Pitted Keratolysis

A Clinical Review

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Background: Pitted keratolysis is a bacterial infection that affects the plantar epidermis. Despite the condition being reported in many countries affecting both shod and unshod populations, there is little guidance for clinicians providing evidence or best practice guidelines on the management of this often stubborn infection.

Methods: Using a structured search of a range of databases, papers were identified that reported treatments tested on patients with the condition.

Results: Most of the literature uncovered was generally of a low level, such as case-based reporting or small case series. Studies were focused mainly on the use of topical antibiotic agents, such as clindamycin, erythromycin, fusidic acid, and mupirocin, often in combination with other measures, such as hygiene advice and the use of antiperspirants. From the limited evidence available, the use of topical antibiotic agents shows some efficacy in the treatment of pitted keratolysis. However, there is currently no suggestion that oral antibiotic drug therapy alone is effective in managing the condition.

Conclusions: Currently, there is no consensus on the most effective approach to managing pitted keratolysis, but a combination of antimicrobial agents and adjunctive measures, such as antiperspirants, seems to demonstrate the most effective approach from the current literature available. (J Am Podiatr Med Assoc 104(2): 177-182, 2014)

Pitted keratolysis (PK) (also known as keratoma plantare sulcatum, keratolysis sulcata, ringed keratolysis, and keratolysis plantare sulcatum) is a descriptive title for a common superficial bacterial infection of the plantar stratum corneum.[1] The infection is characterized by malodor and discrete 1- to 7-mm craterlike pits on pressure-bearing areas[2] that collectively appear as erosions,[3,4] usually along with hyperhidrosis, bromhidrosis, and maceration.[1,4,5]

In this condition, the stratum corneum of the sole becomes infected by a gram-positive organism, usually attributed to *Corynebacterium* species,[6] *Kytococcus sedentarius*,[3,7,8] and *Dermatophilus congolensis*.[9,10] Under suitable conditions of a warm and moist environment,[6] all of these bacteria share a common ability to proliferate and produce keratin-degrading (keratolytic) enzymes that enable them to dissolve the stratum corneum, resulting in tunnel-like pits.[8,10-12]

Pitted keratolysis is a condition that occurs worldwide and that can be seen in both temperate and tropical environments.[3] Although PK is more common in barefooted populations living in tropical regions, Takama et al[4] observed that the clinical manifestations of PK are evident in temperate regions as well, where occlusive footwear is considered to be a cause, associated with poor foot hygiene and maceration.[6]

In temperate and tropical regions, the determinants of the manifestation of PK can be attributed to warmth, humidity (including hyperhidrosis), and the infection of PK-associated bacteria.[13] These aggravating factors are reflected in the published prevalence data, with PK affecting 42.5% of paddy field workers,[14] 23% of coal miners,[15] 13% of athletes,[16] and 2.5% of the general New Zealand adult population.[9] Despite PK being a widespread bacterial skin condition, there is currently no consensus regarding its clinical management. The aim of this paper was to undertake a systematic review of the literature focusing on the clinical management of the condition.

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Methods

An electronic database search was undertaken using OVID (MEDLINE 1946–2012, AMED 1985–2012, and EMBASE 1974–2012). The search was performed by both authors, independently, with the refined keywords *pitted keratolysis* or *keratoma plantare sulcatum* or *keratolysis sulcata* or *ringed keratolysis* or *keratolysis plantare sulcatum*.

After the removal of duplicates, the initial search yielded 97 publications, of which 65 were specific to PK. These papers were reviewed manually, and those that were selected as eligible included a discussion about treatment. The search resulted in 13 papers eligible for inclusion in this review (Table 1). A systematic review or a meta-analysis was initially considered. However, owing to the study types and limited data, this was not possible. Accordingly, a structured review of evidence was undertaken.

Results

Despite PK being a worldwide foot condition, a paucity of literature was noted from the search spanning 66 years. A review of the 13 papers revealed no randomized controlled trials. Papers were predominantly low-level evidence, such as anecdotes, case reports, small case series, and a few uncontrolled, comparative studies. The largest study consisted of 44 participants,[2] with most studies having sample sizes of one to ten participants. The reporting of outcomes in two papers[25,26] was considered of poor quality, ie, based on anecdotes; therefore, these papers were excluded from this review.

