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Diagnosis, and Management**

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Over the Past Decade**

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the European Academy of Dermatology
and Venereology (EADV)**

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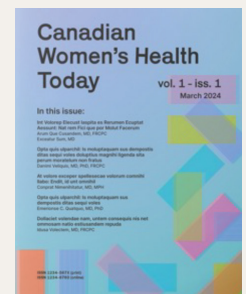
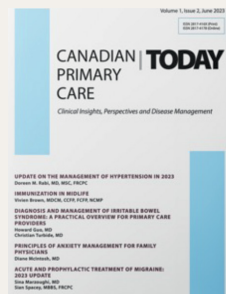
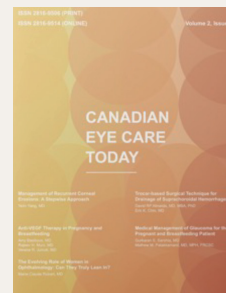
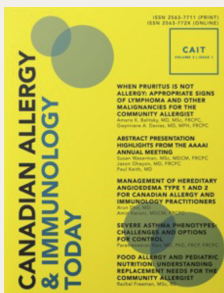
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Systemic Sclerosis: Pathogenesis, Diagnosis, and Management

Anastasiya Muntyanu, MD

Background

Systemic sclerosis (SSc) is an autoimmune fibrosing disease with internal organ involvement leading to significant morbidity and mortality. The average age of diagnosis ranges from 33.5–59.8 years with a strong female predominance (3.8–15 times more common).¹

Epidemiology

Previous studies in Canada have demonstrated a prevalence of 74.4 cases per 100,000 females and 13.3 cases per 100,000 males (Canadian SSc prevalence data, 2003), which accounts for approximately 2,500 males and 14,000 females who are affected by this debilitating condition in Canada.² The highest point prevalence reported in the world, 47/100,000 persons, was observed among Canadian First Nation residents. Globally, the prevalence of SSc is estimated to be between 7–489 cases per million

individuals, with large variability, at least in part, due to differences in diagnosis and in the heterogeneity of the disease.³ Consistently higher case numbers are reported in North America and Australia compared to continental Europe, the United Kingdom, and Japan.³ In the United States, the estimated period prevalence is 50/100,000 persons, and the age-sex adjusted annual incidence was 5.6/100,000 person-years for the years 2003–2008.^{4,5} Globally, the annual incidence has been estimated to be 0.6–5.6/100,000 adults. A recent updated study in Quebec, Canada, showed an overall age-standardized incidence rate of 4.14 cases per 100,000 person-years, with a 4:1 female predominance.⁶ The age-standardized incidence rate increased steadily over time, with an average increase of approximately 4% each year.

Variable geographic distribution has been observed, suggesting that extrinsic/environmental factors may play a role in disease development. For example, in Europe, a north–south gradient was observed with an increased prevalence of SSc in

southern countries.³ Small studies also reported clusters of SSc cases in boroughs near international airports in London, United Kingdom,⁷ a rural community near Rome, Italy,⁸ and in Libby, Montana, where mining activities are predominant.⁹ Other reported clusters include Woodstock, Canada,¹⁰ and the Kahnawake First Nations Community in Quebec, Canada.¹¹ These studies suggest a non-random distribution of SSc cases and highlight the need to further investigate the epidemiology and environmental risk factors for this disease.

Pathogenesis

The pathogenesis of SSc is not fully understood, but it is hypothesized to be due to an environmental trigger in a genetically susceptible host.¹² A three-step hypothesis has been proposed, which includes endothelial cell dysfunction/vasculopathy, inflammation due to immune system dysregulation, and fibrosis (**Figure 1**).¹ The low concordance rate in monozygotic twins and the evidence of geographic clustering suggests the importance of an extrinsic factor leading to disease development.¹³ The nature of such triggers and other factors accounting for the variability in SSc clinical severity and prognosis remains unknown.

Possible external factors that have been studied in SSc include infectious agents, chemicals, occupational or environmental pollutants, and medications/supplements, all of which could affect the immune response and trigger microvascular damage and inflammation, subsequently leading to fibrosis.¹⁵ Air pollution, a frequently studied environmental factor, is known to negatively contribute to many diseases, and was designated by the World Health Organization (WHO) as the primary environmental threat to humanity. It accounts for at least 7 million deaths globally every year.¹⁶ Currently, the highest level of evidence for extrinsic triggers for SSc points to occupational or environmental exposures to silica (18-fold increased risk) and organic solvents (2–4-fold increased risk).^{14,17} Silica exposure was associated with lower survival rates and a more severe disease phenotype, including diffuse cutaneous systemic sclerosis (dcSSc), digital ulcers, interstitial lung disease (ILD), myocardial dysfunction, and positive anti-topoisomerase (ATA) antibodies.¹⁴ Other occupational exposures proposed to increase SSc risk include epoxy resins, asbestos, and particulate air pollution.¹⁴

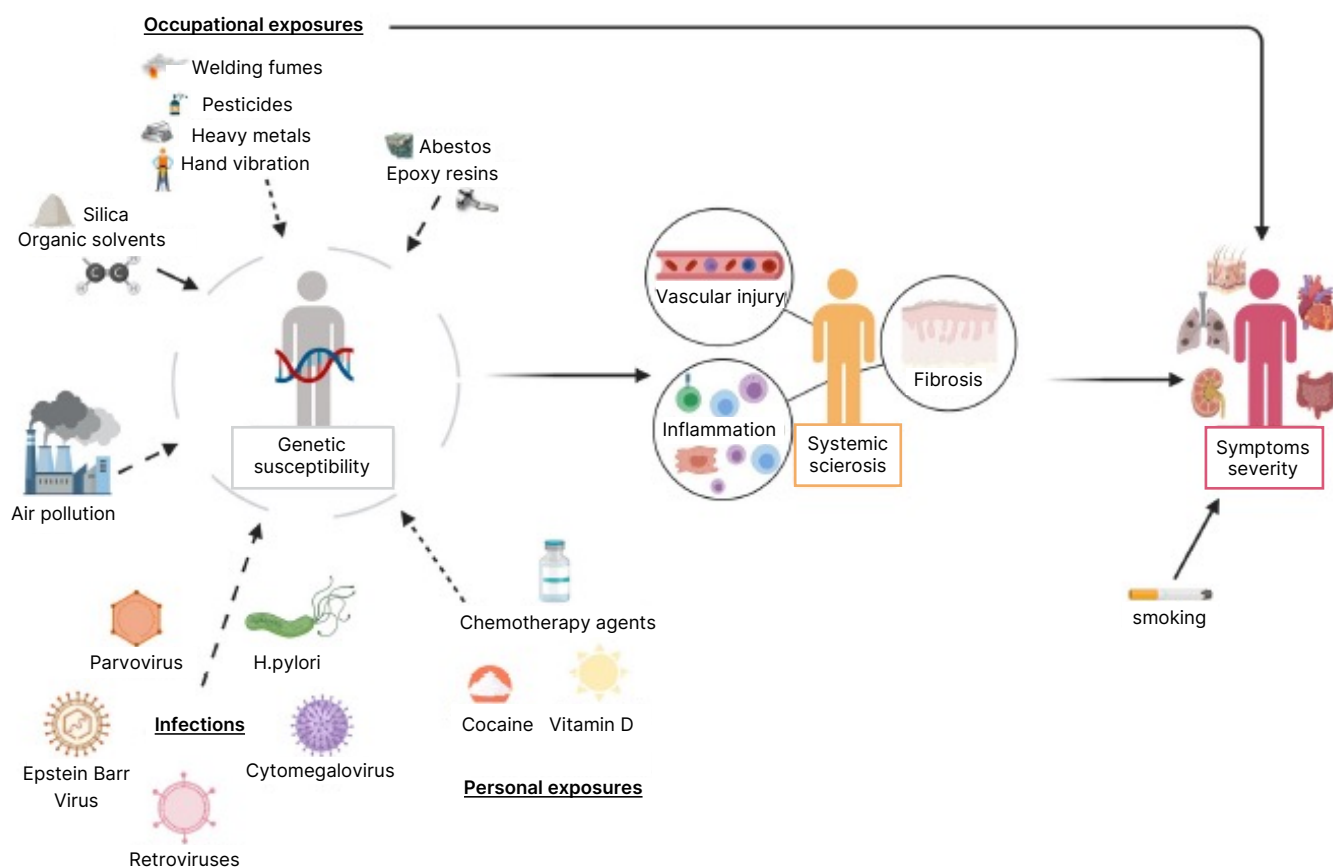


Figure 1. Pathogenesis of SSc and the role of occupational, environmental, and personal exposures to disease development. *H. pylori* - *Helicobacter pylori*. Thick lines—exposures increasing the incidence and/or severity of SSc risk based on observational studies. Dashed lines—exposures with probable increased incidence and/or severity of SSc (limited data). Dotted lines—exposures with anecdotal/unproven data only. Adapted from Ouchene et al.¹⁴

