EMJ EUROPEAN MEDICAL JOURNAL

# DERMATOLOGY

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**Skilarence 30 mg & 120 mg gastro-resistant tablets Active Ingredient: Skilarence 30 mg** Each gastro-resistant tablet contains 30 mg dimethyl fumarate. Also contains 34.2 mg lactose (as monohydrate). **Skilarence 120 mg** Each gastro-resistant tablet contains 120 mg dimethyl fumarate. Also contains 136.8 mg lactose (as monohydrate). **Indication:** For the treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy. **Dosage and Administration:** For oral use. To improve tolerability, it is recommended to begin treatment with a low initial dose with subsequent gradual increases. In the first week, Skilarence 30 mg is taken once daily (1 tablet in the evening). In the second week, Skilarence 30 mg is taken twice daily (1 tablet in the morning and 1 in the evening). In the third week, Skilarence 30 mg is taken three times daily (1 tablet in the morning, 1 at midday, and 1 in the evening). From the fourth week, treatment is switched to only 1 tablet of Skilarence 120 mg in the evening. This dose is then increased by 1 Skilarence 120 mg tablet per week at different times of day for the subsequent 5 weeks. If a particular dose increase is not tolerated, it may be temporarily reduced to the last tolerated dose. The maximum daily dose allowed is 720 mg (3 x 2 tablets of Skilarence 120 mg). *Consult SmPC and package leaflet for the titration table and full method of administration.* **Contraindications, Warnings, etc:** *Contraindications:* Hypersensitivity to the active substance or to any of the excipients listed in SmPC section 6.1. Severe gastrointestinal disorders, Severe hepatic or renal impairment, Pregnancy and breast-feeding. *Precautions:* Skilarence may decrease leukocyte and lymphocyte counts. It has not been studied in patients with pre-existing low leukocyte or lymphocyte counts. Prior to initiating treatment with Skilarence, a current complete blood count (including differential blood count and platelet count) should be available. Treatment should not be initiated if leukopenia below 3.0x109/L, lymphopenia below 1.0x109/L or other pathological results are identified. During treatment a complete blood count with differential should be performed every 3 months. *Leukopenia:* Discontinue treatment if a marked decrease in the total number of white blood cells is at levels below 3.0x109/L. Lymphopenia: If the lymphocyte count falls below 1.0x109/L but is ≥0.7 x109/L, blood monitoring should be performed monthly until levels return to 1.0x109/L or higher for two consecutive blood tests at which point monitoring can again be performed every 3 months. If the lymphocyte count falls below 0.7x109/L, the blood test must be repeated and if the levels are confirmed to be below 0.7x109/L, then treatment must be stopped immediately. Patients developing lymphopenia should be monitored after stopping treatment until their lymphocyte count has returned to the normal range. Infections: Initiation of therapy should only be considered once a pre-existing infection has resolved. If a patient develops an infection during treatment with Skilarence, suspension of treatment should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy. Patients receiving Skilarence should be instructed to report symptoms of infection to a physician. *Progressive multifocal leukoencephalopathy (PML)* Cases of opportunistic infections, particularly of PML have been reported with other dimethyl fumarate-containing products. PML is an opportunistic infection caused by the John-Cunningham virus (JCV) that can be fatal or cause severe disabilities. A modified or weakened immune system as well as genetic or environmental factors can also constitute risk factors. Persistent moderate or severe lymphopenia during treatment with dimethyl fumarate is also considered a risk factor for PML. Patients who develop lymphopenia should be monitored for signs and symptoms of opportunistic infections, particularly for symptoms indicative of PML. Renal and hepatic function should be checked prior to initiation of treatment and every three months thereafter. *Fanconi syndrome:* Early diagnosis of Fanconi syndrome and discontinuation of Skilarence treatment are important to prevent the onset of renal impairment and osteomalacia, as the syndrome is usually reversible. Flushing: Patients should be made aware that they are likely to experience flushing in the first few weeks of taking Skilarence. Lactose: Skilarence contains lactose. 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The efficacy of oral contraceptives may be reduced and the use of an alternative barrier contraceptive method is recommended to prevent possible failure of contraception. Consumption of large quantities of strong alcoholic drinks (more than 30% alcohol by volume) should be avoided because it may lead to increased dissolution rates of Skilarence and, therefore, may increase the frequency of gastrointestinal adverse reactions. Vaccination during treatment with Skilarence has not been studied. Immunosuppression is a risk factor for the use of live vaccines. There is no evidence for Skilarence interaction with cytochrome P450. *Fertility Pregnancy and lactation:* Skilarence is not recommended in women of child-bearing potential not using appropriate contraception. In patients experiencing diarrhoea during Skilarence treatment, the effect of oral contraceptives may be reduced and additional barrier methods of contraception may be necessary. There are limited data from the use of dimethyl fumarate in pregnant women. Animal studies have shown reproductive toxicity. Skilarence is contraindicated during pregnancy and breast-feeding There are no human or animal data on the effects of Skilarence on fertility. Ability to drive and use machines: Skilarence may have a minor influence on the ability to drive and use machines. Dizziness and fatigue may occur. *Consult SmPC and package leaflet for more information.* **Adverse Reactions:** *Very common (≥1/10);*Lymphopenia, leukopenia, flushing, diarrhoea, abdominal pain and distention, nausea. *Common (≥1/100 to <1/10):* Eosinophilia, leucocytosis, headache, paraesthesia, vomiting, dyspepsia, constipation, abdominal discomfort, flatulence, erythema, skin burning sensation, pruritis, fatigue, feeling hot, asthenia, hepatic enzyme increased. *Very rare (<1/10,000):* Acute lymphatic leukaemia, irreversible pancytopenia. *Not known (cannot be estimated from available data) PML, renal failure, Fanconi syndrome. Consult SmPC and package leaflet for other adverse reactions.* **Legal Category:** POM **Marketing Authorisation Number(s):** EU/1/17/1201/001, EU/1/17/1201/004, EU/1/17/1201/007. **NHS Cost:** 30 mg - 42 tablets = £89.04 ; 120 mg - 90 tablets = £190.80, 180 tablets = £381.60 (excluding VAT). **Marketing Authorisation Holder:** Almirall, S.A., Ronda General Mitre, 151, 08022 Barcelona, Spain. **Further information is available from:** Almirall Limited, Harman House, 1 George Street, Uxbridge, Middlesex, UB8 1QQ, UK. Tel: 0800 0087 399. Email: almirall@professionalinformation.co.uk
**Date of Revision:** 06/2017
**Item code:** UKDMF3708

**Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Almirall Ltd.**

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FAE, fumaric acid ester. QoL, quality of life.
*Fumaderm® – a combination of FAEs – is an unlicensed medicine in the UK.[5]

**References: 1.** Skilarence® Summary of Product Characteristics. Almirall. April 2017. **2.** Van de Kerkhof P, *et al.* Treatment with LAS41008 (dimethyl fumarate) improved health-related quality of life and has a positive impact on the patient benefit index in adults with moderate-to-severe chronic plaque psoriasis: results of the BRIDGE study. European Academy of Dermatology and Venereology, Vienna, 28th September – 2nd October 2016. E-poster: P1998. **3.** Mrowietz U, *et al. Br J Dermatol* 2017;176:615–623. **4.** Reich K, *et al. J Dtsch Dermatol Ges* 2009;7:603–611. **5.** British Association of Dermatologists. Fumaric acid esters. 2010. Available at: http://www.bad.org.uk/shared/get-file.ashx?id=84&itemtype=document. Accessed: July 2017.

**This material has been developed and funded by Almirall. Please see Skilarence® Prescribing Information opposite.**

September 2017 UKDMF3757g

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**Abbreviated Prescribing Information for Kyntheum® 210 mg solution for injection in pre-filled syringe** Please refer to the full Summary of Product Characteristics (SmPC) approved in your country before prescribing. This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. **Indication:** Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy. **Active ingredient:** Each pre-filled syringe contains 210 mg brodalumab in 1.5 ml solution. 1 ml solution contains 140 mg brodalumab. **Dosage and administration:** *Posology: Adults:* The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks. Consideration should be given to discontinuing treatment in patients who have shown no response after 12-16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks. Each pre-filled syringe is for single use only. *Elderly:* No dose adjustment recommended. *Hepatic and renal impairment:* No dose recommendations can be made. *Children and adolescents below the age of 18 years:* Safety and efficacy of Kyntheum have not been established. *Method of administration*: Subcutaneous (SC) injection. Kyntheum should not be injected into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by psoriasis. The pre-filled syringe must not be shaken. After proper training in SC injection technique, patients may self-inject Kyntheum when deemed appropriate by a physician. Patients should be instructed to inject the full amount of Kyntheum according to the instructions provided in the package leaflet. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Active Crohn's disease. Clinically important active infections (e.g. active tuberculosis). **Precautions and warnings:** *Crohn's disease*: Exercise caution when prescribing Kyntheum to patients with a history of Crohn's disease. They should be followed for signs and symptoms of active Crohn's disease. If patients develop active Crohn's disease, treatment should be discontinued permanently. *Suicidal ideation and behaviour*: Suicidal ideation and behaviour, including completed suicide, have been reported in patients treated with Kyntheum. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with Kyntheum and increased risk of suicidal ideation and behaviour has not been established. Carefully weigh the risk and benefit of treatment with Kyntheum for patients with a history of depression and/or suicidal ideation or behaviour, or patients who develop such symptoms. Patients, caregivers and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal ideation, anxiety, or other mood changes, and they should contact their healthcare provider if such events occur. If a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behaviour is identified, it is recommended to discontinue treatment with Kyntheum. *Infections*: Kyntheum may increase the risk of infections. Caution should be exercised when considering the use of Kyntheum in patients with a chronic infection or a history of recurrent infection. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, they should be closely monitored and Kyntheum should not be administered until the infection resolves. Kyntheum should not be given to patients with active tuberculosis. Anti-tuberculosis therapy should be considered prior to initiation of Kyntheum in patients with latent tuberculosis. *Reduced absolute neutrophil count*: A decrease in absolute neutrophil count, generally transient and reversible, has been observed in 5.6% of patients receiving Kyntheum. *Vaccinations*: It is recommended that patients be brought up-to-date with all immunisations in accordance with local immunisation guidelines prior to initiation of treatment with Kyntheum. Live vaccines should not be given concurrently with Kyntheum. The safety and efficacy of Kyntheum in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. **Drug interactions:** Live vaccines should not be given concurrently with Kyntheum. **Fertility, pregnancy and lactation:** *Women of childbearing potential*: Use an effective method of contraception during treatment and for at least 12 weeks after treatment. *Pregnancy:* There are no or limited amount of data from the use of brodalumab in pregnant women. As a precautionary measure, it is preferable to avoid the use of Kyntheum in pregnancy. Benefit risk for exposure of the infant to live vaccines following third trimester exposure to Kyntheum should be discussed with a physician. *Breast-feeding:* It is unknown whether brodalumab is excreted in human milk. A risk to the newborns/infants cannot be excluded. Whether to discontinue breast-feeding or discontinue Kyntheum therapy should be decided, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. *Fertility:* No data are available on the effect of brodalumab on human fertility. **Adverse reactions:** *Common (≥1/100 to <1/10)*: Influenza, tinea infections (including tinea pedis, tinea versicolor, tinea cruris), neutropenia, headache, oropharyngeal pain, diarrhoea, nausea, arthralgia, myalgia, fatigue, injection site reactions (including injection site erythema, pain, pruritus, bruising, haemorrhage). *Uncommon (≥1/1,000 to <1/100)*: Candida infections (including oral, genital and oesophageal infections), conjunctivitis. **See SmPC for a full list of adverse reactions. Precautions for storage:** Store in a refrigerator (2°C-8°C). Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light. Kyntheum may be stored at room temperature (up to 25°C) once, in the outer carton, for a maximum single period of 14 days. Once Kyntheum has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 14 days or discarded. **Marketing authorisation number and holder:** EU/1/16/1155/001, LEO Pharma A/S, Ballerup, Denmark. **Last revised:** September 2017

Reporting of Suspected Adverse Reactions
Adverse reactions should be reported according to local guidelines.

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**References:**
1. Kyntheum® (brodalumab) Summary of Product Characteristics. English version, July 2017.
2. Campa M, et al. *Dermatol Ther* 2016;6:1–12.
3. Lebwohl M, et al. *N Engl J Med* 2015;373:1318–28.
4. Supplement to: Lebwohl M, et al. *N Engl J Med* 2015;373:1318–28.
5. Blauvelt A, et al. *J Am Acad Dermatol* 2017;77:372–74.
6. Strober B, et al. *J Am Acad Dermatol* 2016;75:77–81.


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- By achieving **PASI 100** at week 12, a greater proportion of patients experienced no impairment to their **health-related quality of life** from psoriasis (DLQI 0 or 1) versus those with a lower response[6]

* PASI 100 at 12 weeks with Kyntheum® versus ustekinumab: 44% versus 22% (AMAGINE-2) and 37% versus 19% (AMAGINE-3).[3]

September 2017. MAT-12285

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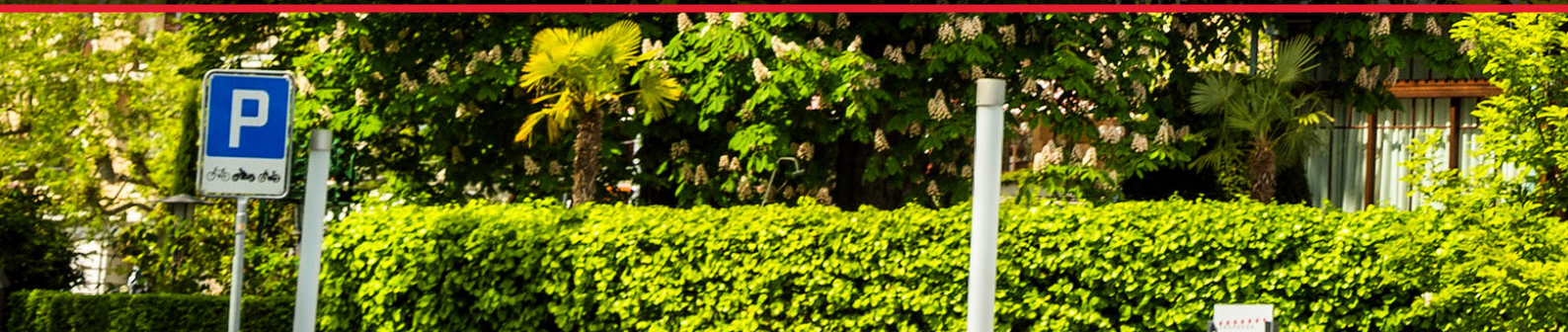

# DERMATOLOGY

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*Front cover and contents photograph: Geneva, Switzerland, home of* EADV 2017. *© Leonid Andronov / 123rf.com*

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- EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research
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**DERMATOLOGY** 5.1
NOVEMBER 2017



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# Welcome

A cheery welcome to each and every one of you joining us for *EMJ Dermatology 5.1*, which takes you through the latest highlights within this ever-evolving field. The 26th European Academy of Dermatology and Venereology (EAVD) congress is summarised within, alongside reviews of some exciting stories brought to you directly from the event. Further into this comprehensive edition, we have interviews with our esteemed Editorial Board, thrilling peer-reviewed articles, and intriguing abstracts from presenters at the EADV congress.

> All of us here at the European Medical Journal hope you enjoy reading *EMJ Dermatology 5.1* as much as we have enjoyed producing it for you.

Surrounded by the stunning Swiss scenery, Geneva, Switzerland, played the perfect host to this year's EADV congress. Novel research from the event, found in our Congress Review section, includes the latest updates on topics such as sunbed use, treatment insights for rosacea patients, sexually transmitted infections, and more. Complementing these, we bring you interviews from members of our *EMJ Dermatology* Editorial Board who discuss their careers and experiences, as well as providing their opinions on the upcoming challenges for the field. We are also delighted to bring you abstract reviews from speakers at the EADV congress, who provide summaries of their most recent, novel research. One abstract, by Moyal et al., discusses the impact of air pollution on the skin and potential protection strategies. With air pollution levels continuously under debate, the findings summarised within this abstract are crucial, both for general public health and specialised dermatologists.

This edition's peer-reviewed articles form the pinnacle of top quality research. Jayarajan and Bulinska, whose article comprises this edition's Editor's Pick, provide an in-depth review into the aetiopathogenesis and management of hidradenitis suppurativa, also known as acne inversa. This disease had previously been considered low priority, but, as the authors highlight, it can have severe psychological effects on the patients. Jayarajan and Bulinska present evidence for exactly why this disease should not be disregarded, giving hope for future management and treatment of the disease. Meanwhile, an article by Ankad and Beergouder takes you on a journey into the current implications for dermoscopy, a specialised microscopy technique. Focussing on six highly prevalent skin conditions, the authors provide a detailed overview of the important characteristics of each condition at a microscopic level, providing important insights which will aid future diagnoses and patient care. These are just two of the excellent articles contained within.

All of us here at the European Medical Journal hope you enjoy reading *EMJ Dermatology 5.1* as much as we have enjoyed producing it for you. We are confident that all the content included within will spark endless, stimulating discussion, which will benefit the future of dermatology therapeutics.

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*Director, European Medical Journal*

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**References:**
**1.** UCB, Our Company. Available at: http://www.ucb.com/our-company/ [Accessed September 2017];
**2.** UCB, Annual Report 2016. Available at: http://www.ucb.com/_up/ucb_com_ir/documents/2016_annual_report_-_ENG.pdf [Accessed September 2017]


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HQ/0817/NU/00058 September 2017

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# Foreword

**Assist Prof Hassan Galadari**

*United Arab Emirates University,*
*United Arab Emirates.*

Dear Friends and Colleagues,

It is with great pleasure that I present to you *EMJ Dermatology 5.1*. This edition of the eJournal contains a comprehensive review of the 26th European Academy of Dermatology and Venereology (EADV) congress, alongside detailed abstract reviews and some of the latest peer-reviewed articles from the field of dermatology.

This year's EADV congress, held in the picturesque city of Geneva, Switzerland, proved to be an incredible success. More than 150 fascinating sessions, led by experts from >30 countries, were featured, including a focus on the use of targeted immune therapies to treat skin disorders; the breadth and quality of these riveting presentations really highlights the complex nature of our field. Details of the congress, including the poignant presentation given by the award-winning photographer Mr Rick Guidotti, can be found in the captivating Congress Review section of this eJournal.

The details of a select number of the ongoing research projects presented at the EADV congress have been outlined by their corresponding authors in the Abstract Review section of this issue and encompass a large variety of topics. I would also like to direct your attention to the series of insightful interviews held with myself and three of my colleagues on the Editorial Board of *EMJ Dermatology*, in which we explain our personal journey through dermatological practice and our hopes for the future of this exciting field.

*EMJ Dermatology 5.1* contains a myriad of high-quality peer-reviewed articles and reviews, two of which emphasise the need for interdisciplinary collaboration when treating skin disease and highlight that, for the patients, the effect of their condition is more than skin deep. Firstly, Jayarajan and Bulinska provide this edition's Editor's Pick; their review of the aetiopathogenesis and management of hidradenitis suppurativa espouses the need for co-operation between dermatologists and plastic surgeons to minimise the psychological damage to the patients following treatment. Secondly, Azambuja's insightful review outlines the need for a collaborative approach between dermatologists, psychologists, and psychiatrists in the treatment of psychodermatoses to achieve the best outcomes for patients.

I am confident that you will enjoy this edition of *EMJ Dermatology*, which contains something to interest everyone and I hope that the captivating abstracts and articles included inside will stimulate lively debate and discussion.

Kind regards,

**Hassan Galadari**

Assistant Professor of Dermatology, College of Medicine and Health Sciences, United Arab Emirates University, Al-Ain, United Arab Emirates

# EADV ANNUAL CONGRESS 2017

PALEXPO,
GENEVA, SWITZERLAND
13TH–17TH SEPTEMBER 2017

## Welcome to the European Medical Journal review of the 26th Annual Meeting of the European Academy of Dermatology and Venerology Congress

**Citation:** EMJ Dermatol. 2017;5[1]:14-26. Congress Review.

A warm welcome to the European Medical Journal review of the 26th European Academy of Dermatology and Venereology (EADV) congress, held from the 13th–17th September 2017.

This year marked the EADV's 30th anniversary, and there was no better place to celebrate the momentous event than in its home city of Geneva, Switzerland. Attracting both dermatologists and aesthetic specialists alike, the picturesque landscape of the Alps and Lake Geneva seemed most appropriate for the backdrop of this year's congress.

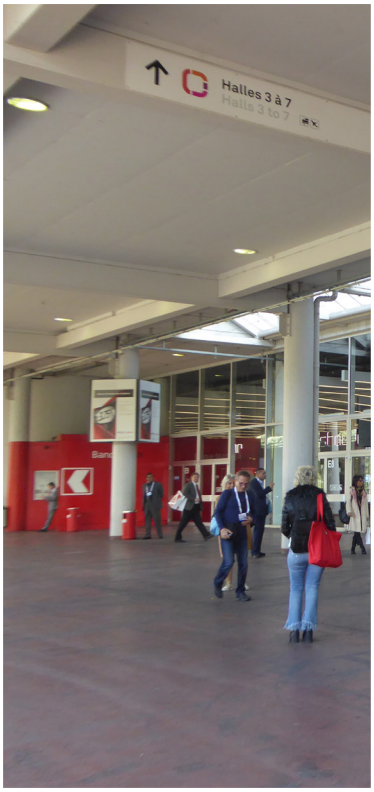
Also residing in the city of Geneva, EADV President Prof Luca Borradori was pleased to welcome attendees to the spectacular Opening Plenary Lecture, in which he presented the highlights of the scientific programme, including the >150 stimulating sessions delivered by contributors from >30 countries. With a large focus over recent years on targeted immune therapies for skin disorders, the EADV scientific committee chose "Clinical immunology: The new immunotherapies" as the key theme for practising dermatologists attending this year's congress. Dedicated to aesthetic and cosmetic dermatologists, the EADV Aesthetic Sunday programme on Sunday 17th September comprised hot topics like "Energy-based devices, including lasers" and "Botulinum toxin".

During the opening session, Prof Borradori was also proud to introduce this year's guest speaker, Mr Rick Guidotti, a well-known fashion and celebrity photographer. The thought-provoking presentation delivered by Mr Guidotti delved into his personal experiences of dermatology in the real-world and his most recent venture, named 'The Spirit of Difference', a project that uses photography to transform public perceptions of people living with genetic, physical, intellectual, and behavioural differences. Continuing the theme of breaking cultural barriers and sparking debate, a Swiss-based theatre troupe was welcomed to the stage to perform a new form of visual theatre. Insights into the human form were portrayed using shadow, light, and creative manipulation of objects, leaving the audience in awe of the stunning spectacle.

After an unforgettable beginning, the remaining 4 days consisted of continued medical education and professional development through a variety of finely-tuned sessions available to delegates. Both new and more experienced dermatologists, as well as nurses and patient organisation representatives, from around the world joined to exchange ideas and experiences, with the overall goal of improving care for patients with debilitating dermatological conditions. In his welcome speech, Prof Borradori also expressed his excitement for the opportunity to collaborate with nurses, describing their role in treating skin disease patients as: "undisputed". He stated: "A strong and constructive relationship with both patients and nurses represents one of the strategic goals of our association." In addition, a key theme throughout the 2017 congress was the acknowledgment of the ongoing involvement of patient advocacy groups in the field of dermatology, and EADV was keen to thank these associations for their contribution to improving patient experience. The Patient Society Village was formed where leading advocacy societies were able to showcase their role and feel the effect of their work on the larger world of European dermatology care.

The outstanding programme of the EADV 2017 congress successfully met the organisation's goal of keeping up-to-date with the ever-changing world of skin diseases, and our following Congress Review section will summarise some of the innovative dermatological research presented in Geneva. With abstract reviews compiled by the presenters themselves, we hope you find our review insightful and educational, whether you were lucky enough to attend the congress and would like to refresh your memory, or if you are reading the data for the first time. As the year ahead promises to be exciting for dermatological practice, we look forward to hearing your ideas and experiences at next year's EADV congress, held in Paris, France.

> "The outstanding programme of the EADV 2017 congress successfully met the organisation's goal of keeping up-to-date with the ever-changing world of skin diseases..."





## Combination Treatment Effectively Treats Rosacea Patients

COMBINATION treatment of rosacea has been found to be effective in treating both the inflammatory lesions and persistent erythema, according to results presented at the EADV 2017 congress. A EADV press release dated 14th September 2017 details the results of a multicentre, randomised, double-blind study assessing the efficacy, safety, and patient satisfaction of combined ivermectin 1% (IVM) cream and brimonidine 0.33% (BR) gel therapy. IVM and BR have been shown to be individually effective at treating inflammatory lesions and persistent erythema symptoms of rosacea, respectively.

Rosacea is a common inflammatory skin disease usually affecting the central areas of the face, including the cheeks, nose, and eyes; the cause of the disease is still under dispute. If left untreated, rosacea could worsen, and therefore, combined with the fact the disease affects highly visible areas of the body, there is a real need to develop an effective treatment that satisfies patients.

The study included rosacea patients with moderate-to-severe persistent erythema and inflammatory lesions. Patients were split into three cohorts, including two active cohorts; the first active group received IVM+BR for 12 weeks (BR and IVM once daily for 12 weeks), the second active group received IVM+BR for 8 weeks (initially with BR vehicle once daily for 4 weeks, followed by once daily BR for 8 weeks and with IVM for the full 12 weeks), and the control group received daily BR vehicle and IVM vehicle for 12 weeks.

A successful treatment was defined as an Investigator Global Assessment score of 0 or 1. Patients receiving either of the active treatments showed superior results for both erythema and inflammatory lesions compared to the vehicle group at 12 weeks (55.8% versus 36.8%; p=0.007). Patients in the active groups also reported similar rates for facial appearance satisfaction after the first 4 weeks of treatment compared to the vehicle group.




> This study develops a comprehensive and early treatment approach to this complex disease.

Lead study author, Dr Linda Stein Gold, Henry Ford Hospital, Detroit, Michigan, USA commented: "This is the first study evaluating the benefit of using both IVM 1% and BR 0.33% in combination to effectively target the multiple features of rosacea," and went on to state: "This study develops a comprehensive and early treatment approach to this complex disease."

## Action Required to Tackle Sunbed Use

TANNING still remains popular amongst many Western populations, particularly young people, despite the health risks being widely publicised. Speaking at the EADV congress, and reported in a EADV press release dated 15th September 2017, Dr Emilie van Deventer, team leader of the radiation programme at the World Health Organization (WHO), Geneva, Switzerland, expressed her concern for the users of sunbeds, pointing out that often the technology is considered a consumer treatment and not seen as a medical device. Although improvements are being made in sunbed regulation, she suggested: "it is time to take more action."

With ultraviolet (UV) radiation being the most significant risk factor for melanoma diagnosis, it is not surprising that 65% of melanomas are caused by UV radiation, and >10,000 melanoma cases in the USA, Europe, and Australia are attributed to sunbed use. Worryingly, >450,000 non-melanoma skin cancer cases are also caused by sunbed use. Interestingly, a French study by Grange et al.[1] found a strong association between an individual having a large number of risk factors for melanoma and their use of a sunbed (p=0.001), and the WHO suggests that an age of <30 years is also a prominent risk factor, reporting: "Evidence of an association between artificially tanning and risk of skin cancer clearly shows that the risk is highest in those exposed to artificial tanning early in life".

> “...the WHO stresses the need for national actions to limit the use of sunbeds, in a bid to reduce the associated health risks such as melanoma and non-melanoma skin cancers and the cost to health systems.”

Understanding why people utilise sunbeds may prove useful in designing public health strategies to reduce their use. Studies have shown that some sunbed users are concerned with health, as well as beauty, however more education is required; interventions should challenge the common misconceptions about health benefits, such as the advantages of increased vitamin D levels associated with tanning. Experts also state that public health strategies that target the appearance of skin cancer are necessary to change the attitudes of sunbed users, since improved body image is a main motivator for tanning. With the high cost-burden associated with melanoma mortality and morbidity, a Belgian analysis[2] highlighted the potential cost-savings of sunbed campaigns, reporting that every €1 invested in a campaign would result in a long-term saving of €3.60. Dr van Deventer explained: “This is why the WHO stresses the need for national actions to limit the use of sunbeds, in a bid to reduce the associated health risks such as melanoma and non-melanoma skin cancers and the cost to health systems.”

Dr van Deventer revealed that Brazil, after a long battle with legislation, shortly followed by Australia in 2016, was the first country to completely ban the use of sunbeds for cosmetic purposes, and many other countries have enforced rules for sunbed operators, including prohibiting unsupervised access. Moving forward, by working with a variety of global organisations, including the United Nations Environment Programme and the Global UV Project, the WHO aims to inform and advise on the health impact and effects of UV exposure, as well as guide national authorities on UV radiation protection.






During a discussion at the EADV congress, Dr van Deventer stated: "information campaigns are good, but not as productive as legislation", highlighting the need for enforced regulation in countries where sunbed use still remains high.

## REFERENCES

1. Grange F et al. Prevalence of sunbed use, and characteristics and knowledge of sunbed users: results from the French population-based Edifice Melanoma survey. J Eur Acad Dermatol Venereol. 2015;29(Suppl 2):23-30.
2. Pil L et al. Burden of skin cancer in Belgium and cost-effectiveness of primary prevention by reducing ultraviolet exposure. Prev Med. 2016;93:177-182.

## Prevention: The Best Cure for Sexually Transmitted Infections

MANAGEMENT of sexually transmitted infections (STI) is becoming more difficult for healthcare providers worldwide due to the increasing prevalence of the conditions and the stronger resistance many of these diseases are having to existing treatments. These issues, and potential solutions, were discussed in a EADV press release dated 15th September 2017.

According to data recently published by the World Health Organization (WHO), there are >1 million new cases of STI every day; for HIV, there were 153,000 new cases in the WHO European Region in 2015, the highest annual number since reporting began in the 1980s.[1,2] A reason for such an increase in cases, particularly with regard to HIV, could be due to the improvement in treatments, removing the 'fear-factor' of acquiring the disease.

Prof Colm O'Mahony, Countess of Chester Hospital, Chester, UK, commented: "The appliance of science has resulted in HIV becoming a chronic long-term condition, no longer feared as it was in the 1980s. Some even believe, wrongly, that it can be cured. This may be one reason why people have become lax on safer sex nowadays. Back in the 1980s, fear was a major factor in changing behaviour. Prevention campaigns were based on it and had a marked effect on STI rates, but, unfortunately, that is history now." In order to improve HIV outcomes and reduce the transmission rate, the WHO recommended that antiretroviral drug treatment be initiated for all individuals infected with HIV, regardless

of their CD4 cell count. The long-term outcomes of this recommendation are still awaited.

Resistance to treatment for STI has also become an increasing problem. In HIV, pre-exposure prophylaxis is available as a preventative measure for persons at risk, including sex workers, but many are unwilling or unable to self-fund the treatment. Syphilis, a condition that has re-emerged in several high-income countries, has acquired resistance to azithromycin 2 g, and it is feared that there will be similar resistance to penicillin in the near future. Additionally, *Neisseria gonorrhoea*, which infects 78 million people every year, has developed resistance to every antibiotic used against it and has retained resistance against previously used antibiotics. Overall, the increasing prevalence of STI, coupled with greater resistance "will make some infections almost untreatable in years to come," according to Prof O'Mahony.

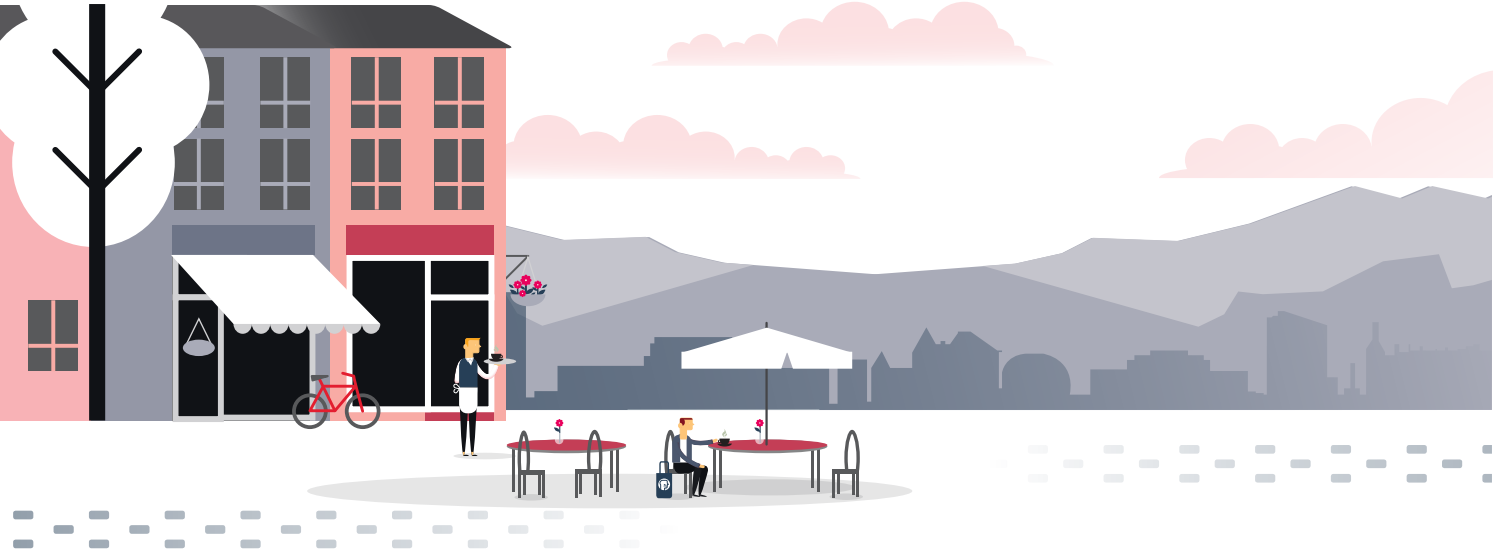
> "Prevention campaigns were based on it [fear] and had a marked effect on STI rates, but, unfortunately, that is history now."

It was in this context that Prof O'Mahony advocated his position that investment in education about sex and relationships is key to ensuring people change their behaviour and engage in safer sex to prevent STI occurring. As Prof O'Mahony pointed out: "Sure, it is difficult to argue why pre-exposure prophylaxis should be available on the NHS when there is a much cheaper solution to the problem, namely changing one's own risk behaviour." Designing awareness-based prevention programmes should therefore be a top priority for governments and education providers.




## REFERENCES

1. World Health Organization. Sexually transmitted infections (STIs). Factsheet. 2016. Available at: http://www.who.int/mediacentre/factsheets/fs110/en/. Last accessed: 27 September 2017.
2. World Health Organization. HIV cases reach over 2 million for the first time in Europe. 2016. Available at: http://www.euro.who.int/en/media-centre/sections/press-releases/2016/11/hiv-cases-reach-over-2-million-for-the-first-time-in-europe. Last accessed: 27 September 2017.



## Can Artificial Intelligence Diagnose Skin Cancer More Accurately Than Doctors?

THE INVOLVEMENT of artificial intelligence (AI) in the diagnosis and monitoring of melanoma is very much at the forefront of development of dermatological practice, according to a press release from the EADV 2017 congress dated 15th September 2017. Medical imaging has been a prominent part of personalising cancer medicine for years, especially in the early diagnosis, treatment, and monitoring of melanoma and skin cancer. Prof Peter Soyer, The University of Queensland, Brisbane, Australia, commented: "Nowadays, new high-tech imaging, combined with AI and decision support systems, will surely redefine the early diagnosis of melanoma and skin cancer!"

A landmark study published in 2017[1] tested machine learning on a convolutional neural network (CNN) for the classification of skin cancer. The CNN was fed information, using only pixels and disease label inputs with data from 129,450 clinical images from 2,032 different diseases. The CNN was then tested against 21 board-certified dermatologists in identification of the most common skin cancers and then the deadliest skin cancer from biopsy-clinical images. Researchers were astonished by the results; CNN performance was equivalent to the dermatologists across both tasks. The CNN was also capable of classifying skin cancers as 'biopsy/treatment is needed' or 'reassure patient/everything is fine.'

> "These devices will change the day-to-day practice of dermatologists."

A next logical step is the progression of such AI technologies to mobile devices, allowing the reach of dermatologists outside of the clinic. Prof Soyer explained that the areas AI development is focussed on are the automated analysis of features in dermoscopy images of skin lesions, identification of potential characteristics of melanoma, and AI being integrated into software for different types of imaging platforms. Prof Soyer also expects that smartphone dermoscopic imaging with built-in AI is likely to be the most accessible method of skin lesion analysis in the future. Some smartphone apps developed for precisely this role are already available to the

public; however, the sensitivity and specificity of these devices range astronomically, from 21–72% and 27–100%, respectively. Prof Soyer explained: "We have to ensure a minimum rate of false-positive and false-negative diagnoses. In the end, we are talking about melanoma, a fatal disease that people die of."

"These devices will change the day-to-day practice of dermatologists. We will more or less exclusively see patients with cancer and suspicious lesions that have been removed. As a consequence, we will have more time for counselling on treatment, etc., because we will not have to see all the patients who have harmless skin lesions," Prof Soyer speculated. He also cautioned that AI technology, despite its massive advantages, will have some drawbacks and stated: "...it cannot process contextual information, like family anamnesis or other symptoms. It does not see the whole patient. For these reasons, I am quite optimistic that human dermatologists will always be needed!"

REFERENCES

1. Esteva A et al. Dermatologist-level classification of skin cancer with deep neural networks. Nature. 2017; 542(7639):115-8.

## Clear Rosacea Patients Have Delayed Time to Relapse

ROSACEA patients who achieve a clear response to treatment experience a delayed time to relapse compared to those achieving an almost clear score, according to a EADV press release dated 16th September 2017 and results presented at the EADV 2017 congress. These findings were obtained from pooled results of four studies evaluating the use of topical therapies for treating the inflammatory papules and pustules of rosacea. Results of rosacea treatment are defined on a 5-point investigator global assessment (IGA) scale; a score of 1 is defined as almost clear and a 0 score is defined as clear.

Study author Dr Guy Webster, Thomas Jefferson University, Philadelphia, Pennsylvania, USA, commented: "Rosacea is a chronic dermatological disease with remissions and exacerbations. Improving treatment options with earlier effective treatment and longer remission times may not only control symptoms, but also delay progression of the disease." He continued to explain: "This first-of-its-kind analysis shows that both remission time and quality of life are improved if patients achieve an endpoint of clear (IGA 0), compared with patients who achieve almost clear (IGA 1)."

> "Improving treatment options with earlier effective treatment and longer remission times may not only control symptoms, but also delay progression of the disease."



Patients with an IGA 0 score were associated with a delayed time to relapse of >5 months compared with IGA 1 patients. Twice as many IGA 0 patients remained treatment free at 8-month follow-up compared to the IGA 1 patients (54% versus 23%). It was commented by the researchers that this prolonged time to relapse may also contribute to improved quality of life and satisfaction with treatment for those IGA 0 patients. An additional one-third of IGA 0 patients reported a clinically meaningful difference (≥4 points) in the dermatology life quality index score than the IGA 1 patients.

Rosacea presents as flushing, permanent erythema, and inflammatory lesions and can affect both men and women equally, usually after the age of 30 years. Despite no specific cause of the disease being known, trigger factors such as spicy food, alcohol, and stress are known to affect the disease severity. Rosacea symptoms are very evident and visible, and as such the disease significantly impacts quality of life of patients in the form of anxiety, embarrassment, depression, and low self-confidence, thus warranting successful, effective treatments that enhance patient satisfaction.

## A Ban on Methylisothiazolinone Finally Passed

The legal concentration of methylisothiazolinone (MI), a preservative used in cosmetics, allowed in wash-off products has been reduced in the European Union (EU), according to a EADV press release dated 15th September 2017 presented at the EADV 2017 congress.

MI, an isothiazolinone biocide, is widely used as a preservative in cosmetics to prevent micro-organism growth in products.

> We dermatologists believe that the maximum concentration should not be higher than 15 ppm for rinse-off products.

Surprisingly for dermatologists, this biocide is commonly used in numerous face and body products, despite its cytotoxic nature. Prior to 2000, MI was used in combination with methylchloroisothiazolinone (MCI); however, due to the observation of allergic reactions since the 1980s, there was a significant need to reassess the guidelines. The initial response to these allergic reactions was to remove MCI from products and use MI in isolation. Due to the less effective nature of MI, concentrations of MI were increased to replicate the antimicrobial nature of the MCI/MI combination.

In 2005, a cap of 100 ppm was enforced for the maximum permitted concentration of MI, which was previously unregulated. However, despite the cap on MI concentrations, severe allergic reactions were continuing to be reported. A multicentre trial of 8,680 and 7,874 patients from Belgium and France, respectively, showed a marked increase in contact allergy caused by MI. Results showed a significant sensitisation rate of ~6.0% in 2012 and an increase to 7.0% in 2013.[1] A continued increase continued to be reported in the literature.

As a result of the continued increase in allergic reports, a ban on using MCI/MI mixture in leave-on cosmetics was also introduced in July 2015, followed by a ban on the inclusion of MI in leave-on cosmetics earlier this year, in February 2017. Despite this positive step in the right direction, Prof An Goossens, Leuven, Belgium explained: "The ban on the use of MI needs to be extended, with stricter regulations on the use of this agent in rinse-off products." In rinse-off products MCI/MI and MI alone can be present in concentrations of up to 15 ppm and 100 ppm, respectively, but dermatologists have been campaigning for a further reduction in legal concentrations.

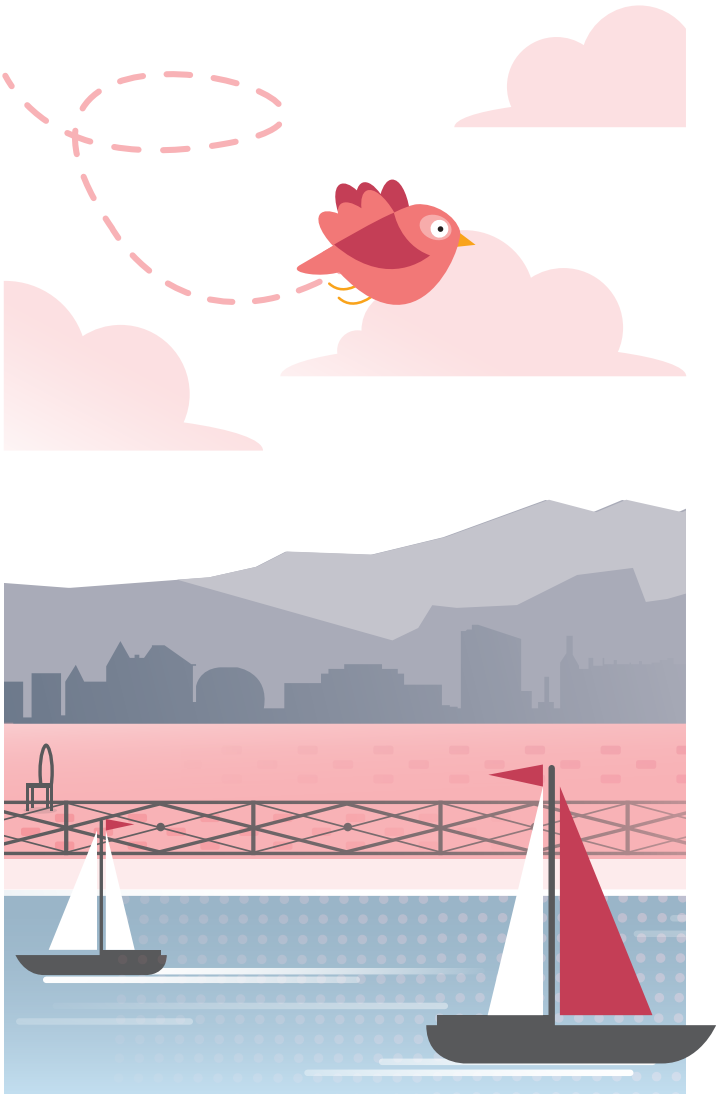



A prospective study at 11 European dermatology departments from 8 countries collected data from the 1st May until 31st October 2015 from patients with positive MI patch tests. MI allergic patients were found to develop an allergic reaction to soap at 100 ppm (10 of 10 patients) and to 50 ppm soap (7 of 9 patients) during 21-day application; no reactions were observed for those using soap without MI. As such, dermatologists believe the limit of 100 ppm for rinse-off products is still too high.

Prof Goossens reported: "We dermatologists believe that the maximum concentration should not be higher than 15 ppm for rinse-off products." As a result of the increased discussion surrounding the use of MI in cosmetic products, dermatologists have gained greater understanding of the effects such molecules in cosmetics can have, even at seemingly low concentrations. As a result of dermatologists' persistence, the maximum concentration of 15 ppm has been agreed upon in the EU earlier this year and is expected to be implemented in April 2018. The passing of new EU legislation on the use of MI in rinse-off cosmetics has been a massive success for dermatologists throughout the continent and will pave the way for other molecules to be reassessed and regulations altered as required, ensuring the public safety.

## REFERENCES

1. Aerts O et al. Contact allergy caused by methylisothiazolinone: The Belgian-French experience. Eur J Dermatol. 2015;25(3):228-33.



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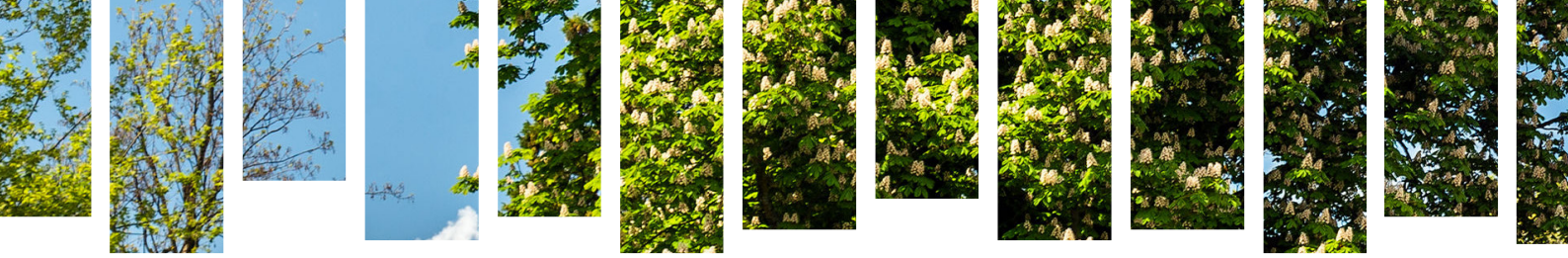



## Hassan Galadari

Assistant Professor of Dermatology, College of Medicine and Health Sciences, United Arab Emirates University, Al-Ain, United Arab Emirates.


**Q:** To begin, could you tell us what first inspired you to pursue a career in dermatology?

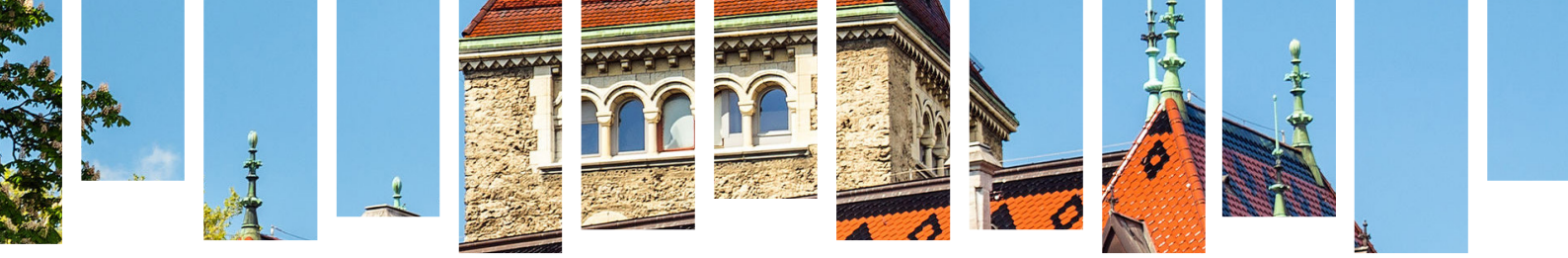
**A:** I have always been a visual person. I have enjoyed looking at pieces of art, or at nature, and have always truly appreciated what I was seeing. In addition to this, I have always been very interested in the sciences. Biology was my favourite subject in school and since I was a child, I knew I wanted to be a doctor. When I got into medicine, I had to make a choice of what to specialise in. Granted, my father is a dermatologist and I was exposed to the subject from the very beginning, I went back to my first passion, which was art and I realised that dermatology allows me to fulfil that artistic calling into a medical field that fits me, and that's why it was dermatology. The nice thing about dermatology is that you help patients with a disease that is visible to them. It is not just a number from a lab test or on a monitor. Patients actually see that your treatment is working for them and that is an utterly fulfilling thing indeed.

**Q:** You work alongside your father, a respected dermatologist in his own right, at the Galadari Derma Clinic, Dubai, United Arab Emirates (UAE). How has working with your father shaped your understanding of dermatology and your training?

**A:** I am going to admit, at first it was a bit rocky. I was this young person who thought I knew it all, extremely ambitious, and all-knowing. My father had been in practice for >25 years when I joined him. We did manage to find common ground in the end and there is a great deal of mutual respect. I enjoy it when he calls me in to see a clinical case and I enjoy doing the same and rely on his expertise when seeing patients. I tell patients that two pairs of eyes are better than one and they do like that. Another thing to note is that I got to experience my father at a completely different level. He was my father first, my teacher, and is now my colleague and friend. It's fun and I would not change it for the world. He never pushed me into becoming a dermatologist, but he made me appreciate the field further by sheltering my other interests. It is a great thing. I now pray that one of my children follows in my footsteps too and I end up getting the chance to be on the other side of the fence.

**Q:** You have been Assistant Professor of Dermatology at the UAE University since 2007. How has the teaching of dermatology changed since your own education and training?

**A:** Teaching is a great calling. Teachers are truly wonderful people who have the knack for making you think and wonder. Not everyone can teach and it takes a special person to be able to do that. I have learned from the best teachers and I strive to be like them one day. Education is a key element in medicine, we never stop learning. It is important to realise that if we tell ourselves that we know it all then we have failed as doctors and failed our patients. In the past, teaching was more teacher driven; now it is student driven. Students have this wide array of information available to them everywhere, from the internet to books and journals, and it is all within a finger push away. I remember we used to slave away in the library; now you do not actually need to go to a physical library, you can sit in the comfort of your own home and access a vast amount of information and publications, all of them up-to-date and peer-reviewed. This is also challenging because, given the amount of information available, you have to be more critical with what you find and what you can do with this information. So now, we have to teach our students the ability to appraise this information and not just take it as dogma.



> “Teaching is a great calling. Teachers are truly wonderful people who have the knack for making you think and wonder.”

**Q:** The field of dermatology has progressed rapidly in recent years. What do you consider to be the biggest or most influential breakthrough?

**A:** There are many. Dermatology is a field that is both medical and surgical. The medical aspect has seen a boom of treatments for psoriasis, atopic dermatitis, and alopecia. There have been many biologics that have been approved for each of the aforementioned diseases with many more in the pipeline. There have also been a number of breakthroughs in melanoma, although we are still awaiting better treatments with better prognostic indicators. As for the surgical/cosmetic aspects, botulinum toxin remains one of the most important breakthroughs since the discovery of penicillin. It has been approved for nearly a dozen indications with more than a hundred still being studied. Botulinum toxin was recently a subject matter and cover story of TIME magazine.

**Q:** Could you tell us if there is a specific dermatological procedure that you find particularly satisfying to perform? Could you share with us one of your more memorable success stories?

**A:** My main area of interest is soft tissue augmentation, specifically the use of fillers. It is the most satisfying treatment or procedure that you can perform on patients. You can literally see the area that has been injected being corrected. There are many memorable stories pertaining to this. One comes to mind in the form of a patient who developed a complication after being injected incorrectly. She presented with areas of neurovascular compromise that was apparent as necrosis. Worse yet, it was the tip of the nose that was injected and the patient was a flight attendant, making the distortion quite apparent. After realising what filler was injected, it was just a matter of dissolving it and making sure that there were no permanent scar formations, which there were not, and the patient was very content.

**Q:** You have spoken in the past about the harmony of beauty and science. Do you believe that aesthetic considerations are generally overlooked in medical debate?

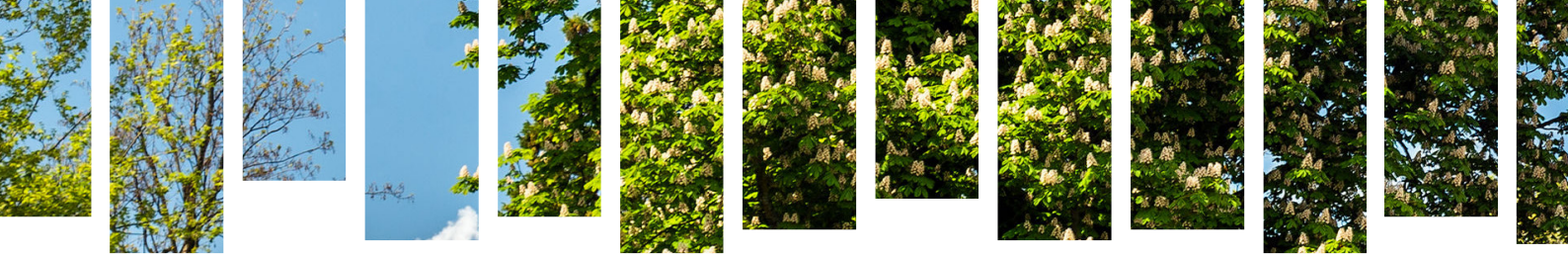
**A:** They are. The medical dermatology community does not look seriously into the aesthetic aspect, especially in Europe. Cosmetic procedures are not performed primarily by dermatologists in that area and patients are treated by general practitioners that dub themselves aesthetic practitioners. This is not the same in the USA, where dermatologists and plastic surgeons hold the larger share of the speciality. These procedures are performed on the skin and, as dermatologists, we should own up to this. We should make sure that practitioners in our field are properly trained and make sure that practices are performed under sound scientific background. Unfortunately, given that the field of aesthetic dermatology is diluted by many, in addition to the influence of industry on the core subject matter, a great many dermatologists have stopped taking the field seriously.

