

# Psoriasis

## Pathogenesis, Assessment, and Therapeutic Update



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### KEYWORDS

• Psoriasis • Biologics • Psoriatic comorbidities • Psoriatic arthritis

### KEY POINTS

- Psoriasis is a chronic condition that affects more than 7 million Americans.
- The disorder has no known cure but today an overwhelming majority of patients can achieve good to excellent control.
- Over the past 2 decades, enhanced understanding of the immunologic basis of psoriasis has led to the development of new systemic agents that have revolutionized the management of this disease.
- There are significant barriers to optimal management, which include expense, patient compliance, and medication safety.
- When dealing with this disease, health care providers should strive to identify the most efficacious treatment associated with the fewest possible adverse events delivered at a reasonable cost.

Psoriasis is a chronic immune-mediated inflammatory disease that affects more than 7 million Americans and 2% to 4% of the population worldwide.<sup>1–3</sup> Affected individuals are impacted both psychologically and physically. Patients with psoriasis are at increased risk of developing anxiety and depression<sup>4</sup> as well as cardiometabolic and rheumatologic comorbidities, all of which can greatly reduce quality of life.<sup>5</sup> Most patients with psoriasis require chronic care, and disease-associated therapeutic management costs billions of dollars on an annual basis in the United States.<sup>6</sup>

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## **PATHOGENESIS**

Psoriasis in predisposed individuals can be triggered by several factors, including infection, medications, and trauma (also known as the Koebner effect). Research over the past 2 decades confirms that psoriasis is a disorder resulting from immune dysregulation.<sup>7</sup> A complex relationship involving macrophages, dendritic cells, T cells, and cytokines induce many of the pathologic changes associated with this disease. Activated cells produce mediators of inflammation, such as tumor necrosis factor (TNF) and interleukins (ILs) 17 and 23, and it is this inflammatory response that eventuates in the skin and joint disease. Understanding the immunologic basis of psoriasis has led to the development of new therapies and a revolutionary approach to management.

## **GENETICS**

Psoriasis has a significant genetic predisposition, with elevated incidence in first-degree and second-degree relatives.<sup>8</sup> Incidence is equal in men and women. In the United States, the prevalence of psoriasis is highest in whites (3.6%) followed by blacks (1.9%) and Hispanics (1.6%).<sup>9</sup> The mode of inheritance is intricate and several chromosomal loci are associated with disease.<sup>10</sup> In genetically susceptible individuals, various antigens are capable of activating T cells, resulting in hyperproliferation of keratinocytes, altered epidermal differentiation, and cutaneous inflammation. One antigen in particular, associated with streptococcal infection, has been causally related to onset and flare of psoriasis.<sup>11</sup>

## **CLINICAL PRESENTATIONS OF PSORIASIS**

Five subtypes of psoriasis are recognized: plaque, guttate, pustular, inverse, and erythrodermic.

Plaque psoriasis (**Figs. 1–3**) is the most common presentation, comprising 85% to 90% of all cases.<sup>12</sup> The condition manifests as well-demarcated erythematous plaques with xerotic, silvery scale that can attain several centimeters in diameter. Removal of scales results in punctate bleeding (Auspitz sign). Individual lesions may be irregular, round, or ovoid and may be sparsely located or occur in a generalized distribution covering a majority of the body surface. The most common locations are the scalp, trunk, buttocks, and limbs. Extensor surfaces, such as the elbows and knees, are frequently involved and may be the first and only presentation of disease. Approximately 80% of patients suffer from mild to moderate disease, which covers less than 10% of the body surface area, whereas the remainder are afflicted with moderate to severe disease.<sup>13</sup>

Guttate psoriasis is characterized by 1-mm to 10-mm, pink to erythematous colored papules, often covered with fine scale (**Fig. 4**). This variant of psoriasis most commonly arises in individuals younger than 30 years and is located primarily on the trunk and the proximal extremities, occurring in less than 2% of patients with psoriasis. Guttate psoriasis may be preceded by group A  $\beta$ -hemolytic streptococcal pharyngitis and may improve or resolve with antibiotic therapy or evolve into plaque psoriasis.<sup>14</sup>

Pustular psoriasis is an uncommon subtype that can be divided into generalized and localized forms. The acute generalized form, also known as the von Zumbusch variant, is a severe and explosive condition accompanied by fever that presents with multiple sterile pustules arising on an erythematous or dusky background (**Fig. 5**). Rapid progression and systemic toxicity may be life threatening. Localized forms of pustular



**Fig. 1.** Well-demarcated erythematous plaques are the hallmark of psoriasis.

psoriasis affect the hands and feet and may be an isolated phenomenon or found in association with plaque psoriasis. Palmoplantar psoriasis is a condition characterized by erythema, fissuring, and scaling. This condition has been linked to cigarette smoking<sup>15</sup> and may improve with cessation.

