

Treatment of Inverse/Intertriginous Psoriasis: Updated Guidelines from the Medical Board of the National Psoriasis Foundation

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ABSTRACT

Inverse or intertriginous psoriasis commonly involves skin fold areas including the axillae, perianal skin, intergluteal cleft, inframammary, genital/inguinal, abdominal, and retroauricular folds. After reviewing the literature for new treatments, a task force was convened to update a consensus on inverse psoriasis therapy. Short-term treatment continues to be low-potency topical steroids. In order to avoid steroid-induced adverse effects, long-term therapy includes topical immunomodulators, calcitriol, and calcipotriene. Second and third-line therapies include antimicrobials, emollients, and tar-based products. Inverse psoriasis resistant to topical therapy has been shown to respond to botulinum toxin injections, excimer laser therapy, and certain systemic agents (such as anti-TNF and anti-IL12/IL23 therapy). Based on promising results from case reports and prior clinical experience, these systemic agents should be strongly considered in inverse psoriasis resistant to topical therapy. However, they need further evidence-based evaluaion. The use of randomized trials and objective severity indices may allow for more robust therapeutic data.

J Drugs Dermatol. 2017;16(8):760-766.

INTRODUCTION

Patients with psoriasis commonly have involvement of the skin fold areas referred to as intertriginous, flexural, or inverse psoriasis. These areas are typically marked by less epidermal keratinization and include the axillae, perianal skin, antecubital fossae, popliteal fossae, intergluteal cleft, inframammary, genital/inguinal, abdominal, and retroauricular folds.[1] According to the Nurses Health Study and Health Professionals Follow-up Study, the frequency of inverse psoriasis among physician-diagnosed psoriasis is 24%.[2] The skin lesions are characterized by shiny, well-demarcated, erythematous plaques with little scaling.[1] Interestingly, inverse psoriasis has been found more commonly in obese individuals and is associated with increased risk for psoriatic arthritis or nail involvement[1,3]; in addition, intertriginous psoriasis occurs in infants and young children, with 4% suffering from localized psoriatic diaper rash.[4] Erythema is also increased in inverse psoriasis due to inflammation and secondary changes from friction, perspiration, and maceration. Stemming from these secondary changes, inverse psoriasis can be diagnostically challenging when also considering candidal intertrigo, tinea infection, irritant, or allergic contact dermatitis.

Although overlap exists between inverse and genital psoriasis, inverse psoriasis is a distinct entity with a similar high burden of disease; in fact, 38% of patients with genital psoriasis did not have flexural skin involvement, characteristic of inverse psoriasis.[5] With respect to genital psoriasis, reported symptoms include itch (86%), pain (44%), burning (49%), dyspareunia (45%), and worsening lesions after intercourse (34%); these symptoms lead to impairments in sexual function and frequency accompanied by fear of sexual relations.[6] In one study, 45.8% of patients did not discuss their genital psoriasis with their physician, indicating low awareness of this condition among physicians.[7] In comparison, the impact of inverse psoriasis has been analyzed with the Inverse Psoriasis Burden of Disease tool; this scoring system identified notable symptoms including negative body image, pain, fissuring, skin maceration, and embarrassment.[8] The tool also demonstrates the greatest impairments in daily activities such as clothing choice and toileting or personal hygiene.[8]

Historically, the primary treatment for inverse psoriasis included low-potency topical steroids.[9] However, there is concern about side effects including atrophy, ulceration, striae, and telangiectasia especially in areas with little epidermal hyperplasia. Therefore, there is an advantage to topical nonsteroidal, systemic, or phototherapy for extensive disease resistant to topicals. New studies have attempted to demonstrate the efficacy of these treatments. This report will summarize these findings while providing an updated consensus on inverse psoriasis therapy.

METHODOLOGY

The literature was reviewed for new reports on inverse psoriasis since the last National Psoriasis Foundation consensus by HK.[10] Articles were obtained from Medline using the following MeSH terms: "psoriasis and skin diseases," "genital diseases, male or female," "anus diseases," "buttocks," "inverse," "flexural," and "intertriginous." 14,054 total articles resulted from this search, and 34 articles were reviewed. Articles were chosen based on documentation of new treatments, modifications or improvements to current management, and/or further trials conducted on current medications for inverse psoriasis. Evidence levels were graded according to guidelines by Shekelle P.G., et al.[11] IA includes evidence from meta-analyses of randomized controlled trials; IB includes randomized controlled trials; IIA includes controlled studies without randomization; IIB includes quasi-experimental study; III includes non-experimental descriptive studies such as comparative studies, correlation studies, and case-control studies; and level IV includes expert committee reports or clinical experience of respected authorities. Importantly, the amount of literature was limited, and study quality varied widely.