**Q:** How important do you believe events like the European Academy of Dermatology and Venereology (EADV) congress are to the field of dermatology? Is there anything about these events that you find particularly useful?

**A:** The EADV congress is an important meeting. It is the most important in Europe and the second largest in the world after the American Academy of Dermatology (AAD) meeting. The meeting helps bring together many specialists from different parts of the world to discuss the latest advances in all areas of dermatology. It is extremely useful for dermatologists to attend this meeting; they can learn from their peers as well as socialise, and exchange experiences.

**Q:** You recently co-authored a paper on the practice of tanning among Emirati youth. With melanoma rates on the rise, could you tell us a little bit about your results and what potential solutions there are to this growing problem?

**A:** Although the UAE is a progressive country, its people’s practices remain conservative. We



conducted a study in which we looked at university students from the UAE and looked at their sun exposure. What we found was that even though the tanning numbers were not as high when compared to the West, it is on the rise due to social influences. That being the case, the rate of melanoma has not changed and I believe that is mainly due to the dark skin tone of the people from the area. That being said, we should still promote safe sun exposure practices.

**Q:** In your opinion, what new challenges are dermatologists going to face in the next few decades?

**A:** Dermatology has been a speciality that has always been overlooked by others in terms of relevance. We should continue to promote our speciality across the medical spectrum and point out the importance of what we do. There have been many bridges that have now been built that connect the field to others, such as rheumatology, plastic surgery, and even obstetrics and gynaecology. This has become apparent in combined speciality congresses as well as joint clinics. This is a great step going forward and that should be encouraged.

**Q:** Lastly, what advice would you give to budding medical students who intend to pursue a career in the field of dermatology?

**A:** Love the field. Own it. Have that passion that drives you and makes you not just look at it as a profession, but more of a calling. The field will treat you well and the patient's gratitude will certainly make your day.

## Francesca Farnetani

Department of Dermatology, University of Modena and Reggio Emilia, Modena, Italy.

**Q:** Firstly, what made you decide to specialise in the field of dermatology?

**A:** The idea of specialising in the field of dermatology matured during my first years of university, because the skin, in its different aspects, provided many opportunities in the field of research and there is still much to discover, with particular regard to diagnostics.

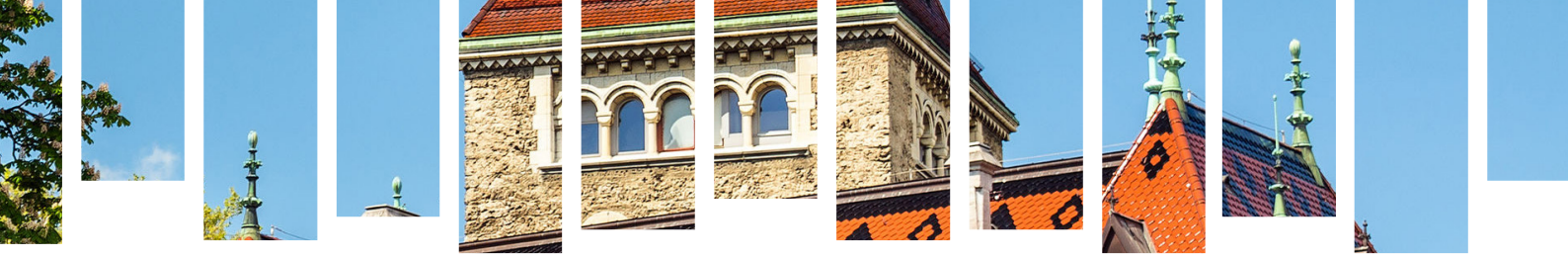
**Q:** Since completing your residency at the University of Modena and Reggio Emilia in 2012, you have stayed on as a research fellow under Prof Giovanni Pellacani. What research are you particularly proud to have carried out at this institution?

**A:** My main research topic is melanoma diagnosis and characterisation. This includes early recognition of skin tumours by means of non-invasive methods like reflectance confocal microscopy (RCM), a new technique enabling the *in vivo* visualisation of skin structures at cellular level resolution for the *in vivo* characterisation of skin tumours at the histological resolution.

**Q:** Could you give us an insight into the research area you are currently working on?

**A:** The acquired experience in the use and interpretation of RCM led to the systematic study of a series of cases characterised by difficult dermoscopic aspects. The possibility of identifying cytological aspects specific to melanoma and of distinguishing tumoural infiltration from inflammatory cells demonstrated the value of this technique in accurate melanoma diagnosis and classification. The possibility of determining an *in vivo* histology through the use of confocal laser microscopy was explored, correlating *in vivo* cytological and architectural features with dermoscopic features and histopathology in many cases of melanoma and other skin tumours, like basal cell carcinoma.

> "I think that the most important step in combatting this disease is the early diagnosis of melanoma..."



> The idea of specialising in the field of dermatology matured during my first years of university, because the skin, in its different aspects, provided many opportunities in the field of research...

**Q:** You are a member of the Italian Society of Dermatology and Venereology (SIDeMAST) and the European Organization for Research and Treatment of Cancer (EORTC) Melanoma Group; what impact do you think societies such as these have on the field?

**A:** The opportunity to be part of such international societies is paramount for the exchange of ideas and experience. Furthermore, they create expert groups, any one of which is able to make a contribution. I strongly believe that with the aggregation of ideas we can have great results.

**Q:** You have a specific interest in the diagnosis and classification of melanoma, and in 2015 you co-authored a paper on skin cancer diagnosis using RCM and the increased accuracy of RCM imaging. Why is being able to diagnose the correct type of melanoma so important regarding treatment?

**A:** Identification of melanoma characteristic features was sometimes difficult but the provision of an *in vivo* histology by confocal laser microscopy gives the opportunity to carry out a correct diagnosis and consequently choose the correct treatment. On the other hand, in cases of a false positive, with the use of confocal laser microscopy it is possible to avoid unnecessary excision.

**Q:** With the incidences of melanoma increasing, what do you think is the most important step in combatting this disease worldwide?

**A:** I think that the most important step in combatting this disease is the early diagnosis of melanoma by the use of confocal laser microscopy. I would recommend that the population has an annual check of any nevi.

**Q:** Earlier this year you were involved with the publication of a paper on the effect of topical vitamin E on skin irritation; what were the take-home messages from this paper and what effect do you hope it will have on the field of dermatology?

**A:** The use of confocal laser microscopy is applicable to different research fields; for example, in this case, we used confocal laser microscopy to monitor the therapeutic response to topical treatments like vitamin E, which is able to reduce inflammation.

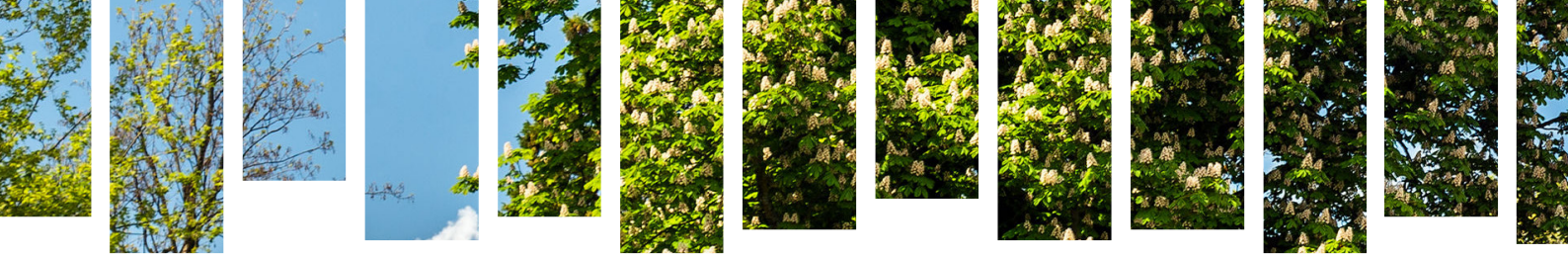
**Q:** Looking to the future, is there a specific area of dermatology or, more specifically, melanoma that you would like to research further?

**A:** To be able to create a melanoma classification by using confocal laser microscopy correlating with the immunohistochemical and genetic aspects of the tumour. In this way we will be able, with only the use of confocal laser microscopy, to understand the immunohistochemical and genetic behaviour of the tumour.

**Q:** In the coming years, what do you think will be the biggest challenge facing dermatologists, and how can the scientific community tackle this?

**A:** I think that the scientific community of dermatologists has two big challenges: the first is advanced metastatic melanoma therapy and its management. In this aspect, I think it is very important to collaborate with oncologists for the diagnosis, management, and follow-up of the tumour. The second is the creation of new aesthetic dermatology techniques from a scientific point of view. In this aspect, I think it is very important to create international guidelines on this topic that is, in many aspects, new and unexplored.

> The opportunity to be part of such international societies is paramount for the exchange of ideas and experience. Furthermore, they create expert groups, any one of which is able to make a contribution.




## Allison Cowin

Professor of Regenerative Medicine, University of South Australia, Mawson Lakes, South Australia; Senior Research Fellow, National Health and Medical Research Council (NHMRC), Canberra, Australia.


**Q:** As a Research Professor at the Cowin Labs and Future Industries Institute (FII), University of South Australia, can you briefly explain your roles and responsibilities?

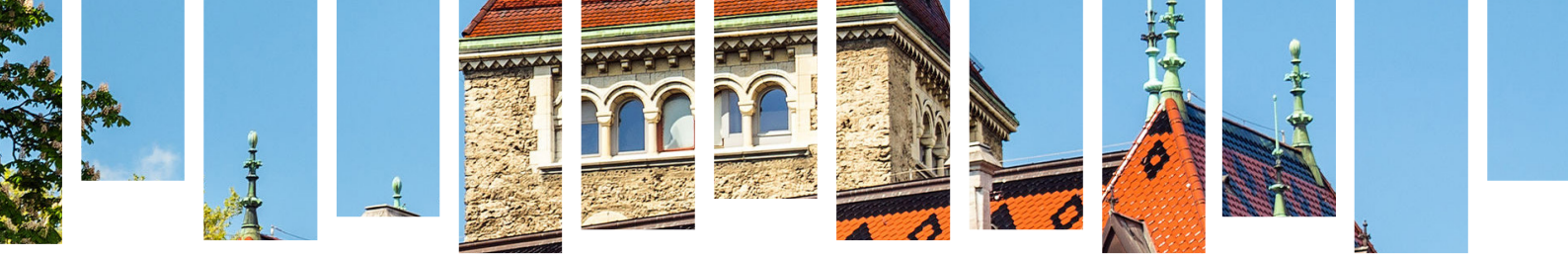
**A:** My regenerative medicine research group consists of 14 members, including staff and students, who are actively developing new approaches and technologies for the treatment of wounds. My group performs both basic and applied research aimed at understanding the mechanisms and processes of wound healing as well as developing new technologies and treatments for improving healing outcomes. My research has been supported by >$12 million in research funding from the National Health and Medical Research Council (NHMRC), the Australian Research Council, the Wound Management Innovation Cooperative Research Centre, the Cell Therapy Manufacturing Cooperative Research Centre, DEBRA Australia, and the Channel 7 Children's Research Foundation, and has resulted in >100 publications, chapters, and patents. My research has been included in the NHMRC's '10 of the best projects' publication and I have received awards including: Women in Innovation: Science award (2016), South Australian finalist in the Telstra Women's Business awards (2015), World Union of Wound Healing Societies (WUWHS): Contribution to Clinical or Preclinical Research (2016), and finalist in the 'Australian Innovation Challenge' (2015).

**Q:** Can you tell us more about the work that is being carried out by the FII and your aspirations for the future of this programme?

**A:** The FII is the University of South Australia's new multi-million-dollar flagship institute focussing on building knowledge and capacity in core future industries and developing the University's internationally competitive research capacity across four key strands: minerals and resources engineering, energy and advanced manufacturing, environmental science and engineering, and biomaterials engineering and nanomedicine. My research is part of the biomaterials engineering and nanomedicine strand, which facilitates connections between chemists, materials scientists, and biomedical researchers to work directly with clinicians and the biotechnology and medical technology industries. This interdisciplinary approach helps us to discover exciting new ways to diagnose, manage, and treat debilitating diseases such as chronic wounds, cancers, and autoimmune diseases.

**Q:** Were you always interested in dermatology, particularly wound care and regenerative medicine? What initially drew your attention to this therapeutic area?

**A:** After completing a PhD at the Department of Medicine, University of Manchester, Manchester, UK, I started my career in wound research with Prof Mark Ferguson in 1994 at the same institution. Prof Ferguson had one of the largest wound research programmes in the world and his team of scientists and clinicians inspired me to focus on developing new approaches to tackle the growing burden of chronic non-healing wounds and scarring. In 1996, I moved to Adelaide, Australia, to join the Cooperative Research Centre for Tissue Growth and Repair and it was there that I first started to work on the role of the cytoskeleton in wound healing. During the >20 years that I have spent in wound healing research, I have been touched by the strength and resilience of the people I have met who live with non-healing ulcers, burns, and fragile skin and it is these people that inspire me to work harder to develop new therapies and approaches to improve the way that wounds heal.



**Q:** You are renowned for your work on the cytoskeletal protein Flightless I (Flii). Can you tell us more about this protein and its impact on tissue repair?

**A:** Flii is a member of the gelsolin family of cytoskeletal proteins that regulate actin by severing pre-existing filaments and/or capping filament ends to enable filament reassembly into new cytoskeletal structures. Flii is also involved in numerous cellular activities, including regulating transcription via coactivation of nuclear hormone receptors and regulation of β-catenin-dependent transcription. Over the past 14 years, my group has investigated the function of Flii in the wound repair process and studied its mechanism of action using *in vitro* and *in vivo* models of wound healing, burn injury, and fibrosis. We were the first to show that Flii is an important inhibitor of wound repair and that, if we reduced Flii expression, we could improve healing. Reducing Flii gene expression in either keratinocytes or fibroblasts increased their proliferation, migration, and adhesion. Flii-deficient mice showed improved re-epithelialisation while Flii-overexpressing mice had impaired wound healing with larger, less contracted wounds, reduced cellular proliferation, and delayed re-epithelialisation. Wounds in Flii-overexpressing mice also had significantly elevated levels of collagen I, and overexpression of collagen is a major contributing factor to excessive scar formation. These studies identified Flii as a central negative regulator of wound repair and suggested that reducing the level of Flii would be a promising approach to improving wound repair and reducing scar formation. This research was included in the NHMRC's '10 of the best' publications and has been widely published in international journals.

**Q:** Can you share some details on the focus of your current research and how you would like your work to progress over the next 5 years?

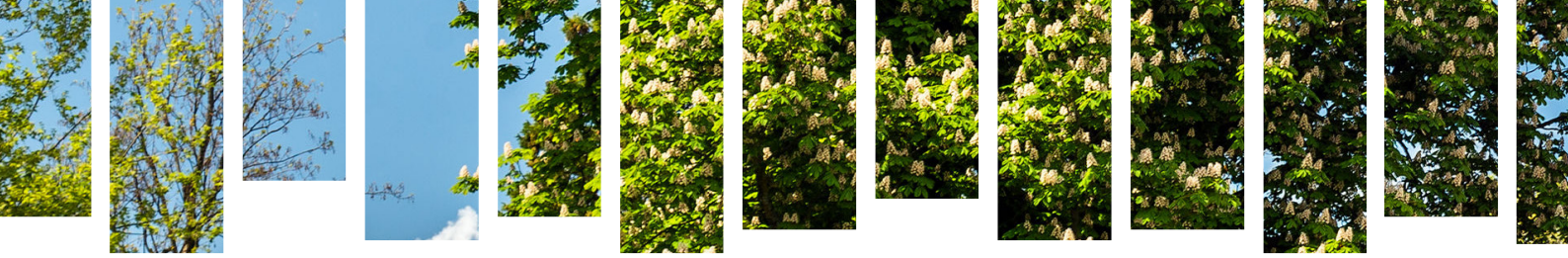
**A:** My current research spans all aspects of wound healing, from chronic non-healing diabetic wounds to burns and hypertrophic scars, as well as the fragile skin condition epidermolysis bullosa. More recently, I have been interested in inflammatory skin conditions, skin cancers, and developing new topical approaches for the treatment of wound infections. Our major focus is the development of a monoclonal antibody that 'mops up' extracellular Flii and improves healing responses. Working with AbRegen Pty Ltd. to commercialise the Flii antibody technology, and with the support of TechinSA, UniSA, and the Wound Management Innovation Cooperative Research Centre, we are progressing these studies towards human clinical trials. Our other projects range from identifying the role of Flii and its binding proteins, LRRFIP1 and LRRFIP2, in skin blistering disorders, such as epidermolysis bullosa, to performing preclinical assessments of cell therapies for the treatment of diabetic wounds. Studies are also progressing with the aim of understanding the role of pericytes in angiogenesis and diabetic wound healing and developing new approaches to resolve excessive inflammation in wounds. Over the next 5 years, I hope to have our antibody therapy approved for the treatment of wounds and have progressed our stem cell therapy for the treatment of diabetic wounds and burn injuries.

**Q:** During your career, what do you feel has been your biggest achievement?

**A:** My biggest achievement has been my Flii programme of research, which has been ongoing for 14 years, has received >$6 million in independent research grants, and has resulted in numerous publications in leading international journals. In addition, Flii research has led to three patent families and is being translated into a clinical product through my spin-out company, AbRegen Pty Ltd.

**Q:** As Program 2 Leader of the Wound Management Innovation Cooperative Research Centre and Project Leader in the Cooperative Research Centre for Cell Therapy Manufacturing, how important do you believe centres such as these are in developing the field of dermatology?

**A:** These large, well-funded centres bring together scientists and clinicians with common goals and encourage blue-sky research to occur that potentially will translate into future therapies and



treatments for patients with wounds and skin conditions. They also bring together industry and end-users, which ensures that the research is kept relevant and focussed and educates the next generation of researchers.

**Q:** Lastly, if money was no object and you could cure one dermatological condition, what would it be and why?

**A:** I would cure epidermolysis bullosa. This skin blistering disease is horrific and children with this condition currently have no respite from the pain and scarring that is associated with their blistered skin. Developing a treatment that will improve healing of these wounds is a personal goal of mine, particularly having met some amazing families and children who live their lives with courage and bravery despite having to endure the impact of their wounds on a daily basis.

> “My biggest achievement has been my Flii programme of research, which has been ongoing for 14 years, has received >$6 million in independent research grants, and has resulted in numerous publications...”

## Jennifer Cather

Director of Modern Dermatology, Co-director of Cutaneous Lymphoma and Graft versus Host Clinics, Baylor University Medical Center, Dallas, Texas, USA.

**Q:** Firstly, could you enlighten us as to whether there was a specific person or event that inspired you to specialise in dermatology?

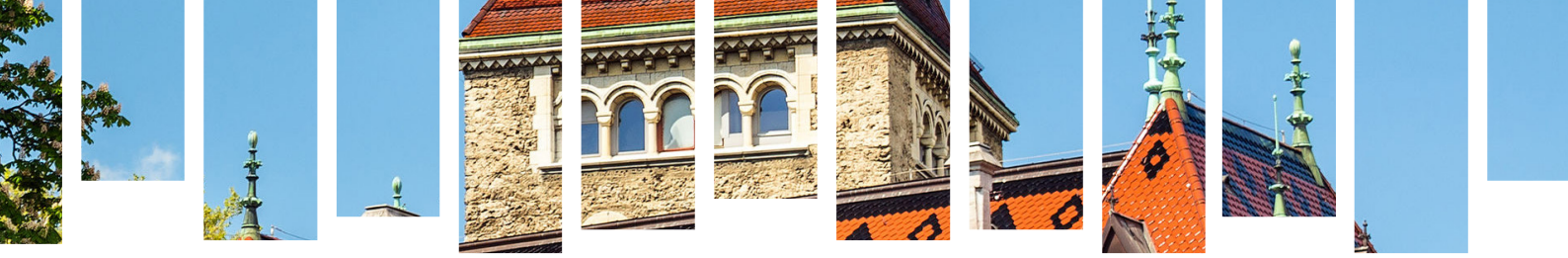
**A:** When I had made the decision to explore switching from internal medicine to dermatology, I was introduced to Madeleine Duvic. She introduced me to dermatologic clinical trials. Her empathy for her patients and her brilliance were inspirational. She inspired me to pursue a career in dermatology.

**Q:** You have written extensively on the topic of psoriasis; what is it about this disease that makes it so problematic for dermatologists?

**A:** Psoriasis is complicated, its impacts are unique and oftentimes far-reaching. A functional patient–physician therapeutic alliance is required for a successful outcome. Agenda setting is an important component during the individual visits. The psychosocial impact of the disease is as important, if not more important, than the visible disease. In our clinic, we use a team approach to help manage the time commitment these patients require for adequate therapy. Many dermatologists do not have the time or experience to employ systemic therapies and therefore patients are often undertreated and have long-term systemic sequelae, such as arthritis and psychosocial stigma.

**Q:** Some skin diseases present themselves early in childhood; what special considerations must be taken into account in these paediatric cases?

**A:** The most important thing I do as a dermatologist for my paediatric dermatology patients is listen to them and educate them. I am often the very first person to whom paediatric patients tell their true feelings. Teaching children to control what they can is my goal. For instance, smoking and obesity can exacerbate psoriasis so starting an early dialogue about healthy lifestyle choices is imperative. Another dynamic that requires finesse is involving the patient’s parents in the appropriate treatment plan. The hardest situation I have encountered is a 16-year-old adopted child with 30% of her body surface area covered by psoriasis. Her mother felt that psoriasis was not worthy of systemic treatment since it was “only a rash”.



> “Psoriasis is complicated, its impacts are unique and oftentimes far-reaching. A functional patient–physician therapeutic alliance is required for a successful outcome.”

**Q:** In your opinion, what has been the most influential dermatological discovery in the last 20 years and what has its impact been on the field subsequently?

**A:** Technology has changed the field of dermatology. Increased understanding of the immune system and the ability to target particular cells or cytokines has revolutionised dermatology. Additionally, lasers are cool as well!

**Q:** You are currently involved in the organisation of a number of clinical trials; are there any results you are particularly looking forward to? How do you hope they will influence the field?

**A:** I am excited about the paediatric psoriasis trials. The results of these trials should help to further define the high-risk paediatric population. By developing earlier interventions, we may be able to spare our paediatric patients from the social and medical consequences of this illness.

**Q:** Many skin conditions, such as melanoma, are becoming increasingly common. Do you consider overcoming this dermatological issue to be a matter of public awareness, government policy, or both?

**A:** I think overcoming this issue will require a multifaceted approach with research at its core. In order to raise public awareness, we need to better understand the science behind the increasing incidence of various skin diseases and skin cancers. The results of this research will allow increased public awareness via education by organisations such as the American Academy of Dermatology (AAD). Ongoing research and education will also inform policy. For example, the government has created policies in the USA that regulate tanning bed use, as more evidence has accrued questioning their safety.

**Q:** Is there a dermatological disease that you feel is academically under-represented and you believe warrants research on a larger scale?

**A:** Cutaneous graft versus host disease (GHVD), a disease with potentially disfiguring and life-threatening consequences, is completely under-funded and under-studied in the USA. We can cure leukaemia and lymphomas with bone marrow transplants but some patients then develop horrible cutaneous GVHD. Additionally, vitiligo and alopecia areata could be helped by some drugs in the marketplace, and I hope the trials go forward.

**Q:** How important do you consider the role of international conferences, like the European Academy of Dermatology and Venereology (EADV) congress, to be with regard to furthering dermatological research?

**A:** I love to work with European dermatologists. I have learned a lot from them and enjoy their perspective. European countries have various forms of managed healthcare and some of their clinical research involves efficiency and allocation of resources. With the increasing costs associated with healthcare in the USA, these factors are becoming more and more important.

**Q:** What challenges do you expect dermatologists to face in the next decade, and how do you think they can best be overcome?

**A:** One of the major challenges we face is access to care. Through improved education and by collaborating as a community, we will help increase the understanding of diseases and raise patient awareness. It can be very difficult to predict what the next decade may bring; however, we will continue to strive to learn to adapt to our patient’s needs.

**Q:** Finally, do you have any words of advice for the next generation of dermatologists?

**A:** Enjoy all aspects of your career. Some of the most important things you learn will be from your patients. You will be humbled, but life without humility would be a life without learning.

# INNOVATION THAT DRIVES YOUR DERMATOLOGICAL FUTURE

## This symposium took place on 14th September 2017 as a part of the 26th European Academy of Dermatology and Venereology (EADV) congress in Geneva, Switzerland


**Chairperson**

**Bernd Bonnekoh[1]**

**Speakers**

**Jorge Juan Fernández García,[2] Christian Surber,[3] Anthony Bewley[4]**

*1. Clinic for Dermatology, Otto-von-Guericke University, Magdeburg, Germany*
*2. E-Health Innovation Department, Sant Joan de Déu Hospital; MOEBIO/d-HEALTH, Barcelona, Spain*
*3. Department of Dermatology, University Hospital of Basel, Basel;*
*Department of Dermatology, University Hospital Zürich, Zürich, Switzerland*
*4. Barts Health NHS Trust; College of Medicine, Queen Mary University of London, London, UK*



**Disclosure:** Prof Surber has acted as a consultant to Actelion Pharmaceuticals, Basilea Pharmaceutica, Bitsplitters, CureVac, Galderma, Janssen Research and Development, LEO Pharma, Regensdorf-Watt, Novartis Consumer Health, Novartis International, Ultrasun, and Spirig Pharma. Dr Bewley has acted as an ad hoc consultant to AbbVie, Almirall, Galderma, Janssen, LEO Pharma, Lilly, Novartis, Stiefel (GSK), and Thornton & Ross, and as a medical advisor to Changing Faces, the National Eczema Society, and the Psoriasis Association. Prof Bonnekoh has functioned as a consultant and/or referent and/or participant in clinical studies for AbbVie, Biogen, Dermapharm, Janssen, LEO Pharma, Eli Lilly and Company, Novartis, Pfizer, and Stiefel (GSK). Mr Fernández has declared no conflicts of interest.
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## MEETING SUMMARY


The main objectives of this symposium were to review the importance of topical therapies in the treatment of psoriasis and the unmet clinical and patient quality of life (QoL) needs that still exist, to discuss the innovation seen with reformulations of existing active pharmaceutical ingredients (API), and to align changes in future dermatology practice with these topical treatment innovations. Mr Fernández introduced the topic of 'looking to the future', with a wide-ranging, big-picture view of the changing face of medical practice and the increasing role of technology, including specific examples of how these trends will affect dermatology practice. Prof Surber built on the theme of innovation to discuss how novel products and approaches can be pursued in dermatology, particularly in the area of topical psoriasis treatments. Prof Surber's presentation and the subsequent talk by Dr Bewley described how innovations can translate into improved patient outcomes in key areas, including psoriasis control, itching, sleep, and overall health-related QoL. Prof Bonnekoh tied the various threads of the symposium together by showing how the new technological and pharmacological options could help clinicians evolve their overall approach to long-term topical management of psoriasis, moving from a more reactive mindset to safe and effective proactive control. Finally, the audience was given the opportunity to ask questions in a brief panel discussion.

# The Future of Medicine Versus the Medicine of the Future: The Future is Already Here

Mister Jorge Juan Fernández García

## How the World is Changing

Although many commentators have attempted to anticipate 'the future of medicine', it is perhaps more relevant to turn the concept around and look towards 'the medicine of the future': the ways in which medical practice will be different from what we know today and the trends that are already being established. In order to provide optimal, patient-centred care, it is important to recognise how the opportunities that are available to physicians and patients are changing, particularly with regard to digital innovations and changes in the ways that people communicate with each other in the delivery of healthcare.

Broadly speaking, healthcare has experienced three major revolutions: the hygiene revolution of the 1800s, the pharmaceutical revolution of the mid-20th century, and the data revolution that is currently ongoing. As medicine becomes more of an information technology, the pace of change is growing exponentially. Although it could be possible to call this 'progress', the term carries the implication that everything will improve, but the relative importance of different institutions and processes will stay the same; what we are experiencing here is more accurately described as 'disruption', where there is more extensive change and some previously essential concepts and organisations may disappear altogether.

## Trends in Healthcare

Among several key trends that physicians should track, virtual visits are on the rise. Indeed, most communications between patients and physicians will likely be digital. An analysis by the Kaiser Permanente company found that consultations by e-mail or through other online platforms have more than doubled in the past 5 years and are on track to outnumber in-person visits by 2018.[1] Since office visits are not declining substantially, these virtual visits represent a complement to in-person care, not a substitution. In dermatology, several online services now exist for patients to receive a virtual consultation with a board-certified physician for a small fee; these services could represent an additional or alternative revenue source for interested dermatologists.

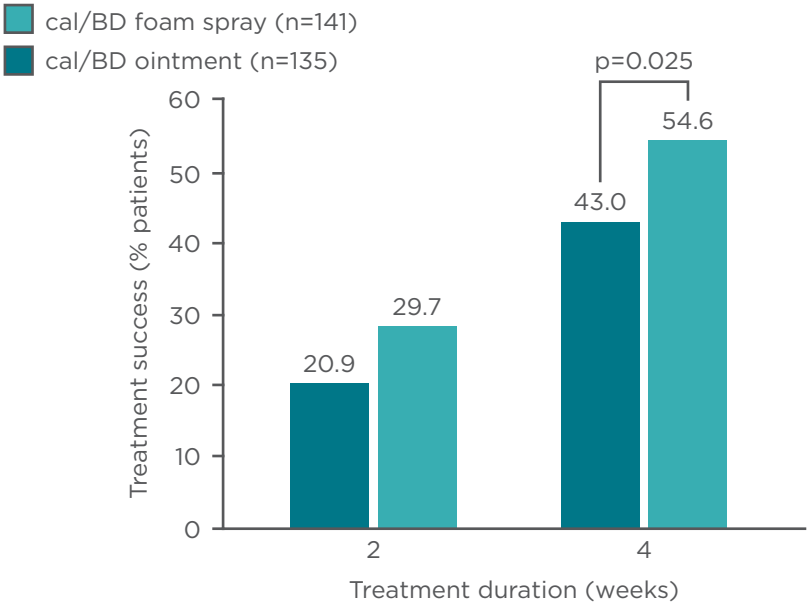
In addition, patient-to-patient interactions are beginning to outpace patient-to-physician interactions, as digital forums and other outlets allow patients to take more ownership of their own health and care. Patients are motivated to share what they have experienced so that they can help others, and physicians should be aware of this dynamic and be prepared to support it with their own clinical expert perspectives. The smartphone will continue to be crucial in providing healthcare. In particular, the development of peripheral devices, such as thermometers and glucometers, will revolutionise the way that patients manage their own monitoring and treatment.

The growth of big data in healthcare is inspiring, but it also presents significant challenges for interpreting the overwhelming quantities of information we are now able to collect. Healthcare is, therefore, becoming less of a science problem and more of an information problem. Since computer algorithms are often faster and more efficient at analysing large datasets than human researchers, our role then shifts towards transforming those data into insights.

Artificial intelligence systems are now being trained to assist in medical diagnosis and treatment. For example, neural networks can evaluate potentially malignant moles for melanoma, with an accuracy rate at least as high as that of experienced dermatologists.[2] Physicians should not fear 'being replaced by robots', rather our focus should be on how clinicians can use their expertise to work most effectively with the strengths and abilities of digital tools in order to create algorithms that will optimise patient care.

## Implications for Dermatologists

The digital revolution is less about healthcare becoming digital and more about shifting towards a patient-centric approach that is driven by digital tools. The overall role of the physician is changing, from that of a 'sage' who holds all the answers, to that of a 'facilitator' who helps co-ordinate the multiple facets of patient care. Dermatologists should reflect on how this could make them a better physician if they delegated certain portions of their role, either to computer algorithms or to the patients. With the rapid pace of change, we have the potential to change the way that healthcare is delivered within the next 2–3 years, as long as we recognise and work effectively with the opportunities that surround us.




| PGA | | Endpoint |
|---|---|---|
| 4 | Severe | |
| 3 | Moderate | |
| 2 | Mild | |
| 1 | Almost clear | |
| 0 | Clear | |

**Figure 1: Treatment success rates with the foam spray and ointment formulations of calcipotriol/betamethasone dipropionate.**
Treatment success: defined as 'clear' or 'almost clear' for patients with a baseline PGA of moderate or severe, and as 'clear' for patients with a baseline PGA of mild.
cal/BD: calcipotriol/betamethasone dipropionate; PGA: Physician's Global Assessment.
*Adapted from Koo et al.*[9]

## Reasons to Apply Topical Formulation Innovation in Psoriasis

Professor Christian Surber

### Topical Treatments for Psoriasis: A Long History of Innovation

For as long as psoriasis has been recognised as a clinical entity, clinicians and researchers have been striving towards better treatment outcomes through topical product innovation. From the early days of arsenic and tar-based topical products through to the development of corticosteroids, phototherapy, retinoids, and immunosuppressive regimens, innovators have aimed to maximise the clinical value of the API and simplify therapy to support patient adherence.[3,4] In addition to new API, we will be able to further improve clinical outcomes by creating novel formulations and vehicle concepts, and by developing application strategies that maximise the impact of existing or new API. This presentation will focus on a recent case showing how a new and unique vehicle or formulation concept can further augment the clinical effect of the fixed-dose combination of calcipotriol and betamethasone dipropionate (cal/BD) in psoriasis.

### What Are Formulations or Vehicles?

The conventional view of topical product formulations or vehicles tends to break products into categories based either on the effect of the vehicle itself (e.g. lubricants, moisturisers), a description of the vehicle format (e.g. ointments, lotions), or a mode of administration (e.g. roll-ons, sprays). The obvious phenomenon that a vehicle can have a significant impact on clinical outcomes led to the false, but widely held, view that for corticosteroids the ointment vehicle format is more potent than the cream vehicle format, and the cream vehicle format is more potent than the lotion vehicle format.[5,6] The fact is, vehicles containing volatile ingredients (e.g. water, alcohol) will change their format once applied onto the skin. This process has been coined as a "metamorphosis of the vehicle".[7] The sum of the vehicle ingredients on the skin after evaporation of all volatile vehicle ingredients is decisive for the behaviour of an API within the vehicle and the impact of the vehicle on the skin barrier function.

### How Can We Innovate with Vehicles?

The fixed-dose combination of cal/BD is available in a number of different vehicle formats, including gels (for the skin and scalp) and ointments.

Recently, these API have been reformulated into a novel foam spray format containing volatile ingredients that instantly evaporate after the product is applied onto the skin, leaving the API and the non-volatile ingredients behind. This metamorphosis of the product affects the behaviour of the API in the vehicle on the skin and, hence, their effect. Once the volatile components have evaporated, the remaining ingredients provide a transient increase in skin permeability through occlusion. On the API side, evaporation of the volatile vehicle ingredients concentrates the API into a supersaturated state, in which there is more drug dissolved in the remaining vehicle ingredients than could be dissolved under normal conditions.[8] Both these phenomena (occlusion and supersaturation) lead to an increase in percutaneous absorption of the API, since the skin becomes more permeable and the concentration gradient of API across the skin increases considerably.

Initial data from clinical trials of the cal/BD foam spray formulation suggest that the novel vehicle can improve patient outcomes relative to the same API in a different vehicle. Compared to the standard ointment formulation of cal/BD, the foam spray was associated with increased rates of treatment success after 4 weeks of treatment (Figure 1).[9]

### How Can We Continue to Innovate?

Although the fixed-dose combination of a vitamin D analogue and a corticosteroid is currently the gold standard for topical management of psoriasis, in the future other novel API may demonstrate similar or even better effects. Regardless of the specific API used, the vehicle or formulation will also be key for treatment success through its effects on both the API itself and the barrier function of the skin. Novel formulations are also crucial for moving towards a patient-centred approach to treatment, since many of the factors that affect patient adherence to topical treatment are related to vehicles and application issues.[10] Looking to the future, topical pharmacotherapy will be further improved through the development of products with improved cosmetic and pharmacologic properties, as well as intelligent digital applications that help patients feel empowered and supported at all stages of their psoriasis journey.

## Why Managing Itch and Psychosocial Comorbidities Experienced by Patients With Psoriasis is so Important

Doctor Anthony Bewley

### Impact of Psoriasis Symptoms and Comorbidities on Patient Wellbeing: Focus on Itch and Psychological Comorbidities

The most commonly recognised and appreciated symptoms of psoriasis (e.g. plaque cracking, flaking/scaling, and erythema) have traditionally served as the clinical focus in psoriasis diagnosis and management. However, psoriasis has many additional symptoms and comorbidities that contribute to the patient's overall wellbeing and are often underestimated.[11] For example, psoriasis was historically thought of as a dermatosis that does not itch, but we now know that itch is a common symptom, present to some degree in >70% of people with psoriasis.[12] Additional physical comorbidities, such as psoriatic arthritis, Crohn's disease, and metabolic syndrome occur more frequently in psoriatic patients than in the general population, with subsequent effects on morbidity and mortality.[13]

Psoriasis is also associated with an increased risk of a number of psychological comorbidities. Depression is widespread in psoriasis patients[14] and this population is twice as likely to have suicidal thoughts than the general public.[15] If applied to the UK population, these statistics would correspond to roughly 300 people annually who choose to die rather than continue living with their psoriasis. Cumulatively, the various comorbidities, symptoms, and stigma of psoriasis significantly impair overall health, psychological state, and QoL over a patient's lifetime.[13] The impact of psoriasis and its comorbidities on patient wellbeing is on par with that of other serious chronic diseases such as cancer, heart disease, and diabetes.[16]

### Focus on Itch and Sleep Disturbances as Determinants of Quality of Life

Itching is one of the five factors most closely associated with reduced mental and emotional wellbeing in people with psoriasis.[16] Patients report that itch has a negative effect on specific elements of QoL, including mood, concentration, and sleep, and that psoriasis-related itch correlates with decreased QoL to a greater extent than pain or fatigue. Since stress, poor mood, and impaired sleep have in turn been identified as key aggravating

factors of itch, many patients face a vicious cycle of inter-related deterioration of both itch and QoL.[17] Insomnia is common in psoriasis patients and can have a major impact on overall QoL and psychological wellbeing. Itching and pain are two of the important factors linked to insomnia in people with psoriasis; effective management of psoriasis and its associated itch and pain, therefore, has the potential to improve sleep and overall QoL.[18]

### The Impact of Effective Psoriasis Control on Itch, Sleep, and Quality of Life

Clinical trials of systemic biologic agents have demonstrated how controlling the cutaneous symptoms of psoriasis (e.g. Psoriasis Area Severity Index [PASI] improvement) can translate into improvements in itch, QoL, and sleep. A post-hoc analysis of the PRISTINE trial found that most patients with moderate-to-severe psoriasis experienced significant improvements in itch scores during 24 weeks of etanercept treatment; patients with the greatest reduction in itch also experienced the highest level of improvement in QoL.[19] Quantity and quality of sleep were also improved with etanercept treatment and these changes translated into further QoL ameliorations.[20]

On the topical therapy side, the novel foam spray formulation of cal/BD holds the potential to provide itch relief, QoL improvements, and sleep amelioration for a broader population. In clinical trials, cal/BD foam spray provided a rapid and marked relief of itch within the first week of therapy.[9] More than one-third (36.8%) of patients reported a 70% reduction in itch by Day 3 of treatment, with most patients (83.5%) achieving this level of itch reduction by the end of the 4-week study; at both time points, itch reduction was significantly greater with the cal/BD foam spray than with its vehicle alone (Figure 2).[21] These improvements in itch also translated into significant reductions in itch-related sleep loss[21] and improvements in overall health-related QoL as measured by the Dermatology Life Quality Index (DLQI).[22]

### Conclusions and Future Directions

With the advent of new data-mining tools and novel approaches to therapy, it is becoming easier for clinicians to provide care that is tailored not only to the patient's clinical signs and symptoms but also to his or her personal experience of the disease. A recent study found that patients on topical psoriasis treatment could be broadly clustered into groups based on their perception of the holistic burden of all aspects of their disease (skin symptoms, comorbidities, psychosocial impact, and treatment experience).[23]

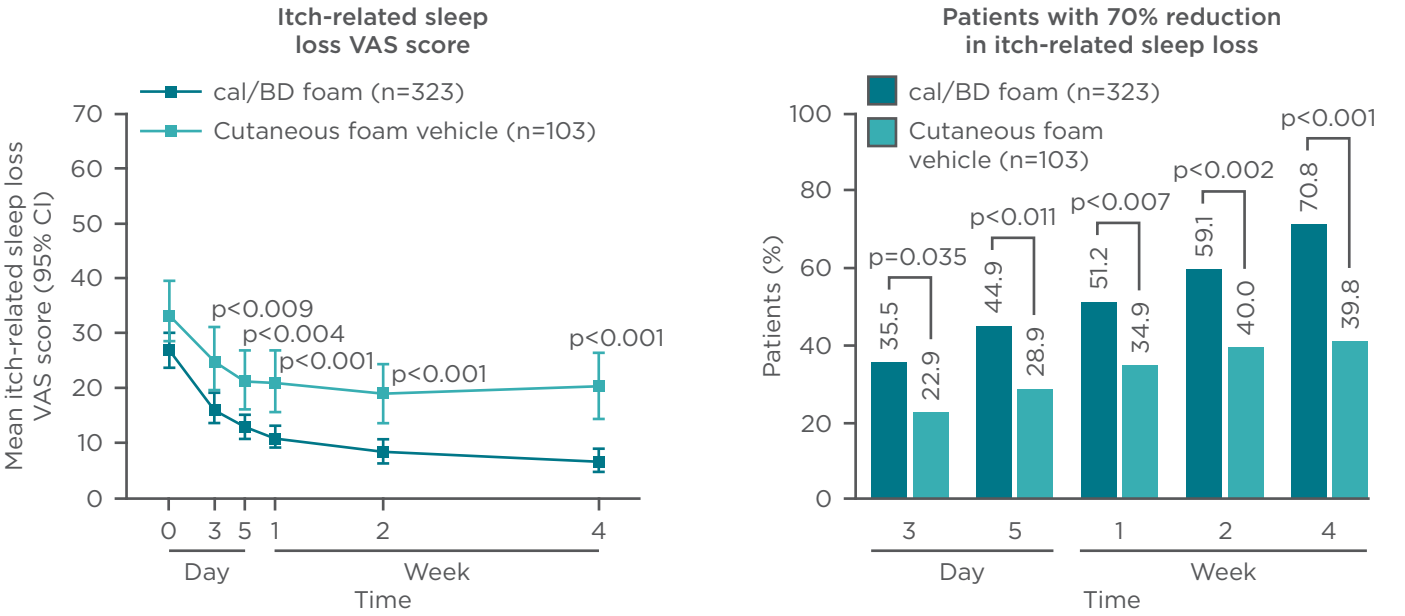



**Figure 2: Improvements in overall itch VAS score and patients experiencing significant (70%) itch reduction with cal/BD foam spray versus vehicle alone.**

cal/BD: calcipotriol/betamethasone dipropionate; CI: confidence interval; VAS: Visual Analogue Scale. *Adapted from Leonardi et al.*[21]

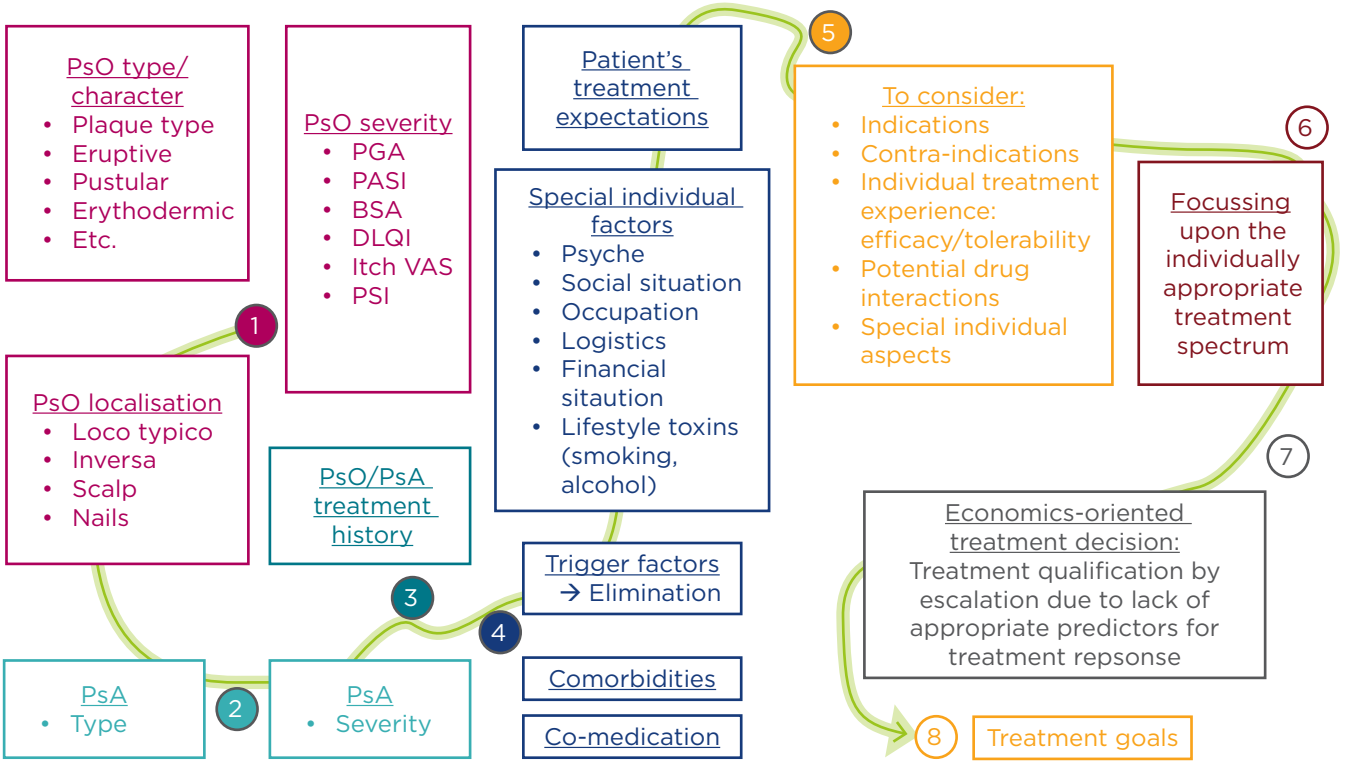



**Figure 3: From multi-parameter psoriasis assessment (1–5), to the treatment decision (6–7), and treatment goals (8).**

BSA: body surface area; DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area Severity Index; PGA: Physician Global Assessment; PsA: psoriatic arthritis; PSI: Psoriasis Symptom Inventory; PsO: psoriasis; VAS: Visual Analogue Scale.

This type of patient profiling and the recognition of patients' different treatment and educational needs is one promising strategy for moving towards more personalised, patient-centred care. Another key approach for optimising patients' holistic wellbeing is the use of multidisciplinary teams that incorporate other facets of psoriasis such as rheumatology and gastroenterology. Finally, many new medications and approaches are under investigation for the management of itch, including antidepressants, hand-held phototherapies, and psychotherapeutic talk therapies.[24] Together, these tools and strategies give dermatologists a wide range of choices for tailoring therapy to provide the greatest improvements in patients' holistic QoL.

## Taking Control Over Psoriasis: From Flare-up to Proactive Management

**Professor Bernd Bonnekoh**

### The Current Topical Psoriasis Treatment Landscape

Since psoriasis is a chronic incurable disease, the treatment plan must consider how best to manage the condition over the course of a patient's lifetime. The current management of psoriasis is extremely complex, with a wide variety of medication options available and a large number of patient factors for physicians to consider in their multi-parameter assessment of the disease (Figure 3). As the integration of big data into clinical practice becomes more widespread, clinicians' reality is moving more towards a shared decision-making framework supported equally by the patient's input, the available treatment and support choices, and the dermatologist's experience and clinical judgement.

Currently, the overall approach to psoriasis tends to use topical products as initial monotherapy for mild-to-moderate disease, and considers adding them as an adjunct to ultraviolet and/or systemic therapy for moderate-to-severe disease. Combinations of topical ingredients can be either sequential or simultaneous (e.g. fixed-dose combinations). In general, a topical product should be applied daily in the initial induction and stabilisation period; however, the approach to longer-term maintenance is more loosely defined

and usually relies on a reactive, on-demand approach to any flares that may occur.

### Moving Towards Safe, Effective, and Proactive Long-Term Topical Use

Topicals will likely remain the cornerstone of treatment for many psoriasis patients; it is, therefore, essential to consider how to use them effectively and promote optimal patient adherence in the long term. Clinical practice guidelines from various national societies offer only indirect recommendations for long-term use of topical medications, and the clinical literature on long-term, proactive topical treatment of psoriasis is likewise very sparse. Given the lack of published material specific to psoriasis, it may be useful to look at the model of a proactive approach in another long-term skin condition: atopic dermatitis. Here, proactive maintenance treatment with tacrolimus ointment twice-weekly, plus additional twice-daily reactive treatment in case of a flare-up, is associated with a significantly delayed time to first flare, compared with standard reactive flare treatment in both children and adults.[25,26]

There appears to be an unmet need in the psoriasis community for this type of proactive approach. A recent survey of dermatologists in Germany indicated that more than half of respondents were using proactive treatment (e.g. once-weekly in nearly cleared lesions) in spite of products not being licenced for this type of use. This practice is supported by a meta-analysis of prospective trials that concluded that long-term maintenance treatment (1–2 times weekly) with two-compound formulations was effective in daily practice, had favourable tolerability and economic benefit, and promoted proactive patient involvement.[27] Further support for the long-term safety and tolerability of fixed-dose combinations is anticipated from the currently ongoing PSO-LONG trial, which is evaluating a twice-weekly maintenance regimen of cal/BD foam spray over a period of ≤52 weeks.

### Looking Towards the Future

Topical therapy is currently built on a solid foundation of effective, tolerable, and easy-to-use products, and the concept of proactive long-term management is starting to become established based on this foundation. In order to improve treatment success and long-term adherence, clinicians can support their patients by setting a clear schedule and empowering patients through knowledge and shared decision-making. As we continue to build this approach into the future, we may also benefit from new drugs, formulations, and modes of application, as well as new digital devices and strategies to keep patients on track and reward them for successfully following their treatment programme.

## Question and Answer Session

**Q:** What advice would you give to dermatologists to help them make the most effective use of the huge amount of information available through big data?

**A:** Mr Fernández suggested that clinicians could focus their research by asking: "What kind of information, if I could find it, would change how I manage the patient?". Dr Bewley added that there will always be a need for clinicians' expertise, especially as more patients research their own conditions online; physicians' expert input can help personalise that information and place it in the appropriate context. He also noted that it is important to recognise that in a consultation there are two experts in the room, the physician who is an expert in medicine, but also the patient who is an expert in his or her own experience of the disease.

**Q:** How can care of psoriasis patients be most effectively co-ordinated between general practitioners and specialists?

**A:** Dr Bewley replied that the 'ownership' of a patient's care should rest with whichever physician is able to provide the most meaningful and appropriate management, whether that is a general practitioner or a specialist. He mentioned that one of the key aspects of psoriasis care is ensuring that the patient's expectations of treatment are understood and that the physician is able to develop a plan to meet those expectations and evaluate treatment success.

**Q:** If a two-compound product containing a steroid is used proactively over the long term, how do we motivate patient adherence to treatment? In atopic dermatitis, this is less of a concern since treatment is non-steroidal.

**A:** Prof Bonnekoh replied that the data for long-term use of two-compound products show no important safety concerns over a period of use of ≤1 year and that anecdotally many dermatologists know of patients who have used topical corticosteroids for decades without any problems. Dr Bewley added that steroid phobia is still

common among patients and that physicians should be careful not to simply dismiss these concerns, but rather to highlight their own experience using these products over the long term. Prof Bonnekoh also mentioned that patient counselling could include examples from other conditions, such as chronic obstructive pulmonary disease, where steroids are routinely used over many years and the safety profile has been well characterised.

## REFERENCES


1. Pearl R. Kaiser Permanente Northern California: Current experiences with internet, mobile, and video technologies. Health Aff (Millwood). 2014;33(2):251-7.

2. Esteva A et al. Dermatologist-level classification of skin cancer with deep neural networks. Nature. 2017;542(7639):115-8. Erratum in: Nature. 2017;546(7660):686.

3. Farber EM. History of the treatment of psoriasis. J Am Acad Dermatol. 1992; 27(4):640-5.

4. Mason AR et al. Topical treatments for chronic plaque psoriasis. Cochrane Database Syst Rev. 2013;(3):CD005028.

5. Cornell RC, Stroughton RB. Correlation of the vasoconstriction assay and clinical activity in psoriasis. Arch Dermatol. 1985;121(1):63-7.

6. Goldsmith LA et al. Fitzpatrick's Dermatology in General Medicine, 8th Edition (2012), New York: McGraw-Hill Education/Medical.

7. Surber C, Smith EW. The mystical effects of dermatological vehicles. Dermatology. 2005;210(2):157-68.

8. Lind M et al. Supersaturation of calcipotriene and betamethasone dipropionate in a novel aerosol foam formulation for topical treatment of psoriasis provides enhanced bioavailability of the active ingredients. Dermatol Ther (Heidelb). 2016;6(3): 413-25.

9. Koo J et al. Superior efficacy of calcipotriene and betamethasone dipropionate aerosol foam versus ointment in patients with psoriasis vulgaris--A randomized Phase II study. Dermatolog Treat. 2016;27(2):120-7.

10. Zschocke I et al. Non-adherence and measures to improve adherence in the topical treatment of psoraisis. J Eur Acad Dermatol Venereol. 2014;28 suppl 2:4-9.

