EMJ EUROPEAN MEDICAL JOURNAL

# DERMATOLOGY

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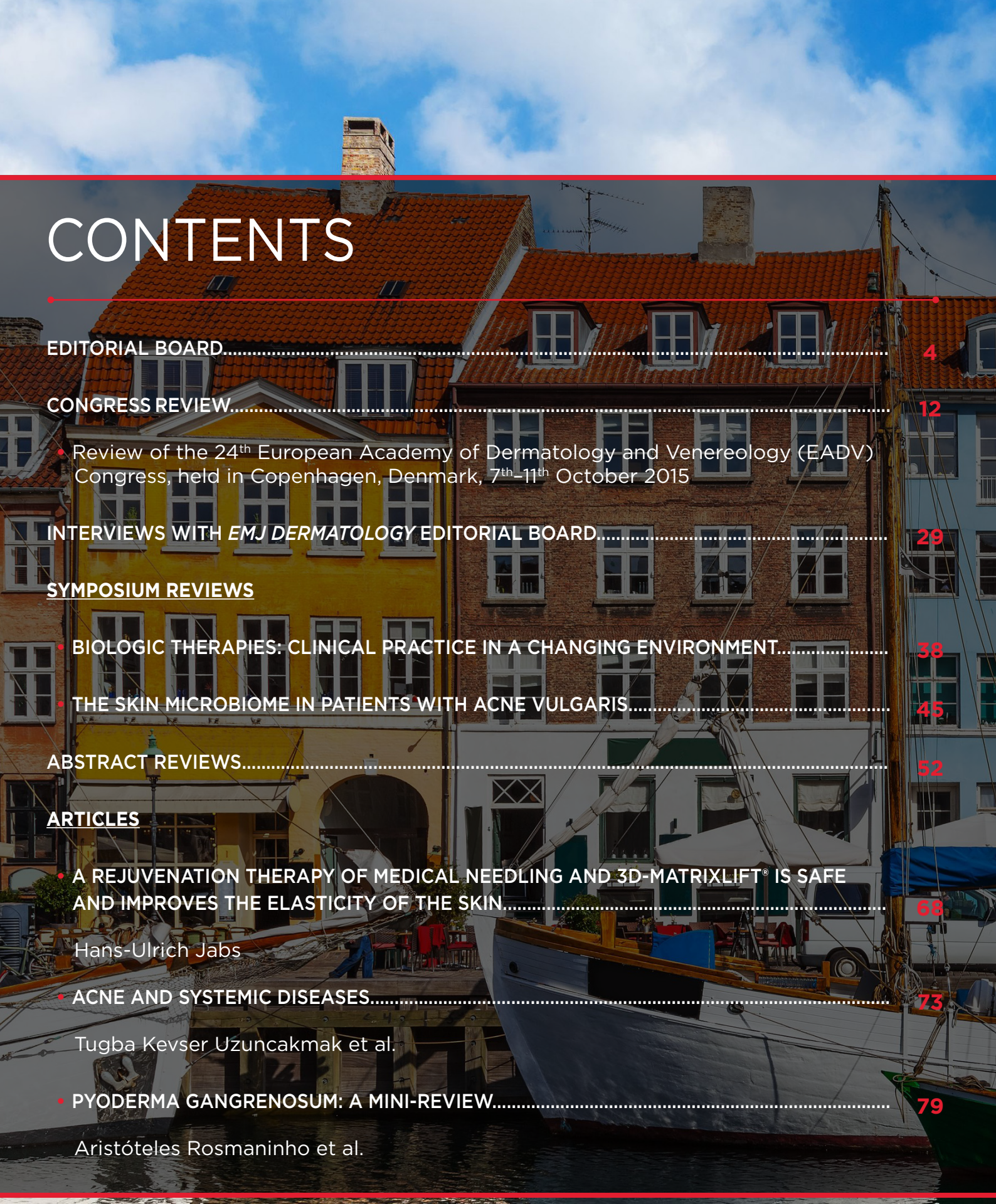
**INSIDE**

Review of

**EADV 2015**

Copenhagen, Denmark



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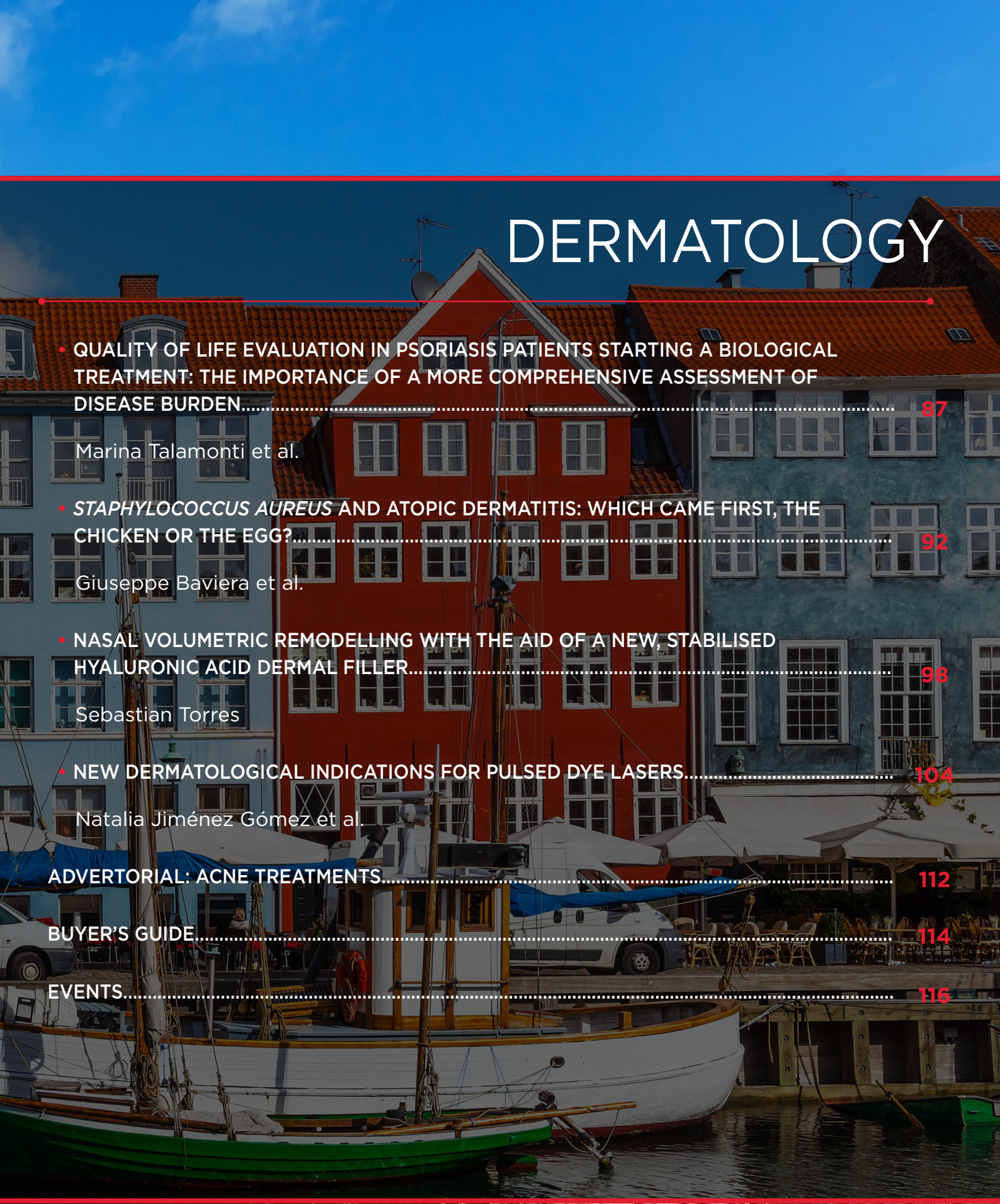

# DERMATOLOGY

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# Dermatology

EMJ GORELY NEW MEDIA

*European Medical Journal*
EMJ Dermatology Vol 3.1
November 2015



The MedBIC,
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# Welcome

Hello and a very warm welcome to *European Medical Journal Dermatology*. In this edition of our eJournal we have included a selection of reviews describing some of the most innovative and impactful advances of 2015, as well as a detailed summary of events taking place at the 24th Congress of the European Academy of Dermatology and Venereology (EADV), which was hosted by Copenhagen, Denmark, from the 7th–11th October.

Home to Medicon Valley, a thriving hub for a multitude of institutions and companies aiming to further medical progress, Copenhagen was the perfect backdrop for the 2015 EADV congress. Once again this meeting provided a variety of novel insights for attendees, and it certainly met its goal of fostering innovation and promoting scientific excellence in dermato-venereology for the benefit of patients with skin diseases. Whether you were lucky enough to attend or not, in the following pages you can now review an assortment of the most important developments and presentations from the congress. We also include a number of interviews with experts in the field who share their perspectives on how medical practice and dermatology are likely to develop in the near future.

This edition also includes a wide range of abstract reviews, which include a report on the immunopathogenesis of vitiligo from Dr Rosalie Luiten, a description of the medical approach to hidradenitis suppurativa provided by Dr John Ingram, and a summary of invasive cutaneous squamous cell carcinoma by Dr Dimitrios Papakostas. Our more comprehensive clinical reviews include an up-to-date summary of the pathogenesis, diagnosis, and treatment of pyoderma gangrenosum, as well as a review on the use of pulsed dye lasers in new dermatological indications by the team based at Ramón y Cajal University Hospital, Madrid, Spain.

We hope that you enjoy this edition of our eJournal and that it serves as a valuable resource for your work. We feel privileged to be a part of delivering the most important updates in this vital field and hope to continue to aid the progress of medical care in Europe and worldwide. Last of all we would like to thank all of you for your continuing support and we hope to bring you more exciting developments in the new year.

Spencer Gore

*Director, European Medical Journal*

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# Foreword

**Dr Marco Romanelli**

*Wound Healing Research Unit, Division of Dermatology, University of Pisa; President Elect, World Union of Wound Healing Society.*

Dear Colleagues,

I wish you a very warm welcome to the latest edition of *European Medical Journal Dermatology*.

For many years, the annual meeting of the European Academy of Dermatology and Venereology (EADV) has provided a venue where the dermatology community may gather to network, learn, and socialise. As a result, the meeting has become the largest and best dermatological conference in Europe. The EADV is committed to providing the highest level of clinical education, science, and information for specialists in dermatology, as well as a number of other allied healthcare professionals who are dedicated to the advancement of dermatology.

> "In addition to the exciting lectures and new and innovative sessions, the meeting delivered all of the outstanding continuing medical education experiences that dermatologists have come to expect."

The 24th EADV Congress, held this year in Copenhagen, made significant advances in dermatological science and research, allowing clinical practice to be grounded in evidence-based principles and guidelines. The EADV scientific committee worked tirelessly to establish what I believe was an interesting and exciting programme of scientific sessions. The meeting encompassed a number of hot topics, including wound healing, angiogenesis, pigmentary disorders, carcinogenesis, autoimmune disorders, cosmetic dermatology, and clinical trials and new technologies.

In addition to the exciting lectures and new and innovative sessions, the meeting delivered all of the outstanding continuing medical education experiences that dermatologists have come to expect. Furthermore, this year's poster sessions highlighted the exceptional research efforts of our presenters, and the free paper sessions were packed with new advances in dermatological research and treatment, keeping all attendees on the cutting edge of dermatological developments.

Inside *EMJ Dermatology* you will find an extensive review covering every aspect of the congress, from the newest scientific breakthroughs coming out of the lab, to pearls of clinical wisdom that you can apply to your practice today.

I would like to take this opportunity to thank the editorial board for their continued support, and our readers for their growing engagement. I fully encourage you to spend some time reading these pages, and to consider this eJournal your trusted source for dermatology research and practice!

Yours sincerely,

**Marco Romanelli**

Wound Healing Research Unit, Division of Dermatology, University of Pisa, Pisa, Italy; President Elect, World Union of Wound Healing Society.

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# CONGRESS HIGHLIGHTS

# DISCUSSIONS

# INTERVIEWS

# WEBCASTS



# Exclusive Videos from the American Society of Clinical Oncology (ASCO) Annual Meeting 2015

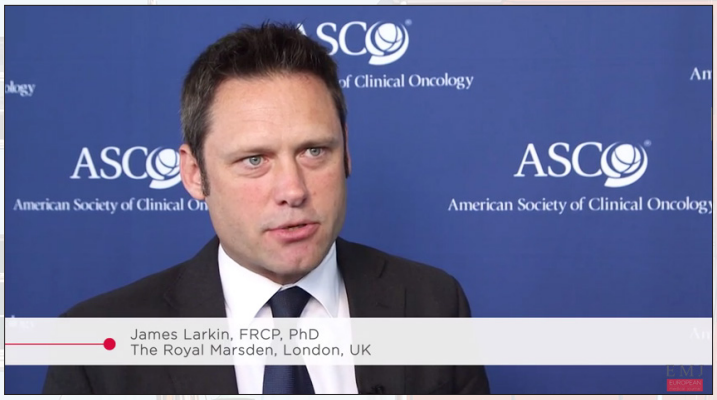
(Click on video clip to view)


## Melanoma Treatment Update at ASCO 2015

Axel Hauschild, MD


## Immunotherapy and Targeted Therapies in Melanoma at ASCO 2015

Caroline Robert, MD, PhD




## Phase 3 CheckMate 067 Trial of Nivolumab in Previously Untreated Advanced Melanoma

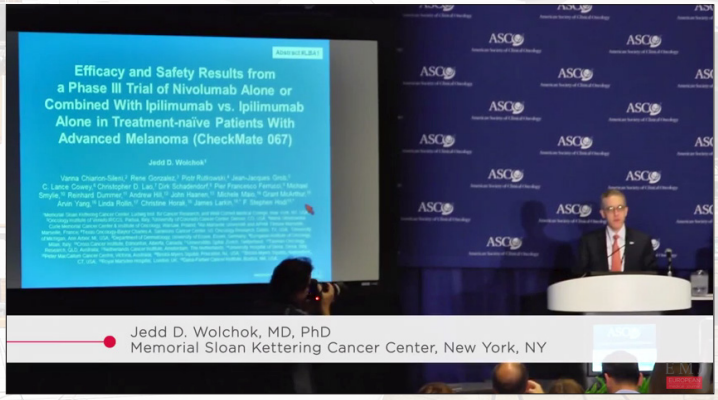
James Larkin, FRCP, PhD


## Phase 3 CheckMate 067 Trial of Nivolumab in Untreated Advanced Melanoma

Hendrik-Tobias Arkenau, MD, PhD


## COMBI-d: Phase 3 Trial of Dabrafenib Plus Trametinib in BRAF V600E/ K-mutated Melanoma

Georgina Long, BSc, PhD, MBBS, FRACP




## Combined Nivolumab and Ipilimumab or Monotherapy Shown Promise in Untreated Melanoma

Jedd D. Wolchok, MD, PhD

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# EADV ANNUAL CONGRESS 2015

BELLA CENTER COPENHAGEN,
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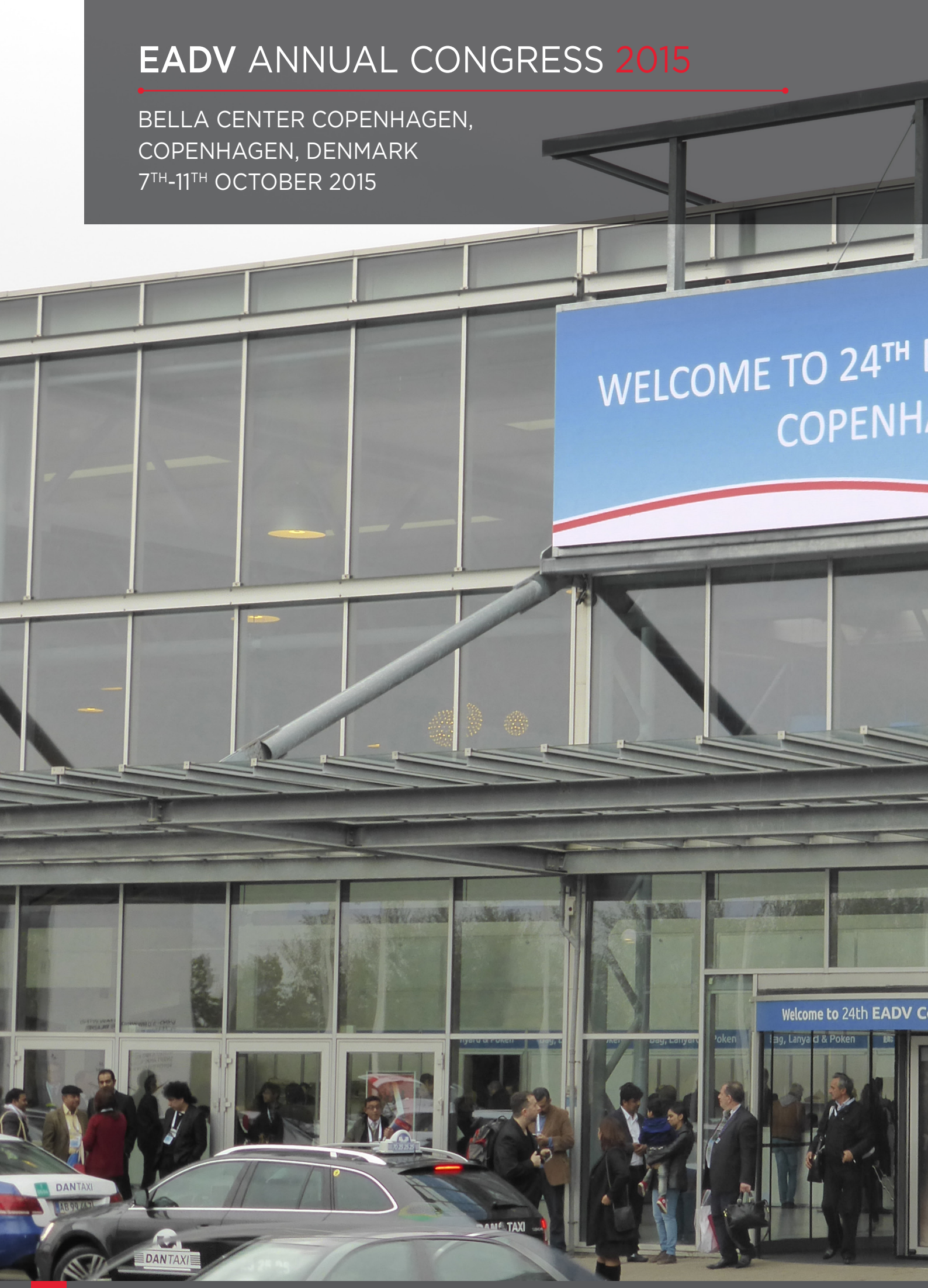


# Welcome to the *European Medical Journal* review of the 24th European Academy of Dermatology and Venereology Congress


This year's edition of the annual EADV congress, the largest dermatology and venereology meeting in Europe, took place in Copenhagen, Denmark, in front of a captivated audience. With 1,000 years of royal history, and a rich and varied mix of cultural attractions, including excellent museums and fine architecture and interiors, the Danish capital provided a glamorous backdrop for this prestigious medical event.

More than 600 renowned speakers from 30 countries around the world featured in 180 sessions during a highly intensive programme at the congress. In his welcome remarks, EADV President Prof Erwin Tschachler acknowledged the growth that this event, and EADV in general, is experiencing. "Both the EADV and their congresses have been continuously developing in scale and scope. Our vision is to foster progress in clinical care and promote scientific excellence related to dermato-venereology for the benefit of patients with skin diseases. We anticipate that the numbers of participants will further increase and that we will reach new audiences and regions," said Prof Tschachler.

A number of awards in recognition of outstanding achievements in the field of dermatology were handed out during the event. In particular, a large number of scholarships for promising young European applicants were announced: 20 obtained the Michael Hornstein Memorial Scholarship, while

a further 11 received the John Stratigos Memorial Scholarship. Meanwhile, there were 8 recipients of the Imrich Sarkany Non-European Memorial Scholarship. The winner of the coveted 'Alumni Club Lecturer of the Year' was Dr Elvira Moscarella (Italy), who subsequently presented a lecture about her professional and scientific career during the Scholarship Ceremony.

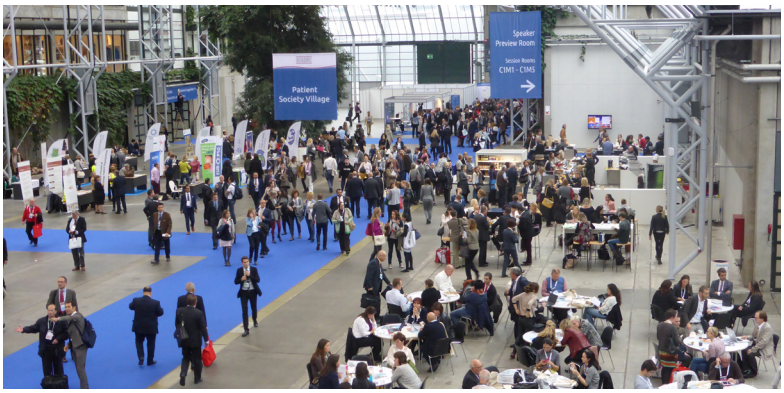
Important research detailing discoveries about major dermatological topics such as skin cancer, inflammation, infectious diseases, and clinical pathological conditions were on display throughout the event, emphasising the vitality of this particular congress to the field of dermatology. In a revamped programme format, the sessions were divided into three different levels of knowledge: 'Training and Educational Forum', to provide real training and teaching for trainees; 'Review and Updates', for an in-depth analysis of important topics; and 'Experts Forum', where the most experienced specialists had a platform to critically examine and debate the most recent developments in the field.

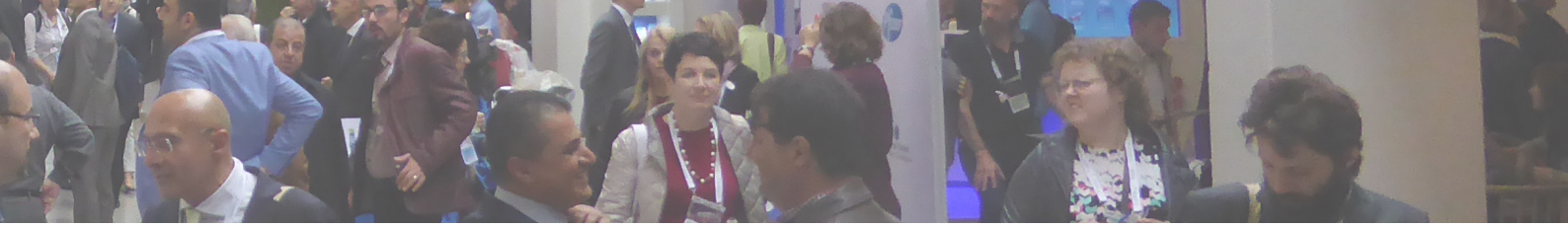
Notable presentations included an overview of our understanding and current treatment options for prominent dermatological conditions such as melanoma, invasive cutaneous squamous cell carcinoma, and purpura fulminans, which are certain to provide medical professionals with an improved understanding and knowledge about tackling such conditions in their patients in the future. Other studies outlined some of the current trends with regard to dermatological conditions and their subsequent implications for public health. This included research displaying the recent prevalence of *Neisseria gonorrhoeae* around the world and the worrying effect that this appears to be having on antibiotic treatments.

Additionally, clinical trial data regarding potential treatment options for dermatological disorders formed a significant part of proceedings. Examples of this include several abstract presentations that examined the use and effects of the drug adalimumab. Another example was the efficacy of the quadrivalent human papillomavirus vaccine in the prevention of low-grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts in HIV-positive women.

The information disseminated throughout the congress is likely to lead to improved treatments for patients in the future, providing a great deal of hope for many. The next instalment of the EADV congress is to be held in Vienna, Austria, next year, and it is expected that even more participants will be able to witness further vital discoveries in 2016.

