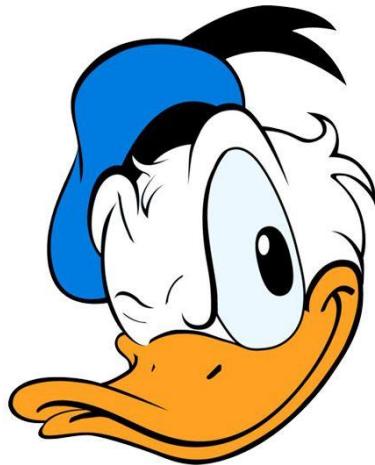


# DERMATOLOGY

## CME

2017





## *Index:*

1. Prevention and management of glucocorticoid-induced side effects.
2. Psoriasis and comorbid diseases.
3. The role of imaging in the management of patients with nonmelanoma skin cancer.
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# Prevention and management of glucocorticoid-induced side effects: A comprehensive review

## A review of glucocorticoid pharmacology and bone health

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and Robert G. Micheletti, MD<sup>a,c</sup>

*Philadelphia, Pennsylvania, and Portland, Oregon*

### Learning objectives

After completing this learning activity, participants should be able to describe key features of glucocorticoid pharmacology and anticipate, prevent, and manage complications of glucocorticoid use affecting bone health.

### Disclosures

#### Editors

The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

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Systemic glucocorticoids are an essential therapy for a range of conditions, but their multiple side effects can produce significant morbidity for patients. The objective of this review is to discuss these side effects while addressing 3 questions: 1) What dose and duration of glucocorticoid therapy should prompt concern for individual side effects?; 2) How should clinicians counsel patients about these complications?; and 3) How can these problems be prevented or managed? To accomplish these objectives, we have created a series of tables and algorithms based on a review of relevant data to guide counseling, prophylaxis, and management of 11 glucocorticoid side effects. The first article in this 4-part continuing medical education series begins with a review of glucocorticoid pharmacology followed by a discussion of bone health (ie, osteoporosis and osteonecrosis). (*J Am Acad Dermatol* 2017;76:1-9.)

**Key words:** glucocorticoids; medication monitoring; osteonecrosis; osteoporosis; pharmacology; side effects; steroids.

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Please note that infectious and other complications of steroid use will be discussed in the third and fourth installments of this Continuing Medical Education feature in the February 2017 issue of the *JAAD*.

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## GLUCOCORTICOID PHARMACOLOGY

### Key points

- **Glucocorticoids are selected based on therapeutic efficacy and side effect considerations, properties that depend on pharmacokinetic and pharmacodynamic parameters**
- **Understanding these parameters may help clinicians manage glucocorticoid side effects for their patients**

There are many options when prescribing glucocorticoids. Prednisone, prednisolone, methylprednisolone, and dexamethasone are all commonly used oral formulations. High-dose pulse glucocorticoid therapy may be required in clinical emergencies or for severe, uncontrolled disease, often in the form of intravenous (IV) methylprednisolone. High-dose dexamethasone may be required in the case of central nervous system emergencies for its enhanced central nervous system penetration.<sup>1</sup> In dermatology, pulse IV methylprednisolone is an option for patients with severe pemphigus vulgaris, pyoderma gangrenosum, and systemic lupus erythematosus. Intraarticular and intralesional formulations, such as triamcinolone acetonide or methylprednisolone acetate, are appropriate for certain conditions. Our glucocorticoid side effect pretreatment screening, ongoing monitoring, and counseling recommendations are shown in Table I.

Glucocorticoids exert their effect by binding to the glucocorticoid receptor, which translocates to the nucleus and targets gene transcription.<sup>2</sup> Nongenomic mechanisms are thought to explain the efficacy of pulse-dose glucocorticoid therapy, because these doses are generally greater than the saturation dose for the glucocorticoid receptor.<sup>1</sup> Oral glucocorticoids are well absorbed after administration and show variable degrees of binding to corticosteroid-binding globulin and albumin.<sup>1</sup> Only free, unbound drug can interact with the glucocorticoid receptor.<sup>1</sup> Prednisone and prednisolone both have dose-dependent pharmacokinetics because of nonlinear protein binding, while methylprednisolone and dexamethasone do not have this same dose-dependency.<sup>1</sup>

Glucocorticoids require a carbon-11 hydroxyl group in order to have activity.<sup>3</sup> The enzyme 11 $\beta$ -hydroxysteroid dehydrogenase controls the availability of glucocorticoids for binding to receptors. Type 1 dehydrogenase converts inactive to active drug and has its greatest activity in the liver.<sup>1</sup> For this reason, topical glucocorticoids, such as cortisone, must be 11-hydroxyl compounds in order to be effective. Cortisone is an 11-keto compound that has no activity topically. The enzyme is also responsible for converting prednisone to its active

form, prednisolone. Type 2 dehydrogenase is found in mineralocorticoid target tissue.<sup>1</sup>

Systemic glucocorticoids are divided into short-, medium-, and long-acting formulations on the basis of adrenocorticotrophic hormone suppression after a single dose.<sup>3</sup> The potency of glucocorticoids is determined by affinity for the intracellular glucocorticoid receptor and duration of action.<sup>3</sup> There is only a weak correlation between circulating half-life, potency, and duration of action.<sup>3,4</sup> Glucocorticoid potencies and duration of action are shown in Table II.

These concepts in pharmacology help explain the therapeutic and adverse effects of systemic glucocorticoids. For example, patients with low protein states are at increased risk of adverse effects from prednisone therapy because the amount of circulating unbound drug is increased.<sup>1,4,6</sup> The dose-dependent availability and clearance of prednisone and prednisolone accounts for the decreased side effects (and diminished efficacy) of alternate-day dosing.<sup>6</sup> Meanwhile, not all individuals metabolize drugs at the same rate; those who are slow metabolizers may suffer increased side effects.<sup>7</sup>

Certain diseases and drug-drug interactions alter glucocorticoid pharmacokinetics.<sup>1</sup> Altered pharmacokinetics are reported in patients with liver disease, renal failure, nephrotic syndrome, severe obesity, and inflammatory bowel disease, but the direction of effect is not necessarily the same for each glucocorticoid.<sup>1</sup> For example, in patients with severe liver disease, the conversion of prednisone to prednisolone is impaired. This effect may be partially offset by a decreased rate of elimination of prednisolone, but it may be prudent to use the active metabolite prednisolone preferentially over prednisone in these patients.<sup>3,6</sup> In patients with severe systemic diseases, it is wise to confer with the patient's other providers before prescribing glucocorticoids.

Clinicians should also be aware of other medications taken by the patient. The coadministration of CYP450 enzyme inducers increases the clearance and decreases the half-life of glucocorticoids, while enzyme inhibitors decrease clearance and increase half-life.<sup>1</sup> Complete lists of CYP450 inducers and inhibitors are readily available, and clinicians are encouraged to review all drug-drug interactions before prescribing new medications.

Glucocorticoid side effects are not limited to systemic oral or intravenous therapy. Injected glucocorticoids vary in their absorption, but high potency injections, or multiple injections that result in glucocorticoid accumulation, can cause systemic side effects. This is true of intramuscular injections, which can increase the risk of adrenal suppression

**Table I.** Side effect–specific pretreatment screening, ongoing monitoring, and counseling recommendations

Counseling
Choose the lowest dose and duration of therapy
Explain side effects of glucocorticoids
Document patient understanding of side effects in the health record; consider asking patient to sign consent to treatment with steroids
Consider prescribing glucocorticoid identification bracelet
Laboratory assessments and screening before initiating therapy/ongoing monitoring
Bone health
Take 1200 mg calcium and 800 IU vitamin D daily
Baseline height and bone mineral density assessment (using DEXA)
Pharmacologic therapy as indicated (see chart)
Annual DEXA scan to monitor bone mineral density
Replete vitamin D and calcium before prescribing bisphosphonate if indicated
Gastrointestinal
Assess history of PUD risk factors, including nonsteroidal antiinflammatory drug use, smoking, history of <i>Helicobacter pylori</i> infection, alcohol use, age >65 years, current or previous PUD, bisphosphonates, and other medications that increase risk of PUD
Prescribe proton pump inhibitor, if indicated
Endocrine
Screen for diabetes with baseline hemoglobin A1c level, finger stick, or basic metabolic panel
Establish baseline electrolytes and renal function with basic metabolic panel
In conjunction with primary care provider, repeat with regular laboratory monitoring
Consider prescribing a glucometer for home glucose monitoring to those taking moderate- or high-dose steroids chronically
Ocular
Ask about history of cataracts and glaucoma
Consider baseline ophthalmology examination
Repeat examinations as indicated
Cardiovascular health
Check blood pressure at every visit
Check fasting lipids as part of regular laboratory monitoring
Vaccinations (see section on vaccinations)
Take immunization history before initiating therapy
If possible, give missing or indicated vaccines before therapy; give live vaccines at least 2-4 weeks before therapy
Infectious
Hepatitis B virus, hepatitis C virus screening
HIV screening
Tuberculosis skin test or interferon-gamma release assay (eg, QuantiFERON-TB Gold) as appropriate
Strongyloides testing as appropriate
Mood and cognitive
Assess for past or current neuropsychiatric disorders
Ask all youth for history of depression and suicidality
Refer any positive findings to primary care provider or psychiatry
If concern for suicidality, urgent referral to emergency services

DEXA, Dual-energy x-ray absorptiometry; PUD, peptic ulcer disease.

and other systemic side effects in a largely dose- and frequency-dependent manner. It is unclear whether individual injections will lead to systemic side effects, but even a single injection can reduce cortisol levels, so clinicians are encouraged to remain aware of this possibility and treat the regular administration of intramuscular steroids as equivalent to that of oral formulations, with all the same side effect considerations. Even intralesional triamcinolone acetonide used for keloids or hypertrophic scars

has been associated with the development of Cushing syndrome, especially when dosed multiple times or at high doses in pediatric patients.<sup>8</sup>

Topical therapy can result in skin thinning, and both topical and inhaled therapy may also result in systemic side effects, such as Cushing syndrome or hypothalamic–pituitary–adrenal axis suppression. The potency of topical corticosteroids depends on the particular molecule and its absorption through the skin, a feature of penetration, concentration,

**Table II.** Glucocorticoid potencies and duration of action

Name	Equivalent dose (mg)	Anti-inflammatory potency	Duration of action (hrs)*
Cortisol (hydrocortisone)	20	1	8-12
Cortisone	25	0.8	8-12
Prednisone	5	4	12-36
Prednisolone	5	4	12-36
Methylprednisolone	4	5	12-36
Triamcinolone	4	5	12-36
Betamethasone	0.75	25	36-72
Dexamethasone	0.75	25	36-72
Fludrocortisone†	—	10	12-36

Data from Axelrod<sup>3</sup> and Nierman.<sup>52</sup>

\*Short acting, 8-12 hours; intermediate acting, 12-36 hours; and long acting, 36-72 hours.

†Not used for glucocorticoid effects.

saturation, and elimination,<sup>9</sup> as well as the location of application.<sup>10</sup> A recent consensus statement and literature review suggested that topical glucocorticoids may rarely be associated with striae, ophthalmologic disease, and short-term hypothalamic–pituitary–adrenal suppression in pediatric patients with eczema. Systemic side effects may also be seen with intraarticular glucocorticoids, although this is encountered more rarely than with systemic formulations and is most likely with repeat exposures and high potency steroids.<sup>11</sup>

### Dose and duration

Specific side effects may develop at different doses and durations of glucocorticoid therapy. In general, the European League Against Rheumatism (EULAR) defines dosing as: low if  $\leq 7.5$  mg prednisone equivalent per day; medium if  $> 7.5$  mg but  $\leq 30$  mg prednisone equivalent per day; high if  $> 30$  mg but  $\leq 100$  mg prednisone equivalent per day; very high if  $> 100$  mg prednisone equivalent per day; and pulse dose if  $\geq 250$  mg prednisone equivalent per day for 1 or a few days.<sup>12</sup> Similarly, the definitions of “chronic,” “long-term,” or “short-term” therapy also vary. One study defines dosing as short-term if  $< 3$  months, medium-term if 3 to 6 months, and long-term if  $> 6$  months.<sup>13</sup> Information regarding dose and duration pertaining to specific side effects is discussed within each section.

## GLUCOCORTICOID-INDUCED OSTEOPOROSIS

### Key points

- Loss of bone mineral density occurs early in the course of glucocorticoid therapy

- All patients regardless of age, sex, dose, and duration of glucocorticoid therapy require counseling, screening, and prophylaxis for glucocorticoid-induced osteoporosis

### Background

Glucocorticoid therapy is the leading iatrogenic cause of secondary osteoporosis.<sup>14,15</sup> Loss of bone mineral density (BMD) in patients who are taking glucocorticoids occurs primarily in the first 6 months of therapy and slows after 1 year.<sup>16</sup> Within the first 3 months of therapy, the risk of fracture increases by as much as 75%, before a significant decrease in BMD.<sup>14</sup>

### Epidemiology and risk factors

Glucocorticoid-induced osteoporosis (GIOP) may occur in 30% to 50% of patients undergoing glucocorticoid therapy.<sup>17</sup> Fractures occur predominantly in regions with a high amount of cancellous bone, especially the lumbar spine and proximal femur, and they may be asymptomatic in a large number of patients.<sup>15,18</sup> The incidence of fracture is strongly associated with daily dose and duration of glucocorticoids.<sup>18</sup> In 1 study, patients taking doses of prednisone  $\geq 7.5$  mg/day had a risk of hip and nonvertebral fracture double that of patients taking prednisone 2.5 mg/day.<sup>19</sup> In the same study, however, there was no threshold dose at which glucocorticoids could be considered safe.<sup>19</sup> Fractures can occur on doses as low as 2.5 to 7.5 mg of prednisone (or equivalent) per day.<sup>20</sup> Alternate-day and intermittent dosing do not decrease the risk of fracture.<sup>21-23</sup> Conversely, there is currently no evidence that osteoporosis medication is needed to prevent fractures for patients on occasional dose-pack prescription glucocorticoids, replacement therapy for hypopituitarism or adrenal insufficiency, or short term high-dose intravenous or oral therapy with  $< 1$  g of cumulative annual exposure.<sup>14</sup> For cumulative prednisolone doses of  $> 1$  g prescribed in short bursts even over the course of 1 year, significant bone loss has been seen.<sup>24</sup> Cumulative corticosteroid dose strongly correlates with loss of bone mineral density.<sup>19,25</sup>

### Evaluation

All clinicians prescribing glucocorticoids should, at the outset of therapy, counsel their patients about osteoporosis and screen for the GIOP risk factors listed in Table III. Those with anticipated therapy lasting  $\geq 3$  months should be screened for osteoporosis (T-score  $\leq -2.5$ ) and osteopenia (T-score between  $-1$  and  $-2.5$ ) at baseline with a

dual-energy x-ray absorptiometry (DEXA) scan, which estimates BMD. Using this information, the patient's risk of fracture should then be estimated. In many instances, clinical history and DEXA findings are sufficient to guide management without the use of specific risk equations. When necessary, however, several tools exist to predict GIOP risk.<sup>14,27,28</sup> The World Health Organization fracture prevention algorithm (FRAX) is a widely used fracture prediction tool (available at: <http://www.shef.ac.uk/FRAX/>). FRAX calculates the 10-year risk of fracture with or without BMD. Importantly, FRAX underestimates fracture risk associated with glucocorticoid use,<sup>14,29</sup> so clinicians who use FRAX should modify the results based on the dose and duration of glucocorticoid exposure and the additional risk factors listed in Table III. Note that because of a lack of data, no current model accurately predicts fracture risk in premenopausal women or men <50 years of age.<sup>30,31</sup> Clinical judgment is required to estimate risk in these patients. Our approach is outlined in Fig 1.

### Prevention and treatment

Clinicians should choose the lowest effective daily dose of steroids for the shortest duration possible and offer lifestyle counseling focused on reducing GIOP risk factors. It is important to emphasize that because significant changes occur within the first 3 months of therapy, clinicians cannot safely wait 3 months to initiate therapies aimed at preventing bone loss and fractures. These measures should be implemented at the outset of glucocorticoid therapy.

### Treatment

**Calcium and vitamin D.** All patients taking any dose of glucocorticoids with an anticipated duration of  $\geq 3$  months should maintain, through diet or supplementation, a total daily calcium intake of 800 to 1200 mg daily and vitamin D of 800 to 2000 units daily with rare exceptions (eg, patients with sarcoidosis may have high levels of activated vitamin D at baseline and may require disease-specific adjustments; patients with a history of hypercalcemia, hypercalcuria, or hypervitaminosis D may warrant adjustment as well; in patients with chronic kidney disease, calcium supplementation should be discussed with a nephrologist).<sup>30,32</sup>

**Bisphosphonates.** Bisphosphonates are first-line therapy for treating GIOP. There is substantial evidence of their effectiveness in preventing and treating bone loss in these patients.<sup>33</sup> Patients most likely to benefit from bisphosphonates are those at highest fracture risk. This includes postmenopausal women and men  $\geq 50$  years of age with established

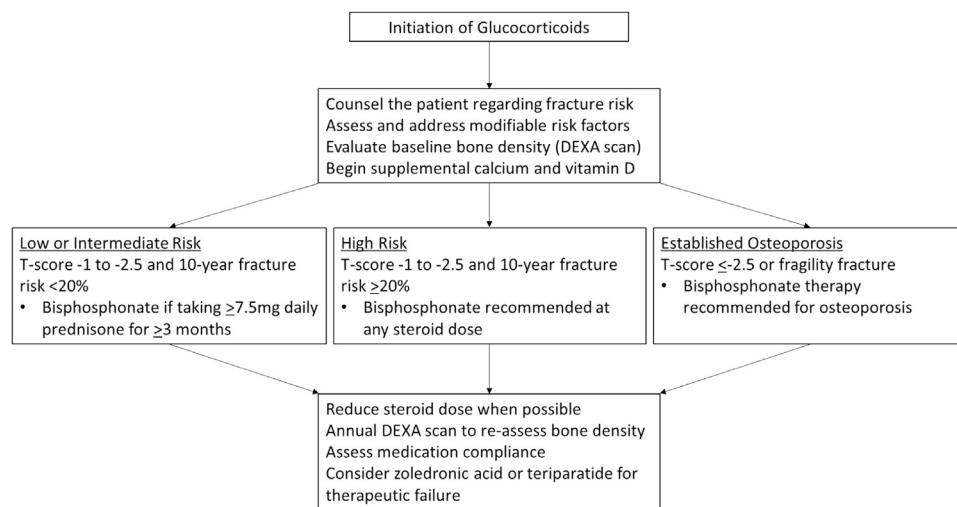
**Table III.** Factors associated with glucocorticoid-induced osteoporosis

Advanced age
Low body mass index
Underlying disease
Previous fracture
Smoking
Excessive alcohol use
Falls
Family history of fracture
High-dose glucocorticoid use
Duration of therapy
Low bone mineral density (as measured by dual-energy x-ray absorptiometry)
Hypovitaminosis D

osteoporosis (a T-score  $\leq -2.5$  or a history of fragility fracture), osteopenia (a T-score ranging from 1-2.5) taking  $\geq 7.5$  mg/day prednisone for  $\geq 3$  months, and osteopenia taking  $< 7.5$  mg/day prednisone who are considered high risk using the FRAX equation. Bisphosphonate therapy in premenopausal women and younger men is less well defined and must be balanced against potential long-term risks and teratogenicity. Nevertheless, it should be considered in patients who are taking glucocorticoids chronically who have accelerated BMD loss or a history of fragility fractures.

Alendronate or risedronate are preferred first-line agents. For patients who cannot tolerate oral medications, IV zoledronic acid may be considered. Bisphosphonates should be avoided in patients with a creatinine clearance of  $< 30$  mL/minute; such patients should be referred to a bone metabolism expert for additional management. Bisphosphonate-specific dosing, administration, and counseling recommendations can be found in Table IV. Of note, bisphosphonates are lipid soluble and may be stored in body fat for months to years; animal studies suggest the potential for fetal harm with abnormal bone development, and clinicians should therefore use caution when considering these medications for premenopausal women who may still become pregnant.<sup>30,34,35</sup>

Osteonecrosis of the jaw (ONJ) and atypical femoral fractures are 2 rare side effects of bisphosphonate therapy of which clinicians should be aware. ONJ is defined as the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks of identification.<sup>36</sup> The estimated incidence among those taking bisphosphonates is between 1 in 10,000 and 1 in 100,000 patients, but is higher for cancer patients who receive larger



**Fig 1.** Approach to treating glucocorticoid-induced osteoporosis using bisphosphonates. These recommendations are most applicable to postmenopausal women and men  $>50$  years of age. Bisphosphonate therapy in premenopausal women and younger men is less well defined. DEXA, Dual-energy x-ray absorptiometry. Adapted from Grossman et al.<sup>26</sup>

**Table IV.** Bisphosphonate therapy

Options for bisphosphonate therapy

- Alendronate: 5 mg daily, 70 mg weekly, or 150 mg monthly (generally the 70-mg weekly dose for treatment is favored)
- Risedronate: 5 mg daily or 35 mg weekly
- Ibandronate: 150 mg/month (only weak recommendation for this medication in glucocorticoid-induced osteoporosis)
- Zoledronic acid: 5 mg once yearly as an intravenous infusion for patients who cannot tolerate oral bisphosphonates (monitor for flu-like symptoms 2-3 days after first injection; can treat with acetaminophen or nonsteroidal antiinflammatory drugs; use with caution in patients with history of atrial fibrillation)

Before initiating therapy

- Consider referring all patients for dental examination; avoid bisphosphonate therapy when dental work is needed
- Correct hypocalcemia and vitamin D deficiencies

Assess for comorbidities that may preclude bisphosphonate use

- Measure serum creatinine: avoid bisphosphonate use if creatinine clearance is  $<30-35$  mL/min, and consider referral to endocrinology or nephrology for additional management

- Ensure patient has no swallowing difficulties and can remain upright for 30 min after taking a bisphosphonate
- Avoid use in patients with active upper gastrointestinal disease

Administration

- Take alone on an empty stomach first thing in the morning with 8 oz of water\*

- Avoid food and drink and other medications or supplements for 30 min after taking alendronate or risedronate and 1 hr after taking ibandronate

- Remain upright for 30 min after taking

- Discontinue if patients develop esophagitis

- Do not prescribe for any patients with swallowing difficulties or with active upper gastrointestinal disease

\*Enteric coated, delayed-release risedronate is taken immediately after breakfast with 4 oz of water.

doses of IV bisphosphonates.<sup>36</sup> Most cases have been reported in patients with underlying osteolytic breast cancer or multiple myeloma.<sup>14</sup> The American Association of Oral and Maxillofacial Surgeons recommends stopping oral bisphosphonates 3 months before and 3 months after a dental procedure if systemic conditions permit.<sup>37</sup> However, stopping bisphosphonates while on glucocorticoids

greatly increases the loss of BMD, and ONJ is rare. To provide perspective, clinicians may consider the following data: to prevent 1 vertebral fracture, the number needed to treat for 8 years is 3; to prevent 1 nonvertebral fracture, the number needed to treat for 8 years is 7; the number needed to harm over 8 years for ONJ is 1000 to 100,000.<sup>38-40</sup> The American Dental Association Council on Scientific Affairs issued an

executive summary in which they stated that the benefit of antiresorptive therapy outweighs the low risk of ONJ.<sup>41</sup>

Atypical subtrochanteric and femoral fractures are also associated with bisphosphonate use. Atypical femoral fractures present with groin or thigh pain unassociated with trauma.<sup>42</sup> According to a report of The American Society for Bone Mineral Research, atypical fractures appear to be more common in patients who have been taking bisphosphonates for >3 years. They also note multiple case series in which patients who are not taking bisphosphonates developed atypical femur fractures.<sup>42</sup> Any patient taking glucocorticoids and presenting with new, dull, or aching pain in the groin, thigh, or hip should have a plain radiograph of the affected side, and the prescribing clinician should communicate with radiology the concern for atypical femoral fracture. Fortunately, this complication is rare; the number needed to harm for atypical femoral fracture is 1282 if receiving bisphosphonates for 8 years.<sup>38-40</sup>

Bisphosphonate drug holidays are not recommended for patients who are at risk for GIOP. Studies guiding such recommendations did not include GIOP, and the results are therefore not generalizable.<sup>14,43-45</sup> A retrospective observational study of patients on extended bisphosphonates for GIOP found that patients who discontinued alendronate after 1 year while remaining on ≥6 mg/day of prednisone had significantly decreased BMD compared to those who remained on alendronate.<sup>46</sup> We recommend continuing bisphosphonates for GIOP while taking glucocorticoids, with annual repeat DEXA scans to monitor BMD.

**Other therapies.** Teriparatide, recombinant human parathyroid hormone; denosumab, a human monoclonal antibody to RANKL; and calcitonin, a parathyroid hormone antagonist, may be considered for patients who cannot tolerate bisphosphonates or who require long-term therapy.<sup>47</sup> These medications should be prescribed by clinicians who are experienced in managing bone disease. Data on hormone-replacement therapy are insufficient to make specific recommendations.

**Monitoring.** In addition to annual DEXA scans to monitor BMD, compliance with bisphosphonate therapy and calcium and vitamin D intake should be regularly reviewed. The importance of smoking cessation, decreased alcohol consumption, and weight-bearing exercise should be discussed. The serum 25-hydroxy vitamin D level should be measured annually.

## OSTEONECROSIS

### Key points

- The risk for developing osteonecrosis increases with cumulative and daily dose of glucocorticoids; however, patients taking any dose of glucocorticoid therapy may develop this side effect
- In patients taking glucocorticoids, clinicians must take note of any complaint of pain, especially in the hip, knee, or shoulder

### Background

Osteonecrosis of the femoral neck, distal femur, and proximal tibia may occur in as many as 40% of patients on long-term or high-dose glucocorticoid therapy.<sup>23</sup> The total cumulative dose and daily dose of glucocorticoids, and likely the underlying condition, affect the risk of developing osteonecrosis.<sup>48</sup> Very short-course, low-dose protocols are only rarely associated with osteonecrosis.<sup>49</sup> In 1 study, the mean daily dose of prednisone exceeded 40 mg/day for ≥1 month in 93% of patients and 20 mg/day in 100% of patients who developed osteonecrosis.<sup>50</sup> In addition, the association between osteonecrosis and Cushingoid features was highly significant.

**Pathogenesis and clinical presentation.** The pathogenesis of osteonecrosis (also called avascular, avascular, or ischemic necrosis or bone infarct) is not known. However, fat embolism, vascular thrombosis, fatigue (stress) fractures, and osteocyte apoptosis triggered by glucocorticoids have all been suggested as underlying mechanisms.<sup>48</sup> Osteonecrosis most commonly occurs in the femoral and humeral heads. Pain is usually the first symptom, but the clinical presentation is variable and depends on the site and size of the infarct.<sup>51</sup> Worsening pain occurs with movement of the affected joint, and as symptoms progress, patients may experience nocturnal pain. Symptoms may present within weeks to months on high-dose oral, intravenous, or intraarticular steroids or with chronic use over time.<sup>49,51</sup>

**Management.** Patients taking any dose of glucocorticoids must be monitored for osteonecrosis, because damage may be irreversible in later stages of disease. Clinicians must take note of any hip, knee, or shoulder pain with or without reduced range of motion. Complaints of joint pain should prompt consideration of osteonecrosis and, if concerned, referral for magnetic resonance imaging of the affected joint and evaluation by the patient's primary care provider, orthopedics, or rheumatology.

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# Prevention and management of glucocorticoid-induced side effects: A comprehensive review



## Gastrointestinal and endocrinologic side effects

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### Learning objectives

After completing this learning activity, participants should be able to describe important gastrointestinal and endocrinologic side effects of glucocorticoid use and devise strategies for preventing and diagnosing these complications in patients taking glucocorticoids.

### Disclosures

#### Editors

The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

#### Authors

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Part 2 of this 4-part continuing medical education series continues with a discussion of the prevention and management of gastrointestinal side effects associated with corticosteroid use, including peptic ulcer disease, gastrointestinal bleeding, and pancreatitis, followed by a review of corticosteroid-related endocrinologic side effects, such as diabetes, adrenal suppression, and Cushing syndrome. (*J Am Acad Dermatol* 2017;76:11-6.)

**Key words:** adrenal suppression; Cushing syndrome; diabetes; gastrointestinal bleeding; glucocorticoids; peptic ulcer disease; side effects; steroids.

## GASTROINTESTINAL SIDE EFFECTS

### Key points

- Glucocorticoid therapy with concomitant nonsteroidal antiinflammatory drug use increases the risk of peptic ulcer disease and gastrointestinal bleeding

- Proton pump inhibitors are an effective means of gastrointestinal prophylaxis, but they are not without side effects

Gastrointestinal (GI) side effects linked to glucocorticoid use include peptic ulcer disease (PUD), GI bleeding, and pancreatitis.

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Please note that infectious and other complications of steroid use will be discussed in the third and fourth installments of this Continuing Medical Education feature in the February 2017 issue of the *JAAD*.

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### Peptic ulcer disease

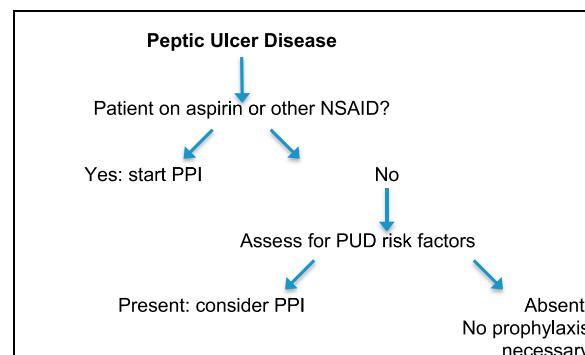
There is conflicting evidence concerning the risk of PUD for patients who are taking glucocorticoid monotherapy. Two metaanalyses found no increased risk of PUD for patients who were taking glucocorticoids, while another found PUD to be a rare complication of corticosteroid therapy, occurring in <0.4% to 1.8% of patients.<sup>1-3</sup> In a nested case-control study of Medicaid patients, there was no increased risk of peptic ulcer disease at any dose or duration of glucocorticoid therapy.<sup>4</sup> Patients who are taking glucocorticoids may experience more symptoms of gastric irritation, yet in 2 separate studies these symptoms did not translate into an increased risk for PUD.<sup>1,5</sup> However, the combination of glucocorticoids with nonsteroidal antiinflammatory drugs clearly increases the risk for PUD. In the same case-control study cited above, there was a significantly increased risk of developing ulcers among patients taking this combination (relative risk, 4.4 [95% confidence interval {CI}, 2-9.7]).<sup>4</sup>

### GI bleed

As with PUD, the concomitant use of glucocorticoids and nonsteroidal antiinflammatory drugs increases the risk of GI bleeding. In 1 study, patients who were taking low-dose aspirin plus high-dose corticosteroid therapy had a relative risk of 4.3 (95% CI, 2.10-9.34) for developing upper GI bleeding compared to those taking low-dose aspirin alone. Patients taking low-dose aspirin with low- or medium-dose corticosteroids, however, did not have increased risk.<sup>6</sup> It is not clear whether glucocorticoid use alone increases GI bleeding.<sup>6-9</sup> A metaanalysis of 71 controlled, randomized trials showed a low but independent risk of bleeding caused by steroids.<sup>2</sup> In the study cited above, patients who were taking high-dose glucocorticoids alone had a slight increased relative risk for developing GI bleed of 1.89 (95% CI, 1.05-3.38).<sup>6</sup> Finally, a metaanalysis comparing glucocorticoid use to placebo found an increased risk of bleeding or perforation limited to hospitalized patients only.<sup>8</sup>

### Pancreatitis

The data linking pancreatitis to glucocorticoid use are similarly mixed. One case-control study found a nearly threefold increased risk of acute pancreatitis among current users of betamethasone, and a slightly lower but still significant risk among those taking prednisolone.<sup>10</sup> The risk reached its highest level in the first 4 to 14 days after the betamethasone was dispensed and 15 to 30 days after prednisolone, with the risk gradually decreasing thereafter.<sup>10</sup> In a randomized, placebo-controlled trial of steroids for



**Fig 1.** Approach to proton pump inhibitor prophylaxis for peptic ulcer disease. *NSAID*, Nonsteroidal antiinflammatory drug; *PPI*, proton pump inhibitor; *PUD*, peptic ulcer disease.

optic neuritis that also evaluated corticosteroid side effects, there was only 1 case of acute pancreatitis among 457 patients.<sup>5</sup> A retrospective chart review of patients with systemic lupus determined that glucocorticoids were not the etiologic agent among those who developed pancreatitis.<sup>11</sup>

### Management and prevention

Patients who must take a combination of glucocorticoids and nonsteroidal antiinflammatory drugs should be prescribed prophylaxis with a proton pump inhibitor (PPI). In patients with other risk factors for PUD, including those with previous peptic ulcer disease, heavy smokers, heavy alcohol users, patients >65 years of age, and patients taking other medications that may increase the risk of PUD, such as bisphosphonates, clinicians may choose to prescribe PPIs. For those taking glucocorticoids alone, without other risk factors, routine use of a PPI is not recommended (Fig 1). Patients should be counseled on the signs and symptoms of upper GI bleed, PUD, and, in the first 2 to 4 weeks of therapy, pancreatitis. These include black or tarry, melena stools, fatigue, pallor, and severe abdominal pain, particularly if the pain is postprandial and radiating to the back or associated with nausea and vomiting.

### PPIs

PPIs are an effective means of prophylaxis for PUD and GI bleeding. Esomeprazole 20 mg and 40 mg, pantoprazole 20 mg and 40 mg, lansoprazole 15 mg and 30 mg, omeprazole 20 mg and 40 mg, and rabeprazole 20 mg are all approved for prophylaxis. All are administered daily before breakfast, and, if needed, a second dose can be given before the evening meal. The choice of which PPI to prescribe comes down to cost, accessibility, and patient preference. However,

**Table I.** Laboratory definitions of diabetes\*

Hemoglobin A1c $\geq 6.5\%$ <sup>†</sup>
Fasting plasma glucose $\geq 126$ mg/dL (7.0 mmol/L) <sup>‡</sup>
Fasting is defined as no caloric intake for $\geq 8$ hours
Two-hour plasma glucose $\geq 200$ mg/dL (11.1 mmol/L) during an oral glucose tolerance test
Random plasma glucose $\geq 200$ mg/dL (11.1 mmol/L) in a patient with symptoms of hyperglycemia

\*The first 3 criteria should be repeated if abnormal. Two abnormal tests indicate a diagnosis of diabetes.

<sup>†</sup>In patients with ongoing steroid treatment, hemoglobin A1c can be used to monitor blood sugars, but not before 3 months of steroid therapy.

<sup>‡</sup>Postprandial hyperglycemia is more common than fasting hyperglycemia with glucocorticoid use, and postprandial testing may therefore be a more sensitive indicator.

drug–drug interactions should also be considered. In recent years, studies have linked PPIs to certain adverse reactions, including an increased risk for enteric infections, such as *Clostridium difficile* colitis, decreased micronutrient absorption, rebound acid hypersecretion, increased fracture risk, chronic kidney disease, and dementia; however, the data are often conflicting.<sup>12–15</sup> The US Food and Drug Administration continues to advise against the combination of omeprazole and clopidogrel out of a concern that the resulting drug–drug interaction will decrease the antiplatelet efficacy of clopidogrel.<sup>16</sup> The data as to the clinical relevance of this interaction remain mixed.<sup>12</sup> However, it may be prudent to select a different PPI in this situation. As with any drug, a PPI should be prescribed only when clinically indicated and at the lowest effective dose. For the purpose of prophylaxis, this should be the recommended once daily starting dose for each specific agent. If the therapeutic response is inadequate, the dose can be increased or given twice daily. If PUD symptoms persist or signs of GI bleeding develop, referral to the patient's primary care provider or gastroenterologist is prudent.

## ENDOCRINE (DIABETES, ADRENAL SUPPRESSION, AND CUSHING SYNDROME)

### Key points

- Glucocorticoid therapy can cause diabetes, adrenal suppression, and Cushing syndrome
- Adrenal suppression is not uncommon among patients who are taking glucocorticoids, and the management of this potentially devastating side effect requires careful consideration

### Diabetes

Glucocorticoids can worsen existing diabetes and cause steroid-induced diabetes. Typical characteristics include an exaggerated postprandial hyperglycemia and insensitivity to exogenous insulin.<sup>17</sup> The

response is dose-dependent. A case-control study of Medicaid patients evaluated the relative risk of starting hypoglycemic therapy while taking glucocorticoids and found an odds ratio of 1.77 (95% CI, 1.54–2.02) for doses  $<10$  mg/day of prednisone equivalent versus 10.34 (95% CI, 3.16–33.90) for doses  $\geq 30$  mg/day.<sup>18</sup> With steroid use, postprandial hyperglycemia (defined as blood glucose  $>200$  mg/dL 2 hours after a meal) is more common than fasting hyperglycemia and is a much more sensitive indicator of steroid-induced diabetes.<sup>19</sup> In an observational study of patients receiving prednisolone for chronic obstructive pulmonary disease, the use of continuous blood glucose monitoring demonstrated hyperglycemia predominantly occurring in the afternoon and evening.<sup>20</sup> Risk factors for steroid-induced diabetes include older age and higher body mass index.<sup>19</sup> Alternate-day dosing is also associated with steroid-induced diabetes.<sup>21</sup>

**Monitoring.** All patients should be counseled regarding the risk of hyperglycemia and the signs and symptoms of diabetes, including polyuria, polydypsia, and polyphagia. Monitoring and treatment should be conducted in conjunction with the patient's primary care doctor or other treating physicians, such as an endocrinologist. Guidelines for when and how to initiate blood glucose monitoring in patients taking glucocorticoids are not clearly delineated in the literature. Consider checking a baseline glycated hemoglobin with presteroid laboratory values; patients with borderline or elevated glycated hemoglobin levels at baseline warrant additional evaluation and closer monitoring. Lifestyle modifications should be encouraged, but these may be insufficient for steroid-induced diabetes,<sup>22</sup> and the underlying disease process may limit exercise capacity. Routine monitoring of blood glucose levels via finger stick or basic metabolic panel should be included with regular medication monitoring or laboratory monitoring of the underlying disease state. In

Adrenal Suppression	
<p>Suppression Likely</p> <ul style="list-style-type: none"> <li>• Patients taking &gt; 20mg/day prednisone or equivalent for <math>\geq</math> 3 weeks</li> <li>• Patients with signs of Cushing's syndrome</li> </ul>	<p>Suppression Unlikely</p> <ul style="list-style-type: none"> <li>• Patients on glucocorticoids for &lt; 3 weeks</li> <li>• Patients taking alternate day doses of prednisone at <math>\leq</math> physiologic doses</li> </ul>

**Fig 2.** Guidelines for assessing the risk of adrenal suppression.

addition, consider prescribing a glucometer to patients who are expected to be taking chronic glucocorticoid therapy, with instructions to check random blood sugar in the afternoons at least 2 to 3 times per week. Glucose readings  $>200$  mg/dL should prompt a phone call to the clinician, more regular blood sugar monitoring, and referral to the patient's primary care doctor or endocrinologist. Laboratory definitions of diabetes are provided in Table I.

**Treatment.** Clinicians should treat to the same glycemic targets in glucocorticoid-induced diabetes as in those with preexisting diabetes. A patient's primary care provider or endocrinologist should manage clinically relevant hyperglycemia. Patients who are taking insulin or sulfonylureas (which increase endogenous insulin production) who are tapering their glucocorticoid dose should be reminded to monitor their blood glucose level closely while tapering, because they are at risk for life-threatening hypoglycemia. The patient's other treating physicians should be kept abreast of such intended changes in the glucocorticoid regimen so that they can provide assistance with monitoring and adjusting these medications.

### Adrenal suppression/steroid taper

Glucocorticoid use suppresses the hypothalamic–pituitary–adrenal (HPA) axis. Too abrupt a withdrawal of glucocorticoids may result in symptoms of adrenal suppression, the steroid withdrawal syndrome, or a recurrence of the underlying condition for which glucocorticoids were prescribed. Symptoms of adrenal suppression include weakness, fatigue, nausea, vomiting, diarrhea, abdominal pain, fever, weight loss, myalgias, arthralgias, and malaise. Adrenal crisis manifests with hypotension, decreased consciousness, lethargy, seizures, coma, and hypoglycemia.

Studies estimate daily physiologic cortisol production at 5 to 7 mg/m<sup>2</sup>/day. Higher doses are considered supraphysiologic.<sup>23–26</sup> Patients should be considered adrenally suppressed if they are

taking doses of prednisone of  $\geq 20$  mg daily for  $\geq 3$  weeks.<sup>27</sup> Clinical signs of Cushing syndrome also suggest adrenal suppression. Patients who are taking glucocorticoids for <3 weeks and those treated on alternate days with doses less than or equal to physiologic levels are less likely to have adrenal suppression.<sup>27–29</sup> However, individual responses to glucocorticoids may be highly varied, and dose and duration of therapy may not adequately reflect HPA axis suppression.<sup>30</sup> For example, patients taking prednisone doses as low as 5 mg/day for a few weeks or 40 mg after even 1 day may show evidence of adrenal suppression, but this is not necessarily clinically relevant.<sup>30–32</sup> Appropriate caution is advised with any taper. Guidelines for assessing the risk of adrenal suppression are noted in Fig 2.

**Tapering.** A systematic literature review found insufficient evidence to recommend any particular strategy for tapering glucocorticoids.<sup>33</sup> Tapering regimens vary with the underlying disease state and should be adjusted based on disease activity and medical comorbidities. Patients experiencing severe glucocorticoid-related side effects while achieving disease control may benefit from more rapid tapers. Patients with ongoing disease activity may require slower tapers. An example taper of long-term steroids for pemphigus vulgaris (assuming disease control) designed to minimize the risk of disease flare and adrenal insufficiency is shown in Table II.<sup>34</sup> In general, below doses of 10 to 15 mg prednisone per day, tapering of chronic steroids should slow to 1 to 2.5 mg every 1 to 3 weeks to account for HPA axis suppression, as warranted by disease activity. In the absence of clear guidelines, clinical judgment and close observation are necessary. Tapers can be managed with or without monitoring morning plasma cortisol levels, and clinicians may choose to switch glucocorticoids to hydrocortisone once a physiologic dose is achieved before continuing to taper.

At any point during a taper, a patient may experience symptoms of adrenal insufficiency or steroid withdrawal syndrome. Steroid withdrawal syndrome

**Table II.** Long-term steroid taper for pemphigus vulgaris\*

For patients taking >40 mg/day prednisone:
Taper steroids by 10 mg/week to 40 mg prednisone daily
Remain on 40 mg/day for 1 week
Starting at 40 mg/day prednisone:
Taper by 5 mg/week to a dose of 20 mg prednisone daily
Stay on 20 mg prednisone daily for 1 week
Starting at 20 mg/day prednisone
Taper by 2.5 mg/week to a dose of 5 mg daily
Stay on 5 mg prednisone daily for 1 week
Starting at 5 mg/day prednisone
Taper by 1 mg/week
Continue taper until patient is off steroids

\*Taper slowly to avoid disease flare and adrenal insufficiency. This taper may be used for other dermatoses requiring high-dose glucocorticoid therapy. However, clinicians must individualize any taper based on disease activity, disease, and underlying comorbidities. This example does not apply to all patients or all diseases but is presented for reference.

is marked by symptoms of adrenal insufficiency (such as weakness, fatigue, nausea, vomiting, etc) in patients with normal HPA axis testing.<sup>35</sup> Patients should be advised of these signs and symptoms and counseled to cease tapering and contact a physician immediately if they develop. The taper should be temporarily halted, and hydrocortisone or an increased dose of the glucocorticoid should be given until the patient stabilizes. The clinician may also choose to test the HPA axis at this time. Patients should resume tapering at a slower rate in 2 to 4 weeks. There are no specific guidelines about rechecking the HPA axis upon resumption of the taper or steroid cessation, but close monitoring and slow taper are advised. Consulting an endocrinologist is also advised for any patient who experiences adrenal insufficiency.

Serious illnesses and major surgeries may require stress dose steroids for patients who have taken glucocorticoids for  $\geq 1$  month.<sup>36,37</sup> Depending on the surgery or illness, various methods of glucocorticoid replacement therapy can be considered. This should be discussed with the patient's surgical or hospital team. Patients need not show symptoms of adrenal suppression before illness or surgery. It is important to ensure that the patient and other providers are aware that the patient is taking steroids and may require dose augmentation to avoid adrenal crisis. Patients who are taking long-term steroids should carry a glucocorticoid treatment card or wear a medic alert bracelet denoting their risk of life-threatening adrenal suppression.

## Cushing syndrome

Classic characteristics of Cushing syndrome include central obesity, redistribution of body fat to truncal areas, supraclavicular fat pads, striae distensae, proximal muscle weakness, fatigue, hypertension, acne, glucose intolerance, muscle atrophy, and psychologic disturbances.<sup>35</sup> Every mode of exogenous glucocorticoid use has been associated with Cushing syndrome. These effects are directly related to the dose and duration of use. Predicting the correct dose and time-course at which Cushing syndrome develops is complicated by the various potencies and half-lives of glucocorticoids; however, even doses as low as 5 mg/day of prednisone can result in Cushing syndrome.<sup>35</sup> In 1 study, the prevalence of Cushing syndrome increased linearly with increasing glucocorticoid dose, from 4.3% to 15.8% to 24.6% among patients taking <5 mg, 5 to 7.5 mg, and >7.5 mg of prednisone daily over the course of 6 months.<sup>38</sup> Medications that interfere with the cytochrome P450 system may prolong the half-life of glucocorticoids, increasing the risk of Cushing syndrome. Management includes reducing the dose and duration of glucocorticoid therapy, as able, to avoid and ameliorate this complication. Clinicians are advised to check drug-drug interactions before prescribing any medication concomitantly with glucocorticoids.

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# Prevention and management of glucocorticoid-induced side effects: A comprehensive review



## Infectious complications and vaccination recommendations

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### Learning objectives

After completing this learning activity, participants should be able to describe important infectious complications of chronic glucocorticoid therapy and implement preventative strategies, including appropriate use of prophylactic agents and routine vaccinations.

### Disclosures

#### Editors

The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

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Part 3 of this 4-part continuing medical education series reviews several important infectious complications of corticosteroid use, including a focus on pneumocystis pneumonia (PCP) prophylaxis, tuberculosis, viral hepatitis, and other infections, followed by a discussion of vaccination recommendations in immunosuppressed patients. (J Am Acad Dermatol 2017;76:191-8.)

**Key words:** glucocorticoids; infections; pneumocystis pneumonia; side effects; steroids; vaccines.

## GLUCOCORTICOIDS AND IMMUNITY

### Key point

- **Glucocorticoids cause significant impairment in immune function, necessitating prophylactic considerations and vaccination recommendations**

Glucocorticoid use affects both adaptive and innate immunity, increasing the risk for acquiring pathogens, reactivating chronic infections, and impacting vaccine recommendations. Adaptive immunity refers to the part of the immune system

that produces lymphocytes (B and T cells) and antibodies. The adaptive immune system works in conjunction with the innate immune system (ie, the part of the immune system that is always present, such as inflammatory proteins, antimicrobial peptides, phagocytic cells, natural killer cells, and physical barriers) to defend against infection and create immunologic memory. Glucocorticoids affect the function of phagocytic cells, downregulate mechanisms involved in antigen presentation, and decrease the effective number of antigen-presenting

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Please note that bone health and gastrointestinal and endocrinologic side effects of glucocorticoid were discussed in the first two installments of this Continuing Medical Education feature in the January 2017 issue of the JAAD.

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cells (macrophages and dendritic cells) and circulating T and B cells. Patients who are taking glucocorticoids are at increased risk for infection by commonly encountered viruses, bacteria, fungi, and less commonly encountered pathogens. Increased vigilance for specific infections and vaccination recommendations relevant to patients who are taking glucocorticoids are reviewed below.

## PNEUMOCYSTIS PNEUMONIA PROPHYLAXIS

### Key points

- **The risk for pneumocystis pneumonia is related to total dose and duration of glucocorticoids; however, the best available evidence suggests that additional risk factors should be present before prescribing pneumocystis pneumonia prophylaxis**
- **Trimethoprim-sulfamethoxazole is an effective prophylactic agent against pneumocystis pneumonia, and it is associated with an acceptably low risk of side effects**

### Overview

Pneumocystis pneumonia (PCP) is a life-threatening complication of immunocompromised patients. It is most commonly seen in patients with HIV/AIDS, but it is also seen in patients who are undergoing high-dose corticosteroid therapy and patients with other significant iatrogenic immunosuppression. Concern for this infection has resulted in the widespread use of PCP prophylaxis in patients with HIV/AIDS. Published guidelines exist regarding the timing and duration of PCP prophylaxis in hematopoietic and solid organ transplant recipients. Special populations—those with certain primary immunodeficiencies, acute lymphoblastic leukemia, and those receiving certain highly immunosuppressive combination chemotherapies or the anti-CD52 monoclonal antibody alemtuzumab—are at substantial risk of PCP and should also receive prophylaxis.

### Estimating risk

Data guiding the use of PCP prophylaxis in dermatologic and rheumatologic patients receiving high-dose corticosteroids and other immunosuppression are less clear. In general, such patients are less immunosuppressed, and ultimately the risk of PCP must be balanced against potential adverse effects of the prophylaxis itself. Accounting for this issue, a metaanalysis concluded that PCP prophylaxis is warranted when the risk of PCP exceeds 3.5%.<sup>1</sup>

Unfortunately, there is no existing risk equation or means of quantifying risk numerically in this way. Among collagen vascular diseases, only granulomatosis

with polyangiitis (ie, Wegener granulomatosis), which is treated with combination high-dose steroids and cyclophosphamide, is associated with a PCP risk >2.5%.<sup>2</sup> Similar incidence data pertaining to dermatologic diseases are lacking, but what is available suggests that the risk in most such patients is low. In 1 study, only 1 (0.5%) of 198 unselected patients receiving immunosuppressive medications for dermatologic conditions developed PCP.<sup>3</sup> In another, 7 of 3921 dermatology patients with connective tissue or immunobullous disease developed PCP, while 327 developed pneumonia due to other causes.<sup>4</sup>

Nonetheless, the mortality associated with PCP infection in non-HIV-infected patients is high (approximately 40%),<sup>5</sup> and prophylaxis is highly effective.<sup>2</sup> While routine PCP prophylaxis in all patients taking glucocorticoids or other immunosuppressive medications may not be justified by the available data, it should be considered on a case by case basis. Dermatology patients who develop PCP tend to represent a highly selected population. This includes patients with systemic lupus erythematosus (SLE), dermatomyositis, or immunobullous disease who are taking ≥1 immunosuppressive agent in addition to moderate- or high-dose corticosteroids and who frequently have other serious comorbidities, such as active cancer, organ transplantation, or interstitial lung disease.

Therefore, in patients taking the equivalent of ≥20 mg of prednisone daily for ≥4 weeks,<sup>6</sup> PCP prophylaxis should be considered, particularly if a second risk factor, such as hematologic malignancy, interstitial lung disease, or another immunosuppressive agent, is present. Alkylating agents, such as cyclophosphamide, are particularly problematic, but other intensely immunosuppressive regimens, such as rituximab or tumor necrosis factor (TNF)-α inhibitors combined with steroids should receive similar consideration.

### Prophylactic regimens

Trimethoprim-sulfamethoxazole 160/800 mg (double-strength) dosed either daily or thrice weekly is the medication of choice. In HIV-negative patients, the rate of adverse events necessitating cessation of the medication is low, about 3.1%.<sup>2</sup> Alternative regimens include atovaquone 1500 mg daily or dapsone 100 mg daily. Some data suggest that sulfonamide antibiotics can exacerbate systemic lupus, so some favor using an alternative agent in these patients. PCP prophylaxis should be continued until the immunocompromised state has resolved; in some cases, this may be some time after the final dose of immunosuppressive medication is given.

## OTHER INFECTIONS

### Key point

- **Glucocorticoid use is associated with an increased risk of bacterial, fungal, and viral infections, including tuberculosis, strongyloidiasis, and hepatitis B virus and hepatitis C virus reactivation**

### Tuberculosis

Prolonged therapy with moderate- or high-dose corticosteroids increases the risk of tuberculosis (TB) reactivation. The Centers for Disease Control and Prevention (CDC) and the American Thoracic Society identified prednisone 15 mg daily for >1 month as the threshold for increased risk based on dosing identified in previous studies as that which suppresses the tuberculin skin test.<sup>7,9</sup> Such patients are considered at increased risk for progression of latent to active TB.<sup>10</sup> However, the lower limit of prednisone dosing that increases risk is not known. In 1 case-control study, the adjusted odds ratio of tuberculosis was 2.8 (95% confidence interval, 1.0-7.9) for <15 mg daily prednisone versus 7.7 (95% confidence interval, 2.8-21.4) for >15 mg daily prednisone (or equivalent).<sup>11</sup> The risk remains elevated in patients who are considered recent users (ie, glucocorticoid use ending 121-180 days before the index event). Patients diagnosed with TB are more likely to smoke, be underweight, diabetic, and have lung disease.<sup>11</sup>

**Management.** The goal of TB testing is to identify patients who are at elevated risk for progression to active TB so that they may receive proper treatment.<sup>12</sup> Screening for TB exposure includes a clinical history focused on TB risk factors, such as known contact with a person infected with TB, exposure to prisons and health care facilities personally or through close contacts, living in or moving from a TB-endemic area, and substance abuse.

Testing for latent TB can be accomplished using a tuberculin skin test (TST; Mantoux tuberculin skin test) or an interferon gamma release assay (IGRA; QuantiFERON-TB Gold [Cellestis/Qiagen, Carnegie, Australia] or T-SPOT.TB [Oxford Immunotec, Marlborough, MA]). TSTs are performed by injecting a purified protein derivative intradermally to elicit a type IV hypersensitivity reaction in patients with cell-mediated immunity to tuberculin antigens.<sup>13</sup> It is interpreted 48 to 72 hours later, and for patients who are taking glucocorticoids, ≥5 mm induration is considered a positive reaction. Doses of glucocorticoids >15 mg for 2 to 4 weeks can suppress tuberculin reactivity and lead to false negative results/anergy.<sup>7,10</sup> A Web-based algorithm has been created to assist interpretation of TSTs (available

from: <http://www.tstin3d.com/>).<sup>14</sup> Another test for latent TB infection is the IGRA, an in vitro blood test of cell-mediated immunity that measures T cell release of interferon gamma (IFN- $\gamma$ ) after exposure to *Mycobacterium tuberculosis*-specific antigens.<sup>13</sup> Two tests are commonly used, the QuantiFERON-TB Gold In-Tube assay and the T-SPOT.TB assay.<sup>13</sup> The US Food and Drug Administration has approved both of these tests for use in the United States. According to the CDC guidelines, IGRAAs are the preferred testing method for patients with previous bacillus Calmette-Guérin exposure (which can cause false-positive purified protein derivative results) or patients who cannot return to the clinic 48 to 72 hours after a purified protein derivative is placed. IGRAAs can be used in any setting in which the TST is used. Routine testing with both TST and IGRA is not recommended. Any patient with a positive test requires a chest radiograph and potentially sputum cultures to determine whether the tuberculosis is latent or active. Positive tests should be referred to an infectious diseases specialist.

### Strongyloides hyperinfection syndrome

Hyperinfection syndrome (HS) is caused by *Strongyloides stercoralis* infection in the setting of immunocompromise. It carries a high mortality rate, ranging from 15% to 87%, and may occur years after exposure to *Strongyloides*, because the parasite can complete its life cycle in a single human host and may persist for decades.<sup>15,16</sup> In developed countries, the most frequent risk factor for HS is exposure of an infected patient to high-dose corticosteroids.<sup>15</sup> Even short courses of steroids over days to weeks may precipitate HS.<sup>17</sup> Risk factors for acquiring *Strongyloides* include travel to or living in endemic areas, which includes tropical and subtropical countries. In the United States, the organism exists in rural Appalachia, but the majority of affected patients are immigrants from endemic areas.<sup>18</sup> Infection may also occur via organ transplantation from an infected person. Symptoms of HS include abdominal pain, nausea, vomiting, diarrhea, intestinal obstruction and ileus, cough, wheeze, dyspnea, hemoptysis, pneumonitis, respiratory failure, and systemic signs, such as peripheral edema, ascites, and Gram-negative bacteremia.<sup>18</sup> A diagnosis of HS can be made by visualization of the organism in sputum or stool on microscopic examination. Peripheral eosinophilia and immunoglobulin G (IgG) antibodies to *Strongyloides* may not be present in immunocompromised hosts. Importantly, most carriers of *Strongyloides* are asymptomatic, and patients may have been exposed remotely and still carry the parasite.

**Management.** Strongyloides screening should be considered in patients with the risk factors noted above who are initiating glucocorticoid therapy. Even patients taking moderate (20–40 mg/day) doses of prednisone chronically may be at risk. The presence of peripheral eosinophilia before treatment can be an important clue; however, eosinophilia may be related to other causes. Screening for IgG antibodies to *Strongyloides* should be performed before initiating therapy in patients with known risk factors or peripheral eosinophilia.<sup>19,20</sup> In endemic areas, in order to prevent HS, some physicians have recommended empiric treatment for *Strongyloides* with ivermectin before initiating glucocorticoids.<sup>21–25</sup>

### Hepatitis B and C viruses

Glucocorticoids have been implicated in the reactivation of chronic hepatitis B in patients receiving chemotherapy for lymphoma, bone marrow transplants, solid organ transplants, and in patients taking glucocorticoids for other conditions, such as asthma or chronic obstructive pulmonary disease.<sup>26–31</sup> Long-term glucocorticoid use increases levels of hepatitis B viral DNA and antibody markers of viremia by interacting with a glucocorticoid responsive element in hepatitis B virus (HBV) DNA and by decreasing T cell function, allowing for increased viremia.<sup>26,32–34</sup> The dose and duration of therapy that increase this risk remain unclear. A study of patients with chronic obstructive pulmonary disease and with positive hepatitis B surface antigen found a significantly higher risk of hepatitis B reactivation only among those receiving ≥3 months of glucocorticoid therapy at doses of prednisolone ≥20 mg/day.<sup>28</sup> Hepatitis B reactivation has also been shown in patients taking glucocorticoids for dermatologic conditions. In a retrospective study of 98 patients with pemphigus vulgaris and dermatomyositis receiving glucocorticoids for >6 months, 4 cases of hepatitis B reactivation were documented, 2 of which progressed to fatal liver failure.<sup>35</sup> Withdrawal of glucocorticoids may result in decreased viremia.

The evidence associating glucocorticoids with elevations in hepatitis C RNA is incomplete. One study found that long-term prednisone at doses <30 mg per day either with or without concomitant azathioprine therapy reduced aspartate aminotransferase and alanine aminotransferase in the first 3 months of therapy, slowed liver fibrosis compared to controls, and had a nonsignificant effect on hepatitis C virus (HCV) RNA.<sup>36</sup> However, other studies have reported increases of HCV RNA in patients taking glucocorticoids.<sup>37,38</sup> The difference may be related to variable glucocorticoid dose, with glucocorticoid therapy in general decreasing

hepatocyte inflammation and higher doses more likely to increase HCV viral load.<sup>36–38</sup>

**Management.** Specialty society recommendations differ as to the dose and duration of corticosteroid use necessitating screening, but clinicians should consider screening for HBV and HCV before initiating immunosuppressive therapy with glucocorticoids, especially if the anticipated dose and duration of therapy are ≥20 mg prednisone daily for ≥4 weeks.<sup>39</sup> This is particularly true for those at increased risk of infection, such as those from Southeast Asia (HBV) and those with a history of intravenous drug use (HCV). Testing for hepatitis B should include hepatitis B surface antigen, surface antibody, and core antibody. A hepatitis C antibody test should be performed to screen for HCV. The CDC now recommends 1-time hepatitis C antibody screening in all patients born between 1945 and 1965, regardless of risk. Patients who have already been screened for HCV do not require repeat testing unless they develop new risk factors. Patients with serologic evidence of HBV or HCV infection should be referred to infectious diseases or hepatology for comanagement while receiving immunosuppressive therapy.

### HIV

The current guidelines recommend routine HIV screening for all persons between 15 and 65 years of age, roughly, but some guidelines differ on the specific age range suggested. One-time screening is reasonable for patients at low risk, and more frequent testing is recommended for those at high risk for HIV infection. When initiating long-term glucocorticoid therapy, it is prudent to review HIV screening history and perform or refer for HIV testing, if indicated. Patients with undiagnosed and untreated HIV infection may be at increased risk of infectious complications with the initiation of chronic glucocorticoid therapy. Any confirmed positive result should prompt a referral to an infectious diseases specialist or a provider experienced in HIV care.

### Herpes zoster virus

Glucocorticoid use has also been associated with reactivation of varicella zoster virus, leading to herpes zoster, or “shingles,” among patients with a variety of underlying conditions, including rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, chronic kidney disease, systemic lupus erythematosus, and autoimmune bullous diseases.<sup>40–43</sup> Immunosuppressed patients who develop shingles are at increased risk for complications, including disseminated disease requiring hospitalization.

**Management.** Patients >50 or >60 years of age (with or without a history of varicella zoster virus infection) who have not received the zoster vaccine should receive it, if possible, at least 2 to 4 weeks before the initiation of moderate- or high-dose glucocorticoids. Patients taking  $\leq 20$  mg prednisone per day (or the equivalent) can safely receive the zoster vaccine at any time.

## VACCINATIONS

### Key points

- Clinicians should assess a patient's vaccination history and address any deficiencies before starting therapy, if possible
- Vaccination recommendations aim to maximize therapeutic response and minimize the risk of active infection from live vaccines

### Overview

The impairment of adaptive immunity by glucocorticoids may cause 2 potential problems during vaccination. The first is that patients may not mount a response to vaccination while taking glucocorticoids, leaving them unprotected from the diseases vaccines are designed to prevent. The second is that patients may develop active infections if exposed to live vaccines. The current recommendations aim to minimize the risk of both potential complications.<sup>44-49</sup> All published recommendations on vaccination of immunocompromised hosts are based on expert opinion because of the limitations of current data. In addition, existing recommendations differ markedly between countries.<sup>45</sup> The recommendations listed below are a combination of the recommendations published by the European League Against Rheumatism,<sup>50</sup> the Advisory Committee on Immunization Practices,<sup>44</sup> the American Society of Transplantation,<sup>43</sup> the Infectious Disease Society of America,<sup>46</sup> and the American Society for Blood and Marrow Transplant.<sup>47</sup> Of note, these recommendations do not apply to patients taking steroids for  $\leq 2$  weeks, patients taking prednisone doses  $<20$  mg per day (or equivalent), patients on alternate-day dosing with short-acting preparations, those on maintenance physiologic doses, nor those receiving steroids topically, by aerosol, or by intraarticular, bursal, or tendon injection. These patients are not considered immunocompromised and should receive vaccinations using the same guidelines as immunocompetent patients.

### Vaccination recommendations

Patients with conditions necessitating moderate or high doses of corticosteroids ( $\geq 20$  mg/day of prednisone) for >2 weeks should be asked about

**Table I.** Vaccinations

Ask about vaccination history during initial visit

*Haemophilus influenzae* B

Hepatitis A and hepatitis B

Human papillomavirus

Influenza

*Neisseria meningitidis*

Rubella (for women of childbearing age)

*Streptococcus pneumoniae*

Tetanus toxoid

Varicella zoster

Administer vaccines or refer to primary care for

vaccinations in accordance with standard scheduling\*

Give preference to live vaccines (eg, measles, mumps, and rubella and varicella). These should be given at least 2-4 weeks before immunosuppression

\*Available at: <http://www.cdc.gov/vaccines/schedules/hcp/imz-adult.html>.

vaccination history to ensure that they are up to date on the following vaccinations: *Haemophilus influenzae* B, hepatitis A virus and HBV, human papillomavirus, influenza, *Neisseria meningitidis*, measles, mumps, and rubella (MMR), *Streptococcus pneumoniae*, and tetanus. The CDC's Recommended Immunization Schedule for Adults provides a detailed explanation of vaccination timing (Table I).<sup>51</sup> Patients who are not up to date on vaccinations should receive them before starting corticosteroids, if possible, so that an appropriate protective immune response may occur. Baseline blood work should also include MMR and varicella zoster virus titers. If titers are low, vaccination is recommended before starting immunosuppression. If the patient has never had varicella nor received the vaccine, the varicella vaccine should be given before treatment with corticosteroids. If the patient is >60 years of age (an age for which the zoster vaccine is recommended in all patients, absent contraindications) and has not received the vaccine, it should be given. If the patient is >50 years of age (an age for which the zoster vaccine is effective but recommended only on a case by case basis), administration of the vaccine should be strongly considered before immunosuppression. If the patient requires several vaccines before treatment, live vaccines (eg, varicella, zoster, and MMR) should take precedence, because they are contraindicated during immunosuppression. Recommendations for delaying corticosteroid treatment after immunization with live vaccines vary because of a lack of data. The minimum wait period recommended is 2 to 4 weeks to allow for immune response to the vaccine and clearance of live virus. All professional societies agree this wait time is imperative for live vaccines

because of the theoretical risk of infection in severely immunosuppressed patients. However, in alignment with data procured from a systematic literature review of vaccine use in patients with rheumatic disease, the European League Against Rheumatism recommendations allow for immunization with inactivated vaccines during times of immunosuppression.<sup>48,49</sup>

Patients who need to start treatment with moderate to high doses of systemic glucocorticoids immediately may be safely vaccinated with inactivated vaccines, with the caveat that their subsequent immunity may be suboptimal. However, those taking doses of corticosteroids equivalent to  $\geq 20$  mg of prednisone daily for  $\geq 2$  weeks should not be given live vaccines. In this clinical scenario, the administration of live vaccines (eg, varicella, zoster, MMR, nasal influenza, vaccinia, oral polio, oral typhoid, bacillus Calmette-Guérin, and yellow fever) should be delayed until the patient is taking doses of prednisone  $< 20$  mg per day (or equivalent) for at least 1 to 3 months.<sup>45,52</sup> These recommendations may change in the near future as additional data are generated about the safety of live vaccines in immunosuppressed patients.<sup>49,53-56</sup>

### Influenza and pneumococcus

An annual seasonal influenza vaccination is recommended for all people  $\geq 6$  months of age. All adults  $\geq 65$  years of age and those  $< 65$  years of age who are immunosuppressed (including those taking doses of prednisone  $\geq 20$  mg/day) should also receive the pneumococcal pneumonia vaccine. Patients taking chronic low-dose steroids, particularly if they are also taking steroid-sparing agents, should also be encouraged to receive the pneumococcal vaccines. According to Advisory Committee on Immunization Practices guidelines, if the patient is pneumococcal vaccine-naïve, he or she should receive the 13-valent pneumococcal vaccine (PCV13) first, followed by a dose of the 23-valent vaccine (PPSV23) at least 8 weeks later.<sup>44,50</sup> A second PPSV23 dose is recommended if 5 years have passed since the first PPSV23 dose was given.<sup>50</sup> Patients previously vaccinated with PPSV23 but not PCV13 should be given PCV13  $\geq 1$  year after the last PPSV23 dose.<sup>50</sup>

### Other vaccines

Patients taking corticosteroids who have not received the yellow fever vaccine before therapy should be counseled to avoid yellow fever-endemic areas.<sup>55</sup> Inactivated travel vaccinations (eg, typhoid, poliomyelitis, rabies, Japanese encephalitis, hepatitis

A virus, HBV, and meningococcus) can be safely administered.<sup>55</sup>

Finally, it is recommended that the patient's close contacts not be immunized with smallpox vaccine or the nasal influenza vaccine.<sup>44,45</sup> If a close contact develops a rash after immunization with the varicella vaccine, the immunosuppressed patient should avoid contact with that person until the rash resolves.<sup>44,45</sup> The patient should also adopt meticulous hand-washing practices when caring for a child who has received the rotavirus vaccine.<sup>44,45</sup>

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# Prevention and management of glucocorticoid-induced side effects: A comprehensive review



## Ocular, cardiovascular, muscular, and psychiatric side effects and issues unique to pediatric patients

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### Learning objectives

After completing this learning activity, participants should be able to describe the ocular, cardiovascular, muscular, and psychiatric side effects of glucocorticoid use and devise strategies to prevent complications in adult and pediatric patients taking glucocorticoids.

### Disclosures

#### Editors

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The final article in this 4-part continuing medical education series reviews the ocular, cardiovascular, muscular, and psychiatric side effects of glucocorticoids and discusses side effects unique to pediatric patients. (J Am Acad Dermatol 2017;76:201-7.)

**Key words:** cataracts; glucocorticoids; glaucoma; growth suppression; side effects; steroid myopathy; steroid psychosis; steroids.

## OCULAR ADVERSE EVENTS

### Key points

- The risk for developing glaucoma and cataracts while taking glucocorticoid therapy appears to be dose-dependent
- When long-term glucocorticoid therapy is planned, clinicians should ask about the history of glaucoma and cataracts and consider referral for ophthalmologic examination

Glucocorticoid use increases the risk of glaucoma and cataracts.<sup>1</sup> The risk appears to be both duration and dose-dependent. In 1 study, glaucoma risk increased with doses >7.5 mg of prednisone per day taken for ≥6 months.<sup>2</sup> A separate case-control study found an increased risk for glaucoma among patients who had taken glucocorticoids within 2 weeks, but not for those who had previously taken glucocorticoids.<sup>1</sup> The risk for glaucoma increased over time and for all doses of

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Please note that bone health and gastrointestinal and endocrinologic side effects of glucocorticoid were discussed in the first two installments of this Continuing Medical Education feature in the January 2017 issue of the JAAD.

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glucocorticoids; however, doses of hydrocortisone  $>40$  mg per day (prednisone 10 mg equivalent) were associated with an almost 2-fold increased risk for glaucoma.<sup>1</sup>

Importantly, patients may not be aware of early visual loss. The increase in intraocular pressure is painless, but it can lead to permanent optic nerve damage. Discontinuation of glucocorticoid therapy leads to reversal of intraocular hypertension within 2 weeks, at which time pressures appear to normalize.<sup>1</sup>

Increased risk for posterior subcapsular cataracts can also be associated with long-term glucocorticoid use.<sup>3</sup> In 1 study, 39% of patients with rheumatoid arthritis developed cataracts, but only at prednisone doses of  $>10$  mg per day for  $\geq 1$  year.<sup>4</sup> In a study of 230 patients with systemic lupus who were taking prednisone for 5 years, only 6 developed cataracts at doses ranging from 8 to 30 mg prednisone per day.<sup>5</sup> Another study of lupus patients found that cumulative prednisone dose was significantly associated with increased risk for cataracts at a reference dose of 10 mg per day for 10 years.<sup>6</sup> This side effect is more likely to occur at higher glucocorticoid doses, but as with other steroid-related complications, even doses  $\leq 5$  mg prednisone per day have been linked to cataract formation.<sup>2</sup> Therefore, there may be no safe dose at which clinicians can disregard this complication completely.<sup>3,7</sup> Other side effects, such as exophthalmos and chorioretinopathy, rarely occur.

**Management.** Clinicians should inquire about personal and family history of glaucoma or cataracts before starting glucocorticoid therapy. All patients for whom long-term glucocorticoid therapy at any dose is planned should have a baseline ophthalmology evaluation, with additional management and regular follow-up based on findings at the initial visit, the underlying disease, comorbidities, and anticipated steroid course (Table I). In the event an ophthalmologic examination cannot be performed in a timely fashion before beginning glucocorticoid therapy, patients can be referred after therapy has started. Given the risk of diabetic retinopathy with poor glucose control and the association of glucocorticoid use with diabetes, adequate diabetes management is also important to mitigate ocular complications of corticosteroids.

## CARDIOVASCULAR/HYPERTENSION/ LIPIDS

### Key point

- **Glucocorticoid therapy may increase the risk of cardiovascular disease, as may the patient's underlying inflammatory condition**

**Table I.** Ocular side effects

Ask about history of cataracts and glaucoma
Consider referral for baseline ophthalmology examination
Follow-up ophthalmologic examination as needed (check intraocular pressure after about 3 months of systemic steroids)

## Cardiovascular

Glucocorticoids may increase the risk of cardiovascular disease. One large case-control study found a dose-response relationship between daily glucocorticoid dose and the risk of heart failure among current users of glucocorticoids, including patients with rheumatoid arthritis, chronic obstructive pulmonary disease, and other conditions. The risk of ischemic heart disease was also increased, but there was not an association with cerebrovascular disease.<sup>8</sup> In a large, population-based study, patients taking  $\geq 7.5$  mg of prednisone per day or the equivalent had a significantly higher composite risk of myocardial infarction, angina, coronary revascularization, hospitalization for heart failure, transient ischemic attack, and stroke.<sup>9</sup> Patients taking glucocorticoids within the preceding 6 months were at increased risk. Continuous use ( $\leq 180$  days between prescriptions) was also associated with higher risk compared to intermittent use.<sup>9</sup> Patients with iatrogenic Cushing syndrome have a higher hazard ratio of developing a cardiovascular event and a higher risk of coronary heart disease and cardiac insufficiency.<sup>10</sup>

The association between cardiovascular disease and glucocorticoid use is confounded by the underlying inflammatory condition, which may increase the incidence of cardiovascular disease because of chronic inflammation and the need for higher doses of glucocorticoids. For example, increased mortality from heart disease has been noted among patients with inflammatory arthritis; however, many patients have been treated with high-dose steroids.<sup>9</sup>

Pulse glucocorticoids, defined as high-dose glucocorticoids delivered over a short period of time, are used to treat severe inflammatory disorders and are also associated with cardiovascular disease. Sudden death caused by pulse dose glucocorticoids has been reported, usually if given over  $<2$  hours, but this tends to occur in patients with underlying cardiac disease or in patients receiving steroids for nondermatologic conditions.<sup>11</sup> Continuous cardiac monitoring should be considered in patients with severe cardiac or kidney disease who are receiving pulse dose glucocorticoids.<sup>11</sup> Patients treated for

dermatologic conditions with widespread cutaneous erosions may benefit from continuous monitoring during pulse therapy because of the potential for electrolyte shifts resulting from loss of skin integrity.<sup>11</sup>

### Hypertension and hyperlipidemia

The mechanism behind glucocorticoid-induced hypertension remains unclear. Increasing evidence supports the notion that activation of mineralocorticoid receptors may not be the primary mechanism. Vascular tone and possibly centrally mediated mechanisms may also play a role.<sup>12</sup>

Glucocorticoid use may result in hyperlipidemia, but the literature is inconsistent.<sup>13</sup> After renal and cardiac transplantation, tapering of steroids mirrors a decrease in cholesterol level.<sup>14</sup> For patients with inflammatory disorders, however, some studies suggest an improved atherogenic profile in corticosteroid-treated patients paralleling decreased disease activity.

**Management.** Cardiovascular risk factors should be aggressively managed in all patients who are taking glucocorticoids. All should receive lifestyle counseling; hypertension and hyperlipidemia should be treated according to current guidelines. Antihypertensive drugs that target vascular resistance may be beneficial.<sup>15</sup> Thiazide diuretics may ameliorate hypertension and may also lower osteoporosis risk by decreasing calcium excretion. However, thiazide diuretics can also cause hyperglycemia, among other side effects. There are no current guidelines for lipid monitoring in patients taking glucocorticoids. Evidence-based recommendations support baseline lipid screening; recommendations for repeat evaluation are less well established outside of transplant recipients. Frequency will vary based on the initial lipid profile, comorbidities, underlying disease state, dose, and duration of glucocorticoid exposure. In the absence of established guidelines, we suggest checking bimonthly lipid profiles in patients taking glucocorticoids chronically unless there is an indication for more frequent monitoring. Lipid-lowering medications should be prescribed in conjunction with a patient's primary care doctor.

## MYOPATHY

### Key points

- **The diagnosis of steroid myopathy is a clinical diagnosis based on characteristic symptoms without a more likely alternative diagnosis**
- **Higher doses of steroids for longer periods of time increase the risk**

- **Clinicians may need to taper glucocorticoid therapy to diagnose steroid myopathy definitively**

### Presentation

Glucocorticoid-induced myopathy presents with painless muscle weakness, followed by atrophy, starting in the proximal lower extremities and spreading to the proximal upper extremities and distal sites.<sup>16</sup> Patients may complain of progressive difficulty standing from a seated position, climbing stairs, and performing overhead activities.<sup>17</sup>

### Mechanism

A wide body of literature exists on the mechanism of glucocorticoid-induced myopathy. In brief, the effect of glucocorticoids on muscle is thought to be both catabolic and antianabolic, causing atrophy of type II muscle fibers through muscle proteolysis and decreased muscle protein synthesis.<sup>18</sup>

### Risk factors

The risk of developing steroid myopathy appears to increase with greater steroid dose and duration,<sup>19,20</sup> but wide variation is reported. In 1 study, prednisone doses of >40 mg per day significantly increased the risk.<sup>21</sup> Fluorinated synthetic steroids, such as dexamethasone, are associated with a greater risk of steroid myopathy than nonfluorinated steroids, such as prednisone and prednisolone.<sup>17</sup> The risk of steroid myopathy may be minimized with alternate day dosing.<sup>21</sup>

### Workup

The diagnosis of steroid myopathy is a clinical diagnosis. Creatinine kinase levels are normal, which helps distinguish steroid myopathy from underlying inflammatory muscle disease. Electromyography is typically unremarkable, with only mild changes in some individuals.<sup>17</sup> Serum markers, such as lactate dehydrogenase and aspartate aminotransferase, are also normal. The clinical utility of creatinuria, suggested in some studies as a marker for steroid myopathy, has been called into question.<sup>21,22</sup> Therefore, one must have a high index of suspicion for steroid myopathy in patients who experience weakness after the onset of glucocorticoid therapy or an increase in glucocorticoid dose. This possibility can be a source of confusion in patients receiving glucocorticoids for dermatomyositis and those taking steroids along with hydroxychloroquine, which can also cause myopathy.

**Management.** When steroid myopathy is suspected, glucocorticoids should be tapered safely, monitoring for a flare of the underlying inflammatory

condition and remaining vigilant for signs of adrenal insufficiency. Improved strength within 3 to 4 weeks helps establish the diagnosis of glucocorticoid myopathy.<sup>16</sup> Various medications, including creatine, androgens, potassium, and vitamins have been investigated for use in steroid myopathy; however, more research is needed before they can be recommended.<sup>17,18</sup> Clinicians may consider switching to nonfluorinated steroids, such as prednisolone or hydrocortisone. Referral to a physical therapist may be warranted.

## MOOD AND COGNITIVE EFFECTS

### Key points

- Glucocorticoids are associated with a range of psychiatric side effects that appear to be dose-dependent
- Clinicians should ask about a history of psychiatric disorders and comanage patients with a psychiatrist when appropriate

### General psychiatric symptoms

Glucocorticoids are associated with mood disorders, anxiety, depression, panic disorder, psychosis, delirium, confusion, and suicide, and they can produce cognitive deficits, especially related to memory.<sup>23,24</sup> These side effects appear to be dose-dependent. Reports suggest that the majority of patients taking moderate- to high-dose glucocorticoids (>10 mg/day, but more often >20 mg/day) will experience some degree of behavioral symptoms.<sup>25</sup> Short-term therapy, as for asthma exacerbation, may lead to hypomania. Euphoria or psychosis is more common with high doses. Depressive symptoms can occur with long-term therapy.<sup>25,26</sup> Previous neuropsychiatric disorders and larger daily doses of glucocorticoids are associated with a greater risk of these side effects.<sup>24</sup>

### Steroid psychosis

Steroid psychosis is a more serious complication that is marked by a range of symptoms, including psychosis, dementia, delirium, depression, and suicidality.<sup>27</sup> Doses <40 mg per day are unlikely to provoke severe psychiatric illness; however, doses >80 mg per day are significantly associated with these effects.<sup>28</sup> Onset of symptoms may occur within a few days to a few weeks of initiating therapy.<sup>27</sup> Symptoms may also arise during glucocorticoid taper.<sup>29</sup>

### Age and sex

In a large epidemiologic study involving >300,000 primary care patients exposed to glucocorticoids, age

**Table II.** Mood and cognitive effects

General recommendations before initiating glucocorticoid therapy
Ask about history of neuropsychiatric disease, paying special attention to any tendency toward self-harm
Consider ongoing mental health screening while taking glucocorticoids
Advise family members to contact clinicians with concern of any change in behavior
Insomnia
Dose glucocorticoids in the morning only, taper dose if possible
Consider low-dose sleep aid, depending on clinical situation
Depression/steroid mania/suicidality
Comanage patient with psychiatrist or primary care physician
Attempt glucocorticoid dose reduction, if possible
Monitor patients closely; urgent inpatient admission for suicidality or severe symptoms

and sex were risk factors for specific behavioral side effects. Women were more likely to develop depression, whereas men were more likely to develop mania.<sup>24</sup> The risk of depression, mania, delirium, confusion, and disorientation increases with age, but the opposite is true of suicidal behavior and panic disorder.<sup>24</sup> The incidence of neuropsychiatric events is highest in the first 3 months of therapy.

**Management.** Patients and their friends and family members should be cautioned about the potential for mood swings, insomnia, emotional lability, rapid speech, increased energy, and related symptoms (Table II). All patients, especially younger ones, should be asked about any history of neuropsychiatric disorders or suicidality before glucocorticoid initiation and during therapy. Clinicians should clearly ask about a history of self-harm and any thoughts or plans for self-harm. Those with histories as noted should be referred to primary care physicians or psychiatrists. Hospital admission should be considered if concern for suicidal thoughts or plans arises.

When patients experience psychiatric side effects, they should be referred promptly to a primary care provider or psychiatrist. Psychiatric symptoms may interfere with treatment of the underlying condition. Those experiencing sleep impairment should take glucocorticoids early in the day rather than in the evening. Dose reduction or tapering and discontinuation of steroids is advised if significant symptoms occur. When that cannot be accomplished because of the underlying condition, anxiolytics and

antidepressants may be prescribed. Expert assistance from mental health professionals is advised for patients who develop psychiatric side effects of glucocorticoid therapy, especially when complications are severe or glucocorticoid regimens cannot be tapered.

## SPECIAL CONSIDERATIONS IN THE PEDIATRIC PATIENT

### Key points

- There is significant overlap in the glucocorticoid complications seen in adult and pediatric populations
- Certain complications, such as cataracts, bone health, and growth suppression, impact the pediatric population more uniquely

### Cataracts

Children taking glucocorticoids may be more susceptible to developing cataracts compared to adults.<sup>30</sup> As such, they may require additional ophthalmologic screening. Physicians should take a careful family history of eye disease when initiating glucocorticoids in pediatric patients and refer them for baseline ophthalmologic examination. Children who experience delayed bone age and growth suppression from steroids are at increased risk of developing cataracts.<sup>30</sup>

### Growth suppression

Glucocorticoid therapy has repeatedly been shown to result in growth suppression among pediatric populations.<sup>31-36</sup> There are multiple mechanisms underlying this complication. Glucocorticoids inhibit bone formation, increase calcium excretion, promote bone resorption, and interfere with nitrogen and mineral balance.<sup>35</sup> In addition, glucocorticoids interfere with growth hormone secretion, growth hormone receptor expression, and growth hormone effect on target tissue.<sup>35</sup> Aside from growth suppression, pediatric bone health may be impacted by osteopenia, which can occur in children on glucocorticoids because of high bone turnover.<sup>37</sup>

Growth suppression is correlated with daily dose, duration, route of administration, and type of glucocorticoid prescribed.<sup>33,35</sup> Glucocorticoid exposure is highly correlated with reduction in growth velocity. Glucocorticoids with high systemic exposure, such as oral prednisolone, cause greater growth suppression than those without significant systemic exposure, such as intranasal fluticasone propionate.<sup>34</sup> The type of glucocorticoid also influences growth suppression because of differences in

half-life.<sup>35,36</sup> For example, prednisone, which has a longer half-life than hydrocortisone, carries a greater risk of growth suppression.<sup>35</sup> Glucocorticoids dosed at physiologic levels (according to some authors, hydrocortisone 12–15 mg/m<sup>2</sup>/day and others hydrocortisone as low as 6 mg/m<sup>2</sup>/day) and alternate-day therapy have been implicated in growth suppression, although the risk appears to be lower.<sup>31,33,35,38</sup> Children who experience growth suppression from glucocorticoid use may not catch up in height even after glucocorticoids are stopped.<sup>33,35,36</sup> Physicians must therefore attempt to wean glucocorticoids as soon as possible in pediatric patients and refer patients to a primary care provider for routine height measurement. Referral to a pediatric endocrinologist for assistance with management is highly recommended for any patient who requires ongoing or repeated doses of glucocorticoids for disease management.

### Diabetes

Physicians must also pay close attention to hyperglycemia and diabetes in pediatric patients who are taking glucocorticoids. These patients can develop medication-induced diabetes without having the same risk factors as children who develop type 2 diabetes. A retrospective study of risk factors for medication-induced diabetes among pediatric patients found that traditional risk factors, such as family history, race, obesity, and acanthosis nigricans, were less often present in medication-induced diabetes than in children with type 2 diabetes.<sup>39</sup> Physicians prescribing glucocorticoids to pediatric populations may therefore need to have a lower threshold to begin testing for and treating this complication.

### Adrenal suppression

Pediatric patients are also at risk for adrenal suppression. As in adults, the dose and duration of glucocorticoid therapy correlate with risk. A review of 59 pediatric patients with inflammatory bowel disease who were taking prednisolone at a median dose of 5 mg daily for 4.7 months found that 20% had adrenal suppression; the rate was higher in patients treated with higher doses and for longer duration.<sup>40</sup> A recent Cochrane review of the hypothalamic-pituitary axis function after glucocorticoid therapy for childhood acute lymphoblastic leukemia found that adrenal insufficiency commonly occurred after cessation of glucocorticoid therapy.<sup>41</sup> It is recommended that children on supraphysiologic doses of glucocorticoids for >2 weeks be considered at increased risk of adrenal suppression.<sup>42</sup> These patients should be weaned to doses that are less

than physiologic as soon as the underlying condition allows, or they can be considered for every other day dosing of glucocorticoids. Repeated short (<7-day) courses of oral steroids may also result in evidence of adrenal suppression by adrenocorticotrophic testing, but it is unclear if this is clinically relevant.<sup>43-45</sup>

In conclusion, side effects of glucocorticoid therapy are a significant source of morbidity and mortality. Managing these side effects requires concerted counseling, prophylaxis, and medication management. The evidence summarized here and in the accompanying tables is provided to help clinicians avoid and ameliorate these complications. Table I in the first article in this series is provided as a quick reference to the main points of discussion. Patients require careful instruction in order to anticipate these effects and alert clinicians to symptoms that may be vague and nonspecific. In this way, clinicians and patients can work together to limit the unintended harmful effects of glucocorticoids while seeking to maximize their therapeutic potential.

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# Psoriasis and comorbid diseases

## Epidemiology



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*See related articles on pages 393 and 531*

### Learning objectives

After completing this learning activity, participants should be able to list at least five comorbidities that are associated with psoriasis, and discuss the supporting evidence and identify psoriasis patients who have the greatest risk of developing cardiovascular disease.

### Disclosures

#### Editors

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Psoriasis is a common chronic inflammatory disease of the skin that is increasingly being recognized as a systemic inflammatory disorder. Psoriatic arthritis is a well-known comorbidity of psoriasis. A rapidly expanding body of literature in various populations and settings supports additional associations between psoriasis and cardiometabolic diseases, gastrointestinal diseases, kidney disease, malignancy, infection, and mood disorders. The pathogenesis of comorbid disease in patients with psoriasis remains unknown; however, shared inflammatory pathways, cellular mediators, genetic susceptibility, and common risk factors are hypothesized to be contributing elements. As additional psoriasis comorbidities continue to emerge, education of health care providers is essential to ensuring comprehensive medical care for patients with psoriasis. (J Am Acad Dermatol 2017;76:377-90.)

**Key words:** cardiovascular disease; chronic kidney disease; comorbidities; Crohn's disease; depression; metabolic syndrome; nonalcoholic fatty liver disease; psoriasis; psoriatic arthritis; lymphoma; infection.

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**Abbreviations used:**

BMI:	body mass index
BSA:	body surface area
CAD:	coronary artery disease
CD:	Crohn's disease
CEC:	cholesterol efflux capacity
CHD:	coronary heart disease
CKD:	chronic kidney disease
CTCL:	cutaneous T-cell lymphoma
CV:	cardiovascular
CVD:	cardiovascular disease
ESRD:	end-stage renal disease
FDG:	fluorodeoxyglucose
FRS:	Framingham Risk Score
HDL:	high-density lipoprotein
IBD:	inflammatory bowel disease
IHD:	ischemic heart disease
MACE:	major adverse cardiovascular events
MI:	myocardial infarction
NAFLD:	nonalcoholic fatty liver disease
NASH:	nonalcoholic steatohepatitis
NMSC:	nonmelanoma skin cancer
OR:	odds ratio
PET/CT:	positron emission tomography/computed tomography
PsA:	psoriatic arthritis
RA:	rheumatoid arthritis
RR:	relative risk or risk ratio
UC:	ulcerative colitis

**INTRODUCTION**

Psoriasis is a common chronic inflammatory disease that affects >7.5 million people in the United States and approximately 125 million people worldwide.<sup>1-3</sup> It has significant impacts on both physical and emotional health-related quality of life comparable to other major illnesses.<sup>4</sup> In the last decade, tremendous progress has been made in furthering our understanding of the genetics, pathophysiology, and treatment of psoriasis. Epidemiologic and basic scientific evidence contributing to our knowledge of the natural history and biology of psoriasis, respectively, have led to the recognition of psoriasis as a disorder with important health implications that extend beyond the skin.

The first observation of comorbid disease among patients with psoriasis was made in 1897 when Strauss<sup>5</sup> reported an association between psoriasis and diabetes. In 1961, Reed et al<sup>6</sup> described a high prevalence of heart disease including coronary thrombosis and myocardial infarction (MI) in postmortem examinations of psoriasis patients with psoriatic arthritis (PsA). Subsequently, in 1978, McDonald et al<sup>7</sup> observed an increased prevalence of venous and arterial vascular disease in hospitalized patients with psoriasis. Now many years later, a quickly evolving body of literature using modern epidemiologic techniques has shown that psoriasis, particularly severe disease, is associated with increased mortality<sup>8</sup> and comorbid disease burden<sup>9,10</sup>

that are hypothesized to be the result of chronic inflammation associated with the skin disease.

We review the epidemiologic data supporting associations between psoriasis and cardiometabolic diseases, gastrointestinal diseases, kidney disease, malignancy, infection, mood disorders, PsA, and other emerging comorbid diseases. Recognition of the comorbid disease burden associated with psoriasis is essential for comprehensive medical care for patients with this chronic skin disorder.

**CARDIOMETABOLIC DISEASE****Key points**

- **Cardiometabolic disease is prevalent among patients with psoriasis, especially those with more severe skin disease**
- **Psoriasis may be an independent risk factor for diabetes and major adverse cardiovascular events; the risk of a major adverse cardiovascular event is greatest among those with severe psoriasis**
- **Chronic systemic, specifically vascular, inflammation may be increased in patients with psoriasis and may contribute to atherogenesis**

**Major adverse cardiovascular events**

Cardiovascular (CV) risk factors are prevalent among patients with psoriasis, and therefore an increased risk of CV disease (CVD) may be expected. However, in 2006, a large, population-based cohort study in the United Kingdom found that psoriasis was associated with an increased risk of MI, independent of traditional risk factors, such as body mass index (BMI), smoking, hypertension, diabetes, and dyslipidemia.<sup>11</sup> Moreover, a dose-response effect was shown, with stronger, more clinically significant risk in patients with more severe disease as defined by receipt of phototherapy or systemic therapies indicated for severe psoriasis. Subsequently, numerous epidemiologic studies have similarly suggested psoriasis to be an independent risk factor for MI, stroke, and death caused by CVD, collectively termed major adverse cardiovascular events (MACE). While a few studies have reported non-statistically significant associations between psoriasis and MACE,<sup>12-15</sup> as discussed in detail elsewhere,<sup>16-18</sup> results from these studies remain consistent with the larger body of work that have found statistically significant associations. To date, many of the studies have been summarized in ≥1 of 8 meta-analyses of psoriasis and CVD (Table 1).<sup>19-26</sup> Two meta-analyses<sup>19,25</sup> specifically examined the risks of MI, stroke, and CV mortality according to psoriasis severity and reported the greatest risks to be among those with severe disease. Risk of MI among patients

with mild psoriasis was found to be significantly increased in both meta-analyses,<sup>19,25</sup> albeit to a lesser extent, suggesting that CV risk is not limited to those with severe disease. Longer duration of psoriasis has also been associated with increased risk of CVD.<sup>27,28</sup> Collectively, these data provide evidence for psoriasis as an independent risk factor for CVD.

Additional analyses have identified the clinical importance of and provided practical measures for the increased risk of MACE associated with psoriasis.<sup>29,30</sup> In a cohort study of severe psoriasis patients in the United Kingdom, Mehta et al<sup>29</sup> found the attributable risk of severe psoriasis on MACE over a 10-year period to be 6.2%. Importantly, in a study to determine the impact of psoriasis on the Framingham Risk Score (FRS), adding psoriasis to the FRS resulted in reclassification of a majority of patients to a higher CV risk category whereby 73% of patients at low risk were reclassified as intermediate risk and 53% of patients at intermediate risk were reclassified as high risk.<sup>31</sup> Putting the psoriasis-associated CV risk into context with other chronic inflammatory diseases, Ahlehoff et al<sup>30</sup> found the increased risk of MACE associated with severe psoriasis to be nearly identical to that conferred by diabetes alone. Similarly, a single observational study of patients with either rheumatoid arthritis (RA) or psoriasis suggests that patients treated with similar systemic treatments (eg, methotrexate) each have similarly elevated risks of MACE, independent of traditional risk factors.<sup>32</sup>

Shared pathophysiologic pathways between psoriasis and CVD, including chronic type 1 helper ( $T_{H}1$ ) T cell- and  $T_{H}17$ -mediated inflammation,<sup>33-38</sup> monocyte and neutrophil modulation,<sup>39-41</sup> increased oxidative stress,<sup>35</sup> endothelial cell dysfunction,<sup>42</sup> increased uric acid,<sup>43,44</sup> angiogenesis,<sup>35</sup> and increased circulating microparticles<sup>45-48</sup> may explain the increased CVD risk associated with psoriasis. In addition, persistent pathophysiologic processes that drive psoriasis (eg, epidermal hyperproliferation, inflammation,<sup>49,50</sup> and angiogenesis) may also exert pleiotropic adverse effects on the CV system that contribute to atherogenesis. Mouse models of psoriasis have shown that chronic skin-specific inflammation has systemic effects, including arterial hypertension,<sup>51</sup> endothelial dysfunction,<sup>51</sup> and vascular inflammation and thrombosis.<sup>38</sup> Studies in psoriasis patients yield similarly consistent findings using [ $^{18}\text{F}$ ]-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), a sensitive tool for measuring vascular inflammation and visualizing macrophage activity *in vivo*. Aortic inflammation measured by PET/CT is a predictor of future CV events and has been shown

to rapidly decrease when patients are exposed to interventions known to lower CV risk (ie, statin therapy), making it an attractive surrogate endpoint to study.<sup>52</sup> Aortic inflammation has been observed to be increased in psoriasis patients in a manner that is independent of CV risk factors and correlates with severity of skin disease,<sup>53</sup> lending further support to the idea that inflammatory pathways in psoriasis exert systemic effects. Lastly, common genetics between psoriasis, diabetes, and CVD, such as CDKAL1, ApoE4, and others, have been suggested,<sup>54-64</sup> and genes relevant to metabolic disease and CVD have been found to be dysregulated in lesional skin and in the serum of psoriasis patients.<sup>64-66</sup> On the other hand, other work suggests that shared genetic pathways are unlikely to explain the association between psoriasis and CVD.<sup>67</sup>

## Obesity

Obesity is an independent risk factor for psoriasis. In studies of incident psoriasis,<sup>68-70</sup> the risk of psoriasis was found to increase with higher BMI.<sup>69</sup> A meta-analysis of 16 observational studies found a pooled odds ratio (OR) for the association between psoriasis and obesity to be 1.66 (95% confidence interval [CI], 1.46-1.89; Table II).<sup>71</sup> Among studies that accounted for psoriasis severity, generally defined by treatment patterns, the pooled ORs for the association between obesity and mild and severe psoriasis were 1.46 (95% CI, 1.17-1.82) and 2.23 (95% CI, 1.63-3.05), respectively. As further support for a relationship between psoriasis severity and obesity, Langan et al<sup>72</sup> performed a cross-sectional study of patients with psoriasis in the United Kingdom for whom information on body surface area (BSA) involvement by psoriasis was available and found a positive dose-dependent relationship between objective measures of psoriasis severity and obesity.<sup>72</sup>

## Hypertension

Hypertension is more prevalent among patients with versus without psoriasis. A meta-analysis of 24 observational studies found a pooled OR for the association between psoriasis and hypertension to be 1.58 (95% CI, 1.42-1.76).<sup>73</sup> The odds of hypertension among patients with psoriasis increased with greater disease severity with ORs of 1.30 (95% CI, 1.15-1.47) for mild and 1.49 (95% CI, 1.20-1.86) for severe psoriasis as defined by treatment patterns.<sup>42</sup> Two cohort studies also observed psoriasis to be associated with an increased risk of incident hypertension.<sup>74,75</sup>

Importantly, studies of patients with hypertension suggest more severe hypertension and poorly controlled blood pressure among patients with

**Table I.** Summary of systematic reviews and meta-analyses assessing the association between psoriasis and major adverse cardiovascular events

Study	Study dates	No. of studies	Total no. of patients		Outcome	Composite measure of association (95% CI)
			Psoriasis	No psoriasis		
Armstrong et al <sup>19</sup> (2013)	January 1, 1980 to January 1, 2012	9	Mild: 201,239 Severe: 17,415	9,914,799	MACE: MI, stroke, and CV mortality	MI Mild psoriasis: RR 1.29 (1.02-1.63) Severe psoriasis: RR 1.70 (1.32-2.18)
					Stroke	Mild psoriasis: RR 1.12 (1.08-1.16) Severe psoriasis: RR 1.56 (1.32-1.84)
					CV mortality	Mild psoriasis: RR 1.03 (0.86-1.25) Severe psoriasis: RR 1.39 (1.11-1.74)
Gaeta et al <sup>20</sup> (2013)	NR	13	1,862,297	43,407,300	CV risk: MI, vascular disease, and mortality	Overall CV risk RR 1.24 (1.18-1.31) MI RR 1.24 (1.11-1.39) Vascular disease RR 1.27 (1.12-1.43) Mortality RR 1.41 (0.97-2.04)
Gu et al <sup>21</sup> (2013)	1966 to October 2012	15	Total (psoriasis + no psoriasis): 6,230,774		MI, stroke, CVD, and CV mortality	MI RR 1.32 (1.13-1.55) Stroke RR 1.26 (1.12-1.41) CVD RR 1.47 (1.30-1.60) CV mortality RR 1.33 (1.00-1.77)
Horreau et al <sup>22</sup> (2013)	1980 to December 211	33	324,650	5,309,087	MI, CAD, and stroke	MI RR—cohort: 1.25 (1.03-1.52); cross-sectional: 1.57 (1.08-2.27) CAD RR—cohort: 1.20 (1.13-1.27); case-control: 1.84 (1.09-3.09); cross-sectional: 1.19 (1.14-1.24) Stroke Cohort: 1.02 (0.92-1.14); cross-sectional: 1.14 (1.08-1.19)

Miller et al <sup>23</sup> (2013)*	Before October 25, 2012	75	503,686	29,686,694	CVD, IHD, cerebrovascular disease, and CV mortality	CVD OR 1.4 (1.2-1.7) IHD OR 1.5 (1.2-1.9) Cerebrovascular disease 1.1 (0.9-1.3) CV mortality 0.9 (0.4-2.2)
Pietrzak et al <sup>24</sup> (2013)	1960 to 2011	14	367,358	9,199,656	CV events: MI, IHD, cerebral ischemic stroke, and sudden cardiac death	OR 1.28 (1.18-1.38)
Samarasekera et al <sup>25</sup> (2013)	1974 to 2012	14	All: 488,315 Mild: 327,418 Severe: 12,854	10,024,815	MI, stroke, and CV mortality	MI All psoriasis: HR/IRR 1.40 (1.03-1.89) Stroke All psoriasis: HR/IRR 1.13 (1.01-1.26) CV mortality All psoriasis: NR Mild psoriasis: HR/IRR 1.34 (1.07-1.68) Severe psoriasis: HR/IRR 3.04 (0.65-14.35) Mild psoriasis: HR/IRR 1.15 (0.98-1.35) Severe psoriasis: HR/IRR 1.59 (1.34-1.89) CV mortality Mild psoriasis: SMR 1.03 (0.86-1.25) Severe psoriasis: SMR 1.37 (1.17-1.60); HR 1.57 (1.26-1.96)
Xu et al <sup>26</sup> (2012)	Database inception to March 2012	7	326,598	5,230,048	Composite of MI and stroke	Composite RR 1.20 (1.10-1.31) MI RR 1.22 (1.05-1.42) Stroke RR 1.21 (1.04-1.40)

CAD, Coronary artery disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; IHD, ischemic heart disease; IRR, incidence rate ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; OR, odds ratio; RR, relative risk or risk ratio.