11. Korman NJ et al. Clinical symptoms and self-reported disease severity among patients with psoriasis – implications for psoriasis management. J Dermatolog Treat. 2015;26(6):514-9.

12. Reich A et al. Interplay of itch and psyche in psoriasis: An update. Acta Derm Venerol. 2016;96(217):55-7.

13. Kimball AB et al. Psoriasis: Is the impairment to a patient's life cumulative? J Eur Acad Dermatol Venereol. 2010;24(9):989-1004.

14. Strohal R et al. Psoriasis beyond the skin: An expert group consensus on the management of psoriatic arthritis and common co-morbidities in patients with moderate-to-severe psoriasis. J Eur Acad Dermatol Venereol. 2014;28(12):1661-9.

15. Dalgard FJ et al. The psychological burden of skin diseases: A cross-sectional multicenter study among dermatological out-patients in 13 European countries. J Invest Dermatol. 2015;135(4):984-91.

16. Rapp SR et al. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol. 1999;41 (3 Pt 1):401-7.

17. Amatya B et al. Patients' perspective of pruritus in chronic plaque psoriasis: A questionnaire-based study. J Eur Acad Dermatol Venereol. 2008;22(7):822-6.

18. Gupta MA et al. Psoriasis and sleep disorders: A systematic review. Sleep Med Rev. 2016;29:63-75.

19. Mrowietz U et al. Pruritus and quality of life in moderate-to-severe plaque psoriasis: Post hoc explorative analysis from the PRISTINE study. J Eur Acad Dermatol Venereol. 2015;29(6):1114-20.

20. Thaçi D et al. Improvement in aspects of sleep with etanercept and optional adjunctive topical therapy in patients with moderate-to-severe psoriasis: Results from the PRISTINE trial. J Eur Acad Dermatol Venereol. 2014;28(7):900-6.

21. Leonardi C et al. Efficacy and safety of a calipotriene plus betamethasone dipropionate aerosol foam in patients with psoriasis vulgaris – a randomized Phase III study (PSO-FAST). J Drugs Dermatol. 2015;14(12):1468-77.

22. Leonardi C et al. The aerosol foam formulation of the fixed combination calcipotriene plus betamethasone dipropionate improves the health-related quality of life in patients with psoriasis vulgaris: Results from the randomized PSO-FAST study. J Drugs Dermatol. 2016;15(8):981-7.

23. Bewley A et al. Identifying individual psychosocial and adherence support needs in patients with psoriasis: A multinational two-stage qualitative and quantitative study. J Eur Acad Dermatol Venereol. 2014;28(6):763-70.

24. Ständer S, Weisshaar E. Medical treatment of pruritus. Expert Opin Emerg Drugs. 2012;17(6):335-45.

25. Wollenberg A et al. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. Allergy. 2008;63(6):742-50.

26. Thaçi D et al. Proactive disease management with 0.03% tacrolimus ointment for children with atopic dermatitis: Results of a randomized, multicentre, comparative study. Br J Dermatol. 2008;159(6):1348-56.

27. Augustin M et al. Topical long-term therapy of psoriasis with vitamin $D_3$ analogues, corticosteroids and their two compound formulations: Position paper on evidence and use in daily practice. J Dtsch Dermatol Ges. 2014;12(8):667-82.

# ADVANCING SCIENCE: DRIVING PROGRESS TODAY FOR A CLEARER TOMORROW

## This symposium took place on 15th September 2017 as a part of the the 26th European Academy of Dermatology and Venereology (EADV) congress in Geneva, Switzerland


**Chairperson**

**Kristian Reich[1]**

**Speakers**

**Caitriona Ryan,[2] Hervé Bachelez[3]**

*1. Skin*flammation™*, Dermatologikum Hamburg, Germany*

*2. St. Vincent's Hospital, Dublin, Ireland*

*3. Saint-Louis Hospital, Paris, France*



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## MEETING SUMMARY

Dermatologists today have more tools than ever at their disposal for managing psoriasis, including newer-generation biologics, which target molecular drivers of psoriatic inflammation that were scarcely known a decade ago. With a deeper understanding of epidermal immunology, we now recognise key pathogenic roles for multiple cytokines and cytokine receptors. Among current treatment targets, we now include not only the tumour necrosis factor pathway, but also interleukins (IL) of the IL-17 family (which are produced by T helper 17 [Th17] cells, among other skin cells) and IL-23 (which polarises the immune response toward Th17 production), as well as the corresponding receptors and intracellular signalling molecules. Rapid and complete skin clearance has become increasingly feasible, as suggested by studies of the newer biologics, including ustekinumab (targeting Th1 and Th17 cell development), secukinumab and ixekizumab (targeting the IL-17A cytokine), and brodalumab (targeting the IL-17 receptor subunit A). Paralleling the improved skin-related outcomes, we see a lightening of the burden of disease that patients experience with this chronic condition.

The bar is being raised when it comes to treatment goals investigated as endpoints in Phase III trials, and we see a shift from control to partial, or even complete, clearance. A similar evolution toward ambitious and personally tailored treatment goals is needed in the clinic. The speakers in this symposium addressed the promise of the new approaches, and the continuing challenge of choosing the optimal therapeutic approach, to ensure that each patient gets the best results from their therapies, whether old or new.

# New Treatments, New Data: Rethinking Future Treatment Goals

Professor Kristian Reich

## Rethinking the Model of Psoriasis Pathogenesis

"Take a fresh look at the IL-17 world," suggested Prof Reich, kicking off this symposium on the future of psoriasis treatment. As an immunologic skin disease, the pathogenesis of psoriasis is traditionally explained by cytokine-mediated crosstalk between dendritic cells and T cells residing in the dermis and epidermis.[1-4] Much clinical research has focussed on cytokines of the IL-17 family and on Th17 cells, which produce IL-17 and appear to collaborate with Th1 cells to drive the characteristic epidermal changes seen in psoriasis. Recently, it has emerged that Th17 cells are less common in active psoriatic plaques than would be expected in this model,[1,2,4,5] suggesting that other IL-17-producing cell types might contribute more to the psoriasis disease process than previously thought.[1,4,6] Indeed, skin keratinocytes release two members of the IL-17 family cytokines, IL-17C and IL-17E, which can trigger an immune response alongside IL-17A.[7-11]

Whatever their cellular source, the IL-17 proinflammatory cytokines transduce their signals through receptors sharing the IL-17 receptor subunit A (IL-17RA), the molecular target of the biologic agent brodalumab.[6] Because brodalumab binds to IL-17RA, this human monoclonal antibody inhibits signalling not only by IL-17A, but also by IL-17F, IL-A/F heterodimer, IL-17E, and IL-17C.[6]

## The Brodalumab Clinical Development Programme

Brodalumab has been studied in one of the largest clinical trial programmes for a new biologic for psoriasis, with 4,464 patients treated in 17 Phase I–III clinical trials.[12-21] From the 8,655 patient-years of brodalumab exposure and 9,174 patient-years of follow-up so far reported,[19-21] most of the available data come from the AMAGINE programme, consisting of three Phase III studies.[22,23]

AMAGINE-1 was a double-blind, placebo-controlled study that tested the efficacy and safety of brodalumab on 661 adults with moderate-to-severe psoriasis.[24] Patients were randomised to brodalumab (140 mg and 210 mg) or placebo every 2 weeks, with an additional dose at Week 1, during the initial 12-week induction phase. During this symposium, the focus was on the results obtained with 210 mg administered every 2 weeks, as this is the approved label dosage. At Week 12, patients meeting the co-primary endpoint of static Physician's Global Assessment of 0 or 1 (sPGA success) were re-randomised to either continue on their current dose or to transition to placebo treatment.[24]

AMAGINE-2 and AMAGINE-3[24] were two identically designed head-to-head Phase III studies in which patients were randomised to receive brodalumab (140 mg and 210 mg), ustekinumab (as per label),[14] or placebo. At Week 12, patients receiving brodalumab in the induction phase were re-randomised to receive a brodalumab maintenance dose of 210 mg every 2 weeks (label dose) or various other maintenance doses.[24] Patients receiving ustekinumab continued to receive ustekinumab every 12 weeks, and patients receiving placebo were transitioned to 210 mg of brodalumab every 2 weeks.

## Clinical Efficacy and Patient Health-Related Quality of Life

In AMAGINE-1, 83.3% of patients treated with 210 mg of brodalumab achieved Psoriasis Area Severity Index (PASI) 75 by Week 12, and 75.7% achieved the co-primary endpoint of sPGA success.[22] However, it could potentially be argued that PASI 75, which implies that patients may continue to experience substantial residual disease, no longer suffices as a treatment goal. In this regard, the more stringent secondary efficacy endpoints of PASI 90 and 100 are of interest.

In AMAGINE-1, 70.3% of patients treated with 210 mg of brodalumab achieved PASI 90, and 41.9% achieved PASI 100 (or completely clear skin) at Week 12.[22] At Week 52, 83.1% of patients who were re-randomised to receive 210 mg brodalumab maintained sPGA success.

This trial setting partially simulated daily clinical practice, in that AMAGINE-1 patients were not allowed to experience a total relapse of the disease. Rather, they were retreated following loss of response, defined as sPGA 2 for at least 4 weeks or sPGA ≥3 at one visit.[22] With retreatment, 97% of patients receiving 210 mg brodalumab recaptured sPGA success (0 or 1) after 12 weeks of retreatment.[22] The PASI 100 response at Week 52 was 67.5% throughout the study in patients on 210 mg brodalumab and who achieved sPGA success (0 or 1) at Week 12 (Figure 1). These results should be seen in context of the study's conservative imputation methodology, whereby patients missing data were assumed to be non-responders.

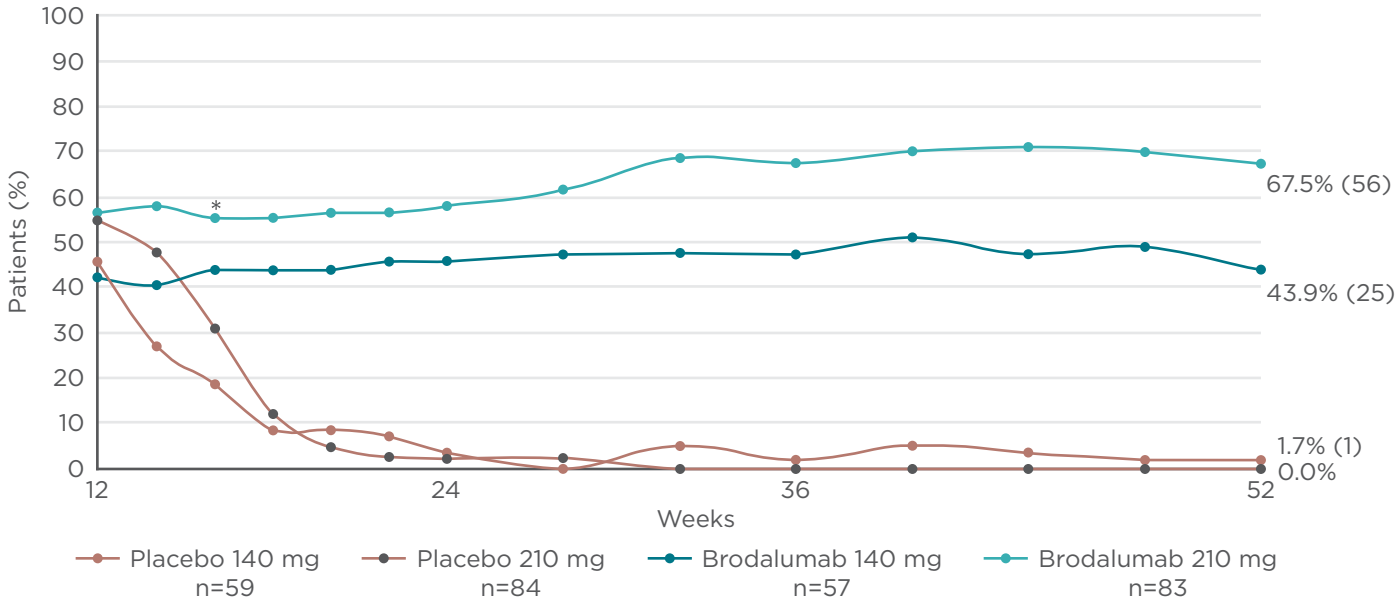


**Figure 1: PASI 100 response rates through Week 52 in patients who achieved sPGA success (0 or 1) at Week 12 (AMAGINE-1).**

All p-values <0.001 for comparisons between brodalumab and withdrawal (placebo) groups at all time points from Week 16–52; *p=0.015 between brodalumab 140 mg every 2 weeks and placebo. Treatment groups were as planned for induction/withdrawal phases, using modified intention-to-treat analysis. Non-responder imputation was used for missing PASI data.

PASI: Psoriasis Area and Severity Index; sPGA: static Physician's Global Assessment.

*Adapted from Papp et al.*[22]

In AMAGINE-2 and AMAGINE-3, significantly more patients achieved PASI 90 at Week 12 with brodalumab 210 mg (70% and 69%, respectively) than with ustekinumab (47% and 48%, respectively).[23] PASI 100 response was also significantly higher with brodalumab 210 mg (44% and 37%, respectively) than with ustekinumab (22% and 19%, respectively).

By Week 12, >55% of AMAGINE patients treated with 210 mg of brodalumab achieved Dermatology Life Quality Index (DLQI) 0 or 1 (55.9%, 60.8%, and 59.0% in AMAGINE-1, AMAGINE-2, and AMAGINE-3, respectively), meaning that the patients were no longer burdened by the disease.[25] Patients were also followed using the Psoriasis Symptom Inventory (PSI), which queries patients on their experience of itch, redness, scaling, burning, stinging, cracking, flaking, and pain.[22,23,26] Researchers calculated the proportion of symptom-free days, defined as the ratio of days the patients reported a PSI total score of 0 and the total number of days with PSI assessments available.[27]

As expected, there was a clear relationship between these patient-reported outcomes and the clinical findings. Thus, 80% of responders who achieved PASI 100, but only 63% of patients with a PASI response between 90 and 100, reported a DLQI of 0 or 1.[27] Likewise, 42% of responders who achieved PASI 100 reported being symptom-free each day between their final visit, Week 12 visit, and the previous visit, compared to 14% of responders whose PASI response was between 90 and 100.

## Safety Profile of Brodalumab

When considering patient treatment with biologic therapies that target the IL-17 pathway, a number of safety events, including *Candida* infections, worsening of Crohn's disease in subjects with active Crohn's disease, and neutropenia are highlighted by experts as identified risks. Safety results from AMAGINE-2 and AMAGINE-3 indicate that these specific safety concerns and other potential safety risks of interest occurred at rates that were consistent with those observed with other biologics and were comparable between ustekinumab and brodalumab.[23]

Suicidal ideation and behaviour (SIB) represents a potential risk for the target population, since rates of depression, anxiety, and suicidal ideation are significantly elevated among individuals with

psoriasis.[28] In the AMAGINE programme, 52-week follow-up, time-adjusted patient incidence rates for SIB were 0.20 and 0.60 per 100 patient-years for brodalumab and ustekunimab, respectively.[25] In the long-term pool of patients treated with brodalumab, there were 4 cases of completed suicide, 1 of which was later adjudicated as indeterminate.[29] These 3 patients showed no consistent pattern between exposure and the timing of suicidal behaviour, and all three cases featured recent and/or longstanding depression or other significant life-stressors.[25] Notably, in the background population, the probability of four suicides occurring in a group the size of the AMAGINE programme over the same time-frame is 26%, and the probability of three suicides rises to 47%[30] (assuming a rate of 0.028 per 100 subject-years based on a meta-analysis of published clinical trials and/or registries for psoriasis).[31]

There has been no mechanistic explanation established between IL-17 pathway inhibition and SIB.[32] Because patients with a history of drug abuse, depression, suicidality, or other psychiatric comorbidities were not specifically excluded from the AMAGINE programme,[33-35] it may be hypothesised that this trial population presents a higher risk for psychiatric comorbidities than in some comparable studies.

Upon review of these data, neither the European Medicines Agency (EMA)[36] nor the U.S. Food and Drug Administration (FDA)[30] identified a causal link between brodalumab treatment and an increased risk of SIB. Indeed, patients treated with brodalumab showed a significant reduction in hospital anxiety and depression scale scores at Week 12 ($p<0.001$ for comparisons between brodalumab and placebo groups).[22] Brodalumab currently has market approval in the European Union (EU), USA, and Japan.

### Conclusions

Overall, the evidence we base our treatment decisions on increasingly suggests that the treatment goal of a life unburdened by psoriasis is both feasible and desirable. Targeting the IL-17 pathway with brodalumab yielded high initial levels of disease clearance that were maintained over ≥52 weeks of treatment. Individuals who achieved clearance or complete clearance were markedly more successful than others in eliminating the disease burden associated with moderate-to-severe psoriasis.

## Beyond the Skin: A Broader View on Disease Facets

**Professor Caitriona Ryan**

Using two hypothetical patient cases, Prof Ryan highlighted different facets of the disease and the impact of comorbidities. Data from the brodalumab development programme were used to illustrate the potential benefits of targeting the IL-17 pathway in the patient-centred management of psoriasis. Both cases featured treatment-experienced patients with moderate-to-severe psoriasis, whose disease was insufficiently controlled despite ongoing treatment with a biologic.

The first case highlights the need for rapid control in a patient expressing desire for complete clearance. The second illustrates the possibility of effective clearance of psoriasis in a middle-aged patient with personal and familial risk factors for cardiovascular disease.

### Case 1: A Patient Requiring Rapid Onset of Action

The first case described a 21-year-old female university student who was experiencing a psoriatic flare that commenced 18 months after initiating adalimumab, with active plaques on her knees, elbows, stomach, and back, as well as inframammary involvement. Body-surface area involved was estimated at 10%. Her poor disease control was a source of anxiety, particularly because she was to be a bridesmaid for her sister's wedding 1 month later.

There was no joint pain and the patient was otherwise healthy. Previous treatments included methotrexate, which she did not tolerate, and phototherapy, which produced a very short duration of remission. She was taking adalimumab at the recommended dose.

Options for achieving control quickly in this patient may have included addition of a topical agent to clear obvious areas, combination treatment with a systemic treatment, or switching to another biologic therapy. In this case, an anti-IL-17 treatment was initiated. At Week 2, the patient achieved <1% body-surface area, with near clearance of psoriasis and only small residual plaques on her back.

#### Rapid onset of action

This outcome, including the rapid achievement of clinically significant disease control, is in line with findings in recent clinical studies of brodalumab in patients with moderate-to-severe psoriasis.

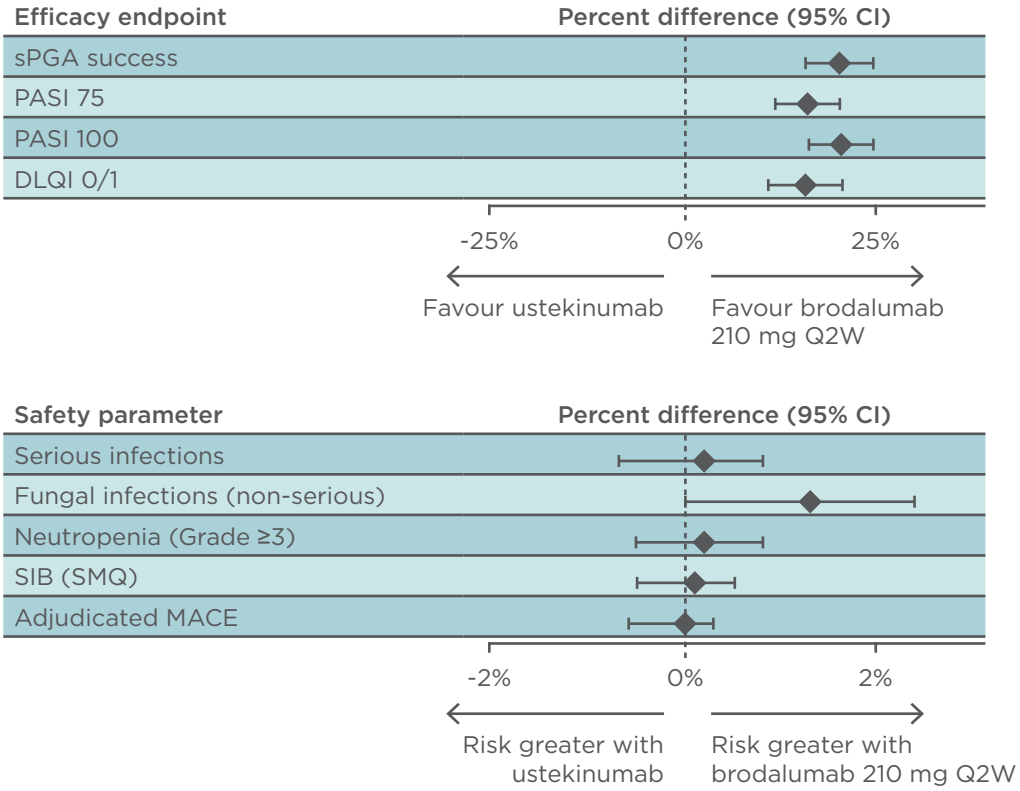


**Figure 2: AMAGINE-2 and AMAGINE-3: Benefit-risk summary plot at Week 52 (ratio comparison).**[31]
CI: confidence interval; DLQI: Dermatology Life Quality Index; MACE: major adverse cardiac events; PASI: Psoriasis Area and Severity Index; SIB: suicidal ideation and behaviour; SMQ: Standardised MedDRA. Query; sPGA: static Physician's Global Assessment; Q2W: every 2 weeks.

At Week 1, a significantly higher number of patients achieved PASI 75 with brodalumab than with ustekinumab.[37] When treated with brodalumab, the median time for 25% of the patients to achieve a PASI 75 response was 2.14 weeks, whereas with ustekinumab, the median time required for the same response was 4.77 weeks.[37] Moreover, the median time to PASI 90 response was shorter in the brodalumab group (6.43 weeks) compared with ustekinumab (12.1 weeks).[38] PASI 100 response was also shorter in the brodalumab group (12.4 weeks) compared with ustekinumab, where the minimum for PASI 100 was not reached within 12 weeks.[38] More than half of patients treated with 210 mg brodalumab throughout the 52 weeks achieved PASI 100 (56% and 53%, respectively, in the AMAGINE-2 and AMAGINE-3 studies) at 52 weeks.[23]

### The follow-up plan

For this patient, the clinical decision was to continue treatment as long as she maintained clearance or near clearance of her disease. "With a new generation of biologics, the bar has been raised," Prof Ryan said. "Our patients deserve to be cleared of their psoriasis."

## Case 2: A Patient with Cardiovascular Risk Factors and a History of Treatment Failures

A 56-year-old salesman had suffered from psoriasis for many years, affecting his face, hands, and genital area, as well as nail involvement. He was a one-pack-a-day smoker with a history of hypertension and a family history of cardiovascular disease. Previous treatment with adalimumab had failed, and he had used ustekinumab for the previous 2 years. However, this patient had never achieved clearance of his facial or genital psoriasis.

Visible disease had lowered his confidence in front of customers, a situation that was affecting his performance at work. There was genital involvement including lichenified, itchy plaques on the shaft of the penis and the entire scrotum. The presence of genital disease was greatly affecting his sexual life with his partner. Because of the potential for profound adverse effects on health-related quality of life and sexual health, patients with genital psoriasis should be specifically asked about their burden of disease, as they may be reticent to volunteer this information.[39]

## Considering comorbidities

More than any other dermatologic condition, psoriasis has been associated with depression, anxiety, and SIB risk.[28,40] Severe psoriasis is also associated with a 50% increased risk of mortality compared with the general population, with cardiovascular death as the most common aetiology.[41,42] When choosing a treatment for a patient, Prof Ryan advised to carefully consider the myriad of conditions associated with psoriasis, including cardiovascular and affective comorbidities.[43] For this case, the treatment plan needed to aim at minimising risk of major adverse cardiac events, as he was a smoker, had high blood pressure, and had a family history of cardiovascular disease.

The treatment options for this patient included continuing his current therapy, possibly with an increased injection frequency (off label treatment), or a switch in biologic therapy. The decision was made to initiate an anti-IL-17 treatment.

## Prior treatment history

Although previous failure on biologic treatment might suggest a poor prognosis with subsequent therapies, brodalumab has shown similar efficacy in biologic-naïve patients as it has in biologic-experienced patients.[37] Treatment with brodalumab allowed 32% of the patients who experienced unsuccessful previous biologic therapy to achieve PASI 100 at Week 12, compared with only 11% with ustekinumab (p=0.0027). In addition, patients with inadequate response to ustekinumab after 16 weeks rapidly achieved and maintained high levels of skin clearance for ≤36 weeks after receiving brodalumab 210 mg rescue therapy; 38% of patients achieved and maintained PASI 100.[44]

A quantitative summary of clinical findings at 52 weeks (Figure 2) demonstrated superior efficacy of brodalumab, relative to ustekinumab, with a similar safety profile.

## The follow-up plan

Having initiated brodalumab in this patient, it is essential to ensure that his facial and genital psoriasis are controlled. His cardiovascular risk remains a concern. Smoking cessation is a priority, as is ongoing monitoring and treatment of hypertension.

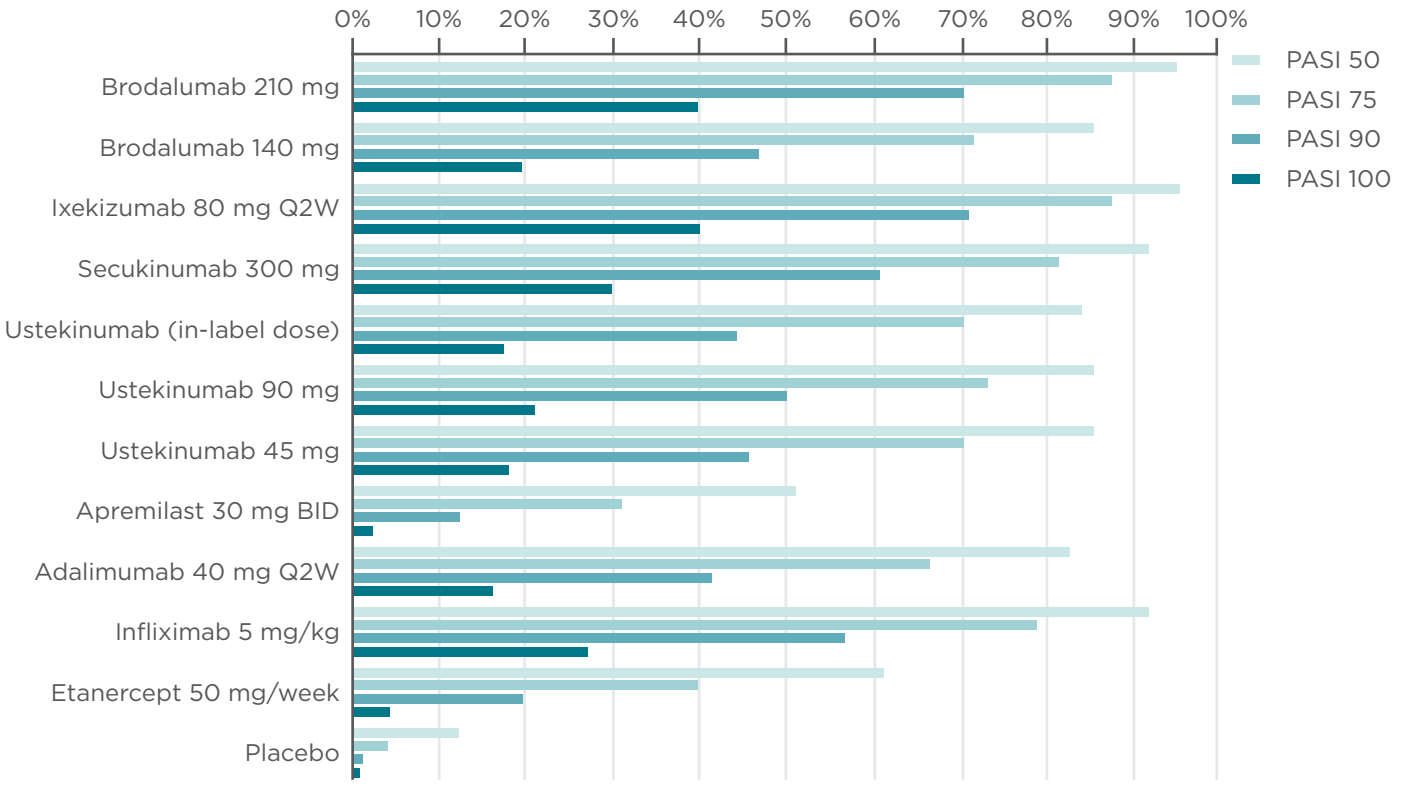


**Figure 3: Meta-analyses of expected probabilities of achieving different treatment outcomes.[50]**
Probabilities estimated based on the unadjusted network meta-analysis.
BID: twice-daily; PASI: Psoriasis Area and Severity Index; Q2W: every 2 weeks.

## Which Drug for Which Patient? The Question of Patient Profiling

Professor Hervé Bachelez

With today's array of newly-developed biologic treatments, clinicians have a wide choice of therapies for their psoriasis patients. Ambitious treatment goals, which have become increasingly feasible with newer treatments, may be key to providing patient outcomes in line with patient expectations. However, to involve patients appropriately in the decision-making process,[45] dermatologists must explain the benefits and risks of the various options clearly; even today, the dermatologist remains a patients' primary source of such information.

The scarcity of real-life data on biologics complicates treatment decisions; therefore, psoriasis patient registries are a potentially valuable resource. In the absence of extensive real-world evidence, European guidelines for treatment of psoriasis are driven by consensus and expert opinion to establish recommendation for clinicians.[46,47] Registries can fill a gap by providing evidence about patients whom we encounter in daily practice but who might be excluded from clinical trials.

### Achieving Skin Clearance Safely: A Fine Balance

With the anti-IL-17 agents, an increasing number of patients can reach complete or almost-complete clearance, making PASI 90 and even PASI 100 an achievable therapeutic goal.[47-49] The odds of a patient reaching PASI 90 or PASI 100 are highest with anti-IL-17 biological agents, according to a network meta-analysis presented at this year's European Academy of Dermatology and Venerology (EADV) congress, which modelled the probability of PASI responses for biologics approved in the EU.[50] Patients have the highest likelihood of achieving PASI 100 when treated with brodalumab, ixekizumab, or secukinumab (Figure 3).

When considering data supportive of treatment safety, registry data will be an invaluable, but not a sovereign, source of data. Important safety issues remain unanswered in randomised clinical trials, and there is a need for newer methods to assess rare risks.[51,52] Moreover, the limited patient population size of clinical trials may lead to failure to discriminate rare adverse drug reactions from background incidence rates. Registry studies could provide such insight, thanks to the larger samples of patients available.[53] Even so, registry findings will require cautious interpretation, as safety signals do not themselves establish a causal link with a given treatment.

Patient priorities will, therefore, remain a crucial factor in deciding among therapies. These priorities may differ somewhat from those of dermatologists. The Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey shed light on physicians' concerns about biologics' long-term safety when initiating or pursuing treatment.[54] Unlike physicians, patients in the MAPP survey expressed little fear of adverse events, but were concerned about tolerability and safety issues that might lead them to discontinue treatment.[55]

Inflammatory bowel disease (IBD) provides an interesting example of the difficulty of evaluating safety in the face of rare events. Isolated cases of new-onset IBD have been observed in the development programmes of all three IL-17-blocking biologics. One confirmed case of IBD (Crohn's disease) occurred in the brodalumab psoriasis development programme,[24] and 19 cases of IBD, mostly *de novo*, were adjudicated (12 of ulcerative colitis and 7 of Crohn's disease) among 4,209 patients exposed to ixekizumab.[13,56] Three cases of IBD (anal fistula, ulcerative colitis, and Crohn's disease) were identified in the secukinumab development programme.[11,57] Interestingly, only brodalumab carries a contraindication for use in patients with active Crohn's disease.[24] Considering that patients with severe psoriasis are at elevated risk of IBD,[58] the occurrence of IBD cases in these clinical trials inevitably raises the question of causality. Data collected so far provides no clear answers, and careful interpretation of results should be observed.

### First-Line Therapies

The selection of a first-line biologic treatment for psoriasis remains a moving target, with no single choice right for all patients. Physicians appear to make this decision on the basis of evidence and expert opinion, taking into account patient factors such as age, cardiovascular risk, tuberculosis screening results, and comorbidities, including joint involvement.[59] There is an undeniable need for real-life registries, which, with robust statistical methodologies, can provide the missing data

necessary to inform patient and clinician decisions regarding treatment options.

## Conclusions

Ambitious treatment goals, such as complete skin clearance, are within reach with today's new therapies. To support patients in setting and achieving their personal treatment goals, clinicians should consider individual patient's comorbidities, as well as their treatment goals, and their engagement in their own treatment. In the future, personalised psoriasis treatment must balance patient's clinical features and individual priorities with the efficacy and safety of the available therapies, as determined by clinical trials and real-world experience.

## REFERENCES


1. Nestle FO et al. Psoriasis. N Engl J Med. 2009;361(5):496-509.

2. Cai Y et al. New insights of T cells in the pathogenesis of psoriasis. Cell Mol Immunol. 2012;9(4):302-9.

3. Harrington LE et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nat Immunol. 2005;6(11):1123-32.

4. Lowes MA et al. Immunology of psoriasis. Annu Rev Immunol. 2014;32: 227-55.

5. Bovenschen HJ et al. Foxp3+ regulatory T cells of psoriasis patients easily differentiate into IL-17A-producing cells and are found in lesional skin. J Invest Dermatol. 2011;131(9):1853-60.

6. Patel DD et al. Effect of IL-17A blockade with secukinumab in autoimmune diseases. Ann Rheum Dis. 2013;72(Suppl 2):ii116-23.

7. Johnston A et al. Keratinocyte overexpression of IL-17C promotes psoriasiform skin inflammation. J Immunol. 2013;190(5):2252-62.

8. Senra L et al. Keratinocyte-derived IL-17E contributes to inflammation in psoriasis. J Invest Dermatol. 2016;136(10): 1970-80.

9. Reich K et al. Evidence that a neutrophil-keratinocyte crosstalk is an early target of IL-17A inhibition in psoriasis. Exp Dermatol. 2015;24(7): 529-35.

10. Gordon KB et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med. 2016; 375(4):345-56.

11. Langley RG et al. Secukinumab in plaque psoriasis - results of two Phase 3 trials. N Engl J Med. 2014;371(4):326-38.

12. European Medicines Agency. EPAR summary for the public: Cosentyx (secukinumab). 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003729/WC500183132.pdf. Last accessed: 10 October 2017.

13. European Medicines Agency. Taltz® Summary of Product Characteristics. 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003943/WC500205804.pdf. Last accessed: 10 October 2017.

14. European Medicines Agency. Stelara® Summary of Product Characteristics. 2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000958/WC500058513.pdf. Last accessed: 10 October 2017.

15. European Medicines Agency. Enbrel® Summary of Product Characteristics. 2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000262/WC500027361.pdf. Last accessed: 10 October 2017.

16. electronic Medicines Compendium. Humira® Summary of Product Characteristics 2003. Available at: http://www.medicines.org.uk/emc/medicine/31860. Last accessed: 10 October 2017.

17. European Medicines Agency. Remicade® Summary of Product Characteristics. 2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf. Last accessed: 10 October 2017.

18. National Institute for Health and Care Excellence (NICE). Psoriasis: assessment and management clinical guidelines. 2012. Available at: https://www.nice.org.uk/guidance/cg153. Last accessed: 10 October 2017.

19. 2.7.4 Summary of clinical safety: brodalumab [common technical document]. AstraZeneca; 21 Oct 2015. Data on File #11.

20. Brodalumab for the treatment of moderate to severe psoriasis: day 120 safety update [common technical document]. AstraZeneca; 6 March 2016. Data on File #5.

21. 2.7.6 - Synopses of individual studies: brodalumab [common technical document]. Data on File #8.

22. Papp KA et al. A prospective Phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. Br J Dermatol. 2016;175(2): 273-86.

23. Lebwohl M et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. N Engl J Med. 2015;373(14):1318-28.

24. European Medicines Agency. Assessment report: Kyntheum (brodalumab). 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003959/WC500232916.pdf. Last accessed: 10 October 2017.

25. Lebwohl M et al. Psychiatric adverse events in brodalumab psoriasis studies. Poster 4908. 75th Annual Meeting of the American Academy of Dermatology, 3-7 March, 2017.

26. Bushnell DM et al. Validation of the Psoriasis Symptom Inventory (PSI), a patient-reported outcome measure to assess psoriasis symptom severity. J Dermatolog Treat. 2013;24(5):356-60.

27. Strober B et al. Clinical meaningfulness of complete skin clearance in psoriasis. J Am Acad Dermatol. 2016;75(1):77-82.

28. Dalgard FJ et al. The psychological burden of skin diseases: A cross-sectional multicenter study among dermatological out-patients in 13 European countries. J Invest Dermatol. 2015;135(4):984-91.

29. Food and Drug Admninistration. Dermatologic and Ophthalmic Drugs Advisory Committee: Errata to Sponsor Briefing Document and errata to Appendix A - narratives and case details for MACE and SIB events. 2016. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM511361.pdf. Last accessed: 10 October 2017.

30. Food and Drug Administration. FDA briefing document: Dermatologic and Ophthalmic Drugs Advisory Committee meeting. Background package for BLA 761032 siliq (brodalumab) injection, 210 mg/1.5 ml. 2016. Available at: https://

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/dermatologicandophthalmicdrugsadvisorycommittee/ucm511357.pdf. Last accessed: 10 October 2017.

31. Food and Drug Administation. Dermatologic and Ophthalmic Drugs Advisory Committee meeting. Sponsor briefing document: brodalumab injection. 2016. Available at: https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/dermatologicandophthalmicdrugsadvisorycommittee/ucm511360.pdf. Last accessed: 10 October 2017.

32. Food and Drug Administration. Dermatologic and Ophthalmic Drugs Advisory Committee meeting. Sponsor briefing document: brodalumab injection. Appendix B: investigations of biologic plausibility of causal relationship between brodalumab and SIB. 2016. Available at: https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/dermatologicandophthalmicdrugsadvisorycommittee/ucm511360.pdf. Last accessed: 10 October 2017.

33. AMAGINE-1: A Phase 3 study to evaluate the efficacy, safety, and effect of withdrawal and retreatment with brodalumab in subjects with moderate to severe plaque psoriasis [clinical study report]. Thousand Oaks (CA): Amgen Inc.; 15 May 2015. Clinical Study Report 20120102. Data on File #1.

34. AMAGINE-2: A Phase 3 study to evaluate the efficacy and safety of induction and maintenance regimens of brodalumab compared with placebo and ustekinumab in subjects with moderate to severe plaque psoriasis [clinical study report]. Thousand Oaks (CA): Amgen Inc.; 30 March 2015. Clinical Study Report 20120103. Data on File #2.

35. AMAGINE-3: A Phase 3 study to evaluate the efficacy and safety of induction and maintenance regimens of brodalumab compared with placebo and ustekinumab in subjects with moderate to severe plaque psoriasis [clinical study report]. Thousand Oaks (CA): Amgen Inc.; 27 March 2015. Clinical Study Report 20120104. Data on File #3.

36. Europan Medicines Agency; Committee for Medicinal Products for Human Use. Summary of opinion (initial authorisation): Kyntheum (brodalumab). 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/003959/WC500228098.pdf. Last accessed: 10 October 2017.

37. Papp K et al. Impact of previous biologic use and failure on efficacy of brodalumab and ustekinumab: A pooled analysis of data from two Phase 3 randomized clinical trials in moderate-to-severe plaque psoriasis (AMAGINE-2 and AMAGINE-3). Presentation 4978. 75th Annual Meeting of the American Academy of Dermatology, 3-7 March, 2017.

38. Blauvelt A et al. Median time to treatment response in patients with moderate-to-severe plaque psoriasis treated with brodalumab 210 mg or ustekinumab: A pooled analysis of data from two Phase 3 randomized clinical trials (AMAGINE-2 and AMAGINE-3). Presentation 5092. 75th Annual Meeting of the American Academy of Dermatology, 3-7 March, 2017.

39. Ryan C et al. Genital psoriasis is associated with significant impairment in quality of life and sexual functioning. J Am Acad Dermatol. 2015;72(6):978-83.

40. Gooderham M et al. A review of psoriasis, therapies, and suicide. J Cutan Med Surg. 2016;20(4):293-303.

41. Ogdie A et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: A population-based cohort study. Ann Rheum Dis. 2015;74(2):326-32.

42. Gelfand JM et al. The risk of mortality in patients with psoriasis: Results from a population-based study. Arch Dermatol. 2007;143(12):1493-9.

43. Yeung H et al. Psoriasis severity and the prevalence of major medical comorbidity: A population-based study. JAMA Dermatol. 2013;149(10):1173-9.

44. Lebwohl M et al. Patients with inadequate response to ustekinumab achieve high levels of clearance after switching to brodalumab. Poster 1800. 26th European Academy of Dermatology and Venereology congress, 13-17 September, 2017.

45. Strohal R et al. A patient-centred approach to biological treatment decision making for psoriasis: An expert consensus. J Eur Acad Dermatol Venereol. 2015;29(12):2390-8.

46. Nast A et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris - Update 2015--Short version--EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2015;29(12):2277-94.

47. Crow JM. Therapeutics: Silencing psoriasis. Nature. 2012;492(7429):S58-9.

48. Puig L. PASI90 response: The new standard in therapeutic efficacy for psoriasis. J Eur Acad Dermatol Venereol. 2015;29(4):645-8.

49. Bachelez H. Interleukin-17 inhibition: A route to psoriasis clearance? Lancet. 2015;386(9993):510-2.

50. Sawyer L et al. Network meta-analysis to evaluate the efficacy of brodalumab in the treatment of moderate-to-severe psoriasis. Poster 1838. 26th European Academy of Dermatology and Venereology congress, 13-17 September, 2017.

51. Nast A et al. Efficacy and safety of systemic long-term treatments for moderate-to-severe psoriasis: A systematic review and meta-analysis. J Invest Dermatol. 2015;135(11):2641-8.

52. Gómez-García F et al. Short-term efficacy and safety of new biological agents targeting the interleukin-23-T helper 17 pathway for moderate-to-severe plaque psoriasis: A systematic review and network meta-analysis. Br J Dermatol. 2017;176(3):594-603.

53. Eichler HG et al. Balancing early market access to new drugs with the need for benefit/risk data: A mounting dilemma. Nat Rev Drug Discov. 2008;7(10):818-26.

54. van de Kerkhof PC et al. Physician perspectives in the management of psoriasis and psoriatic arthritis: Results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis survey. J Eur Acad Dermatol Venereol. 2015;29(10):2002-10.

55. Lebwohl MG et al. Patient perspectives in the management of psoriasis: Results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. J Am Acad Dermatol. 2014;70(5):871-81.

56. Reich K et al. Inflammatory bowel disease among patients with psoriasis treated with ixekizumab: A presentation of adjudicated data from an integrated database of 7 randomized controlled and uncontrolled trials. J Am Acad Dermatol. 2017;76(3):441-8.e2. Erratum in: J Am Acad Dermatol. 2017;77(2):390.e1.

57. Hueber W et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: Unexpected results of a randomised, double-blind placebo-controlled trial. Gut. 2012;61(12):1693-700.

58. Egeberg A et al. Association between psoriasis and inflammatory bowel disease: A Danish nationwide cohort study. Br J Dermatol. 2016;175(3):487-92.

59. Sbidian E et al. Factors associated with the choice of the first biologic in psoriasis: Real-life analysis from the Psobioteq cohort. J Eur Acad Dermatol Venereol. 2017. [Epub ahead of print].

# THE ASSOCIATIONS OF HUMAN LEUKOCYTE ANTIGEN CLASS I AND CLASS II ALLELES IN BULLOUS PEMPHIGOID

**Hui Fang,[1] Xiaodong Zheng,[2] Liangdan Sun,[2] *Gang Wang[1]**

*1. Department of Dermatology, Xijing Hospital, Fourth Military Medical University, Xi'an, China*
*2. Department of Dermatology, No. 1 Hospital and Key Laboratory of Dermatology, Ministry of Education, Anhui Medical University, Hefei, China*
**Correspondence to xjwgang@fmmu.edu.cn*

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Keywords: Bullous pemphigoid (BP), human leukocyte antigen (HLA) Class I, human leukocyte antigen (HLA) Class II, haplotypes.

Bullous pemphigoid (BP) is a complex, multifactorial autoimmune disease characterised by the presence of autoantibodies against BP autoantigens, leading to dermal-epidermal separation with consequent blister formation.[1] Genetic, environmental, and stochastic factors contribute to susceptibility to most autoimmune diseases.[2] Associations of genes, especially human leukocyte antigen (HLA)-DQ and HLA-DR alleles, with BP indicate that genetic predisposition contributes to the disease. Population studies have revealed that HLA Class II alleles are associated with BP in diverse ethnic groups, including British,[3] German,[4] Japanese,[5] Chinese,[6] and Iranian[7] populations. However, BP has previously been found not to have HLA Class I associations. The objective of our study was to evaluate the association of HLA Class I and HLA Class II alleles with susceptibility to BP in the northern Chinese Han population.

We performed genotype investigations for HLA-A, HLA-B, HLA-C, HLA-G, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, and HLA-DRB1 loci in 105 patients with BP by using the Sanger sequence-based typing method. These data were compared with a local control cohort of 1,000 cases. Among the HLA alleles described herein, the susceptibility alleles associated with a high prevalence of BP were HLA-A*01:01 and 11:01, HLA-B*37:01, HLA-G*01:01 and 01:06, HLA-DQA1*01:05 and 05:05, HLA-DQB1*05:01, and HLA-DRB1*10:01 and 11:04. On the contrary, HLA-DQA1*01:02 and 01:03, HLA-DQB1*02:02, and HLA-DRB1*07:01 had significant associations with protection against BP. In addition, the frequencies of haplotypes HLA-DRB1*13/HLA-DQA1*05/HLA-DQB1*03 and HLA-DRB1*15/HLA-DQA1*01/HLA-DQB1*05 in BP patients were significantly higher than those in controls.

Susceptibility to BP is caused by a combination of genetic and environmental factors.[1,8,9] Current thought postulates that a collection of common risk alleles mediates the development of an autoimmune-prone immune system which, when coupled with poorly defined environmental triggers, becomes dysregulated, leading to the development of autoantibodies and the initiation of disease pathologies.[10] Major histocompatibility complex (MHC) Class I and II alleles are often the strongest risk factors associated with autoantibody-mediated diseases. In BP, the activation of antigen-specific B cells and secretion of autoantibodies depends on the interaction between the T cell receptor and classical MHC Class II molecules. Our HLA Class I and Class II profiles of Chinese BP patients, together with the previous reports on populations with BP worldwide, suggest that the alleles and haplotypes reported in this study may play crucial roles in autoimmune responses to BP antigens. In addition, our data indicate that genetic susceptibility differences in ethnic groups are maintained in patients living away from their countries of ethnic origin, underlining the importance of genetic risk factors in this disease. Furthermore, the relationships between the HLA alleles/haplotypes and autoimmune responses to BP antigens remain to be clarified.

## REFERENCES

1. Schmidt E, Zillikens D. Pemphigoid diseases. Lancet. 2013; 381(9863):320-32.
2. Tsai S, Santamaria P. MHC class II polymorphisms, autoreactive T-cells, and autoimmunity. Front Immunol. 2013;4:321.
3. Banfield CC et al. The association of HLA-DQ7 with bullous pemphigoid is restricted to men. Br J Dermatol. 1998;138(6): 1085-90.
4. Büdinger L et al. Identification and characterization of autoreactive T cell responses to bullous pemphigoid antigen 2 in patients and healthy controls. J Clin Invest. 1998;102(12):2082-9.
5. Okazaki A et al. Polymorphisms of HLA-DR and -DQ genes in Japanese patients with bullous pemphigoid. J Dermatol. 2000;27(3):149-56.
6. Gao XH et al. HLA-DR and DQ polymorphisms in bullous pemphigoid from northern China. Clin Exp Dermatol. 2002; 27(4):319-21.
7. Esmaili N et al. Association between HLA-DQB1*03:01 and bullous pemphigoid in Iranian patients. Iran J Immunol. 2013; 10(1):1-9.
8. Zakka LR et al. Role of MHC class II genes in the pathogenesis of pemphigoid. Autoimmun Rev. 2011;11(1):40-7.
9. Lo Schiavo A et al. Bullous pemphigoid: Etiology, pathogenesis, and inducing factors: facts and controversies. Clin Dermatol. 2013;31(4):391-9.
10. Raj P et al. Regulatory polymorphisms modulate the expression of HLA class II molecules and promote autoimmunity. eLife. 2016;5:e12089.


# PSEUDOXANTHOMA ELASTICUM


## *Suzan Demir Pektas

*Department of Dermatology, Faculty of Medicine, Muğla Sıtkı Koçman University, Muğla, Turkey*
**Correspondence to suzandpektas@mu.edu.tr*



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Keywords: Pseudoxanthoma elasticum (PXE), clinical features, histological features, differential diagnosis, treatment.


Pseudoxanthoma elasticum (PXE) is an inherited multisystem disorder characterised by pathological calcification of elastic connective tissue. Females are more commonly affected than males.[1] PXE is caused by mutations in the ABCC6 gene that encodes a transmembrane ATP binding efflux transporter. Skin lesions typically consist of small, asymptomatic, yellowish, or skin-coloured papules in flexural skin areas, that progressively coalesce into larger plaques due to cutaneous laxity.[1,2] Asymptomatic skin manifestations usually occur between the first and second decades of the patient's life.[1] Mucosal lesions of the oral cavity and genital area resemble cutaneous changes. Ophthalmological features of PXE primarily include peau d'orange, comet lesions, angioid streaks, choroidal neovascularisation, chorioretinal atrophies, optic disk drusen, and disciform scars.[1,2] Secondary degenerative and haemorrhagic changes in the macula can be found, frequently leading to severe reduction of visual acuity.[3]

PXE patients can also develop premature atherosclerosis with early, acute myocardial infarctions and gastrointestinal haemorrhage. Alterations in lipoprotein composition were found in plasma samples of PXE patients and bleeding diathesis was also identified.[1,2] Clinical diagnosis, with characteristic histopathological examination, reveals fragmented and distorted elastic fibres in the reticular and deep dermis. These changes are more evident in elastic tissue-specific Verhoeff-van Gieson and Calleja stains.[1,2] The absence of skin alterations does not, however, exclude a diagnosis of PXE.[1] The manifestation of clinical and histological features of classic PXE may be similar to other disorders, such as vitamin K-dependent coagulation factor deficiency, inherited haemoglobinopathies, Paget's disease, Marfan syndrome, cutis laxa, fibroelastolytic papulosis, PXE-like papillary dermal elastolysis, late-onset focal dermal elastosis, and perforating calcific elastosis.[1,2,4]

Therapeutic management is based on prevention and monitoring of complications associated with the disease.[3] Surgery for aesthetic improvement of cutaneous lesions is not routinely performed. However, significant progress has been made in the therapy of ocular complications.[1,5] A diet supplemented with magnesium and vitamin K may slow the progression of the disease.[1,5]

## REFERENCES

1. Marconi B et al. Pseudoxanthoma elasticum and skin: Clinical manifestations, histopathology, pathomechanism, perspectives of treatment. Intractable Rare Dis Res. 2015;4(3):113-22.
2. Decani S et al. Pseudoxanthoma elasticum of the palate: A case report and a brief review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;121(1):e6-9.
3. Marques GF et al. Pseudoxanthoma elasticum: Report of two cases. An Bras Dermatol. 2014;89(5):812-5.
4. Hosen MJ et al. Histopathology of pseudoxanthoma elasticum and related disorders: Histological hallmarks and diagnostic clues. Scientifica (Cairo). 2012;2012:598262.
5. Finger RP et al. Pseudoxanthomaelasticum: genetics, clinical manifestations and therapeutic approaches. Surv Ophthalmol. 2009;54(2):272-85.


# THE IMPACT OF AIR POLLUTION ON SKIN AND RELATED PROTECTION BY THERMAL SPRING WATER


## Dominique Moyal,[1] *Sophie Seité,[1] Susanne Grether-Beck,[2] Jean Krutmann[2]

*1. La Roche-Posay Dermatological Laboratories, Asnières, France*
*2. Institut für Umweltmedizinische Forschung, Düsseldorf, Germany*
**Correspondence to sophie.seite@loreal.com*



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Keywords: Pollution, thermal spring water, inflammatory mediators, pigmentation marker.


In epidemiological studies, it has been shown that exposure to airborne, traffic-related particulate matter (PM) is associated with increased skin sensitivity and signs of skin ageing, including pigment spot formation.[1,2] For example, fine carbon black (Huber 990; H Haeffner & Co. Ltd., Chepstow, UK) and diesel exhaust particles, such as SRM1650 and SRM2975, induce the production of soluble inflammatory mediators (interleukin [IL]-1, IL-6) and skin pigmentation markers (pro-opiomelanocortin [POMC]) in human keratinocytes. Previous studies also indicate that the combination of ultraviolet (UV) radiation and pollution may result in synergistic effects.[2] The aim of this study was to evaluate whether La Roche-Posay Thermal Spring Water (LRP-TSW)[3] was able to inhibit or decrease pollution and UV pollution-induced damage in human keratinocytes.

Gene expression of keratinocytes cultured in cell culture medium MCDB153 dissolved in LRP-TSW was compared to that of keratinocytes cultured in the same medium prepared with deionised drinking water. Total RNA isolation and polymerase chain reaction (PCR) techniques were carried out 24–48 hours after exposure to pollution particles or pollution particles plus UV exposure. Messenger RNA (mRNA) expression of IL-1α/18S ribosomal RNA (rRNA), IL-6/18S rRNA, and POMC/18S rRNA was measured. The PM used in this study were diesel exhaust particles SRM1650 and SRM2975 or Huber 990. Exposure to UV radiation was performed using either a total UV spectrum lamp (solar simulated radiation [SSR]) or under a UVA1 radiation lamp (340–400 nm).