"Our vision is to foster progress in clinical care and promote scientific excellence related to dermato-venereology for the benefit of patients with skin diseases."



# HIGHLIGHTS

## Sun Not the Only Culprit Behind Increased Risk of Melanoma

RESPONSIBILITY for melanoma is often attributed to UV light. However this only accounts for 65% of melanoma cases, with the remainder caused by a variety of multifactorial risk factors, reported Prof Veronique del Marmol, Université Libre de Bruxelles, Brussels, Belgium, at EADV 2015. The World Health Organization defines risk factors as: any attribute, characteristic, or exposure of an individual that increases the likelihood of developing a disease or injury. Risk factors can either be intrinsic or extrinsic.

Intrinsic factors are those that cannot be changed, such as age, sex, and genetics. The main intrinsic factor for melanoma is heritable germline mutations. These make up approximately 10% of all melanomas, with the most common of these being *CDNK2* and *CD4* mutations, which account for 40% of all melanomas of familial origins. Recent advances in sequencing technology have led to the discovery of more familial melanomas, including those with mutations in *BAP1*, *TERT*, *MITF*, and *POT1*. However, these discoveries each account for <1% of familial clustering of melanoma. Half of melanoma-prone families still have unidentified susceptibility genes. One way in which further genes are identified and therapies developed is by studying the cellular pathways in which these genes play a role. Aberrations in these pathways can cause melanoma.

"Even if non-UV related melanomas are rare, we have to be aware of them. They are frequently fatal because of late diagnosis and because there are fewer therapy options for these particular disease subtypes."

Epigenetic factors are those caused by an external source, the most common factor being overexpression of non-coding RNA, specifically miR-21. This factor controls gene expression and plays a vital role in regulating

epigenetic changes, which can begin the process of transformation to cancer cells. Anything that may cause overexpression of miR-21 can be an extrinsic risk factor; suggested causes include air pollution, smoking, Western diets, and sedentary lifestyles. In fact, even drinking milk could increase levels of miR-21, as bovine miR-21 is present in cow's milk and is identical to human miR-21. Sildenafil, a PDE5A inhibitor, is also known to increase risk of melanoma.

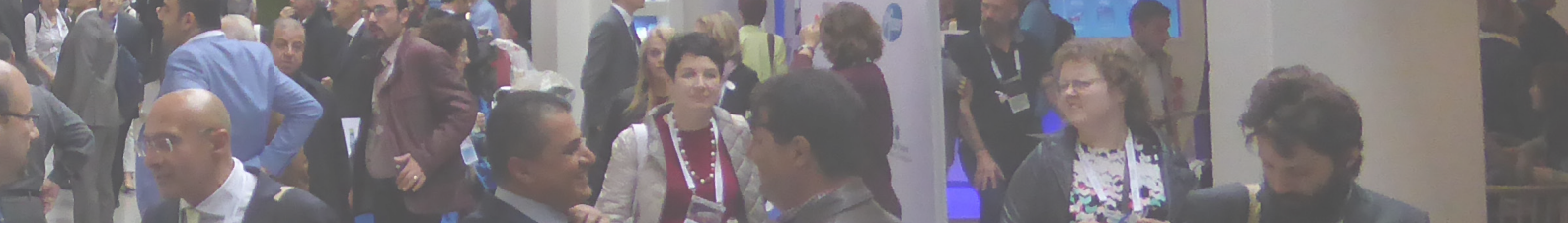
"Even if non-UV related melanomas are rare, we have to be aware of them. They are frequently fatal because of late diagnosis and because there are fewer therapy options for these particular disease subtypes," explained Prof Marmol in an EADV press release dated 9th October. "And we have to be conscious that other risks factors such as lifestyle factors – medications or pollutants – may play a role in the development of these malignancies."

Europe's biggest meeting of dermatology and venereology

## Early Diagnosis of Melanoma May Be Improved with Dermoscopy

OBSERVATION of moles has become a key part of medical care in relation to the prevention and early diagnosis of melanoma. Early detection of melanoma is associated with a good prognosis, as most Stage 1 and 2 skin cancers can be cured. However, the skin is the largest organ of the human body, and therefore its accurate surveillance can be time consuming. Increasingly, technology is being developed that enables not only fast identification of moles and malignancies of the skin, but also comparison between follow-up images at regular examinations. This aids fast diagnosis of *de novo* melanomas at the earliest possible stage, as presented at EADV 2015 and reported in a press release in October.

Melanoma mortality and incidence is rising continuously in Europe Melanomas may arise from pre-existing melanocytic nevi, although the majority of skin cancers develop *de novo*. For this reason, high-risk patients, such as those who have many moles or dysplastic nevus syndrome, should be regularly monitored for signs of skin cancer at close intervals. Application of medical imaging systems, for example those that permit total body mapping and digital dermoscopy, allows for the detection of both new and modified skin lesions that may not be detectable by the naked eye. Meta-analyses have demonstrated the efficiency of dermoscopy in the surveillance and diagnosis of melanomas in the general population. Alongside this, high-definition camera technologies featuring continuous live zoom and optical magnification allow for accurate results and



treatment, as well as documentation of dermatological features.

Further development of these technologies has allowed for documentation of skin lesions on portable devices. Users are able to upload their images onto a specialised application for advice on suspicious moles. It is hoped that these can be used to promote 'self skin-checking' among the general public (an activity which should be practised monthly), to detect new or changing lesions. In turn, this could lead to an increase in the rate of early skin cancer diagnosis.

Excitingly, these technologies are not limited to skin cancer detection, but have wider applications in dermatological practices; for example, in measuring hair loss and growth, visualisation of actinic keratoses, and capillary microscopy.

## Clinico-Imaging to Replace Clinicopathological Diagnosis in Dermatology

CLINICO-IMAGING may represent the future of diagnosing skin diseases, according to Assoc. Prof Giuseppe Argenziano, Professor of Dermatology, Second University of Naples, Naples, Italy, who was responding to questions regarding new developments in dermoscopy at EADV 2015. It is hoped that such a shift in practice will have a positive effect on melanoma mortality rates and on reducing the number of benign skin lesions that are removed.

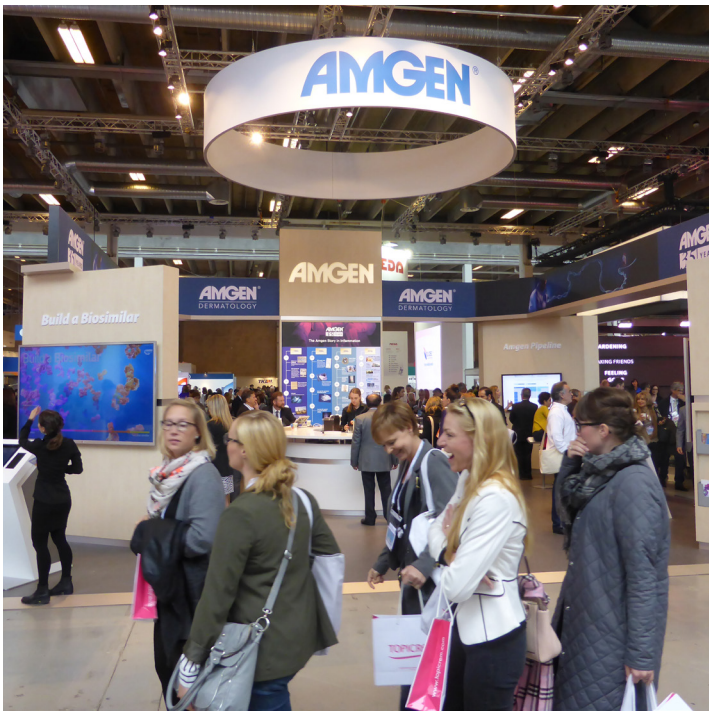
The dermatoscope is arguably the most important diagnostic tool to a dermatologist, according to Assoc. Prof Argenziano. This is not only due to the device being able to reveal a new morphological dimension of pigmented and non-pigmented skin tumours, which has been shown to be superior to examination by the naked eye for early detection of melanomas, but also because it facilitates the diagnosis of many other skin diseases through recognition of an increasing number of skin symptoms.

**Application of medical imaging systems, for example those that permit total body mapping and digital dermoscopy, allows for the detection of both new and modified skin lesions that may not be detectable by the naked eye.**

Early detection of melanoma is crucial, but dermoscopy is not regarded as crucial for its diagnosis. The main reasons why Assoc. Prof Argenziano argues that this attitude is changing are:

- The early identification of melanoma is improved due to the far earlier detection of 'pearly' malignancy signs visible with a dermatoscope compared with the classical features seen by the naked eye
- Spots on the skin that often appear benign when examined by the naked eye can be seen to be suspicious under the dermatoscope, which encourages clinicians to look at lesions that would otherwise be considered clinically banal
- Patients can be routinely monitored by clinicians using a dermatoscope, leading to an improvement in the recognition of melanoma in patients with multiple moles

"Dermoscopy allows early and highly reliable non-invasive clinico-imaging diagnosis. This is the future!" Assoc. Prof Argenziano speculated in a press release dated 9th October.



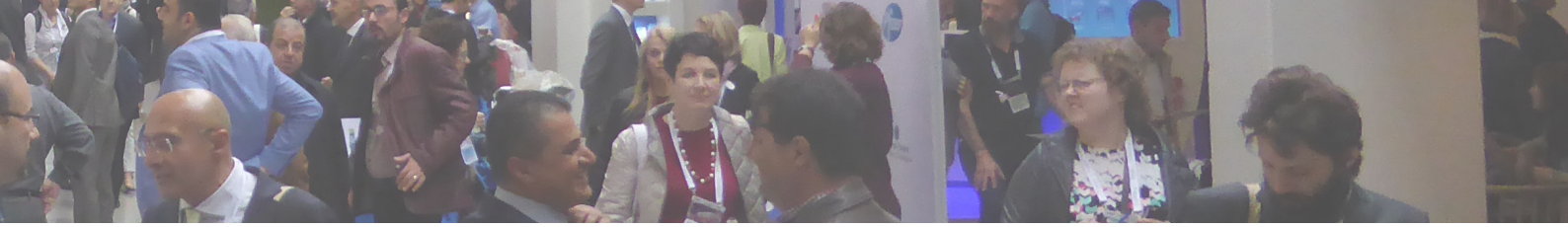

## Advancements in the Documentation of Psoriasis

PSORIASIS patients represent a challenge, even for experienced dermatologists, and patient outcomes are often inconsistent from clinician to clinician. Following the adoption of psoriasis into the agenda of the World Health Organization in 2014, many researchers, doctors, and technology companies have aimed to improve care of psoriasis patients globally, including through the development of body scanning technology. Among the results is PASIvision®, a computer-assisted assessment system launched by FotoFinder at EADV 2015, as reported in a press release in October.

Psoriasis is a common chronic inflammatory disease, characterised by scaly plaques on the skin and in approximately 10% of cases, arthritis. The disease affects 125 million people worldwide (2–5% of the population), is associated with various comorbidities, and can be fatal as extreme inflammation and peeling of the skin may impair the body's ability to regulate temperature and/or act as an effective barrier to infection, although this is rare. Despite all of this, psoriasis is relatively unknown in many countries and patients who have it experience prejudice as well as a range of harmful psychological factors caused by the visibility of the disease. This underlines the need for effective treatment.

**The development of new technologies for the assessment of psoriasis will likely represent an advancement in the standard of psoriasis research and patient care worldwide.**

It is important that patient monitoring and treatment is standardised globally. Currently, the Psoriasis Area and Severity Index (PASI) is the gold standard for diagnosing and gauging the severity of the disease. However, it has limitations; for example, poor sensitivity to change over a relatively small area, and it is difficult to discern dermoscopic patterns in psoriasis by sight alone. Furthermore, PASI is largely subjective as it relies on the opinions of the clinicians and patients. Thus, the development of technologies that can help overcome these limitations and aid in the quantification of psoriasis severity will help to improve accuracy of treatment. Products such as PASIvision therefore represent useful tools that can be utilised to standardise care, improve therapy outcome, and improve measurements of treatment efficacy.



The development of new technologies for the assessment of psoriasis will likely represent an advancement in the standard of psoriasis research and patient care worldwide. Alongside increased awareness of the disease, this will likely improve the quality of life in patients with psoriasis.

## BI 655066 Superior to Ustekinumab in Phase II Psoriasis Study

RESULTS of a Phase II study in psoriasis have demonstrated superior efficacy for the investigational biologic compound BI 655066 compared with ustekinumab, a commonly used treatment for psoriasis. The research findings were presented at EADV 2015 by Dr Kim A. Papp, President of Probity Medical Research, Waterloo, Ontario, Canada.

The Phase II study investigated the efficacy of BI 655066 versus ustekinumab in 166 patients with moderate-to-severe plaque psoriasis, and found that 69% of patients treated with high-dose BI 655066 maintained completely clear (PASI 100) or almost clear (PASI 90) skin after 9 months, compared with 30% of the patients treated with ustekinumab. Skin clearance was also achieved significantly faster and persisted for longer in patients treated with BI 655066 compared with those treated with ustekinumab. Those receiving BI 655066 achieved skin clearance in approximately 8 weeks and maintained it for >32 weeks, whilst those on ustekinumab achieved clearance in approximately 16 weeks and maintained it for 24 weeks. In patients that achieved completely clear skin, almost 3-times the proportion of patients on BI 655066 maintained this after 9 months compared with those on ustekinumab (43% versus 15%, respectively). Regardless of dose, treatment with BI 655066 was associated with a safety and tolerability profile similar to ustekinumab.

In a press release dated 8th October, Dr Papp commented: "These results are striking. They further strengthen our understanding of the potential skin improvement that can be achieved with BI 655066, in moderate-to-severe plaque psoriasis. We saw a third more patients achieve clearer skin in a short time period. And this clearance was maintained longer compared to the commonly used treatment ustekinumab. Achieving clear skin quickly and maintaining clearance is an important goal for patients that have to deal with the daily impact of psoriasis."

Dr Stephen Padula, Therapeutic Area Head Medicine Immunology, Boehringer Ingelheim, Ingelheim, Germany, added: "These Phase II study results represent a major step towards our vision of transforming the treatment of immune diseases and the patients affected by it. We look forward to continued research and are currently planning multiple Phase III studies."


## Adalimumab in Hidradenitis Suppurativa, Psoriasis, and Psoriatic Arthritis

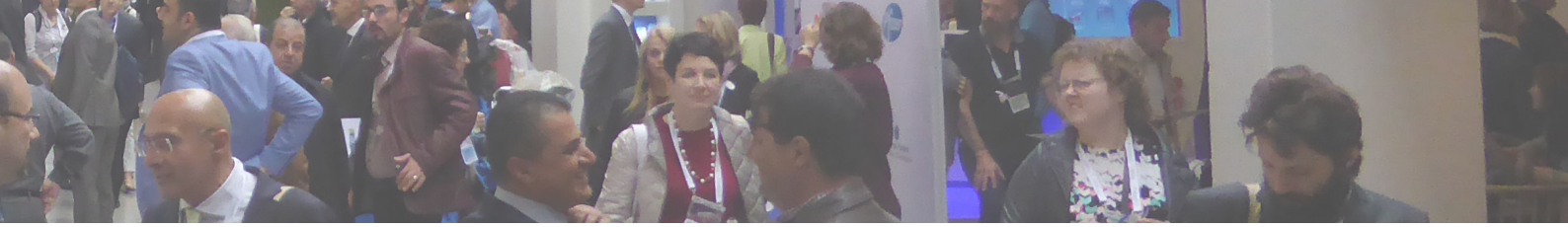
MULTIPLE abstracts describing the safety and efficacy of adalimumab in the treatment of hidradenitis suppurativa (HS), psoriasis, and psoriatic arthritis were presented at EADV 2015 and reported in a press release dated 5th October. The varied studies explored topics ranging from patient attitudes toward TNF inhibitors and conventional therapies to clinical data from Phase III trials in HS patients. These new studies suggest that the drug has an encouraging future and it is hoped that ongoing research will improve the treatment and care of patients with serious dermatological diseases.

These new studies suggest that the drug has an encouraging future and it is hoped that ongoing research will improve the treatment and care of patients with serious dermatological diseases.

HS is a severe, long-term disease that causes painful abscesses and scarring in specific areas, commonly the groin and armpits. Adalimumab has recently been approved for the treatment of HS by several regulatory agencies, including the US FDA and European Medicines Agency. Several of the abstracts presented at EADV 2015 described results from the PIONEER I and II trials, including 'Risk of Flare in Patients with Hidradenitis Suppurativa Treated With Adalimumab for 12 Weeks During PIONEER I and PIONEER II: Two Phase 3, Randomized, Placebo-Controlled Trials' and 'Clinical Meaningfulness of the Hidradenitis Suppurativa Clinical Response Endpoint to Assess Inflammation and Treatment Response in Two Phase 3, Randomized, Placebo-Controlled Trials (PIONEER I & II)'.

Psoriasis and psoriatic arthritis were also addressed in a series of abstracts, including results from the REVEAL, ADEPT, and ALIGN trials. Notable abstracts included: 'Safety and Efficacy of Adalimumab in Combination With Different Doses of Methotrexate in Patients with Psoriatis Arthritis: Subanalysis of ADEPT' and 'Six-Year Interim Results from the ESPRIT 10-Year Postmarketing Surveillance Registry of Adalimumab for Moderate to Severe Psoriasis'.

More than 600 star speakers




Adalimumab is a TNF-inhibiting, anti-inflammatory medication used in adults for the treatment of many conditions, including moderate-to-severe rheumatoid arthritis and moderate-to-severe active Crohn's disease. Paediatric patients with active enthesitis-related arthritis, severe chronic plaque psoriasis, severe active Crohn's disease, or active polyarticular juvenile idiopathic arthritis can also receive the drug. Adalimumab was first approved 12 years ago and is currently being used to treat >940,000 patients around the world. The drug is contraindicated in patients with severe infections such as active tuberculosis, as well as those with moderate-to-severe heart failure. Respiratory infections, injection site reactions, headaches, abdominal pain, and nausea are among the most commonly reported adverse events. The risk of developing serious, possibly life-threatening infections is also, in rare cases, increased with the use of the drug.

## Public Health Crisis in STI Treatment

WORLWIDE, almost 400,000,000 individuals aged 15–49 years acquire one of four of sexually transmitted infections (STIs) every year, including 51 million cases of *Neisseria gonorrhoeae*. This alarmingly high number of cases has severe implications for public health, specifically antibiotic treatments that are used to fight these infections. Dr Colm O'Mahony, Consultant in Genito-Urinary Medicine, Countess of Chester Hospital, Chester, UK, told EADV 2015 about the escalating global STI crisis, reported in an EADV press release dated 9th October.

*N. gonorrhoeae* has developed resistance to all of the antibiotics that have ever been used against it. Bacterial resistance may be acquired through a number of mechanisms: by acquiring plasmids, by transformability (ability to acquire DNA from the environment and incorporate this into the genome), and by standard mutational resistance. Third-generation cephalosporins have previously been implemented in the treatment of the infection, but the inevitable resistance to these drugs began to develop in this species. A strain of *N. gonorrhoeae* (H041 strain) resistant to this antibiotic was first recognised in a female sex worker in Japan in 2011.

A number of efforts are being made to avoid the spread of this resistance, such as adapting the treatment into a dual therapy. The most effective dual therapy is currently ceftriaxone plus azithromycin, but this is not expected to last as resistance to ceftriaxone is predicted in the near future. Other schemes include targeting at-risk groups for resistant infections, while


education and promotion of condom use aim to impede the worldwide emergence of *N. gonorrhoeae*.

The World Health Organization has organised the Gonorrhoea Antimicrobial Surveillance Programme, already established in some nations but awaiting global implementation. A more tentative use of antibiotics in general is also being encouraged, aimed at avoiding resistance development in *N. gonorrhoeae* and other commensal bacteria. Further studies are ongoing to uncover further treatments.

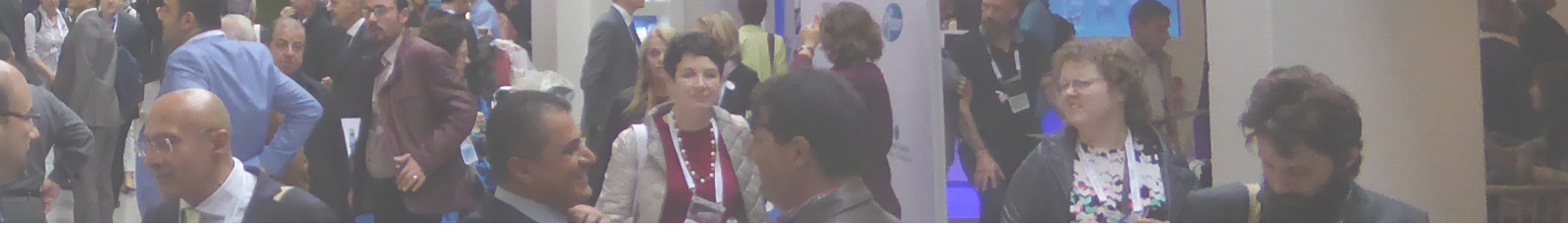
*N. gonorrhoeae* has developed resistance to all of the antibiotics that have ever been used against it.

Furthermore, syphilis, another STI, has developed resistance to azithromycin. This means that for the 5.6 million people infected with syphilis each year, the only treatment option now is injectable penicillin; this is less convenient and more cost-intensive, while many people are allergic to peniciliin. Even more worryingly, 11 new cases of highly resistant gonorrhoea have been discovered this year in Leeds, UK. This strain is completely resistant to azithromycin, and represents a major public health concern.

## European Safety Standard Needed for Tattooing and Permanent Make-up

BODY adornment has been a feature of human culture all over the world for thousands of years. Two of the most popular forms of contemporary body art are tattooing and permanent make-up (PMU), which involve implantation of a colourant into the skin. Although health and safety regulations focussing on hygiene rules to prevent infections such as hepatitis B and HIV (which may be transmitted through contaminated needles) have been established by the Council of Europe (ResAp2008), further health concerns for consumers undergoing tattooing and PMU remain.

"We need a positive list of safe pigments and ingredients. Tattoo inks should at least meet the same standards as cosmetic products."



One concern is the quality and sterility of tattoo inks, which lack proper control. A study by Dr Trine Høgsberg, Department of Dermatology, Copenhagen University Hospital, Copenhagen, Denmark, and colleagues found that 10% of 58 new inks tested were contaminated with bacteria such as Staphylococci and enterococci/*E. coli*. The contaminated inks could cause infection, especially in people at increased risk (e.g. patients with a weak immune system, individuals with heart disease, diabetes). Last August, the FDA identified microbiological contamination in unopened tattoo inks produced by A Thousand Virgins, Inc. The FDA is concerned that tattoo artists are still using contaminated inks from their current stock, despite the company declaring a product recall.

Further concerns include allergies and toxicity: tattoo inks contain a mix of pigments and dyes, additives, nano-particle traces of heavy metals, and impurities from the production process including polycyclic aromatic hydrocarbons. The ingredients and chemicals are improperly labelled in many cases, and the market is poorly regulated. Illegal products of poor quality may be easily purchased online, and some of the pigments used are not deemed suitable for use in cosmetics by the European Scientific Committee for Consumer Products. The ResAp2008 regulations on tattoo and PMU ink composition are thus insufficient to guarantee safety.

"We need a positive list of safe pigments and ingredients. Tattoo inks should at least meet the same standards as cosmetic products," explained Dr Christa De Cuyper, Dermatology Department, AZ Sint-Jan, Bruges, Belgium, in an EADV press release dated 9th October. "We need data on toxicity and biokinetics, and the inks should be tested for their potential toxicity, phototoxicity, substance migration, carcinogenicity, and possible metabolic conversion. We need further research, but as a first step we need a uniform European standard to protect consumers!"

