastic cutaneous squamous cell carcinoma, adenosquamous cutaneous squamous cell carcinoma, and cutaneous squamous cell carcinoma associated with scarring processes

### Dermoscopic clues

Dermoscopy can help to establish the diagnosis of cSCC. cSCC is characterized under dermoscopy by 2



**Fig 1.** **A**, Cutaneous squamous cell carcinoma with dotted and glomerular vessels. **B**, Cutaneous squamous cell carcinoma with hairpin and serpentine vessels. Photographs courtesy of Ashfaq A. Marghoob, MD.

vascular patterns: small dotted vessels and glomerular vessels. Pigmented cSCC in situ can also have small brown globules and a gray-brown homogenous pigmentation on dermoscopic examination.<sup>42</sup> Invasive cSCC tends to have looped/hairpin and serpentine vessels<sup>43</sup> (Figs 1 and 2).

### Histopathologic subtypes

Well-differentiated histologic subtypes with low metastatic potential include keratoacanthoma and verrucous carcinoma. Histologically, keratoacanthomas typically have a crateriform appearance and a large central keratin plug with a pronounced, well-differentiated squamous proliferation. The verrucous carcinoma subtype includes the Buschke–Lowenstein tumor found in the genitalia and groin and epithelioma cuniculatum found on the plantar surface of the foot. Histologically, verrucous carcinomas have an endophytic component with well-differentiated squamous epithelium and pushing borders.<sup>44</sup>

Some histologic subtypes of cSCC bear a poor prognosis. Desmoplastic cSCC is highly infiltrative, recurs 10 times more frequently, and metastasizes 6 times more frequently than other cSCC variants.<sup>45</sup> A prospective cohort study by Brantsch et al<sup>46</sup> found desmoplasia to be a prognostic factor for local recurrence in cSCC (hazard ratio 16.11 [95% confidence interval 6.57-39.49]). The adenosquamous variant, characterized by secretory tubular structures, is another subtype reported to have a high risk of local recurrence, metastasis, and death.<sup>47</sup>

### FACTORS ASSOCIATED WITH LOCAL RECURRENCE AND METASTASES

#### Key points

- **Tumor diameter >2.0 cm is the risk factor most highly associated with disease-specific death**

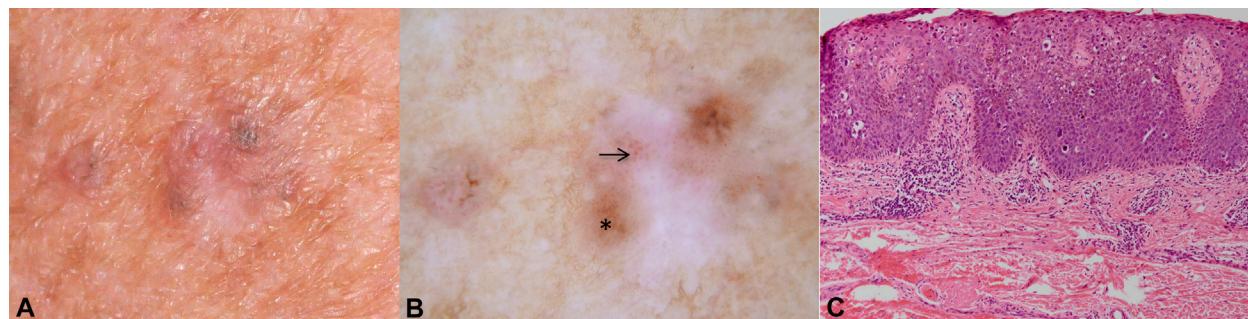
- **Perineural involvement of nerves >0.1 mm in caliber is associated with increased nodal metastases and increased mortality risk**

Lymph node metastases from head and neck cSCC have a high cure rate when identified and treated early.<sup>48,49</sup> Risk factors that predispose an individual to a higher rate of local recurrence and metastasis are discussed below.

**Diameter.** A tumor diameter >2.0 cm doubles the risk of cSCC recurrence and triples the rate of metastasis compared to lesions <2 cm in diameter.<sup>24</sup> Based on a systematic review by Thompson et al,<sup>50</sup> tumor diameter >2 cm is the risk factor most highly associated with disease-specific death and a 19-fold higher risk of death from cSCC compared to tumors <2 cm.

**Depth.** The risk factor most highly associated with recurrence and metastasis is tumor depth, with tumors of Breslow thickness >2 mm having a 10-fold higher risk of local recurrence and tumors extending beyond subcutaneous fat (into deeper layers, such as the fascia, muscle, perichondrium, and periosteum) having an 11-fold higher risk of metastasis compared with more superficial tumors.<sup>50</sup> One study involving 653 patients over a median follow-up of 43 months<sup>46</sup> showed that tumors ≤2 mm did not metastasize; cSCCs between 2.1 and 6.0 mm metastasized 4% of the time; and cSCCs ≥6.0 mm metastasized 16% of the time. The depth of cSCC is sometimes described by tissue plane, rather than millimeters, on pathology reports. In anatomic terms, extension beyond subcutaneous fat is associated with high rates of local recurrence (28%) and nodal metastasis (27%).<sup>51</sup>

**Perineural involvement.** The overall incidence of perineural involvement in cSCC is 2% to 14%.<sup>52-55</sup> Perineural invasion of large-caliber nerves (involved nerves measuring ≥0.1 mm) is associated with increased nodal metastases and disease-specific



**Fig 2.** **A**, Pigmented cutaneous squamous cell carcinoma, clinical image. **B**, Pigmented cutaneous squamous cell carcinoma, dermoscopic image showing focal areas of gray-brown homogenous pigmentation (\*) and dotted vessels (black arrow). **C**, Histopathologic results showing pigmented squamous cell carcinoma in situ with increased melanin deposition throughout the epidermis and melanophages. Photographs courtesy of Harold S. Rabinovitz, MD.

mortality.<sup>54,56,57</sup> Tumors with significant perineural invasion have local recurrence and metastatic risks as high as 47% and 35%, respectively, after wide local excision.<sup>53</sup> Mohs micrographic surgery, which is often combined with radiation therapy, brings the recurrence risk close to 0 and the risk of metastasis to 6%.<sup>54</sup>

**Histologic differentiation.** In 1921, Broders<sup>58</sup> devised a histologic grading system for cSCC from grades 1 through 4 based on the ratio of histologically differentiated versus undifferentiated cells. Grade 1 represents a lesion where 75% of cells are well-differentiated, grade 2 has 50% of cells well-differentiated, grade 3 has 25% to 50% of cells well-differentiated, and grade 4 has <25% well-differentiated cells.<sup>59</sup> In practice, many pathologists use the phrase well-differentiated to mean that nearly all the cells are well-differentiated, moderate differentiation to indicate there are areas without clear keratinization, horn pearls, and other classic features of cSCC, and poor differentiation to indicate that it is difficult to determine a keratinocyte lineage.

The presence of poor differentiation indicates a poorer prognosis, with 1 study indicating a local recurrence risk more than triple (7% vs. 2%) and a metastatic risk approximately double (7% vs. 3%) that of well-differentiated cSCCs.<sup>46</sup>

**Previously treated/recurrent cSCC.** Once a cSCC has recurred, it has a much worse prognosis, with risk of spread to regional lymph nodes and distant metastases cited as 45% for ear cSCC and 32% for lip SCC.<sup>24</sup> Recurrent cSCCs are twice as likely to recur again after excisional surgery when compared with primary tumors.<sup>60</sup> After treatment with Mohs micrographic surgery, recurrent cSCCs can still recur ≤10% of the time.<sup>61</sup>

**Site.** cSCC of the ear has been reported to have a local recurrence risk of 5% after Mohs micrographic

surgery, 19% after non-Mohs modalities, and a metastatic risk of 9% after >5 years of follow-up. SCC of the lip has a reported recurrence risk of 2% after Mohs micrographic surgery, 11% after non-Mohs modalities, and a metastatic risk of 14% after >5 years of follow-up.<sup>24</sup>

**cSCC arising in scar.** cSCCs arising from a leg ulcer, burn scar, radiation dermatitis, discoid lupus, and other chronic wounds have a reported metastatic risk of 26%.<sup>24</sup>

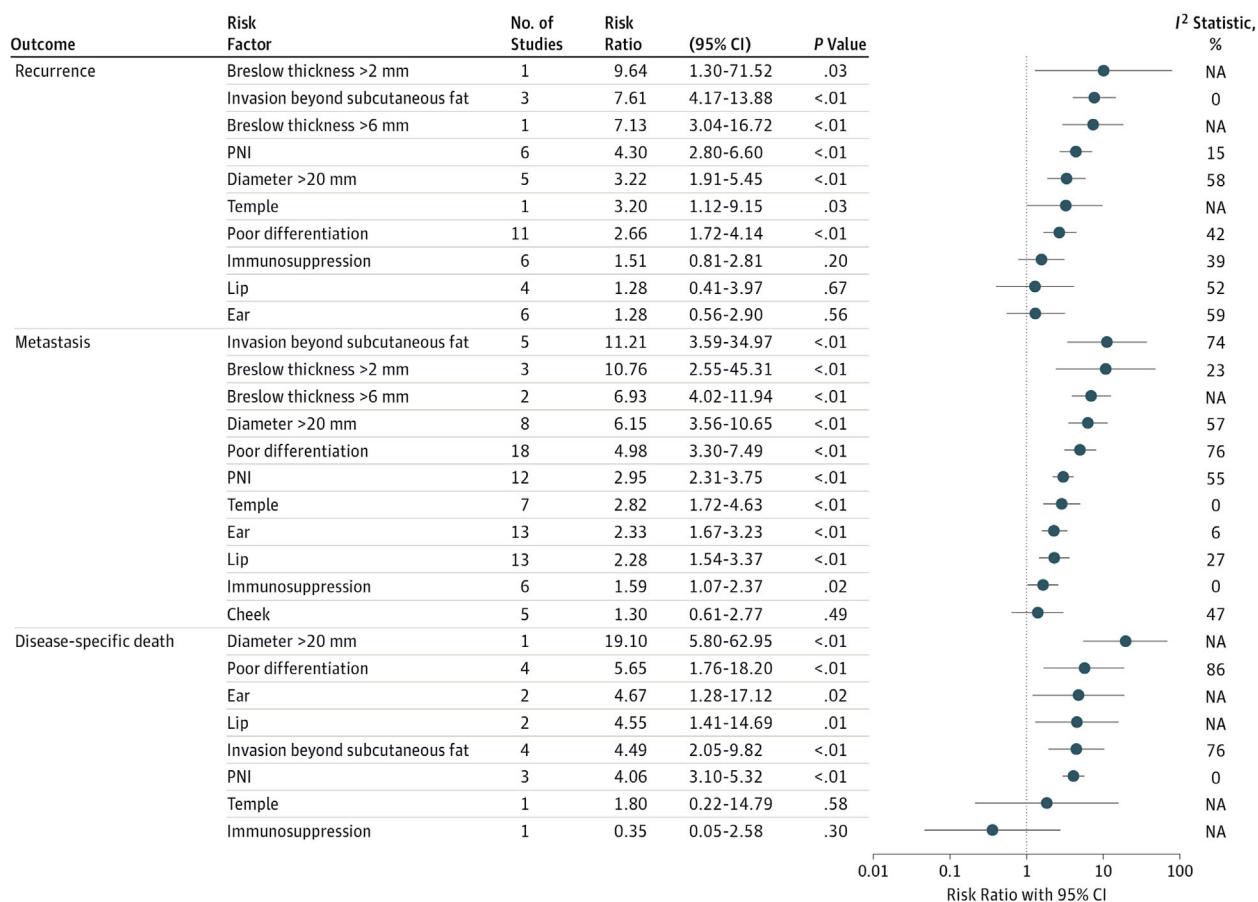
**Immunosuppression.** cSCCs in immunosuppressed patients may display more rapid growth, recur locally in 13% of patients,<sup>62</sup> and have a 5% to 8% risk of metastasis, usually in the second year after excision.<sup>63</sup> Prognosis is usually worse for older patients with tumors located on head and neck skin, when multiple tumors are present, and when there is a history of high exposure to the sun. However, metastases can occur even in patients who undergo transplantation in childhood.<sup>64</sup>

Fig 3, adapted from Thompson et al,<sup>50</sup> summarizes the effect of each high-risk feature on clinical outcome.

## VARIOUS CLASSIFICATION SCHEMES AND CLINICAL APPLICATION

### Key points

- The American Joint Committee on Cancer's (AJCC) most recent staging system, AJCC-8, published in October 2016, uses tumor diameter  $\geq 2$  cm as the distinguishing factor between T1 and T2 tumors
- High-risk features in AJCC-8 staging, which result in upstaging to T3, include tumor diameter  $\geq 4$  cm, minor bone erosion, invasion of nerves 0.1 mm in caliber or in subcutis, or deep invasion ( $\geq 6$  mm or beyond the subcutaneous fat)



**Fig 3.** Effect of each cutaneous squamous cell carcinoma high-risk feature on recurrence, metastasis, and disease-specific death. Obtained with permission from Thompson et al.<sup>50</sup>

- **T4 is reserved for major bone involvement or skull base invasion**
- **An alternative staging system, the Brigham and Women's Hospital (BWH) staging system, contains a high-risk T2b category, which requires the presence of  $\geq 2$  risk factors and includes only about 5% of cSCCs but accounts for 72% of nodal metastases and 83% of deaths from cSCC**
- **The N1S3 nodal staging system, introduced in 2010, specifies that the diameter of metastatic foci in lymph nodes and number of involved nodes play an important role in clinical outcome**

#### How is cSCC tumor staging relevant to my everyday clinical practice?

The goal of cancer staging is to risk stratify patients into groups where patients have similar clinical outcomes within a given group and progressively worse outcomes as the stage increases. Staging can help identify patients that require further work-up, adjuvant radiation, and chemotherapy. In

addition, staging criteria can help select high-risk cSCC patients for inclusion in clinical trials.

#### What are the current staging systems for cSCC?

##### AJCC-8

In October 2016, the AJCC introduced the 8th edition of its cancer staging systems. AJCC-8 includes a revision of the cSCC staging system, which was developed within the head and neck committee and therefore only applies to cSCCs located on head and neck skin and vermillion lip. It is not specified how cSCCs located elsewhere on the body are to be staged. The AJCC-8 staging system classifies cases by local tumor burden (T), nodal status (N), and metastatic disease (M). The T category is based on tumor risk factors that have been shown in multivariate analysis to be independent risk factors for local recurrence, metastasis, or disease-specific death.

**Key features of tumor staging.** Tumor diameter is the key distinguishing feature between T1 and T2 tumors, with tumors 2 to 3.9 cm in clinical

**Table I.** American Joint Committee on Cancer (AJCC) cutaneous SCC staging system for tumors of the head and neck skin 8<sup>th</sup> edition

T category	T criteria	N category	N criteria for pathologic N	M category	M criteria
TX	Primary tumor cannot be identified	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
Tis	Carcinoma in situ	N0	No regional lymph node metastasis	M1	Distant metastasis
T1	Tumor <2 cm in greatest dimension	N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE <sup>+</sup>		
T2	Tumor ≥2 cm but <4 cm in greatest dimension	N2	Metastasis in a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE <sup>+</sup> ; or >3 cm but not >6 cm in greatest dimension and ENE <sup>-</sup> ; or metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE <sup>-</sup> ; or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE <sup>-</sup>		
T3	Tumor ≥4 cm in clinical diameter OR minor bone erosion OR perineural invasion OR deep invasion <sup>†</sup>	N2a	Metastasis in single ipsilateral or contralateral node ≤3 cm in greatest dimension and ENE <sup>+</sup> ; or in a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE <sup>-</sup>		
T4	Tumor with gross cortical bone/marrow, skull base invasion, and/or skull base foramen invasion	N2b	Metastasis in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE <sup>-</sup>		
T4a	Tumor with gross cortical bone/marrow invasion	N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE <sup>-</sup>		
T4b	Tumor with skull base invasion and/or skull base foramen involvement	N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE <sup>-</sup> ; or in a single ipsilateral node >3 cm in greatest dimension and ENE <sup>+</sup> ; or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE <sup>+</sup>		
		N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE <sup>-</sup>		
		N3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE <sup>+</sup> ; or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE <sup>+</sup>		

Obtained with permission from AJCC *Cancer Staging Manual*, 8th edition, Springer International Publishing, New York, New York, © 2017. ENE, Extranodal extension.

\*Extension through the lymph node capsule into surrounding connective tissue, with or without stromal reaction.

<sup>†</sup>Deep invasion is defined as invasion beyond subcutaneous fat or >6 mm (as measured from granular layer of adjacent normal epidermis to the base of the tumor). Perineural invasion is defined as tumor cells within the nerve sheath of a nerve deeper than the dermis or measuring ≥0.1 mm, or presenting with clinical or radiographic involvement of named nerves without skull base invasion.

diameter being T2 and tumors ≥4 cm in diameter being classified as T3 tumors.

Nodal metastases are described by the N category. A solitary parotid or regional lymph node metastasis

measuring ≤3 cm is categorized as N1. Nodes are further classified as N2a to N2c and N3a to N3b on the basis of size, the number of lymph nodes, and the presence of extranodal extension. Metastases in

**Table II.** Brigham and Women's Hospital tumor staging system

Stage	No. of high-risk factors*
T1	0
T2a	1
T2b	2-3
T3	≥4

\*Brigham and Women's Hospital high-risk factors include tumor diameter ≥2 cm, poorly differentiated histology, perineural invasion ≥0.1 mm, or tumor invasion beyond the subcutaneous fat (excluding bone invasion which automatically upgrades tumor to Brigham and Women's Hospital stage T3).

distant organs or sites outside the regional lymph nodes are staged as present (M1) or absent (M0).

**Table I** provides greater detail on the AJCC-8 staging system.

**Strengths.** The new AJCC-8 staging system (2016) is based on multiple studies published since AJCC-7 (2010), which show the most relevant prognostic risk factors for cSCC. The low number of cases meeting T3 and T4 criteria had been a criticism of AJCC-7. The expansion of the T3 category in AJCC-8 will likely lead to more cases and more poor outcomes occurring in this category. The N category currently reflects the evidence-based data showing decreased survival with increasing node size, increased number of nodes, and extracapsular extension.

**Weaknesses.** Given that this staging system has recently been introduced, its prognostic accuracy has yet to be validated. Validation of the full tumor-node-metastasis system will require large population-based cohort studies because of the rarity of cSCC nodal and distant metastases.

**Clinical applications.** cSCCs that are AJCC-8 stage T2 or higher likely have an elevated risk of poor clinical outcomes and may warrant more advanced work-up and management. Staging the nodal basin (via ultrasound, computed tomography scan, or sentinel lymph node biopsy) may be considered for AJCC T2 to T4 cSCCs if a risk of nodal metastasis is considered to be present. We refer the reader to the second article in this continuing medical education series for a more thorough discussion of these options. Clear surgical margins should be obtained whenever feasible. Close clinical follow-up for recurrence should be considered.

### Brigham and Women's Hospital Tumor classification system

The Brigham and Women's Hospital (BWH) staging system, proposed in 2013, offers an alternative tumor (T) classification system (**Table II**) but does not include N or M staging criteria.

**Table III.** Other staging systems for lymph nodes\*

Parotid/neck (O'Brien et al, <sup>67</sup> 2002)	N1S3 (Forest et al, <sup>68</sup> 2010)
Parotid gland	
P1: Node ≤3 cm	I: Single nodal metastasis ≤3 cm
P2: Node >3 cm but ≤6 cm or multiple nodes	II: Multiple nodes with ≥1 node(s) ≤3 cm or single nodes >3 cm
P3: Node >6 cm or facial nerve involvement, skull base invasion	III: Multiple nodes with ≥1 node >3 cm
Neck	
N0: Clinically negative neck	
N1: Single node ≤3 cm (ipsilateral)	
N2: Single node >3 cm, multiple or contralateral nodes	

\*Adapted with permission from O'Brien et al<sup>67</sup> and Forest et al.<sup>68</sup>

**Key features of the BWH T classification.** High-risk features in this T classification system include tumor diameter ≥2 cm, tumor invasion beyond the subcutaneous fat, perineural invasion of nerves ≥0.1 mm in caliber, and poor differentiation. T stage is assigned as follows: T1, 0 high-risk features; T2a, 1 high-risk feature; T2b, 2 to 3 high-risk features; and T3, all 4 high-risk features or bone invasion.

**Clinical applications.** Two studies consisting of a total of 2074 cSCCs showed the BWH T classification to have improved prognostic discrimination over AJCC-7 with BWH T2b cSCCs carrying an elevated risk of nodal metastases (24% and 37%) and disease-specific death (16% and 20%) because of cSCC.<sup>51</sup> Published cases of BWH T2b cSCCs have a sentinel lymph node positivity risk ranging from 29% to 37%.<sup>65,66</sup>

**Strengths.** The BWH T classification takes into account that tumors <2 cm can also metastasize and includes other factors independently associated with poor prognoses on multivariate analysis, weighting these factors as equal to tumor diameter. This appears to result in better prognostication than the AJCC-7 T classification. The majority of poor clinical outcomes occur in BWH stage T2b cSCCs.

**Weaknesses.** The BWH T classification is based on 2 single-institution cohorts. It should ideally be compared against the new AJCC-8 T classification in a larger population-based cohort.

## Are there alternative systems for staging lymph node metastases?

An alternative nodal (N) classification system, developed by O'Brien et al<sup>67</sup> for cSCC, separated parotid and neck disease (Table III). This group showed that patients with cervical nodes  $\geq 3$  cm in diameter or with multiple positive neck nodes had a significantly worse prognosis than those with a single positive node. However, this staging system is complex, and it is unclear whether there is any benefit in separating parotid and neck nodal involvement.

An improved and simplified N classification system, the N1S3 system, was developed by Forest et al<sup>68</sup> in 2010 using a cohort of 215 patients with head and neck cSCC and validated using a different group of 215 patients. This system considers nodes from the parotid and neck together and is simpler than the AJCC-8 nodal staging criteria.

N1S3 N classification is as follows: I, single nodal metastasis  $\leq 3$  cm; II, multiple nodes  $\leq 3$  cm or a single node  $> 3$  cm; and III, multiple nodes with  $\geq 1$  node  $> 3$  cm.

Patients with stage I were reported to have 90% disease-specific survival at 5 years. This percentage decreased to 75% disease-specific survival for stage II disease and 42% survival for stage III disease.

In conclusion, the first article in this series serves as an introduction to the risk factors, histologic features, and staging criteria used to classify cSCC. While there is currently no standard definition of high-risk cSCC, certain patient and tumor characteristics are more likely to lead to poor clinical outcomes. These characteristics are captured in the cSCC staging systems, specifically the AJCC-8 and the BWH T classification systems.

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## Answers to CME examination

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- 1.b  
2.c  
3.c

4. e  
5. d

# Cutaneous squamous cell carcinoma



## Management of advanced and high-stage tumors

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### Learning objectives

After completing this learning activity, participants should be able to evaluate evidence-based literature concerning cSCC preventive therapies; discuss general indications for Mohs surgery in the setting of cSCC; and work up high-risk cSCC and arrive at potential treatment options.

### Disclosures

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While the majority of cutaneous squamous cell carcinomas (cSCCs) can be treated surgically, the additional work-up and treatments indicated for high-risk cSCC remain undefined. In recent years, improvements in tumor staging systems have allowed for the more accurate stratification of tumors into high- and low-risk categories. This insight, along with the publication of cSCC guidelines, brings us closer to the development of a consensus approach. The second article in this continuing medical education series addresses in question and answer format the most common questions related to advanced and high-stage cSCCs, with a simplified flowchart. The questions include the following: 1) Does my patient have high-risk cSCC?; 2) What is the next step for patients with cSCC and palpable lymphadenopathy?; 3) In patients with no clinically evident lymphadenopathy, who are candidates for lymph node staging?; 4) What forms of radiologic imaging can help detect subclinical lymph node metastases?; 5) What is the role of sentinel lymph node biopsy in cSCC?; 6) Which patients with cSCC need adjuvant radiation therapy?; 7) Is adjuvant chemotherapy an option for patients with high-stage cSCC after surgery?; 8) Are targeted and immunologic therapies an option for advanced cSCC?; 9) How often should I follow up with my patient after he/she has been diagnosed with a high-risk cSCC?; 10) What are the options for chemoprophylaxis in a patient with an increased risk of cSCC?; and 11) What chemopreventive measures can be started in coordination with medical oncology or transplant physicians? (J Am Acad Dermatol 2018;78:249-61.)

**Key words:** 5-fluorouracil; imiquimod; ingenol mebutate; acitretin; American Joint Commission on Cancer; Brigham and Women's Hospital staging system; capecitabine; *CDKN2A*; cetuximab; chemotherapy; classification; cSCC; CT; cutaneous squamous cell carcinoma; familial cancer syndromes; high-risk; management; MRI; N1S3 staging; nicotinamide; nivolumab; *NOTCH1*; p53; PD-1; pembrolizumab; photodynamic therapy; radiation therapy; Ras; retinoids; risk factors; sentinel lymph node biopsy; sirolimus; staging.

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**Abbreviations used:**

5-ALA:	5-aminolevulinic acid
5-FU:	5-fluorouracil
AJCC-8:	American Joint Committee on Cancer, 8th edition
AK:	actinic keratosis
ART:	adjuvant radiation therapy
BWH:	Brigham and Women's Hospital
cSCC:	cutaneous squamous cell carcinoma
CT:	computed tomography
EGFR:	epidermal growth factor receptor
MRI:	magnetic resonance imaging
PDT:	photodynamic therapy
SLNB:	sentinel lymph node biopsy

**3. In patients with no clinically evident lymphadenopathy, who are candidates for lymph node staging?**

The risk of nodal metastases is 21% to 30% for BWH T2b tumors and 50% to 67% for BWH T3 tumors.<sup>2,3</sup> We cannot definitively determine which patient population requires nodal staging, and therefore BWH T2b tumors appear to have a nodal metastasis risk higher than the 10% threshold for sentinel lymph node biopsy (SLNB) used for melanoma.<sup>4</sup> In light of this evidence, we recommend nodal staging in the form of radiologic imaging for AJCC-8 T4 and BWH T2b and T3 cSCCs. Radiologic imaging will be discussed in question 4; SLNBs will be discussed in question 5.

**4. What forms of radiologic imaging can help detect subclinical lymph node metastases?**

Radiologic imaging may be a useful tool in the management of high-stage cSCC and can alter management in ≤33% of patients with BWH T2b/T3 stage cSCC.<sup>5</sup> Patients who receive no imaging are often at higher risk of nodal metastases, local recurrence, and death from disease. Computed tomography (CT) is superior for bony and nodal assessment while magnetic resonance imaging (MRI) is more suitable for soft tissue and nerve examination.<sup>6</sup> The use of positron emission tomography/CT increases the sensitivity of nodal detection but is an expensive imaging tool and does not alter management in the majority (77%) of patients with head and neck cSCC with regional nodal metastases.<sup>7</sup> In our practice, we obtain CT imaging of the draining lymph node basin(s) in high-stage cSCC (BWH T2b and T3) cases given the risk of nodal metastases in excess of 20%.

In Europe, ultrasonography is the most commonly used modality for nodal staging in high-risk cSCCs.<sup>8</sup> Breuninger et al<sup>9</sup> recommend ultrasonography to evaluate lymph nodes for tumors >2 mm in thickness and CT or MRI for imaging infiltrative or destructive tumors. Ultrasonography can discriminate extranodal spread of head and neck SCC with comparable accuracy and higher specificity than MRI<sup>1</sup> at a lower cost. In the United States, ultrasound is used less frequently than CT and MRI for cSCC lymph node staging. The accuracy of ultrasonography in pathologic lymph node detection is technique- and operator-dependent. A more in-depth review of radiologic imaging can be found in MacFarlane et al<sup>6</sup> and Humphreys et al.<sup>10</sup>

**QUESTIONS AND ANSWERS REGARDING THE MANAGEMENT OF HIGH-RISK CUTANEOUS SQUAMOUS CELL CARCINOMA****1. Does my patient have high-risk cutaneous squamous cell carcinoma?**

There is no single universal definition of high-risk cutaneous squamous cell carcinoma (cSCC). The risk factors incorporated in the cSCC staging systems (detailed in the first article in this continuing medical education series) can be used as a guide in selecting high-risk patients. In both the Brigham and Women's Hospital (BWH) and the American Joint Committee on Cancer, 8th edition (AJCC-8) staging systems, T1 is considered low-risk disease. BWH T2a also appears to be low-risk while BWH T2b and T3 cases carry a risk of nodal metastases in excess of 20%. AJCC-8 has not yet been evaluated with regard to metastatic risks associated with T2, T3, and T4 cases.

Risk factors not accounted for in either staging system but clinically relevant in risk assessment include immune status, lymphovascular invasion, association with scar or chronic inflammatory disease, and treatment history (ie, primary vs. recurrent cSCC).

**2. What is the next step for patients with cSCC and palpable lymphadenopathy?**

The diagnosis of a high-risk cSCC should involve inspection and palpation of the involved site and the regional lymph nodes. For patients with palpable lymphadenopathy, clinicians can proceed to ultrasound-guided fine-needle aspiration or biopsy confirmation of involved lymph nodes. Ultrasound-guided fine-needle aspiration is reported to have a sensitivity of 80% and specificity of 98%.<sup>1</sup> A positive fine-needle aspiration or biopsy specimen usually prompts lymphadenectomy of the associated nodal basin with or without adjuvant radiation therapy (ART).

**5. What is the role of SLNBs in cSCC?**

Radiologic imaging of the draining nodal basin, generally considered pathologic if ≥1 node(s) are

≥1 cm, is not sensitive enough to detect smaller foci of disease. The concept behind SLNB is that earlier detection of nodal disease at the microscopic stage may increase survival or otherwise positively impact disease management.

SLNB has a high sensitivity and negative predictive value (sensitivity 79%, negative predictive value 96%) for cSCC and is more sensitive than CT or MRI at detecting occult nodal metastases.<sup>11,12</sup> According to 1 study, 7% of patients with cSCC who have negative PET/CT or ultrasonography findings had occult micrometastases detected on SLNB.<sup>13</sup> A systematic review of SLNB in patients with cSCC found an overall positive SLN risk of 14% (32/231 patients) with a false-negative risk of 5%.<sup>14</sup>

The use of SLNB is standard practice in patients with melanoma or breast cancer. The role of SLNB in the staging of high-risk cSCC, however, is just beginning to be studied. Without controlled trials, we cannot yet draw conclusions about its prognostic utility or survival benefit.

What we do know is that mortality associated with BWH T2b/T3 cSCC is a consequence of uncontrolled regional and nodal metastases (rather than distant metastasis) in 85% of cases.<sup>15</sup> Early detection and eradication of nodal disease may therefore significantly impact outcomes. When left untreated, the 5-year survival of cSCC patients with lymph node metastases is 26% to 34%.<sup>16,17</sup> However, if treated early, when only a single node is involved and extracapsular spread has not yet occurred, 5-year survival approaches 70% to 75%.<sup>18</sup> A statistically significant difference in positive SLNB risk exists between patients with BWH T2b lesions and those with BWH T2a lesions (29% vs. 7%,  $P = .02$ ).<sup>3</sup>

The risks involved with SLNB are low and include allergic reaction to the dye, lymphedema, infection, hematoma, and seroma. Given the elevated risk of nodal metastasis and low morbidity of nodal staging, the High-Risk cSCC Workgroup of the Association of Professors of Dermatology suggest that patients with BWH stage T2b and T3 cSCC may be considered for SLNB or ultrasonography while we await trials investigating utility (M. Fox et al, unpublished data, 2017).

Figure 1 demonstrates a proposed strategy for the evaluation and work-up of high-risk cSCC.

## 6. Which patients with cSCC need adjuvant radiation therapy?

Again, the answer is unclear. The benefit of ART has not been directly studied in cSCC; however, ART of the local site may be considered on a case by case basis when surgical margins are uncertain or when

there is high risk of local recurrence (ie, marked single-cell tumor spread at the periphery, lymphovascular invasion, in-transit metastasis, or the invasion of large-caliber nerves [ $\geq 0.1$  mm]).

For regional disease requiring lymphadenectomy, ART of the nodal basin(s) can improve clinical outcomes, particularly if multiple nodes are involved and extracapsular involvement is noted.<sup>19,20</sup> Patients with a single small ( $\leq 3$  cm) involved node without extracapsular extension (AJCC-8 N1) are at low risk for regional failure and death and can be treated with lymphadenectomy alone.<sup>21</sup> In cSCC patients with parotid metastases, ART combined with superficial parotidectomy is superior to superficial parotidectomy alone and is associated with less morbidity than a deep parotidectomy.<sup>22</sup>

## 7. Is adjuvant chemotherapy an option for patients with high-stage cSCC after surgery?

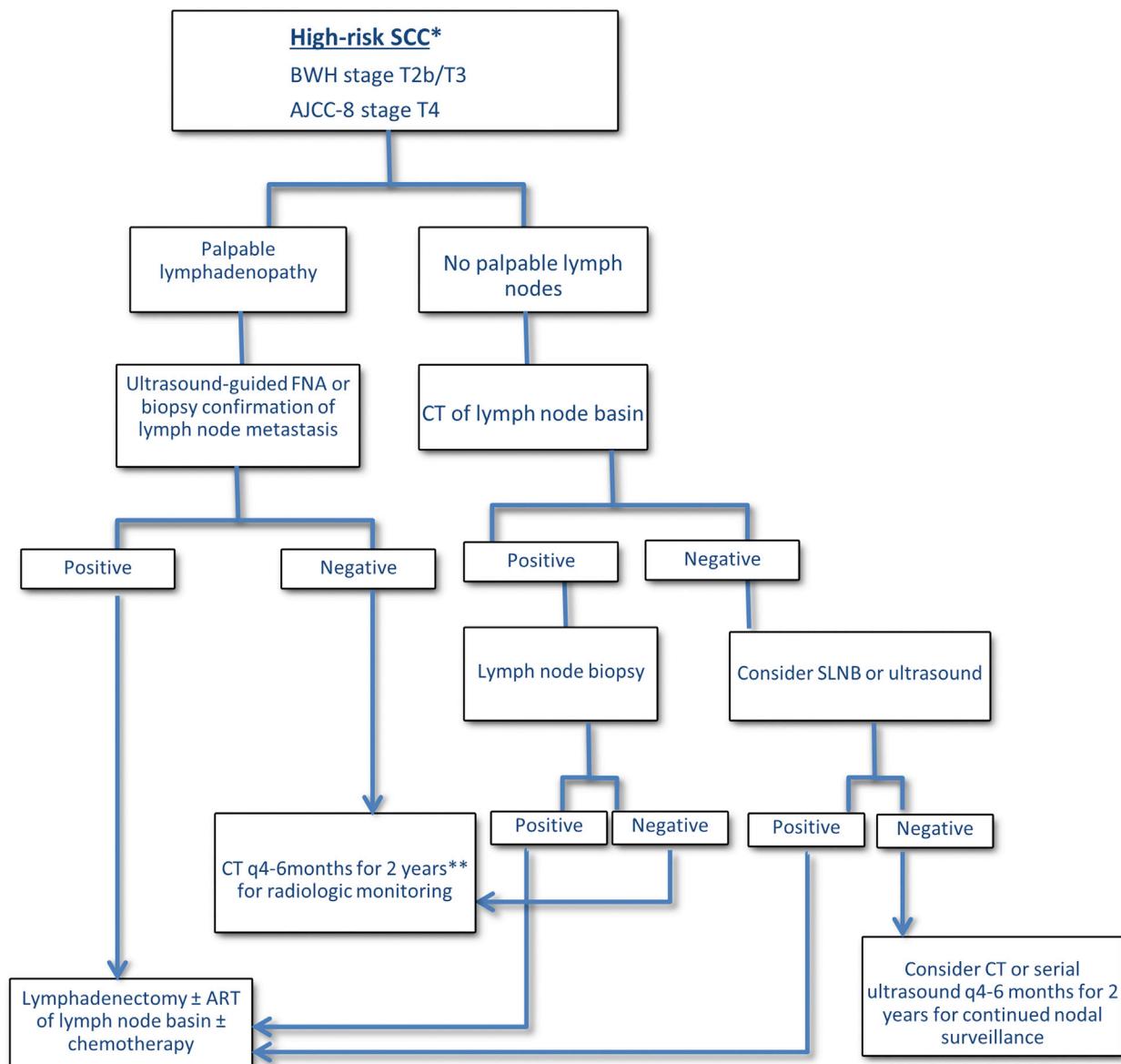
Adjuvant chemotherapy trials have been sorely lacking, and the few studies on this topic have yielded disappointing results. However, for stage III and IV cSCC with nodal or distant metastases, adjuvant chemoradiation results in better recurrence-free survival than adjuvant radiation therapy alone.<sup>23</sup>

There are no drugs approved by the US Food and Drug Administration (FDA) specifically for the treatment of cSCC. Chemotherapy agents, targeted therapies, and immune mediators are currently prescribed off-label. The most commonly used regimens historically for cSCC are 5-fluorouracil (5-FU)/cisplatin, 5-FU/carboplatin, or paclitaxel/carboplatin combinations.<sup>24</sup> Observational studies show  $\leq 80\%$  remission for combination treatments and  $\leq 60\%$  remission for monotherapy.<sup>25-29</sup> However, sustained remissions are rare and traditional chemotherapy is poorly tolerated by frail elderly patients who comprise the majority of those with advanced cSCC. These numbers have also not been confirmed in controlled clinical trials.

## 8. Are targeted and immunologic therapies an option for advanced cSCC?

Targeted and immunologic therapies are now being considered for those with unresectable disease not amenable to radiation and those with distant metastases.

**Epidermal growth factor receptor inhibitors.** Epidermal growth factor receptor (EGFR) is expressed at the cell surface by >90% of cSCCs and is responsible for cell cycle progression, proliferation, survival, angiogenesis, and metastasis via the Ras-Raf-mitogen-activated protein kinase pathway.<sup>30</sup> In 2006, the EGFR inhibitor cetuximab



**Fig 1.** Evaluation and work-up of high-risk cSCC. AJCC-8, American Joint Committee on Cancer, 8<sup>th</sup> edition (staging system); American ART, adjuvant radiation therapy; BWH, Brigham and Women's Hospital (staging system); CT, computed tomography; SLNB, sentinel lymph node biopsy. \*Other notable high-risk features not in staging systems, such as immunosuppression, lymphovascular invasion, associated with scar or chronic inflammatory disease, recurrent tumor, are not included in this flowsheet and may impact a clinician's decision to offer lymph node staging. The flowsheet provides an approach for clinicians' consideration of nodal staging but such consideration is not necessarily limited to AJCC T4 and BWH T2b/T3 cases. \*\*Interval of radiologic monitoring is based on one institution's practice, as there is no available data about the appropriate time interval for monitoring.

was approved by the FDA for the treatment of locally or regionally advanced mucosal SCC of the head and neck in combination with radiation, platinum-based therapy, or 5-FU or as a single agent for patients with recurrent or metastatic mucosal SCC of the head and neck who failed platinum-based therapy. Cetuximab use for cSCC is off-label.

O'Bryan et al<sup>31</sup> studied the use of cetuximab in very high-risk cSCC, which they defined as cSCC with lymphovascular, perineural, parotid, periorbital, cartilaginous, or bony invasion, in-transit metastasis, or regional or distant metastases. In these scenarios, cetuximab can help prevent disease progression, with sustained response after a median of

2.5 years of follow-up.<sup>31</sup> Six of 27 very high-risk patients with cSCC received surgery and cetuximab, with 3 (50%) showing complete response, 2 (33%) with disease progression, and 1 (14%) unable to be assessed because of inability to tolerate infusions. Another phase II study of 36 patients with unresectable cSCC treated with cetuximab for  $\geq 6$  weeks showed an objective response of 25% (3% complete and 22% partial responses) and disease stabilization in 42%.<sup>32</sup> While approximately half of patients respond to EGFR therapy, sustained remissions are uncommon.

Cetuximab is generally well-tolerated, but potential adverse effects include fatigue, malaise, peripheral sensory neuropathy, headache, desquamation, acneiform eruption, xeroderma, rash, diarrhea, weight loss, neutropenia, increased liver transaminase levels, and infection.

**Anti-programmed cell death protein 1 inhibitors.** The immune system plays a large part in cancer surveillance, as evidenced by the commonness of cSCC in patients with immunosuppressive conditions. The programmed cell death protein 1 (PD-1) receptor is a type I transmembrane protein that is found on T cells and that promotes T cell deactivation when it binds with its ligands (PD-L1 or PD-L2).<sup>33</sup> PD-1-inhibiting drugs improve immune surveillance, helping to control the proliferation of malignant cells. PD-1 inhibitors have been investigated for use in the treatment of melanoma, non–small cell lung cancer, prostate cancer, renal cancer, and colorectal cancer.<sup>34</sup> Most mucosal head and neck SCCs have high expression of PD-L1.<sup>35-37</sup> PD-1 inhibition is now being investigated for cSCC as well.

In a case series,<sup>38</sup> 5 patients with unresectable cSCC or basosquamous carcinoma received nivolumab or pembrolizumab. Two patients obtained partial responses and 3 cases experienced stabilization of their disease, with responses observed within 3 months. The longest progression-free survival was 7 months. One patient had a history of liver transplant and 1 patient was HIV-positive, with an undetectable viral load. No significant drug toxicity or adverse events were noted. A second case series found similar results, with 1 patient experiencing complete response and 4 patients with partial response to therapy. The longest progression-free survival was 21 months and the only adverse effect was fatigue, present in 5 of 6 patients.<sup>39</sup> Phase I data of the Regeneron trial on PD-1 showed an overall response rate of 52% and disease control rate of 70% in patients with unresectable locally advanced or metastatic cSCC. Treatment was well-tolerated, with the most common adverse event of any grade being

fatigue (19.2%).<sup>40</sup> A phase II trial is currently underway.<sup>41</sup>

Immunotherapy and checkpoint inhibition therapy hold some promise in the treatment of advanced and unresectable cSCC but should be used with caution in transplant patients. Two case reports document acute antibody-mediated rejection of a kidney allograft after the initiation of a PD-1 inhibitor in renal transplant patients.<sup>42,43</sup> However another report showed that immune-related adverse effects were avoided and kidney allograft was maintained with the preemptive use of oral prednisone 40 mg daily and the use of sirolimus as a replacement for tacrolimus.<sup>44</sup> The benefits of tumor regression must be balanced against the risk of allograft rejection. Because immunosuppressed transplant patients comprise a large fraction of high stage cSCC patients, effective management options with a low risk of organ rejection are needed. Patients with concurrent leukemia and lymphoma are also at risk for aggressive cSCC. Anti-PD-1 therapies may be able to combat both diseases simultaneously in such cases, but this awaits further study.

Table I shows the advanced workup and management strategies for patients with high-risk cSCC.

## 9. How often should I follow up with my patient after he/she has been diagnosed with a high-risk cSCC?

Close follow-up is recommended because >75% of cSCC recurrences occur within 2 years after the initial diagnosis.<sup>2,15</sup> Patients with low-stage cSCC can be seen every 6 months for the first few years after diagnosis. We typically see high-stage (BWH T2b cases) patients every 4 months for skin and lymph node examinations. For patients who are felt to be at particularly high risk for recurrence, repeat imaging (MRI for cases of named nerve invasion; CT of the nodal basin for metastatic concern) every 6 months for 2 years posttreatment may be considered.

## 10. What are the options for chemoprophylaxis in a patient with an increased risk of cSCC?

Patients who form multiple ( $\geq 10$ ) cSCCs have a high risk of nodal disease (26%), mainly because of high-stage tumors that eventually occur.<sup>45</sup> For patients who have had  $\geq 5$  dermally invasive (non–in situ) cSCCs or a single high-stage cSCC, chemoprophylaxis may be considered. Options for chemoprophylaxis are discussed below.

**Field treatment with topical chemotherapy agents.** For patients with field cancerization (widespread actinic keratosis [AK]/cSCC in situ), options

**Table I.** Indications for consideration of advanced workup and adjuvant therapy in high-risk cutaneous squamous cell carcinoma\*

Management strategy	Stage/risk factors for consideration
Imaging	BWH: T2b and T3; AJCC-8: T2, T3, or T4; CT to assess for nodal involvement or bony invasion; MRI to assess for tumor size and depth of invasion, nerve invasion, and central nervous system involvement; and PET/CT to evaluate for nodal and distant metastases
Sentinel lymph node biopsy or ultrasonography of the nodal basin	BWH: T2b and T3; AJCC-8: T4
Adjuvant radiation therapy	Surgical margins positive or unclear; high risk of local recurrence; marked single-cell tumor spread at periphery; lymphovascular invasion; in-transit metastasis; invasion of large-caliber nerves ( $\geq 0.1$ mm), multiple nerves; where there is concern about surgical margins, named nerves; and in combination with lymphadenectomy, for lymph node metastases
Chemotherapy, EGFR inhibitors, and immune checkpoint therapy	Locoregional cSCC not controlled by surgery or radiation; distant metastases

AJCC-8, American Joint Committee on Cancer, 8th edition; BWH, Brigham and Women's Hospital; cSCC, cutaneous squamous cell carcinoma; CT, computed tomography; EGFR, epidermal growth factor receptor; MRI, magnetic resonance imaging; PET, positron emission tomography.

\*Current data are insufficient to provide firm recommendations. The table above provides options for consideration as we await controlled trials.

include topical 5-FU, imiquimod, ingenol mebutate, diclofenac, and topical retinoids. The first 4 agents have been approved by the FDA for the treatment of AKs, and 5-FU has documented high efficacy against *in situ* cSCC as well.<sup>46</sup> Imiquimod and ingenol mebutate are not practical to treat field disease, because the former can lead to cytokine release when applied over large areas. Both products come in packages too small for use on large surface areas.

5-FU is therefore the most common topical therapy for field disease.

For field damage on the arms and legs, 5-FU can be occluded with weekly wraps, which consist of a zinc-impregnated gauze (Unna wrap) covered by a compression wrap and gauze bandages and left intact for 1 week. These 5-FU wraps are changed weekly in clinic for 4 weeks. Alternatively, patients can apply 5-FU in the morning and at bedtime for 4 weeks and provide their own occlusion to extremities with plastic wrap overnight. Before application of these topical therapies, hyperkeratotic crusts should be removed under local anesthesia with a blade or shallow curette to ensure adequate drug penetration.

Data regarding chemopreventive effects of topical retinoids are conflicting. Some studies show that topical retinoids can reduce the number of AKs, either when used alone<sup>47,48</sup> or in combination with other treatments, such as nonablative fractional resurfacing.<sup>49</sup> However, the Veterans Affairs Tretinoin Chemoprevention Trial<sup>50</sup> showed no difference in the number of patients developing invasive cSCC over the follow-up period. A summary of topical chemopreventive therapies is detailed in Table II.

**Photodynamic therapy.** Photodynamic therapy (PDT) is conducted with either 5-aminolevulinic acid (5-ALA) or methylated aminolevulinate as a photosensitizer that is rapidly incorporated into proliferating cells, such as those in AKs and *in situ* cSCC. Upon exposure to a noncoherent light source 1 to 3 hours later, reactive oxygen species are generated and induce destruction of proliferating cells containing the drug.<sup>51</sup>

In the United States, PDT using 5-ALA and 1000 seconds (16 min, 40 sec) of activation by a blue light source was FDA approved in 2001 for the treatment of AKs. This type of PDT protocol can be administered in-office. Some clinicians have advocated for red light PDT (which is commonly available in Europe), especially when treating *in situ* cSCC, because of its longer wavelength and greater depth of penetration.<sup>52</sup>

More recently, daylight PDT has emerged as a protocol equivalent to conventional PDT but associated with less pain.<sup>53-55</sup> In our practice, we advise patients to sit in a shady area within 60 minutes after 5-ALA has been applied. After 2.5 hours in the shady area, the patient is asked to wash the 5-ALA off with soap and water. For the next 48 hours, they are told to wear sun protective clothing (ie, hat, long sleeve shirts, and pants) and to apply a zinc- or titanium-based sunscreen to all areas that are exposed to sunlight.

**Table II.** Topical therapies for cutaneous squamous cell carcinoma chemoprevention and treatment

Therapy	Indications	Frequency of application	Mechanism of action	Adverse effects	Level of evidence*
Topical retinoids <sup>47-50</sup>	Ineffective at preventing cSCC according to VA randomized chemoprevention trial, <sup>50</sup> but other studies show decrease in AK count	N/A	Induces apoptosis of tumor cells; downregulate proliferative keratins K6 and K16	Burning, irritation, erythema, and dermatitis	IB
5-fluorouracil <sup>80,81</sup>	Approved by the FDA in 1970 for treatment of AKs; off-label use: treatment of cSCC <i>in situ</i>	AK: 0.5% cream: apply once daily for up to 4 weeks; 5% cream: apply twice daily for 2-4 weeks cSCC <i>in situ</i> : 5% cream: apply twice daily for 3 to 6 weeks; treatment can be continued for ≤10-12 weeks	Pyrimidine analogue: cytotoxic metabolites are incorporated into DNA and RNA, inducing cell cycle arrest and apoptosis	Erythema, shallow erosions, pruritus, dermatitis, burning sensation, and photosensitivity	AK: IA; cSCC <i>in situ</i> : IB
Imiquimod <sup>82,83</sup>	Approved by the FDA for the treatment of AKs; not practical for treatment of field disease because can have significant side effects when applied to large surface areas	AK: Aldara <sup>†</sup> —apply 2 times/week × 16 weeks Zyclara <sup>†</sup> —treatment consists of 2 cycles (14 days each) separated by 1 rest period (14 days) with no treatment	Induces, synthesizes, and releases cytokines, thereby inducing secretion of interferon-gamma by naïve T cells	Local reactions: erythema, discomfort, erosion, and dyschromia Systemic symptoms: flu-like symptoms, dizziness, headache, and, rarely, urinary retention	AK: IA; cSCC <i>in situ</i> : IB
Ingenol mebutate <sup>84</sup>	Treatment of AKs	Face or scalp: apply 0.015% gel once daily to affected area for 3 consecutive days Trunk or extremities: apply 0.05% gel once daily to affected area for 2 consecutive days Apply 3% gel to lesion area twice daily for 60-90 days	Multiple mechanisms of action, including direct cell death and protein kinase C-mediated inflammatory response	Severe allergic reactions; herpes zoster; eye pain; periorbital edema; headache; mild to moderate erythema, scaling, and dryness	AK: IB
Diclofenac <sup>85</sup>	Treatment of AKs		Nonsteroidal antiinflammatory drug that reduces the production of prostaglandins by inhibiting inducible cyclooxygenase-2	Pruritus, rash, desquamation, elevated liver function tests, flu-like symptoms, and headache	IB
Photodynamic therapy <sup>53-56</sup>	Treatment of AKs	Various protocols	Exogenous photosensitizer and light source induces a porphyria; neoplastic cells accumulate more porphyrins than normal cells	Erythema, blistering, desquamation, and discomfort	IB

AK, Actinic keratosis; FDA, US Food and Drug Administration; cSCC, squamous cell carcinoma; N/A, not applicable; VA, Veterans Affairs.

\*Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥1 randomized controlled trial; level IIA evidence includes evidence from ≥1 controlled study without randomization; level IIB evidence includes evidence from ≥1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

<sup>†</sup>Aldara, 3M Health Care Limited, Loughborough, England; Zyclara, Valeant Pharmaceuticals North America LLC, Bridgewater, NJ.

**Table III.** Oral and systemic agents for cutaneous squamous cell carcinoma chemoprevention

Therapy	Indications	Dosing	Mechanism of action	Adverse effects	Level of evidence*
Nicotinamide <sup>66-70</sup>	Off-label use: decreases AKs and SCCs; can be used by anyone for chemoprophylaxis	500 mg PO BID	Amide form of vitamin B <sub>3</sub> ; enhances the repair of UV light-induced DNA damage; also reduces the level of immunosuppression induced by UV light	None reported; liver failure at high doses (>3 mg/d)	IB
Oral retinoids <sup>58-64</sup>	Off-label uses: cSCC prevention in xeroderma pigmentosum and organ transplant patients; consider in patients who develop 5-10 cSCCs per year; consider for patients on BRAF inhibitors with multiple cSCCs	High-dose isotretinoin (2 mg/kg/d); acitretin 10-30 mg PO daily	Natural or synthetic analogues of vitamin A; bind to specific nuclear receptors and involved in immunomodulation, induction of apoptosis, cell cycle control, inhibition of ornithine decarboxylase, and inhibition of cellular proliferation and keratinization	Dry skin and mucosa, alopecia, increased liver transaminases and triglycerides, decreased night vision, and teratogenicity	IB
Capecitabine <sup>71-73</sup>	Solid organ transplant recipients with multiple cSCCs	950 mg/m <sup>2</sup> on days 1-14 of a 21-day cycle along with 3 times weekly subcutaneous interferon alfa	Converted to active form, 5-FU, in the body	Fatigue, nausea, hand-foot syndrome, gout, and decreased renal function	III
Aspirin and NSAIDs <sup>86</sup>	Preventive effect shown in meta-analysis; however, unclear if benefits worth the potential adverse effects	Variable NSAIDs and dosing frequencies studied	Inhibits COX-2, which results in decreased inflammation and apoptosis of neoplastic cells	Gastrointestinal ulcers and bleeding, kidney failure, nausea, rash, headache, and dizziness	IA
Sirolimus <sup>75-79</sup>	Solid organ transplant recipients—studies show decreased risk of cSCC compared to calcineurin inhibitors	Varies	Inhibits the mammalian target of rapamycin, thereby reducing the growth and proliferation of tumor cells	Myelosuppression, hyperlipidemia, increased susceptibility to infection, peripheral edema, hypertension, headache, rash, and abdominal pain	IB

5-FU, 5-fluorouracil; AK, actinic keratosis; BID, twice daily; COX-2, cyclooxygenase-2; cSCC, cutaneous squamous cell carcinoma; NSAID, nonsteroidal antiinflammatory drug; PO, orally; UV, ultraviolet light.

\*Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥1 randomized controlled trial; level IIA evidence includes evidence from ≥1 controlled study without randomization; level IIB evidence includes evidence from ≥1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

PDT can be used as a definitive treatment for superficial skin cancers. The complete response with 5-ALA is higher than topical 5-FU when measured at 12 months (82% vs. 48%, respectively;  $P = .006$ ) but is a less definitive treatment compared to surgical approaches.<sup>56</sup> Close follow-up is recommended if PDT is chosen as a definitive treatment option. PDT has also been investigated as an adjuvant therapy for *in situ* cSCC incompletely removed by surgery with no recurrences at 12 months in 13 patients.<sup>57</sup>

PDT can be performed in 1 treatment, with an optional repeat treatment 1 to 4 weeks later. Adverse effects of PDT include a sunburn-like reaction with redness, peeling, and discomfort lasting 1 to 2 weeks.

**Oral retinoids.** Retinoids are natural or synthetic analogues of vitamin A that exert their physiologic effects by binding to specific nuclear receptors. As oral agents, their role in the chemoprophylaxis of skin cancer involve immunomodulation, induction of apoptosis, cell cycle control, inhibition of ornithine decarboxylase, and the inhibition of cellular proliferation and keratinization, though the mechanisms are not fully understood.<sup>58,59</sup>

Studies show that oral retinoids can reduce the development of keratinocyte carcinomas in patients with xeroderma pigmentosum<sup>60,61</sup> and in patients who have undergone organ transplants.<sup>62,63</sup> Our threshold for starting oral retinoids includes the development of 5 cSCCs over the course of 2 to 3 years, formation of a single BWH T2b/T3 cSCC combined with field photodamage, or field cancerization that is not well-controlled with topical 5-FU or PDT.

We recommend starting a patient on oral acitretin 10 mg every other day with the dose increased every 4 weeks as tolerated to reach a final oral dose of 20 mg daily. Laboratory monitoring includes a complete blood cell count and assessments of creatinine, lipid panel, and liver function at baseline. A lipid panel and liver function tests should be repeated monthly as the dose is increased, and every 3 months when the patient is on a stable dose. Monitoring of creatinine is also advised for patients with renal dysfunction or kidney transplant.<sup>64</sup> Physicians should inform patients that acitretin is a long-term medication and that discontinuation of the medication is associated with a rapid return to baseline cSCC formation.<sup>65</sup>

**Nicotinamide.** Nicotinamide (also known as niacinamide) is an amide form of vitamin B<sub>3</sub> and enhances the repair of ultraviolet-induced DNA damage.<sup>66</sup> It can also reduce the level of immunosuppression induced by ultraviolet light radiation without altering baseline immunity.<sup>67</sup>

**Table IV.** Consensus guidelines for high-risk cutaneous squamous cell carcinoma

Committees developing guidelines	Topic
American Joint Committee on Cancer, 8th edition <sup>87</sup>	cSCC of the head and neck
National Comprehensive Cancer Network Clinical Practice Guidelines <sup>88</sup>	cSCC
European Dermatology Forum, European Association of Dermato-oncology, European Organization of Research and Treatment of Skin Cancer <sup>19</sup>	cSCC
Association of Professors of Dermatology (M. Fox et al, unpublished data, 2017)	Nodal staging for cSCC
International Transplant-Skin Cancer Collaborative <sup>89</sup>	cSCC in organ transplant recipients

cSCC, Cutaneous squamous cell carcinoma.

The efficacy of oral nicotinamide for the prevention of keratinocyte carcinoma has been demonstrated in a randomized trial of Australian subjects.<sup>68</sup> In this study, 386 immunocompetent participants with a history of >2 keratinocyte carcinomas in the last 5 years were treated with 500 mg of nicotinamide twice daily or placebo for 12 months. The patients in the nicotinamide group had a 30% reduction in the number of new cSCCs and a 13% reduction in AKs in 12 months. The same group has published a similar randomized trial in renal transplant recipients that was underpowered to assess impact on cSCC formation but reported no adverse effects.<sup>69</sup>

When purchasing nicotinamide over the counter, patients should check labels and avoid purchasing nicotinic acid/niacin, which can result in adverse effects (eg, flushing). Side effects of nicotinamide are minimal, but at high doses (>3 g/day) nicotinamide can cause liver failure.<sup>70</sup> The benefits of nicotinamide are promising, but there is a lack of long-term prospective studies documenting its chronic effects on skin cancer prevention. Nevertheless, we are offering it to patients who have had >1 cSCC or who display field cancerization (diffuse AK/*in situ* cSCC).

## 11. What chemopreventive measures can be started in coordination with medical oncology or transplant physicians?

For organ transplant recipients, reducing the number of immunosuppressive agents or replacing these immunosuppressants with sirolimus can be considered by the transplant team if a dermatologist is concerned that skin cancer formation poses a

major risk to the patient's health. Capecitabine is another medication for advanced cSCC that is usually initiated with the help of medical oncology.

**Capecitabine.** Capecitabine is an oral prodrug that is converted to its active form, 5-FU, within tumor tissues, therefore producing less toxicity than intravenous 5-FU. Oral capecitabine can be administered along with subcutaneous interferon alfa to treat advanced cSCC.<sup>71</sup> Capecitabine can also control marked field cancerization in those with diffuse AKs, cSCC in situ, and superficially invasive cSCC.<sup>72</sup> An extremely rare deficiency of dihydropyrimidine dehydrogenase, the enzyme that metabolizes capecitabine, can result in severe toxicity or death. Potential adverse effects include fatigue, hand–foot syndrome, diarrhea, and rarely neutropenia.<sup>73</sup>

**Sirolimus.** Sirolimus is a macrolide that inhibits the mammalian target of rapamycin, thereby reducing the growth and proliferation of tumor cells.<sup>74</sup> Kidney organ transplant recipients who are treated with sirolimus as first-time therapy<sup>75</sup> or who are switched from calcineurin inhibitors to sirolimus display a reduced incidence of skin cancer.<sup>76,77</sup> In addition, for patients who have already had a skin cancer posttransplant, sirolimus can lower the risk of subsequent skin cancer, with no increased risk of overall mortality.<sup>78</sup> Only 1 retrospective study showed a nonsignificant trend toward higher incidence of cSCC in the sirolimus group.<sup>79</sup>

Potential adverse effects of sirolimus include myelosuppression and hyperlipidemia, increased susceptibility to infection, peripheral edema, hypertension, headache, rash, and abdominal pain. Less adverse events have been observed with gradual conversion protocols and lower doses (including the doses used currently in organ transplant recipients).<sup>76,77</sup>

A summary of oral and systemic chemopreventive agents is listed in Table III. Current guidelines and consensus statements for the management of cSCC are summarized in Table IV.

In conclusion, although most cSCCs are cured by clear margin surgery, BWH T2b/T3 cSCCs should be considered for nodal staging. Recommendations for high-stage cSCC will continue to evolve as additional research on this topic is conducted. Clinical trials addressing nodal staging and adjuvant therapy will unquestionably shape future management strategies.

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# Merkel cell carcinoma: An update and review



## Pathogenesis, diagnosis, and staging

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*See related article on page 457*

### Learning objectives

After completing this learning activity, participants should be able to describe the epidemiology of merkel cell carcinoma and be able to identify those at highest risk and with greatest incidence; explain the pathophysiology of merkel cell carcinoma; delineate the clinical characteristics of merkel cell carcinoma; and, when merkel cell carcinoma is suspected, note this on the pathology requisition for the biopsy in order to aid the dermatopathologist in making an accurate diagnosis.

### Disclosures

#### Editors

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Merkel cell carcinoma (MCC) is an uncommon primary cutaneous neuroendocrine cancer. It most commonly presents as an indurated plaque or nodule on sun-damaged skin in elderly patients and is characterized by high rates of local recurrence and nodal metastasis. Survival at 5 years is 51% for local disease and as low as 14% for distant disease, which underscores the aggressive nature of this tumor and challenges in management. Advances in immunology and molecular genetics have broadened our understanding of the pathophysiology of MCC and expanded our therapeutic arsenal. With this comprehensive review, we provide an update of MCC epidemiology, pathogenesis, clinical presentation, diagnostic evaluation and prognostic markers. The second article in this continuing medical education series explores the evolving landscape in MCC management. (J Am Acad Dermatol 2018;78:433-42.)

**Key words:** cytokeratin-20; Merkel cell carcinoma; Merkel cell polyomavirus; Merkel cells.

## EPIDEMIOLOGY

### Key points

- **Merkel cell carcinoma is a rare cutaneous malignancy that most commonly affects elderly white men**
- **Merkel cell carcinoma typically occurs on sun-exposed areas of the head and neck**
- **The incidence of Merkel cell carcinoma is increasing**

The incidence of Merkel cell carcinoma (MCC) has steadily increased over the past 30 years.<sup>1</sup> Epidemiologists have attributed this rise in part to increased reporting and improvements in diagnostic techniques, namely cytokeratin-20 (CK-20) immunohistochemical staining, which was developed in 1992.<sup>1,2</sup> In 2012, MCC was assigned a code in the *International Classification of Diseases, Ninth Revision*, which improved the accuracy of

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**Abbreviations used:**

CK-20:	cytokeratin-20
LT:	large T antigen
MC:	Merkel cell
MCC:	Merkel cell carcinoma
MCV:	Merkel cell polyomavirus
NCCN:	National Comprehensive Cancer Network
PET/CT:	positron emission tomography/computed tomography
SLNB:	sentinel lymph node biopsy
ST:	small T antigen
UV:	ultraviolet

epidemiologic studies incorporating data from population-based registries.<sup>3</sup> Before this, incidence calculations were largely based on the histologic code assigned to MCC in 1986.<sup>4</sup>

The overall age-adjusted worldwide incidence rate for MCC based on population studies from the Surveillance, Epidemiology, and End Results program in the United States and international cancer registries in Europe, New Zealand, and Australia, ranges from 0.10 to 1.6 cases per 100,000 people per year.<sup>5-8</sup> More recent data from Surveillance, Epidemiology, and End Results in 2011 estimated 0.79 cases of MCC per year, or approximately 1600 new cases diagnosed annually.<sup>8</sup> As a point of comparison, for every single MCC diagnosed each year, there are 33 melanomas.<sup>5,9</sup>

The prevalence of MCC varies among ethnic groups and geographic areas. The most typical patient is an elderly white male in his seventies or eighties with a history of extensive sun exposure, although MCC has also been reported in black, Asian, American Indian, and Pacific Islander patients.<sup>1,5,10</sup> MCC is approximately 25 times more common in whites compared to other ethnic groups. Incidence rates based on epidemiologic studies in Northern Europe align closely with US figures, which is not surprising given the ethnic background of that patient demographic. Epidemiologic studies in Africa, Asia, and elsewhere in the Americas have been limited by the exceedingly low numbers of cases reported there. A retrospective chart review of 10 hospitals in China identified 22 cases of MCC, of which all but 1 were of Han Chinese descent.<sup>11</sup>

Geographically, MCC shows a predilection for fair-skinned patients living in areas with high ultraviolet (UV) B light indices. The age-adjusted incidence of MCC in white patients appears to be linearly correlated with the UVB light radiation index, with the highest incidence rates reported in Hawaii.<sup>5</sup> MCC also tends to affect men more than women, in some

studies at a rate of 2:1, although small cohort studies in Finland and China have reported a slightly higher incidence in women.<sup>9-12</sup>

MCC favors the head and neck in all populations except men <65 years of age and in nonwhite ethnic groups. In younger patients, the trunk is the favored site; in African Americans, the lower extremity is most common.<sup>5,8</sup> MCC has been reported in children but is exceedingly rare in younger people; incidence rates for adults 35 to 39 years of age in New Zealand, for instance, have been reported at 0.03 per 100,000 compared with 17.56 for adults >85 years of age.<sup>13-15</sup>

## PATHOGENESIS

### Key points

- **Merkel cells were first described as “touch cells” based on their presumed association with nerve fibers in the skin**
- **A diagnosis of MCC typically requires obtaining a biopsy specimen and immunohistochemical staining because of its nonspecific clinical and histopathologic appearance**
- **The diagnostic and prognostic implications for Merkel cell polyomavirus infection are under investigation and will likely play a role in clinical practice**

Research into the pathogenesis of MCC has generated increasing interest in its presumed cell of origin, the Merkel cell (MC). These so-called “touch cells,” as first described in 1876 by Frederich Merkel, reside predominantly in the basal layer of the epidermis and follicular epithelium and play a role in light touch sensory responses.<sup>16</sup> MCs are also involved in nerve guidance, somatostatin synthesis, and other endocrine and paracrine effects, hence their “neuroendocrine” designation.<sup>17,18</sup> When the pathologist Cyril Toker first identified a primary cutaneous neuroendocrine cancer with a trabecular network and intracellular granules in 1972, he noted that these features were also seen in MCs.<sup>19</sup> For years after his discovery, the terms trabecular and neuroendocrine carcinoma were widely used for these “granular” skin cancers, but with the advent of CK-20 staining and improved immunohistochemical profiling, MCC became the accepted term.<sup>20-22</sup>

Immunohistochemistry has played a major role in characterizing MCC and its potential origins. CK-20, a low-molecular weight keratin expressed normally in gastrointestinal epithelium and some gastrointestinal and transitional cell carcinomas, was the first immunostain used to reliably diagnose MCC.<sup>22</sup> While CK-20 reliably stains both MCs and MCC, several recent studies have used coimmunostaining

techniques to clarify the origin of MCs and their relationship to MCC.<sup>23,24</sup> With the discovery of paired box 5 positivity in MCC, some have argued that MCC is a complete misnomer, in that the cell of origin is actually a pro/pre-B cell rather than a postmitotic MC.<sup>25</sup> For the purposes of this review, we consider MCC a primary cutaneous tumor derived from MCs or their precursors with the caveat that our understanding of this relationship is still evolving.

As with other cutaneous malignancies, the pathogenesis of MCC likely represents a complex interplay of genetic, molecular, and environmental factors. The relationship between UV radiation and MCC, for instance, has been well described in numerous epidemiologic studies.<sup>5,6,26</sup> Psoriasis patients treated with psoralen plus UVA light phototherapy have been shown to develop MCC at a rate 100 times that of the general population.<sup>27</sup> MCC has also been reported at disproportionately higher rates in patients on long-term iatrogenic immunosuppression and those with lymphoproliferative disorders, such as chronic lymphocytic leukemia, HIV/AIDS, organ transplants, and autoimmune disease.<sup>28-39</sup> The predominance of MCC in elderly patients also suggests a role for immunosenescence.<sup>39</sup>

Perhaps our greatest insight into the pathogenesis of MCC stems from the discovery of the MC polyomavirus (MCV) in 2008, when Feng et al<sup>40</sup> at the University of Pennsylvania identified a fusion transcript between an unknown T-antigen and human tyrosine phosphatase in MCC tumor cells, which led to the sequence analysis of the 5387-base pair genome of a previously unknown polyomavirus. The oncogenic potential of this family of small, double-stranded DNA viruses was first shown in murine models in 1953, but no viruses inducing human cancers had ever been conclusively characterized. The polyomavirus sequenced in their laboratory was present in 8 of the 10 MCC tumors sampled and only 8% of control tissues; in 6 of those tumors, viral DNA was integrated into the genome in a clonal pattern, indicating that viral integration preceded clonal expansion of the tumor cells. It was speculated that MCV played a role in tumorigenesis by tumor-associated antigen expression, insertional mutagenesis, or both. In the last 10 years, our understanding of these molecular pathways has been refined.

The polyomavirus genome consists of early and late coding regions that play a role in infectivity. Natural polyomavirus infection is characterized by the expression of early antigens followed by late capsid proteins. In nonlesional skin, MCV does not integrate into human DNA but rather replicates

within the nucleus using the host cell's machinery.<sup>41</sup> In the evolution of MCC, the virus integrates into the genome at a nonspecific binding site and expresses 2 putagenic oncoproteins, the large T-antigen (LT) and small T-antigen (ST). The truncated domain of LT may play a role in shifting the virus' natural behavior from that of replication and virion release to clonal integration and tumorigenesis. LT targets the retinoblastoma tumor suppressor and alters cell cycle progression, thereby contributing to unregulated cell proliferation.<sup>42</sup> The other major driver of oncogenesis in MCV is ST, which has been shown to bind the tumor suppressor protein phosphatase 2A and regulate the mammalian target of rapamycin pathway in nonneoplastic cells; in MCC tumor cells, ST acts on a different pathway, namely the FBXW7-interacting domain.<sup>43</sup> Murine models suggest that ST may be responsible for the initiation of tumorigenesis, while LT maintains it. While the interplay of LT and ST in this oncogenic cascade has yet to be fully elucidated, both antigens show potential as therapeutic targets.

The oncogenic role of MCV in such a rare cancer was in some ways a surprising discovery, because while MCC is a rare cancer, MCV is ubiquitous in human populations. Based on serologic tests, it is estimated that 60% to 80% of the general population is infected with MCV.<sup>44,45</sup> Polyomavirus has been found on normal skin at all body sites and in urine, nasal secretions, and respiratory secretions. Vertical transmission does not occur, but exposure in early childhood is typical.<sup>46</sup> The exact mechanism of how MCV drives oncogenesis in a select number of cases remains the focus of intense study. Integration into the host genome is not part of the polyomavirus' normal life cycle and in fact inhibits its ability to replicate.<sup>47</sup> Given the tendency of MCC to occur on sun-exposed sites, UV radiation may induce mutations in the viral genome that drive oncogenesis, while evasion of the immune response facilitates cellular proliferation.<sup>48</sup> Notably, >80% of MCC tumors downregulate the expression of major histocompatibility complex class I, thereby suppressing immune recognition of MCV-derived peptides by CD8 T cells.<sup>49</sup> In addition, vascular E-selectin expression is reduced in MCC tumors, which compromises the ability of lymphocytes to migrate into the tumor microenvironment.<sup>50</sup>

After viral integration has occurred, MCV induces host cell mutations that give rise to MCC. Advances in DNA sequencing have allowed for the identification of these mutational signatures that elucidate important differences between MCV-positive and MCV-negative MCC, highlighting in particular the abundance of UV-induced mutations in the latter. As



**Fig 1.** A large pink, erythematous nodule with telangiectasias on the forehead.

in melanoma and other skin cancers that are associated with UV radiation, these mutations (namely C-to-T pyrimidine dimers) suggest that at least in MCV-negative tumors, the cell is unable to effectively repair UV-induced damage and subsequently accumulates many more mutations that lead to uncontrolled cellular proliferation. In MCV-positive tumors, in contrast, the acquisition of mutations that drive tumor development may have more to do with the integration of the virus into the genome and its effect on host genes than other external factors.<sup>47</sup> In 1 study using exome sequencing of 49 MCCs, researchers characterized the vast differences in mutational burden that exist between the two: 1121 somatic single nucleotide variants per-exome in MCV-negative tumors compared to only 12.5 variants in MCV-positive MCC, with no mutations in Rb and p53 in the latter.<sup>51</sup> The phosphatidylinositide 3-kinase and Notch pathways were altered in both subsets, which suggests a common—or at least similar—endpoint, independent of viral status. Harms *et al*<sup>52</sup> also compared the molecular genetics of MCV-positive and -negative tumors and identified significant differences in mutational burden (0.4 mutations/mutational burdens in MCV-positive tumors compared to 10 mutations/mutational burdens in MCV-negative tumors). Likewise, several shared deregulated signaling mechanisms among MCV-positive and -negative tumors have also been shown using specific biomarkers such as P-STAT, P-CREB, and NFAT.<sup>53</sup> The characterization of these molecular events and their downstream effects has implications for prognosis and therapy; for example, p63 expression is a negative prognostic indicator, and its prevalence in MCV-negative tumors may explain, at least in part, why those patients have worse outcomes.<sup>54-58</sup>

## CLINICAL PRESENTATION

### Key points

- The clinical presentation of Merkel cell carcinoma is nonspecific and varied, but most

**typical is an erythematous or violaceous nodule on sun-exposed areas on the head or neck in an elderly person**

- Two-thirds of patients with Merkel cell carcinoma present with local disease only, but nodal or metastatic disease at the time of diagnosis is not uncommon

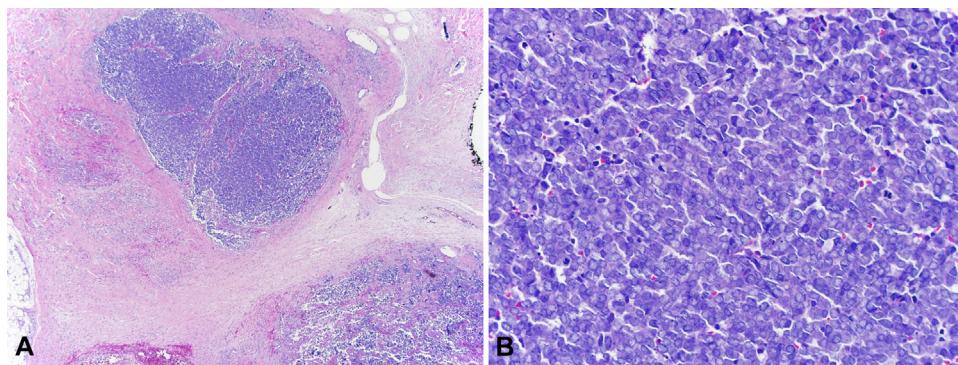
MCC most commonly presents as an erythematous or violaceous, tender, indurated nodule occurring on sun-exposed areas on the head or neck of an elderly white man (Fig 1). Rapid growth with or without ulceration is common. Papules, plaques, and cyst-like structures, pruritic tumors on the lower extremities, pedunculated lesions, subcutaneous masses, and telangiectatic papules have also been reported in the literature.<sup>59-61</sup> MCC in association with scars, squamous cell carcinoma in situ, and other cutaneous malignancies have likewise been described.<sup>62-64</sup> While rare, mucosal MCC is a known clinical entity and exhibits more aggressive behavior than its cutaneous counterpart.<sup>65</sup> Metastatic MCC with no known primary has also been reported and represents 4% of all MCC cases.<sup>66,67</sup> Note that “visceral MCC” with no known cutaneous primary disease is now considered a distinct neuroendocrine carcinoma subtype rather than a variant of cutaneous MCC.