At 24 hours post exposure, we observed a significant ($p<0.05$) upregulation of the proinflammatory marker IL-6 when keratinocytes were exposed to SRM1650 and SRM2975 particles. LRP-TSW significantly ($p<0.05$) reduced this upregulation by 43% and 100%, respectively. At 48 hours post exposure, we observed a significant upregulation of IL-1α expression when keratinocytes were exposed to SRM1650 and SRM2975 particles. LRP-TSW significantly ($p<0.05$) protected against this upregulation by 42% and 53%, respectively. We also observed a significant upregulation of the pigmentation marker POMC with exposure to SRM1650 particles and that LRP-TSW was able to significantly ($p<0.001$) inhibit this upregulation (Figure 1).

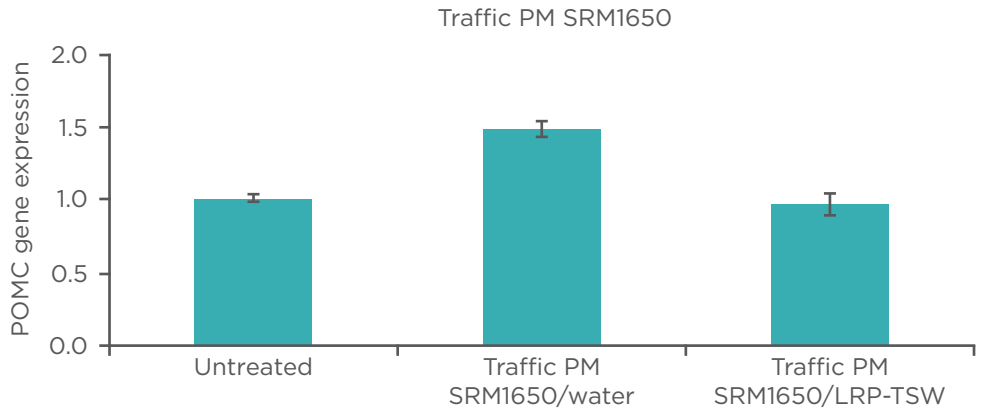


**Figure 1: The upregulation of pro-opiomelanocortin pigmentation marker by exposure to traffic particulate matter SRM1650.**
PM: particulate matter; POMC: pro-opiomelanocortin; LRP-TSW: La Roche-Posay Thermal Spring Water.

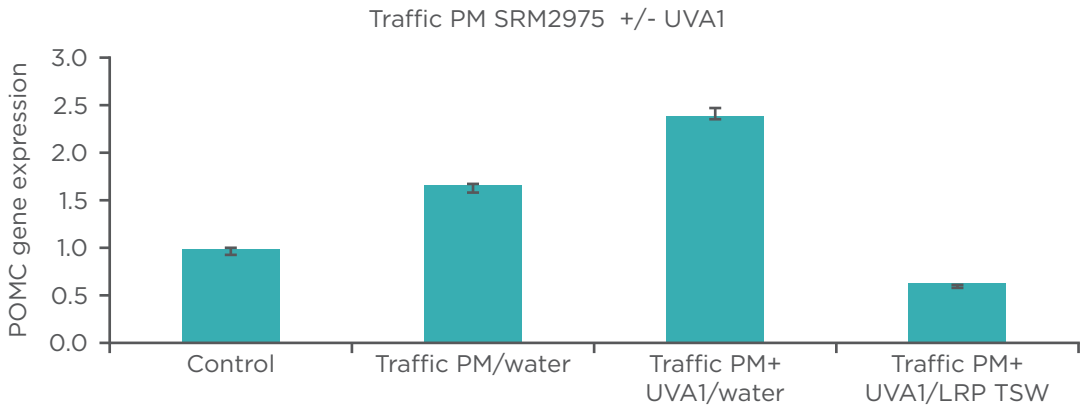


**Figure 2: The upregulation of proopiomelanocortin pigmentation marker by exposure to traffic particulate matter alone and in combination with UVA1.**
LRP-TSW: La Roche-Posay Thermal Spring Water; PM: particulate matter; POMC: proopiomelanocortin; UVA1: ultraviolet A1 radiation.

Keratinocytes were then exposed to PM SRM2975 alone and in combination with SSR. The keratinocyte response suggested increased IL-6 gene expression due to the addition of SSR exposure versus traffic PM alone. LRP-TSW significantly ($p<0.001$) prevented this synergistic effect. When keratinocytes were exposed to the combination of PM SRM2975 and UVA1 radiation (long-UVA) (10 J/cm$^2$), a significant upregulation of POMC was observed, as well as a significant protective effect ($p<0.001$) by the addition of LRP-TSW (Figure 2). Similar protection ($p<0.001$) was noted for the upregulation of IL-1 with PM Huber 990 and UVA1 radiation exposure.

This study confirms that pollution particles are able to induce inflammatory and pigmentation mediators in human keratinocytes and that the combination of these particles with UV radiation has a synergistic effect. We demonstrated that LRP-TSW was able to inhibit inflammatory and pigmentation mediator upregulation by traffic PM alone or in combination with UV radiation. These data confirm the utility of using LRP-TSW to protect the skin against pollution.

REFERENCES

1. Krutmann J et al. Pollution and skin: From epidemiological and mechanistic studies to clinical implications. J Dermatol Sci. 2014;76(3):163-8.
2. Nakamura M et al. Environment-induced lentigines: formation of solar lentigines beyond ultraviolet radiation. Exp Dermatol. 2015;24(6):407-11.
3. Seité S. Thermal waters as cosmeceuticals: La Roche-Posay thermal spring water example. Clin Cosmet and Investig Dermatol. 2013;6:23-8.

# IS THE ANTI-NXP-2 (ANTI-MJ) ANTIBODY A MARKER ANTIBODY FOR DYSPHAGIA IN DERMATOMYOSITIS? A REPORT OF THREE CASES

**Masato Kakeda,[1] *Keiichi Yamanaka,[1] Yoshinao Muro,[2] Hitoshi Mizutani[1]**

*1. Department of Dermatology, Mie University Graduate School of Medicine, Tsu, Japan*
*2. Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan*
**Correspondence to yamake@clin.medic.mie-u.ac.jp*

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Keywords: Dermatomyositis (DM), dysphagia, anti-NXP-2 antibody (Ab), myositis specific antigen.

Dermatomyositis (DM) is an autoimmune myopathy of unknown aetiology and involves the development of characteristic skin manifestations, muscle weakness, and internal organ involvement. Recently, several myositis-specific autoantibodies, the marker antibodies (Ab) for specific clinical manifestations, have been measured by clinical laboratory investigations, and may possibly be used for predicting DM prognosis. The anti-NXP-2 (also known as anti-MJ) Ab has been identified as a myositis-specific autoantibody for juvenile DM with cutaneous calcinosis and severe muscle weakness;[1] however, the clinical manifestations and organ involvement, such as internal malignancy and interstitial lung disease in adult DM patients with anti-NXP-2 Ab, are still unclear. Very recently, close associations between anti-NXP-2 Ab and severe dysphagia in two USA cohorts of adult DM patients were reported.[2,3] Here, we report three successfully treated cases of anti-NXP-2 Ab-positive DM with dysphagia using intensive immunosuppressive therapies, including corticosteroid pulse therapy, tacrolimus (FK506), and high-dose intravenous immunoglobulin therapy (IVIg).

## CASE 1

A 55-year-old Japanese male developed severe dysphagia with thrombocytopenia (16 x$10^9$ /L) and severe generalised subcutaneous oedema on the extremities during the initial treatment for DM with 1 mg/kg/day prednisolone (PSL). Methylprednisolone pulse therapy (1 g/day for 3 days) and IVIg (400 mg/kg/day for 5 days) with platelet transfusion was started. The patient's muscle weakness, thrombocytopenia, and subcutaneous oedema dramatically improved, but the dysphagia did not. Percutaneous endoscopic gastrostomy tube insertion was required for the dysphagia with refractory aspiration pneumonia. Dysphagia was not improved with high dose PSL treatment; however, it was successfully treated after eight courses of monthly IVIg and tacrolimus (4 mg/kg/day) and the patient returned to oral feeding.

## CASE 2

A 70-year-old Japanese male developed severe dysphagia during the initial PSL treatment (1 mg/kg/day) and required a temporal nasogastric tube for feeding. His dysphagia improved with methylprednisolone pulse therapy and tacrolimus (5 mg/kg/day).

## CASE 3

A 25-year-old Japanese female developed mild dysphagia during the tapering of PSL and tacrolimus

from initial daily PSL therapy (0.5 mg/kg/day). Her dysphagia improved with methylprednisolone pulse therapy (0.5 g/day for 3 days) and tacrolimus (4 mg/kg/day).

All three of these cases were diagnosed using the Bohan and Peter's criteria.[4] Anti-NXP-2 Ab was measured using the specific enzyme-linked immunosorbent assay (ELISA).[5] The presence of dysphagia was diagnosed by use of video fluoroscopic examinations. No internal malignancy or cutaneous calcinosis were detected in any of the three patients. Interstitial lung disease was present in Case 2.

Dysphagia is a serious manifestation of severe DM cases and is associated with a high risk of the patient developing aspiration pneumonia and receiving a poor prognosis.[6] Dysphagia develops in 25–84% of adult polymyositis/DM[6] patients and in around 30–40% of juvenile DM patients with anti-NXP-2 Ab.[1,7] In the Mie University Hospital, Tsu, Japan, we treated 22 Japanese adult cases of DM between January 2014 and March 2017. Three of the 22 (14.3%) cases were anti-NXP-2 Ab positive and developed dysphagia. The anti-NXP-2 Ab positive DM patients developed dysphagia more frequently (62.5% and 70.0%) compared with anti-NXP-2 Ab negative DM patients (35.1% and 38.6%) in two recent USA cohorts of DM patients, respectively.[2,3]

Measurement of anti-NXP-2 Ab in DM patients has the potential to be used as a predictor of the severe complication of dysphagia and strict control with intensive immunosuppressive therapy, including corticosteroid pulse therapy, calcineurin inhibitors, and IVIg, should be considered for anti-NXP-2 Ab positive DM cases with dysphagia.

## REFERENCES


1. Espada G et al. Clinical and serologic characterization of an Argentine pediatric myositis cohort: Identification of a novel autoantibody (anti-MJ) to a 142-kDa protein. J Rheumatol. 2009;36(11):2547-51.

2. Albayda J et al. Dermatomyositis patients with anti-nuclear matrix protein-2 autoantibodies have more edema, more severe muscle disease, and increased malignancy risk. Arthritis Care Res (Hoboken). 2017. [Epub ahead of print].

3. Rogers A et al. The cutaneous and systemic findings associated with nuclear matrix protein-2 antibodies in adult dermatomyositis patients. Arthritis Care Res (Hoboken). 2017. [Epub ahead of print].

4. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292(7):344-7.

5. Ishikawa A et al. Development of an ELISA for detection of autoantibodies to nuclear matrix protein 2. Rheumatology (Oxford). 2012;51(7):1181-7.

6. Marie I et al. Intravenous immunoglobulins for steroid-refractory esophageal involvement related to polymyositis and dermatomyositis: A series of 73 patients. Arthritis Care Res (Hoboken). 2010;62(12):1748-55.

7. Oddis CV et al. Clinical and serological characterization of the anti-MJ antibody in childhood myositis. Arthritis Rheum. 1997;40:S139.


# CASE SERIES OF VASCULITIDES: AN ON-CALL EXPERIENCE


***Sue Ann Chan, Donna Thompson**

*Birmingham Skin Centre, Birmingham, UK*
**Correspondence to sueann.chan@nhs.net*



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Keywords: Cutaneous vasculitis, systemic involvement, European Association of Dermatology and Venereology (EADV) congress.


The European Association of Dermatology and Venereology (EADV) annual congress is one of the most prestigious and well-attended dermatology conferences in the world. This year, the EADV successfully held its 26th annual congress in the vibrant city of Geneva, Switzerland on 13th–17th September 2017.

Our team from the Birmingham Skin Centre, Birmingham, UK, was honoured to have the opportunity to present a poster of our research at the congress. We conducted a retrospective review of the records of all patients seen in the emergency dermatology service (emergency clinics and ward reviews) between June and December 2016, to identify patients with cutaneous vasculitis and highlight trends in demographics, clinicopathological features, suspected causes, and clinical outcomes.

Cutaneous vasculitis is a clinicopathological entity induced by various underlying causes, including drugs, infections, and connective tissue diseases, and may also be idiopathic. Dermatological assessment and skin biopsies can help elucidate any underlying aetiologies.

In our case series, six of the nine patients studied had positive urinalysis, demonstrating microscopic haematuria and proteinuria; four of the six urinalysis positive patients had systemic renal involvement with raised urinary albumin/creatinine ratio (≤133.82 mg/mmol) at presentation. The other two patients with initial microscopic haematuria demonstrated resolution in both cutaneous lesions and clearing of microscopic haematuria in subsequent urinalysis (both with normal albumin/creatinine ratio at presentation). One patient was confirmed to have immunoglobulin (Ig)A nephropathy on renal biopsy (perilesional skin immunofluorescence negative), whilst another patient with suspected IgA nephropathy remained under close monitoring given the risks of renal biopsy with comorbidities, including obesity and cardiomyopathy with long-term rivaroxaban.

Suspected causes of vasculitis included streptococcal infection with raised anti-streptolysin O titre (n=2), IgA nephropathy (n=2), and urosepsis (n=1). The patient with sepsis died following transfer to a tertiary hospital for renal dialysis.

Although current literature suggests that, in most instances, cutaneous vasculitis represents a self-limiting, single-episode phenomenon, our case series highlights significant morbidities and one mortality. We wish to raise awareness that patients who showed progression demonstrated abnormal laboratory investigations and urinalysis, and had more florid, cutaneous lesions at the time of diagnosis.

It was very interesting to be able to attend lectures and updates on connective tissue disorders where treatments discussed included hydroxychloroquine, quinacrine, dapsone, methotrexate, thalidomide, systemic steroids, intravenous Ig, acitretin, alitretinoin, photopheresis, and belimumab. It was also educational to be able to view poster presentations from delegates from all over the globe at the EADV congress.

# SUCCESSFUL TREATMENT OF EPIDERMOLYSIS BULLOSA ACQUISITA WITH RITUXIMAB–INTRAVENOUS IMMUNOGLOBULIN COMBINATION

***Nilgun Senturk, Enkhjargal Losol**

*Department of Dermatology,*
*Ondokuz Mayis University, Samsun, Turkey*
**Correspondence to nilsenturk@yahoo.com*

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Keywords: Epidermolysis bullosa acquisita (EBA), rituximab, intravenous immunoglobulin (IVIg).

Epidermolysis bullosa acquisita (EBA) is a rare, sub-epithelial, mechano-bullous blistering disease that usually develops in adulthood. Treatment of EBA with conventional immunosuppressive agents is generally unsatisfactory. At the 26th congress of the European Academy of Dermatology and Venereology (EADV) in Geneva, we presented a case of EBA successfully treated with a rituximab and high-dose intravenous immunoglobulin (IVIg) combination.

A 52-year-old female with a 12-year history of EBA presented with widespread vesiculobullous eruption and milia formation on the trunk and extensor surface of the extremities and scalp accompanied with pruritus (Figure 1). She was unresponsive to prednisolone and azathioprine; therefore, a combination of rituximab (two doses of 1,000 mg, 15 days apart) and human Ig (0.4 g/kg 5 days per month) was added to treatment. At 6-month follow-up, lesions on the extremities had improved almost completely (Figure 2).

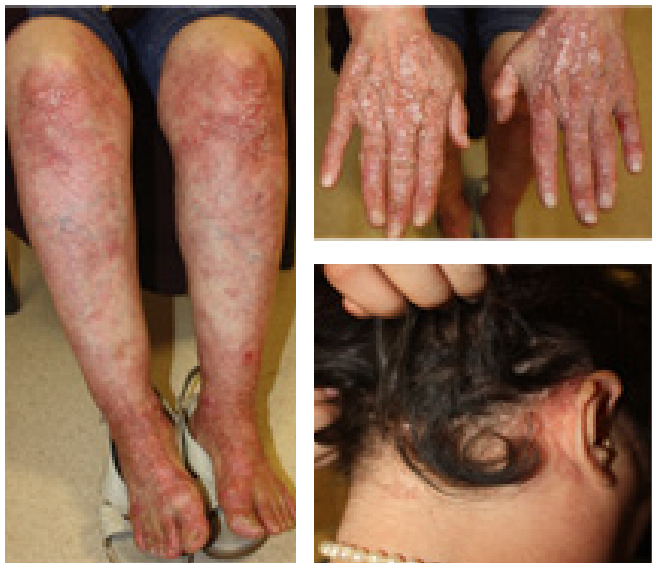

**Figure 1: Widespread milia formation on the lower extremities, hands, and scalp.**

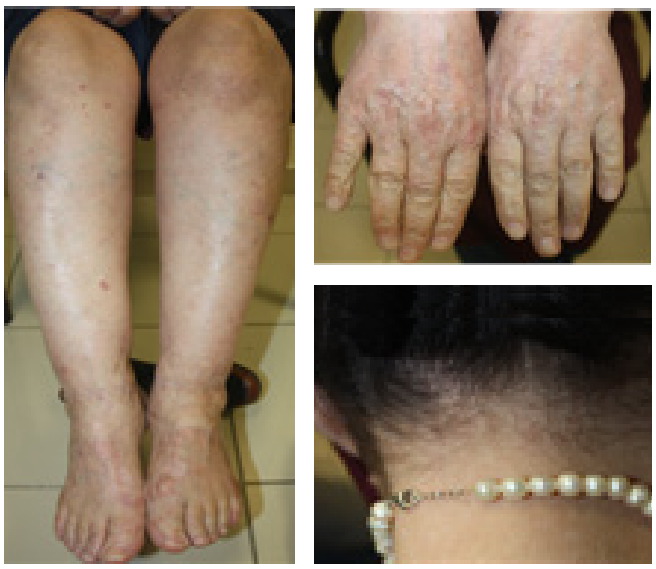

**Figure 2: Clearance of widespread milia lesions on the lower extremities, hands, and scalp after rituximab–IVIg combination treatment.**
IVIg: intravenous immunoglobulin.

Compared with other autoimmune blistering diseases, EBA is generally resistant to conventional treatments; remission induction is quite difficult with the available options such as systemic corticosteroids and immunosuppressive agents. In recent years, much more experience has been gained in the treatment of autoimmune bullous disease with the emergence of novel therapeutic agents. Rituximab and IVIg are new treatment options that can prolong the disease-free interval in patients with an autoimmune bullous disease and have been increasingly used. Rituximab, a monoclonal anti-CD20 antibody targeting immature B cells and memory B cells, can be administered as a monotherapy or in combination with adjuvant agents. IVIg can reduce pathogenic autoantibody levels, and long-term remission can be achieved using IVIg monotherapy in patients with autoimmune bullous diseases. The rituximab–IVIg combination can decrease levels of pathogenic autoantibodies rapidly. A further advantage of this combination therapy is its ability to reduce the risk of infection due to immunosuppression caused by rituximab. The combination of rituximab–IVIg was reported to produce clinical remission in a small number of patients with EBA, which was sustained during the follow-up period. It is suggested that combined/single use of biological agents, such as IVIg and rituximab, is an effective first-line treatment and may protect against the side effects of systemic corticosteroids and immunosuppressive agents.

In conclusion, rituximab–IVIg combination treatment is effective and safe for treating patients with EBA resistant to conventional treatments. IVIg therapy rapidly removes blood pathogenic autoantibodies and reduces the possible risk of infection caused by rituximab. In addition, pathogenic antibody levels can be reduced in the long term by changing the B cell subgroups with rituximab.

## REFERENCES

1. Gupta R et al. Epidermolysis bullosa acquisita. Clin Dermatol. 2012;30(1):60-9.

2. Oktem A et al. Long-term results of rituximab–intravenous immunoglobulin combination therapy in patients with epidermolysis bullosa acquisita resistant to conventional therapy. J Dermatolog Treat. 2017;28(1):50-4.

3. Schmidt E et al. Successful adjuvant treatment of recalcitrant epidermolysis bullosa acquisita with anti-CD20 antibody rituximab. Arch Dermatol. 2006;142(2):147-50.

4. Mohr C et al. Successful treatment of epidermolysis bullosa acquisita using intravenous immunoglobulins. Br J Dermatol. 1995;132(5):824-6.

# COST-EFFECTIVE THERAPEUTIC MODALITIES IN ALOPECIA AREATA

**Ravi Saini, *Mansak Shishak**

*Government Medical College Amritsar, Punjab, India*
**Correspondence to mansakshishak@gmail.com*

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Keywords: Alopecia areata, intralesional corticosteroids, calcipotriol, phenol.

The patches of hair loss in alopecia areata occur as a result of T cell mediated loss of immune privilege. Hair follicles, however, are preserved in alopecia areata; the potential for recovery of hair growth is maintained even in longstanding disease, except when complicated by the cicatricial variant, either iatrogenic or pathologic. Many patients, but by no means all, experience spontaneous regrowth of hair. We believe that treatment is necessary, because it leads to the hastening of hair growth. With this in mind, we compared three cost-effective modalities: intra-lesional corticosteroids, phenol, and calcipotriol. A total of 30 patients, with a minimum of three patches of alopecia on the scalp, were divided into three groups. Group A was injected with triamcinolone acetonide 5 mg/mL at 4-week intervals, Group B underwent phenolisation using pure (88%) phenol once a month, while Group C was treated with topical calcipotriol (0.005%) lotion twice a day. The total duration of treatment was 12 weeks.

## RESULTS

In Group A, 22 (73.3%) cases attained Grade IV improvement, meaning terminal hairs were now present over previous alopecic areas, covering the entire lesional patch. Twenty (66.7%) cases in Group B and 13 (43.3%) cases in Group C attained Grade IV improvement, respectively. Thus, intralesional corticosteroids were found to be more effective than topical phenol, both of which were more effective than topical calcipotriol.

## MECHANISM OF ACTION

- Intralesional corticosteroids act via suppression of T cell-mediated immune attack on the hair follicles.[1]
- Phenol causes epidermal keratin coagulation and releases cytokines during wound healing that neutralise the peribulbar infiltrates, causing regrowth of hair through antigenic competition, thereby decreasing the immune attack on pigmented anagen hairs.[2]
- Calcipotriol (a vitamin D analogue) is immunomodulatory, which acts by binding to specific vitamin D receptors expressed on outer root sheaths, stimulating the terminal differentiation of keratinocytes.[3]

## SAFETY CONCERNS

A concern in phenolisation was the post-inflammatory hyper and hypopigmentation. These effects, although transient, were frequently observed (56.6%). Calcipotriol was found to be extremely safe.

## RECOMMENDATIONS

We recommend that a further study comprising larger sample sizes with adequate follow-up periods be undertaken for a better understanding. Perhaps an ideal approach would be to initiate the treatment with an effective and safe modality i.e. intralesional triamcinolone acetonide (one or two injections) followed by maintenance with topical calcipotriol. Targeted treatments, such as janus kinase inhibitors (ruxolitinib), and interleukin-2 injections have shown good responses and, as such, warrant use in extensive variants such as alopecia totalis. We are hopeful for more extensive clinical trials, including topical targeted treatments, that will bypass the feared systemic ill-effects.

## REFERENCES

1. Porter D, Burton JL. A comparison of intra-lesional triamcinolone hexacetonide and triamcinolone acetonide in alopecia areata. Br J Dermatol. 1971;85(3):272-3.

2. Khar S, Singh N. Alopecia areata treated with phenolisation and intravenous dexamethasone pulses. Int J Trichology. 2013; 5(1):47-9.

3. Kim DH et al. Successful treatment of alopecia areata with topical calcipotriol. Ann Dermatol. 2012;24(3):341-4.

# NEUTROPHILIC DERMATOSIS OF THE HANDS: AN ACRAL VARIANT OF SWEET'S SYNDROME OR A DISTINCT ENTITY?

***Rima Gammoudi,[1] Lobna Boussofara,[1] Nejet Ghariani,[1] Badreddine Sriha,[2] Colandane Belajouza,[1] Mohamed Denguezli,[1] Rafiaa Nouira[1]**

*1. Dermatology department, Farhat Hached Hospital, Sousse, Tunisia*
*2. Anatomopathology department, Farhat Hached Hospital, Sousse, Tunisia*
**Correspondence to rima.gammoudi.28@gmail.com*

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Keywords: Neutrophilic dermatosis of the hand (NDH), Sweet's syndrome (SS), pustulosis.

Neutrophilic dermatosis may have various clinical presentations, but these all share common histopathological manifestations with an aseptic infiltrate of polymorphonuclear neutrophils. Neutrophilic dermatosis of the hands (NDH) is a recently described disorder of which we present two cases and discuss the aetiopathogenic link to Sweet's syndrome (SS).

Patient 1 was a 60-year-old woman, with no relevant medical history, who presented with an acute and painful eruption of both hands with fever preceded by an upper respiratory tract infection. Clinical examination showed erythematous oedematous lesions surmounted by pustules that covered the thenar eminences of both palms (Figure 1A). Histological findings were predominantly neutrophilic infiltration in the dermis with leukocytoclastic vasculitis. A diagnosis of NDH was made and all the lesions disappeared rapidly without relapse under oral prednisone.

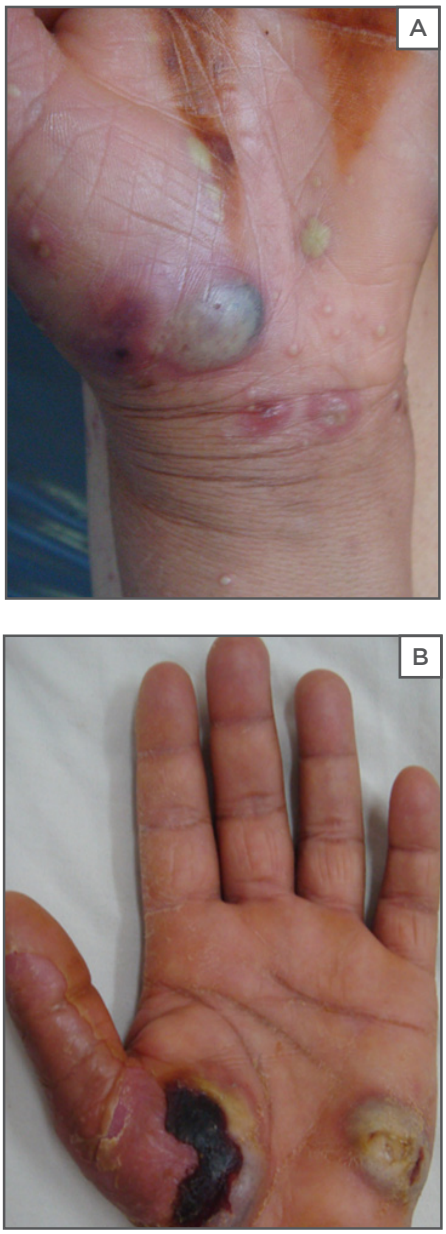


**Figure 1: Erythematous oedematous lesions surmounted by pustular and haemorrhagic bullae over the thenar eminences of both patients.**
A: Patient 1; B: Patient 2

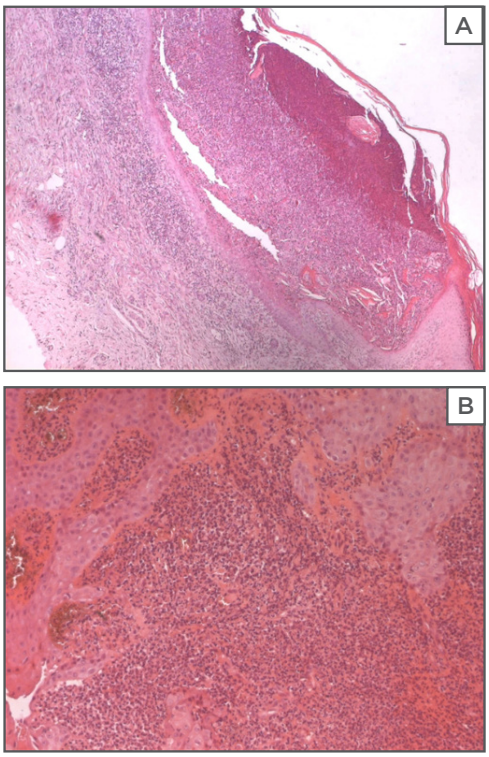


**Figure 2: Diffuse and dense neutrophilic infiltrate in the dermis (haematoxylin and eosin X100).**
A: Patient 1; B: Patient 2.

Patient 2 was a 52-year-old woman who presented with very painful, well-defined erythematous, markedly oedematous plaques and pustular bullae over the thenar eminence of the left hand (Figure 1B). These lesions had gradually progressed for 4 weeks, following percutaneous trauma while handling fish, and failed to respond to several antibiotics. Laboratory investigations showed neutrophil leukocytosis in peripheral blood. A biopsy was taken from a section of the lesion which revealed diffuse and dense neutrophilic infiltrate in the dermis (Figure 2). Based on clinical and histopathological findings, a final diagnosis of NDH was made. The patient responded promptly to treatment with oral prednisone.

NDH is a rare entity that was first described in 1996 by Strutton et al.[1] The eruption observed in our two patients was clinically and histologically suggestive of neutrophilic dermatosis with several similarities to SS: pyrexia, preceding upper respiratory tract infection, cutaneous pathergy, abnormal laboratory values, dense neutrophilic infiltrate, and prompt response to steroids culminating in support that this disease is a localised atypical form of SS.[2] Similar to SS, NDH has also been associated with other conditions including malignancies.[3] However, many findings and observations, both in the literature and in the two presented cases, support that NDH is a distinct entity rather than an acral variant of SS. The most important observation is that many of the reported cases, including the original six described by Strutton et al.,[1] showed marked leukocytoclastic vasculitis. This contradicts one of the two major criteria necessary for a diagnosis of SS, namely dense neutrophilic infiltrate without leukocytoclastic vasculitis.[4] Several other authors[5] have opposed this conclusion, claiming that a secondary leukocytoclastic vasculitis might occur in NDH, and therefore it does not suffice to exclude NDH from the criteria of SS. In addition, cases of NDH usually present with pustular plaques, haemorrhagic bullae, and/or ulcerating lesions, which are uncommon clinical presentations in SS.[5] Our observation was also remarkable through unilateral presentation, which is rarely encountered.[6] The main difference between NDH and SS is the location of lesions, with a remarkable acral distribution in NDH. We also believe that the term NDH is misleading, as it gives the false impression that the disease is confined to the dorsal hands, whereas it also occurs at other sites, such as the palms and soles.

The exact nature of this acute neutrophilic disorder as a variant of SS, pustular vasculitis, an overlap of both these conditions, or a distinct entity remains unclear. This raises questions about the definitive classification of neutrophilic dermatosis and the need for a designation that can include its different clinical and histopathological presentations.

## REFERENCES

1. Strutton G et al. Pustular vasculitis of the hands. J Am Acad Dermatol. 1995;32(2 Pt 1):192-8.

2. Boussofara L et al. [Neutrophilic dermatosis of the hands: Acral sweet syndrome?]. Rev Med Interne. 2015;36(4):287-90. (In French).

3. R Wolf, Y Tüzün. Acral Manifestations of Sweet syndrome (neutrophilic dermatosis of the hands). Clin Dermatol. 2017; 35(1):81-4.

4. Von den Driesch P et al. Sweet's syndrome: Clinical spectrum and associated conditions. Cutis. 1989;44(3):193-200.

5. Brajon D et al. [Neutrophilc dermatosis of the hands]. Ann Dermatol Venereol. 2011;138(10):673-6. (In French).

6. Thatte SS, Aggarwal A. Neutrophilic dermatosis of the dorsal hands: A rare unilateral presentation. Indian Dermatol Online J. 2015;6(5):361-2.

SPECIAL POSTER FEATURE

# CERTOLIZUMAB PEGOL: A FUTURE TREATMENT OPTION FOR PATIENTS SUFFERING FROM PSORIASIS

## This is a summary of the data presented by UCB on 13th–17th September 2017 at the 26th European Academy of Dermatology and Venereology (EADV) congress 2017 in Geneva, Switzerland.

**Disclosure:** Cimzia® clinical data for the treatment of psoriasis and the clinical data relevant to the treatment of women of childbearing age have been submitted to regulatory authorities and are pending approval.
**Acknowledgements:** Prof Alexa B. Kimball, CEO and President at Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center, Inc., Boston, Massachusetts, USA, presented the data from references 10 and 14 at the 26th European Academy of Dermatology and Venereology (EADV) congress as oral and free presentations, respectively. Writing assistance was provided by Afsaneh Khetrapal, ApotheCom, London, UK.
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## Overview

Psoriasis is a chronic inflammatory disease that is associated with a reduction in quality of life (QoL) and professional work productivity.[1-3] Clinical data presented at the 26th European Academy of Dermatology and Venereology (EADV) congress regarding certolizumab pegol (CZP), an Fc-free pegylated anti-tumour necrosis factor (TNF) antibody, demonstrated a clinically meaningful and sustained psoriasis treatment effect associated with maintained improvements in QoL and work productivity.[4-7]

## Patient-Specific Data

Young women affected by psoriasis require safe and effective disease treatments. Control of disease before, during, and after pregnancy may contribute to the prevention of adverse pregnancy outcomes and reduce the risk of post-partum flares. Women who experience worsening of psoriasis during or after pregnancy may require personalised treatment.[8] Anti-TNF treatments are effective therapies that are often stopped during pregnancy and breastfeeding due to limited evidence in this population.

Because of its molecular structure, CZP is not thought to be actively transported across the placenta.[9] The CRIB study used a highly sensitive CZP-specific assay to analyse the level of placental CZP transfer in 14 mother-infant pairs treated with commercial CZP on either CZP 200 mg every 2 weeks (Q2W) or CZP 400 mg every 4 weeks (Q4W), for a locally approved indication (rheumatoid arthritis, axial spondyloarthritis/ankylosing spondylitis, psoriatic arthritis, and Crohn's disease). Mother, baby, and cord blood samples were collected at birth; the baby's blood was further sampled (4 and 8 weeks post-partum). Infant CZP levels were either minimal or below the limit of detection in all blood samples at all time points. At birth, 13 of 14 infants had no quantifiable CZP levels (lower limit of quantification: <0.032 µg/mL) and 1 infant had a minimal CZP level of 0.042 µg/mL (infant/mother plasma ratio: 0.0009) (Figure 1). No infants had quantifiable CZP levels at Weeks 4 and 8 post-partum. The generated evidence indicated no-to-minimal *in utero* fetal CZP exposure, supporting continuation of CZP during the third trimester of pregnancy if required.[10]

Post-partum flares commonly occur in women with rheumatic diseases and in >50% of patients with psoriasis, causing a treatment dilemma.[8,11,12] The CRADLE study used the same CZP-specific assay to analyse the CZP concentration in 137 breast milk samples from 17 breastfeeding mothers requiring post-partum CZP treatment (CZP 200 mg Q2W or CZP 400 mg Q4W).[13] Approximately half the samples, 77 of 137 (56%), had no measurable CZP, 52 (38%) had minute but measurable CZP levels (<0.064 µg/mL), and 8 (6%) had low CZP levels (<0.096 µg/mL). The highest measured CZP concentration in breast milk (0.0758 µg/mL) was

<1% of the expected plasma trough concentration of a therapeutic dose and the median CZP relative infant dose (0.15%) was considered within the safe range for breastfeeding (<10%).[13,14] In both studies, the adverse effects in mothers were consistent with the established safety profile of CZP, and those in infants were consistent with those in unexposed infants of a similar age.

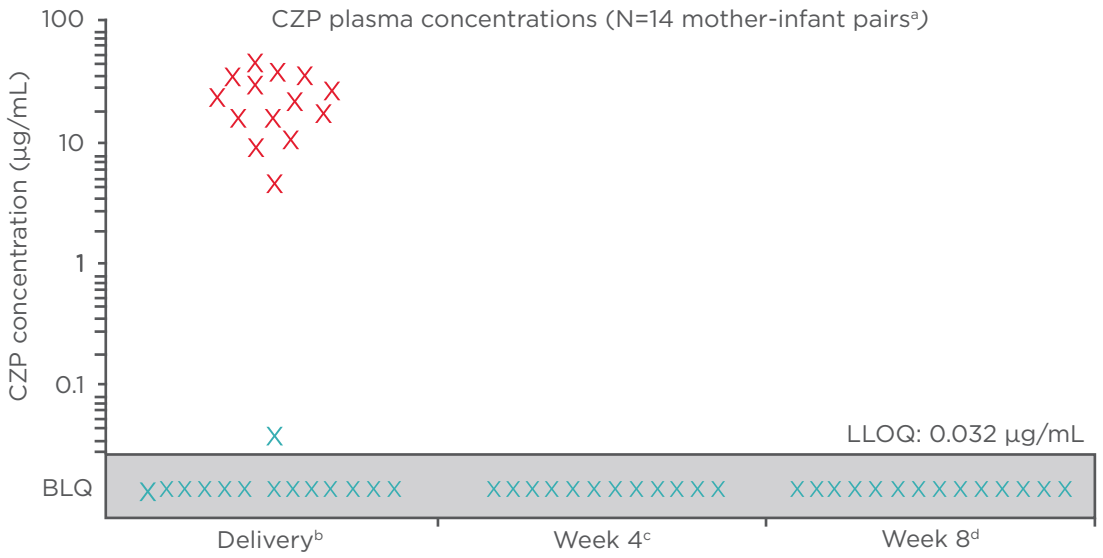


**Figure 1: Certolizumab pegol concentrations for both mothers and infants during the CRIB trial.**

X: maternal concentrations (collected within 24 hours pre or post-delivery).

X: infant concentrations (collected within 24 hours post-delivery).

[a]2 of 16 infants were excluded from the per protocol analysis set, 1 due to missing data at birth and 1 due to implausible pharmacokinetic data at birth (i.e. data not consistent with a paediatric CZP pharmacokinetic model based on the expected range of clearance, volume of distribution, and subsequent elimination half-life); [b] ±24 hours; [c] ±7 days (two samples not collected); [d] ±7 days.

BLQ: below the limit of quantification (<0.032 µg/mL); CZP: certolizumab pegol; LLOQ: lower limit of quantification.

## REFERENCES


1. Armstrong AW et al. Quality of life and work productivity impairment among psoriasis patients: Findings from the National Psoriasis Foundation survey data 2003-2011. PLoS One. 2012;7(12):e52935.

2. Gelfand JM et al. Determinants of quality of life in patients with psoriasis: A study from the US population. J Am Acad Dermatol. 2004;51(5):704-8.

3. Revicki DA et al. Relationship between clinical response to therapy and health-related quality of life outcomes in patients with moderate to severe plaque psoriasis. Dermatology. 2008;216(3): 260-70.

4. Reich K et al. Maintenance of response with certolizumab pegol for the treatment of chronic plaque psoriasis: 48-week results from two ongoing Phase 3, multicenter, randomized, placebo-controlled studies (CIMPASI-1 and CIMPASI-2). EADV P1973. EADV Congress, 13-17 September, 2017w.

5. Thaçi D et al. Certolizumab pegol for the treatment of chronic plaque psoriasis: DLQI and WPAI patient-reported outcomes from two ongoing Phase 3, multicenter, randomized, placebo controlled studies (CIMPASI-1 and CIMPASI-2). EADV P1971. EADV Congress, 13-17 September, 2017.

6. Augustin M et al. Maintenance of response with certolizumab pegol for the treatment of chronic plaque psoriasis: Results of a 32-week re-randomized maintenance period from an ongoing Phase 3, multicenter, randomized, active- and placebo-controlled study (CIMPACT). EADV P1969. EADV Congress, 13-17 September, 2017.

7. Augustin M et al. Certolizumab pegol for the treatment of chronic plaque ssoriasis: DLQI and WPAI patient-reported outcomes from an ongoing Phase 3, multicenter, randomized, active- and placebo-Controlled Study (CIMPACT). EADV P1967. EADV Congress, 13-17 September, 2017.

8. Murase JE et al. Hormonal effect on psoriasis in pregnancy and post partum. Arch Dermatol. 2005;141(5):601-6.

9. Förger F et al. Certolizumab treatment during late pregnancy in patients with rheumatic diseases: Low drug levels in cord blood but possible risk for maternal infections. A case series of 13 patients. Joint Bone Spine. 2016;83(3):341-3.

10. Mariette X et al. Lack of placental transfer of certolizumab pegol during pregnancy: Results from CRIB, a prospective, postmarketing, pharmacokinetic study. Ann Rheum Dis. 2017. [Epub ahead of print].

11. de Man YA et al. Disease activity of rheumatoid arthritis during pregnancy: Results from a nationwide prospective study. Arthritis Rheum. 2008;59(9):1241-8.

12. Ruiz V et al. Psoriasis in pregnancy: A review (I). Actas Dermosifiliogr. 2014; 105(8):734-43.

13. Clowse MEB et al. Minimal to no transfer of certolizumab pegol into breast milk: Results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. Ann Rheum Dis. 2017;76(11):1890-6.

14. Clowse MEB et al. Evaluating transfer of certolizumab pegol into breast milk: Results from a prospective, postmarketing, multicenter pharmacokinetic study [abstract]. Arthritis Rheumatol. 2016;68(suppl 10).

# EDITOR'S PICK

The Editor's pick for this issue is an informative review from Jayarajan and Bulinska, discussing the aetiopathogenesis and management of hidradenitis suppurativa. This debilitating, chronic, relapsing inflammatory condition has been a low priority disease over the last few decades, but it has recently seen an increase in interest. The psychological impact of hidradenitis suppurativa strongly affects the patient's quality of life. A collaborative approach between the dermatologist and the plastic surgeon is needed to achieve the most advantageous outcome in management.

Samantha Warne

# HIDRADENITIS SUPPURATIVA (ACNE INVERSA): A REVIEW OF AETIOPATHOGENESIS AND MANAGEMENT

***Rajshree Jayarajan,[1] Agata Bulinska[2]**

*1. Department of Plastic Surgery, Leicester Royal Infirmary, Leicester, UK*
*2. Department of Dermatology, Leicester Royal Infirmary, Leicester, UK*
**Correspondence to rajshreecj@gmail.com*

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## ABSTRACT

Hidradenitis suppurativa/acne inversa is a debilitating, chronic, relapsing inflammatory condition associated with the development of painful nodules and abscesses progressing to persistently draining sinus tracts. This has a great impact on the psychological aspects of the patient and thus on quality of life. The aetiopathological concepts have vastly evolved with time, as have treatment options. Even with the advancement in management strategies, hidradenitis suppurativa remains a formidable problem for the clinician. A collaborative approach management involving the dermatologist and plastic surgeon is mandatory to achieve the most advantageous outcome. Here, a review of recent literature is presented, including a comparison between various management strategies.

Keywords: Aetiopathogenesis, hidradenitis suppurativa (HS), medical management, surgical options.

## INTRODUCTION

In comparison with other cutaneous conditions, hidradenitis suppurativa (HS) has been labelled a lower priority disease for decades. It has been treated by many different specialities, such as plastic surgeons, emergency medicine, family physicians, and dermatologists. This previously orphaned disease has seen an increase in interest in the last few years.[1]

Lesions are located in the apocrine gland-bearing regions (axilla, inframammary region, groin, and genital area). Disease can develop in any folds of skin, such as the popliteal, but also elsewhere, like the occipital scalp, for example. There are often severe complications in aggravated cases.[2] The prevalence of HS ranges from 0.05–4%, and the condition is observed approximately three-times more often in women than in men, with onset between 20 and 24 years of age. The onset usually develops well after puberty in young adults;[3,4] however, 5% of cases affect children, with the youngest reported case 5 years of age.[5] In children HS is usually associated with family history of HS and/or hormonal imbalance, in contrast to most adult cases.[6,7] The definition of HS as presented in the San Francisco odification of the Dessau criteria[8] reads:

a) Typical, painful nodular lesions which are located deep within the skin. In early stages, the lesions appear as nodules which develop into abscesses with draining sinuses and bridging scars as the disease progresses. In secondary lesions they might be paired with multiheaded open pseudocomedones.
b) Usual topography is within the apocrine gland-bearing regions.
c) It is a chronic and relapsing disease.

Disease severity is measured with the help of Hurley stages,[9] which are often useful to initiate appropriate therapy. Stage I: Abscess formation (single or multiple) without sinus tracts and cicatrisation; Stage II: One or more widely separated recurrent abscesses with tract formation and scars; Stage III: Multiple interconnected tracts and abscesses throughout an entire area.

The psychological impact of HS strongly affects the patient's quality of life in comparison with other inflammatory skin conditions.[10,11]

## PATHOPHYSIOLOGY

The pathogenesis of HS is not fully understood, but genetic factors, smoking, and metabolic syndrome are known to be associated with HS.[12] Histopathological findings demonstrate that the defect is located in the hair follicles, not primarily in apocrine glands. The sequence of the disease development is as follows; initially, infundibular hyperkeratosis appears leading to follicular dilatation accompanied by the formation of cysts. The next stage is characterised by massive inflammation and a local, vivid immune response. This is followed by the fistula, formed of epidermal strands. Early histological examination shows that apocrine sweat glands are not primarily or selectively inflamed.[13] It appears that HS, therefore, is a misnomer.[12]

Immunogenetics of HS has demonstrated the loss of function in three out of four subunits of gamma secretase.[14] Potential target proteins are Type I integral membrane proteins, like Notch, E-cadherin, or CD44. Altered Notch signalling is linked with forming defective follicular keratine-enriched epidermal cysts and T cells as dedicated immune response. It is a feedback inhibitor of activated innate immunity. In summary, inherited or acquired altered Notch signalling could be considered a main factor that contributes to the development of HS.[15]

It is possible that the deficiency in the follicular skin immune response plays a role in the microbial overgrowth associated with HS, but other hypotheses have identified the overactive immune response to normal flora as a possible cause of HS.[16] Recently, Ring et al.[17] expressed the view that bacterial biofilms have an influence on the chronic lesions of HS and believe HS to be reminiscent of well-known biofilm infections. The results from this study suggested that biofilm formation is associated with the inflammation of chronic HS lesions. Biofilm-driven diseases, in turn, are characterised by chronic relapsing lesions reminiscent of infections recalcitrant to antibiotic treatment.[17]

Among other influential factors, tobacco smoke seems to play a vital role in the development of HS. Of the 4,000 chemicals within tobacco smoke, those such as nicotine and other particles, activate keratinocytes, fibroblasts, and immunocytes which, in turn, lead to acanthosis, infundibular epithelial hyperplasia, and cornification in keratinocytes. The chemicals present in tobacco smoke induce proinflammatory cytokines, e.g., tumour necrosis factor (TNF)-α and interleukins (IL), leading to neutrophil chemotaxis and T helper 17 cell induction. Nicotine provokes virulence of *Staphylococcus aureus*[16] by inducing biofilm formation. There are many other negative processes caused by cigarette smoke, making the follicle more susceptible to bacterial infections. Additionally, downregulation of Notch ligands, receptors, as well as downstream effector genes, suggest that smoke further suppresses the already deficient Notch signalling in HS.[13] Hormones are also thought to play a role in the development of HS, and the disease usually develops well after puberty. In paediatric cases, adrenal hyperplasia, premature adrenarche, obesity, and metabolic syndrome were reported.[7] Diagnosing HS in childhood may be a marker of precocious puberty.[6]

Cases of adrenal hyperplasia in both sexes, including in women with polycystic ovaries suffering from HS, have been reported. There are indications that antiandrogens, such as cyproterone acetate and oestrogens, help in HS, while progestogens induce or worsen a pre-existing HS due to their androgenic properties.[18,19] Obesity and metabolic syndrome are also recognised to be strongly associated with HS. The mechanical forces of friction (skin-to-skin and skin-to-clothing) increase follicular occlusion and rupture. In obese individuals, both the mechanism of activating mechanoresponsive genes and

the proinflammatory state are present, which play a role in the development of HS.[12] Danby et al.[20] report that the so-called Western diet can negatively affect people with altered follicular pilosebaceous unit (FPSU). Dairy products have three components that drive the process of FPSU blockage; casein induces the already elevated levels of insulin-like growth factor, while whey and simple carbohydrates raise insulin levels. Acting together or alone, insulin and insulin-like growth factor-1 stimulation depresses the androgen receptor from testes, ovaries, and stressed andrenals, as well as the effects of the FPSU, various contraceptive hormones, and anabolic supplements. In addition to the classical triggers of the FPSU function is 5α-reduced dihydrotestosterone, which is present in the human premenstrual ovary, and at least five others are present in cow's milk (products of bovine placenta and mammary glands). Reducing weight, and possibly withdrawing dairy products and whey, will break the vicious cycle and correct the chronic hyperinsulinaemia, insulin resistance, and all the related downstream problems, such as hyperglycaemia and hypoglycaemia.[20]

Currently, the role of the inflammatory response and the cytokines involved in producing inflammation in HS is being investigated. The key role is attributed to TNF-α, a proinflammatory cytokine, produced by both innate and adaptive immune cells in several autoinflammatory conditions. When HS is treated with inhibitors of TNF-α, such as infliximab or adalimumab, an improvement is usually seen. There are several other agents investigated in the HS pathogenesis, such as IL-1β, IL-10, and IL-17.[21-24]

The entire process of HS development can be summarised as follows: aberrant keratinocytes react with the commensal microbiome, resulting in an altered cytokine and AMP production. The altered production attracts immune cells and triggers an inflammatory cascade; in turn, hyperplastic epithelium causes follicular occlusion and cyst formation. Smoking and false Notch signalling contribute to this process. Cyst rupture allows bacteria and keratin into the dermis, producing a neutrophilic foreign-body type immune response. Finally, abscesses develop, which lead to formation of sinus tracts. Sinus tracts seem to be the HS symptom most resistant to treatment.[12] HS is accompanied by comorbidities such as autoimmune disease, inflammatory disease, and skin cancers developing from non-healing wounds.[25,26]

## INVESTIGATIONS

Even though diagnosis is made by clinical assessment,[8] some investigations are useful in severe cases. If purulent exudate appears, a microbiological (swab) test may be needed. Imaging using ultrasound and magnetic resonance prove useful in assessing the extent of the disease. Routine blood tests might display potential comorbidities and, in an advanced disease (mainly in Hurley Stage III), may show anaemia or hypoalbuminaemia. Polyclonal hypergammaglobulinaemia, elevated C-reactive protein, and other less commonly used inflammatory markers can serve as an additional factor in monitoring severe cases.

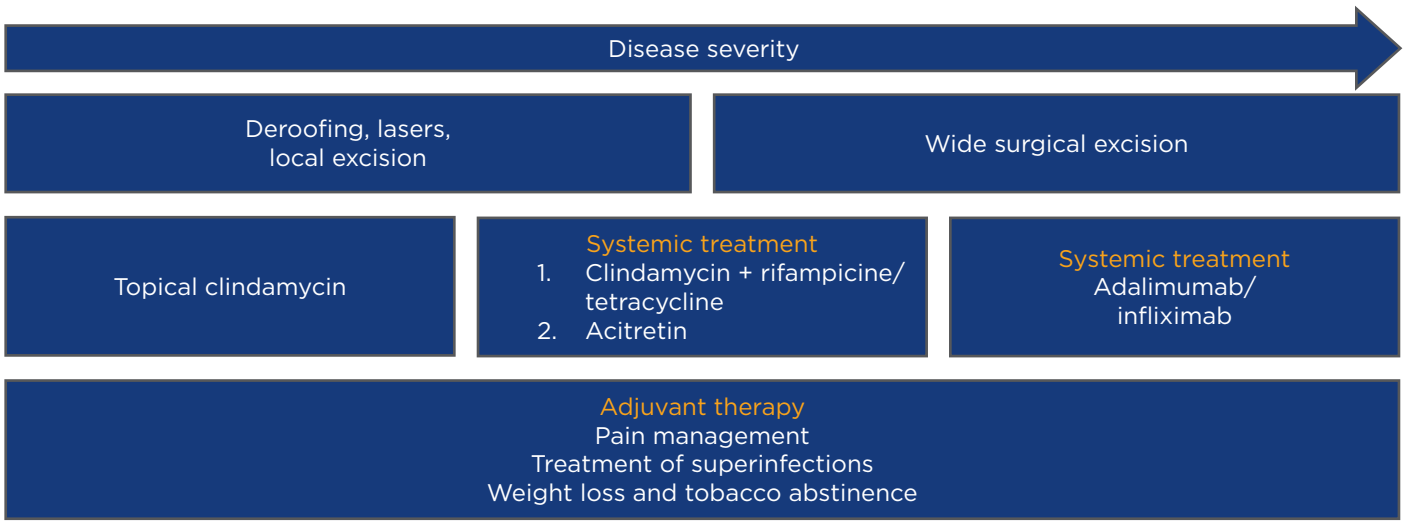


**Figure 1: European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa.**
*Modified from Zouboulis et al.[8]*

## MANAGEMENT

In January 2017, a panel of experts worked out the "European S1 guideline for the treatment of hidradenitis suppurative/acne inversa" (Figure 1),[8] stating that the condition should be treated according to individual assessment. Firstly, Hurley stage should be assessed before a treatment plan for the a patient can be established. The experts advise treating localised recurrent lesions surgically, using classic or laser surgery. When the disease is widespread, the favoured approach is to apply an algorithm, either as monotherapy or combined with surgical procedures.[8]

## MEDICAL MANAGEMENT

Medical therapy can start from skin exfoliants and peels, such as resorcinol.[27] A recent study showed that the use of 15% resorcinol in a group of 12 women suffering from HS reported an improvement compared to the prior use of antibiotics and surgery. Topical clindamycin was tested in double-blinded randomised trials. The most significant effect was observed on superficial lesions, in contrast to deep nodules of abscesses, which did not react positively to the treatment.[28]

The use of systemic antibiotics (such as tetracycline) is advised for HS in Hurley Stage I or II (mild stages). The combination of clindamycin and rifampicin is helpful in more aggravated stages. Antiandrogens proved to be helpful in some cases of HS. Anti-inflammatory therapy plays an important role in the treatment of HS. Intralesional triamcinolone acetonide, as well as a short course of systemic steroids, may be considered prior to surgical management.[29]

Improvement in patients with HS was also achieved using anti-inflammatories such as dapsone or ciclosporin A. Anti TNF-α biologic medications are also very promising for the treatment of HS. Current evidence shows that adalimumab and infliximab prove helpful in HS treatment, with adalimumab being more tolerable. This may not bring about a complete elimination of the disease but is useful as a neoadjuvant with surgery to decrease the extent of surgery required. Other TNF-α inhibitors have also been studied.[30] Isotretinoin and acitretin were also administered to patients with HS but exhibited limited improvement.[8,29]

## SURGICAL MANAGEMENT

Surgical management offers the lowest recurrence rates among all modalities of management for extensive cases. An outcome suggestion so as to have a standard to compare future studies has been put forward by Janse et al.[31] The various modalities of surgical management include: incision and drainage of abscess, deroofing, carbon dioxide ($CO_2$) laser, skin-tissue-sparing excision with electrosurgical peeling (STEEP), and excision followed by direct closure, skin stretching system closure, split skin grafting, split skin grafting plus VAC, local flaps, and free flaps.