Clinical Presentation

Given that many manifestations of SSc are cutaneous, dermatologists play an important role in diagnosis, especially for early onset disease. The disease is classified into the following based on the extent of the skin fibrosis and the pattern of internal organ involvement: limited cutaneous (lcSSc) (the most common form) involving the distal limbs and face; dcSSc, involving the distal and proximal extremities, trunk and face; sine scleroderma, presenting without skin thickening but with internal organ involvement and serologic abnormalities; and overlap disease (e.g. systemic lupus erythematosus, rheumatoid arthritis, polymyositis, or Sjögren's disease).¹⁸ The most commonly affected organs are those with direct exposure to the environment such as the skin, gastrointestinal tract, and lungs.¹⁹ In all forms, and especially in dcSSc, there is significant internal organ involvement leading to increased morbidity and mortality. The 10-year likelihood of survival is less than 65%,¹⁹ and has remained unchanged for the last forty years.²⁰ In fact, SSc has one of the highest mortality rates of any rheumatic disease.¹

Compared to females, SSc in males is more likely to present with a more severe phenotype including dcSSc, cardiomyopathy, ILD, and scleroderma renal

crisis.²¹ Whether these differences are related to sex-hormones or acquired risk factors (e.g. occupational/environmental) requires further investigation. On the other hand, females are more likely to have a younger age of disease onset and an increased rate of peripheral vascular disease and pulmonary arterial hypertension (PAH).²²

Regarding ethnic differences, African American patients are more likely to develop the disease at a younger age and have more severe phenotypes including increased ILD and scleroderma renal crisis.²³

Diagnostic Criteria

The diagnosis of SSc is based on the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) classification criteria, which includes clinical disease manifestations, such as bilateral, symmetric skin thickening proximal to the metacarpophalangeal joints (sufficient criterion), presence of SSc-related abnormalities (e.g. Raynaud's phenomenon, fingertip lesions, telangiectasias, SSc-specific antibodies, abnormal nailfold capillaroscopy) and internal organ involvement (e.g. ILD, PAH) (**Table 1**).²⁴ Patients achieving a score of ≥ 9 are classified as having definite SSc.

Item	Sub Item	Weight/Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)		9
Skin thickening of the fingers (only count the highest score)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to MCP but proximal to the PIPs)	4
Fingertip lesions (only count the highest score)	Digital tip ulcers	2
	Fingertip pitted scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Lung Involvement (Maximum score is 2)	PAH	2
	ILD	2
Raynaud's phenomenon		3
Scleroderma related antibodies (Maximum score is 3)	ACA	3
	ATA	3
	RNAP3	3

Table 1. ACR/EULAR classification criteria for SSc. Patients with a total score of ≥ 9 are classified as having definite SSc. Adapted from van de Hoogen et al.²⁴

Abbreviations: **ACA:** anti-centromere antibodies; **ATA:** anti-topoisomerase/ScI-70 antibodies; **ILD:** interstitial lung disease;

MCP: metacarpophalangeal joint; **PAH:** pulmonary arterial hypertension; **PIP:** proximal interphalangeal joint; **RNAP3:** anti-RNA polymerase III

Since internal organ involvement commonly occurs within the first 3 years, early diagnosis is important. In the last few decades, the availability of nailfold capillaroscopy, which reveals dilated capillary loops and drop out sign, as well as SSc-specific autoantibodies, have allowed an earlier diagnosis of SSc to be made. Very early diagnosis of SSc (VEDOSS) criteria were established in 2011.²⁵ These criteria include the presence of Raynaud's phenomenon, puffy fingers, and positive ANA as early disease features

that predict progression to established SSc.²⁶ Hence, these early features could be helpful in establishing the diagnosis earlier, initiating treatment, minimizing end organ damage, and subsequently improving patient outcomes.

There are several specific autoantibodies that help with the diagnosis, clinical presentation, prognosis, and the exclusion of other conditions that present with skin thickening. ANA is positive in ~95% of patients.^{1,27,28} SSc-specific-autoantibodies include anti-centromere

Antibody	Estimated Prevalence	Subtype of SSc	Main Systemic Associations
ACA	20–25%	lcSSc	• PAH (15–20%) • Esophageal dysmotility and gastrointestinal dysfunction • Low risk of ILD, cardiac and renal disease
ATA	20–30%	dcSSc >lcSSc	• High risk of ILD (early) • PAH • Scleroderma renal crisis • Cardiac • Myositis
PM/Scl	2–4%	Overlap Polymyositis/lcSSc	• Myositis • ILD (50% by 15 years) • PAH (approximately 36% by 15 years) • Cardiac • Renal
To/Th ribonucleoprotein	<5%	lcSSc	• ILD (45%) • PAH (25%)
RNAP-III	1–22%	dcSSc (rapidly progressive)	• Scleroderma renal crisis (early) • Increased risk of malignancy within 3 years of diagnosis • Moderate risk of ILD • PAH (later) • Gastric antral vascular ectasia • Myositis • Less cardiac involvement
U1-RNP	5–10%	lcSSc, overlap syndromes (mixed connective tissue disease)	• Myositis • PAH • ILD
U3-RNP/Fibrillarin	4–10%	dcSSc	• Early severe organ involvement: • PAH (highest risk) • ILD • Scleroderma renal crisis • Cardiac • Small bowel dysmotility • Myositis

Table 2. Summary of autoantibody profiles in SSc and corresponding key systemic associations. Adapted from Jerjen et al.¹

Abbreviations: **ACA:** anti-centromere antibodies; **ATA:** anti-topoisomerase I/Scl-70 antibodies; **dcSSc:** diffuse cutaneous systemic sclerosis; **ILD:** interstitial lung disease; **lcSSc:** limited cutaneous systemic sclerosis; **PAH:** pulmonary arterial hypertension; **PM/Scl:** polymyositis/scleroderma; **RNAP-III:** RNA polymerase III; **U1-RNP:** U1- ribonucleoprotein; **U3-RNP:** U3-ribonucleoprotein

System	Investigation	Explanation	Treatment
General	CBC with differential	Assess for anemia due to malabsorption, iron deficiency, or gastrointestinal blood loss	• Iron supplementation • Nutrition consultation
Lung Involvement	• HRCT of the chest • PFT with DLCO • Bronchoalveolar lavage and lung biopsy can be considered	To be completed at baseline and if clinical symptoms are present or worsening PFTs are identified	• Immunosuppression (mycophenolate mofetil, cyclophosphamide, rituximab) • Nintedanib, tocilizumab – FDA approved • Lung transplant • Autologous HSCT in rapidly progressive ILD
Pulmonary Arterial Hypertension	• Doppler echocardiography • Serum N-Tpro-BNP level • Right heart catheterization	This is recommended for initial screening for PAH	• O₂ • Anticoagulation • Endothelin receptor antagonist • Phosphodiesterase 5 inhibitor • Prostacyclin analogues • Prostacyclin receptor agonist • Soluble guanylate cyclase stimulant • Lung transplant
Cardiac Fibrosis	Echocardiography	Restrictive cardiomyopathy can occur secondary to PAH	• ACE inhibitors
• GI involvement • Esophageal dysmotility • Small bowel involvement	• Barium swallow with small bowel follow through • Manometry • Endoscopy	Evaluation should be guided by symptoms	• PPI • Proton pump inhibitor (ondansetron)
Renal crisis Hypertension	• Blood pressure measurement • Serum creatinine level • Urinalysis with urine sediment		• ACE inhibitors instituted for early treatment but not helpful for prevention
Overlap disease	• CK • Rheumatoid factor • Antibodies to CCP • Anti-double-stranded DNA and/or anti-Smith RNP antibodies	• May be elevated in patients with myopathy or myositis • These antibodies are relatively uncommon in patients with SSc and their presence points toward overlap syndromes with other systemic diseases • Usually in overlap cases there is more significant arthritis compared to SSc	

Table 3. Summary of screening recommendations and treatment approaches based on systemic involvement; *courtesy of Anastasiya Muntyanu, MD*