Evidence

1. The short-term therapy for inverse psoriasis continues to be low to mid-potency topical steroids (Table 1).

2. The recommended long term therapy is preferably tacrolimus or pimecrolimus over calcitriol or calcipotriene (calcipotriol) as listed in Table 2. Based on a study by Ortonne et al, calcitriol is suggested over calcipotriene for flexural psoriasis treatment.[14]

3. Based on anecdotal evidence and case reports listed in Table 4, the use of antimicrobial agents is considered second-line therapy. Antimicrobial therapy can include topical imidazoles; based on clinical experience, antiprotozoal agents such as iodoquinol and combinations with topical steroids have also proven effective in inverse psoriasis.

4. Other recommended second line therapies includes emollients and tar-based products. One case report demonstrated improvement of intertriginous psoriasis with coal tar 2% foam.[28] This is thought to be due to the suppression of keratinocyte differentiation along with anti-inflammatory effects.[28] The use of these agents combined with a low-potency topical steroid may be effective for inverse psoriasis.

5. Treatment modalities that can be used in inverse psoriasis resistant to topical therapy include excimer therapy.[29] As listed in Table 5, case reports have documented improvement in intertriginous psoriasis after therapy with excimer light and tacrolimus.[29] Unfortunately, few studies have evaluated the safety of excimer therapy with drawbacks including the cost and limited availability.[30]

6. Studies listed in Table 6 have evaluated treatment with botulinum toxin type-A. Potential mechanisms include a reduction in perspiration and inhibition of proalgogenic substance release.[31]

7. Other systemic treatments should be strongly considered in inverse psoriasis that is resistant to conventional therapy, involves a large surface area, and/or has a high impact on quality of life based on patient report. Such treatments include methotrexate, anti-TNF inhibitors, anti-IL12/IL23 inhibitors, oral PDE4 inhibitors, and newer anti-IL17 therapy; of the biologic therapies, adalimumab and ustekinumab have shown to be effective in case reports as listed in Table 7. However, etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, and apremilast have been approved for psoriasis therapy and can be considered in inverse psoriasis resistant to topical therapy.[33] With respect to these agents, the consensus committee has noted a strong response based on clinical experience.

FIGURE 1. Treatment algorithm for inverse psoriasis.

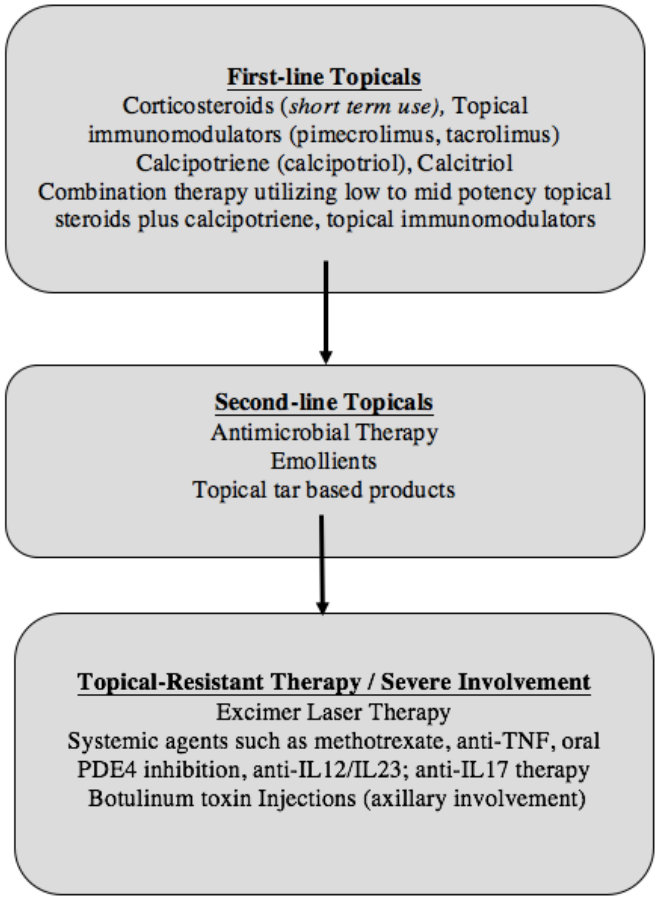

TABLE 1.