### Incision and Drainage

The simplest of all surgical procedures performed on HS is incision and drainage of an acute abscess. This is only a temporary measure to manage the collection of pus; relapse is inevitable because the root cause is not treated.

### Deroofing

This is a procedure by which the extent of the lesion is assessed with a probe and the roof, along with the jelly-like material on the floor of the sinus tracts, are removed by electrosurgical dissection. In a study on 88 deroofed lesions,[32] the recurrence rate was 17%, indicating this is effective as a minimally invasive technique for surgical management. Advantages include a simple, minimally invasive technique, and disadvantages include not that all of the diseased tissue is dealt with, leading to a high risk of recurrence.

### Carbon Dioxide Laser

The sinuses are explored with blunt forceps and then deroofed by evaporation using $CO_2$ laser.[33,34] The slough at the bottom of the tracts are also cleaned up with $CO_2$ laser and left to heal by secondary intention. Advantages include that it can be performed under local anaesthetic and offers an effective method. Disadvantages include that the procedure requires costly equipment and trained personnel.

### Skin Tissue Saving Excision with Electrosurgical Peeling

Described by Blok et al.,[35] this procedure, performed under general anaesthetic, involves initial deroofing of the lesions followed by tangential electrosurgical transection of the involved deeper layers until the whole area is clear of lesional tissue

and fibrosis. The wounds are left open to heal by secondary intention. Advantages of STEEP include that there is a more extensive and complete removal of diseased tissue than deroofing technique, spares healthy tissue, and avoids more extensive procedures like grafts and flaps, and expensive equipment like laser. Disadvantages include that completion of excision of diseased areas may not be thorough, leading to higher recurrence rates than with more extensive surgical procedures, and prolonged healing time from leaving open to heal by secondary intension and thus more scarring results.

## Complete Surgical Excision

This technique is resorted to only after medical management has failed to keep the disease under control. Once the excision has been achieved, there are various options to get the wound to heal. The method selected depends on the extent of area involved, anatomical site, and surgeon's preference.

## Leave Open to Heal by Secondary Intension

Following surgical excision of the involved area, the wound is left to heal by granulation, contraction, and epithelialisation. Secondary intention healing is recommended as a safe and efficient form of healing of postoperative defects in certain areas of the body.[36] This technique avoids the morbidity associated with donor site healing as in grafts and flaps; however, a long duration is required for complete healing and is limited in terms of size of wound.

## Direct Closure

This is applicable only for small areas of involvement, as enough normal skin should be available for a tension-free closure after complete excision of the diseased area. In a study of 92 local excisions with primary closure, 66% had no recurrence.[37] This is usually feasible in Hurley Stages I and II. Direct closure offers the best cosmetic result with minimal postoperative healing problems and because it is usually used for small areas, it can be performed under local anaesthetic. However, it can only be used if the area of involvement is small.

## Sure Closure: Skin Stretching System

This technique, described by Sharma et al.,[38] uses the viscoelastic properties of the skin, so as to stretch the skin by exerting a controlled amount of tension along the wound margins. Known as the skin stretching system, this technique facilitates primary closure of a wound that would have otherwise required either graft or flap. Skin stretching allows closure of a larger wound than that can usually be primarily closed, and the bedside procedure can be performed under local anaesthetic. Although it does give a higher propensity for hypertrophic scar formation, infection of intradermal pin tracts and ischaemic necrosis of skin edges can occur if stretching is not done with caution.

## Split Skin Grafting

If the raw area resulting from excision is too large for a primary closure, the options are either graft or flap. A split skin graft is used, which can be harvested from almost any area as it heals by itself and the graft can be meshed to cover wider areas. Due to it being very thin, the graft moulds well to the contour of the recipient site. Split skin graft, however, does not transfer sweat glands and hair follicles to the recipient site and thus reduces the risk of recurrence at the site postoperatively.[39] The contracture associated with split skin grafts is acceptable in non-flexural areas, like the gluteal region.

Split skin grafting can be combined with negative pressure dressing or vacuum assisted closure.[40]

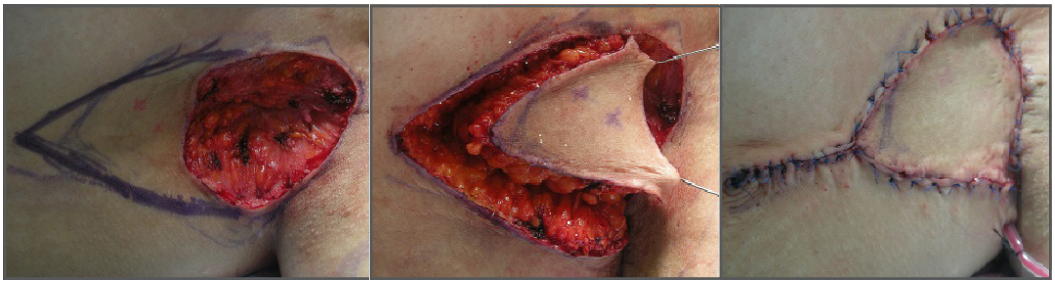

**Figure 2: Thoracic artery perforator V-Y flap.**

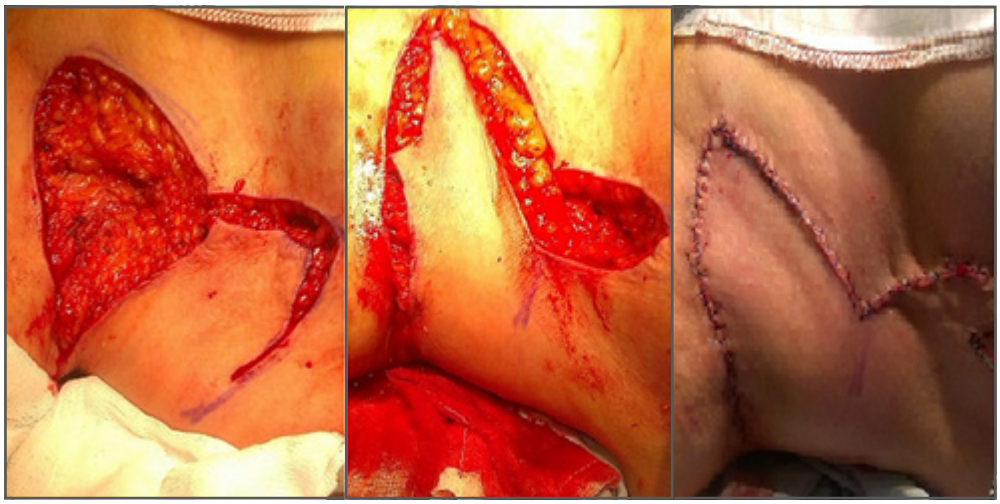

**Figure 3: Limberg flap coverage of areas of hidradenitis suppurativa involving the axilla.**

This method overcomes the difficulties associated with immobilising the grafted area to achieve a good 'take' of the graft postoperatively. A sponge dressing is applied over the non-adherent dressing on the graft and a controlled negative pressure applied allowing adherence of the graft conforming to the contour of the site, preventing shearing, and is also beneficial in drainage of collections between the graft and bed.

Any size defect can be resurfaced in a single procedure and the thin graft moulds to the contour of the recipient site avoiding a bulky appearance. Risk of recurrence on the operated site is low. There is, however, need to have immobilisation of the operated area until the graft is taken up, which usually takes a week. In flexural surfaces, a splint is required to prevent contracture as the graft undergoes secondary contraction after healing and the cosmetic appearance is compromised.

## Flaps

Extensive areas of involvement requiring excision leaves raw areas that need tissue from elsewhere. A flap provides similar tissue with a similar texture and nature as the normal skin of the area. Simple flaps from the adjacent area as either a transposition, advancement, or rotation are commonly used. A transposition flap can be a fasciocutaneous flap, such as a lateral thoracic fasciocutaneous flap.[41] This flap is based on perforators supplying the skin of this region from the lateral thoracic and thoracodorsal arteries. It is a robust flap, large defects can be covered using this flap and it can be raised as an island flap based on the vessels, in which case it is possible to thin the flap to the required thickness.

A thoracic artery perforator V-Y flap[42] is based on the musculocutaneous perforators of the thoracodorsal vessels that supply the skin over the muscle. This can be marked with a hand-held Doppler in the theatre and flap raised based on the perforator position (Figure 2). Compared to a random supply, the V-Y flap[43] allows free movement of the flap into the recipient site. A double V-Y technique,[44] which is perforator based, is helpful if a larger defect needs coverage. Here, one flap from the chest wall and the other from the arm are used in a double opposing manner. A parascapular perforating flap[45] is an option available locally, which provides greater mobility to the flap but involves more tedious dissection.

A Limberg flap (Figure 3) has been described in a case series by O'Brien et al.[46] and Altmann et al.,[47] for coverage of areas of HS involving the axilla. A recent review of Limberg flaps for the same condition has substantiated its usefulness in this situation.[48] Gluteal, perianal, and perineal areas of involvement can similarly be treated with simple fasciocutaneous[49] transposition, rotation, or V-Y flaps. The perianal area is more challenging to reconstruct, especially when the defect is extensive. The extended split superior gluteus maximus musclocutaneous flap described by Kishi et al.[50] is a very good option. Diverting colostomy[51] is indicated occasionally in patients with involvement of these areas undergoing surgery. Medial thigh lift following radical excision of hidradenitis of the groin results in a cosmetically pleasing appearance.

A good functional and aesthetic result has been reported in a series of 15 thigh lifts by Rieger et al.[52] Modified abdominoplasty[53] can be used for HS involving the lower abdomen and groin region, or a combination of abdominal flap and thigh lift[54] if reconstruction of a more extensive area is required.

HS involving gluteal, intergluteal, and perianal areas are usually treated with deroofing, leaving to heal by secondary intention or skin grafts. Superior and inferior gluteal artery perforator flaps[55] are locally available flaps that can be designed for even large defects in this area to facilitate immediate closure, providing excellent quality tissue and good cosmetic appearance in terms of not only the reconstructed area but also the donor site scar. The anterolateral thigh flap[56] and pedicled gracilis myocutaneous flap[57] are other options available for the difficult groin and perineal areas. Advantages of flaps include good colour and texture match, and early mobilisation is possible, unlike grafts; however, they do require more surgical expertise than grafts and could result in a bulky appearance and donor site scars.

A recent systemic review on recurrence rates after surgical management showed the following results: wide excision (13.0%), local incision (22.0%), and deroofing (27.0%). In the wide excision group, recurrence rates were 15% for primary closure, 8% for using flaps, and 6% for grafting.[58] A 10-year study by Kagan et al.[59] of 57 patients involving different areas such as the axilla, inguinal, and perineal region showed no recurrence.

Another relevant report in literature regarding recurrence rates following complete excision is by Balik et al.[60] involving 21 surgeries in 15 patients. Wounds were left open, primarily closed, or skin grafted. A 5-year follow-up showed no recurrence and they concluded that recurrences were due to incomplete excisions. Incomplete excision would inevitably result in a recurrence. Having an array of reconstructive options in the armamentarium gives the surgeon the freedom to avoid limited excisions and to do complete excisions of all disease bearing areas that could result in absolutely no recurrence in the treated area.

## REFERENCES


1. Alavi A. Dermatol. Hidradenitis suppurativa: Demystifying a chronic and debilitating disease. J Am Acad. 2015; 73(5 Suppl 1):S1-2.

2. Jemec GB. The symptomatology of hidradenitis suppurativa in women. Br J Dermatol. 1988;119(3):345-50.

3. Jemec GB, Kimball AB. Hidradenitis suppurativa: Epidemiology and scope of the problem. J Am Acad Dermatol. 2015;73(5 Suppl 1):S4-7.

4. Liy-Wong C et al. Hidradenitis suppurativa in the pediatric population. J Am Acad Dermatol. 2015;73(5 Suppl 1): S36-41.

5. Koshelev MV et al. Concurrent hidradenitis suppurativa, inflammatory acne, dissecting cellulitis of the scalp, and pyoderma gangrenosum in a 16-year-old boy. Pediatr Dermatol. 2014; 31(1):e20-1.

6. Scheinfeld N. Hidradenitis suppurativa in prepubescent and pubescent children. Clin Dermatol. 2015;33(3):316-9.

7. Deckers IE et al. Correlation of early-onset hidradenitis suppurativa with stronger genetic susceptibility and more widespread involvement. J Am Acad Dermatol. 2015;72(3):485-8.

8. Zouboulis CC et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. J Eur Acad Dermatol Venereol. 2015; 29(4):619-44.

9. Hurley H, "Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa, and familial benign pemphigus: surgical approach," Roenigh R, Roenigh H. (eds.), Dermatologic Surgery. (1996), New York: Marcel Dekker, pp.729-39.

10. Matusiak L et al. Psychophysical aspects of hidradenitis suppurativa. Acta Derm Venereol. 2010;90(3):264–8.

11. Janse IC et al. Sexual health and quality of life are impaired in hidradenitis suppurativa: a multicentre cross-sectional study. Br J Dermatol. 2017; 176(4):1042-7.

12. Prens E, Deckers I. Pathophysiology of hidradenitis suppurativa: An update. J Am Acad Dermatol. 2015;73(5 Suppl 1): S8-11.

13. Van der Zee HH et al. Hidradenitis suppurativa: Viewpoint on clinical phenotyping, pathogenesis and novel treatments. Exp Dermatol. 2012;21(10): 735-9.

14. Wang B et al. Gamma-secretase gene mutations in familial acne inversa. Science. 2010;330(6007):1065.

15. Radtke F et al. Notch signaling in the immune system. Immunity. 2010;32(1): 14-27.

16. Nikolakis G et al. Bacteriology of hidradenitis suppurativa/acne inversa: A review. J Am Acad Dermatol. 2015;73 (5 Suppl 1):S12-8.

17. Ring HC et al. Bacterial biofilm in chronic lesions of hidradenitis suppurativa. Br J Dermatol. 2017;176(4): 993-1000.

18. Sawers RS et al. Control of hidradenitis suppurativa in women using combined antiandrogen (cyproterone acetate) and oestrogen therapy. Br J Dermatol. 1986;115(3):269-74.

19. Stellon AJ, Wakeling M. Hidradenitis suppurativa associated with use of oral contraceptives. BMJ. 1989;298(6665): 28-9.

20. Danby FW. Diet in the prevention of hidradenitis suppurativa (acne inversa). J Am Acad Dermatol. 2015;73(5 Suppl 1): S52-4.

21. van der Zee HH et al. Elevated levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNF-α and IL-1β. Br J Dermatol. 2011;164(6):1292-8.

22. van der Zee HH et al. Adalimumab (antitumour necrosis factor-α) treatment

of hidradenitis suppurativa ameliorates skin inflammation: An in situ and ex vivo study. Br J Dermatol. 2012;166(2): 298-305.

23. Schlapbach C et al. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. J Am Acad Dermatol. 2011;65(4):790-8.

24. Dreno B et al. Hidradenitis suppurativa: The role of deficient cutaneous innate immunity. Arch Dermatol. 2012;148(2):182-6.

25. Fimmel S, Zouboulis CC. Comorbidities of hidradenitis suppurativa (acne inversa). Dermatoendocrinol. 2010;2(1): 9-16.

26. van der Zee HH et al. Hidradenitis suppurativa and inflammatory bowel disease: are they associated? Results of a pilot study. Br J Dermatol. 2010;162(1): 195-7.

27. Boer J, Jemec GB. Resorcinol peels as a possible self-treatment of painful nodules in hidradenitis suppurativa. Clin Exp Dermatol. 2010;35(1):36-40.

28. Clemmensen OJ. Topical treatment of hidradenitis suppurativa with clindamycin. Int J Dermatol 1983;22(5): 325-8.

29. Nayaek H, Jemec GBE, "Immunosuppressive Therapy in Hidradenitits Suppuratua," Jemec GBE et al. (eds.), Hidradenitis Suppurativa. (2006), Berlin: Springer, pp. 138-40.

30. Zouboulis CC et al. [S1 guideline for the treatment of hidradenitis suppurativa/acne inversa (ICD-10 L73.2)]. J Dtsch Dermatol Ges. 2012;10 (Suppl. 5):S1-31. (In German).

31. Janse I et al. Surgical Procedures in Hidradenitis Suppurativa. Dermatol. Clin. 2016;34(1):97-109.

32. van der Zee HH et al. Deroofing: A tissue-saving surgical technique for the treatment of mild to moderate hidradenitis suppurativa lesions. J Am Acad Dermatol. 2010;63(3):475-80.

33. Jain V, Jain A. Use of lasers for the management of refractory cases of hidradenitis suppurativa and pilonidal sinus. J Cutan Aesthet Surg. 2012;5(3): 190-2.

34. Lapins J et al. Surgical treatment of chronic hidradenitis suppurativa: $CO_2$ laser stripping-secondary intention technique. Br J Dermatol. 1994;131(4): 551-6.

35. Blok JL et al. Skin-Tissue-sparing Excision with Electrosurgical Peeling (STEEP): A surgical treatment option for severe hidradenitis suppurativa Hurley stage II/III. J Eur Acad Dermatol Venereol. 2015;29(2):379-82.

36. Bieniek A et al. Secondary intention healing in skin surgery: our own experience and expanded indications in hidradenitis suppurativa, rhinophyma and non-melanoma skin cancers. J Eur Acad Dermatol Venereol. 2013,27(8): 1015-21.

37. van Rappard DC et al. Mild to moderate hidradenitis suppurativa treated with local excision and primary closure. J Eur Acad Dermatol Venereol. 2012;26(7):898-902.

38. Sharma M et al. A novel technique for closure of post excisional soft tissue defects of axillary hidradenitis suppurativa. Indian J Plast Surg. 2014; 47(3):465-6.

39. Sugio Y et al. Reconstruction after excision of hidradenitis suppurativa: are skin grafts better than flaps?. Plast Reconstr Surg Glob Open. 2016; 4(11):e1128.

40. Hynes et al. Split-thickness skin grafts and negative-pressure dressings in the treatment of axillary hidradenitis suppurativa. Br J Plast Surg. 2002;55(6):507-9.

41. Mello DF, Helene Junior A. Lateral thoracic fasciocutaneous flap for reconstruction of axillary defects after resection of hidradenitis suppurativa: a series of 10 cases. Re Bras Cir Plást.2016;31(2):186-191. (In Spanish).

42. Rehman N et al. Thoracodorsal artery perforator (TAP) type I V–Y advancement flap in axillary hidradenitis suppurativa. Br J Plast Surg. 2005;58(4):441-4.

43. Sharma RK et al. Reconstruction in extensive axillary Hidradenitis suppurativa with local fasciocutaneous V-Y advancement flaps. Indian J Plast Surg. 2006;39:18-21.

44. Geh JL, Niranjan NS. Perforator-based fasciocutaneous island flaps for the reconstruction of axillary defects following excision of hidradenitis suppurativa. Br J Plast Surg. 2002;55(2): 124-8.

45. Tercedor-Sáncheza J et al. Parascapular perforating flap to treat severe axillary hidradenitis suppurativa. Actas Dermosifiliogr. 2015;106(8): 669-71.

46. O'Brien J et al. Limberg flap coverage for axillary defects resulting from excision of hidradenitis suppurativa. Plast Reconstr Surg. 1976;58(3):354-8.

47. Altmann S et al. Axillary hidradenitis suppurativa: A further option for surgical treatment. J Cutan Med Surg. 2004;8(1): 6-10.

48. Varkarakis G et al. Treatment of axillary hidradenitis with transposition flaps: A 6-year experience. Ann Plast Surg. 2010;64(5):592-4.

49. Kishi K et al. Reconstruction of skin defects after resection of severe gluteal hidradenitis suppurativa with fasciocutaneous flaps. J Plast Reconstr Aesthet Surg. 2009;62(6):800-5.

50. Kishi K et al. Extended split superior gluteus maximus musclocutaneous flap and reconstruction after resection of perianal and lower gluteal hidradenitis suppurativa. J Plast Reconstr Aesthet Surg. 2009;62(8):1081-6.

51. Bocchini SF et al. Gluteal and perianal hidradenitis suppurativa: A surgical treatment by wide excision. Dis Colon Rectum. 2003;46(7):944-9.

52. Rieger UM et al. Hidradenitis suppurativa of the groin treated by radical excision and defect closure by medial thigh lift: Aesthetic surgery meets reconstructive surgery. J Plast Reconstr Aesthet Surg. 2009;62(10):1355-60.

53. Greenbaum AR. Modified abdominoplasty as a functional reconstruction for recurrent hydradenitis suppurativa of the lower abdomen and groin. Plast Reconstr Surg. 2007;119(2): 764-6.

54. Mizukami T et al. Reconstruction for extensive groin hidradenitis suppurativa using a combination of inferior abdominal flap and medial thigh-lift: a case report. Aesthetic Plast Surg. 2014; 38(4):745-8.

55. Unal C et al. Superior and inferior gluteal artery perforator flaps in reconstruction of gluteal and perianal/perineal hidradenitis suppurativa lesions. Microsurgery. 2011;31(7):539-44.

56. Rees L et al. The anterolateral thigh (ALT) flap in reconstruction following radical excision of groin and vulval hidradenitis suppurativa. J Plast Reconstr Aesthet Surg. 2007;60(12): 1363-5.

57. Solanki NS et al. Pedicled gracilis myocutaneous flap for treatment of recalcitrant hidradenitis suppurativa of the groin and perineum. J Wound Care. 2009;18(3):111-2.

58. Mehdizadeh A et al. Recurrence of hidradenitis suppurativa after surgical management: A systematic review and meta-analysis.J Am Acad Dermatol. 2015;73(5 Suppl 1);S70-7.

59. Kagan RJ et al. Surgical treatment of hidradenitis suppurativa: A 10 year experience. Surgery. 2005;138(4):734-40.

60. Balik E et al. Surgical approach to extensive hidradenitis suppurativa in the perineal/perianal and gluteal regions. World J Surg. 2009;33(3):481-7.

# CHRONIC URTICARIA IN CHILDREN: A REVIEW

***Blanca R. Del Pozzo-Magaña**

*Department of Pediatrics, Children's Hospital of Western Ontario, London, Canada*
**Correspondence to brdelpozzo@gmail.com*

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## ABSTRACT

Chronic urticaria (CU) is characterised by the recurrence of hives/angioedema for >6 weeks. It affects children and adults and has a worldwide distribution. In children, CU is substantially less common than acute urticaria but is associated with larger decrease in quality of life. The current classification divides CU into two groups: 1) chronic spontaneous urticaria, which includes idiopathic urticaria (by far the most common type), autoimmune urticaria, and those associated with drugs, food, or additives allergies; and 2) chronic inducible urticaria, constituted by cholinergic urticaria and physical urticarias. Diagnosis of CU is based on the history and characteristics of the lesions. Although laboratory and specific testing could establish the diagnosis of some subtypes of CU, frequently the aetiology is never found; therefore, an extensive workup is not recommended. Once the trigger has been identified, it must be avoided. Specific treatment may be tried, but unfortunately this is not always possible. Currently, the first-line treatment for children with CU are second generation H1-antihistamines (SG-H1AH), such as cetirizine, fexofenadine, desloratadine, and rupatadine, among others. If, after 2–4 weeks, the patient has not improved, an increment from 2 to 4-times the regular dose is recommended. Patients that fail to respond to this treatment may be switched to another SG-H1AH or a second agent, such as H2-antihistamines (e.g., cimetidine, ranitidine), ketotifen, cyclosporine, or a leukotriene receptor inhibitor (e.g., montelukast), may be added to the H1-antihistamine therapy. Recently, omalizumab, an anti-immunoglobin-E monoclonal antibody has been approved in several jurisdictions for patients 12 years or older with recalcitrant CU; however, its high cost has limited its use.

Keywords: Urticaria, chronic urticaria (CU), hives, antihistamines, chronic spontaneous urticaria, urticaria management, physical urticaria.

## INTRODUCTION

Urticaria is a common condition characterised by transient erythematous and oedematous plaques or papules with circumscribed erythematous borders and central clearing, known as hives/wheals. Hives are usually pruritic and their size and location varies, including mucosae. Urticaria can be accompanied by angioedema, which is characterised by poor delimited swelling (deeper oedema of the dermis and subcutaneous tissue) often involving the lips, tongue, eyelids, hands, and feet.[1]

Urticaria results from degranulation of dermal and submucosal mast cells/basophils that release vasoactive mediators such as histamine and lipid mediators (leukotrienes and prostaglandins), which enhance the expression of other cytokines and chemokines and induce an extravasation of fluid into the superficial tissues.[2,3] Hives are the primary lesion of the urticaria but they can also be seen in other inflammatory conditions, such as urticaria pigmentosa, urticarial vasculitis, mastocytosis, and autoinflammatory syndromes; however, because these conditions are not considered within the classification of the urticaria due to their dissimilar pathophysiology, they will not be discussed in this review. Chronic urticaria (CU) is diagnosed when hives and or angioedema are present for >6 weeks.[4]

## CLASSIFICATION OF CHRONIC URTICARIA

Based on the new classification of the Dermatology Section of the European Academy

of Allergy and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA$^2$LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO), CU is classified in two main groups:[5]

1. Chronic spontaneous urticaria (CSU): hives and/or angioedema are present for >6 weeks with or without knowing aetiology.
2. Chronic inducible urticaria (CIU): urticarial symptoms are triggered by specific stimuli.

## EPIDEMIOLOGY AND AETIOLOGY

The frequency of urticaria (acute and chronic) in children is about 2.1–6.7%[2] while CU prevalence ranges from 0.1–13.0%.[6] It is estimated that 20–30% of children who initially present with autoimmune urticaria (AU) develop CU later on.[7] Angioedema and hives are seen together in 50–80% of children with CU.[8,9] A history of atopy or other allergic diseases can be present in up to 40% of this population.[10,11] CU in children has a worldwide distribution, but does not seem to have a sex predilection.[12]

Although the precise pathogenesis of CU remains poorly understood, it is known that urticaria is the result of the mast cell/basophil degranulation triggered by a specific agent. Recently, the role of reactive oxygen species (ROS) and matrix metalloproteinase-9 (MMP-9) in the pathogenesis of CU has been investigated, as they are involved in the inflammatory processes. Dilek et al.[13,14] found that children with CU had plasma levels of both ROS and MMP-9 higher than in healthy subjects and this had a positive correlation with disease activity.

Autoimmunity also plays a role in the pathogenesis of urticaria, since it has been found that at least 30–50% of patients with CU have circulating autoantibodies immunoglobulin (Ig)G against the alpha chain of the IgE receptor.[6,15] Association of CU and autoimmune conditions, such as thyroiditis, is recognised in adults but in the paediatric literature seems contradictory; while some authors have found that 4–7% of children with AU had positive anti-thyroid antibodies;[16] others have found no evidence of this association.[12,17] Other autoimmune conditions that have been associated with AU include Type 1 diabetes mellitus, inflammatory bowel disease, systemic juvenile arthritis, systemic lupus erythematous, and coeliac disease.[15,18]

Infectious agents can also trigger CU. Several cases of *Escherichia coli,* Group A streptococcus, *Chlamydia pneumoniae*, cytomegalovirus, human herpes virus (HHV)-6, Epstein–Barr virus, and *Helicobacter pylori* have been reported.[19,20] Recently, it has been proposed that HHV-6 and HHV-4 act as co-factors in the process of inflammation and autoimmunity observed in CU.[21] The prevalence of parasitic infection (e.g. *Blastocystis hominis, Giardia intestinalis, Dientamoeba fragilis, Enterobius vermicularis, Entamoeba spp.*) in children with CU varies widely, from 1–10%, depending on the country of origin.[10,22,23] Currently, the use of specific treatment for these infectious agents remains controversial, as in many cases CU symptoms persist or recur after the therapy has been discontinued.[23,24]

Allergies to drugs and food or food additives are well-known triggers of CU.[25] Antibiotics and nonsteroidal anti-inflammatory drugs, including aspirin, are the main cause of drug allergies.[3] Among CU patients with food and additives allergies, fruit, vegetables, seafood, colouring agents, preservatives (monosodium glutamate), and sweetener agents have been identified as the main culprits.[19]

Physical and cholinergic urticaria comprise a very particular subgroup of CU known as CIU. It is characterised by the development of hives or angioedema due to a specific physical stimulus such as heat, cold, pressure, vibration, water, ultraviolet light, etc.[26] Rarely, patients may also have a mixed presentation with more than one type of CU.[27]

The literature regarding CU prevalence in children is scarce compared to that of adults; however, a recent systematic review revealed that CSU was the most common type of CU (85%) while patients with CIU represented only 15% of the cases. Within the group of CSU, >55% of the patients had an unknown aetiology (idiopathic), 28.4% had AU; allergies to drugs and foods/additives were found in 25%, and infections were identified in 4.5% of cases.[23] Azkur et al.[16] performed a prospective study in 222 children with CU of which 59.9% had CSU and 40.1% CIU. Within the CSU group, 53.5% had AU, 32.8% had positive 14C-urea breath test for *H. pylori*, and 6.5% had positive stool test for parasites. In the group of CIU, 77.5% had dermographism, 16.8% had cold urticaria, 2.2% had both cholinergic urticaria and solar urticaria, and aquagenic urticaria was present in 1.1% of the

patients.[16] In another study focussed solely on paediatric CIU (N=53), 38% had dermographism, 19% had cholinergic urticaria, 17% had mixed physical subtypes, 9% each had pressure inducible urticaria, cold urticaria, and heat urticaria, and 4% were unspecified.[28]

## CLINICAL PRESENTATION

### Chronic Spontaneous Urticaria

In general, patients with CSU present with frequent hives for >6 weeks, which usually resolve within 24 hours, leaving no mark. Oropharyngeal oedema or angioedema can be seen in ≤80% of patients, but seldom represents a life-threatening condition.[7] In patients with IgE-mediated food or drug allergy, the symptoms are not evident after the first hour after the exposure.[9] Although presentation of parasitic infection-related CSU (PIRCSU) is comparable to non-PIRCSU, the former seems to affect younger children (3–12 years) and the length of the disease is shorter. Also, the prevalence of gastrointestinal symptoms (nausea/abdominal pain) are substantially higher.[22] Overall, patients with AU have no clinical difference among children with non-AU. A couple of studies in children have not been able to find a clinical correlation among levels of antibodies and severity or chronicity of urticaria.[11]

### Chronic Inducible Urticaria

#### Cold Urticaria

Cold urticaria presents with redness, swelling, and itching in unprotected areas of the skin exposed to cold water, ice, or being outdoors in cold weather. The symptoms appear after a few minutes and once the stimulus has been avoided, they resolve within 30–60 minutes. Systemic symptoms, such as headache, fatigue, feeling light-headed, vomiting, or anaphylaxis, are present in ≤50% of patients after generalised cold exposure (e.g. swimming). Association with a recent cryoagglutinins-associated viral infection has also been reported.[29]

#### Heat Urticaria

In contrast to cold urticaria, in heat urticaria hives develop 10 minutes after contact with a heat source (45°C) for ≥5 minutes.[26]

#### Dermographism

Dermographism is characterised by erythema and/or swelling occurring at the sites of friction or minor trauma (e.g. scratching, clothing, clapping). Usually, hives are localised on the surface of the skin and clear after 30–60 minutes. Association with angioedema is rare.[2,26]

#### Solar Urticaria

Patients develop abrupt onset of erythema, hives, itching, and sometimes angioedema in areas that have been exposed to sunlight (ultraviolet light-A and, less frequently, ultraviolet light-B) or other visible light sources. The reaction occurs during or after a few minutes of the exposure, but there can be a latency period of several hours between the irradiation and the first appearance of any symptom.[30] Once the exposure ceases the symptoms resolve after 30 minutes or within the first 24 hours. Interestingly, the wavelength of light that triggers the symptoms varies in each patient. Rarely, full body exposure might lead to systemic symptoms and anaphylaxis.[31,32]

#### Vibratory Urticaria

Rarely seen in children, this type of urticaria is characterised by pruriginous erythema or swelling at the site of a vibratory stimulus, such as running, motorcycling, or electric tools (e.g. lawnmower, pneumatic drill). The symptoms usually appear within minutes of vibration and last several hours after the stimulus has been discontinued. When the stimulus continues, systemic symptoms, such as facial flushing, chest tightness, and an associated generalised feeling of heat, may develop.[33] This urticaria can be caused by a mutation in the ADGRE2 gene, which presents with an autosomal dominant inheritance.[34]

#### Delayed Pressure Urticaria

Unlike the other physical urticarias, delayed pressure urticaria consists of the development of hives/swelling from 30 minutes up to 9 hours after exposure to pressure, such as tight clothing, hammering, sitting down, or carrying heavy shopping bags. Skin lesions also last longer (12–72 hours) than in other types of physical urticaria.[35] Any part of the body may be affected, but the palms, soles, lips, shoulders, arms, and buttocks are usually more frequently involved. Pruritus may be absent or mild; instead patients describe localised pain and a burning sensation.[36] Extracutaneous manifestations, such as flu-like symptoms and arthralgia, may accompany skin lesions.[37]

#### Cholinergic Urticaria

Although it is included within the subgroup of CIU, it is not considered a physical urticaria because it

is triggered by a rise in temperature of the body core/sweating, rather than an exogenous physical trigger acting on the skin to induce the symptoms.[5] Cholinergic urticaria presents as very pruritic point-size papules or hives rapidly after exercising, emotional distress, hot bath, or spicy food, and usually clears within 1 hour.[38] The skin lesions may involve any part of the body; however, the neck, flexor surfaces of the elbows, knees, wrists, and inner thighs are more frequently affected.[7] Like exercise-induced urticaria/anaphylaxis, cholinergic urticaria can be triggered by physical activity, but they might be different entities.[2] Hives in exercise-induced urticaria are usually larger and the risk of anaphylaxis is higher. Angioedema and systemic symptoms can also be present in patients with cholinergic urticaria, but is uncommon.[39]

### Aquagenic Urticaria

Aquagenic urticaria manifests as extremely small pruriginous papules/hives, mostly localised to the neck, upper trunk, and arms. They develop within 5–20 minutes of contact with fresh or salted water, regardless of its temperature.[40] It is rarely seen in small children and it usually develops after puberty (mean age: 11–49 years). Although it presents in both sexes, it seems to be more common in females.[41] A familial presentation has also been reported.[42] Systemic symptoms might present if a large body surface area is submerged for several minutes. Hives last around 20–30 minutes and resolve spontaneously.[43]

## ASSESSMENT OF SEVERITY AND QUALITY OF LIFE IN PATIENTS WITH CHRONIC URTICARIA

Although CU could occasionally represent a life-threatening condition, most of the time symptoms, such as pruritus, hives, or angioedema, resolve promptly without severe complications; however, the recurrence of such symptoms can represent a heavy burden for children and their families. The recent EAACI/GA$^2$LEN/EDF/WAO guidelines for urticaria recommends using the urticaria activity score for 7 days to evaluate the severity of hives and itch in patients with CU. Every day, patients must assign a value from 0–3 to the intensity of the itch (0: none, 1: mild, 2: moderate, 3: severe) and to the number of hives (0: none, 1: <20 hives, 2: 20–50 hives, 3: >50 or large hives). The final score ranges from 0–42. A higher score represents greater severity.[5] Visual analogue scales have also been used to evaluate disease severity in adults and children with CU.[44]

As can be expected, the quality of life (QoL) of children with CU is impaired from a greater to a lesser degree depending on disease severity. Daily activities such as school performance, sleep, personal care, and peer interaction can be affected not only by the symptoms but also by side effects of treatment.[19] Despite the fact that few QoL studies in children with CU have been performed, it is known that CU in children affects QoL similarly to other chronic cutaneous conditions, such as atopic dermatitis.[45] Currently, the Chronic Urticaria Quality of life Questionnaire is the only specific tool that evaluates the severity and impact on QoL in patients with CU.[46] Other instruments used in children with CU include Children's Dermatology Life Quality Index, Dermatology Specific Quality of Life, Skindez-29, and the Urticaria Severity Score (not validated in children).[44,47]

## DIAGNOSIS

Diagnosis is established based on the history and clinical characteristics of the cutaneous and systemic manifestations. Extensive laboratory testing is usually unnecessary and should be guided by symptoms or suspicion of an underlying condition (Figure 1).[48] Either autologous serum skin test (ASST) or basophil activation test (BAT) can be used to diagnose AU.[17] Both tests have a high sensitivity and specificity to detect basophil histamine releasing activity. While ASST is an *in vivo* test, BAT is performed *in vitro*. Recently, Netchiporouk et al.[49] showed that high levels of BAT in children with CU are statistically significantly associated with a higher disease activity. CIU can be diagnosed by specific challenge testing.[50] Skin biopsy is rarely necessary, but it can rule out other conditions when systemic symptoms and skin lesion are not consistent with any type of CU.[9]

## TREATMENT

The goal of treatment is to eliminate the symptoms or reduce their severity/frequency. Eradication or avoidance of triggers (if identified) is the first step;[7] however, in many cases this is not possible or symptoms continue despite specific treatment (antibiotics, anti-parasitic drugs, thyroid hormone replacement).

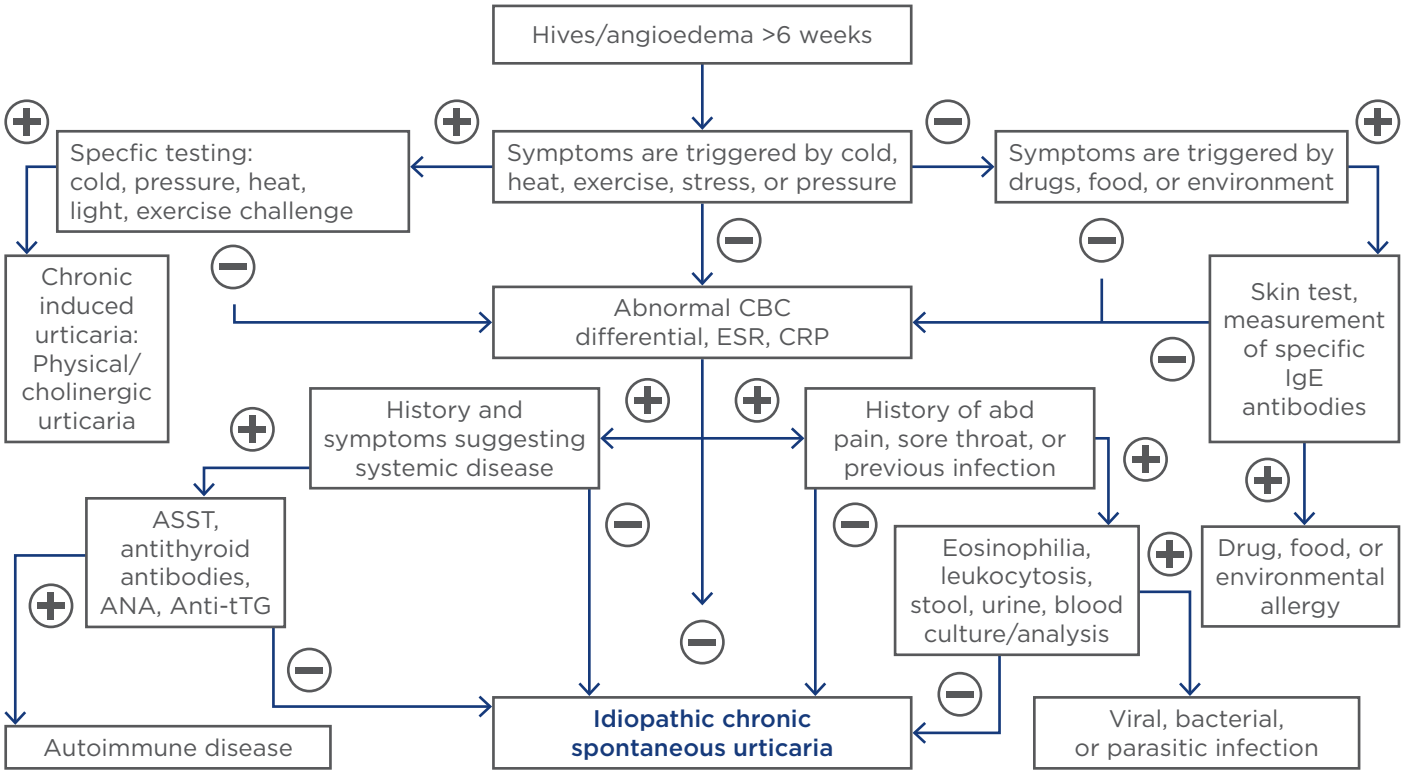


**Figure 1: Diagnosis of chronic urticaria.**

abd: abdominal; ANA: antinuclear antibody; ASST: autologous serum skin test; Anti-tTG: anti-tissue transglutaminase antibody; CBC: complete blood count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IgE: immunoglobulin E.

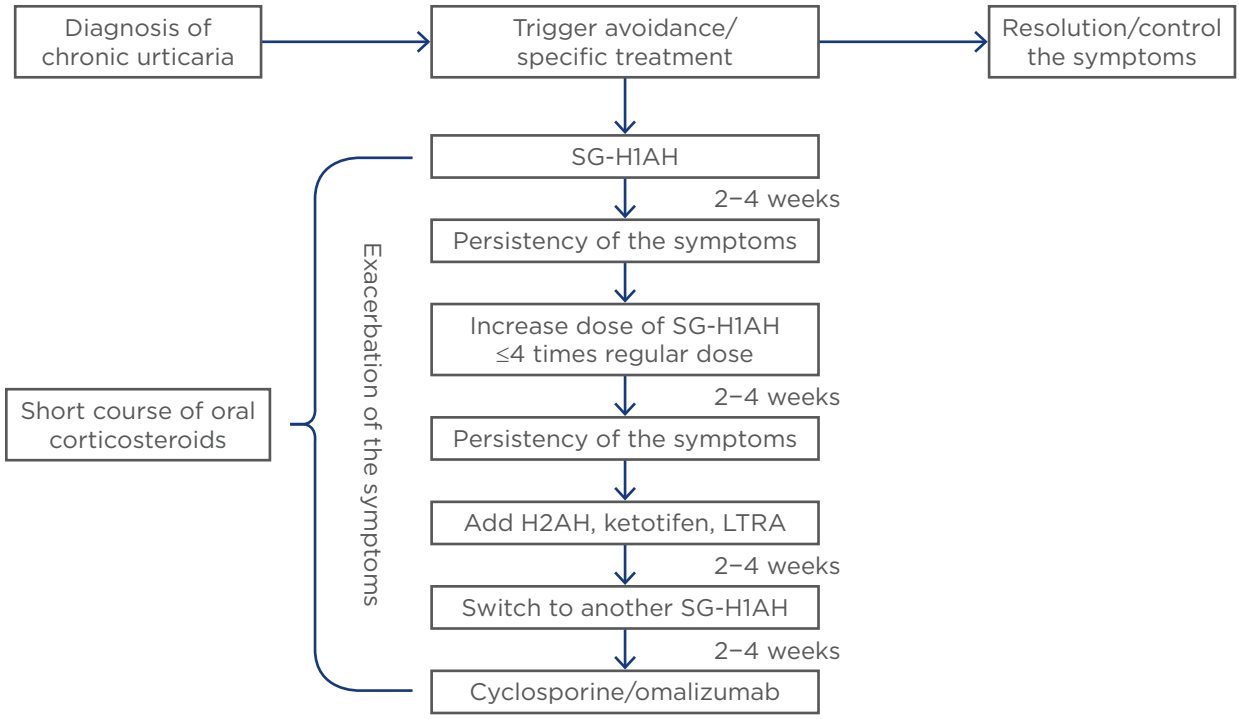


**Figure 2. Treatment steps for children with chronic urticaria.**

Note: this flowchart is a summary of recommendations by several authors included in this review. It is not intended to replace the current guidelines by the EAACI/GA[2] LEN/EDF/WAO.

H2AH: H2-antihistamine; LTRA: leukotriene antagonist; SG-H1AH: second generation H1-antihistamines.

The first-line treatment for CU is antihistamine therapy, as it inhibits the effect of mast cell and basophil mediators on the target tissues.[48] First-generation H1-antihistamines may temporarily relieve the symptoms of CU; however, they are no longer recommended due to undesired side effects (sedation, impairment of alertness and cognition).[2] However, some authors have reported the efficacy and safety of ketotifen (a non-competitive H1-antihistamine and mast-cell stabiliser) in patients with CU.[51]

The new EAACI/GA²LEN/EDF/WAO guidelines strongly support the use of second-generation H1-antihistamines (SG-H1AH) for CU.[5] In children, several studies regarding the safety and efficacy of cetirizine, levocetirizine, loratadine, fexofenadine, desloratadine, and rupatadine have been performed.[52] The regular dosage of SG-H1AH could be increased up to 2–4 times if symptoms are not resolved or improved within the first 2–4 weeks of treatment; if there is still no improvement, another H1-antihistamine could be tried.[53] A few studies performed in children with CU have shown that around 35–38% of these patients required double doses of SG-H1AH, while only 6% and 5% needed triple or quadruple dosage, respectively. Interestingly, younger children seem to respond better to regular doses, while older children require higher doses to achieve resolution of their symptoms.[53,54] Adding an H2-antihistamine (cimetidine, ranitidine) for patients who still have not been able to achieve complete remission of their symptoms has been recommended by some authors, although this remains controversial.[3] For those who have failed monotherapy, next line of treatment includes adding a leukotriene antagonist (LTRA), short course of oral corticosteroids, cyclosporine, or omalizumab.[6]

LTRA, such as montelukast and zafirlukast, have been used successfully in children with asthma or other allergic diseases; however, literature regarding paediatric CU is almost non-existent. In adults, a recent systematic review showed controversial results. As monotherapy, LTRA were better than placebo, but less effective than SG-H1AH, while combined therapy (SG-H1AH+LTRA) showed overall better results.[55-57] Currently, the use of corticosteroids in CU is restricted only for exacerbations and for short periods of time (3–7 days), due to their well-known side effects.[2,5,52]

Cyclosporine has also been used as adjuvant therapy in the treatment of difficult to control CU.[58] Moreover, it has been shown that cyclosporine is more effective in patients with elevated high-sensitivity C-reactive protein. In children, few studies have showed its effectiveness.[59] Doshi et al.[60] reported seven patients treated with cyclosporine after failing high-dose SG-H1AH and corticosteroid therapy. All patients reached cessation of the symptoms within the first 8 weeks of treatment, with no evidence of side effects.[60] Although uncommon, side effects (e.g. infections, hypertension, nephrotoxicity, headache, nausea, abdominal pain) have been reported. Thus, a close monitoring of blood pressure, renal function, and cyclosporine levels is recommended.[61]

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that binds to the constant region of the IgE molecule, avoiding the interaction between free IgE with high and low-affinity IgE receptors. This reduces the levels of IgE and leads to a downregulation of high-affinity IgE receptor expression on inflammatory cells.[62] Lately, the interest in omalizumab as second-line therapy for patients with CU has increased significantly, because several studies and case reports have showed its effectiveness and safety in both adults and children.[63-65] In children, omalizumab is currently approved for moderate-to-severe uncontrolled allergic asthma and CSU (≥12 years). Off-label uses include allergic rhinitis, food allergy, and anaphylaxis, and severe refractory and atopic dermatitis.[66] Improvement of the symptoms can be observed from the first dose; however, to prevent recurrence and obtain complete remission, at least 5 doses are considered necessary.[65] Overall, omalizumab seems to be safe with few side effects reported (mainly mild skin reactions at the injection site and, in rare cases, anaphylaxis), but its high cost has limited its use.[12,66-68] Please see Figure 2 for further information.

## PROGNOSIS

Most children with CU achieve improvement or control of their symptoms within the first 5 years after the diagnosis, although some of them continue to experience the symptoms even longer. However, studies performed in children have dissimilar results. While some authors report a remission rate at one year of 84%, others report only 16–18% for the same period.[69,70] Overall, by the end of Year 5, between 38.4% and 67.7% of the patients are free of symptoms.[10] Children with CIU and AU seem to have symptoms for

longer, but this is also a controversial suggestion as some authors have found no difference among these patients.[2,19]

## CONCLUSION

CU in children is uncommon but represents a challenge for many physicians. The recurrent episodes of hives or angioedema impact the QoL of children and their parents. The diagnosis is based on the clinical characteristics of the symptoms. Extensive work-up is rarely necessary, but specific testing guided by a good history can confirm the diagnosis in many cases. The first line of treatment continues to be SG-H1AH. The emergence of new therapies, such as omalizumab, could represent a hope for patients with recalcitrant CU.

## Appendix

**Table 1: Medications for chronic urticaria in children.**[1,52,60,68,71]

| | Paediatric dosage | |
|---|---|---|
| Cetirizine | 250 ug/kg/twice daily<br>1.25–2.5 mg/twice daily<br>5 mg/once or twice daily<br>10 mg/once daily | 1–2 years<br>2–5 years<br>6–11 years<br>>12 years |
| Desloratadine | 1.25 mg<br>2.5 mg<br>5 mg | >1–5 years<br>6–11 years<br>>12 years |
| Fexofenadine | 30 mg/twice daily<br>60 mg<br>120–180 mg | 2–5 years<br>6–11 years<br>>12 years |
| Levocetirizine | 1.25 mg/twice daily<br>5 mg | 2–5 years<br>6–>12 years |
| Loratadine | 5 mg<br>10 mg<br>Or<br>2–12 years<br><30 kg: 5 mg/once daily<br>>30 kg: 10 mg/once daily | 2–5 years<br>6–>12 years |
| Rupatadine | 10 mg | >12 years |
| Ketotifen | 1 mg/twice daily | 3–18 years |
| Cimetidine | Infants: 10–20 mg/kg/day orally divided over every 6-12 hours<br>Children: 20–40 mg/kg/day orally divided over every 6 hours | |
| Montelukast | 4 mg<br>5 mg<br>10 mg | 2–4 years<br>5–14 years<br>>14 years |
| Ranitidine | 5–10 mg/kg/twice daily | |
| Cyclosporine | 3 mg/kg/twice daily | |
| Omalizumab | 150–300 mg/dose every 4 weeks<br>150–300 mg/dose every 4 weeks | <12 years (off label)<br>>12 years |

## REFERENCES


1. Kulthanan K et al. Clinical practice guideline for diagnosis and management of urticaria. Asian Pac J Allergy Immunol. 2016;34(3):190-200.

2. Pite H et al. Management of childhood urticaria: current knowledge and practical recommendations. Acta Derm Venereol. 2013;93(5):500-8.

3. Choi SH, Baek HS. Approaches to the diagnosis and management of chronic urticaria in children. Korean J Pediatr. 2015;58(5):159-64.

4. Weston W, Orchard, D. Pediatric Dermatology. 3rd ed: Mosby; 2003.

5. Zuberbier T et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy. 2014;69(7): 868-87.

6. Church MK et al. Chronic spontaneous urticaria in children: itching for insight. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology. 2011; 22(1 Pt 1):1-8.

7. Ventilacion L, Leech S. Recurrent

urticaria. Paediatrics and Child Health. 26(7):292-7.

8. Lee SJ et al. Prevalence and risk factors of urticaria with a focus on chronic urticaria in children. Allergy Asthma Immunol Res. 2017;9(3):212-9.

9. Powell RJ et al.; British Society for Allergy and Clinical Immunology. BSACI guideline for the management of chronic urticaria and angioedema. Clin Exp Allergy. 2015;45(3):547-65.

10. Chansakulporn S et al. The natural history of chronic urticaria in childhood: a prospective study. J Am Acad Dermatol. 2014;71(4):663-8.

11. Chang KL et al. Analysis of serum total IgE, specific IgE and eosinophils in children with acute and chronic urticaria. J Microbiol Immunol Infect. 2013;46(1): 53-8.

12. Netchiporouk E et al. Management of pediatric chronic spontaneous and physical urticaria patients with omalizumab: case series. Pediatr Allergy Immunol. 2015;26(6):585-8.

13. Dilek F et al. Oxidative stress in children with chronic spontaneous urticaria. Oxid Med Cell Longev. 2016; 2016:3831071.

14. Dilek F et al. Plasma levels of matrix metalloproteinase-9 in children with chronic spontaneous urticaria. Allergy Asthma Immunol Res. 2016;8(6):522-6.

15. Lara-Corrales I et al. Chronic urticaria in children. Clinical Pediatr. 2009;48(4): 351-5.

16. Azkur D et al. Clinical and etiologic evaluation of the children with chronic urticaria. Allergy Asthma Proc. 2016; 37(6):450-7.

17. Brunetti L et al. High prevalence of autoimmune urticaria in children with chronic urticaria. J Allergy Clin Immunol. 2004;114(4):922-7.

18. Caminiti L et al. Chronic urticaria and associated coeliac disease in children: a case-control study. Pediatr Allergy Immunol. 2005;16(5):428-32.

19. Ghaffari J et al. Chronic urticaria in children: Etiologies, clinical manifestations, diagnosis and treatment. J Pediatrics Rev. 2013;1(2):55-68.

