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REVIEW ARTICLE

# Perioral dermatitis: Diagnosis, proposed etiologies, and management

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## Abstract

**Background and Aims:** Perioral dermatitis is a common cutaneous condition characterized by acneiform facial eruptions often with an eczematous appearance. A granulomatous subtype exists in addition to the classic variant. While topical corticosteroids have been largely implicated in this condition, its etiology is not completely understood..

**Methods:** Using the keywords "corticosteroids," "dermatology," "fusobacteria," "perioral dermatitis," and "periorificial dermatitis," we searched the databases PubMed, MEDLINE, and EMBASE to find the relevant literature. Only articles in English were chosen. The level of evidence was evaluated and selected according to the highest level working our way downwards using the Oxford Centre of Evidence-Based Medicine 2011 guidance.

**Results:** This systematic review found the strongest evidence to support topical corticosteroid misuse as the principal causative factor in the pathogenesis of perioral dermatitis.

**Conclusion:** In terms of treatment, further research is required to robustly investigate promising treatment options including tetracyclines, topical metronidazole, topical azelaic acid, adapalene gel, and oral isotretinoin.

KEYWORDS
corticosteroids, demodex, fusobacteria, maskne, perioral dermatitis

## 1 | BACKGROUND

Perioral dermatitis (POD, also referred to as periorificial dermatitis) is an inflammatory and chronic papulopustular and vesicular dermatitis often affecting children and middle-aged females.[1] Topical or systemic treatment is often used, in addition to identifying the likely cause.[1] The granulomatous form of POD is a more typical presentation in those of African-American ethnicity.[2] In terms of etiology, most dermatologists are aware of its association with corticosteroid use, but less is known about other associations such as infective causes, certain cosmetic products, disruptive skin barrier, dental fillings, and toothpaste reactions. In terms of treatment, options range from topical, systemic or conservative, depending on cause, severity, and patient's choice.[3] In this systematic review, we explore the diagnosis of POD, possible etiologies, and treatment options.

## 2 | METHODS

Using the keywords "corticosteroids," "dermatology," "fusobacteria," "perioral dermatitis," and "periorificial dermatitis," we searched the databases PubMed, MEDLINE, and EMBASE and identified pertinent English language only literature. Our review was conducted in January 2021, and the time period of evidence was collected from the inception of these databases till January 1, 2021. We appraised the level of evidence, utilizing the Oxford Centre of Evidence-Based

  

Medicine 2011 protocol, and assessed the evidence based on its strength from systematic reviews and meta-analyses at the top of the hierarchy to case reports at the bottom.

## 3 | PRESENTATION

POD manifests as pruritic or tender erythematous papules typically in the perioral (sparing of the vermillion) and periorbital areas with occasional genital involvement.[4-6] Perioral involvement is the commonest presentation; hence, the initial term of pod although periorificial dermatitis is a more accurate reflection of the anatomic distribution.[3] Granulomatous periorificial dermatitis (previously named facial afro-caribbean childhood eruption) is another variant characterized by yellow papules, found mainly in children following corticosteroid use.[5] Burning and pain and less commonly pruritus are often present in both variants.[3]

## 4 | DIFFERENTIAL DIAGNOSES

Acne vulgaris, steroid-exacerbated rosacea, and lupus miliaris disseminatus faciei may present in a similar distribution to POD and should be excluded.[4,7] Rosacea usually has a centrofacial distribution with absence of comedones and in some cases rhinophyma or ocular symptoms; the latter which are unusual in POD.[8] Acne vulgaris presents with comedones, papules, pustules, nodules, and cysts which are not typical of POD.[8] In lupus miliaris disseminatus faciei, red-brown papules and nodules and occasionally atrophic small scars are present with spontaneous regression possible.[8]

## 5 | GRADING AND INVESTIGATIONS

The severity of lesions is graded using the POD severity index (PODSI) which takes erythema, papules, and scaling severity into account.[3] The vast majority of patients are diagnosed clinically, but skin biopsies (containing at least one papule) should be considered in unusual presentations or lack of response to treatment.[5]

## 6 | HISTOPATHOLOGY

Histopathology often reveals an eczematous reaction with spongiosis and lymphocytic exocytosis, edema, and sparse lymphocytic perivascular infiltration.[1,8]