## DIAGNOSTIC EVALUATION, STAGING, AND PROGNOSTIC MARKERS

### Key points

- Diagnosis rests on a thorough skin and lymph node examination, a biopsy specimen of suspicious lesions, and histologic assessment by an experienced dermatopathologist
- The revised American Joint Committee on Cancer staging system separates clinical and pathological staging groups and reclassifies the staging for unknown primary tumors
- Obtaining a sentinel lymph node biopsy specimen should be considered for all patients, because one third of patients with clinically localized disease at time of presentation have occult lymph node involvement

The National Comprehensive Cancer Network (NCCN) in the United States proposed specific guidelines for MCC diagnostic evaluation based on a framework of clinical presentation, preliminary work-up, diagnosis, and additional work-up.<sup>68</sup> The NCCN also included a clarification of each point to reflect the evolving landscape of MCC diagnosis and staging; each of these will be discussed in greater detail below. The simplified algorithm for evaluation



**Fig 2.** Typical histopathologic appearance of Merkel cell carcinoma. **A**, Large nodular collections crowded basaloid cells in the dermis and subcutis with foci of necrosis. **B**, High-power magnification shows typical nuclear features with round nuclei with granular chromatin and scant cytoplasm. Scattered mitotic figures are present. (Hematoxylin–eosin stain; original magnification: **A**,  $\times 40$ ; **B**,  $\times 400$ .)

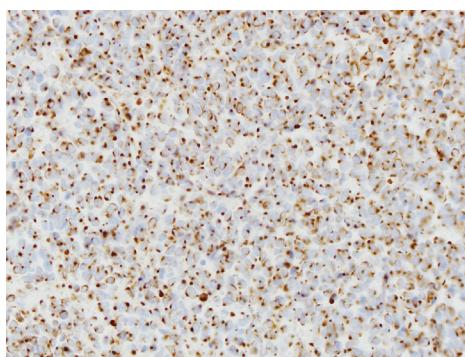
includes the following: 1) skin and lymph node examination; 2) obtaining a biopsy specimen stained with hematoxylin–eosin (including Breslow thickness and evidence of lymphovascular invasion) and immunostaining (including but not limited to CK-20 and thyroid transcription factor-1); 3) obtaining a sentinel lymph node biopsy (SLNB) specimen from patients with negative clinical nodes, preceding excision if possible; 4) fine-needle aspiration or core biopsy first for patients with positive clinical nodes—if negative, consider open biopsy, but if positive, proceed to; 5) imaging as clinically indicated with magnetic resonance imaging, computed tomography (CT), or positron emission tomography (PET)/CT; and 6) consider consultation with a multidisciplinary tumor board.

The clinical examination is the first step in MCC diagnosis. The nonspecific and varied clinical features of this tumor pose certain diagnostic challenges even for the experienced dermatologist. Unlike basal cell carcinoma or melanoma, which may be clinically or dermatoscopically apparent, the “classic” MCC lesion does not exist. For lesions with concerning clinical features, dermoscopy can be helpful in guiding the decision to obtain a biopsy specimen. Sharply and poorly focused vessels, a polymorphous vascular pattern with architectural disruption, milky-red areas on a white sheen, and large caliber arborizing vessels have all been observed in MCC.<sup>69</sup>

For suspicious lesions, tissue sampling should be performed with a shave, punch, incisional, or excisional biopsy; the technique selected depends on the anatomic site, size, and depth of the tumor. A full body skin and lymph node examination should also be undertaken at the time the biopsy specimen is obtained to assess for signs of cutaneous or nodal metastasis.

Histopathologic assessment is critical for MCC diagnosis. On standard hematoxylin–eosin stains, MCC is typically characterized as a dermal tumor with sheets and nests of crowded basaloid cells with a finely granular “salt and pepper” chromatin pattern, indistinct nucleoli, and scant cytoplasm (Fig 2).<sup>70</sup> Numerous mitotic figures and necrotic cells are common. The histopathologic differential includes basal cell carcinoma, melanoma, Ewing sarcoma, neuroblastoma, leukemia cutis, and poorly differentiated carcinoma (eg, metastatic small cell lung cancer). A small cell variant of MCC exhibits overlapping histopathologic features with cutaneous lymphoma, and rarely a large cell phenotype with neoplastic cells containing large, pleomorphic nuclei can be seen. MCC “in situ,” in which the neoplastic cells are limited to the epidermis or follicular epithelium, can be mistaken for squamous cell carcinoma in situ, melanoma in situ, or other pagetoid intraepidermal malignancies.<sup>71</sup> Composite MCCs in which there is a distinct proliferation of neoplastic cells with divergent differentiation (eg, squamous cell carcinoma, basal cell carcinoma, etc) juxtaposed with the MCC occurs frequently in MCCs without detectable MCV infection.<sup>72</sup>

While a diagnosis of MCC can reliably be made in the proper clinical setting (eg, an elderly patient with sun-damaged skin of the head and neck), when classic histopathologic features are present, given the broad differential diagnosis with significant implications for prognosis and management, immunohistochemistry is frequently used to confirm the diagnosis. A combination of neurofilament, CK-20, CK7, and thyroid transcription factor-1 stains has a high sensitivity and specificity in distinguishing MCC from its histopathologic mimics (Fig 3).<sup>70,73</sup> CK-20 stains MCC in both a diffuse cytoplasmic and a



**Fig 3.** Cytokeratin-20 immunohistochemical staining in Merkel cell carcinoma shows a paranuclear dot pattern. (Original magnification:  $\times 200$ .)

paranuclear dot pattern with 75% sensitivity, the latter being more specific for MCC. Neurofilament will help detect CK-20-negative tumors, also frequently exhibiting a paranuclear dot pattern. Most cases of MCC will be CK7-negative, but a significant minority exhibit partial CK7 positivity. Thyroid transcription factor-1 is typically negative in MCC but positive in metastatic small cell lung carcinoma, which can be useful in this context given their similarities on histopathology. MCC is also characteristically positive for other neuroendocrine markers, including synaptophysin, chromogranin, CD56, and neuron specific enolase, but the specificity of these markers is low. For tumors with indeterminant or atypical immunohistochemistry, CAM 5.2, paired box 5, epithelial membrane antigen, MCV large T antigen, and CD56 staining can also be used to narrow the differential diagnosis.<sup>73</sup>

Once the diagnosis of MCC has been established on clinical and histopathologic grounds, appropriate staging should be performed. Patients with palpable nodes should be referred for fine-needle aspiration or core biopsy. For those with clinically negative nodes, the most reliable tool for evaluating the regional lymph nodes is the SLNB. SLNB is recommended because approximately 25% to 30% of patients with a clinically negative lymph node examination have pathologically positive nodes.<sup>74,75</sup> Even patients with small primary tumors have a significant risk of nodal disease, ranging from 14% risk of regional nodal involvement for 0.5-cm tumors to 25% for 1.7-cm (median-sized) tumors; these data are consistent with other recent studies showing that 24% to 42% of patients with small tumors have clinically occult nodal disease.<sup>76-78</sup> However, the impact of SLNB on disease-specific and overall survival remains unclear, because most survival analyses have been based on single-center studies.<sup>79</sup> A recent analysis of 4533 patients in the Surveillance, Epidemiology, and End Results database did show

improved survival with SLNB, but there remains a lack of consensus on this point.<sup>80</sup> In addition, while SLNB carries a lower risk of morbidity than lymphadenectomy, it is well-established in the surgical literature that SLNB is less accurate in the head and neck region compared to the trunk and extremities, because the complexity of the draining nodal basin in the head and neck region confers a higher risk for false-negative results.<sup>68</sup> These potential risks and benefits of SLNB should be discussed and offered to patients who have a clinically negative lymph node examination.

Imaging at the time of diagnosis using magnetic resonance imaging, CT, or PET/CT should be performed as clinically indicated (ie, to identify distant metastases in patients at risk for this or to assess for nodal metastasis in patients who cannot tolerate or who decline SLNB). In 1 retrospective study, 61 patients with MCC were scanned as part of initial management; 48% had a positive finding with either nodal or distant disease detected on PET/CT.<sup>81</sup> However, PET/CT is less sensitive in detecting micrometastatic disease and does not replace SLNB as a staging tool. Imaging proved most useful in patients with distant disease with no clinical primary; in these cases, the identification of distant metastases to bone and other organs affected the treatment plan.

The American Joint Committee on Cancer staging system for MCC was revised in 2017 to help clinicians better stratify patients into groups based on their predicted survival, emphasizing the difference between clinically and pathologically determined staging (Fig 4). This revision also included a change to the N classification for regional metastatic disease to reflect improved prognostication for “unknown primaries.” Patients with clinically detected nodal disease and unknown primary tumor showed improved survival compared to those with an identifiable concurrent primary tumor. Stage IIIA now includes patients with occult nodal disease (T1-4 N1a M0) and those with clinically positive nodal disease with unknown primaries (T0 N1b M0).

MCC is an aggressive tumor with poor prognosis, especially if there is evidence of metastatic disease at presentation. Overall survival at 5 years is approximately 51% for local disease, 35% for nodal disease, and 14% for distant disease.<sup>67</sup> Other prognostic factors for MCC have been described, and immunohistochemistry has evolved as one significant area of study in this regard. In the dermatopathology literature, immunohistochemical features such as evidence of lymphovascular invasion, p53 and p63 immunopositivity, higher mast cell counts, and vascular density in the tumor and surrounding stroma have all been shown to negatively predict survival,

Stage	Primary Tumor	Lymph Node	Metastasis
0	In situ (within epidermis only)	No regional lymph node metastasis	No distant metastasis
I Clinical*	≤ 2 cm maximum tumor dimension	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
I Pathological**	≤ 2 cm maximum tumor dimension	Nodes negative by pathologic exam	No distant metastasis
IIA Clinical	> 2 cm tumor dimension	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
IIA Pathological	> 2 cm tumor dimension	Nodes negative by pathological exam	No distant metastasis
IIB Clinical	Primary tumor invades bone, muscle, fascia, or cartilage	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
IIB Pathological	Primary tumor invades bone, muscle, fascia, or cartilage	Nodes negative by pathologic exam	No distant metastasis
III Clinical	Any size / depth tumor	Nodes positive by clinical exam (no pathological exam performed)	No distant metastasis
IIIA Pathological	Any size / depth tumor	Nodes positive by pathological exam only (nodal disease not apparent on clinical exam)	No distant metastasis
	Not detected ("unknown primary")	Nodes positive by clinical exam, and confirmed via pathological exam	No distant metastasis
IIIB Pathological	Any size / depth tumor	Nodes positive by clinical exam, and confirmed via pathological exam OR in-transit metastasis***	No distant metastasis
IV Clinical	Any	+/- regional nodal involvement	Distant metastasis detected via clinical exam
IV Pathological	Any	+/- regional nodal involvement	Distant metastasis confirmed via pathological exam

\* Clinical detection of nodal or metastatic disease may be via inspection, palpation, and/or imaging

\*\*Pathological detection/confirmation of nodal disease may be via sentinel lymph node biopsy, lymphadenectomy, or fine needle biopsy; and pathological confirmation of metastatic disease may be via biopsy of the suspected metastasis

\*\*\*In transit metastasis: a tumor distinct from the primary lesion and located either (1) between the primary lesion and the draining regional lymph nodes or (2) distal to the primary lesion

**Fig 4.** American Joint Committee on Cancer 8th edition Merkel cell carcinoma staging system. (Reprinted with permission from <https://www.merkelcell.org/wp-content/uploads/2016/10/8th-Edition-Staging-Chart.png> with data from Harms et al<sup>67</sup> and Amin et al<sup>96</sup>)

with p63 expression showing the greatest prognostic value.<sup>82-87</sup> CD34 is an endothelial cell marker that has been used to assess the degree of vascularity in MCC tumors and in 1 study demonstrated a significant association between total vessel score (a higher score indicated stronger CD34 staining) and survival.<sup>84</sup> Lymphovascular invasion can sometimes be seen in routine hematoxylin–eosin-stained sections, but adjunctive immunostaining with D2-40 or CD31 can increase the detection of lymphovascular invasion. Negative clinical prognostic indicators have also been reported; these include male sex, tumor location on the head and neck, tumor size >2 cm, and immunosuppression.<sup>67,74,88-93</sup>

Several small studies since 2010 have shown that MCV-positive MCC confers a better prognosis than its MCV-negative counterpart.<sup>55,94</sup> Given the potential prognostic differences between the 2 tumor types, which have implications for clinical follow-up and surveillance, the implementation of standard tests to reliably establish viral status are under investigation. One such test is the immunohistochemical stain for the MCV large T antigen (antibody CM2B4); in 1 study, multimodal analyses using polymerase chain reaction and the murine monoclonal antibody Ab3 against LT in conjunction with CM2B4 showed even higher sensitivity and specificity for identifying intra-tumoral MCV.<sup>95</sup> Currently, however, there is no consensus clinical test to establish viral positivity in MCC.

MCV baseline serology for prognostic significance and disease surveillance is also being investigated. High antibody titers to known MCV antigens have been shown to reliably correlate with disease recurrence, while low or undetectable levels are associated with remission.<sup>91</sup> These assays reflect our improved understanding of the MCV genome, which encodes several structural proteins, including the major capsid protein (VP1) and two minor capsid proteins (VP2 and VP3), as well as LT and ST.<sup>91</sup> Antibodies to LT are correlated with a high viral burden, while high levels of VP1 antibodies at baseline are associated with decreased risk of recurrence and death; however, VP1 antibodies have failed to show predictive value at later time points.<sup>90-92</sup> As such, the LT antibody is a more clinically useful serologic marker and surveillance tool. This assay is available through the University of Washington and is used to establish a baseline titer at diagnosis and to provide an objective marker for comparison in clinical follow-up.

The first article in this continuing medical education series reviewed the epidemiology, pathogenesis, and clinical presentation of MCC, while also exploring the changing landscape of diagnostic evaluation and staging. The second article in this series continues with a comprehensive review of current management guidelines and promising new therapies in clinical trials.

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# Merkel cell carcinoma: An update and review



## Current and future therapy

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*See related article on page 457*

### Learning objectives

After completing this learning activity, participants should be able to explain the prognosis and treatment options for merkel cell carcinoma and describe evidence-based strategies for the management of merkel cell carcinoma.

### Disclosures

#### Editors

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Merkel cell carcinoma (MCC) is a rare neuroendocrine tumor of the skin associated with a high risk of local recurrence and distant metastases. It most commonly occurs on sun-exposed areas of white patients >65 years of age. The Merkel cell polyomavirus (MCV) is thought to be responsible for malignant transformation in approximately 80% of cases in the northern hemisphere, while ultraviolet radiation-induced DNA damage is implicated in MCV-negative tumors. The overall incidence of MCC is low, with approximately 1600 cases diagnosed annually in the United States. The rate is much higher in patients with lymphoproliferative malignancies, solid organ transplants, and HIV infection. The low overall incidence of this tumor makes it challenging to conduct prospective clinical trials with sufficient power. As a result, most management recommendations are based on case series, retrospective reviews, and expert opinion. The pathogenesis, diagnosis, and staging of MCC was discussed in the first article in this continuing medical education series. This article focuses on current management guidelines and promising new therapies in development. Because of the complexity, aggressive nature, and individuality of each case, MCC is best treated by a multidisciplinary team. (J Am Acad Dermatol 2018;78:445-54.)

**Key words:** immunotherapy; Merkel cell carcinoma; Merkel cell polyomavirus; neuroendocrine tumor.

**M**erkel cell carcinoma (MCC) is a rare neuroendocrine tumor of the skin associated with a high risk of local recurrence and distant metastases. It most commonly occurs on

sun-exposed areas of white patients >65 years of age.<sup>1,2</sup> The Merkel cell polyomavirus (MCV) is thought to be responsible for malignant transformation in approximately 80% of cases in the northern

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**Abbreviations used:**

CLND:	complete lymph node dissection
MCC:	Merkel cell carcinoma
MCV:	Merkel cell polyomavirus
MHC:	major histocompatibility complex
MMS:	Mohs micrographic surgery
NCCN:	National Comprehensive Cancer Network
PD-1:	programmed death receptor-1
PD-L1:	programmed death ligand-1
SLNB:	sentinel lymph node biopsy
TAg:	tumor-associated antigen

hemisphere,<sup>3</sup> while ultraviolet radiation–induced DNA damage is implicated in MCV-negative tumors.<sup>4</sup> The overall incidence of MCC is low, with approximately 1600 cases diagnosed annually in the United States. The rate is much higher in patients with lymphoproliferative malignancies, solid organ transplants, and HIV infection.<sup>5-9</sup> The low overall incidence of this tumor makes it challenging to conduct prospective clinical trials with sufficient power.<sup>10</sup> As a result, most management recommendations are based on case series, retrospective reviews, and expert opinion.

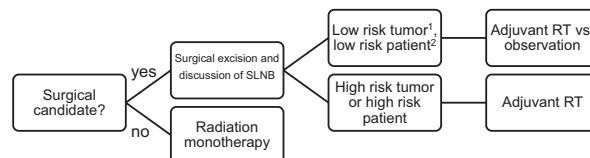
## SURGERY

### Key points

- **Surgical excision with a goal of establishing clear margins is the mainstay of treatment**
- **Obtaining a sentinel lymph node biopsy specimen should be considered for all patients**

Complete surgical excision of the primary site is typically the first step in treating localized MCC (Fig 1). The overarching goal is to establish clear histologic margins when clinically feasible.<sup>11</sup> The optimal surgical margin has not been defined, but in general practice it has ranged anywhere from 1 to 3 cm.<sup>12,13</sup> Some studies have suggested that a reduction in the local recurrence rate is associated with wide margins of 2 to 3 cm,<sup>14-16</sup> while others have shown no difference with margins >1 cm.<sup>17</sup> The current National Comprehensive Cancer Network (NCCN) guidelines recommend excision with 1- to 2-cm margins down to fascia or periosteum (level III evidence).<sup>12</sup> Surgical margins should be balanced with morbidity of surgery. The rate of local recurrence after wide local excision for a localized MCC ranges from 25% to 40%.<sup>13,14,16,18</sup>

Mohs micrographic surgery (MMS) is another surgical option, and MMS offers the primary advantage of complete peripheral and deep histologic margin control while secondarily sparing healthy tissue. Retrospective studies of MMS for MCC have found this technique to be effective, although prospective



**Fig 1.** Management of the primary lesion. <sup>1</sup>Low risk tumor is defined as <1 cm in size, widely excised, and free of lymphatic or intravascular invasion. <sup>2</sup>Low risk patients are immunocompetent. *RT*, Radiation therapy; *SLNB*, sentinel lymph node biopsy.

clinical trials comparing MMS to wide local excision have not been performed.<sup>14,19-22</sup> The reported local recurrence rates after MMS have ranged from 5% to 22%, but the number of studies evaluating the outcomes of MMS for MCC is limited.<sup>13,14,16,18,20-23</sup> If MMS is performed, the central portion of the tumor should be sent for microstaging with permanent sections.

If a sentinel lymph node biopsy (SLNB) is planned, it should be performed before wide local excision or MMS, because surgical excision before SLNB may alter the lymphatic drainage patterns, potentially compromising the accuracy of the test. In anatomic locations where excision would result in substantial functional compromise, or if the patient is not a surgical candidate, radiation monotherapy for treatment of primary tumors is a viable alternative.<sup>24,25</sup>

## MANAGEMENT OF THE DRAINING NODAL BASIN

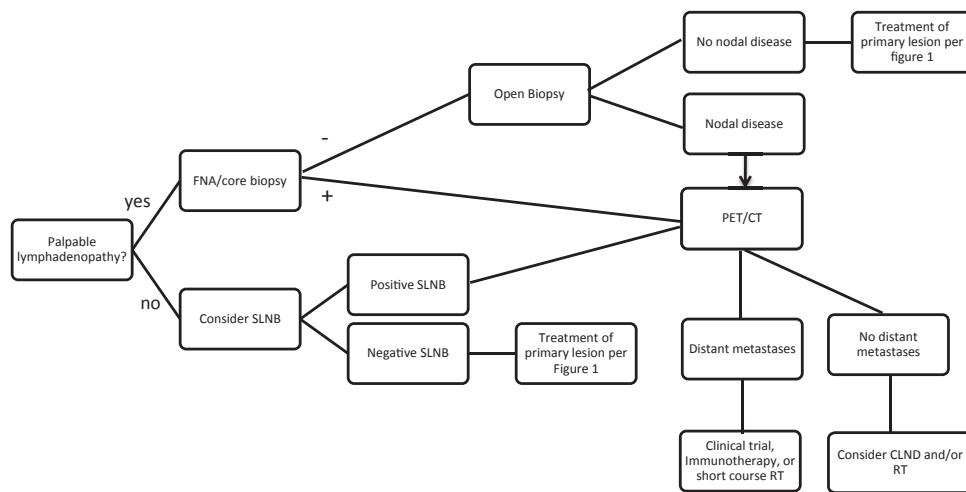
### Key Points

- **One third of patients with clinically negative nodes will have a positive sentinel lymph node biopsy**
- **Sentinel lymph node biopsy is an important prognostic indicator**
- **Sentinel lymph node biopsy helps to identify patients who may benefit from additional regionally directed treatment**

### Sentinel lymph node biopsy

Approximately 25% to 30% of patients without clinically apparent lymphadenopathy will have pathologically positive nodes.<sup>17,26</sup> While larger tumors have higher rates of lymphatic spread, small tumors also carry a notable risk of occult nodal disease (up to 14% in 0.5-cm tumors).<sup>27-29</sup>

SLNB provides important prognostic information and helps to guide management. The 5-year survival for patients with a positive SLNB is 50% to 62%, compared to 60% to 80% for those with a negative SLNB.<sup>17,30</sup> Prognostication is improved by pathologic evaluation of nodal status, which is the rationale for its role in the staging system.<sup>2</sup> As such, SLNB should be



**Fig 2.** Management of the draining nodal basin. *CLND*, Complete lymph node dissection; *FNA*, fine-needle aspiration; *PET/CT*, positron emission tomography/computed tomography; *RT*, radiation therapy; *SLNB*, sentinel lymph node biopsy.

considered in all patients with MCC who do not have clinically detectable nodes unless surgery is contraindicated or declined. Immunostains should be used to increase the sensitivity of lymph node evaluation.

In addition to its prognostic value, SLNB is useful for selecting patients who may benefit from complete lymph node dissection (CLND) or radiation for regional control.<sup>31</sup> A retrospective study of 230 patients found that pathologic confirmation of clinically negative nodal disease (with either elective lymph node dissection or SLNB) was associated with a decreased rate of nodal recurrence (44% recurrence in those with clinically negative nodes vs 11% in those with pathologically negative nodes,  $P < .001$ ) and improved 5-year survival (75%, clinically negative nodes vs 97%, pathologically negative nodes,  $P = .009$ ). Sixty-seven percent of patients with a positive SLNB in this study underwent CLND and 22% of patients with nodal disease received adjuvant radiation therapy, highlighting that pathologic evaluation of nodal status helps to guide further therapy.<sup>17</sup> As a counterpoint, Fields et al<sup>32</sup> did not find a difference in mortality or recurrence in those with positive SLNB when compared to those with a negative SLNB. However, patients with a positive SLNB were more likely to undergo CLND (47% vs <2%,  $P < .01$ ) and receive adjuvant radiation or chemotherapy (60% vs 7%,  $P < .01$ ). The authors concluded that patients with micrometastasis detected on SLNB do not have a difference in outcome compared to those with negative SLNB, but these conclusions may have been confounded by the use of adjuvant radiation therapy to the regional basins. Another explanation is that the more aggressive adjuvant therapy in the SLNB-positive group may have attenuated an increased risk of

recurrence and mortality.<sup>32</sup> However, the impact of SLNB on disease-specific and overall survival remains unclear. An analysis of 4543 patients in the Surveillance, Epidemiology, and End Results database found that SLNB improved survival in univariate analysis; however, this did not remain significant on multivariate analysis.<sup>33</sup> Nodal evaluation has been incorporated into the NCCN guidelines and is frequently performed because of the potential therapeutic and prognostic impact of a positive result (Fig 2). This recommendation is based largely on expert opinion rather than direct outcome data; therefore, it is important to have a thorough discussion of the potential risks and benefits with patients before performing SLNB.

### Clinical lymphadenopathy

Patients with clinically suspicious lymph nodes require pathologic confirmation via fine-needle aspiration or core needle biopsy.<sup>12</sup> If the fine-needle aspiration or core biopsy is unrevealing, an open lymph node biopsy should be performed. If lymphatic spread is discovered, a positron emission tomography/computed tomography scan is indicated to evaluate for distant metastasis (Fig 2).<sup>34,35</sup>

### RADIATION THERAPY

#### Key points

- **Radiation monotherapy is an alternative treatment for the primary lesion in nonsurgical cases**
- **Adjuvant radiotherapy may improve overall survival in patients with localized disease**
- **Short-course radiation may be effective for patients with oligometastatic disease**

### Radiation monotherapy

Definitive radiation monotherapy is an alternative to surgery for patients who are poor surgical candidates or for those in whom surgery would result in significant functional compromise (Fig 1).<sup>25,36-38</sup> However, the outcomes of radiation monotherapy may be inferior compared to complete surgical resection. While the in-field control ranges from 75% to 100%, distant recurrence is increased and the rates of cancer-specific and overall survival are decreased compared to complete surgical resection.<sup>25,38,39</sup> A retrospective review of 43 patients treated with radiation monotherapy found that 53% relapsed outside of the irradiated field and the overall survival at 5 years was 37%.<sup>38</sup> This is similar to an overall survival of 39% in another study of 57 patients treated with curative intent radiation monotherapy.<sup>37</sup> These results should be interpreted in context; the few reports of radiation monotherapy that exist carry significant selection bias. Patients selected for radiation monotherapy often had inoperable tumors or comorbidities that precluded surgical resection, which likely contributed to lower overall survival.

Higher doses of radiation are typically recommended for radiation monotherapy as compared to doses used for adjuvant therapy. Several studies have shown that doses >50 Gy are associated with a significant improvement in relapse- and disease-specific survival.<sup>25,37,40</sup> The NCCN guidelines recommend doses of 60 to 66 Gy for curative-intent radiation, with a wide treatment margin (5 cm) around the primary site. Radiation doses to the primary site after surgical resection should range from 50 to 60 Gy depending on the presence or absence of microscopically positive margins.<sup>12</sup>

### Localized MCC

The benefit of adjuvant radiotherapy for patients with localized MCC who have established clear surgical margins and negative SLNB has been controversial, although recent studies have provided increasing support for its use. The NCCN guidelines state that clinical observation without adjuvant radiotherapy may be considered for a subset of immunocompetent patients with low risk tumors that are <1 cm in size, widely excised, and free of lymphovascular invasion.<sup>1,12,41,42</sup> An analysis of 185 patients with localized MCC and margin-negative excision found that adjuvant radiation to the surgical bed did not improve the rate of local control.<sup>17</sup> Conversely, several studies have suggested that adjuvant radiation in early-stage MCC is beneficial and should be administered expeditiously after surgery.<sup>31,43-46</sup>

In 2016, a retrospective analysis of 6908 cases from the National Cancer Database found that patients with localized disease who received a combination of surgery and radiation had a significant improvement in overall survival compared to those treated with surgery alone, even among those with early-stage primary disease. The relative risk reduction was 29% and 23% for stage I and II disease, respectively (stage I: hazard ratio [HR] = 0.71 [95% confidence interval {CI} 0.64-0.68],  $P < .001$ ; stage II: HR = 0.77 [95% CI 0.66-0.89],  $P < .001$ ). For patients with regional disease, there was no difference in overall survival between the 2 groups.<sup>47</sup> These findings corroborated those of an analysis of 1166 patients in the Surveillance, Epidemiology, and End Results database that found a survival benefit with adjuvant radiation after surgery for localized disease.<sup>48</sup> These studies were unable to distinguish between adjuvant radiation delivered to the primary site, the draining nodal basin, or both, which limited more detailed interpretation of these findings.

The standard practice is to consider radiation to the primary site alone if the SLNB is negative, but to include the nodal basin if the SLNB is positive. Indications for consideration of prophylactic radiation to the draining nodal basin include immunosuppression, extensive lymphovascular invasion, or when the SLNB is not performed or potentially inaccurate. Studies have suggested that adjuvant prophylactic radiotherapy to regional nodes in the absence of SLNB may have a survival advantage.<sup>49</sup>

### MCC with nodal disease

While the optimal management for patients with clinically or pathologically positive nodal disease has not been established, standard treatment options include CLND, definitive nodal radiation, or a combination of the two. There is a paucity of data comparing these 3 options, and most studies are small retrospective reviews or metaanalyses without sufficient power to draw meaningful conclusions. In addition, most studies lack standardized treatment protocols and do not differentiate between clinical lymphadenopathy and occult nodal disease. Keeping these inherent limitations in mind, 2 independent studies found no difference in regional recurrence or overall survival between groups treated with CLND, definitive radiation, or combination therapy.<sup>32</sup> CLND allows for evaluation of a larger number of nodes, which may help to guide the extent of additional radiation fields.

The NCCN recommends adjuvant radiation to the draining nodal basin after CLND in the presence of

**Table I.** Immunotherapies under investigation

Immunotherapy	Mechanism	ClinicalTrials.gov identifier
Ipilimumab	Inhibition of CTLA-4, which activates an antitumor T-cell response	NCT02196961
Adoptive T cell transfer	Technique that involves harvesting, expanding, and reinfusing MCV-specific CD8 <sup>+</sup> T cells	NCT01758458
Intratumoral interferon	Reverses downregulation of MHC-I	NCT02584829
IL-12 DNA electroporation	Induces proliferation of T cells and stimulates production of TNF $\alpha$ and interferon- $\gamma$ . Performed as an intratumoral injection with electroporation to limit systemic side effects of IL-12	NCT01440816
Toll-like receptor-4 agonists	Activates innate and adaptive immune responses	NCT02035657

CTLA-4, Cytotoxic T-lymphocyte associated antigen-4; IL-12, interleukin 12; MCV, Merkel cell polyomavirus; MHC, major histocompatibility complex; TNF $\alpha$ , tumor necrosis factor- $\alpha$ .

multiple involved nodes or extracapsular extension of tumor.<sup>12</sup> Until specific guidelines for patients with nodal disease are better established, the risks and benefits of each treatment option based on site-specific morbidity (ie, axilla vs groin), tumor characteristics, and patient comorbidities should be considered individually for each case.

### Metastatic MCC

Patients with oligometastatic disease may be eligible for short-course radiation therapy. The radiation is given in a limited and convenient fashion to minimize the impact on the patient. The brief course of radiation contributes to cancer control both through direct DNA damage to the tumor cells and immunomodulation. The immunologic effect is thought to be caused by augmented presentation of viral or tumor antigens in conjunction with enhanced T cell priming in the draining lymph nodes. In addition, because the radiation is limited in extent and duration, CD8 T cells recruited to the area are not destroyed by subsequent radiation treatments. This theory has piqued interest in a possible synergistic effect of hypofractionated radiotherapy with the emerging immunotherapies.<sup>50-52</sup>

A retrospective analysis of 26 patients treated with a single fraction of 8 Gy of radiation to 93 metastatic lesions showed an overall response of 94%, with complete response in 45% of tumors. The in-field control was 77% at a median follow-up of 8.4 months. None of the 40 tumors that had a complete response to single-fraction radiation recurred within the 8-month follow-up period. There was a significantly higher rate of in-field progression in immunosuppressed patients compared to immunocompetent patients (30% vs 9%, respectively; odds ratio = 0.24 [95% CI 0.07-0.81],  $P = .02$ ).<sup>52</sup> This approach was well tolerated, with only 2 of 26

patients reporting treatment-related side effects. Another comparative analysis found much higher rates of failure with a single fraction (41%) and recommended 3 fractions of 8 Gy as a strategy more likely to achieve durable local control.<sup>53</sup> Current clinical trials testing combinations of hypofractionated radiation and immunotherapy are using 24 Gy over 3 fractions. Regardless of the specific regimen, it appears that short-course radiation represents an effective and well-tolerated palliative option for metastatic sites of MCC.

Brachytherapy has been reported as a palliative measure for patients with cutaneous metastases. While the cutaneous lesions often respond, patients usually recur outside of the irradiated field. This emphasizes the palliative nature of brachytherapy for MCC, which may be best suited for painful, disfiguring, or ulcerated cutaneous metastases.<sup>54-56</sup>

## CHEMOTHERAPY

### Key points

- **Adjuvant chemotherapy for Merkel cell carcinoma has not been shown to improve survival**
- **In the metastatic setting, responses to chemotherapy are not durable and the side effect profile is poor**

Chemotherapy has been used primarily as palliation in patients with advanced MCC. The most common regimens are carboplatin (or cisplatin) and etoposide or a combination of cyclophosphamide, doxorubicin (or epirubicin), and vincristine. Initial response rates range from 53% to 76%, but these responses are rarely sustained.<sup>44,57-60</sup> The median progression-free survival ranges from 3 to 8 months, with progressive disease developing in 90% of patients at 10 months. In patients who only achieve

**Table II.** Targeted molecular therapy under investigation

Targeted therapy	Mechanism	ClinicalTrials.gov identifier
Somatostatin analogs	Somatostatin receptors are expressed in 76-90% of MCCs. Somatostatin analogs inhibit neuroendocrine tumor growth	NCT01652547 and NCT02351128
Tyrosine kinase inhibitors	Tyrosine kinases are known to play a critical role in the development and progression of several human malignancies. MCC has been shown to express VEGF and PDGF; therefore, inhibition may inhibit tumor growth	NCT02036476 and NCT00655655
mTOR inhibitors	The PI3K/Akt/mTOR pathway regulates cell proliferation. Activating mutations in P1K3C have been identified in 10-17% of MCCs; therefore, inhibition may inhibit tumor growth	NCT00655655 and NCT02514824

MCC, Merkel cell carcinoma; *mTOR*, mammalian target of rapamycin; *PI3K*, phosphoinositide 3-kinase; *PDGF*, platelet-derived growth factor; *VEGF*, vascular endothelial growth factor.

a partial response, the response duration may be as short as 3 months.<sup>57-60</sup> A retrospective study of 6908 patients found that chemotherapy did not improve overall survival in patients with local or regional disease (stage I: HR = 0.79 [95% CI 0.60-1.05], *P* = .11; stage II: HR = 1.14 [95% CI 0.89-1.45], *P* = .30).<sup>47</sup>

Chemotherapy is associated with a high risk of toxicity, particularly in patients >65 years of age. The most common adverse effects are myelosuppression, sepsis, fatigue, alopecia, nausea/vomiting, and renal injury.<sup>58,61</sup> Death from chemotherapy-related toxicities was 7.7% in 1 study.<sup>58</sup>

In the adjuvant setting, the Trans Tasman Radiation Oncology Group (TROG) 96.07 study evaluated radiation in combination with carboplatin and etoposide for patients with high-risk disease, defined as recurrence after initial therapy, involved nodes, primary tumor size >1 cm, gross residual disease after surgery, or occult primary with nodal disease. The 3-year overall survival, locoregional control, and distant control were 76%, 75%, and 76%, respectively. Multivariate analysis indicated that the major factor influencing survival was the presence of nodal involvement. High-grade skin toxicity occurred in 63% of patients and complications from neutropenia (fever and sepsis) occurred in 40% of cases.<sup>62,63</sup> A retrospective analysis of high-risk stage I and II patients by the investigators of this study indicated no benefit to this approach in early-stage disease.<sup>64</sup>

## EMERGING THERAPIES

### Immunotherapy

#### Key points

- **Merkel cell carcinoma locally evades the immune system**

- **Immunotherapy has shown encouraging results in virus-positive and -negative Merkel cell carcinoma**

Genetic and epigenetic alterations lead many cancers to produce antigens that may be recognized by the immune system. The endogenous immune response is often futile, because many tumors develop mechanisms to locally evade the immune system.<sup>65</sup> Advances in immunotherapy have provided a means to activate an antitumor cellular response in some cancers.<sup>66-68</sup> Immunotherapy is of particular interest in MCC because the MCV-positive tumors express viral oncoproteins, and MCV-negative tumors have a high mutational burden associated with neoantigen production, both of which serve as immunotherapeutic targets.

### Immune checkpoint inhibitors

The programmed death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) pathway contributes to local immune evasion by inhibiting T cell activation and impairing the CD8/Treg ratio. Inhibition with PD-1 or PD-L1 blockade reinvigorates T cells and activates an antitumor response.<sup>51</sup> Efficacy of PD-1/PD-L1 inhibition has been shown in several cancers, including melanoma, renal cell carcinoma, bladder cancer, and non–small cell lung cancer.<sup>69-72</sup>

Approximately 50% of MCCs express PD-L1 on their surface, while tumor-infiltrating lymphocytes and circulating MCV-specific T cells express PD-1.<sup>73,74</sup> In addition, PD-1 has been shown to be upregulated in persistent viral infections.<sup>75</sup> These findings provided the rationale for investigating PD-1/PD-L1 inhibitors in MCC.<sup>74,76,77</sup>

A multicenter phase II trial of pembrolizumab, an anti-PD-1 monoclonal antibody, enrolled 26 immunocompetent patients with metastatic or recurrent locoregional MCC. Fifty-six percent of patients treated with pembrolizumab had a partial or complete response (95% CI 35-76%), with a progression-free survival of 67% at 6 months (95% CI 49-86%).<sup>74</sup> Based on this study, pembrolizumab was added to the 2017 NCCN treatment options for metastatic MCC. Nivolumab, a similar monoclonal antibody against PD-1, is also under investigation.

Avelumab is a monoclonal antibody that specifically inhibits PD-L1. A phase II trial of 88 patients with metastatic MCC who were refractory to chemotherapy found that 32% of patients responded to avelumab (95% CI 22-43%), with 82% of responses sustained over an average of 10 months.<sup>78</sup> The US Food and Drug Administration granted accelerated approval to avelumab for the treatment of patients >12 years of age with metastatic MCC; avelumab is now the first treatment for metastatic MCC approved by the US Food and Drug Administration.

Ipilimumab is a monoclonal antibody that inhibits the cytotoxic T-lymphocyte associated antigen-4, which is currently approved for the treatment of unresectable or metastatic melanoma. Cytotoxic T-lymphocyte associated antigen-4 inhibits T cell activation, and its blockade can activate an antitumor T cell response. A phase II randomized trial investigating ipilimumab versus observation in patients with completely excised MCC is currently underway.<sup>79</sup>

Several additional immunotherapies are being investigated in clinical trials, including adoptive T cell transfer, intratumoral interferon, interleukin-12 DNA electroporation, and Toll-like receptor-4 agonists.<sup>80-82</sup> Table I lists these current investigational therapies.

## TARGETED MOLECULAR THERAPY

### Key points

- Potential therapeutic targets for somatostatin analogs, tyrosine kinase inhibitors, and mammalian target of rapamycin inhibitors have been identified in Merkel cell carcinoma and are currently under investigation

The mutational profile of MCV-positive tumors is different from that of MCV-negative tumors. It may be important to consider this biologic distinction when selecting a targeted therapy because driver mutations are more likely to be present in the MCV-

negative tumors that have a high mutational burden. While a recurrent driver mutation has not been identified in MCC, several potential therapeutic targets have shown promise.<sup>83-93</sup> For example, a complete clinical response to the phosphoinositide 3-kinase inhibitor idelalisib has been reported in a patient with stage IV MCC.<sup>94</sup> Somatostatin analogs, tyrosine kinase inhibitors, and mammalian target of rapamycin inhibitors are currently being investigated in clinical trials for the treatment of MCC (Table II).

## SURVEILLANCE

### Key points

- Merkel cell carcinoma carries a high risk of recurrence, metastasis, and death
- Eighty percent to 90% of recurrences occur within the first 2 years
- In Merkel cell polyomavirus-positive tumors, tracking of Merkel cell polyomavirus-TAg-antibody titers is investigational

The diagnosis of MCC portends a high risk of local, regional, and distant recurrence. The 5-year MCC-specific survival ranges from 60% to 87% for local disease, 39% to 62% for nodal disease, and 11% to 20% for metastatic disease.<sup>2,17,18,30,31</sup> The median time to recurrence is 7 to 9 months, with 80% to 90% of recurrences occurring within the first 2 years.<sup>17,31,37,95</sup> The most common site of recurrence is the draining nodal basin,<sup>17</sup> while the most common sites of distant metastases are the liver, bone, brain, lung, and skin.

Because of the aggressive nature and high recurrence rate, patients should be evaluated every 3 to 4 months for the first 2 to 3 years after treatment, which can then be spaced to 6 to 12 months thereafter if the patient is free of disease (level IV evidence). A comprehensive review of systems, skin examination, and lymph node examination should be performed at every visit.

Guidelines for optimal imaging frequency have not been established, and therefore decisions regarding imaging should be based on patient-specific risk factors or symptoms. Routine surveillance imaging should be considered for high-risk patients, including those with nodal disease, high-risk tumor characteristics, or immunosuppression. Positron emission tomography/computed tomography has been shown to have a higher sensitivity compared to computed tomography alone, and has been useful for detecting subclinical disease.<sup>35,96</sup>

An investigational serologic test for the MCV-TAg-antibody is available through the University of Washington (<https://depts.washington.edu/labweb/referencelab/clinical/TestForms/amerk.pdf>).

Serologies are positive in approximately 60% of MCV-positive cases, and titers have been shown to correlate with disease burden.<sup>97</sup> Performing a baseline oncoprotein antibody test while there is evidence of disease may help risk-stratify patients. Those who do not produce oncoprotein antibodies may be at a higher risk of developing recurrence. Validation of the utility of baseline and serial serologies for prognostic significance and disease surveillance is in progress; these tests are considered experimental at this time.<sup>97,98</sup>

In conclusion, the therapeutic landscape of MCC is rapidly evolving with the advent of immunotherapy, targeted molecular therapy, and a growing understanding of MCC biology. The critical role of the immune system in the development and progression of this aggressive malignancy may also provide an avenue for its control. Immunotherapies that oppose the local immune evasion invoked by MCC are being investigated and have shown promising results thus far. Combination therapy should continue to be explored in the future, particularly immunotherapy in conjunction with radiation. Several targeted molecular therapies are being investigated, and may be particularly important in MCV-negative tumors with a high mutational burden. Collaborative efforts to create prospective clinical trials and to better establish the optimal management guidelines should be made. A multidisciplinary approach should be taken for patients diagnosed with MCC, tailoring treatment for individualized therapy.

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# Desquamative gingivitis



## Clinical findings and diseases

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### Learning objectives

After completing this learning activity, participants should be able to define and discuss epidemiology of desquamative gingivitis; describe the clinical presentation of desquamative gingivitis; categorize the differential diagnoses of desquamative gingivitis into recurrent or persistent; and explain the individual diagnoses that can produce desquamative gingivitis.

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Desquamative gingivitis is a clinical finding with several potential etiologies. Among the most common are oral lichen planus, cicatricial pemphigoid, and pemphigus vulgaris, though various other differential diagnoses exist. The presence of desquamative gingivitis often results in poor oral hygiene, which can have downstream consequences, including periodontitis and tooth loss. Though certain mucosal findings may be suggestive of a particular diagnosis, a thorough history, physical examination, and appropriate dermatopathologic assessment is necessary for narrowing this broad differential diagnosis. This article offers a comprehensive review on the subject, including how to differentiate between the different underlying causes and the best methods for diagnosis (eg, how best to obtain mucosal biopsy specimens). In addition, there is minimal information in the dermatology literature on evaluation of oral hygiene and the consequences of poor oral hygiene not only on disease activity but also overall health. Knowledge on appropriate oral cavity inspection and evaluation of dental hygiene is lacking, and this continuing medical education series discusses methods to evaluate for these consequences so that the dermatologist can be better equipped in managing these patients and recognizing complications early on. (J Am Acad Dermatol 2018;78:839-48.)

**Key words:** aphthosis; desquamative gingivitis; erosions; erythema multiforme; immunobullous disease; lichen planus; oral hygiene.

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**Abbreviations used:**

CP:	cicatricial pemphigoid
DG:	desquamative gingivitis
EBA:	epidermolysis bullosa acquisita
EM:	erythema multiforme
GVHD:	graft-versus-host disease
LP:	lichen planus
OLP:	oral lichen planus
PV:	pemphigus vulgaris
SJS:	Stevens-Johnson syndrome
TEN:	toxic epidermal necrolysis

**DEFINITION AND EPIDEMIOLOGY****Key points**

- Desquamative gingivitis describes mucosal inflammation with erythema and especially peeling
- The most common causes are oral lichen planus, cicatricial pemphigoid, and pemphigus vulgaris
- Patients often have secondary reduced oral hygiene practices, leading to more severe gingival inflammation and possible bone loss

Desquamative gingivitis (DG) is a clinical description characterized by an intense erythema of the gingiva with desquamation that can progress to ulceration (Fig 1). The disease can be low-grade, with only mild gingival erythema and edema, or have a more severe presentation, including desquamation, blistering, erosions, and ulceration. Bleeding is commonly seen. DG can be localized or more widespread, which can lead to compromise of gingival structures.<sup>1</sup>

Several different disease processes can lead to DG. The most common are oral lichen planus (OLP), cicatricial pemphigoid (CP), and pemphigus vulgaris (PV), representing 75%, 9%, and 4% of patients with DG, respectively, in 1 study.<sup>2</sup> Other etiologies include erythema multiforme (EM), graft-versus-host disease (GVHD), paraneoplastic pemphigus (PNP), and epidermolysis bullosa acquisita (EBA), among others.<sup>2</sup> Irritant and allergic contact dermatitis can also be potential initiating or exacerbating factors. The most common contactants are mouthwashes, toothpastes, dental materials, and medications.<sup>3</sup>

Though specific diseases are known to underlie DG, reduced oral hygiene caused by gingival discomfort and bleeding on flossing leads to dental plaque accumulation, which typically aggravates the clinical severity of the inflammation. Dental plaque is an accumulation of microorganisms around the teeth in close proximity to the gingiva. This accumulation leads to release of proinflammatory cytokines, such

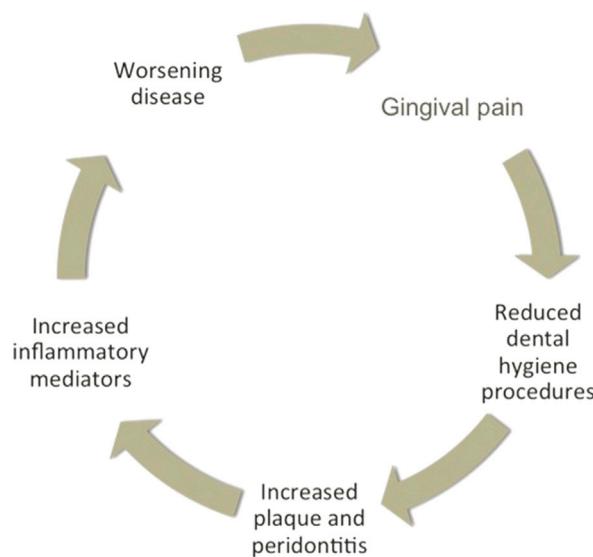


**Fig 1.** Cicatricial pemphigoid. Erythema and desquamation of gingiva. Courtesy of Graham Dermatopathology Library at Wake Forest School of Medicine. All rights reserved.

as interleukin-1 and tumor necrosis factor-alfa, recruitment of inflammatory cells, and periodontal inflammation.<sup>4</sup> These cytokines also upregulate matrix metalloproteases, which can then breakdown collagen and lead to loss of periodontal attachment and bone destruction.<sup>5</sup>

These proinflammatory cytokines are also implicated in the pathogenesis of several etiologies of DG, such as OLP, and periodontal inflammation may not only contribute to the progression but possibly to the onset of disease. More severe periodontal disease is associated with increased OLP lesions and symptoms.<sup>6</sup> Patients with PV who are treated with systemic corticosteroids, antiinflammatory drugs, and immunosuppressive agents actually had improved periodontal parameters.<sup>7</sup> More recently, it has been hypothesized that chronic inflammation induced by periodontitis is implicated in the pathogenesis of various other inflammatory diseases, including Behçet disease.<sup>8</sup> Whether patients with DG develop periodontitis as a result of poor oral hygiene practices secondary to painful brushing, or whether plaque accumulation is the initiating event leading to recruitment of inflammatory cells and later desquamative disease is unknown. Nonetheless, patients with DG often have reduced oral hygiene, which may contribute to reduced ability to control routine inflammatory gingivitis and DG (Fig 2).

Clinical findings of DG can be subtle, which often leads to a delayed diagnosis. Many patients will initially present with bleeding gums after tooth brushing or eating. This is often interpreted as the more common plaque-induced gingivitis, and patients may be erroneously treated with several courses of antibiotics or antifungals without the expected response, and complete resolution will not be possible. In more severe cases, widespread desquamation occurs, leading to stripping of large pieces of gingiva with simple manipulations. This is



**Fig 2.** Cycle of oral hygiene in desquamative gingivitis.

often accompanied by pain and reduced oral intake, which can lead to weight loss and malnutrition.

## CLINICAL PRESENTATION

### Key points

- Clinical findings may be subtle, and when present, Wickham striae and the Nikolsky sign may be suggestive of specific diseases
- Dental plaque, gingival retraction, and tooth loss are consequences of prolonged chronic disease, and gingival health should be assessed at each visit

**Disease-specific findings.** It is usually difficult on clinical features alone to distinguish various diseases associated with DG. Histopathologic and immunopathologic and enzyme-linked immunosorbent assay should be assessed to assign a diagnosis before the institution of systemic therapy.

Wickham striae are lacy, net-like, whitish-gray plaques that are usually found on the buccal mucosa, tongue, and gingiva (Fig 3). Though Wickham striae are the most recognized sign of OLP, they are not always present.<sup>9</sup> The erosive form of OLP can present predominantly with extensive erosions and erythema, but Wickham striae can usually be seen at the periphery of the lesion and may provide a clue to the diagnosis.<sup>10</sup> Other diseases can mimic this finding, including GVHD and oral lichenoid reactions, and therefore Wickham striae are suggestive but not pathognomonic of OLP.<sup>11</sup> Well-healed scars not on gingiva from CP can also produce similar findings.<sup>12</sup> Leukoedema of the bite line often causes confusion, but is a common oral examination finding (Fig 4).



**Fig 3.** Oral lichen planus. Wickham striae. Courtesy of Shailee Patel, MD.

The Nikolsky sign is the production of a blister (or epidermal separation) when lateral pressure is applied adjacent to an active erosion or blister. It is considered suggestive of PV and Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), but can on occasion also be seen in patients with CP.<sup>13</sup> Other features that can aid in distinguishing between PV and CP are the appearance of the ulcers; in patients with PV, they tend to present as more ragged ulcers, while in patients with CP, they are often smooth and blisters are more commonly observable. The Nikolsky sign can aide in distinguishing different forms of pemphigus, because it is often negative in patients with PNP.<sup>14</sup>

Finally, the presence or absence of certain skin findings can aid in narrowing the differential diagnosis (detailed below).

**Long-term consequences.** There are several long-term consequences to periodontal health that occur because of chronic DG and resultant reduced oral hygiene. Because of pain with brushing and flossing and reduced oral hygiene practices, patients with DG have statistically poorer plaque scores.<sup>15</sup> This plaque worsens periodontitis, which can lead to alveolar bone loss and ultimately tooth loss. Patients with DG from PV were found to have significantly poorer plaque scores, probing depth, and clinical attachment levels compared to controls.<sup>15</sup> These parameters were associated with increased clinical disease severity. These findings have also been demonstrated in patients with DG from other causes, including OLP and CP.<sup>4,16–18</sup> Patients with DG have also been found to have higher numbers of carious teeth than healthy controls,<sup>19</sup> increased bone loss,<sup>15</sup>



**Fig 4.** Leukoedema of the bite line.

and increased tooth loss,<sup>17</sup> with an average of 8.5 missing teeth.<sup>20</sup>

Therefore, a proper examination of every patient with DG should include a dental evaluation for dental plaque, gingival recession (evidence of dental root exposure), and tooth loss. Comanagement with a dentist is necessary for additional evaluation for and treatment of secondary periodontal disease. Primary management with any systemic therapy should follow definitive diagnosis and dental workup. A dermatologist comfortable with the administration and monitoring of these medications should direct management. The patient's primary care physician should be updated to assist with monitoring for systemic medication toxicities.

Other long-term consequences from chronic DG include decreased oral food intake as a result of pain with mastication and bacterial and fungal overgrowth. Nutritional evaluation and microbial decolonization procedures should be considered for patients with DG (as discussed in the second article in this continuing medical education series).

## DIFFERENTIAL DIAGNOSIS

### Key points

- Differential diagnosis of DG can be divided into recurrent or persistent diseases
- Screening for involvement of other mucosal sites should be performed in all patients with a thorough review of systems, because the prevalence especially of genital mucosa is high and is associated with significant morbidity

**Diseases with recurrent DG.** *EM.* EM is a mucocutaneous hypersensitivity reaction that presents with skin or mucosal lesions. EM is divided into EM minor and major, depending on the absence or presence of mucosal involvement, respectively, and mucosal involvement can occur alone. The episodes can be self-limited, typically lasting 2 to 6 weeks, or recurrent, classified as recurrent EM.<sup>21</sup> Patients with recurrent EM often have an average of 6 episodes per year, with a mean disease duration of 6 to 10 years.<sup>22,23</sup> The incidence of EM is <1%, and EM occurs more commonly in young adults.<sup>24,25</sup>

EM is no longer considered on the spectrum of SJS/TEN because the former has classic target lesions and involvement of fewer mucosal sites with fewer systemic signs and symptoms. SJS/TEN is characterized by atypical targetoid lesions and areas that range in extent with Nikolsky sign-positive cutaneous erosions. Target lesions of EM and targetoid lesions of SJS both feature identical findings of apoptosis at the dermoepidermal junction histopathologically. In contradistinction to SJS/TEN, which is predominantly caused by medications, EM is medication-induced in <10% of patients, and is often caused by infectious etiologies, the most common being herpes simplex virus, especially in recurrent EM.<sup>24</sup>

Mucosal manifestations are common, and have been reported in 25% to 70% of patients with EM.<sup>22-24</sup> The oral mucosa is most commonly involved. Lesions begin as areas of erythema with edema that progress to erythematous plaques and bullous and erosive lesions with pseudomembrane formation. The labial mucosa, buccal mucosa, nonattached gingivae, and vermillion lip are most commonly affected.<sup>22,23</sup> Other mucosal surfaces can be involved, including ocular, nasal, pharyngeal, laryngeal, and anogenital.<sup>26</sup> These lesions can progress to scarring from secondary trauma or infection, producing significant morbidity. Mucosal involvement often occurs in conjunction with skin involvement, which may provide a clue to the diagnosis when typical and atypical targetoid lesions are found, often in an acral distribution (Fig 5). Mucosal involvement in isolation can make the diagnosis more challenging.<sup>22</sup> Prodromal symptoms can aid in the diagnosis, because these are often seen with EM major and always with SJS/TEN.

*Complex aphthosis/Behcet disease.* Oral aphthosis is a common condition that occurs on nonkeratinized mucosa. The individual ulcers are categorized as minor, major, or herpetiform.<sup>27</sup> Minor aphthae are the most common (~80%), are small (<10 mm), are commonly on the buccal and labial mucosa, nonattached gingivae, and heal without scarring.



**Fig 5.** Erythema multiforme major. Targetoid lesions on the palms.

Major aphthae are larger (>10 mm), deeper, are located on additional mucosal sites, such as the soft palate, tonsils, and pharynx, and heal with scarring. Herpetiform aphthae are grouped and smaller (1-3 mm) and may occur on keratinized surfaces. Aphthae often recur, termed recurrent aphthous stomatitis, which is the most common oral inflammatory disorder.<sup>28</sup> The disease often develops during adolescence or young adulthood, and improves with time, with development of fewer and milder outbreaks.<sup>29</sup>

Recurrent aphthous stomatitis can further be divided into simple or complex, where complex is defined by the almost constant presence of multiple ( $\geq 3$ ) oral ulcers or recurrent oral and genital aphthae and the exclusion of Behcet disease.<sup>27</sup> Complex aphthosis may be primary or caused by an underlying disease, including inflammatory bowel disease, HIV, vitamin deficiencies, or cyclic neutropenia, and these must be excluded.<sup>30</sup> The aphthae often precede the confirmation of other systemic features in those with secondary aphthosis. Behcet disease is another important diagnosis to exclude because it is a chronic, multisystem disease that not only manifests with recurrent oral and genital aphthae, but patients may have ocular, vascular, articular, gastrointestinal, neurologic, and cardiopulmonary involvement, with significant morbidity and mortality.<sup>31</sup> Behcet disease presents



**Fig 6.** Behcet disease. Multiple aphthae. Courtesy of Graham Dermatopathology Library at Wake Forest School of Medicine. All rights reserved.

most commonly in young adults, in the third to fourth decades of life, and oral aphthae are often the only manifestation for 6 to 7 years before another symptom presents.<sup>31</sup> Systemic manifestations and disease confirmation using international criteria usually follow a significant increase in aphthosis in 1 to 2 years.

Clinically, aphthae present as sharply demarcated round or oval ulcers, often with a pseudomembranous base, on the buccal and labial mucosa, sulci, lateral and ventral surfaces of the tongue, soft palate, and oropharynx (Fig 6).<sup>29</sup> The aphthae in primary and secondary aphthosis, as well as in patients with Behcet disease, are indistinguishable, and minor aphthae are the most common presentation in patients with Behcet disease. Exclusion of underlying causes is recommended for all patients with complex aphthosis with herpes simplex virus culture or polymerase chain reaction studies, a complete blood cell count, vitamin B<sub>12</sub>, iron, folate, urinalysis, human leukocyte antigen-B27, and considerations of referral to ophthalmology, gastroenterology, neurology, and rheumatology when indicated.<sup>32</sup>

**Persistent (chronic).** OLP. OLP is a chronic inflammatory disease of the mucosa and the most common cause of DG. The overall prevalence is 0.5% to 2%, with an onset typically between 30 and 60 years of age and a slight female predominance.<sup>9,33,34</sup> The pathogenesis is unknown, but increasing evidence shows that it is likely a T cell-mediated disease that causes tissue destruction by inducing apoptosis of basal keratinocytes

through Fas expression.<sup>35</sup> This aberrant response may be the result of a traumatic, infectious, or medication trigger.<sup>11</sup>

There are 6 clinical variants of OLP, including reticular (Wickham striae), plaque-like, atrophic, erosive/ulcerative, papular, and bullous, although papular and bullous are rarely seen. OLP typically progresses through series of relapses and remissions, but the erosive/ulcerative form is often chronic and persistent. The most commonly affected sites are the buccal mucosa, tongue, gingiva, and labial mucosa; involvement of the palate, floor of the mouth, and upper lip are uncommon.<sup>11</sup> Involvement of the gingiva alone (presenting as DG) is seen in 10% of patients.<sup>36,37</sup>

Screening for other mucosal complaints is imperative because >20% of patients with OLP will have genital involvement<sup>37,38</sup>; esophageal involvement is also becoming increasingly noted.<sup>39</sup> European reports suggest an association with seropositivity for hepatitis C, although this is not confirmed worldwide.

Like cutaneous LP, OLP demonstrates the Koebner phenomenon. Evaluation for a traumatic component to disease, such as ill-fitting dental prostheses or sharp tooth cusps that rub, should be performed. Exclusion of other causes of oral lichenoid lesions, such as lichenoid contact dermatitis with amalgam or dental metals, lichenoid drug reactions, or GVHD should be performed in all patients.

Finally, there is a 0.4% to 9% risk of malignant transformation, most commonly seen in the erosive/ulcerative form, that should be monitored for at each visit, with a biopsy specimen obtained from any unusual or changing erosive lesions.<sup>10,34</sup> We are preparing a report of 500 of our patients seen over a 20-year period with <0.5% incidence of squamous cell carcinoma when the disease is aggressively controlled.

**CP.** CP, also referred to as mucous membrane pemphigoid, oral pemphigoid, and ocular pemphigoid, is a disease phenotype encompassing several autoimmune bullous diseases characterized by subepithelial blisters and erosions with scarring of mucous membranes, skin or both, and linear deposition of immunoglobulin G, immunoglobulin A, or complement component 3 along the epithelial basement membrane zone on direct immunofluorescence. Various subgroups have been described, including antiepiligrin CP, which is associated with malignancy; a purely ocular variant, associated with antibodies to alfa-6, beta-4 integrin; mucosal and skin variant with antibodies targeting bullous pemphigoid antigen 2<sup>40</sup>; a purely oral variant, which tends to follow a more benign course<sup>41</sup>; and finally, a



**Fig 7.** Cicatricial pemphigoid. Mucosal erosion with pseudomembrane formation. Courtesy of Graham Dermatopathology Library at Wake Forest School of Medicine. All rights reserved.

heterogeneous group with involvement of several mucosal surfaces without skin involvement. The overall incidence is low, between 1 in 12,000 and 1 in 20,000 individuals, and it typically presents in older patients between 60 and 80 years of age.<sup>42-44</sup>

The oral mucosa is the most commonly involved site in CP, affecting 85% of patients, followed by conjunctiva (64%) and the skin (24%).<sup>45</sup> The most commonly affected site of the oral mucosa is the gingiva, followed by the buccal mucosa and palate, and the most frequent presentation is of DG.<sup>46,47</sup> Oral involvement typically presents as erythematous patches that progress to bullae, erosions, and pseudomembranous lesions (Fig 7). Healing occurs slowly and often overt scarring in the oral mucosa is not obvious, though it can heal with reticulated white plaques resembling Wickham striae.<sup>48</sup> Involvement of the oral mucosa alone, or with skin involvement only, which is typically confined to the head and upper trunk, is associated with a better prognosis and a better response to treatment. In contrast, involvement of other mucosal sites, such as ocular, genital, nasopharyngeal, esophageal, and laryngeal sites, are associated with a poorer prognosis, because scarring leads to greater loss of function. Ocular disease requires comanagement with ophthalmology, particularly when scarring causes trichiasis, which greatly complicates management.

**PV.** PV is a chronic autoimmune blistering disease characterized clinically by the formation of blisters and erosions on the mucosa and skin, and histologically by acantholysis. PV is associated with antibodies directed against desmosomal cadherins, impairing cellular adhesion, and leading to acantholysis, skin fragility, blistering, and erosion. In mucosal dominant PV, the antibodies target desmoglein 3, which is integral to mucosal integrity, and in mucocutaneous PV, patients also have antibodies targeting desmoglein 1, expressed in



**Fig 8.** Pemphigus vulgaris. Ragged mucosal erosions.

high quantities in the skin of the face, scalp, and upper trunk.<sup>49</sup> These antibodies are pathogenic and are markers of disease activity.<sup>50</sup> The mean age of onset is 50 to 60 years of age, and it is more common in those of Mediterranean or Jewish ancestry.<sup>50,51</sup>

Oral involvement is usually the presenting manifestation of PV and often precedes skin manifestations by several months. Typically, ragged erosions and painful ulcerations are noted along the buccal and labial mucosa, followed by the palate and tongue (Fig 8). These erosions arise from otherwise healthy-appearing mucosa, without surrounding erythema or edema. Bullae are infrequently seen, as they are prone to rupture, but the Nikolsky sign can be elicited adjacent to an active lesion. The ulcerations are persistent and do not spontaneously heal. Nasal and laryngeal mucosal involvement can also occur, presenting as nasal congestion, epistaxis, odynophagia, and hoarseness. In 1 study, ≤49% of patients had symptoms of laryngeal or nasal involvement.<sup>52</sup> Other mucosal sites that can be involved include the conjunctiva, vulva, cervix, urethra, and rectal mucosa, but these sites are rarer.<sup>51</sup>

Skin involvement typically occurs on the scalp, face, and upper trunk, and is rare on the legs.<sup>49</sup> It presents with flaccid bullae and erosions on normal or slightly erythematous skin that heal without scarring but leave residual hyperpigmentation.

Left untreated, PV has a high mortality rate because of skin loss, oropharyngeal ulcerations, nutritional deficiency, inanition, and secondary infection. With the institution of effective therapy, the mortality rate has decreased to much less than 5% to 10%.<sup>50</sup>

**EBA.** EBA is an autoimmune blistering disease characterized by autoantibody production targeting type VII collagen in anchoring fibrils, an important



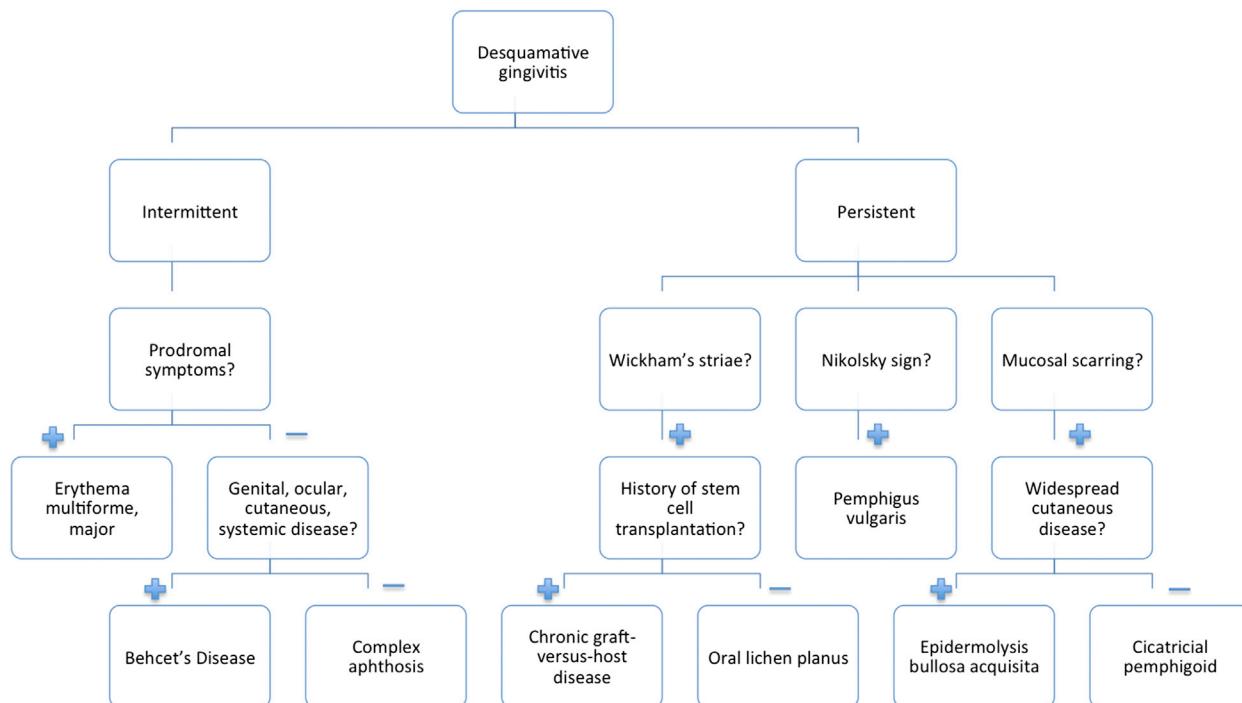
**Fig 9.** Epidermolysis bullosa acquisita. Significant milia and scattered erosions.



**Fig 10.** Paraneoplastic pemphigus. Severe stomatitis.

protein for maintenance of the dermoepidermal junction. EBA has 2 major clinical variants: the mechanobullous variant, which presents similar to heritable epidermolysis bullosa, and the inflammatory variant.<sup>53</sup> The inflammatory variant can resemble various other autoimmune bullous diseases, such as bullous pemphigoid, but is distinguished from this clinically by frequent oral involvement, significant scarring with milia, and poor response to treatment.<sup>54</sup> EBA can also present with principally mucosal involvement, mimicking CP.<sup>55</sup> EBA is exceedingly rare, with an estimated incidence of 0.25 per million people per year.<sup>56</sup>

Mucosal involvement in EBA can present in a variety of manners, ranging from a mild, subclinical variant to severe and life-threatening disease. Mucosal involvement can present with erythema and erosions during the inflammatory phase and progress with time to loss of lingual papillae and scarring of other mucosal sites with development of strictures. In a case series by Delgado et al,<sup>54</sup> 11 of 12 patients with EBA (91.7%) had mucosal involvement, including oral (83%), pharyngeal/laryngeal (55%), nasal (44%), esophageal (40%), and ocular (33%). Complications in EBA are often related to mucosal involvement with the development of esophageal stenosis, laryngeal synechiae, symblepharon, and trichiasis.<sup>54</sup> These complications can occur even in



**Fig 11.** Algorithm for the approach to the patient with desquamative gingivitis.

those patients with subclinical disease, and may develop before symptoms.<sup>55</sup>

Cutaneous lesions in EBA can present as blisters and scarring in areas prone to trauma in the mechanobullous variant; as tense blisters in an erythematous background in the inflammatory variant; or as combinations of both (Fig 9). The distinguishing features of EBA are its refractory nature and poor response to treatment.

**PNP.** PNP, also referred to as paraneoplastic autoimmune multiorgan syndrome, is a condition characterized by severe stomatitis alone or in conjunction with erosions and bullae of the skin in the setting of a known or occult tumor or malignancy. The neoplasms most commonly associated are non-Hodgkin's lymphoma (42%), chronic lymphocytic leukemia (29%), and Castleman disease (10%).<sup>57</sup> It is associated with several autoantibodies targeting both epidermal and dermoepidermal junction proteins, including desmoplakin I, desmoplakin II, envoplakin, periplakin, alfa-2-macroglobulin-like-1 protein, desmoglein 1, desmoglein 3, plectin, and bullous pemphigoid antigen 1.<sup>58</sup> Therefore, it presents with features of both pemphigus (flaccid bullae and erosions) and pemphigoid (tense bullae). It is also associated with a robust inflammatory tissue response, producing analogous inflammatory lesions. PNP is a rare form of pemphigus, seen most commonly in men 45 to 70 years of age.<sup>59</sup>

PNP most often presents with severe, painful mucosal erosions, with preferential involvement of the tongue and intractable stomatitis (Fig 10).<sup>60</sup> In contrast to PV, where unaffected mucosa appears healthy, in PNP the entire oral mucosa is involved with erythema, edema, vesicles, erosions, and ulcerations.<sup>14</sup> Widespread mucosal involvement is common in PNP, including involvement of the esophagus, stomach, duodenum, and colon.<sup>61</sup> Desquamation of bronchial mucosa leads to bronchiolitis obliterans and subsequent respiratory failure, a cause of death in patients with PNP.<sup>62</sup> Cutaneous lesions are polymorphic, presenting as vesicles, bullae, and targetoid patches and plaques, often on acral sites. In the past, patients may have been misdiagnosed with SJS.

The diagnostic criteria include the presence of severe stomatitis, with preferential involvement of the tongue, suggestive histopathologic features and immunofluorescence pattern, and association with an underlying lymphoproliferative disorder.<sup>63</sup> Overall, treatment is poor with a mortality rate of 68% in 1 study.<sup>64</sup> In addition, treatment of the neoplasia is typically not associated with clinical improvement, with the exception being in the setting of Castleman disease.<sup>65</sup>

**GVHD.** GVHD is a multiorgan disease occurring most commonly in patients who have undergone allogeneic stem cell transplantation. Acute GVHD is characterized by cutaneous, gastrointestinal, and

hepatic dysfunction, and typically occurs within the first 100 days of transplantation.<sup>11</sup> Chronic GVHD, on the other hand, can affect multiple organ systems and has overlapping features with autoimmune disease. It typically occurs after 100 days of transplantation, but can occur any time after transplant.

Oral involvement is a frequent manifestation of GVHD, occurring in 33% to 75% of patients with acute GVHD, and ≤80% of patients with chronic GVHD.<sup>66</sup> In acute GVHD, the oral involvement typically occurs in patients with more severe, erosive cutaneous disease as an extension from adjacent skin.<sup>67</sup> In chronic GVHD, the oral lesions typically present similar to OLP, with white, reticulated, sometimes eroded plaques involving the buccal mucosa, gingiva, and lips. Other mucosal involvement is common, including genital and ocular involvement, and should be screened for in these patients.

An algorithmic approach to desquamative gingivitis is shown in Fig 11.

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# Desquamative gingivitis



## Diagnosis and treatment

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### Learning objectives

After completing this learning activity, participants should be able to discuss the best methods for performing mucosal biopsies and indications for additional testing (eg, immunofluorescence); review the pathological findings of diseases that can lead to desquamative gingivitis; explain the importance of dental hygiene in the management of patients with desquamative gingivitis; and discuss disease-specific therapies and evidence-based approaches to management.

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#### Editors

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Desquamative gingivitis is a clinical finding with several potential etiologies, and therefore histologic examination should be performed to confirm the diagnosis before the implementation of systemic therapy. The best methods for obtaining a mucosal biopsy specimen are discussed to aid the dermatologist in approaching these patients, and indications for additional testing, such as immunofluorescence studies, are reviewed. Desquamative gingivitis is uncommon, and there are no systematic guidelines to assist the physician in treatment, producing a practice gap in management. As such, this article focuses on treatment for individual conditions, with emphasis on levels of evidence. An emphasis is also placed on the role of dental care in disease control and the best methods for achieving good oral hygiene. (*J Am Acad Dermatol* 2018;78:851-61.)