Abbreviations: ACE: angiotensin-converting enzyme; CBC: complete blood count; CCP: citrullinated peptides; CK: creatine kinase; DLCO: diffusing capacity for carbon monoxide; GI: gastrointestinal; HRCT: high-resolution computed tomography; HSCT: hematopoietic stem cell transplantation; ILD: interstitial lung disease; PAH: pulmonary artery hypertension; PFT: pulmonary function test; PPI: proton pump inhibitor; RNP: ribonucleoprotein; Serum N-Tpro-BNP: N-terminal pro-B-type natriuretic peptide; SSc: systemic sclerosis

antibodies (ACA), which is associated with lcSSc and PAH, ATA, associated with dcSSc and ILD, and anti-RNAPolymerase (RNAP)-III antibodies, associated with malignancy and renal crisis (**Table 2**).¹ The autoantibodies are typically mutually exclusive. Other autoantibody profiles include Polymyositis/Scl, To/Th ribonucleoprotein, U1-ribonucleoprotein (U1-RNP), and U3-RNP/fibrillarin.¹ A combination of autoantibodies can also help predict survival, timing, risk, and incidence of systemic complications.^{1,29}

Systemic Involvement

Systemic manifestations include pulmonary (ILD or PAH), renal (i.e. scleroderma renal crisis or renal vasculopathy), cardiac (i.e. heart failure, arrhythmias, pericardial effusion, and valve sclerosis), gastrointestinal (i.e. gastroesophageal reflux disease, impaired motility, gastric antral vascular ectasia), and urogenital (i.e. sexual dysfunction) involvement as well as an increased malignancy risk (i.e. cutaneous, breast, bladder, lung, liver, and hematological) (**Table 3**).¹ Regular screening for lung involvement is mandatory and consists of pulmonary function tests as well as a high resolution CT scan (HRCT).³⁰ Cardiac involvement is more common in older patients and in those with ATA antibodies.^{1,31} Scleroderma renal crisis is a severe manifestation that is less common now, given the knowledge that high dose prednisone can precipitate it, as well as the available preventative options such as angiotensin-converting enzyme (ACE) inhibitors.^{32,33} Scleroderma renal crisis typically manifests within the first 5 years of the SSc diagnosis. The most commonly involved internal organ system is the gastrointestinal tract, and most patients with SSc are affected to some degree.³⁴

Management

No curative treatments exist for SSc, and the available therapies may only have a limited effect on slowing disease progression, often with significant side effects.³⁵ Treatment is focused on the disease manifestations that are present. For skin fibrosis, immunosuppressive agents such as mycophenolate mofetil and methotrexate are typically used, with newer agents such as tocilizumab, rituximab, and brodalumab showing early promise in clinical trials.^{30,36} Regarding brodalumab, a clinical trial of 100 patients randomized to brodalumab vs placebo reported that the treatment group showed a rapid, sustained, and significant reduction in skin sclerosis as measured by the modified Rodnan skin score (mRSS) up to 52 weeks.³⁷ Additionally, brodalumab exhibited therapeutic effects on lung/respiratory functions,

formation of digital ulcers, the symptoms of gastroesophageal reflux disease, and quality of life indicators. No additional safety concerns were identified compared to treatment in other disease categories such as psoriasis.³⁷

In recent years, autologous hematopoietic stem cell transplantation has provided tremendous hope.³⁸ This procedure reduces the number of aberrant immune cells and allows re-population with a self-tolerant immune system. This intervention continues to have the largest effect on skin fibrosis to date (e.g., a 10-point greater decrease in mRSS compared to 12 monthly infusions of cyclophosphamide).³⁹ While several studies have shown a decrease in skin involvement, improvements in organ function, quality of life measures, and overall survival,⁴⁰ this procedure is associated with significant risks, which limits its use to certain subsets of patients.

Conclusion

In conclusion, SSc is a complex, autoimmune fibrosing disease that significantly impacts morbidity and mortality due to its multi-organ involvement. The pathogenesis likely involves environmental triggers in genetically predisposed individuals, leading to immune dysregulation, endothelial damage, and progressive fibrosis. The variability in incidence/prevalence rates across regions and globally suggests that geographic/environmental factors could play a role.

Early diagnosis is essential for optimizing treatment, particularly as severe manifestations often develop within the first few years after disease onset. Recent advancements in diagnostic tools, such as nailfold capillaroscopy, SSc-specific autoantibodies, and VEDOSS classification facilitate earlier detection, which may improve outcomes. Management is tailored to specific organ systems, but little is known with regards to disease modification. Continued research is needed to better understand the underlying mechanisms of SSc and to develop targeted therapies that could help reduce the significant disease burden.

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Financial Disclosures

None declared.

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New treatments for acne vulgaris over the past decade

Nikolas MacLellan, MD, FRCPC, DABD

Introduction

Acne vulgaris is a prevalent, chronic inflammatory condition of the pilosebaceous units, commonly affecting adolescents and young adults, though it can persist or develop later in life. Conventional treatments such as retinoids, benzoyl peroxide, antibiotics, and hormonal therapies remain staples in managing acne vulgaris (**Figure 1**). Advances in the past decade have introduced novel treatments for acne vulgaris that may be more effective and tolerable for select populations.

Novel topical therapies

Topical retinoids:

Topical retinoids remain a first-line treatment for managing acne vulgaris. Two newer topical retinoid formulations used to treat acne vulgaris are trifarotene 50 mcg/g cream and tazarotene 0.045% lotion.

Trifarotene was approved in 2019 by Health Canada for the topical treatment of acne vulgaris of the face and/or trunk in patients 12 years of age and

older.¹ Unlike other topical retinoids, trifarotene is a 4th generation topical retinoid that specifically targets the retinoic acid receptor (RAR) gamma, which is the most common RAR isoform, making it more selective than other retinoids. It also has the most clinical data on safety and efficacy in treating truncal acne.² Adverse events are similar to those of other topical retinoids associated with cutaneous irritation that improves with continued therapy.

Tazarotene is a potent topical retinoid that remains highly effective in targeting inflammatory lesions of acne vulgaris. Although tazarotene lotion at doses of 0.05% and 0.1% were approved to treat acne vulgaris, these formulations resulted in more significant side effects given their high potency and are no longer routinely available in Canada to treat acne. Tazarotene 0.045% lotion was approved in 2021 by Health Canada for the topical treatment of acne vulgaris in patients 10 years of age and older.³ Unlike previous formulations, tazarotene 0.045% lotion is formulated with a polymeric emulsification system that helps to

reduce dryness of the skin through its hydrating and moisturizing properties.⁴

Topical clascoterone:

Clascoterone 1% cream was approved by Health Canada in 2023 to treat acne vulgaris in patients 12 years of age and older.⁵ It is the first topical hormonal therapy approved by Health Canada for acne vulgaris. It is an androgen receptor inhibitor that may reduce sebaceous gland activity. Patients treated with clascoterone applied topically twice daily for 12 weeks in two randomized control trials (RCTs) achieved higher investigator global assessment (IGA) scores compared to those using the vehicle. In addition, they experienced few local side effects, similar to those using the vehicle.⁶ Unlike other hormonal therapies used to treat acne vulgaris, clascoterone is safe for use in both men and women. The most common side effects were local skin reactions, such as erythema, scaling and pruritus, but these reactions were reported at similar rates in patients taking the vehicle alternative. Systemic symptoms such as hypothalamic-pituitary-adrenal (HPA) axis suppression and hyperkalemia were not reported with prescription strength therapy.

Topical clindamycin/adapalene/benzoyl peroxide triple-combination:

The latest topical therapy approved by Health Canada to treat acne vulgaris in individuals 12 years of age and older is a gel containing clindamycin phosphate

1.2%, adapalene 0.15%, and benzoyl peroxide 3.1%.⁷ This is the first triple-combination therapy approved by Health Canada, offering three mechanisms of action, including antibiotic, retinoid, and antibacterial. It is applied once daily to the affected areas, which may allow for better compliance than alternative topical regimens that require twice-daily application of multiple products. In two clinical trials, the triple-combination therapy was found to be significantly more effective at reducing both inflammatory and non-inflammatory lesions by week 12 compared to the vehicle. The most frequent side effects were mild local reactions, similar to those observed with other topical therapies used for acne vulgaris.

Topical minocycline:

While not approved by Health Canada, topical minocycline 4% foam is a topical antibiotic that received approval in the United States in 2019 from the Food and Drug Administration (FDA) to treat non-nodular lesions of acne vulgaris in patients 9 years of age and older.⁸ Two clinical trials revealed significant reductions in IGA in patients treated with topical minocycline over 12 weeks, with continued improvement over 52 weeks. The most common side effect reported in these clinical trials was headache. Further, systemic absorption is low, and serious adverse reactions associated with oral minocycline were not observed in clinical studies.