20. Castillo Reguera YM et al. [Helicobacter pylori infection; a rarely suspected and treatable cause of chronic urticaria]. An Pediatr. 2012; 76(4):240-1. (Article in Spanish).

21. Dreyfus DH. Serological evidence that activation of ubiquitous human herpesvirus-6 (HHV-6) plays a role in chronic idiopathic/spontaneous urticaria (CIU). Clin Exp Immunol. 2016;183(2): 230-8.

22. Arik Yilmaz E et al. Parasitic infections in children with chronic spontaneous urticaria. Int Arch Allergy Immunol. 2016;171(2):130-5.

23. Caffarelli C et al. Aetiological factors associated with chronic urticaria in children: a systematic review. Acta Derm Venereol. 2013;93(3):268-72.

24. Shelley WB, Shelley ED. Acyclovir therapy for angioedema and chronic urticaria. Cutis. 1997;59(4):185-8.

25. Ferrante G et al. The care pathway for children with urticaria, angioedema, mastocytosis. World Allergy Organ J. 2015;8(1):5.

26. Trevisonno J et al. Physical urticaria: Review on classification, triggers and management with special focus on prevalence including a meta-analysis. Postgrad Med. 2015;127(6):565-70.

27. Torchia D et al. Multiple physical urticarias. Postgrad Med J. 2008;84(987):e1-2.

28. Khakoo G et al. Clinical features and natural history of physical urticaria in children. Pediatr Allergy Immunol. 2008;19(4):363-6.

29. Hochstadter EF, Ben-Shoshan M. Cold-induced urticaria: challenges in diagnosis and management. BMJ Case Rep. 2013;2013.

30. Roelandts R. Diagnosis and treatment of solar urticaria. Dermatol Ther. 2003; 16(1):52-6.

31. Levi A et al. Successful omalizumab treatment of severe solar urticaria in a 6-year-old child. Pediatr Allergy Immunol. 2015;26(6):588-90.

32. Pérez-Ferriols A et al. Solar urticaria: Epidemiology and clinical phenotypes in a Spanish series of 224 patients. Actas Dermosifiliogr. 2017;108(2):132-9.

33. Pressler A et al. Failure of omalizumab and successful control with ketotifen in a patient with vibratory angio-oedema. Clin Exp Dermatol. 2013;38(2):151-3.

34. Home Genetic Reference. Your guide to understanding genetic conditions – Vibratory urticaria. Available at: https://ghr.nlm.nih.gov/condition/vibratory-urticaria#genes. Last accessed: 4 September 2017.

35. Lawlor F, Black AK. Delayed pressure urticaria. Immunol Allergy Clin North Am. 2004;24(2):247-58.

36. Kobza-Black A. Delayed pressure urticaria. Journal Investig Dermatol Symp Proc. 2001;6(2):148-9.

37. Dortas SD, Jr et al. [Delayed pressure urticaria with systemic manifestations: Case report]. An Bras Dermatol. 2009; 84(6):671-4. (In Portuguese).

38. Bito T et al. Pathogenesis of cholinergic urticaria in relation to sweating. Allergol Int. 2012;61(4):539-44.

39. Del Giacco SR et al. Allergy and sports in children. Pediatr Allergy Immunol. 2012;23(1):11-20.

40. Bayle P et al. Localized aquagenic urticaria: efficacy of a barrier cream. Contact Dermatitis. 2003;49(3):160-1.

41. Wasserman D et al. Aquagenic urticaria in a child. Pediatr Dermatol. 1994;11(1):29-30.

42. Gallo R et al. Localized salt-dependent aquagenic urticaria: a subtype of aquagenic urticaria? Clin Exp Dermatol. 2013;38(7):754-7.

43. Casale TB et al. Aquagenic urticaria. J Allergy Clin Immunol Pract. 2013;1(3): 295-6.

44. Jáuregui I et al. Assessment of severity and quality of life in chronic urticaria. J Investig Allergol Clin Immunol. 2014;24(2):80-6.

45. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. Br J Dermatol. 2006; 155(1):145-51.

46. Baiardini I et al. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). Allergy. 2005;60(8):1073-8.

47. Jariwala SP et al. The urticaria severity score: a sensitive questionnaire/index for monitoring response to therapy in patients with chronic urticaria. Ann Allergy Asthma Immunol. 2009;102(6):475-82.

48. Sussman G et al. Insights and advances in chronic urticaria: a Canadian perspective. Allergy Asthma Clin Immunol. 2015;11(1):7.

49. Netchiporouk E et al. Positive CD63 basophil activation tests are common in children with chronic spontaneous urticaria and linked to high disease activity. Int Arch Allergy Immunol. 2016; 171(2):81-8.

50. Magerl M et al. The definition, diagnostic testing, and management of chronic inducible urticarias - The EAACI/GA(2) LEN/EDF/UNEV consensus recommendations 2016 update and revision. Allergy. 2016;71(6):780-802.

51. Sokol KC et al. Ketotifen in the management of chronic urticaria: resurrection of an old drug. Ann Allergy Asthma Immunol. 2013;111(6):433-6.

52. Fortina AB, Fontana E. Update on antihistamine treatment for chronic urticaria in children. Curr Treat Opt Allergy. 2014;1(3):287-98.

53. Lee XH et al. A stepwise approach in the management of chronic spontaneous urticaria in children. Asia Pac Allergy. 2016;6(1):16-28.

54. Uysal P et al. High-dose anti-histamine use and risk factors in children with urticaria. Turk Pediatri Arsivi. 2016; 51(4):198-203.

55. Generali JA, Cada DJ. Zafirlukast: Chronic urticaria. Hosp Pharm. 2015; 50(10):873-5.

56. Yadav S, Bajaj AK. Management of difficult urticaria. Indian J Dermatol. 2009;54(3):275-9.

57. de Silva NL et al. Leukotriene receptor antagonists for chronic urticaria: a systematic review. Allergy Asthma Clin Immunol. 2014;10(1):24.

58. Criado PR et al. Chronic urticaria in adults: state-of-the-art in the new millennium. An Bras Dermatol. 2015; 90(1):74-89.

59. Ohtsuka T. Response to oral cyclosporine therapy and high sensitivity-CRP level in chronic idiopathic urticaria. Int J Derm. 2010;49(5):579-84.

60. Doshi DR, Weinberger MM. Experience with cyclosporine in children with chronic idiopathic urticaria. Pediatr Dermatol. 2009;26(4):409-13.

61. Marchese M et al. Ciclosporina y su uso en dermatologia. Arch Argent Dermatol. 2014.

62. Holgate ST et al. Anti-immunoglobulin E treatment with omalizumab in allergic diseases: an update on anti-inflammatory activity and clinical efficacy. Clin Exp Allergy. 2005; 35(4):408-16.

63. Maspero JF et al. [Chronic autoimmune urticaria: treatment with omalizumab]. Arch Argent Pediatr. 2009;107(5):452-6. (In Spanish).

64. Asero R et al. Extraordinary response to omalizumab in a child with severe chronic urticaria. Eur Ann Allergy Clin Immunol. 2014;46(1):41-2.

65. Labrador-Horrillo M, Ferrer M. Profile of omalizumab in the treatment of chronic spontaneous urticaria. Drug Des Devel Ther. 2015;9:4909-15.

66. Licari A et al. Omalizumab in children. Paediatr Drugs. 2014;16(6):491-502.

67. Al-Ahmad M et al. Economic burden of refractory chronic spontaneous urticaria on Kuwait's health system. Clinicoecon Outcomes Res. 2016;8:163-9.

68. Ghaffari J et al. Omalizumab (Xolair) in children above 12 years with chronic urticaria: A review of literature. J Ped Revs. 2015;3(1):e152.

69. Shin M, Lee S. Prevalence and causes of childhood urticaria. Allergy Asthma Immunol Res. 2017;9(3):189-90.

70. Sahiner UM et al. Chronic urticaria: etiology and natural course in children. Int Arch Allergy Immunol. 2011;156(2): 224-30.

71. Fitzsimons R et al. Antihistamine use in children. Arc Dis Child Educ Pract Ed. 2015;100(3):122-31.

# PSYCHOSOCIAL ISSUES IN DERMATOLOGY

**Mukku Shiva Shanker Reddy, *Santosh K Chaturvedi**

*Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India*
**Correspondence to skchatur@gmail.com*

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## ABSTRACT

Skin, with its many biological functions, has a unique aesthetic value and determines the self-image and psyche of the person in terms of how they think about themselves. In modern times, smooth-textured flawless skin is a preferred characteristic. Any change in this highly aesthetic organ due to a disease has significant repercussions on personal and social life. There is a bidirectional relationship between dermatological diseases and psychiatric disorders. These can be studied under three categories: psychophysiological disorders, which are dermatologic conditions that fluctuate in clinical severity according to psychological state; primary psychiatric disorders presenting with dermatological manifestations; and dermatological adverse effects of psychotropic medication. Psychiatric disorders are highly prevalent in dermatological patients. Dermatologists should be aware of the psychological factors contributing to or arising from skin disease in common dermatological conditions. Management of psychiatric comorbidities in these patients will help decrease the stigma, stress, and distress, and thus will improve the quality of life of patients and overall treatment success.

Keywords: Skin, psychiatric morbidity, stress, stigma, dermatologist, psychodermatology.

## INTRODUCTION

The skin is the largest organ in the body and serves many functions, including acting as a barrier, immune regulator, and endocrine organ, as well as also having an aesthetic role. There is a strong bidirectional relationship between dermatological diseases and psychiatric disorders. The origin of this relationship may be due to common neurobiological, psychological, and social aspects. Skin diseases account for 12.4% of all the diseases seen by general practitioners.[1] The prevalence of psychiatric morbidity in dermatological outpatients is reported to be 25%.[2] Despite the high prevalence of psychiatric morbidity, it has received scarce attention. Dermatological diseases can increase the risk of developing or worsening an existing psychiatric disorder. The relation between the psychiatric morbidity and skin diseases can be understood in four ways:

- The skin diseases of a chronic nature and disfigurement may frequently affect the quality of life of patient; thus, increasing psychiatric morbidity.
- Less frequently, skin diseases may result from primary psychological diseases, such as obsessive compulsive disorders, impulse control disorders, and delusional disorders.
- Both skin findings and psychiatric complaints may develop secondary to a disease, such as systemic lupus erythematosus.
- Dermatological adverse effects that are due to psychotropics, such as lithium, lamotrigine, and chlorpromazine.

## NEUROBIOLOGICAL LINK BETWEEN MIND AND SKIN

There is an intricate relationship between stress and skin conditions. Stress exerts its effects on skin mainly through the hypothalamic-pituitary-adrenal axis. The skin has developed a fully functional, peripheral hypothalamic-pituitary-adrenal system in which corticotropin-releasing hormone (CRH), adrenocorticotropic hormone, and their receptors are produced in skin cells.[3] CRH is produced in the epidermis and hair follicles by keratinocytes, melanocytes, sebocytes, and mast cells upon stress. CRH inhibits proliferation

by arresting cells at the G0/1 cycle and induces differentiation by calcium influx and the AP-1 transcription pathway.[4] In mast cells, CRH induces degranulation and increases vascular permeability, demonstrating proinflammatory functions.[5] The adrenocorticotropic hormone stimulates interleukin-18 production in skin keratinocytes; interleukin-18 is a proinflammatory cytokine that enhances T cell activity and promotes T-helper type 2 cytokine production.[6]

Stress also induces the release of catecholamines through the sympathetic-adrenal medullary axis, which excretes adrenaline. Adrenaline acts by binding to a variety of adrenergic receptors, leading to decreased skin blood flow, and altered immune and inflammation functions, including lymphocyte trafficking, circulation, proliferation, and cytokine production.[7] The skin also holds a peripheral catecholamine system where adrenaline is synthesised in keratinocytes while the adrenergic receptors are present in both epidermal keratinocytes and melanocytes. Adrenaline, through its action on beta-2 receptors, regulates both epidermal proliferation and differentiation.[8]

The skin is highly innervated and, as such, peripheral nerves can also impact skin health through secreted factors like neuropeptides (substance P) and neurotrophins (NT). Substance P is a stress-related proinflammatory neuropeptide that is released from cutaneous peripheral nerve terminals. Nerve growth factor, one of four NT family members, binds to the high-affinity tyrosine kinase receptors (TrkA, TrkB, and TrkC) and low affinity p75 NT receptor promotes neurogenic inflammation by stimulating cytokine releases from skin mast cells.[9]

Stress also has a negative impact on wound healing. Anxiety and depression are associated with delayed wound healing in chronic wounds[10] and it was found that chronic stress leads to elevated cortisol and dysregulation of healing biomarkers, which contributes to a delay in wound healing.[11]

## PSYCHOPHYSIOLOGICAL DISORDERS

Psychophysiological disorders are when the course of the skin disease is affected by the psychological state of a person or psychological disorders arising due to dermatological diseases. Patients with real and perceived imperfections in important body image areas, such as the face, scalp, hands, and genital area, due to various skin diseases, are prone to distress. Acne, psoriasis, atopic dermatitis (AD), and Hansen's disease are common skin diseases that are well studied with respect to psychosocial health.

### Acne

Acne is one of the most prevalent skin conditions, affecting >85% of teenagers.[12] In 1948, Sulzberger and Zaidens[13] wrote: "There is no single disease which causes more psychic trauma and more maladjustment between parents and children, more general insecurity and feelings of inferiority, and greater sums of psychic assessment than does acne vulgaris." The change in the skin's appearance may give rise to a changed body image that, in turn, is known to lead to anger, fear, shame, anxiety, depression, embarrassment, and stigmatisation within peer groups. Its substantial influence is likely related to its typical appearance on the face and would also explain the increased unemployment rate of adults with acne.[14] In a study carried out in southern India by Durai et al.,[15] it was found acne has a significant impact on quality of life. In another study of Iranian patients, the prevalence of anxiety was 68.3% in patients and 39.1% in the control group.[16] The psychological effect of acne is unique for each patient; therefore, patients should be asked how much their acne bothers them, regardless of how severe it appears to physicians. Acne in adolescence can affect self-image, assertiveness, and the formation of friendships. The face is very important to body image, and as such young men with severe scarring acne are at particular risk of depression and suicide.[17]

### Psoriasis

Psoriasis can be considered a psychosocial skin disease. It is a chronic inflammatory condition of the skin associated with significant morbidity. The prevalence of psoriasis in children ranges from 0–2.1% and in adults it varies from 0.91–8.5%[18] and comprises 2.6% of skin-related visits to primary care physicians.[19] The morbidity in people with psoriasis is due to itching, scratching, bleeding spots, noticeable flakes, and unsightly physical appearance. People affected have poorer social lives, difficulties in getting jobs, and decreased quality of life due to embarrassment and the feeling of physical unattractiveness.[20] The most prevalent psychiatric comorbidities in psoriasis are related to sexual (71%)[21] and sleep problems (50%).[22] In a study conducted in eastern India in a tertiary centre evaluating the psychiatric morbidity in psoriasis patients, 62.5% had psychiatric morbidity,

compared with 18.5% in the control group. Guttate psoriasis had maximum association with psychiatric morbidity (100%), followed by plaque type (63.6%), and palmoplantar type (42.8%). The most common psychiatric symptom in psoriasis patients was anger (58%), followed by discomfort (52%), social problems (52%), cognitive impairment (50%), embarrassment (50%), physical limitation (48%), fear (48%), and depression (44%).[23] In another study from northern India, patients with psoriasis were evaluated in two stages using the mini international neuropsychiatric interview (MINI), and it was found that 45% have psychiatric morbidity, with dysthymia (28.85%) followed by major depression (15.38%) as the next most common psychiatric disorders.[24] In the same study, suicidality was found in 13.6% of patients. Furthermore, certain psychiatric conditions like depression and anxiety can worsen the severity of psoriasis.[25]

### Atopic Dermatitis

AD is a chronic inflammatory skin disease, characterised by pruritic and eczematous skin lesions with a series of exacerbations and remissions. AD onset is commonly during childhood and adolescence. It affects 15–20% of children[26] and constitutes approximately 15% of the skin-related concerns in general practice.[19] Patients with AD experience unrelenting pruritus, which is the primary source of morbidity. Children with AD also experience significant psychosocial and behavioural issues compared to their peers. Parents of children with AD report increased fussiness, irritability, and crying in their children.[27] Daud et al.[28] found children with severe eczema, when compared to unaffected children, had difficulty with psychosocial adjustments and displayed more clinginess and fearfulness. In a study conducted to quantify the mental health burden associated with paediatric AD, it was found that the odds of having attention-deficit hyperactivity disorder was significantly increased in children with AD compared to non-AD controls (odds ratio: 1.87; 95% confidence interval [CI]: 1.54–2.27). In the same study the adjusted odds ratios for depression, anxiety, conduct disorder, and autism were 1.81 (95% CI: 1.33–2.46), 1.77 (95% CI: 1.36–2.29), 1.87 (95% CI: 1.46–2.39), and 3.04 (95% CI: 2.13–4.34), respectively.[29] Adult patients with AD can have substantial salary loss from missed work, as well as financial strain due to multiple medications and possibly consultations with alternative medicine practitioners. In particular, work-related adult hand dermatitis is a common cause of worker compensation benefits and requires workplace modification.

### Hansen's Disease

Hansen's disease (leprosy) is an uncommon skin disease in the Western world, but leprosy cases are still seen in developing nations. Hansen's disease is associated with significant morbidity in the patient and their family. In society, there is significant stigma towards Hansen's disease patients, due to factors such as fear of acquiring disease from patients, disfigurement, and deformities. The psychosocial issues faced by people with leprosy are high, and the rate of divorce, unemployment, displacement from area of residence, and loss of social status are common.[30] Studies have shown that stigma is greater in educated women belonging to a higher socio-economic class staying in a joint family.[31] A study was carried out in south-east Nigeria, where the psychiatric morbidity in leprosy patients was compared to albinism; the prevalence of specific psychiatric disorders among subjects with leprosy was depression (49%), generalised anxiety disorder (18%), and alcohol/drug abuse (16%). Over half (55%) of subjects with leprosy were general health questionnaire (GHQ) positive cases, while 41% with albinism were GHQ positive cases.[32] Hansen's disease complications can cause gross deformities of the face and limbs of infected individuals, as well as crippling disabilities involving sight, touch, and manual dexterity. Cumulative deformities add up to stigma, unemployment, and economic deprivation.[33] In an Indian study evaluating the psychiatric morbidity among inmates of leprosy homes, it was found that 50% of subjects had very high distress as assessed by GHQ-12. Among them, 55.6% of subjects had a psychiatric disorder, the most common being dysthymia.[34] There is a need for comprehensive psychiatric care for people with Hansen's disease. The role of mental health professionals is also important in tackling psychosocial issues related to Hansen's disease.

## PSYCHIATRIC DISORDERS WITH SKIN SYMPTOMS

Psychiatric disorders with skin symptoms are conditions in which there is no primary skin condition. Rather, lesions that are observed on the skin are self-induced because the problem is psychological. Patients with these disorders are more frequently seen in dermatology clinics, as these patients may be unwilling to acknowledge a psychiatric basis for their physical findings.

## Impulse Control Disorders

### Trichotillomania

Trichotillomania (TTM) is characterised by recurrent and persistent urges to pull out one's own hair. A survey of 2,524 college students about TTM demonstrated that the lifetime prevalence rate was 0.6%.[35] The scalp is reported as the most common site affected, followed by the eyelashes, eyebrows, pubic hair, body hair, and facial hair.[36] This self-inflicted hair-loss can range from small, barely noticeable patches on various areas of the body, to total baldness. Despite normal hair density, patients present with different hair lengths, including tapered ends, demonstrating new growth, and blunt ends, representing broken hairs.[37] One important dermatological differential diagnosis is alopecia areata. In alopecia areata, the bare regions of the scalp are smooth, and the scalp is often peach coloured.[38] Psychiatric comorbidities are known to be frequent in TTM and include major depression, generalised anxiety disorder, obsessive compulsive disorder (OCD), other anxiety disorders, eating disorders, and substance abuse.[36] Treatment of TTM includes pharmacologic and non-pharmacologic therapies. Recommended first-line therapy for this psychiatric condition is administration of selective serotonin reuptake inhibitors (SSRI). N-acetylcysteine is also found to be effective for patients with TTM.[39] Non-pharmacologic therapies include behaviour modification through habit reversal therapy, which has been shown to have the highest rate of resolution for TTM.[38]

### Neurotic excoriation

Neurotic excoriations are self-inflicted lesions that typically present as weeping, crusted, or lichenified lesions with post-inflammatory hypopigmentation or hyperpigmentation.[40] This is also known as pathologic skin picking or skin excoriation. The usual sites are the extensor aspects of extremities, scrotum, and perianal regions. It is estimated that 2% of dermatologic clinic patients have the diagnosis of neurotic excoriations.[41] It predominantly affects women, with an age of onset between the third and fifth decade.[42] Medical reasons for pruritus that can induce self-excoriation include urticaria, uraemia, hepatitis, xerosis, cutaneous dysesthesia, and malignancies. The diagnosis requires evaluation of the patient for impulse control disorders and ruling out relevant medical diseases. The first-line treatment for neurotic excoriations may be SSRI, as they can reduce depressive and compulsive symptoms.[43]

### Body dysmorphic disorder

Body dysmorphic disorder (BDD) is a condition in which the patient is preoccupied and distressed with an imagined defect in appearance or an excessive concern over a trivial defect. The prevalence of BDD in many studies varies from 0.75%–12%.[44] Most patients are females who have been affected in their 30s.[44] The affected individuals frequently complain about disfigurement of the nose, ears, and sometimes of the breast, even though there is no objective evidence. This leads to anxiety, insecurity, and tension. In order to reduce anxiety, patients exhibit behaviours such as mirror checking or reassurance seeking.[45] These patients visit cosmetologists or dermatologists for correction of defects. Among BDD patients, 10–14% present to dermatologists requesting cosmetic surgery.[46] The management of these patients is challenging, as they have variable insight about their problems and are also resistant to accepting the psychological nature of their illness.

### Obsessive compulsive disorders

OCD affects 2–3% of the general population. Up to 25% of patients presenting to physicians with skin disease suffer from OCD.[47] In the current classification in the Diagnostic and Statistical Manual of Psychological Disorders (5th edition), obsessive compulsive and related disorders are noted to include OCD, BDD, pathological hoarding, and skin picking.[48] Some of these conditions are already discussed previously. OCD is characterised by obsessive thoughts and compulsive behaviours. Studies have shown that 16% of all OCD patients have washing compulsions.[49] There have been reports of AD irritant toxic dermatitis of the hands in patients with washing compulsions.[47] Therefore, dermatologists seeing patients with hand dermatitis in the presence of compulsive washing should consider OCD in their diagnosis.[45] These patients might take several years before coming to a psychiatrist, causing significant morbidity. Regarding the treatment of OCD, SSRI in combination with behavioural therapy is the standard treatment.

### Delusional infestation

Delusional infestation is a condition where an individual has a firmly fixed, false belief that they are infested with an infectious agent, including infestation with non-living things such as nanobots or fibres. Delusional infestation is favoured over the narrower term delusional parasitosis;[50] it can also

be called Ekbom syndrome. The condition is more common in women in their 5th or 6th decade of life.[51] As part of this belief, patients may perceive parasites crawling or burrowing into their skin. Discrete bruises, nodular pruritus, ulcers, and scars are frequently produced by patients trying to extract the parasite. They commonly seek the attention of dermatologists or physicians and may continue seeking different therapies in search of a cure. In fact, <90% of patients with this condition are seen by dermatologists.[52] Patients affected by delusional infestations are difficult to treat as they have no insight into their illness. Management requires establishing a good therapeutic alliance and antipsychotics.

## DERMATOLOGICAL ADVERSE EFFECTS OF PSYCHOTROPIC MEDICATIONS

Psychotropic medications from all classes have been associated with a broad variety of dermatologic reactions with variable rates of incidence. Psychiatrists should be aware of the potential cutaneous adverse effects of the medications they prescribe.

### Mood Stabilisers

Lithium is one the most common medications used to treat mood disorders. It has been found to cause cutaneous side effects, such as acneiform eruption, psoriasis, folliculitis, and maculopapular eruption.[53] It has been associated with both the onset and exacerbation of psoriasis.[54] In controlled studies, patients treated with lithium developed more cutaneous reactions, particularly acne and psoriasis, with prevalence as high as 45%. Lamotrigine, another mood stabiliser, is an anticonvulsive medication and can cause an uncommon, but serious, rash called Stevens-Johnson syndrome.[55] Stevens-Johnson syndrome has high mortality and morbidity and requires careful attention while using lamotrigine in clinical practice.

### Antidepressants

Antidepressants can cause serious skin adverse effects, but these are rare in routine clinical practice. However, there are case reports of mianserin and bupropion causing erythema multiforme.[56] Fluoxetine[57] and sertraline[58] have also been reported to cause Stevens-Johnson syndrome.

### Antipsychotics

Antipsychotic agents are known to cause adverse cutaneous reactions in approximately 5% of individuals.[59] In particular, chlorpromazine is known to induce skin pigmentation in areas exposed to sunlight.[60] The prevalence of skin pigmentation with chlorpromazine in chronic, hospitalised patients is reported as 1.0–2.9%.[61]

## CONCLUSION

There are significant psychosocial issues in dermatological conditions. Dermatologists are expected to consider quality of life issues along with social aspects, nature of disorder, efficacy, and tolerability of various therapeutic options to optimise the relief and comfort of their patients.[62] There is a high prevalence of psychiatric disorders in patients attending dermatology clinics. Somatisation symptoms occur in dermatology patients, but pure disorders, without other comorbid psychiatric disorders, are rather infrequent. Understandably, persons with cutaneous somatic or bodily symptoms would approach a dermatologist first. Addressing the psychosocial issues is critical in the management and improvement of the quality of life for patients.[63] Here are a few suggestions to achieve this:

- Dermatologists should enquire about psychological distress in the patients.
- Dermatologists should be aware of the psychological issues in common skin diseases.
- Minimum psychiatry training should be given during post-graduate training of dermatologists.
- Good referral systems between dermatology and psychiatry are necessary.
- Both psychiatrist and dermatologist should work together in collaboration, at least in difficult cases.

## REFERENCES


1. Verhoeven EWM et al. Skin diseases in family medicine: Prevalence and health care use. Ann Fam Med. 2008;6(4): 349-54.

2. Picardi A et al. Psychiatric morbidity in dermatological outpatients: An issue to be recognized. Br J Dermatol. 2000; 143(5):983-91.

3. Kim JE et al. Expression of hypothalamic-pituitary-adrenal axis in common skin diseases: Evidence of its association with stress-related disease activity. Acta Derm Venereol.

2013;93(4):387-93.

4. Zbytek B et al. Corticotropin-releasing hormone triggers differentiation in HaCaT keratinocytes. Br J Dermatol. 2005;152(3):474-80.

5. Theoharides TC et al. Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects. Endocrinology. 1998;139(1):403-13.

6. Park HJ et al. Adrenocorticotropin hormone stimulates interleukin-18 expression in human HaCaT keratinocytes. J Invest Dermatol. 2007; 127(5):1210-6.

7. Sanders VM et al. Differential expression of the beta2-adrenergic receptor by Th1 and Th2 clones: Implications for cytokine production and B cell help. J Immunol. 1997;158(9): 4200-10.

8. Gillbro JM et al. Autocrine catecholamine biosynthesis and the beta-adrenoceptor signal promote pigmentation in human epidermal melanocytes. J Invest Dermatol. 2004; 123(2):346-53.

9. Marshall JS et al. Nerve growth factor modifies the expression of inflammatory cytokines by mast cells via a prostanoid-dependent mechanism. J Immunol. 1999; 162(7):4271-6.

10. Cole-King A, Harding KG. Psychological factors and delayed healing in chronic wounds. Psychosom Med. 2001;63(2):216-20.

11. Ebrecht M. et al. Perceived stress and cortisol levels predict speed of wound healing in healthy male adults. Psychoneuroendocrinology. 2004;29(6): 798-809.

12. James WD. Clinical practice. Acne. N Engl J Med. 2005;352(14):1463-72.

13. Sulzberger MB, Zaidens SH. Psychogenic factors in dermatologic disorders. Med Clin North Am. 1948; 32:669-85.

14. Cunliffe WJ. Acne and unemployment. Br J Dermatol. 1986;115(3):386.

15. Durai PCT, Nair DG. Acne vulgaris and quality of life among young adults in south India. Indian J Dermatol. 2015; 60(1):33-40.

16. Golchai J et al. Comparison of anxiety and depression in patients with acne vulgaris and healthy individuals. Indian J Dermatol. 2010;55(4):352-4.

17. Cotterill JA, Cunliffe WJ. Suicide in dermatological patients. Br J Dermatol. 1997;137(2):246-50.

18. Parisi R et al. Global epidemiology of psoriasis: A systematic review of incidence and prevalence. J Invest Dermatol. 2013;133(2):377-85.

19. Julian CG. Dermatology in general practice. Br J Dermatol. 1999;141(3): 518-20.

20. Barankin B, DeKoven J. Psychosocial effect of common skin diseases. Can Fam Physician. 2002;48:712-6.

21. Rieder E, Tausk F. Psoriasis, a model of dermatologic psychosomatic disease: Psychiatric implications and treatments. Int J Dermatol. 2012;51(1):12-26.

22. Shutty BG et al. Sleep disturbances in psoriasis. Dermatol Online J. 2013;19(1):1.

23. Sarkar S et al. Psoriasis and psychiatric morbidity: a profile from a tertiary care centre of eastern India. J Family Med Prim Care. 2014;3(1):29-32.

24. Singh SM et al. Psychiatric morbidity in patients with psoriasis. Cutis. 2016; 97(2):107-12.

25. Connor CJ et al. Exploring the physiological link between psoriasis and mood disorders. Dermatol Res Pract. 2015;2015:409637.

26. Fennessy M et al. The epidemiology and experience of atopic eczema during childhood: A discussion paper on the implications of current knowledge for health care, public health policy and research. J Epidemiol Community Health. 2000;54(8):581-9.

27. Chamlin SL et al. Effects of atopic dermatitis on young American children and their families. Pediatrics. 2004; 114(3):607-11.

28. Daud LR et al. Psychosocial adjustment in preschool children with atopic eczema. Arch Dis Child. 1993; 69(6):670-6.

29. Yaghmaie P et al. Mental health comorbidity in atopic dermatitis. J Allergy Clin Immunol. 2013;131(2):428-33.

30. Kaur H, Van Brakel W. Dehabilitation of leprosy-affected people–a study on leprosy-affected beggars. Lepr Rev. 2002;73(4):346-55.

31. Vyas GK et al. A sociological study of leprosy cases in the Gandhi Kusth Ashram, Jodhpur (Rajasthan). Lepr India. 1982;54(2):324-31.

32. Attama C et al. Psychiatric morbidity among subjects with leprosy and albinism in south east Nigeria: A Comparative Study. Ann Med Health Sci Res. 2015; 5(3): 197-204.

33. Singh GP. Psychosocial aspects of Hansen's disease (leprosy). Indian Dermatol Online J. 2012; 3(3): 166-70.

34. Jindal KC et al. Psychiatric morbidity among inmates of leprosy homes. Indian J Psychol Med. 2013;35(4): 335-340.

35. Christenson GA et al. Estimated lifetime prevalence of trichotillomania in college students. J Clin Psychiatry. 1991; 52(10):415-7.

36. O'Sullivan RL et al. Trichotillomania: behavioral symptom or clinical syndrome? Am. J. Psychiatry. 1997; 154(10):1442-9.

37. Wong JW et al. Primary psychiatric conditions: Dermatitis artefacta, trichotillomania and neurotic excoriations. Indian J Dermatol. 2013; 58(1):44-8.

38. Sah DE et al. Trichotillomania. Dermatol Ther. 2008;21(1):13-21.

39. Grant JE et al. N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: A double-blind, placebo-controlled study. Arch Gen Psychiatry. 2009;66(7):756-63.

40. Ko SM. Under-diagnosed psychiatric syndrome. II: Pathologic skin picking. Ann Acad Med Singapore. 1999;28(4): 557-9.

41. Heller MM, Koo JYM. Contemporary diagnosis and management in psychodermatology® 2011. Pennsylvania, USA: Handbooks in Health Care Co.

42. Zaidens SH. Self-inflicted dermatoses and their psychodynamics. J Nerv Ment Dis. 1951;113(5):395-404.

43. Biondi M et al. Paroxetine in a case of psychogenic pruritus and neurotic excoriations. Psychother Psychosom. 2000;69(3):165-6.

44. Otto MW et al. Prevalence of body dysmorphic disorder in a community sample of women. Am J Psychiatry. 2001; 158(12):2061-3.

45. Mavrogiorgou P et al. Obsessive-compulsive disorder in dermatology. J Dtsch Dermatol Ges. 2015;13(10):991-9.

46. Mufaddel A et al. A review of body dysmorphic disorder and its presentation in different clinical settings. Prim Care Companion CNS Disord. 2013;15(4). pii:PCC.12r01464.

47. Kestenbaum T. Obsessive-compulsive disorder in dermatology. Semin Cutan Med Surg. 2013;32(2):83-7.

48. American Psychiatric Association, "Obsessive-compulsive and related disorders," American Psychiatric Association (eds.), Diagnostic and statistical manual of mental disorders (2013) 5th edition, Arlington: American Psychiatric Publishing.

49. Vythilingum B, Stein DJ. Obsessive-compulsive disorders and dermatologic disease. Dermatol Clin. 2005;23(4): 675-80.

50. Bewley AP et al. Delusional parasitosis: time to call it delusional infestation. Br J Dermatol. 2010;163(1):1-2. Erratum in: Br J Dermatol. 2010; 163(4):899.

51. Wykoff RF. Delusions of parasitosis: a review. Rev Infect Dis. 1987;9(3):433-7.

52. Freudenmann RW, Lepping P. Delusional infestation. Clin Microbiol Rev. 2009;22(4):690–732.

53. Yeung CK, Chan HH. Cutaneous adverse effects of lithium: epidemiology and management. Am J Clin Dermatol. 2004;5(1):3-8.

54. Evans DL, Martin W. Lithium carbonate and psoriasis. Am J Psychiatry. 1979;136(10):1326-7.

55. Parveen S, Javed MA. Stevens Johnson syndrome associated with lamotrigine. Pak J Med Sci. 2013;29(6):1450-2.

56. Herstowska M et al. Severe skin complications in patients treated with antidepressants: a literature review. Postepy Dermatol Alergol. 2014;31(2): 92-7.

57. Bodokh I et al. [Lyell syndrome or toxic epidermal necrolysis and Stevens-Johnson syndrome after treatment with fluoxetine]. Therapie. 1992;47(5):441. (In French).

58. Jan V et al. Stevens-Johnson syndrome after sertraline. Acta Derm Venereol. 1999;79(5):401.

59. Warnock JK, Morris DW. Adverse cutaneous reactions to antipsychotics. Am J Clin Dermatol. 2002;3(9):629-36.

60. Greiner AC, Berry K. Skin pigmentation and corneal and lens opacities with prolonged chlorpromazine therapy. Can Med Assoc J. 1964;90:663-5.

61. Ban TA et al. Neuroleptic-induced skin pigmentation in chronic hospitalized schizophrenic patients. Can J Psychiatry. 1985;30(6):406-8.

62. Chaturvedi SK et al. Stigma experience in skin disorders: An Indian perspective. Dermatol Clin. 2005;23(4):635-42.

63. Connor CJ. Management of the psychological comorbidities of dermatological conditions: Practitioners' guidelines. Clin Cosmet Investig Dermatol. 2017;10:117-32.

# HIDRADENITIS SUPPURATIVA: A RETROSPECTIVE REVIEW OF 13 PATIENTS AND LITERATURE SUMMARY

**Reneeka Persaud,[1] James A. Elliott,[1] Laurie Goodman,[2] Ranjani Somayaji,[3] Morgan Lim,[4,5] *R. Gary Sibbald[1,5-7]**

*1. Toronto Regional Wound Healing Clinic, Mississauga, Canada*
*2. Humber River Hospital, Toronto, Canada*
*3. Cumming School of Medicine, University of Calgary, Calgary, Canada*
*4. Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada*
*5. Trillium Health Partners, Mississauga, Canada*
*6. Dalla Lana Faculty of Public Health, University of Toronto, Toronto, Canada*
*7. Women's College Hospital, Wound Healing Clinic, Division of Dermatology, Department of Medicine, Toronto, Canada*
**Correspondence to rgarysibbald@gmail.com*

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## ABSTRACT

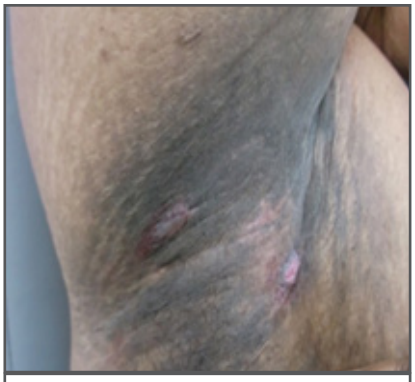
Hidradenitis suppurativa (HS) is an inflammatory skin condition of the follicular pilosebaceous unit that primarily affects flexural areas where apocrine glands are found. This disorder can present as either an acute or chronic disease, with a single subcutaneous nodule or clusters of painful abscesses with purulent drainage in one or more of the following sites: axilla, groin, genital, perianal (more common in males), and under the breasts (more common in females). Over time patients form sinus tracts, fibrosis, and scarring. The onset usually occurs in the early 20s, after puberty. HS can be present for years without being diagnosed and is associated with a diminished quality of life, high morbidity, and substantial healthcare costs. Global HS prevalence is estimated at 1%.

This article reviews a retrospective cohort study of 13 patients assessed by an interprofessional wound care team and discusses relevant literature. Accuracy of referral diagnosis was the primary outcome. Secondary outcomes included demographics and quality of life. In total, 10 patients were female (77%) and the mean age was 33 years. Fewer than half (n=6, 46%) had an accurate diagnosis of HS prior to team assessment. Of these patients, the mean time before a correct diagnosis was 4.2 years. Untreated bacterial damage was diagnosed in the majority of patients (n=9, 69%). There was substantial improvement in pain levels and quality of life in approximately half of the cases. Over time, patients became more actively involved in their care. Our findings show HS diagnosis and management is optimised with an interprofessional team approach.

Keywords: Hidradenitis suppurativa (HS), inflammation, wound care, chronic disease, dermatology.

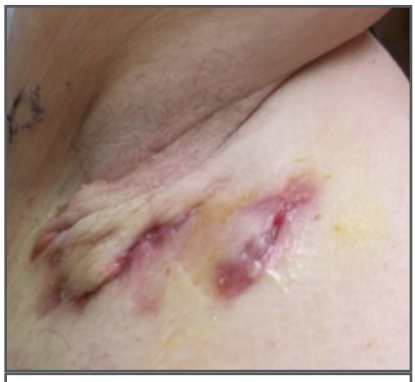
## INTRODUCTION

Hidradenitis suppurativa (HS) is an inflammatory condition that affects the follicular pilosebaceous unit, especially where apocrine glands are found. The axilla, groin, buttocks, genital, inframammary (especially females), and perianal regions (especially males) are primarily affected.[1] HS usually presents as subcutaneous nodules that become painful abscesses with purulent drainage, followed by the formation of sinus tracts, fibrosis, and scarring.[2] Clinical manifestations are classified using the Hurley stages to direct treatment modalities.[3] Severity is graded by a variety of different scoring systems, including the Sartorius score to monitor effectiveness of interventions in clinical trials (Figure 1).[4,5]



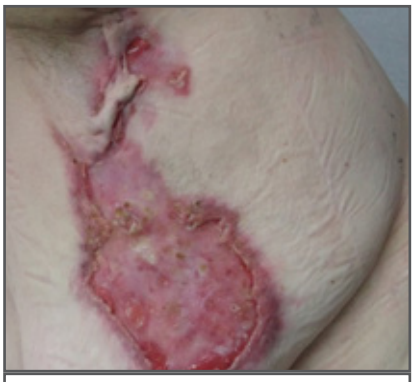
**Stage 1**

Abscess formation, single or multiple, without sinus tracts and scarring



**Stage 2**

Single or multiple, widely separated, recurrent abscesses with tract formation and scarring



**Stage 3**

Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area

| Sartorius score | Description |
|---|---|
| Anatomical region involved | Axilla, groin, gluteal, or other region, or inframammary region left and/or right: 3 points per region involved |
| Number and lesion scores | Abscesses, nodules, fistulas, scars: points per lesion of all regions involved: nodules: 2, fistulas: 4, scars: 1, others: 1 |
| Longest distance between two relevant lesions | For example, between nodules and fistulas in each region, or size if only one lesion: <5 cm: 2, <10 cm: 4, >10 cm: 8 |
| Are all lesions clearly separated by normal skin? | In each region: yes: 0, no: 6 |

**Figure 1: Hurley stages and Sartorius score.**

## PATHOGENESIS, PREVALENCE, AND RISK FACTORS

The pathogenesis of HS is thought to be multifactorial.[6,7] Follicular occlusion and hyperkeratosis are considered the principal initiating causes.[8] The disease has a diverse histological spectrum including: pore occlusion, sinus tracts, epithelial cysts, pyogenic granulomas, and scarring.[9] HS is part of the follicular occlusion tetrad of diseases, along with acne conglobata, dissecting cellulitis of the scalp, and pilonidal sinus disease.[7,9,10] The acute nodules and abscesses of HS usually start in the early 20s after puberty.[2,11,12] The global prevalence of HS is estimated at 1%.[2,13-16] A Canadian population-based survey of 10,200 people calculated the HS prevalence at 3.8%, with an annual incidence of approximately 30 new cases per 10,000 population over a 1-year period.[17] Females are more commonly affected, with a female-to-male sex ratio of approximately 3:1.[14,15,18]

There are strong associations of HS with smoking, high BMI, family history, Type 2 diabetes mellitus, and thyroid disease.[19] Various hormonal and immunological factors such as tumour necrosis factor (TNF) and the interleukin-23/T helper 17 pathway (IL-23/Th17) are involved, although the exact pathogenesis is unclear.[19,20] Smoking is a particularly strong HS risk factor and increases the chance of symptomatic onset and greater severity. The percentage of active or previous smokers with HS has been recorded as ranging from 50–90%.[21-23] A German matched case control study found that current smokers had a 9.4-times greater chance of HS compared to non-smokers or ex-smokers.[22] A greater prevalence and severity of HS have also been reported in patients with high BMIs.[5,21,24,25] Revuz et al.[14] concluded that the relative HS risk increases by 12% for every unit increase of BMI>25. Another retrospective chart review study found 50.6% of patients with HS had metabolic syndrome compared with 30.2% in a matched control group without metabolic syndrome.[25] Familial inheritance of HS is probably autosomal dominant with variable penetrance and expressivity. Approximately one-third of HS patients have a positive family history of HS,[12,26] and this is often associated with an early onset.[18,27,28] HS impacts patients' quality of life in many ways including pain, exudative wounds, odour, shame, embarrassment, and restricted movement.[29-33]

**Table 1: Practice tips for managing hidradenitis suppurativa.**

| |
|---|
| **GENERAL MEASURES** |
| Diagnose and treat comorbidities: diabetes, Crohn's disease, thyroid disease, pilonidal cysts, acne, PCOS |
| Address lifestyle modification factors: smoking cessation, weight loss, avoiding trauma and friction |
| Treat pain appropriately: NSAIDS, opiates |
| Offer psychosocial support |
| Encourage self-care measures: personal hygiene, cleansing |
| Promote optimal local wound care |
| **ANTIMICROBIALS** |
| ***Superficial/localised infection*** |
| **Topical antiseptics** |
| PHMB, povidone iodine 10%, clindamycin lotion, benzoyl peroxide plus clindamycin gel |
| ***Deep and surrounding infection*** |
| **Systemic anti-inflammatory antimicrobials** |
| Tetracyclines 500 mg–2 g daily |
| Doxycycline 100–200 mg daily |
| Clindamycin 300 mg qid +/- rifampicin 600 mg daily |
| **RETINOIDS** |
| Acitretin 10–25 mg daily with supper |
| **IMMUNOSUPPRESSANTS** |
| Cyclosporin A 2–6 mg/kg daily |
| Azothioprine 50–150 mg daily |
| **ANTIANDROGENS** |
| **BIOLOGICS** |
| Adalimumab, infliximab, anti-interleukin-1 inhibitors |
| **INTRALESIONAL STEROIDS** |
| Intralesional triamcinolone acetonide 5–10 mg/mL |
| **SYSTEMIC CORTICOSTEROIDS** |
| Oral prednisolone 0.5–0.7 mg/kg |
| **SURGICAL INTERVENTIONS** |
| Local debridement and curettage |
| Deroofing and removal of amorphous material at the base |
| Incision and drainage |
| Excision: local or wide |
| **THERAPIES** |
| Laser therapy |
| Carbon dioxide laser therapy |
| Photodynamic therapy |

PCOS: polycystic ovary syndrome; PHMB: polyhexamethylene biguanide; NSAIDS: non-steroidal anti-inflammatory drugs; QID: four-times daily.

## DIAGNOSTIC AND TREATMENT CHALLENGES

Early diagnosis and treatment is challenging for clinicians due to the variety of phenotypes, complexity of HS, and lack of randomised controlled trials to guide treatment. A cross-sectional study of 80 Canadian patients with HS documented a 5-year average delay between presentation and diagnosis with some patients living undiagnosed for ≤25 years.[31] This long delay between presentation to diagnosis and subsequent treatment increases associated healthcare utilisation costs, including emergency department visits, outpatient care visits, and diagnostic tests.[29,34,35]

Topical and systemic pharmacological treatments are recommended, including antimicrobials, intralesional corticosteroids, biologics, and, occasionally, anti-androgens.[34,36,37] Anti-inflammatory

antimicrobials, including tetracyclines and clindamycin, have been proven effective.[38-40] Topical or systemic clindamycin or oral tetracycline (including doxycycline and minocycline) are effective for mild disease.[5,41] Second-line therapies include: clindamycin with rifampin, oral retinoids (acitretin is more effective than 13-cis-retinoic acid), and intralesional steroids.[34,39,41] For more severe cases biologics (TNF inhibitors including adalimumab and infliximab [review] and immunosuppressant agent azathioprine) are used.[34] A Cochrane review of 12 randomised controlled trials (615 participants) reported there is moderate evidence of adalimumab and infliximab improving Dermatology Life Quality Index (DLQI) scores.[42] There is also improved quality of life with the biologics.[43] Deep and surrounding infection should be ruled out for any patient with HS receiving biological agents.

Surgical treatment should be assessed early depending on disease severity, anatomical location, and degree of scarring.[41,44,45] Surgical methods include local destruction (cryotherapy, incision and drainage, punch debridement [with curettage], unroofing/deroofing including removal of amorphous debris in the base or else recurrences are common), and local or extensive excision.[34,45]

HS recurrence rates are influenced by many factors, including lifestyle, particularly smoking and obesity, disease severity, anatomical location, local wound care, and treatment. A systematic review and meta-analysis of 22 articles concluded that excisional surgery is the best treatment of severe but localised forms of HS with lower recurrence rates.[46] Local excision with primary closure is associated with higher recurrence rates.[45] Mandal and Watson[47] reported a 69.9% recurrence rate after first surgical intervention with primary closure and low recurrence rates with wide excision and healing by secondary intention. Overall, the literature suggests a comprehensive management plan for HS lesions includes addressing general measures, appropriate use of topical and systemic antimicrobials combined with optimal local wound care, surgical debridement, and intralesional steroid injections (Table 1).[34]

## INTERPROFESSIONAL APPROACH AND WOUND BED PREPARATION

An interprofessional approach, coupled with patient and clinician-directed educational interventions, is crucial for optimal management of HS and its complications.[30,31,35] The Wound Bed Preparation paradigm is a comprehensive, systematic approach to patient management that addresses three main principles: treating the cause, patient-centred concerns, and local skin/wound care.[48] Treating the cause and addressing patient-centred concerns are important to determine if there can be complete resolution of the lesions (healing ability). Wound and skin care can be determined as healable (often with definitive excisional surgery), non-healable (e.g. patient is a heavy smoker, obese, and/or not adherent to treatment), or maintenance (acute or subacute episodes that can be controlled). For local wound care, debridement, infection, and moisture balance must be addressed. The validated NERDS and STONEES criteria can be utilised to diagnose localised (superficial) or deep-surrounding infection.[48,49] Patient-centred concerns commonly include pain and body image issues and should be addressed to ensure patient adherence to treatment. An interprofessional team that follows this paradigm can manage patients with HS in a holistic manner.

## METHODS

### Literature Review

The Cochrane Library, University of York Centre for Reviews and Dissemination database, and PubMed (Medline) databases were reviewed. The MeSH term 'hidradenitis suppurativa' was used in combination with the keywords 'co-morbidities', 'chronic disease', 'wound care', and 'dermatology'. No limit was placed on the publication year and only English language articles were used based on reviewer judgement.

### Study Design, Data Abstraction, and Analysis

A retrospective cohort study of 318 patients with complex and unresolved chronic wounds who were referred between February 2013 and September 2014 to an interprofessional team (Toronto Regional Wound Healing Clinic, Ontario, Canada). The team consisted of an internist/dermatologist physician with expertise in wound care (Dr Sibbald) and three nurses with extensive wound care proficiency. The team had strong communication with primary care physicians and family health teams with referral links to plastic and general surgery, infectious disease specialists, social workers, and certified diabetes educators. Initial comprehensive assessments were approximately 2 hours; follow-up assessments were approximately 30 minutes.

A case report form (CRF) was used to abstract data from paper charts. The CRF was collectively

formulated and pilot tested by the study team. Data were abstracted by a physician (Dr Persaud) and information from the CRF was entered into an SPSS® (Version 23 IBM®) electronic database for analysis. Validation was performed by comparing a random sampling of 10% (n=30) of SPSS case entries against the original paper charts. No discrepancies were found.

### Inclusion Criteria

This review was solely from the 13 patients who had a diagnosis of HS after their initial comprehensive interprofessional assessments (CIA). The diagnosis of HS was based on patient history and clinical presentation. The Trillium Health Partners Research Ethics Board (REB) ID 635 approved this study.

## RESULTS

### Diagnosis, Demographics, Duration, and Comorbidities

HS was diagnosed in 13 (4.1%) of the 318 referred patients with complex wounds. Less than half (n=9, 46%) had a correct diagnosis of HS at time of referral. For those who did not have a prior HS diagnosis (n=7, 54%), the mean time from onset of symptoms to diagnosis was 220 weeks (4.2 years). Patients were predominately female (n=10, 77%; sex ratio ˜3:1), the mean patient age was 33 years, and mean patient BMI was 31.8 (obese). Two-thirds of patients were current or past smokers (n=8, 67%), well above the average smoking rates for Canada. Mean age at HS onset was 22 years (range: 10–40 years). Comorbidities present were diabetes, hypertension, dyslipidaemia, and polycystic ovarian syndrome; all n=2 (15%). There was an almost even distribution between patients presenting as Hurley Stage 1 (n=6, 46%) and Hurley Stage 2 (n=7, 54%). Over two-thirds of patients (n=9, 69%) had a previous surgical intervention related to their clinical presentation.

### Treatment Before and After Comprehensive Interprofessional Assessment

The average number of nursing visits was 3.7 per week (ranging from 0–8 per week). Enterostomal therapists were the most common referring professional (n=7, 54%). The cohort's ability to heal was unknown for 6 patients (46%), but subsequently increased to 100% after the comprehensive CIA.[48]

**Table 2: Results of a retrospective chart review.**

| Parameters | n | % | Parameters | n | % |
|---|---|---|---|---|---|
| **Sex** | | | **Prior HS related surgery** | | |
| Female | 10 | 77 | Yes | 9 | 69 |
| Male | 3 | 23 | No | 4 | 31 |
| **BMI** | | | **Age of disease onset** | | |
| Normal 18.5–24.9 | 1 | 8 | 10–19 years | 7 | 58 |
| Overweight 25.0–29.9 | 6 | 50 | 20–29 years | 2 | 17 |
| Obese ≥30.0 | 5 | 42 | 30–39 years | 3 | 25 |
| **Smoking status** | | | **Location of lesions** | | |
| Current | 6 | 50 | Axilla | 7 | 54 |
| Past | 2 | 17 | Groin | 6 | 46 |
| Never | 4 | 33 | | | |
| **Time of HS diagnosis** | | | **Hurley Stage** | | |
| Before referral | 6 | 46 | 1 | 6 | 46 |
| At team assessment | 7 | 54 | 2 | 7 | 54 |
| **Disease duration at first visit** | | | **Ability to heal at first CIA** | | |
| 0–2 years | 4 | 33.3 | Healable | 12 | 92 |
| 3–5 years | 4 | 33.3 | Maintenance | 1 | 8 |
| 5–12 years | 3 | 25 | | | |
| >12 years | 1 | 8.3 | | | |

HS: hidradenitis suppurativa; CIA: comprehensive interprofessional assessment.

The mean length of time supervised by the team was 10.6 weeks with an average of three CIA during the study period. Wound cultures were carried out for 100% of cases and results received for 85%. Out of the swabs received the following isolates were found: *Pseudomonas aeruginosa*: 8% (n=1), *Proteus mirabilis*: 15% (n=2) mixed gram negative bacteria: 8% (n=1), Group B streptococcus: 8% (n=1), commensal flora: 46% (n=6). The swabs were taken at the first visit; the validated NERDS and STONEES tool was used to clinically identify the presence of infection and antibiotic therapy was prescribed accordingly (systemic antibiotics for deep and surrounding infection; topical antimicrobials for superficial infection). The majority of the cohort (n=9, 69%) had deep and surrounding tissue infection (≥3 NERDS and STONEES criteria). Antibiotics were prescribed for all patients (n=13) based on evidence practice (broad spectrum and anti-inflammatory antibiotics) to address both the infection and inflammatory components of HS. Cotrimoxazole, doxycycline, and metronidazole were the most commonly used antibiotics (n=7, 54%; n=6, 46%; and n=5, 38%, respectively). Most patients were given a combination antibiotic therapy (n=7, 54%). Topical clindamycin with benzoyl peroxide was most commonly used (n=11, 85%), followed by injection of intralesional steroids (n=6, 46%). Dressing regimen was changed at CIA for a majority of the cohort (n=9, 69%). Neither intravenous antibiotic therapy nor biologics were prescribed for the cohort. Most of the visits required acute minor surgical interventions (incision of abscesses and removal of amorphous material from the base or surface curette of sinuses). Other treatments used were: silver sulfadiazine cream, hydrogel, hexachlorophene detergent cleanser, foam with detergent, and silver action exudate absorptive fabric with silver (Table 2).