Evidence for Corticosteroid Treatment

Paper authors	Evidence Type	Study Type	Outcome	Side Effects
Kreuter A, et al[12]	IB	Double blind placebo controlled 1:1:1:1 ratio, 80 patients QD for 4 weeks	Betamethasone valerate 86%/Calcipotriol 62%/ Pimecrolimus 40%/Placebo 21% improvement in modified PASI (P<0.05 for betamethasone vs pimecrolimus)	None reported
Lebwohl MG, et al[13]	IIB	Open label, 20 patients with facial and intertriginous involvement. Fluticasone BID for 2 weeks followed by QD on 2 consecutive days for 8 more weeks.	>50% improvement after 2 weeks in all patients based on physician global evaluation (P=0.106)	None reported

TABLE 2.

Evidence for Treatment With Topical Immunomodulators

Paper authors	Evidence Type	Study Type	Outcome	Side Effects
Kreuter A, et al[12]	IB	Double blind placebo controlled 1:1:1:1 ratio, 80 patients QD for 4 weeks	Betamethasone valerate 86%/ Calcipotriol 62%/Pimecrolimus 40%/Placebo 21% improvement in modified PASI. (P<0.05 for betamethasone vs pimecrolimus)	Pimecrolimus - 5/20 with transient itching and burning
Lebwohl M, et al[15]	IB	Double blind placebo controlled 2:1 ratio, 167 patients treated BID for 8 weeks	Tacrolimus 65% vs placebo 32% clear or almost clear using static severity score (P<0.0001)	No difference between groups
Gribetz C, et al[16]	IIB	Double blind placebo controlled 1:1 ratio, 57 patiens treated BID for 8 weeks	Pimecrolimus 71% vs placebo 21% clear or almost clear using investigator's global assessment (P<0.001)	No difference between groups
Liao YH, et al[17]	IIB	Double blind, parallel 1:1 ratio, 50 patients with facial or genitofemoral psoriasis treated BID for 6 weeks	Tacrolimus 60% vs calcitriol 33% complete or almost complete clearance using phsyician global assessment (P<0.05)	Calcitriol 50% vs tacrolimus 16% perilesional erythema at 4 weeks (P=0.02)
Freeman AK, et al[18]	IIB	Open label, 21 patients treated with tacrolimus BID for 8 weeks	17/21 complete response using physician global assessment (P-value not reported)	2/21 mild itching
Ezquerra GM, et al[19]	IIB	Open label, 15 patients treated with tacrolimus BID for 2 months	Improvement of 12 to 2.2 using modified PASI (P-value not reported)	None reported
Brune A, et al[20]	IIB	Open label, 11 patients treated with tacrolimus BID for 6 months	11/11 had clear response at 30 days (P<0.0001)	1/11 had mild itching
Rallis E, et al[21]	IIB	Open label, 6 patients with psoriasis on glans and 1 with scrotal involvement treated with tacrolimus BID for 10 days	All had improvement at 7 days with 15 recurrences (P-value not reported)	None reported
Bissonnette R, et al[22]	IIB	Open label, 12 patients with genital psoriasis treated with tacrolimus BID for 8 weeks	15.8 to 1.2 improvement in modified male genital PASI at week 8 (P<0.001)	Mild pruritus or burning
Steele JA, et al[23]	III	Retrospective review of tacrolimus BID in 13 patients for 2 weeks	12 had 100% clearance (P-value not reported)	1/13 with burning and irritation

TABLE 3.

Evidence for Treatment With Calcipotriene and Calcitriol				
Paper authors	**Evidence Type**	**Study Type**	**Outcome**	**Side Effects**
Kreuter A, et al[12]	IB	Double blind placebo controlled 1:1:1:1 ratio, 80 patients QD for 4 weeks	Betamethasone valerate 86%/ Calcipotriol 62%/Pimecrolimus 40%/Placebo 21% improvement in modified PASI. (P<0.05 for betamethasone vs pimecrolimus)	Calcipotriol - 2/20 with transient increase in warm, erythema, and irritation
Ortonne JP, et al[14]	IIB	Randomized, investigator-blinded, 30 patients with flexural disease applying calcitriol and calcipotriol to the right or left side BID for 6 weeks	Calcitriol led to 67% improvement in global assessment vs 33% on calcipotriol (P<0.02)	Global assessment showed 80% excellent tolerability with calcitriol vs 57% with calciptriol
Keinbaum S, et al[24]	IIB	Open label, 12 patients BID for 6 weeks	10/12 with improvement in modified PASI (P=0.002)	Minimal irritation
Duweb GA, et al[25]	IIB	Open label, 11 patients BID for 6 weeks	10/11 complete response in physician global assessment (P-value not reported)	None reported

TABLE 4.