## Dermatological Patient Advocacy Alliance to Help Millions

UNIFICATION of many patient advocacy groups is set to bring positive changes to the field of dermatology. The International Alliance of Dermatology Patient Organizations (IADPO) is a new collaboration of the >60 organisations that support millions of patients who have at least one of the >3,000 skin, hair, and nail diseases. IADPO met at EADV 2015 to announce their official launch and release the 'Vancouver Resolution', which aims to raise awareness of, and advocate for, patients with skin diseases. This step towards increased patient centricity hopefully means more patients will be able to receive the care and support they need.

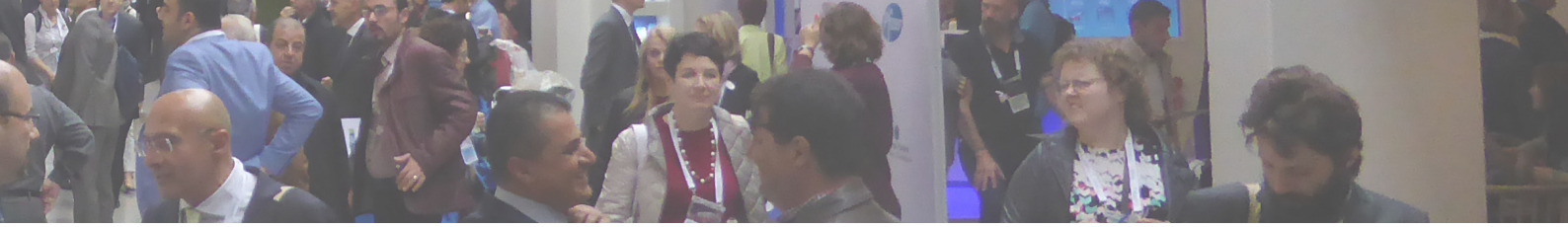

In a press release dated 9th October, Mr Jean-Marie Meurant, IADPO Board Member, France, said: "Beyond the physical suffering, skin conditions and traumas can have enormous psycho-social impacts on those living with these conditions, as well as on their family members." Mr Meurant went on to add: "This psycho-social effect touches people living with virtually all of the skin diseases. Further, because dermatological conditions can be brushed off as being less critical than other kinds of conditions, many skin patients hide and generally do not have a voice."

The new alliance aims to aid organisations that support people living with dermatological conditions, and to increase awareness of how the diseases can impact both individuals and family units. To this end, IADPO will gather regularly in order to share patient outcome information to help contribute to the acceptance of, and respect for, patients. Bringing together multiple dermatological organisations also means more collaborative research can be undertaken, especially in rarer diseases. IADPO also aims to act as an advocate when necessary in order to ensure that patients living with dermatological ailments are able to access the necessary care and treatments. The group hopes to make a global impact by representing dermatological patients at the United Nations and the World Health Organization. Finally, IADPO also aims to implement more specialised training and education for the leaders of member organisations, as well as opportunities to share resources. The newly released Vancouver Resolution affirms these aims by declaring the intent of the dermatological organisations to work together to bring forth patient voices and improve collaboration with physicians and other stakeholders.

"Beyond the physical suffering, skin conditions and traumas can have enormous psycho-social impacts on those living with these conditions, as well as on their family members."

IADPO will be running a multi-year research project to look into the burden of skin diseases. It is hoped that this will follow patient outcomes and aid the IADPO's objectives. Dr Harvey Lui, President of the International League of Dermatological Societies and Secretary General of the World Congress of Dermatology, said: "Patients are central to everything we do as dermatologists. We are enormously proud to have played a role in supporting these dedicated patient leaders at the beginning of their journey."

The admirable intentions of IADPO will hopefully bring more patient voices to the table and increase awareness, reducing the shame and desperation that many patients often feel. This is an important step towards patient



centricity, which is fast becoming a primary value within the medical world in order to ensure that patient care is tailored to meet their preferences, needs, and values. This resolution should make a difference to millions of patients worldwide.

## Dermatological Innovations Could Have Wide-Reaching Impact

INNOVATIVE research addressing a range of diseases from the field of dermatology has been demonstrated at EADV 2015. A number of these results, which address conditions such as psoriasis and skin cancer, are predicted to impact medicine far beyond the field of dermatology, demonstrating the importance and innovative character of this specialty.

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Psoriasis research involving the identification of disease pathways and the development of new targeted drugs, including IL-17 and IL-23 inhibitors, has led to an increased understanding of the origin of inflammatory bowel diseases, rheumatoid arthritis, and multiple sclerosis (MS). It is thought that treatments developed for psoriasis may also be suitable as standard therapy for such diseases. MS, for example, shares an immune-mediated origin with psoriasis, and following an accumulation of long-term safety and efficacy data on fumaric acid formulation (fumarate) usage in the latter disease, fumarates have now been identified as a viable option for MS therapy. Extensive clinical trials assessing the efficacy and safety of dimethyl fumarate administered 2 or 3 times per day in relapsing-remitting MS patients have produced robust, positive results; the placebo-controlled Phase III DEFINE trial, for example, demonstrated a relative reduction of the annualised relapse rate of the low and high-dose regimens in comparison with placebo, with reductions of 53% and 48%, respectively.

Meanwhile, insights into the way skin cancer suppresses immunity and development of the first broadly efficient cancer immunotherapy in dermatology may lead to novel treatment options for other cancers. The anti-programmed cell death-1 (PD-1) antibody, pembrolizumab, is able to delay the progression of metastatic disease by inhibiting the PD-1 immune checkpoint, and has been shown to have antitumour activity in patients with advanced melanoma.


# Intensive 4-day programme

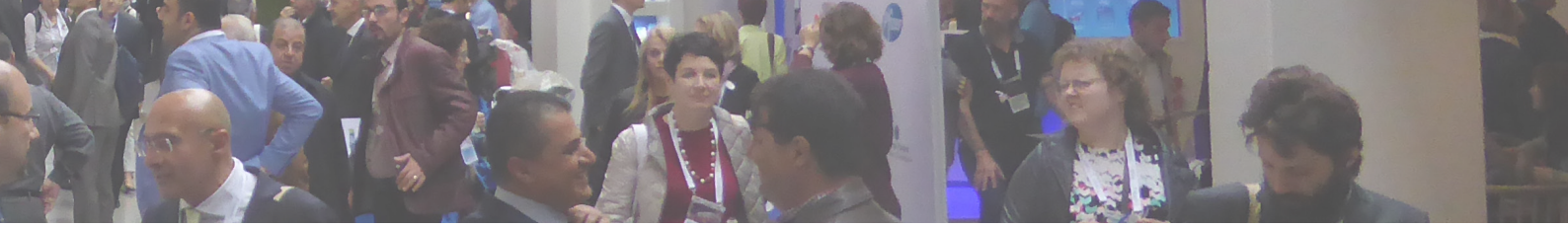
A randomised, Phase III study in which 834 melanoma patients received pembrolizumab every 2 or 3 weeks, or four doses of ipilimumab every 3 weeks, demonstrated that pembrolizumab prolonged overall survival and progression-free survival (PFS) and had less high-grade toxicity than ipilimumab. Estimated 6-month PFS rates were 47.3% for pembrolizumab every 2 weeks and 46.4% for pembrolizumab every 3 weeks, and 26.5% for ipilimumab. Estimated 12-month survival rates were 74.1%, 68.4%, and 58.2%, respectively. The treatment will now be tested as therapy for other malignancies, and it is hoped that patients with lung, bladder, or kidney cancer will benefit from it.

These innovations clearly demonstrate the importance of dermatological research and have identified new treatment options for a range of diseases that extend beyond the field of this specialty. However, there is a downside; new treatment options bring new costs that many healthcare systems will struggle to deal with. Indeed many new treatments for cancer can cost as much as €250,000 per patient. As Prof Martin Röcken, EADV Scientific Programming Committee Chairman, Tübingen, Germany, explained in an EADV press release dated 12th October: "We have to make sure that innovations reach the patients and we have to care that promising treatments do not become too expensive. This is a challenge medical doctors face nowadays."

## Push to Address Challenges Faced by Psoriasis Patients

WORLD Psoriasis Day is held annually on 29th October in order to raise awareness of the symptoms, prejudices, and related issues that people who suffer from psoriasis encounter daily. In line with this, the 24th EADV Congress, held from 7th–11th October this year, focussed its discussions and activities on this disabling skin condition, according to an EADV press release dated 29th October. It is also hoped that the stigma surrounding the disease will start to disappear as a consequence of the push to bring knowledge of psoriasis into the public domain by institutions such as the World Health Organization.

Psoriasis is a chronic skin condition that affects almost 3% of the world's population, from babies to adults. It causes red, flaky patches of skin covered with silvery, dry scales to appear on the body due to the increased production of skin cells. Although the condition is not contagious, it can be inherited and there is no cure, despite the availability of treatments. Alongside the physical symptoms, which range from mild irritation to severe pain from cracking



and bleeding skin, the psychological effects caused by psoriasis can also have a major effect on the patient's quality of life. Due to a lack of understanding regarding the disease, many patients feel ostracised by their peers, or isolate themselves out of a sense of embarrassment, and can often experience anxiety or depression as a result.

Addressing these issues, leading dermatologists discussed the most up-to-date developments in the knowledge and treatment of the condition at the EADV Congress 2015. There was also a Patient Village at the meeting to bring together practitioners and patients with skin diseases. Furthermore, the World Health Organization recently released its 'Resolution on Psoriasis' that, among numerous other objectives, aims to recognise the problems associated with the condition, including the elevated risk of a number of comorbidities, such as cardiovascular disease, diabetes, and liver disease. In addition, they hope to encourage Member States and stakeholders to raise awareness of the disease and fight the stigmatisation of patients, especially by holding events on World Psoriasis Day.


From the ongoing scientific research into treatments to the increased efforts to help patients overcome societal intolerance, more and more is being done by influential bodies to help psoriasis patients improve both their physical and emotional quality of life.

From the ongoing scientific research into treatments to the increased efforts to help patients overcome societal intolerance, more and more is being done by influential bodies to help psoriasis patients improve both their physical and emotional quality of life. Through their dedication and hard work, the progress made by these specialists will hopefully soon be translated to the general public.

## New Sun Creams Target Individual Skin Needs

IMPROVED Eucerin® sun protection products designed to suit different skin types, including oily and acne-prone skin, allergy-prone skin, hyperpigmented skin, photo-aged skin, dry and atopic skin, and children's skin, have been launched to try and help reduce sun-induced skin damage. Prevention of UV exposure was previously the primary concern during the development of such products, but the development of the new range has also considered the variety of skin types present in the general population.

"We select our skin care accordingly, why not take this into consideration when it comes to sun protection?" said Dr Anette Bürger, R&D Eucerin, Beiersdorf AG, Hamburg, Germany, in

a press release. "Targeted formulas can do much more than simply protect skin from the sun's UV rays. By responding to the individual skin needs, they can help to improve skin condition."

Oily, acne-prone skin is highly prevalent in modern society, with more than 80% of all young people and 40% of all adult women across the globe suffering from acne and skin blemishes in its various forms. Adult acne-prone skin is currently the skin condition treated most frequently by dermatologists, and it is estimated that sunlight harms the complexion of one in three patients with acne-prone skin.

The last few years have also witnessed a dramatic increase in sun allergies and light-induced skin reactions, with the most common being polymorphic light eruption (PLE), which is characterised by recurrent, delayed skin reactions ranging from a mild rash to an outbreak of pustules which appear 1 or 2 days following exposure to sunlight. Researchers believe that there is a hereditary tendency towards PLE, and it is known that UV rays cause free radicals to form in the skin, which in turn triggers cell stress. PLE is thought to affect up to 90% of people with sun allergies, with UVA light alone being responsible for the skin reactions due to PLE in 80% of people with sun allergies. The remaining 20% of cases are sensitive to either UVB (12%) or both UVA and UVB (8%).

Hyperpigmentation is another skin complaint that often requires targeted skin care. The condition is caused when UV light activates the enzyme tyrosinase within the skin's melanocytes, causing the conversion of the amino acid tyrosine to melanin. If the exposure to UV radiation lasts too long, occurs too frequently, or is too intense then it can trigger overproduction in some melanocytes, meaning that spots and brown discolourations can appear on the skin in varying shapes and sizes.

The new range of Eucerin sun creams has been developed to specifically target these skin types and conditions. The core element of all of the products is the inclusion of licochalcone A, either alone or in combination with glycyrrhetinic acid or alpha-glucosylrutin extracted from liquorice root (*Glycyrrhiza inflata*), which grows in countries receiving high levels of solar radiation. The plant is able to generate protective molecules that prevent UV-induced damage, and which are also effective for preventing damage to human cells.

"Targeted formulas can do much more than simply protect skin from the sun's UV rays. By responding to the individual skin needs, they can help to improve skin condition."

## Vincenzo De Giorgi

*Professor of Dermatology, Cutaneous Oncology and Skin Surgery, Department of Dermatology, University of Florence, Florence, Italy.*

**Q:** Who or what inspired you to specialise in dermatology and oncology, and which of these two interests came first?

**A:** When I was 12 years old I had a small dermatological problem and my parents took me to a dermatologist. Well, this doctor fascinated me because he looked at me with a big lens and he prescribed a mixture of cream that was prepared in the pharmacy using a 'magic formula' that he had written on a small sheet of paper; already at that time I felt healed! Day by day I recovered from my skin disorder by applying this mixture and it was at that time that I decided to be a dermatologist. It was while I was majoring in dermatology that I became more and more passionate about dermatological oncology.

**Q:** Have there been any changes in the types of skin conditions you see frequently in the clinic now compared with when you started your career?

**A:** I have been a dermatologist for more than 20 years and skin diseases have certainly changed during that time. In my early days in the hospital you could see a lot more infectious disease: many fungal diseases, impetigo, and skin infections in general. Melanomas and skin cancers were often large because they were neglected by both the patient and the physician. The prognosis was also clearly different. Twenty years is not long, but in terms of diagnosis and treatment we have made great strides; just think of the introduction of dermoscopy, video dermoscopy, and confocal microscopy in our clinics. All this allows us to arrive at a more accurate and safer diagnosis, both for the patient and for the physician. Indeed, the introduction of these new non-invasive methods has opened a new dimension in the examination of pigmented skin lesions, especially in the identification of the early phase of cutaneous malignant melanoma. Thanks to all of this we are now able to make increasingly early diagnoses, and the 5-year survival rate for localised melanoma is now 98%.

**Q:** You have extensively studied the presence of genetic mutations in melanoma; what insights has this research yielded and how can this information be translated from the laboratory to the clinic?

**A:** Genetic engineering is becoming increasingly important in the diagnosis, management, and treatment of diseases, particularly tumours. The clinical implications are of paramount importance. They range from the identification of patients most at risk of developing a tumour to identification of cancer patients who are most at risk of disease progression. In the treatment of metastatic melanoma and advanced basal cell carcinoma, we are already talking about targeted therapy that serves to correct the genetic mutation that causes cancer. In the not-too-distant future, I think patients will not be classified and treated for melanoma or prostate cancer, but will instead be classified using the genetic mutation that presents.

**Q:** You have also investigated the use of beta-blockers to prevent the progression or recurrence of melanoma; how did this concept come about and what are the next steps for further evaluating the use of these drugs in this indication?

**A:** The burden of personal and emotional factors in cancer aetiology and outcome has been highlighted several times in the medical and non-medical literature. In the scientific field, the epidemiological and clinical studies have linked psychosocial factors, such as chronic stress and depression, with cancer progression and, to a lesser extent, cancer onset. These effects are mediated through activation of the autonomic nervous system and through the hypothalamic–pituitary–adrenal axis following the release of catecholamines and other stress hormones. Results of experiments conducted *in vitro* confirmed the assumption that stress is a cofactor in melanoma progression.

Among my melanoma patients to date, I have studied those taking beta-blockers due to high blood pressure. These patients had a much higher

survival rate than those who did not take this drug. We then published the first paper regarding the use of beta-blockers in melanoma patients in *Archives of Internal Medicine*. In this study we selected patients who were at higher risk of disease progression based on Breslow's depth >1 mm. A total of 121 patients with thick melanoma were included in the study. Patients were considered treated if they reported beta-blocker use for at least 1 year, whereas untreated patients were those who reported no beta-blocker use. Of the 121 patients with thick melanoma, 30 patients were included in the treated group and 91 patients comprised the untreated group. Overall, 34% of the patients in the untreated group had evidence of disease progression, while only 3% of the patients in the treated group showed progression. This was followed by other studies that have confirmed the protective effect of beta-blockers against melanoma. The development of prospective clinical trials is now critical to definitively clarify the role of beta-blockers in protecting against the risk of melanoma and its progression, and possibly to identify the receptor involved in the protective effect. In particular, as occurred in breast cancer for the oestrogen receptor, it is possible that there are differences in the levels of receptor expression in different subclasses of melanoma and that, therefore, inhibition of adrenergic activation by beta-blockers may have different effects in different subtypes of melanoma. For these reasons, we have planned a multi-centre, placebo-controlled, randomised Phase III trial to test whether propranolol increases overall survival in patients with malignant melanoma at Stage II–IIIA (T2, N0 or N1, M0). This trial will start in Italy in a few months and I am very confident of the results.

**Q:** With the incidence of cutaneous malignant melanoma increasing worldwide, what more do you think could be done to educate people regarding the risks of the sun, sunbeds, etc.?

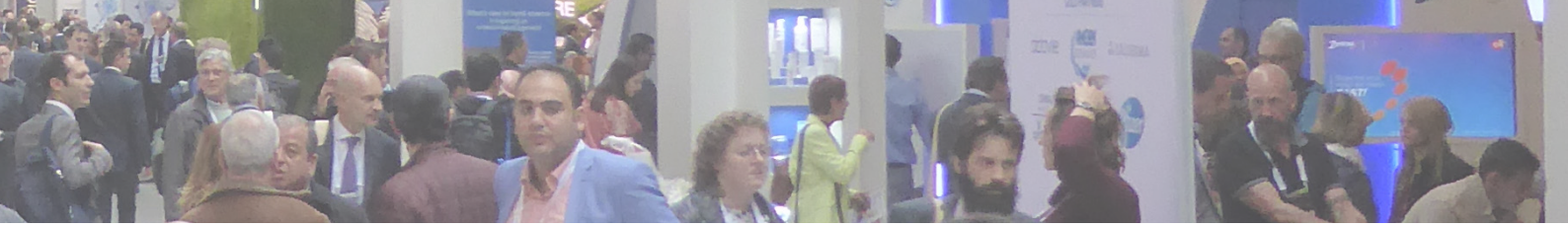
**A:** Primary prevention is very important in the fight against melanoma but it is often overlooked. We need to invest more money in this field. Unfortunately, governments prefer to invest more in basic research and neglect the education of our children with regard to exposure to the sun, which is the only factor currently recognised as a risk for melanoma. We must go into schools, talk to the children, and explain how dangerous sunbeds can be. I think it is also important to dismantle the idea that being tanned is fashionable or 'cool'. Then you have to try to find more of the individuals most at risk, perhaps males between 50 and 70 years of age, in order to implement the call to visit for these population segments. Skin examination by a dermatologist costs little compared with the treatment of a patient with advanced melanoma.

**Q:** The 'human papillomavirus' (HPV) has also been associated with melanoma. Although the relationship is yet to be elucidated, have you noticed any correlation between the introduction of the HPV vaccine and rates of skin cancer in the vaccinated population?

**A:** Data on the power of oncogenic skin HPV are still very limited but appear to be different from those identified for 'high-risk' mucosal HPV. It is therefore appropriate to investigate these mechanisms in order to better understand the possible role of β-HPV in the pathogenesis of non-melanoma skin cancers. Demonstration of the expression of viral oncoproteins in skin biopsies is a very important result. To understand the significance of this finding, however, further quantitative and *in vitro* studies will need to be undertaken in order to analyse in more detail the events that take place inside the infected cells. Licensed HPV vaccines confer type-restricted protection against HPV responsible for genital warts and cervical cancers. However, they do not protect against less prevalent high-risk types or cutaneous HPVs. Over the past few years, several studies explored the potential of developing vaccines targeting cutaneous papillomaviruses. These vaccines were shown to be immunogenic and prevent skin tumour formation in certain animal models. Strategies are currently focussed on finding vaccine formulations that confer protection against a broad range of papillomavirus-associated diseases.

**Q:** Could you please provide a brief outline of your current research themes and what you hope to achieve in the next year or two?

**A:** With my team, I am working hard on research in melanoma on many fronts. The first of these is



epidemiological research to identify patients most at risk of developing these neoplasia, and which aims to allow increasingly early diagnosis.

The search for new diagnostic methods is another area that I follow very carefully. An important strand of my research is oestrogen and melanoma. Our clinical observations show that oestrogen receptor beta expression decreases during melanoma progression, suggesting an inhibitory activity of this protein on tumour cell growth. Our project is now aimed at providing insights into the role of oestrogen receptor beta in preventing growth and metastatic behaviour of melanoma cells.

In the next 2 years I hope to have the results of the randomised, double-blind, placebo versus beta-blockers trial of which I have already spoken. I think the results of this trial will be really helpful for patients suffering from melanoma.

**Q:** Which achievement of your career thus far are you most proud of?

**A:** Several months ago I was appointed president of an Italian foundation that deals with cancer research. This appointment fills me with pride because it was endorsed by both patients and colleagues.

**Q:** What advice would you give to medical students and young physicians considering specialising in dermatology?

**A:** Dermatology is a beautiful and interesting specialty. Perhaps it is the only specialty where the naked eye, experience, and intuition still count a great deal. We have the opportunity to deal with important issues, such as the diagnosis and treatment of melanoma, as well as more superficial matters which may still be important to the patient, such as the treatment of wrinkles and skin ageing. A visit may only last 1 minute or it may last a long time, depending on the pathology. To be a good dermatologist it is not enough to simply study. You must also see many patients during your training period, with a curiosity that should be the basis of any training or cultural growth.

## Raúl Cabrera

*Professor and Chairman, Department of Dermatology, Faculty of Medicine, Clinica Alemana, Santiago de Chile, Universidad del Desarrollo-Clínica Alemana, Región Metropolitana, Chile.*

**Q:** Who or what inspired you to specialise in the field of dermatology?

**A:** I chose dermatology because it is a specialty area that is closely related to immunology, and during my fellowship I discovered that dermatology is a very broad specialty, linked to many other fields of medicine, which sparked my interest even more.

**Q:** How far has the field of dermatology grown since you started your career, and what would you say has been the most memorable or important development in the field?

**A:** Dermatology has changed from being an obscure and underdeveloped specialty to one of the most exciting and pioneering specialties in medicine. The introduction of immunology for the study of blistering diseases and connective tissue diseases in the 1970s and 1980s completely changed the face of dermatology. Monoclonal antibody introduction also opened a new field in immunodermatopathology to further understand various dermatological diseases, such as skin tumours. The outstanding advances in molecular biology introduced in dermatology during the 1990s and in the years after have opened an entirely new world for the understanding of skin disorders.

**Q:** What is the proudest achievement of your career to date?

**A:** An important milestone in my career has been to become a board member of the International League of Dermatological Societies. This appointment has given me a solid position to work for the further development of our specialty, and to help others receive quality healthcare.

**Q:** Research is continually improving the field of dermatoscopy. Do you have any predictions

based on current research about what might be achievable with dermatoscopy in the near future?

**A:** Dermatoscopy has improved our capacity to diagnose dermatological diseases. It is part of the essential armamentarium for any dermatologist. Nowadays, it is included in all dermatological postgraduate residency programmes.

The optics of the new equipment for dermatoscopy is constantly improving and I am sure that we will soon have portable equipment including sophisticated advances that will enable us to have a clinical and pathological view in a single device. Presently, confocal microscopy is improving constantly and will probably be part of this 'single device', which we will have in our hands in the near future.