Hair follicles tend to be edematous with a perifollicular inflammatory infiltrate, and in severe cases, follicular abscesses might be observed. Late papular lesions might reveal connective tissue hypertrophy with hyperplasia of sebaceous follicles. In the dermis, discrete epithelioid cell granulomas of the non-caseating type with perifollicular predominance and sparse Langerhans giant cells might be observed. Caseating granulomas typify the granulomatous subtype of POD.[8]

## 7 | GRANULOMATOUS PERIORIFICAL DERMATITIS

Granulomatous POD is a facial eruption occurring predominantly in pre-pubertal children in the perinasal, perioral, and periocular regions.[9] Lesions tend to be skin-colored or yellow-brown with mild scaling and possible localized erythema. extra-facial lesions including the trunk, extremities, and genitalia have been reported. Epidermal spongiosis, upper dermal granuloma, and perifollicular granuloma surrounded by lymphocytes are the classical histological features.[9]

## 8 | ETIOLOGY

### 8.1 | Corticosteroids

Topical, nasal, inhaled, and oral corticosteroids have been reportedly associated with POD, with the exact pathophysiology not fully understood, with chronic use precipitating more severe presentation (Table 1).[10] POD is often successfully treated initially by topical steroids, although relapse occurs with withdrawal of corticosteroids, leading to long-term reliance and rebound.[11] Topical steroids might alter the microflora of hair follicles, creating a microflora imbalance, contributing to the widely recognized symptoms of POD.[5]

#### 8.1.1 | Topical corticosteroids

In a cross-sectional observational study, 85 280 patients in a dermatology department were evaluated for adverse effects of topical corticosteroids. A total of 370 patients reported adverse effects, of whom 2.7% reported POD as a side effect.[12] In a separate study ($n$ = 200), 75 patients with POD and 125 controls were assessed for their cosmetic and previous topical corticosteroid usage ($p < 0.05$).[13] 25% of patients used topical corticosteroids which were started when the eruption first appeared.[13] In Hogan et al's study, 80 patients with POD were compared with 117 patients with rosacea. 85% of patients with POD and 38% of those with rosacea had used topical corticosteroids previously.[14]

#### 8.1.2 | Oral corticosteroids

Four case reports investigated the association of oral corticosteroids and POD.[15-18] Corticosteroid use following renal transplant was found to trigger POD in patients in one study.[19] In a separate report, a 37-year-old woman with myasthenia gravis treated with oral prednisone at a dose of 100 mg daily in addition to pyridostigmine was diagnosed with POD after three weeks of treatment.[20] Young and colleagues presented two patients who developed childhood granulomatous periorificial dermatitis following growth hormone therapy for short stature which resolved upon discontinuation.[21]

**TABLE 1** Corticosteroids and perioral dermatitis

| Study authors | Study type | Study year | Patient number | Findings | Level of evidence |
|---|---|---|---|---|---|
| Topical corticosteroids | | | | | |
| Meena S, Gupta LK, Khare AK, et al[12] | Cross-sectional observational study | 2017 | 85 280 | A total of 370 patients reported adverse effects, and 2.70% reported perioral dermatitis as a side effect | 3 |
| Dirschka T, Weber K, Tronnier H[13] | Case control | 2004 | 200 | 25.3% of perioral dermatitis patients used topical corticosteroids which were started when the rash first appeared. The patient group had a significantly greater history of atopy (49.3% vs. 15.2%), prick test reactivity (49.3% vs. 8.0%), and specific IgE against aeroallergens (CAP SX1 classes ≥ 2: 50.7% vs. 15.2%) | 4 |
| Hogan DJ, Epstein JD, Lane PR[14] | Retrospective case series | 1986 | 197 | 85% of patients with perioral dermatitis and 38% of those with rosacea had used topical corticosteroids. Those with perioral dermatitis were significantly younger and had a significantly shorter mean duration of eruption before presenting compared with those with rosacea ($p < 0.001$) | 4 |
| Oral corticosteroids | | | | | |
| Garrido PMC, Borges-Costa J[19] | Retrospective cross-sectional study | 2017 | 197 | Patients with renal transplant were investigated for reasons for referral to dermatology over six years. 0.5% of patients were referred to dermatology due to perioral dermatitis | 4 |
| Goss JM, Nord KM, Olarte MR, Grossman ME[20] | Case report | 2007 | 1 | A 37-year-old woman with myasthenia gravis who was treated with oral prednisone and pyridostigmine. She presented with an asymptomatic eruption of 1–2 mm erythematous papules around her mouth and chin. The patient declined treatment waiting for disease resolution as her dose was tapered | 4 |
| Young JY, Na JI[21] | Case report | 2020 | 2 | Patient one developed childhood granulomatous periorificial dermatitis 18 months following growth hormone (GH) therapy for short stature. Patient two also had the same condition after growth hormone therapy. Lesions did not resolve until cessation of growth hormone therapy | 4 |
| Inhaled corticosteroids | | | | | |
| Dubus JC, Marguet C, Deschildre A[15] | Prospective cross-sectional cohort study | 2001 | 639 | Asthmatic children treated with beclomethasone diproprionate or budesonide inhalers were investigated for side effects. 2.9% of children experienced perioral dermatitis, and this was associated with nebulization and younger age | 3 |
| Peralta L, Morais P[16] | Case report | 2011 | 2 | Two patients with allergic rhinitis who developed perioral dermatitis after treatment with intranasal steroid spray | 4 |