\*Systematic review and meta-analysis of the association between psoriasis and CVD and cardiovascular risk factors. Total numbers of studies and patients included are as reported in the full systematic review and meta-analysis, a subset of which is specifically relevant to psoriasis and CVD.

**Table II.** Summary of systematic reviews and meta-analyses assessing the association between psoriasis and cardiovascular disease risk factors

Study	Study dates	Total no. of patients		No. of studies included	CV risk factor	Composite measure of association (95% CI)
		Psoriasis	No psoriasis			
Armstrong et al <sup>71</sup> (2012)	January 1, 1980 to January 1, 2012	201,831	2,119,329	Total: 16 Severity assessment: 5 Incidence: 1	Obesity	Overall: OR 1.66 (1.46-1.89); mild: OR 1.46 (1.17-1.82); severe: OR 2.23 (1.63-3.05); incidence: HR 1.18 (1.14-1.23)
Armstrong et al <sup>73</sup> (2012)	January 1, 1980 to January 1, 2012	309,469	2,384,229	Total: 24 Severity assessment: 5 Incidence: 2	Hypertension	Overall: OR 1.58 (1.42-1.76); mild: OR 1.30 (1.15-1.47); severe: OR 1.49 (1.20-1.86); incidence: HR 1.09 (1.05-1.14); incidence: RR 1.17 (1.06-1.30)
Armstrong et al <sup>78</sup> (2012)	January 1, 1980 to January 1, 2012	404,494	4,640,847	Total: 27 Severity assessment: 5 Incidence: 5	Diabetes	Overall: OR 1.59 (1.38-1.83); mild: OR 1.53 (1.16-2.04); severe: OR 1.97 (1.48-2.62); incidence: RR 1.27 (1.16-1.40)
Ma et al <sup>81</sup> (2012) <sup>†</sup>	January 1, 1980 to January 1, 2012	265,685	2,167,198	Total: 25 Severity assessment: 5 Incidence: 1	Dyslipidemia	Overall OR: 1.04-5.55; mild OR: 1.10-3.38; severe OR: 1.26-5.55
Armstrong et al <sup>89</sup> (2013)	January 1, 1980 to January 1, 2012	41,853	1,357,324	Total: 12 Severity assessment: 3	Metabolic syndrome	Overall OR: 2.26 (1.70-3.01); mild OR: 1.22 (1.11-1.35)*; moderate OR: 1.56 (1.38-1.76)*; severe OR: 1.98 (1.62-2.43)*

CI, Confidence interval; CV, cardiovascular; HR, hazard ratio; OR, odds ratio; RR, relative risk.

\*Reported from single study by Langan et al.<sup>72</sup>

<sup>†</sup>Systematic review only.

psoriasis compared with those without psoriasis.<sup>76,77</sup> In addition, the likelihood of poorly controlled hypertension appears to increase with more severe skin disease, independent of BMI and other risk factors.<sup>77</sup>

## Diabetes

Psoriasis is associated with an increased risk of diabetes, independent of traditional risk factors. A meta-analysis of 5 cohort studies assessing the risk of incident diabetes among patients with psoriasis found a pooled relative risk (RR) for diabetes of 1.27 (95% CI, 1.16-1.40).<sup>78</sup> The risk of diabetes and likelihood of insulin resistance and diabetic complications are suggested to increase with greater psoriasis severity as defined by treatment patterns or BSA affected, respectively, independent of traditional risk factors, such as BMI.<sup>9,72,79</sup> Moreover, diabetic patients with psoriasis appear to be more likely to require pharmacologic management<sup>79</sup> and suffer from micro- and macrovascular diabetes complications than diabetic patients without psoriasis.<sup>80</sup>

## Dyslipidemia

Dyslipidemia may be more prevalent among patients with than without psoriasis. In a systematic review, 20 of 25 included studies found significant associations between psoriasis and dyslipidemia, with ORs ranging from 1.04 to 5.55.<sup>81</sup> Among 3 of the studies included in the systematic review, the ORs for dyslipidemia ranged from 1.10 to 3.38 for patients with mild psoriasis and from 1.36 to 5.55 for patients with severe psoriasis. The directionality of the association between the 2 conditions remains unclear; some studies suggest dyslipidemia may be a risk factor for developing psoriasis.<sup>82,83</sup>

Advanced lipid testing techniques have shown a more atherogenic lipid profile and decreased high density lipoprotein (HDL) cholesterol efflux capacity (CEC) among patients with versus without psoriasis, beyond CV risk factors.<sup>84,85</sup> Increasing psoriasis severity is negatively correlated with HDL CEC in both adults and children with psoriasis.<sup>85,86</sup> HDL CEC is also directly related to coronary artery disease burden in patients with psoriasis<sup>87</sup> and is suggested to be an important proxy for vascular disease.

## Metabolic syndrome

Metabolic syndrome is generally defined by the presence of a combination of central obesity, hypertension, insulin resistance, and dyslipidemia.<sup>88</sup> Studies have found metabolic syndrome and its individual components to be more prevalent among patients with than without psoriasis in both adult and pediatric populations.<sup>89,90</sup> A meta-analysis of 12 observational

studies found a pooled OR of 2.26 (95% CI, 1.70-3.01) for the association between psoriasis and metabolic syndrome, but the analysis was limited by the presence of publication bias due to an absence of smaller studies in the published literature.<sup>89</sup> Importantly, in Langan et al's cross-sectional study<sup>72</sup> in the United Kingdom, the prevalence of metabolic syndrome correlated directly with BSA affected by psoriasis.

## GASTROINTESTINAL DISEASE

### Key points

- Psoriasis may be associated with an increased incidence and prevalence of inflammatory bowel disease, particularly Crohn's disease
- Few studies suggest that psoriasis is associated with an increased prevalence of hepatic diseases, particularly nonalcoholic fatty liver disease

## Inflammatory bowel disease

Common genetic and inflammatory pathways have been implicated in psoriasis and IBD, which includes Crohn's disease (CD) and ulcerative colitis (UC).<sup>59,91-94</sup> The epidemiology of this relationship remains poorly defined. Several studies have observed increased prevalence and incidence of IBD among patients with psoriasis<sup>95,96</sup> and vice versa,<sup>97-99</sup> with varying degrees of association, and a Taiwanese study suggested an absence of association.<sup>100</sup> Cohen et al<sup>95</sup> observed that psoriasis may be more strongly associated with CD than UC (ORs 2.49 [95% CI, 1.71-3.62] and 1.64 [95% CI, 1.15-2.23], respectively). Similarly, a cohort study of US women found an increased risk of CD among patients with psoriasis (RR, 3.86 [95% CI, 2.23-6.67]), while the risk of UC was attenuated and not statistically significant (RR, 1.17 [95% CI, 0.41-3.36]).<sup>96</sup>

## Hepatic disease

Nonalcoholic fatty liver disease (NAFLD) is a common chronic liver disease in Western industrialized countries<sup>100</sup> and encompasses a spectrum of liver disorders from mild hepatic steatosis to nonalcoholic steatohepatitis (NASH). Associations between psoriasis and NAFLD have been reported in the literature. In a meta-analysis of 7 observational studies that were considered low to moderate quality and, for the most part, did not adjust for potential confounding factors, such as metabolic syndrome, NAFLD was found to be more prevalent among patients with versus without psoriasis (pooled OR, 2.15 [95% CI, 1.57-2.94]).<sup>101</sup> Beyond NAFLD, a cross-sectional study in the United Kingdom found that psoriasis was associated with a higher prevalence of

“mild” liver disease, including chronic hepatitis, alcoholic liver disease, and NAFLD (OR, 1.41 [95% CI, 1.12-1.76]).<sup>9</sup> A positive dose-response relationship between psoriasis severity based on BSA involvement and “mild” liver disease was also seen.

## CHRONIC KIDNEY DISEASE

### Key points

- Moderate to severe psoriasis may be an independent risk factor for chronic kidney disease and end-stage renal disease
- The odds of chronic kidney disease increase in a dose-dependent manner with greater psoriasis severity

The term “psoriatic nephropathy” was first introduced based on case reports of glomerulonephritides in patients with psoriasis.<sup>102</sup> Until recently, most studies assessing the association between psoriasis and kidney disease have been small and cross-sectional, with varying results. In a UK cohort study of cause-specific mortality among patients with psoriasis, severe psoriasis was associated with a 4-fold increased risk of death from nephritic or nonhypertensive kidney disease.<sup>103</sup> A Swedish cohort study also found mild psoriasis to be associated with more than a 2-fold increased risk of death from kidney disease.<sup>104</sup> In 2013, another UK cohort study found that severe psoriasis may, in fact, be a risk factor for chronic kidney disease (CKD) and end-stage renal disease (ESRD), independent of traditional risk factors, such as age, sex, BMI, CVD, diabetes, hypertension, hyperlipidemia, and nephrotoxic medications (hazard ratio [HR] for CKD 1.93 [95% CI, 1.79-2.08]; HR for ESRD, 4.15 [95% CI, 1.70-10.11]).<sup>105</sup> A nested cross-sectional analysis of patients with psoriasis for whom information on BSA involvement was available found the prevalence of CKD to increase in a dose-dependent manner with more severe psoriasis. A cohort study in Taiwan similarly found severe psoriasis to be associated with nearly 2- and 3-fold increased risks of CKD and ESRD, respectively.<sup>106</sup>

## MALIGNANCY

### Key points

- Psoriasis, particularly severe disease, may be associated with an increased risk of cancer
- Lymphoma has been most consistently associated with psoriasis, and risk of cutaneous T-cell lymphoma is suggested to be the highest

Patients receiving treatments for severe psoriasis have a 41% increased risk of dying from malignancy

than patients without psoriasis.<sup>103</sup> Risk of malignancy attributable to psoriasis itself remains uncertain. A meta-analysis of 11 observational studies evaluating the risk of malignancy among patients with psoriasis suggested that overall risk of cancer, excluding nonmelanoma skin cancers (NMSCs), is increased (standardized incidence ratio, 1.16 [95% CI, 1.07-1.25]).<sup>107</sup> Greater risks of upper aerodigestive tract, respiratory tract, liver, pancreas, urinary tract cancers, and lymphoma were also suggested.<sup>107</sup> The level of heterogeneity among the included studies was high, making interpretation challenging. In addition, many studies did not account for important confounding factors, such as smoking and drinking, or assess psoriasis treatment effects on the risk of subsequent malignancy, calling into question the validity of attributing the increased risk of cancer to psoriasis alone. A subsequent cohort study of cancer risk among patients with psoriasis in the United Kingdom that included information on BMI, smoking, and drinking also found increased risks of lung cancer, NMSC, and lymphoma, supporting some of Pouplard et al's findings.<sup>108</sup> The greatest risks of cancer were among those receiving treatments for severe psoriasis. The association between psoriasis and lung cancer was lost, however, after stratification by smoking status. Additional studies<sup>109-111</sup> assessing lymphoma risk in patients with psoriasis also found persistently increased risks of lymphoma (1.3- to 2-fold increased risk) even among those without a history of immunosuppressive therapy, although absolute risks remained low. Of the specific lymphoma types, the association between psoriasis and cutaneous T-cell lymphoma (CTCL) was suggested to be the strongest.<sup>108,111</sup> It remains unclear what role psoriasis therapies or misdiagnosis of CTCL as psoriasis may play in explaining this observation.

## INFECTION

### Key points

- Streptococcal pharyngitis is a trigger of guttate psoriasis, and exacerbation of psoriasis in the setting of HIV infection is known
- Psoriasis may be associated with an increased risk of serious infection (ie, infection requiring hospitalization), especially respiratory infections

Infection is the second-leading cause of excess death among patients who are receiving therapies for severe psoriasis, and patients with severe psoriasis have a 65% increased risk of dying from infection than patients without psoriasis.<sup>103</sup> With the advent of targeted biologic therapies, much attention has been

paid to measuring the risk of infection associated with these therapies for psoriasis. However, infection risk attributable to psoriasis itself remains poorly understood. The most well-recognized association between psoriasis and infection is that of guttate psoriasis and streptococcal pharyngitis, which is thought to be caused by molecular mimicry between streptococcal M peptides and human keratins.<sup>112,113</sup> Exacerbation of psoriasis in the setting of HIV infection has also been documented.<sup>114,115</sup> The risk of serious infection among patients with psoriasis has only more recently been evaluated.<sup>116,117</sup> A Dutch cohort study found psoriasis to be independently associated with an increased risk of serious infection (HR, 1.54 [95% CI, 1.44-1.65]) whereby the greatest risk was among patients with severe psoriasis as defined by treatment patterns (HR, 1.81 [95% CI, 1.57-2.08]).<sup>116</sup> Respiratory tract, abdominal, and skin infections were the most common infections among patients with psoriasis. Similarly, a cohort study in Taiwan reported an increased risk of hospitalized pneumonia among patients with psoriasis, independent of other potential risk factors for pneumonia (HR, 1.40 [95% CI, 1.12-1.73]). Severe psoriasis was associated with the greatest risk of hospitalized pneumonia (HR, 1.68 [95% CI, 1.12-2.52]).<sup>117</sup> While neither study had access to information on potential confounders, such as obesity, smoking, and drinking, subsequent cohort studies in the United Kingdom that included this information confirmed that psoriasis is associated with an increased risk of serious infection<sup>118</sup> including hospitalized pneumonia,<sup>119</sup> and further suggested that this risk may increase with greater BSA involvement by psoriasis.

## MOOD DISORDERS

### Key points

- Mood disorders are common among patients with psoriasis
- Psoriasis is associated with an increased risk of depression, anxiety, and suicidal ideation

Psoriasis has a major impact on patients' physical and emotional health-related quality of life comparable to other major illnesses,<sup>4</sup> and this may predispose patients to the development of mood disorders, such as depression, anxiety, and suicidality. Mood disorders, particularly depression, have been suggested to be more prevalent in patients with psoriasis than in the general population (up to 62% prevalence).<sup>120</sup> In a meta-analysis of 98 mostly cross-sectional studies examining the association between psoriasis and depression, patients with psoriasis had more depressive symptoms (pooled standardized mean difference, 1.16 [95% CI, 0.67-1.66]) and were

nearly 1.6-fold more likely to experience depression (pooled OR, 1.57 [95% CI, 1.40-1.76]) than patients without psoriasis.<sup>120</sup>

The risk of depression in psoriasis has been evaluated in 2 cohort studies. In a UK study, psoriasis was found to be associated with increased risks of depression (HR, 1.39 [95% CI, 1.37-1.41]), anxiety (HR, 1.31 [95% CI, 1.29-1.34]), and suicidality (HR, 1.44 [95% CI, 1.32-1.57]).<sup>121</sup> The risk of depression was greatest among patients who were receiving therapies for severe psoriasis (HR, 1.72 [95% CI, 1.57-1.88]). Similarly, a study of women in the Nurses' Health Study<sup>122</sup> found psoriasis to be associated with a nearly 30% increased risk of depression (RR, 1.29 [95% CI, 1.10-1.52]), independent of age, BMI, lifestyle factors, and comorbid conditions.

## PSORIATIC ARTHRITIS

### Key points

- Psoriatic arthritis is an inflammatory arthritis that is present in 6% to 42% of patients with psoriasis
- Psoriatic arthritis is more prevalent among patients with more extensive skin disease
- Approximately 15% of patients with psoriasis have undiagnosed psoriatic arthritis

Psoriatic arthritis (PsA) is the most well-recognized comorbidity of psoriasis and is a heterogeneous inflammatory arthritis characterized by joint or enthesal inflammation and extra-articular manifestations.<sup>123</sup> The prevalence of inflammatory arthritis in patients with psoriasis ranges from 6% to 42% depending on the definitions used and populations studied.<sup>124-137</sup> The prevalence of PsA increases with greater psoriasis severity<sup>124,132,138</sup> and duration<sup>124,139</sup>; however, the severity of skin disease is only weakly associated with severity of joint disease. PsA has been associated with the distribution of psoriasis involvement (ie, scalp, intergluteal, and perianal)<sup>140</sup> and the presence of nail dystrophy, which is suggested to indicate early enthesal inflammation.<sup>123,140,141</sup>

The diagnosis of PsA can be especially challenging. The differential diagnosis includes osteoarthritis, RA, crystal arthropathy (eg, gout or calcium pyrophosphate disease), and fibromyalgia.<sup>123,142-146</sup> Undiagnosed PsA among patients with psoriasis seen in the dermatology setting is prevalent and estimated at 15.5%.<sup>147</sup> PsA generally occurs after the onset of psoriasis<sup>141,147</sup> and can be progressive and result in permanent joint damage. Therefore, early detection is essential because early treatment improves outcomes.<sup>123,148,149</sup> The varied clinical features of and classification criteria for PsA

and its associations with cardiometabolic and other comorbid diseases are reviewed elsewhere.<sup>123,150</sup>

## EMERGING COMORBIDITIES

### Key point

- Other emerging comorbidities of psoriasis include chronic obstructive pulmonary disease, peptic ulcer disease, sexual dysfunction, and obstructive sleep apnea

Additional epidemiologic studies have suggested associations between psoriasis and other emerging comorbid conditions, including chronic obstructive pulmonary disease,<sup>9,151,152</sup> peptic ulcer disease,<sup>9,153</sup> sexual dysfunction,<sup>154</sup> and obstructive sleep apnea,<sup>155-157</sup> among others. Further characterization of known comorbidities and identification of new comorbid disease associations with psoriasis are anticipated as research efforts continue.

In summary, it is essential for both clinicians and patients to recognize the potentially heightened risk of CVD and other comorbidities associated with psoriasis that may increase with greater disease severity and duration. Particularly as psoriasis remains largely undertreated,<sup>158,159</sup> the disease remains active for decades in most patients, potentially placing them at increased risk for associated comorbidities and mortality. Patient and provider education and increased awareness of psoriasis comorbidities are critical to improving the care and quality of life for those living with psoriasis.

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# Psoriasis and comorbid diseases

## Implications for management



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### Learning objectives

After completing this learning activity, participants should be able to determine psoriasis treatment options for patients who also have significant cardiovascular risk factors, such as obesity and/or diabetes; provide appropriate screening for psoriasis patients according to recommended guidelines; and identify optimal treatment regimens for patients with moderate to severe psoriasis and associated cardiovascular, infectious, or rheumatologic comorbidities.

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As summarized in the first article in this continuing medical education series, the currently available epidemiologic data suggest that psoriasis may be a risk factor for cardiometabolic disease. Emerging data also suggest associations between psoriasis and other comorbidities beyond psoriatic arthritis, including chronic kidney disease, inflammatory bowel disease, hepatic disease, certain malignancies, infections, and mood disorders. Recognizing the comorbid disease burden of psoriasis is essential for ensuring comprehensive care of patients with psoriasis. The clinical implications of the comorbid diseases that are associated with psoriasis and recommendations for clinical management are reviewed in this article. (*J Am Acad Dermatol* 2017;76:393–403.)

**Key words:** cardiovascular disease; chronic kidney disease; comorbidities; Crohn's disease; depression; infection; lymphoma; metabolic syndrome; nonalcoholic fatty liver disease; psoriasis; psoriatic arthritis; screening; vaccination.

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**Abbreviations used:**

BMI:	body mass index
BSA:	body surface area
CD:	Crohn's disease
CDC:	Centers for Disease Control and Prevention
CIRT:	Cardiovascular Inflammation Reduction Trial
CTCL:	cutaneous T-cell lymphoma
CV:	cardiovascular
CVD:	cardiovascular disease
FDA:	US Food and Drug Administration
IBD:	inflammatory bowel disease
IL:	interleukin
MACE:	major adverse cardiovascular events
NAFLD:	nonalcoholic fatty liver disease
NMSC:	nonmelanoma skin cancer
PASI:	Psoriasis Area and Severity Index
PUVA:	psoralen plus ultraviolet A light phototherapy
RA:	rheumatoid arthritis
RCT:	randomized controlled trial
TB:	tuberculosis
TNF:	tumor necrosis factor
UC:	ulcerative colitis

**CARDIOMETABOLIC DISEASE****Key points**

- Patients with psoriasis are underscreened and undertreated for cardiovascular risk factors
- At a minimum, patients with psoriasis should be screened for cardiovascular risk factors according to recommendations for the general adult population
- Observational data suggest that treatment with methotrexate or tumor necrosis factor inhibitors is associated with a decrease in cardiovascular events; however, data from randomized controlled trials are not yet available, and data for other psoriasis therapies are lacking

In spite of the evidence supporting an increased prevalence of cardiovascular (CV) risk factors and increased risks of CV disease (CVD) and mortality among patients with psoriasis, data suggest that patients are inadequately screened and undertreated for CV risk factors.<sup>1-5</sup> For example, in a cross-sectional study of National Ambulatory Medical Care Survey data from 2005 to 2009, only 41% of patients with psoriasis versus 66% of those without psoriasis were screened for ≥1 CV risk factor (ie, blood pressure, glucose, cholesterol, or body mass index [BMI]).<sup>4</sup> Specifically among dermatologists, screening for CV risk factors was infrequent (blood pressure, 2.6%; glucose, 1.2%; cholesterol, 4.3%; and BMI, 9.7%). Similarly, a 2015 survey of 127 US dermatologists revealed that <50% screened for

hypertension, dyslipidemia, or diabetes in patients with psoriasis.<sup>5</sup> In addition, in a cross-sectional study of patients with hypertension in the United Kingdom, patients with psoriasis were more likely to have uncontrolled hypertension compared with patients without psoriasis.<sup>3</sup> Together, these data highlight an important health care systems gap in screening for and treating CV risk factors among patients with psoriasis. Therefore, as recommended by clinical practice guidelines,<sup>6,7</sup> dermatologists should, at a minimum, advise patients with moderate to severe psoriasis of their possible increased risk of CVD and recommend that they see their primary care physician for appropriate medical screenings and assessment.

**Major adverse cardiovascular events**

Screening for CV risk factors among patients with psoriasis, particularly those with more severe disease, is essential to minimizing risk of major adverse cardiovascular events (MACE). Screening and management of CV risk factors in patients with psoriasis should, at a minimum, follow recommendations for the general adult population (level of evidence, IB).<sup>6-8</sup> In addition, lifestyle interventions, such as weight loss and smoking cessation, should be encouraged among psoriasis patients who are obese and who are current smokers, respectively (level of evidence, IB). According to the American College of Cardiology and American Heart Association guidelines, CV risk assessment should include evaluation of traditional risk factors every 4 to 6 years among persons 20 to 79 years of age and estimation of 10-year CVD risk among those 40 to 79 years of age (Table I).<sup>9</sup>

Important questions that remain unanswered include what the particular CV risk factor treatment goals should be for psoriasis patients and whether the presence of psoriasis alone warrants different or more aggressive screening and management strategies for CV risk factors compared with the general population. Mehta et al's study<sup>10</sup> of the impact of psoriasis on the Framingham Risk Score found that the addition of psoriasis warranted a change in CV risk factor treatment plans and goals for >60% of patients.<sup>10</sup> Therefore, psoriasis itself—especially severe disease—may indeed necessitate clinically significant changes in prevention and treatment goals for CV risk factors in a similar manner to what has been recommended by the European League Against Rheumatism for patients with rheumatoid arthritis (RA).<sup>11</sup>

Critically, it remains unknown if successful treatment of psoriasis will lower the risk of future CV events. The treatment of psoriasis is currently

**Table I.** American College of Cardiology/American Heart Association guidelines for assessing cardiovascular disease risk factors\*

Age, y	Recommendation	Frequency	Level of evidence
20-79	Check traditional risk factors <sup>†</sup>	Every 4-6 y	IB
40-79	Estimate 10-year risk for Atherosclerotic Cardiovascular Disease <sup>‡</sup> using Pooled Cohort Equations <sup>§</sup>	Every 4-6 y	IB

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

\*Data from Goff et al.<sup>9</sup>

<sup>†</sup>Age, sex, total and high-density lipoprotein cholesterol, systolic blood pressure, use of antihypertensive therapy, diabetes, and current smoking.

<sup>‡</sup>Defined as nonfatal myocardial infarction, coronary heart disease death, and nonfatal and fatal stroke.

<sup>§</sup>Pooled cohort equation for estimating risk takes the following variables into account: sex, race, age, treated or untreated systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, current smoking status, and history of diabetes.

considered to be elective, and systemic treatments are reserved for patients with severe disease that is physically or psychologically disabling to the patient. As a result, the overwhelming majority of patients, even with objectively severe psoriasis, do not receive adequate treatment to control their skin disease.<sup>12-14</sup> This view of psoriasis may be similar to that of hypertension in the 1960s when treatment was considered elective and potentially harmful in the elderly until randomized controlled trials (RCTs) showed improved CV outcomes and decreased mortality among those receiving antihypertensive therapy.<sup>15,16</sup> Unlike hypertension, there are currently no RCTs to prove that psoriasis therapies lower the risk of CVD. Meta-analyses of observational studies suggest that methotrexate and tumor necrosis factor (TNF) inhibitors may lower the risk of CV events in patients with RA.<sup>17-19</sup> Similarly, emerging data from observational studies of psoriasis suggest that methotrexate and TNF inhibitors may lower the risk of CV events in patients with psoriasis<sup>20-22</sup>; however not all studies have observed a protective effect,<sup>23,24</sup> and the observational nature of the studies limits the conclusions that can be drawn. Mixed results from studies of psoriasis therapy effects on the risk of CV events, which have also been observed in the RA population, may be related to differences in study design, uses of different comparator groups, and misclassification of treatment status, and they highlight the need for RCTs to better address this question.<sup>25</sup> Therefore, RCTs evaluating the effects of psoriasis therapy on CVD using rigorous surrogate markers, such as vascular inflammation<sup>26,27</sup> and, ultimately, on CV events are essential. Initial studies in RA<sup>28</sup> and psoriasis<sup>29</sup> suggest that TNF inhibitors may reduce vascular inflammation as measured by 18-fluorodeoxyglucose positron emission tomography-computed tomography.

Multiple studies are ongoing to evaluate the effects of ultraviolet B phototherapy ([ClinicalTrials.gov](#) identifier NCT01553058), TNF inhibition (NCT01553058, 01866592), interleukin (IL) 12/23 inhibition (NCT02187172), and IL-17 inhibition (NCT02690701) on vascular inflammation. Finally, underscoring the importance of testing the inflammatory hypothesis in CVD, the Cardiovascular Inflammation Reduction Trial (CIRT; NCT01594333) is an ongoing RCT studying the effect of methotrexate on the incidence of MACE in patients with type 2 diabetes or metabolic syndrome who have had a previous MI.<sup>30</sup> The CIRT trial is not a study of patients with psoriasis, but it will be important in establishing whether methotrexate treatment of inflammation reduces the residual risk of CVD. If these or other future RCTs reveal a protective effect of psoriasis treatments on CVD, a paradigm shift in the current view of psoriasis therapy will be needed, and support for a causal relationship between psoriasis and CVD would be strengthened.

## Obesity

Obesity may have important effects on psoriasis severity and response to therapies. The impact of weight loss interventions (either diet modification or exercise) on psoriasis severity was assessed in a systematic review and meta-analysis of 7 RCTs of 878 participants.<sup>31</sup> The meta-analysis of 3 RCTs found a significantly greater reduction in the Psoriasis Area and Severity Index (PASI) score among patients receiving the weight loss intervention than those who did not receive the intervention (pooled mean PASI difference,  $-2.49$  [95% confidence interval {CI},  $-3.90$  to  $-1.08$ ]). Similarly, among 4 studies that assessed 75% reduction in the PASI score (PASI-75) as an outcome, more participants in the intervention versus the control group achieved PASI-75 (pooled

odds ratio [OR], 2.92 [95% CI, 1.39-6.13]). Therefore, the current data suggest that weight loss improves psoriasis, but the clinical significance is modest. There was at least substantial heterogeneity among the studies included in the meta-analyses; thus, additional studies are needed to better understand the effects of specific weight loss interventions on psoriasis.

Increased weight and BMI may also negatively impact response to systemic treatments, including biologic therapies and cyclosporine. Subanalyses of data from RCTs have found that higher weight or BMI is associated with poorer response to fixed-dose biologic therapies (ie, adalimumab, etanercept, and ustekinumab 45 mg), whereas the response to infliximab, whose dose is weight-based, does not vary with BMI.<sup>32,33</sup> A US cross-sectional study of patients with psoriasis who were seen in the routine clinical setting supports the RCT findings.<sup>34</sup> The likelihood of having clear or almost clear skin as defined by a 6-point physician global assessment was found to decrease with increasing BMI among psoriasis patients who were receiving adalimumab or etanercept but not among those taking methotrexate. Together, these data suggest that obese psoriasis patients may be underdosed with fixed-dose biologics. Importantly, weight loss may improve response to biologic therapy as suggested by a single RCT evaluating the effect of weight reduction by diet modification on treatment efficacy among obese psoriasis patients who were receiving adalimumab, etanercept, infliximab, or ustekinumab.<sup>35</sup> Another similarly designed RCT also found an improved response to treatment with low-dose cyclosporine among obese patients with psoriasis randomized to a low-calorie versus normal diet.<sup>36</sup> While weight has not been found to have an effect on initial response to treatment with methotrexate, a single-center study suggests that obese psoriasis patients are more likely to experience loss of response to methotrexate than nonobese patients.<sup>37</sup>

Lastly, obese patients with psoriasis may be at increased risk of medication side effects from methotrexate. Nonalcoholic fatty liver disease (NAFLD) is a relative contraindication to methotrexate and is more common among obese patients.<sup>38,39</sup> Being overweight may also be a risk factor for severe hepatic fibrosis among patients with psoriasis who are taking methotrexate.<sup>40</sup> Therefore, it has been recommended that obese patients with psoriasis who are taking methotrexate undergo more aggressive monitoring, including obtaining liver biopsies both at baseline (ie, within 2-6 months of starting therapy) and at a cumulative dose of 1.0 to 1.5 g of methotrexate.<sup>38</sup>

Collectively, these data highlight the importance of providing counseling to overweight and obese patients with psoriasis about weight loss and the impact of their weight on both psoriasis severity and treatment response (level of evidence, IB). In addition, dermatologists should be cautious of methotrexate use in obese patients with psoriasis.

### Hypertension

Given the association between psoriasis and hypertension, patients with psoriasis should undergo at least standard blood pressure screening that is recommended for the general population (Table II).<sup>41</sup> Data suggest that psoriasis patients with hypertension may have more severe hypertension<sup>42</sup> and may be more likely to have poorly controlled blood pressure than hypertensive patients without psoriasis<sup>3</sup>; therefore, appropriate management and monitoring of blood pressure is important to emphasize. Lastly, as hypertension is a well-known potential adverse effect of cyclosporine, dermatologists should use cyclosporine cautiously in patients with psoriasis who have pre-existing hypertension.<sup>43</sup>

### Diabetes

As psoriasis is associated with an increased risk of diabetes, patients with psoriasis should be screened for diabetes at least according to the standard recommendations for the general population (Table III).<sup>44-47</sup> Based on observational data that suggest more aggressive diabetes<sup>48</sup> and greater prevalence and risk of micro- and macrovascular complications<sup>49,50</sup> among patients with than without psoriasis, it may be reasonable to consider more frequent monitoring of diabetes and screening for diabetic complications among psoriasis patients. However, additional studies are needed to support these initial findings and before such recommendations are implemented widely.

### Dyslipidemia

More prevalent dyslipidemia among patients with psoriasis supports lipid screening at least per standard recommendations for the general population (Table I). Hyperlipidemia is a potential adverse effect of treatment with acitretin<sup>51</sup> and cyclosporine;<sup>43</sup> therefore these medications should be used with caution in patients with psoriasis who also have dyslipidemia, and close lipid monitoring is necessary.

In summary, it is essential for both clinicians and patients to understand the possibly heightened risk of CVD in patients with psoriasis, which may increase with greater disease severity and longer duration. At a minimum, screening for and management of CV risk factors in patients with psoriasis

**Table II.** Guidelines for hypertension screening\*

Target population	Screening recommendation	Level of evidence
18-39 years old and blood pressure <130/85 mm Hg without any risk factors <sup>†</sup>	Screen every 3-5 y	IB
Yes to any of the following:		
>40 years old	Screen annually	IB
At increased risk for hypertension <sup>†</sup>		

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

\*Data from the US Preventative Services Task Force.<sup>97</sup>

<sup>†</sup>Risk factors: systolic blood pressure >130-139 mm Hg, diastolic blood pressure >85-89 mm Hg, overweight or obese, and African American.

**Table III.** Guidelines for diabetes screening in asymptomatic patients\*

Target population	Screening recommendation <sup>†</sup>	Level of evidence
Yes to both of the following <sup>‡</sup> :	Screen every 3 y <sup>  </sup>	II-IV

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

\*Data from the US Preventative Services Task Force.<sup>44</sup>

<sup>†</sup>Screen with any one of the following: hemoglobin A1c, fasting plasma glucose, or oral glucose tolerance test.

<sup>‡</sup>Persons who have a family history of diabetes, history of gestational diabetes or polycystic ovarian syndrome, or are members of certain racial/ethnic groups (ie, African Americans, American Indians or Alaskan Natives, Asian Americans, Hispanics or Latinos, or Native Hawaiians or Pacific Islanders) may be at increased risk of diabetes at a younger age or at a lower body mass index and should be considered for earlier screening.

<sup>§</sup>The American Diabetes Association recommends screening for diabetes in adults ≥45 years of age and screening in persons with multiple risk factors regardless of age.<sup>46,98</sup>

<sup>||</sup>More frequent testing may be considered for those with abnormal test results or those at higher risk.

should be according to the recommendations for the general adult population (Tables I-III).<sup>6,7</sup> Continued basic, translational, and epidemiologic research will be essential to support the development of evidence-based psoriasis-specific recommendations for comorbid disease screening and management. In addition, ongoing and future well-conducted RCTs will be necessary to answer the critical question of whether or not treatment of psoriasis itself has an effect on CV disease, events, morbidity, and mortality.

## GASTROINTESTINAL DISEASE

### Key points

- **Adalimumab and infliximab are approved by the US Food and Drug Administration for the treatment of both psoriasis and inflammatory bowel disease (Crohn's disease and ulcerative colitis); ustekinumab is approved for the treatment of both psoriasis and CD**

- **Secukinumab and ixekizumab should be used with caution in patients with both psoriasis and Crohn's disease**
- **Methotrexate and acitretin should be used cautiously in patients with psoriasis and liver disease**
- **Tumor necrosis factor inhibitors should be avoided in patients with psoriasis and moderate to severe alcoholic hepatitis**

### Inflammatory bowel disease

It is important to understand the therapeutic implications of comorbid inflammatory bowel disease (IBD), which is more prevalent among patients with than without psoriasis. Adalimumab and infliximab are approved by the US Food and Drug Administration (FDA) for the treatment of both psoriasis and IBD (ie, Crohn's disease [CD] and ulcerative colitis [UC]), and ustekinumab was also recently approved for the treatment of Crohn's disease. Therefore, these biologics are the treatments of choice in patients with both psoriasis and UC or CD.

Notably, dosing of systemic medications for treatment of CD and UC is often higher than that for psoriasis. Unexpectedly, secukinumab, an IL-17A inhibitor and biologic that was recently approved by the FDA for the treatment of moderate to severe psoriasis, was not only found to be ineffective for treatment of CD but was also suggested to be associated with higher adverse event rates than placebo in a single clinical trial.<sup>52</sup> Exacerbations of CD were observed in clinical trials of secukinumab<sup>53</sup> and ixekizumab<sup>54</sup> for the treatment of psoriasis, and should therefore be used with caution in patients with both psoriasis and CD.

### Hepatic disease

The greater prevalence of NAFLD among patients with psoriasis suggests cautious use of potentially hepatotoxic medications, such as methotrexate and acitretin, in patients with both diseases. As discussed previously, NAFLD is a relative contraindication to treatment with methotrexate, and more aggressive monitoring with liver biopsies obtained at baseline and at a cumulative dose of 1.0 to 1.5 g of methotrexate may be considered (level of evidence, IV).<sup>38</sup> Noninvasive tests to detect hepatic fibrosis, such as various serologic tests and radiologic imaging, such as ultrasound-based elastography, magnetic resonance elastography, acoustic radiation force impulse imaging, and cross-sectional imaging, have also been suggested as promising tools but have yet to be established in the setting of long-term methotrexate use among patients with psoriasis.<sup>55</sup>

Moderate to severe alcoholic hepatitis is a relative contraindication to treatment with TNF inhibitors, specifically etanercept. In a single RCT of etanercept in the treatment of moderate to severe alcoholic hepatitis, higher mortality and serious infection rates at 6 months were detected in the etanercept versus placebo group.<sup>56</sup> Therefore, etanercept and other TNF inhibitors should be avoided in psoriasis patients with moderate to severe alcoholic hepatitis (level of evidence, IB). Importantly, patients with psoriasis, especially those being considered for systemic treatment with potentially hepatotoxic medications, should be screened for alcohol use and counseled appropriately.

### CHRONIC KIDNEY DISEASE

#### Key point

- Patients with more severe psoriasis may warrant closer monitoring for kidney disease, and potentially nephrotoxic medications, such as cyclosporine, should be used with caution

With data suggesting increased risks of chronic kidney disease and end-stage renal disease among patients with psoriasis,<sup>57,58</sup> the risks versus benefits of treating patients with moderate to severe psoriasis with potentially nephrotoxic medications, such as cyclosporine, should be carefully considered. Closer monitoring for renal insufficiency with serum creatinine, blood urea nitrogen, and urinalysis to screen for microalbuminuria may also be considered for patients with psoriasis affecting  $\geq 3\%$  of their body surface area (BSA; level of evidence, III).

### MALIGNANCY

#### Key points

- Tumor necrosis factor inhibitors may be associated with increased risks of nonmelanoma skin cancer and melanoma
- Chronic oral psoralen plus ultraviolet A phototherapy is associated with an increased risk of nonmelanoma skin cancer, particularly squamous cell carcinoma
- Patients with psoriasis on immunosuppressive therapy should adhere to guidelines for age-appropriate cancer screening
- Annual skin cancer screening may be considered in patients with psoriasis who are receiving immunosuppressive medications or phototherapy

The risk of malignancy among patients with psoriasis is most convincing for lymphoma, particularly cutaneous T-cell lymphoma (CTCL), although misdiagnosis of CTCL as psoriasis may at least partially explain this association. Increased risks of other cancers have also been suggested.<sup>62</sup> Malignancy risk is of special concern among patients treated with immunosuppressive systemic therapies or phototherapy. Most studies to date have assessed malignancy risk related to TNF inhibitors received by patients with RA or a combination of immune-mediated diseases (ie, RA, IBD, psoriatic diseases, or ankylosing spondylitis) for which TNF inhibitors are indicated. A meta-analysis of RCTs<sup>63</sup> and observational studies<sup>64</sup> of patients taking TNF inhibitors found no increased risk of internal malignancy, but suggested that risks of nonmelanoma skin cancer (NMSC)<sup>63,64</sup> and melanoma<sup>64,65</sup> may be increased. Skin cancer is also of particular concern among patients who have received phototherapy. The evidence is strongest for an increased risk of NMSC, particularly squamous cell carcinoma, among patients treated with psoralen plus ultraviolet A (PUVA) phototherapy whereby treatment with >200 sessions of PUVA is associated with a 14-fold increased risk of squamous cell carcinoma.<sup>66</sup> The

**Table IV.** Guidelines for age-appropriate cancer screening\*

Malignancy	Age, y	Screen	Frequency	Level of evidence
Breast cancer <sup>99</sup>	50-74	Mammogram	Every 2 y	IA
Cervical cancer <sup>100</sup>	21-65	Papanicolaou smear	Every 3 y	IB
Colon cancer <sup>101</sup>	50-75	FOBT Flexible sigmoidoscopy + FOBT	Yearly Every 5 y (flexible sigmoidoscopy); every 3 y (FOBT)	IB
Lung cancer <sup>102</sup>	55-80 with ≥30 pack-year history and current smoker or quit within 15 y	Colonoscopy Low-dose computed tomography scan of the chest	Every 10 y Yearly	IA

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

FOBT, Fecal occult blood test.

\*Refer to guideline reference documents for full screening recommendations.

risk of melanoma with oral PUVA remains controversial, and increased risk of skin cancer with topical PUVA or narrowband ultraviolet B phototherapy remains unproven.<sup>67</sup>

Especially considering the potential cancer risks and malignancy warnings that accompany adalimumab, etanercept, infliximab, and ustekinumab, it is important that clinicians recommend and patients adhere to age-appropriate cancer screening guidelines (Table IV). Screening and appropriate counseling for important behavioral risk factors for cancer (eg, smoking) is also suggested, and at least yearly skin cancer surveillance may be considered (level of evidence, III-IV). Importantly, malignancy, other than NMSC, is at least a relative contraindication for treatment with immunosuppressive therapies for psoriasis. Guidelines for treatment of RA indicate that treatment with biologics may be cautiously considered in patients with history of malignancy if they have been cancer-free for ≥5 years (level of evidence, III-IV).<sup>68,69</sup> Among psoriasis patients with multiple NMSCs, acitretin may be considered for both psoriasis treatment and its potential chemopreventive effects.<sup>70,71</sup> Lastly, obtaining a skin biopsy should be considered in patients with psoriasis who have atypical lesions or disease that fails to appropriately respond to treatment in order to rule out CTCL.

## INFECTION

### Key points

- Screening for hepatitis B and C and HIV should be considered before starting immunosuppressive therapy in patients with psoriasis

- Screening for tuberculosis before and annually during immunosuppressive therapy in patients with psoriasis is recommended
- Patients with psoriasis are recommended to keep up to date with vaccinations, ideally before receiving immunosuppressive therapies

Infection risk attributable to psoriasis itself and immunosuppressive therapies used to treat moderate to severe disease remains a matter of debate. Observational studies suggest increased risks of serious infections,<sup>72,73</sup> including pneumonia,<sup>74,75</sup> among patients with psoriasis. Both a meta-analysis of RCTs<sup>76</sup> and an observational study<sup>77</sup> have not found higher risks of serious infection caused by TNF inhibitors compared with other systemic therapies; the effects of specific psoriasis treatments on serious infection risk remain unclear. An observational study of psoriasis patients suggests that the risk of herpes zoster may be increased among patients receiving combination biologic and methotrexate therapy.<sup>78</sup> Considering the serious infection warnings that accompany methotrexate, cyclosporine, adalimumab, etanercept, infliximab, ustekinumab, secukinumab, and ixekizumab, it is recommended that patients with psoriasis, particularly those requiring immunosuppressive systemic therapy, remain up to date with their vaccinations according to the Advisory Committee for Immunization Practices (level of evidence, IV).<sup>79-81</sup> As respiratory infections were found to be the most common serious infections in patients with psoriasis,<sup>72,73</sup> influenza and pneumonia vaccinations may be particularly important. Live vaccines should be avoided in patients who are currently taking and are within at least 1 month of starting immunosuppressive therapy.<sup>79</sup>

Infections of special concern, especially in the setting of treatment with immunosuppressive systemic medications, include viral hepatitis B and C, HIV, and tuberculosis (TB). The Centers for Disease Control and Prevention (CDC) and the Medical Board of the National Psoriasis Foundation recommend screening all patients for hepatitis B infection before initiating immunosuppressive therapy with triple serology and baseline liver function tests.<sup>82,83</sup> Screening for hepatitis C is more controversial, but several guidelines recommend screening at least high-risk populations before initiating immunosuppressive, particularly biologic, therapy.<sup>84-86</sup> The CDC also recommends  $\geq 1$  HIV screening test in every person between the ages of 13 and 64.<sup>87</sup> Finally, considering the potential for TB reactivation, particularly with TNF inhibition, whereby the greatest risk may be associated with adalimumab and infliximab,<sup>88,89</sup> TB screening before starting and annually while on biologic therapy has been recommended (level of evidence, IV).<sup>90</sup>

## MOOD DISORDERS

### Key point

- Screening for mood disorders should be considered in patients with psoriasis, particularly those with more severe disease**

Reports of increased risks of depression, anxiety, and suicidality among patients with psoriasis<sup>91,92</sup> suggest that clinicians should consider screening psoriasis patients for depression and suicidality, especially if they have more severe disease. Because both acitretin and apremilast have been labeled with warnings for mood changes and depression, respectively, patients who are taking these medications should be monitored for depression or other mood instability (level of evidence, III).

## PSORIATIC ARTHRITIS

### Key points

- All patients with psoriasis should be screened for psoriatic arthritis**
- The presence of psoriatic arthritis is an indication for systemic therapy**

Psoriatic arthritis is associated with decreased functional ability and quality of life and may result in permanent joint damage. A diagnosis of psoriatic arthritis is an indication for treatment with systemic therapy. Early detection and treatment is essential to prevent progression of this potentially debilitating joint disease.<sup>93</sup> All patients with psoriasis should be asked if they have joint symptoms, including joint

swelling, tenderness, and morning stiffness that lasts for  $\geq 30$  minutes and improves with activity (level of evidence, III-IV). Diagnostic tests and treatment recommendations are reviewed in more detail elsewhere.<sup>94-96</sup>

In conclusion, clinicians and patients must understand the wide range of medical comorbidities associated with psoriasis in order to ensure respective provision and receipt of appropriate screening and treatment in an attempt to reduce morbidity and mortality. Importantly, ongoing and future well-conducted RCTs are necessary to determine the effect of psoriasis treatment on the associated risks of cardiometabolic, renal, malignant, infectious, psychiatric, and other emerging comorbid diseases.

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## Answers to CME examination

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# The role of imaging in the management of patients with nonmelanoma skin cancer

## Diagnostic modalities and applications

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### Learning objectives

After completing this learning activity, the learner should be able to describe commonly used imaging modalities, such as CT, PET/CT, MRI, ultrasound, and lymphoscintigraphy, and discuss their appropriate utilization for management of nonmelanoma skin cancer on the head and neck and identify and select the imaging technique best suited for visualization of different body tissue compartments that may be affected by nonmelanoma skin cancer.

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While uncomplicated cases of nonmelanoma skin cancer can be treated with surgery, destruction, or topical therapy alone, advanced or neglected cases require more complex management decisions. Dermatologists and dermatologic surgeons should be familiar with the imaging techniques relevant to cutaneous oncology and their value in different clinical scenarios. Herein we review imaging modalities used in management of nonmelanoma skin cancer. (J Am Acad Dermatol 2017;76:579-88.)

**Key words:** basal cell carcinoma; computed tomography; dermatofibrosarcoma protuberans; imaging; magnetic resonance imaging; Merkel cell carcinoma; positron emission tomography; radiology; squamous cell carcinoma; skin cancer; ultrasound.

## INTRODUCTION

As the incidence of skin cancer continues to rise, dermatologists and dermatologic surgeons in particular will encounter more aggressive tumors that may require imaging to optimize patient work-up and management. However, radiologic imaging of skin cancer is not a familiar topic to most dermatologists. There are but a few sources

of information found in radiology texts<sup>1</sup> and the dermatologic literature,<sup>2,3</sup> and it remains a knowledge gap in dermatology. In addition to streamlining patient care, an understanding of different imaging modalities will facilitate the use of cost effective imaging resources.<sup>4,5</sup> The objective of this article is to provide a current overview of imaging modalities pertinent to nonmelanoma

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**Abbreviations used:**

18-FDG:	18-fluoro-deoxyglucose
CDU:	color Doppler ultrasonography
CT:	computed tomography
FNAB:	fine-needle aspiration biopsy
MRI:	magnetic resonance imaging
NMSC:	nonmelanoma skin cancer
NSF:	nephrogenic systemic fibrosis
PET CT:	positron emission tomography-computed tomography
SUV:	standard uptake value
US:	ultrasonography

skin cancer (NMSC) and to discuss clinical scenarios where imaging is indicated. For reasons of brevity and relevance to this audience, the discussion will exclude melanoma.

## OVERVIEW OF COMMONLY USED IMAGING MODALITIES

### Anatomic planes of imaging

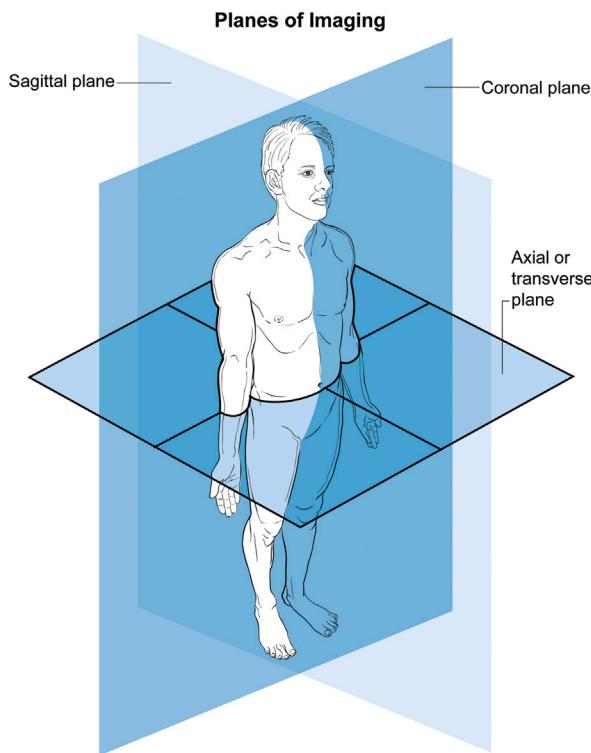
Cross-sectional imaging requires standard nomenclature to refer to the visualized plane. A correct understanding of the terminology used by radiologists is essential in the interpretation of imaging reports and communication. The commonly used anatomic planes in imaging studies (ie, axial or transverse, sagittal, and coronal) are shown in Fig 1.

## COMPUTED TOMOGRAPHY BASICS

### Key points

- **Computed tomography is typically the initial imaging study in the preoperative evaluation of head and neck tumors**
- **Computed tomography scans offer superior spatial resolution compared to magnetic resonance imaging scans and excellent visualization of bony structures and lymph nodes**
- **Computed tomography scans can be quickly performed and are widely available**
- **Computed tomography scans involve exposure to ionizing radiation**
- **Computed tomography scans should be ordered with contrast for tumor imaging**

Computed tomography (CT) scans are the mainstay in the evaluation of advanced cutaneous tumors at most institutions. CT scans are used for showing the soft tissue extent of tumor, bone invasion, and nodal metastases.<sup>1</sup> CT scans use ionizing radiation (radiography) to generate axial images. As the x-ray beam travels through the tissue being imaged, the beam is attenuated and the detector registers the resulting changed radiation level. The degree of beam attenuation reflects tissue density, which is



**Fig 1.** Anatomic planes used in radiologic imaging. Reproduced with kind permission of Springer Nature from Shah K, Onufer J, MacFarlane DF. Imaging of head and neck skin cancer. In: MacFarlane DF, editor. Skin cancer management. New York: Springer Nature; 2010. Illustration by Alice Chen.

expressed in Hounsfield units (HUs).<sup>6,7</sup> By definition, the CT value of air is -1000 HUs and the value of water is 0 HU. Fat has negative values, soft tissue values range from 10 to 50 HUs, and bone is >1000 HUs (Table 1).<sup>8</sup> Intravenous injection of an iodinated contrast agent increases the physical density of blood, enhancing the tissue contrast of vascular structures, organs, and neoplasms.<sup>1</sup> Tumor imaging is significantly improved by contrast administration, in the context of both CT and magnetic resonance imaging (MRI) scans.

CT imaging of specific tissues, such as bone, can be improved by limiting the monitor display to a specific spectrum of the gray scale (ie, bone windows) and by using tailored reconstruction algorithms such that bone invasion can be better identified. For this reason, CT is frequently used to evaluate tumor invasion of cortical bone (Fig 2). A CT scan is usually the first imaging modality used in the evaluation of lymph nodes for tumor staging. Abnormal lymph nodes in the head and neck can be precisely localized and classified.<sup>9</sup> In our experience, lymph nodes <1.0 cm can be identified as metastatic if they show necrosis or abnormal enhancement. A sub-centimeter, abnormal parotid

**Table I.** Relative tissue density in computed tomography scans expressed in Hounsfield units

Substance	Density in Houndsfield units (radiodensity)
Air	-1000
Fat	-50
Water	0
Cerebrospinal fluid	+15
Blood	+30 to +45
Muscle	+40
Bone	+1000 (up to +3000 for dense bone)

Lower density appears black and higher density more white on grayscale images.<sup>8</sup>

**Table II.** Tissue signal characteristics seen on magnetic resonance imaging scans\*

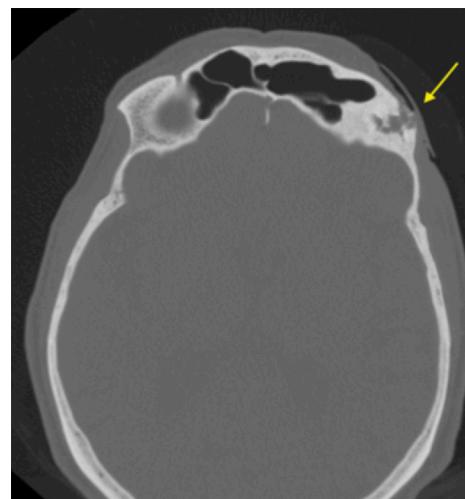
Signal intensity	T <sub>1</sub> -weighted	T <sub>2</sub> -weighted
High	Fat, melanin, hemoglobin, contrast	Fluid (vitreous, cerebrospinal fluid)
Intermediate	Gray matter, muscle	Gray matter, muscle
Low	Fluid (vitreous, cerebrospinal fluid)	
Very low	Bone, calcification	Bone calcification

\*Modified from Mitchell et al.<sup>16</sup>

lymph node in a patient with squamous cell cancer (SCC) detected on CT scan is shown in Fig 3.

**Advantages and disadvantages.** CT is often the initial technique used to image skin cancers with potential extracutaneous involvement because it delivers excellent spatial resolution and is fast and relatively inexpensive. It offers excellent visualization of cortical bone and can detect subtle bone pathology. Some radiologists believe that lymph nodes are better visualized with CT than MRI scans because focal deposits within the nodes can be seen with greater clarity.<sup>1</sup> It provides excellent multiplanar spatial resolution and is a much faster study to perform than MRI. For example, a high-resolution CT scan of the neck from the aortic arch to the vertex (1.25-mm slice thickness) can be performed in 30 seconds. Compared to MRI, CT scans pose fewer safety issues for patients who may be attached to intravenous pumps or monitors. In addition, CT scans can be routinely performed on patients with implanted metal devices. It is less expensive to perform and is generally more widely available than MRI.

Like radiographs, CT scanners use ionizing radiation passed through tissue to generate images. Cumulative exposure with repeat studies can be significant, especially with the high doses required



**Fig 2.** Bony invasion by squamous cell carcinoma. Computed tomography scan, axial view. The arrows show erosive changes of the zygomatic process of the left frontal bone caused by invasion by squamous cell carcinoma.

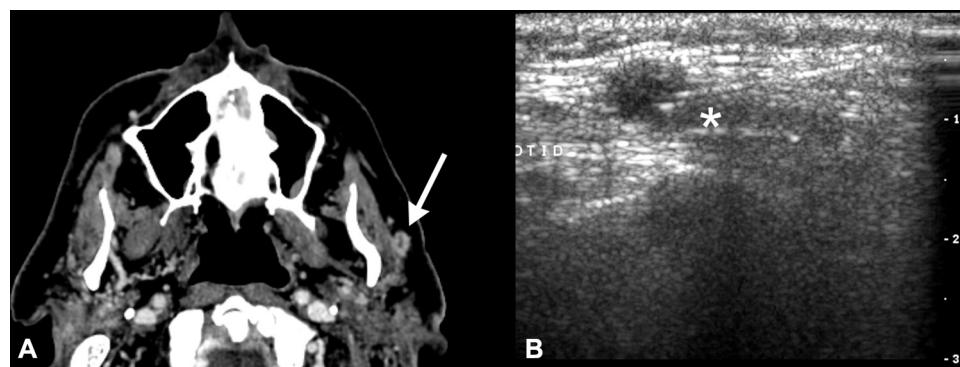
for helical and multidetector systems.<sup>10-12</sup> For example, a high-resolution CT scan of the chest would give an effective radiation dose of 7 millisieverts (mSv), while a chest radiograph would deliver approximately 0.1 mSv.<sup>12</sup> In simple terms, the radiation exposure from 1 chest radiograph is equivalent to the amount of radiation exposure one typically encounters in 10 days in natural surroundings; that of a body CT scan would be equivalent to 1400 hours of transatlantic air travel.<sup>13</sup> Because of the potential threat of radiation to the developing fetus, the risks and benefits of CT versus an alternate modality must be carefully considered and discussed with a pregnant patient. Imaging of radiation-sensitive tissues, such as the thyroid and eye, may pose a relative contraindication in children. Newer algorithms, now becoming more widespread, can allow diagnostic quality CT imaging with lower radiation doses.

The use of iodinated contrast may cause or increase renal insufficiency in at-risk individuals. In addition, hypersensitivity to iodine may be a relative contraindication to the use of contrast, although premedication with solumedrol and antihistamines may permit its use.<sup>14,15</sup> CT is generally less sensitive than MRI for subtle intracranial disease, perineural spread, and imaging of soft tissue tumors.<sup>1</sup>

## POSITRON EMISSION TOMOGRAPHY—COMPUTED TOMOGRAPHY BASICS

### Key points

- Positron emission tomography—computed tomography is an excellent technique for the detection of hypermetabolic tumors, such as squamous cell and Merkel cell carcinomas, in lymph nodes and distant organs



**Fig 3.** Abnormal lymph node on a computed tomography scan. **A**, The computed tomography scan showing enlarged and necrotic parotid lymph node (arrow; axial view). **B**, Obtaining an ultrasonography-guided fine-needle aspiration biopsy specimen of the parotid lymph node. The needle (\*) is seen within the lymph node. Reproduced with kind permission of Springer Nature from Shah K, Onufer J, MacFarlane DF. Imaging of head and neck skin cancer. In: MacFarlane DF, editor. Skin cancer management. New York: Springer Nature; 2010.

- **Positron emission tomography–computed tomography provides both structural and functional data**
- **Positron emission tomography–computed tomography is frequently used to evaluate the presence of occult metastases and monitor head and neck tumors postoperatively**

Positron emission tomography–computed tomography (PET CT) is most frequently used in patients with head and neck malignancies to identify the presence of tumor in lymph nodes and to search for distant metastases.<sup>1</sup> The PET component of PET CT uses the pathway of normal glucose metabolism in cells to detect areas of increased metabolic activity. Radiolabeled 18-fluorodeoxyglucose (18-FDG) is injected intravenously, taken up by cells, and incorporated into metabolic pathways. Malignancies with a high rate of cellular turnover take up greater amounts of the radiotracer. The detection of positrons emitted by areas of high FDG uptake in tissue identifies enhanced metabolic activity of neoplastic cells on the PET scan (Fig 4). The intensity of the signal is measured in standard uptake values (SUVs). The relative SUV can be displayed as a color heat map; higher SUVs generally indicate a greater likelihood of pathology. Anatomic detail and localization is provided by the CT component of the scan (Fig 4, A). The fusion of the 2 images combines form and function (Fig 4, B).

The combination of PET and CT is more sensitive in detecting nodal and distant tumor metastases than each modality separately.<sup>1</sup> PET CT works well in detecting distant visceral metastases,<sup>25,26</sup> occult adenopathy in the head and neck,<sup>27–30</sup> tumor response to therapy,<sup>25,31</sup> and tumor recurrence.<sup>32</sup> PET CT is

most frequently used for staging or surveillance of SCC of the head and neck<sup>25–30</sup> and can detect small volume lymph nodes not visualized on CT.<sup>1</sup> Images of a rapidly growing SCC seen on CT and fused PET CT images (axial view) are shown in Fig 4. The SUV of the tumor on PET is greatly elevated as would be expected for a hypermetabolic tumor. Merkel cell carcinomas (MCCs) are also FDG-avid, and PET CT is routinely used for initial staging to detect occult metastases.<sup>33–36</sup>

The utility of PET CT is limited for slowly growing tumors, such as basal cell carcinoma (BCC). While incidental detection has been reported<sup>37</sup> and large nodular BCCs can show hypermetabolic foci, infiltrative histologic subtypes and slow-growing tumors may not be seen.<sup>38</sup> The smaller cellular aggregates seen with infiltrating BCC may produce too small an SUV to be detected by the PET scanner. Infiltrating tumors, such as dermatofibrosarcoma protuberans may also be less vascular, leading to decreased 18-FDG uptake.

**PET CT: Advantages and disadvantages.** PET CT is particularly helpful in assessing the head and neck postoperatively when scar tissue can distort normal anatomy and obscure visualization of local recurrence or lymph nodes on CT scans alone. Patients with head and neck SCC with nodal involvement are frequently followed with serial PET CT to identify subclinical recurrence, although this practice varies by institution.

The preimaging protocol for PET CT scans requires that patients fast for 4 to 6 hours before radiotracer injection followed by a 1-hour rest period to allow distribution, resulting in greater preparation time. Because PET CT detects all types of increased

glucose uptake, false positives can be seen in areas of infection and inflammation that are unrelated to tumor pathology.<sup>1</sup> In addition, because of the high metabolic demand (and 18-FDG uptake) of the brain, particularly the gray matter, PET CT is not able to assess for cerebral metastasis, often necessitating a separate MRI scan.<sup>1</sup> False negatives can occur with nodes and distant metastases that are <1.0 cm in diameter. Slowly dividing or less metabolically active skin tumors may not be seen.

## MAGNETIC RESONANCE IMAGING: THE BASICS

### Key points

- Magnetic resonance imaging scans have superior soft tissue contrast compared to computed tomography scans
- Magnetic resonance imaging scans allow for the evaluation of perineural invasion
- These scans do not involve ionizing radiation
- Cost, longer imaging time, and sensitivity to motion and magnetic interference can be drawbacks
- Magnetic resonance imaging scans should be ordered with contrast for tumor imaging

MRI scans, in contrast to CT scans, use no ionizing radiation. The first requirement is a strong standing magnetic field, up to 3.0 Tesla (T) clinically, which is used to align the spins of hydrogen protons in soft tissue. A defined pulse sequence is used to change the alignment of spins in specific ways that depend on the tissue composition. As the spins realign to the standing magnetic field, they emit a signal that can be detected and used to generate the diagnostic image. Pulse sequences provide contrast resolution between different tissue types. The most commonly used pulse sequences in skin cancer imaging are T<sub>1</sub>-weighted, T<sub>2</sub>-weighted with and without fat saturation, and T<sub>1</sub> with contrast and fat saturation.

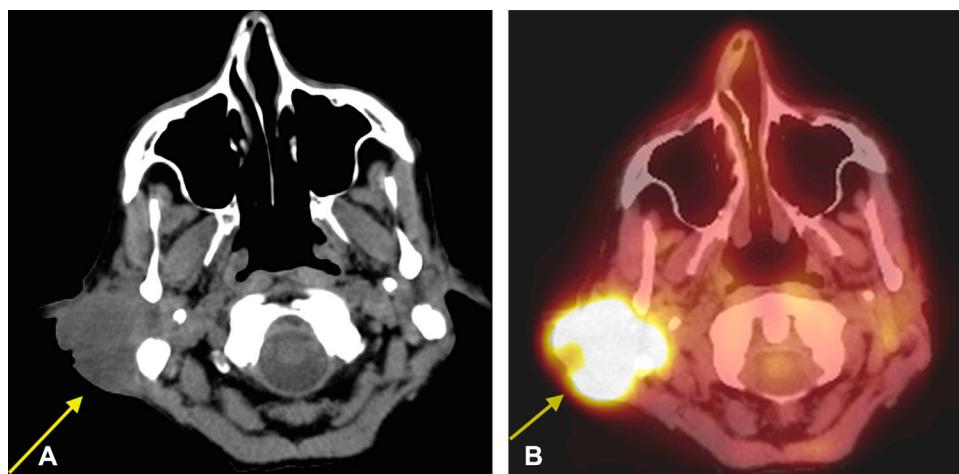
On conventional T<sub>1</sub>-weighted images, a bright signal is seen with fat, blood, and contrast. Muscle and gray matter have intermediate signal intensity. Water-containing fluids, such as cerebrospinal fluid and vitreous humor, have low signal intensity (Table II). On conventional T<sub>2</sub>-weighted images, fluid-containing spaces are bright.<sup>15-17</sup> Fat is bright on both T<sub>1</sub>- and T<sub>2</sub>-weighted images, as is contrast enhancing tumor. Fat signal can be suppressed on T<sub>2</sub>-weighted images and on postcontrast T<sub>1</sub>-weighted images in order to increase the visualization of tumor. Cortical bone generates no signal on any MRI sequence and appears black. Fat suppression is particularly important for orbital

tumors because the bright signal from orbital fat obscures contrast-enhancing pathology.<sup>16</sup> The contrasting appearances of T<sub>1</sub>- and T<sub>2</sub>-weighted images of the normal orbit in the axial plane and the appearance of fat in the orbit are shown in Fig 5. For a concise, well-illustrated review of MRI physics, the reader is referred to *MRI in Practice* by Westbrook et al.<sup>17</sup>

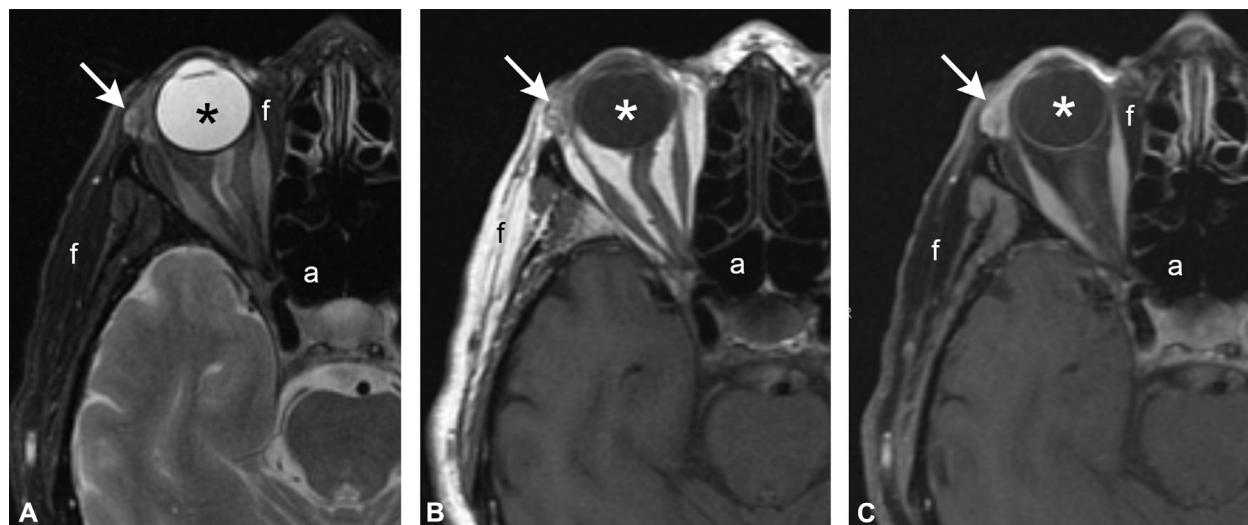
While visualization of the musculoskeletal system for nononcologic indications does not require contrast, the use of contrast is critical for tumor visualization. MRI studies used to evaluate aggressive cutaneous neoplasms will therefore almost always be obtained without and with contrast. MRI contrast typically consists intravenously administered chelated gadolinium compounds. Increased uptake by tumors results in a greater signal on a T<sub>1</sub>-weighted image. Because gadolinium compounds are renally excreted, renal insufficiency is a relative contraindication. Exact exclusion criteria (such as creatinine level >1.5 mg/dL or glomerular filtration rate <30) will vary with the hospital or institution. Nephrogenic sclerosing dermopathy, also known as nephrogenic systemic fibrosis (NSF), has been associated with the use of gadodiamide in the setting of poor renal function.<sup>18</sup> Macrocytic gadolinium contrast agents are considered the safest choice for avoidance of NSF.<sup>18</sup> Hypersensitivity reactions are relatively rare<sup>19</sup> (0.01-0.3%). Premedication with steroids and antihistamines can be used in patients with known hypersensitivity reactions.<sup>14,15</sup> In addition to hypersensitivity reactions, other relative contraindications to the use of contrast include: pregnant or breastfeeding women, use in children, unstable renal impairment, chronic liver function impairment, and hepatorenal syndrome.

**MRI: Advantages and disadvantages.** Unlike CT scans, MRI scans use no ionizing radiation, and exposure risk with multiple studies is not a concern. It has multiplanar capability and is highly sensitive for soft tissue disease with superior resolution compared with other modalities. Typically, systems with stronger magnets (1.5-3.0 T rather than less) offer higher resolution. The ability to apply a large spectrum of specific pulse sequences makes MRI a versatile technique that can be customized to enhance the visualization of different tissues and tumors. The general consensus is that MRI is the most sensitive imaging modality for detecting central nervous system disease and perineural invasion<sup>20,21</sup> that may be seen with aggressive neurotropic cutaneous malignancies.

Because the technique is dependent on the presence of a strong magnetic field, there can be



**Fig 4.** Recurrent squamous cell carcinoma as seen on a positron emission tomography—computed tomography scan. **A**, Soft tissue mass (*arrow*) on the mastoid region seen on computed tomography (axial view) corresponding to recurrent aggressive squamous cell carcinoma. **B**, PET CT at the corresponding level revealed high signal intensity because of increased metabolic activity of tumor.

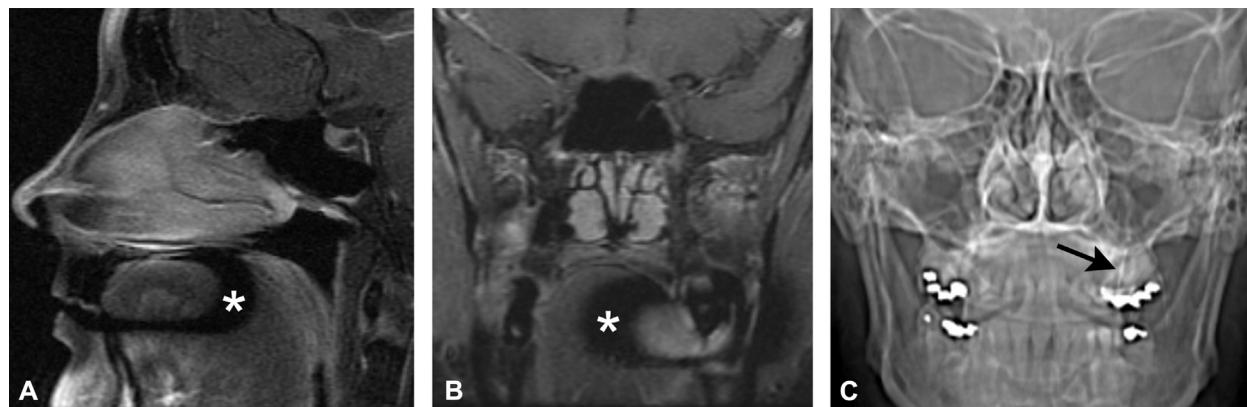


**Fig 5.** T<sub>1</sub>- and T<sub>2</sub>-weighted magnetic resonance imaging scans of a normal orbit. **A**, T<sub>2</sub>-weighted magnetic resonance imaging scan with fat saturation. **B**, T<sub>1</sub>-weighted magnetic resonance imaging scan. **C**, T<sub>1</sub>-weighted magnetic resonance imaging scan with intravenous gadolinium and fat saturation. Fluid appears bright on T<sub>2</sub>-weighted and dark on T<sub>1</sub>-weighted images (\*). Fat (*f*) in the orbit and marrow space appears bright on T<sub>1</sub>- and T<sub>2</sub>-weighted images unless fat saturation is used. Cortical bone and air (*a*) appear dark on all images. Gadolinium administration increases tissue contrast of muscle (extraocular), glandular tissue (lacrimal gland, *arrow*), and tumor, if present. Without fat saturation in the orbit, contrast-enhancing tissue and orbital fat would have indistinguishable signal intensities.

serious MRI compatibility issues with ferromagnetic materials contained in implanted devices, such as pacemakers, cochlear implants, aneurysm clips, or other foreign bodies, such as shrapnel. Like CT, the presence of ferromagnetic materials in tissue can cause scanning artefacts, such as those caused by dental fillings (Fig 6). However, MRI scans can cause

serious patient injury because of the movement or heating of ferromagnetic particles in tissue. Burns have been reported in patients with tattoos created with iron-containing pigments.<sup>22-24</sup>

Other disadvantages of MRI scans include a relatively long scan time (a brain MRI scan without and with contrast can take 40 minutes) and the



**Fig 6.** Dental artefacts on magnetic resonance imaging and computed tomography scans. **A**, Sagittal and **(B)** coronal T<sub>1</sub>-weighted magnetic resonance imaging scans with contrast and fat saturation and **(C)** a scout image conducted with computed tomography. Black oval of susceptibility artefact is caused by a dental implant (\*). Bilateral maxillary and mandibular dental fillings are hyperdense on the scout image, and most do not cause artefacts. The left maxillary osseointegrated implant shows a subtle linear metallic density within the alveolar ridge (arrow).

**Table III.** Ultrasonographic criteria for benign versus malignant nodes\*

Criterion	Benign	Malignant
B scan criteria		
Size	Small	Large
Shape	Oval	Rounded
Hilum	Present	Absent
Echogenicity	Moderate/low	Hypoechoic
Margins	Sharp	Irregular, blurred, and angular
Structural changes (eg, focal cortical nodule, necrosis, reticulation, calcification, and matting)	Absent	Present
Soft tissue edema	May be present	Absent
Doppler criteria		
Flow	Absent	Present
Vessel location	Central	Peripheral
Vascular pedicles	Single	Multiple
Vascular pattern	Regular	Irregular
Impedance valves	Low	High

\*Reprinted with permission from Dudea et al.<sup>41</sup>

necessity to remain motionless during the pulse sequence to avoid motion artefact. This may preclude the scanning of claustrophobic patients and those unable to remain still. Children typically require sedation to obtain a quality study. Compared to CT scans, MRI scans offer relatively poor visualization of subtle cortical bone changes but excellent visualization of marrow changes and soft tissues.<sup>1</sup>

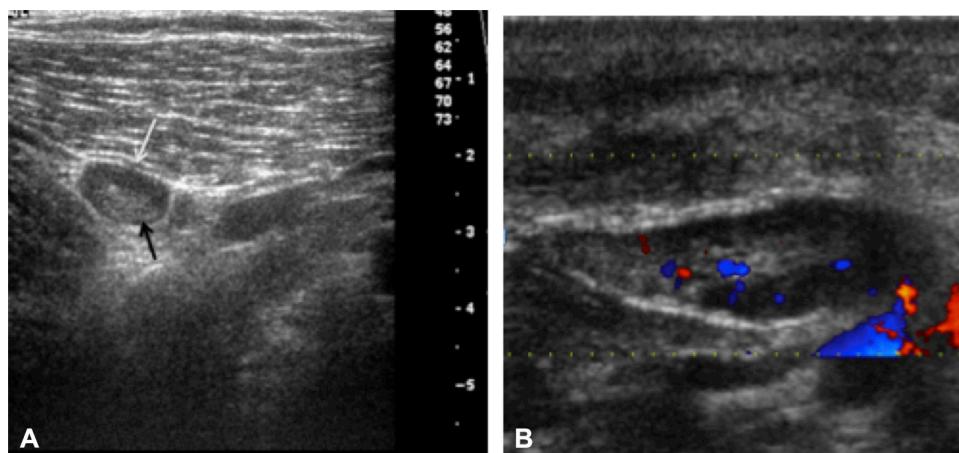
## BASICS OF ULTRASONOGRAPHY

### Key points

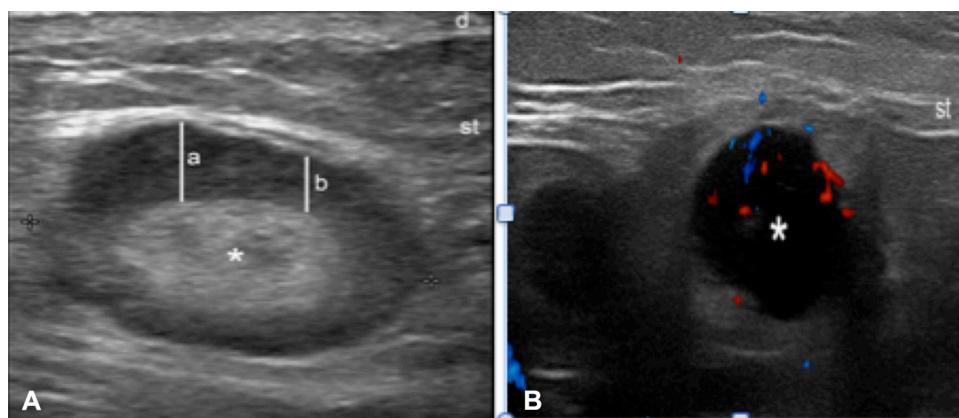
- Ultrasonography is a noninvasive modality
- Ultrasonography can assess regional lymph node characteristics
- Ultrasonography is operator-dependent
- The evaluation of cutaneous tumors with ultrasonography requires specialized equipment

Ultrasonography (US) has been an essential tool in medical diagnosis since its emergence approximately 60 years ago. It can be used to image the primary tumor or assess lymph nodes.<sup>39-44</sup> High-frequency sound waves generated by the piezoelectric crystals in the ultrasound transducer (probe) reflect off tissue, producing an “echo” that is then detected by the transducer. Fluid, such as cerebrospinal fluid and amniotic fluid, is anechoic and appears black. Denser tissues, such as skin and connective tissue, are echoic or hyperechoic and appear bright. The pattern and degree of echogenicity (or echo texture) characterizes different types of tissue and tissue pathology.<sup>43</sup>

In the context of NMSC, US is most frequently used for the evaluation of superficial lymph nodes or masses. A normal neck contains a multitude of lymph nodes of various sizes and depths; those that are superficially located can be well visualized by US, while those in deeper levels of the neck may not be clearly seen because of acoustic interference. Gray scale and color Doppler US (CDU), which allows the study of vascularity in real time and can show the distribution, thickness, vessel type (ie, arterial or venous), and velocity of the blood flow, can help



**Fig 7.** Ultrasonography and color Doppler ultrasonography of a normal lymph node. **A**, Normal lymph node seen on ultrasonography. The oval structure indicated by the white arrow is a normal lymph node seen in a transverse axial orientation. The black arrow shows normal echogenic hilum. **B**, Normal lymph node seen on color Doppler ultrasonography. The lymph node features normal cortex with relatively decreased echogenicity compared to the hilum. The red and blue colors indicate normal blood flow in opposite directions, contained within the hilum.



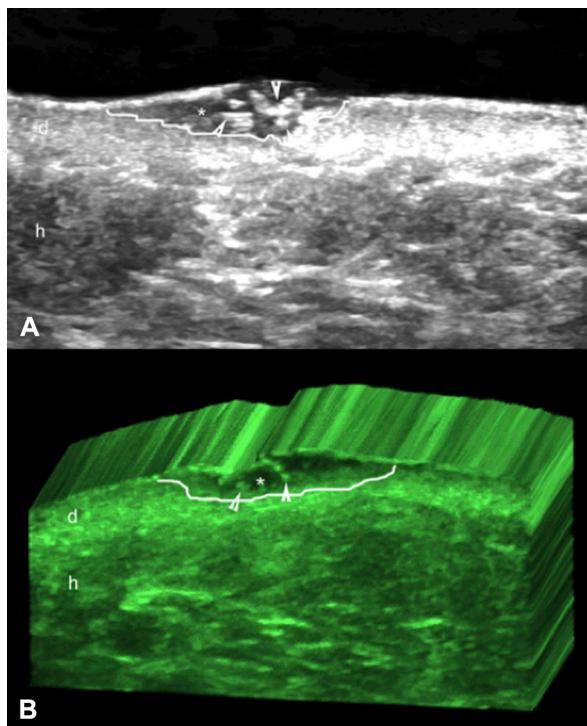
**Fig 8.** Ultrasonography and color Doppler ultrasonography of an abnormal lymph node. **A**, An abnormal metastatic node seen on ultrasonography. There is asymmetric (eccentric) thickening of the cortical region (*a* and *b*, vertical lines) but the hyperechoic center is conserved. **B**, An abnormal metastatic node seen on color Doppler ultrasonography. There is a hypoechoic nodule (asterisk) with eccentric cortical thickening and increased peripheral vascularity. *d*, Dermis; *st*, subcutaneous tissue.

distinguish between benign and malignant lymph nodes (Table III).

Benign lymph nodes are ovoid or flat in the long axis and typically display an echogenic hilum.<sup>39</sup> CDU reveals bidirectional flow in the hilum of normal lymph nodes (Fig 7). In contrast, malignant nodes tend to be larger (>1 cm), rounder in shape, and display necrosis, calcification, matting, and peripheral vascularity.<sup>39,44</sup> Loss of the echogenic hilum and of regular architecture may be noted. On CDU, increased peripheral vascularity is highly suggestive of malignancy (Fig 8).

When suspicious lymph nodes are identified, fine-needle aspiration biopsy (FNAB) with US guidance can be used to sample them; US-guided FNAB has been found to be more sensitive and specific than conventional FNAB.<sup>42</sup>

High-frequency US is beginning to be used for assessment of the morphology and extent of primary NMSC, including depth of the primary tumor.<sup>43</sup> Higher frequency US probes are necessary for the imaging of skin lesions, compared to the imaging of larger and/or deeper structures.<sup>45-48</sup> US reveals NMSC as a hypoechoic lesion (Fig 9).



**Fig 9.** Ultrasonography of basal cell carcinoma on the cheek (transverse axis). **A**, Grayscale image shows hypoechoic dermal lesion (asterisk, outlined) with hypoechoic spots (arrowheads). **B**, Three-dimensional reconstruction of the same lesion (asterisk). *d*, Dermis; *h*, hypodermis.

Hyperechoic foci may be seen within BCC and can be used to identify BCC subtypes.<sup>49-51</sup> Three-dimensional reconstruction of NMSC can also be performed (Fig 9, B). At this time, cutaneous US is a promising technique that is not widely available in clinical practice.

**Advantages and disadvantages of ultrasonography.** US can detect abnormal lymph nodes and can also assist in obtaining a FNAB specimen by assisting with real-time control of the biopsy procedure. Exposure to ionizing radiation is not an issue, unlike fluoroscopy or CT. In addition, the procedure is entirely noninvasive, painless, and has no risk of adverse reaction to contrast agents. US is mobile, does not require confinement or immobilization of the patients, and allows for positioning and interaction with the patient.

One of the major limitations with regard to lymph node evaluation is that US requires an acoustic window (ie, an area allowing visualization) that limits the depth of evaluation because of air or bone. US may not be able to visualize an entire tumor mass or all lymph nodes in the head and neck. While excellent for visualizing superficial parotid or

cervical lymph nodes, US cannot reliably visualize retropharyngeal or nodes deeper in the head and neck, which may require CT or MRI scans.<sup>1</sup> Because US is performed by a technician or physician, abnormal node detection and tumor evaluation is operator-dependent. The availability of high-quality US studies may vary greatly between hospitals and institutions.

In conclusion, different imaging modalities address specific clinical questions. The imaging evaluation should be tailored to specific clinical questions, with an understanding of the strengths and limitation of each modality. Discussion with your radiologist can optimize the imaging process, yield the best information, and promote patient safety. Careful consideration of the clinical context of imaging and of patient limitations will benefit patient care and optimize utilization of resources.

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# The role of imaging in the management of patients with nonmelanoma skin cancer



## When is imaging necessary?

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### Learning objectives

After completing the learning activity, the learner should be able to describe high risk nonmelanoma skin cancers that may be locally invasive or metastatic and list clinical scenarios pertaining to skin cancer where CT, PET/CT, MRI, ultrasound, and lymphoscintigraphy imaging studies are indicated and appropriate for optimal patient care.

### Disclosures

#### Editors

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When treating aggressive skin cancers, pre- and postoperative imaging provides important information for treatment planning and multidisciplinary cooperation of care. It is important for dermatologists to recognize the clinical scenarios where imaging is indicated in the management of skin cancer. We here address the most common indications for imaging in cutaneous oncology and how to best utilize the modalities available. (J Am Acad Dermatol 2017;76:591-607.)

**Key words:** basal cell carcinoma; computed tomography; dermatofibrosarcoma; imaging; magnetic resonance imaging; Merkel cell carcinoma; perineural invasion; positron emission tomography; protuberans; radiology; skin cancer; squamous cell carcinoma; ultrasound.

## INTRODUCTION

While the vast majority of skin cancers can be effectively managed on the basis of clinical features alone, large or aggressive high-risk tumors or those that compromise vital anatomic structures may necessitate radiologic imaging for optimal management. In our experience, the nonmelanoma skin cancers (NMSCs) that most frequently require imaging include squamous cell carcinoma (SCC), basal cell carcinoma

(BCC), dermatofibrosarcoma protuberans (DFSP), and Merkel cell carcinoma (MCC).

SCC may be locally aggressive with the potential for lymph node involvement and distant metastasis. Imaging may be indicated for patients at high risk of SCC, for which criteria include recurrent tumors, tumors >2 cm in diameter or >2 mm in depth, poorly differentiated histology, perineural invasion (PNI), lymphovascular invasion, and

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**Abbreviations used:**

18-FDG:	18-fluoro-deoxyglucose
CDU:	color Doppler ultrasonography
CT:	computed tomography
FNAB:	fine-needle aspiration biopsy
FS:	fat saturation
GAD:	gadolinium
MRI:	magnetic resonance imaging
NMSC:	nonmelanoma skin cancer
NSF:	nephrogenic systemic fibrosis
PET CT:	positron emission tomography—computed tomography
PNI:	perineural invasion
PNS:	perineural spread
SUV:	standard uptake value
US:	ultrasonography

specific anatomic site (eg, the ears, lips, and anogenital regions).<sup>1–5</sup> Multiple criteria greatly increase the risk of recurrence, extracutaneous disease, and mortality.<sup>2,5</sup> The appropriate use of radiologic imaging can result in early identification of tumor progression, improved prognostic accuracy, and early intervention.

While BCC is rarely metastatic, large or aggressive tumors can infiltrate critical anatomic structures, such as the orbit. The deeply infiltrating growth pattern of DFSP can make tumor extent difficult to predict based on a clinical examination alone, especially when located on the head and neck. DFSP can invade skeletal muscle, and preoperative imaging can help guide surgical treatment.

MCC is associated with a high rate of nodal and distant metastasis, and imaging can facilitate staging and adjuvant therapy. Imaging is an indispensable tool for the detection of nodal and distant disease and staging of aggressive cutaneous neoplasms.

The most common indications for imaging studies are summarized in **Table I**.

Computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, radiolabeled 18-fluorodeoxyglucose (18-FDG) positron emission tomography (PET) scans, and ultrasonography (US) are all used in these clinical scenarios. Depending on the clinical scenario and tumor type, ≥1 of these imaging studies may be necessary to adequately assess the extent of locoregional and distant disease. The material presented here can help optimize the evaluation of patients with advanced skin cancers and facilitate communication with other medical specialists involved in the patient's care. Consultation with a radiologist is strongly encouraged to determine the best study or combination of imaging studies for any given patient and to optimize the use of imaging resources (**Table II**).<sup>6</sup> A review of aggressive skin cancer cases in the setting of a hospital-based

**Table I.** Indications for radiologic imaging of skin cancers

Possible bony invasion
Possible orbital invasion
Assessment of the extent of tumor invasion in soft tissue
Staging of lymph nodes and metastatic disease
Evaluation for potential perineural spread
Post operative surveillance for recurrent disease

**Table II.** How to communicate clearly with your radiologist: What they need to know\*

**Tumor characteristics**

Type/subtype of tumor

Primary vs recurrent

Location

**Patient characteristics**

Age

Allergies, particularly to contrast agents

Implantable devices, metal, or other foreign bodies

History of claustrophobia

Renal impairment

Ensure a recent creatinine and/or glomerular filtration rate

Consideration of radiation dose (ie, children, women of childbearing age)

**Imaging-specific considerations**

Primary clinical question (ie, evaluate for extent of lesion, bony invasion, perineural invasion, muscle invasion, etc)

Anatomic structures would you like included

Type of evaluation (ie, preoperative planning, staging, postoperative surveillance, possible recurrence, etc)

History of previous or forthcoming studies (for correlation by the radiologist)

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multispecialty tumor board can also guide decision-making.

**CLINICAL INDICATIONS FOR IMAGING****Bony invasion****Key points**

- **A computed tomography scan is indicated when bony invasion by tumor is suspected**
- **High-resolution bone windows can increase sensitivity of detection**

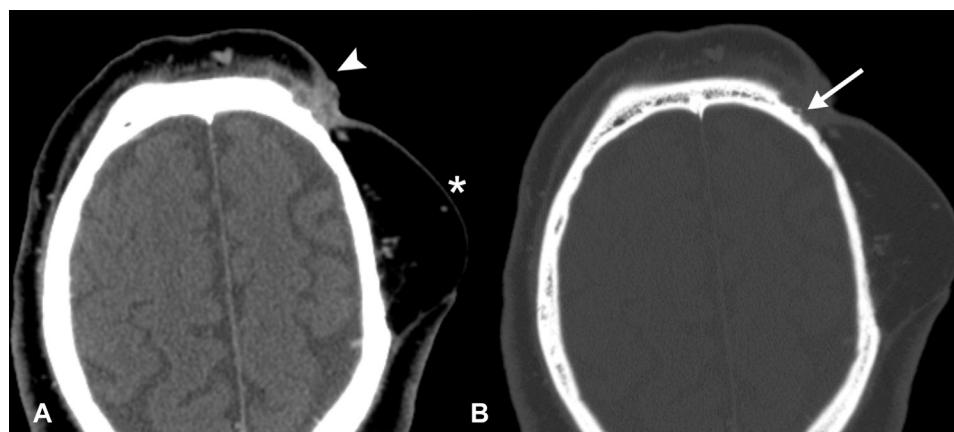
While aggressive skin tumors often follow the path of least resistance along nerves and tissue planes, they may also invade bone. Locally



**Fig 1.** Recurrent squamous cell carcinoma with bony invasion. **A**, Subcutaneous nodule on the left forehead. **B**, Defect after Mohs micrographic surgery extending to periosteum. **C**, Second recurrence of squamous cell carcinoma on the left forehead shortly after radiation therapy. **D**, Computed tomography scan, coronal view. A computed tomography scan with bone windows clearly shows erosive changes (*arrow*) of the zygomatic process of the left frontal bone. **E**, Free flap from the left thigh. Patient after excision of the involved portion of the frontal bone by an ear, nose, and throat specialist and subsequent free flap repair.

aggressive cutaneous SCC of the forehead and scalp may involve underlying cortical bone. Locally advanced BCC have also been reported to penetrate the calvarium, dura, and even the brain with an estimated incidence of intracranial invasion of 0.03%.<sup>7,8</sup> The presence of a firm, fixed tumor mass or focal tenderness over a bony margin is suspicious for bony invasion, and an imaging study is indicated in these cases.

**Case 1.** Bony invasion of the calvarium by SCC can be seen in Fig 1, D. A 64-year-old male renal transplant patient developed a biopsy-proven recurrent SCC on the left forehead (Fig 1, A). The tumor was cleared by Mohs micrographic surgery to the depth of periosteum (Fig 1, B) and the incision was closed with an advancement flap. The patient received postoperative radiation therapy. Several months after completion, he developed a new



**Fig 2.** Squamous cell carcinoma with bony invasion. **A**, Axial postcontrast computed tomography scan at the level of the recurrence shows an enhancing soft tissue mass (arrow) at the margin of a free flap (asterisk). **B**, Bone windows reveal erosion of cortical bone. (Reproduced with kind permission of Springer Nature from Shah K, Onufer J, MacFarlane DF. Imaging of head and neck skin cancer. In: MacFarlane DF, editor. Skin cancer management. New York: Springer Nature; 2010.)

nodule and complained of pain along the left eyebrow (Fig 1, C). A CT scan was ordered to evaluate possible bony involvement. Cortical erosion of the frontal bone was easily seen on CT (bone windows, coronal view; Fig 1, D). The patient was referred to an ear, nose, and throat specialist and underwent resection of the involved frontal bone and placement a free flap from the anterior thigh (Fig 1, E).

**Case 2.** Bony invasion of the calvarium by SCC can be seen in Fig 2. A 70-year-old man presented with a biopsy-proven recurrent SCC on the left temple after wide local excision with a radial forearm flap had been performed 6 months earlier. A CT scan was ordered to evaluate the extent of local recurrence and because of a concern for bony involvement. An extensive soft tissue mass was seen on axial postcontrast images, and clear cortical erosion was appreciated on bone windows.

**Discussion.** A CT scan is the study of choice for the evaluation of cortical bone, while MRI scans provide better evaluation of the bone marrow.<sup>9</sup> High-resolution bone windows on CT scans can provide greater detail. The preoperative evaluation of a locally aggressive tumor may include both MRI and CT scans to determine the extent of soft tissue invasion and evaluate the presence of bony erosion and marrow invasion. Cortical invasion of the skull is typically manifested by loss of the expected architecture of cortical bone. Marrow invasion is better assessed by MRI, which allows imaging of abnormal enhancement or replacement of marrow fat by tumor. While microscopic subclinical bony invasion may not be detectable on a CT scan, biopsy specimens of bone can be obtained when a

high index of suspicion is present based on the presence of pitting or irregular appearance of the calvarium.<sup>7</sup>

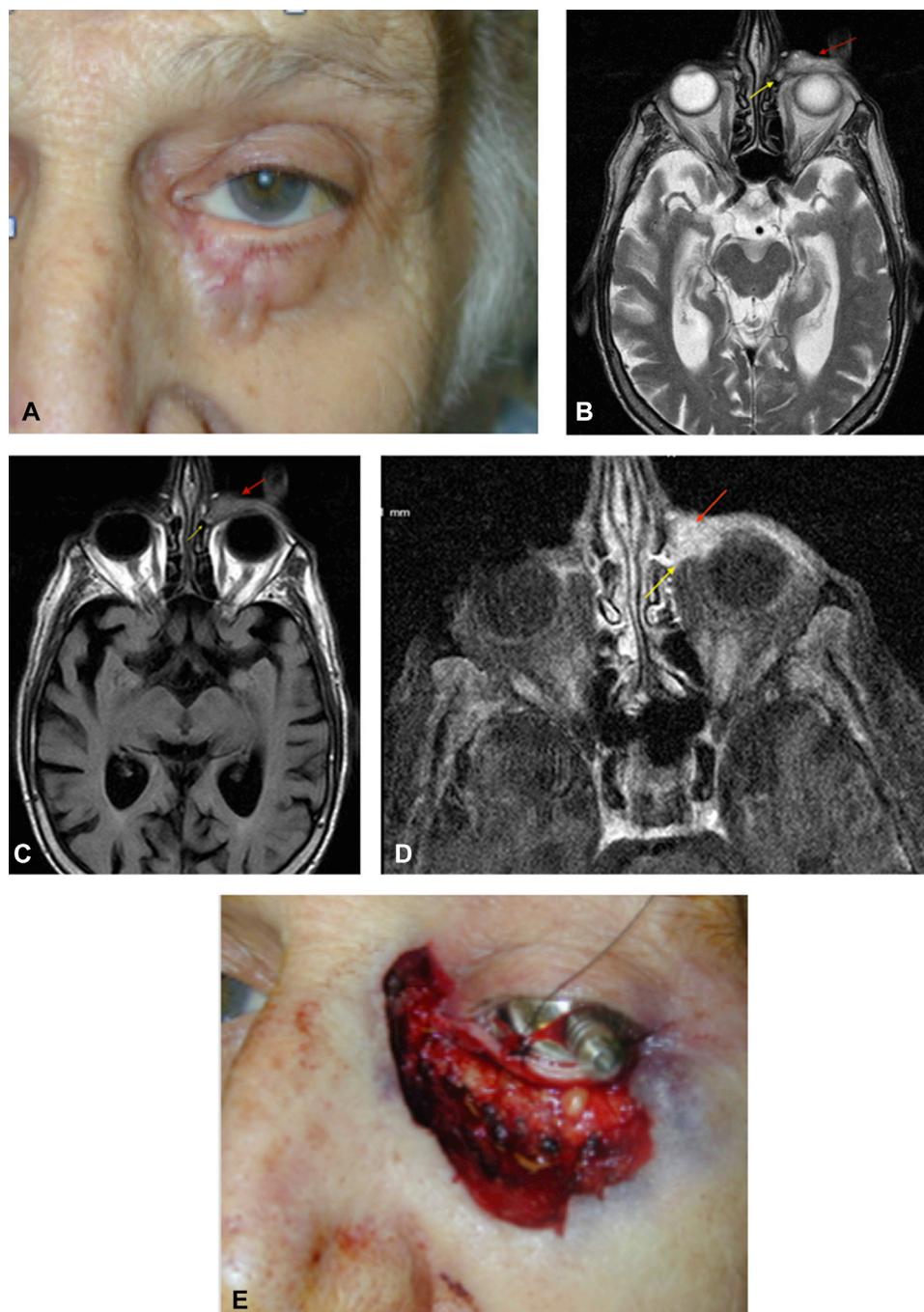
### Orbital invasion

#### Key point

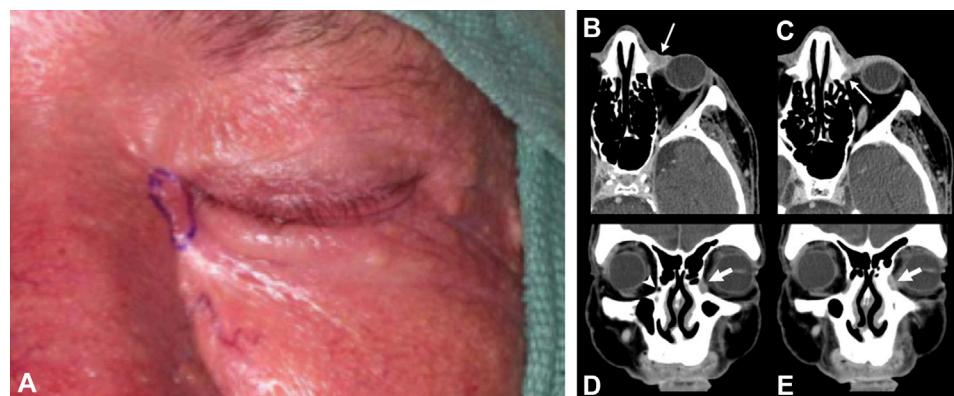
- **Painful, fixed tumors involving the orbital rim or medial canthus or reduced range of motion of the extraocular muscles should prompt imaging to evaluate orbital invasion**

Aggressive skin cancers in the orbital region can invade the orbit by direct extension into orbital contents or retrograde perineural spread (PNS).<sup>10-18</sup> Tumors located at the medial canthus are at particular risk, and clinical signs suggestive of orbital invasion include fixation to bone, reduced ocular mobility, and displacement of the globe.<sup>14,15</sup> Establishing the presence of orbital invasion by cutaneous cancers preoperatively allows for early intervention and coordination with surgical subspecialists, particularly oculoplastic surgeons, ear, nose, and throat specialists, and neurosurgeons.

**Case 3.** Recurrent basal cell carcinoma on the lower eyelid can be seen in Fig 3, A. A 92-year-old man with a history of a recurrent BCC on the lower eyelid had distortion of the canthalculus but no restriction of ocular movement on the clinical examination. An MRI scan was obtained to assess tumor depth and possible orbital invasion (Fig 3, B-D). Because the mass appeared to be preseptal and anterior to the check ligament, Mohs micrographic surgery was performed. The tumor defect extended to the level of preseptal fat pads (Fig 3, E). Additional intraoperative histologic sampling of periorbital fat



**Fig 3.** Recurrent basal cell carcinoma on the lower eyelid. **A**, Large pearly plaque on the left lower eyelid. **B**, T<sub>2</sub>-weighted magnetic resonance imaging scan, axial view, showing infiltrating preseptal mass (*red arrow*). The mass does not appear to extend beyond the medial check ligament (*yellow arrow*). **C**, T<sub>1</sub>-weighted magnetic resonance imaging scan, axial view, showing lower lid mass with infiltration of the preseptal soft tissues (*red arrow*) abutting the medial check ligament (*yellow arrow*). The white high-signal tissue in the orbit represents fat. **D**, T<sub>1</sub>-weighted magnetic resonance imaging scan with fat saturation after gadolinium enhancement. The bright signal from the orbital fat has been suppressed to allow better visualization of the enhancing soft tissue mass (*red arrow*). The check ligament (*yellow arrow*) is again seen and appears intact. **E**, Defect after Mohs micrographic surgery.