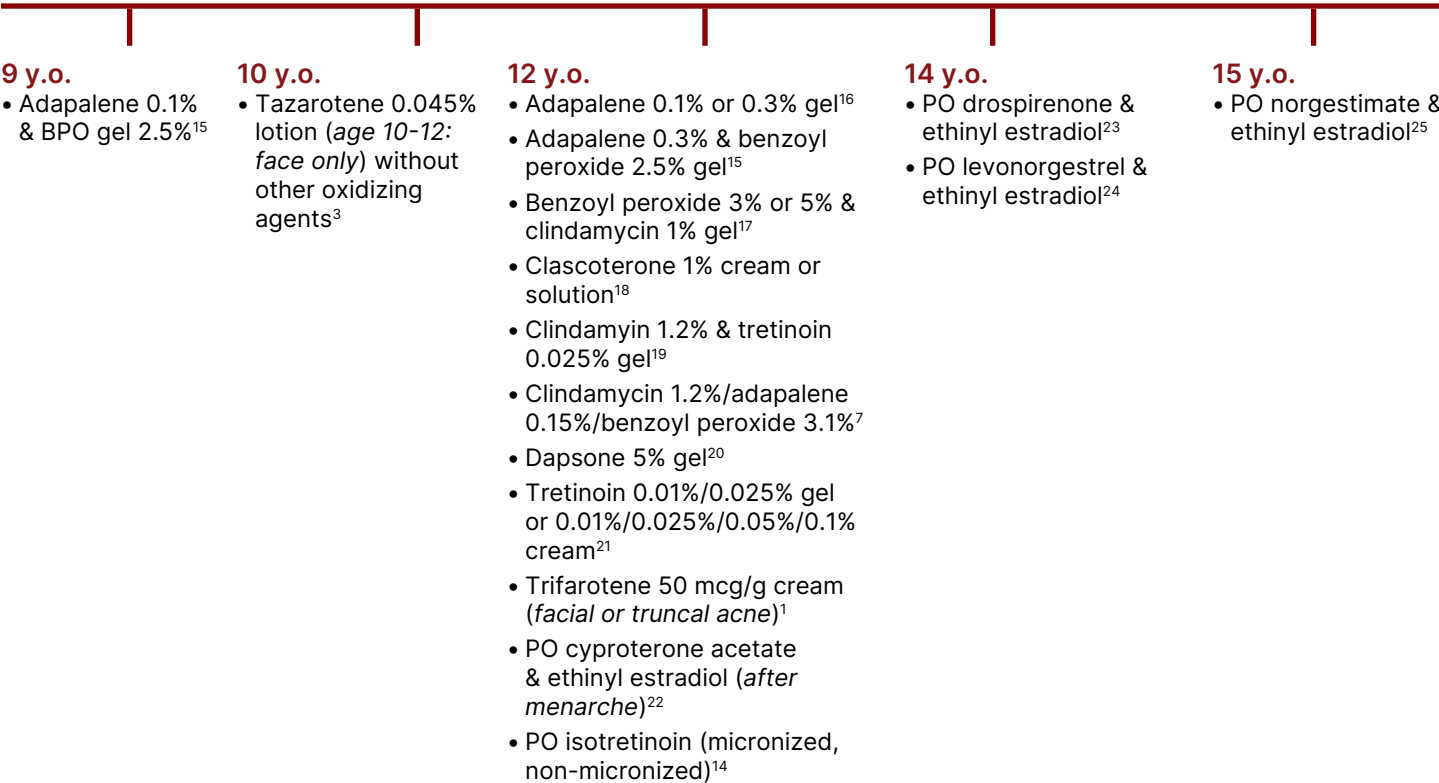


Figure 1. Health Canada-approved pharmacologic therapies for acne vulgaris based on age of approval; courtesy of Nikolas MacLellan, MD, FRCPC, DABD

Novel oral therapies

Sarecycline:

Although not available in Canada, sarecycline is a tetracycline-class oral antibiotic approved by the FDA in 2018 to treat acne vulgaris in individuals 9 years of age and older.⁹ Unlike other tetracycline-based antibiotics, sarecycline has a narrow spectrum of action and demonstrates a lower propensity for inducing antimicrobial resistance and gut microbiome alterations while still achieving a similar therapeutic efficacy to other antibiotics for treating acne.¹⁰ While the most common adverse event reported was nausea, it seems to be associated with fewer instances of diarrhea, fungal overgrowth, and vaginal candidiasis compared to alternate tetracycline antibiotics.

Micronized isotretinoin:

Oral isotretinoin remains the gold standard for treating severe acne vulgaris. However, some oral formulations are poorly absorbed when taken with a low-fat diet, which may result in lower efficacy in selected patients. A new micronized formulation of isotretinoin was approved by Health Canada in 2023 to treat severe nodular and/or inflammatory acne, acne conglobata, and recalcitrant acne in patients 12 years of age and older.¹¹ The micronized formulation provides enhanced bioavailability that results in a comparable rate of absorption and extent of drug exposure under both fasting and fed conditions. This may be a more effective treatment option for younger patients who are on a diet or undergoing intermittent fasting and are unable to achieve the target cumulative dose of at least 120 mg/kg.¹² The side effect profiles are similar between micronized and non-micronized isotretinoin. It is recommended to start micronized isotretinoin at a dose of 0.4-0.8 mg/kg body weight daily, increasing to 1.6 mg/kg per day for a 15- to 20-week duration.

Novel physical therapies

1726-nm laser:

Physical therapies have played a role in managing acne vulgaris for decades. These include photodynamic therapy, visible light therapy, and other surgical methods such as the injection of intralesional triamcinolone acetonide or comedone extraction. In 2023, Health Canada approved a new diode laser with a 1726 nm wavelength to treat acne vulgaris due to its high selectivity for sebaceous glands.¹³ It is postulated to be the first treatment since isotretinoin that significantly reduces sebaceous gland activity while being more tolerable than isotretinoin. The treatment is delivered in 3 sessions every 3 weeks. A prospective,

open-label, single-arm institutional review study that included 104 participants demonstrated that the treatment is safe and effective across all skin types, as observed at 4, 12, and 26 weeks. The study showed a significant, durable reduction in acne lesions in up to 87.3% of participants 6 months post-treatment. Some patients experienced an initial transient eruption in the first 2 to 21 days post treatment (similar to the eruption that occurs after isotretinoin), and some patients experienced temporary perilesional erythema; however, there were no reports of residual erythema, edema, blistering, crusting, or dyspigmentation.

Conclusion

The treatment of acne vulgaris has evolved significantly in recent years, with new therapies offering patients more personalized and targeted options. Health Canada has approved several new treatments for the pharmacologic management of acne, including trifarotene, tazarotene 0.045% lotion, clascoterone, clindamycin/adapalene/benzoyl peroxide triple combination therapy, micronized isotretinoin, and the 1726-nm laser. These treatments offer effective options with improved safety profiles. Additionally, laser and light therapies, along with newer therapies approved by the FDA such as topical minocycline foam and oral sarecycline, offer innovative ways to tackle acne with less systemic involvement and enhanced patient outcomes. As research continues, it is likely that even more effective and safer treatments will emerge, offering renewed hope for patients with acne vulgaris who have long struggled with the psychological and physical impacts of this condition.

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Paradoxical Psoriasis Induced by TNF Inhibitors and Beyond: A Review

David O. Croitoru, MD

Introduction

Paradoxical psoriasis (PP) represents an uncommon but well-documented adverse effect that occurs following exposure to tumour necrosis factor-alpha (TNF- α) inhibitors.¹ There is growing evidence that this reaction may not be class-specific, as the indications for biologic interventions (interleukin [IL]12/23, IL23, IL17, IL4/13) broaden in chronic inflammatory diseases. However, cumulative evidence amongst other classes remains limited to case reports.^{2,3}

The pathogenesis of this reaction to TNF inhibitors has been postulated and experimentally supported as a switch toward interferon (IFN) production by antigen-presenting cells, however, the mechanism with other biologics remains elusive.⁴ The baseline association of classical psoriasis (non-drug induced) with the seronegative rheumatic and gastrointestinal inflammatory diseases treated by TNF inhibitors, initially made this reaction a challenge to define and study. As evidence has grown, PP has been defined as psoriatic lesions that arise *de novo* or as morphologically atypical exacerbations of pre-existing known psoriasis during TNF- α therapy. These lesions may persist and worsen unless treated, commonly requiring systemic therapeutic adjustments. This review explores the epidemiology, pathogenesis, clinical manifestations, and management of PP, with an

emphasis on patient outcomes and recommendations based on primary data, systematic reviews, and contributions from key researchers in the field.