**Key words:** biopsy; desquamative gingivitis; immunofluorescence; oral hygiene; systemic therapy; topical therapy.

## DIAGNOSIS

### Key points

- A biopsy specimen should be obtained from all patients with desquamative gingivitis because it is critical to establishing a correct diagnosis, especially because clinical features are less distinct than on glabrous skin

### Abbreviations used:

DG:	desquamative gingivitis
DIF:	direct immunofluorescence
EBA:	epidermolysis bullosa acquisita
ELISA:	enzyme-linked immunosorbent assay
EM:	erythema multiforme
IIF:	indirect immunofluorescence
PV:	pemphigus vulgaris
TCI:	topical calcineurin inhibitor

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- **Immunofluorescence, both direct and indirect, should be performed for all patients where an autoimmune bullous disease is suspected, both for diagnosis and possibly for monitoring of disease response to therapy**

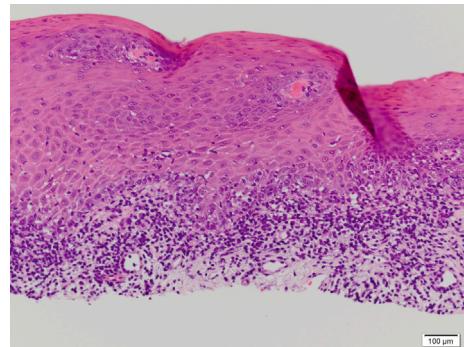
### **Biopsy technique**

Obtaining a biopsy specimen of the gingiva to evaluate for disease, such as lichen planus versus autoimmune bullous disease, requires the same considerations as for disease confirmation of lesions on glabrous skin. If a dermatologist is comfortable with oral mucosal biopsy techniques, then a standard punch biopsy technique can be used. The biopsy specimen can be 3 mm, with the first specimen for routine histology being taken from the edge of the erosion and placed in formalin. The second biopsy specimen should be perilesional, with the specimen being placed in transport medium and sent for direct immunofluorescence microscopic evaluation. If the dermatologist works with an oral medicine specialist with a special interest in gingival disease, an otolaryngologist aware of the above requirements for tissue processing, or obtains gingival elliptical biopsy specimens themselves, an elliptical biopsy specimen is optimal. The specimen should include the lesional and perilesional gingiva, and then be bisected, but it can be difficult to split the specimen without tearing it or losing epithelium in the process. The medial portion, which favors the lesion edge, should be placed in formalin and sent for routine histology as above. The lateral portion, which includes only perilesional mucosa, should be placed in transport medium and sent for direct immunofluorescence microscopic evaluation as above. Clinicians obtaining these biopsy specimens should review them with a dermatopathologist to ensure that the specimen is being collected appropriately.

### **Pathologic findings**

Histopathologic confirmation of the suspected clinicopathologic disease is required before the initiation of systemic therapy. Complete evaluation includes specimen evaluation for routine histology, as well as direct and indirect immunofluorescence microscopy and enzyme-linked immunosorbent assay (ELISA) testing when there is concern for immunobullous disease. Even in the presence of classic findings (eg, Wickham striae), histopathologic confirmation is required to confirm the diagnosis and is important to exclude other concomitant lesions, such as underlying malignancy.

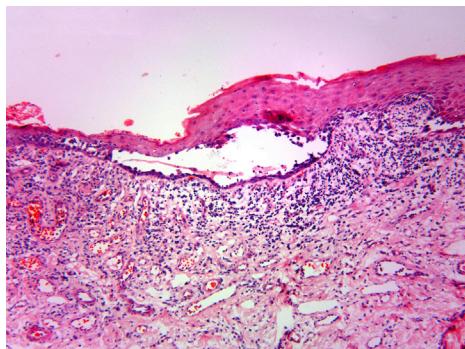
Routine histology demonstrates specific features for several differential diagnoses of desquamative



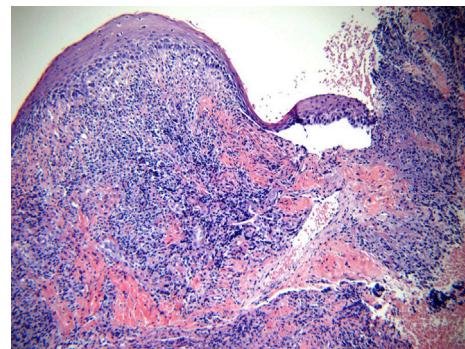
**Fig 1.** Oral lichen planus. Dense, band-like infiltrate at dermoepidermal junction. Courtesy of George Elgart, MD.

gingivitis (DG). Erythema multiforme (EM) demonstrates keratinocyte necrosis, liquefactive degeneration of the basal keratinocytes with basal vacuolar degeneration, and a mixed lymphohistiocytic infiltrate that can demonstrate a lichenoid pattern and obscure the dermoepidermal junction.<sup>1</sup> Biopsy specimens of aphthae are not frequently obtained, but when done, the histology is relatively nonspecific, with lesions demonstrating a neutrophil-predominant infiltrate early and lymphocytes later. When aphthae occur in the setting of Behcet disease (BD), vasculitis changes may be seen, although findings usually overlap with simple aphthae.<sup>2</sup> In oral lichen planus (OLP), the findings are similar to findings from glabrous skin, with hyperkeratosis, saw-tooth rete ridges, liquefactive degeneration of the basal layer, and a dense, band-like infiltrate along the dermoepidermal junction (Fig 1).<sup>3</sup> Ulceration with loss of the epidermis is seen in the erosive/ulcerative form. The mucosal histology of chronic graft-versus-host disease cannot be distinguished from lichen planus, and the clinical context is necessary for the diagnosis.<sup>4</sup> Direct immunofluorescence (DIF) microscopy findings are overall nonspecific in these conditions, and are more helpful for diagnosing autoimmune bullous disease.

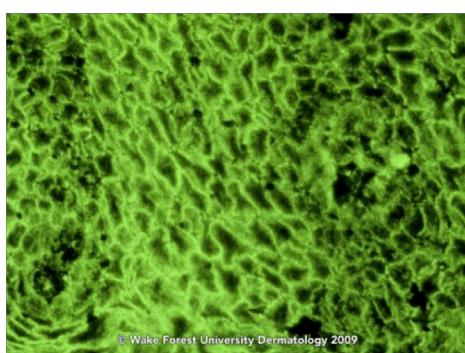
Routine histology in autoimmune bullous disease is helpful in distinguishing between intraepidermal and subepidermal blistering diseases, but ultimate confirmation with immunofluorescence microscopy is required. Pemphigus vulgaris (PV) specimens on routine histology reveal acantholysis and intraepidermal cleft formation, with preservation of the basal layer of keratinocytes (Fig 2).<sup>5</sup> DIF from perilesional skin specimens reveal the intercellular deposition of predominantly immunoglobulin G (IgG) in the epidermis (Fig 3). DIF also reveals these findings on the outer root sheath of plucked anagen hair.<sup>6</sup> Circulating antibodies to desmoglein 3 (and desmoglein 1, if present) are detected by ELISA testing and on indirect immunofluorescence (IIF). Immunoreactants can be seen on human skin,



**Fig 2.** Pemphigus vulgaris. Suprabasilar acantholysis and intraepidermal blister formation. Courtesy of George Elgart, MD.



**Fig 4.** Cicatricial pemphigoid. Subepidermal blister. Courtesy of George Elgart, MD.



**Fig 3.** Pemphigus vulgaris. Intercellular immunoglobulin G deposition within the epidermis. Courtesy of Graham Dermatopathology Library at Wake Forest School of Medicine. All rights reserved.

monkey esophagus, or guinea pig esophagus as substrates, where the characteristic intercellular staining is demonstrated. ELISA is more sensitive and specific than IIF, but the results may not be reliable at high antibody concentrations.<sup>7</sup> Antibody titers demonstrated by IIF and ELISA are not only important for diagnosis but also for disease monitoring, because levels correlate with disease activity and can predict a recurrence before clinical symptoms<sup>8</sup>; however, they are sometimes present in patients with complete remission.<sup>9</sup> Paraneoplastic pemphigus on routine histology can also feature acantholysis and suprabasilar clefting, but is accompanied by a dense, lichenoid infiltrate at the dermoepidermal junction with vacuolar degeneration of the basal layer and blisters both within the epidermis and below the epidermis.<sup>10</sup> DIF specimens demonstrate deposition of immunoglobulins and complement intercellularly within the epidermis, as well as along the dermoepidermal junction, and IIF demonstrates antibodies that bind to several types of epithelia, and is typically confirmed on transitional epithelia of rat bladder.

The antibody titers also can mirror disease activity in paraneoplastic pemphigus.<sup>10</sup>

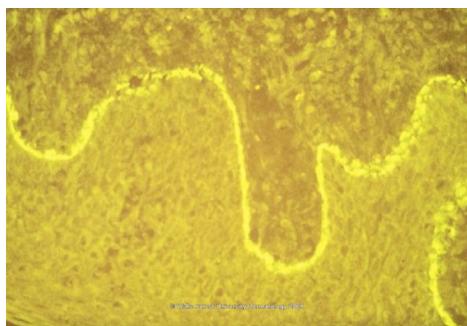
Cicatricial pemphigoid and epidermolysis bullosa acquisita (EBA) are both subepidermal bullous diseases. Cicatricial pemphigoid routine histology specimens show a subepidermal blister with a mixed inflammatory cell infiltrate composed primarily of lymphocytes and histiocytes (Fig 4).<sup>11</sup> Older lesions can feature fibrosis, the histopathologic correlate of scarring. On DIF, there is linear deposition of immunoreactants, most commonly IgG and complement component 3, along the basement membrane zone in most cases (Fig 5), whereas the frequency of IIF positivity is highly variable.<sup>12,13</sup> EBA also shows subepidermal blister formation. In the classical mechanobullous variant, there is minimal inflammatory infiltrate, as opposed to the inflammatory variant, which shows a predominantly neutrophilic infiltrate with variable numbers of eosinophils and lymphocytes.<sup>14</sup> DIF demonstrates IgG or IgA and complement component 3 along the basement membrane zone, in a characteristic u-serrated pattern, which is pathognomonic for antibodies targeting type VII collagen. Circulating antibodies can be detected by both IIF and ELISA, but only 60% of patients have these antibodies.<sup>15</sup> Both cicatricial pemphigoid and EBA demonstrate immunoreactant localization to the floor of the blister when incubated with 1 M NaCl (salt-split skin).

A review of the clinical, histologic, and immunofluorescent features of diseases that can cause DG is presented in Table I.

## MANAGEMENT

### Key points

- Institution and discussion of appropriate oral hygiene measures should be performed for all patients
- Systemic therapies should be instituted after failure of topical therapy, for widespread



**Fig 5.** Cicatricial pemphigoid. Linear immunoglobulin G deposition along the dermoepidermal junction. Courtesy of Graham Dermatopathology Library at Wake Forest School of Medicine. All rights reserved.

### disease, or as first-line therapy in the setting of certain immunobullous diseases

#### Oral hygiene

**Evaluation.** All patients with DG should have a thorough inspection of the oral cavity. The clinician should carefully inspect the gingiva and teeth for accumulation of dental plaque, signs of gingival retraction, evidence of dental root exposure, and tooth loss. Evaluation by a dental professional for the presence and management of caries should also be conducted. All mucosal surfaces should be inspected for the presence of microbial colonization, including evaluation for the white plaques of oral candidiasis, punched-out erosions of herpes simplex virus, or honey-colored crust of impetigo.

**Plaque control.** An effective oral hygiene regimen is critical to the care of patients with DG, and should be performed in addition to disease-targeting therapies. In patients with PV, the institution of an oral hygiene regimen led to significant reduction in bleeding scores and oral pemphigus clinical scores.<sup>16</sup> In patients with OLP, institution of a plaque control program improved not only plaque and gingival bleeding indices, but also pain of OLP lesions and overall disease activity.<sup>17</sup>

Though different protocols have been used for plaque control in studies, some general principles should be applied for all patients with DG. First, all patients should undergo a baseline tooth cleaning with a dental professional comfortable in the management of patients with DG. Second, patients should perform at-home dental cleaning with tooth brushing twice daily. A soft toothbrush is recommended (either manual or electric) while active erosions are present, using a modified Bass technique, where the bristles are placed at a 45° angle to the tooth surface at the edge of the gum, and strokes are performed to the tooth edge. Rough

maneuvers should be avoided. Plaque control should be performed either via gentle flossing or the use of a Waterpik (Water Pik Inc, Fort Colling, CO), which is as efficacious but gentler than flossing. Antiseptic mouth rinse should be performed twice daily, with avoidance of alcohol-based rinses. Periodic teeth cleaning procedures should be performed, and avoidance of local irritants, such as ill-fitting prostheses or unsatisfactory restorations, is critical.

**Decolonization.** Reduced oral hygiene and treatment with local immunosuppressant medications can lead to increased microbial colonization in patients with DG. We recommend institution of an antiseptic protocol with regular antifungal prophylaxis. This can be performed with the twice-daily use of an antiseptic mouth rinse containing hydrogen peroxide and daily use of antifungal troches. We also perform empiric treatment with a short course of an oral antifungal at the time of diagnosis, then as needed for evidence of candidal disease.

#### Medical therapies

**Topical therapies.** Topical therapies are an important component to the therapy of DG. For some diseases, topical therapies alone can be sufficient to control disease when mild to moderate, including EM, complex aphthosis, OLP, and graft-versus-host disease. For immunobullous diseases, systemic therapies are generally required, but topical modalities represent an important adjunctive treatment.

The most commonly used first-line topical therapy is a topical corticosteroid. We prefer either a class 1 or class 2, as a gel, which can sting, or an ointment, which may be seen to wash away but is effective. Ease of application can be facilitated via the use of custom dental trays. Mouth rinses may represent a more functional option for patients with widespread disease; however, we prefer to use topical corticosteroids locally because of *Candida* overgrowth with rinses. Corticosteroid inhalers can be of benefit for patients with oropharyngeal disease. Again, caution is required to prevent oral candidiasis.

Topical corticosteroids have been shown to be beneficial in the management of patients with vesiculocro erosive diseases (level of evidence IIA).<sup>18</sup> In OLP, high-potency topical corticosteroids have been found to be safe and effective (level IA).<sup>19</sup> In patients with atrophic-erosive OLP, topical and systemic corticosteroids have been found to be equivalent treatments, with 68.2% and 69.6% demonstrating complete disease control,

**Table I.** Clinical, histologic, and immunofluorescent findings in diseases causing desquamative gingivitis

Disease	Clinical	Histology	DIF	IFI/ELISA
Erythema multiforme	Erythematous, bullous, erosive plaques Location: labial, buccal mucosa, nonattached gingiva, and vermillion lip Other findings: targetoid lesions Minor, major or herpetiform aphthae Location: buccal and labial mucosa, soft palate, tonsils, and pharynx Other findings: systemic involvement in Behcet disease	Keratinocyte necrosis, basal vacuolar degeneration, and mixed lymphohistiocytic infiltrate Nonspecific; early: neutrophil predominant; late: lymphocyte predominant	Nonspecific	N/A
Complex aphthosis/ Behcet disease				N/A
Oral lichen planus	Wickham striae, erosions, and koebnerization Location: buccal, gingival, and labial mucosa Other findings: genital involvement in 20% Erythematous patches, bullae, and erosions Location: gingiva, buccal mucosa, and palate Other findings: ocular, genital, nasopharyngeal, esophageal, and laryngeal involvement may occur Ragged erosions and ulcerations plus Nikolsky sign Location: buccal and labial mucosa, palate, and tongue Other findings: cutaneous flaccid bullae and erosions, other mucosal surface involvement Erosions, loss of lingual papillae, scarring Location: diffuse Other findings: cutaneous tense bullae, pharyngeal/laryngeal, nasal, esophageal, and ocular involvement	Hyperkeratosis; saw-tooth rete ridges; and dense, band-like infiltrate along dermoepidermal junction Subepidermal blister, mixed inflammatory infiltrate of lymphocytes and histiocytes, and fibrosis in later lesions Acantholysis and intraepidermal cleft formation; preservation of basal keratinocytes	Linear deposition of IgG and C3 along basement membrane zone Desmoglein 3 with or without desmoglein 1	BP180, alpha-6 beta-4 integrin, and laminin 332
Cicatricial pemphigoid				
Pemphigus vulgaris				
Epidermolysis bullosa acquisita				
Paraneoplastic pemphigus				
Graft-versus-host disease				

C3, Complement component 3; DIF, direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay; IgA, immunoglobulin A; IgG, immunoglobulin G; IFI, indirect immunofluorescence; N/A, not available.

respectively.<sup>20</sup> In complex aphthosis, topical corticosteroids are also instituted as first-line therapy, often with a high-potency corticosteroid,<sup>21</sup> although mid-potency steroids have also demonstrated benefit (level IIA).<sup>22</sup> In EM, high-potency corticosteroids can be of benefit for mild disease (level IV).<sup>1</sup> For more refractory lesions, intralesional administration can be used. Adverse effects of topical corticosteroids include mucosal atrophy, oral dryness, and secondary candidiasis. Systemic absorption is thought to be minimal.<sup>23</sup>

Topical calcineurin inhibitors (TCIs) represent an additional topical treatment for DG. TCIs can be delivered via gel, cream, or as a suspension to swish and spit, created by dissolving a 1-mg capsule into a liter of water.<sup>24</sup> TCIs have demonstrated efficacy in patients with OLP, with comparable results to topical corticosteroids (level IA).<sup>19</sup> TCIs have also demonstrated efficacy in complex aphthosis (level III),<sup>21</sup> and for the management of genital aphthae in patients with BD (level IB).<sup>25</sup>

For patients with OLP, topical retinoids can also be used (level IIA), but these are not beneficial for other causes of DG and their use is limited by pain and irritation with application.<sup>26</sup>

**Systemic therapies.** Topical therapy alone is sometimes insufficient to control disease activity. When patients continue to have erosions and pain despite compliance with topical therapy, treatment with systemic therapy is indicated.

EM can either be self-limiting or recurrent. In the recurrent variant, where herpes simplex virus is often implicated in the pathogenesis, treatment and suppression with antiviral therapy is indicated (level IIA).<sup>27</sup> Common regimens include oral doses of acyclovir 400 mg twice daily, valacyclovir 500 mg twice daily, and famciclovir 250 mg twice daily. Treatment with antiviral therapy can reduce the frequency of attacks in recurrent EM, but there is a high rate of recurrence after discontinuation. Therefore, continual treatment for at least 1 to 2 years is indicated for antiviral therapy–responsive patients. This can be followed by a trial of therapy cessation, and reinitiation of therapy if flare occurs.<sup>1</sup> For patients with severe EM major with widespread mucosal involvement, systemic corticosteroids are indicated, but their use remains controversial in the management of EM.<sup>28,29</sup> For patients with refractory EM, anecdotal reports have also described benefit with cyclosporine,<sup>30</sup> azathioprine,<sup>31</sup> dapsone,<sup>32-35</sup> mycophenolate mofetil,<sup>36</sup> and thalidomide.<sup>37-40</sup>

Treatment for complex aphthosis should be initiated with topical therapies, and if refractory, systemic therapy is indicated. Colchicine can be considered a first-line systemic agent, given efficacy

and overall benign safety profile, in patients with complex aphthosis, both with and without BD (level IB).<sup>41-44</sup> Colchicine has been shown to reduce the number of lesions and was equivalent to oral corticosteroids in disease response.<sup>41</sup> Complex aphthosis is a chronic disease, and therefore treatment with oral steroids is not recommended because of side effects from chronic use. Dapsone represents another beneficial treatment option for patients with complex aphthosis, and has demonstrated efficacy in patients with BD (level IB).<sup>45</sup> In patients with BD, dapsone not only reduces the number of oral and genital aphthae, but also treats other systemic manifestations. For patients refractory to these therapies, thalidomide can be used, as it has shown benefit in patients with complex aphthosis with and without BD (level IB).<sup>46-49</sup> Dosing should be performed at the lowest effective daily dose to limit toxicity, and a lower dose of 100 mg/day was shown to be as effective as a dose of 300 mg/day.<sup>46</sup> A retrospective study by Jorizzo et al<sup>21</sup> described the use of a therapeutic ladder for complex aphthosis that included initiating therapy with topical or intralesional steroids, then progressing to colchicine, followed by dapsone, a combination of colchicine and dapsone, and finally low-dose thalidomide (50-100 mg at bedtime) with Risk Evaluation and Mitigation Strategy (REMS) program monitoring in the United States, for refractory patients. In this study, all patients required systemic therapy, and 88% of patients responded overall with this therapeutic ladder. Topical potent corticosteroids are used for breakthrough lesions. Additional therapies that have been evaluated include apremilast, which was found to be effective in reducing oral aphthae in patients with BD compared to placebo alone (level IB).<sup>50</sup>

OLP is often treated with topical therapies, but when refractory, severe, or widespread, systemic therapy is indicated. Systemic retinoids have been shown to be effective in the management of OLP with good overall response rate, but are limited by their toxicity, which leads to high rate of early discontinuation (level IB).<sup>51,52</sup> Antimalarials have also been evaluated in one, small open trial that demonstrated excellent response to therapy in 9 of 10 patients evaluated (level IIB).<sup>53</sup> The onset of effect of antimalarials is slow, requiring 3 to 6 months of treatment before resolution of lesions. In severe or widespread disease, systemic corticosteroids can be used, although systemic and topical corticosteroids were found in 1 study to be equivalent and dramatic disease rebound can occur on tapering.<sup>20</sup> Other therapies that have been reported effective include low-dose weekly methotrexate,<sup>54</sup> cyclosporine,<sup>55</sup>

tumor necrosis factor–alfa inhibitors,<sup>56</sup> and thalidomide.<sup>57,58</sup> A comprehensive therapeutic ladder for patients with OLP was described by Jorizzo et al<sup>59</sup> and recommended after failure of topical therapies with corticosteroids, retinoids, or immunomodulators to progress to oral metronidazole, antimalarials, systemic retinoids, low-dose weekly methotrexate, systemic corticosteroids, cyclosporine, and biological therapies. They used a simplified therapeutic ladder approach of topical tacrolimus to weekly methotrexate to mycophenolate with 82% of patients achieving substantial improvement, and only 8% of patients had no response.

Mild cicatricial pemphigoid involving the oral cavity alone can be treated first with topical therapy, but if unresponsive, or if there is any evidence of ocular, nasopharyngeal, laryngeal, esophageal, or genital mucosal involvement, then systemic therapy is indicated.<sup>60</sup> For mild disease, treatment can be initiated with dapsone, which has shown efficacy in patients with oral cicatricial pemphigoid (level IV).<sup>60-62</sup> For patients with poor response to dapsone, or with severe or rapidly progressive disease, treatment with prednisone at 1 to 1.5 mg/kg/day can be initiated (level IV).<sup>60,63,64</sup> Other immunosuppressive agents that can be used include azathioprine and mostly mycophenolate mofetil.<sup>60,65</sup> Mycophenolate has mostly superseded both azathioprine and cyclophosphamide in these patients. Upon improvement in disease control, weaning of prednisone should be performed while maintaining the other immunosuppressant agent. More recently, rituximab has been used in the management of cicatricial pemphigoid, demonstrating good efficacy. It is often used as adjunctive therapy to additional immunosuppressants, including intravenous immunoglobulin (IVIg).<sup>66-68</sup> IVIg alone has also been used for treatment of cicatricial pemphigoid, and was able to demonstrate efficacy and a corticosteroid-sparing effect.<sup>69-71</sup>

PV is one cause of DG that requires systemic therapy. Treatment is often initiated with oral corticosteroids (level IV),<sup>72</sup> although there is only fair evidence from a recent systematic review to support their implementation as first-line therapy.<sup>73</sup> PV is a chronic disease, lasting several years, and the prolonged used of corticosteroids leads to significant adverse effects and occasionally to death; therefore, initiation of a corticosteroid-sparing agent is critical.<sup>74</sup> This not only reduces cumulative corticosteroid doses, but also enhances the efficacy of the systemic corticosteroid.<sup>75</sup> Azathioprine is one corticosteroid-sparing agent that is traditionally

used in the treatment of PV (level IV).<sup>76,77</sup> No controlled studies have demonstrated efficacy in the treatment of PV, but azathioprine has been shown to demonstrate a corticosteroid-sparing effect superior to earlier immunosuppressant agents.<sup>75,78</sup> Mycophenolate mofetil is another immunosuppressant agent often used as a corticosteroid-sparing agent (level IV).<sup>79,80</sup> Mycophenolate mofetil has demonstrated more rapid and durable responses, as compared to patients treated with systemic corticosteroids alone,<sup>81</sup> and has demonstrated improved efficacy over azathioprine in maintaining disease control.<sup>82</sup> In 1 study, 86% of treatment-resistant and 75% of treatment-naïve patients achieved complete control of disease on mycophenolate mofetil and prednisone.<sup>9</sup> For patients refractory to these therapies or with widespread, severe disease, initiation of therapy with cyclophosphamide or rituximab is recommended (level IV).<sup>9</sup> Cyclophosphamide therapy, in addition to systemic corticosteroids, reduced time to remission and achieved a greater proportion of cases to achieve remission compared with systemic corticosteroids alone, but this was not statistically significant.<sup>83</sup> Rituximab has been demonstrated in several case series to be effective, and some advocate its use as first-line therapy, because clinical remission is reported in 90% to 95% of patients within <6 weeks, with complete remission within 3 to 4 months (level IV).<sup>84-86</sup> Other agents that have been used as adjuvant therapy include dapsone,<sup>87</sup> tacrolimus,<sup>88</sup> IVIg,<sup>86</sup> and plasma exchange.<sup>89</sup> In 1 study with long-term follow-up, combination therapy with 2.5 to 3 g/day of mycophenolate and prednisone 60 mg tapered to 30 mg over 6 months and to 0 over 2 years as tolerated resulted in patients experiencing long-term remission off therapy.<sup>9</sup> Evidence-based studies must follow patients long-term with this possible endpoint.

EBA is typically a treatment-refractory disease with a poor response to systemic therapy. A recent systematic review concluded that no treatment recommendations can be made for EBA in light of the absence of evidence.<sup>90</sup> However, we must treat these patients. Systemic corticosteroids are often used as first-line therapy, and are more effective in patients with inflammatory EBA and IgA-rich EBA (level IV); noninflammatory EBA is often refractory to systemic therapies.<sup>91</sup> Dapsone has been used in the treatment of EBA (level IV), with better response in children.<sup>92</sup> Other therapies used include azathioprine, methotrexate, cyclophosphamide, IVIg, and rituximab. More recently, a case series of 5 patients with EBA who had been resistant to other therapies showed response with rituximab and IVIg

combination therapy.<sup>93</sup> Additional studies are needed to delineate an appropriate treatment protocol for patients with EBA. A therapeutic ladder similar to that used in patients with bullous pemphigoid, including mycophenolate, is often used.

There are no consensus guidelines for the treatment of paraneoplastic pemphigus, and the evidence is limited only to case reports. Treatment of the underlying malignancy is of utmost importance, but this typically does not result in improvement in the disease, with the exception being in the setting of Castleman disease.<sup>94</sup> Often, therapy with rituximab is used, because paraneoplastic pemphigus is often associated with non-Hodgkin's lymphoma, but the therapeutic response is variable.<sup>95,96</sup> Other agents reported (either alone or in combination) include systemic corticosteroids,<sup>97</sup> azathioprine,<sup>98</sup> cyclosporine,<sup>97,99</sup> cyclophosphamide,<sup>100</sup> mycophenolate mofetil,<sup>101</sup> methotrexate,<sup>97</sup> dapsone,<sup>102</sup> IVIg,<sup>97</sup> and plasma exchange.<sup>103</sup> Introduction of immunosuppressive therapy requires coordination with the patient's oncologist.

Management of chronic graft-versus-host disease should be based on additional systemic findings of disease. Topical therapy is sometimes sufficient for oral lesions, but if there is widespread disease involving  $\geq 3$  organs, or if severe mucosal symptoms result in reduced oral intake, systemic treatment is indicated.<sup>104</sup> Systemic therapy is often initiated with systemic corticosteroids followed by extracorporeal photopheresis as adjunctive therapy.<sup>4</sup>

## SUMMARY

The evaluation and treatment of patients with DG, as with the approach to all patients with complex medical dermatoses, requires conscientious attention to precise clinical, histopathologic, and immunopathologic diagnosis. This is complicated by patients often presenting to the dermatologist on some test-altering treatment. Management must be comprehensive and include meticulous attention to oral hygiene, because candidal colonization complicates oral wound healing of erosions and dental plaque is composed of chemotactic bacteria. Our experience favors using potent topical corticosteroids for localized mucosal lesions and tacrolimus 1 mg capsule (dissolved in 1/2 L of water as a 2-minute twice daily "swish and spit" treatment replacing the mixture weekly) for diffuse mucositis as our modification of the Nice, France published method. A therapeutic ladder can be used with systemic therapies including cost as a side effect and arranging treatments from lowest risk/benefit ratio to highest. More severe disease (eg, PV) justifies starting much higher on the therapeutic ladder. We

believe that systemic therapy should be matched with the presumed duration of the disease and that frequent short-term corticosteroid tapers usually complicates disease management because of disease rebound. Patients can present to the dermatologist devastated by the consequences of many of these diseases on their quality of life and fearful after visiting many doctors and after searching the Internet. Proper evaluation and treatment of patients who present with DG can be enormously gratifying for the patient and their family and for the physician and their team.

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# Langerhans cell histiocytosis in children

## History, classification, pathobiology, clinical manifestations, and prognosis

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### Learning objectives

After completing this learning activity, participants should be able to discuss historical perspectives, previous and current classification systems, and former and current perspectives of pathobiology, particularly as they pertain to novel treatment approaches and recognize specific cutaneous and systemic clinical manifestations and the wide range of potential disease courses, ranging from spontaneous resolution to life-threatening multisystem involvement.

### Disclosures

#### Editors

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Langerhans cell histiocytosis (LCH) is an inflammatory neoplasia of myeloid precursor cells driven by mutations in the mitogen-activated protein kinase pathway. When disease involves the skin, LCH most commonly presents as a seborrheic dermatitis or eczematous eruption on the scalp and trunk. Evaluation for involvement of other organ systems is essential, because 9 of 10 patients presenting with cutaneous disease also have multisystem involvement. Clinical manifestations range from isolated disease with spontaneous resolution to life-threatening multisystem disease. Prognosis depends on involvement of risk organs (liver, spleen, and bone marrow) at diagnosis, particularly on presence of organ dysfunction, and response to initial therapy. Systemic treatment incorporating steroids and cytostatic drugs for at least one year has improved prognosis of multisystem LCH and represents the current standard of care. (J Am Acad Dermatol 2018;78:1035-44.)

**Key words:** *BRAF*; Langerhans cell histiocytosis; MAPK; pathway myeloid neoplasia.

## INTRODUCTION

### Key points

- **Langerhans cell histiocytosis is a rare neoplasm of hematopoietic myeloid precursor cells that most commonly affects white male children, with a peak incidence of 1 to 3 years of age**
- **Cutaneous involvement, which is observed in 40% of cases, typically reflects multi-system disease with a 20% mortality**

### Abbreviations used:

ECD: Erdheim–Chester disease  
 LCH: Langerhans cell histiocytosis

The histiocytoses are a group of rare disorders characterized by pathologic accumulation of cells derived from the monocyte, macrophage, and dendritic cell lineage. In 1987, the Working Group of the

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Histiocyte Society classified the histiocytoses as Langerhans cell–related, non-Langerhans cell–related, or malignant,<sup>1</sup> and this classification has been in place for 3 decades. A new classification has been elaborated upon and recently published, and it accounts for the current breakthrough in understanding the molecular mechanisms of most entities.<sup>2</sup> The new classification attempts to integrate clinical and imaging features with pathology and molecular findings.

Histiocytes (tissue macrophages) derive from hematopoietic myeloid progenitors, which further differentiate into monocytes, macrophages, and dendritic cells.<sup>3,4</sup>

Despite their phenotypic resemblance to normal Langerhans cells, which are dendritic cells of the skin and mucosa, the pathologic cells in Langerhans cell histiocytosis (LCH) derive from immature myeloid precursor cells.<sup>5</sup> In the past, they had been erroneously thought to derive from Langerhans cells, the normal dendritic cells of the skin and mucous membranes, because of their phenotypic resemblance and shared markers (eg, positive staining for CD1a, human leukocyte antigen–antigen D related, S-100, and cytoplasmic Birbeck granules).

Among histiocytic disorders, LCH is the most common one, affecting an estimated 4 to 5 per million children 0 to 15 years of age each year.<sup>6,7</sup> Because localized disease often spontaneously regresses, the prevalence is probably higher than reported.<sup>8</sup> The median age of diagnosis is 3.5 years, and the highest incidence rate is observed before 1 year of age, with a decreased incidence observed thereafter.<sup>6</sup> While most prevalent in children, the disorder presents in all ages and has also been reported in the elderly.<sup>9,10</sup> There is a 2:3 male:female ratio.<sup>6,11</sup>

The clinical presentation and subsequent course may vary remarkably, from single-system disease that may resolve spontaneously to treatment refractory multisystem involvement with a 20% mortality.<sup>12</sup> Two thirds of children present with single-system involvement, most commonly of the bone, but also of the skin or lymph nodes.<sup>12</sup> LCH involves the skin in about 25% of cases.<sup>13</sup>

Significant risk factors for LCH include maternal urinary tract infection during pregnancy, feeding problems or blood transfusions during infancy,<sup>14</sup> Hispanic ethnicity, crowding, low education level,<sup>15</sup> neonatal infections, solvent exposure, family history of thyroid disease,<sup>16</sup> and in vitro fertilization.<sup>17</sup> Protective factors include black race,<sup>15</sup> childhood vaccinations,<sup>16</sup> and supplemental vitamins.<sup>14</sup> Association of LCH with other neoplasms has been reported in rare cases.<sup>18</sup>

**Table I.** Histiocytoses classification\*

Disease
Langerhans
Langerhans cell histiocytosis
Erdheim–Chester disease/extracutaneous juvenile xanthogranuloma
Indeterminate cell histiocytosis
Cutaneous and mucocutaneous
Juvenile xanthogranuloma
Adult xanthogranuloma
Solitary reticulohistiocytoma
Benign cephalic histiocytosis
Generalized eruptive histiocytosis
Progressive nodular histiocytosis
Xanthoma disseminatum
Cutaneous Rosai–Dorfman disease
Necrobiotic xanthogranuloma
Multicentric reticulohistiocytosis
Cutaneous histiocytoses not otherwise specified
Malignant
Histiocytic sarcoma
Indeterminate cell sarcoma
Langerhans cell sarcoma
Follicular dendritic cell sarcoma
Rosai–Dorfman disease
Rosai–Dorfman disease
Noncutaneous, non-LCH not otherwise specified
Hemophagocytic lymphohistiocytosis and macrophage activation syndrome
Hemophagocytic lymphohistiocytosis/macrophage activation syndrome

\*Data from Emile et al.<sup>2</sup>

## HISTIOCYTOSES CLASSIFICATION

### Key point

- A recent (2016) histiocytoses classification system divides the histiocytoses into 5 categories: Langerhans (L), cutaneous and mucocutaneous (C), malignant (M), Rosai–Dorfman disease (R), and hemophagocytic lymphohistiocytosis and macrophage activation syndrome (H)

Emile et al<sup>2</sup> recently proposed a new classification of the histiocytic disorders that takes into consideration current knowledge from dendritic cell biology and integrates molecular findings from lesion tissues. Therefore, based on clinical manifestation(s), imaging, histology, and molecular genetics, the histiocytoses are divided into 5 groups (Table I): Langerhans (L), cutaneous and mucocutaneous (C), malignant (M), Rosai–Dorfman disease (R), and hemophagocytic lymphohistiocytosis and macrophage activation syndrome (H).<sup>2</sup>

LCH is assigned to the Langerhans (L) group, together with Erdheim–Chester disease (ECD),

mixed LCH/ECD, extracutaneous juvenile xanthogranuloma, and indeterminate cell histiocytosis. These entities have been grouped together based on similarities in clinical presentation and shared activating mutations in the mitogen-activated protein kinase (MAPK) pathway.<sup>5,19-25</sup> Because of identical histopathology and overlapping clinical phenotype, Emile et al<sup>2</sup> consider ECD a manifestation of extracutaneous juvenile xanthogranuloma with activating mutations in the MAPK pathway. Of note, co-occurrence of ECD and LCH in the same patient seems to be relatively common and may be linked by MAPK pathway mutations, particularly *BRAF*-V600E, in a common progenitor cell. Of patients with ECD, 19% have mixed LCH/ECD and 89% of patients with mixed LCH/ECD have mutations in *BRAF*.<sup>26</sup> Review of the entire classification of the histiocytic disorders is beyond the scope of this paper; interested readers are referred to the article by Emile et al.<sup>2</sup>

### Clinical classification of LCH

#### Key point

- **Langerhans cell histiocytosis is categorized by extent of involvement (single vs multisystem) and presence of risk organ involvement (eg, liver, spleen, or bone marrow)**

Historically, different clinical phenotypes of LCH have been described as distinct entities (eg, eosinophilic granuloma of bone, Hand-Schüller-Christian disease, Letterer-Siwe disease, and Hashimoto-Pritzker disease). Over the years, it became evident that not all cases fit into the originally described strict categories, and most them show overlapping manifestations.<sup>27-44</sup> For example, congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease) has been reported in older patients, and in some cases a prolonged course with resulting sequelae have been described.<sup>38,43-45</sup> Following Farber<sup>46</sup> and Green and Farber's<sup>47</sup> observations in 1941 and 1942 that the different categories present with similar radiologic and histologic findings, Lichenstein and Jeffe<sup>48</sup> in 1953 grouped the different syndromes under the term histiocytosis X, with the X representing uncertainty of the cell origin. Upon development of electron microscopy, Nezelof et al<sup>49</sup> in 1973 identified intracytoplasmic Birbeck granules as specific structures of the normal epidermal Langerhans cells and pathognomonic feature of histiocytosis X lesions and concluded a histogenic relation. Accordingly, histiocytosis X was renamed LCH.<sup>50</sup>

LCH is currently categorized by involvement of single or multiple organ systems, single or multiple

sites within a particular organ system, and the presence of risk organ involvement, which includes the liver, spleen, and bone marrow. Pulmonary involvement is no longer considered a risk organ, as Ronceray et al<sup>51</sup> found it to have no significant impact on survival in a multivariate analysis. Most patients present with single-system involvement (70%). Of patients with multisystem disease, around 50% have ≥1 risk organ involved.<sup>52</sup>

### Pathobiology

#### Key point

- **Current knowledge redefined LCH as an inflammatory myeloid neoplasia driven by activating mutations in the MAPK pathway**

Initially, the pathogenesis of LCH was considered to be a nonneoplastic, inflammatory response.<sup>53-58</sup> The explanation for disease pathogenesis shifted from reactive to neoplastic after Willman et al<sup>59</sup> and Yu et al<sup>60</sup> in 1994 were the first to report clonal expansion of LCH cells. However, it took about 2 more decades until the molecular basis of LCH could be uncovered. Specifically, in their seminal paper in 2010, Badalian-Very et al<sup>19</sup> described the *BRAF*-V600E mutation in 56% of the studied samples. This observation has been subsequently confirmed by other groups, who identified this mutation in 38% to 69% of the studied cases.<sup>24,61,62</sup> The *BRAF*-V600E mutation is an activating mutation that leads to increased rapidly accelerated fibrosarcoma kinase activity and subsequent activation of the RAS-RAF-MEK-ERK-MAP kinase pathway. In the aforementioned study, the RAS-RAF-MEK-ERK pathway was activated in all studied LCH samples, including those with wild-type *BRAF*.<sup>19</sup> Accordingly, mutations in genes encoding other proteins in the pathway—albeit less common mutations—have also been identified.<sup>5,21-23</sup> Considering the pathway's key role in regulating cell growth, differentiation, senescence, and apoptosis, its activation is reflective of LCH's classification as a neoplastic disorder.<sup>63-65</sup>

Despite those molecular findings, LCH is not a classic cancer. It seems that its clinical expression is largely caused by inflammatory properties of the pathologic cellular clone. Murakami et al<sup>66</sup> note that *BRAF* mutations can mediate a prolonged inflammatory response after infection, *Bacillus Calmette-Guérin*, or tobacco use. During inflammation, foreign antigens prompt interleukin-1 secretion by Langerhans cells, and interleukin-1 increases MAPK pathway activity. The physiologic increase in MAPK pathway activity caused by interleukin-1 secretion is exacerbated by *BRAF* mutations.



**Fig 1.** Plain radiography of the skull showing osteolytic lesions of the skull vault in a patient with Langerhans cell histiocytosis.

Accordingly, Berres et al<sup>5</sup> suggested that LCH be considered an inflammatory myeloid neoplasia.

## Clinical manifestations

### Key point

- Isolated cutaneous disease has only been observed in 2% of the total Langerhans cell histiocytosis population
- Of patients presenting to dermatologists with cutaneous disease, 87% to 93% present with involvement of other organ systems

The most commonly affected organs overall are: bone (80%), skin (33%), pituitary (25%), liver (15%), spleen (15%), hematopoietic system (15%), lungs (15%), lymph nodes (5-10%), and the central nervous system excluding the pituitary (2-4%).<sup>67</sup> Systemic signs, such as fever, lethargy, and weight loss, may be noted in patients with either single-system or multisystem disease. Fever has been observed in  $\leq 50\%$  of pediatric patients.<sup>68</sup>

**Skeletal.** Bone involvement is mostly unifocal (75%)<sup>69,70</sup> and most commonly presents as a soft tissue mass presenting with swelling or pain. Any bone may be involved, excluding the hands and feet.<sup>52,71</sup> In both children and adults, the skull is the most common site of involvement<sup>72</sup> (Fig 1). Radiographically, LCH typically mimics multiple myeloma, presenting as either single or multiple osteolytic lesions; however, in contrast to multiple myeloma, LCH lesions may be accompanied by a periosteal reaction.<sup>73</sup>

**Cutaneous.** In considering patients of all ages, skin is the second most frequently involved organ system after bone.<sup>67</sup> Nevertheless, in patients  $< 2$  years of age, cutaneous disease is the most common manifestation.<sup>45,74</sup> Cutaneous involvement is typically representative of multisystem disease,

because 87% to 93% of patients also have systemic involvement.<sup>75</sup> Cutaneous lesions associated with fever (52%), hepatomegaly (52%), splenomegaly (48%), bone damage (39%), and lung damage (36%) are the most common manifestations of systemic involvement.<sup>76</sup> Isolated cutaneous disease accounts for only 2% of total cases.<sup>7</sup>

Patients present with diverse cutaneous findings, which contributes to high rates of misdiagnosis (16%).<sup>76</sup> Lesions may be either circumscribed or spread<sup>77</sup> and there may be either single or multiple lesions<sup>75</sup> (Fig 2).

In Li et al's retrospective analysis<sup>76</sup> of 918 cases of LCH in China (newborns to patients 65 years of age), 510 patients (56%) were reported to have skin lesions, of which 106 patients (12%) presented with cutaneous lesions as the initial disease manifestation. Cutaneous involvement typically presented as pinpoint erythematous or skin-colored papules or pustules. The morphology can mimic a seborrheic dermatitis-like or an eczematous erythematous, skin-colored, or brown petechial rash with or without scale, scabbing, crusting, or purpura. Xanthoma- and vitiligo-like lesions and urticaria were also observed.<sup>76</sup> In infants, a seborrheic dermatitis-like rash on the scalp often causes LCH to be misdiagnosed as seborrheic dermatitis, while groin involvement can present as treatment-resistant, recurring diaper dermatitis.<sup>71</sup> In addition, the wide variety of reported cutaneous morphologies of LCH has also included hypopigmented<sup>78</sup> (Fig 3) or hyperpigmented<sup>79</sup> macules or maculopapular lesions, papulopustular varicella-like eruptions,<sup>80</sup> erythematous, lichenified,<sup>81</sup> or poikiloderma-like plaques,<sup>82</sup> vesicles, vascular tumor-like lesions, purpuric macules, a red-blue nodule,<sup>43</sup> erythematous vesiculopustules,<sup>83</sup> ulcers, hemorrhagic lesions,<sup>84</sup> yellow-orange papules,<sup>82</sup> and violaceous papules and plaques.<sup>85</sup> Lesions are frequently pruritic.<sup>77</sup>

Li et al<sup>76</sup> reported that the trunk, head, and face were the most common sites of involvement. Involvement of the limbs, neck, armpits, groin, perineum, buttocks, and oral mucosa was also prevalent.<sup>76</sup> Other reported sites include the extremities,<sup>75</sup> flexures,<sup>77</sup> retroauricular areas,<sup>82</sup> perianal areas,<sup>85</sup> and genitalia.<sup>86</sup> LCH also has a predilection for sites of previous trauma.<sup>87,88</sup>

Though rare, eyelid involvement can be unilateral or bilateral and may mimic treatment-refractory chalazion.<sup>89-92</sup>

Mucosal lesions (21% isolated skin disease, 52% systemic) are typically noted as ulcers in the genital (Fig 4) or oral mucosa (Fig 5).<sup>13</sup> While oral manifestations are rare, their presence may assist in



**Fig 2.** Langerhans cell histiocytosis. **A**, Widespread and confluent erythematous and purpuric crusted papules and vesicles on the trunk with erythema and maceration of inguinal folds and genitalia of an infant. **B**, Macerated and eroded pink papules with confluence in the suprapubic, inguinal, and genital areas of an infant. **C**, Scattered pink, reddish-brown, and purpuric-appearing papules and nodules on the trunk and extremities of an infant. **D**, Scattered erythematous, crusted, and eroded papules and erythematous patches on the scalp of a child.



**Fig 3.** Self-healing lesions leaving hypopigmentation in a patient with Langerhans cell histiocytosis.

diagnosis.<sup>93</sup> Oral disease may present as gingivitis, bleeding, mucosal swelling, ulceration, pathologic jaw fractures, excessive tooth mobility, and loss of teeth.<sup>94</sup>

Nail involvement is rare<sup>95,96</sup> but can present as subungual pustules, hemorrhage, or hyperkeratosis, purpuric striae, purulent discharge, longitudinal grooving, onycholysis, paronychia, and pitting (Fig 6).<sup>95-98</sup>

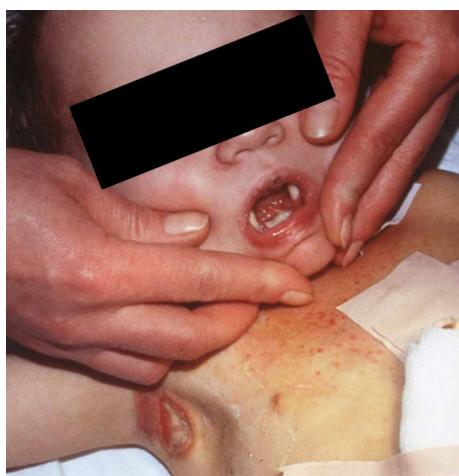
**Endocrine.** Involvement of the hypothalamic–pituitary axis most commonly presents with diabetes insipidus, observed in  $\leq 50\%$  of patients with multisystem disease. Other hormone deficiencies develop in 20% of patients overall. The second most common endocrinopathy is growth hormone deficiency (10%).<sup>99,100</sup> Accordingly, growth should



**Fig 4.** Involvement of the genital mucosa in a teenage girl with Langerhans cell histiocytosis.

be monitored in all LCH patients, particularly in those with diabetes insipidus, who have a 37% and 53% 5- and 10-year risk, respectively, of developing growth hormone deficiency.<sup>101</sup>

Thyroid involvement is rare, with only 75 cases reported in the literature, and may present with either diffuse (59%) or nodular (26%) nontender



**Fig 5.** Ulceration of the oral mucosa with loss of teeth in a toddler with multisystem Langerhans cell histiocytosis.

enlargement. Patients are typically euthyroid (41%), hypothyroid (20%), or subclinically hypothyroid (11%).<sup>102-104</sup>

**Pulmonary.** Isolated pulmonary LCH typically affects adults between 20 and 40 years of age, and at least 90% have a current or past medical history significant for smoking. Isolated pulmonary disease is the major cause of mortality in adults with LCH,<sup>105</sup> with 5- and 10-year survival rates of 74% and 64%, respectively.<sup>106</sup> While isolated pulmonary disease is rare in children (<1%), pulmonary involvement is frequent in multisystem disease ( $\leq 41\%$ ) and typically presents with tachypnea, cough, and chest pain (56%). Symptom severity and time course can vary from asymptomatic to rapidly progressive respiratory failure.<sup>107</sup>

**Hepatic.** Liver involvement is exclusively seen in patients with multisystem LCH. Patients may present with hepatomegaly only or with functional impairment (elevated liver enzymes, hypoproteinemia, and hypoalbuminemia) or jaundice in the context of histiocytosis-induced sclerosing cholangitis.<sup>108-111</sup>

**Lymph nodes.** Lymph node involvement is more frequently implicated in multisystem disease affecting children.<sup>112</sup> Isolated lymph node involvement is rare<sup>13,70</sup> and is typically reported in older children and adults.<sup>113</sup>

## Prognosis

### Key points

- **Prognosis depends on involvement of risk organs (bone marrow, liver, spleen) and response to initial systemic therapy**
- **Multisystem disease is associated with BRAF mutations in early myeloid precursors and young age at initial manifestation**



**Fig 6.** Nail involvement in a patient with Langerhans cell histiocytosis.

**Single-system disease.** Single-system LCH has an excellent prognosis, with a survival rate of nearly 100%. The 5-year recurrence rate is <20%, and recurrence typically involves the same organ system but may involve a different location.<sup>52,70,114,115</sup> Reactivations are usually limited to skeleton and posterior pituitary (diabetes insipidus) and therefore do not affect survival. Considering the typically favorable prognosis and the propensity for spontaneous regression of the bone lesions (typically within 1-3 months), mutilating surgery should be avoided and systemic treatment is not needed in most patients. Cutaneous lesions that regress mostly heal without defects, but may be followed by scarring, hypo-, or hyperpigmentation.<sup>8,71,116,117</sup> Sequelae encompassing diabetes insipidus, hearing loss, and orthopedic defects are observed in  $\leq 24\%$  of patients, but are rarely severe enough to affect quality of life.<sup>117</sup>

**Multisystem disease.** Patients with multisystem disease are at potential risk of mortality and usually need systemic treatment. Recurrence ( $\leq 50\%$ )<sup>52,118</sup> and sequelae ( $> 50\%$ )<sup>117</sup> are also more prevalent in patients with multisystem LCH. The 5-year overall survival rates in patients with single or multisystem disease without risk organ involvement are 100% and 98%, respectively, while survival is  $\leq 77\%$  in patients with risk organ involvement at diagnosis.<sup>52,118</sup> When assessing treatment options, stratification of patients with multisystem disease by risk organ involvement is essential, because high-risk disease is less responsive to therapy and requires more aggressive treatment.<sup>12,119</sup> In addition to the poor prognosis of high-risk disease itself, salvage treatment approaches used in this selected group are more toxic.<sup>118,120-122</sup>

In patients with high-risk disease, initial response to therapy (the first 6 weeks) is particularly prognostic.<sup>123,124</sup> In contrast to patients with an early response to therapy, nonresponders have higher mortality rates (52% vs 17%) and are less likely to experience complete resolution (20% vs 70%).<sup>123,124</sup>

**Associations with multisystem disease.** Both single-system and multisystem disease are associated with *BRAF* mutations. However, in patients with multisystem disease, mutations appear to arise in early myeloid precursors, whereas single-system disease seems to be caused by mutations occurring at a later stage of differentiation (eg, tissue-restricted mature dendritic cells).<sup>61</sup>

High-risk multisystem disease is also negatively correlated with age.<sup>45</sup> It was previously thought that diagnosis at <2 years of age portended a poor prognosis. However, Gadner et al<sup>125</sup> demonstrated that age itself does not predict prognosis, because there was no significant difference in treatment response between children <2 years of age without risk organ involvement and older patients.<sup>125</sup> Accordingly, the association of age with worse prognosis is likely because of the increased prevalence of high-risk multisystem disease in younger patients.

In conclusion, LCH is an inflammatory myeloid neoplasia attributed to activating mutations of the MAPK pathway in all patients. *BRAF*-V600E is the most prevalent mutation. While patients may present with LCH at any age, young children are most commonly affected. The clinical course varies from single-system disease, often with spontaneous resolution, to life-threatening, treatment-refractory multisystem disease. When LCH affects the skin, it typically presents as pinpoint erythematous or skin-colored papules or pustules mimicking eczema or seborrheic dermatitis. Most patients presenting with cutaneous disease also have systemic involvement. Identification of patients with risk organ involvement is essential, because these patients need more aggressive treatment.

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# Langerhans cell histiocytosis in children



## Diagnosis, differential diagnosis, treatment, sequelae, and standardized follow-up

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### Learning objectives

After completing this learning activity, participants should be able to recognize the recommended approach to initial evaluation and diagnosis, treatment, and follow-up in LCH patients; contrast the recommended treatment of single system as compared to multisystem disease and of children as compared to adults; identify and distinguish alternative diagnoses from LCH; and discuss the risk factors and management of potential sequelae.

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A definitive diagnosis of Langerhans cell histiocytosis (LCH) requires a combination of clinical presentation, histology, and immunohistochemistry. The inflammatory infiltrate contains various proportions of LCH cells, the disease hallmark, which are round and have characteristic “coffee-bean” cleaved nuclei and eosinophilic cytoplasm. Positive immunohistochemistry staining for CD1a and CD207 (langerin) are required for a definitive diagnosis. Isolated cutaneous disease should only be treated when symptomatic, because spontaneous resolution is common. Topical steroids are first-line treatment for localized disease of skin and bone. For multifocal single-system or multisystem disease, systemic treatment with steroids and vinblastine for 12 months is the standard first-line regimen. Current research is seeking more effective regimens because recurrence rates, which increase the risk of sequelae, are still high (30-50%) in patients with multisystem disease. An active area of research is the use of targeted therapy directed at the mitogen-activated protein kinase pathway. Adequate follow-up to monitor for disease progression, relapse, and sequelae is recommended in all patients. (J Am Acad Dermatol 2018;78:1047-56.)

**Key words:** BRAF; cladribine; clofarabine; cytarabine; diabetes insipidus; Langerhans cell histiocytosis; steroids; vinblastine.

## DIAGNOSTIC CRITERIA

### Key point

- A definitive diagnosis is made by the combination of clinical presentation, histology, and immunohistochemistry

Obtaining a biopsy specimen is mandatory for a diagnosis of Langerhans cell histiocytosis (LCH), and the skin is an easily accessible site in patients presenting with cutaneous signs; however, because Langerhans cell reactivity is not specific for LCH, the

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diagnosis should be reserved for the appropriate clinical context. Bone marrow aspiration and biopsy specimens are indicated in patients suspected of having multisystem disease presenting with cytopenia to rule out other causes of bone marrow failure.<sup>1</sup>

Histology reveals an inflammatory infiltrate of eosinophils, macrophages, regulatory T lymphocytes ( $\text{FoxP3}^+$  and  $\text{CD4}^+$ ), and multinucleated giant cells. Though eosinophilia is typically a prominent finding (particularly in bone lesions), the presence of eosinophils is not essential for diagnosis. LCH cells have a “coffee-bean” cleaved nuclei, rounded shape, and eosinophilic cytoplasm. Mitotic features and binucleate cells may occasionally be identified, but atypical mitosis and pleomorphism are typically not observed and should raise suspicion towards an alternative diagnosis, particularly Langerhans cell sarcoma.<sup>2</sup>

Skin biopsy specimens reveal predominant involvement of the papillary dermis with minimal involvement of the epidermis. Sinus involvement is essential for diagnosis when biopsy specimens are obtained from the lymph nodes.<sup>2</sup> Megakaryocyte dysplasia, emperipoleisis, and myelofibrosis are prevalent findings on bone marrow specimens, while  $\text{CD1a}^+$  LCH cells are less frequently identified.<sup>3</sup>

Though the detection of Birbeck granules by electron microscopy was once the criterion standard for diagnosis, it was laborious and difficult to reproduce.<sup>4</sup> It became obsolete with the development of staining for CD207 (langerin), which is a monoclonal antibody against Birbeck granules. Diagnosis is now confirmed by positive staining for CD1a and CD207 on immunohistochemistry.<sup>5</sup> Other useful markers include S100, CD68, peanut agglutinin, placental alkaline phosphatase, interferon-gamma receptor, human leukocyte antigen—antigen D related, and CD4. Nevertheless, none of these markers, including CD207 and CD1a, are exclusively specific to LCH, because they are expressed by mononuclear precursors and other derivatives. Therefore, the diagnosis requires a combination of clinical presentation, histology, and immunohistochemistry.<sup>2,6-9</sup>

## DIFFERENTIAL DIAGNOSIS

### Key points

- The diverse cutaneous presentation of LCH generates a broad differential
- Techniques to distinguish LCH from alternative diagnoses include immunohistochemistry, electron microscopy, and cultures

The differential diagnosis of LCH can be broad based on clinical presentation. Histology,

immunohistochemistry, electron microscopy, Tzanck preparations, bacterial, viral, and fungal cultures, and serology can be used to distinguish LCH from alternative diagnoses (Table I).

## EVALUATION AT INITIAL PRESENTATION, RELAPSE, OR PROGRESSION

### Key point

- A thorough history and physical examination for extracutaneous manifestations is indicated in all patients with LCH

The distinction between single-system and multisystem LCH is essential for prognosis and treatment, yet a physical examination and histology are not sufficient for reliable stratification.<sup>2</sup> The uncertainty of clinical course based on clinical and histologic findings warrants thorough evaluation and regular follow-up.<sup>24</sup>

A standardized initial evaluation is mandatory in all patients with LCH to define disease extent and tailor treatment intensity.<sup>25</sup> It includes a thorough history and physical examination with special attention to the skin, lymph nodes, ears, oral cavity, bones, lungs, thyroid, liver, central nervous system, and spleen. Assessment for stunted growth and symptoms of polyuria and polydipsia is also indicated. Recommended laboratory tests include a complete blood cell count, liver function tests, and electrolyte assessment. The minimal requirements for imaging assessment include a skeletal survey, chest radiography, and sonography of the liver and spleen. Additional laboratory tests and imaging are recommended upon specific indications (eg, endocrine evaluation and a magnetic resonance imaging scan of the brain in patients presenting with polyuria and polydipsia<sup>26</sup>).

## CONTEMPORARY TREATMENT APPROACH

### Treatment of cutaneous single-system LCH

#### Key points

- Topical steroids are first-line therapy for lesions few in quantity
- Systemic steroids with vinblastine (12 months) are first-line therapy for diffuse disease

There is no treatment protocol for isolated cutaneous disease. Recommendations are mainly based on case series rather than prospective controlled trials. In children with isolated cutaneous LCH, systemic therapy is only indicated for symptomatic or progressive disease, because isolated cutaneous involvement often resolves spontaneously.<sup>27,28</sup>

**Table I.** Differential diagnosis of Langerhans cell histiocytosis\*

Presenting symptoms	Differential diagnosis	Diagnostic tests
Erythematous scaly or crusted papules and patches, especially on the scalp and trunk	Seborrheic dermatitis, psoriasis, and atopic dermatitis	Skin biopsy for H&E stain
Macerated, erythematous patches localized to the neck, axilla, inguinal folds, or perineum	Intertrigo and inverse psoriasis	Culture, Wood's light examination, potassium hydroxide cytologic examination, skin biopsy for H&E stain
Pustules, vesicles, or petechiae and purpura	Impetigo, dermatophytosis, candidiasis, scabies, herpes simplex, varicella, cytomegalovirus, congenital candidiasis, and congenital syphilis	Culture, Wood's light examination, potassium hydroxide cytologic examination, skin biopsy for H&E stain, serology
Localized yellow or bronze-colored plaques and macules	Lichen aureus	Skin biopsy for H&E stain
Deep, painful acneiform nodules	Hidradenitis suppurativa or follicular occlusion syndrome	Skin biopsy for H&E stain, culture
Erythematous, flesh-colored, ulcerated, or umbilicated papules, plaques, or eroded vesicles isolated to the genitalia, with lesions accompanied by pain or pruritus	Allergic or irritant contact dermatitis, prurigo nodularis, arthropod bites, infectious diseases, such as scabies, herpes simplex, and candidiasis, and malignancies, such as squamous cell carcinoma, malignant melanoma, and extramammary Paget disease	Skin biopsy for H&E stain, culture, Wood's light examination, potassium hydroxide cytologic examination, and immunohistochemistry
Lymph node involvement	Lymphoma, sarcoidosis, Rosai–Dorfman disease, or cutaneous metastasis	Fine needle aspiration cytology, immunohistochemistry, serology, imaging, and skin biopsy for H&E stain
Red-brown papules and nodules with or without crust in a newborn	Erythema toxicum neonatorum, transient neonatal pustular melanosis, congenital leukemia cutis, neonatal erythropoiesis, disseminated neonatal hemangiomatosis, infantile acropustulosis, and the congenital TORCH infections	Wright stain, Gram stain, potassium hydroxide preparation, Tzanck smear, bacterial, viral, and fungal cultures, serology, skin biopsy for H&E stain, immunohistochemistry, flow cytometry, and bone marrow aspiration
Vesicles or eroded papules or nodules in a newborn	Incontinentia pigmenti and hereditary epidermolysis bullosa	Skin biopsy for H&E stain, genetic testing
Multisystem Langerhans cell histiocytosis in newborns, especially patients presenting with a blueberry muffin rash	Cutaneous metastasis, especially leukemia, neuroblastoma, rhabdoid tumor, rhabdomyosarcoma, primitive neuroectodermal tumor, choriocarcinoma, and adrenocortical carcinoma, TORCH infections, and blood dyscrasias	Skin biopsy for H&E stain, immunohistochemistry, bone marrow or lymph node biopsy, imaging, serology, Tzanck smear, and viral culture

H&amp;E, Hematoxylin–eosin; TORCH, toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis.

\*Data from multiple sources.<sup>10–23</sup>

Surgical resection of single lesions for diagnostic purposes is usually sufficient for cure. For lesions few in quantity, medium- to high-potency topical steroids are the first-line therapy. In addition to steroids, other topical treatment options include nitrogen mustard, imiquimod, and phototherapy. For diffuse extensive or symptomatic or progressive cutaneous disease, the combination of systemic

steroids with vinblastine for 6 to 12 months is recommended. First-line therapy is not always effective, with recurrence after discontinuation a common finding.<sup>29,30</sup> Many second-line therapies have been used in individual cases or small case series (eg, methotrexate, 6-mercaptopurine, azathioprine, vinca alkaloids, thalidomide, cladribine, cytarabine; Table II).

**Table II.** Therapies for isolated cutaneous disease\*

Therapy	
Nitrogen mustard	Use should be limited to severe, refractory disease because of the oncogenic potential and high rate of contact sensitivity. Preventative safety measures should be used (ie, focal application with thorough cleansing and sun protection, gloves, face masks, gowns, and specific hospital rooms)
Imiquimod	Case reports demonstrate resolution of lesions in treatment refractory children and adults within 5-6 months. Observed side effects are minimal and include irritation and minor bleeding. There have been reports of no recurrence on 2-year follow-up and recurrence successfully treated again with imiquimod
PUVA	Many case reports have demonstrated either complete or partial resolution in treatment-refractory adults. Resolution with slight hyperpigmentation may be achieved within 2 months. Recurrence may be treated successfully with repeated PUVA. Despite its success in adults, treatment in older children should only be of short duration and is typically contraindicated in children <12 years of age because of toxicity that includes nausea, vomiting, headaches, ocular and hepatic toxicity, photosensitivity, burning, and increased skin cancer risk
NB-UVB	NB-UVB is a safer option that has been effective in children and adults. Side effects, though common, are mild and include erythema, pruritus, xerosis, and burning. Many studies have published promising findings that NB-UVB is not associated with increased skin cancer risk; however, more research is needed to assess for long-term risk
Methotrexate	Methotrexate has led to complete resolution in refractory and recurrent adults within 2 months in a case report and retrospective analysis. Objective improvement was observed within a month in a case series studying combination treatment of methotrexate and prednisone in children. Therapy is well-tolerated, though mild elevation in liver enzymes may be observed
Azathioprine; 6-mercaptopurine	In adults, case reports have reported remission within 14 months with no recurrences on 10-year follow-up. Azathioprine is only considered in children in severe cases. A combination of 6-mercaptopurine with methotrexate has been successful in refractory children
Vitamin A and derivatives	Vitamin A and its derivatives (isotretinoin, acitretin) may result in resolution within 8 months without recurrence on 5-year follow-up (case reports)

NB-UVB, Narrowband ultraviolet B light phototherapy; PUVA, psoralen plus ultraviolet A light phototherapy.

\*Data from multiple sources.<sup>26,29-54</sup>

## Treatment of multisystem LCH

### Key points

- One year of vinblastine/prednisone is first-line therapy in patients with multisystem disease
- A standard of care for patients who do not respond to the first-line regimen has not been established
- Patients with low-risk disease have been successfully cured by application of other single drugs or drug combinations (eg, cladribine, cytarabine, and clofarabine)
- Successful salvage options for those with high-risk disease are a combination of cladribine and cytarabine or a hematopoietic stem cell transplantation

Systemic therapy containing steroids and vinblastine induces response and results in remission in the

majority of patients with multisystem LCH.<sup>55-57</sup> While the intensified therapy used in the LCH-II trial was more effective than that used in the LCH-I trial, the reactivation rate was still too high (Table III).<sup>57</sup>

In the LCH-III trial, patients were given an initial 6-week course of vinblastine and prednisone (with or without methotrexate), with a second initial course given in patients who were only partially responsive after 6 weeks. The initial treatment was followed by continuation therapy with vinblastine, prednisone, and 6-mercaptopurine to a total treatment duration of 1 year. Mortality and recurrence rates were significantly lower than those reported in LCH-I and LCH-II (Table III).<sup>57</sup> Confounding variables in LCH-III to consider include better salvage therapy that treats patients with poor response to initial treatment and improved supportive care.<sup>57</sup>

Therefore, the current standard first-line therapy for patients with multisystem LCH based on the

**Table III.** Comparison of Langerhans cell histiocytosis trial survival and recurrence rates in patients with risk organ involvement\*

Langerhans cell histiocytosis trial	5-year survival rate	5-year recurrence rate
LCH-I	62%	55%
LCH-II	69%	44%
LCH-III	84%	27%

\*Data from Gadner et al.<sup>57</sup>

cumulative knowledge of the LCH I-III trials of the Histiocyte Society consists of 6 to 12 weeks of initial therapy (daily oral steroids and weekly vinblastine injections), followed by pulses of prednisolone/vinblastine every 3 weeks, for a total treatment duration of 12 months.<sup>56-59</sup> Mercaptopurine is added to the prednisolone/vinblastine pulses during continuation therapy for patients with risk-organ involvement. Common toxicities of the first-line therapy are transient and include infection (48%), bone marrow suppression (28%), and hepatotoxicity (25%).<sup>56,57</sup> In addition to being first-line therapy, vinblastine/prednisone has been effective in cases of reactivation in nonrisk organs.

Treatment of patients who do not respond to standard first-line therapy and those who relapse is less well established. Cytarabine seems to be a promising candidate for the second-line treatment of nonrisk LCH. Cytarabine alone or in combination with vincristine and prednisone has also been effective in children with low-risk multisystem disease as either first- or second-line therapy. Initial findings were reported by Egeler et al,<sup>60</sup> who observed complete remission in 13 of 18 (72%) patients with refractory multisystem disease after treatment with vincristine, cytarabine, and prednisone. Subsequently, Morimoto et al<sup>61</sup> studied pediatric patients with multifocal single-system and multisystem disease treated with 6 weeks of induction therapy with cytarabine, vincristine, and prednisolone with 48-week maintenance therapy and cyclosporine, doxorubicin, cyclophosphamide, vincristine, and prednisolone salvage therapy in poor responders. Simko et al<sup>62</sup> recently published a series of patients successfully treated with cytarabine pulses. Testing cytarabine combination therapy with vincristine and prednisone is a key component of the current international clinical trial LCH-IV (NCT02205762).

Patients with risk-organ involvement who fail first-line treatment have a poor prognosis, which justifies treatment that is more intensive.

The current guidelines recommend switching patients with severe disease (hematopoietic or

hepatic dysfunction) who are not responsive to initial therapy to salvage options. Consistent with the recent attribution of disease pathogenesis to defects in myeloid stem cells, salvage therapies in refractory cases derive from leukemia treatment. Indeed, successful salvage options for those with high-risk LCH are a combination of cladribine and cytarabine<sup>61</sup> or hematopoietic stem cell transplantation.<sup>62</sup> The combination of cytarabine and cladribine is the current recommendation for patients with high-risk refractory disease.<sup>28</sup> However, it is extremely myelotoxic and requires expertise and facilities to provide maximal supportive care. Clofarabine is a relatively newer nucleoside analogue used in patients with refractory disease that has demonstrated efficacy in patients with both low- and high-risk disease and in those refractory to cladribine or cytarabine.<sup>28,63</sup> A drawback is its high cost relative to other therapies, but its favorable toxicity profile relative to higher dosages of other therapies or transplant may well offset the cost.<sup>64</sup> A current phase II clinical trial is studying clofarabine in patients with recurrent or refractory disease with and without risk organ involvement (NCT02425904).

Hematopoietic stem cell transplantation is another effective treatment option for patients with severe disease refractory to vinblastine/prednisone or salvage therapy.<sup>63,65-67</sup>

Reduced-intensity conditioning regimens are generally associated with lower treatment-related mortality (22%) and are the preferred option in children with organ dysfunction. However, Veys et al<sup>67</sup> recently reviewed 87 patients who underwent transplantation between 1990 and 2013. They reported a significant difference in survival between patients treated with myeloablative conditioning before 2000 (25% survival) and those treated after (77%). After 2000, they found similar 3-year survival rates in patients treated with myeloablative conditioning (77%) and reduced-intensity conditioning (71%) and did not find a significant difference in transplant-related mortality, although the difference might have been masked by the selection bias of more severe patients obtaining the reduced-intensity regimen.<sup>67</sup> In light of these findings, it is not yet known which conditioning regimen is the optimal choice.<sup>28</sup>

## TARGETED THERAPY

### Key point

- Targeted therapy is still an experimental highly individualized treatment option and an area of active research

**Table IV.** Therapy targeted at the mitogen-activated protein kinase pathway\*

Drug	Target	Efficacy	Side effects
Vemurafenib	BRAF inhibitor	Case reports/series: treatment results in rapid clinical improvement of severe refractory disease within a few days Phase 2 basket study: 43% response rate	Only indicated in severe disease because of association with malignancy, cutaneous side effects are frequent and severe Elevated liver enzymes; QT prolongation
Dabrafenib	BRAF inhibitor	Currently in phase 1 clinical trial in children with LCH	Associated with malignancy, arthralgia, hyperkeratosis, pyrexia, hyperglycemia, hypophosphatemia, and hyponatremia
Trametinib	MEK inhibitor	Case reports/series refractory non-LCH: rapid complete remission still observed on 6-month follow-up	Rash, diarrhea, peripheral edema, central serous retinopathy, and retinal vein occlusion
Cobimetinib	MEK inhibitor	Case reports/series refractory non-LCH: resolution within a month still observed on 6-month follow-up	Diarrhea, nausea, rash, arthralgia, and increased CPK and AST
Sorafenib	ARAF inhibitor	Case reports/series non-LCH: resolution within 3 months	Diarrhea, hypertension, and cutaneous (especially hand-foot skin reaction)

AST, Aspartate aminotransferase; CPK, creatine phosphokinase; LCH, Langerhans cell histiocytosis.

\*Data from multiple sources.<sup>80-91</sup>

Considering that the RAS-RAF-MEK-ERK-MAP kinase pathway is activated in all patients with LCH, including those with wild-type *BRAF*,<sup>68</sup> pharmacotherapy targeting this pathway in patients with known mutations seems a logical option. In addition, alternative treatments are highly needed, particularly in patients with primary refractory disease and in those with multiple recurrences, and *BRAF*-V600E mutations are associated with a higher risk of treatment refractory or recurrent disease in patients with both localized and disseminated disease.<sup>69,70</sup> For instance, patients with *BRAF* mutations have a lower response rate to first-line therapy with vinblastine/prednisone (78% vs 97%) and more require salvage therapy (19% vs 4%).<sup>70</sup> Of note, *BRAF*-V600E mutations are particularly associated with risk organ involvement (88%) as compared to 69% and 44% in patients with multisystem LCH without risk-organ involvement and single-system LCH, respectively.<sup>70</sup> The significant association between *BRAF*-V600E mutations and disease severity is important considering that patients with risk organ involvement are less responsive to therapy and require more aggressive treatment<sup>71,72</sup>; therefore, patients with high-risk disease (risk organ involvement at diagnosis and lack of response to first-line treatment) may be ideal candidates for targeted therapy. *BRAF*-V600E mutations are also prevalent in patients with irreversible neurologic (75%) and pituitary (73%) sequelae.<sup>70</sup> Resistance to treatment and strong association with risk organ involvement and permanent sequelae make it essential to effectively diagnose and treat patients with *BRAF*-V600E mutations.

In addition to their association with high-risk disease, *BRAF*-V600E mutations are also significantly associated with skin involvement.<sup>70</sup> It is therefore essential for dermatologists to be able to distinguish patients with *BRAF*-V600E mutations to refer them to pediatric hematologists or oncologists for aggressive treatment.

Targeted therapy directed at unique mutations in the mitogen-activated protein kinase (MAPK) pathway is an active area of research (Table IV). Targeted therapy must be highly individualized considering that mutations are prevalent in proteins other than *BRAF* and that there are different mutations in *BRAF* alone other than *BRAF*-V600E. Specifically, the RAS-RAF-MEK-ERK-MAP kinase pathway is activated in all patients with LCH, including those with wild-type *BRAF*.<sup>68</sup> Accordingly, mutations in genes encoding other proteins in the pathway, albeit less common, have also been identified. Besides *BRAF*, *MAP2K1* (ie, MAPK/ERK kinase) mutations are the most frequently implicated and have been reported in 33% to 50% of patients with wild-type *BRAF*.<sup>73-76</sup> Mutations in *KRAS*<sup>73</sup> and *ARAF*<sup>76</sup> have also been observed in rare cases. Other *BRAF* mutations and recurrent in-frame deletions, although less frequent, have also been reported.<sup>77,78</sup> Research is still needed to identify the mutations accounting for the remaining 20% to 25% of patients who have wild-type *BRAF* and *MAP2K1*.<sup>79</sup>

The clinical evidence is still limited and has been primarily derived from studies that included only adult patients.<sup>80-83</sup> Additional studies in children are needed to address the most pertinent issues

(eg, spectrum and severity of side effects, appropriate dosing, appropriate treatment duration; is definitive cure with single inhibitor possible at all) before broader clinical use.