**Fig 4.** Recurrent basal cell carcinoma of the medial canthus with involvement of the lacrimal sac (**A**). Computed tomography, post contrast images of the orbit (**B** to **E**). **B**, Axial view. Left medial canthal mass (*arrow*) abutting the periosteum and the attachment of the medial rectus muscle. **C**, The lacrimal sac (*arrow*) appears to be involved. **D**, Coronal view. The left lacrimal sac is enlarged (*large arrow*) while the right is normal (*small arrow*). **E**, Enlargement of the left lacrimal sac (*arrow*). (Reproduced with kind permission of Springer Nature from Shah K, Onufer J, MacFarlane DF. Imaging of head and neck skin cancer. In: MacFarlane DF, editor. Skin cancer management. New York: Springer Nature; 2010.)

by oculoplastics was negative, and the defect was repaired.

**Case 4.** A patient with periorbital BCC can be seen in Fig 4. A 76-year-old man with a history of multiple NMSCs presented with a poorly defined pearly pink plaque in the left medial canthal region (Fig 4, *A*). The patient had a history of Mohs micrographic surgery for BCC at the same site approximately 4 years earlier. On examination, the lesion appeared to be bound down to the underlying periosteum. A CT scan was obtained to further evaluate for bony and orbital invasion (Fig 4, *B*). The imaging showed the mass to be abutting the periosteum and the attachment of the medial rectus muscle but showed no evidence of bony destruction. Postcontrast enhancement of the left lacrimal sac was seen, consistent with tumor involvement.

## Discussion

While the exact rate of orbital invasion by NMSC has not been established,  $\leq 2.5\%$  of periorbital BCCs are associated with orbital invasion.<sup>15,16</sup> Orbital invasion is most commonly seen with tumors located at the medial canthus. Other risk factors include infiltrative or sclerosing histology (83%), PNI (19.3%), and multiple recurrent tumors.<sup>15</sup> Clinical findings of a fixed tumor along the orbital rim or a decreased range of motion of the extraocular muscles should prompt investigation, but a significant number of cases may be subclinical.<sup>15,16</sup>

In 1 series of histologically confirmed cases of orbital invasion, bony destruction on CT scan was seen in 21% of patients, while soft tissue invasion involving the rectus muscle (5 patients), lacrimal sac

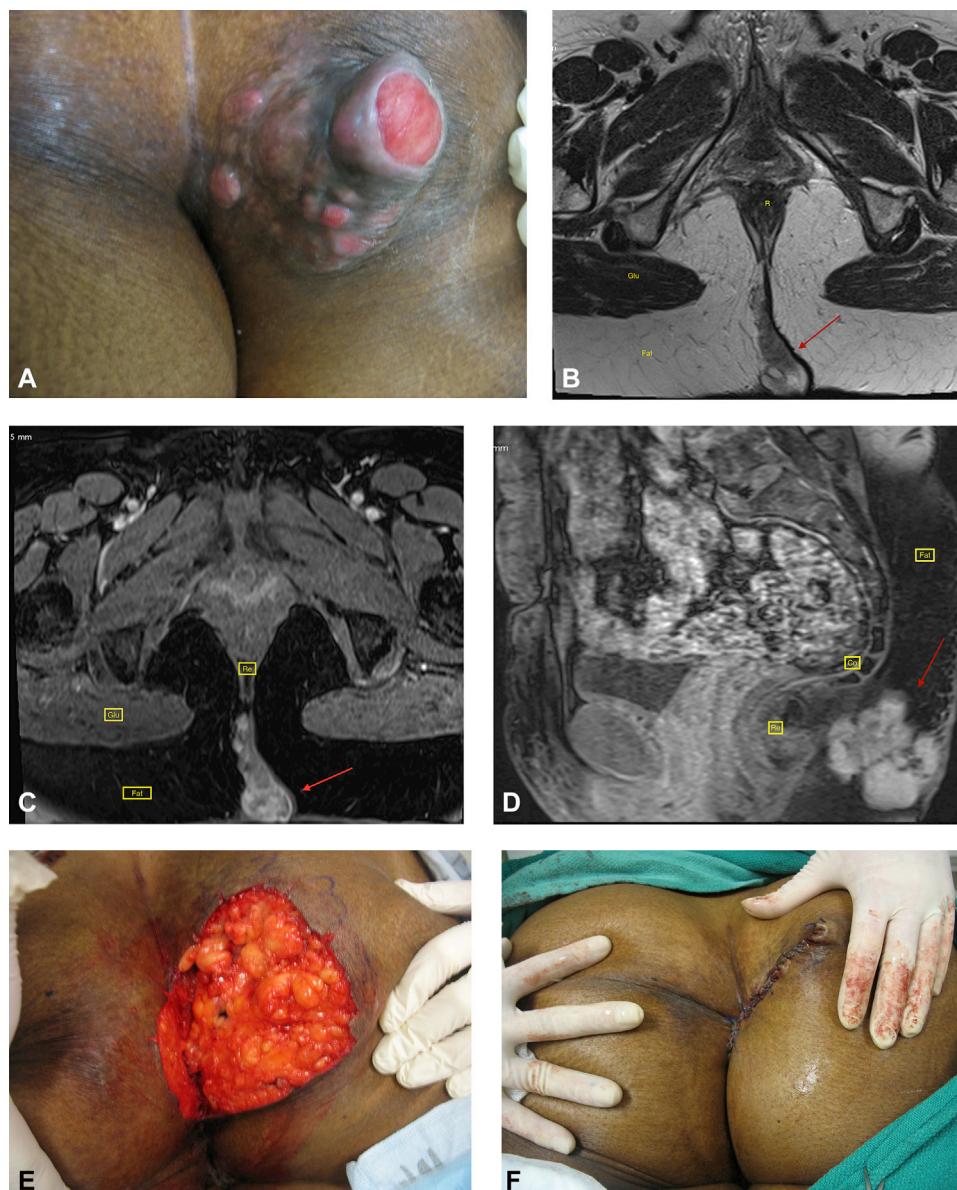
(3 patients), the ethmoid sinus or cribriform plate (4 patients), and the central nervous system (2 patients) was detected in another 21%.<sup>15</sup> CT scans are appropriate for evaluating the bony margins of the orbit,<sup>19</sup> while soft tissue invasion and PNS along the superior orbital wall are best detected by a MRI scan.<sup>20</sup> Because of the bright T<sub>1</sub> signal from intraorbital fat, T<sub>1</sub>-weighted contrast-enhanced fat suppressed images are performed for optimal visualization.<sup>20</sup> Accurate assessment of invasion is critical because involvement of the anterior portion of the orbit may be treated with excision and radiation therapy while bulbar or extensive orbital invasion may require exenteration.<sup>18</sup>

## Assessment of tumor size and depth of invasion within soft tissue

### Key points

- Preoperative imaging of dermatofibrosarcoma protuberans should be considered for large, recurrent tumors with suspected subcutaneous involvement or in critical anatomic locations
- Magnetic resonance imaging is the modality of choice for imaging soft tissue because of its superior resolution
- Magnetic resonance imaging obtained preoperatively may underestimate the margins and depth of extension when compared to histologic margins obtained at the time of surgery

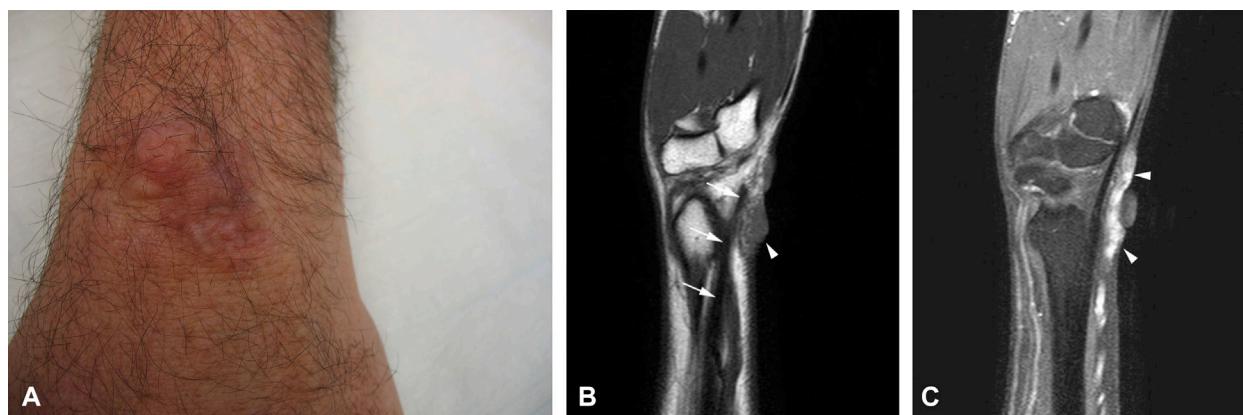
The size and depth of a tumor will greatly impact surgical planning. Infiltrating cutaneous neoplasms



**Fig 5.** **A**, Dermatofibrosarcoma protuberans on the right buttock and gluteal crease. **B**, T<sub>2</sub>-weighted magnetic resonance imaging scan, fast spin echo, axial view. The arrow shows a heterogeneous soft tissue mass. **C**, T<sub>1</sub>-weighted magnetic resonance imaging scan with fat suppression, postcontrast, axial view. The arrow shows an irregularly enhancing mass within the fatty tissue on the right buttock. No involvement of the rectum or gluteal muscles is seen. **D**, T<sub>1</sub>-weighted magnetic resonance imaging scan with fat suppression, postcontrast, sagittal view. The arrow shows an irregularly enhancing mass within the fatty tissue on the right buttock. No involvement of the rectum or gluteal muscles is seen. **E**, Defect after Mohs micrographic surgery. **F**, Repair after Mohs micrographic surgery. Co, Coccyx; Glu, gluteal muscle; Re, rectum.

can be difficult to assess clinically. One particular example is DFSP, which is known to extend through fat and muscle. While large tumors are more likely to invade soft tissue, tumor size alone is not predictive of subclinical extension.<sup>21-23</sup> Microscopic tumor extension may range from 0.3 to 12 cm beyond the clinical tumor margins.<sup>21</sup> On areas with minimal adipose tissue, such as the hands and the

feet, tumor can more easily extend to muscle and even tendon.<sup>24</sup> Imaging can play an important role in planning for reconstruction, particularly when muscle or other critical structures are involved.<sup>24-26</sup> The superior soft tissue contrast of MRI makes it the ideal imaging modality to assess the extent of a soft tissue neoplasm that may involve muscle.<sup>9,27,28</sup>



**Fig 6.** **A**, Dermatofibrosarcoma protuberans on the dorsal aspect of the wrist. **B**, T<sub>1</sub>-weighted magnetic resonance imaging scan shows a longitudinal (sagittal) view of the second extensor tendon sheath (*arrows*). Note the tumor (*arrowhead*) abutting the tendon sheath. **C**, Sagittal T<sub>1</sub>-weighted, fat-suppressed, postcontrast magnetic resonance imaging scan showing enhancement of the tumor (*arrowheads*). (Reproduced with permission from Riggs et al.<sup>24</sup>)

**Case 5.** DFSP on the right buttock. A 65-year-old African American woman presented with an enlarging mass on her right buttock (Fig 5, A). A biopsy specimen was obtained, and histologic examination confirmed the diagnosis of DFSP. Because of the size of the mass and extension to the midline and gluteal crease, an MRI scan was performed to determine the depth of involvement. MRI scans with and without contrast revealed a heterogenous enhancing mass involving the deep fat but sparing the rectum and gluteal muscles (Fig 5, B and C). The tumor was excised using Mohs micrographic surgery (defect shown in Fig 5, D) and closed primarily (Fig 5, E).

**Case 6.** DFSP on the left wrist (adapted with permission from Riggs et al<sup>24</sup>). A 55-year-old man presented with a 10-year history of an asymptomatic, slowly enlarging mass on his left wrist. The physical examination revealed a 6-cm × 7-cm firm, pink, multinodular plaque that felt fixed to underlying soft tissue and tendon on palpation (Fig 6, A). The initial biopsy specimen revealed DFSP extending through the dermis and into the fibrous septa in the subcutaneous fat. An MRI scan revealed a 6.6-cm × 9.2-cm mass in the subcutaneous tissue with decreased signal intensity on T<sub>1</sub>-weighted images relative to the subcutaneous fat (Fig 6, B). T<sub>1</sub>-weighted fat-suppressed contrast-enhanced images showed a high-intensity tumor adjacent to the extensor tendon sheaths. Excision was performed by a hand surgeon and revealed positive deep surgical margins overlying the extensor tendons. Reexcision was performed with partial removal of the extensor tendons of all digits of the left hand. The patient required tendon reconstruction with autologous grafting and a microvascular radial forearm flap.

## Discussion

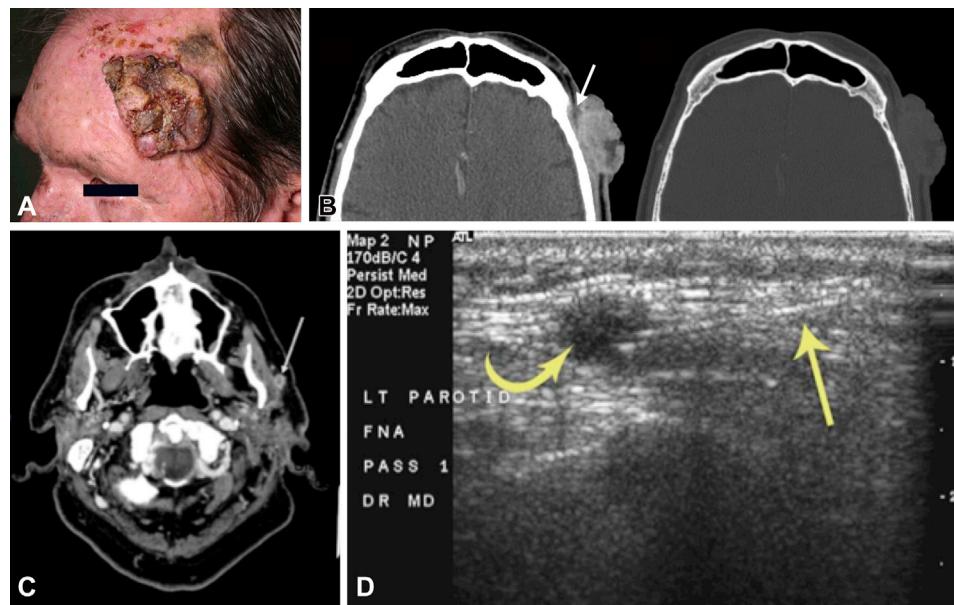
The use of MRI for the evaluation of DFSP was initially described in 1994,<sup>29</sup> and its utility in evaluating subcutaneous extension into fat and muscle has been confirmed in subsequent studies. DFSPs typically have a lower signal intensity than subcutaneous fat on T<sub>1</sub>-weighted images and can be isointense or slightly hypointense compared to skeletal muscle.<sup>25,29</sup> With T<sub>2</sub>-weighted imaging, DFSPs are either hyperintense or isointense compared to fat. Because the brightness of the fat signal on T<sub>1</sub>-weighted images can obscure tumor pathology, fat suppression techniques are routinely used for DFSP.<sup>24</sup>

While MRI is superior to clinical palpation in detecting the depth of penetration of DFSP, it may underestimate the depth and area of involvement compared to histology as the criterion standard.<sup>30</sup> The accuracy and limitations of MRI in predicting tumor extension of DFSP remain unclear. While submillimeter resolution can be achieved with high field strength magnets (4 T) and specialized surface coils, the resolution of a standard study using most commercially available MRI scanners (1.5-3.0 T field strength) may range from 1 to 4 mm. MRI findings of potential deep involvement can facilitate advance collaboration with other surgical subspecialists.

## Tumor staging: Nodal involvement and distant metastases

### Key points

- Computed tomography and magnetic resonance imaging scans are both used to evaluate lymph nodes in the head and neck and offer similar sensitivity and specificity



**Fig 7.** **A**, Squamous cell carcinoma on the left forehead. **B**, Computed tomography (CT) scan with contrast. Axial postcontrast CT scan through frontal sinus (left) shows involvement of the temporalis muscle (*arrow*). Bone windows (right) show no evidence of bony erosion or lymphadenopathy. **C**, Axial postcontrast CT scan through the level of the parotid gland reveals a subcentimeter, enhancing, centrally necrotic preauricular lymph node suspicious for metastasis (*arrow*). **D**, Obtaining an ultrasonography-guided biopsy specimen of the suspected parotid nodal metastasis. The needle (*straight arrow*) approaches the rounded hypoechoic lymph node (*curved arrow*). (Reproduced with kind permission of Springer Nature from Shah K, Onufer J, MacFarlane DF. Imaging of head and neck skin cancer. In: MacFarlane DF, editor. Skin cancer management. New York: Springer Nature; 2010.)

- **Positron emission tomography-computed tomography offers greater sensitivity for detecting hypermetabolic tumors**
- **Positron emission tomography-computed tomography is currently the imaging modality of choice for the staging of Merkel cell carcinoma**

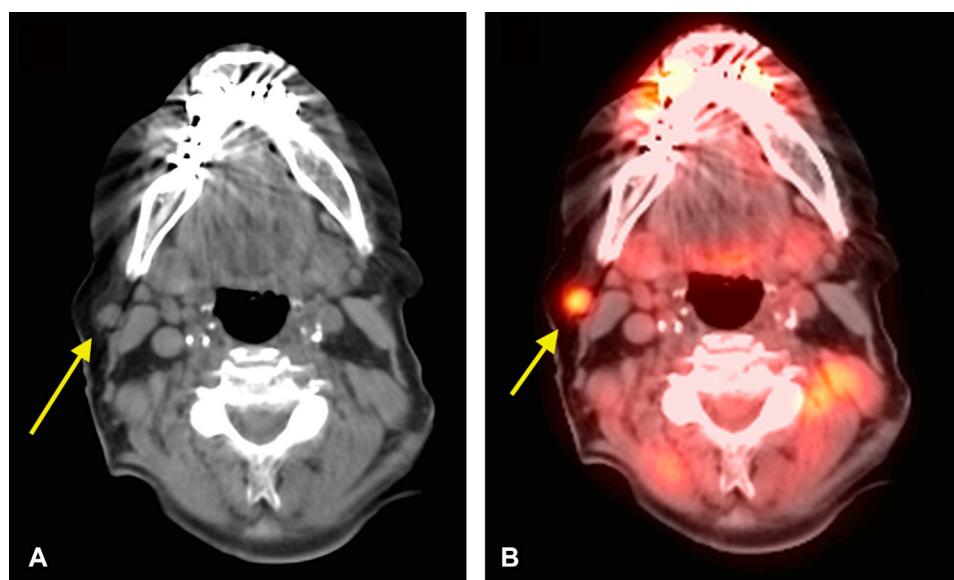
SCC, MCC, and select rare tumors with high rates of metastasis (eg, angiosarcoma and sebaceous carcinoma) most frequently require imaging studies for evaluation of local nodal and distant metastases. Management of these tumors may require the skill of subspecialists, such as otorhinolaryngologists, medical or surgical oncologists, and radiation oncologists. CT and MRI scans are frequently used for the assessment of occult adenopathy associated with head and neck tumors. The majority of imaging studies regarding adenopathy address mucosal tumors, and there are no definitive guidelines for use in the setting of cutaneous neoplasms. US is often used for screening of superficial regional lymph node basins, such as the parotid and cervical nodes, and for guided lymph node biopsy in the setting of palpable nodes. Functional imaging with FDG PET CT may detect smaller hypermetabolic

nodes and is most commonly performed for evaluation of occult adenopathy in the setting of SCC and MCC.<sup>9</sup>

**Case 7.** SCC on left temple with lymph node metastasis (reproduced with permission from Shah, Onufer, and MacFarlane<sup>6</sup>). A 67-year-old man with a 5-year history of a tumor on the left temple was referred for excision (Fig 7, A). A CT scan was obtained preoperatively to evaluate for bone involvement and nodal metastasis. Despite invasion through the temporalis (Fig 7, B), no adenopathy was seen. Five months after his initial surgery, a follow-up CT scan revealed a new left preauricular lymph node that was suspicious for metastasis (Fig 7, C). An US-guided fine-needle aspiration biopsy (FNAB) specimen revealed metastatic SCC (Fig 7, C). The patient underwent a left parotidectomy, confirming metastasis. Left neck dissection on the same date found no cervical nodal metastasis.

## Discussion

Both CT and MRI scans can be used to evaluate lymph nodes. Practically, CT or MRI should be selected based on the imaging requirements of the primary site, because CT and MRI scans have similar



**Fig 8.** Merkel cell carcinoma with positive lymph node seen on a positron emission tomography–computed tomography scan. **A**, Computed tomography scan, axial view. A small submandibular lymph node is seen on the localizing scan (*arrow*). **B**, Positron emission tomography–computed tomography scan. The node (*arrow*) shows increased 18-fluoro-deoxyglucose uptake (standard uptake value, 3.6), consistent with a nodal metastasis.

reported sensitivity and specificity for abnormal lymph nodes.<sup>9,31–33</sup> Lymph nodes are typically categorized by levels I to VI based on anatomic location and depth, which standardizes communication between radiologists, head and neck surgeons, and radiation oncologists.<sup>34–39</sup> The levels most commonly involved by cutaneous tumors are levels I (submental and submandibular), II (upper jugular), and V (posterior triangle of the neck).<sup>37</sup> Lymph nodes above 1 cm along the short axis and above 1.5 cm at the jugulodigastric station are considered abnormal.<sup>40</sup> Using a size cutoff of 1 cm, the sensitivity and specificity of CT and MRI scans are comparable (88% vs 81% and 48 % vs 39%, respectively).<sup>41</sup> At subcentimeter sizes, irregular or intense enhancement, central necrosis, surrounding fat stranding, conglomerated nodes, and asymmetry can be used to suggest metastasis.<sup>35–37</sup> Several studies have shown that necrosis is the most specific or reliable indicator of adenopathy.<sup>41–43</sup> Subtle findings, if at the site of expected nodal drainage, become more worrisome.

The majority of studies pertaining to head and neck imaging are in the setting of patients with mucosal SCC. An examination of 17 studies of cervical nodal imaging using histopathologic correlation found that CT, MRI, US, and US-guided FNAB all had similar sensitivities, ranging from 0.80 to 0.87, although US did have the highest sensitivity.<sup>44</sup> Specificity was highest for US-guided

FNAB at 0.98, as expected. US was next at 0.86, then CT at 0.76 and MRI at 0.63. Data therefore support the fact that US has the highest diagnostic odds ratio.<sup>44</sup> US is, however, a highly operator-dependent modality for architectural evaluation of lymph nodes but can be easily used to guide the biopsy of clinically palpable nodes at most institutions. PET scans may be both more sensitive (87–90%) and specific (94–99%) than US.<sup>45,46</sup> The nodal drainage of cutaneous SCC is anatomically different and less predictable than mucosal SCC but the imaging characteristics of the nodes are comparable.<sup>46,47</sup>

Because data specific for cutaneous SCC are sparse, no precise clinical guidelines exist for radiologic evaluation. New evidence suggests that the use of imaging in high risk cutaneous SCC may improve patient outcome. Ruiz et al<sup>48</sup> found that 46% of high risk SCC cases (T2b/T3) in their institution underwent imaging studies which resulted in treatment changes in 33%. The patients that were imaged had a greater 5 year disease-free survival rate (78%) than patients that did not undergo imaging (51%). This suggests that imaging in these patients results in earlier identification and treatment of advanced disease which, in turn, results in improved outcome. The most frequently used imaging modalities were CT (79%), PET CT (21%) and MRI (19%). Because the study was a retrospective analysis, it may underestimate the positive impact of more sensitive technologies such as PET CT.



**Fig 9.** Metastatic Merkel cell carcinoma. **A**, Maximum intensity projection reconstructed positron emission tomography scan, coronal view. Multiple abdominal nodal metastases are seen (arrow). **B**, Fused positron emission tomography–computed tomography images (coronal view). Arrows indicate hypermetabolic nodes. The patient's palpable lymph nodes showed increased uptake and unsuspected right neck nodal metastases. (Reproduced with kind permission of Springer Nature from Shah K, Onufer J, MacFarlane DF. Imaging of head and neck skin cancer. In: MacFarlane DF, editor. Skin cancer management. New York: Springer Nature; 2010.)

**Case 8.** MCC with lymph node metastasis. An elderly woman with an MCC on the right cheek had a PET CT as part of her initial staging. A small submandibular lymph node is seen on the localizing CT scan (Fig 8, A). Increased uptake (SUV of 3.6) associated with this node is seen on the PET CT fusion image (Fig 8, B), consistent with metastatic disease.

**Case 9.** MCC with distant metastasis (reproduced with permission from Shah, Onufer, and MacFarlane<sup>6</sup>). A 51-year-old man had undergone excision of an MCC on his right thigh. A few months later, a CT scan revealed peripancreatic adenopathy. During chemoradiation, progressive lymphadenopathy was noted. PET CT was obtained

as part of restaging before investigational therapy (Fig 9).

### Discussion

There is no generally accepted recommendation for primary staging of MCC, but PET CT is frequently used for early detection of occult adenopathy and distant metastasis. MCC is a highly proliferative and metabolically active tumor that makes it amenable to staging by PET CT. Reports suggest that PET and PET CT are sensitive in the staging, assessment of treatment response, and continued surveillance of MCC.<sup>49–52</sup> PET CT has been found to have a sensitivity of 86% to 92% and a specificity of 96% to 100%.<sup>53,54</sup> In addition, in a study of 102 patients with

MCC, PET resulted in a change in the management plan in 37% of patients.<sup>55</sup> Specifically, 17% were upstaged over conventional staging because of occult nodal (76%) or distant metastases (24%). Not all MCCs are FDG avid.<sup>53</sup> Nonetheless, PET CT scan has become the generally accepted imaging modality of choice for primary staging of MCC.<sup>56,57</sup> Obtaining a sentinel lymph node biopsy specimen from patients with MCC who present with local disease only after PET CT staging may be warranted, because pathologic staging can help accurately determine prognosis, and more recent data suggest that the number of involved nodes is strongly predictive of survival.<sup>58</sup>

Other imaging modalities used in MCC include US, CT, and MRI. US has been used to evaluate easily accessible lymph nodes, such as in the head and neck region, with an accuracy of 89% to 94%.<sup>59,60</sup> In addition, US has been used to aid in FNAB procedures in patients with MCC.<sup>61,62</sup> A CT scan is a reliable method for the initial staging of patients with MCC.<sup>47,54,59</sup> Finally, MRI may be the modality of choice when evaluating for soft tissue metastasis, invasion of the central nervous system, or invasion of bone marrow.<sup>61,63,64</sup>

### Perineural spread or invasion

#### Key point

- Magnetic resonance imaging is the most sensitive imaging modality for the detection of perineural spread of tumor

PNI is a histologic term that describes the microscopic presence of tumor in the space between the nerve and the nerve sheath.<sup>65</sup> PNS is a phenomenon characterized by tumor cell spread along the loose connective tissue sheath (perineurium) or within the endoneurial spaces of peripheral sensory and motor nerves.<sup>65,66</sup> PNI is present histologically in ≤5% of head and neck skin cancers, including SCC, BCC, desmoplastic melanoma, and microcystic adnexal carcinoma.<sup>12-14,67</sup> Incidental PNI involving small nerves <0.1 mm in diameter is considered low risk, while the involvement of nerves >0.1 mm is associated with a significant risk of morbidity and mortality.<sup>68</sup> While the majority of patients with PNI are asymptomatic, the presence of symptoms—pain, anesthesia, paresthesia, or motor impairments—suggests PNS with involvement of major sensory (cranial nerve [CN] V) or motor (CN VIII) nerves, which warrants additional investigation.<sup>69,70</sup> While the presence of PNS is associated with increased local recurrence and metastasis and decreased survival, local salvage may be possible with early detection and treatment.<sup>68-73</sup> In asymptomatic patients, a high index of suspicion is

needed to identify PNS and should be considered in patients with high-risk tumors.

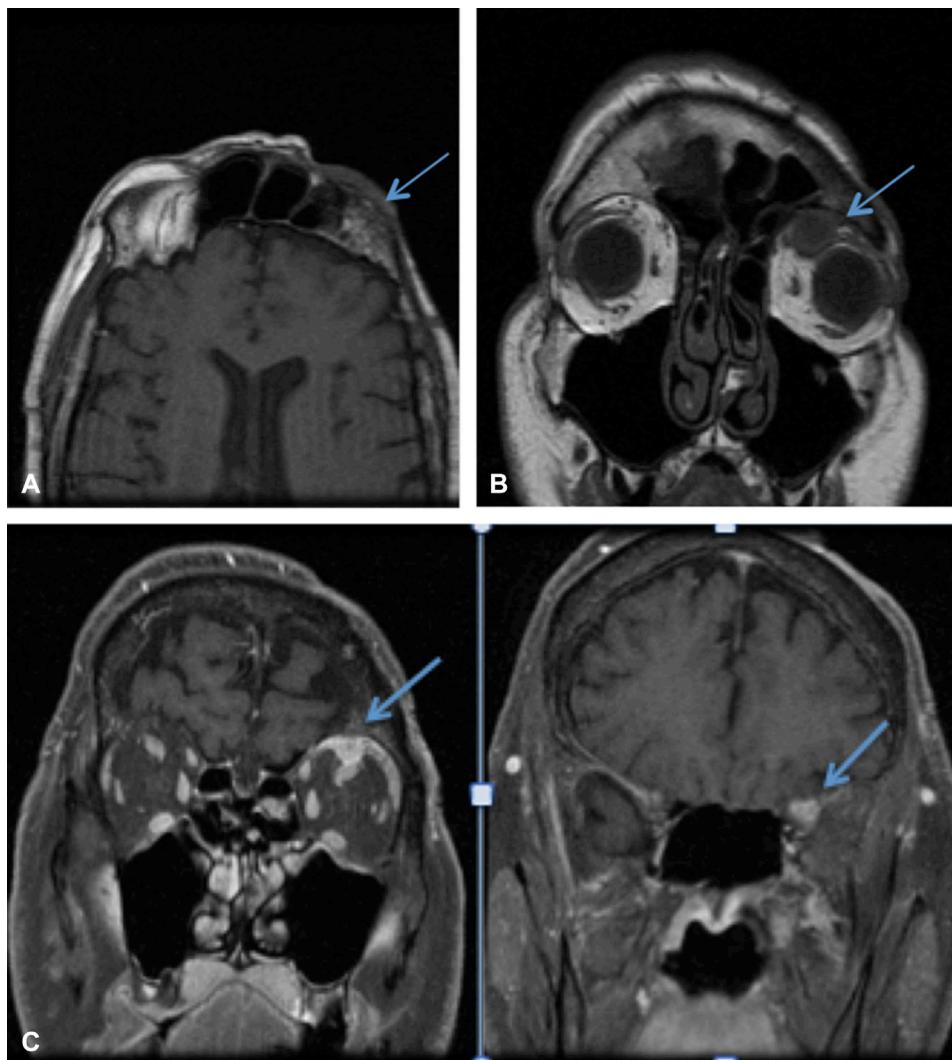
*Case 10.* SCC with PNS (reproduced with permission from Shah, Onufer, and MacFarlane<sup>6</sup>). A 64-year-old man presented with a left supraorbital SCC that was initially treated with primary excision. The lesion recurred locally 7 months later and was treated with radiation therapy. A recurrence approximately 8 months later was treated with Mohs micrographic surgery at an outside facility with a positive margin at the supraorbital nerve. The histologic results revealed an invasive, poorly differentiated SCC. Approximately 10 months later, he presented with headache, proptosis, blurred vision, and V1 paraesthesia. An MRI scan revealed PNS along the V1 division of the trigeminal nerve (Fig 10). The patient underwent stereotactic radiosurgery.

### Discussion

Risk factors for PNI include midface location, male sex, tumor size >2 cm, recurrent tumor, and poorly differentiated histology.<sup>70</sup> Radiologists distinguish between PNI, a histologic phenomenon, and PNS, which affects nerves large enough to be identified by imaging. The most commonly affected nerves are the second and third division of the trigeminal nerve (CN V, V2, and V3) and the facial nerve (VII).<sup>69</sup> Retrograde PNS involving the cranial nerves and the central nervous system can occur insidiously and present years after treatment of the initial tumor. PNS usually progresses in a centripetal fashion towards the skull base, but can spread between the facial and trigeminal nerves via communicating nerves, such as the auriculotemporal, greater superficial petrosal, and vidian (ptygeroid canal) nerves.<sup>71-75</sup>

While there are no clear guidelines for radiologic imaging of patients with presumed PNS, it is generally agreed that high-resolution MRI is the most sensitive imaging modality because of its superior visualization of soft tissue.<sup>67-69,72</sup> In addition to defining tissue planes and determining depth of invasion, MRI is superior at identifying neurotropic tumors.<sup>9,75-77</sup>

MRI findings consistent with PNS include direct and indirect signs.<sup>69-78</sup> Direct signs include enlargement of the affected nerve or contrast enhancement along the nerve<sup>70</sup> and enlargement or erosion of the associated bony foramina.<sup>69,70,72-74</sup> Loss of brightness in the perineural fat pads on the unenhanced T<sub>1</sub>-weighted image may also be a sign of PNS. Loss of the antral fat pad can be indicative of distal V2 involvement, while loss of fat in the stylomastoid foramen can signify distal CN VII involvement.<sup>70</sup> Indirect findings associated with muscle denervation can be a sign of CN VII PNS. Acute denervation can result in hypointense T<sub>2</sub>



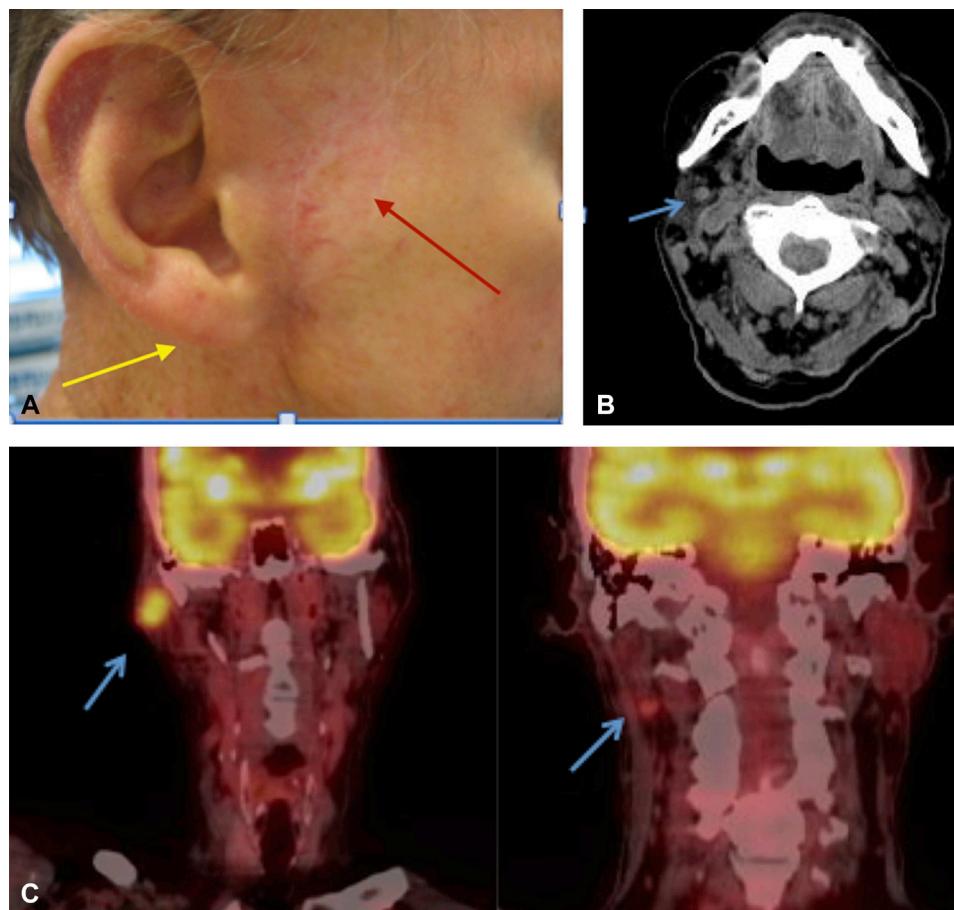
**Fig 10.** Perineural invasion by squamous cell carcinoma. **A**, Noncontrast T<sub>1</sub>-weighted magnetic resonance imaging scan, axial view. Note the decreased signal over the surgical site overlying the frontal sinus (*arrow*). **B**, Noncontrast T<sub>1</sub>-weighted magnetic resonance imaging scan, axial view. Thickening of the left ophthalmic nerve is seen (*arrow*). The bright signal within the orbit represents the surrounding periorbital fat pads. **C**, Contrast-enhanced T<sub>1</sub>-weighted magnetic resonance imaging scan with fat suppression (coronal view) of the orbit and orbital apex. Increased enhancement and thickening of the nerve (*arrow*) is seen within the supraorbital foramen (left) and superior orbital fissure (right). (Reproduced with kind permission of Springer Nature from Shah K, Onufer J, MacFarlane DF. Imaging of head and neck skin cancer. In: MacFarlane DF, editor. Skin cancer management. New York: Springer Nature; 2010.)

signal or excessive enhancement with contrast, while chronic denervation can result in atrophy and fatty replacement of muscle.<sup>72</sup> A CT can also be helpful in the detection of bony changes around the foramina or if there is concern for nerve involvement to the skull base.

Radiologic detection of PNS in the absence of clinical symptoms is rare, and only 22% (17/35) of patients with clinically symptomatic PNS may have radiologically detectable disease.<sup>69</sup> Twenty-one percent to 49% of histologically confirmed cases of

PNI associated with NMSC are not radiologically detectable as PNS.<sup>75-77</sup> This is most likely because the size of the involved nerves and extent of invasion were below the level of resolution of the imaging technique.

The absence of radiologically detectable disease in clinically symptomatic or histologically confirmed PNI is associated with a better prognosis.<sup>69,71</sup> When PNS is seen on MRI scans, survival rates appear to be inversely correlated with the extent of radiologically evident disease.<sup>68,69,78</sup> Overall 5-year survival rates



**Fig 11.** **A**, Recurrent squamous cell carcinoma (SCC). Tenderness and edema of the right ear lobe (yellow arrow) 1 year after excision of a preauricular SCC (red arrow). **B**, Enlarged cervical lymph node on computed tomography scan, axial view. An enlarged level 2 lymph node is present in the right neck (arrow). **C**, Local recurrence of SCC and positive cervical lymph node on a positron emission tomography–computed tomography scan, coronal view. Intense uptake is seen in the right ear lobe (left, arrow) consistent with local recurrence, while the increased standard uptake value of the level 2 lymph node (right, arrow) is consistent with nodal disease.

range from 86% to 90% for patients with imaging-negative PNI<sup>69,70</sup> but only 50% for patients with PNS seen on MRI scans.<sup>70</sup>

Because of the often subtle findings of PNS on MRI scans, clinicians must alert radiologists to specifically search for these findings that may be otherwise missed. In a study of 38 patients with head and neck cancer and histologically documented PNI, 84% of radiologic reports failed to address PNI.<sup>80</sup> The radiologist detected only 10% of cases preoperatively, while 79% were found to have evidence of PNS on retrospective review. Clearly, heightened awareness of PNS results in better detection by the radiologist.

Patients that are clinically symptomatic for PNS with or without radiologically evident disease should be treated aggressively with surgery or radiation. Radiologic evaluation of PNS can help guide therapeutic strategies.<sup>80-82</sup> Collaboration with neurosurgeons or skull-based ear, nose, and throat specialists

may be required to eradicate PNS tracking deep into the central nervous system. Intensity-modulated radiation therapy or proton radiation in the setting of patients with PNS extending to the skull base may also be considered. Chemosensitization before conventional radiation has been reported to improve treatment response.<sup>73</sup>

#### Postoperative surveillance and detection of recurrent disease

##### Key point

- **Positron emission tomography–computed tomography scans are used for postoperative surveillance of patients with recurrent head and neck squamous cell carcinoma because it offers enhanced sensitivity of detection**

Oncologists and surgeons frequently follow their patients with aggressive head and neck malignancies postoperatively with serial imaging studies. The presence of postsurgical fibrosis and alteration of

the normal anatomy may obscure local tumor recurrence on conventional CT or MRI scans. PET CT is particularly useful in this scenario because it is still able to detect recurrent, metabolically active disease in areas with surgically altered anatomy.

**Case 11.** Recurrent SCC with lymphatic invasion. A 65-year-old man underwent excision of a large right preauricular SCC. No palpable lymph nodes were present at the time of presentation. At 18 months postoperatively, the patient complained of soreness of the right ear and swelling of the ear lobe (Fig 11, A). No palpable lymph nodes were present on a physical examination. PET CT was performed and revealed an increased signal within the right earlobe and an ipsilateral level 2 lymph node, indicative of lymphatic spread (Fig 11, B and C). The patient underwent auriculectomy and neck dissection.

## Discussion

Close follow-up of patients with aggressive head and neck SCC is critical for the early detection of recurrent disease. Initial staging of the head and neck can be facilitated with the use of PET CT.<sup>71-84</sup> The scarring, fibrosis, and altered anatomy of the primary site and lymph node basin can make detection difficult on MRI or CT scans. Although false positive rates can be high in the immediate postoperative period because of inflammation and swelling, a PET CT scan can be useful for detecting the early recurrence of head and neck SCC after surgery.<sup>84-87</sup> In 1 study, positive nodes detected on PET CT scan after surgery were histologically positive in 46% and the scan altered management in 15% of cases.<sup>87</sup> Some studies support that FDG PET/CT is more accurate than conventional follow up physical exam in detecting recurrent head and neck SCC and recommend serial scans for early detection.<sup>88</sup>

## CONCLUSIONS

In conclusion, although the majority of skin cancers can be treated without additional information provided by imaging studies, large or aggressive high-risk tumors or those that compromise important anatomic structures may necessitate additional structural and functional information to optimize management.

Depending on the clinical information that is sought, ≥1 imaging studies may be required. In general, CT scans are most useful to evaluate for cortical bone involvement and potentially for nodal staging; MRI scans are best for the evaluation of soft tissue, PNI, and the central nervous system; US can be used to noninvasively evaluate superficial lymph nodes and to guide lymph node biopsy procedures; and PET CT scans are ideal for the evaluation of distant metastases and potentially for postoperative surveillance. While

certain generalizations can be made regarding the utility of each modality, each case must be considered individually. Clinical presentation and circumstances vary in each case, so the imaging work-up should be carefully considered. Ultimately, it is critical to communicate clearly with your radiologist in order to choose the best imaging modality or combination of studies to best evaluate the patient.

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## Answers to CME examination

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# Psychocutaneous disease

## Clinical perspectives



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### Learning objectives

After completing this learning activity, participants should be able to assess the nomenclature and classification of psychocutaneous disease; describe common psychocutaneous diseases/recognize the associated psychiatric/psychosocial comorbidities; and identify appropriate management plans for patients with these diseases.

### Disclosures

#### Editors

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Psychocutaneous disease, defined in this review as primary psychiatric disease with skin manifestations, is commonly encountered in dermatology. Dermatologists can play an important role in the management of psychocutaneous disease because patients visit dermatology for treatment of their skin problems but often refuse psychiatric intervention. This review describes common psychocutaneous syndromes, including delusional, factitious, obsessive-compulsive and related, and eating disorders, as well as psychogenic pruritus, cutaneous sensory (pain) syndromes, posttraumatic stress disorder, and sleep-wake disorders. The updated classification of these disorders in the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* is included. Strategies for management are reviewed. (J Am Acad Dermatol 2017;76:779-91.)

**Key words:** antidepressant; antipsychotic; cognitive-behavioral therapy; drug; pruritus; management; psychotherapy; psychocutaneous.

**P**sychocutaneous disease, defined in this review as primary psychiatric disease with skin manifestations, is frequently encountered in dermatology, with an estimated 30% prevalence of psychiatric comorbidity in the outpatient dermatology setting.<sup>1</sup> Patients with psychocutaneous disease routinely refuse

mental health resources, leaving the burden of care upon the dermatologist. Nevertheless, in a recent survey of dermatologists, only 18% reported a clear understanding of psychodermatology, and only 42% were very comfortable in diagnosing and treating psychocutaneous disorders.<sup>2</sup> In this article, we describe

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**Abbreviations used:**

AN:	anorexia nervosa
BED:	binge eating disorder
BFRBD:	body-focused repetitive behavior disorder
BDD:	body dysmorphic disorder
BN:	bulimia nervosa
CBT:	cognitive behavioral therapy
DA:	dermatitis artefacta
DI:	delusional infestation
DSM-5:	<i>Diagnostic and Statistical Manual of Mental Disorders 5th edition</i>
ED:	eating disorder
HRT:	habit reversal training
OCD:	obsessive-compulsive disorder
OCRD:	obsessive-compulsive and related disorder
ORS:	olfactory reference syndrome
RCT:	randomized controlled trial
SPD:	skin picking disorder
SSRI:	selective serotonin reuptake inhibitors

common psychocutaneous conditions and their categorization in *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5).<sup>3</sup> Appropriate management plans for patients with these diseases are included.

## DELUSIONAL INFESTATION

### Key points

- Delusional infestation is the most common monosymptomatic, hypochondriacal psychosis in dermatology
- Antipsychotic medications have a high response rate

In delusional infestation (DI; also known as delusions of parasitosis), patients have a fixed, false belief that they are infested with parasites or have foreign objects extruding from their skin.<sup>4</sup> It is an “encapsulated” (monosymptomatic) delusion (ie, the sole delusion that the patient experiences). DI is classified as a delusional disorder, somatic type in DSM-5 (diagnostic criteria in Table I). Comorbid psychiatric disease, especially depression, anxiety, and substance abuse, is common.<sup>5</sup>

**Epidemiology.** The prevalence is 5.58 cases per million persons in the hospital and public health setting, and 83.23 per million persons in the private practice setting.<sup>6</sup> Age of onset is bimodal, with a peak prevalence in patients 20 to 30 years of age and >50 years of age.<sup>7</sup> There is a 2:1 female to male ratio among patients >50 years old.<sup>7</sup> Approximately 8% to 12% of patients demonstrate folie à deux (ie, share symptoms with a friend or relative).<sup>8</sup>

**Clinical features and evaluation.** Patients often describe cutaneous dysesthesias attributed to

the infestation, such as crawling, biting, and stinging (“pins and needles” sensation), and elaborate life-cycles of their “parasites.”<sup>9</sup> About half of the patients present with the “specimen sign,” where they bring specimens (eg, skin particles or hair, and rarely insects) as proof of infestation.<sup>10</sup> Patients use eradication that involves the use of pesticides, disinfectants, and topical medications to cure the infestation. Extraction attempts are common, because patients try to remove the organisms with fingernails or tools, producing self-imposed erosions, ulcers, prurigo nodules, and lichenification (Fig 1).<sup>7,9</sup> Patients isolate themselves from friends and family for fear that they can contaminate others.<sup>7,9</sup>

The diagnosis of DI can be established based on the clinical features and history, and after ruling out other etiologies, such as primary skin disease (eg, scabies and bite reactions).<sup>9</sup> Primary formication—the sensation of bugs crawling on the skin (without the belief of infestation) that is often caused by underlying neurologic disease or substance abuse—should be excluded. It is important to rule out other psychopathologies, because DI may occur as a result of an underlying psychiatric disorder or a global mental illness.<sup>9</sup> In addition, dementia, malignancies, cerebrovascular disease, vitamin B12 deficiency, and systemic disorders causing pruritus can produce organic psychosis with formication. Appropriate laboratory evaluations should be performed.<sup>5,9</sup>

**Management.** The first step is building a strong therapeutic alliance with patients that notoriously lack insight and often reject psychiatric care. The goal of the visit is to improve the patient’s condition, not to convince the patient that they are delusional; physicians should neither challenge nor confirm the delusion.<sup>7</sup> Performing initial laboratory tests, obtaining skin biopsy specimens and cultures, and examining patient specimen samples help rule out organic causes of formication and build rapport.<sup>7,9</sup> Once trust is established, patients can be offered antipsychotic agents. Historically, the treatment of choice has been pimozide (1-10 mg/day).<sup>9</sup> Because of pimozide’s extrapyramidal adverse effects, atypical antipsychotic agents, such as risperidone (0.5-6 mg/day), olanzapine (2.5-20 mg/day), quetiapine (25-600 mg/day), and aripiprazole (2-30 mg/day), are increasingly used.<sup>11</sup> Patients with DI often respond to lower doses of antipsychotic medication than patients with schizophrenia or other psychotic disorders. An improved clinical outcome can be achieved in patients who are engaged in antipsychotic treatment.<sup>12</sup>

**Table I.** *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* diagnostic criteria for delusional and factitious disorders

Delusional disorder*
The presence of $\geq 1$ delusions with a duration of $\geq 1$ month
Criterion A for schizophrenia has never been met. Hallucinations, if present, are not prominent and are related to the delusional theme (eg, the sensation of being infested with insects associated with DI)
Apart from the impact of the delusion(s) or its ramifications, functioning is not markedly impaired, and behavior is not obviously bizarre or odd
If manic or major depressive episodes have occurred, these have been brief relative to the duration of the delusional periods
The disturbance is not attributable to the physiological effects of a substance or another medical condition and is not better explained by another mental disorder, such as BDD or OCD
Factitious disorder imposed on self†
Falsification of physical or psychological signs or symptoms, or induction of injury or disease, associated with identified deception
The individual presents himself or herself to others as ill, impaired, or injured
The deceptive behavior is evidence even in the absence of obvious external rewards
The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder

BDD, Body dysmorphic disorder; DI, delusional infestation; OCD, obsessive-compulsive disorder.

\*Diagnostic and Statistical Manual of Mental Disorders, 5th edition, pages 45-47.<sup>3</sup>

†Diagnostic and Statistical Manual of Mental Disorders, 5th edition, page 165.<sup>3</sup>



**Fig 1.** Delusional infestation. Typical self-inflicted lesions include crusted erosions, linear excoriations, and hypopigmented, atrophic scars. Areas reached by the hand are typically affected.

## FACTITIOUS SKIN DISORDER

### Key points

- Dermatitis artefacta is the somatic expression of psychic distress
- Lesion morphology, the patient's personality, and their medical history help establish the diagnosis

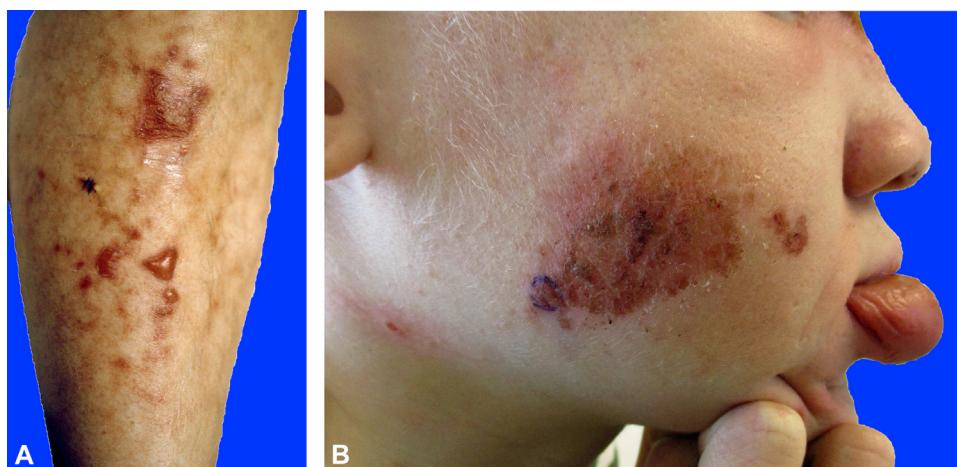
Dermatitis artefacta (DA) is a factitious disorder in which a fully aware patient creates his/her own skin lesions but denies responsibility. DA is classified in the DSM-5 as a factitious disorder imposed on self (diagnostic criteria in Table I) under the category of somatic symptom and related disorders. Patients with DA intend to assume the sick role but are doing so for their own internal psychological motives.<sup>13</sup> Most patients have a history of abuse or neglect

during childhood.<sup>14,15</sup> DA is invariably associated with a comorbid psychological or psychiatric disorder, such as adjustment, depressive, and personality disorders.<sup>14-17</sup>

**Epidemiology.** The prevalence of DA varies from 0.04% to 1.5% in dermatology clinics.<sup>13</sup> There is a female predominance of up to 20:1.<sup>18,19</sup> Although DA can occur at any age, the highest prevalence is around 20 years of age.<sup>20</sup>

**Clinical features and evaluation.** Patients are often anxious, secretive, and reserved in their replies.<sup>13</sup> They classically provide a "hollow history" wherein they offer only vague details about their disorder. They frequently express disappointment with previous providers.<sup>14,15,20</sup> The lesions are monomorphic, appear in crops, and their shape is determined by the method of production. They are generally well-demarcated, with sharp borders and geometric shapes, and do not have the recognizable characteristics or distribution of known dermatoses.<sup>14,20</sup> Clinical presentations include excoriations, ulcers, blisters, panniculitis, localized crusting, eczematous lesions, edema, and purpura and ecchymoses (Fig 2).<sup>20</sup> The most commonly affected sites are the face (34.5%), lower extremities (25%), upper extremities (16.6%), and hands (15.5%).<sup>20</sup>

DA is a diagnosis of exclusion. The differential diagnosis includes skin picking disorder (SPD), malingering, DI, obsessive-compulsive disorder (OCD), and primary skin disease. Patients with SPD do not conceal their role in producing the lesions,



**Fig 2.** Factitious disorder (dermatitis artefacta). The odd, geometric shape of sharply demarcated bullae (**A**), crusted plaques (**A** and **B**), and trauma-induced edematous swelling (lower lip in **B**) in a patient with psychiatric/psychological comorbidity are suggestive of dermatitis artefacta.

and only use their nails/tweezers, whereas DA patients use a range of methods to damage their skin. In malingering, patients are consciously motivated by obvious secondary gain. Primary skin disease, such as pyoderma gangrenosum, and panniculitis should be ruled out.<sup>21,22</sup> Obtaining a skin biopsy specimen is controversial, but may help exclude true skin pathology.

**Management.** DA is therapeutic challenge. The pillars of treatment are: 1) psychotherapy for restructuring the patient's personality, 2) pharmacologic therapy for the psychiatric condition, and 3) treatment of the skin lesions.<sup>20</sup> Creating a supportive, nonjudgmental environment helps establish a friendly relationship with the patient. Providers should set firm boundaries to avoid exploitation, but expect frequent visits, poor compliance, recurrent relapses, and slow progress overall. Although confrontation is to be avoided, at least initially, there may be a point in management where the potential benefits of direct discussion outweigh the potential adverse consequences.<sup>13</sup> Confrontation should be attempted only by those very experienced in psychodermatology. When patients refuse psychiatry referral, the use of psychotropic drugs by the dermatologist can be helpful. Benzodiazepines and buspirone help with anxiety and selective serotonin reuptake inhibitors (SSRIs) with depression and compulsive self-destructive behavior.<sup>14</sup> Antipsychotic drugs, in low doses, such as aripiprazole (2-5 mg/day), pimozide (0.5-1 mg/day), risperidone (0.5-2 mg/day), and olanzapine (2.5-5 mg/day) can help by modulating the dopaminergic dysfunction that may contribute to self-mutilating behavior.<sup>14,20</sup> Dermatologic therapy aims at repairing the skin with emollients and

antibacterial and antifungal agents, as indicated. Occlusive dressings can be used as a diagnostic tool, to prevent self-mutilation, and to aid in skin healing. The prognosis for cure is poor, and the disease tends to wax and wane with the circumstances of a patient's life.<sup>14</sup>

## OBSSESSIVE-COMPULSIVE AND RELATED DISORDERS

### Excoriation (skin picking) disorder

#### Key points

- Excoriation disorder can result in significant tissue damage
- Behavioral therapy and N-acetylcysteine can be helpful

Excoriation disorder, also named neurotic excoriations and pathological skin picking, describes the repetitive picking of skin resulting in noticeable tissue damage. DSM-5 diagnostic criteria are highlighted in Table II. Acne excoriée, a type of SPD, results when acne lesions are scratched and picked (Fig 3). Associated psychopathology (depression, anxiety, or stress) is comparable to severity levels found in trichotillomania and OCD groups.<sup>23</sup> Psychiatric comorbidities include body dysmorphic disorder (BDD; 37% of subjects reporting picking because of dysmorphia), substance use, and borderline personality disorder.<sup>24,25</sup>

**Epidemiology.** Excoriation disorder affects 1% to 5% of the population and shows a female preponderance.<sup>26,27</sup> Onset during childhood or adolescence is most common but can occur later in life as well, typically in patients who are between 30 to 45 years of age.<sup>28</sup>

**Table II.** *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* diagnostic criteria for obsessive-compulsive and related disorders

Trichotillomania (hair-pulling disorder)*
Recurrent pulling out of one's hair, resulting in loss
Repeated attempts to decrease or stop hair pulling
The hair pulling causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
The hair pulling or hair loss is not attributable to another medical condition (eg, a dermatologic condition)
The hair pulling is not better explained by the symptoms of another mental disorder (eg, BDD)
Excoriation (skin-picking) disorder*
Recurrent skin picking resulting in lesions
Repeated attempts to decrease or stop skin picking
The skin picking causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
The skin picking is not attributable to the physiological effects of a substance (eg, cocaine) or another medical condition (eg, scabies)
The skin picking is not better explained by symptoms of another mental disorder (eg, delusions or tactile hallucinations in a psychotic disorder)
BDD <sup>†</sup>
Preoccupation with $\geq 1$ perceived defect(s) or flaws in physical appearance that are not observable or appear slight to others
At some point during the course of the disorder, the individual has performed repetitive behaviors (eg, mirror checking, excessive grooming, skin picking, reassurance seeking) or mental acts (eg, comparing his or her appearance with that of others) in response to the appearance concerns
The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
The appearance preoccupation is not better explained by concerns with body fat or weight in an individual whose symptoms meet diagnostic criteria for an eating disorder
Once BDD is diagnosed, specify if: with muscle dysmorphia; degree of insight (fair, poor, absent/delusional beliefs)

BDD, Body dysmorphic disorder.

\*Diagnostic and Statistical Manual of Mental Disorders, 5th edition, page 133.<sup>3</sup>

<sup>†</sup>Diagnostic and Statistical Manual of Mental Disorders, 5th edition, page 131.<sup>3</sup>

**Clinical features and evaluation.** The face is the most commonly affected site.<sup>29</sup> Individuals generally begin picking over areas of defects, such as acne, scars, scabs, or insect bites.<sup>30</sup> Erosions vary in morphology but are typically grouped at easily accessible sites (Fig 4). Skin lesions and scars tend to have angulated borders. In severe cases, patients may use small utensils, such as tweezers or pins, to dig into their skin.<sup>25</sup> Tissue damage can result in complications, such as infection, bleeding, and severe inflammation.<sup>31</sup> If pruritus is a contributing factor, other etiologies need to be ruled out (see psychogenic pruritus section). Primary psychiatric disorders with secondary excoriations (eg, delusional infestation and DA) need to be ruled out.

**Management.** N-acetylcysteine 1200 to 3000 mg/day significantly reduced skin picking symptoms in a randomized controlled trial (RCT).<sup>30</sup> In addition, cognitive-behavioral therapy (CBT) and habit-reversal training (HRT; aims at replacing an old habit



**Fig 3.** Acne excoriée. Extensive excoriated acne lesions and severe monomorphic atrophic scars on the back, shoulders, and arms in a patient with chronic anxiety.

with a more desirable one) are increasingly showing benefit.<sup>32,33</sup> SSRIs have been studied in controlled trials with mixed results that do not robustly support their efficacy<sup>33</sup>; still, they may help by treating underlying anxiety. Patients with acne excoriée should receive appropriate acne treatment.



**Fig 4.** Skin picking disorder. Crusted inflammatory lesions and extensive hypopigmented linear scars are distributed in areas that can be reached by the hand (**A**). Extensive hypopigmented linear scars are invariably noted on the upper extremities (**B**); the medial aspect is typically less affected.



**Fig 5.** Trichotillomania. Hairs are broken at various lengths. Signs of hemorrhage are secondary to traumatic forced plucking.

## TRICHOTILLOMANIA (HAIR-PULLING DISORDER)

### Key points

- Trichotillomania is the repeated pulling of hair resulting in loss
- Habit-reversal training is the most effective intervention

Trichotillomania is a complex disorder with environmental and genetic etiology. DSM-5 diagnostic criteria are summarized in Table II. Other psychiatric comorbidities include major depression and specific phobia.<sup>34</sup>

**Epidemiology.** Lifetime prevalence is 1% to 4%.<sup>35,36</sup> Hair-pulling typically starts in childhood (average age of onset is 13 years) with a poorer prognosis as it continues into adulthood. There is a female predominance.<sup>37</sup>

**Clinical features and evaluation.** The scalp is the most commonly affected site, followed by the eyebrows and eyelashes.<sup>34</sup> After a hair is pulled, it may be manipulated by twisting it around the fingers

or biting at the hair root (trichophagia). Sidedness of hair loss is determined by the individual's handedness. The alopecic patches are sharply defined, asymmetric, and may assume bizarre geometric patterns.<sup>38</sup> In severe cases involving the vertex (tonsure pattern), the hair at the margins is characteristically spared (Friar Tuck sign).<sup>38</sup> On close inspection, alopecic lesions have broken hairs of different lengths (Fig 5). Characteristic trichoscopic findings include irregularly broken hairs, V-sign (ie, 2 hairs broken at equal lengths from 1 follicular opening), and coiled or flame hairs.<sup>38</sup> Histopathologic findings, such as an increase in catagen hairs, pigmentary casts, traumatized hair bulbs, and trichomalacia, help in diagnosis. Trichotillomania must be distinguished from alopecia areata, tinea capitis, traction alopecia, androgenetic alopecia, trichotemnomania (OCD in which patients cut or trim their hair),<sup>39</sup> and primary psychiatric disorders with secondary hair pulling.

**Management.** HRT is the most effective intervention.<sup>40</sup> SSRIs and clomipramine are well-studied interventions. A metaanalysis found that HRT outperformed clomipramine and SSRI groups, and clomipramine exceeded placebo.<sup>40</sup> N-acetylcysteine 1200 to 2400 mg/day resulted in a ≥50% reduction in pulling in adults,<sup>41</sup> and can be used as an adjunct agent.

## BODY-FOCUSED REPETITIVE BEHAVIOR DISORDER

### Key point

- Body-focused repetitive behavior disorder is linked to obsessive-compulsive disorder

Body-focused repetitive behavior disorder (BFRBD) is characterized by body-focused repetitive



**Fig 6.** Dermatophagia. Chronic biting of the skin, most commonly at the fingers, can cause thickened, discolored papules and plaques.

behaviors (BFRBs) that cause physical injury and significant distress. BFRBs include onychophagia (nail biting), dermatophagia (Fig 6), onychotillomania (nail picking), cheek/lip biting, nose/ear picking, and knuckle cracking. BFRBD is included under “unspecified OC RD” in DSM-5, and has a 21% comorbidity rate with OCD.<sup>42</sup> The presence of BFRBD predicts a worse prognosis for OCD.<sup>42</sup>

**Epidemiology.** Of the BFRBs, only onychophagia has documented prevalence (25-60%) that peaks during puberty.<sup>43</sup>

**Clinical features and evaluation.** Clinical features of BFRBs are variable. Any recurrent picking, peeling, or scratching of the skin may cause complications. Severe nail biting, defined as biting past the nail bed, may cause paronychia and gingival injuries.<sup>44</sup> Habit-tic deformity is caused by rubbing of the proximal nail fold and cuticle area resulting in nail matrix damage. Chronic biting of the skin can cause localized thickened plaques.<sup>45</sup> The differential diagnosis of dermatophagia includes callosities.<sup>45</sup> In cheek biting, there are typically changes in the transverse ridges of the oral mucosa.<sup>46</sup> Cheek biting may imitate candidiasis<sup>46</sup>; the differential diagnosis also includes lichen planus and white sponge nevus.

**Management.** BFRBs may represent solely a cosmetic issue. HRT is used as first-line treatment but with limited evidence. Mild aversion (applying a bitter substance to the nails) outperformed the competing response method (HRT) in the treatment of chronic nail biting.<sup>47</sup> Clomipramine and SSRIs have been used in nail biting with reported efficacy in a small number of case studies.<sup>48</sup> A RCT revealed initial response to N-acetylcysteine 800 mg/day in nail biting as determined by increased nail length after 1 month but no difference was observed after 2 months.<sup>49</sup>

## BODY DYSMORPHIC DISORDER

### Key points

- **Body dysmorphic disorder is associated with significant functional impairment and distress**
- **Cognitive behavioral therapy is first-line treatment, combined with a selective serotonin reuptake inhibitor for severe impairment**

BDD, formerly known as dysmorphophobia, is a distressing or impairing preoccupation with an imagined or slight defect in appearance. DSM-5 diagnostic criteria are highlighted in Table II. Major depressive disorder is the most common comorbidity, followed by social anxiety disorder (social phobia), other OCD, and substance-related disorder. Fifty-eight percent of patients report suicidal ideation.<sup>50</sup>

**Epidemiology.** The point prevalence of BDD in the United States is 2.4%.<sup>51</sup> In a survey, 6.7% of general and 14% of cosmetic dermatology patients had BDD.<sup>52</sup> The median age of onset is 15 to 16 years.<sup>51,53</sup>

**Clinical features and evaluation.** Features are summarized in Table II. The preoccupation is intrusive and time-consuming (occurring 3-8 hours per day in 40% of patients).<sup>53</sup> The face or head is most commonly affected, although any body region can be simultaneously affected.<sup>53</sup> Acne and dyschromia are major concerns among patients.<sup>52,54</sup> Patients believe that cosmetic treatments are the solution to their problem and seek care from cosmetic dermatologists, surgeons, and dentists.<sup>54</sup> In addition, patients often have delusions or ideas of reference, believing that other people stare, laugh, or mock them because of how they look.<sup>53,55</sup>

Cosmetic procedure screening<sup>56</sup> and BDD questionnaires<sup>57</sup> can be used to screen for BDD. Establishing a diagnosis of BDD poses a challenge because patients may have poor insight or are ashamed of their thoughts and feelings and do not disclose them to the physician.<sup>55</sup> Focused questioning to reveal BDD symptoms, associated distress, and effects on the patient’s life is recommended.<sup>58</sup> The differential diagnosis includes social anxiety disorder, major depressive disorder, other OCD, eating disorders (EDs), and psychotic disorders. BDD differs from social anxiety in that social situations are avoided specifically because patients fear they will be ridiculed or rejected because of their physical appearance. BDD differs from other OCD in that in the former, the obsessions and compulsions relate exclusively to appearance.

**Table III.** Skin signs in eating disorders\*

Causes	Skin signs
Starvation <sup>†</sup>	Common: <i>Lanugo-like hair</i> , asterosis/xerosis and follicular hyperkeratosis, alopecia, opaque and fragile hair, carotenoderma, acne, hyperpigmentation, seborrheic dermatitis, acrocyanosis, perniosis, and caries Uncommon: Petechiae, livedo reticularis, generalized pruritus, striae distensae, diffuse reticulate purpura, pellagra, scurvy, acquired acrodermatitis enteropathica, erythema ab igne, pili torti, angular cheilitis, gingivitis, and taste abnormalities
Self-induced vomiting	<i>Perimyolysis<sup>‡</sup></i> and <i>Russell sign</i> (knuckle calluses)
Drug consumption	Adverse reactions to laxatives, diuretics, and appetite suppressants: photosensitivity, fixed drug eruption, urticarial eruptions, and finger clubbing with laxative containing senna
Psychiatric comorbidity	<i>Self-mutilation</i> (eg, skin cutting and burning), trichotillomania, and dissatisfaction with the appearance of the skin

\*Guiding signs shown in italics. The presence of  $\geq 4$  frequent signs and 1 guide sign is enough to suspect an occult eating disorder. Table modified from Strumia.<sup>62</sup>

<sup>†</sup>Starvation-associated skin signs are noted mostly in anorexia nervosa.

<sup>‡</sup>A smooth erosion of enamel on the lingual surface of the teeth from exposure to gastric acid contents.<sup>67</sup>

**Table IV.** Diagnostic criteria for olfactory reference syndrome<sup>76</sup> and psychogenic pruritus<sup>78</sup>

#### Olfactory reference syndrome

A persistent false belief that one emits a malodorous smell; may encompass a range of insight (ie, does not have to be delusional)

The belief causes clinically significant distress, is time consuming (ie, preoccupies the individual for  $\geq 1$  hour per day) or results in significant impairment in social, occupational, or other important areas of functioning

The belief is not better accounted for by another mental disorder or a general medication condition

#### Psychogenic pruritus

##### Three compulsive criteria

Localized or generalized pruritus sine materia (no primary skin lesions)

Chronic pruritus (duration  $>6$  weeks)

No somatic cause

##### Three of 7 optional criteria

A chronologic relationship of pruritus with  $\geq 1$  life events that could have psychological repercussions

Variations in intensity associated with stress

Nocturnal variations

Predominance during rest or inaction

Associated psychological disorder

Pruritus that could be improved by psychotropic drugs

Pruritus that could be improved by psychotherapies

BDD can be comorbid with EDs; however, the only appearance symptom in EDs is the fear of being fat. Finally, while some BDD patients may have delusions related to their appearance, they do not display frank psychosis typical of psychotic disorders.<sup>51,58</sup>

**Management.** Engaging BDD patients in treatment requires an empathetic, nondismissive approach. Although most BDD patients seek cosmetic treatments, rarely does the intervention improve their symptoms; only 2.3% of procedures led to long-term improvements in BDD symptoms.<sup>59</sup> First-line therapy is CBT, with SSRIs being used for additional benefit. CBT and SSRIs were effective in 3 and 2, respectively, RCTs.<sup>53,60</sup> BDD patients require

relatively high doses of SSRIs (eg, fluoxetine  $\geq 60$  mg/day) and longer trial durations, with a mean response time of 6 to 9 weeks.<sup>53</sup>

## EATING DISORDERS

### Key points

- **Eating disorders are psychiatric conditions with skin manifestations, and they require a multispecialty approach**
- **Early identification of skin signs improves prognosis**

EDs in DSM-5 include anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), feeding or ED not elsewhere classified, and other

EDs.<sup>61</sup> Risk factors include female sex, genetic influences, dissatisfaction with body shape, hirsutism, parental concerns about weight, psychosexual impact of puberty, the influence of peers and society, and psychiatric morbidity, such as depression, anxiety, substance abuse, and personality disorders.<sup>62,63</sup> Perfectionism, obsessive-compulsiveness, impulsivity, and sensation seeking are common personality traits in patients with EDs.<sup>64</sup>

**Epidemiology.** Women comprise 90% of the patients. BED is the most common ED in the United States, with a lifetime prevalence of 2%.<sup>65</sup> The lifetime prevalence of AN among women is up to 4%, and of BN 2%;<sup>65</sup> these disorders are relatively rare in men. Both AN and BN are associated with increased mortality.

**Clinical features and evaluation.** EDs have a plethora of skin manifestations (Table III) that can lead to the diagnosis of an occult ED.<sup>62,66,67</sup> AN bears more skin signs than BN. The Russell sign (knuckle calluses) is the most characteristic sign of vomiting in purging type AN. A body mass index of  $\leq 16 \text{ kg/m}^2$  is a critical value at which skin changes occur in AN. Amenorrhea represents a key diagnostic feature in AN, whereas BN has been linked to polycystic ovary syndrome.<sup>62</sup> Self-mutilation may be associated with a suicide risk.<sup>68</sup>

**Management.** Effective and long-lasting management includes psychotherapy combined with attention to medical complications and nutritional needs. CBT is the front-line treatment of choice for BN and BED.<sup>69,70</sup> Psychotherapy and psychopharmacology outcomes for adults with AN are overall disappointing, especially in underweight cases. Enhanced CBT, which identifies triggers and behavior characteristics of EDs, is effective in approximately half of patients with normal-weight BN and atypical EDs, and has yielded a 30% recovery rate in AN.<sup>69</sup> Family-based therapy promotes parental responsibility for treatment adherence and is treatment of choice for adolescents.<sup>69</sup> All skin signs of EDs disappear with weight gain. Olanzapine, a second-generation antipsychotic, may promote weight gain and improve psychological symptoms in patients with AN.<sup>71</sup> Fluoxetine, an SSRI, is approved for BN.<sup>71</sup> Lisdexamphetamine, a stimulant, is the only medication for BED that is approved by the US Food and Drug Administration.<sup>72</sup>

## MISCELLANEOUS DISORDERS

### Key points

- Psychogenic pruritus is itch in the absence of dermatologic, systemic, and neurologic etiologies

- Olfactory reference syndrome, cutaneous sensory (pain) syndromes, and sleep disorders are associated with significant psychiatric pathology
- Posttraumatic stress disorder is associated with skin manifestations

### Olfactory reference syndrome

Olfactory reference syndrome (ORS) is a preoccupation with a false belief that one emits a foul or offensive body odor that is not perceived by others.<sup>73</sup> The DSM-IV considered ORS a type of delusional disorder, somatic type; however, ORS appears under “other specified OCDs” in DSM-5 because it was noted that symptoms can be nondelusional, and similar clinical features can be noted in severe social phobia, BDD, and OCD.<sup>74</sup> Patients with ORS have a wide range of insight and respond to a great variety of treatments, thereby complicating the classification of this disorder.<sup>75</sup> The diagnostic criteria proposed by Phillips et al<sup>76</sup> are highlighted in Table IV. Psychiatric comorbidities include depression, anxiety, social phobia, substance use disorders, OCD, BDD, and cluster C personality disorders (obsessional, dependent, and avoidant).<sup>73,77</sup>

**Epidemiology.** Symptoms develop during early adulthood, with a mean age of onset of 21.1 years.<sup>75</sup> Women experience greater symptom severity than men.<sup>75</sup>

**Clinical features.** Patients commonly engage in time-consuming rituals to rid themselves of their perceived odor, often using perfumes and deodorants excessively. They experience impaired work functions and restrict their travel and social life, avoiding intimacy and physical activity. Lifetime prevalence of suicidal ideation and suicide attempts is 68.4% and 31.6%, respectively.<sup>73</sup> Ideas of reference are a notable feature. In addition, patients frequently seek nonpsychiatric treatments.<sup>75,77</sup> The differential diagnosis includes OCD, BDD, social anxiety disorder, major depression with social withdrawal, psychotic disorders, substance abuse, and medical conditions (ie, neurologic disease).<sup>73-75,77</sup>

**Management.** Case reports and series suggest that SSRIs, neuroleptics, or a combination of SSRIs with antipsychotics may be efficacious.<sup>73</sup> SSRIs have been more effective than neuroleptics. Patients may benefit from psychotherapy and exposure therapy.<sup>73</sup>

### Psychogenic pruritus

Psychogenic pruritus, also termed functional itch disorder, is believed to fall into the continuum of somatic symptom disorders.<sup>78</sup> The diagnostic criteria are summarized in Table IV. Chronic itch carries significant burden, affecting self-esteem and the

**Table V.** Cutaneous sensory (pain) syndromes, posttraumatic stress disorder, and sleep-wake disorders

	Clinical features	Psychocutaneous aspects	Management
Chronic, idiopathic, mucocutaneous pain syndromes (vulvodynia, penodynia, and scrotodynia)	Burning pain unresponsive to conventional treatments <sup>87</sup> ; patients deny the possibility of psychological etiology; in "provoked" vulvodynia, the pain is triggered by physical contact (sexual, nonsexual, or both) <sup>88</sup> ; scrotodynia can be with or without concomitant scrotal erythema ("red scrotum syndrome") <sup>89</sup>	A degree of psychosocial or sexual impairment; patients may report depression, anxiety, and an effect on relationships <sup>90-92</sup>	Education, psychological counseling; sexual counseling (provoked vulvodynia, peno-scrotodynia); multidisciplinary psychodermatology team (vulvodynia) <sup>87</sup> ; pharmacologic therapy: A TCA (ie, amitriptyline 25-150 mg at bedtime) is first -line, <sup>87,93</sup> and second-line is venlafaxine (37.5-225 mg/day), duloxetine (20-120 mg/day), gabapentin (300-3600 mg/day), and pregabalin (50-600 mg/day) <sup>94</sup>
Burning mouth syndrome	Chronic, spontaneous intraoral pain that commonly affects the lips or tongue and lasts >4-6 months <sup>95</sup> ; peri- or postmenopausal women; can be with or without xerostomia and dysgeusia	Psychological stressors, mood or personality disorders <sup>96,97</sup> ; ROS should include insomnia, dysthymia, anxiety, and irritability	Topical clonazepam, capsaicin; systemic clonazepam, doxepin, duloxetine, milnacipran, and paroxetine <sup>95</sup> ; psychiatric interventions (eg, CBT) as monotherapy or adjunctively with pharmacotherapies <sup>95,98</sup>
Posttraumatic stress disorder	Symptoms evolve in the aftermath of an extreme traumatic sensor that overwhelms the individual's coping capacities <sup>99,100</sup> ; persistent re-experiencing of the traumatic event and avoidance of stimuli associated with the trauma; numbing of general responsiveness; persistent symptoms of ↑ arousal (hypervigilance, difficulties with sleep and concentration, irritability, or anger outbursts)	Hyperarousal associated with ↑ cutaneous reactivity (pruritus, hyperhidrosis) and tension-reducing behaviors resulting in self-induced dermatoses (trichotillomania, dermatitis artefacta, onychotillomania, or excoriations) <sup>100</sup> ; hypervigilance associated with dermographism, idiopathic urticaria, or angioedema, <sup>101</sup> and ↑ frequency of psoriasis <sup>102</sup>	Pharmacologic therapy, CBT, hypnosis, EMDR <sup>103-105</sup> , therapy can reduce the severity of related cutaneous conditions, such as dermatitis, psoriasis, urticaria, and self-inflicted dermatoses <sup>103-105</sup>
SWDs	Primary SWDs, such as sleep apnea, deprivation, and circadian rhythm disorders can affect dermatologic conditions <sup>106</sup> ; sleep deprivation inhibits the recovery of skin barrier function and increases proinflammatory cytokines <sup>107</sup>	Psychiatric pathologies are common in primary SWDs <sup>108-110</sup> ; nocturnal pruritus associated with skin conditions may be aggravated by the psychiatric comorbidity in these conditions <sup>111</sup> ; sleep disruption associated with pruritic skin conditions may contribute to the psychologic morbidity observed in these conditions <sup>106,112</sup>	Dermatologists should be aware of the treatment options for insomnia (CBT, self-help measures, and pharmacotherapy) and appropriately refer for specialized management <sup>113</sup>

↑, Increased; CBT, cognitive-behavioral therapy; EMDR, eye movement desensitization and reprocessing; ROS, review of systems; SWD, sleep-wake disorders; TCA, tricyclic antidepressant.

ability to cope with aggression.<sup>79,80</sup> Depression is the most common psychiatric comorbidity.<sup>81</sup>

**Epidemiology.** The incidence is 2% in patients seen in dermatology clinics,<sup>82</sup> and possibly higher in psychiatric patients.<sup>83</sup> There is a female predominance, and the average age of onset is between 30 to 45 years of age.<sup>83</sup>

**Clinical presentation and evaluation.** The face and scalp are the most affected areas; secondary skin manifestations are noted in body areas accessible to the hand. During history taking, episodes of excoriation should be reviewed with respect to onset, location, timing, and precipitants.<sup>83</sup> A review of symptoms should include depression, anxiety, and suicidal ideation. Skin examination may reveal scars, ulcerations, inflammation, and superinfection caused by excoriation.<sup>83</sup> Psychogenic pruritus is a diagnosis of exclusion; dermatologic, systemic, and neurologic etiologies need to be ruled out.<sup>81</sup>

**Management.** Management with antihistamines, emollients, cooling agents, and steroids does not provide long-term relief.<sup>83</sup> Occlusive dressings help prevent scratching. Antidepressants such as paroxetine (20-50 mg/day), fluvoxamine (50-300 mg/day), and sertraline (25-200 mg/day) can mitigate chronic generalized pruritus,<sup>84</sup> and have been successfully used in case series.<sup>85</sup> Doxepin (25-300 mg every night) can be helpful.<sup>86</sup> Patient education, support, and behavior therapies may help control the itch/scratch process.<sup>83</sup>

### Cutaneous sensory (pain) syndromes, posttraumatic stress disorder, and sleep-wake disorders

These disorders are highlighted in Table V.<sup>87-113</sup>

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# Psychocutaneous disease



## Pharmacotherapy and psychotherapy

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### Learning objectives

After completing this learning activity, participants should be able to discuss how to establish a working alliance with the patient who has psychocutaneous disease and most effectively involve the psychiatrist in management; list psychiatric medications used in psychocutaneous disorders; and describe effective psychotherapies for psychocutaneous diseases.

### Disclosures

#### Editors

The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

#### Authors

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Building a strong therapeutic alliance with the patient is of utmost importance in the management of psychocutaneous disease. Optimal management of psychocutaneous disease includes both pharmacotherapy and psychotherapy. This article reviews psychotropic medications currently used for psychocutaneous disease, including antidepressants, antipsychotics, mood stabilizers, and anxiolytics, with a discussion of relevant dosing regimens and adverse effects. Pruritus management is addressed. In addition, basic and complex forms of psychotherapy, such as cognitive-behavioral therapy and habit-reversal training, are described. (*J Am Acad Dermatol* 2017;76:795-808.)

**Key words:** antidepressant; antipsychotic; cognitive-behavioral therapy; drug; management; pruritus; psychocutaneous; psychotherapy.

**M**ost patients with psychocutaneous disease refuse psychiatric intervention, leaving management exclusively to the dermatologist. A direct and empathic approach helps elicit relevant psychiatric information from the patient to formulate a diagnostically driven management plan. It is important for the dermatologist to identify psychosocial factors and psychiatric comorbidity,

and effectively communicate the connection between mind and skin.<sup>1</sup> Rapport develops over the course of several office visits in which the patient feels, with good reason, that the physician is an ally in their struggle to cure the disease.<sup>2</sup> A psychiatry referral approached with sensitivity may be successful.<sup>2</sup> When patient is resistant to pursuing psychiatric treatment, the dermatologist should support the

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**Abbreviations used:**

AED:	antiepileptic drug
CBT:	cognitive-behavioral therapy
EPS:	extrapyramidal symptoms
FDA:	US Food and Drug Administration
HRT:	habit-reversal training
OCRD:	obsessive-compulsive and related disorder
SSRI:	selective serotonin reuptake inhibitor
TCA:	tricyclic antidepressant

patient with a nonjudgmental stance, provide indicated psychotropic medication (the dermatologist should be aware of commonly used psychotropic agents and their adverse effects),<sup>3</sup> and encourage evaluation with a psychiatrist as a supplement to, and not as a replacement for, the therapeutic relationship.<sup>1</sup>

There are data supporting the effectiveness of psychotherapy in psychocutaneous disease.<sup>4</sup> These therapies are described below.

## PHARMACOTHERAPY

### Key points

- Selective serotonin reuptake inhibitors are commonly used to treat anxiety, depression, obsessive-compulsive, and somatic symptom and related disorders
- Tricyclic antidepressants can be used in neuropathic pain and obsessive-compulsive and related disorders; doxepin is a potent antipruritic tricyclic antidepressant

### Antidepressants

Antidepressants are approved for the treatment of depression and variants of anxiety including, panic disorder and posttraumatic stress disorder. The onset of effect for all antidepressants, regardless of class, is 4 to 6 weeks at a therapeutic dose.<sup>5</sup> Dosing recommendations include starting low and titrating slowly. As a general guideline, one may consider starting at half the minimum effective dose and titrating upwards every 14 days. Higher dosing does not hasten the effect, but rather puts the patient at greater risk of adverse effects.<sup>6</sup> If there is no improvement after an adequate trial of  $\geq 6$  weeks, or if the medication is not tolerated, one should switch to a different medication. If there is partial improvement, titrating the dose is ideal. No class of antidepressant has been shown to be more efficacious than another in the treatment of depression.<sup>7</sup> Of note, no antidepressant carries an indication for a specific psychocutaneous condition. Antidepressants are not addictive, but a discontinuation symptom (eg, flu-like symptoms, insomnia, or

imbalance) may occur if they are stopped or tapered too quickly.<sup>7</sup> Treatment should be continued for a minimum of 6 months after therapeutic response.<sup>5</sup> Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are the most commonly used classes of antidepressants in psychodermatology.

**SSRIs.** SSRIs (Table I) are the most common class of antidepressants because of their favorable safety profile.<sup>6</sup> These medications primarily affect serotonin, although this is a simplified version of how they work.<sup>12</sup> Effective dosing for psychocutaneous conditions has not been established. As a general rule, it is typical for obsessive-compulsive and related disorders (OCRD) to require higher dosing.<sup>8</sup> The most common adverse effects include gastrointestinal distress (eg, nausea), insomnia, weight changes, and sexual dysfunction (eg, anorgasmia or reduced libido).<sup>7</sup> When starting an antidepressant of any class in a patient  $< 25$  years old, it is important to monitor for suicide-related events because these medications have been found to be associated with thoughts about suicide and suicide attempts but not completed suicide.<sup>13</sup> This is true particularly at the start of treatment (ie, the first 2 months). If the first SSRI fails, a second SSRI option can be instituted before switching to another class of antidepressant.<sup>14</sup>

**TCAs.** TCAs (Table II) are an older class of antidepressants that act on serotonin and norepinephrine.<sup>5</sup> To a great extent, TCAs have been replaced by SSRIs because TCAs are more sedating and have a broad spectrum of adverse effects. However, they have more antihistaminic properties, which serves useful for pruritic complaints and insomnia.<sup>5</sup> A few of the TCAs are notable for use in psychodermatology. Doxepin carries the most antihistaminergic properties, making it a potent oral and topical antipruritic agent for psychogenic pruritus and prurigo nodularis, respectively.<sup>15</sup> Typically, the dosage of TCA used to treat pruritus is lower than the typical antidepressant dosage. There are case reports of reduction of excoriation and pruritus with doxepin 30 mg/day.<sup>19</sup> Another common TCA used in OCD, including body dysmorphic disorder, is clomipramine.<sup>20,21</sup> Other TCAs have received approval by the US Food and Drug Administration for indications such as neuropathic pain.<sup>16</sup> When a TCA is used as analgesic, the dosage required tends to be less than the dosage required for its antidepressant effect; amitriptyline (25-50 mg at bedtime) is frequently used for pain control.<sup>3</sup>

Of the TCAs, nortriptyline has the most favorable side effect profile, with mortality rates similar to those of SSRIs, and nortriptyline should be

**Table I.** Selective serotonin reuptake inhibitors<sup>5,8-11</sup>

	<b>AEs</b>	<b>Starting dose to target dose (mg/day)</b>	<b>Notes</b>	<b>Monitoring/interactions</b>	<b>Most common uses*</b>
Fluoxetine	Mildly activating, sexual AEs	10-40 (for depression and SSRD <sup>†</sup> ) and 10-80 mg (for OCRD <sup>‡</sup> )	Longest half-life of SSRIs; no discontinuation symptoms	No routine monitoring	<b>MDD, OCD, panic disorder, bulimia nervosa, PMDD, trichotillomania, and excoriation disorder</b>
Sertraline	Mildly sedating, sexual AEs	25-100 (for depression and SSRD) and 25-200 mg (for OCRD)	Effective in chronic anxiety	No routine monitoring	<b>MDD, OCD, panic disorder, PTSD, social anxiety disorder, PMDD, and GAD</b>
Citalopram	Sexual AEs	10-40 (for depression, SSRD, and OCRD)	Cardiac risk in doses >40 mg	Maximum dose 40 mg, consider electrocardiography for higher doses	<b>MDD, OCD, panic disorder, PTSD, and GAD</b>
Escitalopram	Sexual AEs	5-10 (for depression and SSRD) and 5-20 mg (for OCRD)	Purified isomer of citalopram; few drug interactions	No routine monitoring	<b>MDD, GAD, OCD, panic disorder, and PTSD</b>
Paroxetine	Sedating, sexual AEs, and weight gain	20-50 (for depression) and 20-60 (for OCRD)	Second shortest half-life of SSRIs; prone to discontinuation symptoms; higher risk of drug interactions	No routine monitoring	<b>MDD, GAD, OCD, panic disorder, PTSD, social anxiety disorder, and PMDD</b>
Fluvoxamine	Sedating, less sexual AEs	50-150 (for depression) and 50-300 (for OCRD)	Shortest half-life of SSRIs; prone to discontinuation symptoms; most drug interactions of SSRIs	No routine monitoring	<b>OCD and social anxiety disorder<sup>§</sup></b>

This table highlights the most common medications and is not an all-inclusive summary.

AE, Adverse effect; GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; OCRD, obsessive-compulsive and related disorder; PMDD, premenstrual dysphoric disorder; PTSD, posttraumatic stress disorder; SSRD, somatic symptom and related disorder; SSRI, selective serotonin reuptake inhibitor.

\*Conditions in bold indicate that treatment is approved by the US Food and Drug Administration.

<sup>†</sup>SSRDs include somatic symptom disorder, illness anxiety disorder, conversion disorder, factitious disorder, psychological factors affecting medical conditions, other SSRD, and unspecified SSRDs.

<sup>‡</sup>OCRDs include obsessive-compulsive disorder, body dysmorphic disorder, hoarding, trichotillomania (hair pulling disorder), excoriation (skin picking) disorder, substance-induced OCRD, OCRD caused by another medical condition, other specified OCRD, and unspecified OCRD.

<sup>§</sup>Only the extended release form of fluvoxamine has been approved by the US Food and Drug Administration for the treatment of social anxiety disorder.

**Table II.** Tricyclic antidepressants<sup>5,15-18</sup>

Medication	Adverse events	Starting dose to target dose (mg/day)	Notes	Monitoring/interactions	Most common uses*
Clomipramine	High anticholinergic effects, high sedation, moderate orthostatic hypotension, high conduction abnormalities, and weight gain	25-150 (for depression) and 25-250 (for OCRDs)	Most serotoninergic TCA	ECG in women >40 and men >30 years of age or those with preexisting cardiac disease; high risk of lethality in overdose	<b>OCD</b> , BDD, and trichotillomania
Doxepin	Anticholinergic effects, high sedation, less orthostatic hypotension, and fewer conduction abnormalities	25-300 (for depression and OCRDs)	Most antihistaminergic and anticholinergic; effective in treating pruritic skin condition because of these properties	As above	<b>Insomnia</b> , <sup>†</sup> <b>MDD</b> , <b>MDD with psychosis</b> , pruritic skin disease, and excoriation
Amitriptyline	High anticholinergic effects, high sedation, moderate orthostatic hypotension, and high conduction abnormalities	10-150 (for depression and SSRD)	Helpful in insomnia because of sedating effect	As above	<b>MDD</b> , neuropathic pain, fibromyalgia, and headache
Imipramine	Anticholinergic effects, moderate sedation, most orthostatic hypotension, and high conduction abnormalities	50-200 (for depression)		As above	<b>MDD</b> , enuresis, and panic disorder
Desipramine	Fewer anticholinergic effects, less sedation, moderate orthostatic hypotension, and moderate conduction abnormalities	50-200 (for depression)	Monitor weight and BMI	As above	<b>MDD</b> and chronic pain
Nortriptyline	Moderate anticholinergic effects, moderate sedation, least orthostatic hypotension, and fewer conduction abnormalities	25-100 (for depression)	Monitor plasma drug levels; best TCA for use in elderly	As above	<b>MDD</b> and chronic pain

This table highlights the most common medications and is not an all-inclusive summary.

BMI, Body mass index; BDD, body dysmorphic disorder; ECG, electrocardiogram; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; OCRD, obsessive-compulsive and related disorder.

\*Conditions in bold indicate that treatment is approved by the US Food and Drug Administration.

<sup>†</sup>Silenor (Pernix Therapeutics, Morristown, NJ).

considered for use in the elderly.<sup>17,22</sup> With the exception of nortriptyline, therapeutic blood monitoring is not required for TCAs. The most frequent adverse effects result from anticholinergic properties, causing dry mouth, constipation, dizziness, tachycardia, blurred vision, and urinary retention.<sup>5</sup> They are contraindicated in persons with preexisting conduction defects and should be used cautiously in those with preexisting heart disease.<sup>5</sup> These medications are also lethal in overdose and ought to be used carefully in suicidal patients or those with history of suicide.

**Other antidepressants.** Mirtazapine (7.5-30 mg at bedtime) is a noradrenergic and selective serotonergic antidepressant.<sup>5</sup> Because it can cause heavy sedation and weight gain, it is commonly used in geriatric and terminal illness populations. Bupropion XL (150-300 mg every morning) is a selective norepinephrine and dopamine reuptake inhibitor.<sup>5</sup> It has fewer sexual adverse events and is activating. It is helpful for depressed patients with fatigue and poor motivation.<sup>5</sup>

## ANTIPSYCHOTIC AGENTS

### Key points

- Antipsychotic agents can be used in delusional infestation, dermatitis artefacta, and olfactory reference syndrome, and as augmentation therapy in treatment-resistant obsessive-compulsive and related disorders
- Pimozide is a frequently used typical antipsychotic in psychodermatology; atypical antipsychotics used include risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone

Antipsychotic agents (Table III) work by blocking dopamine receptors in the central nervous system. They are used to treat delusional and psychotic disorders by decreasing the excess dopamine neurotransmission believed to drive delusions.<sup>23,24</sup> Typical (first-generation) antipsychotics block the dopamine (D<sub>2</sub>) receptor, and are associated with distressing extrapyramidal side effects, such as dystonia and parkinsonism. Atypical (second- and third-generation) antipsychotics are both dopamine (D<sub>2</sub>) and serotonin (5-HT<sub>2</sub>) receptor antagonists. There is a decreased incidence of extrapyramidal symptoms (EPS) because of the preferential 5-HT<sub>2</sub> receptor activity.<sup>23</sup>

Psychocutaneous disorders can be effectively managed with relatively small doses of antipsychotic medications. It is recommended to initiate therapy at a low dose, and to gradually increase the

dose in order to increase tolerability and allow for adverse effect monitoring.<sup>3,5</sup> There is a risk of dizziness, sedation, and hypotension with most antipsychotics, which can be minimized with slow titration.<sup>5</sup> Patients should be carefully monitored for EPS, because these can become permanent and profoundly disabling.<sup>3,5,23</sup> In addition, in elderly patients with dementia, antipsychotics increase the risk of stroke and transient ischemic attacks.<sup>29</sup> Finally, psychotropic medications can produce a wide spectrum of cutaneous adverse effects, including exanthematous eruptions, skin pigmentation changes, photosensitivity, urticaria, and pruritus.<sup>30</sup>

### Typical antipsychotics

**Pimozide is the most commonly used first-generation antipsychotic in psychodermatology.** The effective dose for psychocutaneous conditions ranges from 2 to 6 mg/day.<sup>3</sup> Careful titration is key to safe usage, with most authors recommending a starting dose of 1 mg/day, followed by slow 0.5- to 1-mg uptitration every 2 weeks until there is an adequate treatment response.<sup>3,23</sup> Once improvement is noted, the clinically effective dosage should be maintained for 1 month, then slowly tapered by 1 mg every 1 to 2 weeks.<sup>3,23</sup> Most patients require 5 to 6 months for induction, treatment, and taper.<sup>3</sup> Adverse effects of pimozide are uncommon at the doses used in dermatology. EPS include stiffness and akathisia, a feeling of inner restlessness.<sup>3,23</sup> EPS can be treated with diphenhydramine 25 mg or benztropine 1 to 2 mg, but it is recommended that patients are switched to a second-generation antipsychotic if EPS occur.<sup>3</sup> Pimozide can cause QTc prolongation with subsequent arrhythmias, and an electrocardiogram is recommended for patients with a history of arrhythmias or cardiac conduction abnormality.<sup>3</sup> However, controversy exists regarding the need for an electrocardiogram with doses <10 mg/day in young and otherwise healthy individuals.<sup>3,31</sup> The long-term use of pimozide can result in tardive dyskinesia, which is potentially irreversible.<sup>3,23</sup>

### Atypical antipsychotics

**Risperidone.** Risperidone is primarily used for the treatment of delusional infestation.<sup>3,23,32</sup> The medication is generally started at 0.5 mg at bedtime, with the dose increased every few weeks up to 4 mg/day on a twice daily schedule until clinical improvement is observed.<sup>3</sup> It retains a high level of D<sub>2</sub> antagonism and therefore can cause hyperprolactinemia, manifested by galactorrhea, amenorrhea, and sexual dysfunction.<sup>25,26</sup> Risperidone can prolong the QT interval and should be used with caution in

**Table III.** Treatment of delusional disorders<sup>3,23-28</sup>

Medication*	Adverse events	Starting dose to maximum dose	Notes	Monitoring/interactions	Psychocutaneous disorders with reported benefit
Pimozide	Severe EPS, QTc prolongation, and anticholinergic effects	1-10 mg/day	Risk of tardive dyskinesia with long-term use	ECG recommended with a history of arrhythmias or cardiac conduction abnormality	DI and DA
Risperidone	Moderate EPS, moderate risk of QTc prolongation, moderate risk of MetS, hyperprolactinemia, and sexual dysfunction	0.5 mg at bedtime to 6 mg/day	May initially cause sedation but resolves within a few days	Parameters of MetS (ie, weight, blood pressure, glucose, and lipid profiles) should be monitored	DI, DA, ORS, TTM, and BDD
Olanzapine	Very sedating, increased risk of weight gain, and significant risk of MetS	2.5 mg at bedtime to 20 mg/day	—	As above	DI, DA, TTM, and BDD
Quetiapine	Very sedating, increased risk of weight gain, moderate risk of MetS, and less risk of CVA in elderly	50-600 mg at bedtime	Useful for elderly population and treatment resistant patients	As above	DI, TTM, and BDD
Aripiprazole	Least sedating, decreased risk of weight gain, less risk of CVA in elderly, and may cause agitation	2-30 mg/day	Can be used as augmentation agent in depression at lower doses	Less risk of MetS, but consider monitoring	DI, neurotic excoriations, ORS, TTM, and BDD
Ziprasidone	Less weight gain and moderate risk of QTc prolongation	20-80 mg twice daily	Slightly less efficacious antipsychotic	As above	DI

This table highlights the most common medications and is not an all-inclusive summary.

BDD, Body dysmorphic disorder; CVA, cerebrovascular accident; DA, dermatitis artefacta; DI, delusional infestation; ECG, electrocardiogram; EPS, extrapyramidal symptoms; MetS, metabolic syndrome; ORS, olfactory reference syndrome; TTM, trichotillomania.

