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## Occlusive Therapy in Atopic Dermatitis

Misha M. Heller<sup>1</sup>, Eric S. Lee<sup>2</sup>, Faranak Kamangar<sup>3</sup>,  
Wilson Liao<sup>4</sup> and John Y. M. Koo<sup>4</sup>

<sup>1</sup>*University of Southern California, Keck School of Medicine, Los Angeles, California*

<sup>2</sup>*University of Nebraska Medical Center, College of Medicine, Omaha, Nebraska*

<sup>3</sup>*University of California Davis, School of Medicine, Sacramento, California*

<sup>4</sup>*University of California San Francisco, Department of Dermatology  
San Francisco, California  
USA*

### 1. Introduction

The treatment of atopic dermatitis (AD) can be challenging for dermatologists and other healthcare professionals. Conventional treatments consisting of emollients and topical corticosteroids are often insufficient for severe and/or refractory AD. Other therapies include systemic corticosteroids, photochemotherapy using psoralen and ultraviolet-A light, and cyclosporine. However, all of these approaches have potentially serious side effects and relative contraindications, especially in children. Over the past two decades, occlusive therapy has been advocated as a safe and effective treatment modality for individuals with acute erythrodermic AD and those with severe and/or refractory AD. (Nicol 1987; Goodyear et al. 1991; Bridgman 1995; Devillers and Oranje 2005)

Occlusive therapy usually involves the application of emollients, antiseptics, or topical corticosteroids under either wet wrap dressings (WWD) or dry wrap dressings (DWD). This consists of moistened open-weave cotton tubular bandages (eg. Tubifast®, Tubigauz®) in WWD occlusion, versus dry gauze, plastic wraps, or hydrocolloid dressings (eg. Duoderm®) in DWD occlusion. (Nicol 1987; Goodyear et al. 1991; Bridgman 1995)

More recently, however, occlusion alone using a hydrogel patch has been utilized. The theory is that a major component in the pathophysiology of AD is barrier dysfunction. In fact, many current therapies target this barrier defect (i.e., pseudoceramide moisturizers and skin barrier emulsions). As such, an ideal repair mechanism would completely eliminate microbe and allergen penetration and transepidermal water loss in AD, both of which lead to xerosis, hypersensitivity, pruritus, and inflammation. The hydrogel patch, therefore, offers an innovative approach to *complete* barrier repair. (Park et al. 2011)

Regardless of the treatment approach, occlusive therapy offers many advantageous such as a cooling effect on inflamed skin, increased penetration of topical agents, enhanced skin hydration, and a barrier to external antigens and trauma (i.e. scratching). Reported disadvantages include the cumbersome and time-consuming nature of the application process, risk of allergic reaction to the occlusive material itself, and possible increased risk of infectious complications such as folliculitis, furunculosis, or cellulitis. An additional concern is that occlusion may cause skin maceration if used incorrectly, or can paradoxically

promote skin dryness if too little topicals are applied. (Nicol 1987; Goodyear et al. 1991; Bridgman 1995; Krakowski et al. 2008)

Occlusion alone of both normal and lesional eczematous skin can result in increased density of cutaneous microbial flora. (Aly et al. 1978; Rajka et al. 1981) Moreover, there is a positive association between *Staphylococcus aureus* (*S. aureus*) colonization and disease severity. (Williams 2000) These findings suggest that occlusion, by increasing the density of *S. aureus*, might push already colonized eczematous skin into the realm of clinical infection. In addition, innate production of cutaneous anti-microbial peptides, such as sphingosine and  $\beta$ -defensin, is depressed in patients with AD such that eczematous skin possesses decreased natural resistance to bacterial invasion (Arikawa et al. 2002; Ong et al. 2002) Thus, evidence of clinically apparent skin infection may be a contraindication to occlusive therapy, as it may exacerbate the infection. (Aly et al. 1978) However, the possibility that *S. aureus* colonization may complicate occlusive therapy has not been adequately addressed to date.

Another concern is that the use of topical corticosteroids under occlusion may relate to an increased potential for absorption and greater incidences of possible adverse effects. Most attention has been focused on the risk of skin atrophy and striae, hypothalamic-pituitary-adrenal (HPA) axis suppression, as well as growth impairment in children.

Ultimately, this chapter aims to examine current evidence on the safety and efficacy of occlusive therapy in the treatment of AD.

## 2. Methods

Studies on the use of occlusive therapy for the treatment of atopic dermatitis were identified in PubMed and Embase Medline databases from January 1966 to April 2011, using the key terms “occlusion,” “occlusive dressings,” “occlusive therapy,” “wet wrap,” “wet dressings,” “dry wrap,” “dry dressings,” “atopic dermatitis,” “dermatitis,” and “eczema.” Key terms were also searched in combination. Reference lists of relevant publications were manually searched for additional relevant studies. The search was limited to original studies and review articles published in English or with English abstracts, in humans. Studies of small size and those that did not use a controlled or randomized study design were included due to the dearth of published literature on this topic. Publications meeting these criteria were then reviewed for study design, population, disease severity or type, study size, efficacy, and safety. The topical agent used, dilution, and type and period of occlusive therapy were also noted, when such information was made available in the publication. In addition, response to therapy was seen as improvement in disease severity or symptoms from baseline, improvement in SCORing Atopic Dermatitis (SCORAD), and/or improvement in Eczema Area and Severity Index (EASI) score, depending on what information was provided. Of note, SCORAD is composite score of eczema severity based on the surface area involved, intensity of symptoms, and subjective symptoms such as sleep disturbance and pruritus. EASI is a 12-point scoring system of disease severity assessing erythema, induration, lichenification, pruritus, and excoriation. Finally, conclusions were drawn from the results of these studies bearing in mind standard clinical practice.