### 8.1.3 | Inhaled corticosteroids

Case reports have reported the link between inhaled corticosteroids and POD.[15,16] Dubus and colleagues investigated asthmatic children treated with beclomethasone diproprionate or budesonide inhalers for side effects.[15] 3% of children experienced POD, and this was associated with nebulization and younger age ($n = 639$). Peralta and colleagues reported two patients with allergic rhinitis who developed POD following treatment with intranasal steroid spray.[16]

Overall, steroid misuse appears likely to have associations with development of POD, with most evidence finding that topical corticosteroids pose the greatest risk. Clinicians and dermatologists must be aware of this risk and prescribe and advise their patients accordingly.

## 9 | INFECTION

Some researchers have posited infectious sources as a cause of POD such as fusobacteria, [17,18,22,23] *Demodex folliculorum* mites,[24] and *Candida albicans*[25] (Table 2).

### 9.1 | Bacteria

The role of fusobacteria in POD was investigated by Berardi and colleagues using toluidine blue staining.[17] Fusobacteria were found in 81% of patients ($n$ = 70) with POD compared with 5% of a cohort with different facial conditions ($n$ = 271).[17]

In a separate study, the profiles of intrafollicular microorganisms were compared in the lesions of perioral, seborrheic dermatitis and control subjects.[18] Tape stripping samples were obtained from eight POD patients, ten seborrheic dermatitis patients, and 31 controls. In the patients with POD and in two control subjects, 20%–70% of their scrapings contained fusobacteria samples. Several normal subjects had hair follicles containing fusobaceria-positive hairs, and the authors suggest that it might not be pathogenic for all hosts.[18] In a separate study, three patients with POD were treated with cefcapene pivoxil hydrochloride hydrate 100–300 mg/day.[22] Patients showed improvement after one to two weeks and were markedly improved, or their disease was resolved after two to five weeks, with no side effects of treatment. All patients were positive for fusobacteria before treatment but were negative afterward.[22] While further studies are needed with larger control groups, nevertheless there are signals that point toward a possible association between fusobacteria and POD.

### 9.2 | Parasitic

The association between *Demodex folliculorum* and POD was investigated in a study.[23] Biopsies from skin in the chin were taken in 82 patients with POD and in 70 control subjects.[23] Patients who had had prior treatment with topical steroids had a significantly higher density of *Demodex folliculorum* mites than patients who had not received previous topical steroid therapy ($p < 0.001$). Mite density increased significantly with duration of treatment with topical steroids ($p < 0.001$).[23] These findings might suggest a complex multifactorial pathogenesis with both corticosteroids and *Demodex folliculorum* playing a role in etiopathogenesis of POD.

### 9.3 | Yeast

In a case report, a 32-year-old woman had POD with *Candida albicans* found in her skin scrapings. The dermatitis cleared with anti-candidal treatment.[24] The evidence supporting any infectious pathogenesis in POD is limited to mainly case series and reports. The role of fusobacteria in POD warrants further investigation, as well as the impact of topical corticosteroids on the presence of *Demodex folliculorum* mites in POD.