\*Listed medications have not been approved by the US Food and Drug Administration for the specific psychocutaneous indication.

patients with a history of conduction abnormality or concomitant use of medications that may prolong the QT interval.<sup>3</sup> Anticholinergic adverse effects of risperidone are minimal, and although it may initially cause sedation, this generally resolves within the first few days of use.<sup>3,25,26</sup>

**Olanzapine.** Olanzapine has one of the highest incidences of weight gain but is overall well-tolerated.<sup>3,25,26</sup> Dosing for psychocutaneous conditions is not well established; therefore, low doses are recommended.<sup>3</sup> The major adverse effect of olanzapine is metabolic syndrome, which increases cardiovascular risk if left untreated.<sup>25,26</sup> Weight, blood pressure, glucose, and lipid profiles should be monitored during therapy.<sup>25,26</sup>

**Quetiapine.** Quetiapine is particularly useful for the elderly and treatment-resistant patients.<sup>3,23</sup> Again, dermatologic dosing is not well established, so low doses are advised.<sup>3,23</sup> Common adverse effects include weight gain, somnolence, mild anticholinergic effects, and orthostatic hypotension.<sup>3,25,26</sup>

**Aripiprazole.** Aripiprazole is a third-generation antipsychotic, its great strength being the relatively low incidence of metabolic disturbances, anticholinergic effects, EPS, and tardive dyskinesia.<sup>23,25</sup> It has been successful in the treatment of delusional infestation and neurotic excoriations.<sup>23</sup>

**Ziprasidone.** Ziprasidone, another third-generation antipsychotic, has also been successful in the treatment of delusional infestation.<sup>27</sup> It has no anticholinergic effects and low likelihood of sedative adverse effects and metabolic syndrome, but is more likely than other atypical antipsychotics to increase QT interval.<sup>28</sup>

## MOOD STABILIZERS AND ANXIOLYTIC, HYPNOTIC, AND MISCELLANEOUS AGENTS

### Key point

- Mood stabilizers and anxiolytic and hypnotic agents have an important place in the therapeutic armamentarium for psychocutaneous conditions

### Mood stabilizers

Mood-stabilizing agents, such as antiepileptic drugs (AEDs) and lithium carbonate are approved for bipolar disorder.<sup>33</sup> AEDs may be of benefit in self-inflicting dermatoses.<sup>34</sup> The use of lamotrigine (12.5–300 mg/day) was effective in skin picking disorder in 1 study<sup>35</sup> but not better than placebo in a subsequent one.<sup>36</sup> Gabapentin, another anticonvulsant, can be used in anxiety and pruritus control (discussed below). Topiramate was endorsed as an antibinge and antipurge agent, and can be used in both bulimia

nervosa and binge eating disorder.<sup>37</sup> Lithium is indicated in poor impulse control, and patients with skin picking disorder can benefit from it. Its use is limited by its broad spectrum of cutaneous adverse effects, including triggering/worsening psoriasis.<sup>38</sup>

### Anxiolytic agents

Antianxiolytic agents can alleviate distress.<sup>5</sup> They can be classified into benzodiazepines and nonbenzodiazepines. Benzodiazepines (Table IV) should be limited to 3- to 4-week courses to avoid potential for abuse and dependence.<sup>3,23,39</sup> They tend to be sedating, and should be used cautiously in patients with sleep apnea. Withdrawal symptoms, including depression, seizures, psychotic episodes, and autonomic system disturbances, can be avoided by using a taper.<sup>23</sup> Withdrawal symptoms must be distinguished from the rebound phenomenon (restlessness, anxiety, or insomnia).<sup>40</sup>

Hydroxyzine, a nonbenzodiazepine anxiolytic, has sedating and anticholinergic effects (Table IV).<sup>5</sup> Buspirone (15–60 mg/day), a nonbenzodiazepine, nonsedating anxiolytic, has a delayed onset of action (2–4 weeks).<sup>4</sup> It has no addictive properties and is a safe option when long-term therapy is required.<sup>41</sup> SSRIs, such as paroxetine, sertraline, fluoxetine, citalopram, and escitalopram, are effective in chronic anxiety at the dosages indicated for depression (Table I).<sup>3,5</sup> Low-dose doxepin and venlafaxine extended release can also be helpful in chronic anxiety.

### Hypnotic agents

Sleep restoration is imperative in increasing a patient's functionality and coping with stress. Zolpidem (5–10 mg orally at bedtime) acts as a partial benzodiazepine but may lead to confusion and tolerance.<sup>42,43</sup> Zaleplon (5–20 mg/day) and suvorexant (5–20 mg/day) have fewer cognitive adverse effects.<sup>42–44</sup> Eszopiclone (1–3 mg/day) and ramelteon (8 mg/day) are indicated for long-term use in insomnia.<sup>42,45</sup>

### Miscellaneous agents

N-acetylcysteine (1200–3000 mg/day) is a promising new treatment for trichotillomania and excoriation disorder.<sup>46,47</sup> It is an over-the-counter glutamate modulator that is generally well tolerated.

## PRURITUS MANAGEMENT

### Key points

- Management of pruritus in the patient with psychocutaneous disease requires an individualistically tailored approach

**Table IV.** Treatment of acute anxiety<sup>x3-5,23,39,40</sup>

Medication <sup>†</sup>	Onset of action	Elimination time (hrs)	Daily dosing (mg)	Maximum dose (mg/day)	Common adverse effects	Notes
Clonazepam	Slow	30-40	0.25-2 daily/twice daily	4	Somnolence, depression, abnormal coordination, and ataxia	Long duration of effect; less risk of rebound anxiety; no active metabolites, therefore easier to taper off
Diazepam	Slow	30-100	2-10 twice or three times daily	40	Drowsiness, fatigue, muscle weakness, and ataxia	Long duration of effect; less risk of rebound anxiety
Lorazepam	Intermediate	10-20	0.5-1 twice or three times daily	6	Sedation, dizziness, weakness, and unsteadiness	Safe in hepatic impairment; no hepatic metabolism
Alprazolam	Fast	12-15	0.25-0.5 twice or three times daily	4	Drowsiness, light-headedness, depression, headache, dry mouth, constipation, diarrhea, confusion, and insomnia	Highest potential for abuse, dependence, and rebound anxiety; use with extreme caution
Hydroxyzine	Intermediate	20	25-50 three or four times daily	600	Drowsiness and dry mouth	Used mostly in the United States; no potential for dependence or withdrawal; anti-itch benefit

This table highlights the most common medications and is not an all-inclusive summary.

\*Adapted from Kotara et al.<sup>5</sup>

<sup>†</sup>Clonazepam is approved by the US Food and Drug Administration for the treatment of panic disorder; other medications listed are approved for anxiety.

### • Psychotropic drug use has expanded the therapeutic options in challenging cases

Pruritus is the presenting symptom in up to half of patients with psychiatric disease.<sup>48</sup> Traditional treatments for itch target the histamine pathway. More recently, neuroactive medications, such as neuroleptics, antidepressants, and opioid receptor modulators, have been used successfully in the management of pruritus, particularly in chronic or generalized cases. These medications are thought to affect the nonhistaminic pathways of itch transmission and central nervous system modulation. They are particularly useful in itch that is of neuropathic or psychogenic origin.<sup>49-51</sup> Topical and systemic therapies for pruritus are highlighted in Tables V and VI, respectively.

### Topical therapies

**Coolants.** When applied to skin, menthol produces a cooling sensation. It relieves itch by activating thermosensitive ion channels that produce the cool sensation and  $\kappa$ -opioid receptors.<sup>49,50</sup>

**Anesthetics.** Capsaicin is used in neuropathic itch.<sup>52,53</sup> It works primarily by desensitizing

peripheral nerve fibers by depleting substance P.<sup>54</sup> Higher concentrations (0.075-0.1%) are more effective.<sup>55</sup> Pramoxine and mixtures of lidocaine and prilocaine cream have been shown to be effective in neuropathic, facial, and anogenital itch.<sup>49,56,57</sup>

**Other antipruritic medications.** Topical corticosteroids and calcineurin inhibitors are not directly antipruritic but relieve pruritus through their antiinflammatory effect.<sup>57</sup> Calcineurin inhibitors are particularly useful in anogenital pruritus.<sup>57</sup> Doxepin can relieve localized itch in patients with atopic dermatitis and contact dermatitis, but has not been efficacious in other causes of itch.<sup>49,58</sup>

### Systemic therapies

**Phototherapy.** Chronic pruritus has improved with several types of phototherapy.<sup>48</sup> Generalized pruritus of unknown origin has improved with narrowband ultraviolet B light phototherapy, while aquagenic pruritus and prurigo nodularis were successfully treated with psoralen plus ultraviolet A light phototherapy.<sup>62</sup>

**Oral antihistamines.** Oral antihistamines are helpful in treating urticaria and acute itch.<sup>49-51</sup> First-

**Table V.** Topical treatment of pruritus

Medication	Concentration	Adverse effects	Types of pruritus with reported benefit
Menthol <sup>49,50</sup>	1-5%	Irritating at concentrations >5%	Acute itch; itch that responds to cold
Capsaicin <sup>52-55</sup>	0.025-0.1%	Transient burning sensation	Neuropathic itch, notalgia paresthetica, brachioradial pruritus, postherpetic neuralgia, PN, UP, pruritus ani, aquagenic pruritus, and pruritus associated with AD
Pramoxine <sup>49,56*</sup>	1%, 2.5%	Irritation and xerosis	Pruritus associated with eczematous dermatitis, anogenital itch, neuropathic itch, and UP
Lidocaine <sup>49,57</sup>	2.5-5%	Irritation and other reactions	Neuropathic itch
Prilocaine <sup>49,57</sup>	2.5%	As above; methemoglobinemia in pediatric patients (rare)	Postburn itch, anogenital itch, and PN
Corticosteroids <sup>57</sup>	Various	Skin atrophy, striae, telangiectasia, folliculitis	Pruritus associated with skin inflammation
Calcineurin inhibitors <sup>57</sup>			
Pimecrolimus	1%	Transient stinging or burning sensation with application	Pruritus associated with AD, contact dermatitis, and facial and anogenital itch
Tacrolimus	0.03% or 0.1%	As above	As above
Doxepin <sup>58*</sup>	5%	Avoid in children; 20-25% risk of sedation	Pruritus associated with AD, LSC, and contact dermatitis
Other medications			
Naltrexone <sup>59</sup>	1%	Well-tolerated	Pruritus associated with AD and other inflammatory skin conditions
Polidocanol <sup>60</sup>	3%	Stinging, itch, irritation	Pruritus associated with AD, contact dermatitis, psoriasis, and idiopathic pruritus
N-palmitoylethanolamine <sup>61</sup>		Well-tolerated	Pruritus associated with AD, PN, LSC, and UP
Aprepitant <sup>61</sup>		Nausea, vertigo, drowsiness	PN, paraneoplastic and drug-induced pruritus, Sézary syndrome, and UP

AD, Atopic dermatitis; FDA, US Food and Drug Administration; LSC, lichen simplex chronicus; PN, prurigo nodularis; UP, uremic pruritus.

\*Approved by the US Food and Drug Administration for the treatment of pruritus.

generation antihistamines help with nocturnal itch.<sup>57</sup> Data are lacking to support the efficacy of antihistamines for pruritic conditions beyond urticaria; however, clinical gestalt suggests that the reduction in pruritus is likely caused by a mild anxiolytic effect associated with sedation.<sup>49,50</sup>

**Neuroleptics.** Gabapentin and pregabalin, structural analogues of the neurotransmitter  $\gamma$ -aminobutyric acid, are commonly used for neuropathic pain/itch, including scalp dysesthesia, notalgia paresthetica, brachioradial pruritus, prurigo nodularis, and postherpetic neuralgia.<sup>49,51,52,63</sup> They are thought to inhibit calcium channels in the dorsal root ganglion and spinal cord, thereby increasing the threshold for neuronal excitation by pruritic stimuli.<sup>63</sup> These medications are of slow onset and may require  $\geq 4$  weeks before clinical effects plateau.<sup>63</sup>

**Antidepressants.** SSRIs, such as paroxetine, fluvoxamine, and sertraline, can improve various types

of generalized pruritus, including psychogenic pruritus.<sup>24,49,51,64,65</sup> The antipruritic effect may be mediated by downregulation of the excitatory postsynaptic 5-HT<sub>3</sub> receptor.<sup>65</sup> Mirtazapine has been effective in various types of pruritus,<sup>49-51</sup> and has a good effect in nocturnal itch in patients with generalized pruritus.<sup>57</sup> The TCAs doxepin and amitriptyline are frequently utilized in neuropathic and psychogenic itch,<sup>49-52</sup> but have not been studied in controlled trials. Doxepin, the most potent anti-histamine available, can help with neuropathic and psychogenic itch but results in significant sedation.<sup>49-52</sup>

**Opioid modulators.** Antipruritic effects can be achieved by blocking the  $\mu$  opioid receptor or activating the  $\kappa$ -opioid receptor. Naltrexone is the prototype  $\mu$  receptor antagonist.<sup>49,66</sup> It reduces pruritus in several skin conditions,<sup>23</sup> especially prurigo nodularis,<sup>67</sup> and has been effective in

**Table VI.** Systemic treatment of pruritus

Medication	Dosing	Adverse effects	Types of pruritus with reported benefit
Phototherapy <sup>48,62</sup> (narrowband UVB and PUVA)	Takes 1-2 months	Sunburn reactions	Chronic itch
Antihistamines <sup>49-51,57</sup>	Variable depending on medication	Sedation, drowsiness, dry mouth, and confusion	Pruritus associated with urticaria and nocturnal itch
Neuroleptics <sup>49,51,52,63</sup>			
Gabapentin	100-800 mg three times daily (maximum 3600 mg/day)	Somnolence, dizziness, fatigue, weight gain, and blurred vision	Postherpetic neuralgia, psychogenic itch, neuropathic itch, UP
Pregabalin	50-100 mg three times daily (maximum 600 mg/day)	As above; gradual taper to prevent withdrawal symptoms	As above; aquagenic itch
Antidepressants <sup>24,49-52,57,64,65</sup>			
Paroxetine	20-50 mg daily	Sedation, dry mouth, and sexual dysfunction	Psychogenic pruritus, UP, CP, and paraneoplastic itch
Mirtazapine	7.5-30 mg at bedtime	Drowsiness, dizziness, dry mouth, constipation, increased appetite/weight gain, and vision changes	As above; nocturnal itch in generalized pruritus
Doxepin	25-300 mg at bedtime	Drowsiness, dizziness, hypotension, dry mouth, urinary retention, and cardiotoxicity	Neuropathic and psychogenic itch
Amitriptyline	10-150 mg daily, or divided	As above	Neuropathic and psychogenic itch
Opioid receptor modulators <sup>23,49,51,57,66-70</sup>			
Naltrexone ( $\mu$ antagonist)	12.5-50 mg daily	GI distress and hepatotoxicity	UP, CP, intractable itch, AD, PN, trichotillomania, self-injury, and neurotic excoriations
Butorphanol ( $\kappa$ agonist, $\mu$ antagonist)	1-4 mg at bedtime (inhaled)	GI distress, drowsiness, and dizziness	Intractable pruritus associated with inflammatory skin disease, non-Hodgkin lymphoma, CP, and opioid use

AD, Atopic dermatitis; CP, cholestatic pruritus; PN, prurigo nodularis; PUVA, psoralen plus ultraviolet light A phototherapy; UP, uremic pruritus; UVB, ultraviolet B light phototherapy.

trichotillomania, cutaneous self-injury, and neurotic excoriations.<sup>68,69</sup> However, its use is limited by its adverse effects and high cost.<sup>57</sup> It is also contraindicated in patients with acute hepatitis or liver failure, and during pregnancy and lactation.<sup>49,66</sup>

**Antipsychotics.** Antipsychotics can help in psychogenic pruritus and pruritus that has a predominantly impulsive quality.<sup>51</sup> Medications, such as chlorpromazine, risperidone, and olanzapine, are often used to augment treatment with an antidepressant or anxiolytic regimen. Olanzapine monotherapy has successfully treated itching related to self-mutilation in patients who have failed other pharmacotherapies.<sup>71</sup>

**Anxiolytics.** Anxiety may incite or worsen symptoms of pruritus. Anxiolytics, such as benzodiazepines and SSRIs, can help reduce itch in patients with an anxious or obsessive-compulsive diathesis.

## PSYCHOTHERAPY

### Key points

- Conducting a psychological assessment and establishing a physician–patient therapeutic alliance improves the outcome of psychotherapy
- There is a plethora of psychotherapeutic modalities but scarce evidence on their comparative efficacy

The psychologic evaluation of the dermatology patient is crucial, and should include an assessment whether a referral to psychiatry and/or psychology is warranted. Patients with psychodermatological issues often benefit from psychotherapy. The most common psychological interventions and psychotherapies are described below.

### Basic therapies

**Psychoeducation.** Providing psychoeducation increases patients' understanding of their condition, improves treatment adherence, and reduces distress, anxiety, shame, and depression associated with the disease.<sup>72</sup> Support groups, in which patients share their problem and provide mutual support for each other, can provide such education and improve quality of life.<sup>4,73</sup>

**Self-help.** Self-help (computer- or literature-based) covers a variety of interventions, including psychoeducation (providing patients with reading material about their illness), specific coping techniques, and self-guided CBT (see below).<sup>74</sup>

**Relaxation.** Most psychocutaneous diseases can be precipitated or exacerbated by stress.<sup>4</sup> Relaxation techniques are used to help cope with stress. They consist of guided imagery, mindfulness, muscle relaxation, avoidance of food indulgence and dehydration, aerobic and water exercise, yoga, and meditation.<sup>4,72</sup>

**Social skills training.** Social skills training helps patients cope with others' reactions to their appearance and develop effective strategies to manage social situations.<sup>72</sup> It also helps patients elicit more positive feedback from others in social interactions, and therefore develop a more positive sense of self.<sup>75</sup>

### Complex therapies

**CBT.** CBT helps alter dysfunctional thought patterns (cognitive) or actions (behavioral) that lead to skin damage or psychological distress.<sup>24</sup> CBT places a strong emphasis on "examining the evidence," and replacing inaccurate thoughts with more accurate ones.<sup>76</sup> For example, in a patient with skin picking disorder, the CBT therapist may challenge a patient who believes that he/she can "pick just a little and then stop" by asking the patient to provide evidence of a time that he/she was able to pick for <5 minutes. CBT is typically conducted once a week for a total of 12 to 20 weeks. Although preliminary results can be seen early into treatment, >20 sessions may be necessary for long-term results.<sup>77</sup> CBT is of significant benefit in OCRDs and somatic symptom disorders.<sup>38,78,79</sup>

**Habit-reversal training.** Habit-reversal training (HRT) aims at replacing an old habit (a recurrent, often subconscious or automatic pattern of behavior) with a new, more desirable one.<sup>80</sup> HRT is the criterion standard for treatment of body-focused repetitive behaviors,<sup>81,82</sup> and may also be helpful in atopic dermatitis, lichen simplex chronicus, pruritus ani, and prurigo nodularis.<sup>83</sup> HRT includes 3 main components: awareness training, competing response training, and social support.<sup>84</sup> Awareness training involves the patient describing the old habit (ie, skin picking or hair pulling), along with its antecedents (ie, triggers/warnings signs before the habit occurs, such as looking in a mirror or stroking the hair). Once the patient is made fully aware of the behavior, its antecedents, and its consequences, breaking the habit becomes much more possible. Competing response training includes teaching the patient behaviors that are physically impossible to do in alongside the old habit (eg, fistling hand with the thumb tucked). Social support involves finding a friend/family member who can gently make the patient aware when he/she is engaging in an old habit and praise the patient for correctly using competing behaviors.<sup>84</sup> Other helpful interventions include stimulus control (eg, covering mirrors, wearing gloves, or wearing shorter hairstyles).<sup>84</sup> Despite positive results, CBT and HRT carry a significant risk of relapse, and their efficacy varies across patients.<sup>85</sup>

**Hypnotherapy.** Hypnotherapy uses the power of suggestion to change habits and thoughts.<sup>4,24,86</sup> By tapping into the subconsciousness to reveal an event, comment, or situation, one can resolve it. Hypnosis can reduce stress and promote deep relaxation, can help deal with childhood issues, and treat anxiety and depression. Skin disorders that may benefit from hypnosis include, among others, acne excoriée, delusional infestation, glossodynia, and trichotillomania.<sup>4,24</sup>

**Biofeedback.** Biofeedback involves measuring and providing auditory and visual feedback of bodily processes including blood pressure, heart rate, galvanic skin response (sweating), muscle tension, and skin temperature.<sup>4</sup> Patients are taught techniques that enable them to control the above involuntary functions, which helps manage stress. Skin diseases improved by biofeedback include, among others, eczema, psoriasis, hyperhidrosis, pain syndromes and Raynaud syndrome.<sup>4,24,86</sup>

**Other interventions.** Family-based therapy promotes parental responsibility for treatment adherence, and has been helpful in eating disorders.<sup>87,88</sup> Motivational interviewing seeks to improve a patient's ambivalence to treatment and resistance to change, and transform ambivalence into positive

emotional changes. Motivational interviewing is suited for addiction treatment because it enhances motivation to recover from substance use.<sup>89</sup> It is also beneficial in eating disorders.<sup>90</sup> Eye movement desensitization and reprocessing serves to reduce trauma symptoms stemming from adverse life experiences, and has been used to treat phobias and posttraumatic stress disorder.<sup>91,92</sup> In this intervention, the patient focuses on a negatively emotionally charged memory or problem area while doing an alternating bilateral activity (eg, following the therapist's fingers moving side to side), during which the patient's eyes move rapidly. The memory recall with eye movement causes a decrease in memory emotionality/vividness.<sup>93</sup>

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# Injectable and topical neurotoxins in dermatology



## Basic science, anatomy, and therapeutic agents

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### Learning objectives

After completing this learning activity, participants should be able to discuss the history, science, safety profile, and new indications of neurotoxins in clinical and cosmetic practice; describe the mechanisms of action of currently available neurotoxins; and explain how to use a more standardized approach to their neurotoxin injection protocol to help minimize complications.

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Botulinum toxin is a potentially deadly anaerobic bacterial toxin that acts by inhibiting release of acetylcholine at the neuromuscular junction, thereby inhibiting contraction of the exposed striated muscle. There are currently 4 botulinum toxin preparations approved by the US Food and Drug Administration (FDA): onabotulinumtoxin, abobotulinumtoxin, incobotulinumtoxin and rimabotulinumtoxin. While significant overlap exists, each product has unique properties and specifications, including dosing, diffusion, and storage. Extensive physician knowledge of facial anatomy, coupled with key differences of the various neurotoxin types, is essential for safe and successful treatments. The first article in this continuing medical education series reviews key characteristics of each neurotoxin, including new and upcoming agents, and provides an anatomic overview of the most commonly injected cosmetic sites. (J Am Acad Dermatol 2017;76:1013-24.)

**Key words:** abobotulinum; anatomy; botulinum toxin; *Clostridium botulinum*; incobotulinum; lower face; neuromodulator; neurotoxin; new indications; onabotulinum; properties; rimabotulinum; RT001; RT002; upper face.

## HISTORY

In the early to mid-1800s, “sausage poison,” now known as botulism, was a major and lethal source of food poisoning in Europe.<sup>1</sup> In 1989, after much investigation and scientific research, *Clostridium*

*botulinum*’s bacterial toxin was approved for a variety of medical uses, including hemifacial spasms, strabismus, and blepharospasm.<sup>1</sup> A serendipitous discovery by ophthalmologist Jean Carruthers in the late 1980s recognized reduced facial wrinkles in

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patients with benign essential blepharospasm who were treated with injectable botulinum toxin.<sup>2</sup> This was first reported at the American Society for Dermatologic Surgery (ASDS) annual meeting in 1991 (Fig 1). Initially met with skepticism, this was closely followed by 2 confirmatory clinical trials of safety and efficacy.<sup>2,3</sup> In 2002, it received approval by the US Food and Drug Administration (FDA) for “temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity.”<sup>4</sup> Subsequently, there has been a rapid acceptance and widespread investigation into additional cosmetic and therapeutic usages for this previously “deadly” toxin that ultimately revolutionized aesthetic medicine.

## BASIC SCIENCE

### Key points

- Botulinum toxin has 7 serotypes purified from the anaerobic, Gram-positive, spore-forming *Clostridium botulinum*
- Botulinum toxins are 150-kDa proteins that are distinguished by the variations in their light chains
- Incobotulinumtoxin is free from complexing proteins
- The mechanism of action involves toxin cleavage of the SNARE protein complex with resultant dysfunction of acetylcholine release at the neuromuscular junction

Seven serotypes (A through G) of botulinum toxin have been identified and purified from differing strains of the anaerobic, Gram-positive, spore-forming *C botulinum*.<sup>5</sup> Type A is the most potent, with types B and F closely following.<sup>2</sup> Types A, B, and E are known causes of food poisoning, and types C and D do not appear to affect the human nervous system.<sup>1,5</sup> Type F is implicated in food poisoning less often, and type G has not been linked to human botulism.<sup>6</sup>

Botulinum neurotoxins are 150-kDa polypeptides that consist of a 100-kDa heavy chain linked with a 50-kDa light chain via heat-sensitive disulfide bonds and noncovalent forces.<sup>5</sup> Different toxin serotypes are distinguished by variations in their light chains.<sup>7</sup> The toxins can be complexed with hemagglutinin and “nontoxic molecule” then dimerized to form a larger compound: 900 kDa for onabotulinum toxin and 500 kDa for abobotulinum toxin.<sup>2,4</sup>

Incobotulinum is free from complexing proteins, weighing 150 kDa.<sup>4</sup> The final active forms act on the peripheral nervous system to inhibit the release of acetylcholine from the neuromuscular junction

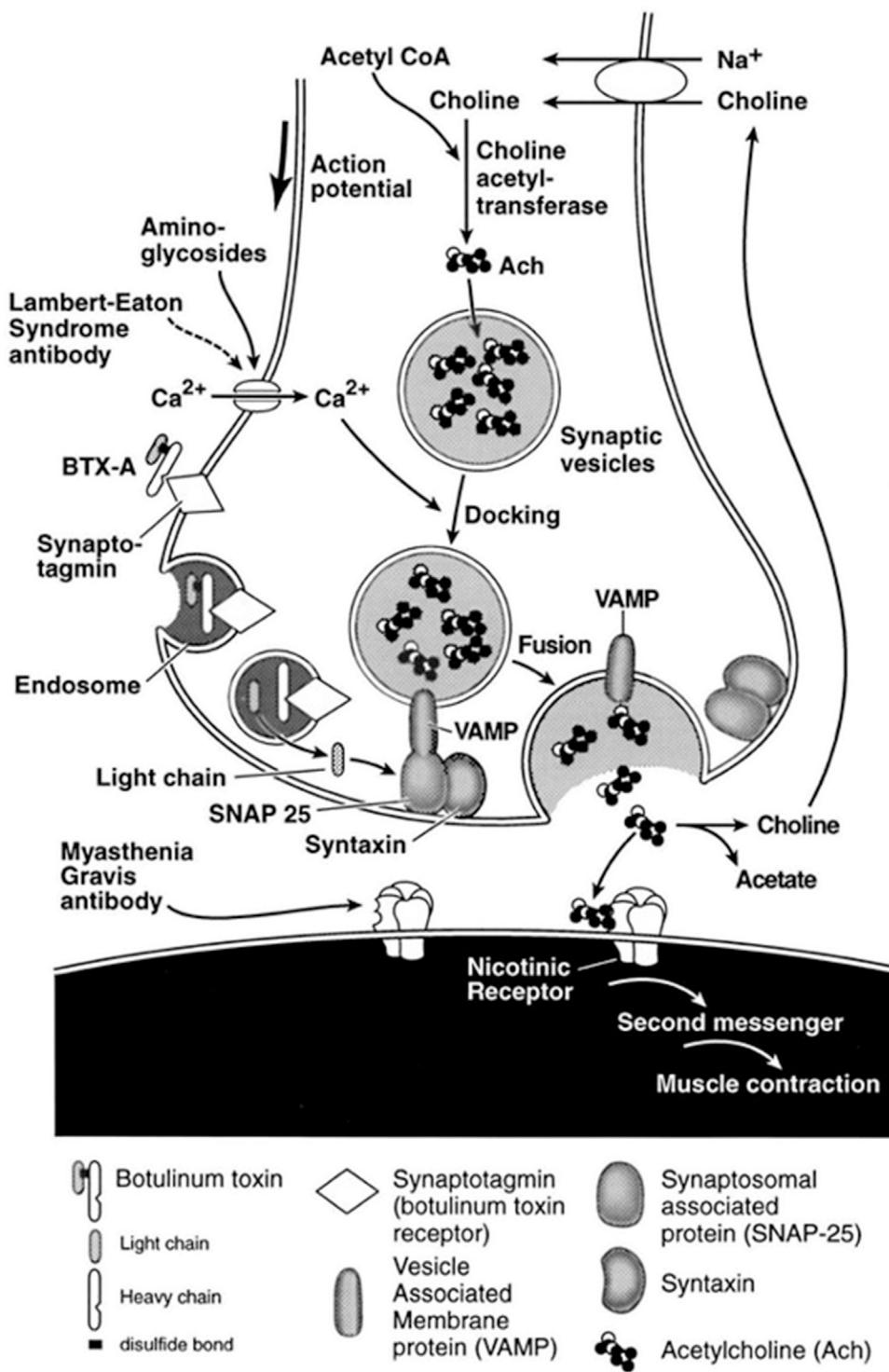


**Fig 1.** The first cosmetic patient treated with botulinum toxin to the glabellar region. **A**, Pretreatment. **B**, Post-treatment. (Courtesy of Jean Carruthers, MD.)

(NMJ).<sup>5</sup> The most common site of action is the presynaptic terminal; however, binding to the autonomic cholinergic ganglia with resultant autonomic effects has been reported in very large doses.<sup>5,8,9</sup>

Once injected, it irreversibly binds to a receptor on the presynaptic terminal of the NMJ, termed synaptotagmin.<sup>5</sup> Through receptor-mediated endocytosis, internalization of the toxin-receptor complex occurs, and the disulfide bond linking the heavy and light chains is cleaved. The light chain then translocates to the cytoplasm, fuses with a toxin-specific protein isoform, soluble NSF attachment protein receptor (SNARE), and cleaves the protein isoform utilizing a zinc-dependent endopeptidase.<sup>5,7</sup> The synaptic fusion complex consists of three main SNARE proteins, synaptobrevin/vesicle-associated membrane protein, 25-kDa synaptosomal-associated protein, and syntaxin.<sup>7</sup> Type A botulinum toxins, most commonly used, cleave 25-kDa synaptosomal-associated protein, while type B toxins catalyze the breakdown of synaptobrevin/vesicle-associated membrane protein (Fig 2). This disrupts the docking, fusion, and release of acetylcholine vesicles into the NMJ, thereby inhibiting muscular contraction.<sup>5</sup>

It has also been suggested that acetylcholinesterase activity is altered with botulinum toxin.<sup>2</sup> While typically confined to the NMJ, staining patterns in treated muscle have shown acetylcholinesterase activity spanning over most of the sarcolemma.



**Fig 2.** Cholinergic neurotransmission and botulinum toxin mechanism of action. BTX-A, Botulinum toxin A. (Reprinted with permission from Huang et al.<sup>5</sup>)

This pattern appears to be temporary, lasting only about 4 to 5 months.

While chemical denervation is thought to be permanent in all exposed NMJs, muscle function is almost always recovered within a few months after exposure. This occurs by neurogenesis, the

formation of axonal sprouts and new motor end plates with the eventual absorption of dysfunctional neurons. This process of reprogramming and reorganization appears to occur within the first 10 days after injection, and by months 3 to 6 have reversed the toxin's effects.<sup>10,11</sup>

## OVERVIEW OF COMMERCIALLY AVAILABLE FORMULATIONS APPROVED BY THE FDA

### Key points

- There are 4 commercially available formulations of botulinum toxin in the United States: onabotulinumtoxin, incobotulinumtoxin, abobotulinumtoxin, and rimabotulinumtoxin
- Each formulation has unique properties, and the neuromodulators are not interchangeable
- Incobotulinumtoxin is unique in its stability at room temperature storage
- Reconstitution with bacteriostatic saline reduces injection discomfort
- Diffusion is suggested to be multifactorial; however, abobotulinumtoxin generally features larger diffusion halos compared to the other type A toxins

There are currently 4 preparations of neuromodulators approved by the FDA (Table I). Three are type A toxins, including onabotulinum, incobotulinum, and abobotulinum; rimabotulinum is type B.

### Onabotulinumtoxin A

Onabotulinum was approved for medical indications in the United States in the 1990s<sup>4</sup> and was purchased by Allergan in 1991, who coined the commonly used name Botox (Allergan, Inc, Irvine, CA).<sup>1</sup>

Onabotulinumtoxin A is a sterile, lyophilized form of botulinum toxin type A, produced from the Hall strain of *C botulinum* bacteria and cultured in a particular medium containing N-Z amine and yeast extract.<sup>5</sup> Lyophilization, or freeze drying, is the process of first freezing a substance and then lowering the surrounding pressure so that the frozen/solid water sublimates to a gas phase. Isolation occurs by a series of acid preparations, forming a crystalline complex consisting of active toxin and hemagglutinin proteins. This preparation is then redissolved in saline and albumin, sterilized, and vacuum-dried.

The 100-unit vial contains 0.5 mg of human albumin and 0.9 mg of sodium chloride in a sterile, vacuum-dried form without preservative.<sup>5</sup> Initially, vials were stored in the freezer before reconstitution because of concerns of toxin heat lability; however, evidence suggests that vials can safely be stored at refrigerated temperatures for  $\leq 36$  months before use.<sup>12</sup> However, upon reconstitution, it is recommended that the product be stored in the refrigerator between 2°C and 8°C.

### Abobotulinumtoxin A

Abobotulinumtoxin A, more commonly known as Dysport (Galderma Laboratories, Fort Worth, TX)

**Table I.** Botulinum toxin agents

Botulinum toxin type A (manufacturer)	Botulinum toxin type B (manufacturer)
Onabotulinumtoxin A/Botox (Allergan, Irvine, CA)	Rimabotulinumtoxin B/Myobloc (Solstice Neurosciences, Louisville, KY)
Abobotulinumtoxin A/Dysport (Galderma Laboratories, Fort Worth, TX)	
Incobotulinumtoxin A/Xeomin (Merz, Frankfurt, Germany)	
Puretox (Mentor Corporation, Santa Barbara, CA)	
Evosyal (Alphaeon, Irvine, CA)	
Linurase (Prolleinum, Aurora, Ontario, Canada)	
Chinese BTX-A/Prosigne/Lantox/Redux (Lanzhou Biological Products Institute, Lanzhou, China)	
Neuronox/Meditoxin/Botulift (Seoul, South Korea)	
Daxibotulinumtoxin A/RT001, topical (Revance Therapeutics, Newark, CA)	
Daxibotulinumtoxin A/RT002, injectable (Revance Therapeutics)	

was the second neuromodulator approved by the FDA in 2009.<sup>4,13,14</sup> This formulation has successfully been in use in >70 other countries since 1990.<sup>7</sup> Abobotulinumtoxin A is supplied in 300- or 500-unit vials and uses a column-based purification.<sup>5</sup> The purified complex is dissolved in a lactose solution also containing human albumin and subsequently sterile filtered and lyophilized, with each vial containing 0.125 mg human serum albumin with 2.5 mg of lactose.<sup>7,15</sup>

Abobotulinumtoxin A is different from onabotulinumtoxin A in terms of units, chemical properties, biologic activity, and weight; therefore, the 2 formulations are not interchangeable and dosing recommendations cannot be based on a single conversion ratio.<sup>4,15</sup> In addition, each neuromodulator has a nonparallel dose response curve, meaning their relative performance is not consistent across a range of dose ratios.<sup>4,16</sup> A given unit of one toxin does not translate to a constant unit relationship with another toxin.<sup>4</sup> It was originally postulated that each unit of onabotulinumtoxin A is equivalent to approximately 3 to 5 units of abobotulinumtoxin A. More recent evidence suggests a ratio closer to 2.5:1 (abobotulinumtoxin:onabotulinumtoxin) is effective for treating rhytides, which parallels the manufacturer's recommendations (Table II).<sup>17</sup> As

**Table II.** Abobotulinumtoxin A dose conversion

Reference	Investigation	Neurotoxin comparison	Dose ratio	Outcome	Suggested conversion
Sampaio et al, 1997 <sup>91</sup>	Clinical study: blepharospasm or hemifacial spasm	Abobot:onabot	4:1	Similar efficacy	4:1
Odergren et al, 1998 <sup>92</sup>	Clinical study: cervical dystonia	Abobot:onabot	3:1	Similar efficacy	3:1
Ranoux et al, 2002 <sup>93</sup>	Clinical study: cervical dystonia	Abobot:onabot	3:1 and 4:1	Abobot > onabot at both doses	≤3:1
Karsai et al, 2007 <sup>94</sup>	EMG activity: forehead	Abobot:onabot	3:1	Abobot > onabot	≤3:1
Cliff et al, 2008 <sup>63</sup>	Anhidrotic effects: forehead	Abobot:onabot	3:1	Abobot > onabot	≤3:1
Kranz et al, 2008 <sup>95</sup>	Anhidrotic effects: abdomen	Abobot:onabot	3:1 and 4:1	3:1 and 4:1 abobot > onabot	2:1
Virgilis-Kalner et al, 2011 <sup>96</sup>	Clinical study: axillary hyperhidrosis	Abobot:onabot	3:1	Onabot > abobot	3:1
Hexsel et al, 2015 <sup>18</sup>	Clinical: anhidrotic effect; EMG: forehead	Abobot:incobot	2.5:1	Clinical/EMG similar; abobot > incobot for anhidrotic effect	2.5:1

Abobot, Abobotulinum; EMG, electromyography; incobot, incobotulinum; onabot, onabotulinum.

with all neurotoxins, the overall recommendation is to match the amount of toxin to the muscle hypertrophy or to use “as much as necessary but as little as possible” to achieve the desired effect.

### Incobotulinumtoxin A

Incobotulinumtoxin A (Xeomin; Merz Pharmaceuticals GmbH, Frankfurt, Germany) is the newest neurotoxin type A available in the United States, achieving FDA approval in 2011.<sup>18</sup> The purification involves separating the neurotoxin from the complexing proteins, yielding a final lyophilized 150-kDa product containing only the active ingredient, 1 mg of human albumin, and 4.7 mg sucrose.<sup>19</sup> It is therefore theoretically less immunogenic. Studies suggest that incobotulinumtoxin and onabotulinumtoxin can be converted in a 1:1 ratio.<sup>18,20-26</sup> Incobotulinumtoxin can be stored at room temperature for ≤36 months before reconstitution. The package insert recommends postreconstitution refrigerated storage at 2°C to 8°C. However, evidence suggests equal product efficacy with 25°C storage (room temperature) for 1 week postreconstitution for the treatment of lateral canthal lines.<sup>27</sup>

### Rimabotulinumtoxin B

Rimabotulinumtoxin B (Myobloc; Solstice Neurosciences Inc, Louisville, KY) is the only type B neurotoxin currently available in the United States, with FDA approval and clinical use almost exclusively in the context of neuromuscular disease, including cervical dystonia.<sup>7,28</sup> It has been used successfully off-label for the treatment of dynamic facial rhytides.<sup>29-31</sup> Unlike its type A counterparts, this preparation is a nonlyophilized and stable liquid

formulation.<sup>29</sup> Rimabotulinumtoxin B was found to have a more rapid onset yet a shorter duration of action (approximately 2 months) compared to the 3 or 4 months with type A toxins, and is associated with more discomfort on injection, limiting its cosmetic use.<sup>4,7,29,31-33</sup> Both dosages of 1:70 and 1:100 units (onabotulinumtoxin A:rimabotulinumtoxin B) produced effective results in the treatment of forehead lines without significant difference.<sup>29</sup> There is no cross reactivity with type A, and it may effectively be used in patients who receive large doses of toxin and are unresponsive to, or have developed neutralizing antibodies to, type A toxins.<sup>2,20,34,35</sup>

The different formulations of botulinum toxins are more similar than dissimilar; however, they are not bioidentical, and therefore it is imperative that the clinician thoroughly understands the properties and clinical performance of each product in order to achieve safe and effective use.

### Reconstitution

Recommendations from the Centers for Disease Control and Prevention regarding the reconstitution of botulinum toxin type A have been challenged. Initial FDA approval specified single-use vials and treatment within 4 hours of reconstitution.<sup>36,37</sup> This was not cost effective and directly conflicted with guidelines from the Centers for Medicare and Medicaid Services, which encouraged the use of 1 vial for multiple patients to prevent product waste.<sup>36</sup> Clinical experience and data have suggested that a single vial may be used for the treatment of multiple patients, assuming that safe reconstitution and injection techniques are practiced.<sup>36,38</sup> The concern for increased risk of infection or contamination of the

product has not been demonstrated in clinical studies or anecdotal reports.<sup>36,39-42</sup> A survey of physician members of the ASDS revealed that a majority maintained their product for 1 week or longer with multiple uses, and no physicians reported any incidence of local infection after botulinum toxin injection.<sup>36</sup> In 2015, a consensus statement was released reconfirming the use of 1 vial for multiple patients, assuming appropriate handling by staff.<sup>38</sup>

Manufacturers recommend using nonpreserved saline for reconstitution. However, numerous randomized controlled trials have shown that use of preserved or bacteriostatic saline has up to a 60% reduction in pain upon injection.<sup>36,43-48</sup> This is because of the preservative benzyl alcohol, which has inherent anesthetic properties.<sup>45</sup> The current physician consensus is to use preservative-containing saline, which improves patient comfort without introducing increased adverse events.<sup>38</sup>

The use of lidocaine as the diluent for botulinum toxin type A has been investigated. In a split-study on axillary hyperhidrosis, the side treated with lidocaine had significantly reduced intraprocedural pain compared to saline, while maintaining effectiveness, duration, and safety of treatment.<sup>49</sup> To date, there is no published comparison of injection pain with bacteriostatic saline/benzyl alcohol compared to lidocaine.

Studies have also shown that toxin refrigerated (4°C) after reconstitution compared to those refrozen (-20°C) showed no difference in the degree or duration of effect up to 120 days after injection.<sup>50</sup>

There is a small amount of product waste per vial of reconstituted toxin because liquid by capillary action will cling to the walls of the vial, the stopper, the syringe, and the needle. In one study, a 5% waste of product per vial on average was demonstrated with the technique of aspirating through the stopper with a larger-bore needle.<sup>51</sup> This loss can be minimized by drawing product from an upright vial with the stopper removed, the bottle tilted at a 30° angle, and using a smaller-bore needle. However, caution should be maintained to avoid blunting the needle tip on the vial floor.

## Storage

Original recommendations designated 4 hours as the maximum shelf-life for the neurotoxins postreconstitution because reduced efficacy beyond this timeframe was noted in animal and in vitro studies.<sup>52</sup> However, clinical studies on humans maintained efficacy if the products are re-refrigerated or refrozen after reconstitution for 1 week to 6 months.<sup>40,50,53-56</sup> In addition, there is evidence that room temperature storage of incobotulinumtoxin A postreconstitution is safe and effective.<sup>27</sup>

Guidelines based on a 2012 ASDS membership survey recommended safe neuromodulator storage and reuse for ≤2 weeks.<sup>37</sup> However, more recent guidelines have expanded this timeframe to 4 weeks postreconstitution with appropriate cold storage of the product.<sup>38,57</sup> Best clinical practice should be used with regard to safe reconstitution, storage, and administration of the neuromodulator. According to the Centers for Disease Control and Prevention, this includes appropriate handling, storing, and managing medications and injection equipment, keeping vials away from immediate patient treatment areas to prevent contamination, dating vials immediately upon opening, and discarding based on manufacturer's data.<sup>58</sup> These revised guidelines allow for improved access to medication with more flexible physician schedules for injection and reduced waste, which directly translates to reduced product (and therefore patient) cost.

## Diffusion

There is a difference in diffusion among the various products, and this may create clinically distinct results. This has been suggested from preclinical animal studies investigating the muscle weakening in mice, which has consistently demonstrated higher potency and reduced diffusion with onabotulinumtoxin A compared to abobotulinumtoxin A.<sup>59</sup> Clinical investigations with equivalent injection volumes largely support this initial finding (Table III).<sup>60-63</sup> While advantageous for treating hyperhidrosis, increased diffusion areas limit precise localization, which may result in a higher risk for unwanted adverse events when treating small facial muscles. Overall, diffusion is suggested to be multifactorial with influence from volume, concentration, and dose.<sup>64</sup> In addition, the interpretation of diffusion studies proves challenging and often unreliable because the widely accepted split-face model cannot account for regional diffusion into the contralateral, untreated side.<sup>65</sup>

## FUTURE TOXINS

### Key points

- A peptide was developed that enables transcutaneous flux of toxin, allowing for a topical formulation on the horizon
- RT002 is a new injectable agent with limited diffusion and longer duration of effect
- Various formulations are available overseas

### Topical agents

Currently formulated complexed neuromodulators are ineffective in penetrating an intact epidermis.<sup>66</sup> A successful mechanism was created

**Table III.** Diffusion properties

Reference	Investigation	Neurotoxin comparison	Study parameter	Greatest diffusion
Trindade de Almeida et al, 2007 <sup>62</sup>	Forehead hyperhidrosis: split-face study	Abobot:onabot	2.5:1, 3:1, and 4:1; isovolumetric	Abobot at all dose ratios
Karsai et al, 2008 <sup>61</sup>	Forehead: clinical and EMG	Abobot:onabot	3:1; isovolumetric	Abobot
Cliff et al, 2008 <sup>63</sup>	Forehead anhidrotic effects: split-face study	Abobot:onabot	3:1; isovolumetric	Abobot
Hexsel et al, 2013 <sup>60</sup>	Forehead clinical, anhidrotic effect, muscle action potentials: split-face study	Abobot:onabot	1:1 (equal unit doses); isovolumetric	Onabot
Ko et al, 2014 <sup>97</sup>	Forehead hyperhidrosis: split-face study	Onabot:abobot: NABOTA	1:2.5:1; isovolumetric	Abobot (onabot and NABOTA similar)
Hexsel et al, 2015 <sup>18</sup>	Forehead anhidrotic effects: EMG, split-face study	Abobot:incobot	2.5:1; isovolumetric	Abobot (however, similar for muscular effects)

NABOTA is a trademark of Daewoong Pharmaceutical Co (Seoul, South Korea).

Abobot, Abobotulinum; EMG, electromyography; incobot, incobotulinum; onabot, onabotulinum.

that allows for the passage of large molecules through an intact epidermis.<sup>67</sup> Recently in phase III clinical trials for the topical treatment of lateral canthal lines, daxibotulinumtoxin A topical gel (RT001; Revance Therapeutics Inc, Newark, CA) contains an albumin-free 150-kDa toxin cream preparation with a poloxamer-based diluent containing a peptide that enables transcutaneous flux of the toxin.<sup>68</sup> A randomized, double-blind, placebo controlled study compared RT001 with placebo at weeks 0 and 4 and followed patients for a maximum of 8 weeks.<sup>68</sup> Initial results were promising as in a second trial, 44.4% of patients achieved a  $\geq 2$  point improvement on the Investigator Global Assessment of Lateral Canthal Line severity scale compared to 0% for placebo after 4 weeks.<sup>69</sup> Results and safety profiles for lateral canthal lines were initially encouraging, eradicating injection site bruising and discomfort.<sup>70,71</sup> However, completion of the phase III trial showed disappointing outcomes and RT001 failed to achieve its endpoint of two points or greater improvement in crow's feet lines after 28 days of treatment.<sup>72</sup>

### Injectable agents

Pending FDA approval are daxibotulinumtoxin A injectable (RT002; Revance Therapeutics Inc), Puretox (Mentor Corporation, Santa Barbara, CA), and Evosyal (Alphaeon, Irvine, CA). Currently, there is no literature on Evosyal. RT002 is a purified 150-kDa injectable neurotoxin coupled with a patented TransMTS peptide that may limit the extent of diffusion and increase the duration of effect.<sup>73</sup> Preliminary studies in mice comparing RT002 to onabotulinumtoxin confirmed that RT002 extended the duration of drug effect by 58% to 100% using

diffusion-matched dosages.<sup>74</sup> A phase I/II clinical study investigated various dosages of RT002 in the treatment of moderate to severe glabellar lines.<sup>73</sup> These results confirmed the preclinical studies. The median duration of response was 7 months. Enrollment has been completed for two large phase III studies for the treatment of moderate to severe glabellar lines in adults. These two pivotal trials will evaluate the efficacy, safety, and duration of RT002 with results anticipated in the fourth quarter of 2017.<sup>75</sup> PurTox (Mentor Corporation) was pursuing phase III trials and expecting FDA approval until Johnson and Johnson acquired Mentor Inc in 2014.

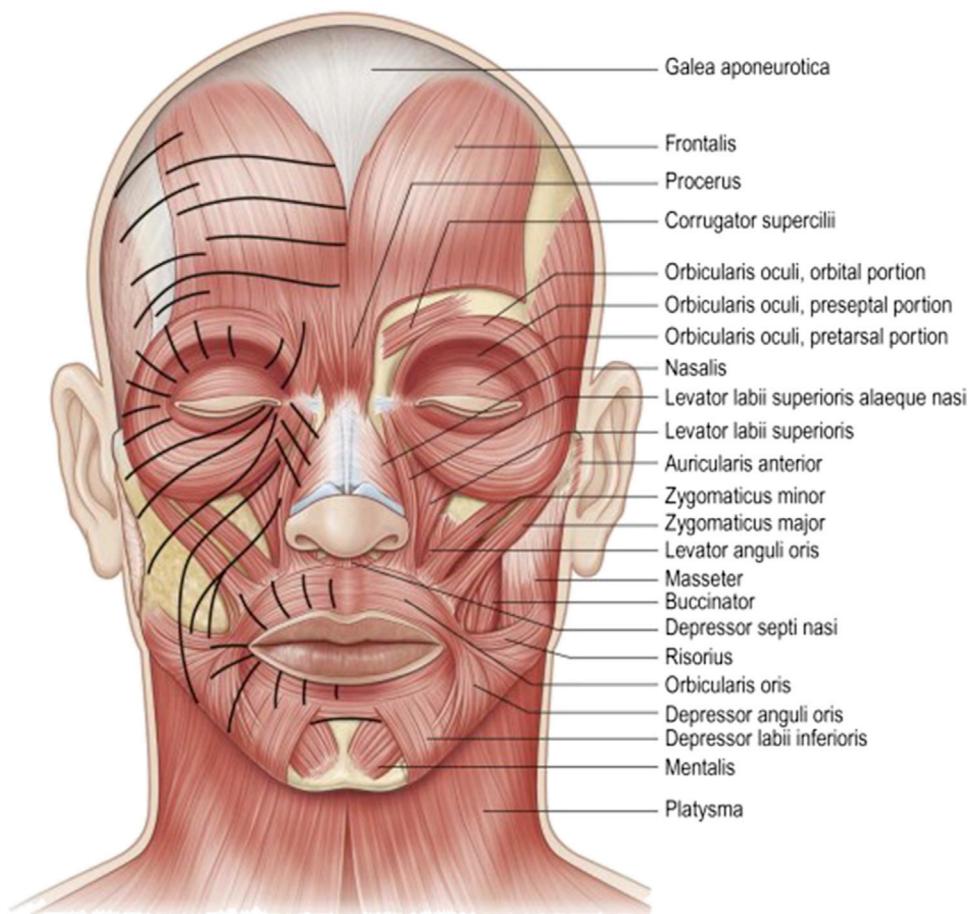
Toxins that are available overseas are Prosigne/Lantox/Redux/CBTX-A (Lanzhou Biological Products Institute, Lanzhou, China) and Neuronox/Meditoxin/Botulift (Medytox Inc, Seoul, South Korea).<sup>67,76</sup> Various formulations available in the United States are marketed under separate names in Europe and overseas.

### ANATOMY

#### Key points

- Appreciating the contraction patterns and the 3-dimensionality of the facial muscles is critical to safe and effective injection
- There are anatomic variations based upon age, location, and sex that must be taken into consideration
- A complete understanding of muscle function and position is crucial to avoid adverse events

All superficial facial muscles work together to form the superficial musculoponeurotic system, which allows for the fluidity of facial movements. Generally, hyperfunctional lines are perpendicular



**Fig 3.** Diagram of relevant facial anatomy. (Reprinted with permission from Kane.<sup>77</sup>)

to the sum vectors of muscle forces.<sup>5</sup> These lines are further accentuated with loss of skin elasticity. There are subtle idiosyncratic variations in anatomy based upon location and sex that can influence the way in which neurotoxin is injected (Fig 3).<sup>77</sup> In addition, appreciating the 3 dimensions of many of these often superficial muscles is critical to effective and safe injection. Many scientific publications focus primarily on “X-Y planes” (horizontal and vertical) for injection, but the muscle depth, the “Z plane,” is also important. Recent studies support the injection of neuromodulators more superficially in the subdermis without a loss of efficacy.<sup>78-81</sup>

### Glabella

The muscles of the glabellar region function as the primary brow depressors, contributing to the vertical and horizontal wrinkles of the medial brow. This group consists of the bilateral corrugator supercilii, depressor supercilii, procerus, and the orbital portion of the orbicularis oculi, with the corrugators arguably having the strongest influence.<sup>5</sup> The winged corrugator muscles, or the “scowl muscles,” overlie the frontal bone near the superomedial

orbital rim and inserts more superficially into the dermis superior to the middle third of the eyebrow.<sup>82</sup> Clinically, this superficial lateral border can be appreciated during muscle contraction as a “dimpled” area. The procerus, or the “snout muscle,” originates on the lower portion of the nasal bone and inserts superiorly on the skin overlying the nasal root. While these muscles are often illustrated as distinct entities, all facial muscles lie in close proximity, and their fibers are often integrated.

### Nasal muscles

The nasalis muscle originates in the maxilla and inserts into the nasal bone. It is comprised of 2 regions: the transverse and the alar portions. The superior transverse portion covers the bridge of the nose, and movement of these fibers results in “bunny lines.” To avoid muscle recruitment when treating the glabellar region, the transverse nasalis muscle is often treated in conjunction.

The alar portion of the nasalis muscle is attached to the nostril cartilage and is responsible for nasal compression. One injection bilaterally can reduce elevation of the nostril corners with less nasal flaring.

The depressor septi nasi muscle originates in the maxilla and inserts into the alar part of the nasalis muscle. As its name implies, its primary responsibility is nasal tip descent. With age there is concurrent nasal tip ptosis, and 1 injection into the base of the muscle, at the columella, has been shown to give subtle nasal tip elevation.

### Frontalis

The frontalis is a broad, thin muscle spanning across the forehead region originating on the galae aponeurotica near the coronal suture and inserting on the superciliary ridge of the frontal bone.<sup>82</sup> It interdigitates with the orbicularis oculi, corrugator supercilii, and procerus muscles. It functions as the “surprise muscle,” and is the main cause of horizontal forehead lines. This thin, wispy muscle only needs small amounts of toxin for clinical effect. Injections consist of superficial blebs directed in 1 or 2 rows spanning from the lateral superior fibers of the frontalis muscle to the midforehead inferiorly ( $\geq 1.5$  cm above the brow) to avoid brow ptosis.<sup>78,79,81</sup> To avoid altering the convexity of the eyebrow arch, the brow depressor muscles (corrugator supercilii, procerus, and lateral fibers of the orbicularis oculi muscles) are usually treated simultaneously or a few days before the frontalis muscle. Treating these agonist and antagonist muscles concurrently maintains the brow in a neutral position.

### Orbicularis oculi

The orbicularis oculi is a large circular band of muscles encircling the orbit. It is composed of the orbital and palpebral portions, inserting onto the inferior and superior aspects of the orbital rim, and radiating outward to insert on the medial and lateral canthal tendons, and fibers of the frontalis, superficial temporalis fascia, corrugators, and procerus.<sup>82</sup> This sphincter muscle functions to close the eyes tightly, while also depressing the eyebrows and directing them medially. Lateral fibers of this muscle are primarily responsible for the lateral canthal lines. To minimize complications, injections should be as superficial as possible as the neuromodulator will then treat the intended muscle groups, which are anatomically superficial to the deeper structures implicated in adverse reactions.

### Lower face (orbicularis oris, depressor anguli oris, and mentalis muscles)

Although not approved by the FDA, neuromodulators have been successfully used for years in the cosmetic treatment of the lower half of the face. The muscles primarily responsible for lower facial rhytides include the orbicularis oris, the depressor

anguli oris, and the mentalis. The masseter muscle is another common cosmetic injection target.

The orbicularis oris is an elliptical muscle that circumferentially extends around the oral aperture, with upper and lower segments joining and inserting laterally at the modiolus and anterior insertion defining the wet-dry vermillion border.<sup>83</sup> Muscle function includes closure and forward protrusion of the lips. This is the primary muscle responsible for hyperdynamic vertical perioral lines, or “whistle, smoker’s, or kissing” lines. Judicious amounts of neuromodulator can achieve temporary effacement of these lines.<sup>83-85</sup>

The depressor anguli oris originates in a deep, fan-like shape at the outer surface of the mandible posterior to the oblique line and courses superiorly to insert superficially into the modiolus.<sup>84</sup> Contraction of this muscle results in depression of the oral commissure, and overactivity may lead to accentuation of the melolental fold or “marionette lines.” This can add to an unwanted resting expression of sadness. Patients are asked to show their lower teeth to assist in the identification of this muscle, and 1 to 2 injections are aimed along the mandibular border about 1 cm lateral to the oral commissure to avoid diffusion into the depressor labii inferioris.<sup>84,86</sup>

The mentalis muscle arises from the incisive fossa on the anterior mandible and inserts more superficially into the medial chin. The 2 muscle bellies create a central V-shaped triangle, with lateral fibers interdigitating with the orbicularis oris and depressor labii inferioris. It functions primarily in lower lip elevation and eversion, and can create unwanted wrinkling and dimpling of the chin with contraction.<sup>83,84</sup>

### Platysma

The platysma is a fine, wispy muscle that encompasses most of the anterolateral neck region.<sup>87</sup> It originates from the superficial fascia of the upper chest, clavicle, and acromial regions and extends superolaterally to interlace with the superficial musculopaponeurotic system, many muscles of the lower face, and the periosteum of the body of the mandible.<sup>88</sup> Inferiorly, it inserts in a fan-like fashion on the second or third rib; however, variations have been reported, with insertion often extending lower than expected.<sup>87</sup> Hyperkinetic activity coupled with loss of tone of this muscle results in vertical banding and horizontal rhytides both in the neck and décolleté regions.<sup>87,88</sup> Injection of both the platysmal bands and the décolleté regions provide not only an improved cervicomental angle but also successful reduction in wrinkling.<sup>87,88</sup> However, injections should be directed superficially,

and at the smallest doses possible to avoid dysphagia,<sup>89</sup> dysphonia, or weakness in neck flexors.<sup>90</sup>

### Axillae/palms/soles

Hyperhidrosis is caused by autonomic neuronal dysfunction in areas with high concentrations of eccrine glands, such as the axillae, palms, and soles, and on occasion, the face and scalp.<sup>90</sup> Eccrine glands are innervated by sympathetic, postganglionic, unmyelinated C fibers, with acetylcholine serving as the primary neurotransmitter. Botulinum toxin blocks the release of acetylcholine. This mechanism of action is well suited for a variety of disorders of sweat production and in a multitude of areas, but is solely approved by the FDA for the treatment of localized, severe axillary hyperhidrosis that is unresponsive to topical therapies. Using a starch iodine test in the axillary vault will delineate the area of excess sweat production, and injections are intradermal and in a grid or targetoid-like pattern.

### SUMMARY

*C botulinum* is an anaerobic, spore-forming bacterium whose toxin has been purified and exploited for both therapeutic and cosmetic uses. Onabotulinum, abobotulinum, and incobotulinum represent the 3 most commonly used formulations within the United States, each exerting effects on the presynaptic terminal to cause neuromuscular blockade and clinically evident muscle relaxation. Physicians embarking on the use of neurotoxins for cosmetic purposes must have a complete understanding of the differences between toxin formulations, including diffusion characteristics, storage requirements, and dosing, because each product has unique chemical properties and is not interchangeable. While these products are overall very safe, a comprehensive knowledge of facial anatomy is crucial to minimize adverse events and maximize patient satisfaction. New and improved agents continue to emerge, boosting patient satisfaction and ultimately expanding the aesthetic armamentarium.

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# Injectable and topical neurotoxins in dermatology



## Indications, adverse events, and controversies

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### Learning objectives

After completing this learning activity participants should be able to compare and contrast botulinum toxin with emerging products not yet on the market; discuss appropriate off-label uses for neurotoxins; list noncosmetic usages of neurotoxins in other medical specialties; and describe how to combine neurotoxin treatment with toxins, lasers, and fillers safely and effectively, while minimizing complications.

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#### Editors

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The use of neuromodulators for therapeutic and cosmetic indications has proven to be remarkably safe. While aesthetic and functional adverse events are uncommon, each anatomic region has its own set of risks of which the physician and patient must be aware before treatment. The therapeutic usages of botulinum toxins now include multiple specialties and multiple indications. New aesthetic indications have also developed, and there has been an increased utilization of combination therapies to combat the effects of global aging. In the second article in this continuing medical education series, we review the prevention and treatment of adverse events, therapeutic and novel aesthetic indications, controversies, and a brief overview of combination therapies. (J Am Acad Dermatol 2017;76:1027-42.)

**Key words:** abobotulinum; adverse events; botulinum toxin; controversies; cosmetic uses; incobotulinum; neuromodulator; neurotoxin; onabotulinum; therapeutic uses.

## THERAPEUTIC INDICATIONS

### Key points

- The therapeutic use of botulinum toxin has spanned across multiple specialties
- Disorders of sweating, flushing, and scar prevention are some of the dermatologic therapeutic usages of neuromodulators
- Other specialties highlighting the use of neuromodulators for therapeutic purposes include psychiatry, neurology,

### ophthalmology, gastroenterology, and urology/gynecology

- Off-label usages are common, and new usages are continuously under investigation
- Hypersensitivity reactions to the product and infection at the site of injection are the only absolute contraindications
- There is a black box warning with the use of neuromodulators regarding the potential spread of toxin and associated adverse events

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Since the discovery of botulinum toxin, indications have rapidly expanded across multiple specialties, including neurology, ophthalmology, dermatology, gastroenterology, psychiatry, and urology.<sup>1</sup> Table 1 and Figs 1 and 2 show non-dermatologic indications for botulinum toxin and ongoing investigations. Many dermatologic indications are reviewed below for each of the botulinum toxin type A agents. Of note, there is a paucity of comparative trials for incobotulinum toxin; therefore, data for each indication are limited.

### Indications approved by the US Food and Drug Administration

Botulinum toxin is approved by the US Food and Drug Administration (FDA) for use in the treatment of axillary hyperhidrosis, glabellar lines, and lateral canthal lines.

**Hyperhidrosis.** Botulinum toxin is widely used for the treatment of localized hyperhidrosis and is approved by the FDA for the treatment of severe axillary hyperhidrosis that is unresponsive to topical therapies. The procedure has minimal patient discomfort and has proven to be of great clinical success, with improvement in patient quality of life.<sup>16-18</sup> The average dose is 50 units of onabotulinumtoxin per axillae.<sup>16,17,19</sup> The duration of effect is variable, reported from 2 to 24 months; however, recent data suggest an increase in the duration of efficacy with increasing repetition of botulinum toxin injections. The median duration of effect from the first injection was 5.5 months compared to the last injection, which was 8.5 months (mean, 4 injection series).<sup>20</sup> Axillary osmidrosis (foul odor) has also been successfully treated with injectable toxin, but the effect is also transient.<sup>21</sup>

Palmar hyperhidrosis is a common off-label site for treatment.<sup>22</sup> The therapeutic effect is less than that seen with axillary treatment.<sup>23-30</sup> In thick acral skin, pain upon botulinum toxin injection can be a significant limiting factor.<sup>22</sup> Pretreatment with ice/cold, vibration, topical anesthetics, nerve blocks (eg, Bier block), and frequent needle change can reduce patient discomfort.<sup>31</sup> On average, the duration of response is 6 months,<sup>32,33</sup> but there may be an increase in the duration of response with repeated treatments.<sup>34,35</sup> Dosages vary between studies, with many showing adequate results with onabotulinum and incobotulinum doses of 50 to 100 units per hand and 100 to 240 units of abobotulinum toxin per hand.<sup>24,36-38</sup> Mild reversible hand grip weakness has been reported; however, there was no alteration in sensation.<sup>39</sup>

Successful treatment with botulinum toxin has been reported in other disorders of sweating,

including Hailey–Hailey disease,<sup>40</sup> the face and back, where compensatory hyperhidrosis tends to occur after thoracic sympathectomy,<sup>41-44</sup> and there have been reports of successful treatment associated with Frey syndrome (sweating on the cheek during chewing as a result of parotid gland injury),<sup>45</sup> granulosis rubra nasi (nasal sweating),<sup>46</sup> and chromhidrosis (colored facial sweat).<sup>47</sup>

**Glabella/lateral canthal lines.** The first cosmetic use approved by the FDA for botulinum toxin in the United States was for the treatment of glabellar lines in 2002.<sup>48</sup> Since that time, the treatment of lateral canthal lines is the only other cosmetic indication to achieve approval despite the widespread clinical use for multiple other indications, which will be separately reviewed. Abobotulinumtoxin and incobotulinumtoxin have also achieved approval for the treatment of glabellar lines, and while lateral canthal lines are not yet approved for these products, treatment of this area has demonstrated similar efficacy to onabotulinumtoxin.<sup>49-52</sup> The average dose for glabellar lines is about 10 to 40 units total of onabotulinumtoxin/incobotulinumtoxin (50-80 units of abobotulinumtoxin), but treatment must be individualized to the anatomy, muscle mass, and sex of the patient.<sup>53,54</sup> Lateral canthal lines generally require 10 to 30 units total of onabotulinumtoxin/incobotulinumtoxin (20-60 units of abobotulinumtoxin), with individual variation in number and location of injection points based on the degree of the wrinkle fanning.<sup>54,55</sup> As with many other facial cosmetic regions, treatment lasts approximately 4 months; however, there are data to suggest that an increased number of treatments over time leads to a greater interval of time between repeat treatments.<sup>49,56</sup> Patient satisfaction with treatment of these areas remains exceptionally high.<sup>54</sup>

### Indications not approved by the US Food and Drug Administration

Nondermatologic approved uses include strabismus, blepharospasm, cervical dystonia, upper limb spasticity, chronic migraine, overactive bladder, and urinary incontinence. Off-label uses in aesthetic medicine include brow lift,<sup>57,58</sup> eye widening,<sup>59</sup> jaw sculpting,<sup>60</sup> minimization of surgical scars,<sup>61</sup> platysmal band reduction,<sup>62</sup> perioral lines, masseter reduction, and palmar hyperhidrosis.<sup>22</sup> A few of the more pertinent dermatologic usages are discussed below.

**Chemical brow lift.** Glabellar injections alone lead to an immediate lateral eyebrow elevation followed by a central and medial brow elevation 12 weeks posttreatment.<sup>58</sup> The mechanism of action

**Table I.** Nondermatologic uses and investigations of botulinum toxin

Specialty	Therapeutic uses
Psychiatry <sup>189-194</sup>	Major depressive disorder and tics/Tourette syndrome
Neurology/musculoskeletal <sup>195-210</sup>	Torticollis, dystonic tics, spastic dysphonia, spasticity related to stroke, essential tremor, Bell's palsy, deformities related to cerebral palsy, cervical dystonia,* upper and lower limb spasticity,* chronic migraine,* neuropathic pain (trigeminal and diabetic neuralgia), postherpetic neuralgia, head and neck cancer survivors with neck contractures postradiosurgical therapy, occupational cramping (ie, writer's cramp), Parkinson disease, myofascial pain syndrome, and ischemic digits
Ophthalmology <sup>48,211-214</sup>	Strabismus,* hemifacial spasm, blepharospasm,* corneal astigmatism, tear film conditions, nystagmus, oscillopsia, and benign eyelid fasciculation
Gastroenterology/upper aerodigestive <sup>215-221</sup>	Chronic anal fissures, diffuse esophageal spasm, anorectal outlet obstruction, rectal spasms, refractory gastroparesis, achalasia not amenable to surgery, laryngeal dystonia, oromandibular dystonia, bruxism, cricopharyngeal spasm, and stuttering
Urology/gynecology <sup>222-227</sup>	Overactive bladder,* neurogenic detrusor overactivity with spinal cord injury and multiple sclerosis, benign prostatic hyperplasia, bladder pain syndrome, detrusor sphincter dyssynergia, provoked vestibulodynia, pelvic floor spasm, and hot flashes

\*Condition for treatment with botulinum toxin approved by the US Food and Drug Administration.



**Fig 1.** Patient with Bell's palsy before (A) and after (B) treatment with botulinum toxin noting improvement in asymmetry. One to 2 units of onabotulinumtoxinA were injected into the zygomaticus, risorius, and orbicularis oris muscles, and 5 to 10 units were injected into the masseter muscle. (Reprinted with permission from Carruthers and Carruthers.<sup>15</sup>)

involves toxin diffusion and partial inactivation of the medial inferior fibers of the frontalis muscle with a consequent increase in muscle tone to the superior and lateral fibers, resulting in unopposed brow elevation. For further temporal brow elevation, targeting the lateral superior fibers of the orbicularis oculi muscle<sup>63,64</sup> results in an average gain of 1.02 mm in the midpupillary line and 4.83 mm from the lateral canthus respectively.<sup>63</sup> Targeting the glabellar complex and the lateral tail of the brow achieves a uniform brow elevation.<sup>53</sup>

**Gummy smile.** Excessive gingival display, "gummy smile," is defined as  $\geq 2$  mm of gingival exposure upon smiling<sup>65</sup> and can be cosmetically displeasing for patients (Fig 3). Hyperactivity of the lip elevator muscles (levator labii superioris alaeque

nasi, levator labii superioris, and zygomaticus minor) is the main contributing factor. Botulinum toxin injections<sup>66</sup> about 3 to 5 mm lateral to each nostril can reduce dental gum show.<sup>67</sup> The injection technique should be tailored to the type of gummy smile. Mazzucco et al<sup>68</sup> identified 4 different types of gummy smile, including anterior, posterior, mixed, and asymmetric. Doses range from a total of 4 to 6 units of onabotulinumtoxin<sup>65-67</sup> to 2.5 to 5 units of abobotulinumtoxin<sup>68</sup> per side. On average, patients achieve a 75% to 85% improvement, with a duration of effect averaging 3 to 6 months.<sup>65,66,68</sup> Asymmetric smile, difficulty in smiling, or overactivation of the depressor anguli oris with depressed oral commissures are reported adverse events, most of which are correctable by further neuromodulator injection.<sup>68</sup>



**Fig 2.** Patient with hemifacial spasm before (**A**) and 2 weeks after (**B**) treatment with botulinum toxin. (Reprinted with permission from Dutton and Fowler.<sup>11</sup>)



**Fig 3.** Patient with excessive gingival exposure (ie, a gummy smile) before (**A**) and after (**B**) treatment with 7.5 units of abobotulinumtoxin to each side. (Photograph courtesy of Doris Hexsel, MD.)

**Masseter muscle.** A youthful face is generally associated with fullness in the upper face with tapering down to the mandible (a heart shape), and masseter muscle hypertrophy can contribute to a heavy appearance in the lower face. Facial shaping with toxin injections was first reported in the Korean literature<sup>62,69-74</sup> (Fig 4). The ultimate cosmetic result may take a few treatments spaced a few months apart to fully realize the change in facial contour because the alteration is largely caused by muscle atrophy.

To define the safety zone for injection and avoid the risorius muscle,<sup>72,75</sup> the location of this large muscle should be appreciated. The anterior and posterior borders of the muscle are identified by palpation with the patient actively clenching their

teeth. To delineate the superior border, an imaginary line can be drawn from the earlobe to the ipsilateral oral commissure, and the lower border of the mandible serves as the inferior border. Depending on the mass of the muscle, 3 to 6 injections are placed directly into the belly of the muscle over the buckled area, directed at the posterolateral corner<sup>69,72,73</sup> or above the border of the mandibular angle.<sup>71,76</sup> Patient satisfaction scores have been exceptionally high, ranging from 80% to 97% at 6 to 10 months postinjection.<sup>69,76</sup> Although an unusual complication of masseter reduction is salivary gland enlargement,<sup>77</sup> hypertrophy of both the parotid and submandibular glands has also been successfully treated with the use of botulinum toxin. Patients



**Fig 4.** A 36-year-old woman before (**A**) and after (**B**) treatment for masseter hypertrophy with 25 units of incobotulinumtoxin per side for over 4 years (7 sessions). (Photograph courtesy of Ki Young Ahn, MD.)

should be advised that there can be a concomitant reduction in oral secretions, resulting in dry mouth.

**Nefertiti lift.** The Nefertiti lift is a variation of administering toxin into the platysma muscle that is also intended to sharpen the jawline. It evolved from platysmal band treatment, but the initial results were inconsistent.<sup>78</sup> Injections are aimed solely at the upper half of the posterior platysma band. Four injections are administered about 1 to 2 cm apart extending down the length of the band<sup>79</sup> with a second series of 4 injections extending from the mandibular angle to the start of the posterior platysmal band.<sup>53,78,79</sup>

**Body contouring (gastrocnemius injections).** Excessive muscular calves can be masculinizing and unwanted in the female patient population.<sup>80</sup> Neurotoxin injections have been successfully used to contour the medial aspect of the calf<sup>80,81</sup> (Fig 5). Injections are placed at the medial head of the gastrocnemius muscle in doses ranging from 32 units of onabotulinumtoxin<sup>81</sup> to 360 units of abobotulinumtoxin<sup>80</sup> per side. The dosing is largely based on the gross size of the contracted gastrocnemius muscle with patients evaluated in the tiptoe position.<sup>81</sup> Reduction in the medial calf is generally noticeable beginning around weeks 1 to 3, with maintenance of response at 6 to 8 months.<sup>80,81</sup> No functional impairment or systemic side effects have been observed.

**Treatment of rosacea/flushing.** Treatment for facial erythema and flushing associated with rosacea includes vascular lasers and topical  $\alpha$ -adrenoreceptor agonists.<sup>82</sup> Topical agents target the  $\alpha$ -adrenoreceptors in the smooth muscle sheath that encases vessel walls. Results are transient, lasting only about 12 hours.<sup>83,84</sup> Botulinum toxin has a similar mechanism of action and successful treatment of facial, neck, and chest flushing have been demonstrated with effects lasting up to 3 months.<sup>85-89</sup>

**Surgical and scar prevention.** Abnormal wound healing and hypertrophic scar formation is commonly seen in areas of high static and dynamic tension. If tension and movement can be minimized, there may be improved cosmesis. When compared to placebo, botulinum toxin injected perioperatively into facial muscles involved in scar widening showed significantly superior scar outcomes.<sup>90-94</sup> A significant reduction in the final appearance of thyroidectomy scars was shown using a placebo controlled split-scar approach, injected early after surgery.<sup>95</sup> In addition, certain types of scarring (rolling acne scars, mildly hypertrophic scars, or atrophic scarring) are amplified with facial movement and may become less noticeable with neurotoxin therapy.<sup>96</sup> A single study treating keloid scars demonstrated equal efficacy compared to intralesional kenalog therapy.<sup>97</sup> The mechanisms behind botulinum toxin's effects on scars are gradually being elucidated, with current in vitro data suggesting direct inhibition by the toxin of fibroblast to myofibroblast differentiation.<sup>98</sup>

### Contraindications

The only absolute contraindications according to the FDA-approved package insert include known hypersensitivity reactions to botulinum toxin or any of the components in the formulation and infection at the proposed injection site, including urinary tract infection or urinary retention for intradetrusor injections.

Treating patients with neuromuscular conditions or patients with preexisting breathing and swallowing difficulties should be avoided given their predisposition for severe muscle weakness, dysphagia, or respiratory compromise. Classified as a category C drug, women who are pregnant, planning pregnancy, or lactating and children under 12 years of age are relative contraindications. While there are documented cases of botulinum toxin injection in pregnant



**Fig 5.** A 53-year-old woman with calf hypertrophy in plantar-flexion both before (**A**) and 6 months after (**B**) treatment with 100 units of incobotulinumtoxin per side. (Photograph courtesy of Ki Young Ahn, MD.)

patients without demonstrated fetal harm, this is not recommended without further confirmatory studies.<sup>99-101</sup> Caution is advised in patients taking medications that interfere with the neuromuscular junction because the effects of the botulinum toxin may be potentiated. These include aminoglycoside antibiotics, cholinesterase inhibitors, succinylcholine, curare-like depolarizing blockers, magnesium sulfate, quinidine, calcium channel blockers, lincosamides, and polymyxins.<sup>102</sup> Avoid injecting into existing inflammatory lesions, such as acne, psoriasis, contact dermatitis, and atopic dermatitis. While not an absolute “contraindication,” it is advisable to reconsider treating patients with unrealistic expectations.

Postmarketing safety data prompted the FDA to issue a black box warning regarding the potential spread of the toxin resulting in “swallowing and breathing difficulties that can be life threatening,” occurring hours to weeks after the initial therapy. Most of these events were from botulinum toxin for cervical dystonia and limb spasticity, and the rare systemic events for cosmetic usages were with excessively high dosages<sup>103</sup> or in patients with

underlying medical conditions that predisposed to the complication.<sup>104,105</sup> However unlikely, it is advisable to discuss and document the black box warning before treatment.

#### **COMBINATION COSMETIC THERAPY: DERMAL FILLERS, LASERS, AND LIGHT SOURCES**

##### **Key points**

- **Combination treatment of neurotoxins and soft tissue augmentation provides greater improvement and longer-lasting results with static facial rhytids**
- **Ideally, injecting toxin and waiting a short period of time before performing filler can reduce the total amount of filler required; however, many patients prefer treatment in the same session for convenience**
- **Neurotoxin combined with energy based devices is superior to either modality alone**
- **Caution is advised injecting toxins concurrently with ablative laser resurfacing as**

## **laser manipulation and postprocedural edema may cause unwanted diffusion**

### **Synergy with fillers**

Neurotoxins do not ameliorate all aspects of facial aging, particularly volume loss. Soft tissue deficiencies are often corrected with the use of dermal fillers, and combination of fillers with neurotoxins can more efficiently and effectively treat the effects of global aging.<sup>106-110</sup>

Treatment of the upper face (forehead and glabella) was initially the purview of injectable neurotoxins, but combination therapy is increasingly used.<sup>110</sup> The effect is muscle and tissue immobilization from the neurotoxin, which allows for a slower degradation of the dermal filler. This allows for less frequent toxin treatments as well as allowing patients a more gradual and natural return to baseline as the products dissipate.<sup>108,111</sup>

Combining toxins and fillers has also been explored for lower facial rejuvenation with similar long-lasting results.<sup>112,113</sup> Patients report more satisfaction with combination treatment, and the side effect profile is comparable with either modality alone.<sup>106,112,114</sup>

Toxin and fillers can be administered in the same treatment session. Ideally, it is advantageous to inject the toxin initially, and then have the patient return when muscle paralysis is complete for soft tissue augmentation. Staging the injection series can often reduce the total amount of filler required.

### **Administration with lasers and lights**

Neurotoxins are also used in conjunction with laser- or light-based therapies. Botulinum toxin is inactivated in vitro at 85°C.<sup>115</sup> Hypothetically, this reduces efficacy with laser treatment, but the opposite is true. When neurotoxins are injected 1 to 7 days before ablative laser resurfacing or intense pulsed light therapy, the combination therapy has proven superior to treatment with energy-based devices alone for the reduction of rhytides.<sup>116-118</sup> In addition, there may be faster reepithelialization with muscle inactivation. In general, toxins should not be injected concurrently with ablative resurfacing because the laser manipulation and postprocedural edema may cause unwanted diffusion. However, if same-day combination therapy is used, it is suggested to perform the laser resurfacing first and the injections afterward.<sup>119</sup>

The diode (800-nm) hair removal laser coupled with neurotoxins has been investigated in axillary hyperhidrosis. No significant differences were observed between treatment groups that had laser

1 week before neurotoxin injections or laser immediately after neurotoxin.<sup>120</sup>

Fractional ablative lasers are being investigated as potential percutaneous drug delivery devices.<sup>121,122</sup> Crow's feet lines treated with a fractional ablative carbon dioxide laser bilaterally with immediate application of concentrated topical botulinum toxin demonstrated statistically significant reduction in periocular rhytides at 1 and 4 weeks compared to laser and placebo.<sup>123</sup>

## **ADVERSE EVENTS AND COMPLICATIONS: PREVENTION, RECOGNITION, AND TREATMENT**

### **Key points**

- **Injection site discomfort, erythema, bruising, and temporary headaches are the most common side effects**
- **Injection into a pilosebaceous unit can reduce pain**
- **Many of the functional/cosmetically displeasing adverse events may be prevented with very superficial, low volume injections**
- **Dysphagia, hoarseness, and neck flexor weakness are rare risks when injecting the platysma**

Neurotoxins have consistently proven to be remarkably safe. Most reactions are a result of injection technique, dosage, or volume, and true allergic reactions are exceedingly rare.<sup>105,124-129</sup> The most common reported side effects are mild and transient, and include injection site discomfort, erythema, bruising, temporary headaches, and, rarely, prolonged migraine headaches.<sup>102,130</sup> Ptosis, ectropion, and diplopia are some of the functional yet uncommon adverse events.<sup>131,132</sup> When compared to placebo, only eyelid sensory disorder (heaviness or tightness), eyelid edema, and ptosis were noted to be significantly more common in the treatment arm.<sup>133</sup> In a recent multicenter study, only 2 of 6200 (0.03%) neurotoxin procedures resulted in complications (hematoma and ptosis), further supporting their remarkable safety profile.<sup>134</sup> The incidence in adverse events has likely declined as experienced injectors have an increased appreciation of facial muscular anatomy and function and awareness of neuromodulator diffusion and activity, leading to improvement in technique.<sup>135</sup>

### **Common local reactions**

There is potential for bruising with any percutaneous injection. Ideally, patients should avoid aspirin, aspirin-containing medications, or nonsteroidal antiinflammatory drugs for ≤1 week before



**Fig 6.** Right-sided blepharoptosis 3 weeks after botulinum toxin injection for frown lines. (Reprinted with permission from Small.<sup>14</sup>)

injection to reduce the incidence of bruising. Adequate lighting to improve visibility and stretching the skin, especially in highly vascular areas, can further minimize bruising.<sup>102</sup> Direct, firm manual pressure on the injection site and the application of ice can also minimize impending bruising. When bruising does occur, a pulse dye laser can hasten recovery.<sup>136</sup>

Discomfort can be minimized with the use of topical anesthetics, the use of small gauge (30-32) needles, reconstitution with bacteriostatic saline, pinching the underlying skin during needle insertion, slowly injecting the solution, and inserting the needle into a pilosebaceous unit.<sup>137,138</sup>

### Eyelid and eyebrow ptosis

Eyelid ptosis is most frequently a result of toxin diffusion through the orbital septum, paralyzing the levator palpebrae superioris muscle<sup>138-140</sup> (Fig 6). This risk can be minimized by injecting the lateral corrugator muscle subdermally, refraining from injecting within a 1-cm region above the superior orbital rim, keeping volumes low, and encouraging voluntary muscular contraction for a few hours after injection to increase muscular uptake and minimize diffusion.<sup>131,138</sup> If ptosis occurs, it is 1 to 2 mm and short-lived, lasting approximately 2 to 4 weeks.<sup>138,139</sup> It can be treated with  $\alpha$ -adrenergic eye drops, such as apraclonidine or phenylephrine, to stimulate contraction of the Müller muscle of the upper eyelid, resulting in elevation of the lash margin.<sup>141</sup> The drops are applied 3 times daily until the effects of the toxin have dissipated.<sup>138,139,142</sup>

Brow ptosis results from either overtreatment of the frontalis muscle or diffusion when treating the glabellar complex. This can result in a "mask-like" face, and the brow may fall over the eye, giving a "hooded" appearance.<sup>138</sup> Injections should remain above the lowest forehead fold upon active contraction of the frontalis muscle. Depth of

injection may influence toxin diffusion,<sup>143,144</sup> but the results are inconsistent.<sup>144,145</sup> When addressing the frontalis muscle, it is important to maintain the brow in a neutral position with a naturally arched shape. This is accomplished by simultaneously treating the brow depressor muscles in the glabellar complex (corrugator supercilii and procerus) and the lateral fibers of the orbicularis oculi and should be considered.<sup>15,102</sup>

When treating the sole brow elevator, the frontalis muscle, another untoward result is the "quizzical" or laterally elevated brow (Mr. Spock brow). This occurs if the lateral fibers of the frontalis are not injected appropriately. The central frontalis activity is reduced, the medial eyebrow is pulled downward, while the lateral brow is still able to contract and pull upwards. To correct this, small aliquots of toxin can be injected into the intact lateral fibers.<sup>138</sup>

### Lateral canthal lines

Ectropion, diplopia, and drooping of the lateral lower eyelid are rare complications thought to be a result of injecting deeply within 1 cm of the lateral bony orbit, causing paralysis of the lateral rectus muscle.<sup>141,146</sup> Upper lip ptosis can occur from injecting too deep or too close to the inferior border of the zygomatic arch, inadvertently affecting the zygomaticus muscle.<sup>102</sup> Actively smiling before injection can demonstrate the contribution of the zygomaticus major to the canthal rhytides; however, patients should not be actively smiling during injection to avoid placement near the zygomaticus major muscle and further reduce risk of inadvertent injection. Each of these complications can be largely prevented with low-volume, very superficially placed injections.

### Lower/midface injections

Injections below the zygomatic arch often result in less profound aesthetic effects than in the upper third of the face. In addition, adverse events can be both cosmetic as well as functional. Therefore, these areas should only be addressed by the physician with comprehensive knowledge in facial anatomy, and it would be prudent to be cautious in patients who are toxin naïve.

Injection of "bunny lines" must remain high on the lateral nasal sidewall above the nasofacial groove in order to avoid inadvertent injection of the levator labii superioris, resulting in upper lip ptosis.<sup>102</sup>

An asymmetric smile may occur if injections into the mentalis muscle are performed too laterally, or if depressor anguli oris injections are too medial, each thereby affecting the depressor labii inferioris muscle<sup>147</sup> (Fig 7). Although patients can be hesitant



**Fig 7.** Complication of lower facial injection. Patient with paralysis of the left-sided lip depressors (likely the depressor labii inferioris) after botulinum toxin injection of the left depressor anguli oris. (Reprinted with permission from Niamtu.<sup>12</sup>)

to receive additional toxin, correction can be accomplished by injecting the contralateral depressor labii inferioris. Injections into the orbicularis oris should remain superficial and in small dosages to prevent lip sphincter weakness and incompetence in the ability to adequately purse the lips.<sup>102</sup> The primary concern when injecting the masseter for muscle hypertrophy is weakening the overlying risorius muscle creating a constrained smile.<sup>75</sup>

### Platysma effects

Diffusion of the toxin into the laryngeal muscles or direct injection into the sternocleidomastoid muscle can result in dysphagia, hoarseness, and weakness in neck flexor muscles.<sup>148,149</sup> Mild weakness has been reported for 1 to 2 weeks after injection of 50 to 200 units of botulinumtoxin A.<sup>150</sup> Severe weakness and dysphagia generally results from larger dosages (mean, 184 units) used in cervical dystonia treatments.<sup>151</sup> These can be largely avoided in cosmetic use with smaller dosages (30-60 total units)<sup>152,153</sup> and precise intrplatysmal toxin placement. If weakness occurs, patients may require psychological support, reassurance, and they may need dietary counseling to aid in swallowing. The effect is temporary and does not signify systemic toxicity, as the estimated lethal dose is upward of 3000 units.<sup>154</sup>

## CONTROVERSIES

### Key points

- The development of neutralizing antibodies is more complex than previously speculated
- Antibodies to toxin type A may not always confer resistance to the other serotypes (ie, type B)

- Proper training requirements should be established and enforced for all physician and nonphysician injectors
- Muscle atrophy remains a topic of debate with regard to the cosmetic use of botulinum toxin

### Neutralizing antibodies

The original theory was that circulating neutralizing antibodies were targeting the foreign complexing proteins, and in 1997, Allergan (manufacturer of Botox) reduced the protein load, resulting in lower rates of immunogenicity.<sup>48,102,155</sup> Recent evidence suggests that antibodies also bind to various epitopes on the toxins themselves, with many antigenic regions coinciding with synaptosome-binding regions, thereby blocking the toxin's ability to bind to neuronal cells.<sup>156</sup>

Immunogenicity is speculated to be dose- and duration of treatment-dependent because many cases were for medical treatments requiring high doses.<sup>157-160</sup> A metaanalysis reported neutralizing antibody formation in dystonia (20%), spasticity (5.9%), urologic patients (2.7%), and other indications (including cosmetics) in 1.1% of a total of 8525 patients.<sup>161</sup> Interestingly, 3.5% of clinically responding patients had neutralizing antibodies, and 53.5% of nonresponding patients in this analysis had detectable antibodies. This highlights the difficulty in correlating antibodies with clinical response and implies an alternative mechanism for resistance.

There are a few sporadic case reports describing secondary immunogenicity in the cosmetic literature.<sup>162-167</sup> Neutralizing antibodies to toxin A may not always confer resistance to the other serotypes of toxin, but a partial resistance may exist with diminished clinical duration.<sup>168,169</sup>

In a rabbit model, repeat injections of incobotulinum toxin (free of complexing proteins), did not show the development of neutralizing antibodies,<sup>135</sup> which confirms a reduced incidence of antibody-related secondary treatment failure.<sup>170-175</sup> There are, however, clinical reports of resistance to incobotulinum toxin after pretreatment with abobotulinum toxin for many years.<sup>176,177</sup>

### Nonphysician injectors

There has been a rapid increase in the number of nonmedical personnel performing botulinum toxin injections.<sup>178-180</sup> In many states, there is often minimal or no regulation regarding who is trained or qualified to perform these procedures.<sup>181,182</sup> Training of nonphysician injectors may vary from direct hands-on physician training to workshops to online courses, or even self-training.<sup>183</sup> In 1 survey

assessing the public perception of competency of procedures, including botulinum toxin injections, dermatologists and plastic surgeons were preferred (combined 89%)<sup>184</sup> and physician assistants and nurse practitioners were chosen only 1.8% of the time. In an email survey to plastic surgeons, 77% believed that nurses were not as capable as plastic surgeons and dermatologists in administering botulinum toxin.<sup>182</sup> This perceived lack of public confidence in nonphysician injectors may be explained by a desire to have a physician perform a procedure, lack of confidence in nonphysician providers for cosmetic concerns, or negative past experiences with nonphysicians.<sup>184</sup> Patients have reported 3 important factors: experience, training, and the medical specialty of the injector.<sup>185</sup> Exposure to cutaneous surgery and cosmetic procedures is a part of the core curriculum of all dermatology residencies,<sup>186</sup> and there are many postresidency procedural fellowship training opportunities.<sup>187,188</sup> Finally, there has been an increase in the number of lawsuits against nonphysician providers, particularly in laser surgery.<sup>2</sup> To ensure continued patient safety and satisfaction, proper training requirements should be enforced, practice guidelines should be established, and patient education should remain a high priority.<sup>182,183</sup>

### Long term implications

Another controversy is the potential for muscle atrophy with repeated injections. While atrophy is the desired endpoint when treating large muscles like the masseter and gastrocnemius, this may not be the goal when addressing smaller facial muscles.<sup>3</sup> In 1 small study assessing muscular response to 20 units of onabotulinum toxin using magnetic resonance imaging, treated patients showed a 46% to 48% volume loss in the procerus muscle at 4 weeks postinjection.<sup>4</sup> This volume reduction remained stable for 1 year, despite clinical effects reversing at 6 to 10 months. No volume reduction was noted in controls.

Additional anecdotal reports have been cited in the medical literature. In patients with migraine headaches, botulinum-induced muscle atrophy and has been noted in the corrugators and in the temporalis muscles.<sup>5,6</sup> In addition, intrinsic hand muscle atrophy occurred after treatment for palmar hyperhidrosis.<sup>7</sup> There was complete resolution of the atrophy, suggesting a temporary effect.

Two-dimensional ultrasound, magnetic resonance imaging volumetric analysis, and histologic assessment revealed muscle atrophy and recovery 6 months to 1 year after 1 single injection for noncosmetic use.<sup>8</sup> It has been postulated that at higher dosages, the atrophy

and remodeling of the contractile proteins may not be completely reversible. In another animal model, recovery of the blocked neuromuscular junction reached 75% within 90 days.<sup>9</sup> In a rabbit study receiving unilateral masseter injections, the paralysis resulted in underloading of the bony structures in mastication with notable, persistent bone loss at the temporomandibular joint.<sup>10</sup>

### SUMMARY

The use of neuromodulators continues to revolutionize medicine. The attractive quality of these agents is partly derived from their remarkable safety profile, minimally invasive approach, and overall ease of use for the physician. New indications are continuously emerging in the dermatologic and nondermatologic literature, expanding the utility and popularity of these products across multiple specialties. As the demand for a more youthful appearance continues to rise, neuromodulators will play a significant role in conjunction with other therapies.

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## New discoveries in the pathogenesis and classification of vitiligo

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*Victoria, Australia; Creteil, France; Detroit, Michigan; Dallas, Texas; and Worcester, Massachusetts*

### Learning objectives

After completing this learning activity, participants should be able to categorize the different forms and presentations of vitiligo; recognize the key features that distinguish active vitiligo; and discuss the mechanisms that influence the initiation and progression of vitiligo.

### Disclosures

#### Editors

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Vitiligo is a common autoimmune disease that progressively destroys melanocytes in the skin, resulting in the appearance of patchy depigmentation. This disfiguring condition frequently affects the face and other visible areas of the body, which can be psychologically devastating. The onset of vitiligo often occurs in younger individuals and progresses for life, resulting in a heavy burden of disease and decreased quality of life. Presentation patterns of vitiligo vary, and recognition of these patterns provides both diagnostic and prognostic clues. Recent insights into disease pathogenesis offer a better understanding of the natural history of the disease, its associations, and potential for future treatments. The first article in this continuing medical education series outlines typical and atypical presentations of vitiligo, how they reflect disease activity, prognosis, and response to treatment. Finally, we discuss disease associations, risk factors, and our current understanding of disease pathogenesis. (J Am Acad Dermatol 2017;77:1-13.)

**Key words:** chemical leukoderma; confetti depigmentation; halo nevi; leukoderma; segmental vitiligo; vitiligo; vitiligo pathogenesis.

**V**itiligo patients are often told that their vitiligo “isn’t a big deal,” that there is “nothing that can be done for it,” and that they “should just

learn to live with it” by their physicians. This is a disservice, because patients often arrive in a dermatologist’s clinic discouraged after years of disease

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progression. Those with long-standing disease (>1–2 years) treated with narrowband ultraviolet B light therapy (NB-UVB) demonstrate lower efficacy compared to patients with recent onset vitiligo.<sup>1–3</sup> Therefore, recognizing vitiligo as a treatable disease and initiating appropriate treatment early is a critical step in helping these patients both physically and psychologically. Despite this, many patients with even long-standing disease can respond to treatment, and so while patients should be encouraged to initiate treatment early in their disease, no one should be discouraged from attempting treatment. New discoveries in the past 5 years have improved our understanding of the disease. The purpose of this review is to empower dermatologists to approach the diagnosis, classification, and management of vitiligo patients in a way that will lead to improved outcomes.

## EPIDEMIOLOGY AND QUALITY OF LIFE

### Key points

- **Vitiligo is common, affecting 0.5% to 2% of the world's population without preference for race or sex**
- **The psychological impact on quality of life is similar to those with psoriasis and atopic dermatitis**

Unlike diseases that require medical treatment for survival, such as juvenile diabetes or thyroiditis, determining the true incidence of vitiligo is challenging, because patients with vitiligo may not seek medical care. A few prospective survey studies, retrospective observational studies, and prospective studies in selected populations, such as those attending dermatology clinics, are available, but these may underestimate or overestimate the incidence, depending on the approach. Based on these studies, vitiligo reportedly affects 0.5% to 2% of the world's population, without clear preference for race or sex, although women may be more likely to present for treatment and respond to surveys.<sup>4–7</sup> Almost 50% of patients present before 20 years of age,<sup>8</sup> and many of these present before 10 years of age.<sup>9</sup>

Vitiligo is not “just a cosmetic condition”—it is a psychologically devastating autoimmune disease.<sup>10–13</sup> Studies have shown that the effect vitiligo has on quality of life, particularly psychological impairment, is similar to other skin diseases, such as psoriasis and atopic dermatitis.<sup>14</sup> The Dermatology Life Quality Index (DLQI) is a simple 10-item questionnaire that aims to measure how much skin diseases impact a patients' life, and scores vary from 0 (no impact) to 30 (highest impact). Differences in DLQI scores are noted in different cultural groups, reflecting the increased



**Fig 1.** Vitiligo koebnerizing within thyroidectomy scar.

stigma and social ramifications of having vitiligo in some communities. For example, DLQI scores were 4.95 in a Belgian study, but 7.06 in Indian patients with a successful treatment outcome and 13.12 in those who failed treatment.<sup>15</sup> Clinicians should take their patients' concerns about vitiligo seriously, having a low threshold for referring patients to counseling services if mood disturbance or significant stress is detected.

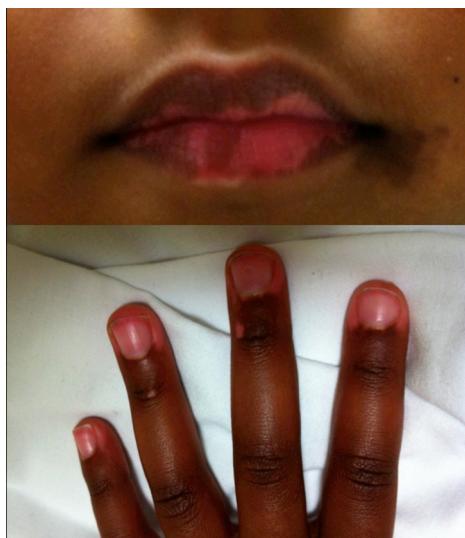
## PRESENTATIONS AND CLINICAL CLASSIFICATION

### Key points

- **Patterns of vitiligo lesions predict progression and treatment responses**
- **The segmental variant of vitiligo is rapidly progressive but stabilizes quickly, and is less responsive to treatment**
- **Progressive disease is marked by inflammatory, trichrome, and confetti-like lesions, as well as the Koebner phenomenon**

Depigmentation of the skin and hair follicles is the clinical hallmark of vitiligo. This results in white, often symmetrical macules and patches, usually increasing in number and size over time, and frequently appearing in visible areas like the face and extremities. In fair-skinned patients, vitiligo is usually first noted in sun-exposed sites because of tanning of unaffected skin. Several factors have been associated with the onset of disease, including severe sunburn, pregnancy, cutaneous trauma,<sup>16</sup> and significant psychological stress.<sup>17</sup> Patients may exhibit the Koebner phenomenon, in which new lesions of vitiligo appear in areas of trauma (Fig 1).

Localized types of vitiligo include focal and mucosal vitiligo. Focal vitiligo refers to an isolated, small, depigmented patch ( $10\text{--}15 \text{ cm}^2$ ) that lacks an obvious, unilateral segmental distribution and does not progress for at least 2 years.<sup>18</sup> The term mucosal vitiligo is typically used when only 1 site in isolation is



**Fig 2.** Lip-tip variant of vitiligo in a young African girl.



**Fig 3.** Universal vitiligo in an Asian man.

noted in the oral or genital region. Acrofacial vitiligo is usually limited to the head, hands, and feet. Distal finger, toe, and facial orifice involvement is often named “lip-tip” vitiligo, commonly seen in South Asia, and is resistant to treatment<sup>19,20</sup> (Fig 2). Universal vitiligo refers to complete or near-complete depigmentation of the skin, which may or may not include body hair ( $\geq 80\%$  of BSA<sup>18</sup>; Fig 3).

Occupational, contact, or chemical leukoderma describes depigmentation that is induced by exposure to phenols or similar chemicals. While



**Fig 4.** Segmental variant of vitiligo on the abdomen of an adolescent boy.

depigmentation initially starts at sites of exposure, the development of remote lesions with progression to a more widespread, typical pattern is common.<sup>21</sup> This disease is indistinguishable from classical vitiligo by clinical examination or histology,<sup>22</sup> and therefore chemical leukoderma does not appear to be distinct from vitiligo, but may be better classified as chemically induced vitiligo.<sup>23</sup>

In segmental vitiligo, the progressive loss of melanocytes results in a unilateral patch of depigmentation that may be arranged in a linear or block-like pattern (Figs 4 and 5).<sup>24</sup> It has been frequently mischaracterized as “dermatomal vitiligo” despite the fact that patterns of depigmentation rarely follow a dermatome. Segmental patterns of vitiligo correlate best with mosaic skin disorders, suggesting that it may be influenced by somatic mutations in developing melanocytes (see section on pathophysiology).<sup>25</sup> The term “dermatomal vitiligo” should therefore no longer be used.

Segmental vitiligo frequently affects the face and progresses quickly over 6 months to 2 years with rapid onset of leukotrichia, but typically stabilizes without treatment. It is 10 times less common than other variants of vitiligo, and early leukotrichia is a hallmark.<sup>24</sup> The majority (87%) of cases occur before 30 years of age, with some reports describing development as early as 6 weeks after birth.<sup>26</sup> This variant is less responsive to treatment than other variants, possibly because of its more frequent association with leukotrichia and the resulting lack of melanocyte reservoirs available for repigmentation.