## SEQUELAE

### Key points

- **The most frequent permanent consequences include diabetes insipidus, anterior pituitary hormone deficits, orthopedic problems, hearing loss, and neurodegeneration**
- **Long-lasting disease activity and recurrences increase the risk for sequelae**

The most frequent sequelae of LCH include diabetes insipidus (24%), orthopedic problems (20%), hearing loss (13%), and neurologic sequelae (11%).<sup>92</sup> After diabetes insipidus, the second most common neurologic sequela is neurodegenerative LCH, which has a varied clinical presentation ranging from asymptomatic magnetic resonance imaging findings (also referred to as “radiologic” central nervous system LCH) to dysphagia, ataxia, dysarthria, altered reflexes, and psychiatric disease.<sup>93</sup> The most common orthopedic sequelae include vertebral collapse and facial asymmetry. Jaw problems, scoliosis, and limb asymmetry may also occur.<sup>92</sup>

Of patients with multisystem disease, 71% develop sequelae, while only 24% of patients with single-system LCH develop sequelae.<sup>92</sup> Among patients with multisystem LCH, sequelae develop in ≤71% of patients with reactivations and only 25% of patients without reactivations.<sup>94</sup> Accordingly, risk factors associated with an increased recurrence rate, such as multisystem disease and *BRAF* mutations, are also associated with an increased risk of developing sequelae.<sup>69,76,95</sup> Neurologic and pituitary sequelae are particularly associated with *BRAF* mutations (observed in 75% and 73% of cases, respectively).<sup>70</sup> An additional risk factor for sequelae is craniofacial bone lesions. Patients with craniofacial bone lesions have a higher risk of diabetes insipidus, neurologic sequelae, and hearing loss.<sup>92</sup>

## STANDARDIZED FOLLOW-UP

### RECOMMENDATIONS

#### Key points

- **Isolated cutaneous LCH should be closely monitored (every 2-4 weeks), particularly if left untreated**
- **Regular follow-up is recommended in all patients; those with isolated cutaneous LCH should be followed every 6 months for 5 years after complete regression**

Observation is recommended in all patients once the diagnosis is clear to monitor for progression to potentially life-threatening, multisystem disease or reactivation of disease that had been responsive to therapy. Eighty-eight percent of reactivations occur within the first 2 years of follow-up, most commonly in the bone, skin, middle ear, and hypothalamus.<sup>94</sup> Nevertheless, it is essential to monitor patients past the initial 2 years, because some of the sequelae (eg, neurodegeneration) may occur many (>10) years after initial diagnosis.<sup>92</sup>

In isolated cutaneous disease, lesions should be assessed every 2 to 4 weeks during active disease with continued assessment for signs of multisystem involvement. After complete regression, follow-up every 6 months is advised for ≥5 years.<sup>30</sup>

In conclusion, LCH is an inflammatory myeloid neoplasia attributed to activation of the MAPK pathway in all patients. Obtaining a biopsy specimen is essential for diagnosis, which is confirmed by positive staining for CD1a and CD207 on immunohistochemistry. Evaluation must include an assessment for extracutaneous involvement to dictate treatment. First-line treatment of multisystem disease consists of steroids and vinblastine for 1 year, while systemic therapy is only indicated for isolated cutaneous disease in symptomatic or progressive cases. Topical steroids are indicated for lesions of minimal quantity, while systemic steroids and vinblastine are recommended for diffuse, symptomatic, or progressive disease. Considering the significance of MAPK pathway activation to disease pathogenesis and the association between *BRAF*-V600E mutations and high risk, treatment refractory, or recurrent disease, individualized targeted therapy directed at mutations in the MAPK pathway, especially *BRAF*-V600E, is an active area of research, and patients with high-risk disease may be ideal candidates for targeted therapy. Regular follow-up for ≥5 years is recommended in all patients to assess for disease recurrence or progression.

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## Dermatoses caused by cultural practices

### Therapeutic cultural practices

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#### Learning objectives

After completing this learning activity, participants should be able to recognize that physicians need to be aware of cultural practices due to increased globalization and awareness of these practices among the general public; identify common dermatologic diseases that can be attributed to therapeutic cultural practices; and identify common dermatologic disease that can be attributed to cosmetic cultural practices.

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With globalization and widespread immigration, physicians increasingly encounter patients from varying backgrounds and diverse customs. Although certain cultural practices are widely performed, there is limited medical literature describing their dermatologic and systemic effects and complications. Population diversity and sharing of traditions make it increasingly important for dermatologists to understand the role of cultural practices and recognize physiologic and pathologic sequelae. In addition, dermatologists are often adjured to assess skin findings that may be mistaken for abuse. Child abuse misdiagnosis can be traumatizing to all those involved, and immigrant families with limited English proficiency may have difficulty explaining their traditional practices. The first article of this 2-part continuing medical education series begins with a review of therapeutic cultural practices, including traditional Chinese medicine, Ayurveda, acupuncture, cupping, moxibustion, and coining, and the clinically relevant complications that may occur. Therapeutic practices can cause a range of complications, including contact dermatitis, heavy metal toxicity, and severe cutaneous adverse reactions. (J Am Acad Dermatol 2018;79:1-16.)

**Key words:** alternative; complementary; globalization; integrative; therapeutic.

## COMPLEMENTARY AND ALTERNATIVE MEDICINE

### Key points

- Complementary and alternative medicine is used worldwide, ranging from a prevalence of 27% to 76% in different populations

#### Abbreviations used:

CAM: complementary and alternative medicine  
RCT: randomized controlled trial  
TCM: traditional Chinese medicine

- Nonvitamin, nonmineral natural products, including fish oil, glucosamine, echinacea,

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## and flaxseed, are the most commonly used complementary and alternative medicines

Complementary and alternative medicine (CAM) includes a variety of practices that are traditionally not considered part of standard conventional medical care. What is defined as CAM often occurs within a cultural context and may have limited scientific evidence supporting its medical use. Complementary medicine is used in conjunction with conventional medical care, whereas alternative medicine is used as a substitute. As few relinquish conventional medicine, the term integrative medicine is increasingly used, which blends conventional medicine, complementary therapies, and lifestyle changes. With the focus on the whole person, CAM includes multiple modalities to improve physical, emotional, and mental health. The most commonly used CAMs are nonvitamin, nonmineral natural products, including fish oil, glucosamine, echinacea, and flaxseed.<sup>1</sup> Vitamin/mineral and herbal supplements are the most commonly used type of CAM in patients with skin disease.<sup>1</sup>

The prevalence of CAM use is high among the US population. According to 2012 data from the Centers for Disease Control and Prevention, 33.2% of adults and 11.6% of children reported using some form of CAM in the previous 12 months.<sup>2,3</sup> The number of annual visits to alternative providers has been estimated at 629 million, which is higher than the number of yearly primary care visits. Women (37.4%) compared to men (28.9%) and persons with higher levels of education (42.6% with a college degree or higher compared to 15.6% with less than a high school diploma) and higher incomes (38.4% of not poor compared to 20.6% of poor) were more likely to use CAM.<sup>2</sup> Rates of CAM use vary by race and ethnicity: non-Hispanic whites have the highest reported usage at 37.9%, whereas non-Hispanic blacks (19.3%) and Hispanics (22.0%) had the lowest usage.<sup>2</sup> CAM is used around the world: 27% of Irish, 60% of Canadian, and 76% of Japanese adults reported use within the previous 12 months.<sup>4-6</sup> Patients with skin disease are also more likely to use CAM compared with the baseline population, with reported lifetime use ranging from 35% to 84.5%; however, it has been reported that only 1.1% to 6% have used CAM specifically for skin disease treatment.<sup>1,7,8</sup>

## TRADITIONAL CHINESE MEDICINE

### Key points

- Traditional Chinese medicine is a multimodal health system that holistically treats

a variety of diseases with individualized therapies

- Dermatologic uses include atopic dermatitis, psoriasis, and vitiligo
- Complications are highly variable, ranging from minor gastrointestinal upset to serious liver, renal, cardiac, and cutaneous toxicity

### Background

Traditional Chinese medicine (TCM) is a form of alternative medicine with 5 branches: acupuncture and moxibustion, herbology, Qigong healing, Tuina therapeutic massage, and dietary therapy.<sup>9,10</sup> It focuses on a holistic treatment regimen that treats each individual based on their mental and physical well-being.<sup>11</sup> Herbal remedies are prescribed as capsules, tablets, pills, powders, decoctions or herbal concentrates, teas, topical ointments, and injections.<sup>12</sup> Individuals obtain TCM from a variety of sources, including hospitals, clinics, pharmacies, chiropractors, herbalists, supermarkets, family, friends, and the Internet.<sup>12,13</sup> In China, TCM accounts for about 40% of health care delivered and is used to treat roughly 200 million patients annually.<sup>14</sup> It is also commonly used in pediatric patients, and more so by those from urban rather than rural areas.<sup>15</sup>

### Therapeutic applications

TCM is prescribed for a variety of diseases, including neurologic, gastrointestinal, obstetric/gynecologic, and dermatologic conditions.<sup>16</sup> TCM users apply topical herbal preparations for a range of ailments, including headaches, abdominal pain, muscle strain, and cutaneous disease (ie, eczema, fungal infections, and arthropod bite reactions).<sup>17</sup> One survey found that between 1990 and 1997, 8.6% persons in the United States used TCM for the treatment of dermatologic disorders.<sup>16,18,19</sup>

Given the focus on individualized therapy, randomized controlled trials (RCTs) determining the efficacy of TCM are difficult to conduct, and, overall, the majority of studies suffer from poor randomization and blinding.<sup>17</sup> In 1 pivotal study, it was shown that ingestion of a 10-herb decoction (*Ledebourreilla seseloides*, *Potentilla chinensis*, *Aelia clematidis*, *Rehmannia glutinosa*, *Paeonia lactiflora*, *Lophatherum gracile*, *Dictamnus dasycarpus*, *Tribulus terrestris*, *Glycyrrhiza uralensis*, and *Schizonepeta tenuifolia*) significantly decreased erythema in adult patients with atopic dermatitis.<sup>20</sup> The available literature on TCM is limited with no overall consensus on its efficacy. A review of the published literature is provided in Table I.

## Complications

Despite the popularized belief that TCM is natural, safe, and has no side effects, there have been numerous reported adverse events. Given the lack of current regulation of TCM, it can be difficult for both patients and prescribers to know exactly what ingredients are included in preparations that can have both intrinsic toxicity along with adulteration, substitution, contamination, and mislabeling.<sup>12</sup> Overall, rates of contamination range from 4.5% to 23.7%.<sup>12,13</sup> In 1 study, 26% of unlicensed products and 8.5% of licensed products were adulterated, showing the possibility of a significant proportion of adulterated medicines passing current testing methods.<sup>13</sup>

Benzodiazepines, corticosteroids, muscle relaxants, diuretics, nonsteroidal antiinflammatory drugs, antihistamines, and acetaminophen have been found in oral herbal medications with a variety of reported adverse reactions, including acute liver failure, dilated cardiomyopathy, and acute respiratory distress syndrome.<sup>17,30-32</sup> Severe cutaneous adverse reactions, including toxic epidermal necrolysis, Stevens–Johnson syndrome, acute generalized exanthematous pustulosis, and drug reaction with eosinophilia and systemic symptoms have additionally been reported with oral preparations.<sup>33-35</sup> Prevalence rates for severe cutaneous reactions per 1000 patients were as follows: overall, 0.32; Stevens–Johnson syndrome, 0.15; toxic epidermal necrolysis, 0.04; and drug reaction with eosinophilia and systemic symptoms, 0.07.<sup>34</sup> Patients can unwittingly overdose on medications if they are using an adulterated traditional medicine and prescribed Western pharmaceuticals. A case of methotrexate toxicity has been reported because of the concomitant use of red clover.<sup>36</sup>

Another safety issue with herbal remedies is that they may contain microbial toxins, pesticides, fumigants, and heavy metals.<sup>12</sup> Heavy metal levels exceeding legal limits of mercury, arsenic, lead, and copper have been found in both oral and topical medications. They are often intentional ingredients, although manufacturing and processing methods may further contaminate medications.<sup>12</sup> In several reports, arsenic toxicity led to the development of squamous cell carcinoma, multiple cases of Bowen disease, palmoplantar keratoses, and pigmentary anomalies.<sup>37,38</sup> Unique cutaneous signs of mercury toxicity include gingivitis, stomatitis, and acrodynia, while cadmium toxicity can cause yellowing of the teeth.<sup>39</sup> In addition, topical herbal medications are well known to cause allergic contact dermatitis and photosensitization.<sup>40-42</sup> Complications that have

been associated with use of Chinese herbal medications are shown in Fig 1 and Table II.

## AYURVEDIC MEDICINE

### Key points

- **Herbal remedies, minerals, specific diets, and blood-letting constitute therapies provided in Ayurveda**
- **Dermatologic uses include psoriasis, molluscum contagiosum, and vitiligo**
- **Toxic levels of inorganic arsenic, mercury, lead, and cadmium have been found**

### Background

Considered India's counterpart to TCM, Ayurveda is practiced in conjunction with Western medicine and other traditional systems, such as yoga, Unani, Siddha, and homeopathy.<sup>89,90</sup> This practice's popularity has transgressed India. In the United States, 750,000 adults have reported Ayurvedic consultation at some point.<sup>39</sup> The basic theory behind Ayurvedic medicine is that there are 3 main forces or doshas, and it is an imbalance of “vaata,” “pitta,” and “kapha” that cause disease. Diagnosis in Ayurvedic medicine requires examining a patient's physique, pulse, and urine in addition to typical history and physical examination techniques.<sup>89</sup> Herbal remedies, minerals, specific diets, and blood-letting constitute therapies provided in Ayurveda. Herbs are often dispensed to patients as entire plants, pastes, pills, suppositories, oils, and lotions, with remedies including minerals containing mixtures of gold, silver, copper, and heavy metals.<sup>52,89</sup>

### Therapeutic applications

Ayurvedic remedies are prescribed for a variety of diseases, including dermatologic disorders. Limited studies exist in the literature. Mehta et al<sup>91</sup> found that 2 Ayurvedic compound medications (navayasa rasayana leha and dhatryadhyo lepa) equally improved the quality of life in patients with psoriasis (67.6–70.3% reported relief).<sup>91</sup> Ayurvedic medications (pratisaraniya knara and bilvadi agada) were found to be efficacious in the treatment of molluscum contagiosum infection in 3 patients who all reported clearance.<sup>92</sup> Working to integrate Ayurvedic and allopathic dermatology treatments, Narahari et al<sup>90</sup> and Ryan and Narahari<sup>93</sup> created protocols for vitiligo and lymphedema. Patients with lymphedema saw a reduction in inflammatory episodes from 80.4% to 8.6% within 2 to 3 weeks and a 39% reduction in limb volume using this multidisciplinary approach.<sup>93</sup>

**Table I.** Summary of traditional Chinese medicine studies for dermatologic use

Study (year)	Study details	Sample size (n)	Conclusions	Level of evidence
Sheehan et al <sup>20</sup> (1992)	Placebo-controlled, double-blind, cross-over trial	40	Topical application of a 10-herb blend significantly decreased erythema (geometric mean score 12.6 compared to 113 for placebo group $P < .0005$ ) and surface involvement (geometric mean score 11.3 compared to 111 for placebo group $P < .0005$ ) in patients with atopic dermatitis	1B
Fung et al <sup>11</sup> (1999)	Placebo-controlled, double-blind, cross-over trial	37	No significant benefit from topical application of the same 10-herb blend used by Sheehan et al <sup>20</sup> in patients with atopic dermatitis (erythema relative risk -0.69, $P = .233$ ; surface damage relative risk -0.69, $P = .518$ ; lichenification relative risk -1.10, $P = .159$ ; scaling relative risk -0.05, $P = .558$ )	3B
Lin et al <sup>21</sup> (2009)	Laboratory case series	6	Indigo naturalis decreased the percentage of proliferating cell nuclear antigen-positive keratinocytes (52.11% vs 26.95%, $P < .005$ ), reduced the number of keratinocytes, ( $57.9 \pm 4.5\%$ , $P < .005$ ), and inhibited cell cycle progression (75.53% of cells in G <sub>0</sub> /G <sub>1</sub> compared to 52.94% in control cells) in a study of psoriasis markers	4
Yu et al <sup>22</sup> (2013)	Metaanalysis	1226 from 8 studies	Combining an herbal medicine bath with phototherapy is efficacious for the treatment of psoriasis; PASI-60 scores significantly reduced in combined group with risk ratio 1.25 (95% CI 1.18-1.32)	1A (of note, studies included of low quality)
Lin et al <sup>23</sup> (2014)	Randomized, observer-blind, vehicle-controlled trial	31	Indigo naturalis is efficacious for the treatment of nail psoriasis (single-hand and modified target Nail Psoriasis Severity Index scores significantly reduced compared to olive oil, $P < .001$ )	1B
Gu et al <sup>24</sup> (2014)	Metaanalysis	1058 from 10 studies	No evidence that topical herbal Chinese medicine is efficacious for atopic dermatitis compared to corticosteroid creams (standardized mean difference -0.05 [95% CI -0.88 to 0.78]); metaanalysis showed topical herbal Chinese medicine was superior to conventional medications (risk ratio 1.19 [95% CI 1.04-1.36])	1A
Liu et al <sup>25</sup> (2015)	Multicenter, randomized, controlled, parallel-group, prospective, assessor-blind trial	220	Use of herbal remedies in patients with atopic dermatitis significantly decreased the mean Scoring Atopic Dermatitis Index ( $P = .002$ at 28 weeks and $P < .001$ at 36 weeks) and significantly improved quality of life ratings ( $P < .001$ )	1B
Chen et al <sup>26</sup> (2015)	Retrospective cohort study	18,024	Concurrent use of TCM reduces exposure to any corticosteroids in children with atopic dermatitis (42.1% vs 34.5% in TCM nonusers with relative risk 0.36, $P < .001$ ) and resulted in shorter duration of steroid use (relative risk 0.37, $P < .001$ )	2B

Yang et al <sup>27</sup> (2015)	Metaanalysis	1342 from 17 studies	Combining herbal medicines with phototherapy is efficacious for the treatment of psoriasis (PASI 60 significantly reduced in combination group 83% vs 59%, RR = 1.35, 95 % CI 1.26-1.45, $P < .01$ ). Despite findings, authors report low quality of evidence	1A (of note, studies included of low quality)
Chen et al <sup>28</sup> (2016)	Metaanalysis	513 from 5 RCTs	Combining herbal medicines with phototherapy is efficacious for the treatment of vitiligo compared to phototherapy alone (risk difference 0.22, 95% CI 0.14-0.29, $P < .00001$ )	1A (of note, studies included of low quality)
Yao et al <sup>29</sup> (2016)	Double-blind, randomized, placebo-controlled trial	17	Combining an oral herbal medication with topical calcipotriol and calcipotriol+betamethasone reduces recurrence of moderate to severe psoriasis vulgaris (17% relapse rate in combined group compared to 67% in placebo group, $P = .118$ )	1B

CI, Confidence interval; PASI 60, 60% reduction in Psoriasis Area and Severity Index score; RCT, randomized controlled trial; RR, relative risk; TCM, traditional Chinese medicine.



**Fig 1.** Traditional Chinese medicine. Erythema multiforme-like eruption after application of a Chinese herbal paste to the right shoulder.

### Complications

Like other forms of CAM, including TCM, those who use Ayurvedic remedies believe them to be safe and without adverse events. However, in 1 study, 30% of patients with contact dermatitis had tried an alternative medicine for their condition and 12% of those were a form of traditional Indian medicine.<sup>94</sup> Heavy metal toxicity has been associated with use of Ayurvedic therapies.<sup>39,53-55</sup> Although some studies have found heavy metal content of the plants used in Ayurveda to be within normal limits, toxic levels of inorganic arsenic, mercury, lead, and cadmium have been found in oral medications.<sup>56</sup> One study investigated the content of 70 products and found concentrations ranging from 5 to 37,000  $\mu\text{g/g}$  of lead ( $\geq 5 \mu\text{g/g}$  in adult venous blood is considered toxic),<sup>95</sup> 28 to 104,000  $\mu\text{g/g}$  of mercury (toxicity level not conclusively defined), and 37 to 8130  $\mu\text{g/g}$  of arsenic (toxic level determined by urine concentration).<sup>54</sup> Toxicity from these heavy metals can lead to permanent disability (Table II).

### ACUPUNCTURE

#### Key points

- Acupuncture stimulates acupoints using needles, pressure, and heat to alter energy flow
- Dermatologic uses include acne, atopic dermatitis, psoriasis, and urticaria
- Complications are highly variable from minor bleeding to infection, anaphylaxis, and rarely death

## Background

Acupuncture is a subset of TCM that involves stimulating specific points on the body, known as acupoints, using needles, pressure, and heat in order to restore balance to the body's energy flow (Fig 2).<sup>96</sup> The underlying philosophy involves altering the vital energy (Qi) between different organs. The predominating styles include the Chinese approach, which involves manual stimulation, and the Japanese approach that does not.<sup>76,97</sup> The popularity of acupuncture has been growing internationally. In the United States, 1.4% of adults reported using acupuncture over the previous year.<sup>98</sup>

Possible acupuncture tools have been found that are believed to date back to 500,000 to 300,000 BC.<sup>99</sup> The term acupuncture encompasses a variety of techniques. Traditional use involves the placement of disposable sterile needles (30-36 gauge) into specific points on the body.<sup>17</sup> Filiform needles are used to puncture acupoints, ear needles to puncture microacupoints on the ear, lancet or blood-letting needles to puncture superficial engorged veins, and cutaneous needles (known as the 7-star or plum blossom needle) to puncture the superficial skin.<sup>97</sup> Electroacupuncture involves electrically stimulating these needles. Other acupuncture variations include bee venom, ah shi point, embedding, ultrasound, laser, aqua, and point application therapy.<sup>61,63,64,66,70,100,101</sup> Nonneedle techniques include acupressure and transcutaneous electrical nerve stimulation.<sup>102</sup>

## Therapeutic applications

Acupuncture has been used to treat a variety of disorders, including dermatologic disorders (acne, psoriasis, atopic dermatitis, acute and chronic urticaria, alopecia, pruritus, rosacea, impetigo, vitiligo, tinea, verrucae, melasma, dermatitis herpetiformis, hyperhidrosis, herpes zoster, and varicella), postherpetic neuralgia, arthritis, systemic lupus erythematosus, leprosy, depression, insomnia, Alzheimer disease, ulcerative colitis, trigeminal neuralgia, breast inflammation, stroke rehabilitation, Bell's palsy, and pain.<sup>59,63,70,96,97,99,103-105</sup> Cosmetic uses include treatment for rejuvenation and rhytides.

Although evidence-based literature is lacking, systematic reviews have found that acupuncture is efficacious in the treatment of nausea and vomiting, histamine-induced pruritus, atopic dermatitis with type I hypersensitivity pruritus, verrucae, primary hyperhidrosis, melasma, and pain.<sup>76,96,103,105-108</sup> It has been shown to be efficacious in 3 RCTs for chronic urticaria ( $n = 61$ , 32, and 40, respectively).<sup>109-111</sup> One study found that acupuncture with point injection of diphenhydramine at

acupoints had a significant therapeutic effect in urticaria compared to acupuncture alone (90.6% vs 68.8% effective rate, respectively,  $P < .05$ ).<sup>110</sup>

Less rigorous study has been conducted for postherpetic neuralgia, acne, and psoriasis. Lewith et al<sup>112</sup> suggested that the low incidence of postherpetic neuralgia seen in China may be because of the routine use of acupuncture in patients with shingles; however, the results of several uncontrolled and 1 controlled study have shown positive, negative, and null results, with the 1 RCT showing acupuncture as effective as placebo ( $n = 62$ ).<sup>97,112-116</sup> In 1 RCT of 36 patients with acne, 12 sessions of either generalized acupuncture or inflammatory lesion targeted acupuncture led to a reduction in the total number of inflammatory lesions, improved subjective symptoms, and improved Skindex-29 scores.<sup>100</sup> Mixed results have been found in psoriasis, with the 1 RCT finding that generalized acupuncture was not superior to sham procedure; however, this was criticized for not properly describing the technique used.<sup>97,99,101,117</sup> Acupuncture has not been found to be efficacious in smoking cessation, weight loss, or secondary Raynaud phenomenon.<sup>76,118</sup>

## Complications

Complications that have been associated with acupuncture therapy are shown in Table II. Some minor complications appear to be quite common.<sup>59,76</sup> Minor complication rates depend on many factors, including acupuncturist expertise and style along with the body area treated.<sup>17</sup> Studies have shown that 0.03% to 38% of cases lead to bleeding, and hematomas occur at a rate between 0.33% to 7.6%.<sup>76</sup> Localized argyria and silica granulomas have both been reported twice, with symptoms sometimes appearing after decades because of the long latency period.<sup>65,72,119,120</sup> Although 1 metaanalysis of 9 prospective studies of almost 250,000 treatments found no cases of local infection,<sup>76</sup> a subsequent review found 204 primary reports and 91 secondary reports of infection associated with acupuncture treatment, with >60% being hepatitis B. As a complication of auricular acupuncture, the second most common infection was that of the external ear.<sup>60</sup> In a case series, infections caused by acupuncture consisted of 5 cases of atypical mycobacterium and 1 case of mucormycosis; however, this study has been criticized for its methodology and overrepresentation of less common types of acupuncture, specifically herbal and bee venom.<sup>59,121</sup>

Acupuncture can also cause koebnerization and pathergy.<sup>73</sup> Severe complications are rare; however,

**Table II.** Summary of therapeutic cultural practices

	Dermatologic complications	Systemic complications
Traditional Chinese medicine	Burning, <sup>19,43</sup> pruritus, <sup>19,44</sup> photosensitivity, <sup>17,19,43,45</sup> contact dermatitis, <sup>17,19,30,40,41,44-46</sup> Stevens-Johnson syndrome, <sup>19,30,33,34,40</sup> Sweet syndrome, <sup>19</sup> pellagra, <sup>19</sup> toxic epidermal necrolysis, <sup>33,34,40,45</sup> acute generalized exanthematous pustulosis, <sup>33,40</sup> drug hypersensitivity syndrome, <sup>33,40</sup> exfoliative dermatitis, <sup>34,44</sup> erythroderma, <sup>19,30,45</sup> drug reaction with eosinophilia and systemic symptoms, <sup>34</sup> and erythema ab igne <sup>47</sup>	Dizziness, <sup>44</sup> chills/fever, <sup>19,44</sup> heavy metal toxicity, <sup>9,12,17,37,38,40,45</sup> gastrointestinal upset, <sup>44,48</sup> liver and renal toxicity, <sup>9,11,19,30,36,44,45</sup> dilated cardiomyopathy, <sup>11,19,30,45</sup> eucalyptus intoxication, <sup>19</sup> yohimbine toxicity syndrome, <sup>19</sup> kava toxicity syndrome, <sup>19</sup> acute respiratory distress syndrome, <sup>30,44,45</sup> and anaphylactic shock <sup>19,33,44,45</sup>
Ayurvedic medicine	Irritant and allergic dermatitis <sup>49,50</sup> and burns <sup>51</sup>	Heavy metal toxicity. <sup>17,39,52-58</sup> weight gain, <sup>57</sup> hypertrichosis, <sup>52,57</sup> depigmentation, <sup>52,57</sup> and sepsis <sup>57</sup>
Acupuncture	Bleeding, <sup>17,59,60</sup> hematoma, <sup>17,59</sup> sweating, <sup>61</sup> dermal spread of breast cancer, <sup>62</sup> foreign-body granuloma, <sup>17,59,63-65</sup> mycobacterial infection, <sup>59,60,66,67</sup> atrophic scarring, <sup>17,68</sup> erythema nodosum, <sup>69</sup> keloids, <sup>59</sup> giant dermatofibroma, <sup>70</sup> cutaneous tuberculosis, <sup>71</sup> localized cutaneous argyria, <sup>60,72</sup> epidermal cysts, <sup>61</sup> prurigo nodularis, <sup>62</sup> lipoatrophy, <sup>59</sup> cutaneous mucormycosis, <sup>59</sup> koebnerization, <sup>60</sup> pyoderma gangrenosum, <sup>59,60,73</sup> infection with herpes simplex virus, <sup>74</sup> and factitial panniculitis <sup>75</sup>	Pain, <sup>60</sup> fatigue, <sup>76</sup> syncope, <sup>61</sup> pneumothorax, <sup>17,60</sup> central nervous system injury, <sup>60</sup> cardiac arrest, <sup>60</sup> hepatitis B and HIV infection, <sup>60</sup> anaphylactic shock, <sup>59,64</sup> and death <sup>60</sup>
Moxibustion	Allergic reactions, <sup>77</sup> erythema ab igne, <sup>78</sup> burns, <sup>17,77,79,80</sup> hyperpigmentation, <sup>77</sup> blistering, <sup>51</sup> pruritus, <sup>81</sup> keloids, <sup>81</sup> cellulitis, <sup>77</sup> abscess, <sup>77</sup> and allergic contact dermatitis <sup>77</sup>	Hepatitis C, <sup>77</sup> fatigue, <sup>77</sup> abdominal pain, <sup>77</sup> headache, <sup>77</sup> pregnancy-related (premature birth, premature rupture of membranes, and preeclampsia) <sup>77</sup>
Cupping	Panniculitis, <sup>17,75,82</sup> ulcer, <sup>83</sup> burns, <sup>79,83,84</sup> koebnerization, <sup>85,86</sup> and erythema ab igne <sup>78</sup>	
Coining and spooning	Contact dermatitis <sup>81</sup> and burns <sup>17,84,87</sup>	Transient microscopic hematuria, <sup>79</sup> cerebellar hematoma with herniation, <sup>79,88</sup> and camphor toxicity <sup>81</sup>

pneumothorax, central nervous system injury, cardiac arrest, HIV infection, anaphylactic shock, and even 12 primary reports of death have been reported.<sup>17,59,60,64</sup> Data from 12 prospective studies surveying a total of >1 million treatments estimates the risk of a serious adverse event with acupuncture to be 0.05 per 10,000 treatments and 0.55 per 10,000 individual patients.<sup>60</sup>

## MOXIBUSTION

### Key points

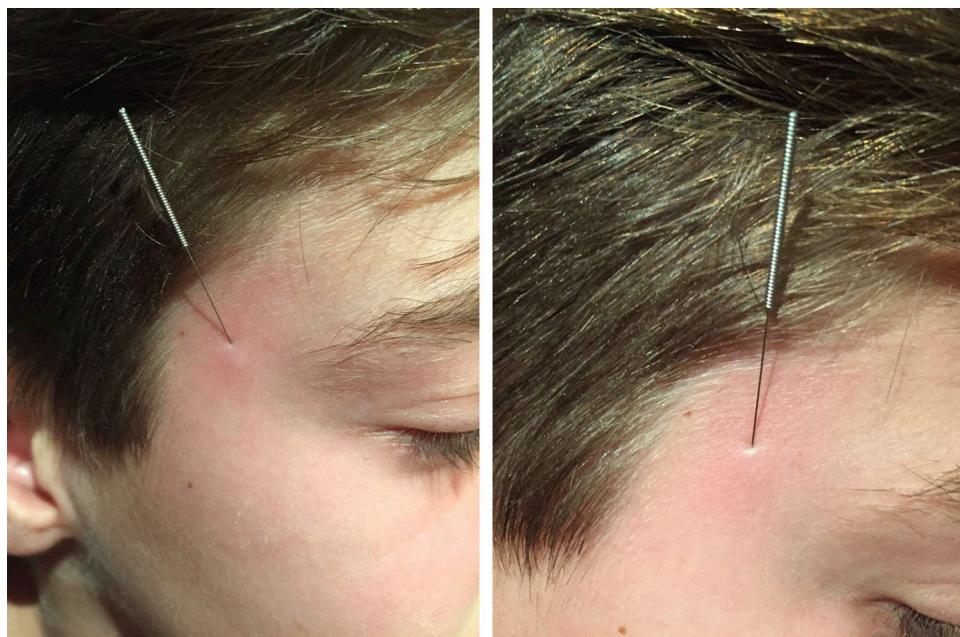
- Moxibustion involves the burning of moxa herb onto or near the skin

- Therapeutic uses range from fever and verrucae to stroke rehabilitation and cancer care

- Lesions classically mimic cigarette burns and can be confused for child abuse

### Background

Moxibustion is a remedy used in various Asian cultures. A similar practice called toullmos is performed in Finland among the Lapp population.<sup>79</sup> In moxibustion, pieces of *Artemisia vulgaris*, known as moxa, are rolled into a cone and burned over acupuncture points (Fig 3). In direct moxibustion, the moxa are burned directly on the skin (Fig 4). They are removed once pain is felt by



**Fig 2.** Acupuncture treatment to the right lateral forehead using filiform needles. Courtesy of Daniel Zancanaro, MD.



**Fig 3.** Moxibustion. *Artemisia vulgaris* known as moxa rolled into a cone. Courtesy of Daniel Zancanaro, MD.

the patient. In indirect moxibustion, the more common practice, insulating materials of 1 to 2 cm of space are placed between the skin and moxa.<sup>77,84</sup> Another technique is to burn moxa on top of acupuncture needles (Fig 4).

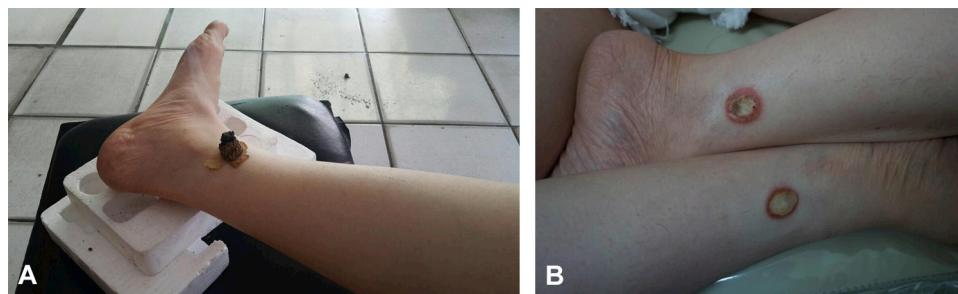
### Therapeutic applications

Practitioners believe moxibustion to be efficacious in treating a variety of disorders, including



**Fig 4.** Direct moxibustion on the upper back and indirect moxibustion using acupuncture needles on the lower back.

fever, abdominal pain, digestive disorders, enuresis, temper tantrums, verrucae, and breech presentation. In addition, it is used for stroke rehabilitation and cancer care.<sup>77,79,80</sup> In 1 published case series, direct moxibustion was found to be effective in treating cutaneous warts, likely because of tissue damage.<sup>80</sup> However, there is still insufficient evidence



**Fig 5.** Moxibustion performed for hemorrhoid treatment with placement of thin slices of ginger below the moxa near the medial ankle (**A**) and subsequent development of third-degree burns on the same area (**B**).

regarding its effectiveness. In a systematic review of 47 RCTs, moxibustion was more effective than medication in 2 ulcerative colitis trials; however, the overall results did not support moxibustion effectiveness for specific diseases because of the limited number, inadequate use of controls, and low quality of studies.<sup>122</sup>

### Complications

Complications associated with moxibustion are included in Table II. Burns have been reported more frequently in patients undergoing indirect compared to direct moxibustion, although this may be because of the greater number of patients undergoing indirect moxibustion rather than an inherent increased risk (Fig 5).<sup>77</sup> Allergic reactions caused by moxibustion may be related to the smoke produced during the process, from volatile oils such as cineole, a-thujone, and sesquiterpene, rather than direct contact with moxa.<sup>77</sup> Patients have also reported fatigue, abdominal pain, and headaches because of smoke inhalation. The lesions caused by moxibustion can be confused with child abuse because it can produce discrete circular or target-like burns with scarring, resembling classic cigarette burns.<sup>79</sup>

## CUPPING

### Key points

- Cupping involves placing cups over the skin to create suction
- Cupping has been used as a method for obtaining epithelial grafts for patients with vitiligo
- Circular bruising and linear purpuric streaks can be mistaken for child abuse

### Background

Cupping is used in Asian cultures and by individuals from Eastern Europe, the Middle East, and Latin America. Although it is used independently, similar to moxibustion, it can be an alternative

technique to stimulate acupuncture points on the body. In dry cupping, a heated cup is placed onto the back, chest, abdomen, or buttocks, and the cooling of air creates a suction that is thought to remove toxins or transfer pathology.<sup>82</sup>

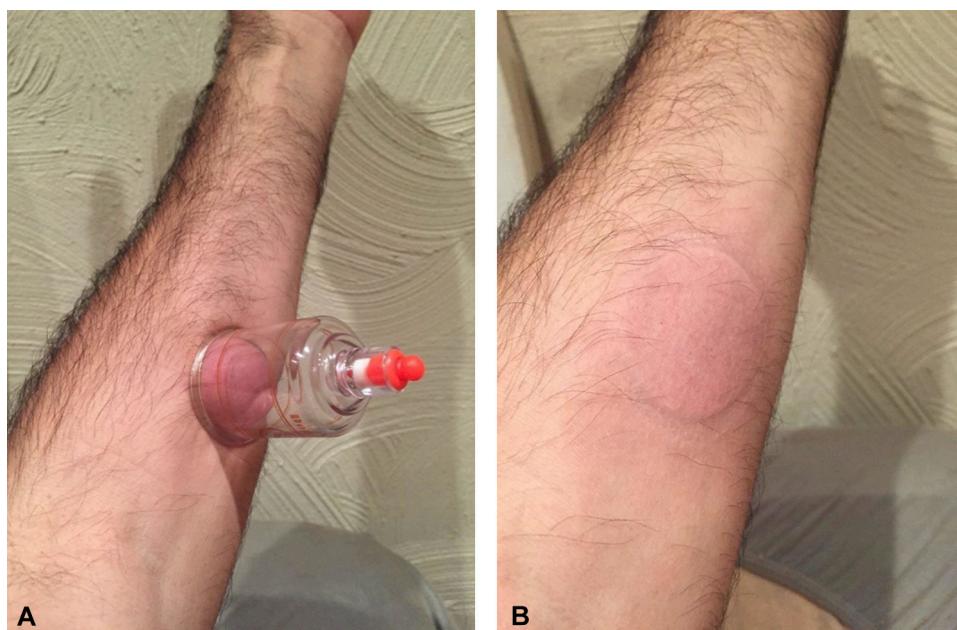
Traditionally, a cotton ball soaked in alcohol is burned inside the glass cup and removed right before placement to create the vacuum. Bamboo and other materials can be used as alternatives to glass. The procedure breaks superficial blood vessels in the papillary dermis, creating ecchymoses, purpura, and petechiae, which is seen as evidence that the ailment is being drawn from the body (Fig 6).<sup>79,82</sup> Wet cupping is a similar procedure in which the skin is first abraded.<sup>79</sup> Moving cupping involves lubricating the area so the cup can be moved to cover larger areas.<sup>82,85</sup>

### Therapeutic applications

Practitioners believe cupping to be efficacious for pain, fever, poor appetite, indigestion, infertility, menstrual pain, acne, eczema, psoriasis, anemia, hemophilia, hypertension, congestion, and stroke rehabilitation.<sup>79,82,83,85</sup> Limited evidence-based medicine exists. Three systematic reviews have been conducted examining the efficacy of cupping for hypertension, stroke rehabilitation, and pain.<sup>123-125</sup> Methodologic shortcomings and poor-quality studies were unable to provide convincing evidence that cupping was effective for these disease entities. More recently, cupping has been developed as a method for obtaining epithelial grafts for patients with vitiligo.<sup>86,126</sup> Awad et al<sup>86</sup> found that 80% of their patients had satisfactory repigmentation of their vitiliginous patches without permanent scarring of the donor sites.

### Complications

Complications that have been associated with cupping include panniculitis, ulcer formation, burns, hyperpigmentation, koebnerization and the



**Fig 6.** Cupping treatment using (A) a glass cup and vacuum with (B) resultant circular ecchymosis. Courtesy of Daniel Zancanaro, MD.



**Fig 7.** Postinflammatory hyperpigmentation occurring 10 days after a cupping treatment in a white man.

development of discoid psoriatic plaques, and erythema ab igne (Fig 7).<sup>78,82,83,85</sup> The lesions produced by cupping can also be mistaken for child abuse stigmata because they produce discrete circular burns with central ecchymosis and petechiae or linear purpuric streaks when moving cupping is practiced.<sup>82,84</sup> This confusion has resulted in at least 1 case of parental suicide.<sup>127</sup>

## COINING AND SPOONING

### Key points

- Coining and spooning involve vigorously rubbing the skin to produce ecchymoses, traditionally in a “pine tree” pattern
- It is a remedy typically used to treat the symptoms of fever, chills, and headache

- These practices can be mistaken for child abuse if the classic patterns are not recognized

### Background

Coining (cao gio in Vietnamese) or spooning (gua sha in Chinese) is a remedy used in Asian cultures, particularly among individuals from the Southeast Asian countries of Vietnam and Cambodia. Oiled skin is vigorously rubbed with the edge of a coin until ecchymoses, petechiae, or purpura are produced, typically in a formation resembling a pine tree (Fig 8). Spoons, metal caps, animal bones and horns, jade, and ginger root may also be used.<sup>79,81</sup> It is believed that this process increases circulation and improves respiration.

### Therapeutic applications

Coining or spooning is used to treat the symptoms of fever, chills, and headache. Practitioners believe that it is also efficacious for seizures, cough, and vomiting.<sup>79</sup> Limited evidence-based medicine is available. One RCT studying breast engorgement ( $n = 54$ ,  $P < .001$ ) showed significant improvement with gua sha compared to traditional breast care.<sup>128</sup> Two RCTs studying pain reported pain reduction ( $n = 40$ ,  $P < .05$ ;  $n = 48$ ,  $P < .001$ ) after 1 gua sha treatment compared to the control group (no treatment and local thermal pad, respectively).<sup>129,130</sup>

### Complications

Complications that have been reported after coining and spooning include transient microscopic



**Fig 8.** Characteristic markings after coining treatment on the (A and B) back and (C) neck.

hematuria, contact dermatitis, minor burns, camphor intoxication, and rare severe events, including cerebellar hematoma with herniation and 1 burn requiring grafting.<sup>79,81,84,87,88</sup> Coining or spooning may also resemble child abuse. In fact, legal action has been taken against 2 families for coining.<sup>131</sup>

## CONCLUSION

In conclusion, in this era of migration and diffusion of cultural customs into mainstream practice, dermatologists need to be familiar with CAM practices and their dermatologic and systemic complications. For example, cupping recently gained significant media coverage because of its popularity among athletes

**Table III.** Rare dermatoses caused by therapeutic cultural practices

	<b>Background</b>	<b>Dermatologic complications</b>	<b>Systemic complications</b>
Aromatherapy and essential oils	Aromatherapy is the use of aromatic essential oils extracted from plants for therapeutic benefit. <sup>17</sup> Essentially, the aromatic herbal remedies of traditional Chinese medicine and its counterpart, Ayurveda, form the foundation of this therapy. Use of aromatherapy and essential oils comes from several Asian cultures, but the practice is now common worldwide. The oils are extracted from all parts of the plant and may be sold unlicensed and be contaminated with heavy metals	Contact dermatitis (allergic and irritant), <sup>17,49,57,132-140</sup> perioral and intraoral dermatitis with cheilitis, <sup>57</sup> chemical leukoderma, <sup>141</sup> hand dermatitis, <sup>57,136,138,140</sup> and localized and disseminated bullous phototoxicity <sup>17,57,135,142,143</sup>	Heavy metal toxicity <sup>143</sup>
Gridding	Gridding is a folk remedy originating from Russia and parts of the former Soviet Union that involves painting a grid-like pattern onto the back with iodine. <sup>81</sup> The warmth and mild burning caused by the iodine application is thought to treat respiratory illness	Chemical burns with maceration or abrasion of the skin have been reported, <sup>81,144</sup> and the hyperpigmented pattern that results on the back can be confused for child abuse <sup>81</sup>	Hypothyroidism <sup>144</sup>
Salting	Salting is a therapy from Turkey that involves scrubbing a neonate's body with table salt in order to deter evil spirits harboring sickness and death <sup>81</sup>	Epidermolysis <sup>84</sup>	Life-threatening hypernatremia <sup>79,84,145</sup>
Toothpaste-induced dermatitis	Toothpaste-induced dermatitis is a rare phenomenon described in India. Rather than using a toothbrush to apply the paste, the teeth are scrubbed with the index finger. Overall, complications are rare because the oral mucosa tends to be resistant to irritants and allergens and common toothpaste ingredients have a low potential for sensitization <sup>146</sup>	Contact cheilitis, <sup>141,146</sup> perioral contact dermatitis, <sup>141,146</sup> and allergic contact dermatitis <sup>141,146</sup> ; implicated ingredients include cinnamic aldehyde, fluorides, balsam of Peru, flavoring agents, fragrance mixtures, sodium lauryl sulfate, peppermint, triclosan, and propylene glycol <sup>146</sup>	

competing in the 2016 Summer Olympic Games. Overall, efficacy of these practices is not well studied, and the lack of regulation can lead to frequent contamination, adverse reactions, and toxicity. In addition, cupping, coining, spooning, and moxibustion may be mistaken for abuse. For other rare dermatoses caused by therapeutic practices, including a summary of aromatherapy and essential oils, gridding, salting, and toothpaste-induced dermatitis, see Table III.

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# Dermatoses caused by cultural practices

## Cosmetic cultural practices

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### Learning objectives

After completing this learning activity, participants should be able to discuss cultural competency and its value in an office- or hospital-based setting; identify common dermatologic diseases that can be attributed to religious practices; and identify common dermatologic diseases that can be attributed to environmentally driven cultural practices.

### Disclosures

#### Editors

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The second article in this continuing medical education series discusses cosmetic practices associated with cultural dermatoses, including hair care, traditional clothing, and skin decorations. Often, the steps individuals take to enhance their physical appearance are determined by cultural perceptions of beauty. Without awareness of cultural practices, a multitude of cutaneous dermatoses may be missed by the dermatologist. Recognition and understanding of patients' cultural backgrounds and habits will allow the practicing dermatologist to offer better counseling and treatment options while providing a more meaningful and understanding physician–patient relationship. (J Am Acad Dermatol 2018;79:19–30.)

**Key words:** cosmetic; cultural competency; globalization.

### HENNA

#### Key points

- Henna is a red dye used for temporarily tattooing the skin and coloring hair, while black henna, an adulterated form, contains para-phenylenediamine, which is a strong skin sensitizer
- The most common complication of henna is allergic contact dermatitis; however, severe cutaneous and systemic adverse events have been reported

#### Abbreviations used:

ACD:	allergic contact dermatitis
CAM:	complementary or alternative medicine
PPD:	para-phenylenediamine

### Background

Henna is a dye made from the plant *Lawsonia inermis* and is used for temporarily tattooing the skin, hair, and nails, an art form that is traditionally

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performed in Hindu and Muslim communities. It is applied for various social events, particularly weddings and Eid celebrations. Natural henna gives the skin a reddish hue from the active ingredient, lawson, and additives like indigo darken the mixture. Unfortunately, although touted as henna, mixtures known as black henna, which contain many other darkening agents and possibly no natural henna at all, are frequently used.<sup>1</sup> Black henna often contains diaminobenzenes and diaminotoluenes, such as para-phenylenediamine (PPD) and p-toluenediamine.<sup>1</sup> PPD, in concentrations ranging from 0.25% to 64%, is used as an additive because it darkens the product and reduces the drying time from hours to minutes.<sup>1-3</sup> Other ingredients that have been found in henna mixtures include heavy metals. Nickel has been found in concentrations ranging from <2.5 ppm to 3.96 ppm and cobalt from concentrations of 2.96 ppm to 3.54 ppm.<sup>2</sup> Although no international standards exist, it has been recommended that products used on the skin should not contain nickel or cobalt at levels >5 ppm; however, a nickel concentration of 0.5 ppm has been sufficient to cause contact dermatitis.<sup>4,5</sup> Coffee, black tea, lemon juice, eucalyptus, clove, mustard oil, vinegar, indigo powder, and even animal urine can be included to alter henna color; fenugreek seeds, okra, and tamarind paste can be included to alter the texture.<sup>6-8</sup>

### Complications

Although rare, natural henna can lead to severe contact allergies.<sup>7,9-12</sup> Complications, particularly allergic contact dermatitis (ACD), most commonly arise when black henna containing PPD is used (Fig 1). Previous sensitization can occur from exposure to different hair dye preparations and by inhaling henna particles.<sup>13</sup> The incidence of allergic reaction among those receiving temporary tattoos can be as high as 2.3%.<sup>14</sup> Permanent sequelae from such reactions includes dyspigmentation, leukoderma, and keloids.<sup>15,16</sup>

Henna application has also been associated with contact urticaria, irritant contact dermatitis, erythema multiforme-like reaction, temporary hypertrichosis, superficial epidermal necrosis, and systemic allergic reactions, such as angioedema.<sup>6,10,14-24</sup> Serious, sometimes fatal, hemolytic crises in patients with underlying glucose-6-phosphate dehydrogenase deficiency have been reported in 4 children.<sup>25</sup> Because of its structural similarity to 1,4-naphthoquinone, it is believed that lawson may act as an oxidant that can prove fatal in glucose-6-phosphate dehydrogenase-deficient persons.<sup>25</sup> Rare cases of acute renal failure and death caused by renal tubular necrosis have been reported.<sup>9</sup>



**Fig 1.** Bullous contact dermatitis on the dorsal surface of the right hand after application of black henna.

Hairdressers and artists are at risk for hand and forearm dermatitis; Khanna et al<sup>26</sup> found that 3.2% of Indian hairdressers and beauticians had positive patch tests to henna mixtures.

Patients suffering allergic reactions to henna should be advised to avoid further contact with henna products and PPD or its cross-reactors, such as latex, rubber, azo dyes, sulfonamides, sulfa drugs, thiazide diuretics, and local anesthetics.<sup>21,27,28</sup> Side effects can be reported to the US Food and Drug Administration hotline for tracking PPD-related reactions.<sup>29</sup>

### THREADING

#### Key points

- Threading is a temporary hair removal technique that uses cotton thread and swift twisting movements
- Complications vary from minor pain and erythema to infections and koebnerization

#### Background

Threading is a temporary hair removal technique that is commonly used in South Asia and the Middle East that has grown in popularity globally. Men most commonly remove hair from the cheek, ear, and forehead, while unwanted facial hair along the eyebrows, upper lip, chin, and cheeks are the most common locations for women (Fig 2).<sup>30,31</sup> Hairs are trapped between cotton threads that are held tightly



**Fig 2.** Threading using cotton thread and swift twisting movements.

in an operator's teeth or around the neck and looped through their fingers. As the operator closes the loop in his or her fingers, the entire hair shaft is extracted from the skin in rapid succession.<sup>31,32</sup> Overall, threading is believed to have several advantages over other hair removal methods, including lower cost, shorter operating time, and less trauma.

### Complications

Common complaints after threading include immediate pain, erythema that subsides within hours, pruritus, edema, folliculitis, irritant dermatitis, and secondary pigmentary changes.<sup>30,31,33-35</sup> Threading can also lead to several infectious dermatoses, including bullous impetigo, verrucae, and molluscum contagiosum; spread of these infections is made easier by the trauma induced by threading which can disturb the epidermal barrier function of the skin.<sup>31,32,34,36,37</sup> Particles of human papillomavirus can be transferred from one area of the body to another, as was the case in a patient with verrucae on her forearm and wrist that spread to her eyebrows after undergoing threading of both areas.<sup>32,34,37</sup> Risk of acquiring these infections can be minimized by training those that perform threading to use aseptic techniques.<sup>31,32,37</sup> Koebnerization can occur in patients with underlying dermatologic diseases, such as vitiligo, psoriasis, or lichen planus. There has been 1 reported patient who developed depigmented patches around the eyebrows after a procedure.<sup>38</sup>

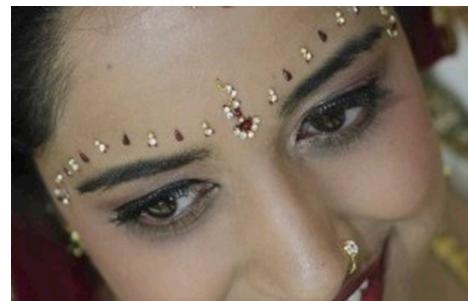
## BINDI AND KUMKUM

### Key points

- **Bindi and kumkum are pigments and adhesives applied to the forehead**
- **Complications include allergic contact dermatitis and chemical leukoderma**

### Background

Kumkum and bindi are pigments and adhesives applied to the forehead. Bindi, meaning dot in Sanskrit, is a decorative adornment worn between the eyebrows, considered the location of the "third



**Fig 3.** Bindi on the forehead and decorative nose piercing on the left nasal ala of an Indian woman.

eye."<sup>39</sup> Although traditionally worn by Hindu women to indicate marital status, the bindi is now popularized and commonly worn as decorative jewelry (Fig 3). Kumkum (also known as sindoor or vermillion) is a powder typically made from turmeric to which slaked lime is added to turn the dried powder from a rich yellow to red color.<sup>39</sup>

Traditionally, kumkum was prepared at home from alkalinized turmeric powder, but kumkum and bindi mixes are more commonly being mass produced with the incorporation of various dyes and chemicals, such as coal tar dyes, toluidine red, erythrosine, lithol red calcium salt, lead oxide, fragrances, groundnut oil, tragacanth gum, parabens, canaga oil, and sandalwood.<sup>39-43</sup> Additionally, bindi that are made of nickel or plastic with an adhesive backing are more commonly used. Allergens associated with bindi include gallate mix, thimerosal, nickel sulfate, Brilliant lake red R, Sudan I, PPD, Kathon CG, benzotriazol, tert-butyl hydroquinone, aminoazobenzene, Disperse Blue 124, and Disperse Blue 106.<sup>42-44</sup>

### Complications

Dermatitis caused by kumkum or bindi can refer to allergic or pigmented contact dermatitis, chemical leukoderma, and foreign body granuloma formation.<sup>42,44,45</sup> Lesions can develop on the forehead, glabella, hair part, abdomen, and neck.<sup>43</sup> Although generally restricted to the site of application, lesions can involve surrounding skin via the spread of kumkum or bindi mix by sweating.<sup>43</sup> Kumkum and bindi can also cause a chemical leukoderma, which occurs when a genetically susceptible individual comes into direct contact with chemicals that are melanocytotoxic. One study found that about 75% of patients who developed chemical leukoderma had first developed ACD to the kumkum or bindi.<sup>46,47</sup> The most common allergen implicated is para-tertiary-butylphenol, which is found in the adhesive of sticker bindis.<sup>40,44,46</sup>

## HAIR OILS

### Key points

- Hair oils are used to soften and provide shine
- Complications include allergic/irritant contact dermatitis and contact urticaria

### Background

Commonly used in India and by African Americans, hair oils are applied directly to the hair and also added to shampoos and conditioners to soften, provide shine, promote hair growth, and prevent hair loss.<sup>9,48</sup> It is thought that the saturated and unsaturated fatty acid content of hair oils inhibit dermatophyte growth.<sup>49</sup> Amla oil is toxic to *Microsporum canis*, *Microsporum gypseum*, and *Trichophyton rubrum*, while coconut oil is toxic to *Trichophyton mentagrophytes*. In addition, coconut oil has been shown to decrease *Staphylococcus aureus* colonization in patients with atopic dermatitis.<sup>9</sup> The antifungal and antibacterial medicinal properties of coconut oil (*Cocos nucifera L*) are attributed to 3 medium-chain fatty acids: lauric acid (most abundant), capric acid, and caprylic acid, which are thought to interfere with the bacterial cell structure and cellular energy production.<sup>50</sup>

### Complications

Some oils that have been associated with various dermatologic complications include mustard oil, argan oil, coconut oil, *Cuscuta reflexa*, *Citrullus colocynthis*, and *Eclipta alba*.<sup>48,51-54</sup>

Complications from using or working with such hair oils include allergic and irritant contact dermatitis and contact urticaria.<sup>51-56</sup> ACD has presented with pityriasis rosea-like lesions in 1 patient.<sup>51</sup> Certain oils with high oleic acid content, such as coconut oil, olive oil, and shea butter, can worsen seborrheic dermatitis as several Malassezia species have high lipase activity, allowing them to use the applied oils for growth.<sup>57-61</sup> Given their occlusive nature, hair oils have been theorized to cause folliculitis; however, no cases have been reported.

Mudichood is a rare dermatosis associated with hair oils that is seen most commonly during the summer months in southern India.<sup>62-64</sup> The term derives from the Malayalam language, translating to “heat of the hair” and represents the comedogenic effect of hairs oils combined with heat, humidity, and occlusion.<sup>65</sup> The traditional practice of maintaining long hair allows for prolonged contact with the neck and upper back, and because of interactions between hair oils that are commonly used in the region (typically coconut or sesame) with the natural heat and humidity, a lichenoid dermatitis forms.<sup>62,66,67</sup>

## HAIR RESTRUCTURING AND STYLING TECHNIQUES

### Key points

- Hair care practices, with heat, chemical, or physical modalities, are used to make the hair easier to style
- Complications include contact dermatitis, hair breakage, and scarring alopecia

### Background

Hair restructuring techniques, with either heat or chemicals, are used by African Americans and Indians to make the hair more manageable.<sup>68</sup> Hot combing consists of the use of a metal comb heated to high temperatures (150–500°F) and slowly pulling it through portions of hair; hair relaxers are chemicals.<sup>69</sup> Both work by disrupting disulfide bonds in keratin. Relaxers are divided into lye and no lye formulations containing sodium hydroxide and calcium hydroxide/guanidine hydroxide, respectively.<sup>70,71</sup> Formaldehyde and its derivatives are also ingredients in hair relaxers marketed as Brazilian keratin treatments.<sup>72</sup> Hair styling techniques include braids (interlocking of ≥3 hairpieces), cornrows (small, tight braids close to the scalp), twists (2 pieces of hair that are twisted together), and locks (twists that are not removed to intentionally form matted ropes of hair).<sup>69</sup>

### Complications

Complications associated with hair relaxers include local irritation, chemical burns, hair shaft dryness, contact dermatitis, hair shaft fragility and breakage, seborrheic dermatitis, infection, hyper- and hypopigmentation of the hair, and scarring alopecia.<sup>71,73,74</sup> Common complications related to thermal straightening include moderate to severe burns, hair breakage and weakening, and severe damage to the hair shaft.<sup>69</sup> Ethnic hairstyling techniques can cause excess tension and traction on the hair, leading to nonscarring and scarring alopecia.<sup>75</sup> Clinically, hair loss typically manifests on the frontal and temporal scalp.<sup>76</sup> Central centrifugal cicatricial alopecia has been associated with application of heat, trauma, and tension (Fig 4).<sup>73,77</sup> Hair relaxers have also been associated with serious and rare dermatologic complications, including Stevens–Johnson syndrome.<sup>78</sup>

## SARI DRAWSTRINGS

### Key points

- Saris and salwaars are traditional outfits worn by South Asian women that close with a drawstring



**Fig 4.** Central centrifugal cicatricial alopecia is characterized by a symmetric, roughly circular patch of scarring alopecia at the vertex and mid-scalp.

- Complications include lichenification, cutaneous infection, koebnerization, and squamous cell carcinoma

### Background

Saris are garments of a length of fabric that is draped around the body, while salwaars are tunic and trouser combinations. These are common traditional clothing worn by women in India, Pakistan, Bangladesh, and Sri Lanka. Under the sari, a petticoat is worn that closes tightly with a drawstring; the pants of salwaars are similarly held up by a drawstring.

### Complications

Sari drawstring complications include blisters from acute friction and pruritus, lichenification, dyspigmentation, cutaneous infection, koebnerization, and rare cases of squamous cell carcinoma from chronic friction. The constant friction and pressure caused by the tightly worn drawstring can create a lichenified, hyperkeratotic, and hyperpigmented band at the waistline.<sup>79</sup> Hyperpigmentation can be interpreted by patients as poor hygiene leading to increased scrubbing during bathing, exacerbating the cutaneous changes.<sup>79</sup> Posttraumatic leukoderma at the waistline can also be seen.<sup>79</sup> The occlusive environment, along with superficial trauma induced by the constant friction, can form an entry point for bacterial and fungal infections.<sup>79</sup> Trauma and pressure induced koebnerization of vitiligo, psoriasis, and lichen planus has also occurred.<sup>79,80</sup> Another rare complication that has been reported is formation of a Marjolin ulcer with development of squamous cell carcinoma, termed “sari cancer” in this case.<sup>79</sup>

## SKIN LIGHTENING

### Key points

- Skin lightening involves the use of creams often containing hydroquinone and corticosteroids to decrease pigmentation

- Complications vary and can be seen in high percentages of patients with duration of use correlated to the number and degree of side effects experienced

### Background

Skin lightening creams and lotions are used by patients with darker skin types to improve overall appearance, portray a higher social level, treat skin blemishes, satisfy a spouse, or increase marital prospects.<sup>81-84</sup> The use of skin lightening agents for cosmetic purposes that are typically restricted for medical use is a common practice worldwide, including Africa, Asia, the Caribbean, the Middle East, and Southern and Central America, with increasing use in North America and Europe.<sup>81-90</sup> In Senegal, 26% of women surveyed currently used skin lighteners, and 36% had used them at some point.<sup>81</sup> Rates up to 73% were reported in other countries.<sup>83</sup> Creams are applied to focal or entire body surface areas multiple times daily. Women who are married, younger, with higher education, or from higher social standing are more likely to use skin lighteners.<sup>81,83,90</sup>

The ingredients contained in these topicals are variable and often not disclosed. Many of the ingredients are prohibited, imported illegally, and sold on the black market. Typical active ingredients in skin lightening agents are hydroquinone and corticosteroids.<sup>81</sup> Other components can include mercury, kojic acid, kojic dipalmitate, 5,5'-dipropylbiphenyl-2,2'-diol, phenylethyl resorcinol, arbutin, aleosin, azelaic acid, salicylic acid, soy proteins, methyl gentisate, licorice root extract, detergents, hypochloride sodium, lemon juice, potash, toothpaste, milk, camphor balls, ascorbic acid, peroxides, and chlorates.<sup>81,83,84,86,90-95</sup> High levels of metals have also been found in skin lightening creams, including cobalt, chromium, nickel, cadmium, lead, copper, aluminum, zinc, manganese, and iron.<sup>90,96</sup> These metals have been found in far excess of the limits for cosmetics and

may have been present as an intentionally added ingredient or as a contaminant from poor production processes.<sup>96</sup>

### Complications

Complications from using skin lighteners have been reported in up to 75% of patients, with duration of use correlated to the number and degree of side effects experienced.<sup>81</sup> A classic sign of overuse is hyperpigmentation over the metacarpal and interphalangeal joints with contrasting hypopigmentation between the joints, possibly because of less efficacy of the skin lighteners on the skin over the joints.<sup>82</sup> Chemical burns mimicking toxic epidermal necrolysis have been described.<sup>97</sup> Each of the main skin lightening ingredients is associated with its own particular set of complications, but because the creams frequently contain ingredients at concentrations that are mislabeled with various unknown additives, it can be difficult to predict the side effects likely to occur with use of any single product. Further complicating the ability to determine causality is the frequent, simultaneous use of multiple topical products.

Hydroquinone competitively inhibits melanin production, acting as a substrate for tyrosinase.<sup>83</sup> Concentrations ranging from 2% to 5% are typically used, but can be much higher. The most feared complication from hydroquinone use is exogenous ochronosis, a paradoxical hyperpigmentation caused by the deposition of homogentisic acid in the skin (Fig 5).<sup>83,85</sup> Duration of use rather than hydroquinone concentration may affect exogenous ochronosis development. Corticosteroids are frequently found at superpotent concentrations in lightening products. They lighten the skin by decreasing endogenous steroid production and its precursors, including melanocyte-stimulating hormone.<sup>83</sup> Mercury products function as skin lighteners by inhibiting tyrosinase.<sup>83</sup> As a preservative, mercury is only allowed at  $\leq 65$  ppm in eye area products and  $<1$  ppm in all other products; however, concentrations ranging from 4.08 to 33,000 ppm have been found in skin lightening agents.<sup>87,98</sup> Acute and chronic complications associated with hydroquinone, corticosteroids, and mercury are included in Table I.

## DECORATIVE NOSE PIERCINGS

### Key points

- Nose piercings are a common body piercing with cultural significance in parts of India
- Common complications include contact dermatitis and infections; rare severe reactions include necrosis and collapse of the nasal wall



**Fig 5.** Exogenous ochronosis on the left malar cheek, nose, and upper cutaneous lip of a Haitian woman, characterized by stippled brown-black macules with surrounding pink hue.

### Background

Decorative nose piercings are common throughout the world, though they have cultural significance in parts of South Asia because they are frequently worn during marriage ceremonies (Fig 3). Although often made with metals like stainless steel, gold, niobium, and titanium that are rarely allergenic, piercings can contain contaminants, such as nickel.<sup>99</sup>

### Complications

Numerous complications can arise from nose piercings, including contact dermatitis, local and systemic infections, and poor cosmesis from keloid formation, necrosis, and collapse of the nasal wall.<sup>99</sup> Piercings through the cartilaginous septum can lead to serious bleeding and septal hematomas which can become secondarily infected with *Staphylococcal* and *Pseudomonas* species, group A B-hemolytic Streptococcal species, *Mycobacterium tuberculosis*, and atypical mycobacterial species.<sup>99,100</sup> More serious systemic infections, including infective endocarditis, can rarely occur in individuals with moderate- or high-risk cardiac conditions.<sup>100</sup> Amateur piercers, nonsterile instruments, and nonhygienic standards were the most common factors influencing whether patients developed complications.<sup>100</sup>

## SCARIFICATION AND TATTOOING

### Key points

- Scarification is the intentional cutting/burning of the skin to produce scars, while tattooing involves marking the skin/mucous membranes with colored materials
- Complications are often infectious

### Background

Scarification is a practice seen in several African societies in which scars are produced by cutting with a sharp knife, stone, or scalpel or burning the skin with a hot metal for decorative and medicinal purposes.<sup>101,102</sup> Keloid formation is often the desired effect in scarification.<sup>103</sup> Certain marks are often made on the face to easily recognize a person's tribal affiliation (Fig 6).<sup>104</sup> In 1 report from Nigeria, 7.2% of

**Table I.** Summary of cosmetic cultural practices

Cultural practice	Dermatologic complications	Systemic complications
Threading	Erythema, <sup>9,30-32,34,36,56</sup> pruritus, <sup>31</sup> folliculitis, <sup>9,30-32,34,36,56</sup> hyperpigmentation, <sup>9,30-32,34,36</sup> bullous impetigo, <sup>9,31,36,56</sup> verruca plana, <sup>9,32,34,37,56</sup> molluscum contagiosum, <sup>9,34</sup> and koebnerization <sup>9,32,34,36,38,56</sup>	
Kumkum and bindi	Allergic contact dermatitis, <sup>9,39-44</sup> leukoderma, <sup>9,41,46,47</sup> and foreign body granuloma <sup>9,45</sup>	
Hair oils	Allergic and irritant contact dermatitis, <sup>9,51-54,56,113</sup> and contact urticaria <sup>52,53</sup>	
Hair restructuring and styling techniques	Contact dermatitis, <sup>70,71</sup> acute scarring alopecia, <sup>55,68,71,72,74,114</sup> central centrifugal cicatricial alopecia, <sup>71,73</sup> and abscesses <sup>70,74</sup>	Uterine leiomyomata <sup>74,115</sup> and Stevens—Johnson syndrome <sup>78</sup>
Sari drawstring dermatitis	Hyperpigmentation, <sup>9,56,79,80</sup> intertrigo, <sup>9,79</sup> pruritus, <sup>79</sup> allergic contact dermatitis, <sup>79</sup> koebnerization, <sup>9,56,79,80</sup> and squamous cell carcinoma <sup>9,56,79</sup>	
Skin lightening Hydroquinone	Exogenous ochronosis, <sup>81-83,85,88</sup> squamous cell carcinoma, <sup>82,83,88</sup> cutaneous sarcoidosis, <sup>85</sup> contact dermatitis, <sup>81-84,86,88,90,92-95,116,117</sup> reticulate postinflammatory pigmentation, <sup>81,82,116</sup> pigmented colloid milia, <sup>83</sup> periorbital hyperpigmentation, <sup>97</sup> pseudo-lupus eruptions, <sup>88</sup> scleral and nail pigmentation, <sup>83</sup> and leukoderma <sup>81,82,88,91</sup>	Cataracts, <sup>83</sup> impaired wound healing and dehiscence, <sup>83</sup> secondary trimethylaminuria, <sup>83</sup> and fetal growth retardation <sup>82</sup>
Corticosteroids	Folliculitis, <sup>83</sup> skin atrophy, <sup>81-83,88,118</sup> purpura and telangiectasias, <sup>81,83</sup> hypertrichosis, <sup>81-83</sup> perioral dermatitis, <sup>83</sup> facial acne, <sup>81-83</sup> excessive striae, <sup>81-83,88,118</sup> dyspigmentation, <sup>81-83</sup> steroid addiction syndrome, <sup>83</sup> allergic contact dermatitis, <sup>82,83</sup> delayed wound healing, <sup>83</sup> susceptibility to numerous infections including tinea corporis/intertrigo/pyoderma/cellulitis/scabies/warts <sup>81-83,88</sup>	Adrenal insufficiency, <sup>82,83</sup> cataracts, <sup>83</sup> glaucoma, <sup>83</sup> Cushing syndrome, <sup>83</sup> electrolyte imbalances, <sup>83</sup> osteoporosis, <sup>83</sup> diabetes, <sup>82,83,88</sup> and hypertension
Mercurials	Dermatitis, <sup>82,87</sup> hyperpigmentation, <sup>82,83,87</sup> and nail dyspigmentation <sup>83</sup>	Pneumonitis, <sup>83</sup> gastrointestinal discomfort, <sup>83</sup> neurologic toxicity such as psychosis and peripheral neuropathy, <sup>83,87</sup> renal toxicity such as membranous glomerulonephritis and proliferative glomerulonephritis, <sup>81,83,87,88</sup> mercurial baboon syndrome, <sup>89</sup> and birth defects, including adverse effects on fetal brain development and low birth weight <sup>87,88</sup>
Henna	Contact dermatitis, <sup>1,6-14,17,20,21,24,27-29,56,119</sup> leukoderma, <sup>9,15,56</sup> erythema multiforme —like reaction, <sup>6,9,18,21</sup> hypertrichosis, <sup>9,19,23</sup> keloids, <sup>9,16,56</sup> angioedema, <sup>9,22,56</sup> and hand eczema <sup>9,26</sup>	Heavy metal toxicity <sup>2,9</sup> and hemolytic crisis <sup>6,9,25</sup>



**Fig 6.** Scarification with tribal markings on the left cheek of an African man.

children had evidence of scarification marks and 12.9% had tribal marks.<sup>104</sup>

Ritual tattooing, opposed to cosmetic tattooing, is the culturally sanctioned process of pigment implantation into the skin. Many cultures have preserved ancient methods of placing tattoos, which often symbolize identification within a certain group and also used to enhance beauty.<sup>102,103</sup> Gingival tattooing is most commonly described among women from Ethiopia where the gingiva are covered in kohl powder before piercing with a needle (Fig 7).<sup>101,105</sup>

### Complications

Complications with scarification include keloid formation (as the desired effect),<sup>103</sup> squamous cell carcinoma,<sup>106</sup> and infection with hepatitis B and C and HIV.<sup>104</sup> Cutaneous complications from tattooing include impetigo, cellulitis, hypersensitivity, scarring, keloid formation, allergic contact dermatitis, contact urticaria, foreign body reaction, abscess formation, and koebnerization.<sup>103,106,107</sup> Infection with hepatitis B and C, HIV, syphilis, leprosy, and leishmaniasis has occurred.<sup>103,105,106</sup> Serious adverse events have been reported, including candida endophthalmitis, systemic zygomycosis, spinal abscess, and retinal vasculitis.<sup>106</sup> Complications are included in Table II.