Epidemiology

The incidence of PP varies by therapeutic agent, clinical context, and patient demographic. Anti-TNF agents, such as infliximab, adalimumab, and etanercept, are frequently implicated. A systematic review conducted in 2022 involving 2,049 cases found that infliximab accounted for over half of the reported cases.⁵ Studies suggest that up to 5% of patients on TNF inhibitors experience PP, with higher rates observed in inflammatory bowel disease (IBD) patients compared to those with other autoimmune diseases. Among patients with IBD, those with Crohn's disease are at over a 1.5 times greater risk of developing PP than those with ulcerative colitis.⁶ Females appear more predisposed to PP, comprising approximately 60-70% of cases.^{6,7} Anti-IL-17 therapies, often prescribed for psoriasis, psoriatic arthritis, and ankylosing spondylitis, are also associated with PP, though the number of reported cases has been significantly lower than that observed with anti-TNF agents. Among the approximately 30 documented cases, most involve IL-17A-specific inhibitors such as secukinumab, with fewer reports for agents such as ixekizumab, the

IL-17A/F inhibitor bimekizumab, and the receptor antagonist brodalumab.⁸ While p19 and p40 inhibitors of IL-12 and IL-23 pathways are commonly described in the treatment of TNF-induced PP, they have also been occasionally described as potential culprits.² Recently, IL-4/IL-13 inhibitors, such as dupilumab, have also been described with a lower frequency of PP following exposure (1-2%) with an increased risk noted in those with a familial or personal history of psoriasis, suggesting that this may represent an 'unmasking' of psoriasis in predisposed patients.³

Pathogenesis

The pathogenesis of PP is distinct from idiopathic psoriasis and hinges on the tight immunological regulation of TNF, IFN, and likely IL-4/13 and IL-17. Evidence suggests that the mechanism for TNF- α induced PP occurs due to TNF inhibition, which causes an overcompensation in interferon-alpha (IFN- α) activity via plasmacytoid dendritic cell activation. This causes a T-cell independent, innate psoriasiform inflammatory response, as well as the recruitment of Th17 and Th1 cells.^{4,9} In contrast, emerging data on the pathogenesis of IL-4/IL-13-induced PP supports the theory that dysregulation of the homeostasis of Th17 and Th2 inflammation is the underlying event for these agents.^{10,11} Both IL-4-R α and specific IL-13 inhibition have been demonstrated to shift toward a Th1/Th17 phenotype, resulting in the development of PP. Patients with this presentation have demonstrated increased relative IL-17A levels in peripheral blood, along with a corresponding increase in IL-23 in lesional skin. Conceptually, it is believed that psoriasis and atopic dermatitis may represent two poles of an interrelated immunological spectrum, with switches hinging on IL-17; emerging translational data may support baseline IL-17A levels as predictive of this immunological switch.¹²

Clinical Manifestations

PP presents with a spectrum of clinical forms, often mirroring classical psoriasis but with some variations. The most frequently observed morphologies include plaque-type (vulgaris) and palmoplantar pustulosis, which can occur either in isolation or with corporal involvement. Other documented forms include inverse, guttate, psoriasiform dermatitis and generalized pustular forms.⁶ Palmoplantar pustules, observed in approximately one-third of cases, may be seen in conjunction with other morphologies simultaneously. Despite the predilection for pustular eruptions, generalized pustulosis is a rare occurrence with <3% of cases described in larger cohorts.¹³ A notable feature of TNF-induced PP, which occurs

in a minority of patients (approximately 10%), is the potential for scalp involvement with regional alopecia, which is not observed in classical psoriasis.^{6,7} This scalp involvement typically manifests as psoriatic erythematous, hyperkeratotic, and sometimes exudative/pustular lesions.

The pleomorphic nature of PP coupled with the variable latency period from initial drug exposure can make the etiology of the eruption challenging to pinpoint. The timing of PP generally occurs within the first year of TNF inhibitor initiation, with an average onset of approximately 11 months in adults and 22 months in children.¹⁴

Factors that predict extensive or severe PP with alopecia include female sex, younger age, smoking, and having Crohn's disease, with a particularly elevated risk among patients on adalimumab.⁶

In rare cases, PP may involve articular manifestations, resembling both arthralgia secondary to IFN upregulation as well as true psoriatic arthritis with synovitis, associated with upregulations in IL-17 and IL-23 pathways.

An important diagnostic consideration for clinicians when managing patients with suspected PP on less commonly described agents (e. g., IL-17) is whether the eruption represents a breakthrough of classical psoriasis or multiple competing pathologies.

Management

Managing PP is often a multidisciplinary decision that involves a reassessment of biologic therapy, without a standard treatment ladder or published guideline. For mild cases, topical therapies may be considered as the first line of treatment, either alone or in conjunction with phototherapy.¹⁵ These include vitamin D agonists, corticosteroids, calcineurin inhibitors, salicylic acid/retinoids, and more recently, phosphodiesterase inhibitors. Discontinuing or alternating biologic therapy is the most straightforward approach, with symptomatic resolution observed in many patients after cessation. However, this decision must be weighed against the risk of exacerbating the underlying inflammatory condition, particularly in patients with severe rheumatoid arthritis or Crohn's disease. Some clinicians will arrange for interval disease staging with synovial exams, serum and stool studies (fecal calprotectin), and/or imaging modalities to define the underlying disease before committing to a management strategy. For patients who cannot discontinue TNF inhibitors, alternative biologic therapies, such as IL-17 or IL-12/23 inhibitors, have shown promise.

In one systematic review on PP in patients with IBD following TNF inhibitor exposure, ustekinumab

resulted in a complete or partial resolution in 83.1% of patients (n=74/89), with 75.4% maintaining their IBD remission.^{13,16} Clinical outcomes following interclass transitions vary, but they are generally favourable, with improved symptom control and reduced lesion progression.

Intraclass switches may also be of benefit but have been associated with persistence or worsening of their PP in large cohort studies. Therefore, this approach should be employed cautiously and on an as-needed basis.

Systemic agents, such as methotrexate or cyclosporine, may also be considered for moderate-to-severe cases using a treat-through approach, though the risk-benefit profile of these treatments must be assessed carefully. Studies underscore the importance of regular monitoring for side effects, particularly when systemic agents are prescribed concurrently with TNF inhibitors. For refractory cases, small-molecule inhibitors such as apremilast, which modulate intracellular inflammatory pathways, have shown potential in small cohort studies but require further validation in larger studies and trials.

Conclusion

PP presents a unique therapeutic challenge, reflecting the complexity of immune modulation through TNF- α inhibition and the polarization of Th17/Th2 immunity. This review highlights the unpredictable epidemiology, complex pathogenesis, and diverse clinical manifestations associated with this condition. Although TNF inhibitors are indispensable for treating various autoimmune disorders, the emergence of PP necessitates ongoing vigilance and a tailored management approach. Current therapeutic options, particularly IL-17 and IL-12/23 inhibitors, offer promising alternatives for managing PP while maintaining disease control of the primary autoimmune condition. Ongoing research into the immunologic mechanisms and long-term outcomes of PP is essential for refining treatment protocols and improving patient care.

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Highlights from the 33rd Congress of the European Academy of Dermatology and Venereology (EADV)

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Introduction

The 33rd congress of the European Academy of Dermatology and Venereology (EADV) was held in Amsterdam, the Netherlands from Sept 24–28, 2024. With over 17,000 participants, this meeting had the highest attendance of any EADV congress to date. The meeting featured over 160 symposia and 20 subspecialty sessions and provided updates and data on new and emerging therapies for a number of skin conditions. This article will highlight interesting findings in atopic dermatitis, psoriasis, and hidradenitis suppurativa (HS).

Reducing the risk of disease comorbidities in psoriasis and atopic dermatitis through biologic therapies

An interesting theme discussed in several late-breaking sessions was the possibility for biologic therapies in atopic dermatitis and psoriasis to reduce the risk of disease comorbidities. Below, I will review presentations by Drs. Armstrong and Irvine, who presented data examining the association of biologic

therapy in psoriasis and the risk of subsequent development of psoriatic arthritis,¹ as well as the impact of biologic therapy in atopic dermatitis and the risk of growth suppression.²

Biologics for psoriasis and the risk of future psoriatic arthritis

Observational studies suggest that approximately one-third of patients with psoriasis develop psoriatic arthritis, with joint changes usually occurring following psoriasis development.¹ This temporal progression from skin to joint involvement was initially described in the nomenclature put forth by the European Alliance of Associations for Rheumatology (EULAR) task force,³ which has been revised by Errichetti and Zabotti, 2023⁴ in **Figure 1**.

Given this temporal progression and the shared inflammatory mediators in the pathophysiology of psoriasis and psoriatic arthritis, it is biologically plausible that early use of biologic agents in this timeframe may delay or prevent the progression to psoriatic arthritis.