In the remaining 11 publications, interventions for PK could be classified as simple remedies, over-the-counter preparations, prescription-only medications, and advanced (or experimental) therapies. A variety of studies used a combined approach in the treatment of the disease consisting of the management of provoking factors (such as hyperhidrosis) and the management of the existing infections.[20,21,23]

Kim et al[2] undertook the largest published study of 44 patients comparing topical benzoyl peroxide, 5%, topical antibiotic clindamycin phosphate, and combination therapy. The mean period to cure was 2.6 weeks, but there was no statistically significant difference in efficacy among the three treatment regimens. Two patients experienced local irritation from benzoyl peroxide, and another two from clindamycin phosphate. Colver[18] undertook a study of topical clindamycin in 15 individuals, using the patient's other foot as a control. Of these participants, 66% (n = 10) showed resolution attributable to the intervention versus 20% (n = 3) in the control group. Burkhart,[17] in a case series of three individuals using topical clindamycin, reported complete resolution within 4 weeks. Topical clindamycin was also used in combination with benzoyl peroxide and antiperspirants on four individuals.[23] After 2 months, complete resolution was noted, with no adverse effects.

Mupirocin is an antibiotic with activity against gram-positive organisms. Two papers[13,22] with a total of five participants report its effectiveness on PK within 2 weeks. One paper[19] reported the use of botulinum toxin in the treatment of two patients with PK and background hyperhidrosis. Both patients were clear within 30 days of treatment.

The use of oral antibiotic drugs in the management of PK was reported in two papers. In a study of ten patients,[21] each received an oral antibiotic (erythromycin or cephalexin) combined with a topical agent (mupirocin, 2%, or topical erythromycin). A good response to treatment was demonstrated in seven patients. Ertam et al[3] also reported a single case study combining oral erythromycin and topical fusidic acid, with the patient responding within 3 weeks of initiating treatment. The use of topical fusidic acid combined with an antiperspirant was also reported in a case.[20] Lesions were reported to be almost completely resolved after 2 weeks of therapy.

Discussion

The literature review identified a paucity of evidence for managing this often stubborn clinical condition. This could reflect the fact that PK may go unrecognized or may not be considered a serious enough infection to warrant substantial investment or investigation. However, there was a diversity of suggested treatment regimens, most relatively untested, reflecting the lack of evidence from clinical research. In this situation, a pragmatic approach would be to consider modifying the exacerbating factors (hygiene, hyperhidrosis, footwear, etc) and, second, treating the infection.

Exacerbating Factors

Bacteria thrive in an environment that is moist, occluded, and warm and are worsened by poor hygiene.[6] Hence, Lockwood et al[27] recommended some specific foot hygiene advice, including wash-

Table 1. Comparison of the Quality of the Evidence, the Interventions, and the Method of Study in the Publications Reviewed

Source, Year	Type of Evidence	Participants (No.)	Treatments Studied/Recommended	Method
Burkhart,[17] 1980	Case report (uncontrolled)	3	Clindamycin hydrochloride, 1%, solution (660 mg dissolved in 55 mL of 70% isopropyl alcohol and 5% propylene glycol)	Apply three times daily
Vazquez-Lopez and Perez-Oliva,[13] 1996	Case report (uncontrolled)	4	Mupirocine ointment	Unspecified
Colver,[18] 1997	Case series (controlled)	15	Clindamycin phosphate, 1%, in isopropyl alcohol and propylene glycol	Apply twice a day to the right sole for 4 weeks; if the right foot was clear at 4 weeks, the patient was asked to apply solution to both feet thereafter, but otherwise continue with the right foot only for a further 2 weeks; clinical assessment at 6 weeks
Tamura et al,[19] 2004	Case report (uncontrolled)	2	Botulinum toxin injection	Injected evenly throughout the plantar aspect
Ertam et al,[3] 2005	Case report (uncontrolled)	1	Combination therapy with oral erythromycin and topical fusidic acid	Unspecified
Khachemoune and Janjua,[20] 2005	Case report	1	Topical fusidic acid cream and aluminum chloride, 20%, solution (antiperspirant) and foot hygiene advice	Apply for 2 weeks
Kim et al,[2] 2005	Comparative study	17	Topical benzoyl peroxide	
		15	Topical clindamycin phosphate	
		12	Combination therapy with topical benzoyl peroxide and topical clindamycin phosphate	
Garcia Cuadros et al,[21] 2006	Case series	10	Oral erythromycin or cephalexyn plus topical mupirocin, 2%, or topical erythromycin; topical clotrimazole was also used for patients with coexisting fungal conditions	Patients were treated with erythromycin or cephalexin (500 mg three times a day) for 10–20 days; mupirocin, 2%, ointment or erythromycin, 4%, solution was also used, and in cases of coexisting fungal conditions, topical clotrimazole was used
Argomaniz and Castillo,[22] 2007	Case report	1	Mupirocin	Topical applications of mupirocin two times a day
Vlahovic et al,[23] 2009	Case reports (uncontrolled)	4	Clindamycin, 1%/benzoyl peroxide, 5%, aqueous gel and foot hygiene advice; aluminum hexahydrate solution given 1 month later	To be applied once per day; once-per-month follow-up; aluminum chloride hexahydrate solution (Drysol [Pearson & Covey Inc, CA]) given in the first follow-up, to be applied sparingly 3 times a week
Kaptanoglu et al,[24] 2012	Case series	9	Erythromycin, 4%, gel	"Patients were controlled weekly and topical treatments were discontinued until symptoms had completely disappeared. All patients reported strict adherence to treatment."[24(p14)]
		19	Erythromycin, 4%, gel + 10% salicylic acid cream + roxytromycine (300 mg/d)	
		13	Erythromycin, 4%, gel + 10% salicylic acid cream + roxytromycine (300 mg/d) + 0.01% potassium permanganate solution	