**TABLE 2** Infection and perioral dermatitis

| Study authors | Study type | Study year | Patient number | Findings | Level of evidence |
|---|---|---|---|---|---|
| Fusobacteria | | | | | |
| Berardi P, Benvenuti S, Genga A, Cecchini F[17] | Case series | 1994 | 340 | Fusobacteria were found in 81% of the 70 patients with perioral dermatitis compared with 5% of the 271 with different facial conditions | 4 |
| Takiwaki H, Tsuda H, Arase S, Takeichi H[18] | Case control | 2003 | 49 | In all patients with perioral dermatitis and in two control subjects, 20%–70% contained fusobacteria samples. | 4 |
| Ishiguro N, Maeda A, Suzuki K, Yamana Y, Fukuya Y, Kawashima M[22] | Case series | 2013 | 3 | All patients were positive for fusobacteria before treatment but were negative after treatment with cefcapene pivoxil hydrochloride hydrate 100–300 mg/day in all patients | 4 |
| *Demodex Folliculorum* | | | | | |
| Dolenc-Voljc M, Pohar M, Lunder T[23] | Prospective case control | 2005 | 152 | Patients who had had prior treatment with topical steroids had a significantly higher density of *Demodex folliculorum* mites than patients who had not received previous topical steroid therapy ($p < 0.001$) | 3 |
| *Candida Albicans* | | | | | |
| Bradford LG, Montes LF[24] | Case report | 1972 | 1 | A 32-year-old woman had perioral dermatitis with *candida albicans* found in skin scraping examination. The dermatitis cleared with anti-candidal treatment | 4 |

## 10 | COSMETICS, MOISTURIZERS, AND SUNSCREENS

The association of cosmetic, moisturizers, and sunscreens with POD was investigated (Table 3).[25,26] A total of 133 patients with POD obtained from dermatologists' records were compared with 99 controls. Using foundation, moisturizer and (unspecified) night cream combinations was found to carry a 13-fold increased risk for POD (OR = 13.5; $p < 0.001$). Moisturizer and foundation combination use was associated with a lower but significant increased risk (OR = 2.9; $p = 0.017$). Moisturizer used alone was not associated with an increased risk of POD, possibly due to fewer occlusive layers being applied.[25] The authors speculate that this pathogenesis was related to an occlusive mechanism with a possible cumulative effect.[25] Cosmetic preparations might affect POD possibly due to their occlusive properties, and greater understanding of this pathogenesis is required.[25] Future studies should investigate the weight of the emollient or cosmetic causing POD, and researchers must exclude the possibility of irritant dermatitis from makeup and cosmetic products.

## 11 | SKIN BARRIER DYSFUNCTION AND ALLERGY

The relationship between skin barrier dysfunction, allergy, and POD was investigated (Table 3).[26] A total of 40 patients with POD were evaluated and compared with control patients ($n = 102$). Transepidermal water loss was measured in three areas of the face which was significantly increased ($p < 0.001$) in all areas of the face in POD patients compared to the control group. The patient group had greater values in terms of history and clinical signs of atopic diathesis, prick test reactivity, and specific IgE aeroallergens such as CAP SX1.[26]

Patients with POD are thought to be "hyper-reactive" with impaired skin barriers especially in the perioral area, which may be explained by thin permeable stratum corneum and an imbalance of intercellular lipids, predisposing susceptible individuals to internal and external irritants that can cause the symptoms associated with POD.[26]

Skin barrier dysfunction has particular relevance in the COVID-19 era in which the widespread use of face masks and personal protective equipment have led to the phenomenon of maske acne or "maskne."[27] It is unclear, however, whether POD is being misdiagnosed as "maskne," with POD possibly caused by irritation from face masks.

## 12 | TREATMENT

In terms of treatment of POD, an individual approach should be taken, based on severity, age, the presence of additional symptoms, and concomitant conditions. In terms of a general approach to treatment, topical corticosteroids should be discontinued, and potential contact allergens should be considered, identified, and avoided where practical. Topical treatments might be used such as calcineurin inhibitors, topical antibiotics, and topical antiparasitics. Systemic treatment such as antibiotics might be used in more severe cases.