At the first comprehensive assessment 38% (n=5) were discharged from the clinic. At the 4-week follow-up visit 15% (n=2) had an increase in wound size, 23% (n=3) had a 30% decrease in wound size, and in 15% (n=2) the size could not be measured or was not measurable (in cases such as nodules or sinus tracts).

### Patient-Centred Concerns

Patient-centred concerns reported by the cohort included impairment of activities of daily living (n=7, 54%), body image compromise (n=6, 46%), and inability to participate in sports and exercise (n=2, 15%). Mean pain score on assessment was reported to be 3.4 out of 10 on the numeric pain scale. No specific tool was used to determine quality of life (general wellbeing, decreased pain levels, increased mobility, improved appetite) since their first visit. They were asked to report if their quality of life had improved, worsened, or was unchanged. Out of the 8 patients that had a second visit, 62% (n=5) reported an improvement in quality of life while 38% (n=3) reported it to be unchanged.

## DISCUSSION

The results from our cohort study are largely consistent with findings in the literature. The majority of patients were females (sex ratio ˜3:1) and most had experienced onset of symptoms in their early 20s. Smoking and obesity were also found to be consistently higher than the general population, supporting their role as HS risk factors.[19,21-25] Smoking cessation, dietitian, and exercise consultations were included in the treatment plan, as recommended by the European Guidelines for management of HS.[41] Other investigational tests were ordered to determine underlying or undiagnosed comorbidities (diabetes mellitus and Crohn's disease).[8,25,27,31,50] Diabetes mellitus was newly diagnosed for one patient of the cohort.

Less than half of the patients (n=6, 46%) had a diagnosis of HS prior to their referral for an interprofessional assessment. Self-reported data from the cohort revealed that these patients had numerous prior surgical interventions, had previously been on multiple short doses of antibiotics, had high pain scores, and required frequent medical attention. This translates to higher healthcare costs as shown in a 2014 North American study that identified the major cost for patients with HS was inpatient costs and more frequent emergency department visits.[33,35] The mean time from onset of symptoms to diagnosis was 4.2 years, ranging from 1–7 years, which is in line with findings from other studies.[11,31,34] The total length of time with HS ranged from 3–10 years, consistent with the chronic forms of this condition. Patients within the cohort had been diagnosed with either Hurley Stage 1 or 2 by the interprofessional team, therefore these results do not accurately represent the distribution of Hurley Stage 3. This could be attributed to the fact that this clinic serves a specific geographical

area of the general population of patients on homecare. These patients were primarily treated for abscesses, chronic wounds, and other diagnoses with the primary diagnosis of HS being missed. In addition, those patients that were accurately diagnosed with Hurley Stage 3 at the primary care level were probably being followed by general and plastic surgeons and not referred to the clinic.

Bacterial damage was not accurately identified at the community level when compared to the interprofessional assessment. The majority of the cohort was diagnosed with deep and surrounding infection utilising a validated tool by the interprofessional team.[49] Secondary infection is not common in HS in general. However, in this population, the majority of patients in the cohort had chronic wounds, were undiagnosed with HS, and were not treated appropriately for infection or optimally for the inflammatory component of HS at the time of consultation. All patients were treated with systemic antibiotics: mainly combination therapy to address both the inflammatory and infection components of HS.[34,37,41,44] Biologics were not required in this patient population, but after treating deep and surrounding infection and optimising local wound care, if deep inflammation persists, patients may benefit from adalimumab or other TNF inhibitors. Surgical management was introduced to the majority of patients prior to referral. Some clinicians favour local surgery for Hurley Stage 2 patients and more extensive surgery for Hurley Stage 3 disease, which should be introduced early in treatment, as outlined in the European Guidelines by Zouboulis et al.[5,41]

A larger proportion reported that their day-to-day activities were affected, mainly due to decreased mobility and pain, followed by embarrassment and body image issues. These findings are also consistent with the literature[29,30,32,50] and a Canadian study that identified a profound effect on patients' lives (DLQI score of 10±8.8), which is higher than for any other comparative chronic dermatological disorder.[33] At the first follow-up interprofessional assessment after adequate pain management,[51] the mean pain score was decreased by >50%.

The interprofessional assessment of these patients allowed for improvements in wound parameters and management. After the first interprofessional assessment, 38% of the patients were discharged from the study and followed-up by a dermatologist. Approximately one-third of the patients (38%) had complete wound closure by the end of the study period.

Utilising the concept of the wound bed preparation paradigm, treating the underlying cause including bacterial damage and persistent inflammation, addressing patient-centred concerns, and appropriate local wound care were the key management strategies to achieve better outcomes.[48]

## STUDY LIMITATIONS

Study limitations include the small sample size, selection bias, and short follow-up time with difficulties in determining remissions and morbidity.

## CONCLUSION

This study corroborates most recorded literature findings. Our cohort was predominantly female, disease onset was typically in the mid-20s, and had a high impact on activities of daily living with a delay in diagnosis. This study was conducted on a difficult-to-treat Canadian population not responding to usual treatment and highlights the difficulty of diagnosing HS early. The effectiveness of an interprofessional team approach, leading to earlier HS diagnosis when compared to standard community care was demonstrated. Key strategies to consider are developing the expertise and diagnostic acumen of primary care physicians and other community providers for persons with HS. A co-ordinated process of care with primary care physicians and interprofessional teams or HS centres of excellence may decrease healthcare costs and improve other health indicators.

## REFERENCES


1. Kurzen H et al. What causes hidradenitis suppurativa? Exp Dermatol. 2008;17(5): 455-6.

2. Alikhan A et al. Hidradenitis suppurativa: A comprehensive review. J Am Acad Dermatol. 2009;60(4):539-61.

3. Hurley H, "Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa, and familial benign pemphigus: surgical approach", Roenigk RK, Roenigk HH, (Eds.), Dermatological Surgery (1988), New York: Marcel Dekker, pp. 729-39.

4. Sartorius K et al. Suggestions for uniform outcome variables when reporting treatment effects in hidradenitis suppurativa. Br J Dermatol. 2003;149(1):211-3.

5. Zouboulis CC et al. European S1 guideline for the treatment of

hidradenitis suppurativa/acne inversa. J Eur Acad Dermatol Venereol. 2015; 29(4):619-44.

6. van der Zee HH et al. Hidradenitis suppurativa: viewpoint on clinical phenotyping, pathogenesis and novel treatments. Exp Dermatol. 2012;21(10): 735-9.

7. Scheinfeld N. Hidradenitis suppurativa: A practical review of possible medical treatments based on over 350 hidradenitis patients. 2013;19(4):1.

8. Scheinfeld N. Diseases associated with hidranitis suppurativa: part 2 of a series on hidradenitis. Dermatol Online J. 2013; 19(6):18558.

9. Jemec GB, Hansen U. Histology of hidradenitis suppurativa. J Am Acad Dermatol. 1996;34(6):994-9.

10. Vasanth V, Chandrashekar BS. Follicular occlusion tetrad. Indian Dermatol Online J. 2014;5(4):491-3.

11. Wang SC et al. Hidradenitis Suppurativa: A Frequently Missed Diagnosis, Part 1: A Review of Pathogenesis, Associations, and Clinical Features. Adv Skin Wound Care. 2015; 28(7):325-32.

12. von der Werth JM, Williams HC. The natural history of hidradenitis suppurativa. J Eur Acad Dermatol Venereol. 2000;14(5):389-92.

13. Canoui-Poitrine F et al. Identification of three hidradenitis suppurativa phenotypes: latent class analysis of a cross-sectional study. J Invest Dermatol. 2013;133(6):1506-11.

14. Revuz JE et al. Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. J Am Acad Dermatol. 2008;59(4):596-601.

15. Jemec GB et al. The prevalence of hidradenitis suppurativa and its potential precursor lesions. J Am Acad Dermatol. 1996;35(2 Pt 1):191-4.

16. Shahi V et al. Prevalence of hidradenitis suppurativa: a population-based study in Olmsted County, Minnesota. Dermatology. 2014;229(2): 154-8.

17. Lachaine J et al. The Prevalence And Incidence Of Hidradenitis Suppurativa In Canada: Results From A Population-Based Survey. Value Health. 2016; 19(3):A123.

18. Canoui-Poitrine F et al. Clinical characteristics of a series of 302 French patients with hidradenitis suppurativa, with an analysis of factors associated with disease severity. J Am Acad Dermatol. 2009;61(1):51-7.

19. Prens E, Deckers I. Pathophysiology of hidradenitis suppurativa: An update. J Am Acad Dermatol. 2015;73(5 Suppl 1): S8-11.

20. Schlapbach C et al. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. J Am Acad Dermatol. 2011;65(4):790-8.

21. Vlassova NH. Emerging trends in hidradenitis suppurativa: A clinical case series. J Am Acad Dermatol. 2012; 66(4):AB51.

22. König A et al. Cigarette smoking as a triggering factor of hidradenitis suppurativa. Dermatology. 1999;198(3): 261-4.

23. Kromann CB et al. The influence of body weight on the prevalence and severity of hidradenitis suppurativa. Acta Derm Venereol. 2014;94(5):553-7.

24. Sartorius K et al. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. Br J Dermatol. 2009;161(4):831-9.

25. Gold DA et al. The prevalence of metabolic syndrome in patients with hidradenitis suppurativa. J Am Acad Dermatol. 2014;70(4):699-703.

26. Al-Ali FMS et al. Hidradenitis suppurativa (or Acne inversa) with autosomal dominant inheritance is not linked to chromosome 1p21.1-1q25.3 region. Exp Dermatol. 2010;19(9):851-3.

27. Schrader AMR et al. Hidradenitis suppurativa: A retrospective study of 846 Dutch patients to identify factors associated with disease severity. J Am Acad Dermatol. 2014;71(3):460-7.

28. Deckers IE et al. Correlation of early-onset hidradenitis suppurativa with stronger genetic susceptibility and more widespread involvement. J Am Acad Dermatol. 2015;72(3):485-8.

29. Lachaine J et al. Resource Utilization and Quality of Life of Patients with Hidradenitis Suppurativa in Canada: Results from a Population-Based Survey. Value Health. 2016;19(3):A125.

30. Matusiak Ł et al. Hidradenitis suppurativa markedly decreases quality of life and professional activity. J Am Acad Dermatol. 2010;62(4):706-8.

31. Kim WB et al. Clinical Features and Patient Outcomes of Hidradenitis Suppurativa: A Cross-Sectional Retrospective Study. J Cutan Med Surg. 2016;20(1):52-7.

32. Gooderham M, Papp K. The psychosocial impact of hidradenitis suppurativa. J Am Acad Dermatol. 2015;73(5 Suppl 1):S19-22.

33. Alavi A et al. Quality-of-life impairment in patients with hidradenitis suppurativa: a Canadian study. Am J Clin Dermatol. 2015;16(1):61-5.

34. Wang SC et al. Hidradenitis Suppurativa: A Frequently Missed Diagnosis, Part 2: Treatment Options. Adv Skin Wound Care. 2015;28(8):372-80.

35. Kirby JS et al. Health care utilization patterns and costs for patients with hidradenitis suppurativa. JAMA Dermatol. 2014;150(9):937-44.

36. Alhusayen R, Shear NH. Scientific evidence for the use of current traditional systemic therapies in patients with hidradenitis suppurativa. J Am Acad Dermatol. 2015;73(5 Suppl 1):S42-6.

37. Rambhatla PV et al. A systematic review of treatments for hidradenitis suppurativa. Arch Dermatol. 2012;148(4): 439-46.

38. Jemec GB, Wendelboe P. Topical clindamycin versus systemic tetracycline in the treatment of hidradenitis suppurativa. J Am Acad Dermatol. 1998; 39(6):971-4.

39. van der Zee HH et al. The effect of combined treatment with oral clindamycin and oral rifampicin in patients with hidradenitis suppurativa. Dermatology. 2009;219(2):143-7.

40. Bettoli V et al. Oral clindamycin and rifampicin in the treatment of hidradenitis suppurativa-acne inversa: a prospective study on 23 patients. J Eur Acad Dermatol Venereol. 2014;28(1): 125-6.

41. Gulliver W et al. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. Rev Endocr Metab Disord. 2016;17(3):343-51.

42. Ingram JR et al. Interventions for hidradenitis suppurativa: a Cochrane systematic review incorporating GRADE assessment of evidence quality. Br J Dermatol. 2016;174(5):970-8.

43. Ingram JR et al. Interventions for hidradenitis suppurativa. Cochrane Database Syst Rev. 2015;(10):CD010081.

44. Kohorst JJ et al. Treatment experience in a local population with hidradenitis suppurativa. J Drugs Dermatol. 2014;13(7): 827-31.

45. Danby FW et al. New and traditional surgical approaches to hidradenitis suppurativa. J Am Acad Dermatol. 2015; 73(5 Suppl 1):S62-5.

46. Mehdizadeh A et al. Recurrence of hidradenitis suppurativa after surgical management: A systematic review and meta-analysis. J Am Acad Dermatol. 2015; 73(5 Suppl 1):S70-7.

47. Mandal A, Watson J. Experience with different treatment modules in hidradenitis suppuritiva: a study of 106 cases. Surgeon. 2005;3(1):23-6.

48. Sibbald RG et al. Optimizing the Moisture Management Tightrope with Wound Bed Preparation 2015©. Adv Skin Wound Care. 2015;28(10):466-76.

49. Woo KY, Sibbald RG. A cross-sectional validation study of using NERDS and STONEES to assess bacterial burden. Ostomy Wound Manage. 2009;55(8): 40-8.

50. Dufour DN et al. Hidradenitis suppurativa: a common and burdensome, yet under-recognised, inflammatory skin disease. Postgrad Med J. 2014;90(1062): 216-21.

51. Horváth B et al. Pain management in patients with hidradenitis suppurativa. J Am Acad Dermatol. 2015;73(5 Suppl 1): S47-51.

# DERMOSCOPY OF INFLAMMATORY CONDITIONS: THE JOURNEY SO FAR

***Balachandra S. Ankad, Savitha L. Beergouder**

*Rajiv Gandhi University of Health Sciences, Bengaluru, India*
**Correspondence to drbsankad@gmail.com*

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## ABSTRACT

The use of dermoscopy in general dermatological practice has recently increased. Its non-invasive nature means it is being practiced frequently by dermatologists to diagnose various skin conditions. Dermoscopy, also known as dermatoscopy, allows dermatologists to quickly visualise skin structures up to the papillary dermis level. The skin patterns seen under dermoscopy are usually due to pigment and vascular structures; melanin and haemoglobin play major roles and give different patterns depending on the skin condition and pathological changes. Many inflammatory diseases are encountered by clinicians in daily practice; at times they are indistinguishable to the naked eye and a biopsy is required to confirm the diagnosis. Dermoscopy is a useful tool in the diagnosis and differentiation of inflammatory skin conditions and is aptly termed inflammoscopy when used in these situations. Inflammoscopy demonstrates the distinct characteristic patterns of many conditions and aids accurate diagnoses. In this article, the importance of dermoscopy in the diagnosis of relatively common inflammatory conditions, such as eczema, psoriasis, lichen planus, pityriasis rosea, pityriasis lichenoides et varioliformis acuta, pityriasis lichenoides chronica, and discoid lupus erythematosus, is highlighted. Here, an overview of dermoscopic patterns in each of these conditions is emphasised.

Keywords: Dermoscopy, inflammatory, psoriasis, lichen planus (LP), pityriasis rosea (PR), pattern, diagnosis.

## INTRODUCTION

Dermoscopy is a non-invasive diagnostic method that aids in the visualisation of surface and subsurface skin structures, leading to accurate diagnoses. In the past, it was used for pigmented lesions to differentiate melanoma from benign melanocytic lesions.[1] Recently, awareness and knowledge of dermoscopy have increased tremendously in many countries. Dermoscopy has expanded its applications not only to inflammatory but also to infectious conditions, with inflammoscopy being the term used for dermoscopic examination of inflammatory conditions.[2] Different names are given to dermoscopy based on the site as well as disease condition; trichoscopy is used for scalp and hair disorders, inflammoscopy for inflammatory conditions, and entomodermoscopy when infestation and infectious conditions are examined under dermoscopy.[3]

Dermoscopy demonstrates the characteristic and often specific patterns of a skin condition, enabling physicians to diagnose the skin disease accurately. All patterns visualised using dermoscopy depend on the location and distribution of melanin and haemoglobin pigment in the skin layers.[4] This paper emphasises the utility of dermoscopy in the diagnosis of inflammatory conditions. In this review, the dermoscopic patterns of psoriasis, lichen planus (LP), pityriasis rosea (PR), prurigo nodularis (PN), eczema, pityriasis lichenoides et varioliformis acuta (PLEVA), pityriasis lichenoides chronica (PLC), and discoid lupus erythematosus (DLE) are described and their importance is highlighted. In inflammoscopy, accurate diagnosis can be made by considering criteria such as scale, lesion colour, type of vessels, and vessel arrangement and background colour.[5]

## STUDY AND DATA SELECTION

Articles and chapters were screened in journals and textbooks, respectively, for information on dermoscopy of inflammatory conditions.

Both original and review articles were included. Articles describing the dermoscopic patterns of inflammatory skin conditions were selected. MEDLINE, PUBMED, and EMBASE were screened up to 2017.

## DISCUSSION

### The Basics of Dermoscopy

Normally, unaided eyes cannot visualise subsurface structures because incident light is reflected and some of this light gets absorbed. This is due to the differences in the refractive indices of the stratum corneum (1.55) and air (1.00), a phenomenon known as specular reflectance or glare. This is prevented by using an interface medium, which is applied onto the skin before a dermoscopic examination. Isopropyl alcohol, water, liquid paraffin, and ultrasound gel are all used as interface media fluids. This type of dermoscopy, wherein the dermoscope comes into contact with skin lesions, is known as non-polarised dermoscopy. Many authors state that contact with the skin surface results in nosocomial infections; this is avoided by using non-contact dermoscopy with polarised lights. The non-polarised method of dermoscopy assists in the recognition of superficial structures such as scales, milia-like cysts, and comedo-like openings, whereas the polarised mode helps in the visualisation of vessels and their arrangement, pigmentation, and dermal collagenous elements. Newer, hand-held dermoscopes have an inbuilt mode that changes from the polarised to the non-polarised technique with a click of a button. This is referred to as a blink sign.[4,6]

### Psoriasis

Psoriasis is a common, chronic, disfiguring, inflammatory, and proliferative condition of the skin, characterised by red, scaly, sharply demarcated, indurated plaques, present particularly over extensor surfaces and the scalp.[7] Lallas et al.[8] studied dermoscopy of psoriasis and described dotted or coiled (glomerular) vessels arranged regularly. Though dotted vessels can be seen in other inflammatory dermatosis, the uniformity and homogenous distribution is characteristic of psoriasis (Figure 1). In histopathology studies, the presence of red dots corresponds with the loops of vertically arranged vessels within the elongated dermal papillae.[8] Errichetti et al.[9] differentiated PLC from guttate psoriasis dermoscopically and stated that orange-yellow structureless areas and dotted and no-dotted vessels are characteristic in PLC, whereas diffuse dotted vessels are specific to psoriasis.

Vázquez-López and Manjón-Haces[7] described the dermoscopic subpatterns of psoriasis as round capillaries (red globules) arranged in irregular circles or rings with a beaded, lacelike capillary appearance, termed red globular rings. These patterns are infrequently observed in a minimal number of cases of plaque psoriasis and are considered diagnostic. Two important additional findings, along with vascular pattern, are the presence of white scales and a light red background. Kibar et al.[10] observed two new dermoscopic signs that are specific to scalp psoriasis, namely signet ring vessels and hidden hairs. Apart from diagnosis, dermoscopy plays an important role in monitoring the disease. The number of twisted vessels visualised using high magnification represents the activity of the disease and the number of these vessels reduces in response to treatment.[11] Errichetti et al.[12] described the dermoscopic patterns in erythrodermic psoriasis, which revealed a monomorphous pattern, with diffusely distributed white-coloured scales and regularly arranged dotted/glomerular vessels on a fairly homogeneous red-coloured background. Although dermoscopy of psoriasis shows dotted vessels, in palmar psoriasis only diffuse scales are visible due to the thickness of these scales. Scales should be scraped in order to see the dotted vessels.[13] Clinical diagnosis of psoriasis is straightforward if the presentation is typical, consisting of silvery-white scales on an erythematous background. Atypical clinical presentations require a biopsy, which is invasive. However, this limitation is overcome by using dermoscopy, because of its non-invasive nature; the role of dermoscopy in the diagnosis of psoriasis is well established.

### Lichen Planus

LP is an inflammatory dermatosis of the mucocutaneous surfaces that can present with a variety of clinical manifestations. Classical lesions of LP present as polygonal, flat-topped, violaceous papules and plaques, superimposed with reticulated white scale, termed Wickham striae (WS). Visualisation of this subtle but specific finding in LP can be enhanced by the application of water or oil to the affected area. Dermoscopy enables the visualisation of WS, which has been assessed as a highly sensitive and specific criterion for the diagnosis of LP (Figure 1). WS correspond

to compact orthokeratosis above zones of wedge-shaped hypergranulosis and acanthosis, centred on acrosyringia and acrotrichia.[8,14] WS is classically seen as white crossing lines on dermoscopic evaluation and defined as 'reticular pattern WS'. Güngör et al.[15] described various other patterns of WS, including leaf veination, circular, radial streaming, linear, globular, annular, perpendicular, veil-like structureless, and a combination of these patterns. Reticular pattern is the most common pattern of WS.

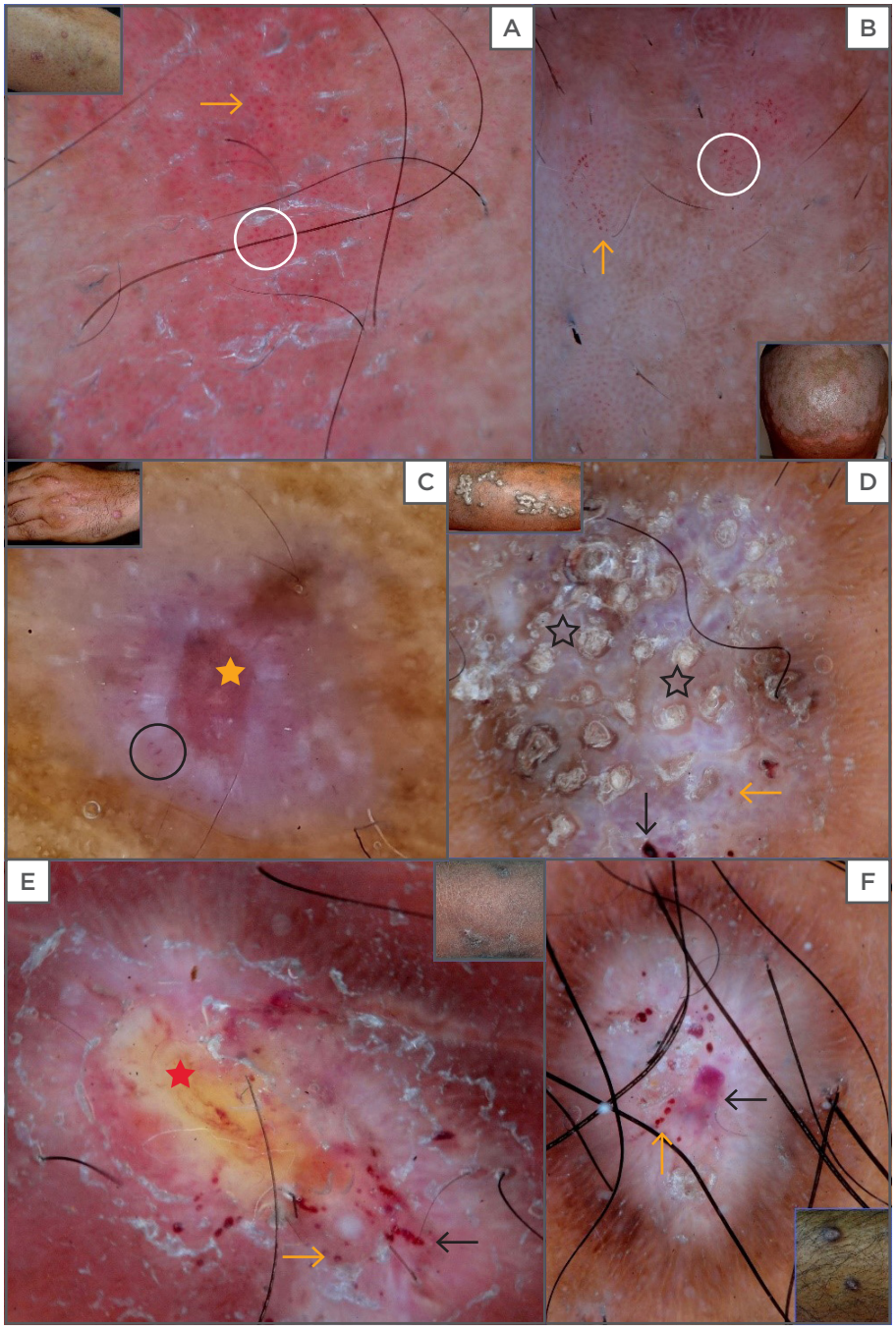


**Figure 1: Dermoscopy of psoriasis shows scaling and regular red dots (orange arrows), which are regular and uniform on the dull red background. Few glomerular vessels (white circle) are noted (A). A red background is not prominent on the scalp (B). Lichen planus reveals annular white ring (Wickham striae); red areas (orange star), and linear vessels (black circle) are present at the periphery (C). Corn pearls (black stars), blue-grey areas, red globules, and peripheral brownish striations are present in hypertrophic lichen planus (D). In prurigo nodularis yellowish areas (red star), white areas, red dots, and clods (black arrows) are present in excoriated lesions (E) as well as bright white areas in a starburst pattern with red dots and clods in late lesions. Note the peripheral brownish striations (F).**

The evolution of LP lesions can be monitored using dermoscopy. Early active lesions show WS arranged in a starburst pattern with a central thick white structure that expands into radial striations towards the periphery. The WS border shows projections of varying sizes, from thin spikes (comb-like appearance) to broad arboriform ramifications that may come together in networks. Prominent linear vessels are usually intermingled with the WS border projections (radial capillaries).[16]

In matured lesions of LP, the arrangement of WS is usually seen as a reticular pattern and vascular structures are well established, appearing as red globules, dots, and linear striations. The pigment pattern appears at this stage as pigmented dots or globules scattered in the lesion.[15] In regressing lesions of LP, WS disappears and the pigmented network becomes more prominent. The pigment pattern at this stage appears as radiating streaks at the periphery of the lesion, grey-black structureless areas, grey-black linear streaks, or grey-black pigment dots. The distribution pattern of grey-black streaks and dots suggests that they represent a previous location of WS.[15] In hypertrophic LP (HLP), corn pearls or comedo-like openings and yellow areas are observed in addition to the aforementioned patterns.[17] Dermoscopy of LP gives many characteristic patterns that differentiate LP from other conditions, and it is particularly helpful in visualising unusual manifestations and LP coexisting with other conditions.

## Prurigo Nodularis

PN is a chronic neurodermatitis that presents with intensely pruritic nodules that are secondary to an intense itch-scratch cycle.[18] Errichetti et al.[19] have noted pearly white areas in the centre, extending peripherally in a starburst pattern in PN. The patterns differ with respect to duration and type of lesion. Early and excoriated lesions show white areas, white scale, yellow erosion/crust, dotted or glomerular vessels, and haemorrhagic spots. Late and hyperkeratotic lesions demonstrate similar patterns in variable frequencies except for yellow erosion (Figure 1).[19] Follicular plugging is an additional feature present in late lesions of PN.[19]

Dermoscopically, nodular scabies, multiple keratoacanthoma, and HLP can be differentiated. Nodules in scabies that indicate mites or burrows appear as a hang glider sign, or show a jet with contrails.[20] Keratoacanthoma presents with a central white crust with peripheral hair pin and linear vessels.[21] HLP shows pearly white areas in the centre that differ from the white area seen in PN. In HLP, white areas do not cover the entire lesion; instead, they extend peripherally and are less prominent. Comedo-like openings are characteristically seen in HLP irrespective of the duration of lesions. Grey-blue globules that correspond to melanin in the dermis are seen in HLP but not in PN.[17]

Peripheral brownish striations extending from white areas are also described as characteristic features of PN. These represent melanin deposited in elongated rete ridges as a result of inflammation. White areas correspond to dermal fibrosis. In the author's experience, yellowish areas (representing discharge), brown and black dots, and globules (representing post inflammatory pigmentation) are new dermoscopic observations in PN. Hence, patterns of dermoscopy in PN vary according to the duration and evolutionary stage of the lesions. Early lesions demonstrate erosion, yellow areas, and 'crusts' and in late lesions, black or brown dots and follicular plugs are visualised. The white, starburst pattern is seen in all lesions irrespective of the lesion duration.

## Discoid Lupus Erythematosus

DLE presents as erythematous patches and plaques with adherent scale and hyperpigmented borders. Photo-exposed areas are most commonly affected, but shaded sites such as the trunk and back are involved in generalised DLE.[22] The patterns of dermoscopy in DLE vary according to the stage of disease. Erythema, perifollicular whitish halo, follicular keratotic plugs, red dots, branching telangiectasia, and white scaling are the most characteristic features of early lesions (Figure 2). These patterns correspond to inflammation, follicular pathology, and vessel involvement.[23] Late lesions demonstrate white-coloured structureless areas, hyperpigmentation in the form of a honeycomb network, perifollicular pigmentation, and a sprinkled pattern with blurred telangiectasias. The white areas represent fibrosis and the pigmentation is due to melanophages.[24] Diffuse hyperkeratosis, dilated follicles, and yellowish scales are examples of less commonly encountered dermoscopic patterns.[25]

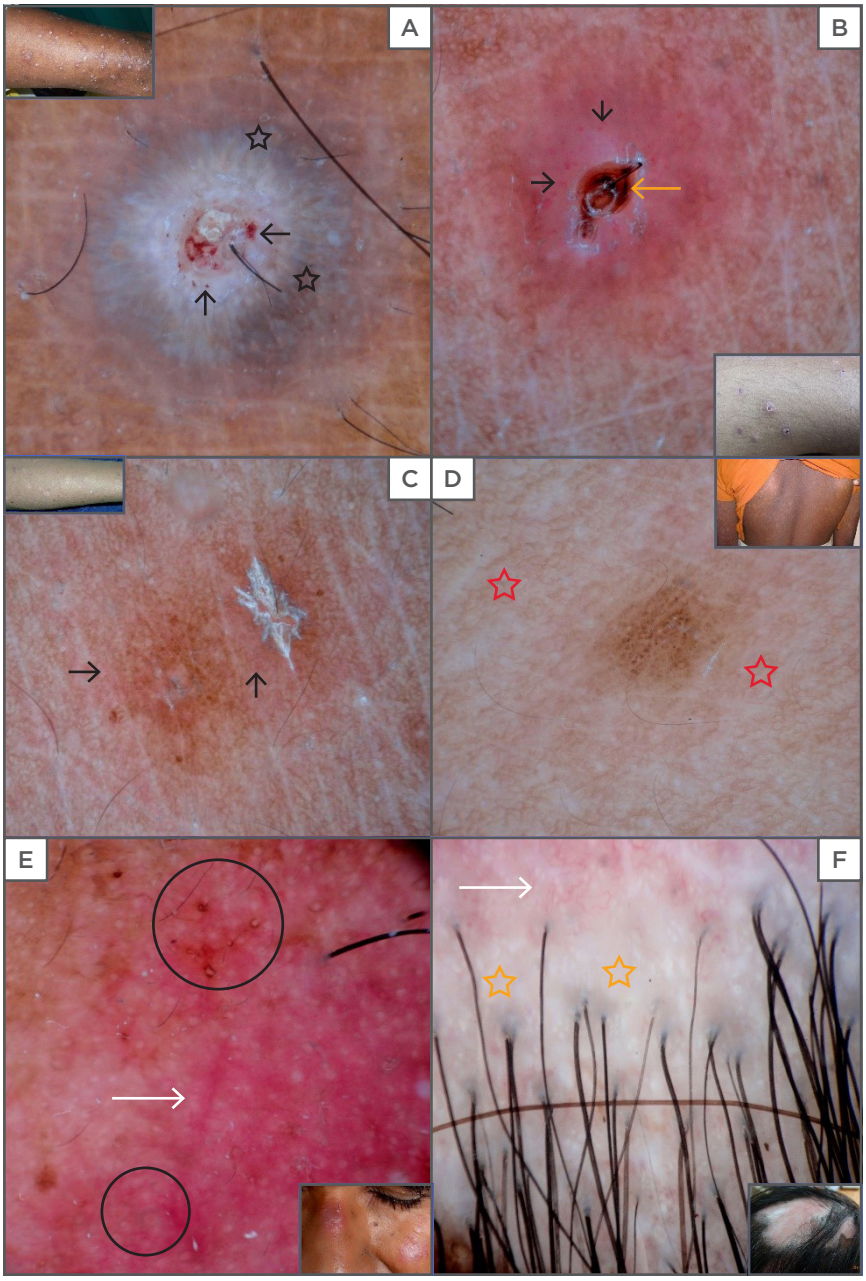


**Figure 2: Dermoscopy of pityriasis lichenoides et varioliformis acuta shows white-yellow, structureless areas with crust, grey-blue radiating strands (black stars), red dots, and globules (black arrows) (A). Amorphous brownish area (orange arrow) and red dots (black arrows) at the periphery are noted (B). Pityriasis lichenoides chronica shows brownish structureless areas and red dots with a micaceous scale (C) and white-coloured areas (red stars) surrounding brown areas are noted (D). Discoid lupus erythematosus shows erythema, dilated follicles (black circles), telangiectasia (white arrows), and scaling (E), as well as the loss of follicular ostia, white areas (orange stars), and telangiectasia (white arrows) (F).**

## Pityriasis Lichenoides et Varioliformis Acuta

PLEVA is an acute inflammatory condition characterised by follicle-oriented pustules and crusts.[26] PLEVA can mimic various skin conditions such as chicken pox, lymphomatoid papulosis, guttate psoriasis, LP, and PR. Dermoscopic patterns give clues to the diagnosis: white-coloured, structureless areas, a central crust, red globules, blue-grey areas, yellow globules, and scaling are described in the literature as features of PLEVA (Figure 2).[27] Authors described dermoscopic patterns in PLEVA that differ between early and late lesions. In the former, an amorphous brownish area around the hair follicles, within a rim of white scale and dotted vessels at the periphery,

are noted; white-coloured, structureless areas and a central crust-plug surrounded by a rim of white scale, red dots and haemorrhages are observed in late phase lesions.[26] Vascular patterns vary from dots, to linear, to haemorrhages and are arranged either in a targetoid or dotted pattern.[26,27] Ankadand Beergouder[26] described new findings that correlated with histopathological changes, including focal blue-grey areas and yellow globules that represent melanin in the dermis and spongiosis and basal cell degeneration, respectively. Dermoscopic patterns correlate well with histopathological changes. Hence, by recognising clinical features and using dermoscopy, the diagnosis of PLEVA can be assumed.

## Pityriasis Lichenoides Chronica

PLC clinically presents as purpuric macules and papules with micaceous scales on the surface that are adherent. Lesions heal with hypopigmented areas especially in skin Type 4, 5, and 6. PLC can be confused with guttate psoriasis and therefore dermoscopy plays an important supportive role in the diagnosis of PLC. The most peculiar dermoscopic findings in PLC include orange-yellowish structureless areas, focally distributed dotted vessels and milky-red globules, and linear irregular and branching vessels (Figure 2).[3] Errichetti et al.[9] described dermoscopic differentiation of guttate psoriasis and PLC. Guttate psoriasis demonstrates regularly arranged red dots on a dull red background, whereas an orange-yellowish background with linear and dotted vessels is characteristic of PLC.

However, in the authors' experience, brown structureless areas and white scaling in the centre, with dotted vessels and hypopigmented areas in the periphery are common, characteristic findings in PLC of melanin-rich skin. Linear vessels are not usually seen. We believe that differences in skin colour are contributing to the different background colours seen in PLC. A brownish background is likely due to haemosiderin deposition (due to extravasated erythrocytes), melanophages (focal basal cell degeneration), and lymphocytic infiltration.

## Pityriasis Rosea

PR is a papulosquamous disease characterised by erythematous papules and plaques with peripheral scaling that is classically described as collarette scaling. Clinical differentiation of PR from dermatophytosis and psoriasis is difficult in unusual presentations.[28] Dermoscopy of PR is well established and both herald and daughter patches demonstrate typical patterns under dermoscopy. It shows diffuse and structureless yellow-orange areas, and characteristic focal white-coloured peripheral scaling (Figure 3). Red dots, different from those seen in psoriasis, may be seen at the periphery but are less evident.[8,28]

These findings ensure dermoscopic differentiation of PR from other papulosquamous conditions. In psoriasis, red dots in regular patterns and scales are seen on a red background. A yellow or brown colour under dermoscopy is a negative factor for psoriasis;[29] however, the authors have observed brownish yellow backgrounds and brown dots in these patients, corresponding to the spongiotic tissue reaction plus haemosiderin deposits from extravasated red blood cells and lymphocytic infiltrate. A pronounced brownish hue on the background is related to the colour of the skin. This peculiar finding is frequently seen in late lesions of PR. Similarly, in early lesions, where pathological changes are not well formed, dermoscopy shows milky-red globules, indicating extravasated red blood cell in the dermis. Brown areas are very minimal suggesting early deposition of haemosiderin in the dermis. It is proven beyond doubt that dermoscopy demonstrates characteristic patterns in PR. Thus, patterns of PR seen under dermoscopy are accurate.

## Eczema

Eczema presents with patches and plaques on the extremities. Clinically, it mimics psoriasis, dermatophytic infection, and LP. Dermoscopy of eczema shows a yellow coloured serocrust and clusters of red dots and white scales (Figure 3). Lallas et al.[8] evaluated the dermoscopic patterns of eczema and opined that patterns may change depending on the stage of the eczema. In the acute stage, yellowish crusts, dotted vessels in a patchy distribution, and focal white scales are seen. In the chronic and lichenification stages, white scales and clusters of red dots are noted.[8]

In one study, dermoscopic patterns of hand eczema and palmar psoriasis were studied extensively. Eczema showed clusters of red dots, whereas psoriasis was characterised by diffusely arranged red dots. Yellow findings were specific to eczema.[13] In all types of eczema, vascular patterns are repetitive and the patchy distribution of red dots is very specific. However, focal white scales, yellowish serocrusts, and white areas are predominantly

seen in acute and chronic stages of eczema, respectively.[13] Yellowish serocrusts correspond to spongiosis and serous discharge and white areas correspond to hyperkeratosis and acanthosis. A yellowish hue is characteristic of acute eczema and is referred to as 'yellow clod' sign.[30]

However, with 10x magnification, the authors have noticed a presence of red dots and globules, especially in asteatotic and subacute eczema, in the same way as that of psoriasis. They are of different sizes and shapes, unlike in psoriasis where they are the same size, both uniform and regular.

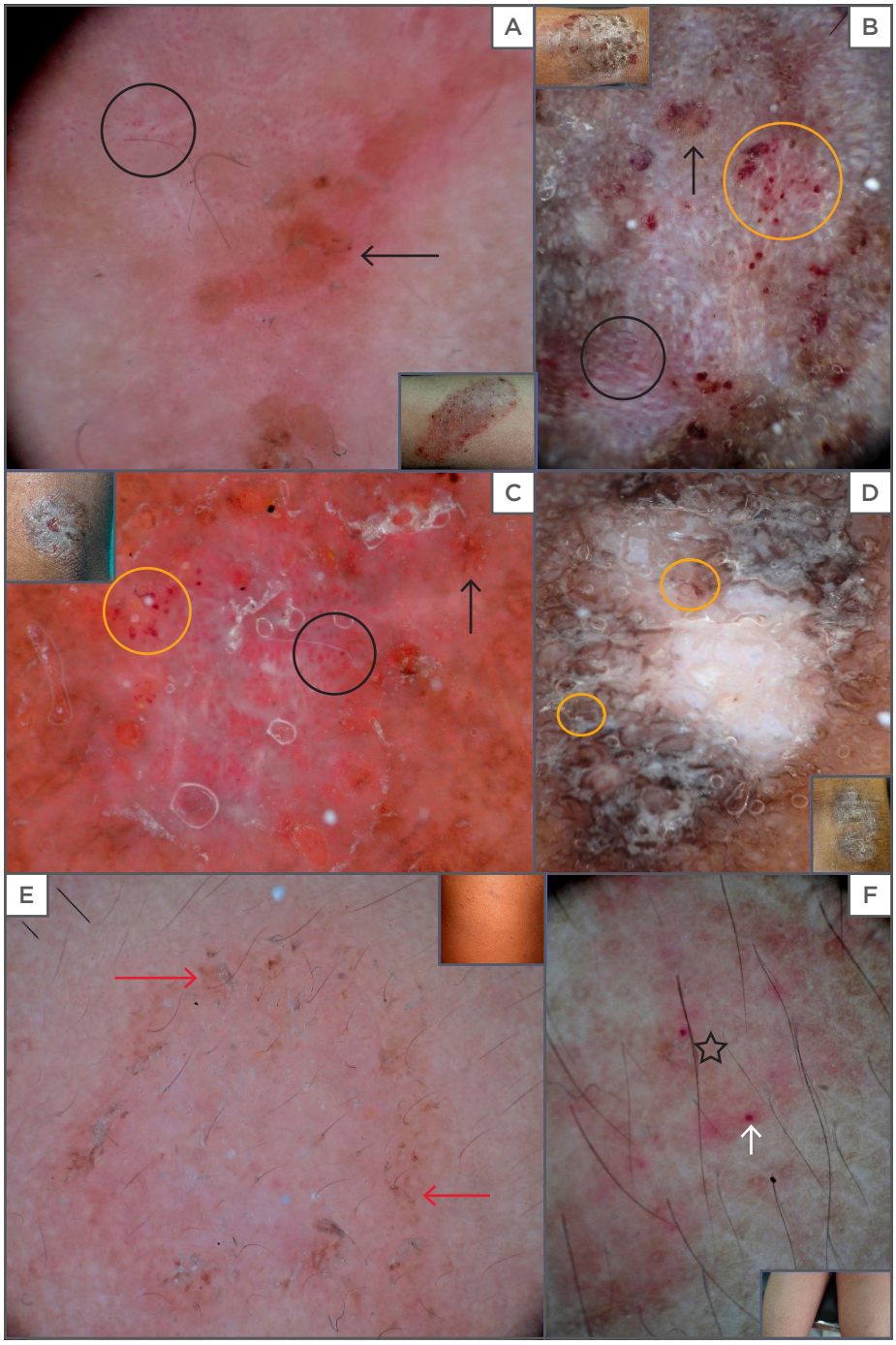


**Figure 3: Dermoscopy of eczema reveals a yellow-orange crust, (A: asteatotic), yellow serocrusts (black arrow), and curvilinear white globules on a white background (B: subacute). Red dots are arranged in a regular (black circle) and cluster pattern (orange circle) (A, B, C, D). Nummular eczema shows focal white scales, a yellow-orange crust, red dots (C), diffuse white areas, and patchily arranged red dots (D: lichen simplex chronicus). Pityriasis rosea is shown by brown dots (red arrows), collarette scales on a yellow-brown background (E: late lesion), scale, and a brown globule (black star); milky pink dots and globules (white arrow) are noted in early lesions (F: early lesion).**

This dermoscopic finding is explained by the fact that chronic scratching and rubbing result in psoriasiform hyperplasia. This results in diffusely arranged red dots over the entire lesion. This is a preliminary finding; further elucidation is required for this observation. Dermoscopy of erythrodermic atopic dermatitis consists of yellowish scales/serocrusts and clusters of dotted vessels on a pinkish background. Non-specific, sparse white-coloured scales may be observed.[12] These findings help clinicians to differentiate inflammatory conditions that present with erythroderma.

## CONCLUSION

Dermoscopy is an *in vivo* method of diagnostic technique that enables the clinician to visualise the skin structures not seen by the naked eye. By supplying higher magnification of a lesion, dermoscopy provides a detailed analysis of the lesion, allowing the accurate diagnosis and treatment. Hence, dermoscopy is considered the stethoscope of dermatologists. Thus, the authors recommend dermoscopic examination of skin lesions in daily practice.

## REFERENCES


1. Fargnoli MC et al. Dermoscopy in the diagnosis and management of non-melanoma skin cancers. Eur J Dermatol. 2012;22(4):456-63.

2. Lallas A et al. Dermoscopy in general dermatology: Practical tips for clinician. Br J Dermatol. 2014;107(3):514-26.

3. Errichetti E, Stinco G. The practical usefulness of dermoscopy in general dermatology. G Ital Dermatol Venereol. 2015;150:533-46.

4. Bowling J. "Non-melanocytic lesions," Bowling J (ed.), Diagnostic dermoscopy-The illustrated guide (2012) 1st edition. West Sussex: Wiley-Blackwell, pp 59-91.

5. Errichetti E, Stinco G. Dermoscopy in general dermatology: A practical overview. Dermatol Ther (Heidelb). 2016; 6(4):471-507.

6. Marghoob AA et al. Observation of chrysalis structures with polarized dermoscopy. Arch Dermatol. 2009; 145:618.

7. Vázquez-López F, Manjón-Haces JA. Dermoscopic features of plaque psoriasis and lichen planus: New observations. Am J Clin Dermatol. 2013;14(1):27-47.

8. Lallas A et al. Accuracy of dermoscopic criteria for the diagnosis of psoriasis, dermatitis, lichen planus and pityriasis rosea. Br J Dermatol. 2012;166(6): 1198-205.

9. Errichetti E et al. Differentiation of pityriasis lichenoides chronica from guttate psoriasis by dermoscopy. Clin Exp Dermatol. 2015;40(7):804-6.

10. Kibar M et al. Dermoscopic findings in scalp psoriasis and seborrheic dermatitis; Two new signs; Signet ring vessel and hidden hair. Indian J Dermatol. 2015;60(1):41-5.

11. Gniadecki R et al. Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. Br J Dermatol. 2011;164:1091-6.

12. Errichetti E et al. Dermoscopy as an auxiliary tool in the differentiation of the main types of erythroderma due to dermatological disorders. Int J Dermatol. 2016;55(12):e616-8.

13. Errichetti E, Stinco G. Dermoscopy in differential diagnosis of palmar psoriasis and chronic hand eczema. J Dermatol. 2016;43(4):423-5.

14. Zalaudek I, Argenziano G. Dermoscopy subpatterns of inflammatory skin disorders. Arch Dermatol. 2006;142:808.

15. Güngör S et al. Dermoscopic patterns in active and regressive lichen planus and lichen planus variants: A morphological study. Dermatol Pract Concept. 2015;5(2):45-53.

16. Vazquez-Lopez F et al. Dermoscopy of active lichen planus. Arch Dermatol. 2007;143:1092.

17. Ankad BS, Beergouder SL. Hypertrophic lichen planus versus prurigo nodularis: A dermoscopic perspective. Dermatol Pract Concept. 2016;6(2):3.

18. Vaidya DC et al. Prurigo nodularis: A benign dermatosis derived from a persistent pruritus. Acta Dermatovenerol Croat. 2008;16:38-44.

19. Errichetti E et al. Dermoscopy of prurigo nodularis. J Dermatol. 2015;42: 632-4.

20. Suh KS et al. Mites and burrows are frequently found in nodular scabies by dermoscopy and histopathology. J Am Acad Dermatol. 2014;71:1022-3.

21. Zalaudek I et al., "Actinic keratosis, Bowen's disease, keratoacanthoma, and squamous cell carcinoma," Marghoob AA et al. (eds.), Atlas of Dermoscopy, 2ndedn. New York: Informa Healthcare, 2012 48-57.

22. Lallas A et al. Dermoscopic patterns of common facial inflammatory skin diseases. J Eur Acad Dermatol Venereol. 2014;28:609-14.

23. Lopez-Tintos BO et al. Dermoscopy in active discoid lupus. Arch Dermatol. 2009;145:358.

24. Inui S et al. Dermoscopy of discoid lupus erythematosus: report of two cases. J Dermatol. 2014;41:756-7.

25. Lallas A et al. Dermoscopy of discoid lupus erythematosus. Br J Dermatol. 2013;168:284-8.

26. Ankad BS, Beergouder SL. Pityriasis lichenoides et varioliformis acuta in skin of color: New observations by dermoscopy. Dermatol Pract Concept. 2017;7(1):5.

27. Lacarrubba F, Micali G. Dermoscopy of pityriasis lichenoides et varioliformis acuta. Arch Dermatol. 2010;146(11):1322.

28. Chuh AA. Collarette scaling in pityriasis rosea demonstrated by digital epiluminescence dermatoscopy. Australas J Dermatol. 2001;42:288-90.

29. Chuh AA. The use of digital epiluminescence dermatoscopy to identify peripheral scaling in pityriasis rosea. Comput Med Imaging Graph. 2002;26:129-34.

30. Navarini AA et al. The yellow clod sign. Arch Dermatol. 2011;147:1350.

# CHRONIC URTICARIAL VASCULITIS AND IMMUNOGLOBULIN G MONOCLONAL GAMMOPATHY: VARIANT SCHNITZLER SYNDROME

**Shilpa Bhartia,[1] *Sujoy Khan[2]**

*1. Department of Hematology and Hemato-oncology, Apollo Gleneagles Hospital Kolkata, Kolkata, India*
*2. Department of Allergy and Immunology, Apollo Gleneagles Hospital Kolkata, Kolkata, India*
**Correspondence to sujoykhan@gmail.com*

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## ABSTRACT

Schnitzler syndrome is a rare acquired autoinflammatory disorder that is characterised by recurrent fevers, bone or joint pains, urticarial rash, and monoclonal immunoglobulin M paraprotein, while the variant form has immunoglobulin G monoclonal paraprotein. The cytokine that appears to cause the inflammatory episodes is interleukin-1β, and blocking this cytokine ameliorates almost all symptoms of this disorder. Physicians should be aware of this disorder so that they can recognise this difficult form of urticarial vasculitis and prevent the complication of amyloidosis.

Keywords: Urticaria, vasculitis, monoclonal paraprotein, Schnitzler syndrome, colchicine.

## INTRODUCTION

Schnitzler syndrome was first described by the dermatologist Dr Liliane Schnitzler in 1972.[1] It is now recognised as a rare acquired autoinflammatory disease of unknown cause that presents with non-specific clinical signs and biochemical features of inflammation over many years (fevers, bone pains, urticaria rash, and classical immunoglobulin [Ig]M monoclonal paraprotein).[2] The histopathological findings of skin biopsies reveal perivascular neutrophil and lymphocytic infiltration into the upper dermis and occasional diffuse neutrophilic infiltration in the middle dermis (neutrophilic urticaria). It is similar to lupus erythematosus, adult-onset Still's disease, and, rarely, autoinflammatory syndromes of the cryopyrinopathies.

We describe a case of variant Schnitzler syndrome (with IgG monoclonal paraprotein), where the patient was treated initially for multiple myeloma, but the treatment was stopped as the urticarial rash progressed into a form of urticarial vasculitis, therefore raising the possibility of Schnitzler syndrome.

## CASE DESCRIPTION

A 37-year-old female was admitted in the Hematology Department of the Apollo Gleneagles Hospital Kolkata, Kolkata, India, with history of recurrent low-grade fevers, flitting arthralgia, and blurring of vision for 1 month. Her medical history revealed generalised arthralgias with occasional multiple large joint pains for 3 years and anaemia for 2 years with recurrent low-grade fevers, for which she received multiple courses of antibiotics with little or no effect. Investigations elsewhere into the anaemia (haemoglobin 6.0 gm/dL) and raised erythrocyte sedimentation rate at 115 mm/first hour had revealed a small paraprotein (quantitated at 8.6 g/L) and 8% bone marrow plasma cells. Immunofixation showed IgG-lambda, for which she had received one dose of bortezomib and dexamethasone.

There was no history of Type 2 diabetes mellitus or hypertension. She was a non-smoker and denied alcohol or illicit drug use. There was no family history of periodic fevers, monoclonal gammopathy, or any family members admitted with pyrexia of unknown origin at any time.