However, the literature to date on this topic is unclear. While many studies show a reduction

of psoriatic arthritis among psoriasis patients on biologics,⁵⁻⁸ some studies show an increased risk.⁹ In her presentation, Dr. Armstrong discussed how significant biases may be impacting these later findings, namely, 1) protopathic bias and 2) survival time bias. For instance, if you consider a typical severe psoriasis patient in your practice who reports joint issues, it is conceivable that you might be more likely to prescribe a biologic agent that also addresses psoriatic arthritis, which could create the impression that the biologic is increasing the risk of psoriatic arthritis. This is referred to as protopathic bias, which is a type of confounding by indication. This bias is likely also at play when comparing different biologic classes. Retrospective studies show that interleukin (IL)-23 agents have the lowest risk of progression to psoriatic arthritis.⁹ However, a more likely explanation is that this

medication class was chosen for these patients due to a perceived lower risk of psoriatic arthritis. Lastly, survival time bias may explain why psoriatic arthritis occurs earlier among psoriasis patients on biologics.⁹ Usually, we prescribe biologics to more severe patients who have "survived" longer with their psoriasis, and are further along on the temporal progression from skin to joint involvement compared to those receiving other treatments.²

Overall, while the evidence to date is inconclusive, it is biologically plausible that biologics for psoriasis might reduce the risk of progression to psoriatic arthritis. Ideally, prospective controlled studies are required to further elucidate this potential association.

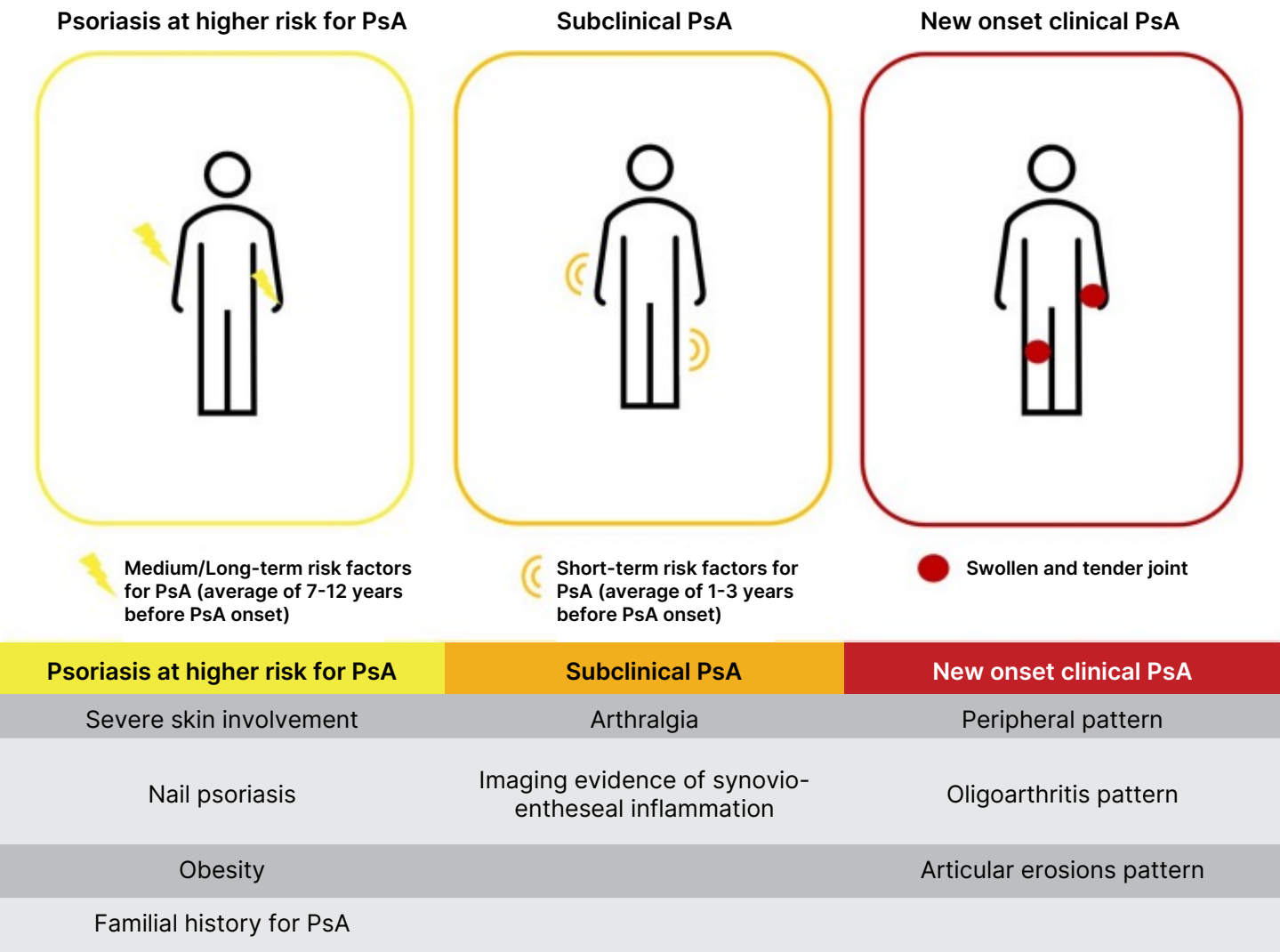


Figure 1. Biologics for psoriasis and the risk of future psoriatic arthritis.

Legend: The transition from psoriasis to clinical psoriatic arthritis (PsA) occurs through two stages: (1) "psoriasis at higher risk for PsA," including patients with a medium-long-term risk (average of 7–12 years) of developing PsA (i.e., those with severe skin involvement, nail psoriasis, obesity, and/or familial history for PsA); (2) "subclinical PsA," including patients with a short-term risk (average of 1–3 years) of developing PsA (i.e., those with arthralgia and/or imaging evidence of synovio-entheseal inflammation). Such phases precede "clinical PsA," which may present with three main patterns, including "peripheral," "oligoarthritis," and "articular erosions"

Source: Errichetti and Zabotti, 2023⁴

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Biologics for atopic dermatitis and the risk of growth suppression

It is well known that patients with severe atopic dermatitis are predisposed to growth suppression.¹⁰ Potential mechanisms for this include chronic inflammation, stress, sleep disruption, and the effects of systemic/systemically absorbed topical corticosteroids. Dr. Irvine from Ireland presented a post hoc analysis from the Liberty-AD PEDS phase 3 trial looking at the role of dupilumab on the growth of children with severe atopic dermatitis.² Children aged 6 to 11 years with severe atopic dermatitis were randomized 1:1 to receive either placebo or dupilumab 300 mg subcutaneously every 4 weeks (both groups were also allowed mild-to-moderate topical corticosteroids). Height was measured at baseline and after 16 weeks of treatment. While growth is expected over this timeframe in children of this age group, the proportion of patients showing at least a five percentile increase in height was consistently and statistically significantly higher in the dupilumab group vs the placebo group. This was observed across all baseline height percentiles (ranging from <25th height percentile to <50th height percentile). Notably, the difference in the proportion of patients reaching this five percentile height increase was quite striking, with some groups reaching over a 25% difference in just a 16-week period.²

Overall, this rigorous and controlled data provides compelling evidence that early treatment with dupilumab for severe AD in childhood can have a quick and meaningful impact on improving growth, which may offer lifelong benefits for these patients (**Figure 2**).

Treatment update for hidradenitis suppurativa

Biologics & small molecules

A number of new biologics and small molecules for HS were reviewed including IL-17, IL-1, tyrosine kinase, and Janus kinase (JAK) inhibitors.