In mild steroid-induced disease, conservative therapy with discontinuation and barrier repair moisturizers might be all that is needed.[3] In moderate disease (according to PODSI score), treatments such as topical metronidazole, erythromycin, and pimecrolimus are recommended. In severe disease, oral tetracycline is prescribed.[6] Systemic isotretinoin could be contemplated as a treatment option for recalcitrant cases (Table 4).[6]

Our review yielded three randomized controlled trials investigating various treatment options for POD.[28-30] In Schwarz and colleague's study, 124 patients with POD were treated twice daily with pimecrolimus cream 1% or vehicle until resolution for up to 4 weeks.[28] Patients treated with pimecrolimus had an average POD severity index score (PODSI) of 2.6 versus 3.5 for those treated with a vehicle treatment (both groups had a baseline score of 5.2). Patients who had a previous history of topical corticosteroid use benefitted most, and patients treated with pimecrolimus reported a greater improvement in dermatology quality of life index (DLQI).[28]

**TABLE 3** Cosmetics, moisturizers, sunscreens, dental fillings, toothpaste, and skin barrier dysfunction and perioral dermatitis

| Study authors | Study type | Study year | Patient number | Findings | Level of evidence |
|---|---|---|---|---|---|
| Cosmetics and sunscreen | | | | | |
| Malik R, Quirk CJ[25] | Case control | 2000 | 232 | Foundation, moisturizer, and night cream were found to carry a 13-fold increased risk for perioral dermatitis (OR = 13.5; p < 0.001) | 4 |
| Skin barrier dysfunction | | | | | |
| Dirschka T, Szliska C, Jackowski J, Tronnier H[26] | Case control | 2003 | 102 | Transepidermal water loss was significantly increased ($p < 0.001$) in all areas of the face in the patient rather than the control group. The patient group had greater values in terms of history and clinical signs of atopic diathesis, prick test reactivity, and specific IgE aeroallergens such as CAP SX1 | 4 |

**TABLE 4** Treatment options for perioral dermatitis.

| Study authors | Study type | Study year | Patient number | Findings | Level of evidence |
|---|---|---|---|---|---|
| Schwarz T, Kreiselmaier I, Bieber T, et al[28] | Randomized vehicle-controlled study | 2008 | 124 | Patients with perioral dermatitis were treated twice daily with pimecrolimus cream 1% or vehicle until resolution for up to four weeks. Patients treated with pimecrolimus had an average perioral dermatitis severity index score of 2.6 versus 3.5 for those treated with a vehicle treatment | 2 |
| Bribeche MR, Fedotov VP, Jillella A, Gladichev VV, Pukhalskaya DM[29] | Randomized vehicle-controlled pilot study | 2014 | 46 | The PODSI was significantly lower in the praziquantel 3% group than in the vehicle group. The mean investigator's global assessment score was significantly greater in the praziquantel group ($p < 0.001$) | 2 |
| Oppel T, Pavicic T, Kamann S, Bräutigam M, Wollenberg A[30] | Randomized, double-blind, vehicle-controlled study | 2007 | 40 | Patients with perioral dermatitis were randomized to receive either pimecrolimus cream 1% or vehicle cream. The PODSI was significantly lower in the pimecrolimus group compared with the vehicle group ($p = 0.005–0.02$) during treatment, but this was not significant at follow-up. At week two, there was a 50% improvement in PODSI in the pimecrolimus group versus 25% in the vehicle ($p = 0.095$) | 2 |
| Ollech A, Yousif R, Kruse L, et al[31] | Retrospective case series | 2020 | 132 | A complete response was found in 68.8% of patients with topical calcineurin inhibitor monotherapy, in 75% of patients taking combinations of topical calcneurin inhibitors and metronidazole, and in 77.8% of patients taking topical calcineurin inhibitors and a systemic antibiotic | 4 |
| Ehmann L, Reinholz M, Maier T, Lang M, Wollenberg A[32] | Open-label clinical trial | 2014 | 51 | Patients who had used the toleriane fluide had a significant improvement in the perioral dermatitis severity index questionnaire over time and subjective complaints such as disease burden, itching, skin distension, and appearance improved with treatment | 3 |
| Liu ZH, Du XH[33] | Prospective open-label clinical trial | 2008 | 50 | Patients were treated with doxycycline 10 mg twice daily and indomethacin 25 mg twice daily for 4 weeks. The steroid dermatitis clinical score decreased significantly from baseline (15.06 ± 4.61 at baseline to 4.52 ± 3.39 at week 6; $p < 0.001$) | 3 |
| Srour J, Bengel J, Linden T, et al[34] | Open, unblinded clinical trial | 2020 | 48 | A skin cream with 4-t-butylcyclohexanol was applied in perioral dermatitis patients for eight weeks. The PODSI decreased significantly over eight weeks (4.71 ± 1.37 to 1.42 ± 1.36; $p < 0.0001$) | 3 |
| Richey DF, Hopson B[35] | Comparative split face | 2006 | 21 | One side of face treated four times weekly with aminolevulinic acid photodynamic therapy (ALA-PDT; 30 min) while the other side was treated with topical clindamycin. 92.1% of the ALA-PDT group had a statistically significant difference in mean clearance of lesions compared with 80.9% clindamycin group ($p = 0.0227$) | 3 |
| Goel NS, Burkhart CN, Morrell DS[36] | Retrospective case series | 2015 | 222 | Treatment of children with perioral dermatitis typically involved combinations of topical metronidazole or sodium sulfacetamide lotion. 71.8% had complete cessation of perioral dermatitis. | 4 |
| Nguyen V, Eichenfield LF[37] | Retrospective chart review | 2006 | 79 | Metronidazole, oral erythromycin, and combination therapy were best for treating primary lesions and secondary presentations such as erythema, scaling, lichenification, telangiectasia, hypopigmentation, or hyperpigmentation versus other therapies or no therapy at all | 4 |