In rare cases, patients may have a typical segmental pattern of vitiligo and then develop additional lesions outside of this region, a presentation labeled mixed vitiligo.<sup>27</sup> Patients with mixed vitiligo exhibit a poor response to ultraviolet light exposure in segmental lesions but a good response elsewhere. Those with halo nevi, leukotrichia, and an initial truncal lesion of segmental vitiligo are more likely to progress to mixed vitiligo



**Fig 5.** Segmental variant of vitiligo on the face and neck of young boy.

**Table I.** Classification of vitiligo

Type	Subtype
Vitiligo	Acrofacial, focal, mucosal (>1 mucosal site), generalized, universal, mixed (associated with segmental vitiligo), and rare variants
Segmental vitiligo/ undetermined/ unclassified	Unisegmental and multisegmental

over time.<sup>28</sup> A 2012 international consensus report<sup>18</sup> recommended that the umbrella term “vitiligo” be used for all forms of vitiligo (Table I) except the segmental variant, which should have a special classification because of its distinct prognosis and response to treatment.<sup>29</sup>

### Halo nevi

Halo nevi (also called Sutton nevi) are characterized by depigmentation surrounding a nevus, forming a halo. While they are common in healthy individuals, they are 8 to 10 times more common in patients with vitiligo.<sup>30</sup> The presence of multiple halo nevi is a marker of cellular autoimmunity against nested melanocytes and may indicate an increased risk of vitiligo in affected individuals, particularly those with a family history of the disease. Individuals with vitiligo who also have congenital or halo nevi reportedly have fewer acral lesions of vitiligo and more central involvement.<sup>25,31</sup>

### Vitiligo in patients with melanoma

Epidermal depigmentation may also be seen in patients with malignant melanoma. It is a good prognostic sign when occurring either spontaneously or when induced by newer melanoma treatments.<sup>32-34</sup> While this phenomenon has been



**Fig 6.** Trichrome pattern on the neck and shoulders.

given descriptive names in the past to differentiate it from vitiligo, the clinical appearance of depigmentation and its histopathology are indistinguishable from vitiligo.<sup>35,36</sup> In addition, similar to vitiligo, the depigmentation in melanoma patients is mediated by autoreactive CD8<sup>+</sup> T cells that attack and kill melanocytes by recognizing melanocyte-specific antigens that directly overlap with vitiligo<sup>37</sup> (see section on vitiligo pathogenesis). Therefore, this process should be characterized as new onset vitiligo in patients with melanoma rather than a distinct entity.

### Clinical markers of disease activity

The most extensively characterized clinical markers of active, progressive disease include the Koebner phenomenon, trichrome lesions, inflammatory lesions, and confetti-like depigmentation. A recent study described greater BSA and a poorer response to treatment when any type of Koebner phenomenon is present.<sup>38</sup> Trichrome lesions (Fig 6) have 3 colors in close proximity—depigmented lesional skin, normally pigmented skin, and a zone of hypopigmented skin, usually at the border. This presentation has been associated with active, rapidly progressing disease.<sup>39</sup> Inflammatory vitiligo (Fig 7) is an uncommon presentation characterized by erythema, scale, and pruritus within hypopigmented or depigmented lesions, particularly at the lesional border. Early histologic studies showed that this presentation has a significant interface dermatitis comprised of T cells.<sup>40</sup> The inflammatory phase may be short-lived, but causes rapid depigmentation. Confetti-like depigmentation has been recently described as a marker of rapidly progressive vitiligo, with patients exhibiting a higher Vitiligo Disease Activity Score and Koebner Phenomenon Vitiligo Score, which correlate with more active, progressive, and aggressive disease.<sup>41</sup> This clinical appearance is characterized by numerous depigmented macules



**Fig 7.** Inflammatory type of vitiligo with erythema and scale.

(1–5 mm in diameter) clustered in groups that are frequently seen at the border of larger existing lesions (Fig 8). These markers of severity are important when assessing the patient and developing a management plan.

## DIAGNOSIS

### Key points

- **Vitiligo is usually a clinical diagnosis**
- **Wood's lamp examination helps to confirm the diagnosis and extent of disease in fair-skinned individuals**
- **The primary differential diagnoses include diseases of hypopigmentation**

Vitiligo is usually a clinical diagnosis, often aided by a thorough history and examination (Table II). Wood's lamp examination of vitiligo reveals a chalky white enhancement of depigmented skin, while hypopigmented skin is not enhanced. Other, inherited causes of depigmentation are often noted at birth, remain stable over time, occur in the context of other developmental or systemic problems, and often demonstrate a positive family history. When diagnosing vitiligo, it is essential to exclude other conditions causing hypopigmentation and depigmentation (Tables III and IV). Rarely, histopathologic examination may be necessary to confirm the diagnosis.

The differential diagnosis of vitiligo includes hypopigmented dermatoses, such as progressive macular hypomelanosis, tinea versicolor, pityriasis alba, and hypopigmented mycosis fungoides. Nevus depigmentosus is the main differential diagnoses of segmental vitiligo and focal vitiligo (Table IV). Nevus depigmentosus is usually present at birth or appears within the first few months of life, grows in proportion to the child, and often appears after first sun exposure, which darkens the surrounding skin and reveals its presence. Unlike segmental vitiligo, the lesions of nevus depigmentosus do not expand over time, are usually hypopigmented rather than depigmented, are not associated with leukotrichia, and typically reveal a jagged border, while vitiligo



**Fig 8.** Confetti-like lesions on the dorsal aspect of the foot.

lesions have a smooth border. No alteration in texture, sensation, or hyperpigmented border is noted. Biopsy specimens reveal approximately normal numbers of melanocytes, but melanin production is decreased.<sup>42</sup> Nevus depigmentosus is off-white under Wood's lamp while vitiligo is chalky white.

### Histology

Lesional skin in vitiligo shows complete or near-complete loss of epidermal pigmentation (Fontana–Masson stain) with an absence of melanocytes at the basal layer.<sup>43</sup> Early lesions demonstrate a subtle interface dermatitis consisting of CD8<sup>+</sup> cytotoxic T cells infiltrating the epidermis in close approximation to melanocytes. The expanding edges of active lesions may reveal a perivascular and perifollicular lymphocytic infiltrate. Electron microscopy of lesional borders reveals vacuolization of melanocytes and keratinocytes. Established lesions show sparse inflammation, likely because the T-cell infiltrate has cleared by the time the epidermis becomes visibly depigmented. In fact, visible depigmentation of the skin may not become apparent for up to 48 days after apoptosis of melanocytes has occurred.<sup>44</sup>

## DISEASE ASSOCIATIONS

### Key points

- **Vitiligo may present with systemic changes, including inflammation of the eye and ear**
- **Autoimmune diseases are more prevalent in patients with vitiligo and their family members**

**Table II.** Approach to history and examination of a patient with vitiligo

History	Examination
Age of onset	Fitzpatrick skin phototype
Location of first lesion	Distribution (whole body with Wood's lamp/light)
Length of stability/rapidity of progression	Morphology
Areas of involvement (including genitals)	Mucosal surfaces (mouth and genitals)
Triggers (especially friction and trauma)	Percent of body surface area involvement
History of AIC	Leukotrichia
Family history of AIC	Trichrome vitiligo
Symptoms of thyroid disease	Koebner phenomenon
Symptoms of other AIC	Confetti-like depigmentation
Contraindications to light therapy (eg, photosensitive dermatoses, claustrophobia, or movement disorders)	Inflammatory lesions (erythema and scale)
Occupation	Stigmata of AIC (especially thyroid disease)
Ability to attend phototherapy	Halo nevi
Depression and quality of life	Repigmentation pattern

AIC, Autoimmune condition.

- Vogt-Koyanagi-Harada syndrome is a rare presentation of vitiligo that also affects the hair, eye, inner ear, and brain**

Patients with vitiligo and their first-degree relatives have an increased prevalence of autoimmune thyroid disease, type 1 diabetes mellitus, pernicious anemia, rheumatoid arthritis, Addison disease, lupus, and Guillain–Barré syndrome, among others.<sup>7,45,46</sup> The increased risk in family members for other autoimmune diseases suggests that genetic predisposition is for autoimmunity in general, rather than specifically for vitiligo. Melanocytes can be found in the uveal tract, retinal pigment epithelium, and membranous labyrinth of the inner ear. Therefore vitiligo, which may affect all melanocytes, may be associated with abnormalities in these organs. In 1 study, 27% of vitiligo patients had retinal pigment epithelium hypopigmentation,<sup>47</sup> while in another >30% had old chorioretinal scars.<sup>48</sup> Bilateral cochlear dysfunction has also been demonstrated in those with vitiligo.<sup>49</sup> Patients with a rare, severe form of vitiligo called Vogt-Koyanagi-Harada syndrome develop skin depigmentation and prominent leukotrichia, but only after presenting with flu-like symptoms, sound-induced ear pain, vertigo, hearing loss, meningitis, and symptomatic uveitis.<sup>50</sup> Alezzandrini syndrome is similar but even more rare, and consists of segmental vitiligo with leukotrichia, hearing loss, and visual changes.<sup>51</sup> These diseases may be caused by an autoimmune attack on melanocytes in multiple tissues, which are normally present in all individuals but usually spared in vitiligo, possibly because of immune privilege in these organs. Of all conditions found in patients with vitiligo, thyroid disease is the most common

(prevalence ~19%),<sup>7</sup> which has prompted some to advocate annual screening for disease through thyroid-stimulating hormone testing and autoantibody screening. A recent study estimated that the risk of developing autoimmune thyroid disease in patients with vitiligo doubles every 5 years, and screening every 3 years was recommended.<sup>52</sup>

## PATHOGENESIS

### Key points

- Vitiligo is an autoimmune disease of the skin that results in a loss of melanocytes**
- Intrinsic defects in melanocytes may initiate disease through innate inflammation**
- The interferon- $\gamma$ -CXCL10 pathway plays a central role in driving autoimmunity in vitiligo**

Vitiligo pathogenesis involves intrinsic defects within melanocytes and autoimmunity that targets these cells.<sup>21,29,53–62</sup> The production of melanin itself is toxic to melanocytes. First, the production of large amounts of protein increases the risk of misfolding of those proteins, which activates a stress pathway within the cell called the unfolded protein response. In addition, the energy requirements for protein production result in the generation of reactive oxygen species from mitochondrial energy metabolism. These 2 pathways appear to be hyperactivated in melanocytes from vitiligo patients, suggesting that these cells are less able to tolerate the demands of melanin production than those from healthy individuals.<sup>57,63</sup> In fact, even healthy melanocytes develop cellular stress when exposed to specific chemical phenols, like monobenzyl ether of hydroquinone (MBEH).<sup>57,64,65</sup> Once melanocytes

**Table III.** Differential diagnosis of vitiligo

Disorder	Clinical presentation	Diagnosis
Congenital conditions		
Piebaldism	Midline depigmentation; present at birth; lesions contain islands of normal pigment	Dominantly inherited; other affected family members
Waardenburg syndrome	White forelock, some with depigmented patches	Other stigmata of the syndrome, including hearing loss
Multiple ash leaf macules of TS	Multiple, well-demarcated, hypopigmented macules	Other cutaneous signs of TS, epilepsy, and other organ involvement
Hypomelanosis of Ito	Blaschkoid hypopigmentation present at birth	May or may not have other stigmata
Inflammatory conditions		
Pityriasis alba	Poorly demarcated hypopigmented macules; scale, erythema may be seen; most commonly in children with skin of color	Does not fluoresce with Wood's lamp; evidence of eczema may be noted
Postinflammatory hypopigmentation	Poorly demarcated hypopigmentation in an area of previous inflammation; may see primary dermatosis (eg, seborrheic dermatitis, eczema)	Decreased number of melanocytes with or without other inflammatory patterns
Lichen sclerosus et atrophicus	Typically on genitals; atrophic skin with or without fissures; figure-of-8 pattern surrounding vaginal introitus and anus	Lichenoid inflammation; epidermal atrophy; sparing of melanocytes
Discoid lupus erythematosus	Head, face, and neck erythematous, scaly macules and plaques with scarring, dyspigmentation and alopecia	Interface dermatitis with sparing of melanocytes
Hypopigmented sarcoidosis	Hypopigmented macules or patches; may be other manifestations of sarcoidosis	Histopathology reveals noncaseating granulomas
Cutaneous malignancy		
Mycosis fungoides (hypochromic variant)	Especially seen in skin of color; bathing suit distribution; with or without scale and signs of inflammation	Epidermotropism; atypical lymphocytes
Infections		
Acquired progressive macular hypomelanosis	Young adults; trunk (especially lower back and axillae)	Wood's lamp may reveal <i>Propionibacterium acnes</i> (pink fluorescence)
Tinea versicolor	Hypopigmentation; trunk	Positive skin scraping with potassium hydroxide preparation; green fluorescence of untreated lesions
Leprosy (tuberculoid or indeterminate)	Hypopigmented, hypoesthetic white patches	Skin smear and biopsy specimen reveal <i>Mycobacterium leprae</i>
Pinta (late-stage)	Depigmented lesions, typically on distal extremities or other exposed part of the body	Rapid plasma reagin—positive; spirochetes on dark-field microscopy or histopathology
Exogenous causes		
Idiopathic guttate hypomelanosis	Exogenous ultraviolet light exposure causing nonprogressive 1-5 mm hypomelanotic macules in older adults; chronically sun-exposed sites; no leukotrichia	
Trauma-induced hypo- or depigmentation	Geometric shapes and history of trauma or surgical intervention	

Any single, unilateral lesion of these diagnoses could also be included on the differential diagnosis of segmental variant of vitiligo.  
TS, Tuberous sclerosis.

**Table IV.** Differential diagnosis of segmental vitiligo

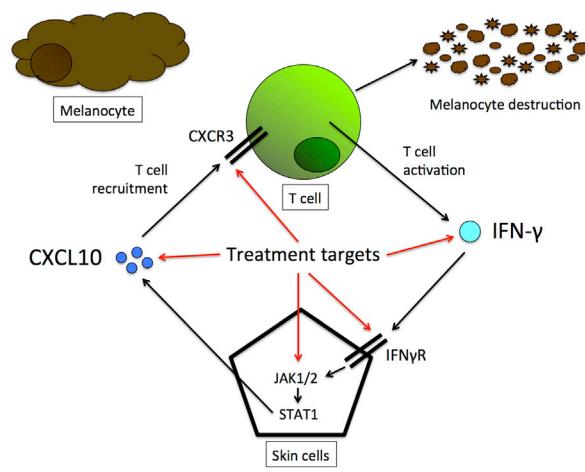
Disorder	Clinical presentation	Diagnosis
Nevus depigmentosus	At birth or first few years of life; grows in proportion to child; usually hypopigmented, has a jagged border, and lacks leukotrichia	Normal number of melanocytes histologically but decreased melanin
Nevus anaemicus	Presents at birth; mostly on the upper aspect of the chest; poorly demarcated white macule with surrounding erythema	Merges with surrounding skin with diascopy; no accentuation with Wood's lamp examination

become stressed, they release inflammatory signals that activate innate immunity, which may represent the initiating event in vitiligo.<sup>64-67</sup>

Studies report aberrant activation of innate immune cells in the skin of vitiligo patients, including recruitment of natural killer cells<sup>68</sup> and inflammatory dendritic cells,<sup>59</sup> suggesting that innate immune activation plays a role in the disease. Antigen-presenting cells probably migrate out of the skin to draining lymph nodes to present melanocyte antigens to T cells and activate them, thus serving to bridge cellular stress and adaptive T-cell responses. Innate cells may also locally secrete cytokines that recruit and activate autoreactive T cells, which then directly kill melanocytes.

Cytotoxic CD8<sup>+</sup> T cells are both necessary and sufficient for melanocyte destruction in the skin of vitiligo patients, and therefore serve as the effector arm of autoimmunity in vitiligo.<sup>69</sup> Vitiligo patients have increased numbers of autoreactive melanocyte-specific, cytotoxic CD8<sup>+</sup> T cells in their blood and skin,<sup>40</sup> and these can be seen infiltrating the epidermis in affected skin. In fact, the degree of CD8<sup>+</sup> cellular infiltration correlates with disease severity.<sup>40,69-71</sup> Specific antigens targeted by CD8<sup>+</sup> T cells in vitiligo have been identified and primarily consist of proteins of the melanogenic pathway, such as gp100, MART1, tyrosinase, and tyrosinase related proteins 1 and 2.<sup>70-73</sup>

Interferon (IFN)- $\gamma$  and IFN- $\gamma$ -induced genes are the predominant cytokine pathway expressed in lesional skin,<sup>74</sup> and IFN- $\gamma$  is required for the recruitment of melanocyte-specific, autoreactive CD8<sup>+</sup> T cells to the skin.<sup>75,76</sup> The IFN- $\gamma$ -induced chemokine CXCL10 and its receptor CXCR3, which is expressed on autoreactive CD8<sup>+</sup> T cells in blood and lesional skin from patients with vitiligo, appear to be critical for T cell recruitment in vitiligo.<sup>74,77,78</sup> Blocking this pathway can both prevent vitiligo onset and reverse established disease in a mouse model. Therefore, interfering with this cytokine pathway may be a viable new treatment strategy (Fig 9).<sup>74,79</sup> The expression of additional cytokines



**Fig 9.** Schematic diagram of current understanding of vitiligo pathogenesis.

has been reported in patients with vitiligo, including tumor necrosis factor- $\alpha$ , interleukin (IL)-6, and IL-17; however, their functional role, if any, is unclear. In fact, patients taking biologics that block tumor necrosis factor- $\alpha$ , IL-12/23, and IL-17 for other diseases have been reported to develop de novo vitiligo or have exacerbated disease.<sup>80-83</sup>

In addition to the pathogenic role of cytotoxic, autoreactive CD8<sup>+</sup> T cells in vitiligo, CD4<sup>+</sup> T regulatory cells (Tregs) appear to play an important role in preventing and controlling disease. Patients with immune polyendocrinopathy and X-linked syndrome, who lack Tregs, are at increased risk for vitiligo.<sup>84</sup> A recent study reported that melanocyte-specific, autoreactive CD8<sup>+</sup> T cells from healthy patients exhibit a phenotype that reflects ongoing Treg-mediated control, while vitiligo patients possess cells that appear to be more activated and lack this phenotype.<sup>85</sup> However, it is currently unclear whether Treg numbers are normal or fewer, whether they have impaired homing to the skin, and whether or not they are functionally altered in vitiligo patients.<sup>86-90</sup> Future studies are required to identify how Tregs function within the skin and exactly how they are defective in human patients with vitiligo.

Some have postulated a role for the nervous system in vitiligo pathogenesis, which is referred to as the “neural hypothesis.” However, the primary basis for this hypothesis is the unilateral distribution pattern of segmental vitiligo,<sup>91</sup> which led to its being labeled “dermatomal vitiligo.” Close observation reveals that the distribution is rarely, if ever, dermatomal.<sup>92,93</sup> Therefore, based on this misidentification and much better supported alternatives, we agree with Ortonne et al<sup>91</sup> that the hypothesis is still without sufficient evidence. In addition, a recent case report revealed that segmental vitiligo exhibits melanocyte-specific T-cell infiltration with an interface dermatitis that is identical to common vitiligo,<sup>94</sup> suggesting that it is also mediated by autoimmunity.

The pathogenesis of segmental vitiligo has recently been hypothesized to include melanocyte mutations that occur during embryologic development, a process called somatic mosaicism.<sup>93</sup> A single mutation in an embryonic melanocyte would be passed on to its daughter cells, which later differentiate into functional melanocytes in the epidermis of the individual. This would result in a unilateral distribution of abnormal melanocytes in a pattern distinct from dermatomes, because melanocytes migrate from the neural crest ventrally in paths that are independent from cutaneous nerves.<sup>95</sup> Based on the fact that intrinsic melanocyte abnormalities contribute to the pathogenesis of vitiligo, it is possible that somatic mutations within stress pathways could contribute to this unilateral manifestation of vitiligo. Then, consistent with the known pathogenesis of vitiligo, these abnormalities may initiate autoimmunity that is limited to the segment of altered melanocytes, sparing normal cells elsewhere. The local field of abnormal melanocytes could explain why segmental vitiligo is resistant to medical treatments but so responsive to surgical ones (discussed in more detail in the second article in this continuing medical education series), because abnormal melanocytes may have difficulty repigmenting the lesions but surgical approaches successfully transplant normal melanocytes to the affected areas, enabling long-term improvement. Additional studies will be required to test this hypothesis and determine whether somatic mutations exist within melanocytes targeted in segmental vitiligo.

## RISK FACTORS

### Key points

- Genetics strongly influence the risk of developing disease
- Environmental factors also contribute, including exposure to phenolic compounds found in household products
- Nonspecific induction of skin inflammation may induce local vitiligo lesions

The risk of developing vitiligo is 0.5% to 2% in the general population, approximately 6% when a first-degree relative is affected, and 23% when an identical twin is affected,<sup>7</sup> suggesting that genetic factors are important elements in developing disease. However, not all identical twins are affected, and therefore nonheritable factors must also play a role, which may indicate a role for exposures in disease pathogenesis, broadly characterized as “environmental factors.”

### Genetics

Vitiligo is inherited in a polygenic pattern, suggesting that multiple alleles contribute to the genetic risk for disease. Indeed, a series of genome-wide association studies and genetic linkage studies have implicated approximately 50 genetic loci as important factors that contribute to vitiligo risk.<sup>96</sup> The overwhelming majority of these genes are immune genes, confirming a critical role for the immune system in vitiligo pathogenesis. Some are known to play a role in innate immunity (*IFIH1*, *CASP7*, *NLRP1*, *TICAM1*, and others), while others are key factors in mediating adaptive immunity (*CTLA4*, *CD80*, *HLA*, *GZMB*, *FOXP3*, and others), confirming a need for both arms of the immune system as discussed above. In addition to immune genes, a small subset of risk alleles is only expressed in melanocytes (*TYR*, *OCA2*, and *MC1R*), supporting a role for melanocytes in initiating disease. In addition, *XBP1* has also been implicated and is a key component of the unfolded protein response cellular stress pathway, which may also be important in initiating inflammation.<sup>96,97</sup> Additional studies through functional genomics will be required to determine the specific roles that each gene plays in driving vitiligo pathogenesis.

### Environmental triggers

The first environmental exposure connected to vitiligo was identified in 1939, when a large number of factory workers developed depigmentation on their hands and remote locations that was caused by the presence of MBEH in their gloves.<sup>98</sup> MBEH is so effective at promoting depigmentation in vitiligo that it is now used to accelerate depigmentation in those with severe disease, resulting in even skin tone.<sup>99,100</sup> A more recent “outbreak” of vitiligo cases (>16,000 cases) was reported in the summer of 2013 in Japan and was determined to be caused by the use of a new skin-lightening agent that contained rhododendrol as the active ingredient.<sup>101,102</sup> Additional chemicals implicated as inducers of vitiligo include 4-tert-butylphenol and 4-tert-butylcatechol, which can be found in adhesive resins, industrial oils,



**Fig 10.** Vitiligo in an area of imiquimod application.

paints, adhesives, and other products.<sup>103,104</sup> A common feature of these chemicals is that all are phenols, bearing a benzene ring with an attached hydroxyl group, which is similar to the amino acid tyrosine, also a phenol. Their mechanism of action appears to be that they act as tyrosine analogs, interfering with tyrosinase and melanin synthesis, inducing additional stress in melanocytes, and resulting in the release of inflammatory factors that initiate autoimmune attack on the melanocytes.<sup>23,57,62,65</sup> However, only a subset of exposed patients appears to be susceptible to depigmentation, as not all those exposed to the chemicals get the disease. The rhododendrol exposure in Japan only affected about 2% of users,<sup>105</sup> suggesting that exposures act on genetically susceptible patients to induce disease.

Recently, Wu et al<sup>106</sup> reported that use of permanent hair dyes increase the risk of developing vitiligo. In this study, even “having ever used” hair dyes increased a woman’s risk of developing vitiligo, and this was increased further with first use before 30 years of age and with longer duration of use. Hair dyes contain multiple phenol ingredients, but the exact chemical ingredients responsible for inducing vitiligo is currently unknown. Additional products implicated in a retrospective study based on patient recall (and therefore susceptible to recall bias) include detergents, topical dyes, and others.<sup>22</sup>

Vitiligo patients are susceptible to skin trauma through the Koebner phenomenon.<sup>107</sup> In addition, imiquimod-induced vitiligo has been reported in patients treated for genital warts, condyloma acuminata, extramammary Paget disease, and basal cell carcinoma<sup>108-110</sup> (Fig 10), and others have reported depigmentation at the site of IFN- $\alpha$  injection for the treatment of hepatitis C.<sup>111</sup> Both skin trauma and imiquimod exposure induce IFN- $\alpha/\beta$  in the skin,<sup>110,112</sup> and therefore depigmentation in these cases may be caused by the ability of IFN- $\alpha/\beta$  to also induce CXCL10<sup>113</sup> which, as

discussed above, promotes the migration of melanocyte-specific, autoreactive T cells into the skin in vitiligo.<sup>74</sup>

In summary, vitiligo is a common skin disease with a large potential impact on patients’ quality of life, and therefore it should not be dismissed as “simply cosmetic.” Distinct subtypes of vitiligo and lesion patterns are important to recognize because they influence prognosis through disease activity, progression, and treatment responses. A variety of other autoimmune diseases are associated with vitiligo, and recognizing this association will help to guide workup and clinical management. Recently, much has been revealed about the pathogenesis of vitiligo and risk factors for disease, which may lead to improved prevention and treatment options.

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# Current and emerging treatments for vitiligo



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## Learning objectives

After completing this learning activity, participants should be able to choose an optimal approach to management of all patients with vitiligo; list the risks associated with treatment for vitiligo; and discuss emerging treatment options for vitiligo.

## Disclosure

### Editors

The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

### Authors

The authors involved with this journal-based CME activity other than Dr Harris have reported no relevant financial relationships with commercial interest(s). Dr Harris has served on advisory boards, as a consultant, or as principle investigator on research agreements with Pfizer, AbbVie, Genzyme/Sanofi, Concert Pharmaceuticals, Stiefel/GSK, Mitsubishi Tanabe Pharma, Novartis, Aclaris Therapeutics, The Expert Institute, Celgene, Biologics MD, and Dermira. Dr Harris' relevant relationship with Pfizer was resolved by nonconflicted reviewers and editors.

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Clinicians should be aware that vitiligo is not merely a cosmetic disease and that there are safe and effective treatments available for vitiligo. It is important to recognize common and uncommon presentations and those with active disease, as well as their implications for clinical management; these were discussed in the first article in this continuing medical education series. Existing treatments include topical and systemic immunosuppressants, phototherapy, and surgical techniques, which together may serve to halt disease progression, stabilize depigmented lesions, and encourage repigmentation. We discuss how to optimize the currently available treatments and highlight emerging treatments that may improve treatment efficacy in the future. (J Am Acad Dermatol 2017;77:17-29.)

**Key words:** afamelanotide; biologics; corticosteroids; excimer lamp; excimer laser; grafting; leukoderma; methotrexate; narrowband ultraviolet light; phototherapy; pigmentation; tacrolimus; treatment; vitiligo.

## MEDICAL TREATMENTS

### Key points

- Potent or ultrapotent topical corticosteroids administered in a cyclical fashion avoids adverse effects

- Topical tacrolimus 0.1% should be used twice daily for affected areas on the face and intertriginous areas
- Narrowband ultraviolet B light phototherapy appears to be safe and effective when >5-10%

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**body surface area is affected; focused narrowband ultraviolet B light phototherapy, such as hand and foot units or excimer laser, is useful in localized disease**

- **Topical tacrolimus 0.1% used twice per week may help prevent relapse after repigmentation is achieved**

Vitiligo is not a “cosmetic disease,”<sup>1</sup> so treatment can and should be offered to patients. The optimal treatment of vitiligo will first depend on the subtype of the disease, percent of body surface area (BSA) involved, effect on quality of life, and the perception of the patient concerning the risk to benefit ratio. For example, in the segmental variant of vitiligo, the disease follows a predictable course, with a phase of rapid spreading and early hair follicle involvement restricted to the affected segment lasting 3 to 24 months. This is usually followed by complete stabilization. The segmental variant is therefore more difficult to treat and requires early medical intervention or a surgical approach late in the disease course. With all types of vitiligo, timing of treatment is an important predictor of success, with early disease responding best.<sup>2</sup>

In contrast to the segmental variant, most cases of vitiligo follow an unpredictable course, with periods of disease progression and quiescence. Early involvement of the hair follicle is uncommon.<sup>3</sup> Spontaneous repigmentation has been described, although this is not the rule. At present, no medical treatment for repigmenting vitiligo has been approved by the US Food and Drug Administration (FDA), and therefore treatments are used off-label. Topical treatments may be applied alone when small areas are involved or when other treatment modalities are not readily available. Phototherapy combined with topical treatment is preferred when >5-10% of the BSA is affected or when focal areas are unresponsive to topical treatments alone.

#### **Topical corticosteroids (level II evidence)**

When selecting a topical steroid, the site of the lesion and age of the patient should be considered. Lesions on the body may be treated with ultrapotent or potent corticosteroids; the face, neck, and intertriginous areas and lesions in children should be treated with either midpotency topical corticosteroids or calcineurin inhibitors (see below). Possible regimens include daily or twice daily application in a cyclical fashion with “days off” (eg, 1 week on then 1 week off for 6 months, or application for 5 consecutive days followed by 2 days off).<sup>4</sup> In practice, these regimens appear to minimize the risk of adverse effects, although evidence-based studies to support this are lacking.

#### **Topical calcineurin inhibitors (level II evidence)**

In recently published guidelines, the European Dermatology Forum group proposed twice daily topical calcineurin inhibitors for head and neck lesions as a first-line approach.<sup>5</sup> This recommendation is based on a combination of its efficacy in these sites and its favorable side effect profile.<sup>6,7</sup> Warnings have been placed on the long-term use of tacrolimus because of a theoretical long-term risk of cancer, despite its repeatedly demonstrated safety.<sup>8</sup> Other than exposure to medically administered phototherapy or excimer laser, photoprotection should be encouraged when using topical immunosuppression. When using a cyclical regimen for topical steroids outlined above, calcineurin inhibitors may be used on the “off” days to provide consistent treatment without increasing the risk of adverse events.

#### **Phototherapy**

There are 2 main indications for the use of whole-body phototherapy in vitiligo: extensive disease (>5-10% of BSA) and rapidly spreading disease. However, patients with smaller areas of involvement and less activity may also require phototherapy in some instances because of its superior efficacy. With all medical interventions, the physical and psychological impact of the disease should be weighed against the risks of a particular treatment, which typically requires physicians to customize the management strategy for each patient. In general, patients should not apply any topical medications or sunscreen before ultraviolet (UV) light therapy in order to avoid reduced transmission of UV light into the skin. Patients should also be vigilant about sun protection to avoid additive effects of sun exposure when receiving UV light therapy treatment.

#### **Psoralen plus ultraviolet A light phototherapy (level I evidence)**

Psoralen plus ultraviolet A light phototherapy (PUVA) was the first phototherapy regimen used in patients with vitiligo. The results were reasonable, but issues with compliance (eg, oculocutaneous protection), side effects (eg, nausea), and an increased risk of skin cancer led to a decline in its use. In a recent Cochrane review, PUVA was deemed inferior to narrowband ultraviolet B light therapy (NB-UVB) in achieving >75% repigmentation in the general population of vitiligo patients.<sup>6</sup> Therefore, PUVA has been largely replaced by NB-UVB, although PUVA may still induce faster repigmentation.<sup>9,10</sup> PUVA may be considered in patients with



**Fig 1.** Vitiligo. Carnation pink color of vitiligo in a patient being treated with narrowband ultraviolet B light phototherapy.

darker Fitzpatrick skin phototypes or those with treatment-resistant vitiligo.<sup>11-13</sup>

#### NB-UVB (level I evidence)

In addition to its immunosuppressive effects, NB-UVB induces melanocyte differentiation and melanin production.<sup>14</sup> In the last decade, NB-UVB has become the first-line therapy for extensive, progressive vitiligo because of its superiority to PUVA and its relative paucity of side effects. It can also be used safely in children and those who are pregnant or lactating. When used alone, repigmentation rates ranging from 40% to 100% have been reported, depending on the location of the lesions.<sup>15-19</sup> Patients should be treated with an optimized, aggressive approach, starting at a safe, low dose (ie, 200 mJ) 2 to 3 times per week with 10% to 20% dose increments. When asymptomatic, light pink erythema (Fig 1) lasting <24 hours is achieved, the optimal dose has been reached and treatment should continue at this dose until erythema disappears. The dose should then be increased again until it returns.<sup>20</sup> The maximum dose of NB-UVB varies depending on Fitzpatrick skin phototype and photosensitivity. There are no established guidelines for maximum dosing for vitiligo, and we therefore recommend increasing the dose until light pink erythema is achieved or until side effects (such as skin burning, sensitivity, peeling, or thickening) develop. A lack of response after 6 months suggests a nonresponsive patient, and discontinuation of treatment should be considered.<sup>11</sup>

#### Targeted UVB phototherapy (level II)

Targeted phototherapy (excimer lasers and excimer lamps) can be considered when <10% of BSA is affected.<sup>2</sup> This therapy is attractive for patients who wish to avoid skin darkening caused by NB-UVB (Figs 2 and 3). Although effective in the repigmentation of stable lesions, this focal therapy



**Fig 2.** Vitiligo. Lesion on the lower leg before excimer laser treatment.



**Fig 3.** Vitiligo. Lesion on the lower leg (with pigmented hairs, which portend a favorable prognosis) after 7 months of excimer laser therapy.

typically fails to stabilize vitiligo because clinically unaffected skin is not treated. In the segmental variant, excimer laser seems to be the most beneficial treatment when used early in the disease course.<sup>21</sup> In a recent retrospective study, 59 patients with the segmental variant, which is typically refractory to treatment, responded well to excimer laser, topical tacrolimus, and short-term systemic corticosteroids for 3 months; almost 50% of patients achieved >75% repigmentation.<sup>22</sup>

#### Oral immunosuppression (level III-2 evidence)

Oral steroids may help stabilize rapidly progressive disease. Oral minipulse therapy (OMP) refers to the discontinuous administration of suprapharmacologic doses of steroids. Randomized controlled trials investigating their efficacy are still lacking, although numerous retrospective studies support their use in progressive disease. The regimen consists of low-dose betamethasone or dexamethasone for 3 to 6 months on 2 consecutive days. It is usually administered in combination with other therapies, including phototherapy.<sup>23</sup> In initial

reports, 5 mg betamethasone/dexamethasone was used on 2 consecutive days per week.<sup>24,25</sup> This was increased to 7.5 mg/day in nonresponders and decreased back to 5 mg/day when disease progression was arrested. The results showed that 89% of patients were stabilized within 1 to 3 months. In another study, dexamethasone 10 mg twice weekly for  $\leq 24$  weeks halted disease progression in 88% of patients after 18.2 weeks.<sup>26</sup> However, 69% experienced side effects, including weight gain, insomnia, acne, agitation, menstrual irregularities, and hypertrichosis.

### Other immunosuppressants and biologics

Limited data are available for the use of other immunosuppressant drugs in vitiligo. In a recent randomized comparative study, low-dose oral methotrexate was reported to be comparable to OMP, and suggested when OMP is contraindicated, although responses were marginal with small study sizes.<sup>27</sup>

Anti-tumor necrosis factor- $\alpha$  drugs have been suggested for the treatment of vitiligo<sup>28,29</sup> despite reports of no benefit and even initiation and worsening with their administration.<sup>30-34</sup> Twice daily oral cyclophosphamide (50 mg) has also demonstrated repigmentation in 29 patients, including those with difficult to treat acral sites, although significant side effects were reported.<sup>35</sup> Although spontaneous remissions are uncommon in patients with vitiligo, treatment recommendations based on uncontrolled studies should be weighed against that possibility.

### Other treatments

**Vitamin D analogs (level III-I evidence).** Most studies have evaluated calcipotriene in combination with other therapies, particularly phototherapy. Calcipotriene may shorten the time to achieve repigmentation and reduce overall cumulative exposure during phototherapy, but it has not demonstrated appreciable repigmentation when used alone.<sup>36,37</sup>

Other treatments for vitiligo appeared to be promising in pilot trials but failed to demonstrate significant efficacy in later controlled trials. Examples include *Polypodium leucotomas*, ginkgo biloba, antioxidants, and pseudocatalase cream.<sup>38</sup>

**Comparative efficacy studies.** *Topical steroids versus calcineurin inhibitors.* There have been a few studies comparing different treatments for vitiligo. In 1 study, tacrolimus ointment 0.1% was compared with clobetasol cream 0.05% in children.<sup>7</sup> This randomized, double-blind, comparative trial revealed 49% repigmentation with clobetasol and 41% with tacrolimus, but the difference was not statistically

significant. Facial lesions responded best, with most patients tolerating treatment well. While small, this study provides evidence of efficacy for the treatment of vitiligo with tacrolimus (level of evidence I, strength of recommendation A).

Another study evaluated 100 children with vitiligo treated with tacrolimus, clobetasol, or placebo ointment.<sup>39</sup> The clobetasol-treated group received intermittent therapy and others continuous therapy; the clobetasol-treated group received clobetasol ointment for 2 months, petroleum jelly for the next 2 months, and clobetasol again for the remaining 2 months. The tacrolimus-treated group received 0.1% ointment for 6 months, and the placebo-treated group received petroleum jelly continuously for 6 months. There was no statistically significant difference between the tacrolimus and clobetasol groups, although facial lesions responded better than nonfacial lesions overall. Both treatments were superior to placebo (level of evidence I, strength of recommendation A).

A small study of 10 patients with bilaterally symmetrical generalized vitiligo treated with clobetasol cream on one side of the body and pimecrolimus cream on the other showed a comparable degree of repigmentation, although small numbers make noninferiority trials like this difficult to interpret.<sup>40</sup> (level of evidence II-I, strength of recommendation B).

**NB-UVB versus PUVA.** NB-UVB therapy has become the predominant form of phototherapy for vitiligo because of its efficacy, relative lack of side effects, and convenience. A study comparing 12 months of twice weekly NB-UVB to twice weekly oral 8-methoxysoralen PUVA demonstrated superior repigmentation, color matching, and fewer side effects in the NB-UVB-treated group.<sup>11</sup> Overall, 64% of the NB-UVB group had  $>50\%$  improvement in BSA affected versus 36% in the PUVA group. The superiority of NB-UVB was maintained 12 months after treatment ended (level of evidence I, strength of recommendation A).

Another investigator-blinded trial of NB-UVB versus PUVA 3 times per week for 6 months was conducted in 56 patients.<sup>41</sup> Median repigmentation was similar between the 2 groups but adverse effects, particularly pruritus, were much lower in the NB-UVB group (7.4% vs 57.2%). The face, neck, and trunk demonstrated the best response in both groups (level of evidence I, strength of recommendation A).

**Combination therapies.** Although antioxidants have been promoted for various skin diseases, including vitiligo, few controlled studies have attempted to determine their true efficacy. In 1 randomized,



**Fig 4.** Vitiligo. Lesion on the upper aspect of the back before narrowband ultraviolet B light phototherapy.

double-blind, placebo-controlled study,<sup>42</sup> patients received a combination of  $\alpha$ -lipoic acid, vitamin C, vitamin E, and polyunsaturated fatty acids or placebo for 2 months. They were then treated with NB-UVB for 6 months. Forty-seven percent of those treated with antioxidants before NB-UVB demonstrated  $>75\%$  repigmentation versus 18% in the placebo plus NB-UVB group. Although this is a single study, this controlled trial supports the use of antioxidants in patients undergoing phototherapy (level of evidence I, strength of recommendation A).

*Evidence for treatment regimens.* There is little evidence to guide clinicians on selecting the optimal frequency, dosing, and duration of treatment for vitiligo. No comparative studies have been performed on one topical dosing frequency versus another, 2 times weekly versus 3 times weekly phototherapy, or on different doses of oral corticosteroids for active vitiligo. Two have studied differences in efficacy between 2 and 3 times weekly treatments with the excimer laser for vitiligo.<sup>43,44</sup> Both concluded that there was no difference in the final degree of repigmentation between the 2 dosing frequencies; however, repigmentation was dependent on the total number of treatment sessions, with earlier onset of pigmentation noted with 3 times weekly dosing. This is likely to be the case for NB-UVB also.

Regarding duration of therapy, a previous study reported a mean 25% improvement after 3 months, 50% after 6 months, and 75% after 9 months of NB-UVB therapy<sup>11</sup> (Figs 4 and 5). The slow but steady improvement when undergoing therapy for vitiligo requires patience and motivation on the part of the patient and clinician. Monitoring improvement requires baseline and serial images at each visit. As long as the patient is improving and side effects are tolerable, treatment can be continued until no further improvement occurs, after which maintenance treatment can be initiated.



**Fig 5.** Vitiligo. Lesion on the upper aspect of the back after 5 months of narrowband ultraviolet B light phototherapy.

*Maintenance therapy.* Given that the risk of relapse in the first year after ceasing therapy is 44%,<sup>45</sup> it may be important to transition patients to maintenance therapy once repigmentation is achieved. In 1 study, all patients achieving  $>75\%$  repigmentation from any modality were treated with either tacrolimus ointment 0.1% or placebo ointment twice weekly. Thirty-five patients were enrolled in this 24-week trial.<sup>46</sup> Lesions on the hands and feet were excluded. Ninety-six percent of those treated with tacrolimus on the head and neck maintained the repigmented areas without relapse, while only 60% on placebo were maintained. Success of the maintenance therapy was independent of initial treatment modality. Topical tacrolimus ointment 0.1% twice weekly can therefore be recommended for maintenance therapy (level of evidence II; Figs 6 and 7). Some have suggested a similar approach with NB-UVB to prevent relapse, but no studies have tested the efficacy of this approach.

## SURGICAL TECHNIQUES

### Key points

- Surgical techniques are most successful in late-stage segmental vitiligo
- Surgery can be considered in those with nonresponsive, stable vitiligo
- Noncultured epidermal melanocyte cell grafting demonstrates superior extent and quality of pigmentation compared with other surgical techniques

Surgical treatments offer some of the best results for stable vitiligo. Repigmentation can improve by  $\geq 68\%$  in certain types of vitiligo with only 1 treatment session.<sup>47</sup> When repigmentation is obtained in these patients, relapse is uncommon.<sup>48,49</sup> Several surgical options exist, which can be classified



**Fig 6.** Vitiligo. Depigmented patch on buttock and scrotum of baby boy that repigmented with topical therapy.



**Fig 7.** Vitiligo. After 13 months of maintenance therapy with twice weekly tacrolimus, pigmentation has been maintained on the buttock and scrotum.

into tissue and cellular grafts. Tissue grafts usually transfer solid tissue from donor to recipient site in a 1:1 ratio. Cellular grafts cover larger surface areas and are composed of suspensions of keratinocytes and melanocytes in a donor to recipient ratio up to 1:10.

### Patient selection

Patient selection is key to success with surgical treatment for vitiligo. Those with stable disease have a superior response to surgical intervention. Patients with segmental disease have better results than those with focal disease who, in turn, fare better than patients with generalized, unstable vitiligo.<sup>50-53</sup>

Disease stability must be evaluated before surgery and is defined by the absence of new or expanding lesions over 6 months to 2 years. Several methods can be used to assess stability, such as patient report, serial photography, and validated scoring systems. These include changes in the Vitiligo Area Scoring Index, Vitiligo European Task Force assessment, and Vitiligo Disease Activity Score. In cases where stability or treatment outcome is uncertain, performing a test procedure with a single punch graft in the center of a stable, depigmented lesion to assess the degree of repigmentation is useful.<sup>53,54</sup>



**Fig 8.** Vitiligo. Lesion on left upper eyelid before treatment.



**Fig 9.** Vitiligo. Lesion on left upper eyelid 9 months after punch grafting. The hyperpigmentation and cobblestone appearance of the punch grafts usually subside with time.

Koebnerization, confetti-like lesions, inflammatory vitiligo, and trichrome vitiligo are also indicators of unstable disease and are discussed in detail in the first article in this continuing medical education series.<sup>52,53</sup>

Recipient site is another variable that should be considered. In general, the head and neck demonstrate a superior response.<sup>55,56</sup> Acrofacial disease and areas over joints respond poorly, possibly because of repeated motion or friction and injury at these locations.<sup>55,56</sup> Patients must be screened for a history of keloids, coagulation abnormalities, bloodborne infections, and other contraindications to surgery, such as severe heart disease.

### Tissue grafts

Minipunch grafts are performed by placing 1- to 1.5-mm punch biopsy specimens from a donor site into a preprepared recipient site (Figs 8 and 9). This technically simple, inexpensive technique does not require specialized equipment but is difficult to perform on large areas, can lead to pigment and textural variations such as cobblestoning, and carries a risk of scarring and keloids.<sup>57-60</sup>



**Fig 10.** Vitiligo. Harvesting of suction blister grafts.

Suction blister epidermal grafting involves the creation and transfer of blister roofs from normal skin (Fig 10) to abraded depigmented skin. Advantages include low cost, use of simple equipment, uniform color match, low rates of scarring, and good efficacy. The time required to create blisters and risk of hemorrhagic blisters are disadvantages.<sup>57-59,61-63</sup>

### Cellular grafts

Cellular grafts can be cultured or noncultured and involve creating a cellular suspension from a thin to ultrathin skin graft. Noncultured options, although complex, do not require a full cell culture laboratory. Therefore, noncultured epidermal suspension (NCES) grafting, also known as a melanocyte keratinocyte transplant procedure, is performed more frequently than cultured melanocyte grafting. It is now considered the criterion standard for vitiligo grafting worldwide.

NCES is performed by harvesting an ultrathin skin graft from a donor site, which is then incubated in trypsin. After removal of the epidermis from the dermis, the epidermis is manually disrupted and then centrifuged to obtain the cellular pellet, which is resuspended in Ringers lactate, applied to the abraded recipient site, and dressed. Movement should be restricted postoperatively to avoid dressing displacement, but bed rest is not required. Dressings are removed between days 4 and 7. This procedure yields good cosmetic results and color match (Figs 11 and 12). Disadvantages include the cost, need for specialized equipment and a skilled team, and limitations of sites that can be successfully treated.<sup>47,51</sup> A new method using epidermal suction blisters for donor skin has also been described.<sup>64</sup> Of note, battery-operated cell harvesting devices have also been developed, offering a self-contained system for cell separation without the need for additional equipment. Head to head comparison studies to standard NCES tissue processing techniques have not yet been performed.<sup>65,66</sup>



**Fig 11.** Vitiligo. Segmental variant of vitiligo on the left upper forehead at baseline.



**Fig 12.** Vitiligo. Segmental variant of vitiligo on the left upper forehead 9 months after noncultured epidermal suspension grafting.

### Comparative efficacy

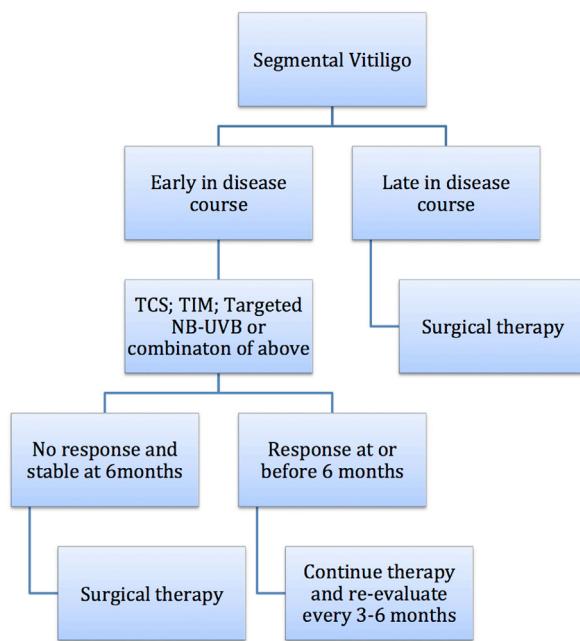
NCES has shown superior extent and quality of repigmentation compared with blister grafting.<sup>67</sup> However, blister grafting and punch grafting are much easier techniques to master and require fewer support staff.

### Camouflage techniques

Camouflage may be an important part of overall patient management given the aesthetic impact of the disease in many patients. Self-tanning agents provide waterproof protection for 3 to 5 days; highly pigmented cover creams require daily application but are lightweight and waterproof. While dermal pigmentation can be achieved with techniques like cosmetic tattooing, potential risks should be carefully considered. These risks include the potential for infection, risk of koebnerizing vitiligo, lack of legislation on tattoo pigments, poor color match, bleeding of color over time, and potential for spread of the lesion beyond the tattoo border.<sup>68</sup>

### TREATMENT ALGORITHM

Treatment for vitiligo should be started as early as possible to maximize efficacy. The type of vitiligo,



**Fig 13.** Treatment algorithm for the segmental variant of vitiligo. *NB-UVB*, Narrowband ultraviolet light phototherapy; *TCS*, topical corticosteroids; *TIM*, topical immunomodulators.

extent and duration of disease, effect on quality of life, and previous treatments should determine the initial treatment approach. The segmental variant, when treated early in the disease course ( $\leq 12$  months), can be initially treated with skin-directed medical therapy. In nonresponsive or longstanding stable disease, surgical therapies should be considered (Fig 13).

The extent of involvement also determines the treatment approach in vitiligo. Localized disease ( $\leq 5\text{-}10\%$  of BSA) is best treated with topical therapy and targeted phototherapy, while a combination of NB-UVB and topical therapy is used to treat more extensive disease ( $> 5\text{-}10\%$  of BSA). OMP can be added for those with clinical signs of aggressive, progressive disease (Fig 14). Efficacy can be assessed at approximately 6 months based on twice-weekly NB-UVB.

## TREATMENT SAFETY

### Key points

- **Topical corticosteroids, when used as directed and with dermatologic supervision, appear to be safe and are usually efficacious for vitiligo**
- **Despite evidence that tacrolimus does not appear to increase the risk of malignancy, its black box warning remains**
- **Long-term administration of NB-UVB does not appear to increase incidence of melanoma or nonmelanoma skin cancers in those with vitiligo**

### Topical therapies

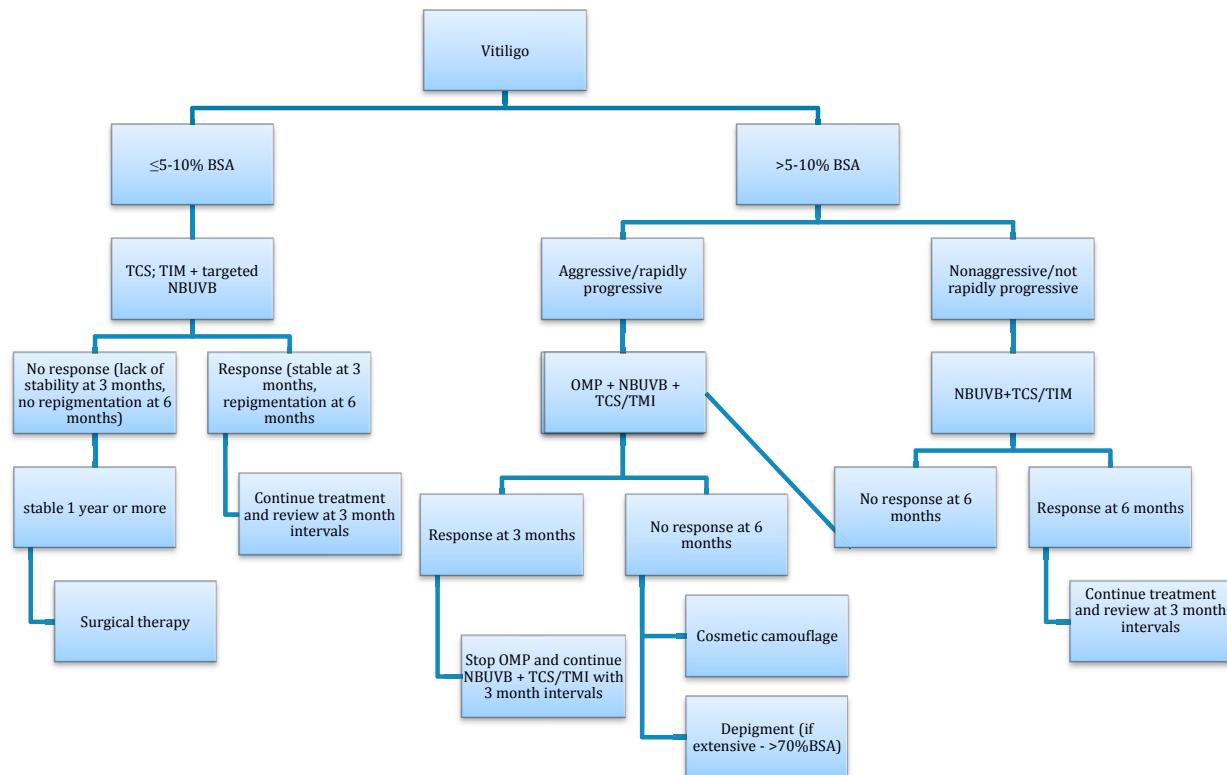
Reported side effects of inappropriate or unsupervised topical steroids include cutaneous atrophy, telangiectasias, hypertrichosis, acne, and striae. However, its side effect profile has been deemed favorable when used as prescribed by dermatologists for atopic dermatitis, in which there is epidermal barrier dysfunction and a greater likelihood of systemic absorption.<sup>69</sup> To minimize the risk of side effects, a sequential discontinuous scheme may be used.

Topical tacrolimus lacks the side effect profile of topical steroids and appears to be much safer, particularly on sensitive areas like the face, genitals, and intertriginous sites. When topical tacrolimus first became available for use, concerns were raised about the risk of malignancies that had been observed in those taking large oral doses to prevent transplant organ rejection. However, a recent systematic review and metaanalysis reporting on the risk of lymphoma in those with atopic dermatitis concluded that it does not appear to significantly contribute to the overall risk of lymphoma in this subgroup of patients.<sup>70</sup> Nevertheless, this black box warning remains and it is still not approved by the FDA, Therapeutic Goods Administration (Australia), or the European Medicines Agency for use in vitiligo. If burning after application of tacrolimus is noted, the concentration may be decreased. While skin flushing may occur immediately after alcohol ingestion and is not always limited to the area of application, it resolves quickly.<sup>71</sup>

### Phototherapy

While an absence of melanin in lesional skin and prolonged administration of phototherapy may give rise to concern about the development of skin cancer in this population, recent evidence suggests that the genetic and autoimmune profile of vitiligo patients confers a degree of protection against melanoma and nonmelanoma skin cancers (NMSCs).<sup>72-78</sup> While prolonged PUVA for psoriasis increases the risk of cutaneous malignancies in white patients, the same has not been noted with NB-UVB.<sup>79,80</sup> Even studies of PUVA for vitiligo do not appear to be associated with the development of NMSCs.<sup>81,82</sup>

While Hexsel et al<sup>83</sup> reported a higher annual incidence of NMSC in those with vitiligo compared with the rest of the population, 5 other studies reveal lower rates of melanoma and NMSC in this population.<sup>84-88</sup> In addition, a 2005 review of the literature suggested that chronic use of ultraviolet B light does not seem to increase the risk of skin cancer.<sup>89</sup> Limitations exist for all of these studies, highlighting the need for well-constructed



**Fig 14.** Treatment algorithm for vitiligo.

prospective randomized controlled trials that span decades.

### Surgical treatments

Complications are rare with most surgical procedures but include pain, hypopigmentation, koebnerization, scarring, and infection.<sup>47,60</sup>

## EMERGING TREATMENT MODALITIES

### Key points

- Afamelanotide enhances the efficacy of NB-UVB in patients with vitiligo
- Targeted immunotherapy has been safe and effective for psoriasis, and a similar treatment strategy may be equally beneficial for vitiligo patients
- The interferon- $\gamma$ -CXCL10 chemokine axis appears to be an important target for the development of new treatments for vitiligo

### $\alpha$ -Melanocyte-stimulating hormone analogues

Afamelanotide is a potent synthetic analogue of the naturally occurring  $\alpha$ -melanocyte-stimulating hormone. It was investigated as an adjunct to NB-UVB in a double blind, multicenter study. Patients treated with NB-UVB plus afamelanotide versus NB-UVB alone achieved repigmentation rates

of 48.64% and 33.26% at day 168, respectively. Side effects included hyperpigmentation, itch, and nausea.<sup>90</sup> Additional studies with this promising treatment are warranted.

### Targeted immunotherapy

In the first article in this series, we outlined recent translational research that has provided insight into possible targets for targeted therapies for vitiligo. In particular, interfering with the interferon (IFN)- $\gamma$ -CXCL10 chemokine axis may be an effective strategy to develop novel, targeted immunotherapies.<sup>91</sup> Significant repigmentation of 2 patients after the oral administration of tofacitinib<sup>92</sup> (a pan-Janus kinase inhibitor [JAK 1/3]) and ruxolitinib<sup>93</sup> (JAK 1/2 inhibitor), which directly inhibit IFN- $\gamma$  signaling, supports this concept. However, repigmentation regressed when the patient discontinued ruxolitinib, suggesting that continuous treatment is required. Importantly, the patient's serum CXCL10 level was reduced during treatment with ruxolitinib, suggesting that JAK inhibition works by targeting the IFN- $\gamma$ -CXCL10 axis, and that it may serve as a biomarker for disease activity and treatment response. A recent case series reported efficacy of topical ruxolitinib in patients with vitiligo, particularly on the face.<sup>94</sup> While these

advances are promising for vitiligo sufferers and dermatologists alike, larger, controlled studies are required to assess the safety and efficacy of targeted therapies for vitiligo.

### Depigmentation

For patients with recalcitrant and widespread (>50% of BSA) vitiligo, depigmentation of the remaining islands of pigment may provide cosmetic improvement that may enhance quality of life. Following its discovery in rubber gloves<sup>95</sup> more than 50 years ago, monobenzylether of hydroquinone (MBEH) has become the most commonly used depigmentation therapy for vitiligo and is currently the only drug approved by the FDA for the treatment of vitiligo in the United States. Depigmentation should only be considered after psychological screening and informed consent about the irreversible nature of the treatment. Patients should be aware that depigmentation cannot be targeted to a single location, but local application frequently depigments the entire skin. MBEH is applied in a 20% concentration twice daily to pigmented skin, and care should be taken to avoid excessive sun exposure, which can result in perifollicular repigmentation. The most common side effect is irritant contact dermatitis, which may be treatment-limiting,<sup>96</sup> and rarely ocular side effects have been reported, such as conjunctival melanosis.<sup>97</sup>

Complete depigmentation may require 4 to 12 months of therapy with potentially longer durations required in patients with skin of color. The concentration can be increased to 30% if responses are not noted after 4 months of treatment, but treatment should be discontinued if no response is seen at 6 months. Once depigmentation is achieved, MBEH can be used a few times per week as maintenance if required.

Recalcitrant areas of pigmentation postdepigmentation therapy may be treated with quality-switched 694-nm laser<sup>98</sup> alone or in combination with methoxyphenol.<sup>99</sup> Mequinol is a phenol derivative thought to produce similar results to MBEH but with a slower onset of depigmentation. Laser and cryotherapy<sup>100</sup> have also been tested in Europe, where the use of MBEH has been restricted.

### SUMMARY

Although it is usually slow to respond and repigmentation may not always occur despite intensive treatment, the variety of management options should be presented to patients who seek treatment. A 2-pronged approach combining stabilization of the disease by reducing the

autoimmune destruction of melanocytes along with stimulation of melanocyte regeneration is likely to produce the best results. Lack of previous success is often the reason for a pessimistic outlook regarding treatment on the part of both the treating physician and the patient; however, education and establishing realistic expectations, a comprehensive treatment plan, and photography at each visit can result in a successful outcome. Recent advances in determining the pathogenesis of the disease have opened exciting new treatment avenues that may herald a revolution in the future treatment of vitiligo.

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# Bedside diagnostics in dermatology



## Viral, bacterial, and fungal infections

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### Learning objectives

After completing this learning activity, participants should be able to describe and perform diagnostic tests that dermatologists can perform at the bedside; select the appropriate bedside technique for diagnosis of specific infectious dermatologic conditions; interpret micrographs to diagnose infectious dermatologic conditions using these bedside laboratory techniques; and judge appropriate situations for utilization of bedside laboratory techniques to save time or money in the timely diagnosis and treatment of patients with important infectious dermatologic diseases.

### Disclosures

#### Editors

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Viral, bacterial, and fungal infections are frequently encountered in clinical practice, resulting in numerous cutaneous manifestations. Although diagnosis of these infections has changed over time because of technological advancements, such as polymerase chain reaction, bedside diagnostic techniques still play an important role in diagnosis and management, enabling rapid and low-cost diagnosis and implementation of appropriate therapies. This 2-part article will review both common and infrequent uses of bedside diagnostic techniques that dermatologists can incorporate into daily practice. This article examines the utility of bedside tests for the diagnosis of viral, bacterial, and fungal infections. The second article in this series reviews the use of bedside diagnostics for parasitic and noninfectious disorders. (J Am Acad Dermatol 2017;77:197-218.)

**Key words:** acid-fast; bedside diagnosis; cytology; Gram stain; slit-skin; Ziehl–Neelsen.

**B**edside diagnostic tests and exfoliative cytology can yield rapid, reliable results that are especially helpful to confirm or exclude dermatologic diseases. Although other tests (including histopathology, polymerase chain

reaction, and culture) play an undeniably important role, dermatologists should be aware of these tests and their potential to help expedite diagnosis in the clinic, on the inpatient wards with complex and critically ill patients, and in resource-limited settings

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**Abbreviations used:**

CBE:	chlorazol black E stain
H&E:	hematoxylin–eosin
HFMD:	hand-foot-mouth disease
HSV:	herpes simplex virus
KOH:	potassium hydroxide
MC:	molluscum contagiosum
PCR:	polymerase chain reaction
SJS:	Stevens–Johnson syndrome
SSSS:	staphylococcal scalded-skin syndrome
TEN:	toxic epidermal necrolysis
VZV:	varicella zoster virus

where other tests are unavailable. The focus of this 2-part continuing medical education series is the use of bedside diagnostic tests for rapid diagnosis of infectious and noninfectious disorders.

## VIRAL INFECTIONS

### Tzanck smear

#### Key points

- **Tzanck smear is an inexpensive, rapid, simple, noninvasive technique that is useful for diagnosing viral and bacterial infections and many inflammatory disorders**
- **A variety of stains are commercially available**

The Tzanck smear was initially introduced by Arnault Tzanck in 1947 for the cytologic examination of vesicular lesions to distinguish between blistering disorders.<sup>1</sup> Since that time, multiple uses have been described, including many in dermatology. As with other techniques, the utility of the tool is dependent on the user's experience.

The Tzanck smear is a simple, relatively noninvasive, rapid, inexpensive test that can be performed easily on multiple sites, including the mucosa.<sup>2–5</sup> For herpetic and other lesions, an early vesicular lesion is preferred for highest diagnostic yield.<sup>6</sup> The desired area is cleaned, the overlying crust or vesicle roof is incised and folded back, the base of the lesion is scraped with a no. 15 scalpel, and the contents are smeared thinly onto a glass slide (*Supplemental Video 1*, available at <http://www.jaad.org>). Specimens are air-dried and should be stained shortly after preparation to avoid cellular swelling and loss of nuclear detail. Depending on the stain used, fixation occurs either with alcohol (which is often incorporated into stains for self-fixing of the specimen) or heat. Stains used include May-Grunwald-Giemsa, Wright–Giemsa, and various modifications of these. These stains typically contain a combination of methylene blue, eosin, and Azure B.<sup>2–5</sup> Numerous stains are commercially available as kits (for example Quik-Dip [Mercedes Medical,

Sarasota, FL], Wright-Giemsa [Sigma-Aldrich, St. Louis, MO], Hemacolor [Millipore Sigma, Billerica, MA], or Diff-Quik [Microptic, Barcelona, Spain]). Different stains result in variable coloring, but the nuclear features are the same. Evaluation of nuclear detail often requires ×20, ×40, or ×100 (oil-immersion) magnification.

### Herpetic infections

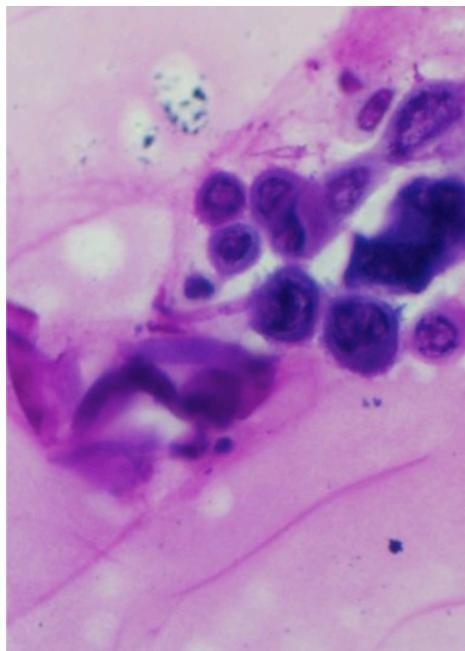
#### Key points

- **Tzanck smear is most sensitive and specific when performed on early vesicular or pustular lesions**
- **Tzanck smear cannot differentiate between herpes simplex viruses 1 and 2 and varicella zoster virus**
- **Key cytologic features of herpetic infection include multinucleate keratinocytes, acantholysis, keratinocyte ballooning, and nuclear margination**

Herpes simplex viruses 1 and 2 (HSV1/2) and varicella zoster virus (VZV or HHV3) are exceedingly common viral infections worldwide. The characteristic clinical appearance of grouped vesicles on an erythematous base involving the orolabial or genital mucosa may not require additional confirmatory testing for HSV 1/2. However, atypical presentations can be a source of diagnostic confusion, especially in immunocompromised patients. Rapid confirmation of infection enables earlier treatment, institution of infection control measures, and avoidance of complications.

Several studies have shown that dermatologists can accurately and reliably diagnose herpetic infection using the Tzanck smear after proper training.<sup>7–9</sup> Diagnosis of herpetic infection depends upon visualization of the characteristic cytologic features. These features include “ballooning” of keratinocytes to sizes as great as 80 μm, multinucleation, and acantholysis. Nuclear changes include enlarged nuclei, peripheral margination of chromatin, nuclear molding, and blurry staining with “ground glass” cytoplasm. Cowdry type A bodies, which are intranuclear inclusion bodies surrounded by a subtle clear halo, are characteristic but may be difficult to find.<sup>6,10,11</sup> (*Fig 1*). Tzanck smears cannot distinguish between HSV1/2 and VZV, and they are less sensitive for old or crusted lesions.<sup>6,11,12</sup>

Several published studies have compared Tzanck to other techniques, including viral culture, polymerase chain reaction (PCR), direct fluorescent antibody, biopsy with cytologic examination and immunohistochemical staining, and electron microscopy.<sup>7,8,12–17</sup> Reported sensitivity ranges from



**Fig 1.** Tzanck smear of a herpetic infection shows multinucleation, margination of the chromatin, and nuclear molding.

40% to 76.9% and specificity up to 100% in comparative studies, depending on the age and stage of the infection and user experience. Tzanck smear of 1- to 3-day-old vesicles has a sensitivity of 78.7% to 100%, compared to 27% to 59.7% for older, eroded, or crusted lesions.<sup>11,12</sup> Tzanck smear performs better than direct fluorescent antibody testing (sensitivity, 50-85%; specificity, 99-100%) and viral culture (sensitivity, 52-93%; specificity, 100%) but is not as sensitive or specific as PCR.<sup>7,11-13,15-17</sup> The sensitivity of PCR is 92.4% to 100% for fresh lesions and 80.7% for older lesions (even up to 1 month), with a specificity of 83.7% to 98%.<sup>8,12</sup> The cost of PCR varies but averages approximately \$80 per specimen, compared to reimbursement for provider interpreted Tzanck smear, for which Medicare pays <\$10.

### Other viral infections

#### Key points

- **The microscopic appearance of molluscum contagiosum is characterized by pathognomonic 30- to 35- $\mu\text{m}$  virally transformed cells called Henderson-Patterson bodies**
- **Cryotherapy and dermoscopy also can help increase diagnostic yield**
- **Characteristic cytologic changes of Orf include Guarnieri bodies and acantholytic cells; in hand-foot-mouth disease, syncytial bodies are typical**

### Molluscum contagiosum

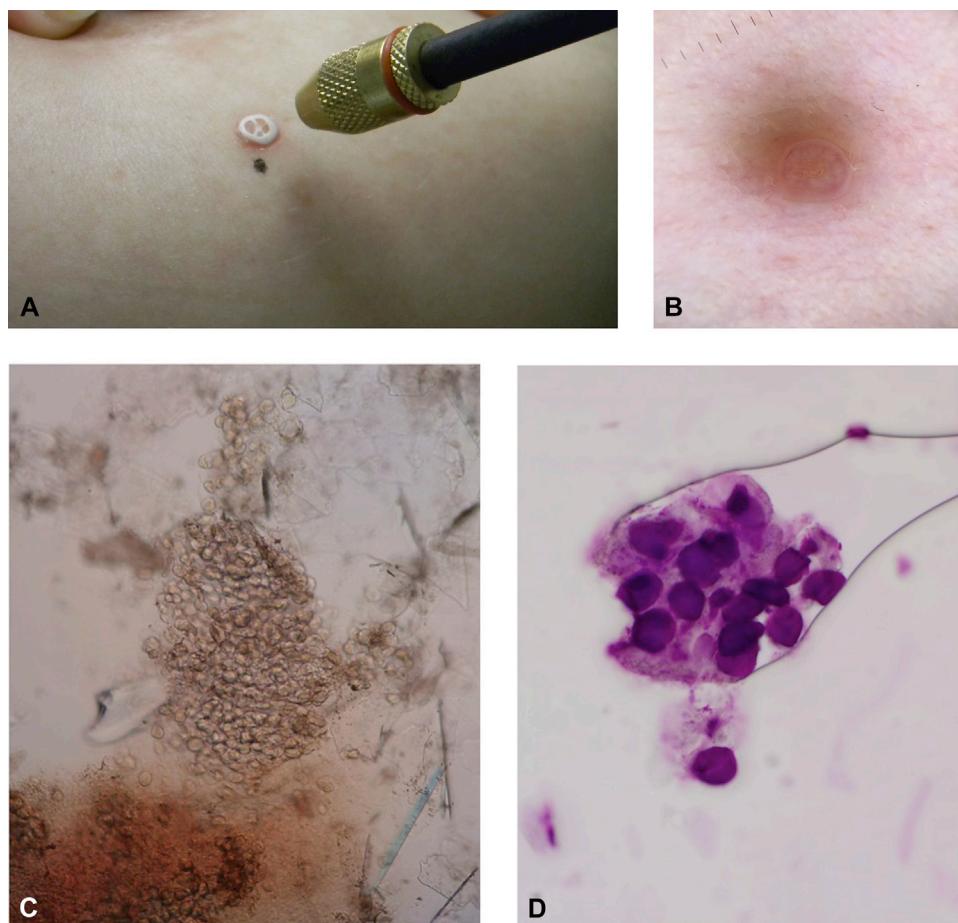
Molluscum contagiosum (MC) is a common childhood viral infection that presents with firm, umbilicated papules. Single or few lesions can also be seen in adults. Widespread, extensive, or "giant" molluscum occurring in immunodeficient states, such as HIV infection, posttransplant, and iatrogenic immunosuppression can be more difficult to diagnose.<sup>18</sup> The differential diagnosis of diffuse umbilicated papules in an immunosuppressed patient also includes cryptococcosis, histoplasmosis, penicilliosis, paracoccidioidomycosis, coccidioidomycosis, and herpetic infection.<sup>18</sup> For less clinically obvious lesions, light cryotherapy to a lesion can accentuate the lesion's central umbilication, with clear change compared to background skin (Fig 2, A). Dermoscopy reveals white or yellow lobules surrounded by a crown of blood vessels that do not cross the centers of the lobules<sup>19,20</sup> (Fig 2, B).

Both Tzanck smear and potassium hydroxide (KOH) preparations also can be used to diagnose MC. To prepare the slide, the central part of the lesion is scraped using a no. 15 scalpel or 3-mm curette, then applied in a thin layer to a glass slide. Either KOH or Tzanck stain is applied. The virally transformed keratinocytes have large inclusions (30-35  $\mu\text{m}$ ), which are ovoid with homogenous basophilic or slightly eosinophilic staining on Tzanck smear (Fig 2, C and D). These Henderson-Patterson, or molluscum bodies, are pathognomonic for MC.

### Other viral infections

Orf (ecthyma contagiosum) and milker's nodules are parapox viral infections that arise mainly in farmers or meat industry workers and result in localized skin infections that resolve spontaneously. Tzanck smear of a lesion reveals eosinophilic inclusions, Guarnieri bodies, acantholysis, necrotic cells, and leukocytes.<sup>11</sup>

Hand-foot-mouth disease (HFMD) is a common, highly infectious, self-limited disease caused by enteroviruses, most commonly coxsackie A16 and enterovirus 71. Atypical, severe presentations have been reported secondary to coxsackie A6.<sup>21</sup> The diagnosis can be made clinically, histologically, or by PCR. Tzanck smear can help differentiate HFMD from herpetic infection. In HFMD, affected nuclei are similarly sized, only slightly enlarged, and are grouped together in a large mass, whereas in herpetic infection, nuclei are much more enlarged, with characteristic changes in nuclear features.<sup>11,22</sup> Key microscopic features of viral infections are listed in Table I.



**Fig 2.** *Molluscum contagiosum* bedside diagnostics. **A**, Cryotherapy shows central umbilication. **B**, Dermoscopy demonstrates white or yellow lobules surrounded by a crown of blood vessels. **C**, Potassium hydroxide preparation demonstrates monomorphic ovoid cells that have been virally transformed. **D**, Tzanck preparation highlights the monotonous, homogenous pigmentation with pink or basophilic cytoplasm. (Photograph in **A** courtesy of Brian Swick, MD.)

**Table I.** Key features of viral infections using bedside diagnostics

Disease	Technique and stain	Microscopic appearance
Herpetic infections (herpes simplex virus or varicella zoster virus)	Tzanck smear performed on base of lesion	Multinucleate keratinocytes, acantholysis, keratinocyte ballooning, and nuclear margination
Molluscum contagiosum	Tzanck or potassium hydroxide	Monomorphic, cuboidal, pathognomonic 30-35 $\mu\text{m}$ virally transformed cells
Hand-foot-mouth disease	Tzanck on base of the lesion	Syncytial bodies: nuclei are similarly sized, only slightly enlarged, and can be grouped together in a larger mass
Orf and milker's nodules	Tzanck on base of lesion	Eosinophilic inclusions, Guarnieri bodies, acantholysis, necrotic cells, and leukocytes

## BACTERIAL INFECTIONS

### Gram stain

#### Key point

- **Gram stain enables rapid confirmation of the presence of bacteria and helps guide early empiric therapy for Gram-positive or -negative organisms**

In 1884, Hans Christian Gram first described the technique for bacterial staining that later would bear his name.<sup>23</sup> This method has since been slightly modified, but the basic principles remain the same. Ionic interactions are responsible for the coloration of bacteria.<sup>24-26</sup> Gram-positive organisms are stained purple by crystal violet, whereas Gram-negative

organisms are stained pink by the safranin counterstain. Atypical mycobacterial organisms can sometimes stain slightly positive or equivocally.

The procedure involves spreading a thin layer of the substance to be identified onto a slide and fixing it either by air-drying or heat. Alcohol can be used to aid fixation. Crystal violet is applied and then rinsed with water or dilute iodine after 30 to 60 seconds. Next, Gram iodine is applied, and the specimen is rinsed again with water after 30 to 60 seconds. Decolorizer, such as acetone or alcohol, is applied until the runoff is clear. Finally, safranin is applied as a counterstain for an additional 30 to 60 seconds. The slide is rinsed and left to dry.<sup>27</sup>

## GRAM-POSITIVE AND -NEGATIVE BACTERIAL INFECTIONS

### Folliculitis

#### Key points

- **Folliculitis is a common inflammation or infection of the hair follicle that can be caused by several bacterial and nonbacterial organisms**
- **Gram stain can provide initial diagnostic clues to the causative organism**

Although folliculitis can be caused by physical or chemical injury, most cases are caused by bacterial, fungal, viral, and parasitic infections. Factors that increase the risk of folliculitis include immunosuppression, chronic kidney disease, diabetes mellitus, poor hygiene, and chronic wounds.<sup>28</sup> *Staphylococcus aureus*, a Gram-positive organism, is the most common cause of folliculitis.<sup>29</sup> Gram-negative folliculitis can occur because of *Pseudomonas*, *Proteus*, *Klebsiella*, *Escherichia*, and *Enterobacter* and can be a complication of chronic antibiotic treatment in acne.<sup>30-32</sup> Gram-negative folliculitis can also occur after exposure to contaminated warm water, most commonly from a spa pool, Jacuzzi, or swimming pool.

In addition to bacterial causes of folliculitis, fungal and noninfectious etiologies exist. These are discussed below and in the second article in this series.

Gram stains are the bedside diagnostic test of choice for folliculitis, although KOH preps of pustular lesions can help rule out fungal etiologies. Initial identification of the causative microbe (usually Gram-positive or -negative cocci or rods) involves Gram stain followed by culture. Gram stain results enable antibiotic therapy to be tailored appropriately pending the final culture results. Tzanck smear also can be useful to

help identify noninfectious causes of folliculitis (discussed in more detail in the second article in this series).<sup>28,33,34</sup>

## GRAM-POSITIVE INFECTIONS

### Key points

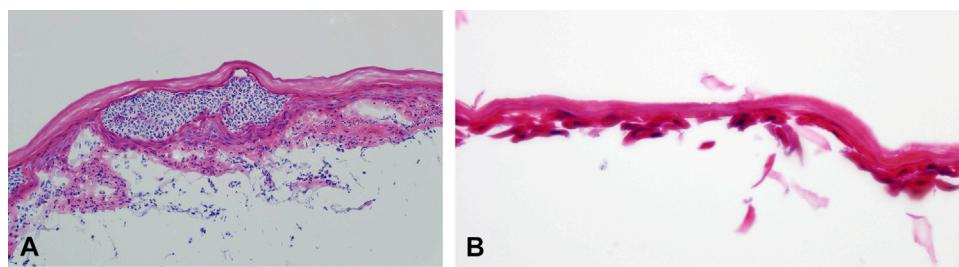
- **Staphylococcal infections can be diagnosed using Gram stain**
- **Frozen section examination can help differentiate staphylococcal scalded-skin syndrome from toxic epidermal necrolysis**

## Impetigo and staphylococcal scalded-skin syndrome

Impetigo is a common superficial skin infection characterized by pustules and honey-colored crusted erosions.<sup>35</sup> Causative organisms of nonbullos impetigo include *Streptococcus* and *Staphylococcus* spp. Bullous impetigo, which presents as small vesicles that evolve into flaccid bullae with clear then purulent fluid, is primarily caused by exfoliative toxin A- and B-producing *S aureus*.<sup>36,37</sup>

A diagnosis of impetigo is based on the clinical presentation, Gram stain, and culture. The Infectious Diseases Society of America guidelines advocate using Gram stain for identification of the causal organism, especially for atypical cases.<sup>38</sup> In addition, Tzanck smear of an erosion or base of a bullous lesion may be used to distinguish bullous impetigo from other clinical mimics, including pemphigus and herpes simplex infection. Typical findings of bullous impetigo include dyskeratotic acantholytic cells with occasional cocci in clusters. Typical findings of pemphigus are discussed in the next article in this series. The sensitivity and specificity of Tzanck preparations for diagnosing impetigo have been reported to be as high as 92% and 100%, respectively.<sup>11</sup>

Staphylococcal scalded-skin syndrome (SSSS), the systemic form of bullous impetigo, is caused by exfoliative toxins A and B, which cleave desmoglein-1 at the epidermal granular layer. SSSS occurs mostly in neonates and children <5 years of age and presents with flexural then generalized erythema and desquamation.<sup>39</sup> Tzanck preparation can help rapidly differentiate SSSS from Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).<sup>39</sup> Tzanck smear reveals broad, superficial, acantholytic keratinocytes, as in bullous impetigo, but typically no bacteria and minimal inflammation are seen.<sup>11,40</sup> This appearance differentiates SSSS from SJS/TEN, in which necrotic, cuboidal basal keratinocytes are diagnostic.<sup>41</sup> Another rapid diagnostic test or alternative biopsy technique that can be performed in lieu of obtaining a biopsy specimen is the “jelly



**Fig 3.** Jelly roll preparation can help differentiate infections. **A**, Bullous impetigo has an intraepidermal split with acantholysis, neutrophils, and cocci forms. **B**, Staphylococcal scalded-skin syndrome demonstrates acantholysis of viable cells with a split in the granular layer. These are differentiated from toxic epidermal necrolysis, which has full-thickness necrosis. (Photograph in **B** courtesy of Brian Swick, MD.)

roll” technique, which involves peeling off a blister roof or scraping it with a blade, wrapping the sample around a cotton swab, placing the sample in sterile saline, and then processing the section in a cryostat, followed by hematoxylin–eosin (H&E) staining. Histopathology is similar to that seen using Tzanck smear (Fig 3) but also shows the level of the split: intraepidermal at the granular layer for SSSS and subepidermal caused by full epidermal necrosis in SJS/TEN.

### Botryomycosis

Botryomycosis is an uncommon chronic skin infection due to masses of bacteria causing subcutaneous nodules that can progress to ulcers or draining sinuses.<sup>42,43</sup> Risk factors include HIV, alcoholism, diabetes, and other immunocompromised states. Trauma, surgery, or foreign body–penetrating injuries may precede infection. Common organisms include *S aureus* and *Pseudomonas aeruginosa*. Other pathogens include other Gram-positive and -negative organisms and anaerobic bacteria; it is rare for multiple organisms to infect a single patient simultaneously.<sup>44,45</sup> The differential diagnosis includes actinomycosis and mycetoma (see other sections).<sup>45</sup>

Microscopic examination of “grains,” clumps of bacteria eliminated through the skin, or purulent material can assist in diagnosis. Gram stain can be performed on either the crushed grains or purulent material and may demonstrate either Gram-positive or -negative bacteria. In addition, Tzanck smear and staining of the crushed grain material will demonstrate suppurative inflammation with neutrophils and histiocytes. Occasionally, islands of radiating amorphous, eosinophilic material will be visible around clumps of bacteria, demonstrating the Splendore–Hoepli phenomenon.<sup>46,47</sup>

## GRAM-NEGATIVE BACTERIAL INFECTIONS

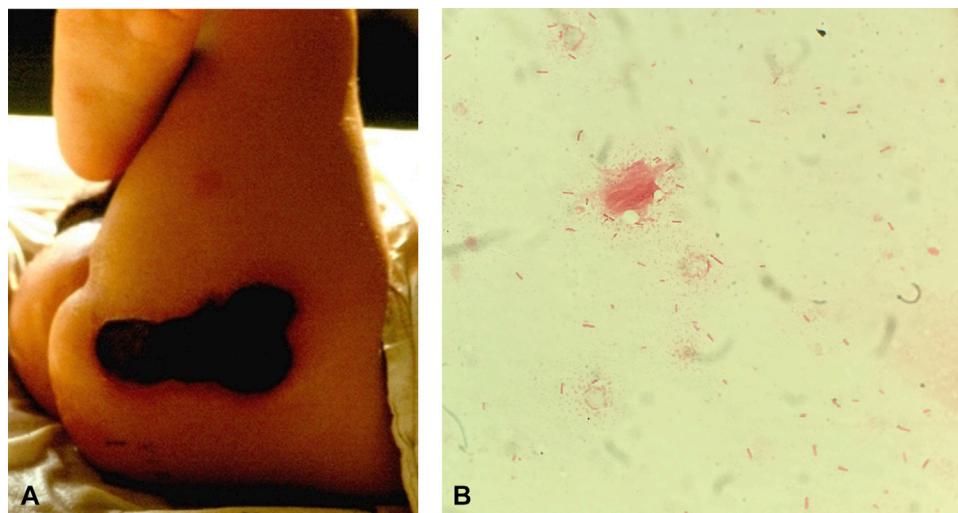
### Key points

- **Ecthyma gangrenosum and meningococcemia are life-threatening conditions caused by Gram-negative bacteria**
- **Rapid diagnosis is possible using bedside touch prep and Gram stain**

### Ecthyma gangrenosum

Ecthyma gangrenosum, which presents as necrotic, purpuric, and occasionally bullous skin lesions in patients with neutropenia or other forms of immunosuppression, is a life-threatening condition classically associated with *P aeruginosa* bacteremia<sup>48–50</sup> (Fig 4, A). Ecthyma gangrenosum can also occur in the absence of bacteremia because of primary inoculation<sup>51</sup> and may secondarily disseminate. Besides *P aeruginosa*, localized or disseminated infection with other Gram-negative bacteria, Gram-positive bacteria, angioinvasive fungi, and viruses can produce similar skin lesions.<sup>52–54</sup>

A diagnosis typically requires obtaining a biopsy specimen and staining with H&E and bacterial, fungal, and acid-fast tissue cultures. Unfortunately, the results of histopathologic examination and culture may not be readily available and can cause a delay in diagnosis and treatment. Touch preparations have been shown to be useful in patients presenting with ecthyma gangrenosum–like lesions and can help guide potentially life-saving empiric treatment. To perform a touch preparation, the underside of a skin punch biopsy specimen is smeared onto 2 glass slides, the first for Gram stain, H&E, or modified Giemsa–Wright stain and the second for KOH preparation with chlorazol black as a counterstain, if available. To avoid contamination, do not use a specimen that will be submitted for tissue culture. Other techniques that



**Fig 4.** Ecthyma gangrenosum. **A**, Clinical appearance with necrotic epidermis and gray to violaceous border, often on the buttocks or upper thighs. **B**, Touch preparation with Gram stain demonstrates numerous Gram-negative rods. (Oil immersion; original magnification: **B**,  $\times 100$ .)

may increase the yield of a touch preparation include smearing the fluid from a hemorrhagic or purulent blister, as well as scraping the edges of the skin defect made from the biopsy specimen with a no. 15 blade and smearing the residue on glass slides. Hemorrhagic necrosis can indicate *P aeruginosa* infection, while diffuse inflammatory cells are more often associated with Gram-positive infections.<sup>55</sup> Bacterial organisms may be visible, and Gram stain can help identify the causative agent (Fig 4, B). A KOH preparation may also reveal fungal organisms, enabling rapid adjustment of therapy (see the section on angioinvasive fungal section below).

### Meningococcemia

*Neisseria meningitidis* is a Gram-negative diplococcus that can cause life-threatening meningitis and meningococcemia. Meningococcal infection can present as purpura fulminans, characterized by noninflammatory retiform purpura, palpable purpuric papules and nodules, or petechial rash, coagulopathy, and altered mental status.<sup>56,57</sup> Early recognition is crucial to reduce mortality and control the disease.

While cerebrospinal fluid (CSF) culture is the criterion standard for diagnosis, bedside Gram staining of representative skin lesions is minimally invasive and can more rapidly confirm the diagnosis.<sup>58,59</sup> One study found that Gram staining of CSF provided diagnostic data in only 4 of 18 patients, whereas Gram stains of skin lesions of those same patients were diagnostic in 12 (86%) of the 14 cases not identified by CSF examination.<sup>59</sup> The results of a skin biopsy procedure may also be

positive even after the CSF has cleared. In meningococcemia, rapid diagnosis can be achieved through either Gram stain of a hemorrhagic vesicle, papule, or macule aspirate or by performing a touch preparation of a skin biopsy specimen and smearing the collected material onto a glass slide. Alternatively, a no. 15 scalpel can be used to scrape the base of a purpuric or hemorrhagic lesion. Gram staining is most likely to be positive when the patient is bacteremic. While a negative result does not rule out meningococcal infection, a positive test revealing Gram-negative diplococci can lead to immediate life-saving intervention.

## ACID-FAST BACTERIAL INFECTIONS

### Acid-fast stains

#### Key point

- **Ziehl–Nielsen and intensified Kinyoun stains are useful for staining acid-fast bacteria**

Before the development of Ziehl–Nielsen stain, visualization of acid-fast bacteria (AFB) was less than ideal because of the presence of mycolic acid inhibiting entry of colorant into the cells. Ziehl–Nielsen stain uses heat to incorporate the stain into cell walls. More recently, other stains have been developed that allow for detection of these bacteria, some of which have advantages over traditional stains.<sup>60</sup>

To prepare Ziehl–Nielsen or Kinyoun stain, a small amount of material approximately 20 mm  $\times$  10 mm is placed in the center of a slide, then dried and fixed, either with or without heat. A small sample works best,

because clumps of organisms make it difficult to observe the characteristics of individual cells. The sample should be placed in the central area of the slide to ensure an even stain. For Ziehl–Nielsen, first a piece of absorbent paper to fit the slide is placed over the sample and saturated with the carbolfuchsin stain. Next, the underside of the slide is heated until steam rises but does not boil. The preparation must be kept moist with stain and steaming for 5 minutes, repeating the heating as needed. The slide is rinsed and then decolorized using 3% hydrochloric acid alcohol (3% hydrochloric acid in 95% alcohol) for 2 to 5 minutes, or until the runoff is clear. A methylene blue or malachite green counterstain is applied for 5 minutes and then rinsed.

Kinyoun stain uses the Kinyoun carbolfuchsin stain initially and does not require additional heat. It is decolorized after 3 minutes with 3% hydrochloric acid alcohol, then rinsed with water and decolorized again. A methylene blue counterstain is applied as with the Ziehl–Nielsen stain.<sup>27</sup> AFB appear red with both stains, and other bacteria stain blue or green depending on the counter stain.

## MYCOBACTERIAL INFECTIONS

### Cutaneous tuberculosis

#### Key points

- ***Mycobacterium tuberculosis* is the most common cause of cutaneous tuberculosis presenting in the skin**
- **Cytology can assist in the identification of acid-fast bacteria**

Cutaneous tuberculosis (TB) is most commonly caused by *Mycobacterium tuberculosis*. Additional etiologic agents include *Mycobacterium bovis* and *Mycobacterium canetti*.<sup>61,62</sup> Cutaneous TB is uncommon but can be seen most frequently in developing countries where TB infection is prevalent.<sup>63,64</sup> Although there are several clinical manifestations of cutaneous TB, scrofuloderma and lupus vulgaris are 2 of the more important forms of cutaneous tuberculosis that lend themselves to bedside diagnosis. Both forms represent active mycobacterial infection in the skin rather than a hypersensitivity reaction to indolent infection. In scrofuloderma, skin lesions are caused by direct extension of underlying TB from lymph nodes, bone, or joints, while lupus vulgaris is a chronic, progressive form of cutaneous TB occurring in patients with a moderate or high degree of immunity.

While obtaining a biopsy specimen and assessing tissue culture are typically performed for cutaneous TB, fine-needle aspiration (FNA) can be used to obtain samples for cytology and can be more

sensitive than histology.<sup>65</sup> Scrofuloderma is more likely than other forms of cutaneous TB to have diagnostic findings on cytology after Ziehl–Neelsen or other AFB staining. Typically, scrofuloderma shows caseating necrosis with or without granulomas.<sup>65</sup> AFB are more likely to be seen when caseating necrosis is present.<sup>65</sup>

As with scrofuloderma, lupus vulgaris is typically diagnosed using culture and histopathology despite the lack of tubercle bacilli in histologic samples.<sup>61</sup> Cytology of FNA of lupus vulgaris skin lesions only rarely has visible AFB organisms and more commonly reveals epithelioid granulomas without caseous necrosis. Nonetheless, cytology samples are more likely to be AFB-positive than traditional histology.<sup>65</sup>

## Leprosy

### Key points

- **Slit-skin smear is useful for diagnosing leprosy**
- **Response to treatment can be monitored with this technique**

**Slit-skin smear.** Leprosy is caused by *Mycobacterium leprae*, an obligate intracytoplasmic parasite of macrophages and Schwann cells that cannot be cultured. The clinical presentation is variable, which can make diagnosis and response to treatment difficult. While PCR is sensitive, it remains expensive and is unavailable in many parts of the world. Slit-skin smear is effective as a bedside diagnostic tool and is used extensively in leprosy-endemic areas.<sup>66</sup>

In the slit-skin smear procedure, a sample is taken from a small incision in the skin. To ensure that an adequate sample is taken, incisions are made in multiple locations, typically the earlobes, elbows, and knees. Samples can also be taken from active lesions.<sup>67</sup> Target sites are first cleaned with alcohol or acetone. The skin is pinched, and a small linear incision is made in the skin. No local anesthesia is typically necessary. Before withdrawing the blade, the wound is scraped to obtain a 5- to 7-mm long sample of dermis and fluid, which is smeared on a slide.<sup>68</sup> The smear is made in a linear or circular manner on the slide, no larger than a pencil eraser (5-7 mm), beginning peripherally and ending in the center, leaving a central “button” (2-4 mm) that can be easily focused upon with the microscope (Supplemental Video 2, available at <http://www.jaad.org>). After drying, slides are placed on a staining rack and flooded with 10% formalin for 15 minutes for fixation. Ziehl–Neelsen or Kinyoun stains are performed as above. Slides should be air-dried rather



**Fig 5.** **A**, Patients on the tuberculoid pole of leprosy have few organisms and a high immune response with few hypopigmented anesthetic lesions compared to those on the lepromatous pole (**B**), who have a low immune response and numerous organisms with indurated plaques. **C**, A slit-skin smear performed on a patient with lepromatous leprosy demonstrates numerous acid-fast bacilli after staining. (Oil immersion; original magnification: **C**,  $\times 100$ .)

than heat-fixed. Repeat smears should be obtained from multiple areas to increase the diagnostic yield. Positive smears are defined by the presence of acid-fast (red) bacterial rods (Fig 5).

Slit-skin smear allows for an estimation of the bacterial index, measuring the number of AFB present. This value is an estimate of the bacterial load and allows for monitoring of disease progression and response to treatment.<sup>68</sup> In multibacillary leprosy (>5 lesions), the sensitivity of slit-skin smear is 59.8%, compared to 85.9% for PCR. In paucibacillary cases, the difference is more substantial (1.8% vs 75.4%, respectively). While cases of lepromatous or histoid leprosy can be diagnosed with 100% sensitivity by either slit-skin or PCR, there is definite increased diagnostic value to PCR in diagnostically challenging cases ( $P < .0001$ ).<sup>66</sup> Still, in cases with high pretest probability and in places where the cost and availability of PCR are an issue, slit-skin smear is a rapid and useful bedside diagnostic test.

#### Buruli ulcer

##### Key points

- Buruli ulcer is caused by *Mycobacterium ulcerans*
- Samples from edematous areas can help improve the diagnostic yield

Buruli ulcer, caused by *M. ulcerans*, is the third most common mycobacterial disease after tuberculosis and leprosy and is frequently observed in Africa and other humid, tropical regions.<sup>69</sup> This condition typically begins with a painless nodule that slowly breaks down to form an ulcer with extensively undermined edges, the result of digestion of the skin and soft tissue by a macrolide toxin (mycolactone). Cases are diagnosed according

to clinical appearance. Microscopic examination of swabs from ulcers or smears from biopsy specimens using Ziehl–Neelsen stain is a first-line test in many endemic countries because of its low cost and rapid results. Sensitivity varies with the clinical lesion examined, ranging from about 40% in the ulcerative form to 60% in the nodular and 80% in the edematous form.<sup>70</sup> Two samples are recommended to confirm the diagnosis.<sup>71</sup> The swabs are more likely to be positive if taken from beneath the undermined edges of ulcers compared to the ulcer center.<sup>71</sup> The sensitivity of PCR and histopathology does not vary with the clinical form of the disease and is as high as 98% and 90%, respectively.<sup>70–72</sup> In many endemic areas, however, there is no access to either confirmatory test.

Table II provides a summary of key diagnostic features for these infections.

## FUNGAL INFECTIONS

##### Key points

- Direct microscopy using KOH is a simple, inexpensive, and fast way to diagnose fungal infections
- The addition of other stains, including chlorazol black E and calcofluor white, may improve the diagnostic yield

Direct microscopy of fungal elements commonly uses KOH to help dissolve the background keratinocytes for enhanced visualization of hyphae or yeast forms. To achieve the highest yield from skin scrapings, identify high-yield sites, such as the leading edge of an annular lesion or pustules, if present. Before scraping, wipe the target area with alcohol to enhance control of the scale and prevent loss to the surrounding environment. A no. 15 scalpel is used to scrape the scale or pustule at a

**Table II.** Key clinical and histologic features of bacterial infections using bedside diagnostics

Disease	Technique and stain	Microscopic appearance
Folliculitis	Tzanck smear followed by Gram stain of pustule	GPC or GNR (oil immersion); eosinophils, pityrosporum
Ecthyma gangrenosum	Touch preparation or slit-skin with both rapid H&E and KOH with chlorazol stain	Hemorrhagic necrosis, GNR, histiocytes, lymphocytes, hyphae if fungal
Botryomycosis	Tzanck smear or Gram stain of lesion edge, ulcer base, or drainage	Balls of GPC or GNR
Meningococcemia	Gram stain of petechial lesions	Gram-negative diplococci
Impetigo/staphylococcal scalded-skin syndrome	Tzanck smear of bullous lesion, "jelly roll" and frozen section for H&E of blister roof; alternatively, Gram stain of purulent material	GPC in clusters or chains, neutrophils, dyskeratotic acantholytic cells; intraepidermal split
Scrofuloderma	FNA with acid-fast stain of lesion	Caseous necrosis with or without granulomas; AFB possible
Lupus vulgaris	FNA with acid-fast stain of lesion	Epithelioid granulomas with occasional necrosis; AFB possible
Leprosy	Slit-skin of earlobes, elbows, knees, and active lesions	Pink to red rods positive with AFB
Buruli ulcer	FNA or touch preparation with acid-fast stain from undermined edges of ulcers	Pink to red rods positive with AFB

AFB, Acid-fast bacilli; FNA, fine-needle aspiration; GNR, Gram-negative rod; GPC, Gram-positive cocci; H&E, hematoxylin–eosin; KOH, potassium hydroxide.

perpendicular angle, and the scale is applied to a focal area of a glass slide. One drop of KOH (10–20%) is applied, and a coverslip is added. If only KOH is used without other dissolving agents, gentle heating of the sample will accelerate the degradation of keratinocytes. One should avoid overheating the sample, because crystals will develop, precluding accurate evaluation. If the KOH contains dimethyl sulfoxide 40%, then heating is unnecessary. To enhance contrast under the microscope and improve visualization, one should reduce microscope illumination by lowering the condenser until epithelial cells are clearly visible (Fig 6). The specimen should be scanned at 4× to find cells and evaluated at 10×, 20×, or 40× magnification to identify fungal elements. If the scale is thick, it may be necessary to break up clumps of cells by gently pushing on the coverslip with the blunt end of a pen.