## 3. Studies on occlusive therapy

There are a total of 19 studies evaluating the use of occlusive therapy in AD (Table 1). Fourteen studies used WWD, 5 of which were randomized controlled trials. All WWD

Study Design	Disease Severity	Size (n)	Population (age)	Type of Occlusion	Treatment Regimen	
					Topical agents*	Frequency & Duration
Goodyear et al., 1991 (Prospective)	Acute erythrodermic eczema	30	Children (9 months – 16 years), inpatient	WWD	HCT 1% or 25% dilution betamethasone cream	Twice daily, x 2-5 days
Mallon et al., 1994 (Prospective)	Chronic severe eczema	21	Children, outpatient with nursing visits	WWD	HCT 0.5% or 10% dilution betamethasone 0.1% cream	Daily, x < 5 days
Abeck et al., 1999 (Prospective)	Acute exacerbated eczema	6	Adults, children	WWD	Chlorhexidine, emollients	Frequency not reported, x 3 days
Wolkerstorfer et al. 2000 (Prospective, left-right comparison study)	Severe AD	31	Children (5 months – 13 years), inpatient	WWD	10-50% dilution fluticasone propionate 0.05% cream	Daily, re-wet every 2 hours, x 1 week
Tang, 2000 (Prospective)	Flare of facial eczema	10	Children (4 - 15 years)	WWD	10% dilution mometasone furoate 0.1% cream or ointment	Daily for 2-3 hours, x “few days”
Pei et al., 2001 (RCT)	Moderate-to-severe AD	40	Children (1 - 15 years)	WWD	10% dilution of mometasone furoate 0.1% ointment or 10% dilution of fluticasone propionate 0.005% ointment	Topical applied once daily, x 4 weeks open application (control group), versus topical applied once daily, x 2 weeks open application and then 2 weeks using WWD (study group)
Schnopp et al., 2002 (RCT, left-right comparison study)	Exacerbated AD	20	Children (2 - 17 years), inpatients	WWD	Mometasone furoate 0.1%, or its vehicle	Twice daily, x 5 days
Devillers et al., 2002 (Retrospective, left-right comparison study)	Refractory AD	26	Adults (6 months – 10 years), children (18 – 61 years), inpatient	WWD	5% (on face), 10% and 25% (on body, adults), 5% and 10% (on body, children) dilution fluticasone propionate 0.05% cream	Daily, re-wet every 2-3 hours, x 1 week
McGowan et al., 2003 (Prospective)	Atopic eczema	8	Children (3 - 8years)	WWD	10% or 25% dilution beclomethasone dipropionate	Daily, x 2-18 weeks (median = 12 weeks)
Beattie and Lewis-Jones, 2004 (RCT)	Moderate AD (requiring HCT 1% or less potent)	19	Children (4 months - 3 years)	WWD	HCT 1%	Topical applied twice daily, x 2 weeks open application (control group), versus topical applied daily, with WWD applied twice daily for the 1 <sup>st</sup> week and then daily for the 2 <sup>nd</sup> week (study group)

Study Design	Disease Severity	Size (n)	Population (age)	Type of Occlusion	Treatment Regimen	
					Topical agents*	Frequency & Duration
Foelster-Holst et al., 2006 (RCT, left-right comparison study)	Severe AD	24	Adults (18-63 years), children (6-16 years)	WWD	Prednicarbat alone or prednicarbat under WWT	Not reported, x 48-72 hours
Hindley et al., 2006 (RCT)	Moderate-to-severe AD	50	Children (4-27 months)	WWD	HCT 1%	Topical applied twice daily, x 4 weeks (control group), versus topical applied daily with WWd for 24-hours for the 1 <sup>st</sup> week and then topical applied twice daily with WWd for 12- or 24- hours for 3 more weeks (study group)
Lee et al. (Prospective)	Severe AD	10	Adults (22 years)	WWD	0.9% saline solution	Daily (8 hours), x 7-14 days
Hon et al., 2007 (Prospective)	Moderate-to-severe AD	6	Children (3 - 15 years)	WWD	Mometasone furoate 0.1%	Overnight, x 3 days
Rajka et al., 1981 (Prospective)	Active AD	10	Adults, outpatient	DWD	None	Not reported, x 24 hours
Geraldez et al., 1989 (RCT)	Lichen simplex chronicus	60	Not reported	DWD	Diflucortolone valerate 0.3% ointment	Twice daily occlusion nightly, x 2 weeks
Volden et al., 1992 (Prospective)	Chronic, therapy-resistant AD	48	Adults	DWD	Clobetasol propionate lotion	Weekly, x 8-18 days
Gauger et al., 2003 (Prospective)	Generalized or localized AD	15	Adults, children (24.6 years), outpatient	DWD	Silver-coated textile	Daily, x1 week
Park et al, 2011 (Prospective)	Generalized or localized AD	15	Adults, outpatient	Hydrogel patch	Triamcinolone 0.1% cream	Hydrogel patch applied daily for 6-8 hours on one lesion, versus topical applied twice daily on another lesion, x 6 weeks

\*Dilution and concentration noted when provided in the article

Table 1. Studies on Occlusive Therapy (HCT = Hydrocortisone, RCT = randomized control trial)



occlusion studies demonstrated efficacy in severe or acute, moderate and chronic AD. Among the 4 studies examining DWD, only one used a randomized controlled design. All, except one, DWD studies demonstrated improvements in AD. There is also one study that used an impermeable hydrogel patch consisting of about 50% water content. The hydrogel patch alone demonstrated improvements in AD, comparable to that of corticosteroid use alone. Increased cutaneous bacterial counts or clinical infections were reported in 4 out of the 15 studies using WWD and all 4 studies using DWD.

### 3.1 Wet wrap dressings

The following is a detailed description of the 14 studies evaluating the efficacy of WWD in the treatment of AD (Table 2). Occlusive therapy was first introduced by Goodyear et al. in 1991. Goodyear et al. (1991) evaluated the inpatient use of WWD occlusion for acute erythrodermic eczema. This WWD technique involved the application of open-weave cotton tubular dressings (Tubegauz®) impregnated with hydrocortisone 1% cream (if child <2 years of age) or 10% dilution of betamethasone valerate (if child > 2 years of age) twice daily. All 30 children responded well to WWD occlusion, with no relapses noted at 2 weeks follow-up. Interestingly, an attempt at long-term home therapy using WWD, following the inpatient therapy, in 5 patients was unsuccessful due to reports of inconvenience, increased bacterial infections, and prolonged HPA axis suppression. (Goodyear 1991)

Mallon et al. (1994) studied the use of WWD in chronic severe eczema in 21 children. Eczema was managed using topical steroid creams (i.e. hydrocortisone 0.5% or 10% dilution betamethosone 0.1% cream) and emollients under WWD daily for less than 5 days. All patients responded well to WWD therapy. The treatment was also well-tolerated. Majority of parents (20/21) reported decreased use topical steroid per week following the introduction of WWD therapy. (Mallon et al. 1994)