(Continues)

TABLE 4 (Continued)

| Study authors | Study type | Study year | Patient number | Findings | Level of evidence |
|---|---|---|---|---|---|
| Noguera-Morel L, Gerlero P, Torrelo A, Hernandez-Martín A[38] | Retrospective case series | 2016 | 15 | Seven patients with perioral dermatitis treated with either a single dose of 200–250 μg/kg oral ivermectin or a compound (three patients) of 1% ivermectin in oil-in-water base cream daily for three months (four patients). Complete or almost complete clearance was realized in all patients treated with both treatment regimes | 4 |
| Boeck K, Abeck D, Werfel S, Ring J[40] | Case series | 1997 | 7 | Seven children with perioral dermatitis were treated with topical metronidazole 1% for 2 weeks and then 2% metronidazole following this. Six of the children had used topical corticosteroids before first presentation. All children had resolution of lesions after three to six months, and this was maintained after 2 years | 4 |
| Rosso JQ[41] | Case reports | 2006 | 2 | A 22-year-old and 42-year-old both with idiopathic perioral dermatitis were treated with ceramide-based gentle cleanser and physiological lipid moisturizer and oral doxycycline 40 mg once daily. After one month of treatment, there was marked reduction of inflammation, pruritus, and no more scaling or erythema with no treatment side effects | 4 |
| Milagre AC, Almeida AP, Rezende HD, Almeida LM, Peçanha MA[42] | Case report | 2018 | 1 | A 9-year-old female with granulomatous perioral dermatitis. Treatment with azithromycin 320 mg/day for 5 days led to resolution of the disease | 4 |
| Hatanaka M, Kanekura T[43] | Case report | 2006 | 1 | An 11-year-old boy with a one-year history of facial papular eruptions presented with multiple monomorphic papules around his mouth, nose, and eyes. He was treated with 0.1% tacrolimus and oral erythromycin (800 mg/day) resulting in flattening of the papules and marked improvement after six weeks | 4 |
| Lucas CR, Korman NJ, Gilliam AC[44] | Case report | 2009 | 1 | A 13-year-old presented with granulomatous periorificial dermatitis. He was treated with erythromycin 400 mg four times daily for six weeks with pimecrolimus 1% cream for his pruritus | 4 |
| von Csiky-Sessoms S[45] | Case report | 2019 | 1 | A 42-year-old with granulomatous periorificial dermatitis diagnosed on biopsy was successfully treated with intralesional triamcinolone (0.2 ml of 5.0 mg/ml with a total dose of 1 mg of triamcinolone) | 4 |

The use of pimecrolimus for POD was investigated by Oppel and colleagues.[30] A total of 40 patients with POD were randomized to receive either pimecrolimus cream 1% or vehicle cream. At week two, there was a 50% improvement in PODSI in the pimecrolimus group versus 25% in the vehicle ($p = 0.095$). DLQI was improved in the pimecrolimus more than in the vehicle group.[30]

In a retrospective case series, a complete response was found in 69% of patients with topical calcineurin inhibitor monotherapy, in 75% of patients taking combinations of topical calcineurin inhibitors and metronidazole, and in 77.8% of patients taking topical calcineurin inhibitors and a systemic antibiotic.[31] Nevertheless, the pimecrolimus studies show that the main value of pimecrolimus is to reduce the PODSI score quickly in the first one to two weeks of therapy, compared with placebo.[28-30] It seems to work only in those who have previously misused topical steroids, with no difference in efficacy in those with no prior topical steroid use. This could be better interpreted as the ability of pimecrolimus, via its anti-inflammatory effect, to reduce the risk of corticosteroid misuse by patients, during the initial symptom flare-up phase of topical steroid withdrawal. The follow-up of the two treatment groups in Schwarz et al's study[28] reveals that at 8 weeks there was no difference between the pimecrolimus arm and the vehicle arm. This implies that the "intervention" of using pimecrolimus is most likely exerting its effect by the withdrawal of previous topical steroid use rather than any primary effect of pimecrolimus on POD.