**Q:** Could you give us a brief overview of the research that you are currently conducting in vitiligo?

**A:** In recent work we studied the 'response speed' of 579 patients to narrowband UVB (UVB nb) light treatment. We found a predictive model of response showing five different 'response speeds' to UVB nb light. We discovered that patients considered in previous reports as being 'non-responders' (<10–20% response after 48 sessions) were mainly 'very low responders' needing more time to respond. At the other end of the spectrum, 7% of the patients were 'very fast responders', and generally needed no more than 24 or a maximum of 48 sessions to achieve a complete response.

**Q:** What are the main external factors that affect the immune system of the skin, and what can people do to protect themselves against these factors?

**A:** UV light decreases the skin's immune response. This change produces the development of a 'good field' to develop skin cancer. If we add the sun as a trigger factor that induces genetic lesions in chromosomes then there is a high potential for developing skin cancer. The best way to protect ourselves is to use appropriate clothing and sunscreen to keep our skin in good health.

**Q:** Being involved in both Chilean and American dermatological medicine, how do you think that the general healthcare in Chile compares with the USA?

**A:** Chile has the best public health index in Latin America. Although resources are greater in the USA compared with Chile, the national healthcare system in Chile has achieved a good basic health standard, and covers any citizen without a private insurance provider. This has made Chile's public health index comparable to those of many European countries.

**Q:** Are there any other areas of dermatology that you are hoping to research in the future?

**A:** Soon we will begin a study to examine the role of the blood's T regulatory cells in vitiligo. We will test if the results of different 'response speeds' to UVB nb light are related to changes in the circulating T regulatory cells.

**Q:** What advice would you give to aspiring young dermatologists?

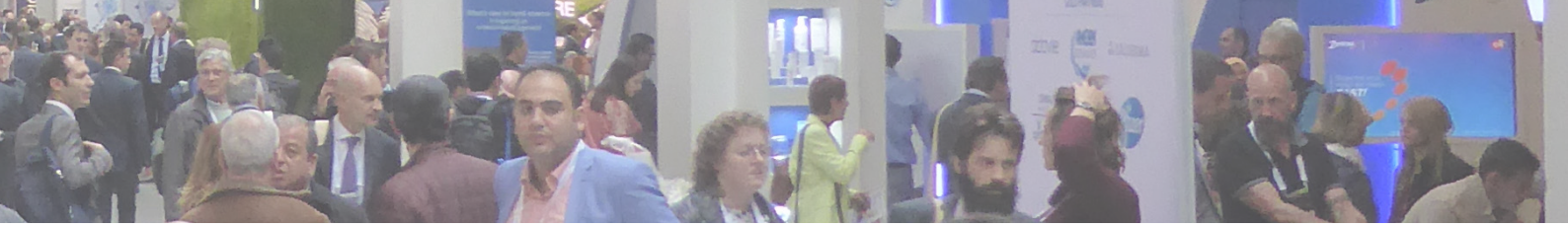
**A:** It is our responsibility to contribute to the continuous growth of this exciting medical specialty. With hard work and detailed study in any of the various fields within dermatology, an aspiring dermatologist may discover a place to make a valuable contribution. In the end, patients will be the benefactors of any young doctor´s achievements and commitment.

## Robert Dellavalle

*Associate Professor of Dermatology and Public Health, Colorado School of Medicine and Colorado School of Public Health, University of Colorado, Aurora; Chief, Dermatology Service Eastern Colorado Health Care System, US Department of Veterans Affairs, Denver, Colorado, USA.*

**Q:** You began your career with a degree in philosophy; how did you get involved with clinical research in skin cancer?

**A:** As an undergraduate I knew that I would only have the interest, energy, and time to read philosophy during undergraduate studies, so I was



interested in doing that, and that led me to study logic and aesthetics, both of which I use daily in taking care of patients and discussing treatment, so I found it to be quite applicable to my daily life. I cannot say that I planned it all out that way; I just had an interest and wanted to do it at that stage in my life. There is no direct relationship between the two.

**Q:** Can you give us a brief overview of any ongoing research projects you are currently involved with?

**A:** I am quite active with the Global Burden of Disease (GBD) project, which is run out of the Institute for Health Metrics and Evaluation (IHME), based at the University of Washington. It is a highly collaborative effort; some have called it the 'Watson' of epidemiology, making reference to IBM's Watson computer that competed on the game show 'Jeopardy' against humans. It is an effort that is all-encompassing, and essentially it is funded by Bill and Melinda Gates, who have donated at least $100,000,000 to date. Christopher Murray has made it his life project to estimate the global burden of disease, of all diseases, and he has called for collaboration with many different specialists, including dermatologists. So I have been working with that group to help estimate the global burden of skin disease for about 8 years now. They have 222 employees and probably about 1,000 collaborators around the world.

The basic idea is to assemble a database of all known, reliable epidemiology data, and then to use that database to answer questions like, in the case of dermatology, 'Where is acne the worst?', 'How does acne disability compare with the disability caused by all other diseases?' Those are just a few of the questions that got me interested in dermato-epidemiology when I started and the answers are in some ways surprising; we thought perhaps that skin cancer might be higher up on the list in terms of causing disability, but it is actually rashes that cause the most disability around the globe. Mainly dermatitis causes the most disability, acne causes the second-most disability, and psoriasis comes in third. So not what I would have expected, and it might have implications for funders of research and for funders of healthcare. There has been very exciting work on many levels with very new tools and terrific open-access databases, which you can go online and find by googling 'IHME'.

**Q:** How long have you been involved with the International Federation of Dermatology Clinical Trials Network (IFDCTN)? How important do you believe research networks such as this are?

**A:** That federation is being led by Howell Williams in the UK, and it is quite important for the reduction of waste in research to make sure that clinical trials actually need to be done and are not answering questions that have already been answered by other clinical trials. It also makes sure that the trials are asking the questions in such a way that they give answers that are meaningful to the patients and not just answers for the sake of finding answers. I think that the federation is crucial to those two aims, of reducing research waste in clinical trials, and finding answers that are meaningful to patients. It is a relatively new endeavour – I have been involved with it very peripherally for about 2 years now – but I think it is a very important effort, and will become increasingly important as we narrow in on reducing waste in clinical research.

**Q:** How important is social media to physicians such as yourself? Do you believe that clinical practices and medical journals could utilise these platforms to improve patient care and education?

**A:** Absolutely! Social media is very exciting on many fronts, and I think that monitoring social media will give us better ideas about what is meaningful and important to patients, and what they are experiencing. I am a very avid believer in the importance of social media for improving doctor–patient communication, as well as improving the dissemination of research results from journals to the public. In that role, I have been a social media editor for the *Journal of the American Academy of Dermatology* for many years. That journal has the most popular Facebook page of any dermatology journal, and this is because we have really put a lot of effort into getting all dermatology results out to the public on social media.

**Q:** You have advocated for a ban on the use of tanning beds by minors. What does the research literature have to offer on this topic, and how may

this type of activity be impacting on the incidence of skin cancer in the general population?

**A:** This is a hot topic around the globe. The World Health Organization analysed the data about 5 years ago and declared that adolescents should not use indoor tanning. Based on that analysis, whole countries, such as Brazil, banned indoor tanning, not only for adolescents but for all ages. Another country that has recently banned indoor tanning for all ages is Australia, and prior to that, Iran. A lot of countries in Europe have also adopted this ban for adolescents, but in the USA it has been regulated on the state level. In the state that I live in, Colorado, there is still no regulation with regard to the age of use for an indoor tanning bed, even though UV light from a tanning bed has been classified as a Type 1 carcinogen and in the literature has been associated with not only melanoma but also basal cell and squamous cell skin cancer.

In the early 2000s, I started to look at the analogies between indoor tanning and cigarettes, because they are both carcinogens that can be sold to minors and it turns out that they both have an addictive component. A lot of the research that has been done in controlling tobacco use can be directly applied to controlling UV indoor tanning. This has been a major public health effort for the past decade. Unfortunately, in Colorado we still do not have any regulations despite my working on this for a long time, but this gives me more work to do in future years.

**Q:** You have made appearances on television, radio, and in print via interviews; how effective are these channels for informing public debate, for example on issues such as sun beds and skin cancer?

**A:** I think our most successful media story has been popularising the new technology of UV photography for detecting hidden sun damage, and using those images to motivate people to stay out of indoor tanning beds. This technology has been around for a while, but we took pictures of legislators at the Colorado state capital and showed them the hidden damage that is not apparent without this photography in an effort to sway them that this is an important issue.

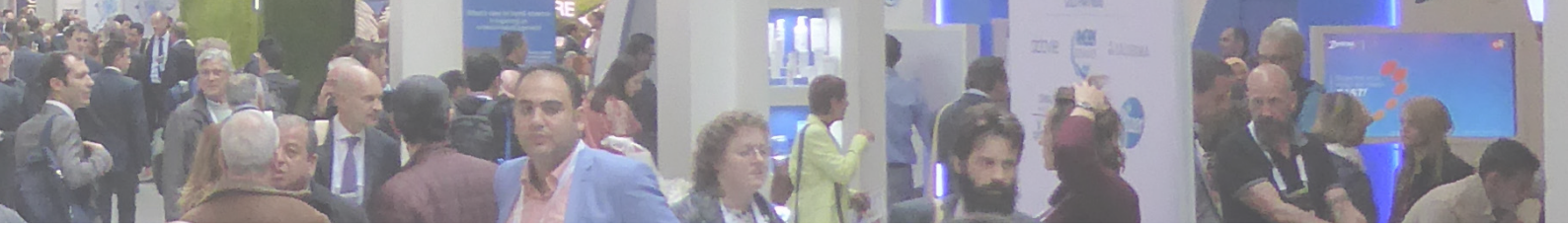
> "Social media is very exciting on many fronts, and I think that monitoring social media will give us better ideas about what is meaningful and important to patients..."

We used the UV photography technique at public health events to show people who use indoor tanning that they have hidden damage that will come out in future years, and should not continue to indoor tan. Seeing these pictures that make your face look really ugly really does motivate people who are concerned about their appearance. The research seems to show that there is no greater intervention that can be done to cause people to stay out of tanning beds than to show them these pictures, if you just have a few minutes to interact with them. That has been a major emphasis of our work, and we have established, along with Neil Box and others here in Colorado, the Colorado Melanoma Foundation to raise money and promote this technology at public health events.

I think you definitely have to be out there, and having a new tool like UV photography can get you on the nightly national news, which is a great coup. But again, a lot of the changing of laws is persistence, doggedness, and luck at the legislative level.

**Q:** Is there any trend in the overall prevalence of inflammatory skin disorders in the general population? If so, could you speculate on the cause(s) of this change?

**A:** The Global Burden of Skin Disease project shows a slight increase in dermatitis over the years. This correlates with the hygiene hypothesis, which suggests that as we gradually get cleaner environments, our immune system adapts to that by becoming more inflammatory, which causes dermatitis. This is one example of a skin disease on the rise, which may be explained by increasing hygiene over the years.



## "I think you definitely have to be out there, and having a new tool like UV photography can get you on the nightly national news..."

**Q:** Are there any particular population groups that are affected by inflammatory skin disorders?

**A:** There are certain countries in Europe that seem to have more dermatitis. The latest 2013 survey highlighted Iceland as being a country that had more dermatitis than others, so we have to monitor that data to see how good it is, and verify it with some in-country observations to make sure that this is actually the case. It does seem like certain countries have more dermatitis than others and I do not know if that is climate-related or genetic, but this is one of the ways in which the GBD project is highlighting areas for further research: targeting hotspots for different skin diseases across the globe.

**Q:** What do you think are the greatest challenges facing dermatologists today?

**A:** In the US, we have ever-increasing bureaucratic burdens as doctors: paperwork that is not related to the doctor–patient experience or the treatment of disease but to payment for services. This, I think, has a great potential for bringing physicians to their knees in terms of making them burn out on things that do not interest them. I think a lot of medical students go into medicine to treat patients, and a lot of paperwork, which is increasing in all realms, is leading to some burn-out and disillusionment. I think that this is the greatest challenge: working through all that paperwork and getting back to the doctor–patient relationship, which matters most.

**Q:** How has medical training changed since you studied to become a physician? The extent of medical knowledge continues to expand and so how challenging is it to maintain standards?

**A:** Medical training has become better in terms of introducing patients to medical training much earlier in the process. When I went to medical school about 25 years ago, you had 2 years of study of sciences where you did not really see patients, and I believe that this has changed so that patients and patient problems are being introduced earlier in the educational process, which is a good thing. Medicine is becoming more complex, and the treatments are becoming more complex and varied. It is going to become ever more important to know how to evaluate the evidence behind the use of medicines and patient preferences, so that we utilise the best medicines in accord with our patients' preferences. I think that a couple of great tools on the horizon that are going to be very helpful are the advent of 'big data' or electronic medical record databases that will better tell us what the patient experience is with every disease, and 'patient decision aids', which use evidence-based medicine to evaluate the options for all the different treatments using algorithms that are understandable for patients and their doctors to help decide what the best treatments for that patient will be. There are even more simplified tools called 'patient encounter aids', which are one-page pieces of paper that go through all of the decision processes for treatment for a disease. I really see these as the future of treatment for many common disorders like acne and psoriasis.

**Q:** What advice would you give to the next generation of physicians, particularly those considering a career in dermatology?

**A:** I think dermatology, at least in my opinion, is one of the best fields in medicine in terms of the challenges that a physician can face, and lifestyle choices that allow flexibility for your personal lifestyle. I think this is the reason that in dermatology we attract some of the best students in the world. There are tremendous opportunities coming about with electronic medical records and databases for answering questions in dermatology and in clinical practice, and it is a very exciting time for targeted therapy for diseases; we know better now what effect an individual treatment will have on our patients. I think we are making progress, providing we do not have too much bureaucracy holding us back.

## Lawrence F. Eichenfield

*Chief of Pediatric and Adolescent Dermatology, Professor of Dermatology and Pediatrics, Rady Children's Hospital, University of California, San Diego School of Medicine, San Diego, California, USA.*

**Q:** Having started your medical career with a degree from Icahn School of Medicine at Mount Sinai, what inspired you to specialise in paediatrics and dermatology?

**A:** While at medical school at Mount Sinai, I was drawn to paediatrics. I enjoyed working with children and understood that when disease was 'fixed' or minimised in a child, the impact could influence a lifetime and beyond. This was an easy choice, especially as my father was a paediatrician and my mother was his office manager – so I grew up in a 'paediatric household'. While in paediatric residency at the Children's Hospital of Philadelphia, I saw how fascinating paediatric dermatology was. I saw Dr Paul Honig, a superb paediatric dermatologist and important mentor for me, doing great work, walking into rooms at what is considered the best children's hospital in the US, and rapidly making a diagnosis that changed the course and management of patients. I also quickly recognised how much research was needed, as there were so many diseases that were chronic, poorly understood, and/or in need of better therapies.

**Q:** How has the field of paediatric dermatology developed since you started your career, and how has this impacted your role within it?

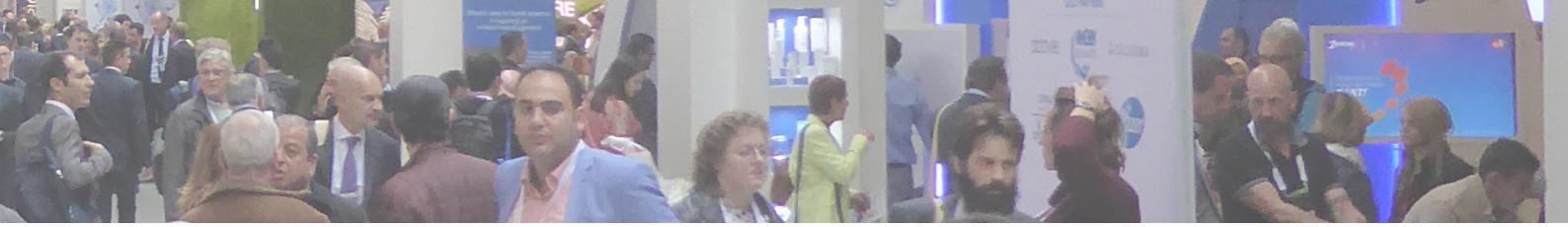
**A:** Paediatric dermatology has grown tremendously in size throughout the world, as the benefits of specialisation have been appreciated by patients, families, training centres, and communities. There are many, many more paediatric dermatologists now throughout the world, and we are fortunate that, despite this growth, we have kept our historic collaborative and mutually supportive sensibility. Procedural paediatric dermatology used to be very limited (treating warts and molluscum, for instance) but now includes a broad set of lasers, light devices, and surgery. The explosion of knowledge of the underpinnings of genetic diseases is incredible. I remember telling parents of newborns with epidermolysis bullosa that "we expect to know mutations soon" that can help us understand and treat different types of Epstein–Barr virus. Now we can order whole exome analysis for genotypic evaluation and are close to the promised genetic interventions that will truly modify or cure. Organised, collaborative research is now being built into the 'genetics' of paediatric dermatology, with groups such as the Pediatric Dermatology Research Alliance (PeDRA) in the US establishing research consortia.

**Q:** It is well known that children tend to have more sensitive skin than adults and are more prone to dermatological issues such as eczema. Do children who develop dermatological issues usually carry these into adulthood?

**A:** Yes and no. Atopic dermatitis (AD) is prevalent in much of the industrialised world, affecting 10–15% of young children, and around 3% (up to 5% in some estimates) of adults. So most children with AD will 'outgrow' at least active eczema, although many may have more sensitive skin, contact allergies, or other atopic phenomena that are seen within the AD population.

**Q:** Allergic asthma is much more common in people who have (or have had) severe AD than the general population. What research is being done and is there a prevailing theory as to the link between asthma and eczema?

**A:** This remains a very tricky area of research. We have some insights into risk factors for AD that are associated with asthma, including filaggrin mutations. Those individuals with AD associated with these mutations have a much higher risk of developing asthma than those without. What 'tracks' the development of airway inflammation and hyperactivity is not known. There is much 'hot' research looking at the onset of inflammation, at T cell sensitisation and effector function and how it may mediate skin and airway inflammation, and



environmental and microbial influences in AD and in asthma. Food allergy is another area of much research, with movement away from avoiding allergenic foods in order to prevent allergy and towards early feeding. There is much work to be done.

**Q:** What are your opinions on the standard of healthcare in the USA since the introduction of 'ObamaCare'? How do you think American healthcare compares to that in the UK and the rest of Europe?

**A:** This could be a whole other interview! The Affordable Care Act has had great benefits in getting insurance coverage to a broad set of the population that did not have it. This is a good thing for the health of the nation. It has also set up forces to try to 'turn a giant cruise ship on a dime', meaning trying to change a massive portion of the economy into new methods of operating, without an organisational structure in place to really do this well. This is a hard, big ship to move! Prescription drug costs are very, very high, including generic drugs, which have gone up by hundreds of percent in cost in the last few years. The US does not pay for or encourage cost-effectiveness studies, leaving 'the market' to figure out if new medications are worth premium pricing, and having healthcare professionals 'feel out' how new drugs work versus older ones. There are no government panels deciding the value of medications; while private insurers may try to do this, they may often just look at short-term costs without impact on health effects over time. These systems are very, very different from Europe and the UK.

**Q:** Do you think that environment-induced dermatological issues are increasing or decreasing in the USA as a whole? What do you think are the main reasons for this?

**A:** We are certainly more aware of them. Part of this is a more complex environment, with much more exposure to metals and chemicals in everyday life, due to modern manufacturing; just look at a shampoo or conditioner bottle and look at the list of agents in it. Contact dermatitis is common in children as well as adults. How environment has influenced rates of AD is still an interesting question without specific answers.

**Q:** Research suggests that vascular lesions most often result from mistakes that occur during embryonic or fetal development, and that these mistakes may be linked to genetic mutations in some cases. Are there any particular groups who are at risk? Why (or why not) might this be the case?

**A:** We are still searching for genetic clues to haemangiomas of infancy and the syndromic haemangiomas, such as PHACE syndrome. Our insights into vascular malformations are coming rapidly; port-wine stains are now known to be associated with *GNAQ* mutations, but like many birthmarks, in mosaic forms. With Sturge–Weber syndrome, the same mutations are present in brain and port-wine stain, showing variability in the tissue lines affected by the mutations. More complex malformations may be seen with or without tissue overgrowth, and a set of patients have been determined to have *PIK3CA* mutations. There is more information coming, which may help us to understand risk factors, but we are not there yet.

**Q:** What are the single most challenging and the most rewarding aspects of your work?

**A:** The most challenging aspect of my work is caring for children with diseases that are debilitating, deforming, functionally impactful, and in some cases deadly, without the tools to 'fix' them. But this also fuels the most rewarding aspects: contributing to research that can advance the field and minimise suffering, and being fortunate to do this with the support and efforts of patients, families, and with a team of dedicated, caring healthcare professionals.

**Q:** What would be your top piece of advice to aspiring paediatric dermatologists?

**A:** Paediatric dermatology is an incredibly rewarding profession! The challenges are there every day in the office or clinic, both with diagnosing and artfully caring for neonates through to young adults. You can contribute to improving health by caring for patients, educating families and other healthcare professionals, contributing to research, establishing best practices, and contributing to innovation. Go for it!

# BIOLOGIC THERAPIES: CLINICAL PRACTICE IN A CHANGING ENVIRONMENT

## This symposium took place on 10th October 2015, as part of the European Academy of Dermatology and Venereology Congress in Copenhagen, Denmark


**Chairperson**

**Matthias Augustin[1]**

**Speakers**

**Matthias Augustin,[1] Leigh Revers,[2] Luis Puig[3]**

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## MEETING SUMMARY


Biological therapies have been in use for treating psoriasis for a decade now, and they have greatly improved disease outcomes and quality of life for patients. The success of biologic therapies has been assisted by the development of evidence-based guidelines for their use, and the achievement of consensus on treatment goals. The future of biologic therapies for psoriasis will be different from the past decade, with new anti-inflammatory targets for antibodies being developed and the increasing availability of biosimilar versions of existing antibodies as patents expire. While reduced costs may exert a pressure to switch to biosimilars, it is important to appreciate that they may not be identical in efficacy. Biologics are large, complex molecules, produced by biosynthetic means, which inherently lead to variations in structure. These slight variations in the manufacture of biologics can lead to clinically relevant changes in efficacy. As more biosimilars become available, their interchangeability becomes an important challenge for use in clinical practice, both between a biosimilar and the originator, and between two different biosimilars. Thus, robust trials of interchangeability are urgently needed. Caution in the use of an increased range of biosimilars will also be needed as switching between drugs can potentially increase immunogenicity and neutralise the drug's efficacy.

The introduction of biologic therapies has been a great achievement in the treatment of psoriasis. The new biologics and biosimilars coming into practice will need to be used with care, for which robust data on safety, efficacy, and interchangeability will be needed, as well as continuing pharmacovigilance.


## The Biologics' Journey

### Professor Matthias Augustin

Psoriasis treatment has changed greatly in the past decade. Before the introduction of biologic therapies, the majority of available treatments were topical, patients spent a long time (over a month) in hospital, and there were no evidence-based guidelines to provide a standardised approach to treatment. Today, psoriasis is a key disease in dermatology, and healthcare has improved markedly. Systemic treatment is standard, inpatient treatment

is rare, guidelines ensure optimisation of both topical and systemic treatment, and patient quality of life is much improved. Patient needs are now the driver for treatment goals,[1,2] and are used in the development of outcomes, instruments, and treatment pathways.[3-7] In Germany, improvements in psoriasis treatment and a reduction in patients with severe disease have been demonstrated over the last 10 years (PsoHealth 1, PsoHealth 2, PsoHealth 3; www.psonet.eu), a result of the implementation and regular review of goals and indicators for quality of care. The introduction of biologic therapies has played a key role in these improvements.

From 2005, with the first approvals of antibody therapies for psoriasis (efalizumab, etanercept, infliximab), to 2015, many more biologics have become available. Concurrently, guidelines to regulate their use, consensus on treatment goals, and registries (www.psonet.eu) to track long-term safety and efficacy have been implemented by the dermatology community to ensure that the best use is made of biologics as they are developed.[4,5] In the next decade, new developments in biologics and biosimilars will need to be incorporated into the goals and guidelines so that we continue to improve outcomes for our patients.