Abeck et al. (1999) treated 6 patients (3 children and 3 adults) with acute exacerbated atopic eczema with basic emollients in combination with chlorhexidine-soaked dressings for 3 days. The study observed improvements in disease severity based on SCORAD score. Patients also reported decreased itch and sleep loss following WWD therapy. In addition, there was a reduction of *S. aureus* counts that paralleled skin improvement. (Abeck et al. 1999)

In a study of 31 children with severe refractory AD, Wolkerstorfer et al. (2000) investigated the efficacy of various corticosteroid dilutions under WWD occlusion. Participants were divided into 3 treatment groups. The first group consisted of 18 children, who were treated with 50% dilution of fluticasone propionate 0.05% (FP) cream under WWD for 2 weeks. In the second group, 5 children with symmetrically localized AD were treated with different dilutions (10%, 25% and 50%) of FP cream on the left and the right side of the body under WWD for one week and then 10% dilution of FP cream under WWD the following week. In the third group, 8 children were treated with 0% (i.e. only emollient), 5%, 10%, or 25% dilutions of FP cream applied to the entire body under WWD. After just one week of therapy, significant improvement in disease severity was observed, without noticeable differences between 5%, 10%, or 25% dilutions of FP cream under WWD. Less improvement was observed in the second week of therapy. In terms of skin infections, mild-to-moderate folliculitis was reported in a large proportion of the children, with 33% (6/18) children in the first group, 40% (2/5) children in the second group, and 63% (5/8) children in the third group. There was also one case of furunculosis in the third group. Interestingly, generalized folliculitis was noted in both of the children treated with only emollient during the first week. These findings suggests that although WWD occlusion may foster bacterial growth,

Study Design	Results		Adverse Events		
	Response to therapy	Additional Information	Infection	Skin Atrophy	Systemic
Goodyear et al., 1991 (Prospective)	All 90-100% clearance	Home maintenance WWD therapy was unsuccessful	N/A	N/A	Transient low morning cortisol levels
Mallon et al., 1994 (Prospective)	“All responded well”	20/21 parents reported using less topical steroids	None	N/A	N/A
Abeck et al., 1999 (Prospective)	Improved SCORAD	Decreased itch and sleep loss	Decreased <i>S. aureus</i> counts	N/A	N/A
Wolkerstorfer et al., 2000 (Prospective, left-right comparison study)	Improved SCORAD, most improvement observed in the 1 <sup>st</sup> week of therapy	No difference between dilutions; dose-response (80%) and adrenal suppression with absolute amount (1.6 g/day)	Folliculitis reported in 6/18 (33%) children in 1 <sup>st</sup> group, 2/5 (40%) children in 2 <sup>nd</sup> group, 5/8 (63%) children in 3 <sup>rd</sup> group. Furunculosis reported in 1/8 (13%) children in 3 <sup>rd</sup> group.	None	HPA axis suppression related to the absolute amount of applied corticosteroid
Tang, 2000 (Prospective)	“Good response”		None	None	N/A
Pei et al., 2001 (RCT)	Improved subjective and clinical scores	No difference between topical agents, one child unable to tolerate WWD	N/A	N/A	N/A
Schnopp et al., 2002 (RCT, left-right comparison study)	Improved SCORAD	Topical corticosteroids are superior to steroid-free emollients under WWWT	Decreased <i>S. aureus</i> counts in steroid group, no clinical infections in steroid or vehicle groups	N/A	N/A
Devillers et al., 2002 (Retrospective, left-right comparison study)	Improved SCORAD	No difference in improvement between dilutions applied to each side of the body	Long-term home treatment: 9 reported cases of infectious complications, including folliculitis, secondary impetigo, <i>Pseudomonas aeruginosa</i> infection, and cellulitis, and conjunctivitis	1 adult (also taking inhaled steroids) with striae	2 children and 1 adult had transient low morning cortisol, and 1 adult (also taking inhaled steroids) developed prolonged HPA suppression
McGowan et al., 2003 (Prospective)	N/A	No change in lower leg length (short-term bone growth) and urinary-DPD (bone turnover marker)	N/A	N/A	N/A

Study Design	Results		Adverse Events		
	Response to therapy	Additional Information	Infection	Skin Atrophy	Systemic
Beattie and Lewis-Jones, 2004 (RCT)	No difference in improvement between treatment groups	Greater HRQoL and sleep improvement in non-WWD control group	Folliculitis reported in 2/10 (20%) children (1 child withdrawn)	N/A	N/A
Foelster-Holst et al., 2006 (RCT, left-right comparison study)	Improved SCORAD in both treatment groups	Significantly better SCORAD improvement in the WWT group	None	None	None
Hindley et al., 2006 (RCT)	Improved SCORAD in both treatment groups	No significant difference observed in SCORAD improvement between two treatment groups	5/23 (22%) children in the WWD group received antibiotics for infective exacerbations of eczema	N/A	N/A
Lee et al. (Prospective)	Improved SCORAD	Epidermal water content increased, transepidermal water loss decreased, increased release of lamellar bodies and restoration of intercellular lipid lamellar structure observed	N/A	N/A	N/A
Hon et al., 2007 (Prospective)	Improved SCORAD	Scratching reduced by 20-60% as assessed by nocturnal wrist motion monitor, improved QoL	N/A	N/A	N/A

Table 2. Outcomes of Studies on Wet Wrap Dressing Occlusion (DPD = deoxypyridinoline, HPA = hypothalamic-pituitary-adrenal, HRQoL = Health Related Quality of Life)



the addition of topical corticosteroids to the treatment regimen appeared to provide some protective benefits. (Wolkerstorfer et al. 2000)

Tang (2000) treated 10 children experiencing a flare of facial eczema with WWD occlusion. Children were initiated on an intermittent treatment regimen involving 10% dilution of mometasone furoate 0.1% cream or ointment under WWD applied for 2-3 hours once daily for a few consecutive days. All parents reported good treatment response. No cutaneous side effects were observed from topical corticosteroid use. (Tang 2000)