Izokibep is a novel IL-17A inhibitor small molecule therapy designed to overcome limitations of traditional monoclonal antibodies. Izokibep is approximately one-tenth the size of monoclonal antibodies, which enables it to reach higher drug concentrations typically only achievable with intravenous administration. Dr. Papp presented data from a phase 3 trial demonstrating an improvement in the HS Clinical Response of 75% (HiSCR75) of 33% (compared to 21% in the placebo arm) after just 12 weeks of treatment.¹¹

Dr. Hunger provided a review of several new and emerging biologics and small molecules for treating HS, including sonelokimab, lutikizumab, remibrutinib and upadacitinib.¹² Sonelokimab is an IL-17A and

IL-17F inhibiting nanobody composed of three domains, two with high affinity for IL-17A and IL-17F, and a third that binds to human albumin, allowing for higher drug concentrations to be reached at sites of inflammatory edema. In a phase 2 trial with 24 weeks of follow-up,¹³ HiSCR75 was achieved in 56.9% of patients (placebo data for 24 weeks was not reported, but 12-week data previously published shows HiSCR75 29% change compared to placebo).¹⁴ Lutikizumab, the first IL-1 inhibitor studied for HS, is a dual-variable domain IL-1 alpha/IL-1 beta antagonist. In phase 2 studies, lutikizumab reached HiSCR75 in 45.9% of patients compared to 17.5% in the placebo group.¹⁵ Remibrutinib, the first agent studied for HS that specifically targets B-cells, is an oral Bruton's tyrosine kinase inhibitor that prevents B-cell conversion to plasma cells. In Phase 2 studies, HiSCR75 was achieved in 42.4% of patients compared to 18.4% in the placebo group.¹⁶ Lastly, data from a retrospective cohort study on upadacitinib was reviewed, showing a HiSCR75 response rate of over 90% after 12 weeks of therapy. Prospective, controlled trials are required to verify this impressive response.¹⁷

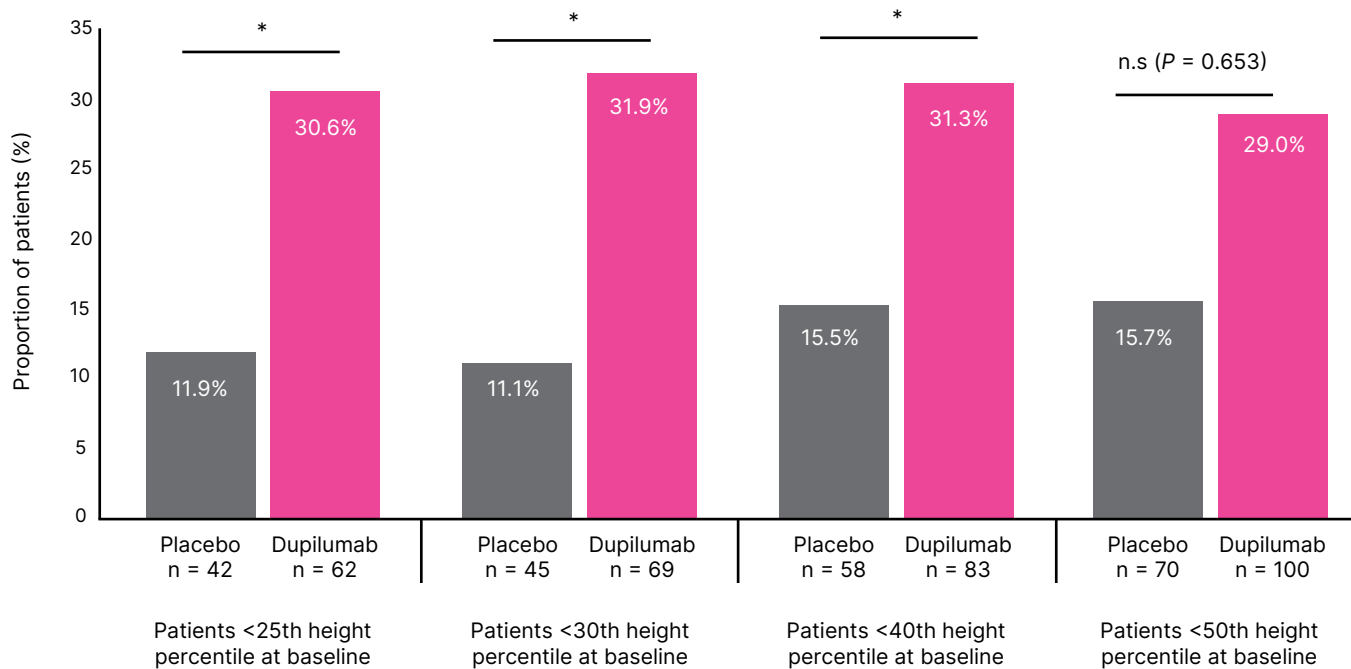
Supportive agents for weight loss

Several sessions examined new supportive therapies for HS, including novel agents to assist in symptom improvement through weight loss. Hughes et al.¹⁸ presented the first published data for the use of semaglutide in HS during a poster presentation. In this retrospective, non-controlled study, thirty HS patients of all severities on various conventional HS therapies were concomitantly treated with semaglutide for weight loss over a mean period of 8.2 months. The mean weight loss was 6.1 kg, with one-third of patients losing at least 10 kg. Patient-reported HS flares decreased from a mean of once every 8.5 weeks to once every 12 weeks, and one-third of patients experienced at least a four point reduction in the Dermatology Life Quality Index (DLQI). Of note, the mean dose of semaglutide used in this study (0.8 mg weekly) is far below the 2.4 mg weekly licenced dose for weight loss (the authors stated supply issues).

In the session by Dr. Hunger described above,¹² the use of oral roflumilast was reviewed in a single-centre prospective study.¹⁹ While weight loss was not the intent of this treatment, it is a common side effect of roflumilast and likely contributed to the improvement in HS scores. The weight loss observed was quite striking and far greater than the semaglutide study described above over a shorter follow-up period (median <4 months). Sixteen patients with HS with insufficient response to topical therapy and oral antibiotics were treated with oral roflumilast at a dose of 500 mcg once daily. They achieved a median weight loss of 9 kg and a corresponding median DLQI

Results

Proportion of patients 6 to 11 years with lower stature at baseline, showing a ≥ 5 -percentile improvement in height following 16 Weeks treatment with dupilumab



*P < 0.05 vs placebo BL, baseline; DUPI, dupilumab; PBO; placebo

Figure 2. Dupilumab vs placebo and growth

Legend: Liberty-AD PEDS phase 3 trial of dupilumab 300mg subcutaneous every 4 weeks vs placebo among patients aged 6-11 years with severe atopic dermatitis with lower stature at baseline. Over 16 weeks of observation, the percentage of patients achieving at least a 5 percentile increase in growth was consistently and statistically significantly higher in the dupilumab group. This was observed across all baseline height percentiles.

Source: Irvine 2024²

License: none

improvement of 12 points. While these studies with different populations and study designs are not directly comparable, the data suggest that both semaglutide and oral roflumilast may be considered as weight loss agents in HS, with greater potential weight loss with roflumilast.

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Practical Tips for Treating Pediatric Dermatology Patients

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The purpose of this paper is to provide strategies to help deliver quality care that meets the unique needs of children and their families in a dermatology outpatient clinic setting. The tools highlighted are simple and fast to implement in a dermatologic office setting. Five separate tips are presented herein.

Tip 1: Dispensing 2 supplies for children living in multiple homes

Many children that we treat live in more than one primary home. Often this means that the family must remember to shuttle treatments back and forth between the homes with the child. This becomes a barrier to proper care, as the family or child could easily forget to bring the treatment to the other home, causing lapses in treatment, and contributing to uncontrolled skin disease. A simple solution is to dispense sufficient medication so that the child has all the necessary treatments at each home, thereby removing the need to shuttle medications between locations. This approach is especially well suited for topical treatments. For example, when treating a child with atopic dermatitis who lives in 2 primary homes, it is beneficial to dispense 2 sets of topical medications—one for flare treatment and one for maintenance

treatment—at each home simultaneously. This helps to streamline things for the family involved as well.

Tip 2: Cryotherapy simplified with an otoscope speculum

The use of otoscope specula for cryotherapy is not new. In her paper, Fern (2004)¹ described a clinical technique where a disposable otoscope speculum was used to focus the spray from the liquid nitrogen canister onto the target skin lesion. In this manner, the disposable otoscope speculum is placed directly on the target lesion and acts to shield the surrounding skin from the liquid nitrogen spray.

This technique is advantageous when using cryotherapy to treat children as well. Verruca vulgaris and molluscum contagiosum are benign cutaneous viruses that commonly infect children. A child may develop a verruca on the eyebrow, the vermilion border of the lip, or in the naris. If active intervention is desired, one option is cryotherapy. Using an otoscope speculum to direct the spray in these situations allows for trickier locations to be treated, as it shields the surrounding skin and structures. Furthermore, children are moving targets and cannot be relied upon to remain still during treatment with cryotherapy. The addition of the otoscope speculum provides a direct touch point

between the young patient and the healthcare provider, as the healthcare provider holds the speculum directly on the patient's skin lesion. This allows the provider's hand to stabilize the speculum and react and move in response to the child's movements. The cryotherapy spray from the liquid nitrogen canister is directed into the otoscope speculum, which channels the spray onto the target lesion (**Figure 1**).

Tip 3: Procedural distraction

Dermatological procedures, such as skin biopsies, are frequently accompanied by a degree of pain; for example, pain associated with the infiltration of local anesthesia. These procedures can be challenging in children and adolescents, but at times they are necessary. Procedural sedation may not be possible or desired in an outpatient setting. The process of overwhelming the senses can help distract the child from the pain of a needle poke in this situation. The goal of overwhelming the senses is to provide abundant sensory stimuli so that the brain does not focus on the pinch or pain from the infiltrating local anesthetic. Examples of potential options to achieve this include listening to music, watching a video, holding a hand or a stuffed animal, singing, or eating a special treat such as a lollipop or popsicle. Ideally several stimuli should be employed simultaneously.