## CULTURAL COMPETENCY

### Key points

- Cultural competency is the set of behaviors and policies physicians use to provide effective cross-cultural care
- Goals include eliminating health disparities, creating open lines of communication, and optimizing health care

Cultural competency involves adopting behaviors and policies that allow physicians to provide effective cross-cultural care with goals of eliminating health care disparities and providing optimal health



**Fig 7.** Gingival tattooing on the left upper gingiva in an Ethiopian woman.

care. This requires respect for the health beliefs, practices, and cultural and linguistic needs of diverse patients.<sup>108</sup> It also requires an understanding of one's own culture and how that affects patient care. Unfortunately, many physicians may lack training or comfort regarding cultural competency topics. According to the National Center for Complementary and Alternative Medicine's 2010 survey, only one-third of respondents had discussed complementary or alternative medicines (CAM) with their health care provider, and in >50% of those cases, it was the patient that brought up CAM rather than the provider.<sup>109</sup> The most common reasons for not discussing CAM were that the health care provider never asked (42%) and that patients did not know that they should discuss it (30%). Other reasons given included a lack of time during the visit, doubts about the provider's knowledge of CAM, fear of dismissal, and lack of comfort discussing the topic.<sup>109</sup> Providers may be wary to discuss topics surrounding race and ethnicity, terms that have variable meaning to people. Avoidance of the topic may seem like an appropriate way to avoid offending patients; however, this practice can limit the ability to have a successful physician–patient relationship.<sup>110</sup>

One way to begin to approach the topic of culture with patients is to incorporate cultural assessment questions during intake at the office. Taylor et al<sup>108</sup> devised a possible set of questions that assess a patient's cultural background and health beliefs that providers may find useful. It is important for physicians to realize that use of alternative medicines does not necessarily mean their patient is wary of conventional medicine. By discussing cultural practices and therapies, providers can foster a comfortable environment for their patients that will likely contribute to trust and, therefore, better compliance with prescribed treatment regimens.<sup>108</sup>

Although this continuing medical education series focused on cultural dermatoses, innumerable other factors are culturally determined and can affect the health and well-being of patients. It is important to

**Table II.** Rare dermatoses caused by cosmetic cultural practices

	<b>Definition and presentation</b>	<b>Dermatologic complications</b>	<b>Systemic complications</b>
Decorative nose piercing	Common worldwide but frequently worn during marriage ceremonies in South East Asia, often made with metals that can contain contaminants (nickel) <sup>99</sup>	Contact dermatitis, <sup>103</sup> granulomatous perichondritis, <sup>99</sup> nasal wall necrosis and collapse, <sup>99</sup> piercing migration or accidental traumatic removal, <sup>99</sup> hypertrophic scars, <sup>106</sup> keloids, <sup>106</sup> embedding of the piercing requiring surgical removal, <sup>99</sup> pyogenic granuloma, <sup>33,100</sup> and staphylococcal/streptococcal/pseudomonal/mycobacterial infections <sup>99,100</sup>	Infective endocarditis, <sup>99</sup> infection with hepatitis B/hepatitis C/HIV/tetanus <sup>99</sup>
Scarification	Practiced in several African societies, scars are produced on the skin for decorative and medicinal purposes <sup>101,102</sup> ; herbalists and native doctors cut the skin with a sharp knife/stone/scalpel or burn the skin with hot metal, most common on the face to denote tribal affiliations	Keloid formation (this is the desired effect) <sup>103</sup> and squamous cell carcinoma <sup>106</sup>	Infection with hepatitis B/hepatitis C/HIV <sup>104</sup>
Tattooing	Placement of tattoos to symbolize identification within a group and to enhance beauty <sup>102,103</sup> ; in Ethiopia the gingiva can be covered in kohl powder and pierced with a needle for tattooing <sup>101,105</sup>	Impetigo, <sup>103</sup> cellulitis, <sup>103</sup> hypersensitivity, <sup>103</sup> scarring, <sup>103,106</sup> keloid formation, <sup>103,106</sup> allergic contact dermatitis, <sup>106</sup> contact urticaria, <sup>106</sup> foreign body reaction, <sup>107</sup> abscess formation, <sup>106</sup> infection with syphilis/leprosy/leishmaniasis, <sup>106</sup> koebnerization, <sup>106</sup> and magnetic resonance imaging-induced burn <sup>106</sup>	Infection with hepatitis B/hepatitis C/HIV, <sup>103,105,106</sup> candida endophthalmitis, <sup>106</sup> systemic zygomycosis, <sup>106</sup> spinal abscess, <sup>106</sup> retinal vasculitis, <sup>106</sup> and cystic macular degeneration <sup>106</sup>

be aware of dietary habits (eg, Muslims fasting during Ramadan may wait to take their medications until they break fast each day), modesty concerns (eg, women of various faiths may request a female physician), family dynamics (eg, Latino families may want to shield elders from poor prognoses), and hair styling (eg, Africans may have unique hairstyling practices incompatible with a provider's recommendations).<sup>101,108,111</sup> Health-related myths that patients believe can also be culturally determined. African Americans are more likely to believe that their skin does not burn, wrinkle, or need moisturizer. They may also believe they are not susceptible to skin cancer.<sup>110</sup> Asians may use hot showers to treat pruritus.<sup>112</sup> In our increasingly diverse nation, dermatologists will see patients with a variety of cultural beliefs. This series of articles aimed to provide a

comprehensive background of the available literature on dermatoses caused by these beliefs. There is still much to be explored.

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# Fat reduction



## Pathophysiology and treatment strategies

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### Learning objectives

After completing this learning activity, participants should be able to describe the pathophysiology driving the development of adipose tissue; recognize the distinct compartments of adipose tissue in each anatomic area; discuss the different available methodologies used for fat removal (invasive, minimally and noninvasive); and choose the appropriate fat removal strategy according to patient profile, goals, and needs.

### Disclosures

#### Editors

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The advances in understanding the pathophysiology and anatomy of adipose tissue together with the emergence of technological innovations in procedures and devices for fat reduction have led to a dramatic rise in patient demand for this procedure. The objective of this continuing medical education series, which is intended for the novice or experienced dermatologist, is to provide an update of the pathophysiology and anatomic considerations of adipose tissue, and detail the liposuction procedure, from patient selection/management to the latest developments in liposuction devices. Information presented was collected from peer-reviewed literature, the latest guidelines of the American Society of Plastic Surgeons, and the authors' personal clinical experience. The goal of these continuing medical education articles is to assist physicians in providing the best clinical care for their patients who are requesting fat reduction. (J Am Acad Dermatol 2018;79:183-95.)

**Key words:** adipose; energy-assisted liposuction; laxity; liposuction.

Patients are increasingly seeking body contouring procedures, such as liposuction, to help them achieve a healthy looking physique with concomitant improvement in self-image.<sup>1</sup> Liposuction is recognized as one of the most common cosmetic procedures performed in the world, and according to 2016 statistics by the American Society for Aesthetic Plastic Surgery

Americans, liposuction was the most pursued surgical procedure.<sup>2</sup>

Liposuction is not a novel means of body contouring (Fig 1). Arpad and Giorgio Fischer<sup>3</sup> founded modern liposuction with the introduction of hollow cannulas and the cross-tunneling technique.<sup>4</sup> In 1977, Yves-Gerard Illouz developed the wet technique.<sup>5,6</sup> A decade later, Jeffrey Klein revolutionized the wet

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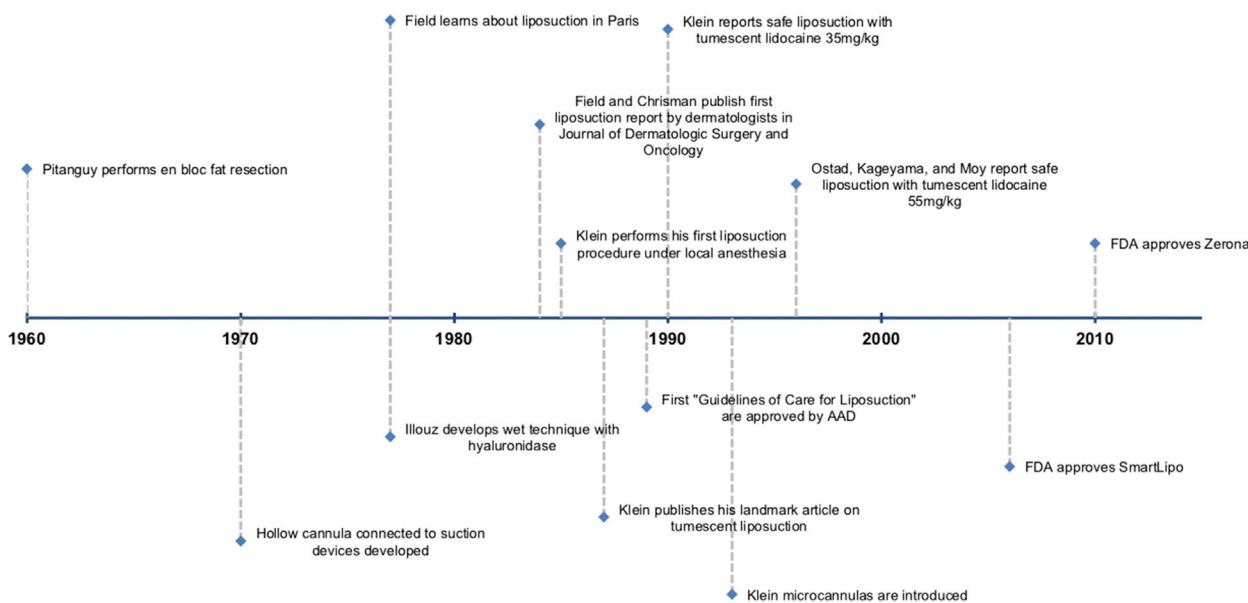
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**Fig 1.** History of liposuction. AAD, American Academy of Dermatology; FDA, US Food and Drug Administration.

technique by developing tumescent anesthesia.<sup>6,7</sup> This allowed for the treatment of multiple adipose areas while extending anesthesia and inducing vasoconstriction, thereby minimizing blood loss and lidocaine toxicity.<sup>7,8</sup> Since that time, several evolutions of the liposuction procedure have been developed.

## ANATOMIC CONSIDERATIONS OF ADIPOSE TISSUE

### Key points

- There are 3 layers of adipose tissue: superficial, superficial fascia, and deep
- The structure and thickness of each layer depends on the anatomic area, gender, and lifestyle
- Adipose anatomy differs according to anatomic area

Liposuction and body sculpting procedures have renewed interest in the anatomy of fat in different anatomic areas. There are 3 layers of fat: a superficial layer, an intermediate membranous layer, known as the superficial fascia, and a deep layer. The depth of each layer depends on an individual's genes, gender, and lifestyle. Liposuction is focused in 2 levels: one in the deep layer to debulk the fat, and a second in the superficial layer to even out the tissue and add definition. The superficial layer is composed of polygonal lobes of fat defined by fibrous septa. The thickness of this layer, assessed by the pinch test, dictates the depth of insertion of the liposuction

cannula. The deep layer contains large, flat lobes of fat, defined by oblique fibrous septa. Distinguishing the superficial from the deep fat layer depends on the anatomic area. For example, in the abdomen, the deep layer is thicker in the periumbilical region, whereas the superficial layer is thicker in the upper abdomen. In the lower body, not only is the division of superficial and deep fat unclear, but the amount of deep fat is minimal. Subsequently, to avoid contour irregularities it is advised to avoid the following areas: the lateral gluteal depression, the infragluteal fold, the inferolateral iliotibial tract, the midmedial thigh, and the infragluteal triangle.<sup>9</sup>

## PATHOPHYSIOLOGY OF ADIPOSE TISSUE

### Key points

- Adipose tissue is an endocrine organ with a key role in regulating metabolism
- Adipose cells secrete bioactive peptides called "adipocytokines"
- Adipose stem cells derived from adipose tissue are being isolated and used in regenerative medicine

Adipose tissue not only insulates the body and stores energy—it also has a dynamic role in multiple endocrine and metabolic functions.<sup>10,11</sup> Fat cells regulate the availability of triglyceride and free fatty acid levels in response to insulin, cortisol, and other hormones, and affect glucose metabolism.<sup>12</sup> Adipose tissue also secretes bioactive peptides, called

**Table I.** Standard questions for patient evaluation for body contouring procedures

Current weight (over the past 3 months)
Weight history (lowest/highest weight, lowest/highest BMI)
Past weight loss method/goal weight/motivations
Nutritional history
Exercise history
Tobacco/alcohol
Pregnancy history/form of hormone replacement/contraception
Cardiac/endocrine/coagulopathy family
Medications
Allergies

BMI, Body mass index.

“adipocytokines,” such as adiponectin, leptin, and tumor necrosis factor–alfa, which act locally and distally through autocrine, paracrine, and endocrine effects.<sup>13</sup> The recent identification of pluripotent stem cells in adipose tissue has been key for the field of regenerative medicine. Applications have been developed for their use in cosmetic indications, such as skin rejuvenation.<sup>14,15</sup>

To date, no study has revealed liposuction resulting in a detrimental effect in human metabolism.<sup>16,17</sup> Some studies have shown no effect, while others have shown improvement of metabolism with liposuction.<sup>18,19</sup> A recent review of the literature investigated the physiologic consequences of liposuction and found that after the procedure there is improvement in insulin resistance and a transient increase in adiponectin and inflammatory markers, but no effect on the lipid profile.<sup>20</sup>

## PATIENT CONSULTATION

### Key points

- Personal and family medical histories are key to assess suitability for treatment and perioperative guidelines
- Patient motivations and expectations need to be defined to exclude psychiatric disorders
- The use of tobacco and certain medications, such as anticoagulants and aspirin, needs to be documented/modified because of the increased risk of complications

The patient consultation session is one of the most important steps of the treatment plan (Table I). A thorough review of personal and family histories, current medications, relevant blood tests, necessary imaging, and further referral to specialist services are all key to ensure patient safety and candidacy for treatment. A standard workup in healthy individuals,

**Table II.** Workup for healthy individuals

Age, y	Test
12-40	CBC
40-60	CBC and ECG
>60	CBC, BUN, glucose, ECG, and CXR

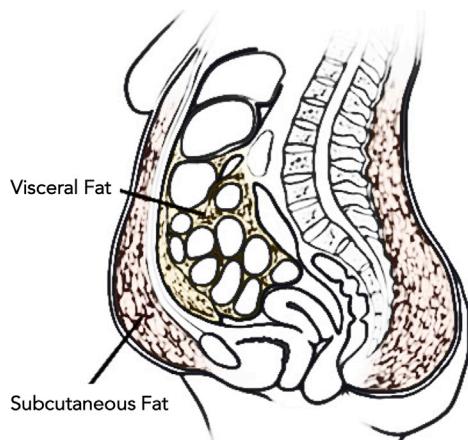
BUN, Blood urea nitrogen; CBC, complete blood cell count; CXR, chest radiograph; ECG, electrocardiography.

**Table III.** Workup for patients with special conditions

Testing	Medical history
Electrocardiogram	Coronary artery disease Congestive heart failure Previous myocardial infarction Hypertension Hyperthyroidism/ hypothyroidism Obesity Deep venous thrombosis Pulmonary embolism Smoking Liver disease Bronchial asthma Congestive heart failure Chronic obstructive pulmonary disease Pulmonary embolism
Chest radiograph	
Electrolytes, glucose, liver function tests, BUN, and creatinine	Diabetes mellitus Chronic renal failure Chronic liver disease Hypothyroidism/ hyperthyroidism
Urinalysis	Diabetes mellitus Chronic renal disease

BUN, Blood urea nitrogen.

depending on their age, is shown in Table II. Table III presents additional testing required in patients with a medical history. The consultation should commence with the patient’s motivation, concerns, and expectations to evaluate the presence of psychiatric disorders, such as body dysmorphic disorder.<sup>21</sup> The presence of an underlying mental disorder, such as body dysmorphic disorder or an eating disorder, needs to be recognized early on. Referral to a psychotherapist/psychiatrist for counseling is advised. This type of patient is particularly challenging to distinguish from a mere “perfectionist.” Certain indications suggesting the presence of a mental disorder include the lack of obvious excess fat, intense preoccupation/obsession with appearance, and a history of having undergone several



**Fig 2.** Superficial versus visceral fat.

cosmetic procedures. Offering aesthetic procedures to patients suffering from such mental disorders should be avoided, because the results will never be satisfactory for the patient and the true clinical pathophysiology will remain unaddressed.<sup>22</sup> When performing a patient evaluation, the candidate's anatomic region for treatment should be assessed for thickness of the subcutaneous layer. The abdomen should be examined for the presence of hernias, and preoperative photographs should be taken.<sup>23</sup> Particularly in men, one must be sure that the fat is above the muscle and not visceral (Fig 2). This can be determined by asking the patient to bend over while the clinician directs muscle contraction.

Liposuction is contraindicated in patients with cardiac implantations (eg, pacemaker or defibrillator), pregnant patients, and patients with bleeding disorders (eg, hemophilia).

Patients with uncontrolled medical problems are not candidates for large-volume liposuction (the removal of 4-5 L of fat in a single session). Medical comorbidities, such as diabetes, hematologic disorders, hypotension, and pulmonary and cardiac disease, should be medically managed to minimize the risk of complications. In patients with diabetes, the primary perioperative goal is to avoid hypoglycemia. Patients with type I diabetes should not administer insulin, while patients with type II diabetes should not take oral hypoglycemia agents the morning of surgery. Moreover, surgical time should not exceed 2 hours. In patients with cardiac disease, liposuction should not be performed 6 months after myocardial infarction. When anesthesia is planned, patients with significant heart disease should undergo surgery at a hospital-based surgical unit, rather than a physician's office, to ensure scrupulous monitoring. Patients with pulmonary conditions need to be evaluated, and asthmatic medications need to be continued up to the

**Table IV.** Postoperative instructions

1	Bedrest is advised for a minimum of 2 days. Normal activities may be resumed after 2-3 days (showers, walking)
2	Compression garments are to be worn for $\geq 3$ weeks
3	Edema and lumps in the areas of liposuction are expected. Gentle massage may be helpful
4	Fatigue and emotional depression after surgery is common
5	Weight gain will replace all the fat that has been removed
6	Pink drainage from the wound is normal and lasts for 1-3 days. Notify your doctor if you experience heavy bleeding
7	If legs get excessively swollen, especially after ambulating, keep them elevated as often as possible during periods of rest
8	Take all medications as prescribed and instructed

time of surgery to minimize pulmonary complications. Any suspicion of allergic reaction to anesthetics needs to be addressed preemptively to avoid complications such as hypotension, bradycardia, nausea, or a loss of consciousness.<sup>24</sup> Patients with controlled hypertension may undergo liposuction and are advised to continue their antihypertension medications up to and including the morning of surgery. Angiotensin-converting enzyme inhibitors, however, should not be taken because they have been associated with hypotension during anesthesia.<sup>25</sup>

The intake of medications and over the counter supplements needs to be addressed, because some medications and supplements can increase the risk of postoperative bleeding or be incompatible with certain agents used as anesthetics. Warfarin, aspirin, fish oils, and vitamins (C and E) are not to be taken at least 2 weeks before and 1 week after surgery because they increase the risk of bleeding.<sup>26</sup> Estrogens (birth control pills and hormone replacement therapy) should be discontinued  $\geq 4$  weeks before until 2 weeks after surgery because they are associated with thromboembolic events. Smoking needs to be stopped  $\geq 2$  weeks before until  $\geq 3$  weeks after treatment.<sup>27</sup> No solid foods should be ingested 10 to 12 hours before surgery, but liquids may be consumed until 2 hours before the procedure. In women, it is advised to avoid performing surgery during the first 5 days of their menstrual period.

Postoperative instructions are summarized in Table IV. Pain medications, an antibiotic, and instructions regarding diet and lifestyle will be given to the patient. It may take  $\leq 6$  months to fully recover from the

**Table V.** Devices for liposuction

Technology	Available devices
Suction-assisted liposuction	HK Surgical (San Clemente, CA)
Power-assisted liposuction	MicroAire (Charlottesville, VA)
UAL	External UAL: Silberg (Wells Johnson, Tuscon, AR), Rich-Mar 510 (Bersco, Seattle, WA), Rich-Mar XUAL (Rich-Mar, Inola, OK) Internal UAL: Sculpture (SMEI), Lysonix (Mentor), VASERlipo (Solta, Hayward, CA)
Laser-assisted liposuction	SmartLipo (1064 nm) SmartLipo Triplex, Cynosure (1064, 1320, 1440 nm) CoolLipo, CoolTouch (1320 nm) SlimLipo, Palomar (929/975 nm) Lipotherme, Osyris (980 nm)
Radiofrequency-assisted liposuction	Bodytite (Invasix, Lake Forest, CA)
Water-assisted liposuction	body-jet (Human Med, Germany)

UAL, Ultrasound-assisted liposuction.

treatment, and any revision should be delayed until 6 months postliposuction. Finally, informed consent needs to be signed by the patient that mandates there has been a detailed discussion about the procedure, recovery, risks, and potential complications.

## FAT REDUCTION TREATMENT STRATEGIES

The liposuction procedure and the various liposuction devices commonly used in the dermatologist's outpatient clinical practice are described below. Complications and their management are discussed in detail in the second article in this continuing medical education series. Table V presents the available devices for traditional or energy-assisted liposuction.

### Overview of traditional suction-assisted liposuction

#### Key points

- Concentrations of anesthesia, sedation, and infiltrating solutions are key to ensuring patient safety and treatment success
- Different cannulas are available depending on the anatomic area and volume to be treated

**Table VI.** Formulas of tumescent solutions

Formula	Ingredients
Tumescent formula	<ul style="list-style-type: none"> <li>• 1 L saline</li> <li>• 50 mL 1% lidocaine</li> <li>• 1 mL epinephrine (1:1000)</li> <li>• 2.5 mL 8.4% sodium bicarbonate</li> </ul>
Modified tumescent formula	<ul style="list-style-type: none"> <li>• 1 L lactated Ringer solution</li> <li>• 50 mL 1% lidocaine</li> <li>• 1 mL epinephrine (1:1000)</li> </ul>

- The tumescent and super wet techniques are the most frequently used and are associated with low risks of complications
- Liposuction is performed from the deep to the superficial fat layers using the cross-tunneling technique

Traditional suction-assisted liposuction consists of aspirating deep and subdermal fat by either the super wet or tumescent methods.<sup>28,29</sup> In these methods, the subcutaneous fat is infiltrated with large volumes of a mixture of normal saline containing anesthetic and vasoconstrictor agents until the target tissue is engorged and tense with fluid. The super wet technique is defined as 1 mL of infiltrate per 1 mL of aspirate, while the tumescent technique is defined as 2 to 3 mL of infiltrate per 1 mL of aspirate. There are 2 main formulas for tumescent infiltration for liposuction: tumescent formula and modified tumescent formula (Table VI). Tumescent formula combines 1 L of normal saline with 50 mL of 1% lidocaine, 1 mL of 1:1000 epinephrine, and 2.5 mL of 8.4% sodium bicarbonate. In this formula, the addition of sodium bicarbonate neutralizes the acidity of lidocaine/epinephrine, reducing the burning/stinging sensation associated with infiltrating solutions, and increases analgesic potency. In the modified tumescent formula, 1 L of lactated Ringer solution is used instead of saline. This has a higher pH, obviating the need for sodium bicarbonate. Both the super wet and tumescent technique have been associated with blood loss of about 1%, and the American Society of Plastic Surgeons Practice Advisory Committee has recommended use of the super wet technique to reduce surgical risk and the need for infiltrating solutions.<sup>30</sup> The American Academy of Dermatology and the American Society for Dermatologic Surgery have recommended safety guidelines that the maximum volume of aspirate is 4500 mL of fat and 5000 mL of total fluid/fat, respectively.<sup>31</sup> If multiple areas require treatment, multiple sessions must be planned.

**Anesthesia.** The choice of anesthesia technique for liposuction depends on patient comorbidities, type of liposuction, anatomic areas, and the amount of expected lipoaspirate. Small-volume ( $\leq 1000$ -mL) liposuction cases can be performed with local anesthesia, with or without mild sedation. Complex, large-volume liposuction and combined cases should be performed under general anesthesia. Current guidelines from the American Society of Plastic Surgeons favor the use of lidocaine ranging from 35 to 55 mg/kg when dispersed in a wetting solution.<sup>32</sup> Despite these recommendations, however, some studies have shown that lidocaine can be omitted from the wetting solution without increased postoperative pain.<sup>32</sup> The presence of vasoconstrictors, such as epinephrine, in the infiltrating solution reduces the risk of bleeding, prolongs anesthetic action, and delays its absorption. The epinephrine dose ranges from 1:100,000 to 1:1,000,000, and although doses as high as 10 mg have been used safely, it is recommended not to exceed 0.7 mg/kg.<sup>33</sup>

**Sedation.** Oral or intravenous sedation is often administered with the goal of reducing surgery-related anxiety, consciousness, or unanticipated pain. Typically, sedatives such as benzodiazepines are combined with narcotic analgesics. Midazolam sedation (1-3 mg) together with fentanyl (25-50 mg) or remifentanil (12.5-25 mg) analgesics are commonly used for small-volume liposuction.<sup>34,35</sup> Analgesics can decrease pain associated with local anesthetic injection or unanticipated breakthrough pain. When using midazolam (with or without fentanyl), blood pressure and oxygen saturation need to be monitored throughout the procedure.

**Intravenous fluids.** Recommendations for one of the most critical aspects of liposuction, perioperative fluid management, vary in the literature. Fluid maintenance depends on the patient's body weight, volume of infiltrated solution, and the total volume of lipoaspirate.<sup>36</sup> Generally, after a 10- to 12-hour period of fasting, an average patient is expected to have lost approximately 1 L of fluid that should be replaced over the first few hours of surgery. The latest guidelines for fluid management<sup>37</sup> are as follows:

- Preoperative fluid losses should be replaced at the discretion of surgeon/anesthesiologist.
- Maintenance fluids during surgery should be replaced based on the patient's vital signs and urine output.
- The super wet technique should be used.
- An additional 0.25 mL of lactated Ringer solution should be given intraoperatively for every 1 mL of aspirate for liposuction volumes  $\geq 5$  L.

**Positioning.** Preoperative markings are made on the patient's skin while the patient is standing. Incision sites are marked to allow cross-tunneling aspiration and limit surface abnormalities.<sup>38</sup> For most procedures, the patient is positioned in the prone or supine lateral decubitus position because this allows access to and mobility for almost all areas to be treated.<sup>39</sup> Pressure points must be adequately padded, and blankets/fluid should be warmed to prevent hypothermia.<sup>40</sup>

**Skin preparation.** The most common skin preparation agents used include products containing iodophors, such as povidone-iodine or chlorhexidine gluconate. Many practices have adopted the use of chlorhexidine gluconate because of its broad-spectrum antimicrobial activity, ease of use, and durability. Some authors also administer first-generation cephalosporin 1 hour before surgery to cover skin flora.

**Cannula selection.** An extensive number of liposuction cannulas are available, and they differ in length and width (Fig 3). Cannula selection depends on anatomic area, volume of lipoaspirate, and whether the cannula is to be used to infuse versus suction fat. Blunt cannulas are commonly used to limit damage to surrounding soft tissues. These have downward-facing openings to prevent the suctioning of superficial fat. Multiple openings allow for the easier extraction of fat and cause less tissue trauma, as repeated movement over a given area is minimized. Generally, 3- to 6-mm cannulas are used for larger treatment areas, while 1.5-, 2.4-, and 3.8-mm cannulas are used in areas such as the face. Recently, power-assisted cannulas have been developed to assist easier removal of fat, with less physical strain on the operating surgeon.<sup>41</sup> Advocates of power-assisted liposuction claim that this technology limits the operating time, reduces operator fatigue, and increases the efficacy of suction. Power-assisted liposuction disadvantages include the additional cost and vibration transmitted to the surgeon's upper extremity.<sup>41-43</sup>

After infiltration, pretunneling of the area to be treated can prevent inadvertent superficial fat removal, thereby minimizing the risk for contour irregularities. Fat is generally suctioned from deep to superficial using a cross-tunneling technique. As the procedure moves superficially, cannula size and suction intensity can be decreased to decrease risk of surface irregularity. The procedure comes to an end when skin pinch testing is  $< 1$  inch, and there is a gritty feeling of the cannula (because of the remaining fibrous septa). Manual massage is conducted with a roller over the treated area to remove excess tumescent fluid, and port sites are sutured. Liposuction patient outcomes studies demonstrated



**Fig 3.** Cannulas used for liposuction. **A**, Infusion cannulas (from bottom to top, one 3-mm diameter with multiple ports and four 2-mm cannulas with various numbers and patterns of ports). Note that the second cannula is bent, because an infusion cannula can be used for aspiration in fibrous tissue toward the end of the procedure to even out superficial fat. The black cylinder at the top is the handle to connect the cannulas to the tubing. **B**, Aspiration cannulas. From bottom to top with 3 ports (Mercedes-type cannula), the first is the most aggressive, 4-mm wide cannula, then two 3-mm cannulas with different lengths. **C**, Cannulas with 1 port (4- and 3-mm diameter) are less aggressive because they have 1 port opening. These cannulas have a spatula tip on the end that makes them preferred for fibrous areas, such as a man's chest. **D**, Ten- and 15-mm cannulas in length (2 or 3 mm in diameter) and 3 ports, which are good for the face, neck, and around the umbilicus.

satisfaction rates at 80%, while 53% rated their appearance as excellent/very good. Weight gain was reported in  $\leq 43\%$  of individuals, with the abdomen being the most common site of fat recurrence. In terms of comfort, 75% of patients reported mild to moderate discomfort.<sup>44</sup> Despite positive results in fat reduction, traditional suction-assisted liposuction has no effect on skin tightening. In fact postprocedure skin laxity may manifest more in anatomic sites such as the abdomen, arms, and inner thighs.<sup>45</sup>

## ULTRASOUND-ASSISTED LIPOSUCTION

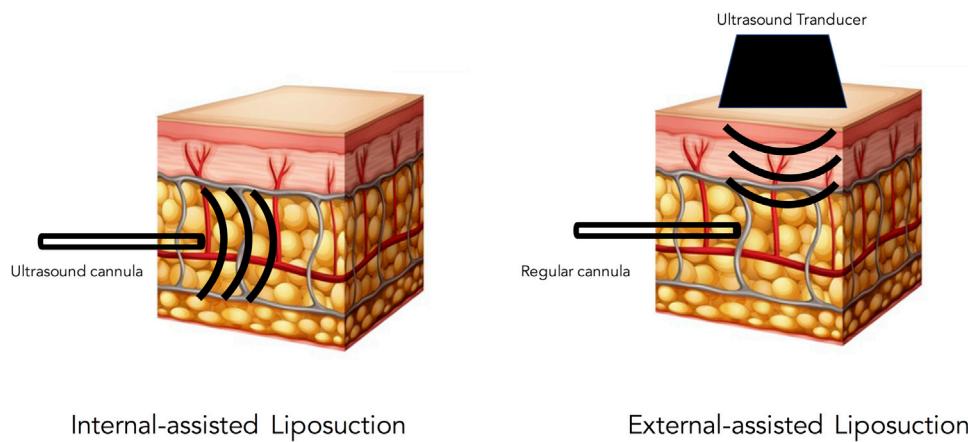
### Key points

- Ultrasound-assisted liposuction uses ultrasonic energy to allow a more selective tissue lipolysis.
- Ultrasound-assisted liposuction can be external or internal.
- Third-generation ultrasound-assisted liposuction devices present a more favorable safety and efficacy profile.

There are 2 types of ultrasound-assisted liposuction (UAL): external, during which the ultrasonic

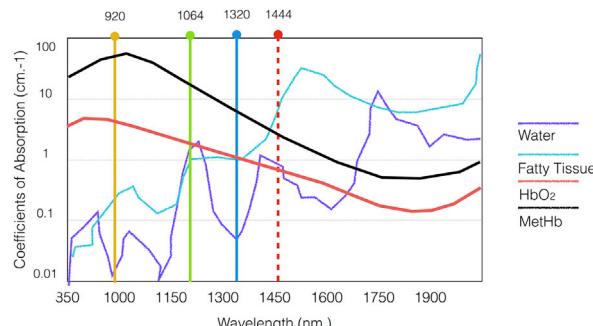
energy is applied through the skin, and internal, during which the ultrasonic energy is applied through a specialized cannula (Fig 4).

In external UAL, transcutaneous application of high-frequency ultrasound is delivered into wetted tissue, followed by traditional liposuction, with the goal of improving the mechanical removal of adipose cells. This procedure is suitable for treating large areas of fibrous tissue because the external ultrasound can allow easier access through it.<sup>46,47</sup> In external UAL, treatment areas are initially infused with tumescent anesthesia. A coupling gel is then applied at the skin-transducer interface, and ultrasound is delivered using continuous circular strokes for 10 minutes on each side. Standard tumescent liposuction is then performed. External UAL is associated with easier aspiration, rapid removal of fat, less postoperative bruising/swelling/blood loss, and a superior skin-tightening effect.<sup>48,49</sup> A study of 500 cases treated with external UAL showed high patient satisfaction and reduced discomfort with the procedure.<sup>50</sup> Overall, external UAL appears to be safe and effective for fat reduction, and the learning curve for the technique is shorter than that required for internal UAL.



Internal-assisted Liposuction

External-assisted Liposuction

**Fig 4.** Internal versus external ultrasound-assisted liposuction.**Fig 5.** Coefficient of absorption of water and fatty human tissue.

A first-generation internal UAL device (Sculpture; SMEI, Casale Monferrato, Italy) used blunt solid probes that were 4 to 6 mm in diameter, followed by aspiration with standard cannulas. After infiltration, UAL was performed from the deep to superficial planes, with the endpoint being loss of tissue resistance and change in the character of the aspirate. However, because of increased reports of skin burns, dysesthesias, and high seroma rates, use of these devices was abandoned. In second-generation devices (Lysonix 2000 [Lysonix Inc, Carpenteria, CA] and the Mentor Contour Genesis [Mentor Corp, Santa Barbara, CA]), the use of hollow cannulas allowed simultaneous aspiration and ultrasound delivery. Emulsification was complete when the aspirate changed from pale yellow to pink or gray. Although superior to first-generation devices, these second-generation devices were not popular. Their large probes ( $\geq 5$  mm) required longer incisions, while the small lumen compromised aspiration efficiency and delivered focused ultrasound that increased the risk of burns. Significant changes in the design of the solid probe were made in third-generation internal UAL devices (VASER; Sound Surgical Technologies LLC,

Louisville, CO). VASER probes require smaller incisions, and grooves near the tip allow for radial dispersion of ultrasound. This results in more effective emulsification with lower total energy application (Fig 3, E).<sup>51</sup> Continuous cannula movement is recommended when using VASER to minimize the potential for focal, secondary thermal injury. This system has allowed for more fat emulsification, less operative time and surgeon fatigue, and protects important structures, such as the blood vessels and nerves.<sup>52,53</sup> Compared with traditional liposuction, third-generation internal UAL is associated with reduced blood loss<sup>54</sup> and low complication rates.<sup>55</sup> VASER has been safely used for body contouring, for the treatment of axillary hyperhidrosis,<sup>56,57</sup> and several studies have shown that UAL can improve contour deformities in areas of excess fibrous tissue, such as the trunk and back.<sup>58,59</sup>

## LASER-ASSISTED LIPOSUCTION

### Key points

- **Laser-assisted liposuction procedures result in both fat removal and skin tightening**
- **The most frequently used wavelengths are 1064, 1320, and 980 nm**

Laser-assisted liposuction (LAL) uses laser technology either while performing liposuction, or in a 2-stage procedure using LAL before liposuction. LAL uses the principles of selective photothermolysis to preferentially lyse adipocytes and stimulate dermal collagen contraction while leaving the surrounding structures unaffected.<sup>60</sup>

The main lasers evaluated for LAL are 1064-nm neodymium-doped yttrium aluminum garnet (Nd:YAG), 1064/1320-nm Nd:YAG, and 980-nm diode lasers. These vary in their relative effectiveness to target collagen, fat, vasculature, hemoglobin, and water (Fig 5).<sup>61-64</sup> LAL devices with lower



**Fig 6.** Laser fiber (approximately 1 mm) encased in cannula.

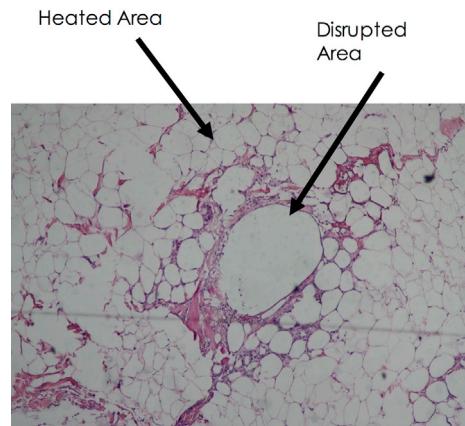
wavelengths are thought to have higher selectivity for lipolysis, but may not be as effective for skin tightening as other modalities, unless combined with another wavelength.<sup>65</sup>

During LAL, a small incision is made and the microcannula is inserted and visualized via transillumination guided by a red beam. Because of the small size of the cannula (1 mm; Fig 6), LAL is considered minimally invasive compared with traditional liposuction techniques. Cosmetically challenging and delicate areas, such as the face, forearm, upper abdomen, and knee, can benefit from LAL.<sup>66</sup>

The first device approved by the US Food and Drug Administration (FDA) for LAL was the 1064-nm Nd:YAG laser (SmartLipo; Cynosure, Westford, MA) that uses a 300- $\mu$ m fiber in a 1-mm diameter cannula.<sup>61</sup> Clinical studies combining the 1064-nm with the 1320-nm laser in a multiplex system (SmartLipo) demonstrated that it is safe and efficacious in both skin tightening and fat reduction. The addition of the 1320-nm laser that converts hemoglobin to methemoglobin makes this laser ideal for highly vascular areas.

The latest-generation LAL device combines the 1064-, 1320-, and 1440-nm wavelengths (SmartLipo Triplex; Cynosure). This wavelength combination is thought to result in greater disruption of subcutaneous fat, mainly because of the incorporation of the 1440-nm wavelength, which is thought to disrupt a larger area with less power (Fig 7). Another LAL device, CoolLipo (CoolTouch, Rosemont, CA) uses a 1320-nm wavelength and is marketed to target small areas, such as the submentum, jowls, and neck (Fig 8).

LAL using diode lasers with wavelengths between 924 and 980 nm penetrate deep into tissue and are thought to be more efficient and powerful than LAL using the Nd:YAG laser.<sup>67</sup> These devices provide



**Fig 7.** Subcutaneous fatty tissue 1 week after treatment with a 4 W 1440-nm device.

greater utility in dense areas containing large fat deposits, such as the thigh and abdomen, and can improve skin laxity. In 2007, the FDA approved the 980-nm laser lipolysis device (Lipotherme; Osiris Medical, Loos, France), which via a 1-mm microcannula integrates a 600- $\mu$ m optical fiber that is inserted into adipose tissues. A study using this laser on approximately 300 patients found that the most advantageous outcome of lipolysis resulted when energy was delivered evenly throughout the superficial, medium, and deep fat layers.<sup>68</sup>

Although disadvantages of LAL include the potential of thermal injury, high equipment cost, and prolonged procedural time, the fat reduction combined with the skin-tightening effect of LAL render it more favorable than traditional liposuction in most cases.<sup>69</sup>

## RADIOFREQUENCY-ASSISTED LIPOSUCTION

### Key points

- Radiofrequency-assisted liposuction uses radiofrequency to heat the dermis and subcutaneous tissue, resulting in fat reduction and dermal contraction
- Radiofrequency-assisted liposuction poses a low risk of complications compared to traditional liposuction

Radiofrequency-assisted liposuction (RFAL) delivers radiofrequency energy that coagulates and liquefies adipose tissue while gently heating the dermis to subnecrotic contractile levels. The BodyTite system (Invasix Ltd, Yokneam, Israel), an FDA-approved RFAL device, has been shown to be safe and effective in the removing of modest volumes of fat while inducing subdermal tissue contraction. In the BodyTite handpiece, RFAL energy is deployed



**Fig 8.** CoolLipo (CoolTouch, Rosemont, CA) Before and After: Photos courtesy of Charles Mok DO.

from an internal cannula to an external electrode, generating focused energy into the adipose tissue and fatty areas. The RFAL handpiece and the hollow internal cannula/probe are attached to suction, so there is simultaneous aspiration of the coagulated and liquefied fat (Fig 9). One of the reported advantages of RFAL is the significant contraction of the skin and soft tissue, which has been reported to be 35% at 12 months, compared with 8% for traditional suction-assisted liposuction.<sup>70,71</sup> A recent retrospective study showed that RFAL for neck and face contouring was a safe procedure, resulting in significant improvement of skin laxity and fat deposits of the cervicomental zone and jowls.<sup>72</sup>

## WATER-ASSISTED LIPOSUCTION

### Key point

- Water-assisted liposuction has a better safety profile than traditional liposuction but does not result in improved skin laxity

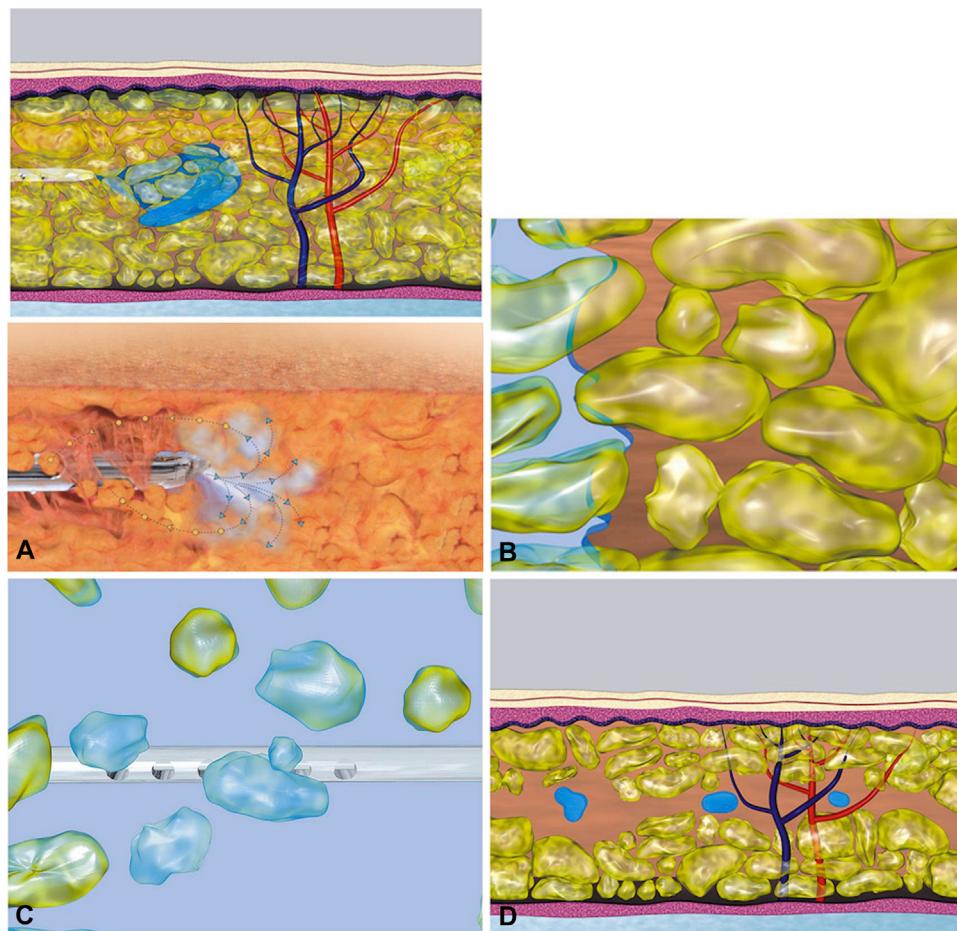
Water-assisted liposuction (WAL) uses a high-pressure jet of water to separate adipose cells and hydrodissect through tissues while preserving important anatomic structures.<sup>73</sup> WAL takes advantage of the tumescent technique but avoids some of its undesirable side effects, such as volume-related electrolyte shifts. This is achieved by using a dual-purpose cannula that emits pulsating, fan-shaped jets of tumescent solution, followed by simultaneous suctioning of the fatty tissue and the instilled fluid. A WAL device, Body-Jet (Human Med, Pomerania,



**Fig 9.** A radiofrequency-assisted liposuction handpiece.

Germany), consists of a pressure system that delivers the infiltration solution into a thin application cannula. Suction is performed with a cannula immediately after infiltration, and no waiting period is necessary because of controlled high infiltration and simultaneous suction (Fig 10). A prospective randomized study comparing traditional liposuction to WAL in 60 patients found that WAL resulted in less ecchymosis and postoperative pain compared to traditional liposuction.<sup>73</sup> In another study evaluating the outcome of WAL for patients with small to moderate adiposities and skin laxity, there were no significant complications and patient satisfaction was high.<sup>74</sup> WAL does not provide inherent skin contraction after adipose aspiration, and therefore there has been limited adoption of this technology in the United States.<sup>75</sup>

In conclusion, liposuction methodologies have become increasingly popular over the last decade because of technological innovations in equipment and evolution of techniques. Aside from reducing adipose tissue, many of the new technologies improve laxity and overall skin quality. Comparative clinical studies using standardized



**Fig 10.** The body-jet (Human Med AG, Schwein, Germany) proposed mechanism of action. **A**, The body-jet cannula is inserted into the adipose tissue. **B**, A water spray softens and releases the fat cells. **C**, Softened fat cells are gently removed in a stream of water. **D**, The volume of fat is reduced and blood vessels and nerves are left intact.

experimental parameters and measurements are still needed to gauge the individual advantages and drawbacks of each new technology and customize treatment depending on individual patient's goals and needs.

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# Injection technique in neurotoxins and fillers: Planning and basic technique

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## Learning objectives

After completing this learning activity, participants should be able to select an appropriate injection technique for a particular patient, clinical condition, and anatomic location; describe the specific preparation, hand position, depth of injection, injection pressure, and intraoperative feedback mechanisms used to deliver an appropriate and effective treatment; and combine appropriate fillers and neurotoxins to improve the overall aesthetic effect.

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Cosmetic dermatologic surgery has evolved to be a minimally invasive field that addresses patient concerns with a multimodal approach while minimizing adverse events and downtime. Within the armamentarium of dermatologic surgery, injections of soft tissue augmentation materials and neuromodulators are key tools for recontouring the aging face. Treatment of the individual patient is preceded by a comprehensive consultation that elicits patient concerns and preferences. A treatment plan is collaboratively developed to correct relevant deficits and retreat as appropriate to maintain the correction. The goal of volumization with fillers is to recreate atrophic subcutis and dermis, thereby filling the deflated face and returning it to a more youthful contour. Neurotoxins can help minimize the emergence of static wrinkles and selectively recontour the face. Treatment techniques for both filler and neurotoxin injections are customized for particular patient needs and are based on the type of deficit and the anatomic location. (J Am Acad Dermatol 2018;79:407-19.)

**Key words:** Bellafill; Belotero; Botox; consultation; Dysport; filler; hyaluronic; injection; Juvederm; neuromodulator; neurotoxin; Radiesse; Restylane; Sculptra; technique; Xeomin.

Cosmetic medicine has been revolutionized by the emergence and acceptance of prepackaged injectable fillers and neuromodulators. Facial rejuvenation was once only available to those who could afford major plastic/reconstructive surgery, but these modalities have now made this process safer, more affordable, and immediate. Dermatology has been at the forefront, the specialty most associated with leading innovation

in fillers and neuromodulators as judged by both primary care physicians and the general public.<sup>1,2</sup>

The purpose of this review is to describe how patients are treated with fillers and neuromodulators. We focus on technique alone because a broader review is beyond the scope of a succinct narrative.<sup>3</sup> We begin by characterizing the cosmetic consultation, treatment selection, and the way treatments are tailored to individual patients.<sup>4</sup> The current thinking

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regarding the process of facial aging is summarized. Finally, the specific maneuvers required for injection of fillers and neuromodulators, respectively, are delineated. The second article in this continuing medical education series discusses the specific injectable products available, particular indications, avoiding and managing adverse events, developing a treatment plan, and combining injectables with other procedures.

## THE CONSULTATION: WHERE AND WHEN TO INJECT FILLER AND TOXIN

### Key points

- Elicit and address patient concerns and preferences in a preinjection consultation
- Smaller volume injections at fewer anatomic sites may allay anxieties in novice patients
- Less patient education is required with neuromodulators, which are associated with briefer downtime and less contour change
- Neuromodulator injections for the upper face are commenced when etched lines begin to emerge

The filler injection process begins with the consultation. Patients who previously received filler and were pleased are easiest. A review of documentation regarding previous treatments helps ensure a comparable outcome in the future. Treatment intervals may be extended as small quantities of filler may persist. The potential utility of novel agents that have been approved by the US Food and Drug Administration since the patient's last visit may be discussed. Patients previously treated by others may be asked what was injected, where, in what amount, and how frequently. Patients may also be asked how they felt about the final look, 2 to 3 weeks after injection, when edema and erythema had subsided. Some injectors believe that patients who have received injectable silicone or other permanent fillers are not good candidates for temporary fillers, which may elicit an idiosyncratic immune reaction. Newcomers to filler injections will typically be more anxious. They are asked what most bothers them about their appearance, and if multiple areas are highlighted, which are most upsetting. The injector can also gently insert their own preferences, noting that they are trying to provide a professional appraisal likely more indicative of the opinion of friends and family. Patients are often alarmed by the immediate change in their facial contour from the first injections and are reassured posttreatment. Patients' overall satisfaction with fillers derives from comparison of the benefits, including youthful appearance, reduced wrinkles, and convenience, versus the costs, including time, expense, downtime, and injection

discomfort. The tolerance of first-time injectees is unknown, and it behooves the injector to begin by injecting modest amounts in one or two areas. In days to weeks, when swelling diminishes, other areas can be injected, and undertreated areas can be touched up.

As with filler, before neuromodulator injections, it is useful to review the patient's history to understand previous treatments. Patients may not remember the method used by other injectors but can communicate the posttreatment features that they found attractive or problematic. This information is used to deduce injection appropriate placement going forward. A history of brow ptosis, preference for brow elevation, or other considerations can guide treatment pattern. Downtime after botulinum injections is negligible as the tiny erythematous macules at injection sites resolve spontaneously, are concealed with makeup, or can be gently massaged away. Patients may be uncertain when they should begin undergoing neuromodulator treatments. It has been suggested that the time to start injecting the upper face is when dynamic creases generated by muscle movement begin transitioning to static creases, or etched lines present even at rest. In patients with fine, fair skin, like redheads, this can occur in the early twenties, while darker patients with ethnic skin may see such a change several decades later.

## MANAGING PATIENT EXPECTATIONS AND DEVELOPING AN ONGOING PLAN

### Key points

- Swelling, redness, and occasional bruising can occur after injections, particularly with fillers
- A predetermined treatment schedule helps maintain the desired cosmetic correction

Patients tend to be satisfied with filler injections if their expectations are coincident with outcomes. Before treatment, patient expectations may be colored by a flawed understanding of the procedure. Common misapprehensions are that injections inevitably cause an unnatural, overfilled appearance, or that fillers are risky. Conversely, patients may have unrealistically rosy beliefs about how little filler is required and how long it may last. Incorrect patient expectations should be explicitly corrected clearly and respectfully. Appropriate counseling keeps patients from unexpectedly having to cancel significant social or work events. Sticker shock, which may be associated with the realization that multiple vials may be required several times a year, can similarly be avoided with clear communication. Satisfied patients tend to return for repeat treatment.

Monitoring retention rates can help an injector assess their own performance in aligning expectations with outcomes. Overall, filler and neuromodulator treatments have been associated with improved psychosocial function and even relief from depression.<sup>5,7</sup>

Quantities injected and the frequency of injections are based on patient-specific factors. To maintain a stable contour, injections of temporary fillers are required at least once annually, and commonly twice or more often. Quantities can be adjusted, with repeat injections often requiring less material. Age-related volume loss causes a gradual increase in the correction amount over the long term.

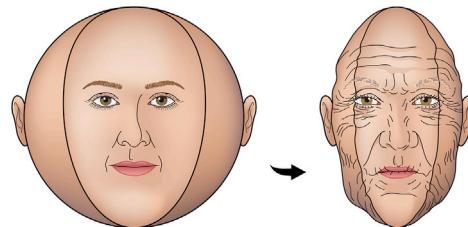
Toxin injections are resisted by a subset of patients who are worried about being injected with a “poison.” Posttreatment concerns are rare with toxin injections, which are not generally associated with swelling, bruising, or other tissue effects. Patient satisfaction with toxin injections is among the highest for a minor cosmetic procedure. Patients are generally not concerned about inconvenience or imprecision. Some patients need to be reassured that there is no physical addiction, and failure to maintain their injection schedule will not result in accelerated signs of aging.

## PLANNING: THE IMPACT OF CHRONOLOGICAL AND PHOTOAGING ON INDICATIONS FOR TREATMENT

### Key points

- Injections help make the patient appear as young as he or she feels while maintaining the natural facial structure
- Filler injections correct atrophied or descended facial fat pads that shape the face
- Volumization is an alternative or complement to skin reduction procedures like facelifts
- Injection-based rejuvenation procedures need to be tailored to the patient's ethnicity

Early analyses of beauty led to now outmoded notions that the ideal face met fixed criteria.<sup>8-19</sup> So-called “golden ratios” were used to define optimal dimensions of the upper and lower face and to specify localization of the nose and spacing between the eyes. More recently, it has been accepted that beauty comes in different forms and sizes. Modern cosmetic interventions aim not to transform patients into idealized figures but rather to help them become fresher, more youthful versions of themselves. The goal is to make patients look more like they feel, given that these two representations may diverge over time. Research suggests that posttreatment patients look several



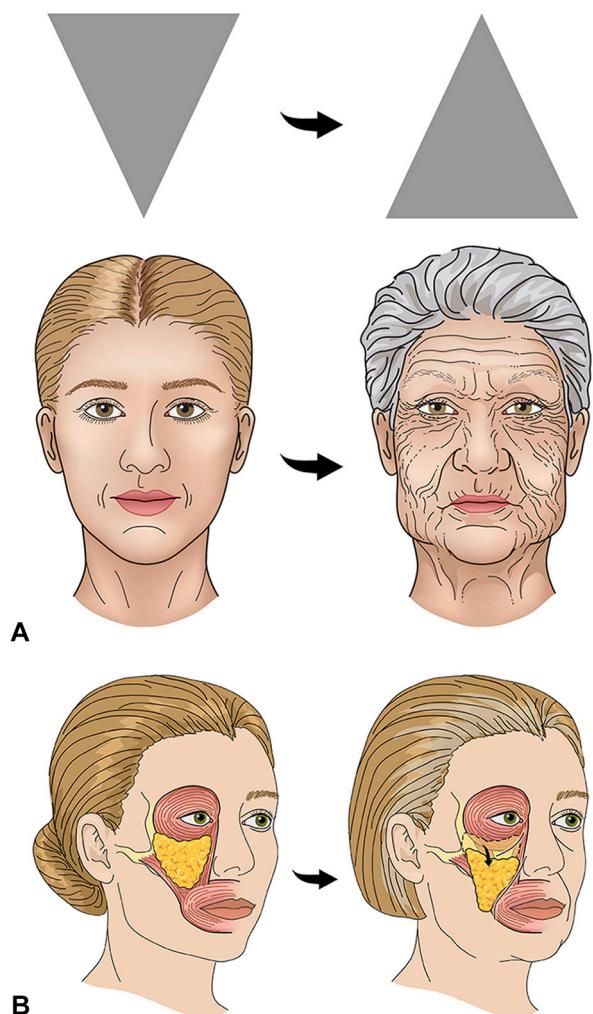
**Fig 1.** Volume loss. Cartoon exaggeratedly shows volume loss associated with aging. Specifically, the aged face (right) is notable not so much for excess skin as for atrophied, reduced, and flaccid soft tissue that results in inadequate inflation of the soft tissue envelope, and a consequent “deflated beachball” appearance.

years younger to others, but fillers are not a time machine. Erasure of aging is not possible, and likely not even desirable.

Historically, the prevailing wisdom was that photoaging and chronological aging produced excess skin and subcutis that could be rectified by skin reduction, like a facelift. With the advent of fillers, the aged facial soft tissue envelope was reconceptualized as analogous to a “deflated beachball” (Fig 1). Deflation, it was posited, could be recontoured by adding filler to replace lost fat. The current opinion is that nonspecific, diffuse reinflation of atrophied areas is not sufficient to improve aged skin, with anatomically appropriate reshaping of facial subunits best able produce an attractive, age-appropriate contour. Fillers are often part of a combination approach including other minimally invasive and invasive techniques.

The youthful face has been represented as an equilateral triangle (Fig 2, A) pointing downwards. Age-related sagging produces an inverted triangle. Cadaver studies have identified fat pads underneath the superficial facial subcutis. Interlocking laterally and supporting the dermis vertically, these pads are subject to gravitational descent with time (Fig 2, B). Infraocular slippage results in the exacerbation of tear trough depressions and nasojugal folds, and subsequent downward and medial rotation accentuates nasolabial folds.

Racial variation impacts skin aging and its correction.<sup>14,20-39</sup> Compared to the aged face in white patients, the aged African American face (Fig 3, A) typically exhibits more midface and eyelid laxity, with pseudoherniation of the orbital fat pads and prominent nasolabial folds. On the neck, blunting of the cervicomental angle is generally more notable than the fine wrinkles in older whites. The African American face tends toward malar hypoplasia and proptosis, and therefore injection into the midface or attempts to camouflage proptosis may be



**Fig 2.** Shift of volume. **A**, The shape of the prototypical youthful face approximates an isosceles triangle with the point aimed downward near the chin, with a wider top at the temples and cheekbones. As we age, this triangular shape inverts; fat pads underlying the skin descend, nasolabial folds and jowls become more prominent, and tear troughs and temporal hollows deepen. **B**, Intraocular fat pads descend and medially rotate with age. The nasolabial folds are augmented as the tear troughs under the eyes deepen.

inappropriate. In Latina patients (Fig 3, B), aging causes a thicker, fuller midface, with excess skin and sagging of the upper and lower eyelids; nasolabial folds may become prominent, but the chin is often recessed. It is important to understand the ethnic starting point of patients to address their aged face. Photographs from youth may show the baseline facial architecture, which may be even more complex in patients with mixed ethnicities.

Racial variation implies different sizes and orientations of facial features. The mouth is less

wide and the mandible is wider in Asian (Fig 3, C) versus white faces. Asian and African noses have a wider base but a less tall tip than noses of white patients. Typical Asian faces have an intercanthal distance greater than those of white patients.

The degree of aging impacts the placement of neuromodulators. Those older than their fifties or with severe photodamage have a weaker frontalis muscle that is treated sparingly to avoid brow ptosis or a “heavy” feeling. Danger zones, like close above the mid-brow or below the eyelid, are injected carefully. Lax lower eyelids exhibit a positive “snap test,” precluding midline injections to avoid scleral show. The snap test is a maneuver to test the elasticity of the lower eyelid skin and muscle. The skin at the center of the lower eyelid is pinched and pulled away from the globe and then released. If the skin spontaneously retracts quickly, the snap test is negative and neurotoxin injections in the mid-lower eyelid will likely be well-tolerated; if retraction occurs slowly, this positive snap test indicates that elasticity is diminished, and localized neurotoxin may result in ectropion. Incipient static creases in a young patient may indicate premature skin aging, and toxin may forestall their imminent deepening. Photographs of older family members may reveal the likely course of aging.

## TIME ALLOCATION FOR FILLER AND TOXIN INJECTION

### Key point

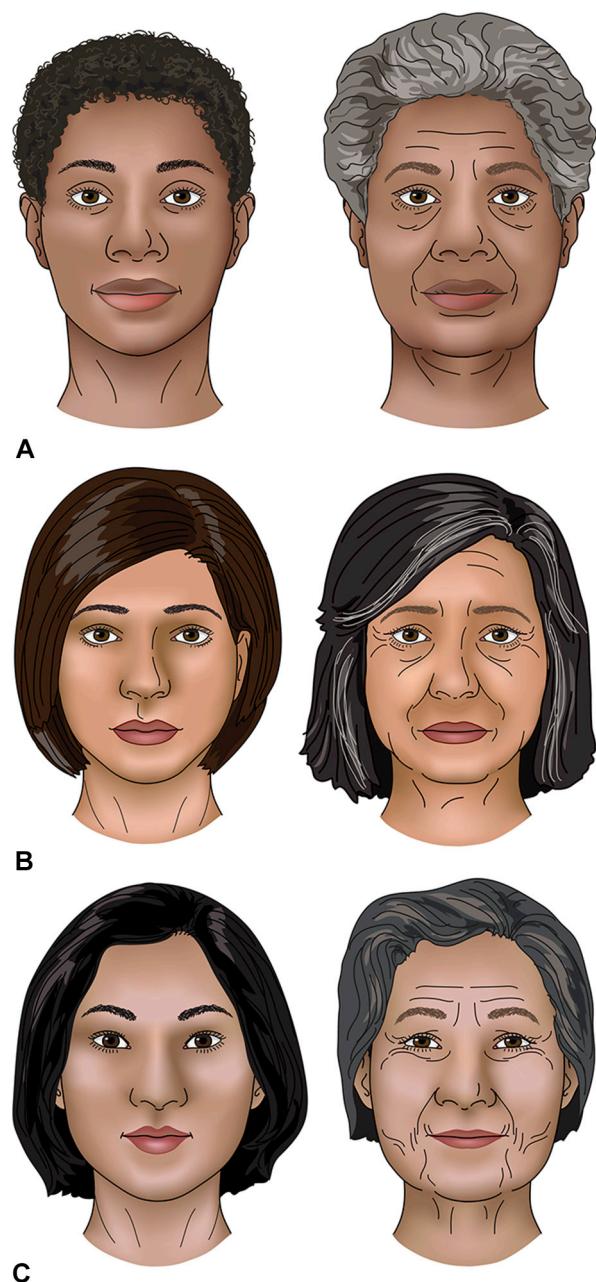
- **Filler injections are time-intensive because contour and symmetry must be preserved**

Relevant work before the delivery of botulinum toxin for mitigation of facial creases includes preinjection preparation, such as selection of toxin, reconstitution and dilution, and mapping of the face. Injection itself is simple and quick. However, the injection of temporary prepackaged injectable soft tissue augmentation materials is more time-consuming, with delivery of even a single vial requiring effort comparable to the planning and execution of an elliptical excision. Overinjection must be avoided, and right to left symmetry must be maintained.

## BASIC INJECTION TECHNIQUES: FILLERS

### Key points

- **Most injectable fillers are placed in the subcutis, with more viscous, thicker fillers placed deeper**
- **Common injection techniques include serial puncture, linear threading, cross-hatching, fanning, and depot placement**



**Fig 3.** **A**, Typical African American faces, young and old. Compared to whites, the young (left) African American face has relative malar hypoplasia. As the typical African American face ages (older face on right, younger on left), fat redistribution and descent, including in the submental area, is more notable than the fine lines, wrinkles, and skin laxity more often seen in aging whites. **B**, Typical Latino faces, young and old. Younger faces (left) tend to be wider and fuller, with thicker subcutaneous fat pads. Like Asians, Latinos have a wider intercanthal distance than whites, with lateral canthi that are higher than medial canthi. Chins can be small and recessed, and noses slightly wide but not overall large in size. As Latinos age (right), thick folds but few fine wrinkles appear as the copious soft tissue sags. Eyelids and eyebrows become heavy and descend,

- **Fillers are layered to correct areas where fine superficial lines overlie deeper volume loss**
- **Filler injection remains more art than science, elevating aesthetic improvement above the erasure of specific lines and depressions**

Most common fillers (Table I) in the United States are “linear fillers,” space-occupying substances injected into the skin to immediately and directly modify contour. No matter their chemical composition, linear fillers can be compared based on rheology, a fluid mechanics term describing their viscosity (ie, resistance, flow, or thickness) and elasticity (ie, stickiness or structure). Some fillers are thicker and require more hand force to eject from the syringe through the needle, with this greater cohesiveness and firmness impacting both how they feel and how likely they are to cause tissue trauma, including swelling and bruising. Thicker, more viscous fillers are injected deeper into the subcutis and offer greater structural support, and often greater *in vivo* persistence.

There is no consensus on the appropriate method for cleansing the skin before filler injection or even whether such preparation is routinely required. Alcohol and chlorhexidine may be used more often than betadine, which can stain clothes and skin. Some practitioners are satisfied if patients simply remove any make-up and wash the treatment area with soap and water. Facial skin, the most common site of filler injection, is generally well-perfused and resistant to infection. Off the face—for instance, when hands are injected with filler—a preparation solution is commonly used.

The depth of injection of linear fillers (Fig 4) is a source of frequent confusion given the ubiquity of the term “dermal fillers,” particularly in the plastic surgery literature. In fact, virtually all linear fillers are injected into the subcutis, usually the high subcutis below the dermis. Deeper injections can be wasteful,

←  
suborbital fat accumulates, and nasolabial folds grow. **C**, Typical Asian faces, young and old. Asians (left) tend to have the widest intercanthal distances and the most slant in the eyes, with lateral canthi markedly higher than medial canthi. Mouths are less wide and mandibles are more prominent and wider in Asians compared to whites. Like Latinos, Asians have broader noses that are less protuberant at maximal elevation. Similar to Latinos and African Americans, Asians age (right) with fewer fine lines, wrinkles, and skin laxity than whites. Sagging fat pads may also be less notable in aging Asians than those of other ethnicities.

**Table I.** Common fillers used in the United States and their properties

Trade name*	Company	Primary material	Concentration	Anesthetic	Rheology						Cohesivity (g/mf)	Crosslinking	FDA-approved indication
					G' (Pa) = elasticity 5 Hz	G' (Pa) = elasticity 0.7 Hz	G'' (Pa) = viscosity 5 Hz	G'' (Pa) = viscosity 0.7 Hz					
Bellafill	Suneva Medical, Inc	PMMA beads, collagen, and lidocaine	20% PMMA microspheres 3.5% bovine collagen	0.3% lidocaine	—	—	—	—	—	—	—	—	Correction of NLFs and moderate to severe, atrophic, distensible facial acne scars on the cheek in patients >21 years of age
Belotero Balance	Merz Pharmaceutical	HA	22.5 mg/mL	None	128 <sup>40</sup>	39 <sup>41</sup>	82 <sup>40</sup>	24 <sup>41</sup>	69 <sup>40</sup>	BDDE cross-linked			Correction of moderate-to-severe facial wrinkles and folds (such as NLFs)
Juvederm Ultra	Allergan	HA	24 mg/mL	None	—	94 <sup>41</sup>	—	35 <sup>41</sup>	—	Hylacross highly cross-linked			Correction of moderate-to-severe facial wrinkles and folds (such as NLFs)
Juvederm Ultra Plus	Allergan	HA	24 mg/mL	None	—	135 <sup>41</sup>	—	38 <sup>41</sup>	—	Hylacross highly cross-linked			Correction of moderate-to-severe facial wrinkles and folds (such as NLFs)
Juvederm Ultra Plus XC	Allergan	HA	24 mg/mL	0.3% lidocaine	244 <sup>42</sup> and 263 <sup>40</sup>	—	76 <sup>42</sup> and 79 <sup>40</sup>	—	78 <sup>42</sup> and 112 <sup>40</sup>	Hylacross highly cross-linked			Correction of moderate-to-severe facial wrinkles and folds (such as NLFs)
Juvederm Ultra XC	Allergan	HA	24 mg/mL	0.3% lidocaine	207 <sup>40</sup>	—	80 <sup>40</sup>	—	96 <sup>40</sup>	Hylacross highly cross-linked			Correction of moderate-to-severe facial wrinkles and folds (such as NLFs) and into the lips and perioral area for lip augmentation in adults over age of 21

Juvederm Volbella XC	Allergan	HA	15 mg/mL	0.3% lidocaine	274 <sup>42</sup> and 271 <sup>40</sup>	174 <sup>43</sup>	41 <sup>42</sup> and 39 <sup>40</sup>	28 <sup>43</sup>	18 <sup>42</sup> and 19 <sup>40</sup>	Vycross tightly cross-linked	Injection into the lips for lip augmentation and for correction of perioral rhytids patients >21 years of age
Juvederm Vollure XC	Allergan	HA	17.5 mg/mL	0.3% lidocaine	317 <sup>42</sup> and 340 <sup>40</sup>	279 <sup>43</sup>	42 <sup>42</sup> and 46 <sup>40</sup>	39 <sup>43</sup>	24 <sup>42</sup> and 30 <sup>40</sup>	Vycross tightly cross-linked	Correction of moderate-to-severe facial wrinkles and folds (such as NLFs) in patients >21 years of age
Juvederm Voluma XC	Allergan	HA	20 mg/mL	0.3% lidocaine	353 <sup>42</sup> and 398 <sup>40</sup>	240 <sup>41</sup> and 314 <sup>43</sup>	40 <sup>42</sup> and 41 <sup>40</sup>	28 <sup>41</sup> and 17 <sup>43</sup>	35 <sup>42</sup> and 40 <sup>40</sup>	Vycross tightly cross-linked	Deep (subcutaneous and/or suprapriosteal) injection for cheek augmentation to correct age-related volume deficit in the midface in patients >21 years of age
Radiesse	Merz Pharmaceutical	Calcium hydroxylapatite	—	None	2782 <sup>42</sup>	1407 <sup>44</sup>	1075 <sup>42</sup>	3498 <sup>44</sup>	225 <sup>42</sup>	—	Correction of moderate-to-severe facial wrinkles and folds (such as NLFs) and also for restoration or correction of the signs of facial fat loss (lipoatrophy) in patients with HIV
Restylane	Galderma Laboratories, L.P.	HA	20 mg/mL	None	—	513 <sup>44</sup> and 565 <sup>41</sup>	—	1192 <sup>44</sup> and 106 <sup>41</sup>	—	BDDE cross-linked	Correction of moderate-to-severe facial wrinkles and folds, such as NLFs, and for submucosal implantation for lip augmentation in patients >21 years of age
Restylane Defyne	Galderma Laboratories, L.P.	HA	20 mg/mL	3 mg/mL lidocaine HCl	—	—	—	—	—	BDDE cross-linked	Correction of moderate-to-severe, deep facial wrinkles and folds (such as NLFs) in patients >21 years of age

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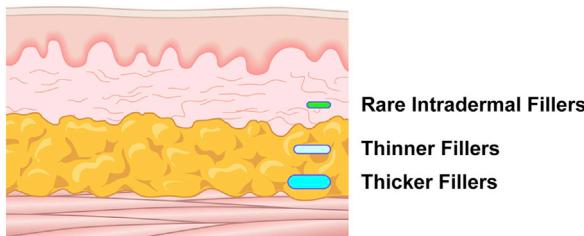
**Table I.** Cont'd

Trade name*	Company	Primary material	Concentration	Anesthetic	Rheology				Cohesivity (gmf)	Crosslinking	FDA-approved indication
					G' (Pa) = elasticity 5 Hz	G' (Pa) = elasticity 0.7 Hz	G'' (Pa) = viscosity 5 Hz	G'' (Pa) = viscosity 0.7 Hz			
Restylane Lyft with lidocaine	Galderma Laboratories, L.P.	HA	20 mg/mL	0.3% lidocaine	—	—	—	—	—	BDDE cross-linked	Correction of moderate-to-severe facial folds and wrinkles, such as NLFs
Restylane Refyne	Galderma Laboratories, L.P.	HA	20 mg/mL	3 mg/mL lidocaine hydrochloride	—	—	—	—	—	BDDE cross-linked	Correction of moderate-to-severe facial wrinkles and folds (such as NLFs) in patients >21 years of age
Restylane Silk	Galderma Laboratories, L.P.	HA	20 mg/mL	0.3% lidocaine	—	—	—	—	—	BDDE cross-linked	Submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids in patients >21 years of age
Restylane-L	Galderma Laboratories, L.P.	HA	20 mg/mL	0.3% lidocaine	710 <sup>42</sup> and 864 <sup>40</sup>	677 <sup>43</sup>	204 <sup>42</sup> and 185 <sup>40</sup>	136 <sup>43</sup>	26 <sup>42</sup> and 29 <sup>40</sup>	BDDE cross-linked	Correction of moderate-to-severe facial wrinkles and folds, such as NLFs and submucosal implantation for lip augmentation in patients >21 years of age
Sculptra Aesthetic	Galderma Laboratories, L.P.	PLLA	367.5 mg in vial	None	—	—	—	—	—	—	For use in immunocompetent patients as a single regimen for correction of shallow to deep NLF contour deficiencies and other facial wrinkles in which deep dermal grid pattern injection technique is appropriate

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BDDE, 1,4-butanediol diglycidyl ether; HA, hyaluronic acid; gmf, grams-force; NLF, nasolabial fold; PLLA, poly-L-lactic acid; PMMA, polymethylmethacrylate.

\*Trade names are property of their respective owners.



**Fig 4.** Depth of injection of linear fillers. Prepackaged injectable soft tissue augmentation materials (often incorrectly referred to as “dermal” fillers) are almost always placed in the subcutaneous tissue. Thinner, less viscous fillers may be best injected in the high subcutis, close to the dermal subcutaneous junction, and thicker, more viscous fillers slightly lower, in the mid-subcutis. Only rarely are a small subset of fillers injected into the dermis; when this is done, small aliquots are used to avoid a Tyndall effect or persistent intradermal nodules.

because the deep subcutaneous space is a capacious sink for large quantities of filler that do not transmit contour change. Intradermal injections are generally technique errors that lead to nodules—violaceous for translucent fillers (because of the Tyndall effect) or skin-toned for white fillers. Inadvertent intradermal injection causes intense back pressure and slow flow. When this occurs, the needle tip should be repositioned into the subcutis. All rules have exceptions, with some thin linear fillers (eg, Belotero [Merz Pharma GmbH, Frankfurt, Germany] and the no longer available human and bovine collagens) appropriate for intradermal injection. Experienced injectors may deliver minute quantities (eg, 0.01-mL aliquots) of less viscous fillers into the dermis to correct irregularities like fine ice pick acne scars, but this is not a routine or recommended approach.

Common injection methods include “linear threading” and “serial puncture.”<sup>8-19</sup> In linear threading (Fig 5, A), the needle is inserted at an acute angle (<90°) and then advanced laterally. Injection can be anterograde (commenced at the point of insertion and continued while the needle is advanced) or retrograde (initiated as the needle is withdrawn from the most distant point). Anterograde injections allow hydrodissection of the tissue, which can facilitate needle insertion, while retrograde injections provide the security of preplanning the course of filler delivery. Benefits of anterograde injection include that the pressure of injection can cleave tissue planes naturally and deposit filler where it is required, without the needle or cannula creating an artifactual tunnel that transects planes or vessel lumina; in addition, because a stream of soft extruded filler precedes the sharper tip of the needle or cannula, tissue trauma may be minimized. On the other hand, retrograde injections may be preferred

because they offer more control over filler placement, with this being placed precisely and exclusively into a preexisting tunnel created by the operator; moreover, because the tunnel for injection already exists, less injection pressure may be needed to expel the filler from the syringe. Whichever method is chosen, injection should be avoided while the needle is traversing the dermis to avoid leaving small, visible intradermal nodules.