Pei et al. (2001) performed a randomized control trial of 40 children with moderate-to-severe AD. Prior to starting the study, all patient were instructed to apply 0.005% flucinolone acetonide cream twice daily for 2 weeks to standardize treatment medications. Patient were then randomized to receive 10% dilution of 0.1% mometasone furoate ointment or 10% dilution of 0.005% fluticasone propionate ointment. These topical agents were applied once a day for 2 weeks without WWD. After this 2-week period of open application, patients were further randomized to receive the same topical agent for 2 more weeks without WWD, or for 2 more weeks under WWD. Only 30 patients (75%) entered into this second phase of the study since their disease severity had failed to improve by more than 50% after the initial 2 weeks of open topical application. In other words, only patients whose disease was refractory to a 2-week period of conventional open therapy continued in the study. Ultimately, there were a total of 27 patients who completed the study. One child receiving fluticasone propionate ointment dropped out of the study because the patient was unable to tolerate WWD. The study found that significantly greater improvements in disease severity and extent in patients using WWD, as compared to controls. These results suggest that WWD may be an effective second-line therapy in children whose disease is refractory to conventional open topical corticosteroids. (Pei et al. 2001)

Schnopp et al. (2002) examined the effect of WWD in a randomized control study of 20 inpatients with exacerbated AD. Children received either a topical corticosteroid preparation (mometasone furoate 0.1%) or a steroid-free preparation (its vehicle) under WWD, applied twice daily for 5 days to the tested area in a left-right study. Disease severity at day 3 and day 5 continuously improved in both groups; however, the mometasone furoate-treated group showed significantly greater improvements. *Staphylococcus aureus* bacterial counts initially decreased during the first 3 days of treatment in both groups. At day 5, bacterial counts continued to decrease in the steroid-treated group, but bacterial counts increased in the vehicle-treated group. There were no reported clinical signs of bacterial superinfection in either the steroid or vehicle groups. The study concluded that WWD were useful in treatment of exacerbated AD, with applications of topical corticosteroids showing better efficacy than steroid-free emollients. (Schnopp et al. 2002)

Devillers et al. (2002) evaluated the use of WWD in refractory AD in 12 adults and 14 children. WWD were applied daily and re-wetted every 2-3 hours for 1 week in an inpatient setting. Patients used 5% dilution of FP cream under WWD on affected areas of the face. As for the body, a side-to-side comparison study was performed, in which adults applied 10% and 25% dilutions of FP cream and children applied 5% and 10% dilutions of FP cream. Disease severity improved dramatically during the one week of inpatient therapy. There was no difference in improvement between dilutions applied to each side of the body. Following inpatient therapy, 8 adults and 13 children continued treatment at home with less potent dilutions of FP cream. Exacerbation of AD occurred in 3 adults and 2 children. Infectious complications included localized folliculitis (4 reported cases), secondary impetigo (2 reported cases), localized *Pseudomonas aeruginosa* infection, cellulitis of the left

cheek in a patient without a facial mask, and purulent conjunctivitis in a patient with a facial mask. These complications may be attributed to variations in standard protocol for WWD application, such as prolonged (>8 hours) occlusion and the frequent rewetting procedure. (Devillers et al. 2002)

McGowan et al. (2003) examined the effects of WWD therapy using topical corticosteroids on short-term growth and bone turnover in 8 prepubertal children, ranging from 3-8 years of age. Tubular bandages were applied over 10% or 25% dilutions of beclomethasone dipropionate for 24 hours each day for 2 weeks. After 2 weeks, frequency of tubular bandages was reduced to overnight use for one week and then as required for the remainder of the treatment period. Occlusive dressings were applied for a median duration of 12 weeks (range 2 - 18 weeks). Short-term growth was assessed by measuring lower leg length velocity by knemometry, while bone turnover was assessed by urinary deoxypyridinoline excretion. (McGowan et al. 2003) (See Section 3.4 Cutaneous and Systemic Side Effects for further discussion of this study)

In randomized control trial, Beattie and Lewis-Jones (2004) compared the use of 1% hydrocortisone under WWD to conventional open therapy in 19 children with moderate, widespread AD. The control group applied 1% hydrocortisone twice daily for 2 weeks, without WWD. In the study group, patients applied 1% hydrocortisone once in the morning for 2 weeks, with WWD twice daily for the first week and then only at night for the second week. Both groups were allowed to apply non-steroidal emollients as often as necessary. Beattie and Lewis Jones (2004) found no difference in clinical improvement between the control group and the study group. The authors, therefore, concluded that conventional open therapy using 1% hydrocortisone and emollients alone appeared to be as effective as using 1% hydrocortisone under WWD for moderate AD. Despite these findings, it is important to note that the use of 1% hydrocortisone is a less potent choice than what is generally used in clinical practice when treating moderate AD. If the authors had evaluated the use of a mid-potency topical corticosteroid under WWD, the degree of improvement between the study and control groups might have been markedly different. In terms of health related quality of life, Beattie and Lewis-Jones (2004) found greater improvements in the non-WWD control group than the WWD group for both the child and the family. Children in the non-WWD control group also reported more sleep than the WWD group, but there was no significant difference for itch between treatment groups. In regards to infections, 2 of the 10 (20%) children in the WWD group experienced folliculitis, one of which had to be withdrawal from the study. There were no reported clinical infections in the non-WWD control group. (Beattie and Lewis-Jones 2004)

Foelster-Holst et al. (2006) conducted a randomized, controlled study of 24 adults and children with acute episodes of AD. This was left-right comparison study, in which patients had skin lesions symmetrically affecting both arms or legs. One arm or leg was randomly treated with the topical prednicarbat (a medium potency corticosteroid), with WWD using a tubular bandage. The other extremity received topical prednicarbat alone. After 48-72 hours of therapy, both groups showed improvement of the local SCORAD, but the improvement in the WWD group was significantly better. No adverse effects were observed in either treatment group. (Foelster-Holst et al. 2006)