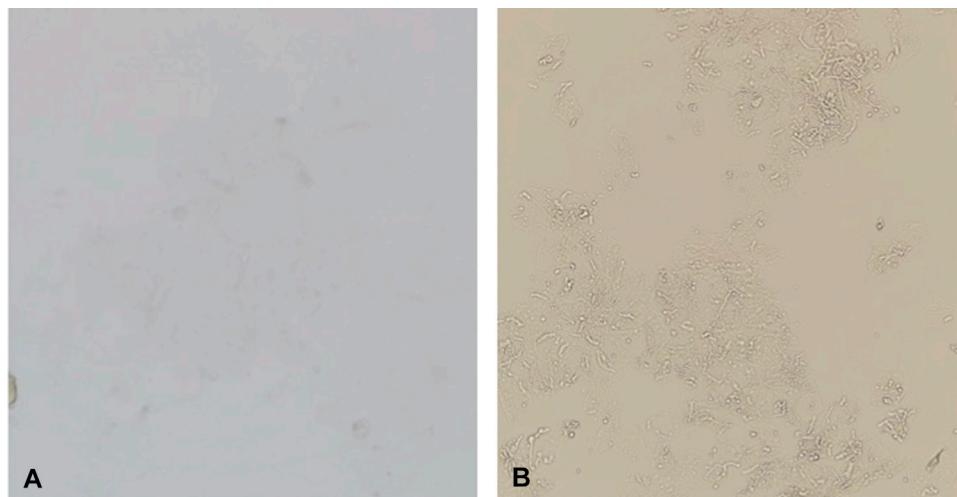
For onychomycosis, obtaining subungual debris, overlying superficial scale (superficial onychomycosis), and the most proximal portion of the nail plate affected will increase the diagnostic yield.<sup>73</sup> When evaluating hair specimens, a Wood's lamp can help identify ectothrix organisms, in which case fluorescing hair should be epilated for evaluation. Scale should be obtained using a no. 15 scalpel. Alternate methods for obtaining scale include using a disposable toothbrush, culturette, or cotton tip. These methods may be safer, easier, and met with less resistance than using a scalpel blade in pediatric populations.<sup>74,75</sup>

Additional staining techniques exist that may be helpful for learners or inexperienced microscopists. Counterstain solutions containing KOH can help provide contrast between the hyphae and spores and background material.<sup>73</sup> Chlorazol black E (CBE) is a chitin-specific stain that turns fungal elements green to turquoise in color and is commercially available with KOH and dimethyl sulfoxide.<sup>76,77</sup> Swartz–Lamkins fungal stain combines KOH and Parker blue ink and stains hyphae blue against the background.<sup>77</sup> Calcofluor white binds to cellulose and chitin and fluoresces when exposed to ultraviolet light; this requires a fluorescent microscope, making it difficult to use in the clinical setting (Fig 7). Alternatively, a twin Wood's lamp light (365 nm) can be placed behind the microscope and shined onto the slide surface. When preparing a sample for evaluation, 1 drop of KOH and 1 drop of calcofluor white are added to the specimen.<sup>78</sup>

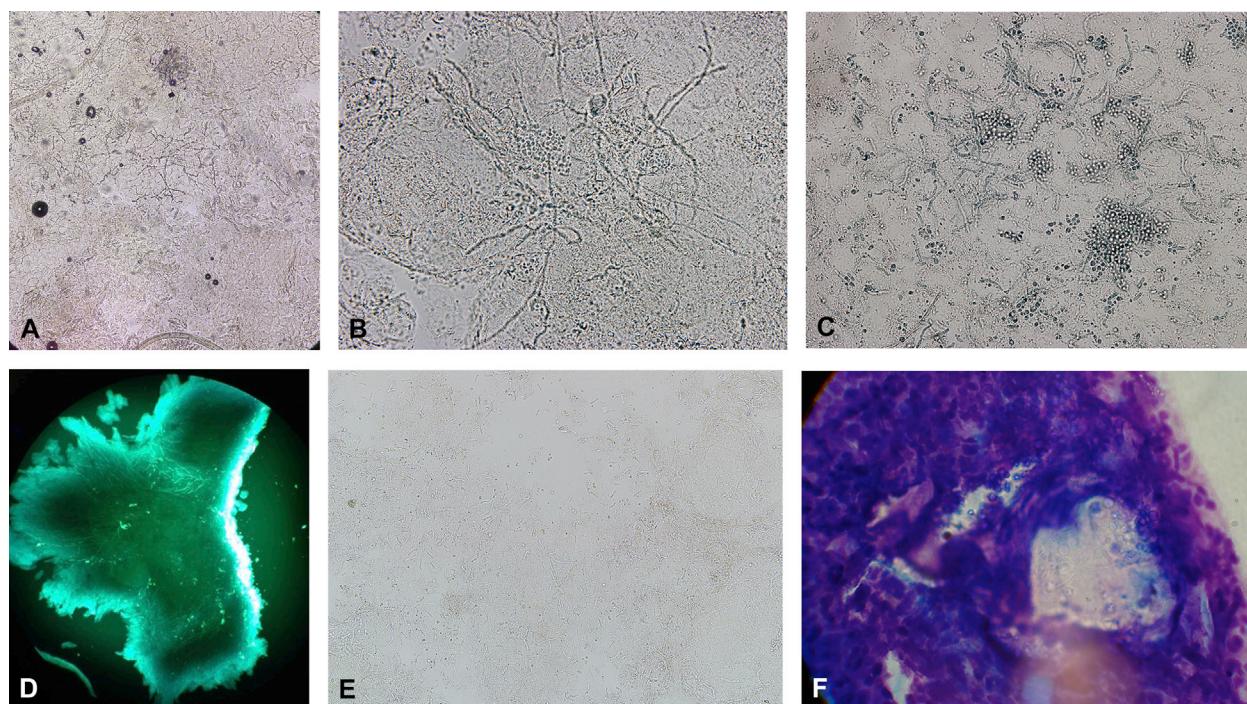
### Superficial mycoses

#### Key points

- Dermatophyte infection can be readily diagnosed using direct microscopy with KOH or CBE
- Candidiasis, pityrosporum versicolor, and pityrosporum folliculitis can be distinguished based upon morphologic appearance



**Fig 6.** Condenser location matters for evaluation. For increased contrast for dermatophytes in potassium hydroxide preparations, the microscope condenser should lowered. When the condenser is up, epithelial cells and fungus will not be visualized (**A**); the same slide can demonstrate organisms with proper condenser position (**B**).



**Fig 7.** Superficial fungal infections can be easily detected using bedside diagnostics. **A**, Dermatophytes are identified by hyphal forms extending past cell walls on potassium hydroxide examination. **B**, Candidal infection can demonstrate spores or pseudohyphae. **C**, Chlorazol black E will cause the fungal forms to be turquoise in color compared to the background. In this case of tinea versicolor, there are short hyphal elements and spores. **D**, Calcofluor white will fluoresce the fungal elements in onychomycosis, making it easier to identify organisms. **E**, Potassium hydroxide preparation of tinea versicolor demonstrates short hyphal elements and spores. **F**, Pityrosporum folliculitis can demonstrate budding yeasts within a pustule or hair shaft. (Photograph in **B** courtesy of Brian Swick, MD. **F**, Potassium hydroxide examination; original magnifications: **A**,  $\times 10$ ; **B**,  $\times 20$ ; **D**,  $\times 4$ ; **E**,  $\times 10$ ; **F**,  $\times 20$ .)

Superficial mycotic infections are caused by dermatophytes, *Candida*, and *Pityrosporum* (*Malassezia* spp.). These are common infections that result in clinically diverse presentations, including tinea capitis, tinea barbae, tinea corporis, tinea pedis, tinea cruris, tinea unguium, tinea versicolor, pityrosporum folliculitis, cutaneous candidiasis, intertrigo, nail unit infection (paronychia), vulvovaginitis, balanitis, thrush, and angular cheilitis. Risk factors for developing superficial mycoses include a history of diabetes mellitus, immunosuppression, antecedent antibiotics, and corticosteroid use.<sup>75</sup> History and clinical appearance may be highly suggestive, but confirmation of diagnosis is important because the differential diagnosis for these infections is broad and includes noninfectious etiologies. The presence of branching, septate hyphae extending across keratinocyte cell walls, within the nail plate, or within the hair shaft is diagnostic of dermatophyte infection<sup>74-76,78</sup> (Fig 7, A-C). Common mimickers include cell borders or membranes that have not dissolved, as well as air bubbles that are small, variably sized, round, and lack budding. Pseudohyphae and yeast forms are seen in candidal infection (Fig 7, B).

Tinea versicolor often can be diagnosed clinically based upon white, pink, salmon, red, tan, or brown patches with slight scale that can be accentuated with a slide, fingernail, or lateral pressure adjacent to the patches.<sup>79,80</sup> Direct microscopy using KOH is the simplest and least expensive way to diagnose dermatophyte infections either with a blade, microscope slide, or with the application of a piece of tape to remove superficial scale. Direct microscopy of tinea versicolor often demonstrates florid yeast forms and short hyphae ("spaghetti and meatballs" or "penne and peas"; Fig 7, E).

Published studies have evaluated the sensitivity and specificity of KOH compared to CBE, calcofluor white, fungal culture, PCR, and periodic acid-Schiff on formalin-fixed tissue with varying results depending on the specimen (eg, onychomycosis compared to skin scrapings) and study.<sup>73,75,76,78,81-87</sup> For superficial skin infections, such as tinea corporis, tinea pedis, and tinea versicolor, KOH, CBE, and calcofluor white have similar results.<sup>78,86</sup> Direct comparisons of KOH and calcofluor white demonstrate similar sensitivities (88% and 92%), specificities (both 95%), positive predictive values (73% and 74%), and negative predictive values (98% and 99%), respectively.<sup>78</sup> For onychomycosis, direct identification with KOH has published sensitivities ranging from 80% to

91%, with false negative reports ranging from 5% to 15%.<sup>75,82,85</sup> Periodic acid-Schiff of the nail plate is reported to be the most sensitive (92-98.8%), with CBE also highly sensitive (94.3%). Fungal culture has an overall lower sensitivity (23.8-79.3%).<sup>82,85,87</sup>

## SUBCUTANEOUS MYCOSES

### Key points

- Chromoblastomycosis is an infection that presents with verrucous nodules and plaques that is most common in tropical and subtropical climates and is characterized by pigmented bodies ("copper pennies") seen on direct microscopy
- Lobomycosis is endemic in rural areas of Central and South America and is characterized by keloidal plaques, which can be diagnosed by direct visualization of single or coupled budding, thick-walled spherules with a thin connection ("pop beads"); the organism cannot be cultured
- Application of vinyl adhesive tape is an alternative method of obtaining a sample suitable for direct visualization

Subcutaneous mycotic infections result from infection with slow-growing fungi affecting the dermis and subcutaneous tissue, resulting in verrucous and keloidal plaques and subcutaneous nodules (Table III). Direct visualization is essential for diagnosis of these entities, which are difficult to culture and most common in resource-limited settings.

Chromoblastomycosis is a subcutaneous fungal infection that most commonly occurs in tropical and subtropical climates. The causative organisms of chromoblastomycosis are extremely slow-growing and difficult to culture, so direct microscopic examination is an essential diagnostic test. Black dots within the verrucous plaques of chromoblastomycosis represent transepidermal elimination of the organism (Fig 8, A). Scraping these pigmented areas with a scalpel blade results in the highest diagnostic yield for KOH preparations. Pigmented bodies, also called sclerotic bodies, muriform bodies, medlar bodies, or copper pennies, are pathognomonic; these are 4- to 12- $\mu$ m globe-shaped, cigar-colored, thick-walled structures with occasional small septate hyphae<sup>88,89</sup> (Fig 8, B).

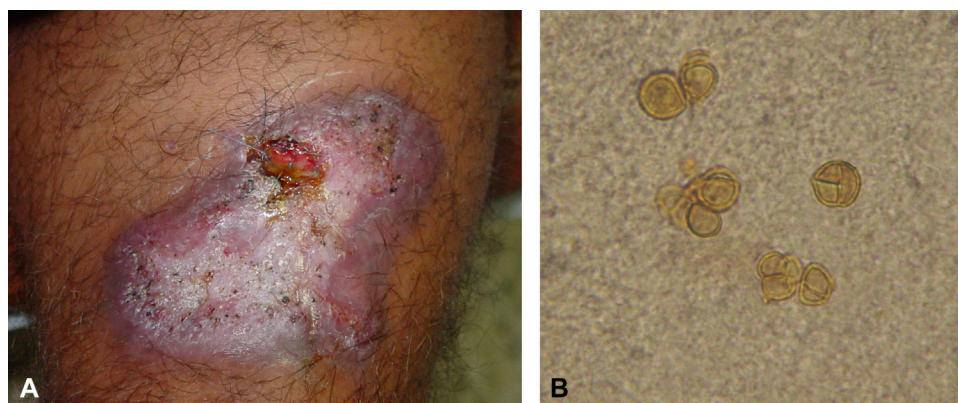
Lobomycosis is endemic in rural areas of Central and South America and is characterized by keloidal plaques. The organism, *Lacazia loboi*, cannot be cultured, so direct visualization is necessary for diagnosis (Fig 9, A). Scraping scale or the keloidal

**Table III.** Key fungal infections with clinical and microscopic features

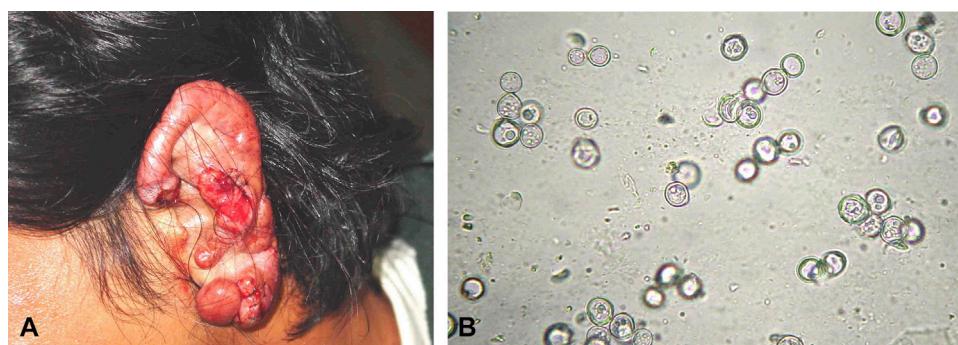
Disease	Clinical features	Microscopic appearance
Superficial mycoses		
Dermatophytes	Erythematous patches with superficial, leading edge scale	Hyphae extending across keratinocyte cell walls, within the nail plate, or within the hair shaft
Candidiasis	Bright red patches with satellite papules and pustules	Pseudohyphae and yeast forms
Pityrosporum (tinea) versicolor	Pink, brown, or pale patches with fine overlying scale, accentuated with stretching of the skin	Florid yeast forms and short hyphae ("penne" and meatballs)
Pityrosporum folliculitis	Red papulopustules	Yeast forms
Subcutaneous mycoses		
Chromoblastomycosis	Verrucous and keloidal plaques and subcutaneous nodules with black dots	4-12 $\mu\text{m}$ globe-shaped, cigar-colored, thick-walled structures with occasional small septate hyphae ("pigmented bodies," copper pennies, or Medlar bodies)
Lobomycosis	Keloidal plaques	9-10 $\mu\text{m}$ single or coupled (2) thick-walled spherules with a thin connection ("brass knuckles or pop beads")
Eumycetoma	Tumefaction (swelling), sinus formation, and grains	Grains macroscopically; thick, broad hyphae, often with septations
Systemic mycoses		
Cryptococcus	Umbilicated papulopustules, cellulitic plaques, ulcers, and abscess	Tzanck: encapsulated 5-10 $\mu\text{m}$ round, dark-walled, pleomorphic yeast with clear gelatinous capsules; India ink stains the background, revealing the extracellular capsule
Histoplasmosis	Oral and perianal ulcerations, umbilicated papules, nodules, and plaques	Small (2-4 $\mu\text{m}$ ), with a pseudocapsule
Blastomycosis	Annular verrucous raised plaques with irregular borders and atrophic central clearing; crusted papules and plaques and subcutaneous nodules	8-15 $\mu\text{m}$ round to oval organisms with thick, double-refractile walls; broad-based, single budding
Paracoccidioidomycosis	Ulcerative and eroded plaques of the oral and perianal mucosa, perioral granulomatous plaques; cutaneous lesions: crusted papules, plaques, nodules, verrucous plaques, or ulcers	Variably sized, 5-50 $\mu\text{m}$ , thick-walled, round cells with narrow (2-10 $\mu\text{m}$ ) budding ("mariner's wheels and Mickey Mouse")
Coccidioidomycosis	Granulomatous papules, plaques, and verrucous lesions; abscesses, chronic ulcers, subcutaneous nodules, and sinus tracts	10-80 $\mu\text{m}$ , variably sized spherules filled with endospores
Angioinvasive mycoses		
Aspergillus	Violaceous, indurated plaques, necrotic eschars, annular "bull's eye" infarcts, and small erythematous macules and papules	Septate, thin hyphae; acute angle branching
<i>Scedosporium</i> spp. and <i>Fusarium</i> spp.		Septate, irregular hyphae with bubbly cytoplasm; branching is 45-90°
Mucomycosis		Ribbon-like, aseptate hyphae with wide angle branching

plaque with a scalpel blade will obtain a specimen; direct visualization with KOH demonstrates 9- to 10- $\mu\text{m}$  single or coupled thick-walled spherules with a thin connection<sup>90-92</sup> (Fig 9, B). Morphologically, these structures have been compared to "pop beads" or "brass knuckles."

The vinyl adhesive tape test has been described as a useful test for chromoblastomycosis, lobomycosis, and paracoccidioidomycosis infections.<sup>91</sup> Instead of using a no. 15 scalpel to scrape the lesion, the sample is collected by applying clear vinyl tape to the lesion, being sure to rub the scaly, crusty areas to remove



**Fig 8.** Chromoblastomycosis. **A**, Clinically, there are verrucous papules and plaques associated with central scarring and numerous dark dots. **B**, Scraping of the dark dots will demonstrate the pigmented spores (Medlar bodies, copper bodies) under potassium hydroxide examination. (Oil immersion; original magnification: **B**,  $\times 100$ .)



**Fig 9.** Lobomycosis. **A**, The clinical presentation are keloid plaques, often on ears or extremities. **B**, Using potassium hydroxide, 9- to 10- $\mu\text{m}$  single or coupled thin-walled spherules with a thin connection will be observed. (Oil immersion; original magnification: **B**,  $\times 100$ .)

the upper layers of the epidermis, then applying the tape to a slide with KOH. Attention should be focused on the black dots on the tissue surface, sites of transepidermal elimination of organisms, and  $>1$  slide should be prepared to increase the diagnostic yield.<sup>91</sup>

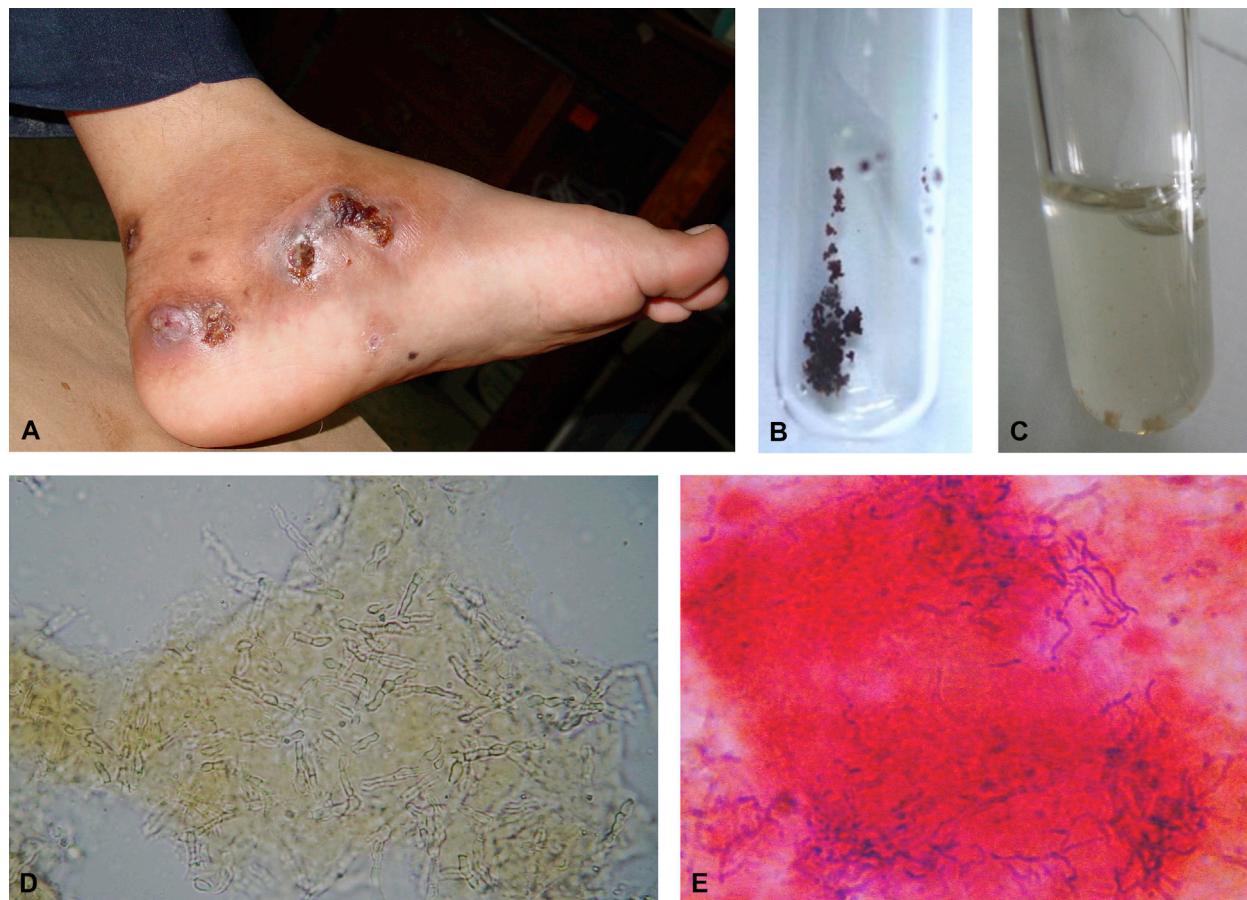
Mycetomas are indolent infections characterized by tumefaction and draining sinuses and caused by either bacteria (actinomycetoma) or fungi (eumycetoma); they are most commonly found in tropical and subtropical locations (Fig 10, A). Botryomycosis has a similar clinical presentation (see bacteria section).<sup>93</sup> Grains eliminated through the sinus tracts can be seen with the naked eye. Direct examination may provide useful information, because certain organisms result in distinct colors. Black grains always signify a fungus is the causative organism<sup>94</sup> (Fig 10, B and C; Table IV). Grains can be obtained by squeezing sinus tracts to promote grain discharge, sometimes with the help of a no. 15 scalpel or forceps. Grains are then applied to a slide, KOH is added, and pressure with another slide or the

blunt end of a pen over a coverslip is used to flatten the grains. Fungi in eumycetomas will have thick, broad hyphae, often with septations<sup>95</sup> (Fig 10, D). Actinomycetomas are characterized by bacteria with thin, fine filaments (Fig 10, E). Additional staining can be performed, including Gram stain or Grocott methenamine silver stain if further identification is needed.

## SYSTEMIC FUNGAL INFECTIONS

### Key points

- Cutaneous lesions may be the presenting manifestation of disseminated fungal infections, including cryptococcosis, histoplasmosis, blastomycosis, paracoccidioidomycosis, and coccidioidomycosis
- Direct microscopy with KOH, CBE, and Tzanck smear can demonstrate differentiating morphologic features that allow for rapid diagnosis that can be confirmed with culture



**Fig 10.** Mycetomas. **A**, The key clinical features are swelling (tumefaction), sinus tract formation, and grains. **B**, Black grains always signify a fungal organism. **C**, Yellow grains could represent bacterial or fungal organisms. **D**, Potassium hydroxide examination of hyphae confirms eumycetoma or a fungal origin. **E**, Gram stain with presence of Gram-positive filamentous bacteria confirms actinomycetoma as the diagnosis. (**D** and **E**, Oil immersion; original magnifications: **D** and **E**,  $\times 100$ .)

**Table IV.** Mycetoma grain color and associated organisms\*

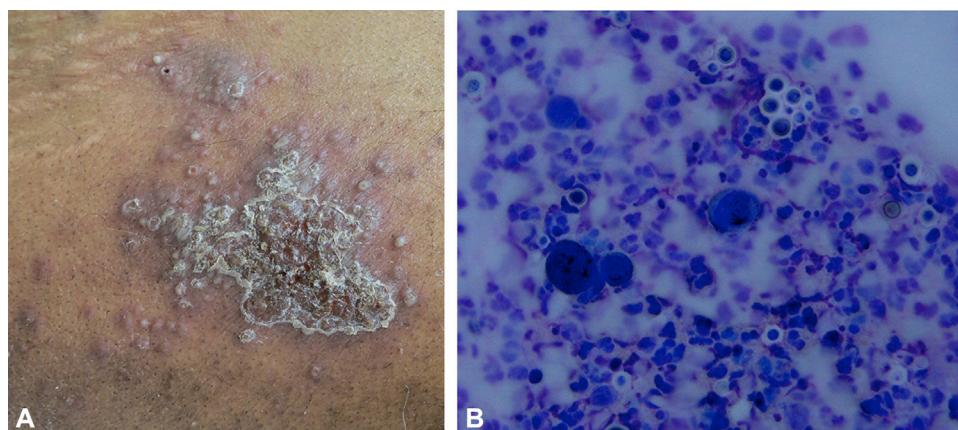
Grain color	Organisms
Black	<i>Madurella</i> spp. ( <i>M mycetomatis</i> , <i>M grisea</i> ), <i>Leptosphaeria senegalensis</i> , <i>Exophiala jeanselmei</i> , <i>Pyrenophaeta romeroi</i> , <i>Curvularia lunata</i> , <i>Phialophora verrucosa</i> , and <i>Phytophthora parasitica</i>
Pale	<i>Pseudoallescheria boydii</i> , <i>Aspergillus</i> spp., <i>Fusarium</i> spp., <i>Acremonium</i> spp., <i>Phaeoacremonium</i> spp., <i>Neotestudina rosatii</i> , <i>Nocardia</i> spp. ( <i>N brasiliensis</i> , <i>N cavae</i> , and <i>N asteroides</i> ), and <i>Actinomadura madurae</i>
Red	<i>Actinomadura pelleiti</i>
Yellow	<i>Streptomyces somaliensis</i>

\*Data from Ramos-E-Silva et al.<sup>92</sup>

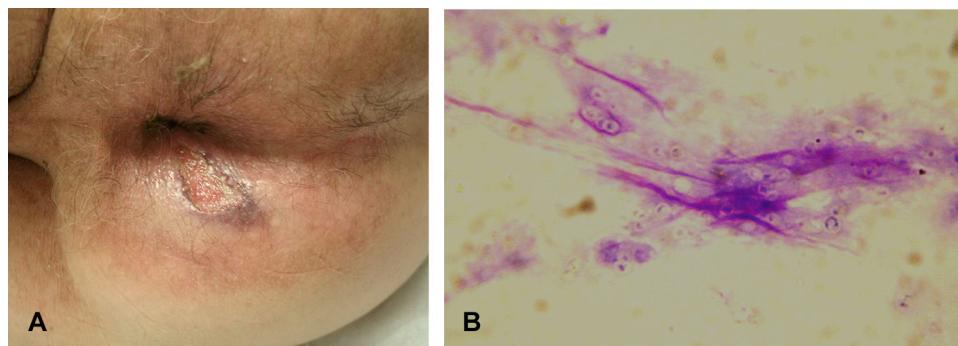
Systemic dimorphic fungal infections that can have cutaneous manifestations include cryptococcosis, histoplasmosis, blastomycosis, paracoccidioidomycosis, and coccidioidomycosis. Primary infection often occurs via inhalation, leading to mild or asymptomatic pulmonary disease. In susceptible hosts, hematogenous dissemination to multiple organs, including the skin, can occur. Importantly,

cutaneous manifestations can be the presenting sign of systemic illness. However, direct inoculation of the skin can also occur, leading to primary cutaneous disease. **Table III** contains an overview of these infections.

Direct microscopic examination can yield rapid diagnosis and enable faster initiation of therapy in patients who are often systemically ill.



**Fig 11.** Cryptococcus. **A**, Numerous umbilicated papules, pustules, and plaques are one of the presentations of cutaneous Cryptococcus. **B**, Tzanck smear demonstrates yeast forms with a gelatinous capsule as demonstrated by a halo. (Original magnification: **B**,  $\times 40$ .)



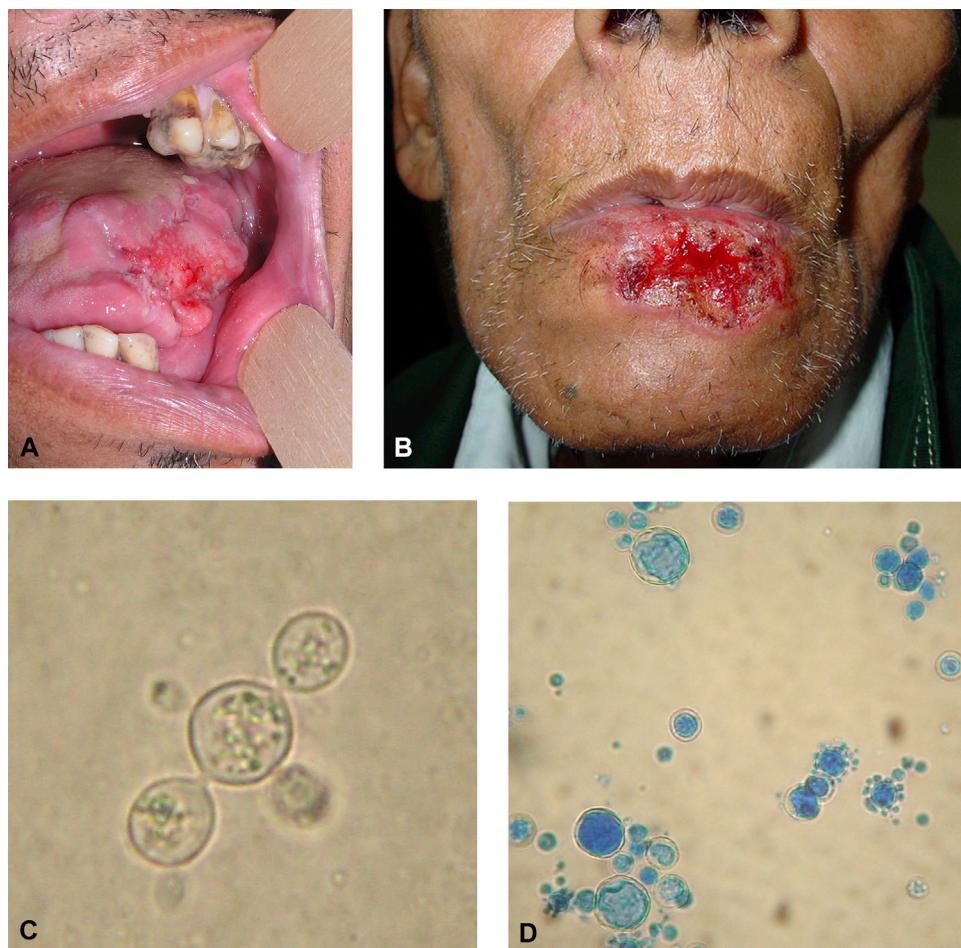
**Fig 12.** Histoplasmosis. **A**, Perianal ulcer, one of the manifestations of histoplasmosis. **B**, Giemsa stain can help highlight the very small organisms that have artifactual clearing around them. (Oil immersion; original magnification: **B**,  $\times 100$ .)

Cryptococcosis is caused by *Cryptococcus* spp., most commonly *Cryptococcus neoformans*, which is found worldwide in bird droppings. It can have varied clinical presentations in immunocompromised patients, including umbilicated, resembling molluscum contagiosum. To obtain a specimen, one can use a no. 15 blade to scrape contents from the center of an umbilicated lesion, crust, papule, or pustule. Tzanck smear demonstrates 5- to 10- $\mu\text{m}$  encapsulated, round, dark-walled, pleomorphic yeast with clear, unstained gelatinous capsules (Fig 11). India ink stains the background, revealing the extracellular capsule.<sup>76,96,97</sup> Capsules stain with methylene blue, Alcian blue, and mucicarmine.

Histoplasmosis (*Histoplasmosis capsulatum*) is found worldwide but is endemic to the Midwest, especially in states that border the Ohio River valley and Mississippi River. Cutaneous lesions include oral and perianal ulcerations, umbilicated papules, nodules, and plaques. Direct microscopic examination of lymph nodes or cutaneous lesions can be

performed using a Tzanck smear (Giemsa stain), which has greater sensitivity than a KOH preparation. On examination, the organisms are small (2-4  $\mu\text{m}$ ), with a pseudocapsule.<sup>76,98</sup> If macrophages are present, engulfed intracellular organisms may be visualized (Fig 12).

Paracoccidioidomycosis is an infection endemic to South and Central America that can present with pulmonary symptoms, lymphadenopathy, and hepatosplenomegaly. It preferentially involves the mucous membranes with ulcerative and eroded plaques of the oral mucosa (moriform or Aguiar-Pupo stomatitis) and oropharynx, perioral granulomatous plaques, and perianal involvement. Cutaneous lesions may appear as scattered crusted papules, verrucous plaques, nodules, or ulcers and result from hematogenous spread in up to 25% of infections<sup>99</sup> (Fig 13, A and B). Direct visualization using a KOH preparation can be more sensitive than culture secondary to contaminating organisms, with a diagnostic yield of >90%. Organisms are variably



**Fig 13.** Paracoccidioidomycosis. **A**, Intraoral involvement is common with ulcerated plaques with small red dots. **B**, Perioral lesions are also common, with similar ulcerated plaques with hemorrhagic crust. **C**, Using potassium hydroxide, variably sized yeast forms with narrow budding can be seen, which may represent a mariner's wheel or Mickey Mouse. **D**, Lactophenol can provide additional contrast compared to background bacterial elements and will color the fungus blue. (Oil immersion; original magnification: **C** and **D**,  $\times 100$ .)

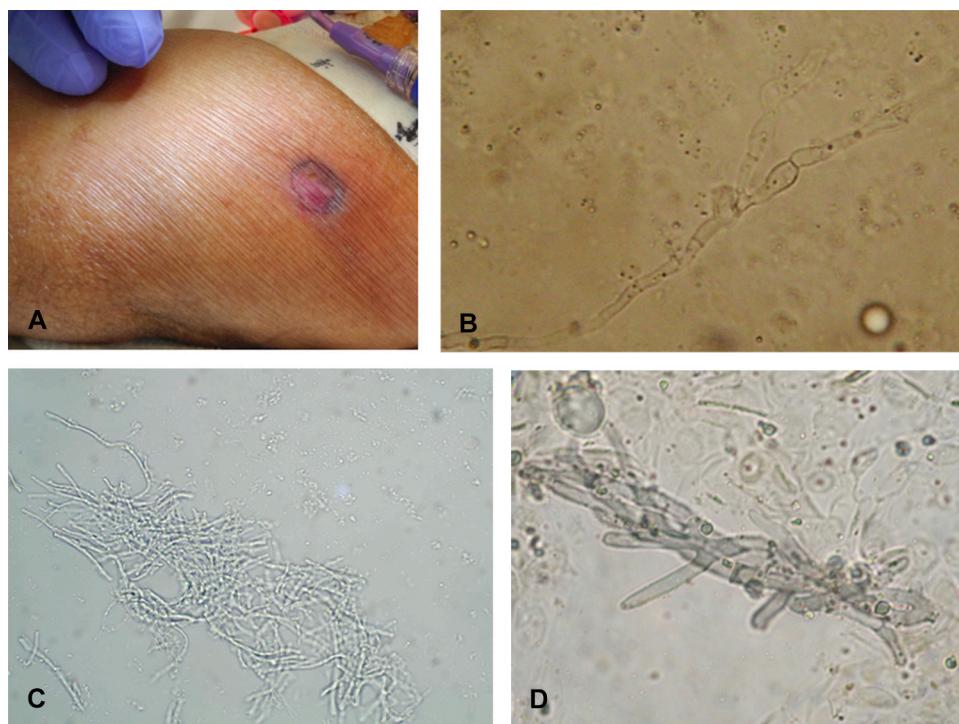
sized, 5 to 50  $\mu\text{m}$ , thick-walled, round cells with narrow (2-10  $\mu\text{m}$ ) budding<sup>76,100</sup> (Fig 13, C). Morphologically, they are said to have a "Mickey Mouse" or "Mariner's wheel" appearance. One can enhance visualization of the fungus with use of lactophenol cotton blue, especially if the specimen has significant contamination. This technique is performed by first adding alcohol to the sample to fix it, then adding the lactophenol/cotton blue stain to the specimen (Fig 13, D). The phenol and lactic acid kill live organisms, while preserving the fungal structures, and the cotton blue stains chitin in the cell walls blue. Another test reported to be successful in the diagnosis of paracoccidioidomycosis is the vinyl adhesive tape method, with technique the same as that used for chromoblastomycosis and lobomycosis.<sup>91</sup>

Blastomycosis is caused by *Blastomyces dermatitidis* and occurs predominantly in North America, with the highest number of reported cases in the Midwest



**Fig 14.** Blastomycosis. Potassium hydroxide examination will demonstrate broad-based budding organisms. (Oil immersion; original magnification:  $\times 100$ .)

and Canada. In the skin, it can present as annular, verrucous, raised plaques with irregular borders and atrophic central clearing (so-called "stadium seating").



**Fig 15.** Angioinvasive fungal infection. **A**, Clinically, there are violaceous papules, plaques, or nodules as the fungus is targeting the blood vessels, resulting in significant hemorrhage. **B**, *Aspergillus* spp. will have septations and demonstrate acute angle branching. **C**, *Fusarium* spp. have smaller and more irregular hyphae with septae and bubbly cytoplasm. The branching will be more variable, from 45° to 90°. **D**, Mucormycosis are irregular, broader (10–25 µm), and aseptate hyphae with wide angle branching. (**B**, Oil immersion; original magnifications: **B**, ×100; **C** and **D**, ×40.)

Crusted papules and plaques and subcutaneous nodules also occur.<sup>101</sup> Direct microscopy with KOH reveals 8-to 15-µm round to oval organisms with thick, doubly refractile walls. Broad-based, single budding is also observed<sup>76,102</sup> (Fig 14).

*Coccidioides immitis* and *Coccidioides posadasii* are the causative organisms in coccidioidomycosis, which is endemic in the western/southwest United States and northern Mexico. Cutaneous manifestations include granulomatous papules, plaques, and verrucous lesions, abscesses, chronic ulcers, subcutaneous nodules, and sinus tracts, characteristically on the head and neck.<sup>103–105</sup> Direct microscopy after KOH or Tzanck smear enables visualization of the organisms, which are variably sized, 10- to 80-µm spherules filled with endospores.<sup>76,104</sup>

## ANGIOINVASIVE FUNGAL INFECTIONS

### Key points

- **Angioinvasive fungal infections (*Aspergillus*, *Fusarium*, *Scedosporium*, *Mucor*, *Rhizopus*, *Cunninghamella*, and *Lichtheimia* [*Absidia*]), are associated with high morbidity and mortality**

### • Early diagnosis of skin lesions using touch preparation can identify life-threatening cases of disseminated infection

*Aspergillus*, *Fusarium*, *Scedosporium*, *Mucor*, *Rhizopus*, *Cunninghamella*, and *Lichtheimia* (*Absidia*) are ubiquitous saprophytic organisms that can cause devastating angioinvasive fungal infection with high morbidity and mortality.<sup>106–109</sup> Risk factors include neutropenia and other forms of immunosuppression. Skin involvement can occur from direct inoculation or, more frequently, from hematogenous spread. Cutaneous manifestations include violaceous, indurated plaques, necrotic eschars, annular “bull’s eye” infarcts, and small erythematous macules and papules<sup>110–114</sup> (Fig 15, A).

Direct microscopic examination can help diagnose these infections. Touch preparation is performed by smearing the base of a punch biopsy specimen on a slide or by scraping a small amount of tissue from the wound base. KOH, CBE, calcofluor white, or other special stains can be used for immediate evaluation.<sup>112,114</sup> The microscopic appearance can predict the causative organism and enable rapid institution of appropriate therapy. *Aspergillus* spp.

have thin, septate hyphae with acute angle branching<sup>95</sup> (Fig 15, B). *Scedosporium* spp. and *Fusarium* spp. also have septae but demonstrate smaller and more irregular hyphae and bubbly cytoplasm; branching is 45° to 90° (Fig 15, C). Mucormycosis (zygomycetes), including *Mucor*, *Rhizopus*, *Cunninghamella*, and *Lichtheimia* (*Absidia*), have irregular, broad (10-25 μm), ribbon-like, aseptate hyphae with wide angle branching<sup>112,114</sup> (Fig 15, D). Distinguishing mucormycosis from other angioinvasive fungal infections is crucially important because these organisms are resistant to voriconazole, the first-line antifungal therapy for *Aspergillus*.

In conclusion, direct, provider-performed microscopy enables rapid diagnosis and early initiation of treatment in numerous viral, bacterial, and fungal infections, providing a therapeutic advantage that is particularly significant in resource-limited and high acuity settings. Development of these bedside diagnostic skills through practice and frequent use is necessary to establish confidence. The second article in this continuing medical education series discusses the use of bedside diagnostic tests for parasitic disorders and noninfectious dermatologic conditions.

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# Bedside diagnostics in dermatology



## Parasitic and noninfectious diseases

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### Learning objectives

After completing this learning activity, the participants should be able to describe and perform diagnostic tests that dermatologists can perform at the bedside; select the appropriate bedside technique for diagnosis of specific parasitic and noninfectious dermatologic conditions using these bedside laboratory techniques; and judge appropriate situations for utilization of bedside laboratory techniques to save time or money in the timely diagnosis and treatment of patients with important parasitic and noninfectious dermatologic diseases.

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In addition to aiding the diagnosis of viral, bacterial, and fungal diseases, mineral oil preparation, Tzanck smear, and other techniques can be used to diagnose parasitic infections, neonatal pustular dermatoses, blistering diseases, Stevens–Johnson syndrome, and a plethora of other benign and malignant conditions, including granulomatous diseases and tumors. In many cases, these techniques are specific, reliable, and easy to perform and interpret. In others, a certain amount of training and expertise are required. In the proper clinical scenario, these tests are rapid, economical, and compare favorably with other diagnostic methods. (J Am Acad Dermatol 2017;77:221–30.)

**Key words:** bedside diagnostic tests; mineral oil preparation; parasitic infections; quality improvement; rapid diagnosis; skin snip; Tzanck smear.

## PARASITES AND MITES

### Scabies

#### Key points

- **Scabies preparation yield is highest in “hot spot” areas, such as the web spaces, flexural wrists, elbows, axillae, umbilicus, waistline, glans penis, and the nipple/areola**
- **Dermoscopy may allow visualization of burrows and mites (delta wing sign), increasing diagnostic sensitivity independently or in conjunction with scabies preparation**

*Sarcoptes scabiei* infestation is common throughout the world, with the highest prevalence in India, Brazil, and Central America. It is a disease of low socioeconomic status, poor nutrition, and poor hygiene, transmitted by direct skin-to-skin contact; in some cases, it is transmitted sexually.

Empiric scabies treatment of patients with pruritic dermatoses is common in primary care and dermatology offices, but confirmation of infestation is useful for the following reasons: 1) to avoid unnecessary treatment, 2) to enable appropriate

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**Fig 1.** Excoriated papules in the web space between the first and second fingers (arrow).

infection control measures and treatment of close contacts and the home environment, and 3) to prevent future diagnostic confusion if symptoms persist. A well-executed scabies preparation can be extremely helpful.

**Scabies preparation.** Despite often severe itching caused by mite saliva, eggs, and feces, etc, the total mite burden in an immunocompetent host is only 10 to 15. Hot spots that are high-yield for scraping include the web spaces, flexural wrists, elbows, axillae, umbilicus, waistline, glans penis, and the nipple/areola (Fig 1). To perform a scabies preparation, a no. 15 scalpel is dipped in mineral oil to provide a viscous surface to which scale, mites, and debris can adhere. Erythematous papules or burrows in “hot spot” areas should be scraped vigorously, and scale is transferred to a glass slide. Scraping several areas can increase the diagnostic yield. Diagnosis depends on visualization of mites, eggs, or feces (scybala) on microscopic examination (Fig 2). Sensitivity of scabies preparation ranges from 46% to 90%, and the negative predictive value is 77%. Specificity is 100% by definition.<sup>1-3</sup>

Mineral oil is not always readily available, so any viscous substance to which scale adheres may suffice. Purell or another alcohol-based cleanser can work well as a mineral oil substitute. If there is significant scale, as in patients with crusted scabies, it may be useful to add a drop of potassium hydroxide (KOH) to the slide to diminish keratinous debris. A modified, pediatric-friendly “curette prep” using a 3-mm disposable curette instead of a no. 15 scalpel to scrape lesions with a gentle scooping motion may provide better control and be less frightening to children.<sup>4</sup> Transparent adhesive packing tape cut to the size of a slide and firmly applied to “hot spot” areas/lesional skin, then rapidly pulled off and transferred to a slide, can replace scraping where appropriate. Sensitivity is 68% and the negative predictive value 85%, with specificity again 100%.<sup>5</sup>



**Fig 2.** A *Sarcoptes scabiei* mite (arrow), ovum (arrowhead), and scybala (asterisk) visible at high power. (Original magnification:  $\times 400$ ).



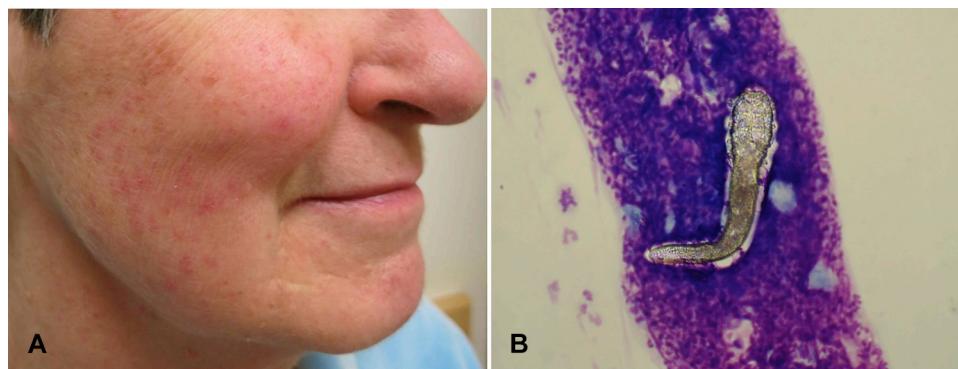
**Fig 3.** Positive “delta wing sign”; mites appear as small triangles on dermoscopy (arrow).

Dermoscopy is a useful adjunctive tool to enable visualization of mites and burrows. On dermoscopy, mites appear as small triangles, the so-called “delta wing sign” (Fig 3).<sup>6</sup> Sensitivity of this method is excellent (83-91%), with a negative predictive value of 85%. Specificity, however, is lower (46-86%), reflecting the potential for false positives. Combining traditional scabies preparation with dermoscopy to locate mites and burrows increases the yield of skin scraping, raising sensitivity from 47% to 84%, while simultaneously decreasing time spent on the procedure.<sup>7</sup>

## Demodex

### Key points

- **Demodex may play a role in rosacea and ocular symptoms, as well as folliculitis in immunocompromised patients**
- **The organism can be demonstrated using scabies preparation or Tzanck smear of an acneiform pustule**



**Fig 4.** **A**, Patient with granulomatosis with polyangiitis on chronic immunosuppression, seen for acute onset of rosacea-like erythematous papules and pustules. **B**, Tzanck smear of the *Demodex* mite appearing as a negative (unstained) image. (Original magnification: **B**,  $\times 100$ ).

*Demodex folliculorum* and *Demodex brevis* are ubiquitous organisms living in the pilosebaceous unit which are associated with eye itching, lid thickening and scaling, madarosis, and rosacea. In immunodeficient states (eg, posttransplant patients or patients with HIV), *Demodex* infestation can mimic folliculitis due to other causes (Fig 4, A), with inflammatory papules and pustules that respond to therapy with topical permethrin or oral ivermectin.<sup>8,9</sup>

*Demodex* can be demonstrated using mineral oil scraping (scabies preparation) or Tzanck smear. In both techniques, a no. 15 scalpel is used to scrape a follicular pustule, and the material is spread onto a glass slide. Whether the slide is unstained or stained using Tzanck (Wright–Giemsma stain), the mite appears clear and elongated. If a Tzanck preparation is used, the organism appears as a negative (unstained) image and may be easier to visualize (Fig 4, B).<sup>10</sup>

### Leishmania

#### Key points

- Cutaneous leishmaniasis frequently presents as ulcerated nodules or plaques on exposed areas
- The “thick drop method,” a modified Tzanck preparation, is the most sensitive light microscopy method for diagnosing cutaneous leishmaniasis
- Intracellular amastigotes appear as a “swarm of bees” within parasitized macrophages

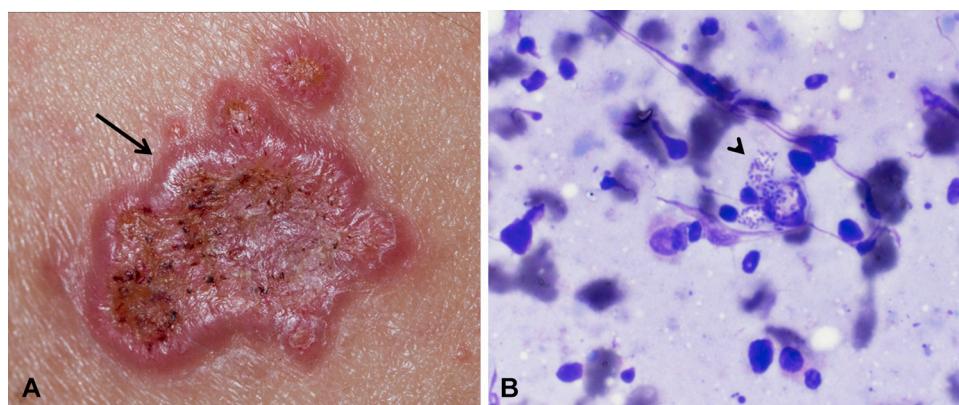
Cutaneous leishmaniasis results from intracellular infection of macrophages by protozoal *Leishmania* species. Cutaneous lesions, which generally present as ulcerated nodules or plaques, occur at sites of inoculation by *Phlebotomus* or *Lutzomyia* sandfly bites. The disease burden is highest in the Middle East and Central and South America.

**Thick drop method.** Rapid bedside diagnosis of cutaneous leishmaniasis can be confirmed using a modified Tzanck preparation known as the “thick drop method.” A no. 15 scalpel is used to nick the inflamed border of the lesion (Fig 5, A), and drops of the oozing blood are placed onto a glass slide or slides. The drop(s) of blood are allowed to dry at room temperature without smearing and are then stained using Wright–Giemsma (Tzanck). Intracellular amastigotes (Leishman–Donovan bodies) are readily detected on microscopy as a light blue, round or oval “swarm of bees” (Fig 5, B). The thick drop method is the most sensitive light microscopy method, with sensitivity ranging from 64% to 77% compared to 44% for punch biopsy specimens and 39% for scraping and smearing a thin layer of material on a glass slide. Specificity is reported at 100% because of the distinctive appearance of the parasite.<sup>11,12</sup> Alternatively, a touch preparation can be prepared from the base of a biopsy specimen, then stained with Wright–Giemsma. The sensitivity of this method is higher than that of biopsy (50–70% overall), enabling diagnosis in cases where the biopsy was ultimately nondiagnostic.<sup>13</sup> Lastly, these bedside scrapings can be used subsequently for polymerase chain reaction (PCR) testing with high sensitivity and specificity, suggesting a kind of practical, algorithmic approach to the diagnosis of cutaneous leishmaniasis, beginning with the thick drop method.<sup>11</sup> Because no fixation or special processing are required, these methods have distinct advantages in resource-limited settings. While PCR is highly sensitive, it is limited by cost and availability.

### Onchocerciasis

#### Key points

- Onchocerciasis (“African river blindness”) can be intensely pruritic and mimic chronic atopic dermatitis



**Fig 5.** **A**, Cutaneous leishmaniasis: an ulcerated plaque with central atrophy and raised border. In the “thick drop method,” a no. 15 scalpel is used to nick the inflamed border (arrow), and drops of blood are placed onto a glass slide to dry. **B**, Intracellular amastigotes (Leishman–Donovan bodies) are readily detected on microscopy as light blue, round or oval “swarm of bees” (arrowhead). (Photograph courtesy of Brian Swick, MD; original magnification: **B**,  $\times 400$ .)

- **The skin snip is relatively bloodless and painless and is the criterion standard for diagnosis worldwide**

Onchocerciasis is the second leading infectious cause of blindness in the world. Cutaneous involvement (onchodermititis) results in intense pruritus and dyspigmentation, mimicking atopic dermatitis. Subcutaneous nodules (onchocercoma) and loss of skin elasticity with loose-hanging skin folds (hanging groin) may also result.

**Skin snip.** The criterion standard of onchocerciasis testing is the skin snip. In this procedure, normal-appearing, nonlesional skin is sampled to look for microfilariae. The highest-yield sites are the iliac crests, the scapulae, and the calves. A syringe with a small needle is held perpendicular to the skin (Fig 6 and [Supplemental Video 1](#), available online at [www.jaad.org](http://www.jaad.org)). The skin is pierced and tented up, and a scalpel is used to snip off a small piece of skin beneath the needle. The depth of snip is approximately that of the superficial dermis. The skin snip is placed on a glass slide in a single drop of normal saline, then incubated at room temperature for 24 hours to allow microfilariae to emerge from the tissue. The organism can then be visualized microscopically with or without staining as an elongated, motile round worm with tapered ends. In settings where the skin snip is performed regularly, specialized tools for sampling may be available.

This method of skin sampling has distinct advantages. It is relatively bloodless and painless, requiring no anesthesia. Few resources (only a syringe, scalpel, slide, and microscope) are required. It is also considered the criterion standard for diagnosis of onchocerciasis worldwide. While the specificity of



**Fig 6.** A skin snip for onchocerciasis is performed on normal skin of the iliac crests, scapulae, and calves using a needle and scalpel without anesthesia.

the skin snip is approximately 100%, sensitivity can be limited (20–50%) in early- or low-intensity infection. A method of taking 6 snips (2 each from the scapulae, iliac crests, and calves) provides the highest diagnostic sensitivity. Antibody and antigen tests, diethylcarbamazine patch test, and PCR are highly sensitive and specific but limited by cost and availability.<sup>14</sup>

Bedside techniques for the diagnosis of parasitic diseases are summarized in [Table I](#).

## DISEASES OF EARLY CHILDHOOD/ PUSTULAR DERMATOSES OF THE NEONATE

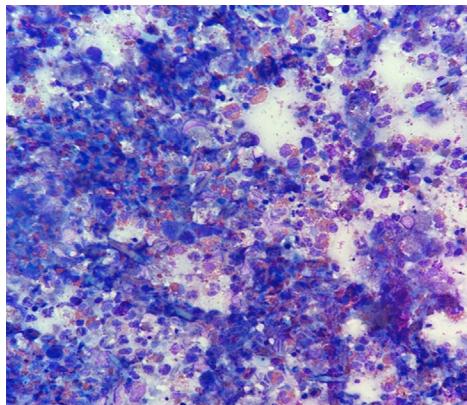
### Key point

- **Tzanck, Gram stain, or KOH preparation can help distinguish benign neonatal pustular dermatoses from potentially life-threatening disseminated infections**

During the neonatal period, the infant is vulnerable to infection; pustules therefore evoke concern. Simple diagnostic tests have the potential to rule out

**Table I.** Parasitic diseases

Disease	Technique	Microscopic appearance
Scabies	Mineral oil preparation	Mites, eggs, and scybala
<i>Demodex</i> folliculitis	Mineral oil or Tzanck smear	Elongated, clear mite
Leishmaniasis	"Thick drop method" or touch preparation with Tzanck smear	Intracellular "swarm of bees"
Onchocerciasis	Skin snip	Elongated, motile round worm



**Fig 7.** Erythema toxicum neonatorum in a newborn and corresponding Tzanck smear showing numerous eosinophils. (Photograph courtesy of Aileen Chang, MD; original magnification:  $\times 400$ .)

or rule in infectious causes, quickly differentiating transient, benign eruptions such as erythema toxicum neonatorum (Fig 7) and transient neonatal pustular melanosis from serious and life-threatening ones, such as neonatal herpes simplex or disseminated candida. The Tzanck smear is an easy, rapid, and sensitive way to evaluate pustules in the neonate; Gram stain and KOH/chlorazol black E preparation may also be indicated. Such testing may quickly identify infectious diseases while sparing healthy neonates more invasive evaluations and potentially harmful interventions for benign, transient conditions (Table II).<sup>15</sup>

### Blistering diseases

#### Key points

- **Tzanck smear can enable differentiation of pemphigus vulgaris from various autoimmune and genetic blistering diseases caused by characteristic cytology**
- **Rapid diagnosis of Stevens–Johnson syndrome/toxic epidermal necrolysis and differentiation from staphylococcal scalded-skin syndrome can be achieved using Tzanck or "jelly roll"**

Bedside diagnostic tests can also be used to differentiate various autoimmune and genetic

blistering diseases, as well as Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and staphylococcal scalded-skin syndrome (SSSS). Doing so accurately requires some degree of familiarity with each entity's diagnostic cytologic appearance, but the sampling technique is the same. In each entity, a Tzanck smear is performed by scraping the freshly denuded base of a blister or erosion, then staining per usual protocol (described in the first article in this continuing medical education series).

In pemphigus vulgaris, characteristic findings include round acantholytic cells, hypertrophic nuclei, basophilic cytoplasm with peripheral rim, and cell adherence or clustering. Additional characteristic findings include chains of white blood cells (streptocytes) and isolated epithelial cells surrounded by a ring of leukocytes (Sertoli rosette). Peripheral fluorescence results if direct immunofluorescence is performed (Fig 8). Advantages of this technique, in addition to the rapidity of diagnosis, include a high degree of sensitivity. Multiple samples from different skin lesions can be sampled to increase yield and include lesions at different stages of disease. Oral erosions may be easier to sample using this method, whereas biopsy specimens of oral erosions may be less reliable.<sup>16,17</sup>

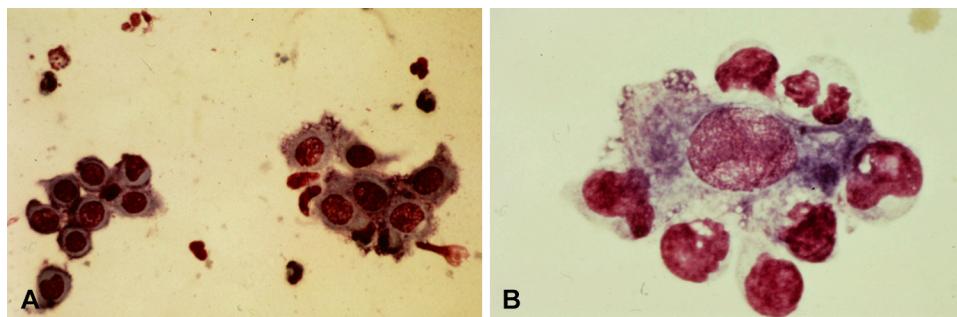
In contrast to pemphigus, Tzanck smear of bullous pemphigoid reveals no specific findings beyond an abundance of eosinophils (Fig 9). There are no acantholytic cells. This serves mainly to differentiate bullous pemphigoid from pemphigus vulgaris. Hailey–Hailey disease is characterized by numerous acantholytic cells, large round keratinocytes, hypertrophic, deeply stained nuclei, and deep basophilic staining at the cell periphery. Unlike pemphigus, cells typically do not cluster, and no streptocytes or rosettes are seen (Fig 10).<sup>18</sup> In Darier disease, one sees acantholytic cells as well as corps ronds and grains.<sup>19</sup>

SJS/TEN is a life-threatening emergency in which a prompt diagnosis is critical. The base of a freshly denuded area (or one induced by the Nikolsky sign) is scraped. While avoiding excess blood and vesicle fluid, the cellular material is spread onto a slide and stained per the Tzanck protocol. The presence of necrotic cuboidal basal keratinocytes with large

**Table II.** Pustular dermatoses in the neonate

Disease	Technique	Microscopic appearance
Erythema toxicum neonatorum	Tzanck smear	Numerous eosinophils
Transient neonatal pustular melanosis	Tzanck or Gram stain	Numerous neutrophils, few eosinophils, and no bacteria
Acropustulosis of infancy	Tzanck or Gram stain	Numerous neutrophils, few eosinophils, and no bacteria
Infantile acne	Tzanck smear	Sebaceous material and <i>Pityrosporum</i> yeast
Incontinentia pigmenti	Tzanck or Gram stain	Numerous eosinophils
Bullous impetigo	Gram stain	Neutrophils and GPC in clusters
Herpes simplex virus	Tzanck smear	Multinucleation, margination, and molding of keratinocytes
Varicella zoster virus		
Candidiasis	KOH preparation	Pseudohyphae and spores

GPC, Gram-positive cocci; KOH, potassium hydroxide.



**Fig 8.** Tzanck smear of pemphigus vulgaris showing (A) round, acantholytic keratinocytes with hypertrophic nuclei, basophilic cytoplasm with peripheral rim, and cell adherence/clustering and (B) isolated epithelial cells surrounded by a ring of leukocytes (Sertoli rosette). (Photographs courtesy of Amit Pandya, MD.)

nuclei and surrounding inflammatory cells suggests SJS/TEN. By contrast, broad superficial acantholytic keratinocytes with small nuclei and a dearth of inflammatory cells suggests SSSS (Fig 11).<sup>20</sup> Alternatively, the blister roof from a patient with SJS/TEN or SSSS can be submitted on saline-moistened gauze (the so-called “jelly roll”) for frozen section processing, revealing full-thickness epidermal necrosis (Fig 12) or intraepidermal necrolysis, respectively (Table III).

### Keratinocytic tumors

#### Key point

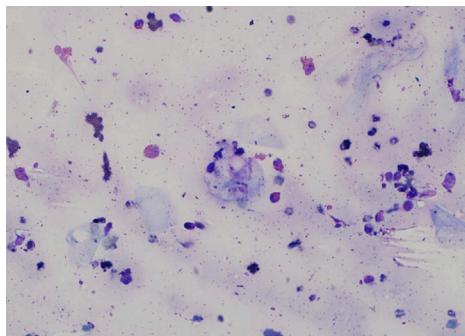
- **Exfoliative cytology using Tzanck is a simple, reliable method for diagnosing common skin cancers in the appropriate clinical setting, including basal and squamous cell carcinoma, which have characteristic cytologic appearances**

Exfoliative cytology has widespread use for the diagnosis of cervical cancer. It may also be used for diagnosis of skin tumors in the appropriate setting. Ulcerated lesions can be scraped directly, while the edge of nonulcerated papules or plaques should be nicked with a scalpel before scraping the lesion

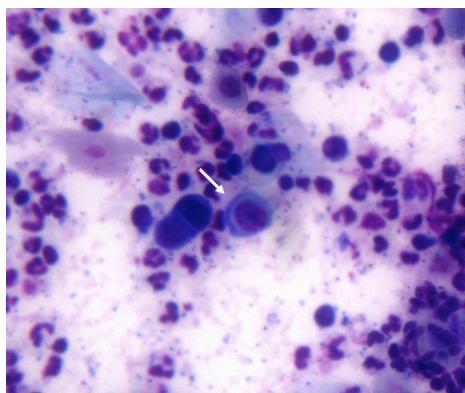
surface. Removal of slough or scab, pretreatment of keratotic lesions with petroleum jelly, and scraping down to the papillary dermis may all increase the likelihood of getting a sufficient sample and increase the diagnostic yield. Material should be scraped onto a glass slide then stained per the Tzanck protocol and viewed immediately.

Basal cell carcinoma (BCC), which may resemble several benign lesions clinically, looks cytologically much like the familiar histologic appearance on review of the biopsy specimen—packed clusters of atypical, strongly basophilic basaloid cells with uniform large size clump together with peripheral palisading (Fig 13). The diagnostic reliability of cytology for diagnosis of basal cell carcinoma is high. A metaanalysis of 8 primary studies showed that of 1261 biopsy-proven BCCs, cytology was 97% sensitive and 86% specific.<sup>21</sup>

Squamous cell carcinoma (SCC), which can sometimes be difficult to differentiate from other benign and malignant lesions (eg, psoriasis), exhibits pleomorphic isolated cells with hypertrophic, hyperchromic, lobulated or multiple/mitotic nuclei. Cytoplasmic staining may be vacuolated or otherwise unusual (Fig 14). For SCC, Tzanck smear is most reliable for nodular, soft, ulcerated,



**Fig 9.** Tzanck smear of bullous pemphigoid reveals no specific findings beyond an abundance of eosinophils. Compare to pemphigus vulgaris shown in Fig 8. (Original magnification:  $\times 400$ .)



**Fig 10.** Tzanck smear of Hailey–Hailey disease showing acantholytic cells, large round keratinocytes, hypertrophic nuclei, and peripheral basophilic staining (arrow). Unlike pemphigus vulgaris, cells do not cluster, and no streptocyes or rosettes are seen. (Original magnification:  $\times 400$ .)

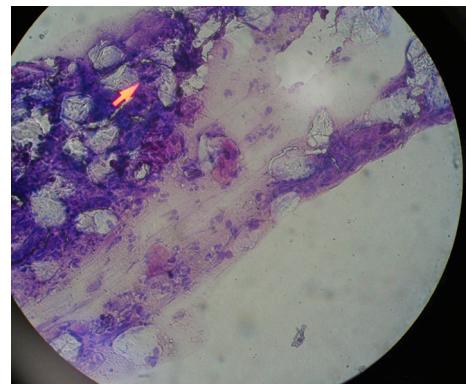
nonkeratotic, and mucosal lesions and is less reliable for keratotic or verrucous lesions with extensive scale.<sup>17</sup>

Tzanck smear for the diagnosis of BCC and SCC is simple and reliable and can represent significant time and cost savings. It allows diagnostic confirmation at the initial visit and may be a more conservative means of diagnosis for cosmetically sensitive sites or multiple lesions. It may be appropriate when planning to treat immediately with destruction or with a nonsurgical modality.<sup>21</sup> However, it should not be considered equivalent to or a replacement for obtaining a biopsy specimen in most circumstances where pathology services are readily available.

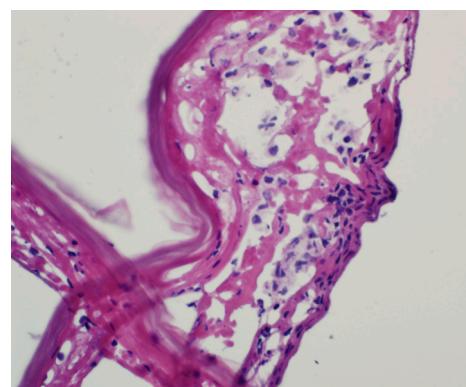
## OTHER BENIGN AND MALIGNANT TUMORS

### Key point

- **Tzanck smear/exfoliative cytology can be used to diagnose a great variety of other benign and malignant cutaneous disorders**



**Fig 11.** Tzanck smear of staphylococcal scalded-skin syndrome showing broad superficial acantholytic keratinocytes with small nuclei and a dearth of inflammatory cells. (Original magnification:  $\times 400$ .)



**Fig 12.** Frozen section processing of the blister roof from a patient with Stevens–Johnson syndrome revealing full-thickness epidermal necrosis. (Original magnification:  $\times 400$ .)

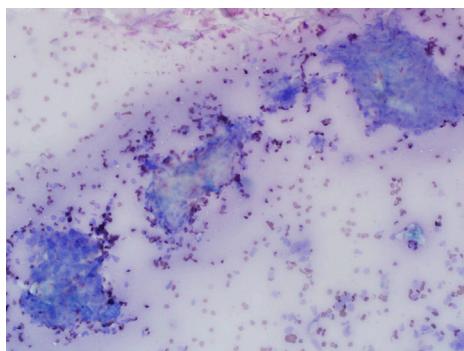
In addition to BCC and SCC, the Tzanck smear can be used to diagnose a variety of other malignant and benign tumors, granulomatous, and other diseases, including: Paget disease, melanoma,<sup>22</sup> erythroplasia of Queyrat,<sup>18,23</sup> mastocytoma,<sup>24</sup> and histiocytosis<sup>18,23,25</sup>; sarcoidosis, granuloma annulare, necrobiosis lipoidica, foreign body granuloma, and juvenile xanthogranuloma<sup>12</sup>; clear cell acanthoma,<sup>26</sup> spongiotic dermatitis,<sup>19,27</sup> seborrheic keratosis, melanocytic nevus, dermatofibroma, vellus hair cyst, and verruca (Table IV).<sup>22</sup>

The utility of these techniques is limited by the expertise and comfort level of the operator and should not replace formal histology. However, there is evidence to suggest that the diagnostic reliability of the Tzanck smear for these entities can be high. The diagnosis of erosive vesiculobullous and ranulomatous lesions can be made reliably with brief training, showing substantial agreement between experienced and less experienced operators

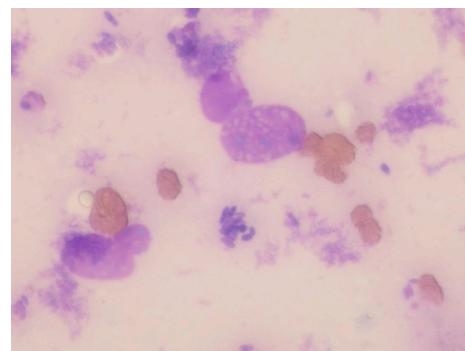
**Table III.** Blistering diseases (Tzanck smear)

Disease	Microscopic appearance
Pemphigus vulgaris	Acantholytic cells, hypertrophic nuclei, basophilic cytoplasmic rim; cell adherence, streptocyte, and Sertoli rosette; immunofluorescence
Bullous pemphigoid	Abundant eosinophils; otherwise nonspecific
Hailey–Hailey disease	Acantholytic cells, hypertrophic nuclei, basophilic cytoplasmic rim; no adherence, streptocyte, or rosette; nonfluorescent
Darier disease	Corps ronds and grains (hyaline pink round and ovoid bodies)
HSV and VZV	Multinucleation, molding, and margination of nuclear chromatin
SJS/TEN	Necrotic cuboidal basal keratinocytes, large nuclei, and inflammatory cells
Staphylococcal scalded-skin syndrome	Acantholytic broad superficial keratinocytes, small nuclei, and no inflammation

HSV, Herpes simplex virus; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; VZV, varicella zoster virus.



**Fig 13.** Tzanck smear of basal cell carcinoma showing clusters of atypical, large, basophilic basaloid cells that clump together with peripheral palisading. (Original magnification:  $\times 200$ .)



**Fig 14.** Tzanck smear of squamous cell carcinoma with pleiomorphic isolated cells with hypertrophic, hyperchromic, lobulated or multiple/mitotic nuclei and vacuolated cytoplasm. (Original magnification:  $\times 400$ .)

( $\kappa = 0.79$  and  $0.68$ , respectively). The accurate evaluation of tumoral lesions appears to require more experience, showing only moderate agreement ( $\kappa = 0.50$ ). When applied to pigmented lesions, the accuracy of the Tzanck smear appears to be similar to that of dermoscopy, with an overall diagnostic accuracy of  $90.5\%$ , and superior with respect to differentiating melanocytic from nonmelanocytic pigmented lesions.<sup>22</sup> While not replacing obtaining a biopsy specimen, exfoliative cytology can be a useful adjunct to traditional methods like dermoscopy or biopsy, particularly when pathology services are unavailable (as in resource-limited settings) or when results are needed in a timely fashion.<sup>28</sup>

## WET MOUNTS IN THE DIAGNOSIS OF VULVOVAGINAL DISEASES

### Key points

- Pseudohyphae or budding yeast confirm the presence of vaginal candidiasis
- The presence of clue cells and absence of lactobacilli can help confirm bacterial vaginosis

The evaluation of a patient with vulvovaginal diseases often necessitates the use of bedside diagnostics to complement clinical examination. The evaluation of scale, pustules, and vesicles in the vulvar area can be performed using the methods previously discussed. Examination of vaginal secretions, or a “wet mount,” may also provide useful information. Wet mount preparations are performed by collecting vaginal secretions with a cotton-tipped applicator from the blades of a speculum, from the secretions pooled within the vagina, or from the vaginal walls. The cotton-tipped applicator is touched or swiped onto a glass slide to create a thin layer of the secretions, followed by application of a drop of normal saline and a coverslip.<sup>29</sup>

The wet mount provides information on the morphology of epithelial cells, inflammatory cells, and the presence of organisms, both colonizing and infectious. The range of normal findings includes mature epithelial cells, which are large, polygonal cells with abundant cytoplasm and small nuclei, and parabasal cells, which are smaller and rounder

**Table IV.** Malignant and benign tumors and other diseases (Tzanck smear)

Disease	Microscopic appearance
Basal cell carcinoma	Clustered large, atypical, basaloid cells with peripheral palisading
Clear cell acanthoma	Keratinocytes with multiple small cytoplasmic vacuoles
Dermatofibroma	Spindle-shaped fibroblasts
Erythroplasia of Queyrat	Cellular and nuclear polymorphism and enlarged nuclei
Foreign body granuloma	Foreign body giant cells and foreign material
Granuloma annulare	Palisading granulomas and mucin
Histiocytosis	Large pale cells with large reniform nuclei
Juvenile xanthogranuloma	Foamy Touton giant cells
Mastocytoma	Abundant irregularly shaped mast cells; reddish purple granules
Melanocytic nevus	Dermal- and epidermal-type nevoid cells
Melanoma	Atypical nevoid cells; multinucleation, irregular molded nuclei
Paget disease	Large, round cells; microvacuolated cytoplasm; large, eccentric nuclei
Sarcoidosis	Granuloma formation and Langerhans type giant cells
Seborrheic keratosis	Hyperkeratosis and horny cysts
Spongiotic dermatitis (vesicular)	Numerous tadpole cells
Squamous cell carcinoma	Pleomorphic isolated cells with hypertrophic, hyperchromatic, lobulated or multiple/mitotic nuclei and vacuolated cytoplasm
Vellus hair cyst	Numerous vellus hairs within cyst contents

immature epithelial cells with large nuclei. Parabasal cells can be seen in inflamed skin or atrophic, estrogen-deficient vaginal epithelium and represent a disorder in maturation.<sup>29</sup> Lactobacilli, which are small rods of varying lengths that can attach end-on-end to each other, constitute normal bacterial flora in the vagina. Leukocytes in a ratio of 1:1 with epithelial cells also are considered normal. Increased numbers can be seen in infections such as *Trichomonas* or in inflammatory dermatoses.<sup>29-31</sup>

Other abnormal findings can provide a definitive diagnosis. Pseudohyphae, yeast forms, or budding yeast confirm the presence of *Candida* species.<sup>29-31</sup> The presence of clue cells, which are epithelial cells with bacteria adherent to the cell wall so that they appear ragged, together with a lack of lactobacilli, can help confirm the diagnosis of bacterial vaginosis (which is diagnosed on the basis of  $\geq 3$  clinical criteria: milky, copious vaginal discharge, pH  $> 5$ , positive whiff test, and identification of clue cells).<sup>29-31</sup>

## CLINICAL LABORATORY IMPROVEMENT AMENDMENTS CERTIFICATION

### Key point

- Clinical Laboratory Improvement Amendments certification helps ensure minimum performance standards for provider-performed procedures

The Centers for Medicare and Medicaid Services regulates all human clinical laboratory testing through CLIA. The objective of CLIA is to ensure quality laboratory testing by establishing minimum

performance standards and quality control. This jurisdiction extends to provider-performed procedures, such as scabies preparation, KOH preparation, and Tzanck smear (as well as those performed by other specialties, such as wet mount, urinalysis, and arthroscopic fluid analysis, etc). For the purposes of clinical decision making, providers should be certified and compliant by CLIA standards, with regular competency and quality control checks. While certification is not difficult, an understanding of CLIA requirements is necessary.<sup>32</sup> Once certified, standard bedside diagnostic tests are billable. Nonstandard applications of these and other techniques discussed in this manuscript are not among those certified by CLIA.

## DISCUSSION

Bedside diagnostic tests can provide rapid answers to important clinical questions, including diagnosis of common and uncommon infectious diseases as well as a wide variety of benign and malignant dermatologic conditions.<sup>28,33</sup> Bedside tests can complement more expensive and time-consuming tests. They are rapid, practical, and economical, well-tolerated, repeatable, and suitable for difficult surfaces like the face, genitals, and mouth. They may be particularly valuable in resource-limited settings, on inpatient wards, and in the clinic.

Each technique is easily performed but requires expertise in interpretation. Dermatologists, with training in surgery and pathology, are well-equipped to carry out and interpret these tests but may need

special training to interpret some of them accurately, such as for cutaneous tumors. Like dermoscopy, and despite their limitations, bedside tests are a useful adjunct to the clinical examination. When used appropriately, these techniques provide unique efficiency and operational autonomy.

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# Etiologies and management of cutaneous flushing



## Nonmalignant causes

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### Learning objectives

After completing this learning activity, the participant should be able to describe the recommended diagnostic workup for uncommon serious causes of cutaneous flushing and describe the best management practices for causes of flushing.

### Disclosures

#### Editors

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The flushing phenomenon may represent a physiologic or a pathologic reaction. Although flushing is usually benign, it is prudent that the physician remains aware of potentially life-threatening conditions associated with cutaneous flushing. A thorough investigation should be performed if the flushing is atypical or not clearly associated with a benign underlying process. The diagnosis often relies on a pertinent history, review of systems, physical examination, and various laboratory and imaging modalities, all of which are discussed in the 2 articles in this continuing medical education series. This article reviews flushing associated with fever, hyperthermia, emotions, menopause, medications, alcohol, food, hypersensitivity reactions, rosacea, hyperthyroidism, dumping syndrome, superior vena cava syndrome, and neurologic etiologies. (J Am Acad Dermatol 2017;77:391-402.)

**Key words:** blushing; climacterium; dumping syndrome; emotional flushing; fever; flushing; hot flush; hypersensitivity reactions; hyperthermia; hyperthyroidism; menopause; rosacea; SVC syndrome.

### HISTORY

The concept of the flushing reaction dates back to 1839 when T. H. Burgess published a report on blushing. He proposed that blushing was a uniquely human trait designed by the creator in “order that the soul might have sovereign power of displaying in the cheeks the various internal emotions of the moral feelings.”<sup>1-3</sup> Charles

Darwin further discussed blushing in the *Expression of the Emotions in Man and Animals* in 1872.<sup>1,2,4</sup> E. J. Tilt coined the term “flush” in 1882. In 1890, descriptive works were provided by Henry Campbell.<sup>1,5</sup> It was not until 1980 that research began unraveling the pathophysiology of the complex mechanisms of flushing.<sup>1</sup> This delay may be explained by the fact that flushing reactions

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were viewed primarily as emotionally rooted and cosmetic for some time. The association of flushing and specific chemical mediators of various disease processes sparked a renewed interest in the subject of flushing.<sup>2</sup>

## DEFINITION/DISTRIBUTION/ANATOMY

Flushing is defined as visible reddening of the skin accompanied by a sensation of warmth.<sup>2,6-8</sup> Synonyms of flushing include hot flashes, hot flushes, hot blooms,<sup>1</sup> and blushing.<sup>2</sup> Classic areas of flushing are the face, ears, neck, and upper aspect of the chest (Fig 1).<sup>1,2,6-9</sup> The greater visibility of flushing in these areas is caused by the superficial nature of the cutaneous vasculature and an increased vascular capacitance for dilation in these regions. Variations in the stratum corneum, a thin papillary dermis, flatter epidermal rete ridges, wider diameter of blood vessels, and subpapillary plexus closer to the skin surface contribute to increased visibility in these blush regions.<sup>8</sup>

Vasodilation of flushing is mediated by nerves or vasoactive substances acting on vascular smooth muscle. The transient nature of flushing is related to variances in the vascular response of the blush areas. There are 4 neurally mediated vascular responses in the face: (1) sympathetic vasoconstrictor fibers have a tonic constricting influence on the vessels of the ears, lips, and nose, while sparsely supplying other areas of the face; (2) sympathetic vasodilation of the face during heat, stress, and emotion; (3) parasympathetic vasodilation with reflexes in the facial and glossopharyngeal nerves increase blood flow to exocrine glands, the eyes, nose, and mouth during irritation of these tissues; and (4) axon reflexes release vasoactive peptides from sensory fibers that contribute to a local inflammatory response.<sup>10</sup>

## PHYSIOLOGIC FLUSHING

### Key points

- Physiologic forms of flushing are classified as benign cutaneous flushing
- The most common forms are thermoregulatory, emotional, and extrinsic-mediated
- Extrinsic agents, or substances that have been topically applied, ingested, or systemically administered, are a frequently encountered cause of flushing, and in many cases, extrinsic mediators exacerbate flushing in patients who are predisposed

### Thermoregulatory flushing

Thermoregulatory flushing is caused by fever and hyperthermia.<sup>6</sup> During febrile episodes, body heat



**Fig 1.** A 54-year-old woman with idiopathic flushing.

is dissipated using a mechanism of cutaneous vasodilation and perspiration. Some patients are exceptionally sensitive to this pathophysiologic mechanism.

Hyperthermia can be induced by exercise or exogenous heat, such as a warm environment or ingestion of hot substances.<sup>6</sup> Ingestion of hot food and beverages can increase the temperature of the oropharyngeal cavity and cause flushing by a countercurrent exchange model. Increased heat in the mouth dissipates to the tissues surrounding the oral cavity, including the internal jugular vein and common carotid artery. The increased temperature of the blood flowing through this vasculature is transferred to the internal carotid artery and base of the brain. The body's thermostat, the anterior hypothalamus, reacts to slight changes in temperature of the arterial supply. This triggers heat dissipation via autonomic reactions, such as flushing and sweating.<sup>11</sup> Thermoregulatory flushing also occurs in climacterium because of circadian cycling of core body temperature.<sup>1,6,7</sup>

Thermoregulatory flushing can be controlled by resetting the body's thermostat. This can be accomplished by applying cold compresses to the face or neck, drinking ice water, or holding ice chips in the back of the mouth. Any mechanism that cools the oropharyngeal cavity for periods of >30 min can lead to countercurrent-induced central cooling, which increases the hypothalamic tolerance to hyperthermia.<sup>6</sup>

### Emotional flushing

Emotional flushing is temporally related to situations of emotional distress or embarrassment. Women are affected more than men.<sup>12</sup> Emotional flushing is typically resistant to medications.<sup>6,12</sup> Management with beta blockers has been attempted, but data on efficacy are lacking.<sup>6</sup> Treatment options include psychological modification in the form of biofeedback, paradoxical intention, and

hypnosis therapy.<sup>1,6</sup> Patients who undergo biofeedback have increased control of spontaneous flushing episodes but not of flushing provoked by ingestants.<sup>13</sup>

Bilateral endoscopic transthoracic sympathectomy (BETS) can be considered in certain refractory and distressing cases of flushing, but it is not a first- or second-line treatment option. Patient satisfaction varies, and it is not uncommon for patients to develop postprocedure adverse reactions of compensatory hyperhidrosis or gustatory-induced perspiration. Other risks include Horner syndrome and postoperative pneumothorax.<sup>14-18</sup>

### Climacteric flushing

Climacterium, or menopause, is a common condition affecting women in their fifth through seventh decades of life. It is associated with hot flushes, which are frequent brief episodes of flushing, sweating, and the sensation of overheating, often accompanied by palpitations and anxiety.<sup>6</sup> The flush distribution involves the chest, head, and neck.<sup>1,19</sup> Episodes last a few minutes and may occur up to 20 times per day. Alcohol, hot beverages, heat, and stress can trigger flushing.<sup>6,9</sup> Hot flushes may cause nighttime awakenings, which can lead to sleep disruption, fatigue, and irritation.<sup>1,7</sup> The flushing will usually subside after months to several years.<sup>1,19</sup>

Primary menopausal hot flushes are typically a result of age-related loss of ovarian function.<sup>6</sup> Secondary causes include surgery (ie, oophorectomy)<sup>7,9</sup> and pharmacotherapy after adolescence. A number of medications can induce a pharmacologic menopause reaction, including antiestrogen medications (ie, tamoxifen, clomiphene citrate, and 4-hydroxyandrostenedione), gonadotropin-releasing hormone agonists (ie, leuprolide and treptorelin), and danazol.<sup>6</sup> Alternatively, withdrawal from hormone replacement therapy can induce symptoms.<sup>2,7,19</sup> Occasionally, females in their thirties can develop cyclic flushing episodes associated with their menses. Flushing occurs during the week before the onset of menses.<sup>6</sup>

Primary treatment involves behavioral and lifestyle modifications, such as avoiding triggers and maintaining a cool body temperature.<sup>19,20</sup> Pharmacologic therapy is instituted if these fail or if symptoms are distressing.

Paroxetine, a selective serotonin reuptake inhibitor, was approved by the US Food and Drug Administration in 2013 for nonhormone treatment of vasomotor symptoms. It is approved at 7.5 mg nightly. Selective serotonin reuptake inhibitor

therapy has a quicker effect on vasomotor symptoms than depressive symptoms.<sup>21</sup> Fluoxetine, sertraline, citalopram, escitalopram,<sup>22</sup> and venlafaxine<sup>20,23-25</sup> have also been studied for the management of vasomotor symptoms of menopause. Studies have shown significant improvement of hot flushes, making it a good alternative to hormone replacement therapy.<sup>20</sup> Gabapentin has also shown benefit as a nonhormonal treatment.<sup>20,24-26</sup>

Because hormonal changes are implicated as causative, symptoms can resolve with administration of hormone therapy. Hormone replacement therapy is often beneficial for short periods of time in patients with severe climacteric symptoms.<sup>6,7,20,24</sup> There are controversies and risks associated with hormone replacement therapy, warranting discussion with the patient's gynecologist or endocrinologist.<sup>19,24</sup>

Bazedoxifene is a third-generation selective estrogen-receptor modulator with tissue-selective activity. Combination therapy with bazedoxifene and conjugated estrogens (Duavee; Pfizer, New York, NY) at 20 mg/0.45 mg daily is approved for treatment of moderate to severe vasomotor symptoms associated with menopause. This is a progestin-free hormone therapy option for postmenopausal women. Studies showed a 74% decrease in hot flush frequency.<sup>27</sup>

Central adrenergic and opioid pathways may also play a role in treatment.  $\alpha$ -2 adrenergic agonism with clonidine<sup>2,6</sup> and opioid antagonism with naloxone have been proposed as adjuncts for treatment of climacteric flushing. However, more recent studies of clonidine have shown little or no benefit in the treatment of menopausal hot flushes.<sup>19,20</sup> A recent review concluded that vitamin E, evening primrose oil, acupuncture, and exercise also have no benefit. Black cohosh has contradictory evidence. It is to be used cautiously in patients with a personal or family history of breast cancer because of its estrogenic properties.<sup>25</sup> In refractory cases of menopausal flushing, stellate ganglion blockade may be considered.<sup>28</sup>

Although rare, men can also undergo climacterium, or andropause. Climacteric flushing in males results after an acute drastic decrease in testosterone levels. Primary male climacterium is rare and occurs during aging. Secondary causes are more common and occur after surgery or with drug therapy.<sup>6</sup> Surgical causes include orchectomy, which is performed for advanced prostate carcinoma, or after testicular vascular compromise from bilateral hernia repair.<sup>6,29</sup> Antiandrogen agents, such as flutamide and gonadotropin-releasing hormone agonists (ie, leuprolide acetate), may precipitate a drop of testosterone and induce associated flushing.<sup>6,30</sup>

**Table I.** Medications associated with flushing

Antiemetics: metoclopramide and alizapride
Antimicrobials: vancomycin, rifampin, and metronidazole
Brimonidine
Calcium channel blockers: Nifedipine, verapamil, and diltiazem
Calcitonin
Catecholamines
Chemotherapeutic agents: $\alpha$ 2-interferon, cyclosporine, cisplatin, dacarbazine, doxorubicin, mithramycin, and tamoxifen
Cholinergic medications, such as antihelminthic agents and metrifonate
Contrast media
Disulfiram
Glucocorticosteroids (oral, intraarticular, and epidural)
Gold (nitritoid reaction)
Hormonal agents: thyrotropin-releasing hormone, corticotropin-releasing hormone, cyproterone acetate, bromocriptine, and leuprolide acetate
Morphine, opiates
Nonsteroidal antiinflammatory drugs
Pilocarpine
Serotonin agonists (selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants): caution for serotonin syndrome
Vasodilators: nicotinic acid/niacin, nitroglycerin, phosphodiesterase type 5 inhibitors (ie, sildenafil), prostaglandins, amyl nitrate, and butyl nitrite

Adapted from Izikson et al.<sup>33</sup>

Treatment involves androgen replacement if appropriate. Other options include megestrol, estrogen analogues, gabapentin, venlafaxine, or paroxetine.<sup>31</sup> Although various treatment options exist, evidence is preliminary or limited and none are approved by the US Food and Drug Administration at this time.<sup>30</sup>

### Topical extrinsic mediators of flushing

Topical application of cinnamic aldehyde, a common fragrance additive in foods and topical products, can induce flushing. Urticaria and stinging may also develop. Similar cutaneous vasodilation may occur with topical compounds that include sorbic acid and methylnicotinate. This is mediated by prostaglandin D2 production and can be reduced by preemptive administration of aspirin, a cyclooxygenase 1 inhibitor.<sup>32</sup> There is a controversial association of topical brimonidine with flushing.

### MEDICATIONS

Several medications have been associated with flushing, and a partial list is provided in Table I.

Flushing severity ranges from asymptomatic to extremely uncomfortable, with mild to severe redness. Distress caused by flushing can lead to medication noncompliance.

The etiology of flushing with medications varies depending on the class and mechanism of each drug. For instance, opiates trigger flushing by release of histamine. Therefore, antihistamines are a feasible treatment modality for opiate-induced flushing. Other medications act as vasodilators or cholinergic agents. The route of medication delivery can also cause flushing. Intraarticular steroid injections cause flushing because of capsular distention of the joints.

Flushing caused by niacin or nicotinic acid may be prevented with long-acting preparations of niacin or with aspirin therapy.<sup>6,7,9</sup> This may in turn improve compliance with therapeutic doses of niacin.<sup>6</sup>

Please refer to Litt's Drug Eruption Reference Manual for a complete list of drugs that may cause flushing.<sup>34</sup>

### Serotonin syndrome

Serotonin syndrome (SS) is a potentially life-threatening condition caused by excess serotonergic activation of the central nervous system and peripheral receptors. Patients with SS can present with any of the following symptoms: altered mental status, autonomic hyperactivity, and neuromuscular irritability. The complete triad may not be present in all patients. Other symptoms and signs include tremor, diarrhea, tachycardia, shivering, diaphoresis, mydriasis, nystagmus, hypertonicity, clonus, hyperreflexia, hypertension, hyperthermia, hyperactive bowel sounds, agitation, hypervigilance, pressured speech, spasms, salivation, flushing, delirium, neuromuscular rigidity, and coma. In severe cases, metabolic acidosis, rhabdomyolysis, elevated serum aminotransferase levels, seizures, renal failure, and disseminated intravascular coagulation can occur.

SS can result from therapeutic drug use, overdose, or drug interactions. Serotonergic drugs include selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and opiates. Inciting factors can also include triptans, antibiotics, antiemetics, over the counter cough syrup, herbal remedies, or illicit drugs, such as 3,4-methylenedioxymethamphetamine (ecstasy). Symptom onset is rapid and occurs within minutes to hours. There are no laboratory tests to confirm the diagnosis.

Treatment involves discontinuation of the serotonergic agents, supportive care, and in some cases, benzodiazepines, 5-hydroxytryptamine receptor 2A antagonists, such as cyproheptadine,

sedation, neuromuscular paralysis, and intubation in life-threatening situations.<sup>35,36</sup>

## Alcohol

Alcohol ingestion may result in “dry” flushing in patients with aldehyde dehydrogenase gene polymorphisms, which are common in Asians and people of Mongoloid lineage. Therefore, the term “Oriental flushing” has been used. A deficiency or inactive form of aldehyde dehydrogenase causes increased acetaldehyde levels, resulting in slower alcohol metabolism and cutaneous flushing.<sup>37,38</sup> After drinking small amounts of alcohol, these patients may also develop decreased blood pressure, elevated heart rate, dizziness, lightheadedness, fatigue, anxiety, headache, weakness, nausea, or vomiting.<sup>38-41</sup> Studies have shown that pretreatment with antihistamines,<sup>40</sup> aspirin, or naloxone decrease the flushing associated with alcohol ingestion in this patient population.<sup>39</sup>

There have been numerous attempts to link alcohol-induced flushing with other comorbidities. Currently, there are limited cohorts that suggest an increased risk of insulin resistance,<sup>42</sup> hypertension,<sup>43</sup> and metabolic syndrome.<sup>44,45</sup> It has also been proposed that such patients are more susceptible to liver damage and esophageal cancer.<sup>46</sup> Alcohol in this population, as compared to those who do not flush with alcohol ingestion, has a negative effect on triglycerides and less positive effects on high-density lipoprotein cholesterol.<sup>45</sup>

Alcohol-induced flushing is typically diagnosed by assessing the patient’s history of alcohol intake. An ethanol patch test can be used to produce localized erythema, which is suggestive of a potential flusher.<sup>39</sup> However, the patch test has limitations in those homozygous for the gene and requires genotype testing for definitive diagnosis.<sup>47</sup>

Alcohol may also exacerbate flushing associated with malignancies, such as carcinoid, mastocytosis, lymphoreticular malignancies, and medullary thyroid disorder; these will be discussed in detail in the next article in this series.

## FOOD

### Key point

- Nitrites, sulfites, and capsaicin can cause flushing

### Food additives

Nitrites are found in deli meats or cured meats and may provoke flushing and headache.<sup>6</sup>

Sulfites are a common preservative and antioxidant additive used in food and pharmaceuticals.

These additives can be found in foods (dried fruits and vegetables, pickled onions, and jams/jellies), drinks (bottled soft drinks, wine, and beer), cosmetics (hair dyes, creams, and perfumes), and medicines. Topical, oral, or parenteral exposure can cause dermatitis, urticaria, flushing, hypotension, abdominal pain, diarrhea, angioedema, bronchoconstriction, or anaphylaxis in sensitive individuals.<sup>48</sup> Symptom onset is rapid, occurring within 2 to 15 minutes. The mechanism is believed to be a neural reflex of the irritant receptors in the nose, pharynx, and esophagus, which produces a cholinergic efferent response. Certain anticholinergic drugs have been shown to prevent sulfite reactions. Many sulfite-sensitive individuals are asthmatics. Deficiency of the sulfite oxidase enzyme can be found in some sulfite-sensitive patients. In these patients, treatment with cyanocobalamin (vitamin B12) can protect against sulfite reactions. Avoidance is the best preventative measure for those who are sensitive to nitrites and sulfites.<sup>49</sup>

Spicy foods containing capsaicin, the active compound in red pepper, can cause flushing in sensitive individuals.<sup>1,6</sup> Spicy and sour foods induce gustatory flushing by activating a neural reflex of the trigeminal nerve. In these cases, flushing may be unilateral.<sup>1</sup>

Monosodium glutamate (MSG) is used as a flavor enhancer and is commonly added to Chinese food. MSG-induced flushing is controversial. Several studies have shown that MSG is an unlikely cause of flushing in many individuals. It is likely that other concomitant dietary agents (nitrates, sulfites, or peppers), thermal heat, or the coingestion of alcohol trigger flushing when eating foods containing MSG. A true MSG reaction causing flushing is rare, if it occurs at all.<sup>50</sup>

### Fish poisoning

Histamine fish poisoning has also been referred to as scombroid fish poisoning, pseudoallergic fish poisoning, histamine toxicity, or mahi-mahi flush.<sup>51</sup> Improper refrigeration of fish allows overgrowth of bacteria that converts histidine to histamine. Although scombroid-type fish (mackerel, tuna, skipjack, bonito, and albacore) were originally associated with the syndrome, nonscombroid fish (salmon, mahi mahi, amberjack, marlin, yellowtail, herring, sardine, anchovy, and bluefish) frequently cause illness as well. Cooking the fish does not prevent poisoning.<sup>6,52</sup> Symptoms begin within 10 to 30 minutes of ingestion and include flushing of the face and upper torso, headache, sweating, oral burning, abdominal pain, nausea, vomiting, diarrhea, and possibly urticaria. Often the patient will

report the fish tasting metallic, tangy, peppery, or bitter. Patients who are taking medications that inhibit histamine metabolism, such as monoamine oxidase inhibitors or isoniazid, may be at increased risk.<sup>53</sup> The diagnosis is clinical and a history of fish ingestion is key.<sup>6,53,54</sup> The majority of cases are mild, resolve quickly (within 8 hours), and do not require treatment. Severe cases respond well to treatment with H<sub>1</sub> and H<sub>2</sub> antihistamines and supportive care.<sup>6,51,53,54</sup>

Ciguatera fish poisoning is another fishborne illness that occurs after ingesting a fish that contains ciguatoxin, a heat-resistant toxin produced by the marine algae *Gambierdiscus toxicus*. Cooking does not destroy the toxin. Causative fish include sea bass, snapper, grouper, amberjack, hogfish, surgeonfish, or barracuda. The symptoms include flushing, pruritus, abdominal pain, vomiting, diarrhea, myalgias, and weakness. Neurological symptoms, such as dyesthesia and ataxia, also occur. Symptom onset occurs within a few hours of ingestion and is usually self-limiting. Symptoms can persist for days to weeks, and residual effects can last for years. An immunoassay allows for the ciguatoxin to be detected in the fish tissue. There is no cure, and treatment involves symptomatic management. Public health authorities should be notified immediately if a case is suspected.<sup>6</sup>

## INFUSION REACTIONS AND HYPERSENSITIVITY REACTIONS

Infusion reactions occur with the infusion of blood products or medications. This may arise via immunologic or nonimmunologic mechanisms. Acute hemolytic reactions after a blood transfusion may manifest with flushing, fever, hypotension, lower back pain, wheezing, or anxiety. Acute transfusion reactions occur within 24 hours of a blood transfusion and may be associated with immune or non-immune-mediated hemolysis.<sup>55</sup> The transfusion should be stopped immediately and workup performed per the institution's protocols.

Flushing can be encountered during the rapid infusion of certain medications, such as vancomycin, ciprofloxacin, amphotericin B, rifampicin, and teicoplanin. This is caused by histamine release.<sup>56</sup> Other symptoms can include a rash or pruritus. The medication should be discontinued immediately and a dose of 50 mg of diphenhydramine should be given, either intravenously or orally. Once the skin changes abate, the infusion can be reinstated at a lower rate.

Infusion of monoclonal antibodies or chemotherapeutic infusions can produce infusion reactions

by various mechanisms.<sup>57</sup> Pretreatment with antihistamines or corticosteroids is recommended to reduce the frequency and severity of hypersensitivity reactions. Patients should be closely monitored during and after the infusion. For a mild reaction, such as flushing, chills, or temperature <38°C, it is important to stop the infusion and assess the patient. Supportive care should be given with acetaminophen, antihistamines, and fluids if needed. If symptoms resolve, the patient can be rechallenged with a reduced infusion rate, adequate premedication, and a desensitization protocol if indicated. For severe reactions, such as hives, fevers, chills, chest pain, drastic changes in blood pressure, angioedema, or anaphylaxis, the medication should be discontinued and supportive care initiated. In these cases, the infusion should not be restarted.<sup>58</sup>

Flushing may also accompany a hypersensitivity reaction, most notably a type I or anaphylactic hypersensitivity reaction. This is caused by an immediate immunoglobulin E-mediated reaction. Allergens include insect envenomation, food allergies (particularly nuts, fish, and shellfish), medications, plants, or pollen.<sup>59</sup>

## ROSACEA

Rosacea is a common inflammatory dermatologic condition. Facial flushing is often present in patients with rosacea (Figs 2 and 3). Telangiectasias, skin textural changes, inflammatory papules, and pustules may also be seen. Patients typically complain of burning, stinging, itching, pain, dryness, or swelling.<sup>60,61</sup> Triggers include stress, exercise, heat, spicy foods, hot beverages, and alcohol.<sup>60,62</sup> The 4 subtypes of rosacea (erythematotelangiectatic, papulopustular, phymatous, and ocular) are diagnosed clinically.<sup>60,61</sup> The diagnosis and management of rosacea was reviewed in 2015 by Two et al.<sup>60,62</sup>

Moisturizing, sun protection, and avoidance of triggering factors are essential. In addition, there are many pharmacologic treatment options. The US Food and Drug Administration has approved topical sodium sulfacetamide, azelaic acid, metronidazole, ivermectin, oxymetazoline hydrochloride, and brimonidine for rosacea treatment.<sup>61-63</sup> Brimonidine is a selective alpha-2 adrenergic receptor agonist with vasoconstrictive activity.<sup>61,62</sup> However, a minority of rosacea patients experience significant vasodilation or flushing upon withdrawal of brimonidine.

Systemic therapies include tetracyclines, beta-blockers, and isotretinoin. Studies have shown that certain beta-blockers, such as propranolol and carvedilol, decrease the flushing and erythema of



**Fig 2.** A 43-year-old woman with flushing associated with rosacea.

rosacea by vasoconstriction of dermal blood vessels. Beta-blockers have also been shown to decrease anxiety and tachycardia, both of which can trigger flushing.<sup>62</sup>

Pulsed dye laser and intense pulsed light therapy have been shown to decrease flushing associated with rosacea. Destruction of excessive cutaneous vasculature and decreased blood flow is the likely mechanism.<sup>61,64</sup> The Q-switched 595-nm neodymium-doped yttrium aluminium garnet laser has been used for the off-label treatment of rosacea.<sup>65</sup> In addition, small studies have shown improvement of rosacea symptoms<sup>66</sup> and decreased facial flushing<sup>67</sup> after treatment with long-pulsed 1064-nm neodymium-doped yttrium aluminium garnet laser. Botulinum toxin A injection also appears to reduce flushing in rosacea.<sup>61,68,69</sup>

## SYSTEMIC CONDITIONS

### Key point

- Various systemic conditions have been associated with flushing, including hyperthyroidism, dumping syndrome, superior vena cava obstruction, and neurological causes



**Fig 3.** Flushing associated with rosacea.

Various systemic conditions have been associated with flushing. These include hyperthyroidism, dumping syndrome, superior vena cava (SVC) obstruction, and neurologic causes (Table II).