Evidence for Treatment With Antimicrobial Therapy				
Paper authors	**Evidence Type**	**Study Type**	**Outcome**	**Side Effects**
Flytstrom I, et al[26]	IV	Bacterial fungal cultures in 32 psoriatic patients with no topical treatment in intertriginous areas, 13 psoriatic patients treated with topical steroids in intertriginous areas, and 19 patients with no psoriasis	Untreated psoriatic patients were colonized by S. aureus more often than the control group. (P<0.005) Candida was not found.	-
Hughes J, et al[27]	IV	Anecdotal	-	-

TABLE 5.

Evidence of Treatment With Excimer Therapy				
Paper authors	**Evidence Type**	**Study Type**	**Outcome**	**Side Effects**
Carrascosa JM, et al[29]	IV	Case report, 308 nm excimer light treatment for 22 sessions with subsequent tacrolimus for 2 weeks	90% improvement with addition of tacrolimus, mild relapse observed 1 month after treatment	Intense pain with mild eyrthema and hyperpigmentation with dose of 950 mJ/cm^2
Mafong EA, et al[30]	IV	Case report, 308 nm excimer light treatment 2 times per week.	Complete clearance after 3 weeks. Remission of 6 months.	Mild sensation of warmth

TABLE 6.

Evidence of Treatment With Botulinum Toxin Type-A				
Paper authors	**Evidence Type**	**Study Type**	**Outcome**	**Side Effects**
Zanchi M, et al[31]	IIB	Open label, botox treatment with total dosage of 50-100 U	Subjective improvement in 13/15 according to 10-point visual scale (P-value not reported)	None reported
Saber M, et al[32]	IV	Case report, 100 U botox injection	Improvement of psoriasis in axillae	None reported

TABLE 7.

Evidence of Treatment With Adalimumab and Ustekinumab				
Paper authors	**Evidence Type**	**Study Type**	**Outcome**	**Side Effects**
Ješe R, et al[34]	IV	Case report, adalimumab	Almost complete regression	None reported
Campos MA. et al[35]	IV	Case report, ustekinumab	Significant improvement in pruritus, erythematous lesions	None reported

DISCUSSION

In accordance with the prior National Psoriasis Foundation review, the recommended short-term (2-4 weeks) therapy for acute exacerbations of inverse psoriasis continues to be low to mid-potency topical steroids.[10] Based on a double-blind, placebo-controlled study comparing betamethasone to calcipotriene and pimecrolimus, topical steroids have proven more effective for inverse psoriasis.[12] However, topical steroids should be used with caution to minimize tachyphylaxis or such adverse effects as atrophy, telangiectasia, and striae. Thus, the frequency of steroid application should be slowly discontinued if possible. After 2-4 weeks, options for continued therapy include less potent topical steroids such as fluticasone or other first-line agents like calcitriol, calcipotriene, pimecrolimus, or tacrolimus. These agents can be used in combination with low-potency topical steroid one or two times per week for maintenance dosing.[13] Proper dispensing and patient education can also decrease the incidence of adverse events.

Long-term topical therapy for inverse psoriasis can include tacrolimus, pimecrolimus, calcitriol, or calcipotriene to avoid local steroidal effects. The efficacy of these medications has been documented in open prospective, randomized, and blinded studies.[12,14-25] Among these studies, one randomized, double-blinded study has shown both greater efficacy and fewer side effects with tacrolimus compared to calcitriol, suggesting its preferred use in inverse psoriasis.[17] Furthermore, a randomized, investigator-blinded, left-right comparison demonstrated greater efficacy and tolerability with calcitriol over calcipotriene.[14] With the use of these first-line medications, the patient should be educated regarding such adverse effects as perilesional erythema and edema, but these problems have generally been transient and minor. When these symptoms are persistent, one can use topical steroids for a short time; in the long-term, the patient should be transitioned back to a topical immunomodulator or calcitriol.

Second-line therapy for inverse psoriasis includes emollients, tar-based products, and antimicrobial therapy.[9,26,28,36] The evidence for these therapies is anecdotal or based on case reports. In general, emollients are not associated with adverse effects and have been beneficial in plaque psoriasis, suggesting its use in milder skin fold involvement. Tar-based products are used less frequently due to the potential for irritation; however, the case report documenting improvement with coal tar 2% foam may favor this vehicle of administration.[28] Additional methods of reducing irritation may include dilution or combination with topical steroids.