Hindley et al. (2006) carried a randomized, control trial to investigate the efficacy of WWD as compared to conventional topically applied corticosteroids. This 4-week study consisted of a total of 50 children with moderate-to-severe eczema. In the conventional treatment group, patients had emollients applied as needed and 1% hydrocortisone ointment (or more

potent topical steroids, if necessary) applied twice daily. In the WWD treatment group, patients had wet wraps applied daily for a 24-hour period over 1% hydrocortisone ointment (or more potent topical steroids, if necessary) during the first week, followed by wet wraps applied for a 12- or 24-hour period depending on disease progress for the remaining three weeks. When wet wraps were applied for only a 12-hour period, 1% hydrocortisone and emollients were used during the non-wet wrap period. Both treatment groups demonstrated improvement in overall SCORAD scores; however, there was no significant difference between the conventional and WWD treatment groups. Five out of 23 (22%) children in the WWD treatment group required antibiotics for skin infections, as compared to none of the children in the conventional treatment group. The authors conclude that 4-weeks of maintenance WWD treatment may be associated with more skin infections than conventional treatment. (Hindley et al. 2006) However, it is important to realize that in clinical practice, physicians usually do not use WWD for maintenance therapy of AD over a 4-week duration. Instead, physicians are more likely to use WWD in settings of acute generalized eczematous flares for 3-7 days to induce disease remission. (Williams 2006) Lee et al. (2007) examined the therapeutic efficacy of WWD and the mechanism behind its therapeutic efficacy in treatment of AD. Ten patients with severe AD received WWD (without steroid treatment) for 7-14 days. SCORAD was used to assess AD severity, immediately following the end of treatment and 7 days after termination of treatment. Transepidermal water loss, water content in the corneum, and lipid amount of skin surface were also measured. The SCORAD was significantly reduced after WWD therapy. Additionally, epidermal water content was increased and transepidermal water loss was decreased following WWD therapy; these results were maintained 1 week after terminating therapy. In atopic lesions, increased release of lamellar bodies and restoration of intercellular lipid lamellar structure was observed. The authors speculated that increased secretion of lamellar bodies induced with WWD occlusion may lead to recovery of the abnormal epidermal barrier and clinical improvement in AD. (Lee et al. 2007)

In a clinical study of six children with moderate to severe AD, Hon et al. (2007) tested the efficiency of WWD occlusion using Tubifast® garments with mometasone furoate 0.1% cream. Short-term use of WWD occlusion over 3 days demonstrated improvement in disease severity based on SCORAD. In addition, a wrist motion monitor was used to measure nocturnal itch, which showed that average scratching activity was significantly reduced by 20-60% on day 3 of treatment. Furthermore, WWD was effective in improving quality of life in these children. (Hon et al. 2007)

Since its introduction by Goodyear et al. (1991) nearly two decades ago, WWD occlusion has been extensively used as a relatively safe and effective treatment modality for children with acute erythrodermic AD and those with severe and/or refractory AD. The most effective topical corticosteroid to be used is still uncertain, but 10% dilutions of potent topical corticosteroid are most commonly used. Protocols on administration and duration of WWD occlusion can vary between studies. (Oranje et al. 2006) (See Table 3)

Advantages of WWD occlusion include a rapid therapeutic response, reduction in itch and sleep disturbances, and a possible decreased topical corticosteroid use. Disadvantages include high cost, the need for specialized training, increased potential for topical corticosteroid absorption, and increased incidences of folliculitis and other cutaneous infections. (Oranje et al. 2006)

However, the application of WWD has become less time-consuming and more feasible for home use with development of Tubifast® garments manufactured by Medlock Medical®

(available since 2003). With the introduction of these garments, wet wrapping can be done in 20–25 minutes. Tubifast garments® are available as tights for babies aged 6–24 months, vests for children 6 months through 14 years, and socks and leggings in all sizes. These washable garments are absorbent, holding enough water to remain moist for hours, and are elastic and able to conform to the contours of the body. (Page 2005)

1. Choose the appropriate width of the tubular bandages and cut these to size to fit the affected body areas (i.e. arms, legs, trunk). Alternatively, Tubifast® garments can be used.
2. Apply the appropriate dilution of topical corticosteroids (e.g. fluticasone propionate 0.05% cream, mometasone furoate 0.1% cream) on the involved skin. In general, diluted steroids in emollients of 1:9 are applied to the face of all patients and body of infants, while diluted steroids in emollients of 1:9 or 1:3 are applied on the body of adults.
3. Wet the pieces of tubular bandage in lukewarm water. Alternatively, if Tubifast® garments are used, then the inner garment is moistened using a plant sprayer.
4. Apply the first layer of wet tubular bandages. Connect the arm and leg pieces to the trunk. Apply the facial mask, if necessary. Alternatively, if Tubifast® garments are used, the inner garment is moistened using a plant spray.
5. Apply the second layer of dry tubular bandage. Again, connect the arm and leg pieces to the trunk. Apply the facial mask, if necessary. Alternatively, if Tubifast® garments are used, a second dry Tubifast® garment is placed over the wet one.
6. Re-wet the tubular bandages every 2-3 hours. Alternatively, if Tubifast® garments are used, re-wet the inner Tubifast® garment every 2-3 hours.
7. Repeat procedures #1-6 (described above) daily.
8. After 7 days of occlusive therapy, the dilution of topical corticosteroids (e.g. fluticasone propionate 0.05% cream, mometasone furoate 0.1% cream) is applied on the involved skin for 4-7 consecutive days.

Table 3. Protocol for Wet Wrap Dressing occlusion

Finally, in a review article, Devillers and Oranje (2006) made the following conclusions regarding WWD occlusion with a grade C of recommendation. 1) WWD using cream or ointment and a double layer of cotton bandages, with a moist first layer and a dry second layer, is an efficacious short-term treatment for children with severe and/or refractory AD. 2) The use of WWD with diluted topical corticosteroids is a more efficacious treatment than wet-wrap dressings with emollients only for children with severe and/or refractory AD. 3) The use of WWD with diluted topical corticosteroids is a safe intervention treatment for children with severe and/or refractory AD for up to 14 days, with temporary systemic bioactivity of the corticosteroids as the only reported serious adverse effect. 4) Lowering the absolute amount of applied topical corticosteroid to once daily application and further dilution can reduce potential risks. (Devillers and Oranje 2006)

### 3.2 Dry wrap dressings

DWD occlusion in AD has been less well studied (Table 4). Specifically, Rajka et al. (1981) examined the effect of dry occlusion on skin microbial flora. Occlusion using plastic film was applied to 10 patients with AD. A significant increase in the density of *S. aureus* was observed after 24 hours of dry occlusion. Notably, 2 of the 10 patients had tiny pustules or crusts following dry occlusion. But, there were no reports of AD exacerbation. (Rajka et al. 1981)