### Hyperthyroidism

Hyperthyroidism may be associated with facial flushing.<sup>70-72</sup> Symptoms include tremor, emotional lability, irritability, anxiety, tachycardia, heat intolerance, perspiration, weakness, and weight loss in spite of normal or increased appetite. The skin is warm, moist, and smooth. A physical examination may also reveal atrial fibrillation,<sup>73</sup> goiter, nail abnormalities, ophthalmopathy, pretibial myxedema, or acropachy.<sup>70-72</sup> Laboratory evaluation includes thyroid-stimulating hormone, free T4, T3, and thyroid antibodies. Definitive treatment of the underlying disease should be referred to a specialist; however, beta-blockers may be used in the interim to control symptoms.<sup>73</sup>

### Dumping syndrome

Dumping syndrome is a complication of esophageal, gastric, or bariatric surgery, resulting in rapid gastric emptying of large particles to the small intestine. This causes a fluid shift from the intravascular space to the intestinal lumen, which leads to vasomotor and gastrointestinal symptoms. Abdominal pain, fullness, borborygmi, nausea, vomiting, diarrhea, flushing, palpitations, tachycardia, perspiration, weakness, fatigue, dizziness, and syncope may occur after ingestion of a meal.<sup>74-78</sup> A clinical diagnosis is based on postprandial symptoms, and may be confirmed with a modified oral glucose tolerance test. Gastric emptying studies or endoscopy can also aid in diagnosis. Medical management includes dietary modification, acarbose for hypoglycemia, and slow-release

**Table II.** Neurologic causes of flushing

Autonomic hyperreflexia
Riley-Day syndrome (familial dysautonomia)
Brain tumors
Spinal cord lesions
Diabetic autonomic neuropathy
Migraines
Cluster headaches
Trigeminal neuralgia
Trigeminal nerve damage
Paroxysmal extreme pain disorder
Erythromelalgia
Auriculotemporal syndrome (Frey syndrome)
Autonomic epilepsy
Harlequin syndrome
Horner syndrome
Holmes-Adie syndrome
Ross syndrome
Streeter syndrome
Parkinson disease (nonmotor "off" states)
Multiple sclerosis
Infantile neuroaxonal dystrophy
Pure progressive autonomic failure
Postural orthostatic tachycardia syndrome
Secondary neurologic involvement caused by systemic conditions: systemic lupus erythematosus and sarcoidosis

Adapted from Izikson et al.<sup>33</sup>

octreotide if dietary changes are not sufficient. If these fail, patients may require remedial surgery or continuous enteral feeding.<sup>77,78</sup>

### Superior vena cava obstruction

SVC syndrome results from the obstruction of blood flow through the superior vena cava. The clinical presentation depends on the location, degree of occlusion, and acuity of obstruction. Symptoms include flushing, head and neck swelling, upper extremity swelling, distended neck and chest veins, dyspnea, cough, hoarseness, dysphagia, chest pain, syncope, and headache.

Most cases are caused by malignancy, usually lung cancer or lymphoma.<sup>79,80</sup> Less common causes include substernal goiter,<sup>81</sup> thrombosis or fibrosis of central venous catheters, pacemaker wires, fibrosing mediastinitis, and aortic aneurysms.<sup>79,80</sup>

Diagnosis is suggested by a positive Pemberton sign. The Pemberton maneuver is performed by having the patient raise both arms until they touch the sides of the head. The patient will develop pronounced facial flushing and edema, usually within 1 minute.<sup>81,82</sup> This sign indicates impeded venous outflow from the head and neck caused by

compression of the SVC.<sup>81</sup> Computed tomography is the imaging modality of choice.<sup>80,82</sup> Treatment should be tailored to the underlying cause of compression and restoring blood flow.<sup>79,80</sup>

### Neurologic causes

Various neurologic disorders are associated with flushing and are outside the scope of this article. A list of causes is given in Table II. Warning signs of neurologic causes of flushing include unilaterality, seizure disorder, headache, pain, or other associated neurologic findings. A good reference to review is Freeman et al.<sup>83</sup>

### Autonomic hyperreflexia

Autonomic hyperreflexia, also known as autonomic dysreflexia, typically occurs in quadriplegics and paraplegics with spinal cord disruption at or above the T6 level.<sup>83-86</sup> It has also been seen after brainstem tumor resection involving the area of the fourth ventricle,<sup>84</sup> traumatic brain injuries, and in severe spinal multiple sclerosis.<sup>86</sup>

Disruption of descending sympathetic pathways allows afferent sympathetic stimuli from skin and other viscera to trigger a widespread sympathetic response.<sup>84-86</sup> Noxious stimuli below the level of the spinal cord lesion cause paroxysmal acute hypertension, bradycardia or tachycardia, cardiac dysrhythmias, throbbing headache, and anxiety. Cutaneous manifestations include flushing, piloerection, and diaphoresis above the level of the cord lesion.<sup>83-86</sup>

Episodes are elicited by visceral and somatic noxious stimuli from the bladder, rectum, cervix, stomach, or skin.<sup>83,85,86</sup> Examples include bowel or bladder distention,<sup>85,86</sup> suprapubic bladder pressure, gastric ulcers,<sup>84</sup> uterine contractions,<sup>85</sup> cutaneous pressure ulcers, tight clothing, sunburns, ingrown toenails, surgical procedures, position changes, or immersion into cold water.<sup>86</sup>

At rest, baseline blood pressure and plasma catecholamine levels are lower than controls; however, during reflexive episodes, blood pressure may increase 3-fold and plasma catecholamines also increase but levels still remain below those found in normal subjects.<sup>86</sup> Adverse outcomes include hypertensive crisis resulting in encephalopathy, cerebrovascular hemorrhage,<sup>85,86</sup> retinal hemorrhage, seizures, or death.<sup>86</sup> In patients with paralyzing spinal cord lesions and flushing, it is prudent to perform a thorough review of systems and a physical examination to exclude any obvious noxious stimuli.<sup>84,85</sup> Advise patients to partake in

proper skin care, regular bowel/bladder programs, and frequent position changes.<sup>86</sup> The use of adequate regional or general anesthesia and analgesia is recommended during procedures even if the patient has no sensation in that region.<sup>85,86</sup>

### Auriculotemporal syndrome

Auriculotemporal syndrome, also known as Frey syndrome, is typically unilateral facial flushing and sweating in the auriculotemporal distribution in response to gustatory stimuli, such as eating or drinking. Damage to the auriculotemporal nerve usually occurs during surgery or trauma to the parotid gland.<sup>6,83,87-89</sup> The likely mechanism is posttraumatic regenerated parasympathetic nerve fibers misdirected along sympathetic pathways to cutaneous vessels causing flushing and to sweat glands causing sweating.<sup>83,87-89</sup> Thermography and a Minor starch-iodine test can aid in diagnosis.<sup>90</sup> Treatment is rarely necessary,<sup>88</sup> but includes botulinum toxin A<sup>91</sup> and topical scopolamine or aluminum chloride. In refractory cases, surgical intervention is an option.<sup>83,92,93</sup>

In infants, the syndrome may result as a sequela of forceps-assisted delivery, may be unilateral or bilateral, and typically does not involve sweating. Childhood cases usually resolve spontaneously and do not require treatment.<sup>87-89,92</sup> Many of these cases are misdiagnosed as food allergies, oral allergy syndrome, or allergic contact dermatitis.<sup>87,92,94</sup>

### Harlequin and Horner syndromes

Harlequin syndrome is a physiologic flushing on the dependent half of the body caused by vasomotor instability in some newborns.<sup>95</sup>

Acquired Harlequin syndrome is a separate entity with acute onset of hemifacial flushing and sweating triggered by exercise, heat, or emotion.<sup>96</sup> It is caused by disruption of cervical sympathetic nerves from trauma, tumor growth, or stroke.<sup>97</sup> Unilateral flushing occurs on the normally innervated side while the pathological nonflushed side is caused by the lack of vasomotor response to sympathetic stimuli.<sup>95,97</sup>

The “Harlequin sign” is a compensatory unilateral flushing and sweating reaction caused by contralateral sympathetic denervation.<sup>96,98</sup> This can be seen with Horner syndrome, in addition to ipsilateral miosis and ptosis.<sup>98-100</sup> Patients with Harlequin syndrome have normal ocular sympathetic innervation,<sup>96</sup> distinguishing it from Horner syndrome.

Imaging modalities of the head, neck, and thorax may be needed to exclude malignancy or carotid artery thrombosis.<sup>100</sup>

### Other neurologic disorders

Pain disorders, such as migraines, cluster headaches, and trigeminal neuralgia, can cause neurovascular disruption via trigeminal activation and neurovascular reflexes, thereby inducing flushing.<sup>6,10,101-103</sup>

Table IV in the second article in this continuing medical education series contrasts selected common causes of flushing against other potentially worrisome causes.

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# Etiologies and management of cutaneous flushing



## Malignant causes

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### Learning Objectives

After completing this learning activity, participants should be able to describe the varied presentations of cutaneous flushing and list the potential etiologies of cutaneous flushing.

### Disclosures

#### Editors

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The second article in this 2-part continuing medical education series reviews the following malignant causes of flushing: mastocytosis, medullary thyroid carcinoma, pheochromocytoma, carcinoid tumors, gastroenteropancreatic neuroendocrine tumors, bronchogenic carcinoma, vasointestinal polypeptide secreting tumors, and renal cell carcinoma. The information provided will allow physicians to better distinguish patients who have worrisome presentations that require a more thorough investigation. Appropriate diagnostic workup and treatment options for these malignancies are reviewed. (J Am Acad Dermatol 2017;77:405-14.)

**Key words:** bronchogenic carcinoma; carcinoid syndrome; carcinoid tumor; flushing; gastroenteropancreatic neuroendocrine tumor; mastocytosis; medullary thyroid carcinoma; pheochromocytoma; renal cell carcinoma; vasointestinal polypeptide—secreting tumor.

**F**lushing may be caused by the release of vasoactive intrinsic mediators produced by malignancies. It is important to consider malignancy in patients presenting with nonphysiologic causes of flushing. These include flushing episodes associated with concurrent systemic symptoms, those that involve extensive portions of the body, or episodes that do not resolve within minutes.

## MASTOCYTOSIS

Mastocytosis is a clonal neoplastic proliferation of mast cells that can occur in various organs. The disease may range in severity from simple skin lesions to advanced mastocytosis, which can cause multiple organ failure. According to the World Health Organization's classification, there are 7 categories of mastocytosis: cutaneous, indolent systemic, systemic

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mastocytosis with associated clonal hematologic non–mast cell lineage disease, aggressive systemic mastocytosis, mast cell leukemia, mast cell sarcoma, and extracutaneous mastocytoma. Approximately 80% of patients with mastocytosis have skin involvement. In systemic mastocytosis, >50% of patients have skin lesions and almost all have bone marrow involvement. Clinical features of systemic mastocytosis include constitutional symptoms of fever, fatigue, weight loss, and diaphoresis; skin manifestations, such as pruritus, urticaria, and dermatographism; mast cell mediator symptoms, such as flushing, headache, syncope, hypotension, tachycardia, and gastrointestinal distress; and musculoskeletal complaints of myalgia, arthralgia, bone pain, and pathologic fractures.<sup>1</sup> Mast cell mediators responsible for these clinical features include histamine, prostaglandin D2, tryptase, and leukotriene C4.<sup>2</sup> Flushing is mediated by histamine and prostaglandin D2.<sup>3,4</sup>

Characteristic yellow-tan to reddish-brown macules and papules found mainly on the trunk and lower extremities<sup>2</sup> as well as Darier's sign, which is urtication of the lesion upon rubbing, may be evident on examination.<sup>1,2</sup> When obtaining a skin biopsy specimen from a patient with suspected mastocytosis, local anesthesia without epinephrine should be injected below the biopsy site to avoid degranulation.<sup>3</sup>

Laboratory evaluation is needed in cases of flushing or other systemic complaints. Serum total tryptase levels >20 ng/mL are suggestive of systemic mastocytosis and are used as a minor criterion for diagnosis.<sup>1</sup> Plasma and urinary histamine, urinary histamine metabolites (N-methylhistamine<sup>3,5</sup> and N-methyldimidazoleacetic acid),<sup>5</sup> and urinary prostaglandin D2 metabolites<sup>3,4,6</sup> are elevated. Patients may have concurrent anemia, leukocytosis, eosinophilia, neutropenia, and thrombocytopenia.<sup>1</sup> Obtaining a biopsy specimen from bone marrow is strongly recommended in adults because there is almost always bone marrow involvement in patients with systemic disease.<sup>1-4,7</sup> The World Health Organization criteria for diagnosis of systemic mastocytosis can be found in Table I.<sup>1</sup>

More than 90% of adults and 80% of children with mastocytosis have a gain-of-function mutation in c-kit. It is most commonly a missense activating mutation at codon 816 causing substitution of Val for Asp,<sup>1,2,7</sup> which leads to augmented mast cell proliferation and survival.<sup>2</sup>

Patients should avoid triggers and mast cell degranulators, including temperature extremes, stress, pressure, friction, alcohol, opioids, dextran, iodinated radiocontrast dyes, aspirin, and nonsteroidal antiinflammatory drugs.<sup>3,4,8</sup>

The mainstay of treatment is oral H<sub>1</sub> and H<sub>2</sub> antihistamines.<sup>3,8</sup> Cutaneous blood vessels have H<sub>1</sub> and H<sub>2</sub> receptors, which are responsible for histamine-induced vasodilation and vascular permeability.<sup>2</sup> Because of this, combination H<sub>1</sub> antihistamine (ie, hydroxyzine, diphenhydramine, or nonsedating cetirizine) and H<sub>2</sub> antihistamine (ie, cimetidine, ranitidine, or famotidine) may be used to treat flushing associated with mastocytosis. These medications also provide relief of pruritus and gastric hypersecretion and act as prophylaxis for hypotensive and anaphylactic episodes.<sup>2,3,9</sup>

Aspirin and nonsteroidal antiinflammatory drugs, which decrease prostaglandin synthesis, can be an effective therapy for flushing in certain patients with mastocytosis. However, because these antiinflammatory agents can also provoke mast cell degranulation and vascular collapse, they should be started at low test doses under close monitoring in a hospital setting.<sup>3,4,8</sup>

Oral psoralen plus ultraviolet A light phototherapy has been shown to control flushing and pruritus. Leukotriene antagonists, cromolyn sodium, and corticosteroids may also be used in the treatment of mastocytosis. Patients with anaphylactoid episodes require a self-injectable epinephrine device (ie, EpiPen [Mylan NV, Canonsburg, PA]). Surgical excision may be considered for solitary lesions. Aggressive forms of systemic mastocytosis may necessitate chemotherapy with interferon- $\alpha$  or cladribine.<sup>2,9</sup> Imatinib is recommended in patients with systemic mastocytosis associated with chronic eosinophilic leukemia and Fip1-like1/platelet-derived growth factor receptor- $\alpha$  fusion.<sup>2,10</sup>

## MEDULLARY THYROID CARCINOMA

Medullary thyroid carcinoma (MTC) represents a neuroendocrine malignancy of the parafollicular C cells of the thyroid.<sup>11</sup> Because the cells are of neural crest origin, they secrete a variety of active amines and peptides, including calcitonin, prostaglandins, histamine, corticotropin, corticotropin-releasing hormone,<sup>11,12</sup> serotonin, substance P, levodopa, katacalcin,<sup>12</sup> and vasoactive intestinal peptide.<sup>13</sup> Patients may complain of weight loss, fatigue, flushing, sweating, diarrhea, and a mass at the base of the neck producing subsequent dysphagia or hoarseness.<sup>14</sup> Flushing occurs as a result of secreted vasoactive mediators and involves the face and upper extremities.<sup>11,12</sup> Flushing is protracted and can occur with perspiration, discoloration, and telangiectasias.<sup>12</sup>

MTCs can be sporadic or caused by inherited mutations in protooncogenes, such as in multiple endocrine neoplasia (MEN) 2A and 2B. MEN 2A and

**Table I.** World Health Organization criteria for the diagnosis of mastocytosis

Diagnosis of systemic mastocytosis requires the major criterion and 1 minor criterion or $\geq 3$ minor criteria
Major criterion: Multifocal, dense infiltrates of mast cells ( $\geq 15$ mast cells in aggregates) in bone marrow and/or other extracutaneous organ(s)
Minor criteria: In biopsy specimens of bone marrow or other extracutaneous organs, $>25\%$ of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or, of all mast cells in the bone marrow aspirate smears, $>25\%$ are immature or atypical; activating point mutation at codon 816 of <i>KIT</i> in bone marrow, blood, or another extracutaneous organ; mast cell expression of CD2 and/or CD25 in addition to normal mast cell markers; or serum total tryptase persistently exceeds 20 ng/mL (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid)

Adapted from Horny et al.<sup>1</sup>

2B are autosomal dominant neoplastic disorders affecting multiple endocrine glands. They are caused by a mutation in the rearranged during transcription (RET) protooncogene.<sup>11,13,14</sup> MEN 2A may be associated with pheochromocytoma, parathyroid tumors, and cutaneous amyloidosis. MEN 2B may be associated with pheochromocytoma, mucosal neuromas, and Marfanoid habitus.<sup>13,14</sup> Patients with sporadic disease typically present with a symptomatic thyroid mass.<sup>11,13</sup> Cervical lymphadenopathy, when present, implies locally progressive disease.

Calcitonin levels will be elevated with MTC and correlate with tumor burden. Levels  $>100$  pg/mL have nearly a 100% positive predictive value of diagnosing MTC. Levels of 10 to 40 pg/mL are seen with lymph node metastases, and levels  $>150$  pg/mL are seen with distant metastases. Rising calcitonin is often the first indication of persistent or recurrent disease.<sup>13,14</sup> Serum procalcitonin has been shown to have similar diagnostic accuracy for screening and risk stratification of MTC.<sup>15</sup> Chromogranin A and carcinoembryonic antigen may also be elevated in MTC and can be used to monitor for recurrence. Carcinoembryonic antigen levels  $>100$  ng/mL are indicative of distant metastases. Thyroid nuclear scanning and fine needle aspiration are additional diagnostic tools.<sup>13</sup> Immunohistochemical staining for calcitonin, chromogranin A, or carcinoembryonic antigen increases the accuracy of fine needle aspiration diagnosis.<sup>13,14</sup>

Surgical and endocrinology consultations should be obtained if the diagnosis is suspected. Symptoms of flushing and diarrhea may be treated medically with somatostatin analogs.<sup>13</sup> Curative treatment is total thyroidectomy with lymph node dissection. It is important to exclude and treat other components of MEN. A pheochromocytoma should be removed before thyroidectomy to decrease the risk of intraoperative complications.<sup>11,13</sup> Patients with metastatic disease may be treated with tyrosine kinase inhibitors, such as vandetanib<sup>13-15</sup> and

cabozantinib, which target the RET and vascular endothelial growth factor receptors.<sup>14,15</sup> Familial cases are diagnosed by genetic testing for RET mutations and require prophylactic thyroidectomy before the development of MTC.<sup>13</sup>

## PHEOCHROMOCYTOMA

Pheochromocytoma is a rare neuroendocrine malignancy that presents with flushing and potentially life-threatening hypertension caused by excessive catecholamine release from chromaffin cells of the adrenal medulla. Paragangliomas are similar but arise from extraadrenal autonomic neural ganglia.<sup>16,17</sup>

Patients experience labile blood pressure with either sustained or episodic hypertension. Paroxysmal attacks include flushing, pallor, tachycardia, palpitations, sweating, tremor, headache, chest pain, or abdominal pain. Patients may also develop apprehension, anxiety, or a sense of impending doom.<sup>11,16</sup>

Catecholamines have both  $\beta$ -adrenergic effects (vasodilation, flushing, diaphoresis, and tachycardia) and  $\alpha$ -adrenergic effects (vasoconstriction and hypertension).<sup>16</sup> The face has predominantly sympathetic vasodilator fibers, which results in the stereotypical vasodilatory flushing.<sup>18</sup> These tumors may also produce other flushing mediators, such as vasoactive intestinal peptide (VIP),<sup>19</sup> calcitonin gene-related peptide,<sup>20</sup> and adrenomedullin.<sup>21-23</sup>

During examination, the clinician may note postural hypotension caused by volume contraction, and the patient may exhibit pallor. Caution should be exercised when examining the abdomen. A paroxysmal attack can be triggered by deep abdominal palpation,<sup>11,16</sup> exercise, and straining.<sup>16</sup>

Because catecholamines (epinephrine, norepinephrine, and dopamine) are metabolized within the chromaffin tumor cells, measurement of both catecholamines and their metabolites should be performed. Initial biochemical testing should include plasma-free or 24-hour urinary fractionated

metanephrides.<sup>24</sup> Caffeine, nicotine, exercise, and certain medications can give false results.<sup>16</sup> Other general laboratory features include polycythemia, hyperglycemia, hypertriglyceridemia, and hypercalcemia. Patients should be referred to an endocrinologist or surgeon for further work-up.

In patients with findings concerning for MEN syndrome, serum parathyroid hormone and calcium levels can be used to rule out hyperparathyroidism.<sup>19</sup> Genetic testing, including screening for the RET protooncogene, should be discussed with patients.<sup>16,24</sup> Pheochromocytoma can also occur in patients with Von Hippel–Lindau syndrome, neurofibromatosis,<sup>16,17</sup> and hemihypertrophy syndromes.<sup>17</sup> Patients with known germline mutations predisposing to pheochromocytomas may benefit from periodic biochemical testing.

Imaging modalities should be performed after laboratory studies have confirmed the diagnosis and include abdominal computed tomography scans, magnetic resonance imaging, nuclear scintigraphy, or positron emission tomography scans.

It should be cautioned that beta-blockers may cause unopposed alpha receptor activity, which could amplify the hypertensive effects of catecholamines. Alpha blockade should be administered before any beta blockade. Surgical resection is the treatment of choice.<sup>11,16,24</sup> Pheochromocytomas are usually benign, and most can be removed laparoscopically.<sup>16,24</sup> Sunitinib and everolimus are targeted molecular therapeutic options for advanced disease. For metastatic malignant tumors, ablation or embolization procedures have shown success for palliative therapy.<sup>16</sup>

## CARCINOID TUMORS, CARCINOID SYNDROME, AND GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS

Carcinoid tumors are neuroendocrine tumors (NETs) of enterochromaffin cells that may originate in a variety of organs, typically the intestine and bronchus.<sup>25,26</sup> The small intestine, rectum, and lung are the most common sites.<sup>26</sup> Functional tumors secrete excess vasoactive substances and hormones, which cause a constellation of symptoms known as carcinoid syndrome.<sup>25,26</sup> Carcinoid syndrome has two presentations: typical and atypical. The typical presentation is the most common and consists of flushing, diarrhea, abdominal pain, right-sided valvular heart disease, cardiac fibrosis, bronchospasm, wheezing, dyspnea,<sup>26,27</sup> and pellagra dermatitis.<sup>28</sup> Pellagra cutaneous features include skin fragility, erythema, and hyperpigmentation, primarily over the shins and knuckles. The primary

mediator is serotonin (5-hydroxytryptamine). Flushing is attributed to serotonin, tachykinins (kallikrein and substance P), and prostaglandins.<sup>26</sup>

In the atypical syndrome, patients present with prolonged flushing, headache, palpitations, and bronchoconstriction. The mediators involved in the atypical syndrome usually include histamine and 5-hydroxytryptophan instead of serotonin.<sup>27</sup>

Carcinoid syndrome is dependent on the anatomic location of the tumors. The typical syndrome is evident in midgut (jejunal, ileal, and cecal) tumors and those with hepatic metastases. The atypical presentation is more common with foregut (bronchial, gastric, and duodenal) tumors.<sup>25</sup> Flushing may be triggered by exercise, stress, pain, anger, alcohol, and some foods.<sup>11,25</sup>

The appearance of the flush by carcinoid tumors is unique. Flushing associated with bronchial carcinoid tumors is bright pink-red, confluent, involves much of the body, and can persist for hours to days. Associated features include facial edema, chemosis, hypotension, and oliguria. Gastric carcinoid tumors cause a reddish-brown flush with variegated borders that occur with wheals over the entire body, including the palms and soles, which can be pruritic.<sup>11</sup> The flushing associated with foregut tumors is mediated by histamine.<sup>29</sup>

With midgut carcinoid tumors, the flush is cyanotic,<sup>11,28,29</sup> lasts for seconds to minutes, and is typically confined to the face, neck, and upper aspect of the trunk.<sup>11</sup> Patients may eventually develop thickened skin, telangiectasias, and blue discoloration of the face and neck, most notably of the malar region.<sup>11,26,28</sup> The flushing associated with midgut tumors is mediated by serotonin, tachykinins, and prostaglandins.<sup>29</sup>

Chromogranins, neuron-specific enolase, and pancreatic polypeptide are nonspecific tumor markers of NETs.<sup>27</sup> Serum chromogranin A (CgA) is elevated in carcinoid tumors<sup>25,27</sup> and often correlates with tumor burden.<sup>26</sup> It is the most important general marker of NETs and should be measured in patients with a suspected tumor.<sup>27</sup> Falsely elevated CgA may occur in patients with atrophic gastritis, inflammatory bowel disease, renal insufficiency, and with steroid or proton pump inhibitor use.<sup>26,27</sup> Neuron-specific enolase is frequently elevated in poorly differentiated NETs, which is helpful because CgA is often low to normal with this type of tumor because of the loss of secretory function of the cells. Pancreatic polypeptide is used in the diagnosis of pancreatic nonfunctioning NETs.<sup>27</sup>

Serotonin is inactivated in the liver and excreted in the urine as 5-hydroxyindole acetic acid (5-HIAA).

**Table II.** Causes of elevated or falsely decreased 5-hydroxyindoleacetic acid

Causes of elevated 5-hydroxyindoleacetic acid
Malabsorption syndromes, such as Whipple disease, celiac sprue, and stasis caused by chronic intestinal obstruction
Occasionally seen in healthy individuals
Foods: Pineapples, plums, bananas, eggplants, tomatoes, avocados, and walnuts
Medications: Phenacetin, reserpine, cisplatin, fluorouracil, and melphalan
Causes of falsely decreased 5-hydroxyindoleacetic acid:
Renal impairment
Tumor production of undetectable indole acids
Medications: Monamine oxidase inhibitors, tricyclic antidepressants, chlorpromazine, heparin, isoniazid, levodopa, and methyldopa

**Table III.** Other rare causes of flushing

Acute arsenic intoxication
Basophilic granulocytic leukemia
Ganglioneuroma
Homocystinuria
Leigh syndrome
Malignant histiocytoma
Neuroblastoma
POEMS syndrome
Postherpetic gustatory flushing and sweating
Rovsing syndrome

POEMS, Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin abnormalities.  
Adapted from Izikson et al.<sup>49</sup>

Therefore, with liver metastases or bulky retroperitoneal disease, serotonin is secreted directly into the systemic circulation and bypasses hepatic metabolism.<sup>25,26</sup>

Twenty-four-hour urine 5-HIAA will be elevated in 50% of patients with carcinoid tumors.<sup>25</sup> Levels of 5-HIAA >25 mg are indicative of carcinoid.<sup>11</sup> Special handling is required for specimens and mandates that the patient be sent to a laboratory equipped to handle these specimens. It is recommended that 2 consecutive 24-hour samples be collected and the mean value of the 2 samples be used for diagnosis.<sup>27</sup> Certain factors can elevate or falsely decrease 5-HIAA levels (Table II).

Flushing and tumor progression are inhibited by the somatostatin analogs octreotide and lanreotide, which decrease secretion of vasoactive mediators.<sup>25,26,30</sup> Some tumors are surgically resectable. Other treatment options include embolization, interferon- $\alpha$ , and various chemotherapy modalities.<sup>11,25,30,31</sup>

## BRONCHOGENIC CARCINOMA

Bronchogenic carcinoma is the most common cause of cancer death in the world. Patients develop

cough with or without hemoptysis, chest discomfort, and weight loss. Most cases are associated with a history of cigarette smoking.<sup>32</sup>

Flushing may occasionally be associated with bronchogenic carcinoma and is possibly caused by the production of VIP<sup>33,34</sup> or adrenocorticotrophic hormone.<sup>35</sup> Other cases may be caused by superior vena cava syndrome. The disease is often metastatic at diagnosis.<sup>32</sup>

## VASOINTESTINAL POLYPEPTIDE-SECRETING TUMORS

VIP-secreting tumors, also known as VIPomas, are rare NETs. The majority arise from the pancreas.<sup>36,37</sup> VIP causes intestinal secretion of water and electrolytes, stimulation of hepatic glycogenolysis, inhibition of gastric acid secretion, and vasodilation of peripheral blood vessels.<sup>33</sup>

VIPomas present as Verner–Morrison syndrome, also known as pancreatic cholera. This syndrome consists of large-volume watery diarrhea, hypokalemia, and achlorhydria or hypochlorhydria.<sup>27,33,34,36–40</sup> The mediator is VIP.<sup>33,34,37,40</sup> Resultant hypovolemia and acidosis are common.<sup>39–41</sup>

Flushing associated with VIPomas is caused by the vasodilatory effects of VIP.<sup>36,39,40</sup> Other variable features of the syndrome include lacrimation, rash, enlarged gallbladder, hypotension, hyperglycemia, hypercalcemia, hypomagnesemia, and hypokalemic myopathy or nephropathy.<sup>33,36,37,39,41</sup>

Initially, diarrhea may be intermittent but eventually it becomes continuous. Diarrhea persists during fasting.<sup>40,41</sup> With VIPomas, the stool is isotonic with plasma,<sup>40</sup> and stool pH can be as high as 8 because of bicarbonate excretion.<sup>41</sup> Stool volume is >1 L/day and usually exceeds 3 L/day. Stool volume <700 mL/day essentially rules out the syndrome.<sup>39–41</sup> Diagnosis is based upon stool volume, the secretory nature of diarrhea without an osmolar gap, and an elevated plasma VIP level. VIP

**Table IV.** Common causes of flushing

Diagnosis	History	Physical	Location of flushing	Laboratory evaluation
Benign	Triggered by emotions, exercise, food, or ingestants		Face, neck, or upper chest	Noncontributory
Fever	Febrile, chills, and symptoms indicative of underlying illness	Perspiration	Face, neck, or upper chest	None needed unless assessing for leukocytosis
Rosacea	Triggered by heat, spicy foods, or stress; concurrent skin changes	Cutaneous papules, pustules, telangiectasias; may have ocular findings	Limited to the face	Noncontributory
Climacterium	Female: profuse perspiration, recurrent brief episodes Male: gonadal surgery, antiandrogen therapy	Perspiration	Head, neck, and chest	Usually none needed; elevated follicle-stimulating hormone
Neurologic	Asymmetric distribution; stigmata of migraine or neurologic dysfunction	Perspiration, anhidrosis, pupil changes, or other neurologic dysfunction	Unilateral face or body	Based on underlying cause, imaging modalities
Hypersensitivity/anaphylaxis	Bronchospasm, nasal congestion, and sense of doom	Hypotension; angioedema or urticaria		Serum tryptase
Carcinoid	Abdominal cramping, diarrhea, headache, lacrimation, and bronchoconstriction	Facial telangiectasia if chronic; lacrimation	Widespread flushing; bright red or red-brown color; may develop cyanotic facial appearance	24-hour urine for 5-hydroxyindoleacetic acid
Pheochromocytoma	Paroxysmal palpitations, chest/abdominal pain, headache, and sense of doom	Episodic or sustained hypertension		24-hour urine for fractionated metanephrenes, norepinephrine, epinephrine, dopamine, and vanillylmandelic acid
Mastocytosis	Abdominal pain, diarrhea, fatigue, and weight loss	Hypotension; may have lesions consistent with cutaneous mastocytosis with Darier sign		Serum tryptase; 24-hour urine for N-methylhistamine
Renal cell carcinoma	Flank pain and hematuria	May have palpable abdominal mass		Urinalysis; imaging modalities
Medullary thyroid carcinoma	May be associated with multiple endocrine neoplasia (pheochromocytoma and hyperparathyroidism)	Thyroid nodule; perspiration; discoloration or telangiectasias	Face, neck, chest, and arms	Calcitonin level; radioimmunoassay for calcitonin after intravenous calcium/pentagastrin

	Watery odorless diarrhea that persists despite fasting; lethargy and weakness	Hemoptysis, chest pain, and positive smoking history	May have abnormal pulmonary findings or positive Pemberton sign	Comprehensive metabolic panel; fasting vasoactive intestinal peptide; imaging modalities Imaging modalities
Adapted from Izikson et al. <sup>49</sup>				

levels are typically >500 pg/mL with VIPomas.<sup>39</sup> Normal plasma VIP levels are 0 to 190 pg/mL. In between episodes of secretory diarrhea, VIP levels may be normal.<sup>40</sup>

Many patients have metastatic disease at the time of diagnosis.<sup>37-41</sup> Various imaging modalities are available, including computed tomography, magnetic resonance imaging, endoscopic ultrasound, and somatostatin receptor scintigraphy using radionuclide-labeled octreotide.<sup>36,38,39,42</sup>

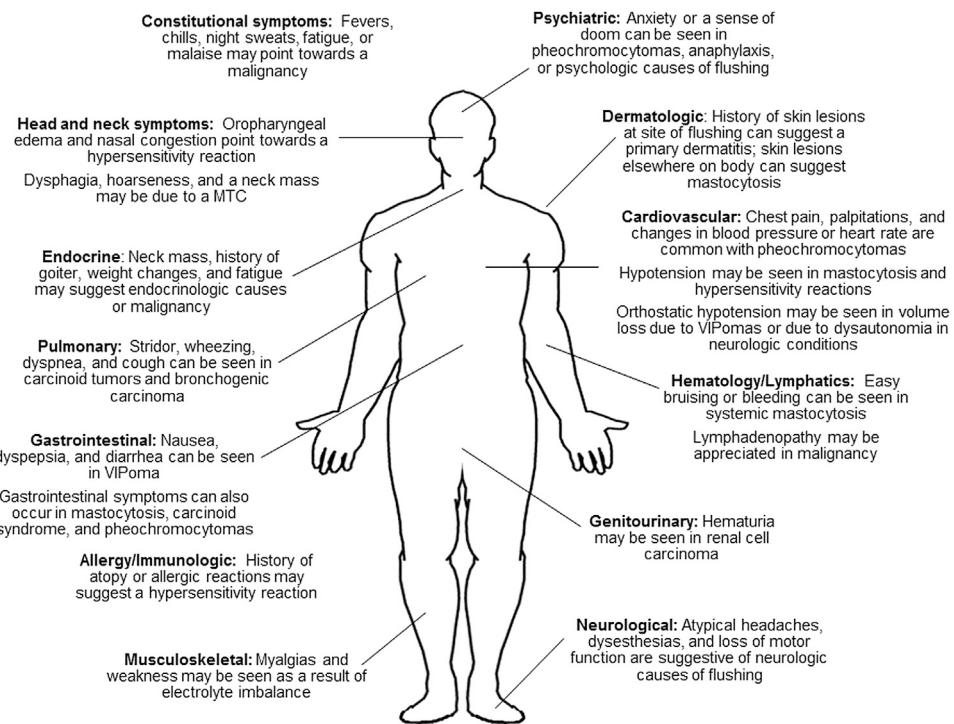
Most cases are sporadic.<sup>37</sup> However, VIPomas can be a component of MEN1,<sup>38,40,41</sup> an autosomal dominant neoplastic condition with mutation of the menin gene on chromosome 11q13. Various neoplasms are associated with MEN1, including parathyroid, pancreatic, and pituitary.<sup>38,39</sup>

First-line treatment is surgical resection, if feasible.<sup>37</sup> Somatostatin analogues can be used for symptomatic management.<sup>37,39,41,42</sup> Chemotherapy and hepatic arterial embolization for metastases are options.<sup>40,41</sup>

## RENAL CELL CARCINOMA

Renal cell carcinoma (RCC) originates from the renal epithelium and constitutes 85% of renal cancers.<sup>11,43</sup> Less than 10% of patients present with the classic triad of gross hematuria, flank pain, and palpable abdominal mass.<sup>11,43,44</sup> Approximately 40% of patients have none of these symptoms.<sup>44</sup> More than half of RCCs are discovered incidentally on radiographic imaging.<sup>43,44</sup> Often, patients will present with nonspecific symptoms of fatigue, fevers, weight loss, or cachexia. Associated laboratory abnormalities may include anemia, erythrocytosis, leukocytosis, eosinophilia, thrombocytosis, hypercalcemia, or abnormal liver function tests. Some tumors secrete alpha fetoprotein, which may be elevated.<sup>45</sup> Smoking, obesity, and hypertension are risk factors for developing RCC.<sup>43,44</sup> Gross or microscopic hematuria is an important clinical feature and should be worked up in order to rule out malignancy.<sup>43</sup>

RCC can produce hormones and hormone-like substances, such as parathyroid hormone-related peptide, prolactin, renin, prostaglandins, and gonadotropins.<sup>45</sup> Flushing associated with RCC can be caused by the release of prostaglandins.<sup>11,46</sup> Aspirin can inhibit flushing attacks that are provoked by prostaglandin secretion.<sup>46</sup> Treatment of choice is nephrectomy; however, in certain cases, such as metastatic disease, immunotherapy or therapeutic agents that target the vascular endothelial growth factor receptor or the mechanistic target of rapamycin pathway may be used.<sup>47,48</sup>



**Fig 1.** A pertinent review of systems can aid the practitioner in determining which of the many causes of flushing may be afflicting a patient.

**Table V.** Common malignancies associated with flushing: Clinical findings and laboratory markers

	Mastocytosis	Carcinoid syndrome	Pheochromocytoma	Central nervous system	Other
Clinical findings					
Flushing	X	X	X	X	
Blood pressure	May be low		Hypertension	May be low or high	VIPoma is associated with hypotension
Oropharyngeal edema/congestion			X		
Dysphagia	Rare	Esophageal carcinoid			Medullary thyroid carcinoma
Cardiac disease		X		X	
Pulmonary	X	X			Bronchogenic carcinoma
Gastrointestinal	X	X	X	X	VIPoma
Laboratory markers					
Serotonin/5-hydroxyindoleacetic acid		X (24-hour urine for 2 consecutive days)			
Total tryptase	X				Hypersensitivity/anaphylaxis
Histamine	X				
Metanephhrines			X		
Vanillylmandelic acid			X		
Norepinephrine			X		
Vasoactive intestinal peptide					VIPoma
Creatinine		X (obtained to ensure adequate urine collection)			

VIPoma, Vasointestinal polypeptide—secreting tumor.

There are numerous other causes of flushing (Table III).

In conclusion, the flushing phenomenon may represent a physiologic or a pathologic reaction (Table IV). Although flushing is usually benign, it is prudent that the physician remain aware of potentially life-threatening conditions associated with cutaneous flushing. A thorough investigation should be performed if the flushing is atypical or not clearly associated with a benign underlying process. The diagnosis often relies on the use of a thorough history, review of systems (Fig 1), physical exam, and various laboratory and imaging modalities (Table V). It should be noted that treatment to simply reduce flushing is not sufficient to combat the underlying causes.

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# Postinflammatory hyperpigmentation: A comprehensive overview



## Epidemiology, pathogenesis, clinical presentation, and noninvasive assessment technique

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### Learning objectives

After completing this learning activity, participants should be able to recognize characteristics of PIH and similar conditions; discuss the pathogenesis of PIH and similar conditions; and describe how to perform an objective evaluation for PIH.

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Postinflammatory hyperpigmentation (PIH) commonly occurs after various endogenous and exogenous stimuli, especially in dark-skinned individuals. PIH is one of the most common complications of procedures performed using laser and other light sources. The severity of PIH is determined by the inherent skin color, degree and depth of inflammation, degree of dermoepidermal junction disruption, inflammatory conditions, and the stability of melanocytes, leading to epidermal and dermal melanin pigment deposition. The depth of melanin pigment is the key factor to predict prognosis and treatment outcome. Epidermal hyperpigmentation fades more rapidly than dermal hyperpigmentation. Various inflammatory disorders can eventually result in PIH. The evaluation of pigmentation using noninvasive tools helps define the level of pigmentation in the skin, pigmentation intensity, and guides therapeutic approaches. This first article in this 2-part series discusses the epidemiology, pathogenesis, etiology, clinical presentation, differential diagnoses, and investigation using noninvasive assessment techniques that objectively determine the details of pigmentation. (J Am Acad Dermatol 2017;77:591-605.)

**Key words:** colorimetry; hyperpigmentation; hyperspectral imaging; melanin; melanocytes; photography; racial/ethnic; reflectance confocal microscopy; reflectance spectroscopy; skin phototypes.

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## INTRODUCTION

### Key points

- Postinflammatory hyperpigmentation can occur in all skin phototypes but is most common in dark-skinned individuals
- Certain dermatoses can cause postinflammatory hyperpigmentation without noticeable inflammation

Postinflammatory hyperpigmentation (PIH) is a common, acquired pigmentary disorder caused by cutaneous endogenous inflammation, external injury, or cutaneous procedures.<sup>1,2</sup> In each individual, inflammatory dermatoses can produce clinical hyperpigmentation, hypopigmentation, or both. PIH presents locally in previous areas of inflammation. When erythema subsides, a hyperpigmented macule or patch that can range in color from tan to black is left behind. PIH tends to occur most noticeably among individuals with Fitzpatrick skin phototypes (SPTs) III to VI.<sup>3-5</sup> Although PIH is easily diagnosed from the patient's history and the presence of inflammation, several dermatoses lead to PIH without noticeable inflammation. Visual assessment is one of the criterion standards for evaluating PIH, but it is subjective and has interobserver variability. The use of noninvasive techniques can avoid this limitation. This article presents an overview of the epidemiology, risk factors, pathogenesis, etiology, clinical manifestations, and certain hyperpigmentation disorders resulting in PIH. In addition, the evaluation of PIH using noninvasive objective assessment techniques that provide more reliable, reproducible outcome measurements are also discussed.

## EPIDEMIOLOGY

### Key points

- Dark-skinned individuals constitute most of the world's population
- The increasing percentage of individuals with skin of color in the United States makes a better understanding of skin of color–related cutaneous disorders important
- In individuals with skin of color, postinflammatory hyperpigmentation is one of the most common complications of procedures performed using laser and other light sources

Dark-skinned individuals, commonly referred to as patients with skin of color (SOC), constitute most of the world's population. They include Africans, African Americans, Native Americans, Hispanics, Latinos, people of Caribbean descent, Pacific

Islanders, East Indians, Pakistanis, Eskimos, people of Middle Eastern descent, Koreans, Chinese, Vietnamese, Filipinos, Japanese, Thais, Cambodians, Malaysians, Indonesians, and Aleuts.<sup>6</sup> In 2000, individuals with SOC represented 30% of the US population, and by 2050, the US Census Bureau has estimated that a minimum of 50% of Americans will be those with SOC.<sup>7</sup> It is therefore important and relevant that a better understanding of cutaneous disorders related to SOC be obtained.

El-Essawi et al<sup>8</sup> reported that uneven skin tone and skin discoloration are 2 of the most concerning skin problems among Arab Americans, with >50% of the survey participants expressing such concerns. Among 3000 Latino patients, the incidence of hyperpigmentation and melasma was reported to be between 6.0% and 7.5%.<sup>9</sup> In a study conducted in Singapore, PIH tended to occur among Asians with darker skin, showing the importance of the degree of constitutive cutaneous pigmentation in the development of PIH.<sup>10</sup> Alexis et al<sup>11</sup> reported that dyschromia was 1 of the top 5 disorders in 1412 African Americans, whereas this diagnosis was not among the top 10 diagnoses in white patients.

PIH is also the most common complication of laser resurfacing in those with SOC.<sup>12</sup> Chan et al<sup>12</sup> reported a PIH prevalence of 11.1% to 17.1% among Asians who had undergone fractional laser resurfacing. The incidence of PIH after ablative fractional carbon dioxide laser treatments in SPT IV patients was as high as 92%,<sup>13</sup> compared with 23% in patients with SPT I to III undergoing similar procedures;<sup>14</sup> in SPT I to III patients exposed to deep fractional carbon dioxide laser treatments, PIH was observed in only 1.2% of patients.<sup>15</sup>

## PATHOGENESIS AND ETIOLOGIES

### Key point

- Intensity of postinflammatory hyperpigmentation is determined by the inherent skin color, degree and depth of inflammation, degree of disruption at the dermoepidermal junction, inflammatory conditions, and stability of melanocytes

Pigmentary alteration from preceding inflammatory dermatoses can lead to hyperpigmentation, hypopigmentation, or both, relying on the number and function/activity of melanocytes after inflammation. Inflammation that affects the dermoepidermal junction tends to develop dyspigmentation. The difference of these responses is not well-clarified. Ruiz-Maldonado and Orozco-Covarrubias<sup>16</sup> proposed an “individual chromatic tendency” hypothesis. After cutaneous inflammation or injury,

*Abbreviations used:*

DRS:	diffuse reflectance spectroscopy
HSI:	hyperspectral imaging
PAHPI:	post-acne hyperpigmentation index
PIH:	postinflammatory hyperpigmentation
SOC:	skin of color
SPT:	skin phototype
UV:	ultraviolet

melanocytes can respond with normal, increased, or decreased melanin production depending on the unique property of the melanocytes of that individual, resulting in the development of varying degrees of dyspigmentation.<sup>16</sup> It is proposed that this reaction is genetically determined and not related to the patient's SPT. Various inflammatory dermatoses affect different melanocyte responses. Melanocytes in lesions of lichen planus and lupus erythematosus have been described to have variable shapes and peculiarly branched dendrites.<sup>17</sup> In contrast, diseases that do not affect the epidermis primarily, such as erythema nodosum, show only a moderate increase in normal-appearing melanocytes.<sup>17</sup> In PIH, the characteristic response of melanocytes to inflammation is increased activity, hyperplasia, and hypertrophy.<sup>17</sup> When inflammation occurs, increased melanocytic activity leads to increased melanogenesis, with the melanin being transferred via dendrites to the neighboring keratinocytes. Moreover, this epidermal ultraviolet (UV)-protective melanin can enter the dermis via a damaged basal cell layer and is phagocytized by macrophages, forming melanophages. Both processes can occur within the same injury.<sup>18</sup>

Cutaneous inflammation results in generation of eicosanoids from cell membranes, which include prostaglandins E<sub>2</sub> and D<sub>2</sub>, leukotrienes B<sub>4</sub>, C<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub>, and thromboxane B<sub>2</sub>. In vitro, these metabolites have been found to increase the size of melanocytes and melanocyte dendritic proliferation.<sup>19,20</sup> Leukotriene C<sub>4</sub> has been shown to increase tyrosinase activity.<sup>19</sup> Cytokines and inflammatory mediators (eg, interleukins 1 $\alpha$  and 6, tumor necrosis factor- $\alpha$ , endothelin-1, stem cell factor, basic fibroblast growth factor, superoxide, and nitric oxide) also stimulate melanin production.<sup>19,21,22</sup>

The wide range of PIH etiologies includes inflammatory dermatoses, infections, and reactions to medications, therapeutic procedures, burns, and trauma. These are summarized in Table I.

## CLINICAL PRESENTATION

### Key points

- **Epidermal postinflammatory hyperpigmentation tends to be light to dark brown, whereas**

**gray to black coloration is seen with dermal postinflammatory hyperpigmentation**

- **The clinical characteristics can guide the treatment options and prognostic outcome**

There are 2 clinical forms of PIH: epidermal and dermal.<sup>4,23</sup> Epidermal hyperpigmentation tends to be light to dark brown, whereas dermal hyperpigmentation tends to have a blue-gray coloration (Figs 1 and 2).<sup>24</sup> Much of the clinical appearance of PIH is related to the depth of the pigmentary alteration. This is a result of the Tyndall effect of light scattering. Shorter wavelengths scatter more, and therefore the light redirected back to the eye is predominantly the shorter blue wavelengths of visible light, leading to the consequential blue hue. The depth of dermal melanophages is the most important factor in the response to treatment. Epidermal PIH usually disappears spontaneously within months or years, whereas dermal PIH has a more prolonged course and may be permanent. Intense, repetitive inflammation tends to produce a long-lasting PIH with a dark color. As with a fixed drug eruption, initial lesions present with erythema and evolve to brown, whereas repeated reactions usually leave a slate gray discoloration.<sup>25</sup>

## CERTAIN DERMATOSES PRESENT WITH HYPERPIGMENTATION

### Key point

- **Postinflammatory hyperpigmentation must be differentiated from other hyperpigmented conditions, especially in the cases of unnoticeable inflammation and atypical presentation**

Hyperpigmentation admixed with inflammatory lesions make the diagnosis of PIH straightforward. However, inflammation can be subtle or unnoticeable by naked eyes, and only PIH persists. Table II summarizes the features of certain hyperpigmentation disorders (Figs 3-9).<sup>26-35</sup> Clinically, some of these can mimic PIH (eg, melasma, drug-induced hyperpigmentation, exogenous ochronosis, and UV-induced tanning). Problematic pigmentary conditions are reviewed below.

### Melasma

Melasma is a common, acquired hyperpigmentation found predominantly in females with SPTs III to IV. It usually presents as brownish patches with an irregular border on the sun-exposed areas of the face; however, it may also be found on the neck and arms. Melasma is not usually associated with inflammation. There are 3 types of facial melasma:

**Table I.** Dermatologic conditions that can cause postinflammatory hyperpigmentation

Inflammatory dermatoses	Acne/acneiform eruption Pseudofolliculitis barbae Eczema Atopic dermatitis Irritant contact dermatitis Allergic contact dermatitis Pigmented contact dermatitis Photoallergic contact dermatitis Lichen simplex chronicus Insect bites Papulosquamous disorders Psoriasis Pityriasis rosea Lichen planus/lichen planus pigmentosus Lichenoid dermatitis Erythema dyschromicum perstans Connective tissue disease Lupus erythematosus Vasculitis Morphea/scleroderma Atrophoderma of Pasini and Pierini Vesiculobullous disorders Pemphigus Bullous pemphigoid Dermatitis herpetiformis Impetigo Viral exanthem Chickenpox Herpes zoster Dermatophytosis Syphilis Pinta Onchocerciasis Phototoxic dermatitis Morbilliform eruption Erythema multiforme Fixed drug eruption Stevens-Johnson syndrome/toxic epidermal necrolysis Lichenoid drug eruption Chemical peel Dermabrasion Cryotherapy Laser treatment Intense pulsed light treatment Mycosis fungoides Neurotic excoriation Sunburn Trauma Friction
Infections	
Drug reactions	
Dermatologic procedures	
Miscellaneous	

centrofacial (which is the most common type), malar, and mandibular. Increased melanocyte activity in patients with melasma results in hypermelanosis in the epidermis and dermis.<sup>36</sup>

### Acne-related postinflammatory hyperpigmentation

Dyspigmentation and scarring are commonly found in patients with SOC.<sup>37</sup> Acne-related PIH is sometimes more bothersome than the acne itself. PIH can occur without clinical evidence of significant inflammation, even in patients with mild to moderate acne.<sup>38</sup> PIH is mainly located in the epidermis. The cheeks and mandibular area are mostly involved.<sup>39</sup> PIH persisted for ≥1 year for <50% of the patients and for >5 years in 22.3% of patients.<sup>39</sup>

### Lichen planus pigmentosus

Lichen planus pigmentosus is an uncommon variant of lichen planus. It is characterized by the gradual onset of violaceous, slate gray to black macules and patches mainly on the face (mostly involving the forehead and temporal area), neck, axillae, antecubital fossae, and upper extremities (Fig 3). Erythematous borders may be observed in early lesions. Histopathologically, fully developed lesions show basal cell vacuolation, a few necrotic keratinocytes, and variable lichenoid lymphocytic infiltration. In contrast, late lesions characteristically show an atrophic epidermis, basal vacuolation with prominent melanin, and melanophages.<sup>29</sup>

### Erythema dyschromicum perstans

Erythema dyschromicum perstans, also called ashy dermatosis, is a rare pigmentary condition that begins with an active erythematous border that later disappears, leaving oval or round, polycyclic, slate gray macules and patches on the trunk, proximal extremities, and neck (Fig 4). In contrast to lichen planus pigmentosus, it more commonly involves sun-protected sites. The etiology is poorly understood. Some associations have been reported, such as the ingestion of ammonium nitrate, hepatitis C virus, and HIV infection.<sup>40</sup> Histopathology in the early active stage is characterized by low-grade interface dermatitis, resembling those seen in the subtle form of lichen planus. Late lesions show melanophage aggregation in the papillary dermis.<sup>24</sup>

### Reihl melanosis

Reihl melanosis, also known as pigmented contact dermatitis, is commonly seen in young to middle-aged women with dark skin. Repetitive



**Fig 1.** Epidermal postinflammatory hyperpigmentation (PIH). **A**, Trichloroacetic acid–induced PIH in a patient with Fitzpatrick skin phototype (SPT) III. (Courtesy of Sasima Eimpunth, MD, Bangkok, Thailand.) **B**, Psoriasis with PIH in a patient with SPT IV. **C**, Acne vulgaris with PIH in a Thai woman with SPT III. **D**, PIH from acne vulgaris in an African American man with SPT V. **E**, PIH after laser hair removal in an American woman with SPT IV.

contact with allergens in cosmetics, textiles, and pharmaceuticals (eg, fragrances, dyes, and bactericides) is thought to be the cause.<sup>41</sup> It is characterized by reticulated and diffuse, brown-to-gray pigmentation on the forehead, temporal and zygomatic regions of the face and neck, and is usually seen at sites exposed to the putative contactant (Fig 5). It is likely a subtle contact dermatitis that results in PIH. Patch and photopatch testing should be performed in patients suspected to have Reihl melanosis.<sup>42</sup> Early lesions show interface dermatitis, and older lesions show melanin incontinence in the papillary dermis.

### Hyperpigmented mycosis fungoides

Hyperpigmented mycosis fungoides is a rare variant of mycosis fungoides that commonly occurs in dark-skinned patients and sometimes presents only with hyperpigmented patches or plaques without the typical findings of mycosis fungoides.<sup>43</sup> Histopathology of hyperpigmented mycosis fungoides includes interface change, epidermotropism, melanophages, and melanin incontinence in the dermis, which can differentiate it from PIH.<sup>43</sup>



**Fig 2.** Dermal postinflammatory hyperpigmentation from chronic actinic dermatitis in an African American man with Fitzpatrick skin phototype V.

### DIAGNOSIS AND CLINICAL EVALUATION

#### Key points

- Visual assessment, Wood's lamp examination, and obtaining a skin biopsy specimen remain the simple and important diagnostic and evaluation methods for postinflammatory hyperpigmentation and similar conditions

**Table II.** Features of dermatoses associated with hyperpigmentation

Conditions	Epidemiology	Etiology	Presentation	Histopathology	Management*
Hyperpigmentation disorders that mimic PIH					
Melasma	Common in SPTs III-IV; occurs in women more than men	Multifactorial factors: UV radiation, hormonal therapy, pregnancy, genetics, and drugs, such as phenytoin	Symmetrical, irregular border, brownish patches on sun-exposed areas (especially the face)	Increased epidermal ± dermal melanin	Bleaching agents, tranexamic acid, chemical peels, and lasers and light
Drug-induced hyperpigmentation	All race and age groups	Various medications, such as antimalarials, chemotherapy, amiodarone, and minocycline; heavy metals	Slowly progressive eruption, circumscribed or generalized hyperpigmentation; may be seen: melanonychia and mucosal pigmentation	Depends on causative agent: increased epidermal ± dermal melanin ± heavy metal deposition	Discontinue the offending drugs, bleaching agents, oral isotretinoin, and Q-switched laser <sup>26,27</sup>
Exogenous ochronosis	In dark-skinned, young to middle-aged women	Prolonged use of high concentrations of hydroquinone, frequently associated with intense sun exposure	Paradoxical darkening of the skin with blue-black papules on application sites	Banana shapes, yellow-brown globule in dermis	Discontinue the offending drugs, dermabrasion, chemical peel, CO2 laser, and Q-switched laser <sup>28</sup>
UV-induced tanning	Common in SPTs III-VI	Delayed response to UVA/UVB exposure, with increased melanogenesis	Hyperpigmentation on sun-exposed areas	Increased epidermal melanin	Photoprotection
Hyperpigmented mycosis fungoides	Common in dark-skinned patients	Unknown	Hyperpigmented patches or plaques commonly in sun-protected areas	Epidermotropism, interface change, melanophages and melanin incontinence	Skin-directed therapies
Hyperpigmentation disorders that result in PIH	Common in SPTs III-V and young to middle-aged adults	Unknown	Oval or irregular slate-gray to black macules and patches either on sun-exposed areas or intertriginous sites	Interface dermatitis, mainly increased dermal melanin	Topical corticosteroids, topical tacrolimus/pimecrolimus, hydroxychloroquine, mycophenolate mofetil, and oral isotretinoin <sup>29,30</sup>

Erythema dyschromicum perstans	Common in SPTs III-IV and young adults, especially in the second to third decades of life	Unknown	Oval or irregular slate-gray macules and patches on the neck, trunk, and proximal extremities; erythematous border may be seen in early lesions	Interface dermatitis, mainly increased dermal melanin	Oral corticosteroids, topical tacrolimus, antibiotics, dapsonc, clofazamine, antimalarials, isoniazid, griseofulvin, and UV light <sup>31,32</sup>
Rehl melanosic	Common in darker skin types and young and middle-aged adults	Unknown, but possibly allergens in cosmetics and textiles producing type IV cytotoxic reaction	Brown to gray facial pigmentation, predominantly on the lateral aspects of the face and neck	Interface dermatitis, mainly increased dermal melanin	Avoid suspected allergens, bleaching agents, and chemical peels
Periorbital hyperpigmentation	Common in dark-skinned populations	Multifactorial: genetic, anatomic, vessels, and pigmentation	Bilateral, symmetrical darkening of periorbital skin, including the eyelids	Increased epidermal $\pm$ dermal melanin	Bleaching agents, chemical peels, lasers and light filler, autologous fat transplantation, and blepharoplasty <sup>33</sup>
Frictional melanosis	All race and age groups	Repeated friction	Brownish pigmentation, commonly over bony prominences	Mainly dermal melanin	Discontinue aggressively rubbing with nylon brushes or scrub pad, chemical peels, and Q-switched laser <sup>34,35</sup>
Phytophotodermatitis	All race and age groups	Contact with plants containing furocoumarins	Patterned hyperpigmented patches at contacted sites	Increased epidermal melanin and dermal melanophages	Avoidance of offending agents, topical corticosteroids, and bleaching agents

CO<sub>2</sub>, Carbon dioxide; P/H, postinflammatory hyperpigmentation; SPT, skin phototype; UVA, ultraviolet A light; UVB, ultraviolet B light.

\*Photoprotection should be advised in all conditions.



**Fig 3.** **A** and **B**, Lichen planus pigmentosus on the neck of an African American woman with Fitzpatrick skin phototype V. **C** and **D**, Lichen planus pigmentosus in a Thai woman with Fitzpatrick skin phototype IV.

- **Subjective rating scales of pigmentation can be used in routine clinical practice and require only minimal training**

Visual assessment of PIH is easily performed by comparison with the baseline normal skin color. Examination with a Wood's lamp is a simple and useful diagnostic step. A Wood's lamp emits UV and visible light from 320 nm to 450 nm, with a peak at 365 nm. The light emitted by the Wood's lamp is absorbed by epidermal melanin; therefore, epidermal PIH is enhanced and appears darker compared with unaffected normal skin. Because minimal UV light penetrates the dermis, dermal PIH is not highlighted during the Wood's lamp examination. In patients with SPTs V to VI, a Wood's lamp examination may show ambiguous results because of the constitutively high concentration of melanin in the epidermis.<sup>16</sup> In cases of uncertain primary inflammation or diagnosis, obtaining a skin biopsy specimen might be necessary to exclude other conditions that cause hyperpigmentation (Table II).<sup>26-35</sup> Specimens should contain normal and hyperpigmented skin for optimal interpretation, and Masson-Fontana staining of the melanin can aid



**Fig 4.** Erythema dyschromicum perstans on the abdomen of a Thai woman with Fitzpatrick skin phototype IV.

the diagnosis. Histopathology of PIH reveals superficial dermal melanophages, including increased epidermal melanin without basal cell vacuolization. However, postinflammatory hypopigmentation also shows dermal melanophages with decreased epidermal melanin. The term "postinflammatory pigmentary alteration," therefore, is described in histopathology based on superficial dermal melanophages, not epidermal melanin, and refers to both PIH and postinflammatory hypopigmentation.<sup>44</sup>

Other tools for evaluating PIH include the Taylor hyperpigmentation scale<sup>45</sup> and the post-acne hyperpigmentation index (PAHPI).<sup>46</sup> The Taylor



**Fig 5.** Riehl melanosis (pigmented contact dermatitis) in a Thai woman with Fitzpatrick skin phototype V. Patch test was positive for herbal cream. (Courtesy of Waranya Boonchai, MD, Bangkok, Thailand.)



**Fig 6.** Exogenous ochronosis in a patient with melasma.

hyperpigmentation scale is a visual rating scale that assesses skin color and monitors hyperpigmentation after therapy. The tool consists of 15 uniquely colored plastic cards that span the full range of skin colors and is applicable to individuals with SPTs I to VI. Each plastic card contains 10 bands of increasingly darker gradations of skin color that represent progressive levels of hyperpigmentation.<sup>45</sup> The Taylor scale has not been validated. The PAHPI was introduced and validated by Savory et al<sup>46</sup> to



**Fig 7.** Frictional dermatitis after repeated rubbing with coarse towel. Note the accentuation at the ribs. (Courtesy of Ryoichi Kamide, MD, Tokyo, Japan.)



**Fig 8.** Minocycline-induced hyperpigmentation. Note the violaceous discoloration on the lateral aspect of the upper lip.



**Fig 9.** Ultraviolet light-induced tanning in a patient with scleredema who received 40 treatments of medium-dose ultraviolet A1 light ( $50 \text{ J/cm}^2$ ).

evaluate PIH caused by acne vulgaris. Three parameters are scored: PIH lesion size, median lesion intensity compared with surrounding skin (ie, slightly darker, moderately darker, significantly

**Table III.** Summary of noninvasive assessment techniques in postinflammatory hyperpigmentation

Noninvasive technique	Assessment	Clinical use
Wood's lamp	Melanin	Distinguish epidermal and dermal pigmentation; epidermal pigmentation is darker
Ultraviolet light photography	Epidermal melanin	Enhances visualization of epidermal pigment
Parallel-polarized light photography	Skin surface details	Enhances visualization of wrinkle, fine lines, texture, scale, and elevation
Cross-polarized light photography	Melanin and vasculature	Enhances visualization of pigmentation and vasculature
Colorimetry	Melanin and vasculature	Quantifies relative pigmentation and erythema
Diffuse reflectance spectroscopy	Melanin and vasculature	Quantifies relative pigmentation and erythema
Hyperspectral imaging	Melanin and vasculature	Enhances visualization and assists in quantification of relative pigmentation and erythema
Reflectance confocal microscopy	Histologic detail	Visualization of pigmentation, pigmented tumor, and inflammatory cells; assists in identifying lesion borders; quantitative information can be obtained through image analysis

darker), and the number of PIH lesions. The PAHPI is a summation of these 3 scores, with a possible score ranging from 6 to 22.<sup>46</sup>

## NONINVASIVE ASSESSMENT TECHNIQUES

### Key points

- Noninvasive objective technologies for post-inflammatory hyperpigmentation assessment are reliable and reproducible
- These technologies help obtain valuable quantitative information of the lesion and augment clinical assessment of postinflammatory hyperpigmentation
- Some training for operating and interpreting the output of these technologies is required

Clinical assessment and color monitoring of PIH during treatment is challenging.<sup>47</sup> Noninvasive objective technologies supplement the clinical assessment and provide more reliable, reproducible outcome measures for PIH. These techniques include polarized light photography, colorimetry, diffuse reflectance spectroscopy (DRS), hyperspectral imaging (HSI), and reflectance confocal microscopy (Table III).

### Polarized light photography

Photography is a valuable tool in both the research and clinical assessment of PIH. UV light photography incorporates illumination of the area to be imaged by UV light (320–400 nm) and collection of reflected light by a camera lens that has a UV-transmitting filter and a visible and infrared blocking filter attached to it. It enhances visualization of epidermal melanin. Polarized light photography provides greater in-depth information than regular photography. It

involves the use of a linear polarizer on the illumination source and the camera lens. The polarizer on the camera lens can be oriented either parallel or perpendicular to the polarizer on the illumination source, which would then generate parallel or perpendicular (also known as cross-) polarized light photographs, respectively. Whereas parallel polarized light photography enhances surface features, such as wrinkles and fine lines, perpendicular or cross-polarized light photography augments subsurface features, such as pigmentation and vasculature, by reducing the surface glare (Fig 10).<sup>48</sup>

Although pigmentation is easily observed clinically in patients with lighter skin, this is not the case for those with dark skin. Cross-polarized light photography provides the much-needed contrast for dark skin by minimizing the appearance of constitutive epidermal pigmentation, and therefore, assists in the diagnosis of pigmentary disorders. In taking photographs over a period of time, care must be taken to ensure consistent ambient lighting and patient positioning to obtain reliable, accurate comparisons. Cross-polarized light photography has been shown to be a valuable, reliable noninvasive technique for assessing patients with acne vulgaris and melasma<sup>49,50</sup> as well as their responses to treatment. It has also been reported to provide better differentiation between erythematous halos and PIH in dark-skinned individuals compared with visual clinical examination alone.<sup>50</sup>

### Colorimetry

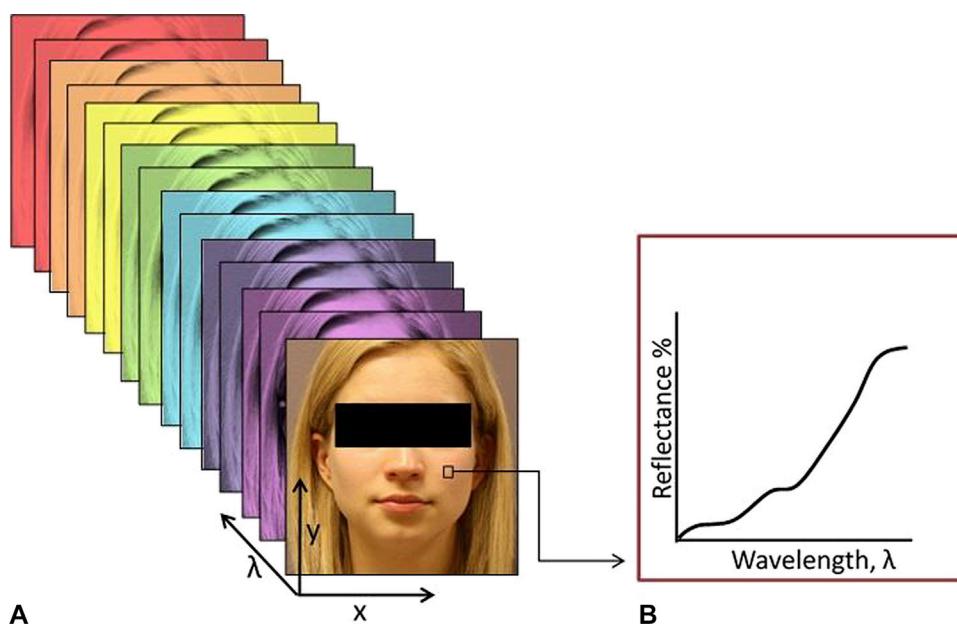
Tristimulus colorimetry, a specific combination of red, green, and blue light (3 stimuli) that corresponds



**Fig 10.** **A**, Parallel polarized image (left) enhancing surface features, such as wrinkles (arrow). Cross-polarized image (right) enhancing subsurface pigmentation. **B**, Parallel polarized image of patient with skin of color (left). Cross-polarized image of patient with skin of color (right), enhancing variation in pigmentation.

to a particular color, has been used for the *in vivo* quantitative evaluation of erythema and pigmentation.<sup>51,52</sup> A colorimeter homogenously illuminates the specimen under the aperture with intense white light covering the entire visible spectrum. Information from reflectance spectra of the specimen is converted to  $L^*$ ,  $a^*$ , and  $b^*$  values, as defined by the standard Commission International de l'Eclairage system ( $L^*$  corresponds to luminance, or darkness to lightness;  $a^*$  represents the green-to-red color component; and  $b^*$  represents the blue-to-

yellow color component, corresponding to the complementary colors of the red, green, and blue pairs<sup>53</sup>). Together, these values represent the color of the specimen at a threshold lower than that of visual detection. For PIH, an increase in the  $L^*$  value, corresponding to lightening of the skin color, indicates an improvement. When collecting measurements, uniform gentle pressure should be applied when placing the probe on the skin to avoid skin blanching, which may result in inaccurate readings. Colorimetry has often been used as a primary



**Fig 11.** **A**, Schematic of hyperspectral data cube with spatial information (x- and y-axis) and spectral information ( $\lambda$ -axis). The frames are much more numerous than in this schematic depiction. **B**, Spectral information corresponding to a selected region of interest.

evaluation tool to assess treatment responses in patients with facial and axillary hyperpigmentation, vitiligo, psoriasis, and melasma.<sup>54-56</sup>

#### Diffuse reflectance spectroscopy

DRS is an in vivo measurement technique used to compute the concentration of complex biomolecules present in the skin. With DRS, apparent absorption spectra are calculated from the collected reflectance spectra of the interaction of light and skin. The incident light spectra depend on the lamp used and can be UV, visible, near-infrared (280–800 nm), or just visible light (400–700 nm). DRS quantifies the biochemical concentrations of skin chromophores, melanin, oxyhemoglobin, and deoxyhemoglobin using their known absorbance characteristics. The DRS probe must be placed perpendicular to the skin while applying uniform but gentle pressure to avoid skin blanching. In addition, because of the small probe size (a diameter of approximately 2.5 mm), enough readings must be obtained to capture the variance of normal skin and that within the lesion. Because DRS can quantify the concentrations of melanin, it is another important tool in the assessment of PIH.<sup>57-59</sup>

#### Hyperspectral imaging

HSI provides the combined advantages of digital imaging and spectral information. The HSI system incorporates a uniform illumination source, for instance Lowel Vip Pro-light halogen tungsten

lamp (Lowel-Light Manufacturing, Inc, Hauppauge, NY) and Lite panel LED panels, a hyperspectral camera with sensor like Philumina-VNIR/400H (PhiLumina, LLC, Gulfport, MS) capable of detecting absorbance in the wavelength range of 400 to 1000 nm, and a computer.<sup>60</sup> The hyperspectral data cube consists of spatial and spectral information corresponding to any specific region of interest in the digital image (Fig 11). It uses the same principles as DRS to extract the optical properties of tissue by fitting the collected reflectance spectra, thereby providing spectral information associated with each pixel. Unlike multispectral imaging, where each pixel is associated with spectral information corresponding to a few specific bands of wavelength, HSI collects numerous narrow spectral bands and provides continuous spectral measurements. This provides high sensitivity and enables HSI to account for even subtle changes in reflectance spectra. This aids in quantifying optical properties of the skin, including melanin concentration, blood concentration, and dermal scattering.

Measurements using HSI require no direct contact of the probe with the skin; therefore, HSI overcomes the limitation of capillary constriction and skin blanching that may occur with colorimetric or DRS measurements. Unlike DRS or colorimetry, it can collect information on large lesions because spectral information is extracted from a digital image. Because it is a noncontact setup, care should be taken to avoid any stray light entering the detector. In

addition, the setup must be calibrated each time the illumination source is moved relative to the detector. The data files obtained are large. These limitations must be accounted for when selecting an appropriate measurement technique. Because of its promising technology, it has been used in studies related to skin cancer,<sup>61-63</sup> skin pigmentation, and vascular structures.<sup>64,65</sup>

### Reflectance confocal microscopy

Reflectance confocal microscopy is highly correlated with histology.<sup>66</sup> Near-infrared light from a diode laser is focused on the tissue. This incident light is reflected, because of inherent differences in the refractive index of the cellular structures (including melanin, collagen, and keratin), and is collected by the photodetector. With the use of a pinhole, only the reflected light from the plane of interest can enter the detector, resulting in a high-resolution image. A z-scan can be performed, which involves image collection at regular intervals while precisely moving perpendicular to the epidermis. It helps collect a stack of images that can be used to reconstruct a 3-dimensional image of the sample.<sup>67</sup> A lateral resolution of about 1 μm can be achieved with near-infrared light, implying that features ≥1 μm in size can be seen distinctly. It is a valuable tool for in vivo diagnoses of facial skin, where many patients are hesitant to undergo procedures to obtain biopsy specimens. However, confocal microscopy is significantly more costly than conventional microscopy, and a significant amount of training needs to be done to be proficient with confocal microscopic examination and interpretation. Another limitation is the depth of penetration, which is only down to the superficial dermis. It has been used successfully to identify malignant and benign features of melanoma.<sup>68,69</sup> Because melanin provides a natural contrast, it has been used for diagnosing and testing treatment efficacy in pigmentation disorders, such as vitiligo, melasma, melanoma, and pigmented nevi.<sup>70-73</sup>

In conclusion, PIH is common and remains problematic in patients with SOC. Epidermal hyperpigmentation tends to be associated with a better prognosis than dermal hyperpigmentation. Visual examination and a Wood's lamp evaluation are convenient ways for PIH evaluation. Polarized light photography, colorimetry, DRS, and other noninvasive tools help obtain quantitative information of the lesion and augment clinical assessment of PIH; however, the use of these noninvasive technologies requires training to be proficient. The application of this technology helps improve the evaluation of PIH assessment and the treatment outcomes. Treatment

of PIH is based upon the depth of pigmentation and associated primary inflammatory dermatoses, which will be discussed in the second article in this continuing medical education series.

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# Postinflammatory hyperpigmentation: A comprehensive overview



## Treatment options and prevention

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### Learning objectives

After completing this learning activity, participants should be able to describe currently available medications, surgical treatments, and laser treatments for PIH; list possible side effects for PIH medication, surgical treatment, and laser treatment regimens; and discuss photoprotection methods to alleviate the PIH.

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#### Editors

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Postinflammatory hyperpigmentation (PIH) occurs after various dermatoses, exogenous stimuli, and dermatologic procedures. The clinical course of PIH is chronic and unpredictable, although the probability of resolution of epidermal hyperpigmentation is better than those of dermal hyperpigmentation. PIH can be prevented or alleviated. When it does occur, the underlying inflammatory conditions should be sought and treated as the first step to reduce the progression of inflammation and PIH (which is an inflammatory consequence). If the inflammatory conditions subsides or there is no evidence of inflammation at the time of diagnosis, the treatments of PIH should be considered as the next step. Understanding the available treatment options helps the physician choose the appropriate treatment for each patient. Having a reproducible model for PIH is essential for the development of treatment modalities. The second article in this 2-part continuing medical education series on PIH specifically addresses the evidence that supports medical and procedural treatments of PIH and other forms of acquired hyperpigmentation. It also describes a PIH model and provides an algorithm for clinical practice along with discussion about the prevention of PIH. (J Am Acad Dermatol 2017;77:607-21.)

**Key words:** bleaching agent; botanical; chemical peeling; hydroquinone; hyperpigmentation; laser and light; melanin; photoprotection; sunscreen; trichloroacetic acid.

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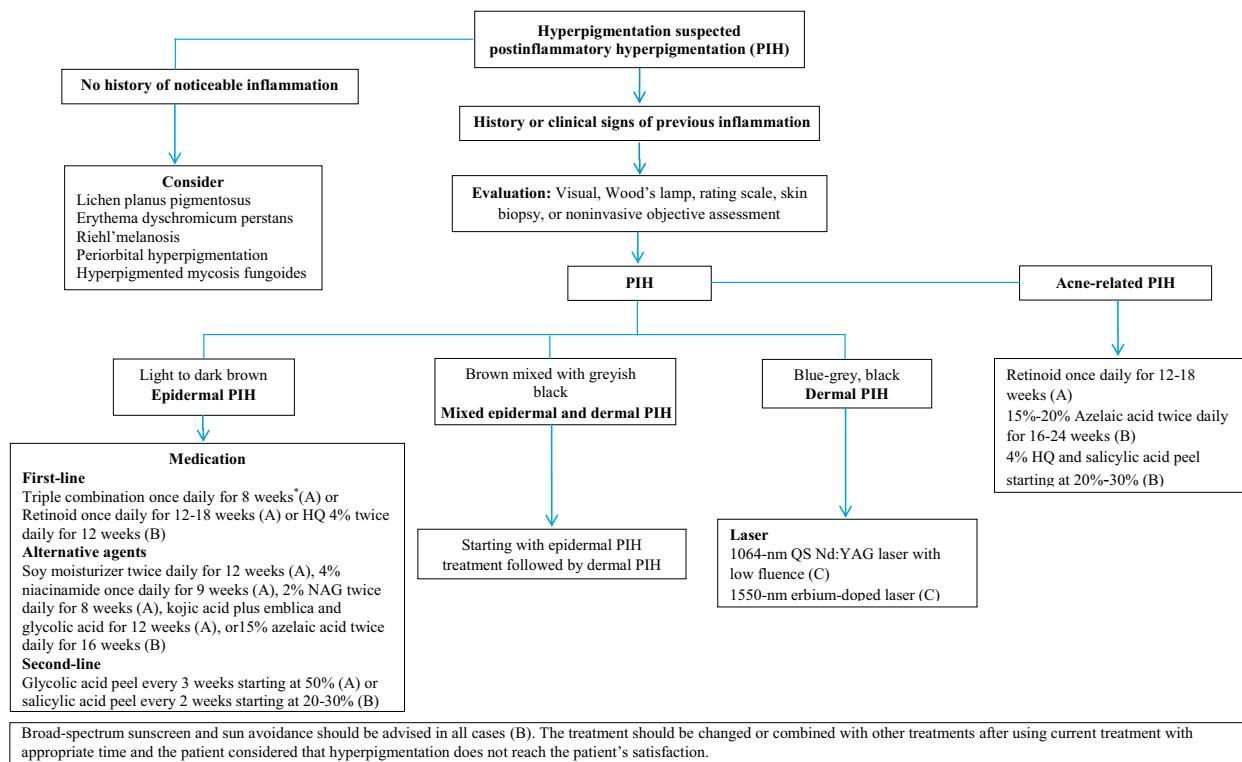
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**Fig 1.** Algorithm for the diagnosis and treatment of postinflammatory hyperpigmentation.

Postinflammatory hyperpigmentation (PIH) is a common skin disorder with significant psychological impact.<sup>1</sup> There is a limited understanding of its pathogenesis and the therapeutic modalities that are used to manage this condition. While there have been numerous studies of hyperpigmentation, few have specifically focused on PIH. In this article, we discuss the available evidence regarding the treatment of PIH and provide an algorithm for clinical practice (Fig 1). If data are not available for PIH, we refer to other commonly acquired types of hyperpigmentation. For future research, a reproducible, controlled stimulus that induces PIH would provide a useful tool for studies to better understand the molecular pathogenesis of this disorder and a criterion standard on which to test various treatment modalities for their efficacies.

## POSTINFLAMMATORY HYPERPIGMENTATION MODEL

### Key point

- Trichloroacetic acid–induced postinflammatory hyperpigmentation can be used as a model for evaluating treatment interventions and subsequent outcomes

Isedeh et al<sup>2</sup> created a model of induced PIH using trichloroacetic acid (TCA). This *in vivo* model was validated versus naturally induced PIH using acne as the causative agent. Validation consisted of comparing the clinical, histologic, and spectroscopic properties of TCA-induced and naturally occurring acne-induced PIH. The acne- and TCA-induced PIH exhibited similar clinical, spectroscopic (colorimetry and spectroscopy), and histologic characteristics starting at day 28.<sup>2</sup> The TCA-induced PIH model can be used for the future study assessing new treatments in PIH.

## MEDICAL TREATMENT

### Key points

- Small numbers of randomized controlled trials have proven the efficacy in reducing pigmentation for patients with postinflammatory hyperpigmentation
- A combination treatment appears to be more effective than monotherapy

Melanogenesis is a complex process. In melanosome, tyrosinase converts precursor L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA) by hydroxylation. L-DOPA is converted to L-DOPA quinone by an oxidation process, which then transforms to

*Abbreviations used:*

DOPA:	dihydroxyphenylalanine
GA:	glycolic acid
L-DOPA:	L-3,4-dihydroxyphenylalanine
NAG:	N-acetyl glucosamine
PIH:	postinflammatory hyperpigmentation
QS:	Q-switched
RCT:	randomized controlled trial
TA:	tranexamic acid
TCA:	trichloroacetic acid
UV:	ultraviolet

eumelanin or pheomelanin. Eumelanin and pheomelanin are transferred to surrounding keratinocytes by phagocytosis at the tip of the melanocyte dendrite.<sup>3</sup> Tyrosinase is the key regulatory and rate-limiting enzyme in melanogenesis; it requires copper as a cofactor.

Various agents have been proposed to interfere at different steps in melanogenesis. The mechanisms of action of these agents include inhibition of melanin production and melanosome transfer, increased keratinocyte turnover, and antiinflammatory and antioxidant effects.<sup>4</sup> Medical and procedural treatments for PIH and other hyperpigmentation disorders with their mechanisms of action are summarized in Table I. Table II lists topical bleaching agents that are available in the US market. Table III summarizes the treatment outcomes related to PIH as reported in the published literature.<sup>5-20</sup>

## HYDROQUINONE

### Key point

- Combination products containing hydroquinone, retinoic acid, and corticosteroids are the most effective medical treatment for postinflammatory hyperpigmentation based on the evidence from melasma treatment

Hydroquinone is the criterion standard skin-lightening agent. It acts as a tyrosinase inhibitor by blocking the conversion of DOPA to melanin. It can degrade melanosomes and destroy melanocytes.<sup>21</sup> Hydroquinone products are unstable; they rapidly oxidize and turn brown. When hydroquinone becomes discolored, its activity is decreased, and it should be discarded.<sup>22</sup> A concentration of 2% to 4% hydroquinone is commonly used to treat hyperpigmentation.<sup>23,24</sup>

Combination products enhance the efficacy and decrease the side effects of hydroquinone.<sup>25</sup> The Kligman formula (5% hydroquinone, 0.1% tretinoin, and 0.1% dexamethasone) was developed in 1975 and was shown to be effective for treating melasma, ephelides, and PIH.<sup>16</sup> A modified Kligman formula

(4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide [Tri-Luma; Galderma Laboratories, Fort Worth, TX]) was shown to be effective and safe in a multicenter, randomized, investigator-blinded study that included 641 patients with melasma. At week 8, 26% of patients had significant, complete clearing compared with other treatment groups. A 75% reduction in melasma and pigmentation was observed in >70% of patients.<sup>26</sup> This triple combination is well-tolerated and can be used for all Fitzpatrick skin phototypes (SPTs).<sup>27</sup> A formulation of 4% hydroquinone with 0.15% retinol entrapped in microsponge reservoirs, with good efficacy and safety profile, has been used successfully for treating melasma and PIH.<sup>14</sup> Microsponges are used to prolong the duration of exposure to the active agents and to minimize skin irritation via the gradual release of hydroquinone.<sup>14</sup>

Common short-term side effects of hydroquinone include irritation, contact dermatitis, and postinflammatory hypopigmentation.<sup>23</sup> Ochronosis is the most common long-term complication, usually occurring in African patients who have been exposed to high concentrations ( $\geq 4\%$ ) of hydroquinone along with exposure to high doses of sunlight,<sup>28,29</sup> although it has also been reported to occur with a low concentration (2%).<sup>30</sup> Carcinogenicity of hydroquinone has been reported in animals, but there is no established increased risk of cancer in humans.<sup>31,32</sup> Because of these adverse effects and the controversy involved, hydroquinone has been withdrawn from European and Japanese markets. In the United States, over-the-counter hydroquinone concentration is restricted to 2%, and 4% hydroquinone is available by prescription.<sup>22,23</sup>

## Mequinol

Mequinol, a 4-hydroxyanisole, is a hydroquinone derivative that has been approved in the United States and Europe.<sup>22</sup> It is a substrate for tyrosinase, acting as a competitive inhibitor in melanin formation without toxicity to melanocytes. Large clinical studies demonstrated efficacy of combination 2% mequinol and 0.01% tretinoin cream mostly in solar lentigines with minimal side effects.<sup>33-37</sup>

## NONHYDROQUINONE AGENTS

### Key point

- Nonhydroquinone agents have an excellent safety profile and can be used as monotherapy, alternative, or adjunctive treatments to other medical or procedural treatments

**Table I.** Treatment options for hyperpigmentation and their proposed mechanisms of action

Treatment	Mechanism of action				
	Tyrosinase inhibition	Melanosome transfer inhibition	Increased epidermal turnover	Antioxidation	Other
Hydroquinone	●				
Mequinol	●				
Retinoic acid	●	●	●		
Azelaic acid	●				
Arbutin/deoxyarbutin	●				● Melanosome maturation inhibition
Licorice	●				
Kojic acid	●				
Soy		Interacts with copper	● PAR-2		
Ascorbic acid (vitamin C)	●	Interacts with copper		●	
Niacinamide			●		
<i>N</i> -acetyl glucosamine	●				
Aloesin	●				
Mulberry				●	
Rucinol	●				
Emblica	●			●	
Pycnogenol				●	
Mulberry	●			●	
Coffeeberry				●	
Green tea	●			●	
Silymarin	●			●	
Grape seed extract				●	
Orchid				●	
Belides			●	●	
Tranexamic acid				●	
<i>Polypodium leucotomos</i>				●	
Glutathione	●			●	
Chemical peel			●		
Dermabrasion			●		
Pigmented-specific laser					● Destroys melanin

PAR-2, Protease-activated receptor 2; UV, ultraviolet.

## Retinoids

Retinoids can inhibit melanogenesis by increasing keratinocyte turnover, reducing melanosome transfer, and inhibiting tyrosinase transcription. Topical retinoids are available in 3 forms: tretinoin, adapalene and tazarotene. For PIH, retinoids are effective when using as monotherapy or in combination with other agents. Tretinoin cream 0.1% application once daily for 40 weeks in dark-skinned patients significantly improved the clinical outcomes, as shown by colorimetry and histology, compared with those in the placebo group. Improvement was first evident at 4 weeks.<sup>5</sup> After 40 weeks, colorimetry showed 40%

lightening of the skin compared with placebo. Common side effects include erythema, irritation, and desquamation (called “retinoid dermatitis”).<sup>5</sup> Adapalene is frequently used to treat acne vulgaris and causes less irritation than tretinoin. The efficacy of 0.1% adapalene gel was evaluated in a 12-week, open-label study of 65 African patients with acne vulgaris and associated PIH. The severity of PIH significantly decreased at weeks 4, 8, and 12 compared with baseline.<sup>15</sup> Tazarotene was assessed for PIH treatment in a randomized controlled trial (RCT) of 74 dark-skinned patients who had acne; 0.1% tazarotene cream was significantly more

**Table II.** Topical bleaching agents available in the US market

Ingredient	Selected representatives of US brand*	Remark
Hydroquinone	Eldoquin, Lustra, Obagi Skin Lightening Complex	—
Mequinol	Solage	2% Mequinol and 0.01% tretinoin
Retinoic acid	Retin-A, Avita, Renova, Aberel, and Aknoken Differin	Tretinoin Adapalene Tazarotene
Azelaic acid	Avage, Fabior, and Tazorac	—
Arbutin/deoxyarbutin	Azelex and Finacea	—
Licorice	Biopelle brightening cream Timeless Skin Care skin lightening cream Osmotics Lighten Fx 3X Dark Spot Remover Obagi nu Derm Blend Fx Skin Ceuticals Phyto + NeoStrata HQ Skin Lightening Gel Vichy ProEven Total Dark Spot Corrector	7% Arbutin and 3% phytic acid Arbutin, vitamin C, kojic acid, and licorice Arbutin and niacinamide Arbutin, vitamin C, vitamin E, and lactic acid Arbutin and kojic acid Licorice, 3% kojic acid, and 2% HQ Licorice, vitamin C, vitamin E, and salicylic acid
Kojic acid	NeoStrata HQ Skin Lightening Gel Biopelle KNR serum  PCA Skin Pigment Gel HQ Free Glytone Fading Lotion Skin Ceuticals Phyto + La Roach-Posay Mela-D Pigment Control	3% Kojic acid, 2% HQ, and licorice 2% Kojic acid, 4% niacinamide, vitamin E, and 0.15% retinol Kojic, azelaic and lactic acid, and resorcinol 1% Kojic, 2% HQ, and glycolic acid Kojic acid and arbutin 2% Kojic acid, Lipo-Hydroxy Acid, salicylic acid, and glycolic acid
Soy	MD formulations Vit-A-Plus Illuminating Serum  Ambi Even & Clear Daily Moisturizer SPF 30 Neutrogena Visibly Even Daily Moisturizer Aveeno Active Naturals Positively Radiant Daily Moisturizer	Soy, vitamin C, vitamin E, glycolic acid, retinol, grape and mulberry extract, and licorice Soy, vitamin C, and vitamin E
Ascorbic acid (vitamin C)	Biopelle XCP brightening serum  SkinCeuticals C E Ferulic serum  SkinMedica Lytera Skin Brightening Complex Dermelect Cosmeceuticals Beautone Enlightening Facial Serum Obagi Professional-C serum 20% strength	10% Vitamin C, 2% phytic acid, green tea extract, and grape extract 15% Vitamin C, 1% vitamin E, and 0.5% ferulic acid Vitamin C, vitamin E, licorice, retinol, phytic acid, and niacinamide Vitamin C, emblica, licorice, and arbutin
Niacinamide	Biopelle KNR serum  La Roach Posay Pigmentclar Intensive Dark Spot Correcting Serum Olay Total Effects Tone Correcting Moisturizer L'Oreal Youth Code Dark Spot Serum Corrector	4% Niacinamide, 2% kojic acid, vitamin E, and 0.15% retinol Niacinamide, ferulic acid, salicylic acid, and ginkgo biloba Niacinamide, vitamin E, and N-acetyl glucosamine Niacinamide, vitamin C, and vitamin E
N-acetyl glucosamine	Olay Total Effects Tone Correcting Moisturizer	Niacinamide, vitamin E, and N-acetyl glucosamine
Aloesin	Jan Marini Transformation Cream	—
Mulberry	Docteur Renaud	—
Rucinol	Noreva IKEN Depigmenting Serum and Cream	—
Emblica	Lumixyl Topical Brightening Creme	Emblica and licorice

Continued

**Table II.** Cont'd

Ingredient	Selected representatives of US brand*	Remark
Pycnogenol	Venus Pycnogenol Cream Swanson Premium Pycnogenol Wrinkle Cream	Rose hip oil Pycnogenol, vitamin B5, vitamin E, vitamin C, soy, thyme extract, and cinnamon extract
Coffeeberry	Revaleskin Intensive Recovery Treatment	1.5% coffeeberry extract formulation
Green tea	MD Formulations Moisture Defense Antioxidant Hydrating Gel	Green tea ( <i>Camellia oleifera</i> ) extract and licorice
Silymarin	Silymarin in Skin Actives Scientific	—
<i>Polypodium leucotomos</i> extract	HelIOCARE	—
Glutathione	Kyowa's Oxidized Glutathione	—

This is a representative but not an exhaustive list.

HQ, Hydroquinone; LHA, lipo-hydroxy-acid.

\*Brand names are trademarks of their respective manufacturers.

effective against PIH in overall disease severity, intensity, and area of hyperpigmentation within 18 weeks. Its side effects are mild, including trace erythema, burning, and peeling.<sup>6</sup>

### Azelaic acid

Azelaic acid is derived naturally from *Pityrosporum ovale*. As a depigmenting agent, it acts as a direct or indirect inhibitor of tyrosinase.<sup>38</sup> Azelaic gel 15% (Finacea and Skinoren; Bayer HealthCare, Whippany, NJ) is approved in the United States for treatment of rosacea.<sup>22</sup> In acne-related PIH, azelaic acid gel 15% twice daily was assessed in an open-label, 16-week study in 20 dark-skinned patients. Alleviation of PIH was seen at 4 weeks, and complete clearance was noted in 31% of patients at the end of the study.<sup>17</sup> In a randomized, double-blind, vehicle-controlled study, 52 dark-skinned patients with melasma and other facial hyperpigmentation (acne-induced PIH, drug-induced hyperpigmentation, and idiopathic melanosis) underwent application of 20% azelaic acid (n = 25) or vehicle (n = 27) twice daily for 24 weeks. Azelaic acid significantly reduced pigmentary intensity measured by the investigator's subjective scale ( $P = .021$ ) and chromameter analysis ( $P = .039$ ) and produced greater global improvement than the vehicle at the end of the treatment period ( $P = .008$ ). Side effects included mild local burning or itching.<sup>39</sup>

### Kojic acid

Kojic acid is produced by many species of fungi (eg, *Aspergillus oryzae*, *Penicillium* spp., and *Acetobacter* spp.). It inhibits tyrosinase by chelating copper at the active site of the enzyme.<sup>40</sup> Kojic acid is available in concentrations ranging from 1% to 4%.<sup>41</sup> A 12-week, double-blind study of 80 multiethnic

patients with mild to moderate facial dyschromia were randomly assigned to treatment with a combination of kojic acid, emblica extract, and glycolic acid (GA) versus 4% hydroquinone cream. The results showed similar efficacy in both groups.<sup>7</sup> Therefore, the combination of kojic acid, emblica extract, and GA appears to be a good alternative to 4% hydroquinone for reducing pigmentation.

### Soy

The soybean is a legume that is native to East Asia. Soybean-derived serine protease inhibitor, soybean trypsin inhibitor, and Bowman–Birk protease inhibitor can inhibit protease-activated receptor 2. Protease-activated receptor 2 is expressed on keratinocytes and mediates the phagocytosis of melanosomes by keratinocytes.<sup>42</sup> Soybean has also been shown to inhibit ultraviolet (UV) B-induced pigmentation.<sup>43</sup> A double-blind, parallel, vehicle-controlled study in 65 women with moderate facial photodamage showed that a soy-based moisturizer containing nondenatured soybean trypsin inhibitor and Bowman–Birk protease inhibitor applied twice daily for 12 weeks was significantly more effective than the vehicle alone for removing mottled hyperpigmentation, blotchiness, dullness, and fine lines and for improving skin tone and overall skin appearance.<sup>8</sup>

### Arbutin/deoxyarbutin

Arbutin is a glycosylated hydroquinone extracted from the bearberry plant. It inhibits tyrosinase activity and melanosome maturation without melanotoxic effects. Higher concentrations are correlated with greater action, although paradoxical hyperpigmentation has been seen.<sup>44</sup> Deoxyarbutin, a synthetic form, causes greater inhibition of tyrosinase.<sup>45</sup> Arbutin and deoxyarbutin are available in Japan and

**Table III.** Studies related to the treatment of postinflammatory hyperpigmentation

Treatment	Author, year	Conditions	Study design	Subjects	Treatment protocol	Pigmentation assessment methods	Outcomes	Level of evidence*
Retinoid (tretinoin)	Bulengoo-Ransby et al. 1993 <sup>5</sup>	PIH	RCT	n = 54 (black patients)	0.1% tretinoin vs vehicle cream applied daily for 40 wks	Colorimetry, IGA scale, histology, and clinical photograph	Significant alleviation of clinical outcome and improved colorimetry and histology in treatment vs placebo group	IB
Retinoid (tazarotene)	Grimes and Callender, 2006 <sup>6</sup>	PIH and acne	RCT	n = 74 (dark-skinned patients)	0.1% tazarotene vs vehicle cream applied daily for 18 wks	Pigmentation intensity and lesion area	Significantly reduced pigmentation, overall disease severity, intensity, and area of hyperpigmentation in treatment vs placebo group	IB
Kojic acid	Draelos et al. 2010 <sup>7</sup>	Facial dyschromia	RCT	n = 80 (multiethnic patients)	Combination of kojic acid, emblica extract, and glycolic acid vs 4% HQ cream applied twice daily for 12 wks	Clinical assessment and dermospectrophotometry	Similar efficacy between both groups	IB
Soy	Wallo et al. 2007 <sup>8</sup>	Facial photodamage	RCT	N=65	Soy moisturizer vs vehicle cream applied twice daily for 12 wks	Clinical assessment, colorimetry, and digital photograph	Significant alleviation of mottled hyperpigmentation, dullness, fine lines; improved overall texture, overall skin tone, and overall appearance in treatment vs control groups	IB
Niacinamide	Lee et al. 2014 <sup>9</sup>	Facial hyperpigmentation	RCT	n = 42 (Asian)	2% niacinamide + 2% tranexamic acid vs vehicle cream applied twice daily for 8 wks	Mexameter, chromameter, pigment intensity score (1-10), and clinical photograph	Combination treatment was significantly more effective in reducing pigmentation than the vehicle	IB

Continued

Table III. Cont'd

Treatment	Author, year	Conditions	Study design	Subjects	Treatment protocol	Pigmentation assessment methods	Outcomes	Level of evidence*
Niacinamide	Castanedo-Cazares et al, 2013 <sup>10</sup>	Axillary hyperpigmentation	RCT	n = 24 (SPTs III–V)	4% niacinamide vs 0.05% desonide vs placebo applied at night	Colorimetry, clinical grading score, histology, and image analysis	Both niacinamide and desonide produced significantly better results than placebo as measured by colorimetric and Physician Global Assessment score; desonide had a better depigmenting effect than niacinamide	IB
N-acetyl glucosamine	Bissett et al, 2007 <sup>11</sup>	Facial hyperpigmentation	RCT	n = 50 (Japanese) n = 105 (white)	2% NAG vs vehicle controls applied twice daily for 8 wks 2% NAG + 4% niacinamide vs 4% niacinamide alone vs vehicle control, applied twice daily for 8 wks	Digital image and visual perception system	Reduced facial hyperpigmentation in treatment group More effective lightening with combination treatment compared with others	IB
N-acetyl glucosamine	Kimball et al, 2010 <sup>12</sup>	Facial hyperpigmentation	RCT	n = 202	2% NAG + 4% niacinamide vs vehicle cream control applied daily for 8 wks; SPF 15 sunscreen used in both groups	Facial color image analysis, visual perception system and melanin-specific imaging and analysis	Combination treatment was significantly more effective in reducing the area of facial spots and hyperpigmentation than the vehicle	IB
Chemical peel	Burns et al, 1997 <sup>13</sup>	Facial PIH	RCT	n = 16 (SPTs IV–V)	6 serial glycolic acid peels every 3 wks plus topical treatment (2% HQ/10% glycolic acid gel twice daily and 0.05% tretinoin cream at night vs topical treatment applied for 22 wks	Clinical photograph, colorimetry, and Hyperpigmentation Area and Severity Index	Peel group tended to have more reduced pigmentation than the control group in terms of more rapid and greater lightening	IB

HQ	Grimes, 2004 <sup>14</sup>	Melasma and PIH	Open-label study	n = 25 (dark-skinned patients)	Microentrapped 4% HQ with 0.15% retinol applied twice daily for 12 wks	Colorimetry, disease severity, pigmentation intensity, and lesion area	Statistically significant alleviation of disease severity, lesion size, and pigmentation	IIIB
Retinoid	Jacyk and Mpofu, 2001 <sup>15</sup>	PIH and acne	Open-label study	n = 65 (African patients)	0.1% adapalene gel applied daily for 12 wks	Number and density of hyperpigmentation	Degree of PIH significantly alleviated at wks 4, 8, and 12 compared with baseline	IIIB
0.1% tretinoin + 5% HQ + 0.1% dexamethasone (Kligman formula)	Kligman and Willis <sup>16</sup>	PIH, melasma, and others	Open-label study	n = 18 (PIH)	Applied daily or twice daily for 12 wks	Clinical assessment	12/18 cases had satisfactory response	IIIB
Azelaic acid	Kircik, 2011 <sup>17</sup>	Acne with PIH	Open-label study	n = 20 (dark-skinned patients)	15% azelaic acid gel applied twice daily for 16 wks	IGA scale	Alleviation of PIH at 4 wks; 31% of patients showed complete clearance at the end of study	IIIB
Chemical peel	Grimes, 1999 <sup>18</sup>	Acne, PIH, melasma, and enlarged pores	Open-label study	n = 25 (SPT V-VI)	Pretreated with 4% HQ for 2 wks before peeling with salicylic acid (20–30%) every 2 wks for 5 treatments	Clinical photograph and grading score	Moderate to significant improvement occurred in 5/5 patients with PIH and 4/6 patients with melasma; decreased the intensity of hyperpigmentation and the lesional area, and improved skin texture	IIIB
1064-nm QS Nd:YAG laser Fractional 1550-nm erbium-doped laser	Kim and Cho, 2010 <sup>19</sup> Katz et al, 2009 <sup>20</sup>	Procedure-related PIH PIH on neck	Case series Case report	n = 5 (Asian) n = 1 (SPT IV)	1064-nm QS Nd:YAG laser with low fluence 1550-nm erbium-doped Fraxel laser using density of 880–1100 MTZ/cm <sup>2</sup> for 3 sessions at 4- to 8-wk intervals	Clinical photograph	Excellent response >95% clearance of PIH with no postprocedural complications or recurrence after third treatment	III IV

IGA, Investigator's Global Assessment; HQ, hydroquinone; NAG, N-acetyl glucosamine; PIH, postinflammatory hyperpigmentation; QS, Q-switched; RCT, randomized controlled trial; SPF, sun protection factor; SPT, Fitzpatrick skin phototype.