Inverse psoriasis, also known as flexural or intertriginous psoriasis, is characterized by lesions situated within the skin folds and affects between 3% and 7% of individuals with this disease.<sup>16</sup> Due to the moist and warm nature of these areas, psoriasis localized to folds tends toward erythematous patches with minimal scale (**Fig. 6**). Common sites include the axillary, genital, perineal, and inframammary areas.

Erythrodermic psoriasis (**Fig. 7**) may evolve from chronic plaque disease or develop acutely de novo. It occurs in less than 2% of cases and may involve the entire skin surface.<sup>17</sup> Chills and hypothermia can result from altered thermoregulation and fluid loss may precipitate dehydration. Extensive cases may eventuate in sepsis.

## NONDERMATOLOGIC MANIFESTATIONS

Nail disease (psoriatic onychodystrophy) occurs in a majority of persons with psoriasis (**Figs. 8–10**).<sup>18</sup> Fingernails are involved in approximately 50% of all patients and toenails in 35%.<sup>13</sup> Abnormal nail plate growth results in pitting, subungual hyperkeratosis, and the oil-drop sign. Pits are depressions within the nail plate and are the most common nail finding in psoriasis, although not specific for this disease.<sup>19</sup> Subungual hyperkeratosis results from the deposition of cellular debris under the nail plate. Over time

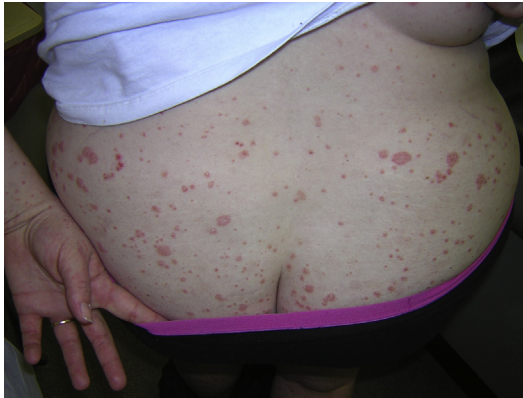


**Fig. 2.** Plaques of psoriasis manifesting thick adherent scales, which markedly impede penetration of topical therapies.

the nail thickens and becomes more brittle. The primary differential diagnosis is onychomycosis. Oil-drop spots result from psoriatic lesions contained within the nail bed. These are translucent yellowish to pink discolorations that resemble drops of oil under the nail surface.



**Fig. 3.** Scalp psoriasis affects more than 50% of individuals with this disorder. The condition may present with fine scale or, in more severe cases, with thick, crusted plaques that extend onto the forehead and posterior neck.



**Fig. 4.** Guttate psoriasis arises suddenly, concentrates on the trunk, and may be preceded by streptococcal pharyngeal infection.

### ARTHRITIS

Psoriatic arthritis (PsA) is a chronic seronegative inflammatory joint arthritis that affects approximately 25% to 30% of individuals with psoriasis.<sup>20</sup> Similar to rheumatoid arthritis, PSA has the potential for joint damage and disability. The condition affects men and women equally and has a peak age of onset of between 35 and 45 years of age. The prevalence increases in individuals with more extensive skin disease. In a majority of patients, skin psoriasis precedes PsA; however, in approximately 15%, the reverse is noted.<sup>21</sup>

PsA may be asymptomatic or associated with pain, tenderness, and swelling of the joints and surrounding ligaments and tendons. The pattern of joint involvement associated with PsA is variable. Unique to PsA is the DIP predominant pattern, which occurs in approximately 10% of patients and primarily in men.<sup>22</sup> Approximately 30% of PsA patients experience asymmetric oligoarticular arthritis with involvement of a large joint, such as the knee, and a few small joints of the hands or feet, often in association with dactylitis. Also common, especially in women, is the polyarthritis



**Fig. 5.** Pustular psoriasis manifests as clearly defined white pustules arising on an erythematous base. The condition usually arises acutely and be precipitated by medications including lithium and nonsteroidal anti-inflammatory drugs.





**Fig. 6.** Inverse psoriasis involves the axillae and intergluteal and crural folds. The male and female genitalia may also be affected. The skin is erythematous and usually devoid of scale.

pattern involving the fingers, wrists, toes, and ankles in a symmetric distribution. The most debilitating form of PsA is called arthritis mutilans, characterized by bone absorption and deformity.

Associated with PsA may be enthesitis, or inflammation at the site of tendon or ligament insertion into bone. Common sites include the insertion zones of the plantar fascia, the Achilles tendons, and ligament attachments to the ribs, spine, and pelvis.