All children are different, and it is important to mention that this quantity of sensory stimulation would not be appropriate for all children. Also, these techniques for overwhelming the senses and distraction should not replace other strategies to minimize the pain of local anesthesia infiltration, (i.e., such as selecting a smaller needle diameter, slow speed of infiltration, etc.)

Tip 4: Table salt for the treatment of pyogenic granulomas

Pyogenic granulomas are benign acquired vascular neoplasms that can be problematic because of their tendency to grow quickly and bleed. The standard of care for treatment is surgical removal. This allows for histopathologic confirmation of the diagnosis, and distinction from malignant neoplasms.

Sometimes, non-surgical treatment options are desired. Effective non-surgical treatment of pyogenic granulomas with topical beta-blockers, such as topical timolol applied twice daily, is well documented. Topical imiquimod is another option, however, the resulting inflammatory reaction limits its clinical application.²

Recently, table salt has been investigated as a therapeutic option for pyogenic granulomas. Daruwalla et al.³ described the use of topical table salt for this purpose (**Figure 2**). In their study, soft paraffin was used to create a well around the target pyogenic granuloma, and topical table salt was placed within the well. This was then secured with tape. This process was repeated daily. Their study of 50 patients included 15 pediatric patients. The results indicated a decrease in bleeding by day 3.7 (mean). They achieved 100% resolution of pyogenic granulomas after a mean of 14.7 days, with a single recurrence of pyogenic granuloma reported 11 months later. Adverse events included difficulty with the application site, mild burning if the pyogenic granuloma was eroded, and surrounding eczema.

Table salt has also been demonstrated as an effective treatment for umbilical granulomas in infants.⁴ In a study of 17 infants, table salt was applied to a cleaned area with a wet toothpick in the clinic. The treated area was secured with surgical adhesive

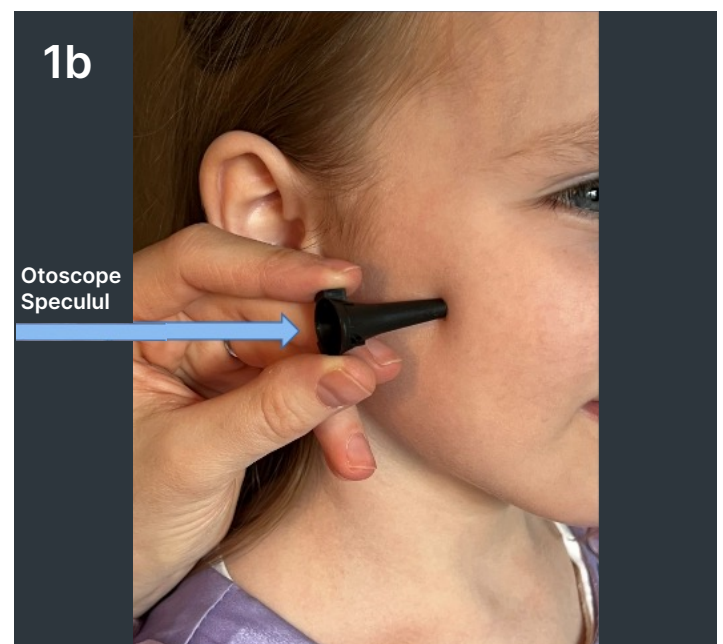
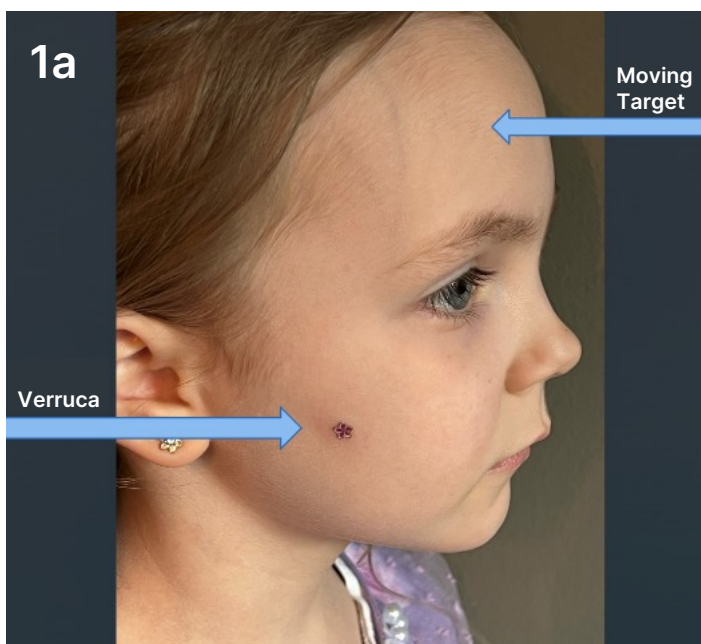




Figure 1 A-C: Using cryotherapy with an otoscope speculum; *courtesy of Genvieve Gavigan, MD.*

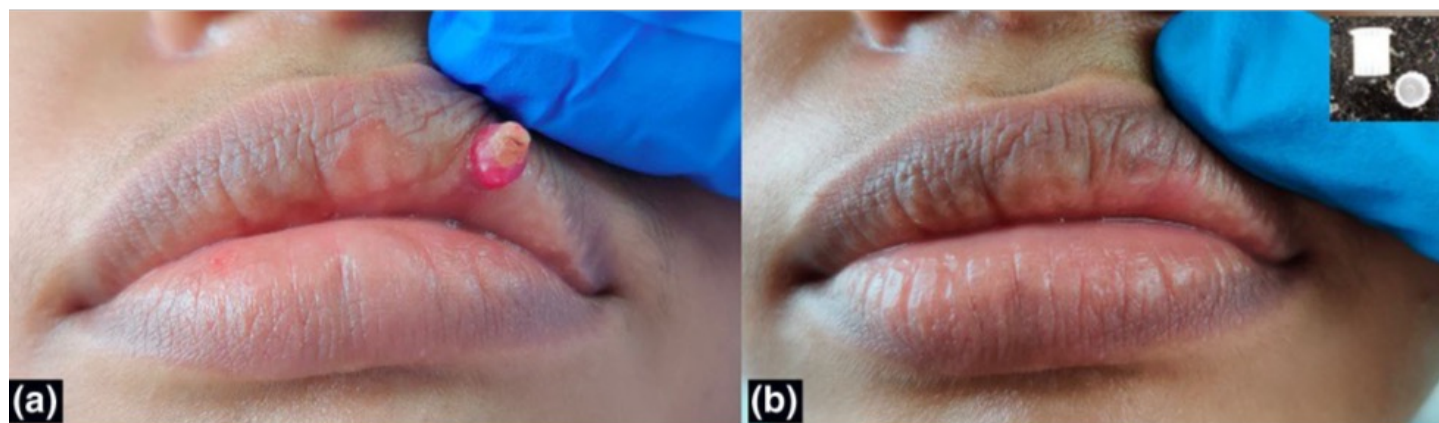


Figure 2 A-B: The use of common salt for the treatment pyogenic granuloma; *from Daruwalla et al., 2021*

tape. After 24 hours, all 17 infants showed complete resolution of their umbilical granulomas.

The mechanism of action by which salt treats pyogenic granuloma and umbilical granuloma is through the creation of a hyperosmolar environment, which desiccates and shrinks the pyogenic granuloma or umbilical granuloma.^{3,4}

Tip 5: Tools to learn how to swallow pills

Learning to swallow medication pills is a life skill. Yet, it can be scary and difficult to master for many children. Dr. Bonnie Kaplan has created an online learning program, based on her research to assist children and their families to learn this problematic skill. Her video, "How to Swallow Pills by Dr. Bonnie Kaplan", is available in YouTube. In it, she outlines a stepwise method that can be practiced at home. At first, children practise swallowing water while positioning their heads in 5 different ways (head turned to the left, head turned

to the right, head looking up, head looking down, and head looking straight ahead). Next, the same 5 head positions are used when swallowing a small hard candy. It is recommended to spend 30 minutes to learn the technique and to practice for 14 days (about 5 minutes each day) to achieve the skill of swallowing pills. This video also describes possible pitfalls and additional methods to help remedy them.⁵

In conclusion, five practical and easy-to-implement tips were reviewed. Taken together, these tips may ameliorate the tolerability of cryotherapy and skin biopsies in children, providing real-world strategies for treating dermatologic conditions and prescribing medications to children.

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