The past decade has also demonstrated the safety of tumour necrosis factor (TNF)-alpha antagonists in psoriasis. Long-term safety data for adalimumab from global clinical trials, including over 20,000 patients with a variety of immune-mediated inflammatory diseases, show a markedly positive safety profile for patients with psoriasis and psoriatic arthritis.[8] Rates of serious adverse events and serious infections were low, and mortality was similar to or lower than expected for the general population. A slightly higher incidence of malignancies in patients with psoriasis was confirmed by a Finnish study, which showed that risk for malignancy and comorbidity in psoriasis patients was altered compared with the general population.[9] European psoriasis registries, coordinated under the PsoNet organisation (www.psonet.eu), show no negative safety signals for adalimumab, or for TNF antagonists as a class, compared with systemic treatments.

The development of biosimilars is an area of growth for many pharmaceutical companies, due to the reduced cost of development compared with new drugs. How will the influx of biosimilars change healthcare for psoriasis? Further uptake of biosimilars will mostly depend on regulation and reimbursement. Treatment of biosimilars by regulatory agencies varies globally; while the EU has nearly 10 years of experience in licensing biosimilars, the US lags behind. Regulatory agencies require biosimilars to demonstrate similarity in quality, safety, and efficacy to a licensed reference biotherapeutic product in a clinical trial and in post-marketing surveillance, as the complex manufacturing process means that the biosimilar will not be identical to the reference product and it cannot be assumed to behave identically. The interchangeability of the biosimilar and reference product should also be addressed. The majority of payors have little knowledge of biosimilars, but according to a survey of German healthcare stakeholders,[10] the potential for less costly biosimilars to generate savings in healthcare systems is being explored.[11] There may be pressure from payors to make greater use of biosimilars through prescribers' budgets, and dermatologists will need to balance this pressure against patient needs. Treatment guidelines are now being rewritten to address the issues and opportunities in adopting biosimilars.

## Structure to Function: The Importance of Consistency

### Professor Leigh Revers

Biologics are important and highly effective in the treatment of psoriasis and other immune-mediated inflammatory diseases.[12] Biologic drugs are active pharmaceuticals synthesised by living organisms, consisting of large whole proteins and complex assemblies, and cannot be synthesised chemically. This has important implications for their use, and for producing copies of them, i.e. biosimilars. With the upcoming expiry of a number of patents for successful biologics, many competitors will look to profit from making their own versions.

Biologics are largely therapeutic monoclonal antibodies, and the precise way in which these most complex of drugs exert their clinical effects is not fully understood. Infliximab and adalimumab bind soluble TNF-alpha, preventing downstream signalling responses such as cytokine release, apoptosis, T cell activation, or inflammation. However, they can also act on membrane-bound TNF-alpha, triggering effects such as antibody-dependent cell-mediated cytotoxicity.[13] These differing mechanisms of TNF-alpha inhibition all contribute to the efficacy of the biologic in a

patient, and patients will vary in their response, depending to some extent upon their particular genetic polymorphisms. This degree of unpredictability in the efficacy of the reference biologic creates an additional challenge when attempting to demonstrate that a different manufacturer's version, which is known to contain minor but detectable compositional differences, has the same therapeutic value.

There are crucial differences between small-molecule drugs and biologics, which are important when considering biosimilars in comparison with generic drugs. Small-molecule drugs are simple, uniform, chemically synthesised structures, whose molecular structures are predictable and straightforward to characterise. Biologics are large, complex, heterogeneous molecules produced by living organisms (i.e. they are mixtures), whose three-dimensional structure is more easily perturbed; their chemical structures are variable and far more difficult to characterise completely. Monoclonal antibodies, in particular, are especially large molecules; all of these proteins undergo post-translational modification when produced by cells, resulting in a range of versions with different sugar chains attached (known as glycoforms).[14] Such post-translational glycosylation has been found to affect the potency of monoclonal antibodies (Figure 1).[15] This has raised concerns that differences in the relative proportions of glycoforms among biosimilars and the reference biologic may lead to differences in efficacy in individual disease settings, as exemplified by Health Canada's ruling that restricts the indications for a biosimilar of infliximab.[16] In some cases, engineered glycosylation may improve the clinical activity of a biologic, as in the case of lenograstim, a glycosylated version of filgrastim. These biologics that have been altered for improved clinical performance are sometimes referred to as 'biobetters'.[17]

Importantly, post-translational modifications are known to be highly sensitive to changes in the manufacturing process, and process variations between one manufacturer and another are inevitable. Thus, even slight alterations in manufacturing processes can lead to clinically relevant changes in potency or efficacy, the effects of which can range from benign to severe.[18,19] Manufacturers of reference products, such as adalimumab, have recently begun publishing manufacturing consistency data over the product's lifecycle. It has yet to be seen whether biosimilar manufacturers can achieve a similar level of consistency. With the emergence of multiple manufacturers of biosimilars, there is the inherent potential for divergence among these drugs as manufacturing drift occurs over time, which could be a future problem for clinicians (Figure 2).

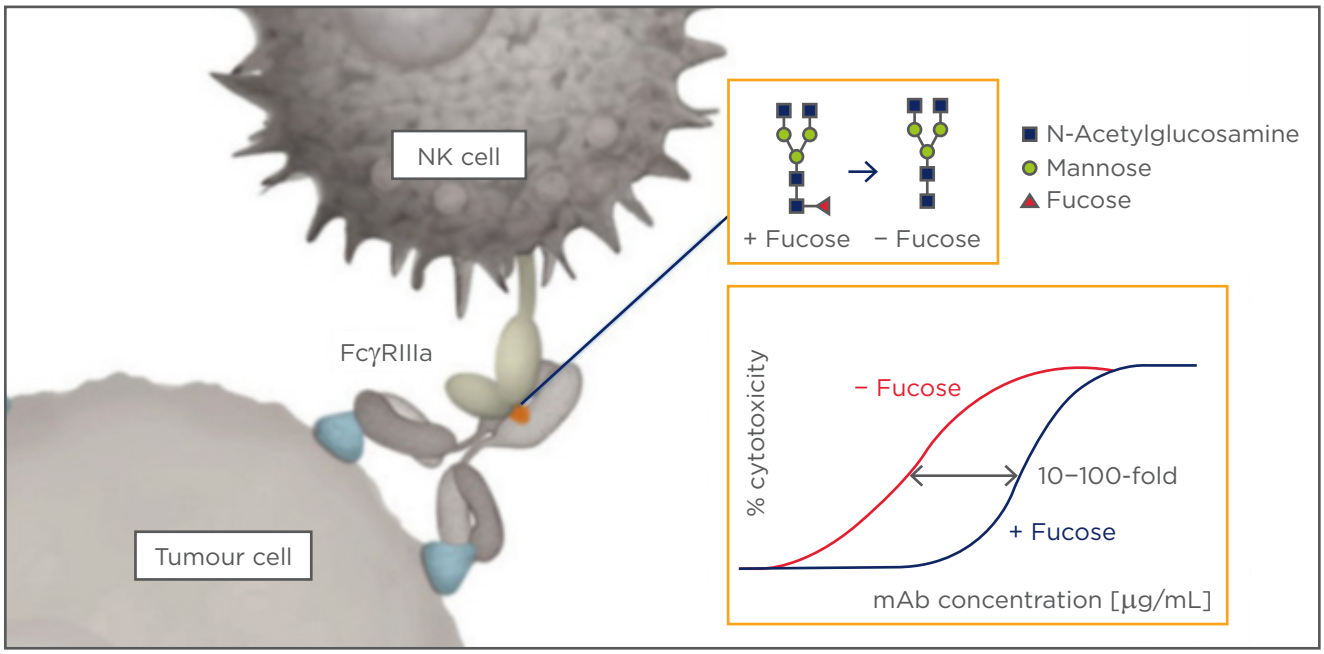


**Figure 1: Differences in glycoforms can affect the potency of antibody-dependent cell-mediated cytotoxicity, as shown here in the recruitment of natural killer (NK) cells to the site of a tumour.[15]**
mAb: monoclonal antibody.

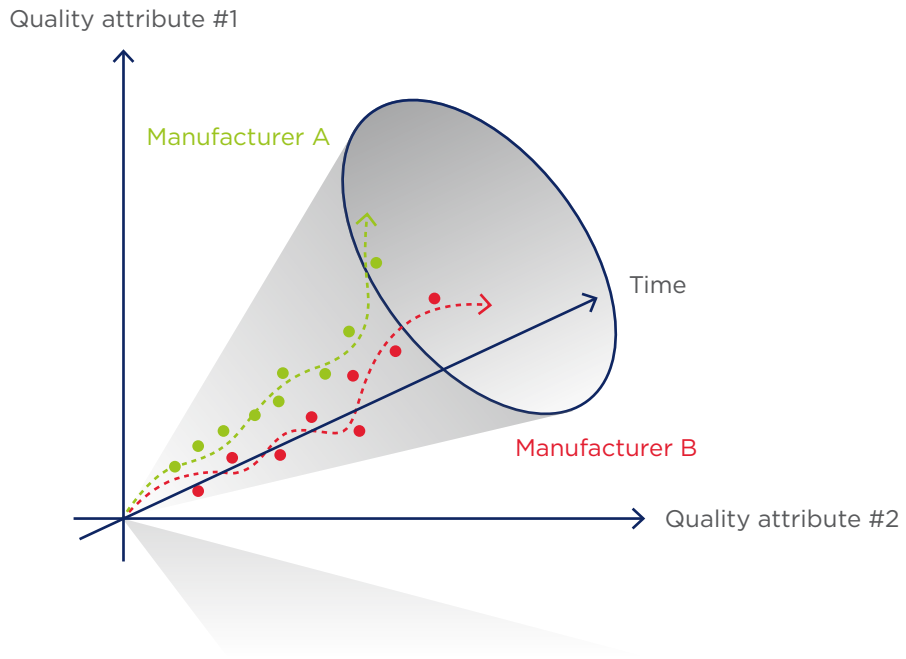


**Figure 2: Multiple manufacturers' inherent drift will cause divergence in product structure.**

With large numbers of biosimilars anticipated in the near future, there will be an increased need for regulatory vigilance to ensure the continued consistency of these products over the long term.

In summary, biosimilars are not generics: they are far larger and more complex. The challenge for the manufacturers is to ensure continued, parallel product consistency into the future, and, as more biologic therapy patents expire over the next 5 years, this will become an extremely important issue.

## The Changing Environment – What Does This Mean for Clinical Practice?

### Professor Luis Puig

The increasing availability of biosimilars to established biological therapies for psoriasis expands clinicians' choice, but how can we make the right treatment choices? There is a need to understand the comparability of biosimilars and for evidence to support switching from one to another. The European Medicines Agency (EMA) requires a full clinical trial to demonstrate safety and efficacy for each indication of a new biologic therapy, whereas for biosimilars the key regulatory requirement is availability of clinical data to prove comparable safety and efficacy to the reference biologic.[20] While interchangeability with the originator product is inherent in generic drugs due to the reproducibility of their manufacture, granting of biosimilar status by a regulatory body does not necessarily imply interchangeability.[21-23] There is a large number of biosimilars in development and approaching registration; therefore we need to be able to assess how to use them in practice.

For clinicians, an important issue in clinical practice is that of switching from a reference biologic to a biosimilar (or vice versa), or from one biosimilar to another (although from regulatory requirements a biosimilar can only be considered similar to the reference product and not to any other biosimilar). Patients may be switched due to failure of a biologic, i.e. inadequate response or intolerable adverse events, to a different biological agent, either within the same class (e.g. anti-TNF monoclonal antibody) or to a different class, which can be safe and effective.[24-27] However, switching from a reference biologic to its biosimilar (or vice versa) when there is a lack of efficacy is not sensible because the antidrug antibodies (ADA) underlying the loss of efficacy will cross-react with the biosimilar.[28,29] Non-medical switching, when a patient is switched to a different biologic or biosimilar although their current therapy is effective and well tolerated, is usually a result of intended cost savings or patient preference.[30] There are very few clinical data for this situation, making it difficult to assess the clinical and health economic consequences of this practice.[31] While the available data

(mainly for epoetin) suggest that switching seems to be relatively safe, it is difficult to design large trials to prove the absence of adverse effects due to non-medical switching of biosimilars. However, some trials suggest that non-medical switching may be associated with loss of response and increased healthcare utilisation.[32,33]

Assessing the interchangeability and automatic substitution of biosimilars is an important issue. The FDA requires biosimilar manufacturers to demonstrate that switching between a biosimilar and its reference product during the course of treatment does not cause loss of efficacy or safety issues. An interchangeable biologic can be substituted by a pharmacist for its reference without prior permission from the original prescriber. The EMA, however, does not evaluate interchangeability. A review of switching in clinical trials within the classes of erythropoetin, growth hormone, or granulocyte colony-stimulating factor concluded that patients could be safely switched from one product to another, but the data in this study were limited. Studies were generally too short to identify any long-term side effects, and the trials were not designed to identify switching-related adverse events.[34] More data are needed from appropriately-designed trials.

Study designs to compare the efficacy of reference drugs and biosimilars include transition studies, from the reference to the biosimilar; substitution studies, with a single crossover between biosimilar and reference; and interchangeability studies, with multiple switches between biosimilar and reference.[35] Studies evaluating a single-sided switch from the reference product to the biosimilar cannot be regarded as demonstrating interchangeability or switching. The ongoing NOR-SWITCH study is one such example, which aims to investigate potential differences in the rate of loss of response between patients continuing to receive infliximab and those switched to a biosimilar (NCT02148640, www.clinicaltrials.gov). The use of transition study design and the total of 250 patients in each arm means that the rate of loss of response in the two arms could be as different as 11% and 30% and still be considered statistically comparable. The PLANETAS open-label study extension, also a transition study, concluded that there was no significant difference between infliximab and a biosimilar in the development of ADA and loss of efficacy, although the data do suggest a trend towards a difference between the reference and the biosimilar.[36] The question of the level of difference we would consider adequate to demonstrate no change in safety and efficacy is yet to be resolved. Furthermore, while biosimilars are each compared with their reference product, studies comparing one biosimilar to another are not performed, making it difficult to know whether switching between biosimilars is safe.[37]

Repeated switches between biosimilars and originators may increase immunogenicity with potentially negative effects.[29] Immune responses to a biologic can influence its safety and efficacy,[38] and cannot be predicted from the chemical characterisation of the product.[28] Switching and intermittent exposure to a biologic is prone to increase immunogenicity,[28] and psoriasis (or its treatment with biologics in monotherapy) may be associated with a higher risk of immunogenicity than other immune-mediated inflammatory diseases.[39] Data from a comparison of infliximab and a biosimilar in patients with inflammatory bowel disease suggest that there is likely to be cross-reactivity.[40] Immunogenicity should always be assessed in switching studies, as it can cause serious adverse events, as well as drug neutralisation and loss of efficacy. Differences in immunogenicity are best determined by immunogenicity analysis in the most immunocompetent patient population.[41,42]

Traceability will be important for pharmacovigilance in order for adverse events developing after several months of treatment to be correctly attributed. This will be possible only through large pharmacovigilance databases and through specific studies and registries, as well as the use of individually identifiable product names and batch numbers.[43] However, centralised databases may not be available in many countries, and problems with reliable labelling do occur, such as with a recent withdrawal of an incorrectly labelled infliximab biosimilar in Spain. Given the limitations of post-authorisation data, it is currently not possible to conclude an absence of risk for switching between biologics and originators.[29,34] Therefore, more trial data are needed for us to use the upcoming range of biosimilars confidently in clinical practice.

## Q&A session

### How do you foresee potential divergence in structure in a world with several biosimilar manufacturers?

Prof Revers replied that it will be a challenge to the regulatory agencies. Healthcare professionals would have a role to play in ensuring that the use of individual biosimilars is tracked when products

are substituted; lot numbers will be important in tracking any problems that may arise due to subtle structural differences in the biosimilars. Manufacturers with a great deal of experience in producing biologics are likely to be able to meet regulatory requirements, and one might have greater confidence in their biosimilars.

My hospital has mandated a switch for all patients on a biologic to a biosimilar – is this a good idea, and what should I watch out for?

Prof Puig replied that it depended on the balance of cost savings versus the risk of losing drug response or immunogenicity of adverse events.

How are different batches and biosimilars captured in registries?

Prof Puig replied that, in Spain, the trade names are used. Prof Augustin agreed that this was also the case in Germany but that unfortunately they did not have the means to record batch numbers.

Doesn't the monitoring of critical quality attributes by manufacturers maintain consistency between lots and prevent the divergence referred to by Prof Revers?

Prof Revers responded by questioning what should be considered to be a critical quality attribute for the biosimilars. A quality attribute is something that is measured physically or chemically for a molecule, and the problem with monoclonal antibodies is that we are not completely sure how they work so it is difficult to determine a set of critical quality attributes. He suggested that some divergence is essentially unavoidable over time, which is why tracking batches of different manufacturers' biosimilars is important.

Will biologics be chemically synthesised in the future?

Prof Revers replied that, while synthesising single chain proteins was possible, it is expensive, and the synthesis of complex structures including antibodies was still at least 15 years away.

Do you think that the guidelines will need to be rewritten now that we have biosimilars?

Prof Puig replied that they would have to be adapted, since, if the regulatory agencies have approved a biosimilar, it can be used.

Should we preserve what we have achieved in the last decade and move forward only when we have solid clinical evidence, in particular for patients with good disease control?

Prof Puig replied that it depended on the healthcare system, and the problem of gaining evidence was that in some cases the population size that would be required would be too great. Prof Revers added that he thought in the future there may be less reliance on complex monoclonal antibodies, and that smaller chemical drugs would be developed that targeted the same mechanisms and have the same clinical effect while reducing some of the problems such as cross-reactivity and variation in production.

In Europe, why haven't authorities like the EMA considered the issues of interchangeability?

Prof Revers replied that the risks with switching biologics and issues with interchangeability were always a concern with such complicated biological molecules, and that this might be part of the reason why the FDA has taken so long to develop guidelines.

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# THE SKIN MICROBIOME IN PATIENTS WITH ACNE VULGARIS

## This symposium took place on 9th October 2015, as part of the European Academy of Dermatology and Venereology Congress in Copenhagen, Denmark


**Co-Chairs**

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## MEETING SUMMARY


Similar to some other tissues such as the gut, the skin is colonised by a dense community of commensal microorganisms. Maintaining the balance of this diverse flora may be important for healthy skin. Changes in the composition of cutaneous microbial communities have been linked to several chronic inflammatory skin diseases, including atopic dermatitis, psoriasis, and acne. Acne is a chronic inflammatory disease that affects the pilosebaceous follicle. The association between *Propionibacterium acnes* and acne vulgaris has been well established, but very few studies have investigated the total facial skin microbiota of acne-affected patients. Three-dimensional topographic analyses and microbiome profiling have, however, revealed differences in microbiome composition between healthy skin and acne lesions, as well as natural differences in microbial colonisation between the sebaceous gland and surface skin.[1] Furthermore, bacterial communities of the skin are involved in immune homeostasis and inflammatory responses important in the development of all acne lesions.[2] This improved understanding of the interactions between skin microbiota and the innate immune response in acne may provide a platform to design efficacious treatment strategies, specifically concerning the role of dermocosmetics to protect the skin microbiome.


## The Cutaneous Microbiome: A Master for Healthy Skin and an Underestimated Factor in Skin Diseases

### Professor Thomas Bieber

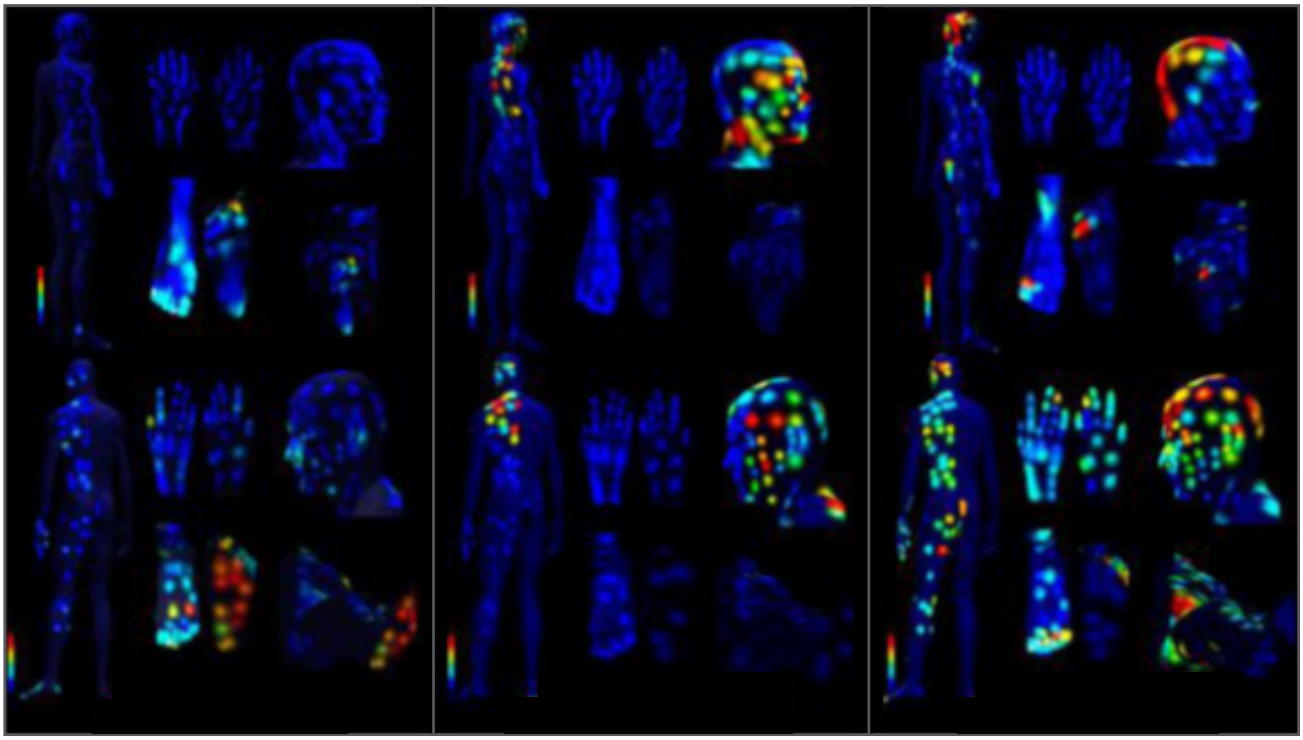
Since the discovery of microbes on the human body, much information on their composition has been gathered. However, the role of this collection of bacteria, fungi, and viruses remains a mystery. As well as the skin, most organs with an external surface are heavily colonised with different kinds of microbes, bacteria, fungi, and viruses. This 'microbiome' contains $10^{14}$ organisms, representing 10-times more cells than the human body itself,[2] and is often referred to as our 'second genome' owing to its fingerprint-like unique composition of diverse organisms. The microbiome can be localised to three zones of the human body: sebaceous areas and those sites that are dry or moist, each of which

represents differing ecological conditions and are therefore favoured by different kinds of microbes.[2]

The microbiome is strongly influenced by environmental signals and conditions. Microbiota on the skin are determined at birth and vary depending on the method of birth (natural or caesarean section) and the extent of contact with the mother shortly thereafter,[3,4] whereas the microbiota of the gut are largely dependent on early-life feeding habits.[5,6] Thus, certain events during human development are crucial in determining the basis of an individual's microbiome, which will ultimately adapt and change over the years.[7] In addition to the sex and age of a person, genetics, environmental factors (both climatic and geographic), immune response, lifestyle (e.g. occupation and level of hygiene), and underlying disease play a critical role in driving and regulating the composition of the microbiome.[8]

Microbiota have been linked to various diseases, including inflammatory bowel disease, diabetes, obesity, rheumatoid arthritis, and various allergies,[9,10] as well as neuropsychiatric diseases related to the gut–brain axis.[11] However, not all microbes are harmful. When considering the skin, microbes are present on the surface as well as deep within the epidermal compartment owing to connections with structures such as the sebaceous glands.[12] Interestingly, microbiota have been found to be in close dialogue with other cell types, including resident immunologically important cells (e.g. T cells). In addition, it has been shown that microbes in contact with Langerhans cells bridge the innate and the adaptive immune system, allowing local production of antimicrobial peptides (AMPs)[1] to counteract pathogenic microbes or even protect against atopic sensitisation and inflammation.[13] One example is *Staphylococcus epidermidis*; these bacteria themselves produce high amounts of AMPs to control the growth of pathogenic *S. aureus* strains.[14] Although diverse colonisation is key for good health, as microbes consistently deliver signals that contribute to the education of our immune system, skin is the most vulnerable organ to environmental changes, with the most unstable microbiota compared with those of the gut or other niches of the body.[15]

New technology provides 3D topography of the skin that allows visualisation of the microbiome, and the associated metabolome, for the first time (Figure 1).[1] These visualisation methods will greatly aid in developing new approaches for the design of therapeutic compounds and cosmetics.