ing socks and shoes at higher than 60°C, using antibacterial washing solutions, ventilating occupational shoes, and reducing friction to avoid hyperkeratosis. Despite there being little evidence, notionally, environmental modification may help improve PK. Antiperspirants are usually preparations based on aluminum salts that when applied on the plantar surface are able to block the hyperactive sweat glands, thus achieving temporary anhidrosis. Although some publications have anecdotally recommended a particular antiperspirant, such as aluminum chloride hexahydrate, 20%,[5] or aluminum hydroxide, 20%, lotion,[27] it is likely that other antiperspirants (not deodorants) containing active ingredients based on the same pharmacologic principles will achieve comparable results.

Treatment of the Infection

For the management of PK, topical antiseptics could be proposed as the first-line intervention as they can usually be purchased as over-the-counter remedies or in pharmacies without a prescription or consultation from a physician.

Benzoyl peroxide has antibacterial and keratolytic properties and is effective against aerobic and anaerobic organisms.[28] In addition, the keratolytic properties of benzoyl peroxide also enhance its own skin penetration to achieve improved clinical outcomes.[29] In the study by Kim et al,[2] topical benzoyl peroxide therapy was found to have clinical efficacy comparable with topical clindamycin phosphate (antibiotic cream). In the same comparison study, benzoyl peroxide was also found to have efficacy comparable with combination therapy using topical benzoyl peroxide and clindamycin phosphate. All three therapies yield a mean period to cure of 2.6 weeks. The results suggest that some cases of PK may be managed through its use.

Topical Antibiotic Agents (Prescription-Only Medications)

Of all of the published papers, the use of topical antibiotic agents was the most investigated treatment. As a superficial bacterial infection, it is conceivable that PK should respond to this modality. Topical antibiotic agents studied included clindamycin[2,17,18] and mupirocin,[13,22] and some success was reported. Topical fusidic acid was also used in conjunction with oral erythromycin in one case report[3] and aluminium chloride, 20%, solution in another case report.[20] Complete resolution was reported in both reports.

Overall, topical clindamycin is generally preferred because it is more commonly available in pharmacies and is more affordable than mupirocin or fusidic acid. In comparing fusidic acid and mupirocin, fusidic acid is generally preferred. A study by Rennie[30] based on data collected in Canadian hospitals between 1999 and 2005 showed a significantly lower rate of methicillin-susceptible *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* resistance to fusidic acid compared with mupirocin. In fact, cases of methicillin-resistant *Staphylococcus aureus* resistance associated with mupirocin were already noted since the start of its clinical use.[31]

Oral Antibiotic Agents (Prescription-Only Medications)

There is currently no evidence supporting the use of systemic antibiotic drug monotherapy for the management of PK based on this review. Although the use of systemic antibiotic agents for a bacterial condition such as PK seems to be sound, in practice, drug delivery to the plantar epidermis may be clinically insignificant. In PK, resident bacteria live in the stratum corneum. Oral antibiotic drugs will be therapeutic only if they are able to reach this layer in an active form. The modes of drug delivery include 1) passive diffusion through the epidermis, 2) secretions from sebaceous glands, and 3) perspirations via eccrine sweat glands.[32]

In a study by Marples and Kligman[32] on the effects of oral antibiotic agents on microflora of non–palmar-plantar areas of human skin, holocrine excretions from sebaceous glands (sebum) were determined as the primary carrier of oral erythromycin, tetracyclines, and clindamycin to the skin surface. However, as an area devoid of sebaceous glands, drug delivery to the plantar surface may be limited.