Study Design	Results		Adverse Events		
	Response to therapy	Additional Information	Infection	Skin Atrophy	Systemic
Rajka et al., 1981 (Prospective)	N/A	No reports of AD exacerbation	Increased <i>S. aureus</i> density, 2/10 (20%) with pustules or crusts	N/A	N/A
Geraldez et al. 1989 (RCT)	Significantly greater improvement in pruritus and lichenification in non-occlusive control group		Control group: none reported, versus Treatment group: 2/30 (7%) with pustular lesions and 1/30 (3%) with erythema	N/A	N/A
Volden et al., 1992 (Prospective)	44/48 (92%) complete resolution, 4/48 (8%) partial remission (>50% clearance)	Instant relief from scratching	Mild folliculitis reported in 2/48 (4%) of adults.	None	N/A
Gauger et al., 2003 (Prospective)	Improved SCORAD, versus constant in control group		Decreased <i>S. aureus</i> density in silver-coated textile group, versus constant or increased in control group	N/A	N/A

Table 4. Outcomes of Studies on Dry Wrap Dressing Occlusion

Geraldez et al. (1989), in a randomized controlled study of 60 patients with lichen simplex chronicus, observed more infections and other adverse events in patients treated with diflucortolone valerate 0.3% ointment under occlusion as compared those treated without occlusion. Among the patients using dry occlusion, 2 patients (7%) developed pustular lesions surrounding the affected sites, one (3%) had erythema, and one (3%) had hyperpigmentation. None in the control group experienced any side effects. The control group also reported greater improvements in both pruritus and lichenification. The authors noted that the difference in the observed efficacy may be due to poorer absorption of the ointment that tended to adhere to the plastic occlusive material. Furthermore, the adverse events seen in the treatment group may have resulted from the combination of both the ointment vehicle and the nature of the plastic occlusive material that created an over-occlusive environment, thereby favoring microbial proliferation and/or contact sensitization. (Geraldez et al. 1989)

Volden et al. (1992) treated 48 patients with chronic, therapy-resistant AD, with once-weekly application of clobetasol propionate lotion under hydrocolloid (Duoderm®) occlusive dressings. Of the 48 patients, 44 (92%) had complete resolution of lesions, and 4 (8%) had partial response (defined as >50% clearance). There were also 2 (4%) patients with mild folliculitis. The authors conclude that adverse events were both mild and infrequent. (Volden 1992)

Gauger et al. (2003) further addressed the concern of skin colonization with *S. aureus* using occlusion therapy for AD. A side-to-side comparative study of 15 patients with generalized or localized AD was performed, in which the flexures of the elbows were covered with silver-coated textiles on one arm and cotton on the other arm for one week. The study found a significant decrease in *S. aureus* colonization on the lesions covered with silver-coated textile just 2 days after initiation of therapy and lasting until the end of the treatment. Additionally, a significantly less amount of *S. aureus* was observed on the silver-coated textile sites than the cotton sites at the end of the treatment. Clinical improvement further correlated with the reduction of bacterial colonization. Thus, the silver-coated textile appeared to not only improve active lesions of AD, but also mitigate the potential pro-microbial effects of dry occlusion alone. (Gauger et al. 2003)

Ultimately, DWD occlusion appears to improve disease severity and is perhaps most beneficial in chronic treatment-resistant eczematous lesions. However, there is too little data to determine whether occlusion, in particular DWD occlusion, predisposes skin bacterial growth. But, it seems reasonable to conclude that the addition of antimicrobial topical agents (e.g. antiseptic or silver preparations) to occlusive therapy might be helpful in countering the potential risk of infection. (Abeck et al. 1999; Gauger 2006)

### 3.3 Hydrogel patch

In a pilot study of 15 patients, Park et al. (2011) evaluated the efficacy and safety of a hydrogel patch for AD treatment. The hydrogel patch used in this study was composed of an adhesive, thin, flexible, hydrogel layer on an impermeable urethane surface. Unlike hydrocolloid dressings (e.g. Duoderm®) with low water content, the hydrogel patch consisted of approximately 50% water. In this 6-week study, patients applied the hydrogel patch over one lesion for 6-8 hours daily and triamcinolone (TAC) 0.1% cream twice daily to another lesion. Erythema, induration, lichenification, excoriation, and total EASI scores significantly improved compared to baseline in both the hydrogel patch and TAC groups.



Improvement in pruritis was observed in both treatment groups, but was only statistically significant in the TAC group. At week 4, there was no significant difference in all sub-scores between the patch and TAC groups (except pruritus, as stated above). Improvement was maintained after discontinuing treatment for 2 weeks. No adverse events from steroid use occurred. This study appears to demonstrate that instant correction of the dysfunctional skin barrier with the hydrogel patch can improve signs and symptoms of AD comparable to TAC 0.1% cream. Thus, the hydrogel patch may provide a new approach to occlusive therapy without the potential risks of topical corticosteroid use (Park et al. 2011)

### 3.4 Cutaneous and systemic side effects

Topical corticosteroid use can cause both cutaneous and systemic side effects, most significantly laboratory adrenal insufficiency. Risk factors include the use of high potency corticosteroids, occlusive or prolonged therapy, and application to thin- or barrier-compromised skin lesions. (Levin and Maibach 2002) Occlusive therapy with topical corticosteroids does not appear to be associated with an increased incidence of local non-infectious side effects, such as skin atrophy and striae. This is most likely because nearly all studies have examined limited treatment durations and diluted topical corticosteroids. However, several studies demonstrated either lowering of morning cortisol levels (Hartmann and Lahmann 1977; Goodyear et al. 1991), loss of diurnal cortisol rhythm (Hartmann and Lahmann 1977), or overt laboratory HPA suppression with WWD (Wolkerstorfer et al. 2000; Devillers et al. 2002). Importantly, nearly all cases of decreased cortisol levels proved to be transient, returning to normal ranges within weeks of discontinuing therapy.