*Staphylococcus* *Propionibacterium* *Corynebacterium*

**Figure 1: Three-dimensional topography of the skin microbiome.[1]**

## How *P. acnes*, the Microbiome, and the Innate Immunity Interact in Acne

**Professor Brigitte Dréno**

Acne is a chronic inflammatory disease affecting the pilosebaceous follicle. Three main factors are implicated in the development of acne lesions: firstly, sebaceous glands are stimulated via activation of several receptors, including those for androgens, neuropeptides, insulin-like growth factor 1, and peroxisome proliferator-activated receptors; secondly, the combination of hormonally stimulated sebum production, abnormal keratinisation of the pilosebaceous duct, and formation of comedones; and thirdly, an inflammatory immune response to *P. acnes*, a gram-positive bacterium that results in activation of innate immunity and the development of an inflammatory reaction. Inflammation is crucial in the development of acne and could potentially contribute to the development of scars. The bacterium has been located in active lesions and also found to underpin the development of persistent post-inflammatory hyperpigmentation via the stimulation of alpha melanocyte-stimulating hormone and interleukin (IL)-1.

*P. acnes* is a commensal bacterium of the pilosebaceous follicle microbiome that plays a physiological role by inhibiting invasion by pathogenic bacteria such as *S. aureus* and *S. pyogenes*. In addition, *P. acnes* maintains the acidic pH of the sebaceous gland and the skin by hydrolysing triglycerides, releasing free fatty acids, and secreting propionic acid.[8] This helps to maintain the physiological profile of the sebaceous microbiome in both a quantitative and qualitative manner. Recent improvements in DNA sequencing technology, together with the publication of metagenomic analyses by the Human Microbiome Project Consortium,[16,17] allowed the identification of a 16S rRNA gene, which includes hypervariable regions that provide species-specific signature sequences, permitting the identification and classification of bacteria.[18] *P. acnes* has been characterised as an anaerobic bacterium that grows particularly well in the sebaceous areas of the forehead, retroauricular crease, and back.[18,19] Furthermore, metagenomic studies have highlighted that acne is a non-infectious disease that results from shifts and imbalances in microbiota of the skin.[18,19]

*P. acnes* interacts with the innate immune system to promote inflammation in two different ways. The skin acts as an immunological barrier and a first-defence mechanism against infection. *P. acnes* directly modulates innate immunity by identifying pathogen recognition patterns and activating innate immune responses via Toll-like receptors,[20,21] peroxisome-activated receptors,[22,23] intracellular NOD-like receptors 1–3, retinoic acid-inducible gene-like intracellular receptors, and AMPs, thus regulating cutaneous inflammation.[22] Optimal skin health and innate immunity are maintained when the microbiome and the immune system of the skin are balanced. The second mechanism by which *P. acnes* activates cutaneous innate immunity is by quantitatively and qualitatively modifying the cutaneous microbiome. Hyperseborrhoea, starting during puberty, induces proliferation of specific *P. acnes* subtypes, *S. epidermidis*, and corynebacteria, which creates an imbalance in the microbial make-up of the skin that stimulates the activation of cutaneous innate immunity, including the secretion of IL-1β by keratinocytes and monocytes, and development of inflammatory lesions.[8,24] Additional secretion of IL-17 by monocytes in the dermis and follicular metalloproteinases are also implicated in destruction of the follicle and scarring.

Recent studies have shown that acne is not necessarily the result of the proliferation of *P. acnes*, as *P. acnes* predominates on both normal and disease-associated skin.[25] Genomic comparison of *P. acnes* strains has allowed identification of different profiles of commensal *P. acnes* subtypes between healthy skin and acne lesions, demonstrating phenotypic and functional differences of *P. acnes* as a commensal in health and as a pathogen in acne.

Skin care plays an important role in acne, as repeated cleansing of the skin results in modification of the natural protective barrier. The natural defence system of the skin can be altered by using detergents that disrupt the skin lipid barrier and induce marked loss of AMPs, allowing proliferation of *S. epidermidis* and attenuation of the innate immune response. Therefore, the main purpose of cosmetics for skin care in acne is to maintain the protective barrier function by maintaining cutaneous pH, hydration, and lipid film to protect the skin barrier and the microbiome.[26]

Research into cosmetics that support the natural defences of the skin is ongoing. A recent study demonstrated the benefits of cosmetic AMPs in the suppression of antibacterial, antiviral, and

anti-inflammatory activity, thus maintaining skin homeostasis and suppressing bacterial resistance by inhibiting the pro-inflammatory IL-1 pathway.[27] Furthermore, treatment with vitamin B12, B3, and ceramide has demonstrated benefits with regard to modulation of the transcriptome of the skin microbiome in acne pathogenesis,[28] delaying extracellular signal-regulated protein kinase activation, and reducing melanin synthesis via alpha melanocyte-stimulating hormone and inhibition of the IL-1 inflammatory pathway.[29]

## The Skin Biome: A New Player in Acne Management

### Doctor Sophie Seité

In collaboration with L'Oréal Research and Innovation and the University of Boulder (Boulder, Colorado, USA), La Roche-Posay has initiated studies to analyse the microbiomes of various face skin surface areas of acne patients compared with healthy individuals. Superficial intrapersonal sampling of inflammatory lesions and non-inflammatory lesions in close, non-affected areas, coupled with amplification of the 16S rRNA specific to each bacterium in the skin samples allows identification of the bacterial landscape at the surface of the skin of acne patients and assessment of the quantity and the diversity of the superficial microbiome.[30] Three outcomes were considered to be of the greatest importance: differences between the microbiomes of superficial acneic and normal healthy skin in two individuals, differences in the microbiomes of an inflammatory lesion and adjacent unaffected skin of the same individual, and variability between the microbiome of a non-inflammatory lesion and adjacent unaffected skin of the same individual.

Bacterial biodiversity seems lower on the skin surface of the cheeks of healthy individuals compared to patients with acne possessing the same skin type, age, and gender, particularly following treatment.[30] The main difference in the phyla present on both skin types is the quantity of actinobacteria (including the *Propionibacterium* genus), which are observed at higher levels in healthy skin of healthy individuals, together with firmicutes and proteobacteria. The lower levels of actinobacteria present on acneic patients translate into increased levels of firmicutes and proteobacteria, even on unaffected skin (Figure 2).[30]

The comparison of unaffected skin with non-inflammatory and inflammatory lesions sampled from acne patients revealed similar profiles of phyla. Whereas the level of actinobacteria was similar across the three sampled sites, the abundance of proteobacteria was lower for both lesions compared with unaffected skin. Conversely, firmicutes were observed at a higher level on non-inflammatory lesions in comparison with unaffected skin. This increased quantity of firmicutes was mainly due to a significant rise in staphylococci in both lesions compared with unaffected areas (Table 1). When comparing healthy individuals with those affected by acne, propionibacteria made up 38% and less than 2% of the skin phyla, respectively.[31]

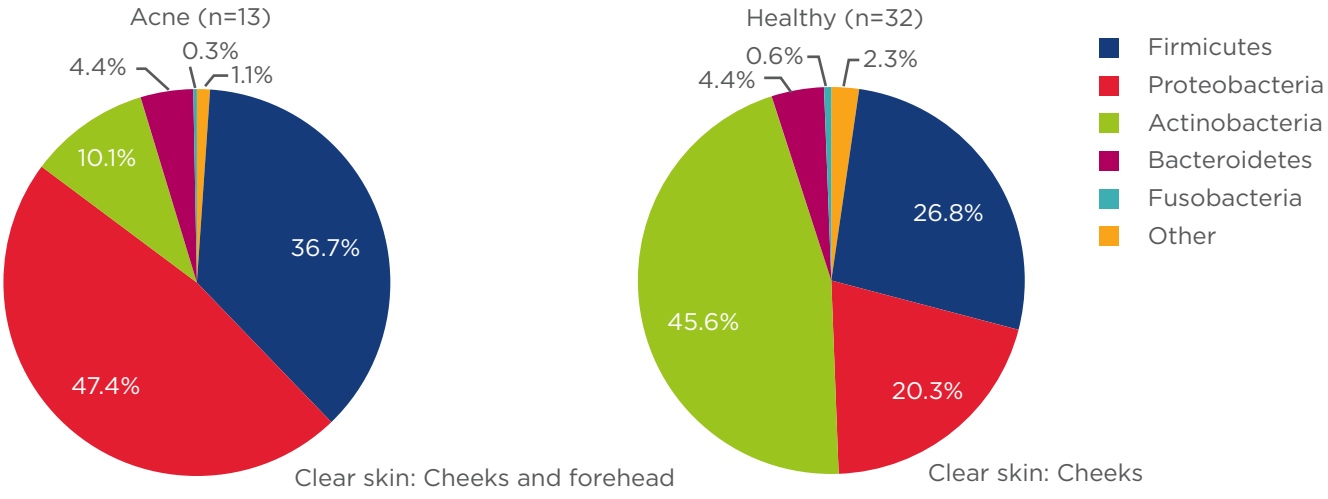



**Figure 2: Phylum-level comparison of the microbiomes of healthy skin (cheeks) and acne-affected skin (skin without any lesion - cheeks and forehead).**

**Table 1: Phyla profiles of non-inflammatory lesions (NIL), inflammatory lesions (IL), and unaffected skin (UAF) taken from acne patients.**

| PHYLUM | GENUS | NIL (%) | IL (%) | UAF (%) |
|---|---|---|---|---|
| Actinobacteria | | 13.61 | 14.15 | 13.75 |
| | *Propionibacterium* | 1.04 | 1.20 | 1.36 |
| | *Corynebacterium* | 7.93 | 8.54 | 7.71 |
| Firmicutes | | 52.01* | 49.27 | 47.01 |
| | *Staphylococcus* | 33.87* | 34.00* | 26.85 |
| Proteobacteria | | 28.90* | 31.30* | 34.10 |

*p<0.05 vs UAF, n=26.

The differing severity of acne was reflected in the proportion of staphylococci, without apparent differences for propionibacteria or *P. acnes*. Therefore, while the bacterial microbiota of follicles from acne-affected patients are dominated by *P. acnes*,[32] current data indicate that the microbiota of the skin surface are dominated by staphylococci relating to the severity of acne.

When assessing the effect of topical treatment with 4% erythromycin or a dermocosmetic on the skin surface microbiota of acne-affected patients, both agents significantly decreased the number of non-inflammatory and inflammatory lesions after short-term use. These benefits may be the result of a significant reduction in actinobacteria, particularly corynebacteria and propionibacteria, after antibiotic treatment and a smaller effect on staphylococci and propionibacteria following treatment with the dermocosmetic used in this study. Therefore, dermocosmetics targeting staphylococci in monotherapy or in combination with additional treatments provide an effective treatment strategy to manage more widely the microbiotic imbalance observed on the skin surface of patients affected by acne.

**Q&A session**

The effect of method of birth and influences immediately afterwards on the microbiome are well understood. To what extent does the microbiome change throughout a person's lifetime?

Prof Bieber: It is important to note that past studies were based on swab sampling, whereas in current studies cutaneous swabs or scratching can be performed to analyse samples, allowing us to assess more carefully and distinguish between the skin surface microbiome and the follicular microbiome. It has been suggested that standardised microbiomes could be used to correct the composition of the skin biome following birth by caesarean section. However, the composition of the microbiome is largely dependent on genetic and epigenetic pressures. Manipulation of the microbiome is likely to be transient and would require long-term and consistent application of agents designed to change the microbiome of the skin.

What was the make-up of the agent used as dermocosmetic?

Dr Seité: The study presented was based on a cosmetic (Effaclar Duo[+], La Roche-Posay) containing β-lipohydroxy acid, salicylic acid, linoleic acid, niacinamide, and piroctone olamine, and which has been shown to be very effective in the treatment of acne, mainly via rebalancing the skin surface microbiome without eradicating *P. acnes* and with no risk of inducing *P. acnes*-resistant strains.

Does each individual harbour different phenotypes of *P. acnes* or is a single phenotype involved in the development of acne?

Prof Dréno: Different phenotypes of *P. acnes* are involved in the development of the skin disorder and this is very individual to each patient. The severity of acne most likely depends on the ratio of the various phenotypes, as well as the predominant phenotype, as the effect on innate immunity activation can vary.

Can different skin diseases, such as acne and psoriasis, be explained by differences in microbiota?

Prof Bieber: The development of cartographic analysis of the microbiotic composition of various

body regions will aid greatly in establishing 'concrete' profiles that will aid the treatment of specific skin disorders. However, the question remains whether changes in microbiomic composition are a cause or the result of skin disorders. The unexpected finding of staphylococci on the acneic skin surface, as presented during this symposium, may be interpreted as a secondary phenomenon owing to a particular kind of inflammation that favours the growth of bacterium in unexpected regions of the skin. Furthermore, topical antibiotic treatment used in acne-affected patients may lose its activity due to bacteria becoming resistant. However, many topical antibacterials appear to have an additional benefit as anti-inflammatory compounds.

Dr Seité: One limitation of studies assessing the microbiome is the inability to evaluate antibiotic resistance of *P. acnes* or staphylococci. Therefore, antibiotics can induce the development of bacterial resistance but are also, as demonstrated in this study, unable to manage the microbiotic imbalance observed on the skin surface of patients affected by acne.

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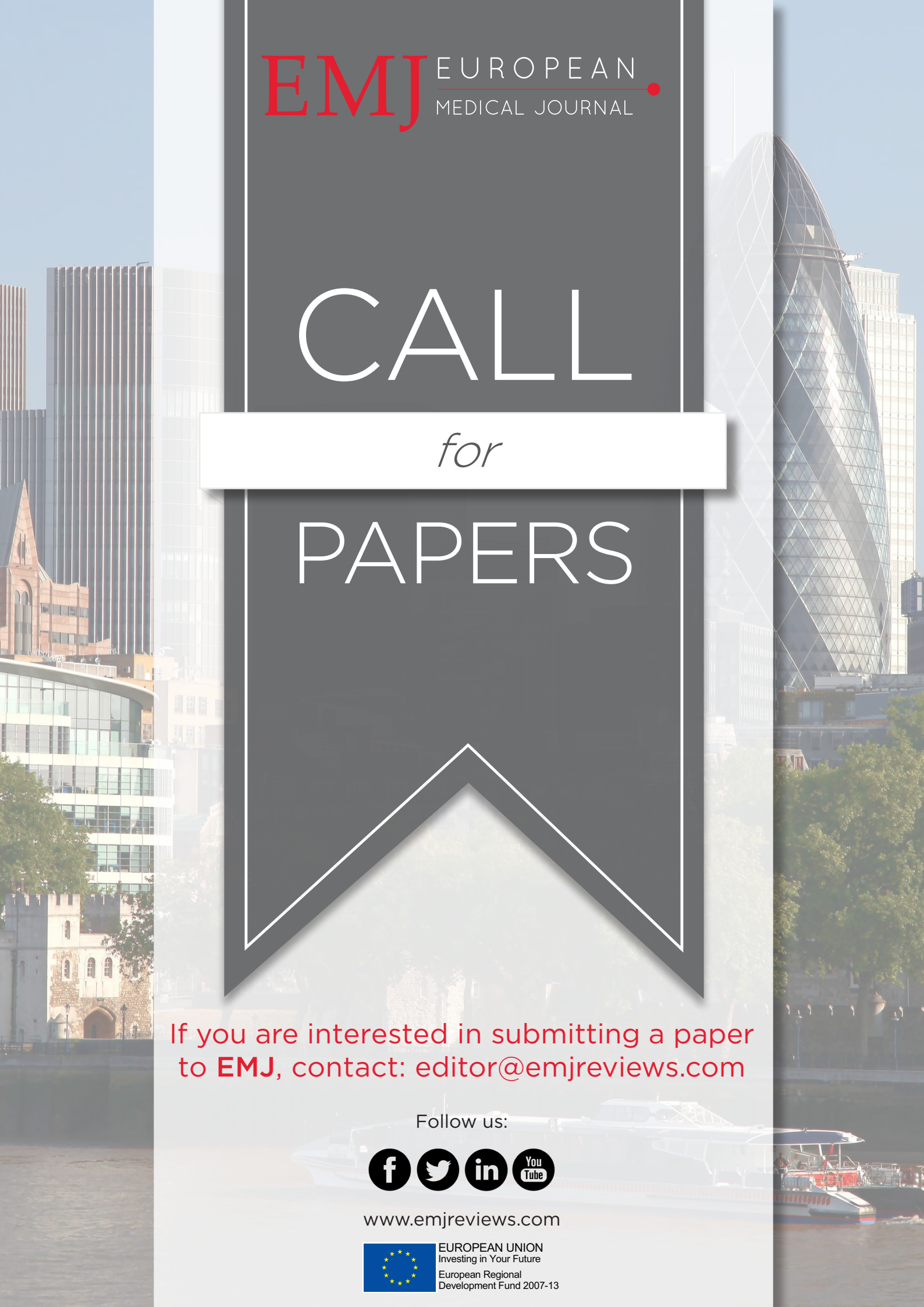
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# INVASIVE CUTANEOUS SQUAMOUS CELL CARCINOMA

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Invasive cutaneous squamous cell carcinoma (cSCC) accounts for nearly 20% of non-melanoma skin cancer, with a steady increase in incidence over the past decades. It usually develops from precursor lesions such as actinic keratosis or Bowen's disease, but may also develop *de novo*. Recent studies emphasise the role of a number of clinical and histological characteristics in risk evaluation, including: a tumour diameter of >2 cm, a tumour depth of >6 mm, immunosuppression, location, differentiation, and histological subtype. High-risk cSCC demonstrates metastatic potential in the lymph nodes, lungs, brain, and liver.

The diagnosis is set histologically with a biopsy punch or an excisional biopsy after initial clinical evaluation and dermoscopy. Dermoscopy can be a helpful tool along with optical coherence tomography and reflectance confocal microscopy in evaluation of tumour characteristics prior to biopsy. Lymph node ultrasound should be advised for the diagnostic workup of high-risk tumours. The role of fine needle aspiration cytology and particularly of the sentinel lymph node biopsy (SLNB), though well validated in the diagnosis of melanoma, remains controversial. However, most major guidelines tend to consider SLNB or even advise it in the setting of clinical trials.

Surgical excision remains the mainstay of treatment and is rarely contraindicated, even in older patients who can be managed in a day hospital setting in most cases. Standard excision with adapted safety margins ranging from 5 mm for low-risk tumours up to 10 mm for high-risk tumours demonstrates excellent results in many cases. However, in the case of high-risk tumours, or if functional impairment is feared, Mohs surgery could be preferred in spite of the elevated costs. Radiotherapy remains a fair alternative in the treatment of small, low-risk cSCC, or if surgery is contraindicated or refused from the patient. Radiotherapy can also be discussed in the case of advanced tumours, nodular disease with extracapsular expansion, or in the adjuvant setting.

In the therapeutic approach of advanced or metastatic disease, progress is slow; treatment is still based on chemotherapeutic platinum-based regimes, with polychemotherapy demonstrating better results than monochemotherapy. However, remissions are short-lived in most of the cases.

Interestingly, EGFR is overexpressed in cSCC, and targeted treatments with EGFR inhibitors, such as cetuximab, have emerged as second-line treatments in recent years. Though results are promising, a major breakthrough such as the one seen in basal cell carcinoma with vismodegib is yet to be achieved. Combinational treatments of EGFR inhibitors with VEGFR, IGFR, and mTOR inhibitors promise better results in the years to come and should be evaluated in the context of clinical trials.

# DERMOSCOPY OF MUCOSAE

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Few studies have been conducted on the dermoscopy features of healthy and pathological mucosae due to three main reasons: 1) patient embarrassment associated with the dermoscopic examination of genital mucous membranes; 2) lack of dermoscopic equipment allowing visualisation of lesions located intraorally; and 3) the rarity of malignant melanoma (MM).

Mucosals represent 1–8% of all MMs, but melanoses (or 'melanotic macules', benign pigmentations of the mucosae due to a hyper-pigmented basal layer of the epithelium) are common and it has been estimated that 20% of women have pigmented lesions of the vulva. For this reason, dermatologists are often asked to give their advice on pigmentation

of the mucosae. The differential diagnosis between MM and melanosis is challenging because melanoses can be highly pigmented and large, mimicking MM. However, there are some clinical clues that help in the differential diagnosis: melanoses are often multiple and bilateral, and can involve different areas (genital sites, oral sites, and nails). Moreover, melanoses occur in younger patients and are never raised. The few studies on dermoscopy of the mucosae mainly focus on the differential diagnosis between melanoses and MM, and have found that melanosis can present with parallel-line (or 'fingerprint'), circle (or ring-like), reticular-like, structureless (or homogeneous), or globular-dotted patterns, whereas MMs are mainly characterised by a multicomponent pattern and polychromia (three or more colours). Parallel-line and circle patterns are quite specific for melanosis, whereas the other dermoscopic patterns can also be found in MM. When they are found in MM, however, they are usually irregular, combined, and associated with multiple colours.

Blum et al.[1] found that the presence of structureless grey, white, or blue areas is a clue for the diagnosis of MM; these criteria displayed 100% sensitivity and 82.2% specificity in their series. However, the authors evaluated only 11 MMs and only 1 *in situ* MM and it is possible that some early MMs may not exhibit these criteria. Our group recently found that, similar to MM, melanoses can also appear grey in colour under dermoscopy.[2] We found that half of melanoses present as grey in colour (either alone or associated with brown colouring), but few melanoses are characterised by structureless grey areas. Moreover, we demonstrated that the grey colour in melanoses is due to the presence of melanin-laden melanophages in the upper dermis.

With regard to the dermoscopic features of inflammatory diseases, there are only case reports present in the literature and there remains a lot of research to be undertaken in this field.

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# TWO-YEAR EFFICACY OF QUADRIVALENT HUMAN PAPILLOMAVIRUS VACCINE IN THE PREVENTION OF LOW-GRADE CERVICAL, VULVAR, AND VAGINAL INTRAEPITHELIAL NEOPLASIAS AND ANOGENITAL WARTS IN HIV-POSITIVE WOMEN

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## Background and Objectives

A quadrivalent human papillomavirus (HPV) L1 virus-like-particle vaccine against HPV Types 6, 11, 16, and 18 has been shown to be effective for the prevention of cervical and genital disease related to these HPV types in HIV-negative women already infected with ≥1 of these HPV types at the time vaccination is offered. Interaction between the two sexually transmitted infections appears to be related to the alteration of cell-mediated immunity in HIV-infected persons, increased susceptibility, and possibly reactivation of latent HPV infection.

The aim of our study was to evaluate the prophylactic efficacy of the quadrivalent HPV vaccine in preventing low-grade cervical, vulvar, and vaginal intraepithelial neoplasias and anogenital warts (condyloma acuminata) in HIV-positive women.

## Materials and Methods

Thirty-one HIV-positive women were vaccinated with the quadrivalent HPV vaccine. The HPV

DNA status of the participants was determined using polymerase chain reaction before and after immunisation.