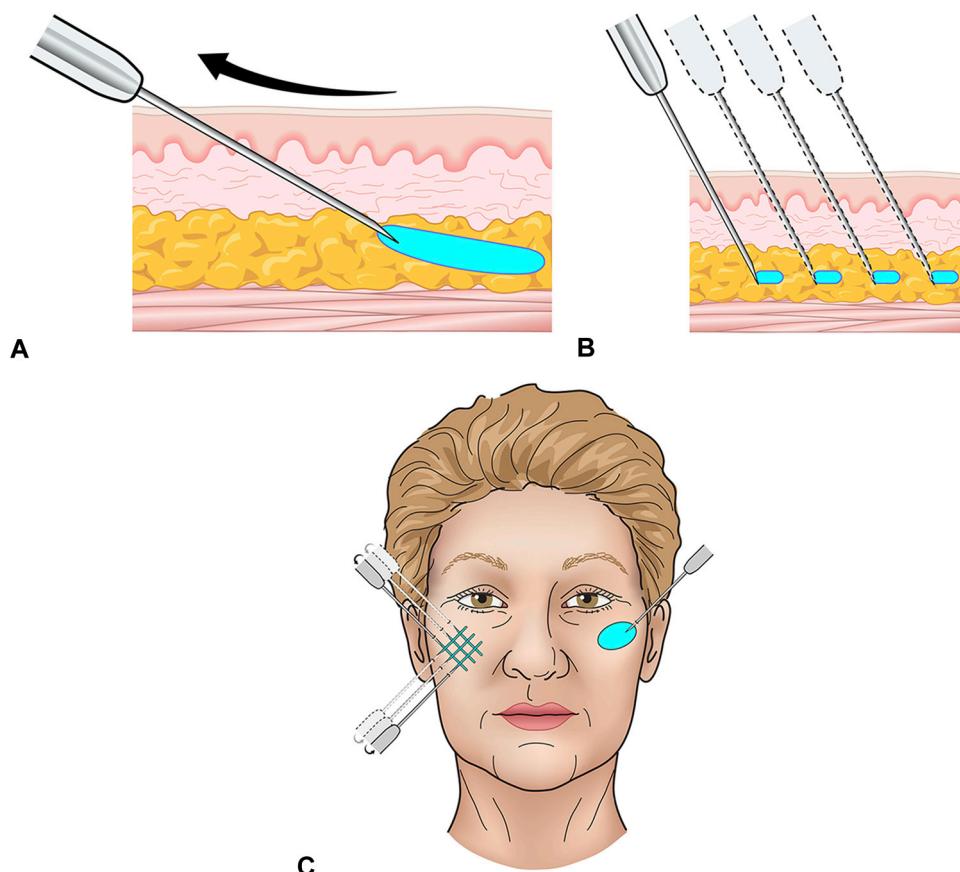
Serial puncture (Fig 5, B) is a subtly different technique comprised of numerous small injections. Each injection perforates the dermis followed by extrusion of a droplet of filler into the high subcutis. The needle is then withdrawn, repositioned a small distance away, and the process is repeated. Unlike linear threading, serial puncture does not rely on much lateral movement of the needle within the subcutis.

The benefits of serial puncture include (1) less risk of needle trauma because the needle enters and exits without horizontal displacement that could nick vessels; (2) precise delivery to each locus; and (3) suitability for small defects. The benefits of linear threading include (1) fewer skin entry points per unit area; (2) even, uniform delivery of filler; and (3) a diminished risk of intradermal injection given fewer insertions.

The angle of insertion during filler placement is a matter of physician preference. In general, serial puncture may predispose to a perpendicular approach and linear threading a narrower angle of incidence, which lends itself to lateral advancement. Alternatively, vertical insertion may be followed by lateral redirection to enable linear threading. Such an approach reduces intradermal travel, minimizing the likelihood of transection of dermal vessels. Conversely, vertical injections can induce excessively deep placement because the needle tip is poorly visualized.

Injection methods frequently used for large areas and deep soft tissue defects like atrophied cheeks include “cross-hatching” and “depot injections” (Fig 5, C). Cross-hatching can literally entail the placement of a row of linear threads, followed by another row at right angles. To minimize trauma, injectors may select a fanning pattern, whereby an arc of linear threads emanate from a single injection point. After each thread, the needle is retracted, redirected a few degrees, and pushed forward again. Fans can be propagated from several entry points to create a cross-hatching pattern.

Depot injections solve the same problem in an altogether different way. Rather than dispersing a wafer of filler in the superficial subcutis, depots



**Fig 5.** **A**, Linear threading. The needle is inserted at a shallow angle almost parallel to the skin, and as the needle is advanced and/or withdrawn, a long, continuous stream of injectant is delivered. Multiple threads may be placed in a given area. Benefits include the need for fewer entry punctures, and risks, less precision in placement. **B**, Serial puncture. The needle is reinserted and removed, and small aliquots delivered, at numerous points along a wrinkle or other area to be treated. Benefits include precision of placement. Risks, because of the need to repeatedly ascertain the correct depth of injection, include the possibility of inadvertent injection into the intradermal plane. **C**, Cross-hatching and depot. In cross-hatching (patient's right), linear threads are placed in a criss-cross manner, perpendicular to each other, to intensely and uniformly fill a tissue plane in a broad target area. Cross-hatching permits the injection of larger volumes into larger areas while maintaining a smooth, even contour. Depot injections are a single large bolus of injectant, and are often placed deep, just above the bony margin at the level of the periosteum. Depots can dramatically fill one specific area, or they can be massaged to spread less noticeably fill a broader, wider area.

create a nodule of filler deep at the center of the defect. Manual compression is used to spread this evenly. Requiring one injection per site, depots may help reduce insertion-associated pain, bruising, and palpable dermal nodules. Spreading of the depot can, however, induce pain and bruising. Multiple smaller depot injections may therefore be preferred. Intraoral depot injections may further minimize cutaneous trauma, but such injections may be less precise and prone to bacterial colonization. Biofilms resistant to antibiotics can be created as the oral flora enter the subcutis.

Dilution of fillers with lidocaine has been used to control pain and adjust filler thickness. Hyaluronic

acid derivative fillers (eg, Restylane, Juvederm) and injectable calcium hydroxylapatite (Radiesse) are approved by the US Food and Drug Administration for delivery in combination with lidocaine and supplied in premixed syringes. Off-label modifications include further dilution with additional lidocaine, using female-to-female syringe adaptors. When fillers are diluted, care is taken to ensure that the resulting mixture is of uniform consistency. Finer solutions may be useful for superficial defects and reduce bruising. Filler function is not impeded by addition of lidocaine.<sup>45,46</sup> Very dilute mixtures will be largely lidocaine, which will be resorbed, suggesting the need for a subsequent touch-up procedure.

Different fillers can correct a multipart defect. For instance, a fine line may overlie a deep crease at the nasolabial fold. Thicker filler material may be injected into the mid-subcutis to elevate the deep crease, and thinner filler may be pushed under the dermis to efface the fine rhytid. Layering can be accomplished with different filler materials or different dilutions of the same.

Similarly, treatment of different indications may require different techniques. For instance, acne scars may be corrected with serial puncture delivery of small aliquots into the reticular dermis or superficial subcutis. Nasolabial folds may be directly corrected using a variety of methods, including serial puncture, linear threading, or cross-hatching of the entire area in layers, with different fillers. Upper cheek and lower face augmentation may require cross-hatching, fanning, or even deep depot injections to sculpt the facial contour. Infraorbital correction of tear troughs or nasojugal folds may be best accomplished with linear threading through a cannula, thereby minimizing the number of entry sites and therefore of inadvertent cutaneous trauma that may manifest as ecchymoses.

The facial skin is a 3-dimensional structure of parallel planes connected by soft tissue ties. This complex layer cake deforms in unexpected ways. For instance, a marionette line at the oral commissure may be unresponsive to filler, and further injection may deepen it. Therefore, in areas of thin tissue or at hypermobile regions, it is prudent to inject small quantities at intervals of several weeks or months. In this manner, the soft tissue scaffold at the site is gradually strengthened. Spaces between assimilated filler provide room for additional injectable material. Injection technique has shifted from a focus on filling specific depressions to a preference for more diffuse volumization that reshapes the face. Experienced injectors use fillers to treat entire “zones,” augmenting the mid- and upper cheeks, inflating temple hollowing, and blending perioral rhytids. Augmenting the upper face restores the youthful facial contour while providing lift that softens nasolabial creases. Zone injecting has its limits. No amount of upper face filler can entirely obscure perioral, perinasal, and periorbital lines, which do require some degree of direct correction.

While basic filler techniques are easily explained, the placement of filler remains more art than science. Frequent practice coupled with a sense of proportion allows skillful injectors to create natural, age-appropriate contours. While sufficiency of filler is important, more is not always better. Overinflation may camouflage aging at the cost of creating a cartoon-like appearance. Very deep injections of

copious quantities of linear fillers can diffuse in unpredictable ways, sometimes resulting in successful elevation of a region, and sometimes in decreased efficacy and volume enhancement at undesired locations. Fashion impacts soft tissue augmentation, with the recent emphasis on exaggerated upper cheek volumization giving way to the popularity of thick lips in young women. However, most patients prefer a natural appearance that conceals the visible signs of aging without adding the telltale signs of a trip to the dermatologist.

## BASIC INJECTION TECHNIQUES: TOXINS

### Key points

- Neuromodulator injections are used to minimize upper face lines, including vertical glabella rhytids, horizontal forehead lines, and crow's feet
- Commonly treated muscles include the frontalis, the procerus, the corrugators, and the orbicularis oculis
- Short, small-bore needles minimize injection trauma
- More concentrated neurotoxin solutions have their effect closer to the point of injection (ie, have a narrower action halo), and more dilute solutions impact skin further away (ie, have a wider action halo) but with a relatively lesser degree of effect

The technique for the use of botulinum toxin<sup>8-19</sup> for facial rhytids owes its invention and refinement to the work of two pioneers, Jean and Alastair Carruthers. Initial dermatologic uses for botulinum toxin included the reduction of upper face rhytids, notably those of the glabella, forehead, and crow's feet.

Injections are typically placed symmetrically in the upper face, commonly into the frontalis, procerus, corrugators, and orbicularis oculis. Short, small-bore needles are inserted at acute to perpendicular angles. Superficial dermal injections bruise less often because fewer vessels are traversed. Deeper injections at the periosteum may elicit a disconcerting audible popping sound, but they also minimize the visible intradermal papules at the sites of injection. The longer persistence of deeper injections remains unproven.

The smallest effective dose is used to avoid unwanted outcomes like asymmetry, brow or lid ptosis, ectropion, or mouth or lip asymmetry. Electrophysiologic guidance is not used to place botulinum toxin into facial muscles. Distance from external anatomic landmarks may be used instead since anatomic variation is modest. Common

configurations for injections can be expressed in stylized diagrams.

Reconstitution volume, dilution, and distance of effect from the point of injection are related concepts. Botulinum toxin type A, whether ona-, abo-, or inco-, is provided dehydrated from the manufacturer, and must be mixed with sterile normal saline before injection. Per 100-unit vial of ona- and inco-, and per 300-unit vials of abo-, the quantity of saline used for reconstitution varies widely, from 1 to 10 mL. Concentrated solutions result in a smaller action halo around the point of injection.

### Variation in technique

As discussed above, injection treatments are designed to address individual patient features while being age-, ethnicity- and sex-appropriate. The methods described are not exhaustive but are rather a set of basic tools.

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# Injection technique in neurotoxins and fillers: Indications, products, and outcomes

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## Learning objectives

After completing this learning activity, participants should be able to describe the specific signs and symptoms that can be used to detect an incipient adverse event during or after injection of fillers and neurotoxins; describe the corrective strategies that can be initiated to mitigate the consequences of such an event; and identify demographic and other risk factors for such adverse events.

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Injectable fillers and neuromodulators are used for a range of indications pertaining to the correction of facial aging and disfigurement. Fillers can correct soft tissue loss, depressed scars, and atrophy or asymmetry induced by systemic or local disease. Neuromodulators correct muscle-mediated skin creases, reshape the face, and address right–left functional asymmetry. Among the prepackaged injectable fillers approved by the US Food and Drug Administration are hyaluronic acid derivatives, calcium hydroxylapatite, and poly-L-lactic acid; neuromodulators include three types of botulinum toxin type A and one type of type B. Adverse events associated with injections are typically mild, easily managed injection pain, followed by redness, swelling, and bruising. Asymmetry, nodules, ptosis, and intravascular occlusion are less common. Filler and toxin injections are part of a complete treatment plan. Reinjection is typically required to maintain the clinical effect, and combination treatment with laser and energy devices can enhance the aggregate effect. (J Am Acad Dermatol 2018;79:423–35.)

**Key words:** adverse event; asymmetry; Bellafill; Belotero; Botox; Dysport; filler; hyaluronic; indication; injectable; Juvederm; neuromodulator; neurotoxin; pain; Radiesse; Restylane; Sculptra; Xeomin.

## RANGE OF INDICATIONS

### Key points

- **Fillers have diverse indications, including the correction of age-related soft tissue loss, depressed scars, and atrophy or asymmetry induced by systemic or local disease**

- **Neuromodulators are used for the treatment of muscle-mediated skin creases, for reshaping of the face by selective muscle relaxation, and for the correction of right–left functional asymmetry**

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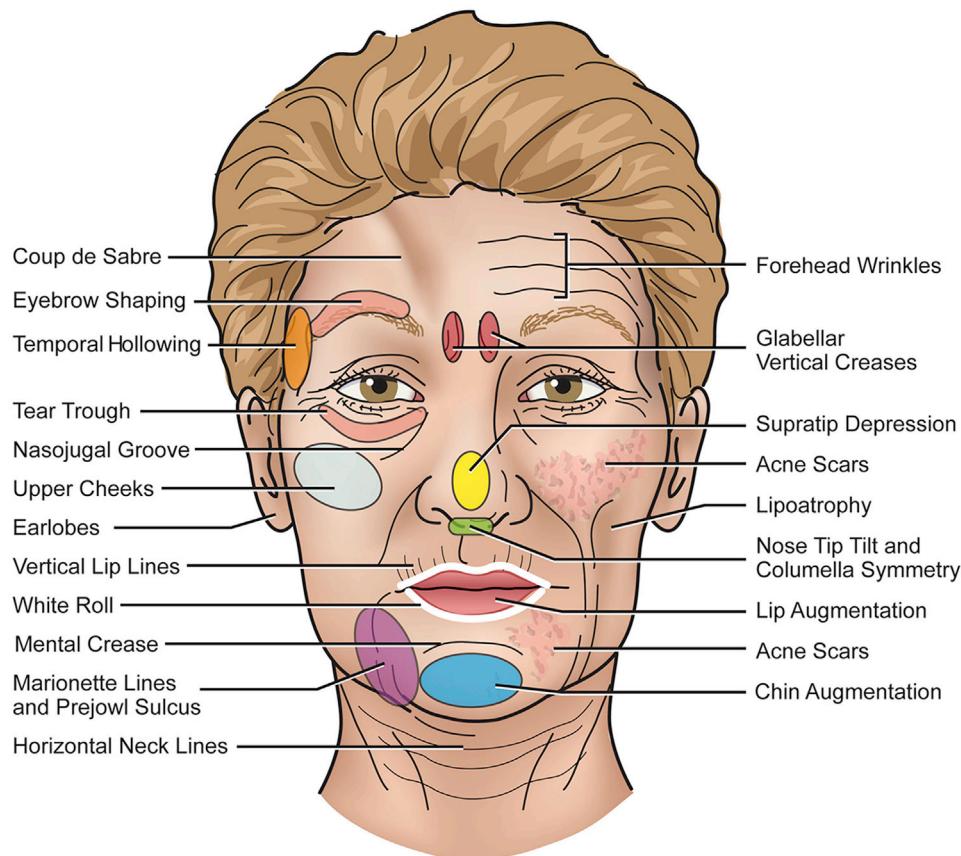
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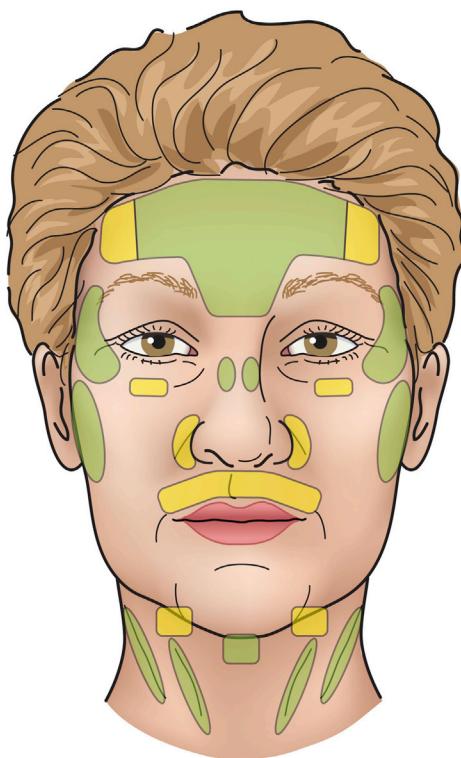
**Fig 1.** Common locations where filler materials are injected.

Although only a minority of routine uses are on-label according to the US Food and Drug Administration (FDA), temporary injectable fillers are medically indicated for a range of dermal and subcutaneous contour abnormalities (Fig 1).<sup>1-16</sup>

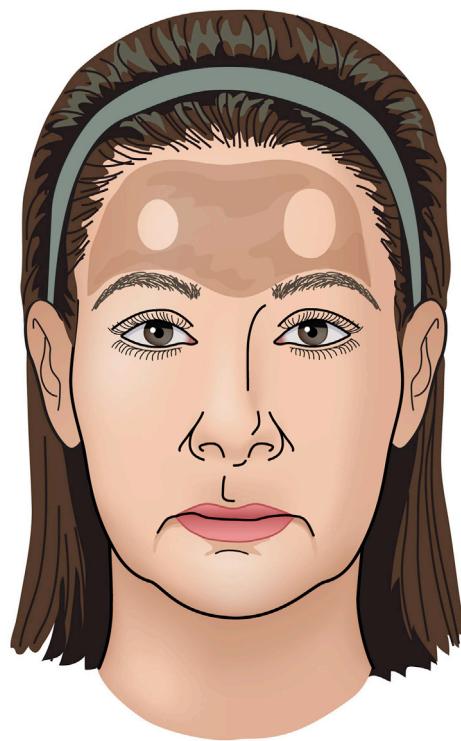
On the face, fillers can correct aging-related volume loss causing forehead horizontal creases, glabella vertical lines, temporal hollowing, recessed eyebrows, upper cheek atrophy, tear troughs, nasojugal folds, midface atrophy, nasolabial folds, vertical lip lines, lip thinning, preauricular fat atrophy, earlobe thinning, marionette lines, mental creases, and jawline irregularities. Depressed scars, whether caused by disease, injury, or iatrogenic processes, are amenable to lifting with filler. While fillers are commonly used for rolling scars, other acne scars, including ice pick and boxcar scars, are also modifiable. Skin biopsy and surgical scars can be filled, with small nasal dorsal pits a particularly suitable indication. Primary and secondary subcutaneous fat atrophy, including coup de sabre, HIV lipoatrophy, and progressive hemifacial atrophy, are amenable to fillers. Other uses include the improvement of cicatricial ectropion and correction of right-left

facial asymmetry. Off of the face, fillers can smoothen scars and depressions. Body indications include horizontal creases of the neck (ie, “necklace” lines), fine rhytids of the upper chest and décolletage, and dorsal hand atrophy.

Botulinum toxins were first approved by the FDA for the treatment of glabella lines, but now are used for various aesthetic purposes (Fig 2) both on and off the face.<sup>17-32</sup> Toxins can treat muscle-mediated dynamic horizontal forehead lines, periorbital smile lines (ie, “crow’s feet”), upper and lower lip vertical rhytids, and cobblestoned mental creases. Toxins can also reshape the face by selective muscle relaxation. Specific uses include upturning the upper lip, rounding a square mandibular contour, and widening the eye aperture to an almond shape. Injections can raise or lower a point on the face, thereby elevating the nasal tip, raising or lowering the brow, lifting drooping oral commissures, and lowering the lip to prevent show of the gums. Injections reduce scar formation in healing surgical or traumatic wounds. Like fillers, toxins can also correct facial asymmetries caused by disease, injury, or man-made causes. Off of the face, indications include platysmal banding upon tooth clenching and chest rhytids.



**Fig 2.** Neuromodulator injections are safely placed at many facial anatomic sites (green shaded areas). Certain other areas (yellow shaded areas) are safe to inject if appropriate precautions are observed. Injections above the lateral brow should be placed to avoid brow ptosis or heaviness; at the mid-lower eyelid, injections should be avoided in older patients with small muscle weakness that can result in ectropion; perinasal injections for correction of a gummy smile and injections on the upper cutaneous lip for vertical lip rhytids are performed symmetrically around the midline, in small doses, taking into account any preexisting right–left asymmetries to avoid a lopsided final appearance; injections on the jawline to raise the lip corners are at or lateral to the prejowl sulcus as much more medial injections can result in lip asymmetry.



**Fig 3.** Action halos of equivolumic, equipotent injections of abobotulinumtoxinA (patient's right), and ona- or incobotulinumtoxinA (left), respectively.

onabotulinumtoxinA (Botox; Allergan Inc, Dublin, Ireland), abobotulinumtoxinA (Dysport; Galderma, Lausanne, Switzerland), and incobotulinumtoxinA (Xeomin; Merz Pharma GmbH & Co KGaA, Raleigh, NC).<sup>33–40</sup> While each has the same core composition, associated complexing proteins differ. There is at most a 3% difference in effectiveness between ona- and inco-toxins. Abo-toxins reconstituted in equipotent, equivolemic solutions have a broader action halo (Fig 3), meaning activity occurs further out from the point of injection.<sup>41,42</sup> Reconstituting toxins in a dilute solution also widens the action halo, regardless of the toxin.<sup>43</sup> Typical dilutions for type A toxins range from 1 to 10 mL per standard vial (100 units of ona- or inco-toxins; 300 units of abo-toxin). Very concentrated solutions offer specific benefits, including precision because of minimal diffusion and the minimal induration of intracutaneous blebs after injection; however, the loss of a few drops of material during reconstitution and preparation is a significant concern. More dilute solutions also offer benefits, notably the ability to treat a wider area with a smaller dosage, but very dilute solutions may create a degree of imprecision because of dilution and also leave visible blebs after injection. Type A toxins are more similar than different but are not considered generic equivalents because of their biologic

## DIFFERENT INJECTABLE PRODUCTS

### Key points

- **Neurotoxins approved by the FDA include onabotulinumtoxinA, abotulinumtoxinA, incobotulinumtoxinA, and rimabotulinumtoxinB**
- **Equivolumic, equipotent solutions of abo-toxins have a wider action halo than those of ona- and inco-toxins**
- **Injectable prepackaged temporary skin fillers approved by the FDA include hyaluronic acid derivatives, calcium hydroxylapatite, and poly-L-lactic acid**

Fillers and toxins are available in different chemical formulations. There are three botulinum toxin type A drugs that are approved by the FDA:

complexity. Unit potency is equivalent between ona- and inco-toxins, with 1 unit of each of these approximately as potent as 2.5 units of abotoxin.<sup>39,44</sup> The only type B available in the US is rimabotulinumtoxinB (Myobloc; Solstice Neurosciences, San Francisco, CA).<sup>37</sup> This is used much less often because it is associated with a shorter duration of action.<sup>45</sup>

In the United States, temporary prepackaged injectable skin fillers include hyaluronic acid (HA) derivatives, calcium hydroxyapatite (CaHA), and poly-L-lactic acid (PLLA).<sup>46-48</sup> All are biocompatible, biodegradable, and unlikely to migrate from the point of injection. Fillers may be linear fillers that work primarily through direct filling, the space-occupying effect of the mass of the injectant. Some fillers, notably PLLA, function mostly by stimulating fibrosis that causes neocollagenesis. That being said, even linear fillers induce some neocollagenesis, and stimulatory fillers have a small direct effect.

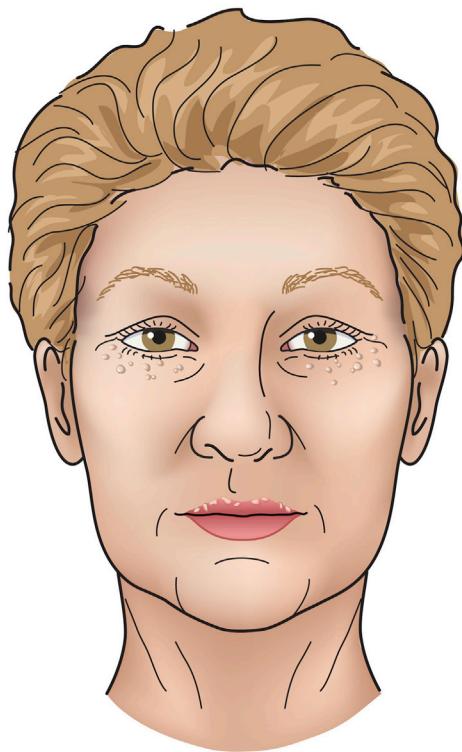
Rheology, the study of how materials react and deform under mechanical stress, can be used to characterize and differentiate filler materials.<sup>49-52</sup> The underlying chemistry is not self-evident, but four parameters, G\* (measures hardness), G' (measures elastic properties), G'' (measures viscous properties), and tanδ (ratio of viscous to elastic) can be used to characterize each filler. All fillers need to be viscoelastic, sufficiently viscous to be injectable, and sufficiently elastic to retain some shape when they are placed in the skin. Another important characteristic is cohesivity, a measure of internal adhesion forces, which describes a substance's resistance to vertical compression or spreading. Harder fillers are typically injected more deeply, with the hardest even at the level of the periosteum. Fillers with high cohesivity are used in areas like the upper cheekbones, deeply creased nasolabial folds, nasal dorsum depressions, and chin notches, where the filler needs to retain its contour and shape, or ability to project; on the lower cheeks and in fine lines, less cohesive fillers can spread to create a soft, diffuse correction that looks natural even when deformed by underlying muscle motion. A further discussion of comparative rheology and cohesivity is beyond the scope of the current review but has been extensively clarified in the literature.

HA (ie, hyaluronan) is a glycosaminoglycan that occurs naturally in body tissues, including the skin. HA derivatives that are fillers include a range of products of different viscosities and stiffness (ie, as measured by G'). Softer, less viscous products are used the lips, eyelids, and superficial wrinkles. Harder, more viscous products are placed in the deep subcutis, or on the periosteum, for cheek

augmentation and correction of temple recession. Depending on the filler, injection needles or cannulas of at least 27- or 30-gauge are required. Hyaluronics, like other fillers, last longer on the upper face, where decreased muscle motion slows disintegration and resorption. The duration of clinical correction ranges from 6 months to >1 year, depending on the specific filler and the anatomic site. In the lower eyelid, prehydrated, less dense HA products help avoid delayed translucence caused by postinjection swelling. While small aliquots of the finest HA fillers can be injected intradermally, usually HAs are injected below the dermal subcutaneous junction, like other injectable fillers. The enzyme hyaluronidase dissolves HA fillers in cases of asymmetry, overinjection, or adverse events like intravascular injection. Significantly, adjacent native hyaluronan is affected only temporarily and is quickly replaced.

Commercially available forms of hyaluronidase include Amphadase<sup>53</sup> (bovine; Amphastar Pharmaceuticals, Rancho Cucamonga, CA), Vitrase<sup>54</sup> (ovine; Bausch and Lomb, Tampa, FL), and Hylenex<sup>55</sup> (human recombinant; Halozyme Therapeutics, San Diego, CA). Removal of an entire injected implant of HA typically requires an injection of several dozen to 100 units, with undiluted enzyme being most effective. Recently, it has been found that delayed-onset nodules attributable to long-lasting fillers comprised of cross-linked low- and high-molecular weight HAs (ie, based on Vycross technology) are more resistant to hyaluronidase and require multiple repeat treatments, each of several hundred units.<sup>56</sup> Injections of as little as 3 units of enzyme are sufficient to dissolve focal areas of excess filler in areas of thin skin, such as the infraorbital area.<sup>57</sup> CaHA, a constituent of bone mineral, is also an eponymous skin filler. Tiny spherules (25–45 μm) of synthetic calcium hydroxyapatite are combined with a neutral gel matrix that dissipates after injection. Biodegradation of CaHA occurs over the better part of a year. CaHA is radio-opaque and may be visible on radiologic imaging. Like firmer, thicker HA products, CaHA is injected into the deeper subcutis, not the lips and eyelids (Fig 4). Injection instruments are of 27- to 28-gauge. Excess injection is corrected by a stab incision followed by extrusion via manual compression.

PLLA is a synthetic polymer used in other medical implants and sutures. PLLA filler is a powder that is reconstituted with sterile water before injection. Injected particles settle into the subcutis, and the water is resorbed. Over several months, the PLLA particles function as minute foreign bodies that stimulate peripheral neocollagenesis. A typical regimen is three injection sessions 2 months apart. Like CaHA, PLLA is



**Fig 4.** Thicker, more viscous, and more fibrosis-inducing fillers are generally not injected into the body of the lips or the skin of the lower eyelids to avoid persistent nodules (lips) or syringoma-like papules (eyelids).

appropriate for injection into the subcutis and less so for fine lines, lips, or eyelids (Fig 4). PLLA does not induce an immediate correction, and the postinjection contour can worsen as water is resorbed, before neocollagenesis manifests in 1 to 3 months. Posttreatment, patients massage the affected area (immediately after injection, and then for 5 minutes, 5 times a day, for 5 days) to prevent nodules. To avoid clotting of the 25-gauge needles or cannulas used for injection, reconstitution is often with larger volume of sterile water than specified in the package insert, and the mixture is stored for 48 to 72 hours before injection.

A filler approved by the FDA that may have some degree of permanent persistence is a polymer, polymethylmethacrylate (PMMA).<sup>58-63</sup> Approved for use in the United States in 2006, this material consists of 20% PMMA microspheres of 30 to 50  $\mu\text{m}$  in diameter suspended in 3.5% bovine collagen and 0.3% lidocaine. Injections are placed in tunnels at the dermal subcutaneous junction. Within a month postinjection, the collagen carrier is resorbed, and fibrosis begins around the remaining polymer beads. Despite the potential for persistent correction because of the longevity of the polymer, adoption of this filler has been slow in the United States

because of concern regarding the perceived potential for delayed and intractable granulomas. Supporters of the product have argued that an improved manufacturing process ensures that the currently available microspheres have an extremely smooth surface and are  $>20 \mu\text{m}$ , with these characteristics ensuring a low risk of immune induction, bacterial colonization, and granuloma formation. A 5-year cohort study found only a 1.7% risk of granuloma formation, of which half had fully resolved by the end of the study.<sup>59</sup> Despite this evidence, skeptics remain concerned that granuloma risk remains higher than reported, with several case series of granulomatous adverse events reinforcing this perception.

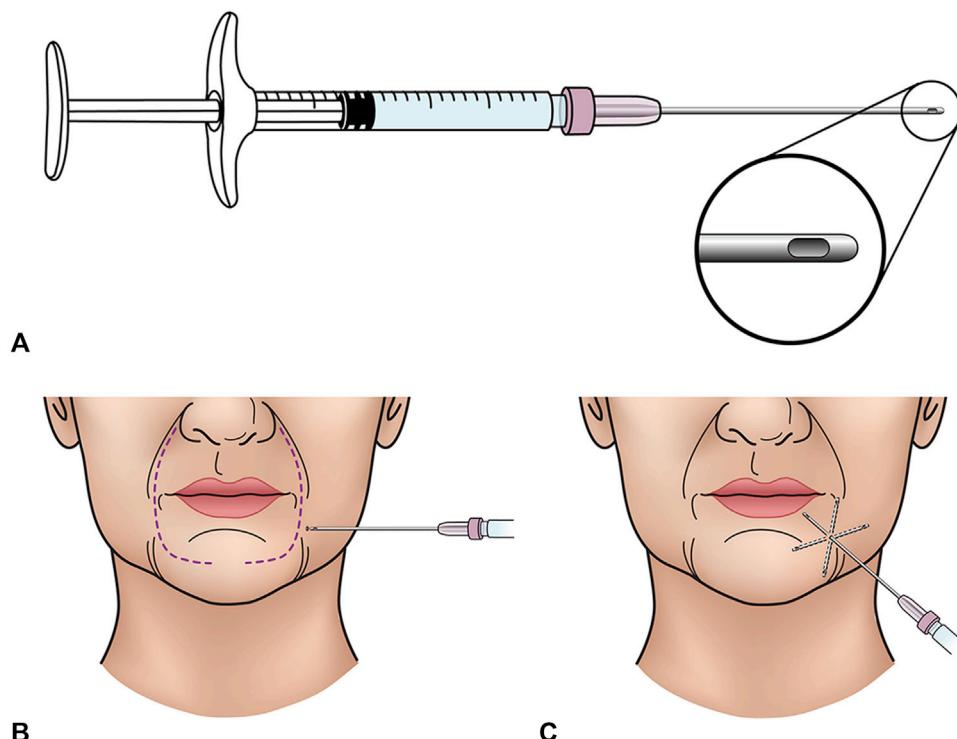
## PAIN MANAGEMENT

### Key points

- To mitigate injection pain, many fillers come premixed with small quantities of lidocaine
- Other methods to reduce injection pain, include ice, topical anesthetic, vibration, nerve blocks, and the use of ultrafine needles or microcannulas
- Injection of botulinum toxin reconstituted with preserved saline containing benzyl alcohol is less painful than injection of toxin reconstituted with saline without preservative

Injections of filler and toxins can be uncomfortable. Patients are awake and able to perceive injection pain. Moreover, injections are usually a series of insertions. Filler injections, in particular, can be protracted, with the needle tip coursing within the dermis and subcutis for many seconds or even minutes, often through sensitive periorificial skin. Finally, receiving toxin and filler injections to modify appearance is usually entirely volitional, and declining the injections is therefore a reasonable alternative.

Intraoperative discomfort during filler and toxin injections can be managed.<sup>64-73</sup> Many hyaluronics (eg, Restylane, Juvederm) and injectable CaHA (ie, Radiesse), are provided premixed with small quantities of lidocaine. While injection of such a slurry does not mitigate pain of the initial stick, subsequent injections hurt less as the skin numbs. Adding more lidocaine to a prepackaged filler can enhance pain relief or improve flow characteristics; this is off-label, but routine practice. Topical ice is a quick and inexpensive means for additional pain control.<sup>69</sup> An ice pack may also be self-administered by the patient before treatment. Forced cold air or contact cooling provide similar benefits.<sup>70,72</sup> Topical



**Fig 5.** Cannulas. **A**, To avoid bruising and minimize the risk of intravascular spread, blunt-tipped cannulas with side ejectant ports can be attached to filler syringes in lieu of needles. **B**, To insert a 27-gauge cannula into the marionette line, a 25-gauge needle is used to puncture the skin, and the cannula is inserted through this minute hole. **C**, A single cannula entry site may be sufficient to treat an entire unilateral anatomic area. The cannula is withdrawn and reinserted in different directions.

mixtures of anesthetics (eg, lidocaine 2.5% and prilocaine 2.5% cream or compounded formulas) can be applied, often under occlusion, for 30 to 60 minutes to areas pending injection, provided the patient has sufficient time to wait in the office. Infraorbital or mental nerve blocks, while simple to instill and providing outstanding pain control in the perioral area, may make patients numb for hours.<sup>73</sup> Adjuvant intralesional anesthetic injections at the filler site are avoided because they distort the local anatomy and reduce the subcutaneous space available to receive filler. The gate control theory of pain posits that transmission of vibration may inhibit concurrent signaling of pain through colocalized thin pain fibers.<sup>74</sup> In practice, it requires skill or a helper to hold a vibration device while devoting appropriate care to the injection process. Distraction is another approach for controlling patient perception of pain, with patients using headphones to listen to music, squeezing a compressible ball, or being entertained by a brisk monologue initiated by the medical staff.

The diameter, length, and tip shape of the instrument used to deliver the injectant is also a consideration. Needles selected are typically the smallest

bore, between 25- and 32-gauge depending on the filler type, consistent with unimpeded extrusion. Short, 0.5-inch needles require less travel through the skin, but larger 1- or 1.25-inch needles may enable fewer needle sticks. Serial puncture technique is combined with perpendicular needle sticks to minimize pain. Microcannulas, blunt-tipped metal cylinders with a side port, can be used in lieu of needles. Puncture with a larger bore needle precedes the insertion of a microcannula through this hole. Once the microcannula has been inserted, a large area can be treated from that single point.

Botulinum toxin injections are generally less painful than filler injections. Aqueous solutions of toxin do not significantly injure or compress adjacent tissues. Measures to mitigate toxin injection pain are therefore modest. Ice or topical anesthetics may be used for sensitive patients. Small-bore needles, such as 31- and 32-gauge needles, may reduce injection pain.<sup>64</sup> Reconstitution of botulinum toxin with sterile saline that contains benzyl alcohol reduces pain by approximately one-half compared to reconstitution with saline without preservative.<sup>67</sup> While the use of nonpreservative containing saline is on-label, and that of saline with benzyl alcohol is off-label, both

practices are consistent with the current standard of care.

## AVOIDING ADVERSE EVENTS

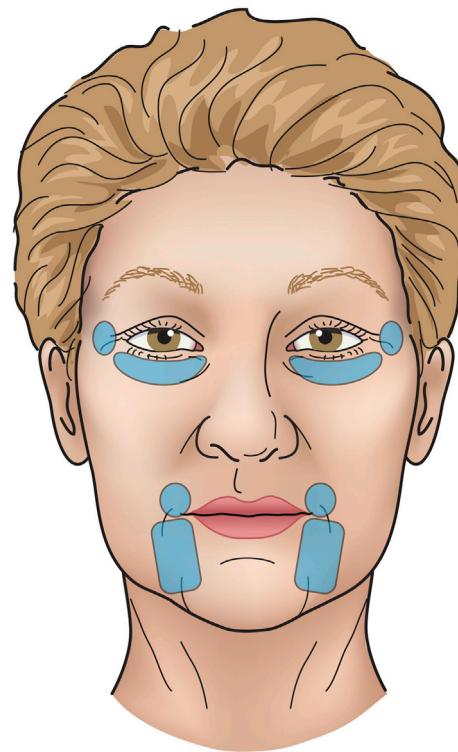
### Key points

- Common unwanted effects of filler injections are redness and swelling; bruising, nodules, and asymmetry can also occur
- Inadvertent intravascular injection of filler results in pain and delayed reticulated erythema. This usually resolves without sequelae, but can leave a scar
- Rarely, intravascular filler injection causes retrograde movement into the retinal artery and unilateral blindness
- Neuromodulator injections produce mild redness and swelling that quickly abates
- Minor adverse events after neuromodulator injections include brow or eyelid ptosis and transient headaches
- Storage and reuse of reconstituted neuromodulators is safe and effective

Fillers and botulinum toxin are extremely safe, with exceedingly low rates of adverse events when used by expert, board-certified dermatologist injectors.<sup>36,74-107</sup> Injectable nonpermanent fillers do not require skin testing before use and are generally considered nonimmunogenic.

The injection technique is designed to minimize common but troublesome unwanted events, including erythema, edema, ecchymoses, and nodules. Erythema and edema are routine after filler injections. Edema severity is contingent on the filler quantity, thickness, and hygroscopic character. Ecchymoses can occur in the perioral and periorbital areas, which have fragile small vessels. Nodules are typically associated with inadvertent injection of an excessive bolus and are rarely immunogenic granulomas.

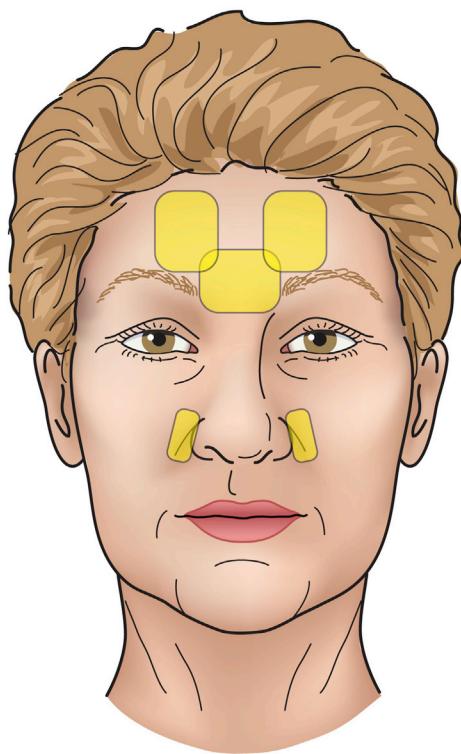
Pre-emptive adjustment of an injection technique can prevent unwanted events. Modest volume injections, followed by a touch-up procedure several weeks later once edema has receded, can limit the degree of peak edema after injection. Cannulas (Fig 5, A-C) assist the injector in avoiding sharps trauma and bruising (Fig 6).<sup>80,103</sup> Fewer passes with a needle or cannula can similarly curtail microvascular injury. Vitamin K, arnica, and bromelain may also prevent or treat injection-related bruising.<sup>96-101</sup> Prompt treatment of ecchymoses, as with the pulsed-dye laser at nonpurpuric settings, can speed resolution.<sup>97,100,101</sup> Not injecting into the dermis reduces the likelihood of nodule creation. Similarly, control of injection volume and experience



**Fig 6.** Areas at high risk for bruising after filler injection.

with the filler substance being used reduce the chance that too much filler will be injected at any given point, leaving a bump behind. If a lump has occurred, resolution is hastened by massage,<sup>107</sup> injection of dilute corticosteroid, or incision and extrusion. Immediate posttreatment asymmetry may be attributable to injection-related edema, which will resolve spontaneously. Persistent lumps, like those associated with longer-lasting HA fillers, may require repeated, high-dose injections of hyaluronidase or energy device treatment to disrupt them.<sup>79,81</sup>

In rare instances, filler injections may result in adverse events more concerning than transient redness, swelling, bruising, and bumps. These include intravascular and perivascular injections that induce vascular compression and tamponade, leading to tissue destruction.<sup>77-79,81,82,95,102</sup> Abundant superficial vasculature in the glabella and perinasal regions renders these locations particularly susceptible to filler-associated vaso-occlusion (Fig 7). Nicking of a vessel by the filler needle or deposition of filler in a cuff around the vessel is associated with pain and blanching. Symptoms may be difficult to distinguish from the baseline discomfort and tissue whitening of uncomplicated filler injections. However, in the case of vaso-occlusion, affected patients may call the office the next day complaining of unremitting pain. Extremely rarely,



**Fig 7.** Fillers should be injected cautiously, slowly, superficially, and in modest quantities to avoid intravascular spread. On the forehead, glabellar and forehead injections can inadvertently pierce the supratrochlear arteries and its tributaries. Perinasally, and on the nose, the angular artery and many smaller vessels are at risk.

filler injections can enter a vessel proximal to the glabella and proceed by retrograde movement into the central retinal artery, then spraying microemboli into the retina. Sharp, acute pain occurs concurrently with complete unilateral vision loss, which can be permanent if not recognized and treated immediately.<sup>5</sup> Protocols are available to address cases of intravascular injection (Table I).<sup>82,105,106</sup>

Slow, superficial injections of filler reduce the likelihood of a vaso-occlusive episode.<sup>95</sup> Even if a vessel is perforated, gradual injection can deliver a forward force less than the back pressure in the vessel, thereby preventing introduction of filler into the lumen. Total injection volumes and numbers of individual needlesticks are minimized in regions at risk of vascular injury. Pulling back on the syringe before injection reveals a red flash if the tip has been mistakenly positioned within a vessel; however, because of the small caliber of the needles used and the high viscosity of many fillers, the absence of a red flash does not mean that a vessel has not been compromised.<sup>77</sup> Staff education is also important. If

**Table I.** Management of local vaso-occlusion caused by fillers\*

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If hyaluronic acid filler, inject >100 units of hyaluronidase <sup>†</sup>
Warm compresses
Apply and massage in nitropaste
Initiate oral aspirin
Hyperbaric oxygen (if available)
Other possible interventions: low-molecular weight heparin, cold compresses
Follow patient closely

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\*Based on information from Goodman et al<sup>108</sup> and Cohen et al.<sup>105</sup>

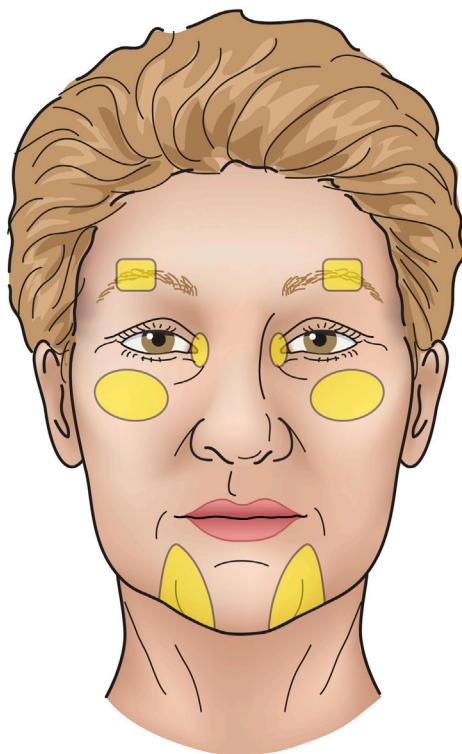
<sup>†</sup>May be beneficial even if the filler is not hyaluronic, because temporary dissolution of native hyaluronan may relieve occlusive pressure.

consistent with vaso-occlusion, patient calls complaining of pain instigate an effort to have the patient come in for evaluation. If an HA was used, prompt instillation of hyaluronidase may reduce tissue damage. In general, occlusion is better avoided than treated, because delayed detection usually reduces treatment effectiveness.

Adverse events with botulinum toxin injections are uncommon. Barely visible erythematous macules at the site of injection usually resolve spontaneously within hours and are well-concealed by makeup. Brow ptosis and eyelid ptosis are avoided (Fig 8) by not injecting low and close to the midbrow.<sup>83</sup> Eyelid ptosis is treated by eyedrops containing apraclonidine (Iopidine),<sup>90</sup> an  $\alpha_2$  adrenergic agonist. Not injecting under the middle lower eyelid in older individuals with skin and muscle laxity reduces the risk of scleral show and ectropion. Midface injections can impact the zygomaticus muscle and cause unilateral lip droop (Fig 8). On the lower face, injections are placed symmetrically around the midline to preserve right-left symmetry. Injections to correct gummy smiles and injections of the depressor anguli oris for relief from lip droop are performed precisely with modest volumes of toxin.

Patients who have had headaches after toxin injections are told they headaches may recur after retreatment. Fortunately, the headaches resolve spontaneously. Alternatively, some patients may notice the relief of preexisting headaches after injection of the forehead with toxin.<sup>78,104</sup>

Infection or contamination is not a risk when neuromodulators and fillers are used in accordance with the standard of care, which diverges in some cases from the obsolete recommendations in the package insert. Storage of reconstituted botulinum toxin, and subsequent reuse of the residual contents of one vial in additional patients, is safe and routine practice among expert injectors.<sup>85,89</sup>



**Fig 8.** Neuromodulators are not typically injected at certain anatomic sites. Injections at or below the midbrow can cause eyebrow and even eyelid ptosis; medial canthal injections can diffuse into the intrinsic muscles of the eye and also cause ptosis; upper cheek injections far below the lower eyelid can denervate the zygomatic major, leading to lip droop; and injections of the midchin area that are far medial to the vertical line defined by the oral commissures can also result in mouth and lip asymmetry.

## ASYMMETRY AFTER INJECTION

### Key points

- Asymmetry after filler injections is often transient, self-correcting, and may be associated with temporary swelling
- Since right–left asymmetries often exist before treatment, standardized pretreatment photographs should be obtained

One common patient complaint after toxin or filler injections is right–left asymmetry. It is important for both physician and patient to be aware that facial asymmetries are likely to exist before injection, as natural, normal variations. Standardized pretreatment photographs can help to document these and help clarify the additive effect of the procedures. Typical sets of standardized photographs include a symmetrically lit front view and 45° side views; these can be obtained at rest and also at maximal frown or smile.<sup>109</sup> Photographic equipment used may be a turnkey solution provided by a specialized vendor

(eg, Canfield) or a custom solution in a clinic room or dedicated photographic suite.<sup>110</sup> It is helpful if pictures are available in an accessible format (print or online) so that they can be promptly reviewed with patients when indicated. When asymmetry was not preexisting and appears after the injection procedure, the patient and doctor should discuss whether, and how, this should be addressed. It is often prudent to wait 1 to 2 weeks to allow edema and erythema resolve fully. Importantly, efforts to correct a minor persistent asymmetry may give rise to another asymmetry. Patients may be reminded that perfect symmetry is neither an achievable nor desirable goal.

## FREQUENCY OF INJECTION

### Key points

- Neuromodular injections are repeated every 3 months in novice patients, and as infrequently as every 4 to 6 months in experienced patients
- For filler injections, anatomic site and the filler type impact retreatment frequency, which varies from 4 to 6 months to 9 to 12 months
- Temporarily or permanently discontinuing neuromodulators or fillers does not render patients worse off than if they never had such injections

Patients often want to know how often fillers or toxins should be injected. Relevant considerations include the severity of the defect, cost and willingness to pay, patient schedule and convenience, patient preference regarding the degree of correction, the individual's specific rate of metabolism and biodegradation, and the details of the treatment plan.

When a patient receives toxin for facial rhytids repeatedly, the duration of action is enhanced. The effect, which starts by lasting about 3 months, can eventually remain for 4, 5, or even 6 months. For fillers, the site is a consideration, with glabella and infraorbital injections persisting longer than perioral and nasolabial fold injections. Some patients may choose to receive injections several times a year to maintain the aesthetic effect. Others may prefer to receive injections once or twice a year, possibly in preparation for social seasons, like summer or the winter holidays. Postinjection edema may resolve in such a way as to leave an underfilled appearance. To counteract these late effects, a touch-up treatment may be planned several weeks after an injection session.

## COMBINATION TREATMENTS

### Key points

- **Fillers and toxins can be used in combination, as can energy devices**
- **Combination treatments may have synergistic effects**

Fillers and toxins are safely and effectively used in combination.<sup>111-117</sup> On the face, toxins reduce dynamic creases while fillers correct static creases at rest. The concurrent use of fillers and toxins at the same site, if indicated, is common practice.

Fillers and neurotoxins can also be used with energy devices.<sup>111-117</sup> Lasers, lights, radiofrequency devices, and therapeutic ultrasound for improving fine skin texture, correcting brown and red discoloration, tightening skin, or reducing fat can be applied directly over recently injected skin. Stacked treatments of this type do not appear to disrupt previously placed filler or cause skin injury.

Multiple treatments at the same visit may not be preferred by all patients. Discomfort and swelling may be greater if more procedures are performed, with increased posttreatment down time. Extreme edema may motivate diffusion of toxin, with possible unwanted clinical effects. If fillers and energy devices are delivered in succession, it is unclear which should be injected first. Some believe that fillers should be first because energy devices induce edema that may obscure the endpoint for fillers. Alternatively, any impact on the filler of deeply penetrating energy devices can be prevented by starting with energy devices.

## MEASUREMENT AND OPTIMIZATION OF PATIENT OUTCOMES

### Key point

- **Methods currently under development to improve the measurement of cosmetic outcomes include refined patient-reported outcome measures and core outcome sets for facial appearance**

It is incontrovertible that filler and neurotoxin injections for facial treatment are safe and effective. Due to their accessibility, they are also a democratizing force and a cultural phenomenon. Dermatologists have been integral in bringing these innovations to fruition and refining their use.

Additional advances in minimally invasive facial soft tissue augmentation are likely forthcoming. To understand how best to improve current treatments and design new options, dermatologists are gathering data pertaining to safety and effectiveness. Patient-reported outcome measures are enabling

practitioners to augment their observations with patient-provided feedback regarding the subjective experience of undergoing treatment. Core outcome sets, which are agreed-upon minimum sets of outcomes, are being developed so that in the near future diverse clinical trials of facial soft tissue augmentation will be able to collect similar data points, allowing for pooling of data across studies and a better understanding of what works.<sup>118</sup>

The holy grail of soft tissue augmentation is autologous cellular correction, wherein a patient's own cells would help reverse aging, senescence, or injury. This may entail adaptation of adipose-derived stem cells to recapitulate facial soft tissue, or the solution may be something more exotic that has yet to be considered.

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# Urticaria: A comprehensive review



## Epidemiology, diagnosis, and work-up

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### Learning objectives

After completing this learning activity participants should be able to recognize the various type of urticaria; recall diagnostic strategies for confirming the diagnosis; and describe the key histopathology features involved in the diagnosis of urticaria.

### Disclosures

#### Editors

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Urticaria is a common clinical condition presenting with wheals (hives), angioedema, or both. Urticaria has a complex pathogenesis, along with a high disease burden, a significant impact on quality of life, and high health care costs. The first article in this continuing medical education series covers the definition, classification, epidemiology, diagnosis, and work-up of urticaria, taking into account the recent literature and the best available evidence. (*J Am Acad Dermatol* 2018;79:599-614.)

**Key words:** acute; angioedema; chronic physical urticaria; histopathology; hives; inducible urticaria; testing; urticaria; wheals.

Urticaria presents with wheals (hives), angioedema, or both, and has a lifetime prevalence of about 9%.<sup>1,2</sup> The appearance of pruritic, erythematous dermal swellings that blanch with pressure, indicating the presence of vasodilation and superficial dermal edema, is characteristic of wheals.<sup>3</sup> Angioedema is caused by similar pathologic alterations that occur in the reticular dermis and subcutaneous tissue, with poorly defined swelling and burning.<sup>4</sup> One-third of patients present with both hives and angioedema, 30% to 40% present with isolated hives, and 10% to 20% with isolated angioedema.<sup>1,5,6</sup>

### Abbreviations used:

ASST:	autologous serum skin test
AU:	acute urticaria
CSU:	chronic spontaneous urticaria
CsA:	cyclosporine
CU:	chronic urticaria
DPU:	delayed pressure urticaria
NSAID:	nonsteroidal antiinflammatory drug

The spinothalamic tract is thought to play an important role in the pathway of pruritus.<sup>7</sup> Primary afferent neurons, also known as pruriceptors, detect itch-inducing substances like histamine and chloroquine.<sup>8</sup> The most well-known pruritogen is

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histamine; however, non-histaminergic mediators also exist.<sup>9</sup> Initially it was thought that the nerve fibers only responded to histamine/nonhistamine stimulus, but it is now accepted that these fibers can also be stimulated by noxious stimuli.<sup>7</sup>

Urticaria has a complex pathogenesis and a significant impact on quality of life.<sup>1,10</sup> Urticaria-related costs may be as high as \$1750 to \$2050 per patient per year.<sup>11,12</sup>

## CLASSIFICATION

### Key points

- Urticaria cases are classified as either acute or chronic**
- Chronic urticaria is defined if daily or almost daily wheals or angioedema are present for >6 weeks**

Urticaria can be classified according to duration and etiology,<sup>13</sup> although ≥2 types of urticaria can coexist in the same patient (Table I).

## ACUTE URTICARIA

### Key points

- Acute urticaria has precipitating factors in <50% of cases**
- When present, the most common triggers are infections, drug reactions, and food intolerance**

Acute urticaria (AU) is defined by the occurrence of spontaneous wheals or angioedema for <6 weeks.<sup>13</sup> In acute cases, it is important to exclude anaphylaxis in the presence of respiratory, gastrointestinal, or neurologic symptoms or hemodynamic instability.

Eliciting factors have been found in <50% of cases, with upper respiratory infections being the most common trigger (40%), followed by drug reactions (9.2%) and suspected food intolerance (0.9%).<sup>15</sup> Among infectious agents, upper respiratory tract agents, *Mycoplasma pneumonia*, and parasitic infections have been commonly reported in children,<sup>16</sup> while viral hepatitis and infectious mononucleosis are important culprits in adults.<sup>17-19</sup>

## CHRONIC URTICARIA

### Key points

- Chronic urticaria may be subclassified into chronic spontaneous urticaria or chronic inducible urticaria**
- Up to 30% of cases are associated with functional immunoglobulin G antibodies to the high-affinity immunoglobulin E receptor FcεRIα or to immunoglobulin A**

**Table I. Classification of urticarias\***

Type	Clinical feature or type
Acute urticaria	
Chronic urticaria	
Chronic spontaneous urticaria	Spontaneous appearance of itchy wheals, angioedema, or both for ≥6 weeks because of known <sup>†</sup> or unknown causes
Chronic inducible urticaria	
Physical urticaria	Symptomatic dermographism <sup>‡</sup>
Cold urticaria <sup>§</sup>	Cold contact urticaria <sup>  </sup>
Delayed pressure urticaria <sup>¶</sup>	Solar urticaria
Heat urticaria <sup>#</sup>	Heat contact urticaria
Vibratory angioedema	
Other inducible urticaria	Cholinergic urticaria
Contact urticaria	
	Aquagenic urticaria

\*Modified from data presented by Zuberbier et al<sup>13</sup> and Margerl et al.<sup>14</sup>

<sup>†</sup>For example, autoreactivity; that is, the presence of histamine-releasing autoantibodies (also called urticaria factitia).

<sup>‡</sup>Dermographic urticarial.

<sup>§</sup>Cold contact urticarial.

<sup>||</sup>Pressure urticarial.

<sup>#</sup>Heat contact urticaria.

- Among patients in which an etiology is suspected, infections, drugs, food, and psychological factors are the most commonly associated**
- Chronic inducible urticaria is characterized by its ability to be triggered consistently and reproducibly in response to a specific stimulus**

Episodes of daily or almost daily wheals or angioedema lasting for ≥6 weeks are designated as chronic urticaria (CU).<sup>13,20</sup> CU must be distinguished from acute intermittent urticaria/angioedema, where episodes only last hours or days but recur over months or years.<sup>21</sup>

Chronic inducible urticaria (CIndU) represents a subgroup of CU where urticaria is induced by a determined stimulus rather than occurring spontaneously. If no inducible factor is present, the process is termed chronic spontaneous urticaria (CSU). Among this subgroup, 30% to 40% of patients present with autoantibodies, suggesting an autoimmune basis. These cases would be categorized as chronic autoimmune urticaria (CaU) (European guidelines) or as antibody-associated CU (US guidelines).<sup>22</sup>

**Table II.** Comparison of the recommendations of the EAACI/GA2LEN/EDF/WAO international guidelines and the US practice parameters for confirming the subtypes of chronic inducible urticaria

Subtype	EAACI/GA2LEN/EDF/WAO international guidelines <sup>14</sup>	Joint Task Force on Practice Parameters <sup>22</sup>
Aquagenic	Wet cloth at body temperature applied for 20 min	Water compress at 35°C applied to the skin of the upper body for 30 min
Cholinergic	Exercise and hot bath provocation	Provocative challenges that raise core body temperature (exercise and hot water immersion 42°C or methacholine intradermal challenge)
Cold	Cold provocation and threshold test (ice cube, cold water, and cold wind). Extended diagnostics based on history: CBC with differential, ESR, CRP, or cryoproteins	Cold stimulus (eg, an ice cube on the forearm for 5 min) applied and observe for wheal-and-flare reaction during rewarming of the skin
Contact	Cutaneous provocation test. Skin tests with immediate readings (eg, prick test)	
Delayed pressure	Pressure test and threshold test	Challenge with 15 lbs of weight suspended over the shoulder for 10 or 15 min and monitor for development of delayed angioedema
Heat	Heat provocation and threshold test	See cholinergic urticaria
Solar	Ultraviolet and visible light of different wavelengths and threshold test. Extended diagnostics based on history: rule out other light-induced dermatoses	Phototesting to various wavelengths of light
Dermatographism	Elicit dermatographism and threshold test (dermographometer). Extended diagnostics based on history: CBC with differential, ESR, or CRP	Stroke the skin with a firm object, such as a tongue blade
Vibratory angioedema	Vortex	Vortex mixer applied to forearm for 4 min

CBC, Complete blood cell count; CRP, C-reactive protein; EAACI, European Academy of Allergy and Clinical Immunology; EDF, European Dermatology Forum; ESR, erythrocyte sedimentation rate; GA2LEN, Global Allergy and Asthma European Network; WAO, World Allergy Organization.

## CHRONIC SPONTANEOUS URTICARIA

Neither European nor US guidelines recommend extensive laboratory testing. Other testing can be performed based on the patient's history (Table II).<sup>20,22</sup> In cases where an etiology is suspected, infections are the most commonly associated.<sup>1,13</sup>

### Infections

Bacterial, viral, parasitic, or fungal infections have been implicated as underlying causes of CSU.<sup>23-27</sup> The frequency and relevance of infectious etiologies varies according to the patient population and geographic location.<sup>28,29</sup> Such is the case of *Anisakis simplex*, a sea fish nematode that has been linked to recurrent spontaneous urticaria in the Mediterranean.<sup>30</sup>

The relationship of *Helicobacter pylori* and CSU has been proposed, and a protein component has been shown to induce mast cell degranulation.<sup>31</sup>

Clinical data are unclear; some studies show an association, while others do not.<sup>32-34</sup> A few studies have shown that *Helicobacter* eradication may improve CSU, but the verdict is still unclear.<sup>16,35,36</sup>

### Food

Patients frequently associate foods and food additives with symptom onset; however, type I allergy seems to be a rare cause of CSU.<sup>20</sup> Food allergy as a cause may, however, be considered in patients with intermittent symptoms, typically within 1 hour of exposure.<sup>21</sup>

About 20% of CSU patients have positive prick testing to food allergens, the most common being hazelnut, potato, apple, oatmeal, pork, beef, and seafood.<sup>37-39</sup> In <2% of cases, immunoglobulin E (IgE) allergy is confirmed.<sup>1,40,41</sup>

Another condition is alpha-gal anaphylaxis, which occurs after susceptible patients bitten by a

**Table III.** Cutaneous manifestations in aspirin/NSAID-exacerbated diseases

Disease	Baseline	Clinical features	Proposed mechanism	Cross-reactivity between groups
NECD <sup>60,61</sup>	CSU	Exacerbation of hives/angioedema minutes to 4 h after exposure; NECD in 12–30% of patients with CSU	Increased leukotrienes and PGD2	Yes
NIUA <sup>60,61</sup>	Healthy	Hives/angioedema 1–6 h after exposure	COX-1 inhibition	Yes
Immediate hypersensitivity to aspirin or single NSAID <sup>60,61</sup>	Healthy	Urticaria, angioedema, or anaphylaxis, minutes to 1 h after exposure	IgE-mediated	No

COX, cyclooxygenase; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; NECD, NSAID-exacerbated cutaneous disease; NIUA, NSAID-induced urticaria/angioedema; NSAID, nonsteroidal antiinflammatory drug; PGD2, prostaglandin D2.

tick develop sensitization to galactose-alpha-1,3-galactose, found in milk and red meat, which then causes a delayed reaction manifesting as urticaria and, in severe cases, anaphylaxis.<sup>21,42,43</sup> Most authors have not found pseudoallergens (eg, food additives and some spices) to be the cause of CU, but a few studies have advocated the relevance of food intolerance as a triggering factor of CSU.<sup>35,44–46</sup> Some studies have shown ≤30% resolution 10 to 14 days after removal of pseudoallergens from patients' diets.<sup>45,47</sup>

## Drugs

The most commonly implicated drugs in CU are angiotensin-converting enzyme (ACE) inhibitors and nonsteroidal antiinflammatory drugs (NSAIDs).<sup>48–51</sup>

ACE inhibitor–induced angioedema and urticaria is caused by the nonimmunologic accumulation of bradykinin and other neurokinins.<sup>52</sup> The incidence may be as high as 0.68%, and can occur from weeks to years after treatment is initiated.<sup>53</sup> Risk factors include African American heritage (4–5 times greater than the incidence in white patients), female sex, atopy, and cigarette smoking.<sup>54</sup> In the event of angioedema, the ACE inhibitor must be discontinued.<sup>55</sup> The majority of patients improve significantly after withdrawal of ACE inhibitors, but episodes may persist for several months.<sup>56–58</sup> Management is the same as CU, and recently the bradykinin antagonist icatibant has shown significantly faster resolution of symptoms than standard therapy with corticosteroids and antihistamines.<sup>59</sup>

**Table III** lists cutaneous manifestations in aspirin/NSAID-exacerbated diseases. NSAID-exacerbated cutaneous disease manifests as exacerbation of symptoms in patients with a history of CSU after intake of an NSAID. NSAID-exacerbated cutaneous disease can be found in 12% to 30% of patients with

CSU.<sup>60,61</sup> NSAID-induced urticaria/angioedema, on the other hand, develops in the absence of urticaria history.

In the case of immediate hypersensitivity to aspirin or a single NSAID, symptoms develop rapidly after exposure to the drug.<sup>62</sup> Drugs most commonly implicated include NSAIDs of the pyrazolone class (metimazole), acetic acid (diclofenac), or propionic acid derivatives (ibuprofen).<sup>60</sup>

## Emotional stress

Patients with CSU experience high rates of anxiety, depression, and somatoform disorders, with half being affected by at ≥1 of these conditions.<sup>63</sup> In addition, psychiatric comorbidity appears to be an additional factor in the impairment of quality of life in CSU patients,<sup>21</sup> but it is uncertain if emotional stress/anxiety is the cause or consequence of CSU.<sup>64</sup>

## Chronic autoimmune urticaria (antibody-associated urticaria)

About one-third to one-half of patients with CSU show a positive response against their own serum (positive autologous serum skin test [ASST]).<sup>65</sup> IgG antibodies to the high-affinity IgE receptor Fc $\epsilon$ R $\alpha$ , or less commonly IgG antibodies to IgE, have been documented.<sup>35,60–69</sup> There seems to be an increased risk for thyroid disorders (hypothyroidism more often than hyperthyroidism), diabetes mellitus type I, systemic lupus erythematosus, and rheumatoid arthritis in patients with CaU.<sup>65</sup> Although these autoantibodies are of academic interest, as some studies report a more intense refractory course, their clinical relevance remains unclear.<sup>67,70,71</sup>

There is also an increased frequency of human leukocyte antigen subtypes DRB\*04 (DR4) and DQB1\*04 (DQ8) among patients with CaU, providing additional evidence of an autoimmune etiology.<sup>72,73</sup>

There is no clear evidence of increased risk of malignancy in CSU,<sup>74</sup> although 1 study did show twice the risk, especially for hematologic neoplasms.<sup>75</sup>

### Chronic inducible urticaria

CIndU is a unique subgroup of CU where patients develop urticaria symptoms exclusively and reproducibly in response to a specific stimulus. Signs and symptoms are usually localized to exposed areas, and with the exception of delayed pressure urticaria (DPU), lesions last <2 hours. It is not uncommon for patients to exhibit multiple CIndU.<sup>14</sup> CIndU is responsible for 20% to 30% of all cases of CU and can be associated with CSU in 14% to 36% of cases.<sup>2,76</sup>

According to the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/Urticaria Network eV consensus from 2016, there are 2 subtypes: physical urticaria (physical trigger) and other inducible urticarias (Table I).<sup>14,77</sup>

CIndUs are diagnosed based on the patient's history and the results of provocation testing (Table IV). CIndU patients may develop systemic signs and symptoms during provocation testing, such as dizziness, vertigo, vomiting/diarrhea, wheezing, and even anaphylactic shock.<sup>14</sup>

### Bradykinin-mediated angioedema

Heredity angioedema (HAE) and acquired angioedema are bradykinin-mediated vasodilation and increased capillary permeability.<sup>100</sup> HAE types I (85%) and II (15%) are caused by deficient levels of C1 inhibitor or a dysfunctional C1 inhibitor, respectively.<sup>101,102</sup> Patients with HAE type III, on the other hand, have normal C4 and C1-inhibitor levels. These patients are typically females, demonstrate frequent exacerbations with estrogen, and their angioedema is more prominent in the face and oropharynx.<sup>103,104</sup> Contrasting with the hereditary forms, patients with the acquired variant are older at presentation, predominantly male, and have a predilection for the face, but also the abdomen and genitalia.<sup>105-107</sup>

## EPIDEMIOLOGY

### Key points

- Urticaria is a common worldwide disease
- Chronic urticaria develops in 20% to 45% of patients presenting with acute urticaria
- Most forms of urticaria are more common in females

Estimates of the lifetime prevalence for any type of urticaria range from <1% to 24%, depending on

the age range, method of sampling, and geographic location.<sup>1,21,108</sup>

AU and CU are more common in women.<sup>109-113</sup> Most studies have found male:female ratios of 1:2, although this difference is less evident in the elderly, children, and for cholinergic urticaria and DPU.<sup>1,11,35,114,115</sup>

The lifetime prevalence of AU ranges from 12% to 24% in Europe.<sup>116-118</sup> Point prevalence ranges from 0.1% to 0.6%.<sup>119,120</sup> CU develops in about 20% to 45% of individuals presenting with AU.<sup>1,111</sup> A study using a large American commercial insurance database found that the 1-year period prevalence for CU was 0.08%,<sup>11</sup> while European data report that the 1-year period prevalence for CU ranges from 0.38% to 0.8%.<sup>1,111,117</sup> The prevalence and incidence for other types of urticaria is lower (eg, the incidence for acquired cold urticaria in Central Europe is approximately 0.05%).<sup>78</sup> Among patients with physical urticaria, the most common type is symptomatic dermographism (40-73%), while solar urticaria, heat urticaria, and vibratory angioedema are more rare.<sup>14,35,121</sup> CU is most common between the ages of 25 and 55 years.<sup>119</sup> In half of patients, the symptoms will be present for <2 years, and in <20% of patients the symptoms last >10 years.<sup>1,110</sup> However, patients suffering from physical urticarias seem to have longer disease processes, with 1 study showing that only 16% were free of symptoms after 1 year.<sup>122</sup>

Urticaria appears to be less common in children than in adults.<sup>123</sup> Urticaria prevalence of any type in children is around 3.4% to 5.4%.<sup>124</sup> The incidence of AU ranges from 2 to 73 per 100,000 emergency department referrals.<sup>116</sup> The prevalence of childhood CU is 0.1% to 0.3% in the United Kingdom.<sup>125</sup>

## ETIOLOGY AND CLINICAL CLASSIFICATION

### Key points

- Mast cells and basophils are the primary inflammatory cells involved in urticaria pathogenesis
- Mast cell activation may be caused by immunologic or nonimmunologic factors. Functional anti-IgE or anti-FcεRIα subunit antibodies are found in ≤50% of patients with CU
- Prostaglandin release, rather than histamine mediation, seems to be involved in contact urticaria

Mast cells and basophils are the major effector cells involved in the development of urticarial lesions.<sup>126</sup> Degranulation releases preformed vasoactive mediators, primarily histamine.<sup>36</sup> Disease

**Table IV.** Characteristics of chronic inducible urticarias

Type	Subtype	Definition	Subtypes	Incidence	Provocation testing	Comments
Physical urticaria	Symptomatic dermatographism <sup>2,14,77</sup> (dermographic urticaria or urticaria factitial)	Wheals, and in rare cases angioedema, caused by shearing forces on the skin (rubbing, scratching, or scrubbing)	NA	PU is the number 1 cause; 1-5% in the general population	Firm stroke of the skin with a blunt object	Differentiate from simple dermographism or white dermographism
	Cold urticaria (acquired cold urticarial or cold contact urticaria) <sup>2,14,77-81</sup>	Rapid onset of itchy wheals after contact cooling and rewarming of the skin	1. Idiopathic 2. Familial a. CAPS b. PLAID 3. Acquired	PU is the number 2 cause; up to one-third of all PU cases	Ice cube test	Aquatic activity is a common trigger. Severe cases may lead to anaphylaxis. Counsel patients against swimming
	Heat urticaria (heat contact urticaria) <sup>14</sup>	Sudden appearance of itchy wheals after heat contact of the skin	N/A	Exceptionally rare	Hot stimulus to the skin of volar forearm	Differentiate from cholinergic and solar urticaria
	Delayed pressure urticaria <sup>14,77,82</sup>	Angioedema occurring after application of a sustained pressure stimulus to the skin	N/A	37% of patients with CSU	Suspension of weights over the shoulder; application of rods on thigh, or forearm; dermographometer	Develops 6-8 h after, and lasts up to 72 h. Systemic symptoms relatively common (malaise and arthralgia)
	Solar urticaria <sup>14,77,83-87</sup>	Development of urticaria within minutes after a brief exposure to sunlight, usually 5-10 min	1. Type I: abnormal chromophore 2. Type II: abnormal circulating IgE antibodies to a normal chromophore	Rare	Provocation phototesting	Chronically light-exposed skin (face and dorsal surface of the hands) is usually resistant
	Vibratory angioedema <sup>14,82,88-89</sup>	Itching and swelling, within minutes at the site of skin exposure to vibration	1. Idiopathic 2. Hereditary: - activating mutation ADGRE2	Very rare	Laboratory vortex mixer	Common triggers: mowing, motorcycle rides, horse riding, or biking; seems to be exaggeration of normal response to dermal vibration

Other inducible urticarias	Cholinergic urticaria (generalized heat urticaria) <sup>14,77,90-92</sup>	Pruritic wheals, angioedema, and/or anaphylaxis, precipitated by an increase in core body temperature	1. Sweat allergy type: hypersensitivity to leaked sweat components, probably antigen secreted by <i>Malassezia globosa</i> 2. Decreased sweating type: direct effect of acetyl choline in degranulation of mast cells	5-7% of CU and 30% of CIndU	Moderate physical activity	Triggers: exercise, passive warming, emotional stress, and hot and spicy foods or beverages; numerous, short-lived, tiny wheals surrounded by a large flare reaction
	Adrenergic <sup>93-95</sup>	Pruritic wheals after stress-induced release of epinephrine and norepinephrine	N/A	Very rare	Intradermal injection of 5 ng adrenaline or 3-10 ng noradrenaline	Antihistamines are minimally effective. Respond better to beta-blockers like propranolol
	Aquagenic urticaria <sup>14,77,78,96,97</sup>	Urticaria after contact with any source of water, independent of temperature	1. Classic: water as carrier for epidermal antigen 2. Salt-dependent aquagenic urticaria: osmotic pressure changes	Very rare	Water compress to skin	Differentiate from aquagenic pruritus, cholinergic urticaria, cold urticaria, and heat urticaria
	Contact urticaria <sup>14,98,99</sup>	Development of urticarial lesions, systemic involvement, and in some cases anaphylaxis within minutes after contact to an exogenous agent	1. NICU: prostaglandin release 2. ICU: IgE-mediated hypersensitivity. Requires previous exposure	Variable	Open controlled application testing; skin prick test; closed patch tests	NICU triggers: plants (eg, stinging nettle), animals (eg, jelly fish), or chemicals (eg, cinnamon aldehyde, sorbic acid). ICU triggers: latex, plants, animal products, drugs, cosmetics, and chemicals. Certain occupations seem to be at higher risk ( $\geq 90\%$ of cases). Most frequently affected were health care workers, food handlers, hairdressers, and dental assistants

CAPS, Cryopyrin-associated periodic syndromes; CIndU, chronic inducible urticaria; ICU, immunologic contact urticaria; NICU, nonimmunologic contact urticaria; PLAID, phospholipase C $\gamma$ 2 gene-associated antibody deficiency and immune dysregulation; PU, physical urticaria.

activity has been correlated with a significant increase in serum C-reactive protein, interleukin-6 (IL-6), IL-6 soluble receptor, and matrix metalloproteinase-9, independent of the presence of a positive ASST or circulating histamine-releasing factors.<sup>123,127</sup> Sleep and circadian rhythm have been implicated in IL-6-mediated processes, and some authors hypothesize that this could be the cause of increased severity of urticaria symptoms at night, when physiological concentrations of IL-6 and IL-6 soluble receptor increase.<sup>128</sup>

### Mast cell-dependent urticaria

Mast cells can be activated by immunologic or nonimmunologic factors. Among the immunologic triggers, IgE-mediated immediate hypersensitivity reaction is the classic mechanism of mast cell activation.<sup>129</sup> This accounts for some cases of acute or episodic urticaria, such as contact urticaria to latex or AU from foods.<sup>130</sup>

IgE is less important in CU, as demonstrated by the lack of correlation between IgE levels and disease severity.<sup>131</sup> CU may also be associated with the presence of functional anti-IgE or anti-Fc $\epsilon$ RI antibodies in  $\leq 50\%$  of patients.<sup>132</sup> This can be assessed functionally by the ASST. A positive ASST indicates a subset of patients with an increased risk of developing urticaria due to endogenous causes.<sup>133</sup> It has also been found to correlate with disease severity and with patients who have multiple intolerances to NSAIDs.<sup>71</sup> The ASST is the only generally available test to screen for autoantibodies against either IgE or Fc $\epsilon$ RI.<sup>134</sup> To achieve disease control, these patients might need higher doses of antihistamines or additional immunomodulators. Therefore, this assay is a useful tool in patients who are not responding to traditional therapy. However, the significance of a negative test remains unclear, and some studies have demonstrated low sensitivity of the ASST with a high false-positive rate; therefore, ASST is not a first-line test during the initial work-up.<sup>71</sup> However, the clinical relevance of these antibodies is still unclear, because therapies to treat CU are effective in the presence or absence of these antibodies.