Specifically, Goodyear et al. (1991) found that 0900 hour cortisol levels were suppressed immediately after treatment with WWD, but returned to normal 2 weeks following therapy. Following this observation by Goodyear et al. (1991) of a transient lowering of morning cortisol levels (Goodyear et al. 1991), Wolkerstorfer et al. (2000) decided to examine the effects of different corticosteroid dilutions under WWD occlusion on HPA axis suppression in children with severe refractory AD. Only 3 out of the 18 children in the first treatment group (i.e. 50% dilution of FP cream) and none of the 5 children in the second treatment group (i.e. 10%, 25% and 50% dilutions of FP cream) demonstrated HPA axis suppression based on 0900 hour serum cortisol measurements following 2 weeks of WWD occlusion. In the third treatment group (i.e. 0%, 5%, 10%, or 25% dilutions of FP cream applied to the whole body), children demonstrated HPA axis suppression based on 0600 hour serum cortisol measurements, which was associated with the absolute amount of applied corticosteroid. To be more specific, a dose-response relationship was observed with an absolute amount of topical corticosteroid applied. Patients using  $800 \mu\text{g m}^{-2}$  daily (equivalent to 1.6 g FP 0.05% cream) had an approximately 80% improvement, while patients using absolute amounts  $>957 \mu\text{g m}^{-2}$  daily had no greater improvement. Patients using absolute amounts  $\leq 800 \mu\text{g m}^{-2}$  daily had no suppression of the HPA axis. This suggests that weaker dilutions of topical corticosteroid may have a lower risk of HPA axis suppression, while still maintaining comparable efficacy to more potent dilutions of topical corticosteroid. (Wolkerstorfer et al. 2000)

Similarly, Devillers et al. (2002) found a significant decrease in early-morning serum cortisol levels following 1-week of inpatient WWD therapy. Transient cortisol levels below the normal range were observed after 4 days in 3 children and after one week in 2 adults. One

adult, who also taking inhaled steroids, developed prolonged suppression of the HPA axis, in combination with several abdominal striae. (Devillers et al. 2002)

As for the effect of occlusive therapy using topical corticosteroids on bone development, McGowan et al. (2003) examined short-term growth and bone turnover in prepubertal children undergoing WWD occlusion for AD. Knemometry, a technique estimating the distance between the heel and knee of the sitting child, was used as a non-invasive measurement of lower leg length, in combination with 24-hour urinary deoxypyridinoline excretion to evaluate bone turnover. Lower leg length and urinary deoxypyridinoline levels for all children remained similar in pre-treatment measurements and during therapy. This suggests that WWD occlusion for a limited duration does not impact growth parameters. (McGowan et al. 2003)

#### 4. Occlusion in clinical practice

Occlusive therapy, in particular WWD occlusion, can be useful as a 'stepped-up' therapy in controlling acute erythrodermic AD or as a second-line therapy for severe and/or refractory disease. There is limited convincing data that WWD occlusion is superior to conventional open application of topical corticosteroids. However, occlusive therapy represents an important alternative to currently available, but often undesirable standard treatment modalities for AD. A few drawbacks of standard therapies include dependency on super-potent topical corticosteroids, frequent and inconvenient sessions of phototherapy, and serious systemic side effects with oral medications (e.g. nephrotoxicity with cyclosporine use).

Based on the studies on occlusive therapy, it appears that the greatest benefits of topical corticosteroids under occlusion is achieved during the first week of therapy. This suggests that if used as 'rescue' therapy for acute flares or intermittently for maintenance, durations of up to 1 week might be adequate (Wolkerstorfer et al. 2000; Pei et al. 2001). Anecdotally, long-term effects are thought to be sustained when WWD occlusion are continued with emollients for 2–4 more weeks to improve skin hydration (Nicol 1987). Variations in protocol regarding duration of WWD occlusion and rewetting procedures possibly contributed to differences observed in efficacy and incidence of infection. It may, therefore, be advisable to limit occlusion to less than 8 hours duration, apply WWD no more than twice daily, and avoid rewetting procedures.

It is difficult to ascertain the extent to which occlusion may promote bacterial colonization. However, the use of anti-bacterial agents, when applied alone or under occlusion, appears to not only inhibit bacterial colonization, but also reduce disease severity. (Abeck et al. 1999; Brockow et al. 1999; Gauger 2006) Thus, it seems logical that antibacterials, whether topical or systemic, might be a beneficial adjunct to occlusive therapy helping to decrease the potential risk of clinical infection. As such, topical antibacterials in combination with topical corticosteroids under occlusion may be useful when treating small areas of skin for a limited period of time, while systemic antibacterials in combination with topical corticosteroid under occlusion may more be appropriate when treating larger areas of involvement. Yet, the use of antibacterials must be weighed against the potential risk of antimicrobial resistance and contact sensitization. (Williams 2000; Zhai and Maibach 2001)

More specifically, according to Williams (2000), there are three categories of patients with AD: 1) those with obvious clinical infection, in whom anti-staphylococcal therapy is essential, 2) those with mild disease and a lower density of *S. aureus* colonization, in whom no evidence supports additional benefit of anti-staphylococcal therapy, and 3) those with fissured or

cracked eczema without overt signs of infection such as crusting or folliculitis. (Williams 2000) While the latter group of patients carry an intermediate to high levels of *S. aureus*, studies are contradictory regarding the clinical benefits of anti-staphylococcal therapy in these patients. Clinicians may choose to institute antimicrobial therapy, in combination with topical corticosteroids under occlusion. If poorly responsive to WWD occlusion, addition of corticosteroid with topical or oral antibiotics has been helpful anecdotally, suggesting that subclinical infection or heavy colonization may impede response to topical corticosteroids. (Nicol 1987) Despite half a century of topical corticosteroid use in eczematous skin, the clinical criteria for the addition of a topical antimicrobial agents remains to be determined.

In terms of the concern for adrenal suppression with topical corticosteroids under occlusion, the minimal available data suggests that a decrease in cortisol levels can occur, but these effects are generally transient. The use of mid- or high-potency corticosteroid, an ointment vehicle, occlusion, and a disrupted skin barrier are all contributing factors that can increase the risk of systemic side effects including this possibility of adrenal suppression. Of note, there has been only one suggested fatal case of adrenal insufficiency from topical corticosteroid use. However, the details of this case are limited. It is known that the patient was an 11-year old girl with generalized psoriasis being treated with betamethasone cream under occlusion for a prolonged durations. However, the concentration and the exact quantity of betamethasone cream applied, as well as the duration of therapy are unknown. (Levin and Maibach 2002)