### Results and Conclusion

The rate of protection against HPV16/18 with a three-dose schedule was high (≥84%) and the cross-reactive antibody responses against HPV31, HPV33, and HPV45 were evaluated at 6, 12, and 24 months. In summary, the quadrivalent HPV vaccine provided sustained protection against low-grade lesions attributable to the HPV types included within the vaccine and a substantial reduction in the burden of these diseases through 24 months of follow-up. These results support vaccination of this population without prescreening.

## ADDITIONAL REVIEW OF MOHS SLIDES TO OPTIMISE MOHS MICROGRAPHIC SURGERY

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The success of Mohs surgery partly depends on correct interpretation of slides. This retrospective study determined how often pathologists detected incompletely excised basal cell carcinoma (BCC) on Mohs slides in 1,653 BCCs treated with Mohs surgery.[1] Thereby, we determined risk factors for incompletely excised BCCs. Incompletely excised BCCs were detected in 31 cases (2%), in which defects >20 mm in diameter were an independent risk factor (odds ratio: 3.58, 95% confidence interval: 1.55–8.28). Other studied variables (i.e. aggressive subtype, previously treated BCC, location on nose, and >2 Mohs stages) did not affect the risk of incompletely excised BCCs. This study showed that the additional review of Mohs slides increased accurate interpretation, especially in large BCCs. Therefore, the additional review of Mohs slides might prevent skin cancer recurrence.

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## A RETROSPECTIVE CASE–CONTROL STUDY OF PATIENTS WITH INTRINSIC ATOPIC DERMATITIS

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**Introduction:** Atopic dermatitis (AD) can be classified into extrinsic and intrinsic forms. The criteria for extrinsic AD are coexistence of either asthma, hay fever, specific IgE against a common inhalant or food allergen, or elevated total serum IgE. Patients with the intrinsic form are characterised by absence of asthma and allergic rhinitis, absence of both positive standard skin prick tests and specific IgE to common atopic allergens, and normal serum IgE levels.[1,2] The background of the intrinsic form remains unclear. Two hypotheses exist: either patients could be genetically fixed for an extrinsic or intrinsic form, or patients may change their status from an intrinsic form to an extrinsic form of AD.

**Methods:** To provide an answer to these questions, we performed a retrospective case–control study in 867 consecutive AD patients who attended our out-patients department between 1999 and 2004. The ratio between extrinsic and intrinsic AD, the gender ratio, and whether the intrinsic form developed immediate-type hypersensitivities or allergies in the observation time were analysed. Data obtained included personal and family history. Total and allergen-specific serum IgE, atopy patch

test (APT), and skin prick test with a standard panel of inhalant allergens were performed. Using these diagnostic criteria, all patients were classified as having either extrinsic or intrinsic AD. The intrinsic patients were followed up until study termination in 2013, for an average of 6.3 years.

**Results:** A total of 867 patients were included; 806 (92.96%) showed elevated total or allergen-specific serum IgE levels for typical atopic allergens. Sixty-one patients (7.04%) did not show elevated serum IgE levels and no specific antibodies against cat and dog epithelia, house dust mites, latex, timothy grass, rye, birch, and mugwort (Sx1 allergens). During further analysis, 38 (62.29%) of the initial 61 patients could be defined as having an intrinsic form of AD. Therefore, 23 patients (37.7%) with a former intrinsic AD were reclassified: 11 patients due to positive skin prick tests, 12 patients due to *in vitro* IgE diagnostics, but none in relation to elevated total serum IgE. Atopy patch testing was performed in 31 of our 61 intrinsic AD patients and 2 patients showed positive test reactions. The percentage of intrinsic AD in relation to extrinsic AD was 4.38% versus 95.61%, respectively. The average age of our intrinsic patients was 27.83 years. This was significantly younger than the extrinsic patient group, in which the average age was 33.73 years. The distribution of gender showed a male to female ratio of 19:48 (male: 21.3%). Until the study's termination in 2013, 38 patients showed no immediate-type hypersensitivity in skin prick tests and, in a total of three serum samples, no elevation in levels of total (<100 kU/L) and specific IgE (<0.35 kU/L) against typical atopic allergens were found.

**Conclusion:** We discovered that intrinsic AD is rare in our tertiary centre. Intrinsic AD is predominantly seen in young women, which confirms the data obtained from other centres. The reason for this remains unclear. The significantly younger average age of intrinsic AD patients is in line with the concept of an 'AD march'. During the 6.3-year observation period, 23 of our 61 initially intrinsic patients were reclassified as extrinsic. The APTs were positive in a small percentage of our intrinsic AD patients (6.45%, n=2). This was not completely unexpected as this test is known to be more specific for AD than skin prick tests, and targets the T cell-mediated component of AD. From published data, we know that approximately 50% of the extrinsic AD patients in our institution develop a positive APT reaction.[3] An AD march is detectable in almost one-third of our patients with an initial diagnosis of intrinsic AD within an observation time of 6.3 years.

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# MEDICAL APPROACH TO HIDRADENITIS SUPPURATIVA

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With over 30 medical treatment options available for hidradenitis suppurativa (HS), often supported by only limited evidence, selecting the optimum therapy can be challenging. The recently published European S1 guidelines recommend a stepwise approach based on disease severity, commencing with topical clindamycin, followed by oral tetracyclines, then oral rifampicin and clindamycin in combination, acitretin for males and infertile females, and finally, considering biological therapy for more severe disease unresponsive to other therapies.[1] Adjuvant therapy includes pain management, which is a relatively neglected component of HS care and has been included in the top 10 priorities in a recent HS research priority setting partnership conducted between HS patients and clinicians.[2] Weight loss and smoking cessation are additional recommendations when relevant.[1]

**Table 1: Multidisciplinary team members to provide holistic care.**

- Dermatologist
- Dermatology nurse
- Plastic surgeon
- Wound healing expert
- Vulval expert
- Clinical psychologist
- Chronic pain expert

**Table 2: Top 10 tips for medical management of hidradenitis suppurativa.**

1. Advise weight loss and smoking cessation (if relevant)
2. Manage pain
3. Develop a multidisciplinary team approach
4. Measure outcomes, including pain and quality of life
5. Topical clindamycin
6. Oral tetracyclines
7. Oral clindamycin and rifampicin
8. Acitretin for males
9. Avoid isotretinoin (unless treatment of concomitant acne vulgaris is needed)
10. Infliximab/weekly adalimumab

The randomised controlled trial (RCT) evidence for HS interventions has recently been summarised in a Cochrane Review.[3] The review included 12 RCTs with 615 participants, investigating 15 different interventions. The median number of participants for the included studies was only 27 and so imprecision resulted in a downgrading of evidence quality for most of the studies when assessed using GRADE methodology. Another issue that limits meta-analysis of HS trials is the heterogeneity of outcome measures. In terms of physician-reported outcomes, the Hurley staging system is a widely used measure for baseline disease severity, but is relatively unresponsive to change. More recent scoring systems, such as the Sartorius and HiSCR scales, involve a lesion count. Patient-reported measures include a pain score on a visual analogue scale and quality of life, measured with a dermatology specific instrument.

Ideally, HS management should be coordinated by a multidisciplinary team to provide holistic care for patients (Table 1). A list of top 10 tips for the medical management of HS is provided in Table 2. Surgical therapy, ranging from limited to more extensive excision, can run parallel to medical care, as outlined in the S1 guidelines.[1]

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# A NEW PARADIGM FOR MONITORING CLINICAL PROGRESS IN HIDRADENITIS SUPPURATIVA

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Hidradenitis suppurativa (HS) is a chronic autoinflammatory disease manifesting in recurrent, painful, and deep-seated nodules and abscesses with variable heterogeneous phenotypic presentation. The recent surge in HS research has provided invaluable understanding of many facets of this disease; however, large gaps continue to exist in pathogenesis, epidemiology, classification and staging systems, monitoring, treatment, and relevant comorbidities. Our Liverpool clinic has recognised that current measurement tools still do not reflect the burden of disease that patients experience, as they lack longitudinal responsiveness and correlation to disease severity. Until a new scoring system is achieved, it is our impression that the only reliable assessment is a comprehensive patient review through the use of routine blood tests including inflammatory markers, cytokine analysis, Dermatology Life Quality Index (DLQI), genetic sequencing, ultrasound imaging, comorbidity assessment with specific importance

placed on insulin resistance, and lipid and androgen dysfunction.

The central concept underpinning HS is the inflammasome, first conceptualised by Jürg Tschopp in Switzerland as a model for interleukin-1 beta (IL-1β) processing. This group of protein complexes recognise stimuli that control the production of proinflammatory cytokines, which regulate important aspects of inflammation, tissue repair, and tissue death. Assembly of the inflammasome is induced by dysregulation of endogenous (including notch receptor, gamma secretase, and tumour necrosis factor-alpha [TNF-α] polymorphisms; endogenous hormones; and insulin resistance) and exogenous (including smoking, visceral adiposity, dietary factors, and the microbiome) signals that result in IL-1β release. Tissue analysis of cytokines in patients affected with HS show high levels of IL-1β in involved and peripheral skin.

HS would benefit from a specific biomarker for diagnosis, prognosis, comorbidity assessment, prediction of relapse, and for tailoring individual patient therapy. Given the complexity and heterogeneous nature of HS, it is unlikely that a single cytokine will meet all of these criteria, and instead multiple biomarkers may represent a more realistic approach for the future of personalised medicine in HS. Our Liverpool clinic has commenced cytokine panel testing for HS patients using the following cytokines: TNF-α, IL-1, IL-17, IL-8, IL-10. Further testing, with S100 protein as a biological marker of progress, is intended.

Bacteria are a major contributor to the inflammatory cycle observed in HS. They most likely trigger a cascade of pathogen-associated molecular patterns, leading to inflammasome activation and IL-1β release. The most common species found on bacterial analysis of superficial and deep lesions of HS patients are coagulase-negative staphylococci (CNS) and *Staphylococcus aureus*. Numerous studies have shown that CNS can cause severe infection, especially in immunocompromised patients and those with intravascular devices and foreign body devices. CNS may have true pathogenic properties in HS. It is this concept that has led our Liverpool clinic to commence bacterial analysis of HS lesions to specifically include CNS.

Approximately one-third of HS patients have been shown to have a genetic basis to their disease, presenting early and with a positive family history. In familial cases, HS shows an autosomal dominant pattern of inheritance and appears to be genetically heterogeneous. The pathogenesis of HS appears to involve mutations in genes encoding for gamma secretase transmembrane complex and the notch receptor. Gamma secretase targeted therapy is a potential new focus for the management of HS. The restoration of the notch signalling pathway in these individuals could bring much anticipated relief to HS patients who suffer significant disabilities as a result of their chronic inflammatory condition. In collaboration with our international colleagues in Genova, Italy, we have commenced genetic analysis using a newly developed 41-gene panel for autoinflammation.

Accurate analysis of lesions in HS patients with ultrasound is vital to assessment and monitoring. Our Liverpool clinic has found use of this tool essential in assisting with classification and scoring of disease, analysis of relationship to pain, and for pre-surgical review to ensure accuracy of surgical excision. More often than not, ultrasound results show far more extensive disease than those found on clinical examination.

In conclusion, our team suggests the following in assessment and monitoring of HS patients:

- Regular clinic reviews and provision of education
- Collection of phenotypic variables
  - Demographic details: Body mass index, waist circumference, family history
  - Past medical history: Smoking, acne, ductal carcinoma *in situ*, inflammatory bowel disease (IBD), pyoderma gangrenosum, polycystic ovary syndrome, hyperlipidaemia, ischaemic heart disease, diabetes mellitus, insulin resistance, depression, obesity, squamous cell carcinoma, malignancy, rheumatological factors, genetic factors
  - Disease specific: Disease onset, sites involved, lesion types, classification of disease (typical versus atypical, etc.), current and previous/failed medications/therapies
  - Measurement of quality of life: DLQI
- Collection of biochemical variables
  - Full blood count, urea, electrolytes, and creatinine; liver function tests, C-reactive protein, erythrocyte sedimentation rate,

androgen levels, glucose tolerance test (including glucose and insulin levels), fasting cholesterol (including low density lipids, high density lipids, total cholesterol, and triglycerides)
  - If for systemic or biologic agents: Tuberculosis, HIV, hepatitis B, hepatitis C
- Comorbidity assessment
  - Cholesterol, insulin resistance, androgen dysfunction, smoking, depression, IBD
- Cytokine analysis (pre and post-therapy)
  - TNF-α, IL-1, IL-17, IL-8, IL-10
- Bacterial swabs
  - At initial assessment and flare-up reviews
  - Specific request for review of CNS
- Lesion ultrasonography
- Genetic analysis

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# BE AWARE OF SYSTEMIC NEUTROPHILIC SKIN DISEASES

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It was the English dermatologist Robert Douglas Sweet who in 1964 first described a disease that was characterised by the sudden onset of raised erythematous plaques accompanied by general malaise and fever. His name for the disease, 'acute febrile neutrophilic dermatosis', was soon replaced by the shorter name 'Sweet's syndrome' (SS). An interesting observation was that the dense neutrophilic infiltrates in the dermis were characterised by a lack of obvious vasculitis.

In the following years it soon became clear that approximately 50% of these cases had a severe associated disease. 'Parainflammatory' cases are associated with well-known inflammatory diseases such as rheumatoid arthritis, ulcerative colitis, and Crohn's disease, as well as with infections such as tonsillitis, mycobacterioses, or infectious urinary disease. 'Paraneoplastic' cases refer to those associated with haemoproliferative diseases such as leukaemia, lymphoma, and paraproteinaemia with or without plasmacytoma, as well as malignant solid tumours such as adenocarcinomas of different origins. Pregnancy is also a risk factor, whereas drug use is only a very rare causative factor.

It soon became clear that this characteristic spectrum of associations was typical not only for SS, but also for a range of rare dermatoses, e.g. pyoderma gangrenosum, some sterile pustular diseases, erythema elevatum diutinum, and neutrophilic urticarial dermatosis. Furthermore, it should be noted that these diseases are systemic in nature and the involvement of, for example, the liver, lung, kidney, or central nervous system can be dramatic and life-threatening. The major problem is that the patients appear to have severe signs of a systemic infection but do not profit from antibiotic treatment.

The pathogenesis, i.e. how different circumstances can lead to these clinically heterogeneous neutrophilic infiltrates in the skin and other organs, remained an enigma for a long time. It is clear that neutrophils migrate along chemotactic gradients. They usually enter the skin by being activated, either by antigen–antibody–complement complexes in classical small vessel vasculitis, or by the presence of highly activated TNF-α and interleukin (IL)-8. The latter are primarily released after activation of the primary cytokine IL-1 (α and β).

In pyoderma gangrenosum and erythema elevatum diutinum, for example, there is clear-cut histological evidence for the presence of vasculitis, which is substantiated by direct immunofluorescence findings in which IgA, IgG, IgM, and C3 can frequently be seen on vessel walls. It is therefore not surprising that, similar to Behçet's disease, a dramatic pathergy phenomenon might occur, which may lead to a rapid enlargement of wounds after surgery; 'postoperative Cullen gangrene' is an example of this problem. In SS or neutrophilic urticarial dermatosis, however, a lack of vasculitis is a hallmark. A likely explanation of this phenomenon comes from recent research on innate immunity. For example, it has been shown that certain defects in the biology of the inflammasomes present in neutrophils and macrophages can lead to uncontrolled and overwhelming IL-1 activation from inactive intracellular pools of pro-IL-1β. This release can lead to sterile neutrophilic infiltrates in the skin and other organs, periodic fever symptoms, arthralgias, and elevated levels of C-reactive protein as an inflammatory marker. All of these can be demonstrated in SS and neutrophilic urticarial dermatosis, for example, making it likely that this pathway might play a fundamental role in these diseases.

Corticosteroids are the main therapeutic option. They lead to a rapid clearing of all skin and other symptoms, including those in internal organs. The problem is the chronicity of some of the diseases, especially pyoderma gangrenosum. Adding immunosuppressive treatment such as dapsone, cyclosporine A, azathioprine, or cyclophosphamide can be of help, but is associated with certain toxicity and side effects. In our hands, biological treatment with either anti-TNF agents, intravenously given immunoglobulins, or $CD20^+$ cell-eliminating rituximab can lead to substantial healing or long term remission in severe cases. With regard to the new insights concerning the pathogenesis of the condition, it is attractive to speculate how biological anti-IL-1 treatments such as anakinra may work. There are limited data currently available, but there is an upcoming paper by Prof Lars French and his group from Zurich describing how anti-IL-1-treatment can be of help in some cases of pyoderma gangrenosum.

The take-home message should be that the major aim for all physicians is to be aware of these cases, especially in those dramatic situations with high fever and all the symptoms of an acute infection. The challenge is to prevent the patients with vasculitic variants, especially those with pyoderma gangrenosum, from undergoing surgery. If surgery is performed and a dramatic but primary, sterile, aggressive gangrene occurs at the site of operation then this should be stopped by early and adequate immunosuppressive treatment.

# IMMUNOPATHOGENESIS OF VITILIGO

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Vitiligo vulgaris is an acquired disorder characterised by expanding, depigmenting lesions of the skin, which form due to the disappearance of melanocytes. Several factors are involved in the pathogenesis of vitiligo, such as genetic predisposition, neurochemical factors, and toxic metabolites interfering with melanin metabolism, all of which lead to an autoimmune reaction directed against melanocytes (convergence theory).[1] Vitiligo patients also suffer from other autoimmune diseases (e.g. thyroid disease)[2] more frequently than the general population and produce autoantibodies against melanocyte antigens.[3] Genetic analyses have shown associations between vitiligo and 27 genes, 23 of which are immune-related and

4 of which are pigmentation genes.[4] Furthermore, repigmentation therapies such as steroids and UV irradiation have an immunosuppressive effect. These observations all support the role of autoimmunity in vitiligo.

The goal of our research is to gain a better understanding of the autoimmune pathology of vitiligo, the mechanism underlying the breaking of tolerance to self-antigens, and the effector mechanism of melanocyte destruction. We have demonstrated that T cells infiltrating the perilesional skin of expanding vitiligo lesions recognise melanocyte differentiation antigens, which leads to T cell activation.[5] By culturing vitiligo perilesional T cells with nonlesional skin biopsies taken from the same patient, we have demonstrated that melanocyte-specific T cells can kill melanocytes within the skin tissue, indicating that depigmentation in vitiligo is autoimmune-mediated.[5]

The cause of the autoimmunity in vitiligo is not well understood. Skin-bleaching compounds, such as the monobenzyl ether of hydroquinone or monobenzone, can cause skin depigmentation that spreads beyond the application site; this depigmentation is indistinguishable from vitiligo. We investigated how monobenzone is able to induce vitiligo by using biochemical, cellular, and immunological studies.[6,7] Monobenzone specifically interacts with the enzyme tyrosinase in melanocytes. This interaction triggers a series of cellular effects (oxidative stress, alteration of cellular proteins, and increased release of exosomes and melanocyte antigens) that selectively induce autoimmune reactions against melanocytes. In particular, monobenzone is converted by tyrosinase to a reactive quinone that binds to tyrosinase and other adjacent melanosomal proteins, which increases their immunogenicity.[7] Exosomes and melanocyte antigens are adequately taken up by dendritic cells, which are activated and able to present these antigens to T cells and prime anti-melanocyte immune responses. The resulting T cell responses also react with unexposed melanocytes.[7] The spreading of these T cells throughout the body can cause skin depigmentation at sites distant from the original monobenzone exposure. 4-tertiary butylphenol (4-TBP) is another phenolic compound associated with skin bleaching and vitiligo. In a patient with 4-TBP-induced vitiligo, we observed T cell responses reactive with 4-TBP-exposed melanocytes, indicating that autoimmunity is also found in 4-TBP-induced vitiligo. These studies indicate that phenols such as monobenzone can induce autoimmune reactions against pigmented cells.

We have extensively studied the positive relationship between vitiligo and melanoma regression. In a questionnaire-based study of 1,300 vitiligo patients of 50 years and older, and controls, we found that vitiligo patients have a 3-fold decreased lifetime risk of developing melanoma.[8] Vitiligo can also occur in melanoma patients and is referred to as melanoma-associated leukoderma (MAL). We have shown that these patients display autoimmune reactivity against both melanocytes and melanoma cells.[9,10] Interestingly, antibody responses against MART-1 (melanoma antigen recognised by T cells 1) are frequently found in these patients, but are absent in vitiligo patients.[10] Our systematic review and meta-analysis demonstrated that melanoma patients who develop MAL/vitiligo as an immune-related adverse event during various types of immunotherapy show significantly longer progression-free and overall survival than patients without vitiligo (hazard ratio [HR] for disease progression: 0.51, $p<0.005$; HR for risk of death: 0.25, $p<0.003$).[11] Taken together, these results indicate that vitiligo is a clinically relevant marker for the prognosis of melanoma patients.

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# SEPTIC VASCULITIS AND PURPURA FULMINANS

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Purpura fulminans is a symptomatic diagnosis. It is an acute thrombotic disorder that manifests as blood spots and discolouration of the skin due to coagulation of blood in vessels, leading to skin necrosis and often to disseminated intravascular coagulation. Septic vasculitis is a term used when vascular changes occur within sepsis. Sepsis can be best defined as an overt inflammatory response to various bacteria, other pathogens, and injuries (such as sterile inflammation). Sepsis can lead to a condition termed systemic inflammatory response syndrome, which results in multiple organ dysfunction syndrome. Thrombotic vasculopathy can develop through various mechanisms. The underlying cause is usually complex and is often not revealed in individual patients. We presented cases with skin symptoms indicative of acute thrombotic vascular changes due to different clinical conditions.

The first patient was a 21-year-old male who presented with asymmetric, large purpuric lesions with central blue discolouration, and who had a previous history of deep venous thrombosis for which he underwent a thorough investigation by haematologists. He was undergoing treatment with acenocoumarol when the lesions suddenly developed. He had a fever and symptoms of an acute upper respiratory infection immediately before his purpuric lesions developed. He was given 2 U fresh frozen plasma (FFP), which resulted in rapid regression of his lesions. His thrombophilia screen revealed increased homocysteine levels and a homozygous *MTHFR* mutation. His protein C level was normal, but he had decreased protein S activity.

Acute infections (such as gram-negative sepsis, meningococcus, and *Streptococcus pneumoniae*) can induce an endothelial cell disease with vascular leakage and peripheral thrombotic syndrome. Hereditary or acquired protein C or protein S deficiency and antithrombin III deficiency (neonatal) can lead to purpura fulminans, as can cases of benign infection (such as varicella or scarlet fever), in which purpura fulminans can develop in response to the pathogenic role of acquired protein S antibodies. This condition is called idiopathic or benign postinfectious purpura fulminans. Protein S deficiency can be hereditary, and only free protein S works as a cofactor. In Type 1, both bound and free protein S levels are decreased; in Type 2, protein S levels are normal but the protein is dysfunctional, resulting in decreased protein S activity; and in Type 3, free protein S levels are decreased. Acquired protein S deficiency occurs in vitamin K deficiency, which can be due to treatment with coumarins, and can develop in autoimmune diseases (such as systemic lupus erythematosus) as well as in severe chronic infections.

Our patient's acenocoumarol therapy was switched to low-molecular-weight heparin and he was given intravenous antibiotic therapy. Based on our experience with the beneficial therapeutic effect of FFP on his purpuric lesions, we now regularly administer FFP to patients with early dermatological signs of purpura fulminans and have found that FFP administered on the basis of the appearance of early dermatological signs has a good therapeutic effect. We start with 2 U and, according to the symptoms apparent on the skin, repeat the dose as necessary. Early lesions have blue central discolouration and advanced lesions when tissue necrosis has developed are

black; therapies are much less effective and mortality high in these cases.