Nonimmunologic mechanisms that can directly activate mast cells include radiocontrast media, opiates, neuropeptides (eg, substance P), and certain foods.<sup>135,136</sup> Reactive oxygen species seem to be another cause of mast cell degranulation; recent evidence suggests that low levels of reactive oxygen species play a role in cell signaling, aiding in the exocytosis of granules content from mast cells.<sup>68,137</sup>

Complement 3a (C3a), C4a, and C5a function as anaphylatoxins by interacting directly with the surface of mast cells to trigger histamine release.<sup>138</sup>

### Mast cell-independent urticaria

There are situations where urticaria does not involve mast cells or histamine.<sup>98</sup> A common example is the development of contact urticaria to sorbic acid, cinnamic acid, cinnamic aldehyde, methyl nicotinate, or dimethyl sulfoxide.<sup>139</sup> These cases do not respond to antihistamines, but rather to acetylsalicylic acid and NSAIDs.<sup>50</sup> It has been proposed that pathogenesis involves prostaglandin release from the epidermis rather than histamine release from mast cells.<sup>98</sup>

### Other mechanisms

Increasing evidence suggests that adipokines such as lipocalin 2 affect immune responses and CU. Lipocalin 2 and urticaria activity have a negative association, suggesting an antiinflammatory effect of lipocalin 2 in CU.<sup>140</sup>

The role of the coagulation pathway in CU came to light when it was found that the autologous plasma skin test had a higher positivity than the ASST.<sup>141</sup> Patients with CU show activation of the extrinsic pathway of the coagulation and fibrinolysis cascade, both of which correlate with disease exacerbation.<sup>142,143</sup>

Together, these findings show the complex pathogenesis of urticaria, beyond simple histamine release or mast cell activation, as previously understood.

## DIAGNOSIS

### Key points

- **Urticaria is characterized by the presence of wheals or angioedema. A detailed history and physical examination are essential in excluding alternative diagnoses and in guiding additional investigations**
- **Individual lesions lasting >24 hours, associated purpura, tender wheals, or the presence of systemic symptoms should prompt further work-up, including obtaining a skin biopsy specimen**

### History and physical examination

A detailed history is essential, and should document the frequency, circumstances of onset, triggers, duration of individual lesions, pattern of recurrence, duration of attacks, whether lesions are itchy or painful, and if episodes are associated with systemic symptoms. Detailed drug and family history, as well as response to treatment, are important. In addition, severity using the urticaria activity score or a visual analogue scale, can be assessed at baseline to use as a gauge for response to treatment.<sup>22</sup>

**Table V.** Recommended history intake\*

## Pertinent questions

1. Time of onset of disease
2. Frequency/duration of and provoking factors for wheals
3. Diurnal variation
4. Occurrence in relation to weekends, holidays, and foreign travel
5. Shape, size, and distribution of wheals
6. Associated angioedema
7. Associated subjective symptoms of lesions, for example pruritus and pain
8. Family and personal history regarding urticaria or atopy
9. Previous or current allergies, infections, internal diseases, or other possible causes
10. Psychosomatic and psychiatric diseases
11. Surgical implantations and events during surgery, for example after local anesthesia
12. Gastric/intestinal problems
13. Induction by physical agents or exercise
14. Use of drugs (ie, nonsteroidal antiinflammatory drugs, immunizations, hormones, laxatives, ear and eye drops, and alternative remedies)
15. Observed correlation to food
16. Relationship to the menstrual cycle
17. Smoking habits (especially use of perfumed tobacco products or cannabis)
18. Type of work
19. Hobbies
20. Stress
21. Quality of life related to urticaria and emotional impact
22. Previous therapy and response to therapy

\*Data from European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization 2013 urticaria guideline.<sup>13</sup>

A list of pertinent questions suggested by the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization guidelines<sup>13</sup> can be found in **Table V**.

Individual wheal lesions resolve within 24 hours, although the episode usually persists for several days, with new wheals occurring in different areas (**Fig 1**).

Angioedema is a sudden, pronounced, poorly defined swelling in deeper dermal, subcutaneous, or submucosal tissue. Lesions tend to be fainter in color, painful (particularly with delayed pressure



**Fig 1.** Acute urticaria. (Photograph courtesy of Pete Smith, MD, Griffith University, Brisbane, Queensland, Australia.)

**Table VI.** Diseases with urticarial lesions

Syndromes presenting with wheals and/or angioedema	Cryopyrin-associated periodic syndromes, including familial cold autoinflammatory syndrome, Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, and articular syndrome; Schnitzler syndrome; Gleich syndrome; and phospholipase C <sub>g</sub> 2-associated antibody deficiency
Diseases related to urticaria	Urticarial vasculitis; serum sickness-like reaction; bradykinin-mediated angioedema, including hereditary angioedema and angiotensin-converting enzyme-induced angioedema; mastocytosis; bullous pemphigoid; and arthropod bites

angioedema), and last 48 to 72 hours. The lips, tongue, eyelids, genitalia, and rarely bowel are also affected. In some cases, angioedema can be associated with wheals, and these 2 can be difficult to separate, especially around the eyelids; in other cases, it may be mistaken for joint swelling. Isolated angioedema is clinically significant because some of these patients will have nonhistaminergic angioedema.<sup>144</sup>

For physical urticarias, the distribution pattern and morphology can give important clues for identifying potential triggers.<sup>145</sup> Patients with DPU

**Table VII.** Syndromes presenting with wheals or angioedema

Syndrome	Mechanism	Clinical features
Cryopyrin-associated periodic syndromes <sup>152</sup>	<i>NLRP3</i> mutation and increased interleukin 1 $\beta$	Urticarial rash from birth, which is persistent and migratory. Systemic symptoms: fever, arthralgia, arthritis, malaise, and conjunctivitis. FCAS: short-term, for a few hours after cold exposure; MWS, longer episodes and unknown triggers; NOMID/CINCA: early onset. Association with bony overgrowth, mental retardation, optic nerve malformation, and chronic aseptic meningitis
Schnitzler syndrome <sup>153</sup>	N/A	Recurrent, asymptomatic/mildly pruritic wheals, recurrent fever, bone and joint pain, increased erythrocyte sedimentation rate, and monoclonal IgM gammopathy
Gleich syndrome <sup>154,155</sup>	N/A	Recurrent episodes of angioedema and eosinophilia; most associated with increased serum IgM
Phospholipase Cg2–associated antibody deficiency <sup>156</sup>	Phospholipase C $\gamma$ 2 (temperature-dependent intracellular signaling)	Life-long cold-induced urticarial; variable antibody deficiency, increased risk of infections, autoimmunity, and granulomatous disease

FACS, Familial cold autoinflammatory syndrome; IC, intracellular; IgM, immunoglobulin M; MWS, Muckle–Wells syndrome; NOMID/CINCA, neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, and articular syndrome.

usually complain of severe burning and pain, as well as systemic symptoms, such as arthralgias and malaise.<sup>146</sup> Lesions are induced when pressure from walking, tight clothes, sitting, or leaning is applied to sites like hands, feet, trunk, and buttocks.<sup>147</sup> For cold contact urticaria, the development of wheals occurs within minutes of cold contact. Extensive exposure (ie, swimming in cold water) can lead to systemic reactions, including shock.<sup>148</sup> Heat contact urticaria is rare<sup>145</sup>—wheals develop within a few minutes of exposure but resolve within a couple hours.<sup>14</sup> Solar urticaria appears on skin that is exposed to visible or ultraviolet light. When a large enough area is exposed, syncope, wheezing, and even anaphylaxis can be observed.<sup>149</sup>

The physical examination should also include any signs of residual purpura. When evaluating residual lesions, it is important to evaluate areas that are hard to reach by patients, because scratching can result in residual purpura or postinflammatory hyperpigmentation. If there is doubt, marking individual lesions and asking patients to monitor their duration can help differentiate between urticaria and urticarial vasculitis (UV). However, 50% of UV cases may present with lesions that are <24 hours old, making unresponsiveness to conventional antihistamines the main differentiating factor.<sup>150</sup>

In patients with isolated wheals associated with fever, joint/bone pain, or general malaise, autoinflammatory disease or UV should be considered as alternative diagnoses.<sup>77,151</sup> However, ≤16% of patients with CU report systemic symptoms associated

with flares. The most frequent symptoms are asthenia, arthralgias, and abdominal pain, in ≤30% of cases. Headache, myalgias, retrosternal oppression, dyspnea, rhinorrhea, and ocular irritation are seen with less frequency.<sup>1,110</sup>

### Differential diagnosis

Urticaria can be part of several syndromes, and urticaria-like lesions can be found in various skin conditions; therefore, associated skin lesions and systemic signs and symptoms are crucial in achieving the correct diagnosis. Table VI lists urticarial diseases, Table VII summarizes the mechanism and clinical features of syndromes presenting with wheals or angioedema, and Table VIII shows the main dermatologic conditions that can present with urticaria-like lesions in addition to other clinical clues. An algorithm for the differential diagnosis of urticarial lesions is found in Table II.

### HISTOPATHOLOGY

#### Key points

- Histopathologic findings are usually mild, including sparse perivascular and interstitial mixed inflammatory infiltrate and upper dermal edema
- If vascular damage is present, UV needs to be considered

Histopathologic findings can vary depending on chronicity, site (lesional vs uninvolved skin), and even subtype.<sup>163</sup> Although most cases are easy to

**Table VIII.** Diseases related to urticaria

Disease	Clinical features	Histopathology
Urticular vasculitis <sup>157</sup>	Urticular lesions >24 h; residual purpura; more painful than pruritic angioedema in ≤40%; systemic symptoms: fever, arthralgia, arthritis, malaise, lymphadenopathy, and renal and liver involvement	Subtle findings; fibrinoid necrosis of vessel walls, karyorrhexis, extravasation of red blood cells, and endothelial swelling
Serum sickness-like reactions <sup>158,159</sup>	Urticular lesions >24 h; fever, arthralgia, myalgia, arthritis, lymphadenopathy, glomerulonephritis, myocarditis, and neuritis; 1-2 weeks after antigen exposure (heterologous serum, or certain infections or drugs)	Leukocytoclastic vasculitis
Mastocytosis <sup>160</sup>	Urticular lesions; reddish-brown macules and papules; positive Darier sign (urticular reaction elicited by stroking lesion)	Uniformly spaced mast cells filling papillary dermis with or without reticular dermis; scattered eosinophils
Sweet syndrome (acute febrile neutrophilic dermatosis) <sup>161</sup>	Urticular plaques >24 h; fever, leukocytosis; systemic symptoms: arthralgia, malaise, headache, and myalgia	Dense neutrophilic infiltrate in the papillary dermis; pronounced dermal edema
Bullous pemphigoid <sup>162</sup>	Elderly patients; multiple, erythematous, urticarial, pruritic, plaques with or without tense blisters	Subepidermal band of inflammatory infiltrate, with an abundance of eosinophils; perilesional DIF: linear complement 3 with or without immunoglobulin G at the BMZ
Insect bites	Long-standing urticarial lesions; central punctum	Variable; intraepidermal and papillary dermal edema; wedge-shaped perivascular and interstitial infiltrate: lymphocytes, eosinophils, and neutrophils

BMZ, Basement membrane zone; DIF, direct immunofluorescence.

diagnose clinically, a biopsy specimen should be obtained if there is doubt. A universal feature across all urticarial biopsy specimens is the presence of a mixed cellular perivascular infiltrate surrounding the dermal postcapillary venules.<sup>164</sup> AU is associated with a more intense leukocytic infiltrate, an increased erythrocyte sedimentation rate, and leukocytosis.<sup>129</sup> Neutrophils are especially prominent in acute urticaria, in contrast to DPU, where the main infiltrate is composed of eosinophils in the reticular dermis.<sup>165</sup> Although distinctive pathological elements can be identified in different types of urticaria, the variability of these elements in individual lesions prevents their use as a sole diagnostic tool.

Angioedema shows similar findings; however, the reticular dermis and subcutaneous tissue are involved.<sup>10</sup>

Mast cells do not appear to be increased in number, although some reports have found up to a 10-fold increase in mast cell numbers in cases of CU.<sup>163,166</sup> There is controversy about the significance of the inflammatory infiltrate in urticarial lesions.

Some authors have found an association between a predominantly eosinophilic inflammatory infiltrate and greater clinical severity scores,<sup>166</sup> while others found the same association with predominantly neutrophilic infiltrates.<sup>167</sup>

Vascular damage is not a finding of urticaria, and, if present, UV needs to be considered. UV affects the superficial vascular plexus and shows features of leukocytoclastic vasculitis, although the histologic findings tend to be subtle. Mild or focal fibrinoid changes are apparent only in few sections, and unlike classic leukocytoclastic vasculitis, neutrophils and karyorrhexis are mild. Immunofluorescence reveals vascular deposition of immunoglobulins and complement.<sup>77</sup> In patients with CU who are unresponsive to H<sub>1</sub> antihistamines, obtaining a skin biopsy specimen to assess for inflammatory infiltrates may therefore be warranted.

## WORK-UP

### Key points

- In most cases of AU, extensive diagnostic work-up is not warranted

- For CU, a limited routine diagnostic work-up is recommended in a case-by-case basis
- A skin biopsy specimen may be helpful in cases of refractory urticaria or when alternative diagnoses are suspected

### Acute urticaria

**Skin testing or immunoassays.** In general, no diagnostic work-up is necessary in the evaluation of AU. Further work-up may be warranted when allergic causes of AU are suspected. IgE-mediated reactions can be confirmed by skin-prick testing or chloramphenicol fluoroimmunoassay.

### Chronic urticaria

**Laboratory testing.** Extensive laboratory testing is not recommended in the evaluation of CU because it rarely identifies the cause or affects long-term management.<sup>13,22,168</sup> Both the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization international guidelines and the Joint Task Force on Practice Parameters recommend testing for underlying causes based on patient history (Table V) as well as specific tests to help elucidate the specific subtypes of CIIndU (Table II).<sup>13,22</sup>

**Skin biopsy.** Obtaining a skin biopsy specimen is not recommended in patients with CU.<sup>22</sup> A skin biopsy should be considered in patients with refractory CU, when UV or other nonurticarial immunologic skin diseases are being considered, and in patients who are unresponsive to H<sub>1</sub> antihistamines to determine if there is a predominance of neutrophils.<sup>22,169</sup>

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# Urticaria: A comprehensive review

## Treatment of chronic urticaria, special populations, and disease outcomes

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### Learning objectives

After completing this learning activity, participants should be able to develop an initial treatment plan for a patient with acute or chronic urticaria; identify second-, third-, and fourth-line treatment options when initial treatments are ineffective; discuss outcomes of the disease; and describe possible disease course with patients.

### Disclosures

#### Editors

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Second-generation antihistamines are considered first-line agents in the treatment of chronic urticaria because of their safety and efficacy profile. Some patients require higher doses of H<sub>1</sub> antihistamines alone or in combination with other classes of medications, including H<sub>2</sub> antihistamines, leukotriene receptor antagonists, or first-generation H<sub>1</sub> antihistamines. One major therapeutic advance has been omalizumab, a humanized monoclonal anti-immunoglobulin E that was recently approved by the US Food and Drug Administration for the treatment of chronic urticaria that is unresponsive to H<sub>1</sub> antagonists. In addition, the second article in this continuing medical education series outlines several evidence-based alternative treatments for urticaria and the differences in recommendations between 2 major consensus groups (the European Academy of Allergy and Clinical Immunology/World Allergy Organization and the American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force). (J Am Acad Dermatol 2018;79:617-33.)

**Key words:** acute; antihistamines; children; chronic; corticosteroids; elderly; leukotriene receptor antagonists; management; omalizumab; quality of life; urticaria.

### H<sub>1</sub> ANTIHISTAMINES

#### Key points

- Second-generation antihistamines are considered first-line agents because of their safety and efficacy profile

- For nonresponsive patients, higher than recommended doses of antihistamines are an acceptable option
- First-generation antihistamines have similar efficacy to second-generation antihistamines, but sedation makes them less favorable

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**Table I.** Efficacy of histamine H<sub>1</sub> receptor antagonist randomized, double-blind, placebo-controlled studies

Study	N	Duration, weeks	Treatment	Comments
Breneman et al <sup>9</sup>	187	4	Cetirizine 10 mg vs astemizole* 10 mg vs placebo	Cetirizine was superior to astemizole in reducing the number of wheals Both agents were statistically superior to placebo at relieving CSU symptoms based on weekly patient rating
Nettis et al <sup>10</sup>	100	6	Levocetirizine 5 mg vs placebo	Complete symptom resolution in 53% of patients taking levocetirizine at the study endpoint compared with 0% in the placebo group
Finn et al <sup>11</sup> and Nelson et al <sup>12</sup>	489 and 418	4	Fexofenadine 20, 60, 120, and 240 mg† and placebo	Same study design for both trials Efficacy results were similar in the 60-, 120-, and 240-mg groups. All dosages were statistically superior to placebo and the 20-mg group in reducing mean pruritus score, mean number of wheals, and mean TSS when compared to baseline values
Kaplan et al <sup>7</sup>	255	4	Fexofenadine 180 mg vs placebo	Once-daily dosing of fexofenadine was superior to placebo for improvement in mean number of wheals, pruritus severity scores, and in TSS
Handa et al <sup>13</sup>	97	4	Cetirizine 10 mg vs fexofenadine 180 mg	Cetirizine showed superior overall efficacy, determined by subject rating on an analog scale Complete symptom resolution in 52% of patients taking cetirizine at the study endpoint compared with 4.4% in the fexofenadine group
Leynadier et al <sup>14</sup>	61	4	Mizolastine 10 mg vs loratadine 10 mg	Both agents had a similar reduction in urticarial episodes Mizolastine was associated with a greater reduction in the number of wheals compared to loratadine
Ortonne et al <sup>3</sup>	137	6	Desloratadine 5 mg vs placebo	Desloratadine was superior to placebo in improving pruritus scores

TSS, Total symptom score.

\*Astemizole was removed from the market due to the rare but possible QTc prolongation and subsequent arrhythmia side effect.

†Twice daily dosing.

Second-generation antihistamines (sgAHs), such as loratadine, desloratadine, fexofenadine, cetirizine, levocetirizine, azelastine, and bilastine (not available in the United States) are considered first-line treatment for mild to moderate chronic urticaria (CU).<sup>1,2</sup> Several randomized controlled trials (RCTs) have demonstrated a high level of safety, efficacy, and tolerability.<sup>3-7</sup> Once daily dosing is recommended over an as-needed regimen to maximize clinical response and improve quality of life.<sup>8</sup> When comparing the efficacy of individual agents (Table I),<sup>3,7,9-14</sup> some studies<sup>2,13,15-18</sup> suggest the superiority of certain sgAHs over others, but data are limited.<sup>19</sup> More than 50% of patients with CU do not respond to sgAH doses that have been approved by the US Food and Drug Administration.<sup>20</sup> For these patients, higher than recommended doses are considered reasonable.<sup>2,19,21</sup> In fact, 2 to 4 times the “normal” doses are frequently needed with sgAHs. Anecdotal experience points to the fact that

starting with the “normal” dose rarely is effective for patients with urticaria. Patients can be told to escalate the doses every few days if they have no side effects but do not respond to current dosages. Nonetheless, there are few clinical trials supporting this recommendation.<sup>12,22-25</sup> However, European and US guidelines recommend increasing sgAH doses 2- to 4-fold because of their tolerability, safety, and efficacy in many patients.<sup>1</sup> First-generation antihistamines (fgAHs) are clinically effective and act rapidly in adults.<sup>26</sup> However, they are associated with increased sedation, leading to impaired motor skills, because of their ability to cross the blood-brain barrier.<sup>17,27,28</sup> Nonetheless, studies have shown tolerance to performance impairment after 3 to 5 days of therapy.<sup>26,29,30</sup> These agents can cause excessive dryness and gastrointestinal side effects, such as constipation, because of their anticholinergic activity.<sup>31</sup> The original sgAHs, such as terfenadine and astemizole, caused Torsades de

*Abbreviations used:*

ASST:	autologous serum skin test
AU:	acute urticaria
BB-UVB:	broadband ultraviolet B
CSU:	chronic spontaneous urticaria
CsA:	cyclosporine
CU:	chronic urticaria
DPU:	delayed pressure urticaria
fgAH:	first-generation antihistamine
LTRA:	leukotriene receptor antagonist
MMF:	mycophenolate mofetil
NB-UVB:	narrowband ultraviolet B
PUVA:	psoralen plus ultraviolet A light phototherapy
RCT:	randomized control trial
sgAH:	second-generation antihistamine
UAS:	urticaria activity score

Pointe because of the inhibition of CYP3A4B, resulting in increased drug accumulation.<sup>32,33</sup> However, cardiac side effects with fgAHs and newer sgAHs are exceedingly rare.<sup>34</sup>

## H<sub>2</sub> ANTIHISTAMINES

### Key points

- H<sub>2</sub> antihistamines can be added to H<sub>1</sub> antihistamines for patients with refractory chronic urticaria
- However, the quality of evidence for the aforementioned dual therapy is low

Because of their tolerability, H<sub>2</sub> antihistamines can be added when monotherapy with H<sub>1</sub> antihistamines is not sufficient.<sup>2,19,35</sup> Most studies proving the efficacy of concomitant use of H<sub>1</sub> and H<sub>2</sub> antihistamines have been conducted with cimetidine.<sup>36-38</sup> Early studies found that cimetidine increased the half-life of H<sub>1</sub> antihistamines, which may explain its benefit in CU.<sup>36,37</sup> A recent Cochrane review including 4 small trials (n = 144 patients) found evidence that diphenhydramine in combination with ranitidine was more effective than diphenhydramine alone. However, the limited evidence and variation between the trials prevented the authors from achieving solid conclusions.<sup>39</sup> There is differing opinion regarding the use of H<sub>2</sub> antihistamines; some still advocate this combination therapy because it is safe and affordable,<sup>2,40</sup> while others believe that it has no therapeutic benefit either alone or in conjunction with sgAH.<sup>20</sup>

Although not a true antihistamine, doxepin, a tricyclic antidepressant, has combined H<sub>1</sub>, H<sub>2</sub>, and muscarinic blocking activities, which makes it an alternative agent in the treatment of CU especially those cases refractory to high doses of antihistamines.<sup>41</sup> In a crossover study of 50 patients comparing doxepin and diphenhydramine, Greene et al<sup>42</sup> noted that 43% of patients taking doxepin had

complete resolution of their urticaria lesions compared to 5% of the patients taking diphenhydramine. On a smaller double-blind crossover trial study of 24 patients, Harto et al<sup>43</sup> compared doxepin to mequitazine. There was no significant difference in efficacy when compared with each other, but both were superior to placebo.

## LEUKOTRIENE MODIFIERS

### Key points

- Leukotriene receptor antagonists have shown mixed results in the treatment of chronic urticaria
- In spite of this, leukotriene receptor antagonists remain a treatment option for patients not responding to second-generation antihistamines because of their safety and tolerability

Leukotriene receptor antagonists (LTRAs) such as zafirlukast and montelukast as well as the 5-lipoxygenase-inhibitor zileuton have shown beneficial effects in the treatment of CU.<sup>19</sup> The results of several RCTs have yielded mixed results, with some showing greater efficacy<sup>44,45</sup> and others less efficacy<sup>46,47</sup> than sgAHs. Studies with positive results include 2 small (n = 51 and n = 30 patients) RCTs in which montelukast was more effective than cetirizine and placebo, respectively, in patients with nonsteroidal antiinflammatory drug-exacerbated CU.<sup>45,48</sup> Negative studies include 1 crossover RCT trial lasting 12 weeks that demonstrated no statistical difference between zafirlukast and placebo in 46 patients<sup>49</sup> and another RCT that found no differences between the montelukast and placebo groups in 160 patients with mild chronic spontaneous urticaria (CSU).<sup>46</sup> Therefore, firm recommendations on the use of LTRA are lacking. Nonetheless, these drugs may provide a reasonable alternative to patients who are unresponsive to antihistamines in view of their excellent safety profile.<sup>50</sup> Nettis et al<sup>44</sup> and Bagenstose et al<sup>51</sup> demonstrated that aspirin or food additive intolerance or a positive autologous serum skin test in patients with CSU may predict a good response to LTRA.

## SYSTEMIC CORTICOSTEROIDS

### Key points

- Corticosteroids have a high efficacy in refractory chronic urticaria despite the shortage of large controlled studies
- Corticosteroids should be used for short periods and at the lowest effective dose; long-term use is not recommended because of known adverse effects

Systemic corticosteroids are frequently used in the treatment of CU that is refractory to antihistamines, despite the lack of large controlled trials.<sup>2,19</sup> A recent study examining financial resources in CU found that oral corticosteroids were used in 54.7% of patients.<sup>52</sup> Although there is general agreement among several consensus groups that use of corticosteroids for long periods of time is not recommended,<sup>19,21,53</sup> there are differing opinions regarding the dose and duration. Daily or every other day low-dose prednisone (20 mg/10 mg or the equivalent) for 3 to 6 months until control is achieved is advocated by some,<sup>54</sup> while other protocols suggest starting at 15 mg daily and decreasing by 1 mg each week.<sup>2</sup> In a recent retrospective study of 750 patients, 47% of patients with antihistamine-resistant CU who were treated with oral prednisone for 3 days were able to obtain remission.<sup>55</sup> An additional 9% responded after a second course of systemic corticosteroids.<sup>55</sup> One of the main problems with long-term therapy is hypothalamic-pituitary axis suppression once therapy is stopped; therefore, tapering is required.<sup>55,56</sup> Other notable side effects include osteopenia/osteoporosis, cataracts, glaucoma, fatty liver, glucose intolerance, and atrophy of the skin, among others.<sup>57</sup> Nevertheless, the data suggest that tapering is not necessary in patients who are taking the equivalent of  $\leq 40$  mg of prednisone daily for up to 3 weeks.<sup>56</sup> A recent study of 641 patients with CSU demonstrated that oral corticosteroids, when used as initial therapy or in addition to  $\geq 1$  antihistamine, did not change the disease course. Disease duration, aggravating factors, and treatment were evaluated each visit and there was no significant difference in the time required to reach stable long-term control between patients treated with H<sub>1</sub> antihistamine monotherapy versus combination therapy with oral corticosteroids.<sup>58</sup>

## IMMUNOSUPPRESSIVE AGENTS

### Key points

- When high-dose corticosteroid therapy is needed for longer periods of time, immunosuppressive agents should be considered
- Various immunosuppressant drugs have been used for the treatment of refractory chronic urticaria, with cyclosporine being the most studied

Several case reports, case series,<sup>59-61</sup> and various controlled trials<sup>62-65</sup> have investigated the efficacy and safety of cyclosporine (CsA) in CU; most of the studies have shown favorable effects. Vena et al<sup>65</sup> performed the largest of these studies by evaluating the response to CsA in 99 patients with CSU. After 8 and 16 weeks, symptom scores were significantly

better in the CsA group compared to placebo. Two patients had to discontinue the study because of hypertension.<sup>65</sup> Because of study design limitations, potential side effects, and cost, both the US task force and the European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA2LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) have issued a weak recommendation for the use of CsA in patients with CU.<sup>2,19</sup> The EAACI/GA2LEN/EDF/WAO recommends a weight-based dose of 4 mg/kg/daily, while many experts use a 200-mg daily dose of CsA.<sup>19,66</sup> Because the bioavailability of different formulations of CsA varies between different preparations, it is recommended to continue the same formulation throughout the course of therapy. Patients who are taking CsA should have regular monitoring of their blood pressure, kidney function, and lipids.<sup>66</sup> Another calcineurin inhibitor, tacrolimus, was found to be effective in patients with refractory CU in a small open-label prospective study of 19 patients with unremitting disease. Doses used varied between 0.05 and 0.2 mg/kg/day divided into 2 daily doses for 12 weeks, with 70% of patients achieving clinical response. When response occurred, it was between 5 and 10 days. Side effects included abdominal pain, diarrhea, headache, and paresthesia, and resulted in discontinuation in 2 patients.<sup>67</sup>

Methotrexate has been described as an effective therapy according to anecdotal reports.<sup>68,69</sup> The beneficial effects of methotrexate may be antiinflammatory and immunosuppressive. However, in a recent RCT of 49 patients with CSU from India, Sharma et al<sup>70</sup> found that 15 mg of methotrexate weekly for 3 months did not provide any additional benefit over H<sub>1</sub> antihistamines.<sup>70</sup>

Mycophenolate mofetil (MMF) has been used in at least 32 patients to date.<sup>71-74</sup> An open-label study of 9 patients with refractory CU taking MMF 1 g twice daily for 12 weeks found improvement in symptom scores along with a diminished need for continuous corticosteroid use.<sup>72</sup> The largest retrospective series to date reported 90% improvement in 19 patients with CU (most refractory to other alternative therapies) with doses that ranged from 1 to 6 g/day. After 14 weeks of treatment, 60% of patients achieved disease control.<sup>74</sup> The most common adverse effects were gastrointestinal tract symptoms, found in 20% to 50% of patients, with no significant adverse events or laboratory abnormalities.<sup>72,74</sup>

Mizoribine, a related purine biosynthesis inhibitor, has also been successfully used in a patient with chronic autoimmune urticaria, achieving complete resolution at a dose of 150 mg daily for 6 months.<sup>75</sup>

There have been a small number of reported cases in which azathioprine was used successfully in CU; in 1 small single-blind RCT for patients with CU with positive autologous serum skin tests, small doses of azathioprine (50 mg/day) for 8 weeks were found to significantly decrease disease intensity and the need for rescue antihistamines with few side gastrointestinal side effects.<sup>76-79</sup>

Intravenous and oral cyclophosphamide have demonstrated efficacy in several case reports with patients with CU and demonstrated superiority to antihistamines in a small parallel group study. Doses have varied between 500 to 1500 mg intravenously every 2 to 4 weeks<sup>80</sup> and 50 to 100 mg orally daily.<sup>81,82</sup>

### Biologic agents

Originally approved for the treatment of severe allergic asthma, omalizumab is a recombinant humanized IgG monoclonal antibody against serum IgE,<sup>20</sup> and has recently been approved for the treatment of patients with CU who are unresponsive to H<sub>1</sub> antihistamines. The mechanism of action for omalizumab in CU is currently unknown but is postulated to work, in part, by preventing IgE binding to the high-affinity Ig E receptor FcεRI, as well as downregulating these receptors on mast cells and basophils, which may reduce their activation and release of bioactive mediators.<sup>83</sup> The evidence supporting the use of omalizumab is of higher quality than other antiinflammatory and immunosuppressant agents that are currently used for patients with CU who are unresponsive to H<sub>1</sub> antihistamines.<sup>19</sup> Three phase III and 2 phase II studies have demonstrated the efficacy and favorable safety profile of omalizumab (Table II).<sup>84-88</sup> The phase III pivotal studies found that both 150 and 300 mg of omalizumab are effective in reducing itch and the number of wheals related to CU.<sup>84-86</sup> Approximately 35% to 40% of subjects achieved complete relief and another third achieved partial relief after both the 3- and 6-month trials.<sup>85,87</sup> In both trials, the 300-mg dose appeared to be more effective than the 150-mg dose. Based on these results and the safety of omalizumab, experts recommend starting appropriate patients on 300 mg per month and continuing for 4 to 6 months to determine if the medication is effective.<sup>89</sup> If no therapeutic effect is seen within 6 months, it is unlikely to be achieved.<sup>90,91</sup> Efficacy has also been reported in isolated cases of physical urticaria, including solar urticaria, with inconsistent results.<sup>92,93</sup> A small (10-patient) phase II study using omalizumab 300 mg in patients with refractory solar urticaria resulted in 2 patients (20%) achieving control of their solar urticaria after 12 weeks. As with

CSU, the improvement in solar urticaria was lost when omalizumab was stopped.<sup>94</sup>

### ALTERNATIVE AGENTS

#### Key points

- Several alternative agents have been used in patients with CU that is refractory to antihistamines
- Supportive evidence is limited to small open-label studies or poorly designed RCTs

#### Dapsone

Dapsone is a sulfone antimicrobial that is mainly used in neutrophilic cutaneous diseases because of its antineutrophilic effects.<sup>95</sup> Possible therapeutic effects in CU may be related to decreased synthesis of leukotriene B4 and prostaglandin E2, and interference with CD11b.<sup>96-99</sup> Evidence for dapsone in CU is limited to case reports, case series, and 2 RCTs.<sup>98,100,101</sup> In these studies, dosing of 50 to 100 mg daily was used in patients with CSU, although 1 small open-label series demonstrated a good response with 25 mg daily.<sup>101</sup> One study showed that daily dapsone at 100 mg per day had a significant improvement in symptoms compared to placebo. Of the 22 patients enrolled in the trial, 9 patients showed ≥50% improvement in weekly itch score and 7 patients showed a ≥50% improvement in weekly hive score. The response was sustained even after discontinuation of treatment in 3 patients.<sup>102</sup> The initial response is usually observed in 3 to 4 weeks, but an effect can be as early as 1 week.<sup>95,102</sup> Dapsone was shown to be effective in treatment of delayed pressure urticaria in a small retrospective study of 22 patients, with a 74% response rate.<sup>103</sup> However, 50% of patients with CU who took dapsone developed side effects requiring 5.5% to discontinue treatment; 2.7% of these side effects were categorized as serious.<sup>66</sup> The most common side effect was an asymptomatic drop in hemoglobin level, followed by increased liver transaminases, headache, blood dyscrasias, and asymptomatic methemoglobinemia.<sup>66,95,104</sup> Before treatment initiation, a glucose-6-phosphate dehydrogenase level should be obtained because of the risk of severe hemolysis. A complete blood cell count and liver function tests should also be obtained at baseline and monitored regularly while patients are undergoing treatment.<sup>95,100,105</sup>

#### Sulfasalazine

Sulfasalazine is an antiinflammatory 5-aminosalicylic acid derivative.<sup>95</sup> The potential mechanisms of action relevant to CU include decreased leukotriene and prostaglandin production,

**Table II.** Phase II and III omalizumab trials in chronic urticaria

Name	Study type	N	Duration	Comment	Outcomes	Results of primary endpoint, 95% CI (SD)
ASTERIA I	Phase III randomized, double-blind, placebo-controlled	319; omalizumab 75 mg (n = 78), 150 mg (n = 80), 300 mg (n = 81), and placebo (n = 80)	24 weeks, with 16 weeks' follow-up	1. CSU patients who remained symptom- atic despite appro- priate treatment with H <sub>1</sub> antihistamines 2. 6 subcutaneous injections at 4-week intervals 3. Additional H <sub>1</sub> antihistamines allowed after week 12 4. Diphenhydramine 25 mg was allowed as rescue medication	Primary endpoint: week 12 change from baseline in weekly ISS	Compared with placebo, mean weekly ISS was reduced from baseline to week 12 by 2.96 points in the 75-mg group, 2.95 points in the 150-mg group, and 5.80 points in 300- mg group
ASTERIA II	Phase III randomized, double-blind, placebo-controlled	323; omalizumab 75 mg (n = 82), 150 mg (n = 82), 300 mg (n = 79), and placebo (n = 79)	24 weeks, with 16 weeks' follow-up	1. CSU patients who remained symptomatic despite appropriate treatment with H <sub>1</sub> antihistamines 2. 3 subcutaneous injections at 4-week intervals 3. Diphenhydramine 25 mg was allowed as rescue medication	Primary endpoint: week 12 change from baseline in weekly ISS	Compared with placebo, mean weekly ISS was reduced from baseline to week 12 by 0.81 points in the 75-mg group, 3.00 points in the 150-mg group, and 4.70 points in 300-mg group

GLACIAL	Phase III randomized double-blind, placebo-controlled	335; omalizumab (n = 252) and placebo (n = 83)	24 weeks, with 16 weeks' follow-up	1. CSU patients who remained symptomatic despite treatment with H <sub>1</sub> antihistamines, plus H <sub>2</sub> antihistamines, LTRAs, or both	Primary endpoint: percentage of participants with adverse events	No statistical difference was found between both groups. Adverse events were reported by 83.7% of patients taking omalizumab and 78.3% by the placebo group
				2. 6 subcutaneous injections at 4-week intervals		
				3. Diphenhydramine 25 mg was allowed as rescue medication		
X-QUISITE	Phase II randomized, double-blind, placebo-controlled	49; omalizumab 75-375 mg (n = 27) and placebo (n = 22)	24 weeks	1. CSU and immunoglobulin E (against TPO) positive anti-bodies patients who remained symptomatic despite antihistamine treatment.	Primary endpoint: week 24 change from baseline in mean weekly UAS	At week 24, there was a mean reduction in UAS score from baseline of -7.8 (10.52) with omalizumab and -7.9 (11.52) with placebo
				2. 6 or 12 subcutaneous injections at 4- or 2-week intervals		
				3. Loratadine or clemastine were allowed as rescue		
MYSTIQUE	Phase II randomized, double-blind, placebo-controlled	90; omalizumab 75 mg (n = 23), 300 mg (n = 25), 600 mg (n = 21), and placebo (n = 21)	4 weeks, with 12 weeks' follow-up	medications	Primary endpoint: week 4 change from baseline in mean weekly UAS	Both the 300-mg group -19.9 (12.3) and the 600-mg group -14.6 (10.7) showed greater improvement vs the placebo group -6.9 (9.8); no meaningful difference was observed for the 75-mg group -9.8 (11.75)
				1. CSU patients who remained symptomatic despite treatment with H <sub>1</sub> antihistamine.		
				2. A single subcutaneous injection		
				3. Diphenhydramine 25 mg was allowed as rescue medication		

CI, Confidence interval; CSU, chronic spontaneous urticaria; ISS, Itch Severity Scale; LTRA, leukotriene receptor antagonists; SD, standard deviation; TPO, thyroid peroxidase; UAS, Urticaria Activity Score.

**Table III.** Multiple validated tools to determine the effect of urticaria on quality of life

Tool	Type	Details	Available in multiple languages	Reference
CU-Q2oL	Retrospective	<ul style="list-style-type: none"> <li>• CU-Q2oL was developed and validated to assess the health-related quality of life in patients with CU</li> <li>• 23 items divided into 6 quality of life domains</li> <li>• 5-point scale (1, not at all; 5, very much) with multiple options for how much the patient has been troubled by each item</li> </ul>	Yes	Engler et al <sup>109</sup>
USS	Prospective	<ul style="list-style-type: none"> <li>• USS evaluates quality of life measures relevant to CU and the amount and type of medication required to control urticarial symptoms</li> <li>• 12 questions</li> <li>• 7-point scale (0, not at all; 7, very much) measuring degree of symptoms</li> </ul>	No	Wedi et al <sup>114</sup>
UAS-7	Prospective	<ul style="list-style-type: none"> <li>• UAS-7 has been developed to assess disease severity and control in patients with CU</li> <li>• Severity of itching (0-3 points) and the number of wheals (0-3 points) are recorded daily for a maximum score of 6 points, for 7 days</li> <li>• A score of &lt;7 in 1 week indicates control of disease, while a score of &gt;28 in 1 week indicates severe disease</li> </ul>	Yes	Sams Jr et al <sup>115</sup>
UCT	Retrospective	<ul style="list-style-type: none"> <li>• UCT has been developed to assess disease control in patients with CU</li> <li>• 4 items</li> <li>• 5 answer options each scored 0-4 points, with high points indicating low disease activity and good disease control</li> <li>• Minimum and maximum UCT scores range from 0-16, with 16 points indicating complete disease control</li> </ul>	Yes	Lawlor et al <sup>119</sup>

CU, Chronic urticaria; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; UAS, urticaria activity score; UCT, urticaria control test; USS, urticaria severity score.

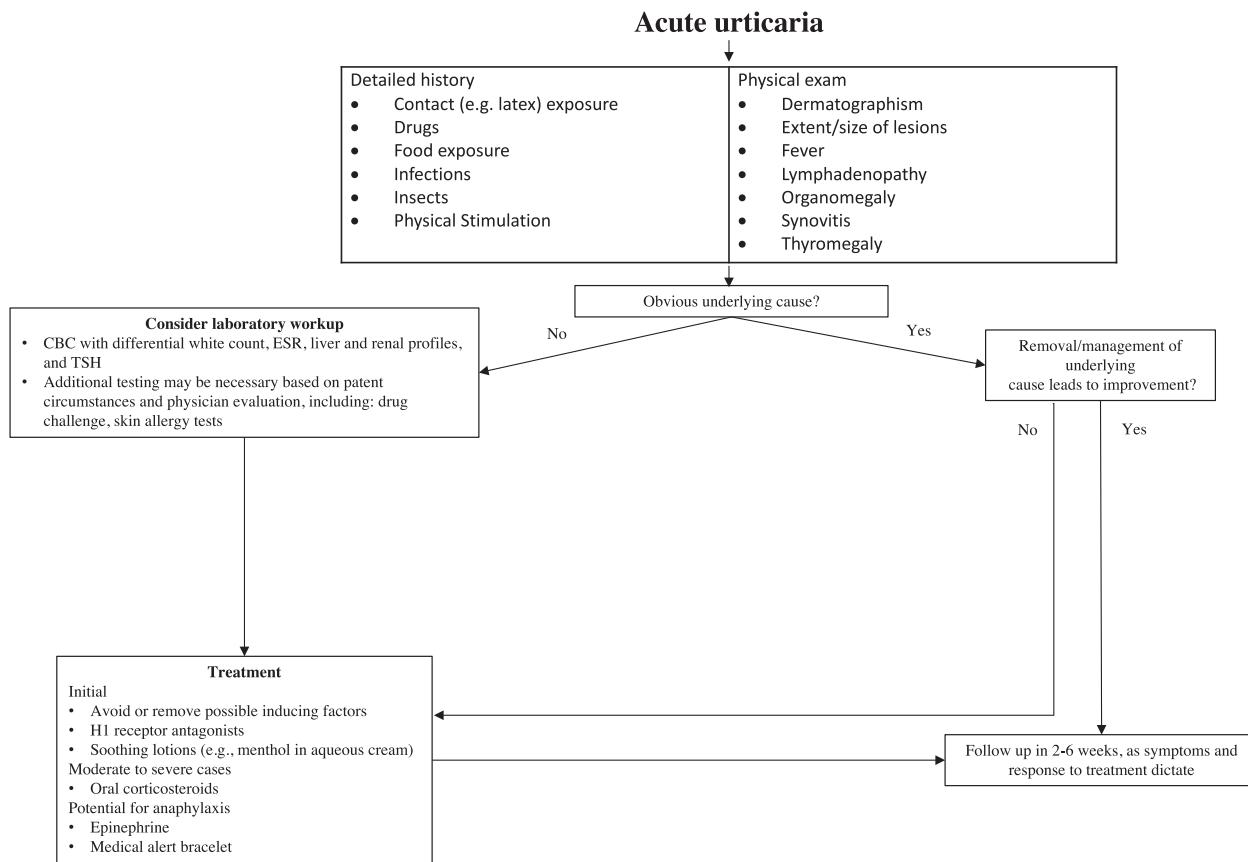
inhibition of IgE-mediated mast cell degranulation, reduction of histamine release, and inhibition of B lymphocyte proliferation.<sup>95,106</sup> Efficacy data for the use of sulfasalazine in CU are limited to case reports, case series, and a single retrospective case study.<sup>103,107-110</sup> Sulfasalazine is usually started at a dose of 500 mg/day and increased weekly by 500 mg up to a total of 4 g, as tolerated, until achieving symptom control.<sup>106</sup> Therapeutic responses typically occur within 1 month. Doses above 2 g/day have been associated with increased side effects without additional benefit.<sup>95,100,103,106</sup> In addition, anecdotal evidence points to sulfasalazine rarely causing side effects in doses <2 g but providing little benefit at <1 g. It has also been noted that patients rarely need >3 g, and side effects become common above this dose.

McGirt et al<sup>106</sup> successfully treated 19 patients with antihistamine-unresponsive CSU with sulfasalazine for 3 years. Although 37% (7 patients) had adverse effects, no serious side effects were reported.<sup>106</sup> The

most frequent side effects are nausea, diarrhea, dyspepsia, abdominal pain, and anorexia, which typically occur early and are often dose-related.<sup>95</sup> Headache, myalgia, and flu-like symptoms are also frequent.<sup>66</sup> Laboratory monitoring includes a complete blood cell count and liver function tests. Sulfasalazine is contraindicated in patients with hepatic, renal, and hematologic dysfunction.<sup>111</sup>

### Hydroxychloroquine

The immunomodulatory effects of hydroxychloroquine are partly related to interference with antigen presentation by major histocompatibility complex class II molecules.<sup>95</sup> The effects related to urticaria pathogenesis are still unknown.<sup>112</sup> Data related to hydroxychloroquine are limited to case reports and a small randomized, double-blind, placebo-controlled trial of 21 patients that showed quality of life improvement despite only a marginal change in urticaria activity scores.<sup>105,112</sup> Hydroxychloroquine is dosed at 200 mg twice daily and may take 2 to



**Fig 1.** Acute urticaria treatment algorithm. *CBC*, Complete blood cell count; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *TSH*, thyroid-stimulating hormone.

3 months for the full effect. Although considered a safe drug, its use in CU has been associated with side effects in 16% of patients, with discontinuation in 7% as demonstrated in a retrospective study of 217 patients with CSU.<sup>66</sup> The most common adverse effects are diarrhea, abdominal cramps, and nausea.<sup>66</sup> Other common side effects include vision changes, which are usually reversible, and headache.<sup>95</sup> The risk of retinopathy, which may be irreversible, increases after 5 years of use and, therefore, a baseline ophthalmologic evaluation is recommended within the first year, and follow-up examinations annually after 5 years.<sup>100,104,105</sup> Patients with existing ocular problems, such as retinopathy, may be more susceptible to these side effects.<sup>113</sup>

Chloroquine reduces histamine release in the serum of patients with autologous serum skin test-positive CU,<sup>114</sup> and in doses of 250 mg daily has successfully treated isolated cases of solar urticaria<sup>115</sup> and delayed pressure urticaria.<sup>116</sup>

### Colchicine

Data on colchicine efficacy in CU are limited to a few case reports and a single case series, where most

patients showed histologic findings of neutrophilic infiltrates or urticarial vasculitis.<sup>104</sup> Colchicine has a number of antiinflammatory effects, including inhibition of neutrophil chemotaxis and downregulation of adhesion molecules.<sup>117</sup> Colchicine also has the capability to inhibit histamine release and interleukin-1.<sup>118</sup> Colchicine is dosed at 0.3 to 0.6 mg twice daily.<sup>118,119</sup> Although 1 randomized trial showed no efficacy in cases of delayed pressure urticaria,<sup>119</sup> a recent retrospective study by Amin et al<sup>120</sup> demonstrated complete control in 18% of patients treated with colchicine suffering from CU refractory to antihistamines and LTRA. A total of 221 patients were included in the study with aims of identifying patient-specific characteristics and medications associated with urticaria control. The average time to achieve control was  $1.4 \pm 2.7$  years, which required 1 to 3 classes of medications. In addition, they concluded that colchicine was more effective when used in physical urticarias, excluding dermatographism.<sup>120</sup> The most common adverse effects are gastrointestinal, which are dose-dependent, and include diarrhea ( $\leq 77\%$  of patients), nausea, vomiting, and abdominal pain.<sup>121,122</sup> Rare, but possibly serious, adverse events include

**Table IV.** The European Academy of Allergy and Clinical Immunology/World Allergy Organization and the American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology guidelines on the diagnosis and management of chronic urticaria

	EAACI/GA2LEN/EDF/WAO international guidelines	US practice parameters
Diagnosis		
History and physical examination	Evaluate for psychiatric/psychosomatic disease, surgical implantations, and postsurgical events	Evaluate for psychiatric/psychosomatic disease, surgical implantations, and postsurgical events
Laboratory evaluation	Limited (eg, CBC with differential, CRP, or ESR)	Patient-dependent; consider CBC with differential, CRP, or ESR, liver enzymes, and TSH; clinical utility of these tests has not been established
Tests for evaluating differential diagnosis based on patient history	<p>Autoinflammatory disease strongly suspected</p> <ul style="list-style-type: none"> <li>Consider CRP or ESR; testing for paraproteinemia (adults); screening for neutrophil-rich infiltrates in the skin biopsy specimen; performing gene mutation analysis for hereditary periodic fever syndromes</li> </ul> <p>HAE suspected</p> <ul style="list-style-type: none"> <li>Complement C4, C1-INH levels and function, and C1q and C1-INH antibodies</li> <li>Gene mutation analysis if above tests unremarkable</li> </ul> <p>Mean wheal duration &gt;24 hours</p> <ul style="list-style-type: none"> <li>Obtain biopsy specimen of lesional skin to assess for signs of urticarial vasculitis</li> </ul> <p>Infectious diseases</p> <ul style="list-style-type: none"> <li><i>Helicobacter pylori</i></li> </ul> <p>Miscellaneous</p> <ul style="list-style-type: none"> <li>Type I allergy, trial pseudoallergen-free diet for 3 weeks; conduct ASST</li> </ul>	<p>Laboratory tests</p> <ul style="list-style-type: none"> <li>Antinuclear antibody, rheumatoid factor, or anticitrullinated protein, complement activity tests</li> <li>Cryoglobulin levels</li> <li>Hepatitis B and C serologies</li> <li>Serologic or skin testing for immediate hypersensitivity</li> <li>Stool analysis (ova and parasites)</li> <li>Thyroid autoantibodies to TSH receptor, thyroglobulin, and thyroid peroxidase</li> </ul> <p>Imaging</p> <p>Chest radiography or imaging studies</p> <p>Procedures</p> <ul style="list-style-type: none"> <li>Obtain skin biopsy specimen</li> <li>Physical challenge tests</li> </ul>
Management		
Step 1	<ul style="list-style-type: none"> <li>Second-generation antihistamines</li> <li>Avoid triggers like drugs (eg, NSAIDs) and physical factors</li> <li>Increase dosage of second-generation antihistamines up to 4-fold</li> </ul>	<ul style="list-style-type: none"> <li>Second-generation antihistamines</li> <li>Avoid triggers like drugs (eg, NSAIDs) and physical factors</li> </ul>
Step 2		<p>One or more of the following:</p> <ul style="list-style-type: none"> <li>Advance the dose of second-generation antihistamine used in step 1</li> <li>Add another second-generation antihistamine</li> <li>Add an H<sub>2</sub> receptor antagonist</li> <li>Add a leukotriene receptor antagonist</li> <li>Add a first-generation antihistamine to be taken at bedtime</li> </ul>
Step 3	<ul style="list-style-type: none"> <li>Add another drug: cyclosporine, montelukast, or omalizumab</li> <li>Give short course (&lt;10 days) of oral corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>Advance the dose of first-generation antihistamine</li> </ul>

Continued

**Table IV.** Cont'd

	EAACI/GA2LEN/EDF/WAO international guidelines	US practice parameters
Step 4	—	<ul style="list-style-type: none"> <li>• Cyclosporine or omalizumab</li> <li>• Biologics, additional antiinflammatories, or immunosuppressants</li> </ul> <p>≤1-3 weeks</p>
Use of oral corticosteroids	≤10 days	

ASST, Autologous serum skin test; C1-INH, C1-inhibitor; CBC, complete blood cell count; CRP, C-reactive protein; CSU, chronic spontaneous urticaria; EAACI, European Academy of Allergy and Clinical Immunology; EDF, European Dermatology Forum; ESR, erythrocyte sedimentation rate; GA2LEN, Global Allergy and Asthma European Network; HAE, hereditary angioedema; TSH, thyroid-stimulating hormone; WAO, World Allergy Organization.

neutropenia, thrombocytopenia, pancytopenia, myelosuppression, transaminitis, myoneuropathy, and renal dysfunction (in individuals with a history of renal insufficiency).<sup>95</sup>

### Ultraviolet phototherapy

Ultraviolet light phototherapy is thought to work by decreasing histamine release from mast cells.<sup>123</sup> Studies on psoralen plus ultraviolet A light (PUVA) phototherapy have returned inconsistent results, but broadband ultraviolet B light (BB-UVB) and narrow-band UVB (NB-UVB) phototherapy are more promising.<sup>124-126</sup> With regard to PUVA, Khafagy et al<sup>126</sup> treated 12 patients to a maximum of 20 sessions (3 sessions/week) with a mean cumulative dose of 76 J/cm<sup>2</sup> and found significant improvement in the duration of wheals and the number of days patients reported itching.<sup>126</sup> On the other hand, Olafsson et al<sup>124</sup> compared the efficacy of PUVA versus UVA plus placebo in 11 patients during a maximum period of 2 months (2 sessions/week) with a mean cumulative dose of 88 J/cm<sup>2</sup>. They concluded that PUVA was no better than UVA in the treatment of CU.<sup>124</sup> A Canadian questionnaire study also found neutral/ineffective results.<sup>127</sup>

In a study of 43 patients treated with BB-UVB 5 times a week, it was demonstrated that BB-UVB treatment was 90% effective (measured as remission or improvement of symptoms). After a follow-up period of ≤2 years, many patients (26) had lasting effects, but 13 relapsed within 5 months of therapy discontinuation.<sup>128</sup> Studies using NB-UVB have shown a significant reduction in the urticaria activity score as early as the ninth session.<sup>123,125,126</sup> Engin et al<sup>125</sup> randomized 81 patients with CU into a NB-UVB plus levocetirizine group and a levocetirizine control group. Patients were assessed at sessions 10, 20, and at 3 months of follow-up. The reduction in urticaria activity score and visual analogue scale was statistically significant in both groups, but the NB-UVB group demonstrated a maintained urticaria activity score improvement (after 3 months of

phototherapy discontinuation) that was not observed in the levocetirizine control group.

## SPECIAL POPULATIONS

### Key points

- The management of urticaria in pregnant or lactating women and children is largely the same as for nonpregnant adults
- In pregnant or lactating women, antihistamines should be used at the lowest effective dose for the shortest period of time possible
- In children, second-generation rather than first-generation antihistamines should be used and corticosteroids should be avoided or used sparingly

### Pregnancy or breastfeeding

The management of urticaria in pregnant or lactating women is largely the same as for nonpregnant adults, but H<sub>1</sub> antihistamines should be used at the lowest effective dose for the shortest period of time possible given the largely unknown effects on the developing fetus and on excretion in breast milk.<sup>129</sup> Cetirizine, loratadine, and levocetirizine are US Food and Drug Administration pregnancy category B, while desloratadine and fexofenadine are category C.<sup>130</sup> Notably, a prospective RCT on the use of loratadine in pregnancy found no increased risk of congenital anomalies compared to other antihistamines or controls.<sup>131</sup> Similarly, there is consensus that diphenhydramine, a fgAH, is safe during pregnancy.<sup>132</sup>

### Children

The management of urticaria in children is largely the same as for adults with the caveats that sgAH rather than fgAH should be used because of the latter's sedating effects, and corticosteroids should be avoided or used for short periods of time (<10-14 days) whenever possible because of growth-related side effects.<sup>53,133</sup>

## Elderly

The use of antihistamines in the elderly is accustomed by multiple factors, including comorbidities, polypharmacotherapy, and organ insufficiency.<sup>19,134,135</sup> fgAHs are more lipophilic, which means they can cross the blood–brain barrier. In addition, they tend to be anticholinergic, antiserotonergic, and antidopaminergic, which can cause or worsen urinary retention, arrhythmias, peripheral vasodilatation, postural hypotension, tachycardia, and mydriasis.<sup>134</sup> sgAHs do not cross the blood–brain barrier and are therefore a better choice.<sup>2,19</sup> However, some of them require dose adjustment if the patient has renal or hepatic impairment.<sup>134,135</sup>

Levocetirizine requires dose adjustments in cases of moderate to severe renal insufficiency. Mizolastine is contraindicated in patients with liver insufficiency and with the use of systemic azole antifungals and macrolide antibiotics or drugs able to prolong the QT interval. Ebastine is contraindicated in severe liver failure and caution needs to be taken not to exceed 10 mg/day in patients with mild to moderate liver failure.<sup>135</sup>

## OUTCOMES

### Key points

- **Most cases of acute urticaria resolve**
- **Sixty-seven percent of cases of chronic urticaria in children remit spontaneously within 5 years**
- **Urticaria significantly impacts quality of life because of associated pruritus, sleep disturbances, drug-related side effects, and concerns about physical appearance**
- **Multiple, validated, patient-reported outcome tools have been developed to help gauge the effect of urticaria on quality of life and to help guide and assess the response to treatment**

### Disease course

About 80% of cases of AU resolve in <6 weeks.<sup>136,137</sup> Reports on the proportion of cases that recur or become chronic are limited, with studies estimating a 20% to 30% transition to CU.<sup>138,139</sup> In children, the data are similar; a prospective study of 57 infants with 2 years of follow-up showed that 30% of patients experience recurrent or chronic urticaria.<sup>140</sup> Reports on the natural history of CU are variable, depending on the age of the patient, type of urticaria, and center where the patients were seen.<sup>19</sup> Only a few studies deal with the duration of treatment in CU. Quaranta et al<sup>141</sup> found that 32% of patients were symptom-free after a 3-year treatment period in a study on 86 patients

with CSU. Kozel et al<sup>142</sup> reported that 47% of 78 patients with CSU had remission within 1 year. Similarly, Champion et al<sup>143</sup> found that 45% of 554 patients with CSU still had symptoms after 1 year. Remission rates of CU at 5 years have been found to be 67.7% and 29% in children and adults, respectively.<sup>144,145</sup>

## Patient-reported outcomes

Urticaria can have a significant impact on quality of life because of the associated pruritus, sleep disturbances, and drug-related side effects.<sup>146</sup> Patients with CU and severe disease are more severely impacted.<sup>146,147</sup> The severity of CU is commonly assessed by using objective instruments, such as visual analogue scales.<sup>148</sup> The impact on health-related quality of life has been traditionally assessed using generic, dermatology-specific, or urticaria-specific patient-reported outcome measures.<sup>149</sup> Patient-reported outcomes that are urticaria-specific have been shown to be superior to less specific instruments in measuring the impact urticaria has on patients' quality of life and how the patients' level of disease responds to treatment.<sup>149</sup>

## Quality of life

Because of the strong effect CU has on quality of life, multiple patient-reported outcome tools have been developed to quantify the effect of urticaria and to help guide and assess the response to treatment (Table III).<sup>149</sup>

## Treatment approach

Treatment guidelines for CU have been published by the EAACI/WAO and the American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force, which share many similar recommendations but have some notable differences.

**Acute urticaria.** A stepwise approach to the treatment of AU is shown in Fig 1.<sup>19,139,150</sup>

**Chronic urticaria.** A stepwise approach to the treatment of CU, as specified by the international guidelines and US practice parameters, is shown in Table IV.<sup>19,21</sup>

Although the Joint Task Force Practice Parameter treatment algorithm is widely accepted in the United States, its step-by-step approach is not tailored to patient-specific characteristics (ie, serologic, physical, or histologic traits). No clinically effective treatment algorithm(s) are available, based on the presence or absence of specific patient characteristics.<sup>19,151,152</sup>

Few studies have tried to identify patient-specific clinical characteristics associated with control of CU in adults.<sup>120,153,154</sup> Amin et al<sup>120</sup> found that physical urticarias, the presence of dermatographia, and a neutrophil-rich infiltrate on a skin biopsy specimen were markers associated with more recalcitrant disease. Kozel and Sabroe<sup>152</sup> reported that patients with physical urticarias (not including pressure, cold, solar, and aquagenic urticaria) may respond better to an H<sub>1</sub> antagonist. Both of these studies agreed that patients with dermatographia were more likely to respond to fgAHs or sgAHs.<sup>120,152</sup> Patients with a neutrophilic infiltrate responded best when treated with dapsone (5 times greater odds of control) than cyclosporine and other immunosuppressants.<sup>120,155</sup> Patients with thyroid autoantibodies, which make up 20% to 30% of the CU population,<sup>156-158</sup> had a 3 times greater odds of control with fgAH or sgAH than LTRA or H<sub>2</sub> antagonists.<sup>120</sup> Amin et al<sup>120</sup> also found that the best overall control of CU was achieved when using a sgAH plus LTRA and that white patients were up to 7 times more likely to have a favorable response to LTRA or doxepin.

## Differences between US and European guidelines

Differences exist primarily for terminology and treatment recommendations. Table IV compares the guidelines in terms of the diagnosis and management of CU.<sup>19,21,53</sup>

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# Lichen planus and lichenoid dermatoses



## Clinical overview and molecular basis

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### Learning objectives

After completing this learning activity, participants should be able to recognize clinical features characterizing lichen planus and other lichenoid disorders in patients; classify lichenoid conditions into their respective categories and subtypes; distinguish between the various lichenoid dermatoses despite the significant overlap in clinical presentation; and describe underlying molecular mechanisms for lichenoid skin diseases.

### Disclosures

#### Editors

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Deriving from the Greek word *λειχήν* for “tree moss” and the Latin word *planus* for “planar,” lichen planus is a relatively uncommon and heterogeneous cutaneous disorder that typically develops in middle-aged adults. Despite the significant clinical burden associated with the disorder, little well-conducted molecular research has been undertaken, possibly because of heterogeneity impeding consistent and confident phenotyping. The multiple variants of lichenoid disease bear overlapping clinical and pathologic features despite manifesting as distinct clinical disorders. The first article in this 2-part continuing medical education series provides a comprehensive overview of the clinical and pathologic characteristics of cutaneous lichenoid dermatoses and links these manifestations to recent advances in our understanding of the underlying pathobiology of such diseases. (J Am Acad Dermatol 2018;79:789-804.)

**Key words:** lichen planus; lichenoid inflammation; lichenoid variants; molecular basis of lichenoid inflammation.

## CUTANEOUS LICHEN PLANUS

### Key points

- Cutaneous lichen planus represents a relatively uncommon dermatosis, affecting <1% of the population

- Consisting of polygonal, pruritic, planar papules or plaques, lichen planus is a heterogeneous papulosquamous eruption of variable morphologic manifestation but a consistent histologic phenotype

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**Abbreviations used:**

LP:	lichen planus
LPP:	lichen planopilaris
NLP:	nail lichen planus
HCV:	hepatitis C virus
LDE:	lichenoid drug eruption
LPLK:	lichen planus–like keratosis
LS:	lichen sclerosus
BP:	bullous pemphigoid
LE:	lupus erythematosus
IL:	interleukin
IFN:	interferon
HLA:	human leukocyte antigen
SNP:	single nucleotide polymorphism

- **The etiology of lichen planus remains elusive, although immune dysregulation, infectious, environmental, and genetic factors may play a role in disease pathobiology**

### Epidemiology, clinical features, and diagnostic considerations

With an estimated incidence of <1%,<sup>1</sup> cutaneous lichen planus (LP) is thought to make up 0.4% to 1.2% of all dermatology referrals and features.<sup>2–4</sup> It is an inflammatory dermatosis mainly affecting adults of any sex and ethnic origin, and only rarely has it been reported to involve children; the remainder of this series focuses on disease as manifested and treated in adults.<sup>1,5,6</sup>

Cutaneous LP typically presents as a papulo-squamous eruption with flat-topped, violaceous, papular lesions of varying size, often described using the “six P’s” (purple, pruritic, polygonal, planar, papules, and plaques) and characterized by the classic Wickham striae (Fig 1, A).<sup>5,7</sup> The distribution of the eruption is usually localized to the extremities,<sup>8</sup> but may rarely be generalized<sup>4,9</sup> or adopt a Blaschkoid,<sup>10</sup> intertriginous,<sup>5</sup> or dermatomal<sup>11</sup> configuration. The majority of cutaneous LP cases will remit within 1 to 2 years,<sup>12</sup> unlike subtypes involving mucosal and densely follicular sites, where lesions tend to persist for a longer duration. From our perspective, testament to this is the observation that our tertiary specialist clinics are occupied with challenging chronic cases of oral, genital, and appendageal disease, whereas classic cutaneous disease does not appear to be as burdensome, demands less regular clinical input, and is only seen in the general clinic service.

There are a number of characteristic pathologic findings that allow confirmation of a clinical diagnosis of LP.<sup>13,14</sup> The epidermis may show hyperkeratosis without parakeratosis, and apoptotic keratinocytes (Civatte bodies) can be seen at a lower level (Fig 1, B).<sup>13,14</sup> The epidermis itself may show

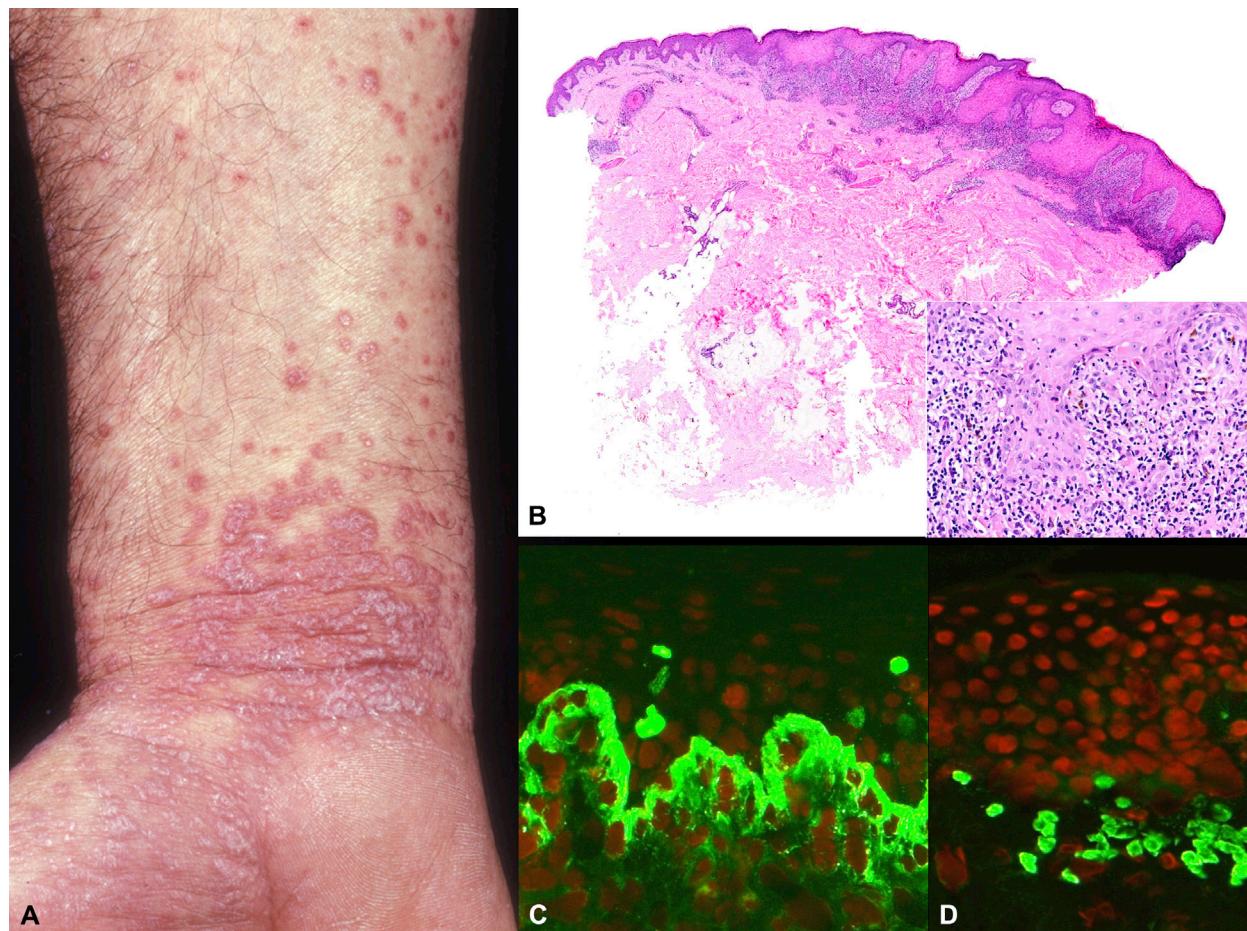
“wedge-shaped” hypergranulosis, with a characteristic “saw tooth” appearance of the rete ridges.<sup>13,14</sup> At the dermoepidermal junction, small clefts (known as Max Joseph spaces) may be observed along with band-like lymphocytic infiltration.<sup>13,14</sup> Apoptotic keratinocytes are also found in the papillary dermis, as eosinophilic colloid bodies. As the dermoepidermal junction is disrupted, pigment incontinence occurs, linked to the increased presence of melanophages.<sup>13,14</sup> Direct immunofluorescence staining in the biopsy specimen is helpful, because lesions of LP characteristically and consistently display a bright “shaggy” band of fibrinogen along the dermoepidermal junction, as well as colloid bodies staining with any of the autoantibodies immunoglobulin M (IgM), IgG, IgA, and C3 (Fig 1, C and D).<sup>13</sup>

Although experienced physicians are able to diagnose cutaneous LP clinically, a biopsy specimen of the skin is useful for confirmation of a clinical diagnosis, and punch or shave biopsy specimens are normally adequate.<sup>15</sup> We tend to resort to histopathologic evaluation in rare cases of diagnostic uncertainty, but we consistently explore possible risk factors for hepatitis C virus (HCV) infection. A systematic drug history to look for culprits is also relevant in the clinical history, as are symptoms suggestive of other regional lichenoid involvement. Such symptoms comprise oral or genital erosions or pain, dysphagia or odynophagia, alopecia, and trichodynia, and the physical examination should comprehensively look for the corresponding and supportive clinical signs at the scalp, oral cavity, and genitalia, respectively. Dermoscopy can be used to highlight Wickham striae,<sup>16</sup> which complement the clinical history, in differentiating idiopathic LP from drug-induced disease (lichenoid drug reaction).<sup>17</sup> The clinical history is also vital in diagnosing clinically reminiscent conditions, such as chronic graft-versus-host disease.<sup>18</sup>

### MORPHOLOGIC VARIANTS OF CUTANEOUS LICHEN PLANUS

#### Key points

- **Being morphologically heterogeneous, lichen planus may be hyperkeratotic, annular, bullous, pigmented, or atrophic**
- **Lichenoid variants are plentiful and comprise lichenoid drug eruption, lichen planus–like keratosis, lichen nitidus, lichen sclerosus, and lichen striatus**
- **Overlap syndromes refer to lichen planus coexisting with a distinct second clinical entity**



**Fig 1.** Lichen planus. **A**, Wrist. Characteristic polygonal flat-topped erythematous papules with shiny surfaces coalescing into plaques. **B**, Histopathology of a hypertrophic lesion showing irregular epidermal hyperplasia with a dense lichenoid lymphohid cell infiltrate. *Inset*, Higher magnification showing lymphocytic exocytosis with vacuolar interface changes and individual dyskeratotic keratinocytes (Civatte bodies) with papillary dermal lymphocytes admixed with histiocytes and melanophages. **C**, A linear "shaggy" band of fibrinogen deposition at the basement membrane zone. **D**, Colloid bodies in the papillary dermis staining for immunoglobulin A. (**B**, Hematoxylin–eosin stain; **C**, fibrinogen; **D**, immunoglobulin A; original magnifications: **B**,  $\times 40$  and *Inset*,  $\times 200$ ; **C**,  $\times 400$ ; **D**,  $\times 400$ .) Clinical image courtesy of St. John's Institute of Dermatology.

Cutaneous LP does not always manifest in a classic presentation, because there is an array of LP variants that possess distinct clinical characteristics.

Actinic LP is a morphologic variant of high prevalence in tropical countries such as India, East Africa, and the Middle East<sup>8</sup>; therefore, it is sometimes referred to as LP subtropicus. Sun-exposed areas display discoid macules, papules, or plaques with a hyperpigmented focus and encircling hypopigmentation.<sup>5</sup> The violaceous plaques observed in annular LP have a thin rim of activity with a clear, and occasionally atrophic, center. These lesions may develop on the penis (Fig 2), scrotum, and intertriginous regions amongst other sites, including the lips (Fig 3).<sup>19</sup>

Atrophic LP, one of the rarer cutaneous LP variants, typically affects the legs<sup>5</sup> and manifests as small violaceous, annular papules that progressively enlarge. These lesions develop central atrophy and histology of the papillary dermis characteristically shows destruction of elastic fibers, which may or may not be accompanied by a lymphocytic infiltrate.<sup>20-22</sup> In the bullous subtype, bullae or vesicles tend to be restricted to areas already affected by cutaneous LP, and frequently develops on the lower extremities.<sup>5</sup> Bullous LP can resemble an overlap syndrome of LP and bullous pemphigoid (BP) known as LP pemphigoides.<sup>23</sup> The hypertrophic variant of LP presents with extremely pruritic, hyperkeratotic flat-topped plaques affecting the



**Fig 2.** Lichen planus of the penis. **A**, Glans penis. Annular patch with central clearing and white shiny peripheral edge. **B**, Histopathology showing epidermal atrophy with an overlying compact horn and a dense lichenoid lymphoid cell infiltrate in the papillary dermis. (Hematoxylin–eosin stain; original magnification: **B**,  $\times 400$ .)

wrists, interphalangeal joints or the anterior lower legs (Fig 1, A). This subtype can commonly present in a symmetrical pattern. Polygonal papules may encircle the original lesion. A visual clue that can be used to differentiate hypertrophic LP is its resemblance to the extrusive forms of igneous rock.<sup>24</sup> Squamous cell carcinoma may arise in sites affected by chronic hypertrophic LP.<sup>25</sup> Inverse LP manifests as poorly defined erythematous lesions with pigmentation, usually involving the axillae, inguinal creases, inframammary creases, and neck and limb flexures.<sup>5</sup> LP pigmentosus is characterized by minimally pruritic, hyperpigmented macules typically on intertriginous or sun-exposed areas. The degree of pigmentation varies from slate gray to dark brown patches, and inverse LP and LP pigmentosus are more often observed in individuals with darker skin.<sup>26</sup> When lesions are primarily distributed on skin fold areas, this rare variant is known as LP pigmentosus inversus.<sup>27</sup>

Of the above morphologic variants, we most commonly encounter the hypertrophic type, followed by LP pigmentosus, the latter almost exclusively in association with cases of frontal fibrosing alopecia.