In a separate study, the efficacy and tolerability of praziquantel 3% ointment used for 4 weeks of treatment as a monotherapy was investigated in 46 patients with POD.[29] The PODSI was significantly lower in the praziquantel group than in the vehicle group. The mean investigator's global assessment score was significantly greater in the praziquantel group ($p < 0.001$). The treatment group had a greater improvement in DLQI, and no treatment adverse events were reported in either group.[29] Treating patients with praziquantel led to a decrease in chitinase 3-like 1 (CH3L1) protein secreted by inflammatory cells. Increased serum levels of CH3L1 have been reported in other inflammatory conditions, and therefore, praziquantel is thought to have target inflammatory aspects of POD patients.[29] This trial was only single-blinded, and as for pimecrolimus, at eight weeks, there was no difference between the praziquantel and vehicle groups with PODSI = 1.1 at week eight in the treatment group and 1.2 in the placebo group ($p > 0.01$). This indicates that withdrawal of all topical applications, including steroids and cosmetics, could be the main mediator of therapeutic effect, with some quicker improvement in the treatment group.

Four open-label clinical trials ($n = 170$) found benefits with Toleriane Fluide® twice daily for eight weeks (L'Oreal Germany, Dusseldorf, Germany).[32] Benefits were also found with doxycycline 10 mg twice daily and indomethacin 25 mg twice a day for four weeks,[33] skin cream containing 4-t-butylcyclohexanol twice daily for eight weeks,[34] and aminolevulinic acid photodynamic therapy four times a week for six months.[35] There were decreases in the PODSI and DLQI and improvements in patient satisfaction with these treatments.

The final studies were case reports and therefore were of lesser quality evidence and reported various therapeutic options for POD. Treatments reported include combinations of topical metronidazole and sodium sulfacetamide lotion,[36] or oral erythromycin,[37] or a single dose of 200–250 μg/kg oral ivermectin,[38] or 20% azelaic acid.[39]

Topical metronidazole 1% monotherapy treatment was reported as an efficacious treatment option with minimal reported side effects.[40] Doxycycline in doses of 40–100 mg has been used with marked responses and no reported side effects.[41] In separate case reports, oral clarithromycin (250 mg/day),[7] azithromycin 320 mg/day for 5 days,[42] and combination of oral erythromycin 800 mg/day and 0.1% tacrolimus[43] or pimecrolimus 1%[44] markedly improved lesion appearances. Intralesional triamcinolone (0.2 ml of 5.0 mg/ml) successfully treated one patient's lesions.[45] A case report presented a patient successfully treated with oral isotretinoin (10–20 mg daily).[9]

Treatments were mainly presented in case reports, and studies are of poor quality with low levels of evidence and small numbers of patients.

Pimecrolimus seems to work only in those who have previously misused topical steroids, with no difference in efficacy found in those with no history of prior topical steroid use. Only a single randomized controlled trial from Ukraine supported the use of praziquantel 3% ointment, a largely unavailable and rarely used therapy.[29] Topical metronidazole, erythromycin, oral tetracycline, and systemic isotretinoin require further investigation with large blinded randomized controlled studies. This might prove difficult given the fact that conservative approach with moisturizers and discontinuation of corticosteroids might result in resolution of POD.[28-30]

## 13 | CONCLUSION

POD has been associated with several etiologies, namely, misuse of topical or inhaled corticosteroids, infection with fusobacteria, in response to cosmetics, dental fillings or toothpaste, and possibly due to skin barrier dysfunction. This systematic review identified the urgent requirement to find stronger evidence to support the treatment of this condition with randomized controlled trials. Further research is required to fully elucidate the pathogenesis of POD. This could allow for the development of better treatment guidelines and hence patient outcomes.

### CONFLICTS OF INTEREST

None declared.

### CONSENT FOR PUBLICATION

All authors have approved this final submitted version of the manuscript and consent to its submission for consideration of publication.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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