Passive diffusion of systemic antibiotic drugs across the non–palmar-plantar epidermis is suggested to be unlikely given the highly impermeable layer of stratum corneum.[32] However, there is currently no known drug diffusion study of antibiotic agents across the plantar region. Structural studies of human epidermis[33] have found that the stratum corneum is four to nine times thicker on the soles than on other parts of the body. In addition, the palmar-plantar epidermis comprises an additional three to five layers of partially keratinized dead keratinocytes, known as the stratum lucidum.[33] Therefore, it can be suggested that drug delivery via passive diffusion through the plantar surface may

be even more unlikely. Drug diffusion data from acne studies cannot be extrapolated to the epidermis of the feet.[6] Overall, whether oral antibiotic agents achieve sufficient intracorneal inhibitory concentrations remains unclear.[6]

Advanced Therapies

In the study by Tamura et al,[19] subcutaneous injection of low-dose botulinum toxin into multiple sites in the plantar region to induce deliberate anhidrosis was practiced. Both patients in the study were previously unresponsive to topical and systemic antibiotic drug therapies. Complete anhidrosis and subsequent complete recovery of PK was achieved in both patients.

Given the high cost of botulinum toxin preparations, the expertise required to administer botulinum toxin therapy, and the pain associated with multiple subcutaneous injections, this therapy may be considered in cases unresponsive to more traditional therapies.

Combination Therapies

In some countries, the combination of benzoyl peroxide and clindamycin as a topical agent is also used as treatment for acne vulgaris. Individually, clindamycin has both bactericidal and bacteriostatic activity against a range of bacteria, including aerobic gram-positive cocci.[34,35] Similarly, benzoyl peroxide has antibacterial and keratolytic properties and is effective against aerobic and anaerobic organisms.[28] In combination, the therapeutic efficacy was found to be greater than their individual effect in the treatment of acne vulgaris.[36]

Vlahovic et al,[23] in a case report, experimented with the novel use of clindamycin, 1.2%, with benzoyl peroxide, 5%, aqueous gel (Duac; Stiefel Laboratories, Inc, Research Triangle Park, North Carolina) for the treatment of PK, along with general foot hygiene advice. At 1 month, all four patients experienced significant improvements in the lesions and in hyperhidrosis and malodor associated with PK. With the subsequent use of antiperspirant (aluminum hexahydrate solution), the symptoms completely resolved within 1 month. None of the four patients experienced adverse effects. Kim et al,[2] in a clinical comparative study of benzoyl peroxide and clindamycin phosphate, also demonstrated the effectiveness of the combination but found that the outcomes using the individual agents as monotherapy were not significantly different.

Simultaneous Use of Oral and Topical Antibiotic Agents

In the case report by Ertam et al,[3] the patient was directly treated with a combination of oral erythromycin and topical fusidic acid, with curative results within 3 weeks. However, the therapeutic outcome could have been attributed to the topical fusidic acid alone, and it is argued here that the study does not justify any therapeutic efficacy of oral erythromycin as independent monotherapy.

In a more recent study by Kaptanoglu et al,[24] 41 patients diagnosed as having PK were allocated to three parallel treatment groups: 1) erythromycin, 4%, gel only (a topical antibiotic drug); 2) erythromycin, 4%, gel, salicylic acid, 10%, cream, and roxythromycin (300 mg/d) (topical and oral antibiotic drugs); and 3) the addition of 0.01% potassium permanganate solution combined with the treatment in group 2. Patients were reviewed weekly, and a 1-year follow-up was performed. Despite the larger sample size, the study had vague reported outcomes, with a single general statement: "Treatment lasted between one and eight weeks (mean 19 days)." The report did not evaluate the outcome of the individual treatment groups and their comparative efficacies.

The overall clinical outcome was a mean period to cure of 19 days, equivalent to 2.7 weeks. Based on the data in Table 1, it is noted from the study by Kim et al[2] that the mean period to cure of PK using simple topical management strategies, such as topical benzoyl peroxide or topical clindamycin gel, was 2.6 weeks. By integrating the study outcomes of Kim et al[2] and Kaptanoglu et al,[24] there seems to be a clinical implication that the additional use of oral roxythromycin (300 mg/d), 10% salicylic acid cream, and 0.01% potassium permanganate did not contribute to enhanced clinical outcome in terms of the mean period required for complete clearance of PK.

Conclusions

A review of the evidence for the treatment of PK revealed little robust research in this area. Strategies such as drying preparations and antimicrobial agents were suggested, but little evidence exists to recommend any one particular treatment, although reports using antibiotic agents (such as topical clindamycin) seem to be successful based on the limited evidence available. No evidence was presented suggesting a role for oral antibiotic drug

monotherapy with this condition, which currently remains unresearched.

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