One aspect of inverse psoriasis treatment includes the possible role of microorganisms. In fact, there is data to suggest that cutaneous and streptococcal throat infections can cause inflammation and flares of psoriasis;[37-39] although recent reports on the lack of Candida in intertriginous areas seem to refute this.[26,40] The idea of microbial-induced inflammation, however, is further supported by a report demonstrating decreased $CD161^{+}$ cells in the dermis of inverse psoriasis patients possibly linked to microbial overgrowth.[41] Indeed, if there is increased bacterial colonization in skin-fold areas, culture, especially in children with recurrent secondary infections, and antimicrobial therapy could be beneficial. Such agents as topical imidazoles, ciclpriox, and naftifine may be optimal options due to the spectrum of both antibacterial and antifungal activities.[42] Using topical imidazoles or antifungal agents alone or in combination with a low-potency topical steroid may be effective in treating inverse psoriasis by reducing microbial colonization and inflammation. Anecdotally, certain antiprotozoal agents such as iodoquinol and combination preparations with hydrocortisone have also been effective in inverse psoriasis.

Of the inverse psoriasis subtypes, perianal psoriasis deserves additional comment. The secondary irritation and propensity to develop a lichen simplex-type reaction may lead to a Koebner reaction with worsening psoriasis and pruritus. In order to break this cycle, proper hygiene, topical therapy, and loose-fitting clothes are indicated.[43] When concerned about perianal psoriasis, one should also contemplate an unrelated or concurrent allergic contact dermatitis to agents such as wipes, which may cause chronic dermatitis at this site.

With inverse psoriasis resistant to topical therapy, one may consider botulinum toxin treatment which has shown efficacy in one case report and an open label trial; this form of treatment is theorized to work through the reduction of inflammatory neuropeptides and perspiration in intertriginous areas.[31,32] Also, excimer laser therapy has been shown to be effective in case reports with minimal side effects.[29,30]

Lastly, systemic agents such as methotrexate, anti-TNF, anti-IL12/IL23 inhibitors, oral PDE4 inhibitors, and anti-IL17 can be considered. While these therapies have been evaluated for plaque psoriasis, their use in inverse psoriasis has not been well-studied. Our literature review revealed two case reports demonstrating efficacious treatment with adalimumab and ustekinumab.[34,35] Further randomized control studies need to evaluate the efficacy and safety of biologics for inverse psoriasis. However, based on clinical experience, these agents have shown significant efficacy and should be strongly considered in patients suffering from severe, topical-resistant inverse psoriasis.

As mentioned previously, this review is limited by the lack of clinical trials in inverse psoriasis. For example, the number of patients in these studies is small and there are few meta-analyses or randomized, controlled trials. The authors of this report hope that future studies will add to the limited body of knowledge. In these future clinical studies, it is important to use a psoriasis severity index inclusive of inverse and genital psoriasis along with patient-reported outcomes. The Comprehensive Assessment of the Psoriasis Patient is one such index that takes into account non-plaque phenotypes and incorporates patient-derived, patient-reported outcomes.[44] The use of this index could possibly allow for more robust drug development.

CONCLUSION

The primary treatment for inverse psoriasis continues to be low-potency topical steroids for short periods (less than 2-4 weeks).[10] However, in order to avoid steroid side-effects with long-term treatment, topical therapies such as tacrolimus, pimecrolimus, calcitriol, or calcipotriene should be considered. Second and third-line therapies such as antimicrobial therapy, emollients, and tar-based products have been used anecdotally. Severe involvement that is resistant to topical therapy can be treated with botox injections, excimer laser therapy, or systemic agents; despite anecdotal evidence demonstrating the strong clinical efficacy of biologic treatment, we currently have limited knowledge on the effects of biologics on intertriginous or genital psoriasis. With randomized controlled trials and incorporation of objective severity indices inclusive of non-plaque phenotypes, we hope further treatment assessment can be performed.

DISCLOSURES

Dr Siegel is employed by the National Psoriasis Foundation. The Foundation receives unrestricted financial support from AbbVie, Inc, Amgen, Inc, Celgene Corporation, Eli Lilly and Co, Janssen Biotech, Inc, LEO Pharma Inc, Novartis Pharmaceuticals, and Pfizer, Inc.

Dr. Van Voorhees has served as a consultant and/or investigator for the following companies including: AbbVie, Amgen, Aqua, Astra Zeneca, Celgene, Corrona, Dermira, Jannsen, Leo, Lilly, Merck, Pfizer, and Valeant. Dr. Merola has served as a consultant, speaker, board of director member, advisory board member, and/or investigator for the following companies including: AbbVie, Amgen, Biogen IDEC, Boehringer Ingelheim, Jannsen, Leo, Eli Lilly, Merck, Mollinckrodt, Novartis, Pfizer, and UCB. Hasan Khosravi has no conflict of interests to declare.

This work was funded by the National Psoriasis Foundation, Portland, OR.

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