Several strategies may be used to limit the potential for such complications. Possible options include using occlusive therapy only intermittently, reducing topical corticosteroid potency gradually as inflamed skin improves, and applying occlusion only once-daily. Studies have demonstrated that twice-daily application of topical corticosteroids to be no more effective than once-daily regimens and more prone to systemic side effects. (Lagos and Maibach 1998; Green et al. 2005) In addition, diluting topical corticosteroids may be helpful in reducing the risk of serious side effects. However, such preparations may alter the physiochemical properties of the agent and may not serve to reduce disease activity. (Haigh and Smith 1991; Gao and Li Wan Po 1994; Ohtani et al. 2002; Kizu et al. 2004) Furthermore, the application of a hydrogel patch, which appeared to have similar efficacy as topical corticosteroid use, may potentially serve as an ideal method of treating AD while avoiding topical corticosteroids. (Park et al. 2011) But, additional studies on the efficacy of the hydrogel patch in the treatment of AD are needed. Ultimately, if prolonged topical corticosteroid use is required in certain patients with refractory disease, adrenal function may be monitored using morning plasma cortisol and urinary steroid levels, in combination with rapid ACTH stimulation testing, while evaluating the patient for cutaneous atrophy or Cushingoid features (Levin and Maibach 2002). But, the rare occurrence of topical corticosteroid-induced Addison's disease makes this suggestion impractical for most patients.

Topical immunosuppressive agents such as pimecrolimus or tacrolimus under occlusion have not yet been studied extensively. These agents might represent a valuable non-steroidal alternative, though systemic absorption should be measured to confirm that immunosuppressive levels have not been reached. An open-label study evaluating topical pimecrolimus cream 1% in the treatment of chronic hand dermatitis showed that twice-daily application under occlusion was safe and effective, resulting in low pimecrolimus blood levels. (Thaci et al. 2003) Beyeler et al. (2006) reported a case of a female patient treated with tacrolimus 0.1% ointment under occlusion with Unna's paste boots (zinc bandages), whose

serum levels had reached 12.9  $\mu\text{g}/\text{l}$  after 5 days of treatment, corresponding to high-dose immunosuppression. Beyeler et al. (2006) attributed the increased systemic absorption to the combination of severely damaged skin barrier function, application of tacrolimus to a large surface area, and occlusion under zinc bandages. (Beyerler et al. 2006)

The wide variation in occlusive techniques and predominance of uncontrolled trials with small sample sizes make direct comparison of studies evaluating the safety and efficacy of occlusive therapy difficult. Limited numbers of studies using control groups restricts the conclusions that can be drawn regarding the benefit of occlusive therapy versus conventional therapies. However, it can be concluded that occlusive therapy has been shown, both formally and anecdotally, to be very effective in severe or exacerbated AD. It, therefore, offers an important alternative or adjunct therapy to more commonly used approaches. The randomized controlled trials described in this chapter resulted in divergent outcomes regarding infectious complications and efficacy. Differences could be related to the study populations (i.e. exacerbated versus moderate AD) or different topical corticosteroid application regimens.

While the exact mechanism of action of occlusive therapy is still unknown, a recent pilot study demonstrated significant down-regulation of 7 serum chemokines following WWD occlusion for 1 week in 6 children with severe AD. Of these, 4 chemokines are considered to be potential serum markers for the disease activity of AD. (Ong et al. 2008) In another study evaluating WWD occlusion using diluted tacrolimus and fluticasone propionate cream in APOC1 mice with AD, WWD occlusion improved transepidermal water loss, reinforcing that this may be one of the therapeutic aspects of occlusive therapy. (Oranje et al. 2009)

Future studies should evaluate the efficacy of occlusive therapy versus open topical corticosteroid application with measurements on the differences in systemic absorption. Studies should also investigate the impact of varying the durations of occlusive therapy. Given the number of protocols utilizing inpatient or specialized nurse-assisted visits, it would be useful to understand the contribution of professional supervised application. To our knowledge, no studies to date have evaluated occlusion as preventive therapy (i.e., to prevent disease flares and maintain cutaneous hydration).

## 5. Conclusion

WWD occlusion may be a reasonable first-line therapy for acute exacerbations of AD and second-line therapy for refractory disease. DWD occlusion appears to be efficacious having relatively low risk of infectious complications and may be particularly useful in treatment of chronic AD lesions. However, it remains unclear if occlusive therapy offers significant advantageous over conventional open therapy. The risk of infection associated with occlusive therapy, while greater than open therapies, seems to be manageable and may be mitigated by limiting the duration of occlusion, avoiding rewetting and perhaps adding antibacterial agents. Transient changes in morning cortisol levels and rare clinical HPA suppression seen with the use of topical corticosteroids under occlusion are concerning side effects, but are likely related to corticosteroid potency and the absolute amount applied. The hydrogel patch offers an innovative approach to the treatment of AD instantly correcting the barrier defect, and it may have similar efficacy as topical corticosteroids without the systemic risks. Further controlled studies are needed to better evaluate the risks and benefits of these occlusive modalities in the treatment of AD.



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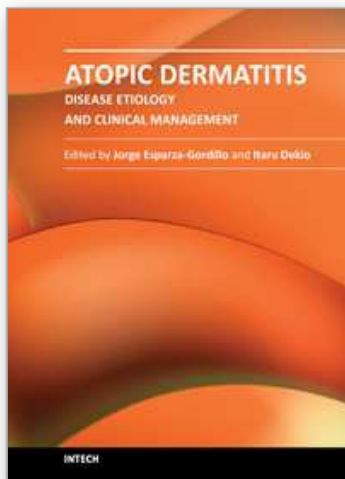
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## **Atopic Dermatitis - Disease Etiology and Clinical Management**

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Atopic Dermatitis is a common disease characterized by inflamed, itching and dry skin. This relapsing allergic disorder has complex etiology and shows a remarkably high clinical heterogeneity which complicates the diagnosis and clinical management. This book is divided into 4 sections. The first section (Disease Etiology) describes some of the physiological mechanisms underlying Atopic Dermatitis, including alterations in the immune system and the skin-barrier function. The important role of host-microorganism interactions on the pathophysiology of Atopic Dermatitis is discussed in the second section (Microorganisms in Atopic Dermatitis). An overview of the clinical diagnostic criteria and the disease management protocols commonly used is given in the third section (Diagnosis and Clinical Management). The last section (New Treatments) describes new therapeutic approaches that are not widely used but are currently being studied due to preliminary evidence showing a clinical benefit for Atopic Dermatitis.

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