**Fig. 7.** Erythrodermic psoriasis is an uncommon variant that covers much of the body surface, including the face and hands. Patients may present with fever, chills, and dehydration.



**Fig. 8.** Nail deformity secondary to psoriasis. Nail psoriasis is a common manifestation of this disease and may present with onycholysis, pitting, and discoloration.

Dactylitis, or sausage digit, is a combination of enthesitis of the tendons and ligaments accompanied by synovitis involving a whole digit. The toes are most commonly affected.<sup>23</sup>

### COMORBIDITIES

Several prospective and retrospective studies have validated the association of psoriasis and PsA with diabetes, hyperlipidemia, hypertension, atherosclerosis, and myocardial infection.<sup>24–28</sup> The chronic inflammatory response that underlies psoriasis is believed to play a key role in the pathogenesis of these adverse events as well. Because such conditions adversely affect morbidity and mortality in patients with psoriasis, comprehensive management best includes screening, monitoring, and,



**Fig. 9.** The oil drop discoloration is a clinical finding specific for psoriasis.



**Fig. 10.** Pitting of nails frequently accompanies psoriasis and most commonly affects the fingernails.

when indicated, prompt intervention. Treatment strategies for controlling moderate to severe disease may have a favorable impact on cardiovascular endpoints.

## TREATMENT

Treatment goals are control and improvement of disease and symptoms. More recently, dampening of the chronic inflammatory response has been advocated to decrease overall morbidity and mortality. A survey by the National Psoriasis Foundation revealed that a significant proportion of individuals with moderate to severe psoriasis receive no treatment or are undertreated.<sup>29</sup> Factors for this disparity include the high cost of medications and difficulty accessing medical specialists experienced in disease management, namely dermatologists and rheumatologists.

### *Topical Therapies*

Topical therapies are a mainstay in the management of mild disease.<sup>30</sup> Disadvantages include the time required for application, local adverse reactions, and incomplete lesion clearance.

Topical corticosteroids are considered first-line therapy for less extensive disease due to their anti-inflammatory properties. Initial treatment often entails use of superpotent formulations, which are available as creams, ointments, gels, lotions, and foams. Examples include clobetasone, betamethasone, and halobetasol. Use for extended periods of time, on the face, axillae, and crural areas or under occlusion, may induce atrophy, telangiectasias, and striae. Midpotency topical steroids, such as triamcinolone, mometasone, and fluticasone, are commonly used as maintenance therapy. The least potent topical steroid, hydrocortisone, is available without prescription (up to 1%) and is safe to use for extended periods on the face and body folds.

Vitamin D analogs, calcipotriene, calcipotriol, and calcitriol, are other first-line topical agents with proved efficacy in the treatment of psoriasis. Calcipotriene/betamethasone dipropionate combines a vitamin D analog with a high-potency topical steroid for enhanced efficacy. Vitamin D analogs affect cellular differentiation and proliferation.

Tazarotene is a vitamin A derivative approved to treat psoriasis. This medication diminishes epidermal turnover and inflammation. Erythema, burning, and pruritus may limit use and the drug is contraindicated during pregnancy.



### **Phototherapy**

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Cabinet-based UV light therapy has been used for decades to treat widespread psoriasis or disease that is refractory to topical therapies. Wavelength in the narrowband-UV-B spectrum is the preferred phototherapy modality and is safe to use in both children and pregnant women.<sup>31</sup> Treatment is ideally performed 3 times per week over a several-month period. Home-based units are available and effective. The efficacy of narrowband-UV-B may be enhanced in combination with other treatment modalities.

### **Oral systemic therapies**

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Acitretin (Soriatane) is an oral retinoid with daily dosing that ranges from 10 mg to 50 mg. Retinoids modulate epidermal proliferation and differentiation and exhibit anti-inflammatory properties. The drug is teratogenic and must not be taken by pregnant women or those contemplating pregnancy within a 3-year time frame. Skin and lip dryness and hair loss are the most common adverse events. The drug can elevate serum triglycerides, necessitating periodic laboratory monitoring.

Apremilast (Otezla) is a phosphodiesterase type 4 inhibitor approved in 2014 for the treatment of moderate to severe psoriasis and PsA. The medication is taken twice daily, at a dose of 30 mg. In clinical studies, a response equal to or greater than 75% was achieved in 29% to 33% of patients. Routine laboratory studies are not required. The most common adverse events are diarrhea and nausea, which tend to dissipate with continued therapy.