\*Level of evidence: IA, evidence from metaanalysis of randomized controlled trials; IB, evidence from at least 1 randomized controlled trial; IIA, evidence from at least 1 controlled study without randomization; IIIB, evidence from at least 1 other type of experimental study; III, evidence from nonexperimental descriptive studies; IV, evidence from expert committee reports or opinions and/or clinical experience of respected authorities. IGA scoring system was not validated.

the United States as over-the-counter products.<sup>45</sup> In an open study of 33 patients with epidermal melasma, a combination of 3% arbutin, 4% niacinamide, 1% bisabolol, and 0.05% retinaldehyde applied once daily significantly reduced Melasma Area and Severity Index scores and total melasma area over 60 days of treatment.<sup>46</sup>

### Licorice extract

Licorice is extracted from the root of *Glycyrrhiza glabra*, a legume that is native to southern Europe and Asia. The active ingredients, liquiritin and isoliquiritin, inhibit tyrosinase and disperse melanin.<sup>22</sup> A split-face study of 20 patients with melasma using 20% liquiritin cream twice daily compared with controls showed that 70% of the patients had an excellent response.<sup>47</sup>

### Ascorbic acid

Ascorbic acid (vitamin C) is an essential nutrient with antioxidant properties. It interacts with copper to reduce conversion of L-DOPA to L-DOPA-quinone, which reduces melanogenesis. Ascorbic acid is rapidly oxidized and highly unstable. It is a mild skin-lightening agent with an excellent safety profile.<sup>48,49</sup> In melasma, a 16-week, split-face, RCT compared 5% ascorbic acid versus 4% hydroquinone cream in 16 patients.<sup>48</sup> Hydroquinone produced a better response than the ascorbic acid in terms of subjective improvement (93.0% vs. 62.5%); however, no significant difference in the colorimetric measurements was seen in both groups.<sup>48</sup>

### Niacinamide

Niacinamide is an amide form of niacin (vitamin B<sub>3</sub>). It inhibits melanosome transfer to keratinocytes.<sup>50</sup> A combination of 2% niacinamide and 2% tranexamic acid (TA) as a moisturizer demonstrated efficacy in 42 Asian women with facial hyperpigmentation. At 8 weeks, mexameter, chromameter, and clinical assessments all showed reduced irregular pigmentation.<sup>9</sup> A 9-week, RCT was performed in 24 women (SPTs III to V) with hyperpigmented axillae. Subjects were randomly assigned to apply 4% niacinamide cream, 0.05% desonide cream, or placebo once daily. Both niacinamide and desonide cream produced significantly better colorimetric and physician global assessment scores than the placebo.<sup>10</sup>

### N-acetyl glucosamine

N-acetyl glucosamine (NAG) is an aminomonosaccharide produced in vivo via addition of an amino group to glucose.<sup>51</sup> It inhibits glycosylation of tyrosinase, which accounts for its pigment-

lightening ability. NAG is usually used in 2% concentration as monotherapy or in combination with niacinamide.<sup>41</sup> Many studies have demonstrated the efficacy of NAG monotherapy or NAG/niacinamide combination in facial hyperpigmentation in Asian patients.<sup>11,12</sup>

## ORAL AGENTS

### Key point

- Evidence supporting the efficacy of oral treatment of postinflammatory hyperpigmentation is limited

### Tranexamic acid

TA is a plasmin inhibitor. It is used to reduce blood loss caused by abnormal fibrinolysis. It has also exhibited effectiveness in patients with melasma in several studies with good safety profiles.<sup>52-55</sup> The proposed mechanism is that TA inhibits UV-induced plasmin activity in keratinocytes, which results in a reduction of free arachidonic acid and prostaglandins, and thus decreased melanocyte tyrosinase activity; therefore, melanogenesis is reduced.<sup>56</sup> Oral TA 750 mg/day combined with topical TA for 8 weeks showed beneficial effects in patients with melasma.<sup>54</sup> The mean melanin index score decreased and epidermal pigmentation, number of blood vessels and mast cells, evaluated histologically, were also decreased.<sup>54</sup>

Unlike oral TA, topical TA showed no significant effect on melasma.<sup>57,58</sup> In a split-face RCT in 23 women with bilateral epidermal melasma, topical 5% TA gel applied twice daily for 12 weeks showed no difference in reducing pigmentation compared to vehicle.<sup>57</sup>

### *Polypodium leucotomos* extract

*Polypodium leucotomos* is a tropical fern native to Central and South America. Its extract has been shown to have antioxidative and immunomodulatory effects. *P leucotomos* extract has been reported to be photoprotective against UVB- and psoralen plus UVA light phototherapy-induced phototoxicity.<sup>59,60</sup> Therefore, it might have a potential benefit on minimizing the development of PIH. One RCT showed no significant difference of pigmentation reduction in melasma when *P leucotomos* was added to sunscreen use. Sunscreen provided a 14% improvement in the darkness component of melasma.<sup>61</sup> However, *P leucotomos* extract can be used as an adjunct to topical sunscreen in melasma.<sup>61</sup>

### Other botanical agents

Several botanically derived agents have exhibited lightening effects in patients with epidermal

melasma and UV-induced hyperpigmentation. These include rucinol, emblica, pycnogenol, mulberry, coffeeberry, green tea, silymarin, grape seed extract, orchids, and belides.<sup>4,62-71</sup> Pycnogenol is derived from the bark of the French maritime pine. It has potent antioxidant and antiinflammatory properties. Oral intake of pycnogenol reduces areas of melasma and pigmentary intensity.<sup>72</sup> Grape seed extract contains proanthocyanidin, a potent antioxidant. Oral intake of grape seed extracts (67 mg of grape seed extract) 3 times daily for 6 months was reported to be effective in reducing hyperpigmentation in patients with melasma.<sup>73</sup> Although these agents produced promising results, additional studies regarding the treatment of PIH are needed.

## PROCEDURAL TREATMENT

### Key points

- **Procedural techniques, including chemical peeling, dermabrasion, laser, and intense pulsed light therapy, are considered adjuncts to topical medications**
- **These treatments should be applied with caution because they can also worsen post-inflammatory hyperpigmentation, especially in dark-skinned patients**

### Chemical peel

Chemical peel facilitates the absorption of topical bleaching, increases epidermal turnover, and decreases epidermal melanin. Superficial peeling agents include GA, salicylic acid, Jessner solution (ie, salicylic acid, lactic acid, and resorcinol), 20% TCA, and tretinoin. Superficial peeling removes the stratum corneum, whereas medium and deep peeling affects the papillary and reticular dermis, respectively. These deeper peeling agents cause irritation, which can subsequently lead to PIH. Therefore, superficial peeling agents are the preferred agents for the treatment of PIH.

In 1 study, dark-skinned patients with PIH underwent GA (50-68% concentration)-induced serial peels 6 times every 3 weeks plus once-daily topical treatment (2% hydroquinone/10% GA/0.05% tretinoin cream). This regimen produced more rapid reduction in pigmentation than topical treatment alone.<sup>13</sup> Salicylic acid peel (20-30%) every 2 weeks was shown to be effective in 25 dark-skinned patients with acne ( $n = 9$ ), PIH ( $n = 5$ ), melasma ( $n = 6$ ), and enlarged pores ( $n = 5$ ). All patients were primed with 4% hydroquinone for 2 weeks and underwent 5 peeling sessions. Moderate to significant improvement using serial photographs evaluation were seen in 88% of patients. All PIH patients

had improvement while melasma had improvement in 66% of cases.<sup>18</sup>

For TCA peel, a comparison study in 100 patients with melasma using 10% to 15% TCA peels ( $n = 32$ ) and 55% to 75% GA peels ( $n = 68$ ) every 2 weeks until significant improvement occurred showed that at 3 months, the TCA-treated group had more rapid improvement of chronic pigmentation, which had been present for 1 to 3 years. However, irritation and relapse at follow-up at 3 months were more common in the TCA group than the GA group.<sup>74</sup>

### Laser and light

Several laser types have been studied for the treatment of PIH and other hyperpigmentation, with variable results. These studies suffer from small sample size, nonstandardized outcomes, and limited controls. Lasers and light sources studied include pigmented specific laser (Q-switched [QS] ruby, QS alexandrite, and QS neodymium-doped yttrium aluminium garnet [Nd:YAG]), intense pulsed light, and fractional photothermolysis. The QS-ruby and QS-alexandrite lasers have been reported to worsen lesions and are not recommended for dark-skinned patients.<sup>75-77</sup> In contrast, QS-ruby laser has shown efficacy in reducing sclerotherapy-induced hyperpigmentation.<sup>78</sup>

In PIH resulting from cosmetic procedures, low-fluence 1064-nm QS Nd:YAG with a 6-mm spot size produced an excellent response in 5 cases.<sup>19</sup> QS-Nd:YAG 1064 nm has been reported to be effective in patients with melasma. A split-face, randomized study compared the combination of low-fluence ( $3.0\text{-}3.8\text{ J/cm}^2$ ) QS Nd:YAG laser with a 6-mm spot size for 5 sessions at 1-week intervals and 2% hydroquinone versus 2% hydroquinone alone in 22 Asian patients. After 5 laser treatments, colorimetry and Melasma Area and Severity Index scores confirmed statistically significant alleviation of melasma compared to baseline. Mottled hypopigmentation developed in 3 cases; however, melasma recurred at 12 weeks after the last treatment in all patients.<sup>79</sup> Katz et al<sup>20</sup> treated 1 PIH patient with 1550-nm erbium-doped Fraxel laser using a density of 880 to 1100 MTZ/cm<sup>2</sup>. The patient achieved >95% clearance after 3 treatment sessions without side effects.<sup>20</sup>

## PHOTOPROTECTION

### Key point

- **Visible light can induce hyperpigmentation, especially in dark-skinned individuals**
- **Broad-spectrum sunscreen should be applied regularly on areas of postinflammatory hyperpigmentation at sun-exposed areas**

Effect of pigmentation induced by UV light is well recognized, especially in dark-skinned individuals. Photoprotection should be provided during PIH treatment. Patients should be advised to apply broad-spectrum sunscreen with sun protection factors of  $\geq 30$ , to seek shade when outdoors, to use physical photoprotection (eg, clothes, wide brimmed hats, and driving gloves), and when appropriate, to have UV-protective films applied to window or automobile glass. Regular usage of sunscreen in patients with skin of color for 8 weeks showed the improvement of dyschromia and skin darkening as measured by colorimetry.<sup>80</sup> Apart from UV light, visible light (400-700 nm) has been shown to induce pigmentation in those with SPTs IV to VI.<sup>81</sup> This pigmentation is darker and more sustained than that induced by long-wavelength UVA.<sup>81</sup> Therefore, visible light with UV protection might aid in PIH and other pigmentary conditions. Sunscreen containing large particles (ie, nonmicronized) inorganic materials (titanium dioxide and zinc oxide) offers visible light protection, but the white appearance after application is cosmetically unacceptable. Iron oxide is another pigmented ingredient that acts as a UV-visible light filter.<sup>82,83</sup>

## PREVENTION OF POSTINFLAMMATORY HYPERPIGMENTATION

### Key point

- Postinflammatory hyperpigmentation caused by dermatologic treatment is preventable by taking measures before, during, and after the procedure

PIH associated with inflammatory dermatoses can be alleviated by promptly and adequately treating the underlying condition while concomitantly treating the PIH. In acne-related PIH, topical retinoid is the best option because of its antiinflammatory and bleaching properties. Bleaching creams can be prescribed along with an acne regimen, especially in dark-skinned individuals.<sup>84</sup> PIH derived from dermatologic procedures can be prevented before, during, and after treatment. Photoprotection measures as outlined above should be practiced for at least 2 weeks before the procedure.<sup>85,86</sup> Preoperative treatment with a topical bleaching cream (eg, hydroquinone, tretinoin, GA, and vitamin C) has been shown to be ineffective in decreasing the occurrence of PIH.<sup>87</sup> Pretreatment with a bleaching cream, however, allows the patient to become familiar

with the medication in case it is required after the procedure.

Ablative laser has a higher risk of causing PIH than nonablative laser. Parameter settings affect the outcome of PIH.<sup>88</sup> For solar lentigines, aggressive irradiation with an obvious whitening endpoint using QS laser has been shown to have the same efficacy as the treatment protocol using milder irradiation (resulting in slight, immediate whitening); however, the aggressive protocol resulted in significantly more PIH.<sup>88</sup> Epidermal cooling can also minimize epidermal injury.<sup>89</sup>

The short-term use of topical corticosteroids has shown promise in reducing the incidence of PIH after ablative fractional resurfacing. A split-face comparison study of 40 patients (SPT IV) undergoing fractional carbon dioxide laser for acne scars was performed. Subjects applied 0.05% clobetasol propionate ointment twice daily on the first 2 days followed by petrolatum jelly for the rest of the week to 1 side of face, and applied petrolatum jelly alone for 7 days to the contralateral side. The clobetasol-treated side had significantly less PIH compared to the petrolatum jelly side.<sup>90</sup> The use of sunscreen with antioxidants starting on the first day after ablative fractional skin resurfacing can decrease the incidence of PIH at 1 week postoperatively.<sup>91</sup> Even with special protection, PIH remains a common adverse effect in dark-skinned patients. Therefore, counseling and written informed consent are mandatory in all cases. The choice of laser and its parameters (energy/density) should be tailored carefully for each patient.

In conclusion, there are still tremendous gaps in the understanding of the basic science of PIH. There are no in vitro models of PIH, but the skin PIH model described above may provide a platform for basic science. In addition, there are limited studies in PIH treatment, with most of the data obtained from studies in patients with melasma. Studies should be undertaken that focus on PIH as the primary condition. These future studies should evaluate a variety of elements of study design and outcome measures. These include different degrees of severity of PIH in the studied subjects, the concurrent use of other treatments (eg, sunscreen or bleaching agents), noninvasive methods of PIH assessment, standardized follow-up periods, and larger sample sizes. The previously described skin PIH model can be applied in treatment evaluation. In addition, studies of laser combined with topical or oral antioxidants should be further conducted. The goal would be to develop clinical trials informed by basic science using standardized

outcome measures. This effort would boost treatment options for this disease.

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# Spectrum of orocutaneous disease associations

## Immune-mediated conditions

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### Learning objectives

After completing this learning activity, participants should be able to recognize the important and close relationship between the skin and the mucosal tissues inclusive of GI disorders and inflammatory disorders; recognize and differentiate the mucosal manifestations of multiple dermatologic conditions; and describe the pathophysiology of how oral disease may potentially manifest on the skin, and vice versa.

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There are a number of diseases that manifest both on the skin and the oral mucosa, and therefore the importance for dermatologists in clinical practice to be aware of these associations is paramount. In the following continuing medical education series, we outline orocutaneous disease associations with both immunologic and inflammatory etiologies. (*J Am Acad Dermatol* 2017;77:795-806.)

**Key words:** chronic ulcerative stomatitis; Crohn's disease; immune-mediated conditions; linear immunoglobulin A bullous dermatosis; lupus erythematosus; mucous membrane pemphigoid; oral cavity; orocutaneous disease; paraneoplastic pemphigus; pemphigus vulgaris; rheumatoid arthritis; scleroderma.

## ORAL ANATOMY

The normal anatomy of the oral cavity is comprised of the lips anteriorly, the cheeks laterally, the floor of the mouth inferiorly, the oropharynx posteriorly, and the palate superiorly. It includes the lips, gingivae,

teeth, hard palate, cheek mucosa, and tongue (Fig 1). The lip has an interior wet vermillion and is lined with a stratified squamous, nonkeratinized epithelium together with an outer dry vermillion, separated from each other by the red line. The outer dry lip

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is composed of stratified squamous, keratinized epithelium. The cheeks are lined by mucosa that is nonkeratinized, although in some places it can be parakeratinized. The gingivae and hard and soft palates are lined with a keratinized stratified squamous epithelium (masticatory mucosa).

## GRANULOMATOSIS WITH POLYANGIITIS

### Key points

- **Granulomatosis with polyangiitis, formerly known as Wegener granulomatosis, is a systemic immune-mediated condition characterized by the presence of antineutrophil cytoplasmic antibodies**
- **Hyperplastic gingivitis with the appearance of overripe strawberries is characteristic of this disease**
- **Granulomatosis with polyangiitis is responsive to a 2-phase treatment plan beginning with a remission induction phase followed by a maintenance phase**

### Etiology

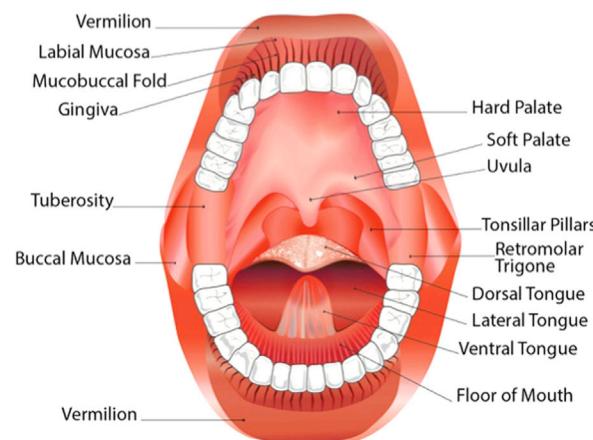
Granulomatosis with polyangiitis (GPA) is a systemic, immune-mediated process characterized by the presence of circulating antineutrophil cytoplasmic autoantibodies.<sup>1–6</sup> Antineutrophil cytoplasmic autoantibodies target proteinase 3 and myeloperoxidase, causing neutrophil activation and degranulation.<sup>7–9</sup> While all ages can be affected, patients are most commonly affected in the sixth and seventh decades of life.<sup>6</sup> The cause of GPA is unknown, although a genetic predisposition relating to human leukocyte antigen (HLA)-DPB1\*0401, the  $\alpha 1$ -antitrypsin gene *SERPINA*, or the proteinase 3 gene *PRTN3* together with exposure to environmental or infectious agents has been suggested.<sup>10,11</sup>

### Oral manifestations

The oral cavity is affected in  $\leq 62\%$  of patients with GPA, with 5% to 6% of patients citing oral lesions as a presenting complaint.<sup>8</sup> Hyperplastic gingivitis of the upper anterior gingiva is most common and characteristically resembles overripe strawberries.<sup>10,12</sup> Other oral manifestations can include painful ulcerations of the palatal or gingival mucosa, tooth mobility, poor healing after tooth extraction, cranial nerve palsies, and parotid gland swelling.<sup>1,6,8,10,13</sup> Table I shows the differential diagnosis of GPA.<sup>14</sup>

### Cutaneous manifestations

Up to 50% of patients present with nonspecific cutaneous manifestations, including palpable purpura, subcutaneous nodules, pustules, vesicles,



**Fig 1.** Normal oral anatomy.

**Table I.** Differential diagnosis of granulomatosis with polyangiitis

#### Differential diagnosis

Vasculitides: Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis
Granulomatous disease: sarcoidosis, Crohn's disease
Systemic lupus erythematosus
Nasal natural killer/T-cell lymphoma
Langerhans cell histiocytosis
Lymphomatoid granulomatosis
Blood dyscrasias: leukemia, lymphoma
Granulomatous infectious disease: tuberculosis, deep mycoses
Drug-induced gingival changes

or petechiae commonly involving the extremities.<sup>10,12</sup> Alopecia can occur during active disease because of vasculitis of the scalp.<sup>10</sup>

### Treatment

Treatment is divided into remission induction and maintenance phases.<sup>4,6,7,15</sup> The criterion standard GPA therapy combines prednisone and cyclophosphamide and typically brings symptoms under control within a week.<sup>7,8,15</sup> Intralesional steroid injections may relieve gingival symptoms.<sup>1</sup> Azathioprine and methotrexate are the principal agents of the maintenance therapy regimen.<sup>2,6,7,16</sup>

## PEMPHIGUS VULGARIS

### Key points

- **Pemphigus vulgaris is an immune-mediated disorder characterized by immunoglobulin G autoantibody production against desmoglein-1 and -3 desmosome antigens**



**Fig 2.** Pemphigus vulgaris. Persistent erosions in the upper labial mucosa.

- **Bullae and painful, nonhealing erosions present in the mouth, pharynx, and skin**
- **Treatment plans should focus on suppression of immune autoantibody production**

#### Etiology

Pemphigus vulgaris (PV) is a rare immune-mediated chronic blistering disorder that results from immunoglobulin G (IgG) autoantibody production toward and against the desmosomal components desmoglein-1 and desmoglein-3.<sup>17,18</sup> The resulting dysfunction of these cell adhesion molecules results in acantholysis of suprabasilar keratinocytes.<sup>19</sup> Although the cause of autoantibody production is unknown, a genetic predisposition is associated with HLA-DRB1\*0402 and HLA-DQB1\*0503 haplotypes.<sup>18-23</sup> Triggers of outbreaks in genetically predisposed individuals include drugs, physical agents, viruses, hormones, food, and stress.<sup>19,22,24</sup>

#### Oral manifestations

The oral mucosa is the initial site of involvement in 70% to 90% of cases.<sup>25</sup> Areas subjected to frictional trauma are most affected, such as the buccal mucosa, palate, lower lip, and tongue (Figs 2 and 3); however, any area of the oral cavity can be involved.<sup>21,25</sup> Bullae rupture quickly, producing nonhealing ulcerations. Desquamative gingivitis is also a common feature, often associated with sore throat, hoarseness, and odynophagia.<sup>2,24,26-28</sup> Because of pain, poor oral hygiene and hemorrhage lead to increased dental plaque and progression to periodontal disease.<sup>20</sup>

#### Cutaneous manifestations

Subsequent to its oral manifestations, flaccid bullae may present at any location on the skin, but the scalp, face, axillae, trunk, and groin are most susceptible. Bullae rupture easily because of its suprabasal membrane location, resulting in painful erosions and crusting.<sup>17,22</sup> Mucosal involvement of the urethra, penis, vulva, cervix, and anus can also be



**Fig 3.** Pemphigus vulgaris. Lower labial edema and hemorrhagic crusts caused by extensive blistering.

observed in patients with PV. The Nikolsky and Asboe-Hansen signs are commonly observed on physical examination and are suggestive of PV.<sup>17,22</sup> Direct immunofluorescence studies demonstrate the presence of IgG antibody and complement component 3 (C3) deposition along the cell surface within the intercellular space.<sup>29</sup>

#### Treatment

Because first-line therapy for PV has traditionally been high-dose systemic corticosteroids, sparing therapies aimed at reducing corticosteroid dosage include azathioprine, cyclophosphamide, methotrexate, cyclosporine, and mycophenolate mofetil. Topical therapies have limited efficacy because of their inability to impact the production of autoantibodies. Intravenous immunoglobulin has also been used with some success. Most recently, rituximab has been used with excellent results, yielding remission in many individuals.<sup>30,31</sup>

### MUCOUS MEMBRANE PEMPHIGOID

#### Key points

- **Mucous membrane pemphigoid consists of a heterogeneous group of immune-mediated chronic blistering conditions caused by immunoglobulin G, immunoglobulin A, or complement component 3 deposition along the basement membrane**
- **Mucosal tissues of the oral oropharynx, nose, penis, vulva, or anus are commonly involved**
- **Patients are stratified into low- and high-risk treatment groups based on distribution of lesions beyond the oral mucosa**
- **Immunosuppressive therapy is imperative to reduce autoantibody production and improve the clinical status**

#### Etiology

Mucous membrane pemphigoid (MMP) consists of a heterogeneous group of rare, immune-mediated



**Fig 4.** Mucous membrane pemphigoid. Large sloughing ulcer on the left cheek mucosa.

conditions sharing a common chronic subepidermal blistering phenotype. Bullae formation is attributed to linear deposition of IgG, immunoglobulin A (IgA), or C3 along the mucosal and epithelial basement membranes.<sup>32,33</sup> This disease commonly manifests after the fourth decade of life, with women being affected more frequently than men. Several antibody targets have been identified in the hemidesmosome and basement membrane. It is likely that each disease subtype corresponds to a different target antigen.<sup>34-36</sup> An increased incidence of MMP is observed in patients with HLA-DR4 and HLA-DBQ1\*0301 haplotypes.<sup>37-39</sup>

### Oral manifestations

The gingivae are the most common site for MMP, occurring in about 94% of patients with MMP.<sup>40</sup> Clinically, oral lesions present with multiple erythematous bullae, erosions, or ulcerations that can occur at any location in the oral cavity, including the gingivae, buccal mucosa, palate, pharynx, labia, or tongue.<sup>40</sup> Ruptured bullae tend to form irregularly shaped erosions with a yellowish slough and surrounding inflammation (Fig 4).<sup>41</sup> Notably, these tend to heal without scarring. Desquamative gingivitis is a common clinical manifestation of patients with MMP; however, this finding is associative, not diagnostic.<sup>40,42,43</sup> In addition, bleeding, pain, dysphagia, or odynophagia are common presenting symptoms.<sup>41,44</sup>

### Cutaneous manifestations

Mucosal tissues of the nose, vulva, penis, or anus may be involved with scarring and more serious complications.<sup>41,45</sup> Skin involvement is uncommon, occurring in ≤25% of patients, and is restricted to the face, neck, scalp, axillae, trunk, and extremities.<sup>41,42,45</sup> Cicatricial alopecia may present on the scalp.<sup>46</sup>

### Treatment

Patients are categorized into low- and high-risk groups based on restriction of disease to or

extending beyond the oral mucosa.<sup>45</sup> In low-risk patients, topical high-potency corticosteroid gel may be sufficient to reduce symptoms, but can also be combined with dapsone.<sup>45</sup> Systemic corticosteroids are used in high-risk cases or in patients who are unresponsive to topical therapies.<sup>47,48</sup> As in PV, steroid-sparing agents can also be used alone or in combination with steroids, including cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate, and cyclosporine.<sup>41,49,50</sup> In refractory cases, both intravenous immunoglobulin and rituximab have been used separately or in combination, with excellent responses.<sup>51-53</sup>

## PARANEOPLASTIC PEMPHIGUS

### Key points

- Paraneoplastic pemphigus is a severe immune-mediated chronic blistering disease associated with an underlying neoplasm and immunoglobulin G autoantibodies targeting desmoglein or plakin family antigens
- Oral lesions are seen in almost all cases, while flaccid cutaneous bullae may present subsequently
- An approach to treatment should consider the underlying neoplasm, autoimmune phenomena, and secondary complications associated with compromised skin barrier function

### Etiology

Paraneoplastic pemphigus (PNP) is a rare, life-threatening immune-mediated bullous condition commonly associated with lymphoproliferative neoplasms.<sup>54-56</sup> There is a lack of consensus regarding the defining characteristics of this disease, although mucosal lesions, detection of IgG autoantibodies against Dsg or plakin family antigens, and the presence of an underlying neoplasm constitute a constellation of shared features.<sup>57-59</sup> HLA antigen allele type HLA-DRB1\*03 may confer susceptibility to PNP.<sup>60</sup> While the pathogenesis of this condition is unknown, 5 hypotheses are to be considered: (1) tumor autoantibody production,<sup>61</sup> (2) cross-reactivity of tumor antigens,<sup>62</sup> (3) epitope spreading,<sup>62,63</sup> (4) elevated levels of interleukin-6,<sup>64</sup> and (5) T cell-mediated pathology.<sup>65,66</sup>

### Oral manifestations

Oral lesions are seen in almost all cases of PNP, with painful stomatitis traditionally the first symptom.<sup>54,56</sup> Presentation is highly variable, and typically includes longstanding painful erythematous erosions or ulcerations of the oropharynx, nasopharynx, tongue, or esophageal mucosal

membranes, often extending to the vermillion of the lip.<sup>67</sup> Unlike PV, PNP lesions do not show ragged superficial erosions and are much more necrotic.<sup>54</sup>

### Cutaneous manifestations

Flaccid cutaneous bullae typically present before mucosal lesions. Because of the heterogeneity of cutaneous manifestations, 5 clinical variants have been established: (1) pemphigus-like, (2) bullous pemphigoid-like, (3) erythema multiforme-like, (4) graft-versus-host disease-like, and (5) lichen planus (LP)-like.<sup>68</sup> Lesions may occur anywhere on the skin, but have a predilection for the upper body. The mucosa of the penis or vagina may also be involved.<sup>69</sup>

### Treatment

An approach to treatment must first consider the underlying neoplasm as well as autoimmune phenomena and secondary complications. Resection of the tumor is imperative, leading to a decrease in serum IgG autoantibody titer.<sup>70</sup> High-dose corticosteroids is the traditional first-line treatment.<sup>56</sup> Azathioprine, cyclosporine, and mycophenolate mofetil may be used as combination therapy to reduce steroid dosage.<sup>56,71-73</sup> Rituximab and intravenous immunoglobulin have been used successfully in several cases.<sup>68,74,75</sup> Secondary infection and pain caused by compromised skin barrier function should be treated with appropriate antibiotics and analgesics.

## LINEAR IMMUNOGLOBULIN A BULLOUS DERMATOSIS

### Key points

- Linear immunoglobulin A bullous dermatosis is an immune-mediated subepidermal dermatosis caused by immunoglobulin A deposition along the lamina lucida
- Oral involvement is reported in 80% of cases, and characteristic cutaneous “collarettes” form on extensor surfaces of the limbs, buttocks, and genitalia
- Linear immunoglobulin A bullous dermatosis is typically responsive to dapsone, with corticosteroids, azathioprine, or cyclophosphamide being added in unresponsive cases

### Etiology

Linear IgA bullous dermatosis (LAD) is an immune-mediated subepidermal dermatosis caused by IgA deposition along the epidermal basement membrane. A bimodal distribution of disease incidence peaks at ages <5 and >60 years, constituting 2 disease variants.<sup>22,76</sup> This condition is idiopathic, but can be precipitated by infection, ultraviolet light radiation, drugs, or neoplasm.<sup>77,78</sup>

Vancomycin is the most commonly implicated cause of drug-induced pathology.<sup>79</sup> IgA autoantibodies target a variety of antigens localized to the lamina lucida of the basement membrane zone.<sup>80</sup> An association between this disease and HLA haplotypes B8, CW-7, and DR3 has been established.<sup>81</sup>

### Oral manifestations

Oral involvement is reported in ≤80% of patients with cutaneous lesions. Clinical manifestations may range in severity from a few lesions to more severe disease involvement. The hard and soft palates are the most commonly affected sites, followed by the tonsils, buccal mucosa, tongue, and gingiva.<sup>82</sup> Bullae, erosions, or ulcerations develop in the oral mucosa and may extend to surround the mouth. In addition, desquamative gingivitis can present alone or in conjunction with the aforementioned lesions and cannot be clinically distinguished from gingivitis because of LP, pemphigoid, and other mucocutaneous disease.<sup>83</sup>

### Cutaneous manifestations

Cutaneous symptoms include pruritic, annular papules, vesicles, or tense bullae seen in clusters most commonly on the elbows, knees, genitalia, and buttocks.<sup>79</sup> New lesions characteristically form “collarettes” or a “string of pearls” appearance around the periphery of older lesions. Excoriations caused by itching can induce crusted papules.

### Treatment

LAD generally responds well to treatment. Dapsone may be first-line therapy against LAD, initially in low doses to control bullae formation.<sup>79</sup> In cases where dapsone is inadequate to control symptoms, corticosteroids, azathioprine, or cyclophosphamide should be considered.<sup>79</sup>

## LUPUS ERYTHEMATOSUS

### Key points

- Cutaneous lupus erythematosus is a more common condition than systemic lupus
- A wide spectrum of oral manifestations can be found in lupus erythematosus, including mucosal and nonmucosal lesions

### Etiology

Systemic lupus erythematosus (SLE) is an immune-mediated disease that has the potential to affect multiple organs, including the skin. The etiology of SLE remains unknown, but multiple factors, such as immunologic, environmental, genetic, and hormonal dysregulation, are known to play a role in the pathogenesis of the disease. Genome-wide association studies (GWASs) have

yielded numerous candidate genes. Those conferring the highest risk are deficiencies in the early components of the complement (C1q, C4A and B, C2) and mutations in *TREX1*. Antinuclear antibodies are positive in virtually all patients with SLE. Anti–double-stranded DNA and anti-Smith are highly specific antibodies for SLE.<sup>84,85</sup>

### Oral manifestations

Oral involvement ranges from 9% to 54% in SLE and 3% to 20% in localized cutaneous disease.<sup>86-89</sup> Although oral ulcers appear in both American College of Rheumatology and Systemic Lupus International Collaborating Clinics classification criteria, the oral manifestations in SLE are much broader, including erythematous patches, cheilitis, honeycomb and discoid plaques, and LP-like lesions.<sup>88,90</sup> Commonly, patients present with multiple oral lesions located on the buccal mucosa, hard palate, and lips.<sup>91</sup> Obtaining an oral biopsy specimen and using direct immunofluorescence is recommended, because the characteristic histopathology can aid in the diagnosis.<sup>92</sup>

### Cutaneous manifestations

Discoid lupus erythematosus is the most common subtype of cutaneous lupus erythematosus (CLE) and classically presents with erythematous scaly plaques with prominent follicular plugging commonly found on the face, scalp, and ears. Given the involvement of the epidermis and both the papillary and reticular dermis, discoid lupus erythematosus frequently leads to permanent scarring and atrophy.<sup>86,92</sup>

Subacute CLE is a photosensitive, nonscarring dermatosis that is clinically characterized by small erythematous and scaly papules with a psoriasiform or annular appearance. Despite the photosensitive nature of subacute CLE, the midfacial skin is usually spared, with the most common locations being the upper aspect of the chest and extensor aspects of the arms.<sup>86,92</sup>

The hallmark of the acute CLE is the presence of the butterfly rash. This is a transient, bilateral malar erythema frequently induced by ultraviolet light exposure and universally associated with systemic disease. The involved skin is usually warm and mildly edematous, with multiple telangiectasias and occasional scaling.<sup>86,92</sup>

### Treatment

The American Academy of Dermatology guideline of care for CLE recommends avoidance of sunlight exposure and the use of sunblock with a sun protection factor  $\geq 15$ . Topical and intralesional corticosteroids are also recommended. First-line

systemic therapy consists of antimalarials, dapsone, and prednisone.<sup>93</sup> High- and medium-potency corticosteroids and calcineurin inhibitors are the most used topical therapies for all CLE subtypes.<sup>94</sup> Despite the significant differences observed among the participants, corticosteroids and antimalarials are still considered the most effective systemic treatments for patients with CLE.

### CROHN'S DISEASE

#### Key points

- The most common sites of oral involvement in Crohn's disease are the lips, gingiva, and vestibular sulci
- Obtaining biopsy specimens from these sites is generally uncomplicated, and these specimens are diagnostic
- The treatment of oral manifestations is generally the same as that of the underlying intestinal disease

#### Etiology

Crohn's disease (CD) is a disorder of unknown etiology that is characterized by transmural inflammation of the gastrointestinal (GI) tract. GWASs have found at least 71 susceptibility loci that result in a dysfunction of both the innate and adaptive immune response toward a diminished diversity of commensal microbiota.<sup>95,96</sup> An imbalance between the effector T cells ( $T_{H}1$ ,  $T_{H}17$ ) and regulatory T cells of thymic origin (nTreg) and the inducible (iTreg) T cells in the GI mucosa prompts inappropriate recruitment of leukocytes, and changes in the protein expression of epithelial tight junctions increase the intestinal permeability. In genetically predisposed individuals, the most studied environmental trigger is smoking, increasing significantly the risk of developing the disorder.<sup>97,98</sup>

### Oral manifestations

In a review of 79 patients with CD, two-thirds experienced oral lesions in the first 3 decades of life, with a median age of presentation of 22 years.<sup>99</sup> The most common sites of involvement are the lips, gingiva, and vestibular sulci. A most characteristic finding is a persistent, firm, painless swelling of the labial, buccal, or facial tissues.<sup>96</sup> The oral equivalent of the intestinal cobblestone lesions is a corrugated edema or thickening of the vestibular mucosa, which is usually accompanied by linear or serpiginous ulcerations.<sup>100</sup> Underlying chronic inflammation usually leads to hyperplastic gingivitis, tissue tags, and polypoid masses. Additional oral findings include aphthous ulcerations, angular cheilitis, and glossitis.

### Cutaneous manifestations

Cutaneous manifestations include contiguous perianal CD, reactive lesions (such as erythema nodosum [EN] and pyoderma gangrenosum [PG]; Fig 5), nutritionally related skin changes, and the unusual metastatic CD. Chronic and multiple perianal fissures, sinus tracts, and fistulas are the classic presentation of perianal CD and occur in more than one-third of the patients.<sup>101</sup> EN (Fig 6) is significantly and independently associated with a diagnosis of CD, female sex, and extraintestinal manifestations, such as eye and joint involvement and concurrent PG. EN presents as painful, erythematoviolaceous nodules located most frequently on the anterior aspects of the lower extremities. Histologically, EN is a granulomatous septal panniculitis without vasculitis. PG is neither an infectious nor gangrenous process, but instead is a painful neutrophilic dermatosis characterized by rapidly enlarging ulcers on the pretibial area. Neither EN nor PG has been shown to have an association with the severity of the underlying inflammatory bowel disease.<sup>98</sup>

### Treatment

In many cases, a short-term use agent (ie, steroids, anti-tumor necrosis factor- $\alpha$  agents) is used to achieve rapid symptom relief. Long-term control is usually achieved with combinations of thiopurines and methotrexate.<sup>96</sup> Oral manifestations of CD usually respond well to treatment directed at the intestinal disease.<sup>102</sup> Symptomatic relief consists of triamcinolone acetonide in orabase or a potent steroid gel, 2 to 4 times daily until the ulcer is healed. The use of tumor necrosis factor- $\alpha$  inhibitors, particularly infliximab, has been tested in case series and small case reports of recalcitrant mucosal ulcerations with favorable results.<sup>103</sup>

## SCLERODERMA

### Key points

- The main orofacial manifestations of scleroderma are a reduction in oral aperture, widening of the periodontal ligament, and xerostomia
- General treatment focuses on internal organ involvement, with response in cutaneous manifestations being less evident

### Etiology

The etiology of scleroderma remains unknown. Environmental triggers, including viral infections and toxins, may lead to disease expressions in genetically predisposed individuals. The strongest genetic risk factor is an HLA haplotype bearing the alleles DQ7, DR2, DQA1\*0501, or DQB1\*0301.<sup>104</sup>

GWASs in white populations have identified susceptibility loci in gene regions for CD247, interferon regulatory factor 5, and signal transducer and activator of transcription 4.<sup>105</sup>

### Oral manifestations

Orofacial manifestations of scleroderma have a female preponderance (84.5%) with a mean age of 40.2 years, 10 years on average after the diagnosis of the systemic disease,<sup>106</sup> and include limitation of mouth opening (69.8%), widening of the periodontal ligament (67.3%), xerostomia (63.4%), telangiectasias (36.2%), and bone lesions (34.5%). In fact, the number of missing teeth was significantly associated with xerostomia, worse hand function (as a manifestation of sclerodactyly), and the presence of gastroesophageal reflux disease.<sup>107</sup>

### Cutaneous manifestations

The classification criteria for scleroderma<sup>108</sup>—skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints—is an important diagnostic criterion, but it is not an early sign of the disease. Many patients experience an early edematous phase, accompanied by pitting edema of the fingers. Fingertip lesions include digital tip ulcers (Fig 7) and pitting scars, usually caused by calcinosis and a loss of finger pad substance. The Raynaud phenomenon is a common complaint frequently leading to digital ulcerations.

### Treatment

Because of the wide spectrum of clinical manifestations, treatment must be individualized to the specific organs involved. Treatment of Raynaud phenomenon involves educating patients about keeping their hands warm and avoiding smoking, as well as the use of calcium channel blockers or phosphodiesterase type 5 inhibitors. In patients with diffuse skin sclerosis and visceral involvement, the intensity of the therapy depends on the latter, which generally leads to only a modest benefit on skin thickening.<sup>109,110</sup> Treatment of periodontal disease in patients with scleroderma does not differ from that of other patients.<sup>106</sup>

## CHRONIC ULCERATIVE STOMATITIS

### Key points

- Characterized by painful oral lesions
- The criterion standard for diagnosis is a direct immunofluorescence of the affected tissue
- Hydroxychloroquine is the drug of choice in limiting the disease, producing long-term remissions even after its discontinuation



**Fig 5.** Pyoderma gangrenosum in a patient with Crohn's disease. Deep ulcer with a well-defined, gun metal gray hue border and surrounding erythema in the lateral aspect of the ankle.



**Fig 6.** Erythema nodosum. Tender erythematous nodules on the extensor aspect of the shin.

### Etiology

The etiology of chronic ulcerative stomatitis (CUS) is only partially understood. In vitro studies have shown that IgG autoantibodies against the protein  $\Delta\text{Np}63\alpha$  explain the subepithelial detachment at the basement membrane, characteristic for the oral ulcerations seen clinically.<sup>111</sup> Direct immunofluorescence remains the criterion standard for the diagnosis.<sup>112</sup> A classic finding in the biopsy specimen is a speckled, intranuclear deposition of IgG in the basal and parabasal cells, with a stratified epithelium-specific antinuclear antibody pattern (Fig 8).<sup>113</sup>

### Oral manifestations

CUS is characterized by chronic painful oral erosions seen anywhere in the oral cavity, with the tongue, buccal mucosa, and gingiva being the most commonly affected sites.<sup>114</sup> A common clinical presentation is the development of progressive painful erythematous gingival erosions, with progression to ulcers and vesicles.

### Cutaneous manifestations

In a review of 35 patients, skin lesions were present only in 5.1% of cases.<sup>114</sup> Skin manifestations resembling LP have been reported in some patients.

Similar immunofluorescence findings may be found in skin.

### Treatment

An important distinguishing factor of CUS compared with other ulcerative conditions is that the former is usually refractory to treatment with topical corticosteroids. Conversely, CUS has a striking response to hydroxychloroquine, with 70% of patients developing complete remission or disease-free status even after discontinuation of therapy.<sup>114</sup> Side effects, such as retinopathy, aplastic anemia, agranulocytosis, and myopathy, should be closely monitored.

## RHEUMATOID ARTHRITIS

### Key points

- The most common oral manifestations of rheumatoid arthritis are Sjögren syndrome, temporomandibular joint dysfunction, and periodontal disease
- The treatment of the oral manifestations is the treatment of the systemic disease, with a current trend moving toward early aggressive treatment with disease-modifying anti-rheumatic drugs

### Etiology

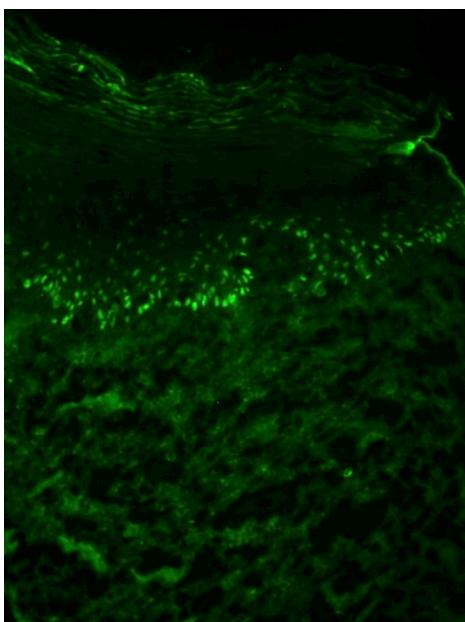
Rheumatoid arthritis (RA) results from an interaction between genes and the environment, leading to autoreactivity and synovial inflammation. Genes contributing to the susceptibility and severity of RA include the class II major histocompatibility complex, with HLA-DR4 being most prominent.<sup>115</sup> Smoking can modify proteins through citrullination, leading to the production of anticitrullinated protein antibodies that can initiate inflammation by fixing complement.<sup>116</sup> Once the immune-mediated process is established, the synovium organizes itself into an invasive tissue that degrades cartilage and bone, leading to the specific signs and symptoms of RA.

### Oral manifestations

Oral manifestations include secondary Sjögren syndrome and xerostomia, temporomandibular joint dysfunction, periodontal disease, and methotrexate-induced ulcers. Depending on the definition, symptomatic xerostomia and secondary Sjögren syndrome can occur in  $\leq 30\%$  of patients with RA.<sup>117,118</sup> Different studies have estimated the prevalence of temporomandibular joint dysfunction in patients with RA to be  $> 50\%$ .<sup>119,120</sup> A case control study including 57 patients with RA and 52 healthy controls found a significant association of periodontitis in the RA group after adjusting for



**Fig 7.** Scleroderma. Extensive digital ulceration with loss of substance from the finger pad caused by calcinosis.



**Fig 8.** Direct immunofluorescence in chronic ulcerative stomatitis. Positive speckled intranuclear deposition of immunoglobulin G in the basal and parabasal cells.

age (odds ratio = 8.05 [95% confidence interval, 2.93–22.09]).<sup>121</sup>

### Cutaneous manifestations

The most common cutaneous manifestation of RA is the rheumatoid nodule,<sup>122</sup> a firm, painless, skin-colored lesion that can be solitary or multiple and lie deep subcutaneously in areas prone to mild trauma, such as the extensor surface of forearms, fingers, occiput, back, and heel.<sup>123</sup> Rheumatoid vasculitis, a complication occurring in <1% of patients with RA,<sup>124</sup> may manifest as ulcers, petechiae or purpura, gangrene, and digital infarcts.<sup>125,126</sup> Leg ulcers occur in 10% of patients with RA.<sup>127</sup> These are often found to be multifactorial, with vasculitis and venous insufficiency as the main determinants.<sup>128</sup>

### Treatment

Because most of the articular damage occurs early in the course of the disease,<sup>129,130</sup> it is recommended that all the patients diagnosed with RA initiate therapy early with a disease-modifying antirheumatic drug (DMARD). Classic DMARDs include methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine. Biologic DMARDs used in RA include TNF- $\alpha$ , the interleukin-1 receptor antagonist anakinra, the interleukin-6 receptor antagonist tocilizumab, and the Janus kinase inhibitor oral tofacitinib. Several studies have demonstrated that treatment aimed at specific targets in RA has better efficacy than treatments without a predefined goal.<sup>131–133</sup>

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# Spectrum of orocutaneous disease associations

## Genodermatoses and inflammatory conditions

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### Learning objectives

After completing this learning activity, participants should be able to recognize the important relationship between the skin and the oral cavity with respect to genodermatoses.

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The oral cavity and cutaneous organ systems share a close embryologic origin. Therefore, there are numerous dermatologic conditions presenting with concomitant oral findings of which the dermatologist must be aware. The second article in this continuing medical education series reviews inflammatory orocutaneous conditions and a number of genodermatoses. It is essential for dermatologists to be familiar with oral cavity manifestations associated with dermatologic diseases for prompt diagnosis, management, and appropriate referral to stomatology and dentistry. (J Am Acad Dermatol 2017;77:809-30.)

**Key words:** amyloidosis; Behcet disease; burning mouth syndrome; cutaneous manifestations; Darier disease; genodermatoses; inflammatory; lichen planus; nevoid basal cell carcinoma syndrome; oral cavity; orocutaneous diseases; Peutz-Jeghers syndrome; sarcoidosis; sclerosis complex; tuberous erythema multiforme.

## GENODERMATOSES

The genodermatoses are a group of rare, inherited, single-gene skin disorders that are often

associated with a variety of other medical abnormalities. The epidermis of the skin and the enamel and dentine components of the teeth share a common

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embryologic origin. As such, many genodermatoses frequently present with preceding or concomitant manifestations of the oral cavity.<sup>1,2</sup> It is therefore imperative for the dermatologist to identify and recognize lesions of the oral mucosa for prompt diagnosis and treatment of these often multisystemic diseases. Table I shows the genodermatoses associated with both cutaneous and oral findings, highlighting the pertinent clinical findings, pattern of inheritance, and implicated gene.

## INFLAMMATORY CONDITIONS

### Darier disease

#### Key points

- Darier disease is an autosomal dominant keratinization disorder associated with mutations of the *ATP2A2* gene
- Cases can be hereditary or sporadic
- Topical retinoids are effective treatments

#### Background

Darier disease (DD) is an autosomal dominantly inherited keratinization disorder affecting the skin, nails, and mucous membranes. It is caused by mutations of the *ATP2A2* gene, which encodes a sarco/endoplasmic reticulum adenosine triphosphatase type 2 calcium pump located within the endoplasmic reticulum.<sup>26,27</sup> Sporadic mutations occur in up to two-thirds of cases.<sup>28</sup> Prevalence rates range from 1 in 30,000 to 1 in 100,000 individuals.<sup>29,30</sup>

#### Clinical

**Skin.** DD has a peak onset around puberty and is characterized by yellow to brown, greasy, keratotic papules involving the seborrheic areas of the face, scalp, and chest (Fig 5). Known trigger factors include excessive sweating, ultraviolet light exposure, mechanical trauma, humidity, high temperatures, pregnancy, and friction.<sup>27,28</sup>

**Oral cavity.** The hard palate is the most commonly affected oral site, followed by the gingiva, buccal mucosa, and tongue. Lesions include whitish papules with a central depression with aggregation to form nodular plaques. The palate often exhibits a fine to coarse “pebbly” appearance resembling nicotinic stomatitis. More severe forms are similar to papillary palatal hyperplasia.<sup>6</sup> Obstructive sialadenitis has been reported in ≤30% of cases and often involves the parotid gland.<sup>31</sup>

**Systemic.** DD may be associated with neuropsychiatric disorders, including bipolar affective disorder, mental retardation, epilepsy, encephalopathy, and schizophrenia.<sup>27</sup> Moreover, urogenital abnormalities, such as polycystic kidneys, hypoplastic

gonads, and renal and testicular agenesis, are occasionally reported.<sup>32</sup>

#### Therapy

Treatment of DD includes removal of exacerbating factors. Topical retinoids are effective, and in combination with a mid-potency steroid or emollient can decrease irritation. Oral retinoids are indicated for more severe forms. In addition, topical antibiotics, salicylic acid, and antifungals can reduce infection and the associated foul odor.<sup>27,28,33</sup>

## TUBEROUS SCLEROSIS COMPLEX

#### Key points

- Tuberous sclerosis complex is an autosomal dominant neurocutaneous disease caused by mutation of the hamartin or tuberin genes
- Facial adenoma sebaceum, epilepsy, and mental retardation are the classic clinical triad
- The skin and oral cavity are involved in most cases
- Baseline management involves neurologic, cardiac, renal, ophthalmic, dermatologic, and dental evaluation

#### Background

Tuberous sclerosis complex (TSC) is an autosomal dominant, multisystemic, neurocutaneous disease caused by mutations of the *TSC1* or *TSC2* genes or hamartin and tuberin, respectively.<sup>34</sup> The incidence is approximately 1 in 5000 to 1 in 10,000 births and is classically characterized by the clinical triad of facial adenoma sebaceum, epilepsy, and mental retardation.<sup>35</sup> Seven percent to 37% of patients have a positive family history, and de novo mutations are common.<sup>36</sup>

#### Clinical

**Skin.** TSC is associated with numerous skin findings, with hypomelanotic macules being the most common (90-98%). These lesions often involve the trunk and buttocks, and are best observed under a Wood's lamp.<sup>37</sup> Hypomelanotic macules presenting with infantile focal seizures should raise suspicion for TSC.<sup>36</sup> Bilateral facial angiofibromas are hamartomatous nodules often distributed in a butterfly pattern over the malar eminences and nasolabial folds, giving a ruddy appearance to the cheeks (Fig 6).<sup>38</sup> The shagreen patch presents as irregularly shaped, thickened patches with a roughened surface. In addition, yellow-brown to flesh-colored forehead fibrous plaques are present in approximately 36% of patients.<sup>35,36,38</sup>

**Table I.** Genodermatoses

Genoderm	Inheritance	Gene defect	Oral findings	Skin findings	Pertinent signs	Notes
Papillon–Lefèvre syndrome <sup>3,4</sup>	Autosomal recessive	<i>CTSC</i> gene on 11q14	Periodontitis with severe gingivitis after eruption of both primary and permanent dentition; alveolar bone resorption	Hyperkeratosis of the palms, soles, knees, and elbows	Infections seen in children with neutropenia; painful chewing because of looseness, hypermobility, and migration of teeth	Periodontitis with severe gingivitis, alveolar bone resorption, and loss of deciduous and permanent teeth
Darier disease <sup>5,6</sup>	Autosomal dominant	<i>ATP2A2</i> gene on 12q23-34	Papules with a central depression and cobblestone pattern affecting the palate; blockage of salivary ducts resulting in obstructive sialadenitis; itching, malodor, and pain	Skin-colored or yellow-brown keratotic papules with a warty texture involving predominantly seborrheic areas that may coalesce to form large crusted plaques; palmar keratoses	Nail changes: white and red longitudinal bands, ridges, and subungual hyperkeratosis; red and white longitudinal bands with a V-shaped nick at free margin of the nail; neuropsychiatric abnormalities, such as epilepsy and mood disorders; focal suprabasal acantholysis and dyskeratosis with eosinophilic corps ronds and grains in the stratum spinosum and stratum corneum on skin biopsy specimen	Painless whitish papules with cobblestoning of oral mucosa
Tuberous sclerosis <sup>7,8</sup>	Autosomal dominant	<i>TSC1</i> (hamartin) on 9q34; <i>TSC2</i> (tuberin) on 16p13.3	Enamel pitting on the facial aspect of the anterior permanent dentition; gingival fibrous papules; hemangiomas; high-arched palate; bifid uvula	Hyperpigmented macules (ash leaf spots); angiofibromas; brown fibrous plaque on the forehead	Ungual fibromas; shagreen patch; retinal hamartomas; angiomyolipomas; glioneural hamartomas; cortical tubers; subependymal nodules; white matter heterotopias; infantile cognitive defects	Enamel pits, gingival fibromas

Continued

**Table I.** Cont'd

Genoderm	Inheritance	Gene defect	Oral findings	Skin findings	Pertinent signs	Notes
Sturge—Weber <sup>9,10</sup>	Somatic activating mutation	GNAQ gene	Maxillary hypertrophy with occlusion deformity and cross-bite; gingival hypertrophy	Cutaneous capillary malformation (port wine stain) on forehead and upper eyelid with extension bilaterally of the face and trunk	Facial capillary malformation and associated leptomeningeal capillary-venous malformation; visual field defects; focal neurological defects; glaucoma; seizures	Maxillary hypertrophy (occlusion deformity, cross-bite), gingival hypertrophy
Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu) <sup>11,12</sup>	Autosomal dominant	<i>ENG</i> on 9q34.1 (HHT1); <i>ACVR1</i> on 12q11-14 (HHT2)	Telangiectasias of the oral and vermillion mucosa, tongue and lips (Fig 1); hemorrhagic ulcers and vesicles on the gingival and oral mucosa	Cutaneous telangiectasias, mostly on the fingertips, but can occur anywhere	Epistaxis; mucocutaneous telangiectasias; iron deficiency anemia; visceral and pulmonary AVMs; cerebral AVMs with a high risk of hemorrhagic stroke	Telangiectasias on vermillion, oral and nasopharyngeal mucosa
Goltz syndrome (focal dermal hypoplasia) <sup>13</sup>	X-linked dominant	<i>PORCN</i> gene	Hypodontia; enamel hypoplasia and dysplasia; microdontia; abnormal eruption and position of teeth; cleft lip or cleft palate less common	Atrophy; pigmentation; fat herniation; nail dystrophy; alopecia; papillomas along the lines of Blaschko	Limb malformation/skeletal abnormalities (lobster claw hands); microphthalmia; craniofacial abnormalities; mild intellectual disability	90% females, almost always lethal in males; hypodontia, oligodontia; small teeth with dysplastic enamel
Lipoid proteinosis (Urbach—Wiethe disease) <sup>14,15</sup>	Autosomal recessive	<i>ECM1</i> gene on 1q21	Hoarseness (vocal cord infiltration); pearly deposits in the mucosa; hard, enlarged, stiff and woody tongue; gingival hypertrophy; thickened lips (Fig 2)	Acneiform scars between yellowish waxy skin (recurrent blister healing); hyperkeratosis of the palms, soles, elbows, and knees; diffuse alopecia with varicelliform scarring; moniliform blepharosis (beaded papules) on upper and lower eyelids	Moniliform blepharosis; nail dystrophy with hemorrhagic blisters at the distal extremities; recurrent crops of vesicles, bullae, macules, papules, and nodules on the skin; concentric smooth muscle and basement membrane layering of blood vessels with visceral bleeding caused by hyaline deposition	Hoarse cry because of vocal cord infiltration; large, wooden tongue

Gardner syndrome (a variant of FAP) <sup>16</sup>	Autosomal dominant	<i>APC</i> gene on 5q22.2	Osteomas of the mandible; unerupted teeth; supernumerary teeth; dentigerous cysts; odontomas	Epidermal cysts; fibromas; lipomas; pilomatrixomas	Osteomas are the first described lesion; increased risk of extracolonic malignancies; desmoid tumors; hypertrophy of retinal pigment epithelium; nasal angiofibromas; adrenal adenomas	Odontomas, supernumerary teeth, central or periosteal osteomas
Peutz–Jeghers syndrome <sup>17,18</sup>	Autosomal dominant	<i>STK11/LKB1</i> gene on 19p13.3	Mucosal hyperpigmentation presenting as dark macules on the gingiva, hard palate, and mucosa of the cheek and lower lip	Cutaneous hyperpigmentation on facial and body surfaces that fade as the patient ages	Hamartomatous polyps in the small intestine, most commonly jejunal, stomach, and large bowel; mucocutaneous lesions	Mucocutaneous lesions causing patches of hyperpigmentation in the mouth and on the hands and feet; the oral pigmentation are the first on the body to appear, and thus play an important part in early diagnosis; intraorally, they are most frequently seen on the gingiva, hard palate and inside of the cheek; the mucosa of the lower lip is almost invariably involved
Cowden syndrome <sup>19</sup>	Autosomal dominant	<i>PTEN</i> gene on 10q	Oral papillomas (Fig 3); cobblestone appearance on lips, gingival, labial, and buccal mucosa, oropharynx; fissured tongue	Facial trichilemmomas; acral keratosis; palmoplantar keratoses punctata	Multiple hamartomatous syndrome; abnormalities in the thyroid, breasts and GI tract predisposed to malignant hamartomatous neoplasms	

Continued

**Table I.** Cont'd

Genoderm	Inheritance	Gene defect	Oral findings	Skin findings	Pertinent signs	Notes
MEN IIB <sup>20</sup>	Autosomal dominant	<i>RET</i> oncogene on chromosome 10	Mucosal neuromas on tongue and lips, may involve buccal, palatal, gingival, nasal, and laryngeal mucosa; thickened "blubbery" lips; open-bite deformity (skeletal apertognathia); dental diastema (gap)	Cutaneous neuromas on the eyelids, conjunctivae, and corneas; marfanoid habitus	Mucocutaneous neuromas; thickened eyelids; hypertrophied lips; skeletal abnormalities—notably the spine; dolichocephaly (hull-shaped skull); pes cavus; increased risk of pheochromocytoma and medullary thyroid carcinoma	
DEB <sup>21</sup>	Autosomal dominant and recessive	<i>COL7A1</i> gene on 3p21.3	Vesiculobullous lesions and erythema of the oral-pharyngeal mucosa and esophagus; hoarseness; erosive gingival lesions; decay of the dentition	Widespread blistering lesions; loss of fingernails and toenails; thickening of the palms and soles; scalp blistering; atrophic scarring of the skin	High risk of squamous cell carcinoma; dominant disease is less severe than recessive DEB	May have blistering, erosions in oral cavity (with/without secondary hoarseness) and esophagus
Pachyonychia congenita <sup>22</sup>	Autosomal dominant	<i>KRT16</i> (keratin-16) or <i>KRT6A</i> (kertain-6A) on chromosome 12	Oral leukoplakia with a milky appearance on the tongue and buccal mucosa; natal teeth; angular stomatitis	Subungual hyperkeratosis with thickening of the distal nail; palmar and plantar hyperkeratoses; hyperhidrosis; follicular hyperkeratosis; friction blisters	Hypertrophic nail dystrophy; Natal teeth (PC-2), oral palmoplantar hyperkeratoses; oral leukoplakia	Natal teeth (PC-2), oral leukokeratosis (PC-1, not premalignant)—tongue, buccal mucosa
Nevoid basal cell carcinoma syndrome <sup>23</sup>	Autosomal dominant	<i>PTCH1</i> (patched 1) on chromosome 9	Keratocystic odontogenic tumors; intraoral BCCs	Multiple BCCs and epidermal cysts of the skin; palmar or plantar pits	Classic triad of multiple BCCs, keratocysts in the jaws, and bifid ribs; calcified falx cerebri; enlarged head circumference; ocular hypertelorism	Keratocysts and interestingly, BCCs have been reported intraorally in this syndrome
White sponge nevus (of Cannon; hereditary mucosal leukokeratosis) <sup>24</sup>	Autosomal dominant	<i>KRT4</i> on chromosome 12; <i>KRT14</i> on chromosome 17	Bilateral white plaques that are thickened, spongy and folded on the buccal, labial, and gingival mucosa	Perigenital and perianal nevi	Multiple mucosal and genital nevi	

Hereditary benign intraepithelial dyskeratosis. <sup>25</sup>	Autosomal dominant	Chromosome 4q35 duplication	White plaques on the oral mucosa ( <b>Fig 4</b> )	Conjunctival (bulbar) epithelial white plaques and abnormalities	White plaques on the bulbar Rosenthal syndrome, occasionally seen in association with Cowden syndrome, pachyonychia congenita, and acromegaly (in the setting of macroglossia)
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ACVR1, Activin receptor-like kinase 1; BCC, basal cell carcinoma; COL7A1, collagen type VII alpha1; CTSC, cathepsin C; DEB, dystrophic epidermolysis bullosa; ECM1, extracellular matrix protein 1; ENG, endoglin; FAP, familial adenomatous polyposis; G/J, gastrointestinal; GNAQ, guanine nucleotide binding protein G alpha q; HHT, hereditary hemorrhagic telangiectasia; MEN 1B, multiple endocrine neoplasia type 2b; PTEN, phosphatase and tensin homolog; STK11/LKB1, serine/threonin kinase.



**Fig 1.** Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu). Punctiform telangiectatic lesions in the dorsal aspect of the tongue.



**Fig 2.** Lipoid proteinosis. Yellow, waxy infiltrates of the buccal mucosa and gingiva associated with cobblestoning of the lips.

**Oral cavity.** Dental pitting is the most frequent oral and distinguishing finding (**Fig 6**).<sup>35,39</sup> Oral fibromas on the gingiva appear as multiple pink, dome-shaped papules with a papillomatous appearance. Diffuse gingival overgrowth can also occur. Oral lesions are predominantly asymptomatic.<sup>40</sup> Of note, oral fibromas occur in the general population with a reported prevalence of 12 per 1000 individuals >35 years of age, but are generally fewer in number.<sup>40,41</sup>

### Diagnosis

Mutation of the *TSC1* or *TSC2* genes in normal tissue is diagnostic, but unidentifiable in up to 25% of patients.<sup>42</sup> A definitive clinical diagnosis is based on the presence of ≥2 major features, or 1 major and at ≥2 minor features (**Table II**).<sup>43,44</sup>

### Management

Early neurologic evaluation is crucial, and all patients suspected of TSC should undergo magnetic



**Fig 3.** Cowden syndrome. Cluster of smooth, white-pinkish papules in the buccal mucosa.



**Fig 4.** White sponge nevus (of Cannon). Thick, sponge-like plaque involving the buccal mucosa, gingiva and anterior pillar of the oropharynx.

resonance imaging.<sup>43</sup> Hypomelanotic lesions require stringent ultraviolet light protection. Sun exposure may contribute to the formation of facial angiofibromas.<sup>45</sup> Therapies inhibiting the mammalian target of rapamycin, such as sirolimus (rapamycin) and everolimus (RAD001), are effective treatments for TSC tumors and skin lesions.<sup>46</sup> Surgical intervention may be necessary in the case of functional impairment and disfigurement.

## NEVOID BASAL CELL CARCINOMA SYNDROME

### Key points

- Nevoid basal cell carcinoma syndrome is a rare autosomal dominant disorder caused by a mutation of the *PTCH1* tumor suppressor gene
- The classic clinical triad is multiple basal cell carcinomas, odontogenic keratocysts, and skeletal anomalies
- Multidisciplinary management and close monitoring is essential

### Background

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin–Goltz syndrome, is an autosomal dominant disorder caused by mutations of the



**Fig 5.** Darier disease. Coalescent, yellow-brown, scaly papules in seborrheic areas of the face and scalp.



**Fig 6.** Tuberous sclerosis. Multiple facial angiofibromas in association with dental enamel pits.

*PTCH1* tumor suppressor gene. The classic triad of multiple basal cell carcinomas (BCCs), odontogenic keratocysts (OKCs), and skeletal anomalies is characteristic.<sup>47,48</sup> Prevalence rates range from 1 in 60,000 to 1 in 256,000 individuals.<sup>47,49</sup> Forty percent of cases result from a de novo mutation.<sup>49</sup>

### Clinical

**Skin.** NBCCS gives rise to multiple cutaneous BCCs presenting predominantly between puberty and 35 years of age.<sup>47–49</sup> The number of BCCs can range from a few to thousands, and they appear predominantly on sun-exposed surfaces.<sup>47,49</sup> Milia are associated, mostly on the face.<sup>49</sup> Palmar and plantar pits are common and are more visible after soaking the patient's palms in warm water.<sup>47,49,50</sup>

**Oral cavity.** OKCs are present in >90% of patients with NBCCS who are >40 years of age.<sup>49,50</sup>

**Table II.** Tuberous sclerosis major and minor clinical features

Major features	Minor features
Angiofibromas $\geq 3$	Dental pits $\geq 3$
Hypomelanotic macules $\geq 3, \geq 5$ mm	Intraoral fibromas $\geq 2$ "Confetti" skin lesions
Ungual fibromas $\geq 2$	Nonrenal hamartomas
Shagreen patch	Multiple renal cysts
Multiple retinal hamartomas	Renal achromic patch
Cortical dysplasias	
Subependymal nodules	
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangioleiomyomatosis	
Angiomyolipoma $\geq 2$	

Adapted from Northrup et al<sup>44</sup> (level IV evidence).



**Fig 7.** Nevoid basal cell carcinoma syndrome. Panoramic radiograph of odontogenic keratocysts. Bilateral teeth displacement caused by cysts in the mandibular body.

OKCs are often an incidental radiographic finding, demonstrating unilocular or multilocular radiolucencies commonly at the posterior body, angle, or ramus of the mandible (Fig 7).<sup>47,48</sup> Associated symptoms include swelling, displacement of the overlying dentition, mild pain, or unusual taste.<sup>47,49</sup> Rare cases of OKCs have progressed to ameloblastomas and squamous cell carcinomas (SCCs), with potentially fatal outcomes.<sup>48,50</sup> Additional oral findings include impacted teeth, mandibular prognathism, dental ectopy, or dental agenesis.<sup>48</sup>

**Systemic.** Skeletal anomalies, such as fused ribs, scoliosis, spina bifida, and cysts within long bones, are notable. Central nervous system calcification (falx cerebri) is common, presenting after 20 years of age. Various ophthalmic, urogenital, gastrointestinal (GI), or cardiac problems may also be present and assist with diagnosis.<sup>47-50</sup>

### Diagnosis

The diagnosis of NBCCS is based on the presence of 2 major criteria or 1 major criteria and 2 minor criteria (Table III).<sup>47,49</sup>

### Management

Management of NBCCS is multidisciplinary in conjunction with genetic counseling.<sup>51</sup> Surgical excision of BCCs is performed for limited lesions. Imiquimod cream 5% (level IIB evidence), photodynamic therapy (level IV evidence), and oral vismodegib (level IB evidence) are alternative treatments.<sup>47,51-54</sup> OKCs are treated with local resection of the cysts and satellite microcysts, or enucleation and curettage of the surrounding bone.<sup>23,49</sup> Many cysts undergo decompression (marsupialization) followed by more conservative removal.<sup>23,50</sup> Lifelong screening is essential.

### PEUTZ-JEGHERS SYNDROME

#### Key points

- Peutz–Jeghers syndrome is a rare, autosomal dominant disorder associated with a mutation of the serine/threonine kinase gene on chromosome 19p13.3
- It is characterized by gastrointestinal hamartomatous polyposis and mucocutaneous pigmentation
- Management includes close monitoring for malignancies, particularly of the gastrointestinal tract, pancreas, and breast

### Background

Peutz–Jeghers syndrome (PJS) is a rare autosomal dominant disorder characterized by GI hamartomatous polyposis and mucocutaneous pigmentation.<sup>17,18</sup> Hereditary disorders represent 70% of cases, with 30% occurring sporadically.<sup>55</sup> The incidence of PJS is between 1 in 50,000 and 1 in 200,000 births, often arising in childhood or early adulthood.<sup>18,56</sup>

### Clinical

**General.** PJS is the second most common hereditary GI polyposis syndrome after juvenile polyposis. It is characterized by histologically distinct hamartomatous polyps with nondysplastic epithelium and epithelial infolding. GI polyps arise in 88% to 100% of patients with PJS, predominantly in the small intestines.<sup>56</sup> Large polyps can cause recurrent intussusception, leading to bleeding and abdominal pain.<sup>57</sup> There is an 80% risk of malignancy by 70 years of age involving the GI tract, pancreas, breast, uterine, cervix, ovary, lung, and thyroid gland, including a 39% risk of colorectal cancer.<sup>56-58</sup>

**Mucocutaneous.** Mucocutaneous pigmentation is a classic hallmark of PJS in 95% of cases.<sup>17,56</sup> Lesions are painless, melanin-pigmented patches on the tongue, buccal, or labial mucosa that cross the vermillion border (Fig 8).<sup>17,18,56</sup> Other sites include the

**Table III.** Nevoid basal cell carcinoma syndrome criteria

Major features	Minor features
<ul style="list-style-type: none"> <li>• &gt;2 BCCs or &gt;1 under 20 years of age</li> <li>• OKC as proven by histology</li> <li>• &gt;3 palmar or plantar pits</li> <li>• Bilamella calcification of the falk cerebri</li> <li>• Bifid or fused ribs</li> <li>• First-degree relatives with NBCCS</li> </ul>	<ul style="list-style-type: none"> <li>• Macrocephaly after height adjustment</li> <li>• Congenital malformations: cleft lip or palate, frontal bossing, hypertelorism</li> <li>• Other skeletal abnormalities</li> <li>• Radiological abnormalities</li> <li>• Ovarian fibroma</li> <li>• Medulloblastoma</li> </ul>

BCC, Basal cell carcinoma; NBCCS, nevoid basal cell carcinoma syndrome; OKC, odontogenic keratocysts.  
Adapted from Kiwilsza and Sporniak-Tutak<sup>49</sup> and Lo Muzio.<sup>47</sup>



**Fig 8.** Peutz–Jeghers syndrome. Melanotic macules grouped in the vermillion and perioral region.

face, palms, soles, digits, perianal area, and rarely the intestinal mucosa or nail plate.<sup>55,56</sup> Unlike oral mucosal lesions, skin pigmentation often fades with age.<sup>17</sup>

## Management

The risk of malignancy makes early diagnosis and surveillance crucial. The American College of Gastroenterology advises patients who present with mucocutaneous pigmentation, ≥2 histologically characteristic GI hamartomatous polyps, or a family history of PJS to be evaluated. A positive diagnosis warrants continuous surveillance of the GI tract, pancreas, breast, and other high-risk organs. Colonoscopy and esophagogastroduodenoscopy should be performed at 8 years of age and repeated every 3 years if polyps are present (level IV evidence from expert committee). Lung cancer screening in PJS smokers is recommended. Currently, prophylactic surgery or chemoprevention is not recommended (level IV evidence).<sup>56</sup>

## BURNING MOUTH SYNDROME

### Key points

- Burning mouth syndrome is a chronic, idiopathic condition of the oral mucosa in the absence of clinical, laboratory, and imaging findings

- Most commonly seen in postmenopausal females, it is a diagnosis of exclusion
- Treatment options include antidepressants, benzodiazepines, topical analgesics, and cognitive behavioral therapy

### Background

Burning mouth syndrome (BMS) is a chronic, idiopathic condition of the oral mucosa in the absence of clinical, laboratory, and imaging findings. It is more prevalent in women than men (7:1), affecting predominantly postmenopausal females.<sup>59</sup> Prevalence rates for the general population are 0.7% to 15%.<sup>60</sup>

### Classification

BMS can be classified into 3 subtypes based on symptom presentation (Table IV).<sup>61</sup>

### Clinical

The burning sensation of BMS is typically bilateral and symmetrical, with fluctuations in intensity. The most common site of involvement is the anterior two-thirds of the tongue, followed by the dorsal and lateral tongue borders, anterior hard palate, and mucosal surfaces of the lips. Symptom onset may be spontaneous or follow an infection, dental procedure, or traumatic life stressor.<sup>60</sup> Concomitant symptoms include xerostomia, dysesthesia (disagreeable sensation), and altered taste.<sup>59,60</sup> Nonspecific health complaints are common in patients with BMS, including neck pain, headache, dizziness, depression, anxiety, and irritable bowel syndrome; their association is unclear.<sup>62-64</sup>

### Diagnosis

BMS is a diagnosis of exclusion. Secondary causes of nutritional deficiencies (eg, iron, folate, and B vitamins), medications, systemic illnesses, infections (fungal and bacterial), mucosal disease, and contact stomatitis must be excluded. Combined with clinical history, various studies including salivary flow,

**Table IV.** Burning mouth syndrome classification

Type 1	Type 2	Type 3
Daily symptoms	Daily symptoms	Intermittent symptoms
Burning absent upon waking	Burning present upon waking	Burning in an unpredictable pattern
Burning maximal in evening	and persistent throughout the day	

Adapted from Lamey.<sup>61</sup>**Table V.** Therapies for idiopathic burning mouth syndrome

Topical	Systemic	Behavioral
Capsaicin oral rinse or preparation (level IB)	Alpha-lipoic acid: 200-800 mg/day (level IB)	Cognitive behavioral therapy (level IB)
Lysozyme-lactoperoxidase oral rinse (level IB)	Gabapentin (level IB)	Psychotherapy (level IB)
Lycopene-enriched virgin olive oil (level IB)	Lafutidine (level IB)	Tongue protector (level IB)
Aloe vera (level IB)	Clonazepam: 0.5-3 mg/day (level IB)	
Low laser therapy (level IB)	Trazodone (level IB)	
Benzydamine hydrochloride topical anesthetic (level IB)	Paroxetine (level IB)	
Lidocaine lingual nerve block (level IB)	Sertraline (level IB)	
	Ctuama capsules (level IB)	

Level IB evidence includes evidence from at least 1 randomized controlled trial.

contact sensitivity, taste function, and blood tests can aid in the diagnosis.<sup>60,65</sup>

## Management

Reported treatment options are listed in Table V.<sup>66-69</sup>

## BEHÇET DISEASE

### Key points

- Behçet disease is a systemic vasculitic disorder characterized by episodic aphthous ulcers, uveitis, genital ulcers, and skin lesions
- It is more common in females and individuals living between Eastern Asia and the Mediterranean Sea
- Treatment options include corticosteroids (topical or systemic), topical anesthetics, antiinflammatory agents, and systemic immunomodulators

### Background

Behçet disease (BD) is a systemic, multiorgan disorder occurring in the third decade of life in both men and women; it is characterized by unpredictable relapsing and remitting episodes of acute inflammation.<sup>70</sup> Major symptoms include oral aphthous ulcers, genital ulcers, uveitis, and skin lesions. It is most common in Asian and Euroasian populations residing along the old Silk Route between the Mediterranean and Eastern Asia.<sup>71</sup> Prevalence rates are between 1 in 1000 and 1 in 10,000 people in this geographic region, compared to 0.12 to 0.64 per



**Fig 9.** Behçet disease. Major aphthous ulceration in the labial mucosa.

100,000 people in Western countries.<sup>72,73</sup> The etiology is unknown, but environmental and genetic factors are implicated in its pathogenesis. The HLA-B51 allele located on chromosome 6p is a strongly associated risk factor for BD and is highly prevalent among individuals of Asian descent.<sup>71</sup>

### Clinical

**Mucosal.** Oral ulceration occurs in 92% to 100% of patients and traditionally precedes other clinical signs by years.<sup>70</sup> These lesions are painful and manifest on the tongue, buccal and labial mucosa, gingiva, as well as the soft and hard palates, pharynx, and tonsils. Ulcers are typically round with well-demarcated, erythematous borders and a yellowish-tan pseudomembrane (Fig 9); they typically heal without scarring within 10 days.<sup>71,74,75</sup> Painful genital

**Table VI.** Treatment options for Behcet disease

Topical	Systemic
Triamcinolone acetonide (level III)	Colchicine: 0.5-2 mg/day (level IB)
Fluocinonide gel (level III)	Apremilast (level IB)
Prednisolone tablets in 20 mL water (level III)	Methylprednisolone 1 g, 1-5 days (level IB)
Tetracycline mouthwash: 250 mg/5 mL water (level IB)	Azathioprine: 2.5 mg/kg body weight/day (level IB)
Sucralfate: 1 g/5 mL suspension (level IB)	Diaminodiphenyl sulfone: 100-150 mg/day (level IIA)
Pimecrolimus (level IB)	Thalidomide (level IB)
Chlorhexidine (IIA)	Zinc sulfate (level IIA)
Dexamethasone ointment (level IB)	Cyclosporine A: 3-4 mg/kg/day (level IB)
Lidocaine topical anesthetic: 2-5% (level III)	Etanercept (level IB)
Silver nitrate (level IB)	Infliximab (level IIA)
Pentoxyfylline (level IB)	Methotrexate: 7.5-20 mg/week (IIA)
Minocycline (level IB)	Benzathine penicillin: 1.2 MU/3 weeks (level IB)
Tetracycline (level IB)	Rebamipide: 300 mg/day (level IIA)
CO <sub>2</sub> laser (level IIB)	Interferon- $\alpha$ (level IB)

Level IB evidence includes evidence from at least 1 randomized controlled trial. Level IIA evidence includes evidence from at least one controlled study without randomization. Level IIB evidence includes evidence from at least one other type of experimental study. Level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies.

ulcers occur in 57% to 93% of patients, frequently appearing on the scrotum in men or vulva in women.<sup>71</sup> These lesions are deeper with irregular margins and heal with possible scarring in 10 to 30 days.<sup>74,75</sup>

**Skin.** Erythema nodosum-like lesions (15-78%) and papulopustular lesions (28-96%) are the most commonly observed cutaneous findings.<sup>70</sup> These lesions do not ulcerate and heal within 2 to 3 weeks. Other cutaneous lesions resemble Sweet syndrome, erythema multiforme, palpable purpura, pyoderma gangrenosum, furuncles, and abscesses.<sup>70,71,75</sup>

**Systemic.** Additional systemic symptoms include bilateral uveitis, hypopyon (anterior chamber of eye inflammation), nondeforming arthritis or arthralgias, papilledema, pyramidal signs, GI discomfort, and thrombophlebitis of major vessels.<sup>74</sup> Mouth and genital ulcers with inflamed cartilage syndrome meets the criteria for BD and relapsing polychondritis. Patients with this condition can also have auricular chondritis, nonerosive inflammatory polyarthritis, nasal chondritis, respiratory tract chondritis, and ocular inflammation. Overlap of relapsing polychondritis with BD suggests a common underlying pathogenic mechanism.<sup>76</sup>

## Diagnosis

The diagnosis of BD is based on the presence of  $\geq 2$  of the following: recurrent genital ulceration, skin lesions, eye lesions, and a positive pathergy test. The absence of oral lesions makes BD highly unlikely.<sup>75</sup>

## Therapy

Treatment options for BD are shown in Table VI.<sup>70,71,75,77-79</sup>

## LICHEN PLANUS

### Key points

- Lichen planus is a chronic inflammatory disease most commonly affecting the skin and oral and genital mucous membranes
- Predisposing risk factors include genetic, infectious, medications, autoimmunity, and trauma
- Diagnosis is made clinically and histopathologically, with topical corticosteroids first-line treatment for milder cases and systemic therapies for more severe cases

## Background

Lichen planus (LP) is a chronic mucocutaneous inflammatory disease affecting the squamous epithelium of primarily the oral and genital mucous membranes, but also the skin, scalp, nails, esophagus, and conjunctiva. It is more common in females and often occurs in the fourth decade of life for cutaneous disease and fifth decade of life for oral disease.<sup>80</sup> Prevalence varies by geographic location, with rates between 0.5% to 2% in the general US population. Oral LP (OLP) has a prevalence between 0.5% to 2.2%. Forty percent to 70% of patients with cutaneous LP present with oral lesions, with  $\leq 35\%$  of patients presenting with purely oral disease.<sup>80-83</sup>



**Fig 10.** Lichen planus. Flat-topped, violaceous papules covered by reticular, white lines (Wickham striae).



**Fig 11.** Lichen planus. Extensive area of atrophic depapillation on the dorsal aspect of the tongue with associated areas of white, reticular patches.

### Etiology

Both LP and OLP are considered T cell–immune-mediated diseases. Associated factors include genetic, infectious, dental materials, medications, stress, neoplasms, allergies, autoimmunity, diabetes, hypertension, and trauma. Patients with LP have a 5.4% increased prevalence of hepatitis C virus compared to unexposed patients, making screening for hepatitis C virus essential.<sup>84</sup> Associations with HLA-A3 and -B5 are documented.<sup>85</sup>



**Fig 12.** Lichen planus. Cluster of polygonal-shaped papules coalescing into a plaque in the lower lip.

### Clinical

**Skin.** Cutaneous lesions of LP are characterized by the 6 Ps: planar (flat), purple, polygonal, pruritic, papules, and plaques (Fig 10). Lesions are usually pruritic and may follow lines of trauma (Koebner phenomenon). Forms of LP include linear, annular, atrophic, actinic, acute, hypertrophic, inverse, ulcerative, and vulvovaginal.<sup>82,84,86</sup>

**Oral.** The most common pattern of OLP is the reticular type, which is characterized by radiating white-gray papules forming a fine, lacy, reticular pattern (Wickham striae). Lesions are typically painless, bilateral, and symmetrically located on the buccal mucosa, gingiva, and less frequently the tongue (Fig 11), lips (Fig 12), floor of the mouth, or palate. Other forms include erosive, bullous, atrophic, plaque-like, papular, and pigmented OLP.<sup>82</sup> Complications are painful erosions, secondary infection, sensitivity to heat, and burning sensation.<sup>84</sup> The malignant potential of OLP is controversial, with reported rates for transformation to oral SCC of 1% to 2%, carcinoma in situ up to 28.5%, and micro invasive carcinoma of 30% to 38%. However, the exact risk of transformation remains unknown.<sup>87,88</sup>

**Genitalia.** LP presents on the genitalia as violaceous papules on the glans penis, penile shaft, scrotum, and perineum. In females, lesions can be atrophic, leukoplakic, or erythroplakic. Pruritus, dyspareunia, and burning are often present. Oral and genital involvement in women is defined as vulvovaginal gingival syndrome.

### Therapy

Management of LP is symptomatic, with appropriate therapy of underlying conditions (eg, hepatitis C). Cutaneous LP may resolve spontaneously within 1 to 2 years, with high-potency topical corticosteroids as first-line therapy.<sup>84</sup> Surgical removal may be



**Fig 13.** Necrotizing sialometaplasia. Well-demarcated posterior hard palate ulcer featuring ischemic borders.

required for high-risk dysplastic areas. A variety of additional topical and systemic therapies are potential second-line options.<sup>80,81,84,89,90</sup>

## NECROTIZING SIALOMETAPLASIA

### Key points

- Necrotizing sialometaplasia is an uncommon, self-healing lesion occurring in salivary glands after infarction
- It may resemble a malignancy and can be misdiagnosed histologically as mucoepidermoid carcinoma or squamous cell carcinoma
- Diagnosis is based on clinical history and histopathology

### Background

Necrotizing sialometaplasia (NSM) is an uncommon reactive lesion of the salivary glands. It is a self-limited condition that can be misdiagnosed as a malignant neoplasm, such as mucoepidermoid carcinoma or invasive SCC. NSM classically involves the minor mucoseroous glands of the posterolateral hard palate. Additional sites include the parotid, sublingual, and submandibular glands, nasal cavity, trachea, tongue, tonsils, gingiva, larynx, and buccal mucosa. The skin is rarely involved.<sup>91,92</sup> Less than 1% of oral biopsy specimens are reported to represent NSM, and approximately 65% of cases occur in men.<sup>92</sup>

### Etiology

NSM is hypothesized to be caused by the stress of a local blood vessel supplying a salivary gland, leading to ischemia. Subsequent infarction causes coagulation necrosis of the involved gland. The ducts, however, are more resistant and undergo florid squamous metaplasia. Proposed stressors include chemical injury, surgical interventions, infections, local anesthesia, bulimia, radiation, smoking, and alcohol.<sup>93-95</sup>



**Fig 14.** Erythema multiforme. Target lesions in the extensor aspect of the forearm with both intact and ruptured central vesicles.

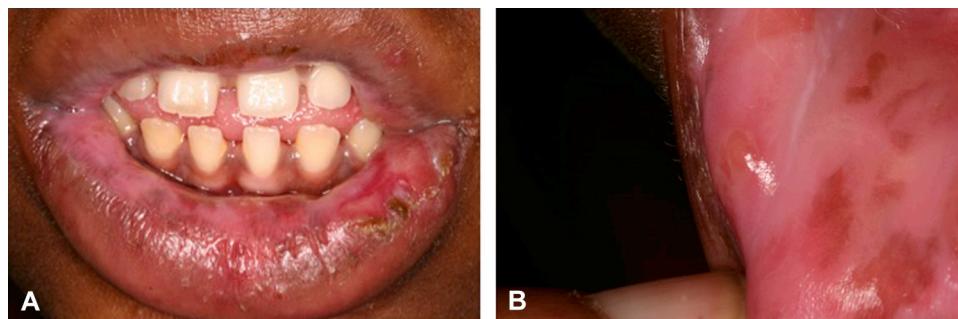
### Clinical

**Oral.** NSM appears as a nonhealing, painful ulcer with well-demarcated, erythematous, or rolled borders (Fig 13). The posterior hard palate is the most common site, followed by the junction of the hard and soft palates. Most lesions are unilateral and range in size from 0.7 to 6 cm. Infarction of the gland induces painful swelling, which evolves into tissue breakdown and ulceration within days. Symptoms can persist for up to 3 weeks to 3 months.<sup>91,96</sup> On histologic examination, pseudoepitheliomatous hyperplasia and squamous metaplasia of the ductal cells may be confused for SCC or mucoepidermoid carcinoma, but preservation of the lobular architecture and identification of coagulation necrosis of the gland are distinguishing diagnostic features of NSM.<sup>96</sup>

**Skin.** This rare clinical entity is referred to as eccrine squamous syringometaplasia. It results from mucinous metaplasia of the ductal epithelium of sweat glands in response to various reported triggers, including chronic ulcers, skin tumors, cytotoxic agents (ie, cytarabine and doxorubicin), radiation, viral infections (ie, cytomegalovirus, HIV, and varicella zoster virus), hemodialysis, medications, and trauma. Clinical presentation is highly variable and may exhibit erythematous, crusted papules with ulceration located on the neck, chest, abdomen, extremities, and genitalia. Histologically, lesions may resemble NSM, demonstrating squamous metaplasia of the intralobular ducts, hyperkeratosis, dermal fibrosis, and lymphocytic infiltrate.<sup>97-99</sup>

### Management

The diagnosis of NSM is based on clinical history and obtaining a biopsy specimen. Immunohistochemistry can aid in distinguishing lesions from a malignancy, with hematoxylin–eosin staining the criterion standard for histopathologic diagnosis. Treatment is not required because



**Fig 15.** Oral erythema multiforme. **A**, Markedly swollen lips with crusted erosions and fissuring. **B**, Small, unruptured vesicle in the oral mucosa associated with postinflammatory hyperpigmentation in the adjacent mucosa.

lesions typically resolve spontaneously or heal by secondary intention after obtaining a biopsy specimen. Nonresolving or recurrent lesions should be reevaluated.<sup>91,96</sup>

## ERYTHEMA MULTIFORME

### Key points

- Erythema multiforme is an episodic inflammatory condition of the skin and mucous membranes characterized by the classic “targetoid” lesion
- Oral lesions are present in  $\leq 70\%$  of cases and present as edematous and erythematous macules, vesiculobullous lesions, and erosions
- Diagnosis is generally made clinically
- Treatment includes removal of the underlying cause, corticosteroids, immunomodulators, supportive care, and antiviral prophylaxis for recurrent cases

### Background

Erythema multiforme (EM) is a self-limited, episodic inflammatory condition of the skin and mucous membranes. It is characterized by acute-onset, erythematous, and edematous papules that rapidly evolve into concentric “target” lesions (Fig 14). EM major and minor are differentiated based on the presence of mucosal involvement and prodromal symptoms. Oral cavity lesions are seen in  $\leq 70\%$  of cases.<sup>100</sup> EM can affect the mouth exclusively, sharing clinical features with primary herpetic gingivostomatitis.

### Etiology

A recent history of herpes simplex virus (HSV) infection (66% HSV-1 and 28% HSV-2) accounts for  $\leq 70\%$  of recurrent cases.<sup>100</sup> Many other viral, bacterial, fungal, and parasitic infections have been

associated as triggers. A reported 58% of EM cases are linked to medications, with a variety of drugs implicated (eg, cephalosporins, sulfonamides, phenobarbital, hydantoin, and penicillin). Other potential predisposing factors include trauma, hypocomplementemia, ultraviolet light radiation, and systemic illness.<sup>100,101</sup>

### Clinical

**Oral EM.** Oral EM occurs most frequently in children and young adults. Episodes can recur from every few days to annually, with the duration lasting from 10 days to 6 weeks. Frequently recurrent cases are associated with increased morbidity, while other cases can be self-limited.<sup>102,103</sup> Oral lesions present with diffuse mucosal erythema, bullae, ulcerations, erosions, or nonspecific erythematous changes involving any part of the oral cavity (Fig 15).<sup>104</sup> The lips become swollen, with crusted erosions typically involving the vermillion border and buccal and labial mucosa.<sup>105</sup> Targetoid lesions can also be seen on the lips, but are rarely found on the oral mucosa. Involvement of the gingiva may have features of desquamative gingivitis, but oral EM is distinguished clinically by its explosive acute onset. When EM is restricted to the oral cavity, it can be mistaken for other inflammatory, vesiculobullous, and dysplastic diseases.<sup>102</sup> Complications of extensive mucosal involvement include dehydration, keratitis, conjunctival scarring, visual impairment, airway damage, pneumonia, esophagitis, and strictures. Renal, myocardial, and hematologic damage are rarely reported complications.<sup>106</sup>

### Diagnosis

Diagnosis is often clinical. Histology, immunofluorescence, and immunostaining can help distinguish oral EM from other vesiculobullous disorders, toxic

epidermal necrolysis, drug hypersensitivity reactions, polycyclic urticaria, and viral stomatitides.

### Therapy

Treatment is predominantly symptomatic and includes topical antiseptics, antihistamines, corticosteroids, and anesthetic solutions for erosions (all level III evidence). Severe cases of EM may require intravenous fluids and systemic corticosteroids (no high-quality studies).<sup>107</sup> Known or suspected triggers should be appropriately treated, with prophylactic antiviral treatment valuable for individuals with HSV-associated EM.<sup>100,101</sup>

## SARCOIDOSIS

### Key points

- **Sarcoidosis is a systemic granulomatous disease affecting the lungs, liver, spleen, eyes, skin, parotid glands, and lymph nodes**
- **The presence of noncaseating granulomas on the biopsy specimen, appropriate clinical context, and exclusion of other causes of granulomatous inflammation is diagnostic**
- **Topical, intralesional, and systemic corticosteroids are traditional first-line treatments with tumor necrosis factor- $\alpha$  inhibitory biologic agents used for recalcitrant cases**

### Background

Sarcoidosis is a systemic granulomatous disease of unclear etiology characterized histologically by noncaseating granulomas. Affected organs include the lungs, liver, spleen, eyes, skin, parotid glands, and lymph nodes. Sarcoidosis is considered the “great imitator” because it can be misconstrued for numerous skin conditions.<sup>108,109</sup> Cutaneous lesions affect approximately 25% of patients, while involvement of the oral cavity is relatively rare.<sup>108,110</sup>

### Epidemiology

This multiorgan condition frequently occurs between 20 and 40 years of age, with a higher incidence in females.<sup>109</sup> A genetic predisposition is suggested based on the demonstration of familial aggregation and variations in disease susceptibility between racial groups.<sup>111</sup> The highest incidence in the United States is among African American females (39.1/100,000), followed by African American males (29.8/100,000), white females (12.1/100,000), and white males (9.6/100,000).<sup>112</sup>

### Etiology

*Mycobacterium tuberculosis* has been found in sarcoidal lesions, indicating sarcoidosis as an

immune form of tuberculosis.<sup>113</sup> Other infectious causes are also implicated.<sup>114,115</sup> Additional risk factors include chemical agents (ie, beryllium, aluminum, and titanium), medications (ie, interferons), environmental antigens, smoking, and autoimmunity.<sup>108,109</sup> HLA-B8 and -DR3, as well as genes coding the HLA class 1 and 2 molecules, are associated with sarcoidosis.<sup>116</sup>

### Clinical

**Skin.** Cutaneous lesions have a predilection for sites of injury, such as scars or tattoos. Common lesions include red/violaceous, brown, or hypopigmented macules or papules often involving the knees, trunk, central face, and extremities. Larger plaques (>1 cm) predict a more chronic course of disease and can cause scarring or permanent alopecia of the scalp.<sup>115,117</sup> Erythema nodosum is the most common nonspecific lesion and is associated with acute and benign disease. When present, it may be the sole cutaneous manifestation, often occurring in association with bilateral hilar lymphadenopathy.<sup>117</sup>

Lupus pernio is a specific variant characterized by red/violaceous indurated plaques with mild scaling of the nose, central face, and cheeks. It is strongly associated with sarcoidosis of the respiratory tract and sinuses, and indicates a chronic, severe course of disease.<sup>117</sup> Darier–Roussy or subcutaneous sarcoidosis affects the reticular dermis and subcutaneous tissue, causing firm, nontender, mobile nodules that are typically present on the arms. This variant is associated with nonsevere cases of sarcoidosis.<sup>108</sup>

**Oral.** Oral sarcoidosis may be the first or only symptom of disease. The buccal mucosa is the most commonly affected site, followed by the gingiva, lips, floor of the mouth, tongue, palate, and submandibular gland.<sup>110</sup> Lesions present as painless ulcerations or nodules, gingivitis, gingival hyperplasia, and gingival recession. Rarely, bone involvement progressing to alveolar bone loss can occur. The salivary glands, particularly the parotid gland in 6% of patients, can also be affected more frequently in females, and presents as bilateral painless swelling.<sup>118</sup> Heerfordt syndrome encompasses parotid gland enlargement, fever, uveitis, and facial palsy.<sup>110,119-121</sup>

### Diagnosis

Sarcoidosis is a diagnosis of exclusion. The presence of noncaseating granulomas on the biopsy specimen, appropriate clinical context, and exclusion of other causes of granulomatous inflammation is



**Fig 16.** Oral amyloidosis. Soft yellow nodules in the gingival and alveolar mucosa.



**Fig 17.** Amyloidosis. Macroglossia.

diagnostic. Radiologic findings on chest radiography or a computed tomography scan include bilateral hilar lymphadenopathy, paratracheal lymph node involvement, and pulmonary infiltrates. Pulmonary function tests demonstrate diminished lung volume and vital capacity. Laboratory testing may show an elevated erythrocyte sedimentation rate, increased angiotensin-converting enzyme, hypercalcemia, elevated liver enzymes, or anemia.<sup>108,110</sup>

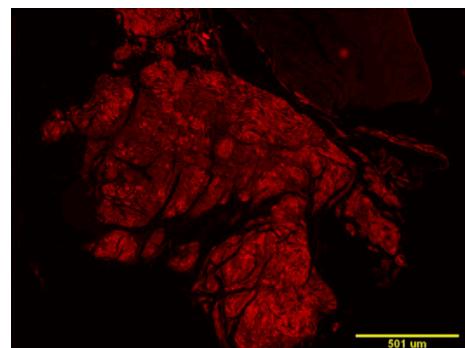
## Therapy

Corticosteroids are the most common treatment for sarcoidosis. Cutaneous lesions may initially be treated with intralesional triamcinolone injections (5-10 mg/mL) every 3 to 4 weeks, or topical steroid therapy (level III evidence). Systemic corticosteroids are required for systemic, progressive, or severely disfiguring cases (level III evidence).<sup>122-127</sup>

## AMYLOIDOSIS

### Key points

- Amyloidosis is caused by the abnormal extracellular deposition of a proteinaceous material within single or multiple organs
- The clinical appearance of mucocutaneous findings is variable, with the diagnosis based on amyloid deposition in biopsy specimens



**Fig 18.** Biopsy specimen of a patient with oral amyloidosis. Characteristic orange-red color under light microscopy when stained with Congo red.

- Treatment involves management of the underlying cause as well as immunomodulators, CO<sub>2</sub> laser, dermabrasion, acitretin, amyloid-lowering agents, and surgical excision

### Background

Amyloidosis refers to the abnormal extracellular deposition of fibrillar proteinaceous material. The main subtypes of systemic amyloidosis include amyloid light-chain associated with plasma cell dyscrasias, amyloid A related to chronic inflammation, and a transthyretin mutation associated with old age.<sup>128</sup> The skin is involved in ≤40% of patients with systemic amyloidosis.<sup>129</sup> Oral involvement is rare and occurs as part of systemic amyloidosis, or more commonly as localized amyloidosis.<sup>130</sup>

### Clinical

**Systemic amyloidosis.** The mucocutaneous findings of systemic amyloidosis most commonly present as smooth, waxy, nontender and non-pruritic papules, nodules, and plaques, often with a hemorrhagic appearance. Petechiae, purpura, and ecchymoses can occur spontaneously or after minor trauma. Purpura of the periorbital region (raccoon eyes) after the Valsalva maneuver, coughing, vomiting, or proctoscopy are characteristic findings.<sup>129,131</sup> Macroglossia is a common oral finding and is frequently associated with amyloid light-chain and hemodialysis-associated amyloidosis. The lateral tongue borders exhibit numerous tooth indentations and the surface can be smooth, or present with fissuring, ulceration, and hemorrhage.<sup>130,132-134</sup>

**Localized oral amyloidosis.** The characteristic findings of localized oral amyloidosis appear as multiple soft nodules of the tongue, lip, and cheek (Fig 16). Lesions can be hemorrhagic and may

resemble benign tumors, such as schwannomas, neurofibromas, neuromas, and granular cell tumors.<sup>134,135</sup> Macroglossia is also common, leading to difficulty with chewing and speaking (Fig 17). Involvement of the major and minor salivary glands can result in swelling and xerostomia.<sup>130,136</sup>

## Diagnosis

The presence of amyloid deposition on a biopsy specimen is diagnostic, with the rectum and abdominal subcutaneous fat the traditional biopsy sites in addition to the tongue, salivary gland, and other intraoral sites.<sup>136</sup> Histology and microscopy cannot differentiate between various amyloid precursors, which is important for determining treatment. Staining with various aniline dyes, such as Congo red, which shows the characteristic apple-green birefringence under polarized light, is more sensitive and specific for determining the amyloid precursor (Fig 18).<sup>137</sup> Other techniques, including mass spectrometry and scintigraphy, may aid in amyloid typing.<sup>138,139</sup>

## Therapy

Treatment of the underlying disease is the primary management of systemic amyloidosis. In addition, numerous agents have been implemented with variable success.<sup>137</sup> CHPC, a drug that targets the serum amyloid P component of amyloid fibril, has demonstrated promising effects in an exploratory study (level IIB evidence).<sup>140</sup> Another open label, phase 1 study tested an IgG anti-SAP antibody in 15 patients after first using CPHPC, with a reduction in amyloid levels noted (level IIB evidence).<sup>141</sup>

Cosmetic treatment of oral lesions includes surgical excision, CO<sub>2</sub> laser, dermabrasion, electrodesiccation and curettage, and cryotherapy (level III evidence). Case reports document adequate initial results, but amyloid deposition frequently persist in the dermis and recurrent lesions following treatment are common.<sup>130,142-145</sup> Acitretin alone, or combined with psoralen plus ultraviolet A light phototherapy (level III) is reported to improve skin lesions and severe pruritus over the long term.<sup>146-149</sup>

In conclusion, there are many dermatologic diseases associated with oral cavity findings. It is imperative for dermatologists to be able to recognize and manage oral manifestations of cutaneous disease. Moreover, dermatologists play an important role in early workup, diagnosis, treatment, and multidisciplinary collaboration, aiding in the prevention of disease progression and serious complications.

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