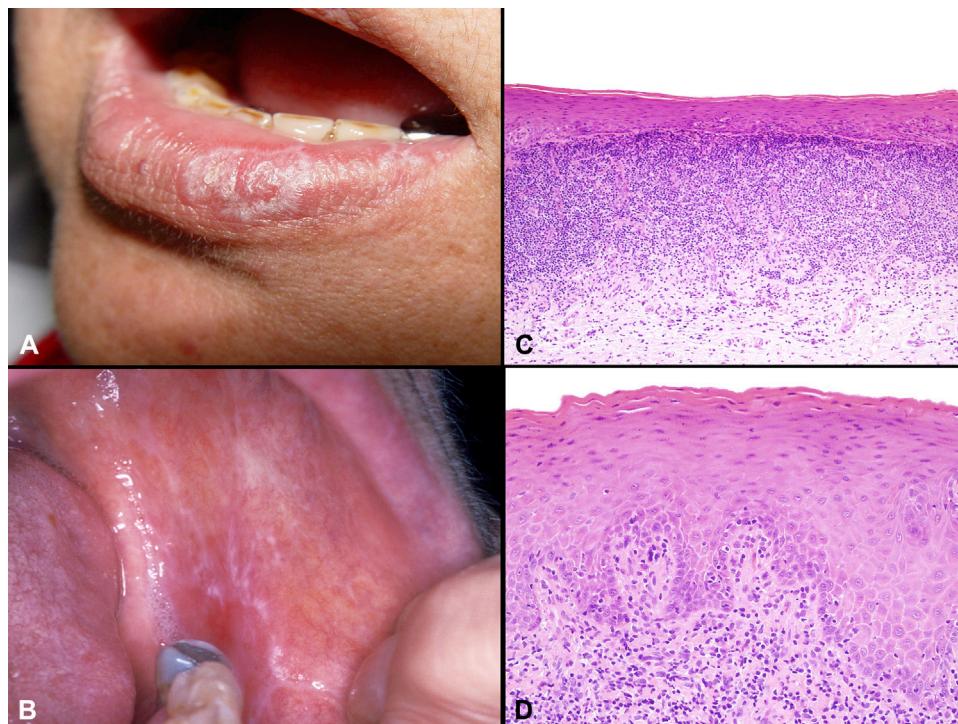
### Regional and appendageal subtypes

There are 3 different specialty clinics in our center, each devoted to and hosting a large patient cohort for each of these subtypes, and each subtype can be more debilitating and treatment-refractory than classic cutaneous cases of LP.

**Oral LP.** Oral LP, a lichenoid subvariant affecting the oral mucosa (Fig 4), is a chronic, relapsing and remitting disorder, and is generally thought to confer a higher morbidity than many of its cutaneous counterparts.<sup>28,29</sup> This condition is often diagnosed by dentists, who subsequently refer these patients to dermatologists for treatment. Indeed, given that oral LP is frequently associated with cutaneous lichenoid disease, examination of the oral cavity should therefore be a routine part of patient evaluation in dermatology clinics. Whether asymptomatic reticular or highly distressing erythematous and erosive, specialist assessment and work-up (clinical and histopathologic) is required and should be sought as appropriate.

**Genital LP.** Genital LP, involving glabrous or mucosal skin, may affect men and women alike and may be encountered by a variety of medical specialties, including gynecology, genitourinary medicine, urology, and primary care, although dermatologists should be involved and lead care as early as possible. Penile LP tends to present with a papular or annular morphology, whereas females tend to develop highly debilitating erosive disease, whether in isolation or as part of erosive vulvovaginogingival syndrome.<sup>30–32</sup> There are many variations in clinical presentation, and it is important to be aware of the more common manifestations of genital LP (Fig 5) while also remembering to consider the genital areas in history-taking and clinical examination when evaluating for LP affecting other body regions. Diagnosis may be reached by clinical assessment, although histopathologic evaluation may be undertaken in challenging cases.

**Follicular LP.** Follicular LP, or lichen planopilaris (LPP) for loyal Latin scholars, is the prototype of primary lymphocytic cicatricial alopecias and is associated with inflammation-driven hair follicle destruction, culminating in scarring hair loss that involves the scalp and other body areas (Fig 6, A and C).<sup>33,34</sup> Histopathologically, LPP is characterized by perifollicular lymphoid cell infiltration and perifollicular fibrosis (Fig 6, B). It has been postulated that the underlying immune privilege collapse at the level of the hair follicle bulge culminates in epithelial hair follicle stem cell loss and irreversible cicatricial hair loss, in a process germane to alopecia areata but occurring at the more



**Fig 3.** Annular lichen planus. **A**, Lower lip. Annular plaque with central clearing and raised purple to white shiny borders. **B**, Oral lichen planus. Lacy reticular network of white coalescing papules. Clinical image courtesy of St. John's Institute of Dermatology. **C**, Squamous mucosa with confluent parakeratosis and with underlying dense lichenoid lymphoid cell infiltrate. **D**, Higher magnification detail on the lichenoid interface changes and lymphocytic exocytosis. (Hematoxylin-eosin stain; original magnification: **C**,  $\times 100$ ; **D**,  $\times 200$ .)

superficial anatomic level of the isthmus.<sup>34</sup> LPP is heterogeneous per se and comprises classic multifocal LPP, Graham-Little-Piccardi-Lasseur syndrome, and the distinct and almost exclusively of female predilection and postmenopausal onset frontal fibrosing alopecia variants (Fig 6).<sup>34</sup> We have argued and proposed elsewhere<sup>34</sup> that the term frontal fibrosing alopecia is a misnomer, because it restricts in linguistic terms an immune system-mediated autoinflammatory disease characterized by widespread body, eyebrow, facial, occipital lichenoid, and alopecic involvement to the geographic territory of the frontovertex. By the same token, perhaps LPP should be more precisely defined as classic, frontoparietalis, occipitalis, totalis, and universalis, in a manner on par with its nonscarring, albeit deeper dermal, autoimmune counterpart alopecia areata.

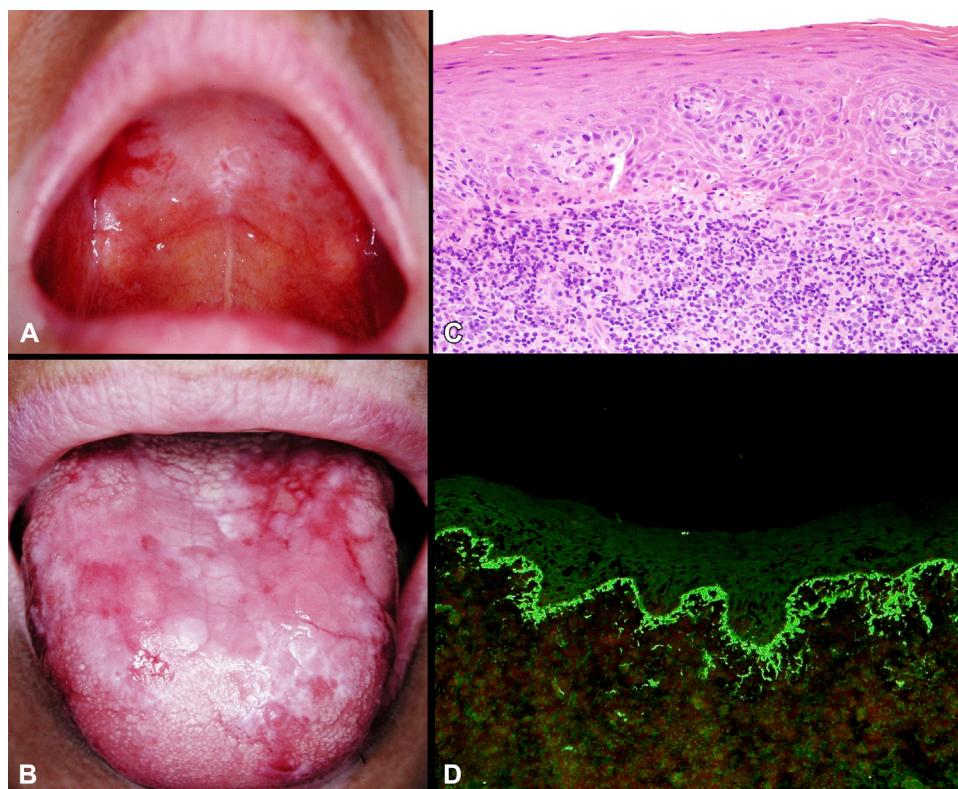
**Nail LP.** Although the nails show lichenoid involvement in  $\leq 25\%$  of patients with LP,<sup>35-38</sup> isolated nail LP is rare,<sup>39</sup> with no accurate epidemiologic figures. Classic clinical signs comprise nail thinning, longitudinal ridging and fissuring, distal splitting, trachyonychia, and erythema of the lunula.<sup>35,36</sup> Nail LP may lead to severe erosion of the

nail bed along with severe and permanent onychodystrophy caused by scarring (Fig 7, A).<sup>39</sup> The diagnosis can be reached clinically in most cases, but where there is clinical uncertainty, histopathology of the nail matrix, demonstrating all the classic lichenoid findings (Fig 7, B and C), is usually conclusive.<sup>39</sup>

#### Other lichenoid dermatoses

The lichenoid dermatoses discussed below are individually rare eruptions but collectively important clinically. Histologic and dermoscopic evaluation is often essential in diagnosis, and key features thereof are presented in Table I.

**Lichenoid drug eruption.** Also known as drug-induced LP, lichenoid drug eruptions (LDEs) are often clinically identical to cutaneous LP and occur as an adverse reaction to various medications, while certain drug culprits (Table II) have also been implicated in oral and photodistributed involvement, the latter possibly because their spectrum of activity coincide with the wavelength of ultraviolet B light (290-320 nm).<sup>17,40-47</sup> We find that although LDEs morphologically mirror classic cutaneous LP, they tend to be more polymorphic, lack Wickham striae,



**Fig 4.** Ulcerative (erosive) lichen planus. **A**, Extensive ulceration involving the hard palate and (**B**) the dorsal aspect of the tongue. **C**, Histopathology showing squamous mucosa with parakeratosis and a dense lichenoid lymphoid cell infiltrate. **D**, A linear “shaggy” band of fibrinogen deposition at the basement membrane zone. (**C**, Hematoxylin-eosin stain; **D**, fibrinogen; original magnifications: **C**,  $\times 200$ ; **D**,  $\times 100$ .)

and show more pronounced desquamation with psoriasiform or eczematous morphology, as also reported in the literature.<sup>48</sup> LDEs usually arise several months (or even years) after the initial exposure to the perpetrating medication. The underlying basis for this delay remains unclear but is likely to be influenced by many variables, including the dose, medication class, drug–drug interactions, and other host factors.<sup>43</sup> There is no gender bias and LDEs tend to affect older adults (40–60 years of age).<sup>17,49,50</sup> LDEs typically settle within weeks or months of withdrawing the culprit, although resolution can be seen sooner or while the patient remains exposed to the medication.<sup>51,52</sup>

We routinely perform histologic assessment, and this usually shows lichenoid interface dermatitis,<sup>50,53,54</sup> although there are distinguishing features, such as eosinophilia, which is frequently present (Table I). Patch testing persistently yields high false negative rates and therefore are not regularly performed. At best, only half of all cases receive a meaningful result,<sup>55–57</sup> and we do not often conduct this unless there is dilemma on which drug

needs to be discontinued with potentially clinically meaningful implications.

**Lichen nitidus.** Lichen nitidus, described as inflammatory and often intensely pruritic, is a variant we see relatively uncommonly, especially in isolation. It presents with small, skin-colored papules that can be flat-topped, rounded, shiny (or minimally scaly), hypo- or hyperpigmented (depending on skin tone), and can affect any site, most commonly in children or young adults.<sup>58–65</sup> It has been reported to koebnerize,<sup>66</sup> and nail manifestations, such as pitting and splitting, are common.<sup>67</sup> Lichen nitidus has been associated with a range of diseases, such as Crohn’s disease, Down syndrome, atopic dermatitis, and congenital megacolon, and it is important to recognize it in such contexts.<sup>68–70</sup> Familial forms of lichen nitidus have also been reported, lending support to the notion of inherited pathology,<sup>71,72</sup> although no orchestrated attempt at genetic dissection has been reported. For diagnosis, we tend to corroborate clinical evaluation with histologic evaluation: the characteristic lichenoid lymphohistiocytic infiltrate is



**Fig 5.** Erosive vulval lichen planus. **A**, Bilateral vestibular erosions with hyperkeratotic lacy edge on lower right labium minus. **B**, Histopathology taken across the edge of the erosions shows compact orthokeratosis, hypergranulosis, irregular “saw-toothing,” vacuolar interface change, and a dense lichenoid lymphoid cell infiltrate filling the papillary dermis. (Hematoxylin-eosin stain; original magnification: **B**,  $\times 400$ .) Clinical image courtesy of Dr Fiona Lewis, St. John’s Institute of Dermatology.

seen filling the papillary dermis in a pattern known as the “ball and claw” in dermatopathology (Table I).

**LP-like keratosis.** We encounter LP-like or benign lichenoid keratosis (LPLK) in mole clinics because these are typically solitary, scaly plaques ranging from pink to violaceous to pigmented<sup>73</sup> on the upper extremities, trunk, and other sun-exposed areas.<sup>74</sup> LPLK is thought to arise from a regressing seborrheic keratosis or solar lentigo. Some of the proposed triggers include dermatitis, medications, mild trauma, and sun exposure. Dermoscopy can be of diagnostic value in LPLK, revealing remnants of the original seborrheic keratosis or lentigo (which fade with time), telangiectatic vasculature, and clusters of gray spots.<sup>75</sup> LPLK may be misdiagnosed as psoriasiform or as superficial basal cell carcinoma, although histologically, it is highly similar to LP but often shows parakeratosis, which can be an important distinguishing feature to bear in mind. Clinicopathologic correlation is essential for accurate

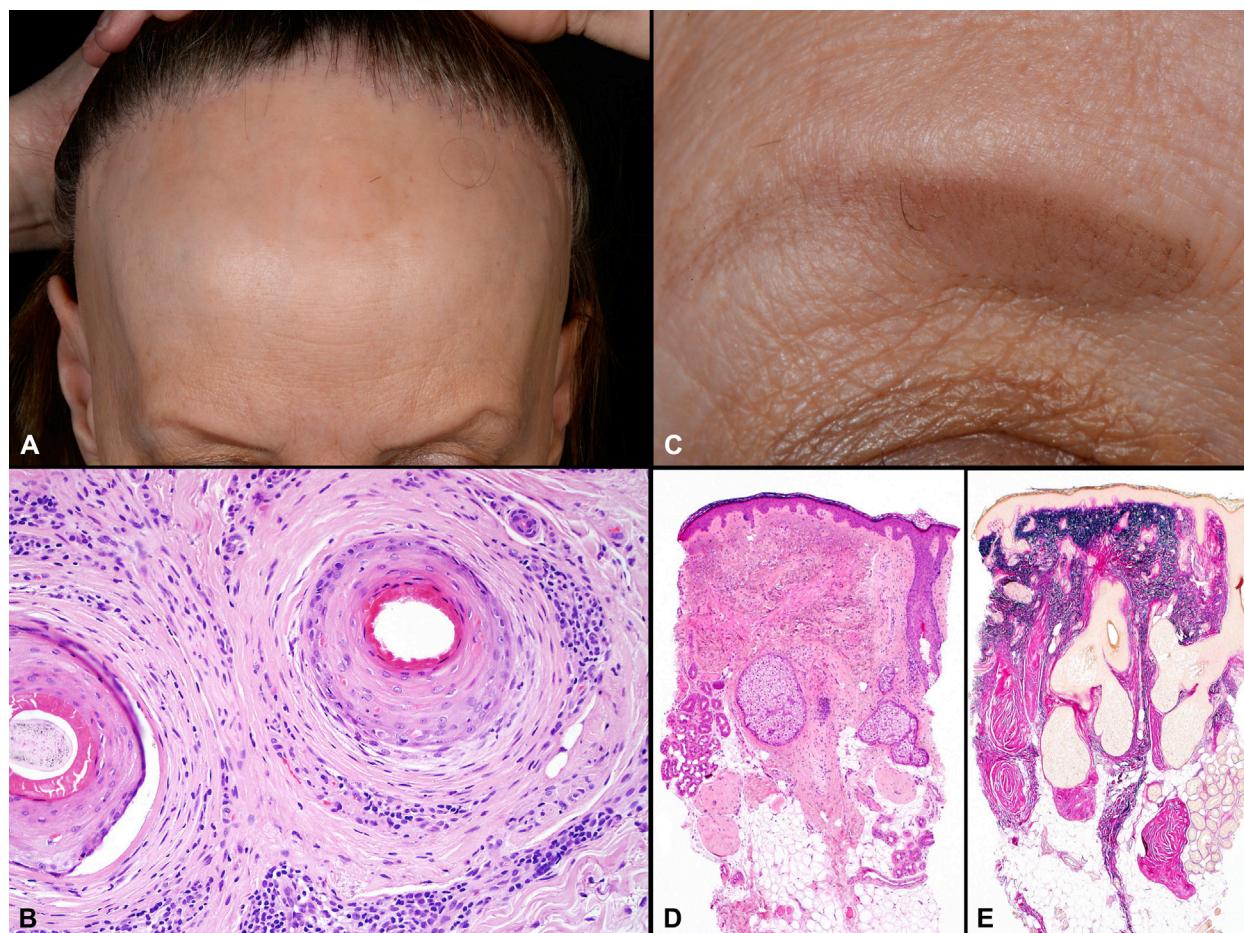
diagnosis, because LPLK is frequently a solitary lesion in its distribution and may raise concern of actinic damage of a preneoplastic nature.

**Lichen sclerosus.** Lichen sclerosus (LS) is a relatively common dermatosis that usually involves the perianal and genital regions but can also manifest extragenitally (Fig 8). Individuals of any age or sex can be affected in a biphasic manner, but the disease is most often detected in later life. Women are thought to be 10 times more likely to be affected than men.<sup>76-81</sup> An association with autoimmune diseases (eg, alopecia areata, pernicious anemia, and thyroid disease) has been reported,<sup>80-82</sup> and our (adult) clinical cohorts do seem to corroborate the published literature. LS may develop in conjunction with or following other immune-mediated cutaneous disorders,<sup>76,81,83-86</sup> although the underlying pathobiology is most likely multifactorial.<sup>87,88</sup> Men who have been circumcised in infancy seldom develop penile LS (also called balanitis xerotica obliterans), lending support to the notion that foreskin may be an obligate part in pathogenesis, whereby susceptible epithelium is allowed to be in prolonged contact with occluded urine.<sup>89</sup> LS may increase the risk of developing squamous cell carcinomas in the involved area<sup>90-94</sup> and, although it can be diagnosed clinically, obtaining a skin biopsy specimen is desirable, especially given the neoplastic transformation potential and warranted surveillance.<sup>93,94</sup>

**Lichen striatus.** Lichen striatus is a rare, asymptomatic, self-limiting eruption of cryptic pathogenesis that develops most commonly in children (5-15 years of age). Lesions are characterized by red or pink papules that coalesce into a scaly, erythematous linear configuration, often in a Blaschkolinear distribution.<sup>95,96</sup> Lesions may be pruritic and develop most frequently on the neck or limbs, but may also affect the trunk, abdomen, thighs, and buttocks,<sup>97</sup> and a collection of nail signs may be seen.<sup>98</sup> A diagnosis is typically made based on clinical evaluation, but obtaining an accompanying biopsy specimen and histologic analysis are valuable for excluding other differential diagnoses (Table I).<sup>99,100</sup>

### Overlap syndromes

Overlap syndromes are conditions where patients present with characteristics of a second and distinct clinical entity alongside cutaneous LP, such as BP and lupus erythematosus (LE). Unlike bullous LP, where blisters are confined to chronic LP erosions, in LP pemphigoides, bullae can arise on existing LP lesions or healthy skin. Clues to distinguish LP pemphigoides from BP include a younger age of



**Fig 6.** Frontal fibrosing alopecia variant of lichen planopilaris. **A**, Scalp. Recession of the frontotemporal hairline with hyperkeratotic papules perifollicular erythema and loss of eyebrows. **B**, Histopathology of horizontally oriented scalp biopsy specimen. Isthmus. Perifollicular fibrosis with perifollicular lichenoid cell infiltrate. Dyskeratotic keratinocytes are present in the follicular epithelium. **C**, Eyebrow. Higher magnification showing almost complete loss of hair. **D**, Histopathology of vertically oriented eyebrow biopsy specimen. Hair loss with dermal solar elastosis and fibrous tracts (follicular scars) extending into the subcutaneous tissue. **E**, Elastic stain highlighting the solar elastosis in the papillary dermis and demarcating the fibrous tracts with absence of elastic fibers. (**B-D**, Hematoxylin–eosin stain; **E**, elastic van Gieson stain; original magnifications: **B**,  $\times 400$ ; **D**,  $\times 40$ ; **E**,  $\times 40$ .)

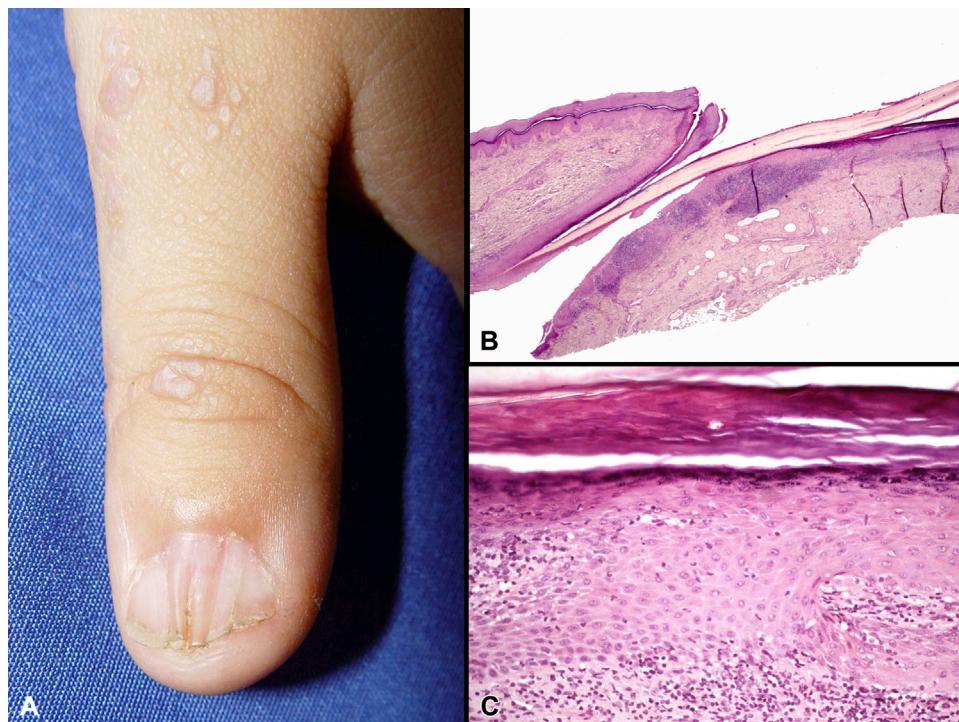
onset (40s) and milder lesions principally affecting the extremities,<sup>101</sup> although we invariably resort to obtaining a skin biopsy specimen, in which linear deposits of IgG or C3 at the dermoepidermal junction are detectable by direct immunofluorescence staining, as also reported in the literature.<sup>102</sup> LP—lupus erythematosus is rare and presents with mixtures of verrucous or lichenoid lesions in the head, neck, trunk, and upper extremities. These lesions show clinicopathologic characteristics that resemble both LP and LE.<sup>103</sup>

#### Etiology and molecular basis

There is relative paucity of well-conducted, hypothesis-driven investigative research in LP,

despite its relative prevalence and the therapeutic challenges it often comes with in clinical practice, all stemming primarily from agnosia on molecular targets for drug development. The undertaken studies have focused on the putative role of 4 domains in pathogenesis, and each of these is discussed below.

**Immune dysregulation.** As with many other inflammatory dermatoses, immune dysregulation has been suggested to be strongly relevant in the pathophysiology of LP. It is postulated that activated T cells, principally cytotoxic CD8<sup>+</sup> cells, launch an immune attack against basal keratinocytes, assisted by CD4<sup>+</sup> helper T cells via secretion of T<sub>H</sub>1 cytokines.<sup>8</sup> The basement membrane is breached



**Fig 7.** Nail matrix lichen planus. **A**, Nail scarring with dorsal pterygium. Flat-topped polygonal papules of lichen planus are also present on the dorsal aspect of the thumb. **B**, Histopathology showing a dense lichenoid lymphoid cell infiltrate involving the nail matrix. **C**, Higher magnification detail with lymphocytic exocytosis and vacuolar interface changes. (Original magnifications: **B**,  $\times 20$ ; **C**,  $\times 400$ . Histopathology photographs courtesy of Professor P. A. Fanti, University of Bologna, Bologna, Italy.) Clinical image courtesy of St. John's Institute of Dermatology.

when CD8<sup>+</sup> cells inflict injury on keratinocytes, allowing the inflow of additional CD8<sup>+</sup> cells in a self-perpetuating process of basal keratinocyte destruction. This vicious loop is presumed to be the underlying basis of the chronicity of LP,<sup>104</sup> although there is no adequate explanation of why classic cutaneous LP is usually self-limiting while its follicular or mucosal counterparts persevere for significantly longer. In LP, Toll-like receptor-mediated activation of the innate immune response results in the production of proinflammatory myeloid dendritic cells, regulatory T cells, and polyfunctional T cells.<sup>105</sup>

Various factors have been shown to be up- and down-regulated in the inflammatory process, comprising a milieu of adhesion molecules, inflammatory and proapoptotic mediators, and cytokines and growth factors (including interleukin [IL]-1 $\alpha$ , IL-6, IL-8, interferon [IFN]- $\gamma$ , tumor necrosis factor- $\alpha$ , vascular endothelial growth factor, transforming growth factor- $\beta$ 1, caspase-3, and Bcl-2).<sup>8,106-118</sup>

From a pharmacologic perspective, important chemokines involved both at tissue and systemic

level comprise CXCL9, CXCL10, and CXCL11.<sup>119,120</sup> There is increasing evidence to suggest the important role of type I IFNs and accumulation of plasmacytoid dendritic cells and the IFN- $\alpha$ -inducible protein known as myxovirus resistance 1 protein in the process, has recently been implicated.<sup>121-128</sup> Recently, transcription factor Brn2 has been proposed to be of relevance in keratinocyte differentiation and thus in the pathogenesis of LP. Injection of Brn2 into rat skin leads to histopathologic features that resemble human LP. In addition, Brn2 also attracts T lymphocytes and has been shown to be present in almost all cell nuclei of the thickened epidermis in LP.<sup>129</sup>

It is still unclear what exactly spurs the upstream regulators to action and why it so happens in certain individuals and not others, but dissecting the molecular signature of the process is helpful in identifying “druggable” molecular targets. To add to the complexity, a link between endocrine and immune changes caused by stress and LP has also been postulated, as evidenced by the differential expression of factors such as neopterin, sIL-2R, sFasL, sIL-6R, and IL-18 compared to controls.<sup>130</sup>

**Table I.** Lichenoid dermatoses and their key histologic features

Lichenoid variant	Key histologic features	Key dermoscopic features
Lichenoid drug eruption	<ul style="list-style-type: none"> <li>Lichenoid interface dermatitis; colloid or Civatte bodies, lymphocytic infiltrate in the papillary dermis, pigmentary incontinence with dermal melanophages</li> <li>Focal parakeratosis with focal interruption of the granular layer, cytid bodies in the cornified and granular layers, and present eosinophil</li> <li>Prominent necrotic keratinocytes, plasma cells and eosinophils, exocytosis of lymphoid cells into upper epidermis and deeper perivascular infiltrate would be more typical of lichenoid drug eruption than lichen planus</li> </ul>	<ul style="list-style-type: none"> <li>Lack of Wickham striae</li> </ul>
Lichen planus–like keratosis	<ul style="list-style-type: none"> <li>Lichenoid lymphocytic infiltrate, similar to lichen planus; parakeratosis can be a key distinguishing feature, clinicopathological correlation is essential to diagnosis</li> </ul>	<ul style="list-style-type: none"> <li>Fissures and ridges (brain-like appearance)</li> <li>Milia-like cysts and comedo-like openings</li> <li>Telangiectatic vasculature</li> <li>Clusters of gray spots</li> <li>Punctate hemorrhages</li> </ul>
Lichen nitidus	<ul style="list-style-type: none"> <li>“Ball and claw” appearance with focal dense lymphohistiocytic infiltrate in the papillary dermis close to the epidermis; Langerhans giant cells in the infiltrate, elongated rete ridges that “clutch” the infiltrate; erythrocytes subepidermally (if hemorrhagic or purpuric) or eosinophilic material within the dermis with occasional cell in the epidermis (if perforating variant)</li> </ul>	<ul style="list-style-type: none"> <li>Clusters of gray spots</li> <li>Punctate hemorrhages</li> <li>Keratin plug surrounded by annular cloud-like, smooth area</li> <li>Well-demarcated depressions with surrounding thin scale on palmoplantar sites</li> </ul>
Lichen sclerosus	<ul style="list-style-type: none"> <li>Lichenoid infiltrate in dermoepidermal junction and compact hyperkeratosis</li> <li>Papillary dermis edema, replaced by dense homogenous fibrotic change as lesions mature</li> </ul>	<ul style="list-style-type: none"> <li>White structureless foci</li> <li>Comedo-like openings with telangiectasia</li> </ul>
Lichen striatus	<ul style="list-style-type: none"> <li>Acanthotic epidermis, dense or sparse lichenoid infiltrate</li> <li>Numerous melanophages in the superficial dermis, apoptotic keratinocytes throughout all epidermal layers and infiltrate normally extending to involve eccrine structures</li> </ul>	<ul style="list-style-type: none"> <li>Well delineated white structure</li> <li>Yellow keratotic, cerebriform structures featuring red dots (corresponding to dermal capillaries)</li> </ul>

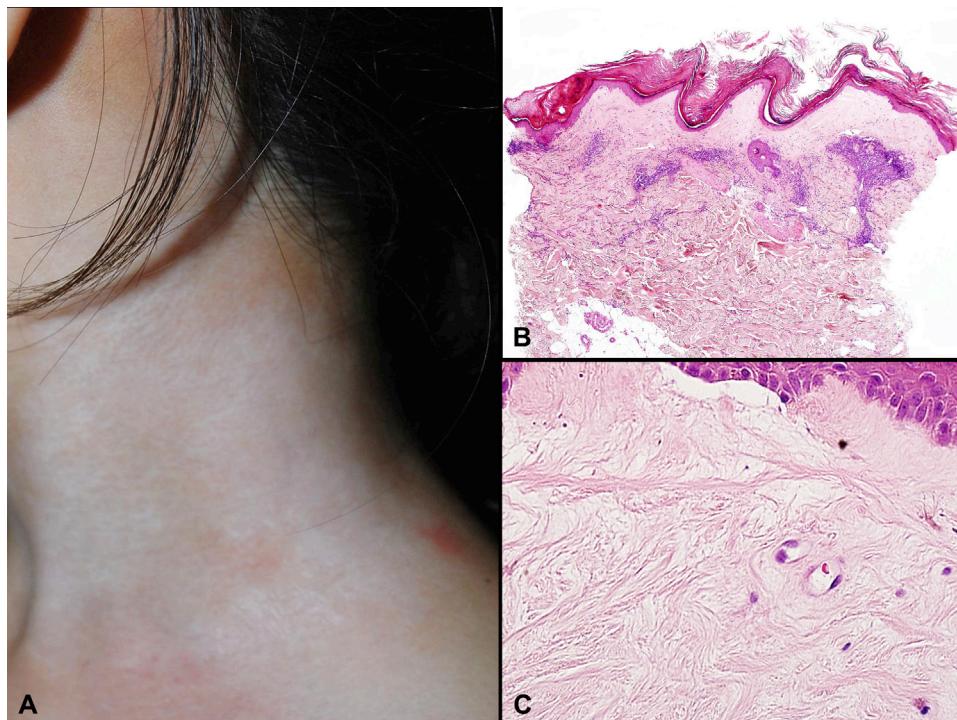
**Association with infection.** LP has been associated with HCV infection, but whether there is underlying causality remains ambiguous. Although studies have demonstrated that affected patients are more likely to be HCV positive, this association is highly variable across different populations and countries.<sup>131,132</sup> IFN therapy for HCV has also been tied to the initiation or worsening of LP lesions.<sup>133</sup> And although a contentious issue, routine screening for HCV should probably not be recommended, except in individuals at high risk for HCV infection, due to the risks of morbidity and transmission that

exist with this infection.<sup>131-137</sup> We take an individual approach to this issue by performing a focused clinical enquiry to seek high-risk behaviors and thereby screen identified individuals who might be at risk. Numerous other viral pathogens have been associated with LP, including hepatitis B virus,<sup>138</sup> varicella zoster,<sup>139,140</sup> and human herpesviruses-6 and -7.<sup>122</sup> LP eruptions have also been reported to develop after vaccination, especially hepatitis B virus immunization.<sup>141,142</sup>

**Genetic associations.** There may be a genetic predisposition to idiopathic LP, because multiple

**Table II.** Drug-induced lichen planus: Drug culprits and their associated lichenoid manifestation

Drug culprit	Association
Angiotensin-converting enzyme inhibitors, antimalarials, $\beta$ -blockers, gold, lithium; mercury amalgam, methyldopa, penicillamine, quinidine, sulfonylureas, thiazide diuretics, tumor necrosis factor- $\alpha$ , or tyrosine kinase inhibitors	Classic cutaneous lichenoid drug eruption
Angiotensin-converting enzyme inhibitors, allopurinol, anticonvulsants, antiretrovirals, gold, ketoconazole, or nonsteroidal anti-inflammatory drugs	Cutaneous and oral lichen planus
Carbamazepine, chlorpromazine, diltiazem, ethambutol, quinidine, quinine, tetracyclines, and thiazide diuretics	Photodistributed lichenoid drug eruption



**Fig 8.** Lichen sclerosus et atrophicus. **A**, Neck. Irregular-shaped white atrophic patches. **B**, Histopathology showing hyperkeratotic horn, epidermal atrophy, and a patchy lichenoid lymphocytic infiltrate with pale, hyalinized papillary dermis. **C**, Higher magnification on the hyalinized edematous papillary dermis. (Hematoxylin–eosin stain; original magnifications: **B**,  $\times 40$ ; **C**,  $\times 400$ .)

familial cases have been reported in the literature<sup>143–145</sup> and familial occurrence has been estimated to be as high as 10.7%.<sup>146</sup> Currently, most genetic loci identified for LP have been associations to the HLA region. These include HLA-A5 and HLA-A3,<sup>147,148</sup> HLA-B7,<sup>143</sup> HLA-DR1,<sup>149,150</sup> HLA-DR10 in Arab individuals,<sup>150</sup> and HLA-DRB1\*01:01 in Sardinian and Mexican populations.<sup>151,152</sup> Associations to HLA-B5 and HLA-B8 have also been reported.<sup>153</sup> The HLA-A28 haplotype has been associated with nondiabetic Israeli Jewish individuals with LP and

carbohydrate intolerance.<sup>154</sup> Though several studies have sought to explore a possible link between the -308 G/A polymorphism in the tumor necrosis factor- $\alpha$  gene with LP, a metaanalysis has concluded that this variant was associated with oral LP (without HCV infection) but not cutaneous LP.<sup>155</sup> This genetic heterogeneity has led to the hypothesis that cutaneous and solely mucosal LP may have distinct pathogenetic mechanisms.

Recently, a genome-wide association study has comprehensively interrogated the major

histocompatibility complex region and identified novel genetic associations to 8 diseases, including LP.<sup>156</sup> Six single nucleotide polymorphisms (SNPs) were found to be associated (odds ratio 2.0-2.5) and the HLA-DQB1\*05:01 haplotype was also strongly associated with LP. These 6 SNPs have previously been implicated in multiple sclerosis, type I diabetes, and other immune disorders.<sup>157-161</sup> Interestingly, LP risk had previously been associated with multiple sclerosis and type I diabetes.<sup>162,163</sup> Four of these SNPs were validated in a replication cohort; however, many of these variants were found to be in partial or strong linkage disequilibrium, leading the authors to suggest that these SNPs probably tag for a single functional variant or haplotype. The most significant SNP, rs1794275, implicated the HLA-DQB1 and HLA-DQA2 haplotypes with an odds ratio of 2.5 (95% confidence interval 1.8-3.4).<sup>156</sup> It is worth noting that the HLA-DQB1\*05:01:01 haplotype had previously been implicated in vulvovaginogingival syndrome, a variant of LP.<sup>164</sup>

**Environmental risk factors.** As discussed in greater detail earlier, a wide spectrum of drugs has been associated with lichenoid eruptions that can greatly resemble LP. Apart from medications, other environmental influences have been associated with cutaneous LP. Psychological factors that have been associated with LP include stress, depression, and anxiety, and they may all play a role in pathogenesis.<sup>130,165,166</sup> LP-like dermatitic eruptions have been associated with exposure to substances in color film developers,<sup>167</sup> methacrylic acid esters,<sup>168</sup> and dimethylfumarate in sofas,<sup>169</sup> and radiotherapy may also trigger LP-like lesions,<sup>170</sup> although we have yet to see a case of a clear-cut environmental association with any of the aforementioned putative triggers.

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# Lichen planus and lichenoid dermatoses

## Conventional and emerging therapeutic strategies

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### Learning objectives

After completing this learning activity, participants should be able to describe briefly the evidence-based therapeutic options available for lichen planus and related disorders and discuss emerging therapies and reflect on recent molecular advances in related disorders that might contribute to advancing therapies in lichen planus and variants.

### Disclosures

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Having reviewed the diverse clinical subtypes of lichenoid disease and the postulated molecular basis thereof in the first article in this 2-part continuing medical education series, we discuss herein the existing and emerging treatment strategies in the most common clinical forms of lichenoid inflammation and provide an overview of their pharmacodynamics and evidence base. The scope of this review is not to exhaustively discuss treatment modalities for all lichenoid variants discussed in the previous article of this series. Instead, the focus will be on frequently encountered subtypes of lichen planus and on linking mechanisms of disease with mechanisms of drug action. Future directions and potential avenues for translational research will also be discussed. (J Am Acad Dermatol 2018;79:807-18.)

**Keywords:** emerging drugs for lichenoid inflammation; lichen planus therapeutics; lichenoid variant therapeutics.

## LICHEN PLANUS: DISEASE BURDEN AND NATURAL HISTORY

### Key points

- Lichen planus is associated with significant morbidity, especially the mucosal, erosive, and appendageal subtypes**

- Although cutaneous lichen planus is known to resolve spontaneously, there are many persistent, treatment-refractory clinical variants**

Whether genital, oral, follicular, or classic cutaneous, lichen planus (LP) is associated with

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**Abbreviations used:**

LP:	lichen planus
LPP:	lichen planopilaris
NB-UVB:	narrowband ultraviolet B light
NLP:	nail lichen planus
PUVA:	psoralen plus ultraviolet A light phototherapy
RCT:	randomized controlled trial
TCI:	topical calcineurin inhibitor
TCS:	topical corticosteroid

significant morbidity among affected individuals, both physical and psychological.<sup>1</sup> The considerable impact on patient quality of life may result from symptoms related to active inflammatory, often erosive disease, such as intense pruritus, burning, trichodynia, or odynophagia.<sup>2</sup> Aside from the symptomatic aftermath, the impact of disfiguring lesions, especially associated with some cicatricial variants,<sup>3</sup> can also be detrimental to psychological well-being. Certainly, the side effects associated with potent systemic immunosuppressants or prolonged courses of topical corticosteroids may per se impact patient quality of life, and therefore the benefit-to-risk ratio should always be considered carefully before initiating therapy.

Most cases of classic cutaneous disease are thought to resolve spontaneously within 1 to 2 years, although mucosal and appendageal disease tends to be more persistent and refractory to treatment.<sup>4,5</sup> Oral, hypertrophic cutaneous and genital lichenoid disease have been thought to bear the potential for malignant transformation in some individuals; nevertheless, there is marked inconsistency among published studies and no consensus has been reached.<sup>6,7</sup> We tend to take an individualized approach when it comes to surveillance for carcinogenesis but, in practical terms, refractory cases are followed up and thus monitored regularly for neoplastic transformation.

## CONVENTIONAL THERAPEUTIC STRATEGIES

### Key points

- **Conventional treatment agents for lichenoid disease include topical and systemic corticosteroids, phototherapy, retinoids, topical calcineurin inhibitors, and systemic immunosuppressants**
- **Oral, genital, and follicular LP are less likely to resolve spontaneously and are more likely to require systemic treatment**
- **Well-conducted clinical research is sparse, although the lack of evidence does not necessarily indicate a lack of efficacy**

LP collectively represents a significant and unresolved clinical entity that has been sparsely researched, and therefore the evidence base underlying many of the currently used treatment modalities remains by and large inadequate. The evidence base alongside the basic pharmacology of conventional, commonly used treatment strategies will be reviewed separately for each broad clinical lichenoid subtype. An overview of conventional therapeutic strategies, their pharmacodynamics, and evidence base is provided in Table I.

### Cutaneous LP

**Topical and systemic corticosteroids.** The aim of treatment in the self-limiting classic cutaneous LP is to accelerate resolution while providing symptomatic relief from pruritus. Medium- to high-potency topical corticosteroids (TCSs) are the standard first-line treatment choice for this purpose, primarily reflecting physician experience and confidence with prescribing these agents rather than robust clinical trial data.<sup>10</sup> Commonly used TCSs include clobetasol propionate, fluocinolone acetonide, betamethasone dipropionate, and triamcinolone acetonide, the latter also delivered as an intradermal injectable in stubborn cases of hypertrophic cutaneous LP.<sup>72</sup> We generally recommend ointment-based formulations because of the added emollient benefit and the less complex formulation compared to creams. Application of topical steroids can only be practicable if the body surface area involvement is <10% to 15%, above which systemic options may be preferable.

Systemic corticosteroids, whether oral or intramuscular, may be used for TCS-resistant cases of LP, with prednisone typically being used at a dose of 30 to 60 mg/day for a treatment period of variable duration, depending on severity and refractoriness by clinical impression. A placebo-controlled randomized clinical trial (RCT) of patients with TCS-refractory disease has demonstrated that a 10-day course of prednisone at 30 mg/day is associated with significantly improved clinical outcomes.<sup>9</sup> We tend to use treatment regimens of up to 4 to 6 weeks in our center for severe cases of LP, but treatment duration tends to be shorter for less severe cases. The adverse effects of systemic steroid therapy should be borne in mind, particularly when administered for an extended duration, and blood pressure monitoring and regular urinalysis for glucosuria is common practice for many physicians. Repeated courses of corticosteroids should be (and are) generally avoided where possible, but clinical signs of chronic steroid exposure and toxicity should be looked for, with appropriate surveillance

**Table I.** Proposed mechanisms of action and comments on evidence base for commonly used conventional and less commonly used experimental treatment modalities for lichenoid inflammation

Modality	Mechanism of action	Comments	Level of evidence
Cutaneous lichen planus			
Topical and systemic corticosteroids	Nonspecific suppression of a multitude of proinflammatory mediators at a gene expression, protein, and cellular level <sup>8</sup>	Small (n = 38) but well-conducted double-blind, placebo-controlled, RCT for prednisone <sup>9</sup> ; evidence for medium to potent topical agents mostly empirical <sup>10</sup>	IB (systemic corticosteroid therapy) and IV (topical corticosteroids)
Photo(chemo)therapy	UV radiation exerts immunomodulation by triggering the photoproduct generation, interfering with DNA replication (PUVA) and synthesis; culminates in cell cycle arrest and suppression of inflammatory presence <sup>11</sup>	RCT of UVB vs corticosteroids (N = 46) <sup>12</sup> ; evidence for PUVA from retrospective study of small sample size (N = 28) <sup>13</sup>	IB (narrowband UVB) and III (PUVA)
Retinoids	Downregulates epidermal cell maturation and inflammatory pathways via effects on retinoic acid receptor <sup>14</sup>	Randomized, double-blind, placebo-controlled trial on acitretin (N = 65) <sup>14</sup>	IB (acitretin)
Sulfasalazine	Antiinflammatory effects via metabolites (5-aminosalicylic acid and sulfapyridine) interfering with arachidonic acid metabolism; inflammatory cytokine production; leukocyte function; and free radical scavenging <sup>15</sup>	Randomized, double-blind, placebo-controlled trial (N = 52) <sup>16</sup>	IB
Griseofulvin	Mostly unknown; in vitro antiinflammatory effects not replicated in vivo; main in vivo effect observed on polymorphonuclear cell migration <sup>17</sup>	Randomized, double-blind, placebo-controlled trial (N = 38) <sup>18</sup>	IB
Azathioprine	Converted to 6-mercaptopurine, a purine metabolism antagonist exerting immunosuppressive effects via effects on (rapidly proliferating) B and T cells <sup>19</sup>	Reports of cases <sup>20</sup>	IV
Methotrexate	Inhibits tetrahydrofolate reductase and interferes with purine and pyrimidine synthesis, although its antiinflammatory effects are mediated via enhancing adenosine release and effects at cellular, protein, and immune response level <sup>21</sup> ; inhibiting effects on JAK/STAT pathway recently described <sup>22</sup>	Nonrandomized, uncontrolled, small sample-sized studies <sup>23,24</sup>	IIB

Continued

**Table I.** Cont'd

Modality	Mechanism of action	Comments	Level of evidence
Topical calcipotriol	A vitamin D analogue exerting antiproliferative effects on keratinocytes and immunomodulatory actions via the nuclear vitamin D receptor expressed on lymphocytes, macrophages, and Langerhans cells; direct cellular effects via an increase in intracellular calcium <sup>25</sup>	Randomized open-label controlled trial comparing calcipotriol and betamethasone (N = 31) <sup>26</sup>	IB
Thalidomide	Inhibits TNF $\alpha$ * and suppresses lymphocytic response <sup>27</sup>	Small sample-sized, uncontrolled cases	IIB
Adalimumab	TNF $\alpha$ blocker	Case report <sup>28</sup>	III
Apremilast	Inhibits PDE4 and leads to the accumulation of intracellular cAMP, which activates protein kinase A and suppresses downstream, such as TNF $\alpha$ , interferon- $\gamma$ , IL-2, -5, -8, and -12 <sup>29,30</sup>	Open-label case series (N = 10) <sup>30</sup>	IIB
OLP			
Topical and systemic corticosteroids	As above	Triple-blind RCT evidence for TCSs <sup>31-33</sup> ; triple-blind study (N = 30) demonstrating superiority of clobetasol propionate (0.05%) vs TCI tacrolimus orabase (0.3%) and triamcinolone acetonate (0.1%) <sup>34</sup>	IB (topical corticosteroids)
Topical calcineurin inhibitors	Inhibit T cell activation via multiple effects at the transcription factor level <sup>35</sup>	No evidence for pimecrolimus vs placebo (Cochrane metaanalysis of 3 RCTs) <sup>36</sup> ; no evidence for tacrolimus superior to TCSs <sup>37</sup>	IA
Topical and systemic retinoids	As above	Placebo-controlled RCTs <sup>6,38</sup> for use of topical retinoids; small series for oral retinoids	IB (topical retinoids) and IIB (systemic retinoids)
Sulfasalazine	As above	Uncontrolled study (N = 21) demonstrates benefit of topical sulfasalazine in steroid-refractory OLP <sup>37</sup>	IIB
Azathioprine Hydroxychloroquine	As above Permeates cell membrane and concentrates in cytoplasmic vesicles of macrophages and other antigen-presenting cells resulting in intravesicular pH elevation, which may downregulate autoantigenic immune response; also modulates Treg-related gene expression <sup>40,41</sup>	Case series <sup>39</sup> Open-label study (N = 10) <sup>42</sup>	IIB

Continued

**Table I.** Cont'd

Modality	Mechanism of action	Comments	Level of evidence
MMF	Inhibits IMPDH in activated B and T lymphocytes, antagonizing purine synthesis and T and B cell proliferation <sup>43</sup>	Retrospective study <sup>43</sup> (N = 10) for OLP	III
Biologics (adalimumab, etanercept, infliximab, alefacept, basiliximab, efalizumab, and rituximab)	Adalimumab, etanercept, and infliximab block TNF $\alpha$ ; alefacept blocks CD2 on T cell membrane, thereby blocking T cell activation; basiliximab inhibits IL-2; efalizumab inhibits lymphocyte activation by interfering with the CD11a subunit of lymphocyte function-associated antigen 1 (withdrawn in 2009); rituximab interferes with CD20 on B cells <sup>44-46</sup>	Overall, scant evidence; single case reports for each molecule <sup>44-46</sup>	III
Topical thalidomide	As above	Randomized, double-blind, positive controlled trial for topical thalidomide <sup>47</sup>	IB (topical thalidomide)
Purslane	Likely multifactorial mechanism of action <sup>48</sup> ; antiinflammatory constituent alkaloid recently reported <sup>49</sup>	Randomized, double-blind, placebo-controlled trial (N = 37) <sup>48</sup>	IB
Curcuminoids	Antiinflammatory effects, <sup>50</sup> including systemic IL-6-lowering effects <sup>51</sup>	Randomized, double-blind, placebo-controlled trial (N = 20) <sup>50</sup>	IB
ECP	Complex immunomodulatory properties including induction of lymphocyte apoptosis <sup>52</sup>	Nonrandomized, uncontrolled study (N = 12) <sup>52</sup>	IIB
BCG-PSN	Immunoregulatory effects via T cell subset modulation <sup>53</sup>	RCT (N = 56) <sup>53</sup>	IB
Genital lichen planus			
Topical corticosteroids	As above	Descriptive, prospective, cohort study (N = 114) <sup>54</sup> ; recommended in national guidelines <sup>55,56</sup>	III
PUVA	As above	Nonrandomized, uncontrolled study (N = 12)	IIB
PDT	Direct effects on highly proliferating immune cells, where photosensitizer accumulates <sup>57</sup>	Randomized, double-blind, controlled trial demonstrating superiority of PDT vs topical corticosteroids (N = 20) <sup>58</sup>	IB
MMF	As above	Single case report of erosive female genital lichen planus (N = 1)	III
Follicular lichen planus			
Topical, intralesional, and systemic corticosteroids	As above	Case series, <sup>59-61</sup> but also parallel-group, assessor-blinded, randomized trial (N = 60) <sup>62</sup>	IB

Continued

**Table I.** Cont'd

Modality	Mechanism of action	Comments	Level of evidence
Hydroxychloroquine	As above	Retrospective studies of efficacy only <sup>63,64</sup>	III
MMF	As above	Found to be beneficial in retrospective study (N = 12) <sup>65</sup> , although a RCT demonstrated inferiority to TCS (clobetasol) <sup>62</sup>	IB (MMF vs TCS) and III
Cyclosporine	Block T lymphocyte function <sup>66</sup>	Small series (N = 3) observed benefit in follicular lichen planus <sup>67</sup>	III
Doxycycline	Tetracycline antibiotic with antiinflammatory properties <sup>68</sup>	Mixed treatment response in small series (N = 4)	III
Nail lichen planus			
Topical, intralesional and systemic corticosteroids	Nonspecific antiinflammatory effects, as above	Sporadic cases; retrospective study (N = 67) <sup>16</sup>	III
Altretinoin	First-generation retinoid; mode of action as above	Case reports <sup>69,70</sup>	III

cAMP, Cyclic adenosine monophosphate; ECP, extracorporeal photophoresis; IL, interleukin; IMPDH, inosine monophosphate dehydrogenase; JAK/STAT, Janus tyrosine kinase/signal transducer and activator of transcription; MMF, mycophenolate mofetil; OLP, oral lichen planus; PDE4, phosphodiesterase type 4; PDT, photodynamic therapy; PUVA, psoralen plus ultraviolet A light phototherapy; RCT, randomized controlled trial; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; TNF $\alpha$ , tumor necrosis factor–alfa; Treg, regulatory T cell; UV, ultraviolet.

\*TNF $\alpha$  is thought to be upregulated in lichen planus (see Tziotzios et al<sup>71</sup>).

measures put in place as necessary. The mode of action of corticosteroid therapy is rather nonspecific by exerting immunosuppressive and antiinflammatory effects through regulating a milieu of proinflammatory mediators at gene, cytokine, and cellular levels.<sup>8</sup> The lack of pharmacologic specificity underlies the plethora of side effects, testament to the notion that research toward targeted treatments is a necessity.

**Photo(chemo)therapy.** Photo(chemo)therapy has been used for its complex immunosuppressive effects in inflammatory dermatoses, including cutaneous LP, for many years.<sup>11</sup> Recently, RCT data have demonstrated superiority of phototherapy over oral corticosteroids; in a study of patients with TCS-refractory disease, a 6-week course of narrowband ultraviolet B light phototherapy (NB-UVB) was associated with a 52% complete response rate versus 13% with a similar duration of oral prednisone therapy,<sup>12</sup> although the latter was used at a slightly lower dose than typically used in common practice. A retrospective cohort study suggested that NB-UVB and psoralen plus ultraviolet A light phototherapy (PUVA) are of comparable clinical efficacy in cutaneous LP,<sup>13</sup> although NB-UVB is often preferred at our center over PUVA because of its more convenient administration mode and favorable safety profile.<sup>72</sup>

**Retinoids.** Systemic retinoids have been used successfully in cutaneous LP, with acitretin being the most commonly used drug. The pharmacologic effects of acitretin are thought to be effected via the activation of retinoic acid receptor subtypes, controlling epidermal maturation and inflammatory responses in the skin.<sup>14</sup> A placebo-controlled double-blind RCT in patients with cutaneous LP reported that an 8-week course of acitretin (30 mg/day) was associated with significantly greater disease remission.<sup>14</sup> A higher adverse event incidence was nonetheless reported in the treated arm,<sup>14</sup> the occurrence of which in clinical practice may explain why acitretin and other systemic retinoids are not commonly used in patients with cutaneous LP despite evidence of efficacy. Various case series have cited the beneficial effects of other oral retinoids, including etretinate, isotretinoin, and tretinoin, although their actual usage in practice is limited.<sup>10</sup>

### Oral LP

**Topical and systemic corticosteroids.** TCS therapy is first-line therapy for localized forms of oral LP.<sup>31-33</sup> Potent or highly potent TCSs, comprising preparations based on clobetasol, triamcinolone, betamethasone, fluocinonide, fluticasone, and prednisone, have been shown to be effective and

safe.<sup>31-33</sup> These preparations are commonly applied twice daily either neat (eg, clobetasol propionate 0.05%) or mixed with orabase (eg, triamcinolone) for 1 to 2 months, before tapering to a maintenance regime subject to clinical response.<sup>72</sup> Corticosteroids can also be injected intralesionally, although there are few data to suggest any benefit other than case series reports.<sup>73,74</sup> Systemic therapy, usually with oral glucocorticoids, may be considered in cases of sufficient severity or that remain refractory to topical treatments, though the evidence is sparse, with no adequate placebo-controlled studies conducted.<sup>75</sup> Because of the side effects associated with systemic steroid use, oral glucocorticoids are used on a short-term basis before commencing or reverting to topical therapy.<sup>76</sup>

**Topical calcineurin inhibitors.** Topical calcineurin inhibitors (TCIs) have been of interest primarily because of their steroid-sparing antiinflammatory properties. These effects are thought to be through blockage of T-cell activation via effects at the transcription factor level.<sup>35</sup> The published accounts on efficacy have been somewhat contradicting: a 2012 metaanalysis of 3 RCTs concluded that there was no evidence that pimecrolimus provided benefit over placebo.<sup>36</sup> Subsequent accounts were mixed but were more positive by reporting that TCIs were noninferior<sup>77-79</sup> or superior<sup>80-82</sup> an alternative to topical corticosteroids in oral LP. Pimecrolimus was found to somewhat outperform tacrolimus in a 2014 RCT<sup>83</sup> but not in a later study, where they were found to be pharmacodynamically equipotent.<sup>84</sup> These findings were affirmed in 2017 in a randomized open-label study,<sup>85</sup> a 3-arm pilot RCT,<sup>77</sup> and a subsequent metaanalysis,<sup>86</sup> and, in fact, many experts realize and report that tacrolimus is associated with better clinical outcomes than pimecrolimus in practice. Side effects of TCIs include local irritation and burning, particularly on eroded skin, prohibiting their wider use in erosive disease,<sup>80</sup> but otherwise their side effect profile is not less favorable than that of chronically used TCSs. Their favorable steroid-sparing pharmacodynamics encouraged their increasingly widespread use in clinical practice.<sup>87-89</sup>

**Topical and systemic retinoids.** Retinoids are known to exert their immunomodulatory properties by direct effects on T cells via the nuclear retinoic acid receptor.<sup>90</sup> Topical retinoids are an alternative to TCSs in nonerosive oral LP and are recommended as second-line therapy in oral LP by the World Workshop in Oral Medicine IV. Although 0.1% topical preparations of both tretinoin and isotretinoin have demonstrated efficacy in

placebo-controlled RCTs,<sup>6,91</sup> a comparative study showed inferiority to TCS therapy, albeit with a relatively low potency retinoid preparation.<sup>92</sup> Side effects include local irritation, photosensitivity, and teratogenicity,<sup>10</sup> and disease relapse 2 to 5 weeks after discontinuation limits the wider uptake of topical retinoid therapy in practice.<sup>91</sup> Systemic retinoids, such as etretinate and isotretinoin,<sup>38,93-96</sup> have been used in the treatment of oral LP, but their benefit-to-risk ratio is suboptimal and their clinical utility minimal, although alitretinoin may be more promising.<sup>97</sup>

### Genital LP

The treatment of genital LP is, in principle, similar to that of its oral mucosal counterpart. The major objective of therapy is to prevent or minimize scarring, synechiae, and vaginal stenosis in women and phimosis in men. While standard antipruritic measures can be used for symptomatic relief, TCSs are widely used as the initial line of therapy in genital LP.<sup>98</sup> An initially intensive regime, typically with clobetasol twice daily for 1 to 2 months, aims to assertively arrest the inflammatory process before tapering to a maintenance regime of twice to thrice weekly. The above treatment strategy is germane to the recommended therapeutic approach for lichen sclerosus<sup>99</sup> and is supported by data from case series.<sup>54</sup> The intravaginal application of emollients can help in reducing friction and pain, while foam and suppository corticosteroid formulations can be used in anal disease.<sup>100</sup>

In cases of treatment-resistant, severe, genital disease, systemic (oral) corticosteroid therapy can be used in the form of a tapering course followed by maintenance topical therapy. Topical retinoids are irritating and rarely tolerated in erosive (ano)genital disease. There have been retrospective studies and case reports of genital LP responding to TCIs<sup>101,102</sup> which, despite being associated with burning on eroded skin, are better tolerated than topical retinoids and are used widely for genital LP.

### Follicular LP

The objective in treating follicular LP or lichen planopilaris (LPP) and its variants is to arrest the inflammatory process as early as possible to minimize epithelial hair follicle stem cell loss via inflammation-driven apoptosis, while also controlling associated symptoms and awaiting spontaneous clinical remission.<sup>103</sup> Topical potent and ultrapotent corticosteroids are frequently used as first-line therapy in clinical practice, and there is reasonable evidence to support established clinician familiarity.<sup>59,60,62</sup> Intralesional corticosteroid therapy

is used by many clinicians despite lack of strong evidence and concerns about scalp skin atrophy in cases of prolonged use.<sup>61</sup> A dual regime of an ultrapotent and a potent topical corticosteroid instead, daily for 6 to 8 weeks, followed by tapering to thrice weekly or as per skin response, is favored by some clinicians. Systemic steroids (30-80 mg daily of prednisone or equivalent) are often administered in aggressive, rapid disease and sometimes systemic cyclosporine (3-10 mg/kg/day), although their actual evidence base is sparse.<sup>104-106</sup> A tapering course of prednisone (commencing with 40 mg daily) in addition to TCS therapy may be prescribed when there is a prominent inflammatory base for LPP, while also introducing hydroxychloroquine. The latter is thought to downregulate the immune response to autoantigens while also modulating regulatory T cell-related gene expression.<sup>40,41</sup> Its immunomodulating effect can be of benefit in LPP, and its relatively good overall adverse effect profile<sup>63,64,105</sup> renders it a preferred therapeutic option in this context. Tetracycline antibiotics can be used in cases where hydroxychloroquine is either not tolerated or contraindicated and is our preferred second-line agent,<sup>61,63</sup> followed by mycophenolate mofetil<sup>62,63,65,106</sup> and cyclosporine.<sup>67,107,108</sup>

### Nail LP

Despite the significant functional and cosmetic impact associated with nail LP, there is significant scarcity of evidence-based treatments. The objective to prevent or minimize permanent scarring is on par with follicular LP, and it is similarly important to arrest the inflammatory process as soon as possible to achieve the best overall outcome. Intralesional, topical, and systemic corticosteroids are favored as first-line, with the latter being reserved for cases in which the extent of involvement goes beyond a few nails.<sup>16,109</sup> Alitretinoin has also been reported to be of benefit.<sup>69,70,110</sup> For many dermatologists, including the authors, pulsed or short and tapering systemic corticosteroid treatment is preferred to intralesional delivery because of its efficacy and convenience, while we have also found that occlusion enhances the efficacy of moderately and highly potent topical corticosteroids.

## EXPERIMENTAL AND EMERGING THERAPEUTIC STRATEGIES

### Key points

- Many treatment modalities have been used experimentally to treat cutaneous, mucosal, and follicular LP, such as sulfasalazine, mycophenolate mofetil, azathioprine, griseofulvin, and adalimumab

- Most attempted treatment strategies have not progressed to clinical practice because of suboptimal benefit-to-risk ratios
- The prerequisite to success for any future advances is molecular insight into the pathobiology of the condition

### Cutaneous LP

There is a plethora of experimental agents that have not made it to standard clinical practice either because of unfavorable benefit-to-risk ratios or because of unconvincing overall cost effectiveness. An example of such a drug is sulfasalazine, which has not yet been widely adopted as mainstay treatment despite the relatively good evidence base and lack of serious side effects.<sup>111,112</sup> Griseofulvin seemed promising in early trials<sup>18,113</sup> but was later researched only sporadically<sup>114,115</sup> before being reported to be inferior to hydroxychloroquine.<sup>116</sup> Antifungals such as itraconazole and terbinafine, thought to interfere with inflammatory cytokines, have also been investigated and showed some benefit but were never followed-up more thoroughly.<sup>117-119</sup> Systemic immunosuppressive antiinflammatory agents, such as azathioprine and methotrexate, have been used with success in generalized, severe forms of LP and they tend to only be resorted to in such cases, given their associated toxicity.<sup>20,23,24</sup> Topical calcipotriol has been found to be noninferior to a potent TCS in a randomized controlled trial,<sup>120</sup> although there are inconsistent reports about its efficacy.<sup>26,121</sup> By immunomodulating effects on multiple cytokine and immune targets, including interferon-gamma loops, thalidomide has been postulated as efficacious in treating LP,<sup>27,122</sup> although it has not been further researched or developed. Adalimumab has been reported to be efficacious in cases of cutaneous LP,<sup>28</sup> although tumor necrosis factor-alfa blockade is not always therapeutic<sup>123,124</sup> and its precise role in lichenoid inflammation is not fully understood. Phosphodiesterase 4 is a key enzyme to cyclic adenosine monophosphate processing in several immune cell types,<sup>29</sup> and apremilast, an oral phosphodiesterase 4 inhibitor, has been reported to be effective in treating cutaneous LP.<sup>30</sup>

### Oral and genital LP

As mucosal and cutaneous disease share the same molecular underpinning, there is considerable overlap in therapies used in experiments in both conditions. Agents such as sulfasalazine, azathioprine, hydroxychloroquine, mycophenolate mofetil, tumor necrosis factor-alfa inhibitors and

other biologics, and topical thalidomide have been studied in oral and genital lichenoid inflammation and are of varying efficacy.<sup>39,42,44-47,112,125</sup> Pharmacognosy-derived agents, such as purslane<sup>48</sup> and curcuminoids,<sup>50</sup> have been demonstrated to be clinically efficacious in oral LP, although an uptake in clinical practice following larger-scale studies has not yet materialized. The list of experimental drug therapies for mucosal lichenoid disease would be incomplete without mentioning PUVA,<sup>126</sup> extracorporeal photochemotherapy,<sup>52</sup> and intralesional bacillus Calmette-Guérin,<sup>53</sup> which, although practically obsolete and reserved for refractory cases, may provide insights into the molecular signature of disease and how this might determine pharmacodynamic responses. Photodynamic therapy has also been reported to be of benefit in genital disease, although it is still regarded as experimental and is not widely used.<sup>57</sup>

### Follicular LP

While molecular research into the pathogenesis of follicular LP and its variants is as sparse as or perhaps sparser than in the other lichenoid inflammatory conditions, there has been an example whereby gene expression studies formed the basis of adopting an experimental treatment in clinical practice.<sup>127</sup> The implication of peroxisome proliferator-activated receptor gamma in the etiopathogenesis of LPP encouraged clinicians to use pioglitazone, a peroxisome proliferator-activated receptor gamma receptor agonist, for refractory cases. Controversy soon arose about whether the gene expression studies were relevant,<sup>128</sup> and reports of inconsistency in clinical outcomes when treating LPP with pioglitazone followed.<sup>129</sup> By the same token, finasteride was reported to be of help in patients with frontal fibrosing alopecia after overinterpretation of the clinical benefit in reversing the androgenetic element coexisting with frontal fibrosing alopecia, a claim that was later dismissed and failed the litmus test in clinical practice.<sup>130,131</sup> These scenarios highlight how significant and sought after well-conducted molecular research is in the modern era of evidenced-based therapeutics by informing pharmacodynamics and enabling targeted drug development and utilization.

### FUTURE DIRECTION

The profound morbidity associated with most forms of LP necessitates clinically efficacious therapies. The latter will only arise if robust molecular research elucidates novel pathways that inform targeted drug development and therapeutics. In many respects, the desired objective would be to

achieve molecular dissection of the etiopathogenesis of LP before exploring gene expression and druggable targets for targeted therapeutics in a manner germane to the disease. Large-scale studies aimed at gleaning fresh insights into the mechanistic basis of lichenoid inflammation will need to be orchestrated, with the aid of modern multiomic technologies that can help inform specific molecular pathways. There is paucity of such investigative approaches, possibly because of the lack of commercial interest and relative dearth of research funding to support basic scientific exploration before moving forward to conceptualizing and experimenting or testing appropriate molecular targets in clinical trials.

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## Case Report

# Acute Methotrexate Toxicity: A Fatal Condition in Two Cases of Psoriasis

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We describe two fatal cases of low dose methotrexate (MTX) toxicity in patients with psoriasis, emphasizing the factors that exacerbate MTX toxicity. The first patient was a 50-year-old male of psoriasis on intermittent treatment with MTX. After a treatment-free period of six months, he had self-medication of MTX along with analgesic for joint pain for one week which followed ulceration of the lesions, bone marrow suppression, and eventually death. The second patient was a 37-year-old male of psoriasis, who has taken MTX one week earlier without prior investigations. He had painful ulcerated skin lesions and bone marrow suppression. On investigations, he showed high creatinine level and atrophied, nonfunctioning right kidney on ultrasonography. In spite of dialysis, he succumbed to death. MTX is safe and effective if monitored properly, but inadvertent use may lead to even death also. Prior workup and proper counseling regarding the drug interactions as well as self-medication should be enforced.

## 1. Introduction

Methotrexate (MTX), when used in low doses, has anti-inflammatory and immunosuppressive action. Low dose MTX is an effective and safe treatment for psoriasis being used for more than 50 years [1]. Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration [2]. It is also affected by concomitant ingestion of certain drugs which are protein bound like non-steroidal anti-inflammatory drugs (NSAIDs), sulfonamides, and barbiturates. This demands careful monitoring of renal function tests and blood counts, along with carefully looking for mucosal lesions or ulcerations in skin to identify acute MTX toxicity. Failure to adhere to guidelines may lead to severe toxicity, even death. There are few publications mentioning adverse reactions of MTX, but very few are there mentioning fatality because of such a safe drug. Here, we report two cases that died of MTX toxicity because of just not abiding by the standard protocol.

## 2. Case Reports

**2.1. Case 1.** A 50-year-old male presented with generalized skin lesions with ulcerations along with erosions over lips and oral cavity and difficulty in swallowing for 2 days. He also had fever with chills.

He was a known case of psoriasis for 5 years, on MTX (7.5 mg) once weekly for two years. He was under remission and stopped MTX six months earlier. He had aggravation of lesions along with knee joint pains for two weeks. He took oral MTX (7.5 mg/day) daily for one week along with some pain killers by himself. After two days he developed ulcerations over existing lesions along with erosions on lips and oral cavity (Figure 1).

The patient was conscious with body temperature 103°F, pulse rate 120/minute, and normal respiration and blood pressure. Cutaneous examination revealed generalized multiple annular ulcerated plaques with mucosal erosions. On admission, investigations showed myelosuppression (Hb 6.7



FIGURE 1: Ulceration over psoriatic lesions with crusting on lips (Case 1).



FIGURE 2: Pustules on face with mucositis in oral cavity (Case 2).

gms, WBC 1200, and 69,000 platelet count) with normal renal and liver profile.

Patient was diagnosed as a case of acute MTX toxicity and treated with intravenous antibiotics and leucovorin and neukine (GM-CSF) injection subcutaneously. He was investigated periodically which showed persistent myelosuppression which was worsening day by day. He was supported with packed cell volume and platelet transfusions. On the fifth day, he was transferred to the intensive care unit for better monitoring. His platelet count increased to 45000/mm<sup>3</sup> and WBCs to 1300/mm<sup>3</sup> on the 10th day. His liver function deteriorated with bilirubin 8.1 grams on the 10th day. Unfortunately, he expired due to acute respiratory failure after six hours of onset on the 10th day.

**2.2. Case 2.** A 37-year-old male, a known case of psoriasis, presented with complaint of reduced oral intake due to painful lesions in the oral cavity, along with fever and chills for three days. He also complained of pain with ulceration in the existing lesions. On careful history taking, it was revealed

that he took an unknown amount of oral MTX one week back without prior investigations.

On examination, he was conscious but febrile with 102°F temperature with normal vitals. Cutaneous examination showed ulcerated and necrotic psoriatic plaques with erythema and tenderness. There were few new pustules on chest and face (Figure 2). He also had crusting and fissuring of the lips along with erosions in oral cavity. On admission, investigations suggested bone marrow suppression (hemoglobin 8.2 grams, WBC 1600 cells/mm<sup>3</sup>, and platelet count 1,06,000 cells/mm<sup>3</sup>) and altered renal functions (blood urea 72 and creatinine level 4.8).

Based on the clinical and laboratory findings, he was diagnosed having MTX toxicity and was covered with broad spectrum empirical antibiotics and injectable leucovorin. Sodium bicarbonate was added to aid in the excretion of drug by alkalinization of the urine and was hydrated aggressively. Despite aggressive therapy, there was gradual worsening with odynophagia/dysphagia and the blood counts still falling with no improvement in the renal functions. The patient was transferred to medicine ward. He was given platelet transfusions and taken for dialysis for two days, during which he succumbed to death.

### 3. Discussion

Low dose MTX in psoriasis rarely produces toxicity, and most of such cases occur due to failure to adhere to the recommended guidelines [1]. The risk of toxicity is greater if additional methotrexate is administered sooner than the usual scheduled weekly dose [3]. In the first case, it was a self-administration of the higher, consecutive dose which acted as a precipitating factor.

MTX toxicity has its impact on skin, gastrointestinal mucosa, liver, kidneys, and bone marrow. Ulcerations in skin due to MTX toxicity are restricted to the psoriatic plaques probably because of higher uptake of methotrexate by the hyperproliferative psoriatic plaques than normal skin [4]. Both of the cases presented with ulceration on existing plaques of psoriasis.

Pancytopenia due to MTX is attributed to the patients with renal dysfunction, presence of infection, folic acid deficiency, hypoalbuminemia, concomitant use of drugs such as trimethoprim, and advanced age [5]. Both of our patients had mucositis along with myelosuppression as a presenting feature of MTX toxicity. The probable cause of myelosuppression in the first patient could be advanced age, concomitant use of NSAID, and inadvertent use of MTX dose, while, in the second patient, it was renal dysfunction which was not picked up before initiation of the treatment.

Drugs can increase the risk of methotrexate toxicity either by decreasing renal elimination of methotrexate (aminoglycosides, cyclosporine, nonsteroidal anti-inflammatory agents, sulfonamides, probenecid, salicylates, penicillins, colchicines, cisplatin, and other renotoxic drugs) or by displacing methotrexate from protein binding sites in the plasma (salicylates, probenecid, sulfonamides, barbiturates, phenytoin, retinoids, sulfonylureas, and tetracyclines). NSAID

taken for joint pain had contributed to the MTX toxicity in the first case.

Unfortunately, we could not measure the drug level of MTX because of lack of facility. But the common feature in both of them was inadvertent dosage of MTX which is the major contributory factor for the toxicity.

It is a must to avoid self-administration of such drugs. There should be proper counseling of the patient for not taking the drugs on their own without consulting a dermatologist as well as not to combine with any other drug without taking doctors' consent. Selling such drugs without prescription should be banned.

The second case had consumed MTX without following the standard investigative as well as therapeutic protocol. Already compromised renal functions were missed out and impairment in renal clearance could have played a role in MTX toxicity. Prior workup is mandatory for MTX which is otherwise really safe and effective in cases of psoriasis.

## Key Messages

Pretreatment investigations are a must if MTX is to be prescribed. Proper monitoring and strict avoidance of self-administration of MTX are mandatory. Coadministration of the drugs like NSAIDs should be judicious.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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