Cyclosporine (Neoral) is a calcineurin inhibitor that dampens T-cell activation. The drug is administered on a daily basis, in a dosing range of 2.5 mg/kg to 5 mg/kg; works rapidly; and has the highest efficacy of all systemic therapies. Cyclosporine may raise serum triglycerides and blood pressure. Long-term use may cause renal impairment and periodic laboratory monitoring is mandatory.

Methotrexate has been used to treat psoriasis for more than 50 years. The drug inhibits epidermal cell division and is usually administered on a once-weekly basis with dosage varying between 5 mg/wk and 25 mg/wk. The drug is immunosuppressive and should not be used in patients with active infections. It is contraindicated in pregnancy but safe to use in pediatric patients. Hepatotoxicity is the most common serious adverse event and is most likely to occur in persons who are obese or diabetic.

### **Biologics**

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Biologic agents are protein-based compounds made from living cells that mitigate against inflammatory agents involved in the pathogenesis of psoriatic plaques and arthritis. These medications allow physicians to directly target mediators of the immune system that induce psoriasis and have revolutionized therapy for this disease. Currently approved biologic agents for the treatment of psoriasis include the following:

- TNF inhibitors: adalimumab (Humira), etanercept (Enbrel), and infliximab (Remicade)
- IL-12/23 inhibitors: ustekinumab (Stelara)
- IL-17 inhibitor: secukinumab (Cosentyx)

#### **Adalimumab**

Adalimumab is a recombinant IgG1 antibody that binds specifically to TNF- $\alpha$  and blocks its interaction with key cell surface TNF receptors. The drug was approved to treat psoriasis in 2008. For psoriasis, an initial dose of 80 mg is given subcutaneously followed 1 week later by 40 mg, with this dose then continued every other week.

**Etanercept**

Etanercept is a fusion protein approved in 2004 for the treatment of psoriasis. It inhibits binding of TNF- $\alpha$  and TNF- $\beta$  to cell surface TNF receptors. The drug is administered by subcutaneous injection. For psoriasis, the starting dose is 50 mg twice weekly for 3 months, followed by 50 mg weekly.

**Infliximab**

Infliximab is a chimeric IgG1 $\kappa$  monoclonal antibody specific for human TNF- $\alpha$  approved to treat psoriasis in 2006. The drug neutralizes TNF- $\alpha$  by inhibiting binding to receptor sites. For plaque psoriasis, the recommended dose is 5 mg/kg given as an intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter.

**Ustekinumab**

Ustekinumab is a human IgG1 $\kappa$  monoclonal antibody that binds to the p40 protein subunit used by both IL-12 and IL-23 cytokines. Approved in 2009 to treat psoriasis, the drug is administered subcutaneously with dosage dependent on weight. For patients under 100 kg, the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. Heavier individuals are treated with 90 mg at the same dosing schedule.

**Secukinumab**

Secukinumab was approved to treat psoriasis in January 2015. The drug is a human IgG1 $\kappa$  monoclonal antibody that binds and inhibits IL-17A. The recommended dose is 300 mg by subcutaneous injection at weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks.

Concerns have been raised about potential long-term sequelae associated with systemic and biologic psoriasis therapies<sup>32</sup>; fortunately, the safety track record to date is favorable regarding incidence of serious infections, major cardiac events, and malignancies.<sup>33</sup> When using immune-modulating agents, initial screening should include assays for hepatitis B, hepatitis C, and tuberculosis, with testing for tuberculosis exposure repeated on a yearly basis.

Psoriasis is a complex disorder that involves genetic, environmental, and immunologic factors.<sup>34</sup> The disorder has no known cure but today an overwhelming majority of patients can achieve good to excellent control. A multitude of promising therapies are in the pipeline,<sup>35–37</sup> some nearing Food and Drug Administration approval. There are significant barriers to optimal management, which include expense, patient compliance, and medication safety. When dealing with this disease, health care providers should strive to identify the most efficacious treatment associated with the fewest possible adverse events delivered at a reasonable cost.

Podiatrists may encounter several variants of psoriasis, including the palmar-plantar subtype, nail disease, and arthritis. Palmar-plantar psoriasis may be debilitating and is often refractory to topical therapies (ultrapotent topical steroids, retinoids, and calcipotriol) necessitating phototherapy, oral systemics (ie, acitretin or methotrexate), or biologics. Painful or disfiguring nail distortion may respond to intralesional steroid injections administered to the nail base as well as to systemic or biologic therapy. A multidisciplinary approach to achieve ideal control is highly recommended and should include a dermatologist, for management of moderate to severe skin and nail disease, and a rheumatologist, for management of joint disease. Given the significant comorbidities associated with psoriasis, such as diabetes, hypertension, and hyperlipidemia, consultation with other specialists may be prudent as well.

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