**Table 1: Laboratory investigation results at admission and subsequent review.**

| Variable (Reference range) | At admission | 3 months later |
|---|---|---|
| Haemoglobin (12.0–15.0 g/dL) | 6.1 | 12.2 |
| Mean corpuscular volume (76–96 fL) | 68.0 | 85.1 |
| White cell count (4.0–10.0x10$^9$/L) | 9.5 | 9.3 |
| Platelet count (150–400x10$^9$/L) | 216 | 151 |
| Neutrophil count (2.0–7.5x10$^9$/L) | 7.2 | 7.6 |
| Lymphocyte count (1.5–4.0x10$^9$/L) | 2.2 | 2.3 |
| Monocyte count (0.02–1.0x10$^9$/L) | 0.04 | 00 |
| Eosinophil count (0.01–0.06x10$^9$/L) | 0.02 | 0.01 |
| Erythrocyte sedimentation rate (0–20 mm/1st hr) | 46 | - |
| Sodium (136–145 mEq/L) | 137 | - |
| Potassium (3.5–5.2 mEq/L) | 4.1 | - |
| Urea (15–39 mg/dL) | 22 | - |
| Creatinine (0.6–1.3 mg/dL) | 0.6 | - |
| C-reactive protein (0–8 mg/L) | 25 | - |
| ALT (SGPT) [10–42 U/L] | 19 | - |
| AST (SGOT) [10–40 U/L] | 28 | - |
| Alkaline phosphatase (42–98 U/L) | 90 | - |
| Calcium (8.6–10.2 mg/dL) | 8.6 | - |
| Phosphorus, inorganic (2.5–4.5 mg/dL) | 3.3 | - |
| Vitamin B12 (211–946 pg/mL) | 168 | - |
| Ferritin (10–120 ng/mL) | 41.2 | - |
| Serum iron (50–170 µg/dL) | 21 | - |
| 25-OH-Vitamin D (def <20 ng/mL) | 46 | - |
| Anti-cyclic citrullinated peptide (<5 U/mL) | 0.5 | - |
| Antinuclear antibody (Hep-2 cell line 1:100) | Negative | - |
| Anti-neutrophil cytoplasmic antibody | Negative | - |
| Direct Coombs test | Negative | - |
| Serum free light chain (kappa) (3.3–19.40 mg/L) | 28 | - |
| Serum free light chain (lambda) (5.71–26.30 mg/L) | 30.3 | - |
| SFLC ratio (0.26–1.65) | 0.94 | - |
| Serum protein electrophoresis | M spike 10 g/L | - |
| Serum protein immunofixation | IgG-lambda | - |
| Bone marrow | 8% plasma cells | - |

ALT (SGPT): alanine aminotransferase (serum glutamic-pyruvic transaminase); AST (SGOT): aspartate aminotransferase (serum glutamic oxaloacetic transaminase); def: deficiency; IgG: immunoglobulin G; SFLC: serum-free light chain.

Her laboratory results showed low haemoglobin at 6.1 g/dL, a white cell count of 9,500/mm$^3$, platelet count of 216x10$^9$/L with elevated erythrocyte sedimentation rate at 48 mm/1st hour (Table 1). The findings of low serum iron and vitamin B12 levels confirmed the diagnosis of a mixed haematinic deficiency anaemia. She was started on broad-spectrum antibiotics that were discontinued after admission when infections were ruled out. Complete blood count after 3 days of admission showed white cell count 10,600/mm$^3$ with neutrophilic pleocytosis (82%). The patient continued to complain of joint pains, but anti-cyclic citrullinated peptide antibody analysis was negative with normal X-ray of shoulder and knee joints.

A rheumatological consultation led to the suggestion of a seronegative spondyloarthropathy and ophthalmological consultation indicated possible episcleritis. Following this, it was advised to start administering the patient Homide eye

drops (homatropine-hydrobromide) twice daily and prednisolone acetate ophthalmic suspension eye drops.

A whole body bone scan (20 mCi of technetium 99m-methyl diphosphonate [99mTc-MDP] given intravenously and images obtained after 3 hours) showed increased tracer uptake in both sacroiliac joints, right more than left (Figure 1). Serum protein electrophoresis showed monoclonal gammopathy and serum protein immunofixation confirmed the paraprotein as IgG lambda. Positron emission tomography with computed tomography (PET-CT) imaging showed diffuse [$^{18}$F]-2-fluoro-2-deoxy-D-glucose (FDG) uptake in both tonsils (standard uptake values [SUV] maxright 6.0 and left 5.6), mild FDG avid subcentimeter size bilateral cervical level IIA nodes were seen, the largest measuring 11x8 mm (SUV max 2.7), and mildly FDG avid left inguinal lymph node (SUV max 4.1), all of which were considered to be either infective/inflammatory in nature. FDG avid cysts were seen in both ovaries; the largest left ovarian cystic lesion measured 12x9 mm (SUV max 5.1) and was considered to be corpus luteal cysts. There was no abnormal uptake to suggest active metastatic disease or any myelomatous deposits.

As the patient was suffering from iron deficiency and vitamin B12 deficiency, she was given iron infusion and a single dose of vitamin B12 1 mg injection. She was discharged on folic acid 5 mg and ferrous gluconate tablets with a plan to review in the outpatient clinic.

She was seen 5 weeks after being discharged, when she complained of increased joint pains, recurrent diffuse pruritic maculopapular lesions over her face, abdomen, and upper extremities, with daily attacks over 4 weeks. She, however, had an excellent response to haematinic therapy with a rise in haemoglobin of 5 g/L. At this point, an immunology referral was made with a provisional diagnosis of urticarial vasculitis.

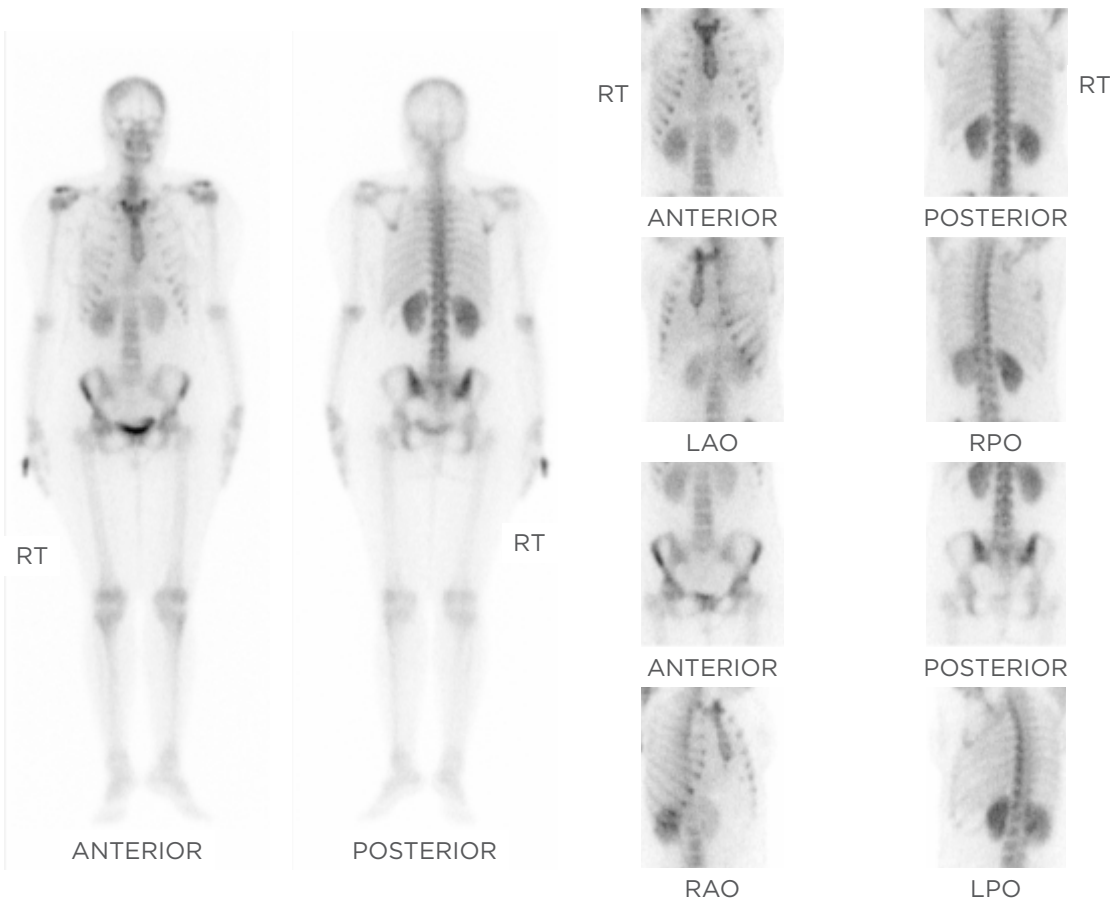


**Figure 1: Whole body bone scan using 20 mCi of 99mTc-MDP with images obtained after 3 hours showing increased tracer uptake in both the sacroiliac joints, right more than the left.** 99mTc-MDP: technetium 99m-methyl diphosphonate; LAO: left anterior oblique; LPO: left posterior oblique; RAO: right anterior oblique; RPO: right posterior oblique; RT: right.

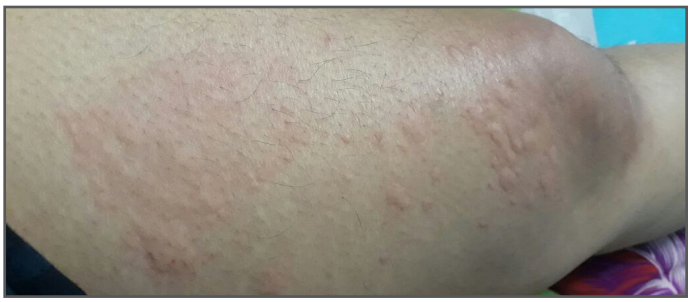

**Figure 2: Urticarial rashes of variable nature that is characteristic of Schnitzler syndrome, as exhibited by our patient.**

The patient revealed that she now suffered outbreaks with variable intensity almost on a daily basis, with no identifiable triggering factors. She mentioned that the lesions cleared up in 24 hours, leaving no marks or scars, while new lesions had appeared almost daily. The physical examination at this time revealed diffuse pruritic maculopapular lesions over her face, thorax, and upper extremities, sparing her palms, soles, and mucous membranes. There was evident synovitis affecting both wrists, ankle, and knee joints, but no overt arthritis. She refused skin biopsy.

She was started on high-dose antihistamines and a 10-day course of oral steroids that controlled the urticaria. However, after 3 weeks, bone pains with fevers were reported almost on a daily basis (maximum temperature recorded was 40°C) and urticaria relapsed with more of a burning than an itching sensation, which now lasted 48–72 hours (Figure 2).

Based on the clinical presentations and laboratory results, the diagnosis of Schnitzler syndrome was made as she fulfilled the diagnostic criteria: both major criteria (chronic urticarial rash/intermittent fever and monoclonal paraprotein) and three out of five minor criteria (arthralgias, bone pain, and elevated erythrocyte sedimentation rate). There was no evidence of hepatosplenomegaly or lymphadenopathy and there was perhaps a transient phase of neutrophilic leucocytosis. She was counselled regarding the diagnosis of Schnitzler syndrome and discussed starting anti-interleukin 1 therapy (anakinra). Serum amyloid A and C-reactive protein levels were measured to ascertain disease activity at 10 weeks from diagnosis, which showed borderline raised serum amyloid A at 6.91 mg/L (normal, <6.4 mg/L) and normal C-reactive protein at <0.50 mg/L.

Anakinra could not be started due to financial constraints; colchicine 0.5 mg twice daily was started with long-acting non-sedating anti-H2 blocker fexofenadine 180 mg, which led to almost complete resolution of symptoms in about 6 weeks from starting treatment. She has since presented on two further occasions with florid urticaria requiring short-term steroids and remains on long-term colchicine therapy.

## DISCUSSION

Schnitzler syndrome is categorised under orphan disease and remains largely underdiagnosed. Studies from Mayo Clinic, Rochester, Minnesota, USA, suggest that Schnitzler syndrome may be present in ≤1.5% of patients with a monoclonal IgM in serum,[3] while the variant form with monoclonal IgG probably remains undiagnosed. The most comprehensive review to-date is by de Koning,[4] who reviewed 281 cases of Schnitzler syndrome from 25 countries that showed a male:female ratio of 1.5, median age at onset of 51 years, with the delay in diagnosis exceeding 5 years in most cases. In a previous case series of 94 patients by the same author, only 5 patients (5.3%) experienced symptoms before the age of 35 years,[5] while a recent paper of 11 patients from Belgium (between 1995 and 2015), reviewed using the Strasbourg criteria, had only 2 patients who presented before the age of 35 years and all had IgM paraprotein (kappa light chain in 10 patients, while only one had lambda light chain).[6] Our case is probably the first from India and has other interesting features: a young age onset of Schnitzler syndrome (37 years compared to median age 51 years), episcleritis as an unusual presentation, variant form of IgG-lambda monoclonal paraprotein, and fever and monoclonal paraprotein preceding onset of urticaria. Our patient had opted for naturopathy as a treatment option for almost a year and was avoiding several foods in her diet, which would explain the relatively severe anaemia and excellent response to haematinic replacement therapy (i.e. nutritional anaemia), and objectively no evidence of bone marrow infiltration. It is, therefore, not unusual that the presence of the severe anaemia and monoclonal paraprotein had prompted physicians to initially use bortezomib and dexamethasone to treat as multiple myeloma, with the presence of anaemia and bone pains satisfying two of four 'CRAB' features (hypercalcaemia, renal impairment, anaemia, bone pains). As patients with

Schnitzler syndrome may occasionally receive full courses of chemotherapy for multiple myeloma before the diagnosis of Schnitzler syndrome is suspected,[7] awareness of this entity needs to be increased.

It is perhaps always a concern of physicians and patients whether chronic (idiopathic) urticaria may be a manifestation of an underlying malignancy, especially a haematological malignancy. Among known significant disease associations with urticaria, monoclonal gammopathy of undetermined significance (MGUS) appears to be associated with urticaria in about 144.8 per 100,000 patient-years.[8] A study using the Mayo Clinic electronic database (1994–2001) of 1,639 patients presenting with chronic urticaria found 47 of 797 patients evaluated for existence of monoclonal protein had MGUS, 142 had a malignancy, and 24 had both.[9] This study concluded that patients presenting with chronic urticaria at an older age (>56 years) were more likely to have associated underlying MGUS. The variant form of Schnitzler syndrome with IgG paraprotein has not been described extensively, apart from a few reports,[10-14] but the clinical presentation and laboratory features of inflammation are very much similar to the well-described form with IgM paraprotein. A relatively new form of IgG monoclonal gammopathy-related acquired autoinflammatory syndrome (proposed as Mullins' syndrome) is, however, distinct from Schnitzler syndrome with features of neutropenia, complement activation, and resistant to anti-IL1 (anakinra) therapy with no mutations in any of the known periodic fever-related syndrome genes.[15]

Almost all patients with Schnitzler syndrome will present with urticaria-like dermatoses at disease onset, which are typically recurrent, last 24–48 hours, and the symmetrical nature of the rash differentiates them from chronic spontaneous or the physical/inducible urticarias. These dermatoses present with more of a burning pain than itching and generally respond poorly to antihistamines.

**Table 2: Treatment options for Schnitzler syndrome with strength of recommendation.**

| Treatment | Strength of recommendation |
|---|---|
| Prednisolone | Acute attacks only |
| NSAID and anti-H2 blockers | Acute attacks only, minimal relief |
| Colchicine[2,4-6,22,23] | Moderate to high |
| Combinations of prednisolone, dapsone, and sulfasalazine | Not effective |
| IL-1 receptor antagonists,<br>such as anakinra[13,17-20,24]<br>During flare ups: 100 mg sc<br>Daily doses of 100 mg sc preferred<br><br>Other IL-1 receptor antagonists are:<br>canakinumab, rilonacept | Strength of recommendation: high<br><br>Treatment option: Monotherapy only |
| Thalidomide | Low: risks probably outweigh benefits[13,25] |
| Immunoglobulin therapy | Not recommended |
| Proteosome inhibitors | Not recommended |
| Anti-TNFα | Not beneficial |
| Hydroxychloroquine | Not beneficial |
| Ciclosporin | Not beneficial |
| Rituximab | Low: paraprotein reduction with elimination of autoreactive B cells certain; but uncertain effect on urticarial symptoms[24] |
| Interferon alpha (proposed to increase IL-1 antagonist levels) | Successful in a report,[26] while not beneficial in others[23] |
| Tociluzumab (anti-IL-6) | Beneficial in three cases[27] |

Notes: Strength of recommendation is mainly based on case reports, case series, and single-centre experience, as referenced.
IL: interleukin; NSAID: non-steroidal anti-inflammatory drugs; sc: subcutaneous; TNFα: tumour necrosis factor alpha.

Our patient presented with urticarial lesions after the arthralgia, which has been documented in another report.[6] The skin lesions did not show a temperature-related effect; hence, cryoglobulin testing was not performed. Angioedema is uncommon in this condition. Intermittent fever, not periodic, affects nearly 75% of patients and may range from daily episodes to a few times in a year. As there was no family history of periodic fevers, or fevers with features of amyloidosis, genetic testing for periodic fever related syndromes (such as Muckle-Wells syndrome or tumour necrosis factor-related autoinflammatory syndromes) was not done in this case. Joint pains usually precede the skin rash in Schnitzler syndrome, and involve larger peripheral joints (knees, hip, back) without arthritis. Bone pains affect >50% of patients and typically involve the shins, including long bones, the hips, and back. A bone scan is, therefore, a helpful screening tool if Schnitzler syndrome is suspected, with typical findings of osteosclerosis especially involving the knees and pelvis.[16] There have been reports of patients with Schnitzler syndrome having unusual symptoms, such as intercostal neuralgia with headache and pancreatitis,[4] which may be similar to the finding of episcleritis in our patient. We think that inflammation due to IL-1β can affect any site, as seen with patients with cryopyrin-associated periodic syndromes who develop episcleritis, and this manifestation may have been due to untreated Schnitzler syndrome. It is therefore important that complications of Schnitzler syndrome, as with any autoinflammatory syndromes/diseases, are avoided, for example, amyloid A amyloidosis. Furthermore, there should be mandatory follow-up to detect the development of haematological malignancies, such as Waldenström's macroglobulinaemia.[6]

The treatment options of Schnitzler syndrome are outlined in Table 2, with most experts recommending that the first-line treatment for patients with significantly reduced quality of life or evidence of persistent elevation of inflammatory markers/high risk of amyloidosis should be anakinra or with canakinumab.[17] Canakinumab is a human monoclonal anti-human IL-1β antibody of the IgG1/kappa isotype.[18-20] It binds to human IL-1β and neutralises its activity by blocking its interaction with IL-1 receptors. We used colchicine as primary treatment option in our patient given the cost restraints with anakinra. Colchicine is a tricyclic alkaloid that inhibits microtubules and is the preferred treatment of choice in familial Mediterranean fever, where it markedly reduces episodes of fever and prevents amyloidosis; a similar mechanism of action may be at play in Schnitzler syndrome given the modest efficacy of this drug. Colchicine is also known to stabilise proteinuria in patients with amyloid nephropathy. However, it is now clear that symptoms in Schnitzler syndrome are most likely related to the monoclonal paraprotein and thus this disease should be classified under monoclonal gammopathy of cutaneous significance.[21]

In our limited experience, we recommend colchicine as the first-line therapy for management of Schnitzler syndrome. Anti-H1 blockers and colchicine have now been prescribed long-term for our patient, with short rescue courses with corticosteroids when required, but continuous assessment with complete blood count, C-reactive protein, urine routine examination every 3 months, and paraprotein levels every 6 months has been recommended for long-term follow-up including monitoring for treatment-related complications.

## REFERENCES


1. Schnitzler L et al. Urticaire chronique, lesions osseuses, macroglobulinemie IgM: Maladie de Waldenstrom? Bull Soc Fr Dermatol Syphiligr. 1974;81(4):363.

2. Simon A et al. Schnitzler's syndrome: Diagnosis, treatment, and follow-up. Allergy. 2013;68(5):562-8.

3. Jain T et al. Schnitzler syndrome: An under-diagnosed clinical entity. Haematologica. 2013;98(10):1581-5.

4. de Koning HD. Schnitzler's syndrome: Lessons from 281 cases. Clin Transl Allergy. 2014;4:41.

5. de Koning HD et al. Schnitzler Syndrome Study G. Schnitzler syndrome: Beyond the case reports: Review and follow-up of 94 patients with an emphasis on prognosis and treatment. Semin Arthritis Rheum. 2007;37(3):137-48.

6. Vanderschueren S, van der Veen A. The Schnitzler syndrome: Chronic urticaria in disguise: A single-centre report of 11 cases and a critical reappraisal of the literature. Clin Exp Rheumatol. 2017; 35(1):69-73.

7. Barbosa NS et al. Chronic urticarial eruption associated with monoclonal gammopathy. Am J Hematol. 2015; 90(4):365-6.

8. Bida JP et al. Disease associations with monoclonal gammopathy of undetermined significance: A population-based study of 17,398 patients. Mayo Clin Proc. 2009;84(8):685-93.

9. Karakelides M et al. Monoclonal gammopathies and malignancies in patients with chronic urticaria. Int J Dermatol. 2006;45(9):1032-8.

10. Nashan D et al. Chronic urticaria, arthralgia, raised erythrocyte sedimentation rate and IgG paraproteinaemia: A variant of Schnitzler's syndrome? Br J Dermatol. 1995;133(1):132-4.

11. Pascual-López M et al. Schnitzler's

syndrome with monoclonal IgG kappa gammopathy: Good response to cyclosporin. J Eur Acad Dermatol Venereol. 2002;16(3):267-70.

12. Akimoto R et al. Schnitzler's syndrome with IgG kappa gammopathy. J Dermatol. 2002;29(11):735-8.

13. de Koning HD et al. Beneficial response to anakinra and thalidomide in Schnitzler's syndrome. Ann Rheum Dis. 2006;65(4):542-4.

14. Patel S et al. Chronic urticaria with monoclonal IgG gammopathy: A clinical variant of Schnitzler syndrome? Ann Allergy Asthma Immunol. 2012;109(2): 147-8.

15. Longhurst HJ et al. Mullins' syndrome: A new gammopathy-related autoinflammatory syndrome resistant to anakinra. QJM. 2015;108(6):497-501.

16. Niederhauser BD et al. Imaging findings in 22 cases of Schnitzler syndrome: Characteristic para-articular osteosclerosis, and the "hot knees" sign differential diagnosis. Skeletal Radiol. 2014;43(7):905-15.

17. Kaplan AP. Biologic agents in the treatment of urticaria. Curr Allergy Asthma Rep. 2012;12(4):288-91.

18. de Koning HD et al. Successful canakinumab treatment identifies IL-1β as a pivotal mediator in Schnitzler syndrome. J Allergy Clin Immunol. 2011; 128(6):1352-4.

19. Vanderschueren S, Knockaert D. Canakinumab in Schnitzler syndrome. Semin Arthritis Rheum. 2013;42(4):413-6.

20. Krause K et al. Efficacy and safety of canakinumab in Schnitzler syndrome: A multicenter randomized placebo-controlled study. J Allergy Clin Immunol. 2017;139(4):1311-20.

21. Lipsker D. Monoclonal gammopathy of cutaneous significance: Review of a relevant concept. J Eur Acad Dermatol Venereol. 2017;31(1):45-52.

22. Barešić M et al. Different therapeutic paths (colchicine vs. anakinra) in two patients with Schnitzler's Syndrome. Arch Rheumatol. 2016;31(4):377-80.

23. R Lin, S Jagannath. Treatment of Schnitzler's syndrome with colchicine: A case report. The Internet J Asthma. 2004;4(1).

24. Eiling E et al. Schnitzler syndrome: Treatment failure to rituximab but response to anakinra. J Am Acad Dermatol. 2007;57(2):361-4.

25. Worm M, Kolde G. Schnitzler's syndrome: Successful treatment of two patients using thalidomide. Br J Dermatol. 2003;148(3):601-2.

26. Schartz NE et al. Report of a case of Schnitzler's syndrome treated successfully with interferon alpha 2b. Dermatology. 2002;205(1):54-6.

27. Krause K et al. Complete remission in 3 of 3 anti-IL-6-treated patients with Schnitzler syndrome. J Allergy Clin Immunol. 2012;129(3):848-50.

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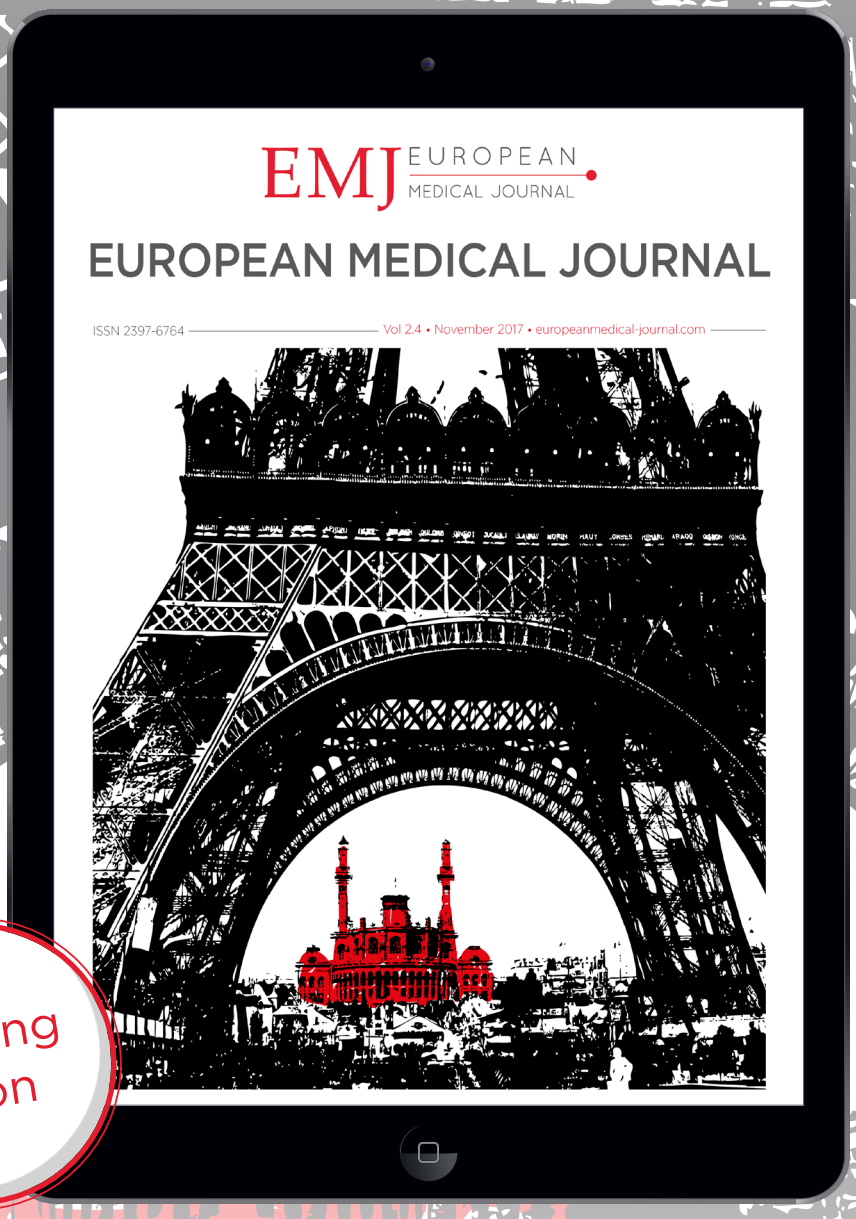


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# MIND–BODY INTEGRATIVE TREATMENT OF PSYCHODERMATOSES

***Roberto Doglia Azambuja**

*Brasilia University Hospital, Brasilia, Brazil*
**Correspondence to robertodoglia@gmail.com*

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## ABSTRACT

The mind–skin interaction has been progressively clarified by recent research that has focussed on psychoneuroimmunology. This article focusses on brain–cell communication by means of chemical messengers and the changes in the skin they provoke under stress, providing an origin to dermatoses linked to the mind, called psychodermatoses. The author refers to three types of psychodermatoses: those caused by prior psychiatric disturbances, those that cause psychologic disturbances by their aspect, and those that are influenced by emotional states. This article highlights the four simple and natural mind–body anti-stress techniques of posture, diaphragmatic breathing, muscle relaxation, and meditation that every doctor can teach to patients, which will enable them to face stressful situations and therefore protect themselves against the negative psychological effects of stress. Several therapeutic behaviours in the doctor–patient relationship are recommended to build a patient's trust in their doctor and to encourage the patient to play an important part in their treatment process. It is emphasised that the treatment of psychodermatoses needs to be co-operative, integrating specialists in dermatology, psychiatry, and psychology. Dermatologists take care of the skin alterations, while psychiatrists are involved with the associated mental disturbances and are able to prescribe a large range of psychopharmaceuticals to treat anxiety, depression, post-traumatic stress disorder, and compulsive states. Psychotherapists try to correct erroneous behaviours and false feelings, employing cognitive-behavioural therapy, analytic and reprogramming techniques, and also hypnosis, in order to rid patients of psycho-emotional perturbations and facilitate successful outcomes in the skin.

Keywords: Psychodermatology, psychoneuroimmunology (PNi), stress, mind–body, doctor–patient relationship, biopsychosocial.

## INTRODUCTION

The mind–body interaction has always been evident. Some normal physiological events demonstrate how thoughts have physical consequences in the body, for example:

- Flushing of the cheeks in embarrassing situations, whether the problem be real or imaginary. Simply thinking of the situation is enough to unintentionally provoke rubefaction.
- Paleness of the skin and muscle contraction when thinking of a serious threat.
- Having hair on the body stand on end, or a 'skin crawling' sensation, when in the presence of something an individual perceives as a phobia, for example, a snake.
- Tachycardia and tachypnoea under stress.
- Vasodilation when one feels an overwhelming rage, with the skin turning red.
- Activation of the salivary glands upon imagination of a palatable food source, for example if one imagines fresh lemon juice on the tongue. The lemon is only an idea, but the salivation that occurs is perceptible.

All individuals are aware of these effects through their own observations and experiences: scientific proof is not required of them to assure the public that these phenomena are real. These processes take place in the mind but alter the body's physiology. It is an evidence-based fact that the mind acts over the body and has the power to cause perceptible changes within it. Meanwhile,

these clear phenomena have so far been ignored by dualistic medicine, which stated that the mind and body were two separated entities and wholly independent from one another (Cartesian paradigm). It was only in 1991 that the medical pluralism was recognised, when the National Institutes of Health (NIH) established the Office of Alternative Medicine, which was intended to explore the scientific basis for the effectivity of other types of medicines from outside of the biomedical model.[1,2]

Research carried out by psychologist Dr Robert Ader and pathologist Dr Nicholas Cohen in 1970 discovered the ways in which mental events influenced the physical alterations of the body, particularly the immunologic and endocrine functions, in the form of pavlovian conditioning. In 1975, they published an article on their findings and started a new field of science, called psychoneuroimmunology (PNI).[3] Their work promoted the transformation of the materialistic, mechanistic, and reductionist biomedical concepts, and brought to light the biopsychosocial or integrative concept in which health and disease are viewed as a continuum and the dynamic result of mind, emotions, culture, heredity, and environmental interaction. This integrative model encompassed several medical specialties, such as endocrinology, gastroenterology, cardiology, and dermatology. With reference to the skin, it resulted in a broadened knowledge of how the skin functions in combination with emotional states and psychological activity. A new understanding was conceived, called 'psychodermatology', the principles of which are a) the mental and emotional mechanisms involved in the genesis, maintenance, and worsening of dermatoses; and b) the mental, emotional, and social consequences of skin diseases.

Starting with PNI, the concept evolved so that the mind and body constituted a functional unit with bidirectional communication, where nothing happens in one without impacting on the other.[4] Likewise, the mind and skin are constantly communicating so that cutaneous physiology is influenced by thoughts, and cutaneous sensations are delivered to the brain, interpreted, and recognised by the mind. The brain is the command centre where the transductions of subtle energy in chemical messengers takes place.[5]

## MIND–SKIN CONNECTION

The mind–skin relationship uses the same pathways as all tissues and organs. Thoughts of stress are transduced from vibrational signs in chemical substances and activate the paraventricular nucleus of the hypothalamus, and the closely related locus coeruleus nucleus in the brain stem. The hypothalamus secretes corticotropin-releasing hormone that reaches the pituitary gland where it stimulates adrenocorticotropin hormone liberation. This hormone acts as a messenger to the adrenal glands, which are induced to secrete cortisol and small amounts of adrenaline. The locus coeruleus has a neuronal connection with the paraventricular nucleus and activates the sympathetic nervous system to secrete noradrenaline, stimulating the production of adrenaline and noradrenaline by the adrenal glands. These catecholamines, as well as cortisol, target the skin cells directly, affecting their performance and the innate and adaptive immune systems present within the skin.[6] Furthermore, via nerves and circulation, a large number of chemical messengers are sent from the brain as neurotransmitters, neurohormones, and neuropeptides, their compositions depending on the thoughts processed in the central nervous system. Thoughts may be unpleasant, like worries, or pleasant, such as the idea of achieving a goal. Unpleasant thoughts drive the anterior pituitary to create a state of alertness and tension, known as the 'fight-or-flight' reaction, while pleasant thoughts stimulate the posterior pituitary to secrete calm and satisfaction hormones, leading to a relaxation response.

Cutaneous cells express receptors for every chemical messenger sent from the brain and respond to all received stimuli, producing the same substances that come from the brain, such as adrenocorticotropin hormone, corticotropin-releasing hormone, serotonin, prolactin, and substance P.[7-9] In a situation where the organism is exposed to stress, increased concentrations of chemical messengers flow to the skin, where they exert their action by changing the skin functions and provoking a number of disorders, examples of these include evident worsening of dermatoses, impairment of wound healing,[10,11] activation of sebaceous and sweat glands, alteration of recovery of the stratum corneum barrier,[12] decrease in antigen presentation function of the Langerhans cells,[13,14] neurogenic inflammation by substance P liberation in nerve endings, reduction of hair growth,[15-17] and/or acceleration of cutaneous carcinogenesis induced by ultraviolet light.[18]

These facts indicate that the mind, nervous system, and skin constantly communicate by means of

chemical messengers and their receptors, named the psychosomatic network.[19] These messengers are the chemical equivalents of thoughts and each thought generates a biochemical state in the body. This is not a fact that occurs by chance, or only under special conditions, but takes place as a physiological event all the time.

## PSYCHODERMATOSES

Cutaneous events that involve the mind–skin interaction are called psychodermatoses and have been observed and reported since the era of Hippocrates.[20] What is new, however, is the light modern science is shedding on the link between emotional stresses, psychiatric disease, mediators, and functioning of skin cells, all of which are jointly involved in the pathogenesis of dermatoses. In a general sense, psychodermatoses are classified into three groups: Group 1: dermatoses originating from a primary psychiatric disturbance; Group 2: psychiatric disturbances caused by disfiguring dermatoses; and Group 3: dermatoses that are triggered, exacerbated, or maintained by psychological states.[21-23]

In Group 1, the primary alteration exists in the mind or in the central nervous system function, and skin alterations come thereafter. The most commonly observed dermatoses in this group are delusions of parasitoses, dermatitis artefacta, psychogenic excoriations, trichotillomania, bromhidrosis, malingering, body dysmorphic disorders, somatoform disorders, psychogenic pruritus, lichen simplex chronicus, and acne excoriée. A variety of psychological processes form the basis of these dermatoses, with the most frequently observed being depressive, obsessive-compulsive, post-traumatic, delusional, and body dysmorphic disorders, as well as personality disorders and social phobia.[24]

Group 2 includes dermatoses that give rise to mental and emotional instability. In these cases, the presence of the skin condition causes anxiety, depression, suicidal thoughts,[25] and feelings of fear, worry, embarrassment, impatience, anger, sadness, frustration, and/or distress. Sometimes patients isolate themselves from social contact and change the clothes they wear in order to hide the skin defect. Any sort of dermatosis can elicit these effects, but it is mainly seen in cases of psoriasis, vitiligo, acne, alopecia areata, rosacea, seborrhoeic dermatitis, hyperhidrosis, melasma, hypertrichosis, ichtyosis, and hidradenitis suppurativa.[26-29]

Group 3 is composed of dermatoses that are influenced by worries, post-traumatic stress, fear, negative thoughts, sadness, anxiety, and/or discouragement. Depending on the patient's psychological constitution, these and other emotional variances can start, maintain, or worsen dermatoses through changes in immunomediators. The conditions that are most likely to receive these influences are psoriasis, atopic dermatitis, seborrhoeic eczema, prurigo nodularis, lichen planus, chronic urticaria, alopecia areata, pruritus,[29,30] and herpes simplex infections.[31]

## INTEGRATIVE CARE

Due to the interaction of psychoemotional factors and the skin, it is mandatory that healthcare professionals care for both areas, pursuing an integrative, mind–body treatment. The dermatologist's role is to have knowledge of the pathogenetic mechanism of these dermatoses to allow the ability for them to manage the conditions, focussing on the cutaneous lesions. Depending on the nature and severity of the psychological or psychiatric impairment, the dermatologist should suggest that the patient has a consultation with a psychologist, psychiatrist, or both. No specialist has the skill to master dermatologic, psychotherapeutic, and psychiatric expertise combined, along with the techniques to apply these specialisms to each particular clinical case. Even if the dermatologist does have these abilities, they would not have enough time to give sufficient attention to each individual patient. Therefore, the collaboration among dermatologists, psychiatrists, and psychologists, is necessary for the effective treatment of psychodermatoses cases.

## THE DOCTOR–PATIENT RELATIONSHIP

The most valuable help that the dermatologist can provide to their patients is the way they relate to their experiences. A healthy doctor–patient relationship is the simplest resource that can help the patient to gain a sense of satisfaction and happiness, for their own benefit.[32,33] Some aspects of this relationship that should be followed by the doctor are:

- Welcome: How the doctor receives the patient, preferably with a friendly posture and a smiling face.
- Listen: The doctor should listen to what the patient has to say about the reason for their visit and pay strict attention to the significance

of their words, speculating what may be behind them.
- Qualify the complaints: The doctor must make it clear that they value the importance of the patient's complaints in relation to their everyday lives.
- Empower the patient: The doctor should indicate what the patient can do to help themselves without help from the doctor.
- Avoid iatrogenic words: The doctor should never say "that condition has no cure" or other words that can give the patient negative feelings and expectations; remember that the patient's body reacts to their beliefs and to the doctor's convictions.[34]
- Lead the patient to perceive things that are beyond the available evidence.
- Warn about the effects of the imagination: Mental images may have the potential to become reality, so it is always better to have positive mental thoughts.
- Encourage the patient to have faith in themselves to change their condition.
- Make a diagnosis, but do not make a prognosis; often the doctor's predictions will not be fulfilled and this can cause stress in the patient if the alternative consequence is disastrous.
- Touch: Ensure the patient knows they can rely on the doctor for help through verbal support. Provide physical support where appropriate; however, never invade the patient's space if there is no permission to get closer. The patients who have received a supportive embrace from their doctor have had the sensation that the visit lasted double that of the time it actually did.[35]

## MIND–BODY ANTI-STRESS RESOURCES

Stress, perceived as the set of abnormal reactions that an organism is forced to accomplish in order to adapt to a threatening situation, is the origin of many illnesses; the number of cases of stress-related illnesses is increasing since research provides greater knowledge of the mind–body communication pathways. This allows patients a greater understanding of the stress mechanisms and enhances their ability to efficiently deal with it. Stress influences the brain, glands, hormones, immune system, heart, and lungs to provide energy, oxygen, muscle strength, fuel, resistance to pain, mental acuity, and temporary defence against infections. Meanwhile, when chronically activated, it leads to damage in the organism and exacerbates disease.[36,37]

Nobody is free from stress; however, it is possible to adopt methods of adapting to stress to protect oneself from its consequences. This can be achieved by adopting natural attitudes that allow relaxation of the muscles and maintenance of slow and calm breathing to keep the brain alert. These attitudes can be taught to the patient by every doctor during a consultation and they will make a significant difference to their lives if incorporated into their daily routine. There are four procedures that patients can adopt to reduce their stress levels:

- Erect posture, including a straight spinal column, shoulders slightly backwards, chin up, face directly forward, and arms hanging down. This position favours movement of the chest to ensure proper breathing and psychologically it makes the person feel confident and self-aware.
- Diaphragmatic breathing involving calming inhalations that are deep and slow, dilating the abdominal wall so that the diaphragm is forced down and the inhaled air reaches the lower part of the lungs.
- Muscle relaxation to consciously and progressively relieve muscle tension from the feet to the eyelids and then staying in this physical state for a number of minutes.
- Meditation is a well-studied technique that has proven, positive results on the brain physiology and functioning. There are numerous forms of meditation; the most commonly used forms in medicine are transcendental meditation and mindfulness meditation. Regular meditation practice maintains the person in a relaxed state of alert.

These four attitudes lower stress and reduce the burden on the immune, endocrine, cardiovascular, and nervous systems, consequently favouring overall health.[38]

## SPECIALIST CO-OPERATION

Psychological and emotional states in relation to dermatoses are increasingly being demonstrated. They are not accidental and are in fact part of the patient's clinical picture. Therefore, all disease aspects should be treated together, since each one influences the others. The skin alterations that appear as eczema, excoriations, tears, cuts, bites, burns, wounds, scars, and alopecic areas are

the dermatologist's field of action. In cases of dermatoses secondary to psychiatric problems, improvement of the condition depends on the control of the mental state. When the dermatosis itself gives rise to secondary emotional perturbations, the patient will only regain tranquillity as the skin recovers to its normal appearance. In cases of dermatoses aggravated by stress, there is a mutual influence between the improvement of one factor and the subsequent improvement of the other.

The psychiatrist, after performing the psychodiagnosis,[39] has access to a range of psychopharmaceuticals, used to control psychoses and emotional and psychological disturbances that lead to cutaneous problems, such as neuroleptics, antidepressants (tricyclic and selective serotonin reuptake inhibitors, noradrenaline-serotonin reuptake inhibitors, noradrenaline-dopamine reuptake inhibitors, and presynaptic antagonists), anxiolytics (benzodiazepines and nonbenzodiazepines), antihistamines with central effect, and hypnotics.[39] All of these medications cause a variety of side effects and have specific characteristics. Their correct use needs to be performed by a dermatologist who is experienced in the management of these substances, or by a psychiatrist, the healthcare professional best qualified to prescribe these medications to help relieve patient symptoms.

Emotional disturbances associated with psychodermatoses demand psychotherapies. In order to treat these conditions successfully, the psychotherapist should have an interest in dermatology, in the role skin diseases exert on the patients' psyche, and in the power psychoemotional problems possess in initiating cutaneous reactions. Post-traumatic stress, mood disturbances, negativity (preference for bad results), conflicts, difficulties in decision-making, worries, sadness, losses, discourage, frustrations, mourning, anger, and other unpleasant emotions powerfully influence the skin, as well as originating from skin conditions. In these situations, psychotherapy is essential and patients using psychiatric medication have a more favourable prognosis when also attending psychotherapy sessions.[40-43] There is a diverse range of psychotherapies that can be useful for patients. The most commonly practised are analytic therapies, like psychoanalysis, cognitive-behavioural therapy, transactional analysis, Gestalt-therapy, bioenergetics analysis, and many more. Clinicians can also rely on the so-called 'mind reprogramming' therapies, examples of which are eye movement desensitisation and reprogramming, neuro-linguistic programming, thought field therapy, and emotional freedom techniques, all of which give fast results. It is important to acknowledge that no single type of psychotherapy is applicable to all patients or will give the same outcome in every case. Whether the results will be positive is very much based on the individual. Another method of treatment is hypnosis, which can be used in a large number of dermatologic issues, potentially providing impressive improvements and even cure.[44-47]

Ideally, the three specialists discussed in this review should attend joint consultations in a liaison clinic in order to merge their biomedical and biopsychosocial views. The patient should not know who is a dermatologist, psychiatrist, or psychologist, therefore avoiding possible refusal of the patient to liaise with any specialist type.[48,49] This is the most efficient way to deal with psychodermatoses, although it is rarely feasible in the majority of hospitals.

## CONCLUSION

As mentioned, PNI has continuously contributed to clarifying how mental processes influence the organism and how the mind is influenced by the body. In regard to the skin, we now understand the mechanisms by which many, if not all, dermatoses are linked to the mind. This understanding has led to the creation of the concept of psychodermatoses and the understanding that their treatment needs to be accomplished by integrating specialists in skin and psychology for consistent results; this would best be performed in liaison consultations.

## REFERENCES


1. Castro MG et al. Mind and body concept through history. Psicol em Estudo. 2006; 11(1):39-43.
2. Narahari SR et al. Evidence-based integrative dermatology. Indian J Dermatol. 2013;58(2):127-31.
3. Ader R, Cohen N. Behaviorally conditioned immunosupression. Psychosom Med. 1975;37:333-40.
4. Kumar R, Yeragani VK. Psyche and soma: New insights into the connection. Indian J Psychiatry. 2010;52(Suppl 1): S233-9.
5. McEwen BS. Brain on stress: How the social environment gets under the skin. Proc Natl Acad Sci USA. 2012;109 Suppl 2: 17180-5.
6. Hall JMF et al. Psychological stress and

the cutaneous immune response: Roles of the HPA axis and the sympathetic nervous system in atopic dermatitis and psoriasis. Derm Res Pract. 2012:403908.

7. Suárez AL et al. Psychoneuroimmunology of psychological stress and atopic dermatitis: Pathophysiologic and therapeutic updates. Acta Derm Venereol. 2012;92(1):7-15.

8. Chen Y, Lyga J. Brain-skin connection: Stress, inflammation and skin aging. Inflamm Allergy Drug Targets. 2014;13(3): 177-90.

9. Slominski AT et al. Key role of CRF in the skin stress response system. Endocr Rev. 2013;34(6):827-84.

10. Christian LM et al. Stress and wound healing. Neuroimmunomodulation. 2006; 13(5-6):337-46.

11. Gouin JP, Kiecolt-Glaser JK. The impact of psychological stress on wound healing: Methods and mechanisms. Immunol Allergy Clin North Am. 2011; 31(1):81-93.

12. Garg A et al. Psychological stress perturbs epidermal permeability barrier homeostasis. Arch Dermatol. 2001; 137(1):53-9.

13. Kleyn CE et al. The effects of acute social stress on epidermal Langerhans' cell frequency and expression of cutaneous neuropeptides. J Inv Dermatol. 2008;128(5):1273-9.

14. Madva EN, Granstein RD. Nerve-derived transmitters including peptides influence cutaneous immunology. Brain Behav Immunol. 2013;34:1-10.

15. Arck PC et al. Neuroimmunology of stress: Skin takes center stage. J Invest Dermatol. 2006;126(8):1697-704.

16. Ito T. Hair follicle is a target of stress hormone and autoimmune reactions. J Dermatol Sci. 2010;60(2):67-73.

17. Hadshiew IM et al. Burden of hair loss: Stress and the underestimated psychosocial impact of telogen effluvium and androgenetic alopecia. J Invest Dermatol. 2004;123(3):455-7.

18. Parker J et al. Chronic stress accelerates ultraviolet-induced cutaneous carcinogenesis. J Am Acad Dermatol. 2004;51(6):919-22.

19. Pert CB. Neuropeptides and their receptors: A psychosomatic network. J Immunol. 1985;135(2 Suppl):820s-6s.

20. França K et al. Psychodermatology: A trip through history. An Bras Dermatol. 2013;88(5):842-3.

21. Koo J, Lebwohl A. Psychodermatology: The mind and skin connection. Am Fam Physician. 2001;64(11):1873-8.

22. Jafferany M. Psychodermatology: A guide to understanding common psychocutaneous disorders. Prim Care Companion J Clin Psychiatry. 2007;9(3): 203-13.

23. Sharma BYK et al. Skin and psyche: Diversionary symbiosis. MJAFI. 2005; 61(2):163-6.

24. Gupta MA, "Psychiatric comorbidity in dermatological disorders," Walker C, Papadopoulos L (eds.), Psychodermatology: The Psychological Impact of Skin Disorders (2005) New York: Cambridge University Press, pp.29-43.

25. Dalgard FJ. The psychological burden of skin diseases: A cross-sectional multicenter study among dermatological out-patients in 13 European countries. J Invest Dermatol. 2015;135(4):984-91.

26. Huynh TT. Burden of disease: The psychosocial impact of rosacea on a patient's quality of life. Am Health Drug Benefits. 2013;6(6)348-54.

27. Moon HS et al. Psoriasis and psycho-dermatology. Dermatol Ther (Heidelb). 2013;3(2):117-30.

28. Tasoula E et al. The impact of acne vulgaris on quality of life and psychic health in young adolescents in Greece. Results of a population survey. An Bras Dermatol. 2012;87(6):862-9.

29. Moynihan J et al. Psychoneuroimmunology: The example of psoriasis. G Ital Dermatol Venereol. 2010;145(2):221-8.

30. Arck P, Paus R. From the brain-skin connection: The neuroendocrine-immune misalliance of stress and itch. Neuroimmunomodulation. 2006; 13(5-6):347-56.

31. Horn EE. Psychological distress, emotional stability, and emotion regulation moderate dynamics of herpes simplex virus type 2. Ann Behav Med 2015;49(2):187-98.

32. Poot F. Doctor-patient relations in dermatology: obligations and rights for a mutual satisfaction. J Eur Acad Dermatol Venereol. 2009;23(11):1233-9.

33. Dixon DM et al. The physician healer: Ancient magic or modern science? Br J Gen Practice. 1999;49(441):309-12.

34. Spiegel D. Healing words. Emotional expression and disease outcome. JAMA. 1999;281(14):1328-9.

35. Carey B. Evidence that little touches do mean so much. New York Times. 2010. Available at: www.nytimes.com/2010/02/23./health/23.mind.html. Last accessed: 25 September 2017.

36. McEwen BS. Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators. Eur J Pharmacol. 2008; 583(2-3):174-85.

37. Pang S et al. Chronic stress suppresses the expression of cutaneous hypothalamic-pituitary-adrenocortical axis elements and melanogenesis. PLOS ONE. 2014;9(5):e98283.

38. Stahl JE et al. Relaxation response and resiliency training and its effect on healthcare resource utilization. PLoS One. 2015;10(10):e 0140212. Erratum in: PLoS One. 2017;12(2):e0172874.

39. Ghosh S et al. Psychiatric evaluation in dermatology: An overview. Indian J Dermatol. 2013;58(1):39-43.

40. Harth W et al. "Psychopharmacological Therapy in Dermatology," Harth W et al., Clinical Management in Psychodermatology (2009), Berlin–Heidelbert: Springer-Verlag, pp 239-58.

41. Müller MC, Ramos DG. Psychodermatology: An interface between psychology and dermatology. Psicol ceinc prof. 2004;24(3).

42. Fried RG, Hussain SH. Nonpharmacologic management of common skin psychocutaneous disorders. Dermatol Ther. 2008;21(1)60-8.

43. Papadopoulos L, "Psychological therapies for dermatological problems," Walker C, Papadopoulos L (eds.), Psychodermatology: The Psychological Impact of Skin Disorders (2005), New York: Cambridge University Press, pp.101-15.

44. Shenefelt PD. Psychological interventions in the management of common skin conditions. Psychol Res Behav Manag. 2010;3:51-63.

45. Tausk F, Whitmore SE. A pilot study of hypnosis in the treatment of patients with psoriasis. Psychother Psychosom. 1999;68(4):221-5.

46. de Zoysa P. Psychological interventions in dermatology. Indian J Dermatol. 2013;58(1)56-60.

47. Shenefelt PD. Hypnosis in dermatology. Arch Dermatol. 2000; 136(3):393-9.

48. Shenoi SD et al. Our experience in a psychodermatology liaison clinic at Manipal, India. Indian J Dermatol. 2013; 58(1):53-5.

49. Basavaraj KH et al. Relevance of psychiatry in dermatology: Present concepts. Indian J Psychiatry. 2010;52(3): 270-5.

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- HYUNDAE MEDITECH CO., LTD.
- IFC
- ILOODA CO., LTD.
- ISISPHARMA
- IVATHERM
- JAMJOOM PHARMA
- JANSSEN
- JAPAN BIO PRODUCTS CO., LTD.
- JEISYS MEDICAL INC.
- JETT MEDICAL
- JOHNSON & JOHNSON CONSUMER
- KAI EUROPE GMBH
- KERNEL MEDICAL
- KING LASER TECHNOLOGY
- KORUST CO. LTD.
- KREUSSLER PHARMA

# Dermatology

- K-SURGERY
- LA ROCHE-POSAY
- LABORATOIRE BIODERMA
- LABORATOIRE DERMATOLOGIQUE ACM
- LABORATOIRES BAILLEUL INTERNATIONAL
- LABORATOIRES DERMATOLOGIQUES D'URIAGE
- LABORATOIRES PIERRE FABRE DERMO-COSMÉTIQUE
- LASEROPTEK
- LASERVISION GMBH & CO. KG
- LEO PHARMA
- LILAC LABORATOIRES
- L'OREAL PARIS
- LUMENIS
- LUMINERA DERM
- MARTIDERM
- MAVIG GMBH VIVASCOPE SYSTEMS
- MEDAC GMBH
- MESOESTETIC PHARMA GROUP
- MIRADRY
- MIXA
- NEAUVIA
- NEOSTRATA COMPANY, INC.
- NEWPONG CO., LTD.
- NIUU MEDICAL AESTHETIC
- NOMARD LTD.
- NOREVA LABORATOIRES
- NOVACLINICAL
- NOVARTIS
- NOVELLA CLINICAL
- NOVOXEL
- OMNILUX
- PAN RC GROUP PCL
- PENINSULA MEDICAL
- PFIZER
- PROINNOVERA GMBH
- PROTECT – LASERSCHUTZ GMBH
- Q-SKIN SCIENCE/AK PHARMA
- QUANTA SYSTEM SPA
- QUANITIFICARE
- QVENTIS GMBH
- RA MEDICAL SYSTEMS, INC.
- READY MEDICAL
- REFORM SKINCARE
- REGEN LAB
- SAINT GERVAIS MONT BLANC
- SANDOZ
- SANOFI GENZYME AND REGENERON
- SCITON
- SEOULINMEDICARE CO., LTD.
- SESDERMA
- SHENB
- SILHOUET-TONE
- SKINCEUTICALS
- SKYMEDIC
- SNJ
- STIEFEL, A GSK COMPANY
- STORZ MEDICAL AG
- SUISSELLE SA
- SYNERON CANDELA
- TAV TECH
- THE HYDRAFACIAL COMPANY
- THERMI, AN ALMIRALL COMPANY
- TKL RESEARCH, INC.
- TPM TABERNA PRO MEDICUM GMBH
- UNITE MEDICAL LIMITED
- VENUS CONCEPT
- VICHY LABORATOIRES
- VISIOMED AG
- VISUALDX
- VIVOSIGHT
- VONAGE LABORATOIRES/ ELLARO
- VYDENCE MEDICAL
- WALDMANN – MEDICAL DIVISION
- WONTECH CO., LTD.
- YERIM ENGINEERING CO., LTD.
- ZIMMER MEDIZIN SYSTEME GMBH