Our experience with purpura fulminans patients, all of whom are adults, points to the importance of thyroid dysfunction (both hypo and hyperthyroidism) in the development of this condition. Thyroid disease can be a triggering factor of vasculopathies as hypothyroidism enhances the tendency for thrombosis. In hypothyroidism, thrombocyte numbers can either be normal or decreased, and coagulation factor synthesis can be decreased, including proteins C and S. In hyperthyroidism, thromboembolic events are also more frequent. Thrombocytopenia may be present in these cases, antithrombotic antibodies can form, there is increased phagocytic activity, splenomegaly, increased synthesis of hepatic proteins, increased thrombin activity, and decreased levels and function of proteins C and S.

# COMPLEX VASCULAR MALFORMATIONS: FROM DIAGNOSIS TO THERAPY

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Vascular anomalies are localised lesions consisting of malformed lymphatic and/or blood vessels with important chronic morbidity. They have been overlooked for a long time, and the old medical literature is confusing. With a clear clinico-histological classification[1] and recommendations from the International Society for the Study of Vascular Anomalies,[2] this field has made considerable progress during the past 20 years. Moreover, genetic dissection of the inherited forms, understanding of the multifocal lesion appearance in them, and extrapolating and demonstrating that tissular mutations explain the somatic forms have given an unprecedented clinico-genetic classification for the complicated and often complex anomalies.[2]

Our studies started with a rare inherited form of venous malformation. Such lesions can appear in any body part or organ, and cause pain, discomfort, bleeding, and destruction of adjacent body structures. Sclerotherapy and surgery are the main treatment options, but are rarely curative because of the extensiveness of the lesions.[3] A genetic approach allowed us to identify the chromosome and thereby the mutated gene, *TIE2*.[4] Further studies demonstrated that somatic 'second hits' accompany the inherited mutation, and lesions only develop in areas where the two mutations are present. This led us to realise that individuals with the much more common sporadically occurring lesions had a strong tissular mutation also affecting the same *TIE2* gene.[5-7]

Identification of the causes allowed us to subsequently develop cell culture models, in which the variant Tie2 receptors were expressed, to study the effects of the variant proteins. They all increased Tie2 kinase activity and downstream intracellular signalling via the PI3K/AKT/mTOR pathway.[8,9] Moreover, as no animal model existed for venous malformation, we decided to introduce the cells expressing a variant Tie2 receptor into immunocompromised mice to see if the cells had the capacity to form a lesion; this turned out to be the case.

As the Tie2 receptor mutations increase mTOR activation, the well-known mTOR inhibitor rapamycin became a drug of interest to test for inhibition of the effects of the variant proteins. In cells and mice, rapamycin was capable of dampening the activating effects of the variant Tie2 receptors. Moreover, patients' symptoms (pain) significantly decreased and quality of life significantly increased in a clinical pilot study.[10] Thus, the loop from patients, via the laboratory and back to patients (20 years later) was achieved with the first molecular therapy for the lesions. This example will surely be followed by many others for other vascular anomalies, and hopefully also other disorders. The era that genetic research has promised for so long has finally started.

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# INFANT SKIN MATURATION PROCESSES AND THE ROLE THAT SKIN MAY PLAY IN INFANT COGNITIVE DEVELOPMENT

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To have 'baby skin' is frequently considered a cosmetic aspiration for adults, but the fact that infant skin is prone to developing dermatological conditions, including atopic dermatitis, diaper/nappy dermatitis, skin infections, and irritant contact dermatitis, is often overlooked.

While infancy is recognised as a critical period of development for the whole organism, the skin was, until recently, considered to be fully developed and functional a few weeks following birth, representing a period of adjustment to the atmospheric environment. However, accumulating evidence published over the last decade has clearly demonstrated that infant skin structure, function, and composition continue to change during the first years of life in a process that is now known as 'skin maturation'.[1,2] Comparison of healthy infant skin with that of adults shows that its water-handling properties and, importantly, its barrier function are weaker. This can be ascribed, at least in part, to denser surface micro-relief lines, thinner epidermal layers, smaller corneocytes, smaller quantities of amino acids within the stratum corneum, and higher levels of lactate. Moreover, the composition and population diversity of the skin microbiome changes during the first years of life and is different to that of adult skin.[3]

During the same period, there is a rapid development of the infant brain. Neuron cell numbers and density of neuronal synapses dramatically increase in the first few years, which is further characterised by high plasticity (e.g. synapse formation, pruning, reinforcement).[4] This process manifests as the characteristic patterns of emotional, social, and cognitive development that occur during infancy.

Evidence of a connection between the development of the skin and the brain can be deduced from observations made at different levels. At the cellular level, for example, the cells that give rise to the brain and the epidermis (neurons and keratinocytes, respectively) are of common ectodermal origin. This common origin explains the similarities observed at the molecular level. For example, they share common communication pathways: neurotransmitters (e.g. corticotropin-releasing hormone, proopiomelanocortin, adrenocorticotropic hormone, and melanocortin) and receptors (parathyroid hormone-related peptide and α, β, and γ-melanocyte-stimulating hormone).[5]

Clinical evidence also shows that, through touch, skin can play an important role in the emotional and social development of an infant. For example, massage can bring about several benefits to healthy infants: it reduces stress (shown by crying frequency and saliva cortisol levels),[6] improves sleep,[7] increases daily weight gain,[6,8] enhances

psychological and social development (such as mother–infant interaction behaviours),[6,9,10] and improves cognitive development.[10] Recent work has shown that the sensation of touch, as stimulated within a multisensory-enriched environment, can have a positive impact on important cognitive outcomes in at-risk populations, such as premature infants and children with autism.[11] Therefore, the role of the skin–brain axis that has previously been identified in adults also appears to play a very important role during infant development.

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# PROBIOTICS AND NUTRACEUTICALS IN AESTHETIC DERMATOLOGY


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The natural ageing process is characterised by the slow progression of a constant, sub-acute, and asymptomatic inflammatory condition called low-grade chronic inflammation (LGCI). The efficiency of the psycho–neuro–endocrine–immune mechanisms of regulation and control, and the consequent ability to regulate homeostasis essential for the maintenance of good health, begins to decline at around 50 years of age, while the levels of pro-inflammatory cytokines characterising LGCI start to grow, reaching very high levels in advanced age and thereby increasing the chances of fatal diseases arising. This progressive and physiological inflammatory status, called inflammaging, reflects the loss of adaptive abilities of the organism to endogenous and exogenous stimuli, which is typical of ageing. In particular, the skin ageing process is influenced by factors such as the physiological processes of the progressive impairment of cell and endocrine functions related to age and by numerous environmental and behavioural factors.

Stress, incorrect lifestyle, alcohol abuse, smoking, and above all an improper diet are powerful inflammatory triggers responsible for the LGCI pathological phenomenon that can accelerate and anticipate the inflammaging onset; the inflammatory process reduces cellular functionality and activates the oxidative stress phenomenon with consequent production of oxygen free radicals. Cellular senescence, oxidative stress, and reduced mitochondrial activity cause the degeneration of all cell subsets of the skin tissue.

One of the most delicate pieces of apparatus from an inflammatory point of view is certainly the gastrointestinal tract. The intestine and skin are closely related as the fundamental constituents of the gut–skin axis. Gastrointestinal disorders such as increased intestinal permeability caused

by damage to the intestinal epithelium, or alteration/destruction of commensal microbiota, often contribute to the onset of skin diseases characterised by a strong inflammatory component and accelerate the processes of skin ageing. Therefore, protection of the gastrointestinal tract is essential in managing the physiological process of inflammaging and, consequently, to maintain the skin in optimal condition from both an aesthetic and a functional point of view. Diet is the main parameter on which we can act to protect intestinal function: a healthy and balanced diet is a critical step in reducing the risk of developing LGCI.

Dietary supplementation represents an opportunity to optimise the diet through use of dietary supplements of the highest quality, designed and formulated with the aim of contributing to the maintenance of intestinal homeostasis while at the same time preserving the delicate qualitative and quantitative balance of intestinal microbiota. Recent studies have demonstrated the protective role on mucosal monolayer junctional systems and microbiota exerted by bovine colostrum in association with extracts from the pulp of the *Morinda citrifolia* fruit. These act on the intestine, interpreted as a neuro–immune–endocrine microcosm, which clearly appears to be one of the key steps in the restoration and protection of the physiological harmony of the gut–skin axis and, therefore, for the maintenance of the proper functions of the skin.

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# EPIDEMIOLOGY OF BODY ART

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The term 'body art' refers to all the forms of external and voluntary modifications that are applied to the human body. Body art ranges from tattoos to piercings, but can include more extreme modifications including intradermal and subdermal implants, scarification, tongue splitting, etc. To some extent, non-reconstructive cosmetic surgery and other aesthetic treatments, and even bodybuilding and body painting, could be considered to be part of the spectrum of body modification or body alteration. For this presentation during the EADV congress, we focussed only on the epidemiology of body piercing (BP) and tattooing.

BP can be performed on virtually any part of the body. By our definition, soft earlobe piercing is not considered a BP. The prevalence of BP is highly variable according to study settings and may vary from 4–51%. Obvious biases emerge according to the time and location of a study and/or the definition of 'piercings'. A study based in Italy found that the prevalence of BPs increases by up to 20–25% in high schools and universities. According to studies in Australia, Germany, and the USA, if a broader population is considered, the prevalence is close to 7–14%. In 2005, a study based in England found that 10% of adults surveyed (classed as those >16 years) possessed a (non-soft earlobe) BP. The study found that women predominated each age group, and that 50% of women aged 16–24 years have a BP. The choice of anatomical site varied by gender.

Unfortunately, one in five piercings are done by 'non-specialists'. BPs are associated with high-risk behaviours such as alcohol use (odds ratio [OR]: 5.5, 95% confidence interval [CI]: 1.1–11.2), smoking (OR: 3.1, 95% CI: 1.6–5.9), drug-use in men (OR: 2.2, 95% CI: 1.3–4.0) and in women (OR: 4.1, 95% CI: 2.7–6.2), and sexual behaviours. A less consistent association has been found between BP and depression, suicide ideations, and suicide attempts. A possible relationship between personality traits and self-reported psychopathological symptoms, such as anger expression, impulsivity, and thrill

seeking, has also been suggested. However, these results have to be analysed with caution as: 1) the studies are based on adolescents or college students for whom such risk behaviours are more frequent, and 2) there is likely to be a small size effect in those studies. In addition to this, other factors should also be considered such as the number of BPs and body modifications, the placement of the BP, the age of acquisition, the rapidity with which new piercings are obtained, etc.

Tattooing is defined as the introduction of pigments and dyes into the dermis to obtain a permanent design. Nowadays, 10–20% of the general population in Western countries are tattooed. This population encompasses a young generation born from the end of the 1970s to late in the 1980s. Social factors are strong as 70–90% of people with tattoos have friends and/or family members with tattoos. The number of tattoos is usually correlated to the number of tattooed friends. Nowadays, women are quite often tattooed. Most people with tattoos get their first before the age of 25–35 years, and 90% of these individuals go to a professional tattoo parlour. Home tattooing represents (at the lowest) 2–3% of cases, where the individual acknowledges it. No differences are found in the marital status or sexual orientation of tattooed and non-tattooed individuals. The associated high-risk behaviours mainly include tobacco and recreational drug use (cannabis). There is no increase in sexually transmitted diseases amongst this population. The same level of caution should be applied for tattoos with regard to interpretation of psychological studies. Tattooed individuals usually see themselves as sexier, more rebellious, and more attractive than non-tattooed individuals. Meanwhile, those without tattoos rate tattooed individuals as being more rebellious, less attractive, and less sexy. The negative perceptions associated with tattoos may lead to issues in the professional practice and personal lives of those with tattoos, as they tend to get judged by others more negatively.

Lastly, the market for tattoo removal has boomed over the past years. Fourteen percent of those with tattoos are said to regret ≥1 of their tattoos (though regret is different from removal itself). In a study completed in a French laser removal clinic, 25% of those attending the clinic said that they had been dissatisfied immediately after receiving their tattoo, and stressed the importance of choosing the tattooist wisely, as well as planning the tattoo carefully.

Although 10–20% of the general population is tattooed, it should not be considered a 'trend' anymore. The tattooed population is a young population, aged 20–40 years (b.1975–1990), and will grow old with their tattoo(s). In the long-term, we should expect more tattoo-related complications to be reported, as the long-term health issues related to tattoo ink remain unknown. The question of the safety of laser removal and the possible production of by-products is also open. Tattooing is still associated with negative (social) perceptions and could be a marker of risk behaviour in some sub-groups that remain to be defined.

During the workshop, Prof Jorgen Serup showed the extent of body modifications that are available, including corneal tattooing, scarification, tongue splitting, and stretching that stress the question of long-term risks. The other presentations were rather more 'conventional' and included the possible complications of BP and laser tattoo removal techniques. The audience's questions were mainly focussed on the possible long-term health risks associated with the inks used in tattooing, for tattooed individuals.

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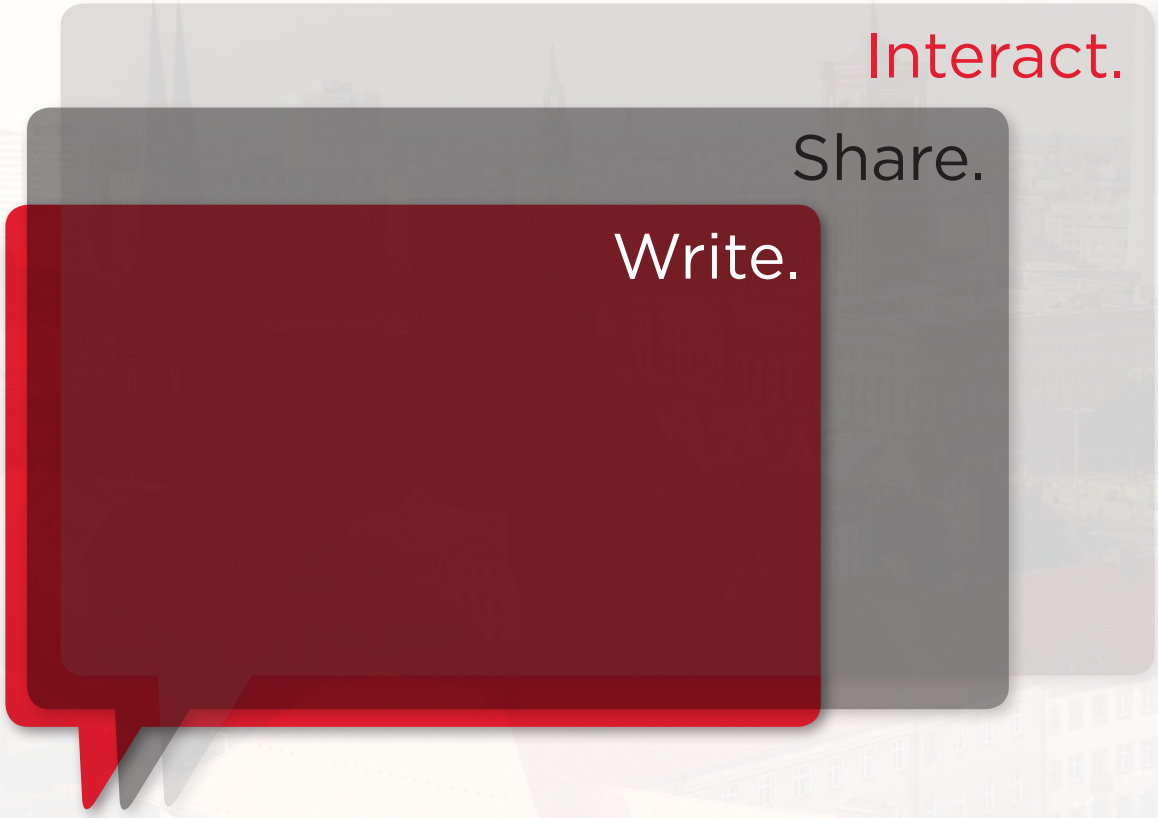


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# A REJUVENATION THERAPY OF MEDICAL NEEDLING AND 3D-MATRIXLIFT® IS SAFE AND IMPROVES THE ELASTICITY OF THE SKIN

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## ABSTRACT

The use of platelet-rich plasma and growth factors is emerging as an anti-ageing regimen for the skin. We tested the safety and efficacy of 3D-MatrixLift®, a new treatment regimen for skin rejuvenation that combines medical needling and the application of a stem cell and growth factor-rich solution with irradiation by LED light. A total of 15 participants were enrolled in a single-centre, prospective pilot study. The elasticity parameters of the skin increased significantly after five rounds of treatment, with no signs of adverse effects. 3D-MatrixLift improves the elasticity of the skin and can be used safely in combination with medical needling for skin rejuvenation.

Keywords: 3D-MatrixLift, medical needling, rejuvenation.

## INTRODUCTION

Measuring approximately 2 $m^2$, the skin is the largest organ of the human body. The outer skin layer, the epidermis, is a dynamic system that is constantly proliferating and differentiating. The most important function of the skin, besides many others such as temperature regulation, sensory perception, and protection against harmful substances and mechanical impacts, is as a hydration barrier that prevents the dehydration of the skin and the organism and maintains the osmotic balance of the inner tissues. During ageing, the physiological regeneration process slows down and the ability to bind water is reduced. As a result, the skin loses its elasticity, becomes increasingly cracked, and barrier damage and wrinkles occur (intrinsic ageing). Furthermore, the skin is damaged by environmental factors such as smoking and UV radiation (external ageing).

Several studies have shown that physiological growth factors improve the signs of skin ageing.[1-5] One source of growth factors is platelet-rich plasma (PRP), an autologous concentration of human platelets suspended in a small volume of plasma. PRP contains constituents including platelet-derived growth factor, transforming growth factor, vascular endothelial growth factor, epidermal growth factor, and fibroblast growth factor.[6,7] In recent years, PRP has become increasingly attractive for skin rejuvenation as it has been shown that PRP promotes tissue remodelling in aged skin.[8-10]

3D-MatrixLift® is a new treatment regimen for skin rejuvenation that combines a new cell separation technique using human blood with irradiation by LED light and medical needling. Differential centrifugation separates platelets, leukocytes, and mesenchymal stem cells from erythrocytes. The concentrated cell suspension contains growth factors and is enriched with trace elements such as copper, zinc, magnesium, and amino acids including glycine and arginine which influence epigenetic factors.

Mesenchymal stem cells are undifferentiated adult stem cells that self-renew and differentiate into cell types of their cell linage (multipotency). Age-associated accumulation of mutations in the mitochondrial DNA of adult stem cells has been

proposed to be responsible for the age-associated defects found in elderly humans. Hashizume and colleagues[11] found that ageing is controlled not only by mutations but also by epigenetic regulation. They showed that reprogramming of aged fibroblasts restored age-associated mitochondrial respiration defects, indicating that ageing is reversible and is controlled by epigenetic factors. Treatment of aged fibroblasts with glycine modified epigenetic regulation and effectively prevented these ageing phenotypes.[11] There are a number of clinical case reports that describe stem cell use in dermatology, including a report by Rigotti and colleagues[12] that describes the successful use of adult stem cells for treating severe radiodermatitis.

Irradiation of the 3D-MatrixLift solution by LED light in the blue spectrum (440 nm) stimulates the synthesis of nitric oxide (NO). Gaseous NO has recently emerged as a key player in the mediation of epigenetic changes associated with cell cycle arrest and differentiation. Many other nuclear factors involved in proliferation and differentiation of skin cells are directly regulated by NO.[13] Blue light irradiation photolytically generates NO from nitrosated proteins, which are known to initiate differentiation and vasorelaxation in skin cells and in smooth muscles. Nitrosated proteins and amino acids such as arginine are light receptors and signal transducers. NO inhibits neutrophil migration, rolling, and adhesion in inflammation and induces apoptosis in keratinocytes. NO protects against cellular damage by reactive oxygen species and stimulates regeneration of the skin.[14-21]

Medical needling is performed with an automated device that penetrates the skin with fine needles, thereby creating channels for improved absorption of topically applied compounds through the top layer of the skin. This is important as large (>20 kDa) and hydrophilic (>500 Da) molecules penetrate poorly into the hydrophobic stratum corneum.[22,23] Therefore, medical needling is necessary to improve absorption and subsequent pharmacological effect. Furthermore, medical needling in itself improves the appearance of the skin through a process called percutaneous collagen induction.[24-32] Percutaneous collagen induction is based on the natural inflammation reaction of the skin after an injury. This reaction induces the release of growth factors, epigenetic factors, and cytokines that stimulate the synthesis and deposition of new collagen and elastin in the upper dermis. This leads to remodelling of the skin structure and an improved appearance.[25-30,32-35]

The 3D-MatrixLift regimen also includes an irradiation step of the treated skin area by LED light in the blue and red/infrared spectra. It has recently been shown that red/infrared irradiation is a safe and effective method to increase intradermal collagen and to rejuvenate the skin.[32] At the same time, the anti-inflammatory effects of LED energy at 633 nm and 830 nm have been well documented in the treatment of psoriasis and in acceleration of wound healing.[33] Furthermore, Papageorgiou and colleagues[35] successfully used phototherapy with blue and red LED light for the treatment of acne vulgaris.

As a large number of human populations grow older, an increasing number of individuals want to be treated for signs of ageing with a safe and effective procedure. Therefore, the aim of this study was to evaluate the efficacy and safety of 3D-MatrixLift in the treatment of ageing skin.

## MATERIAL AND METHODS

### Study Design and Participants

The study was conducted at the Private Practice for Functional Medicine in Lindenthal, Cologne, Germany. A total of 15 healthy adult participants were recruited for this single-centre, prospective pilot study (14 women, 1 man). Participants were 38–69 years of age (mean: 55 years). Written informed consent was obtained from each patient. Exclusion criteria were: open skin infections and wounds, florid acne, neurodermatitis, and psoriasis. Medical and cosmetic histories were documented and a photo of the facial skin was taken.

### 3D-MatrixLift

A total of 8 mL of autologous whole blood was collected from each patient into a sterile CPT™ Cell Preparation Tube (BD Becton Dickinson) and centrifuged according to the manufacturer's instructions. A density gradient is formed in the CPT tubes during differential centrifugation. After centrifugation, the mononuclear cells, adult stem cells, and platelets were re-suspended in a small volume of plasma, mixed with 0.5 mL of a trace elements/amino acid solution, and transferred to a sterile syringe via a closed transfer system. The 3D-MatrixLift solution was subsequently irradiated with LED light (Kernel, China) for 5 minutes at 440 nm to stimulate NO synthesis. Half of the

solution was used immediately after preparation, while the other half of the solution was stored at 4°C for 1 week in closed sterile syringes and used for the next treatment.

## Non-Invasive, Objective Skin Elasticity Measurements

The measurement of skin elasticity was performed with the CUTOMETER® Dual MPA 580 (Courage + Khazaka Electronic GmbH, Cologne, Germany). In accordance with the manufacturer's instructions, the measurement was taken from the right temple and the right cheek before the start of the treatment and 10 days after the last treatment. The parameters R0 and R2 were determined; R0 represents the passive behaviour of the skin force and R2 represents the gross elasticity.

## Treatment

Participants received five treatments at 1-week intervals. First, the face was cleaned and disinfected. A topical anaesthetic cream (lidocaine 23% and tetracaine 10%) was then applied for 15 minutes. Any excessive anaesthetic was then removed and physiological saline solution was applied to smooth the medical needling treatment. Medical needling was carried out using Revive MN (MT.Derm GmbH, Berlin, Germany), which is an automated medical needling device. The needle length of the 6 point needle plate cartridge was adjusted to 0.5 mm and the skin was perforated through circular movements at a speed of 150 per minute. After medical needling treatment, the 3D-MatrixLift solution was applied to the treated areas for 5 minutes. The treated area was subsequently irradiated with LED light (Kernel, China) for 3 minutes at 440 nm and then for an additional 3 minutes at 640/830 nm to photostimulate the skin. CUTANOVA - Cream Nanorepair (Dr. Rimpler GmbH, Wedemark, Germany) was applied to the treated areas to regenerate the skin barrier.

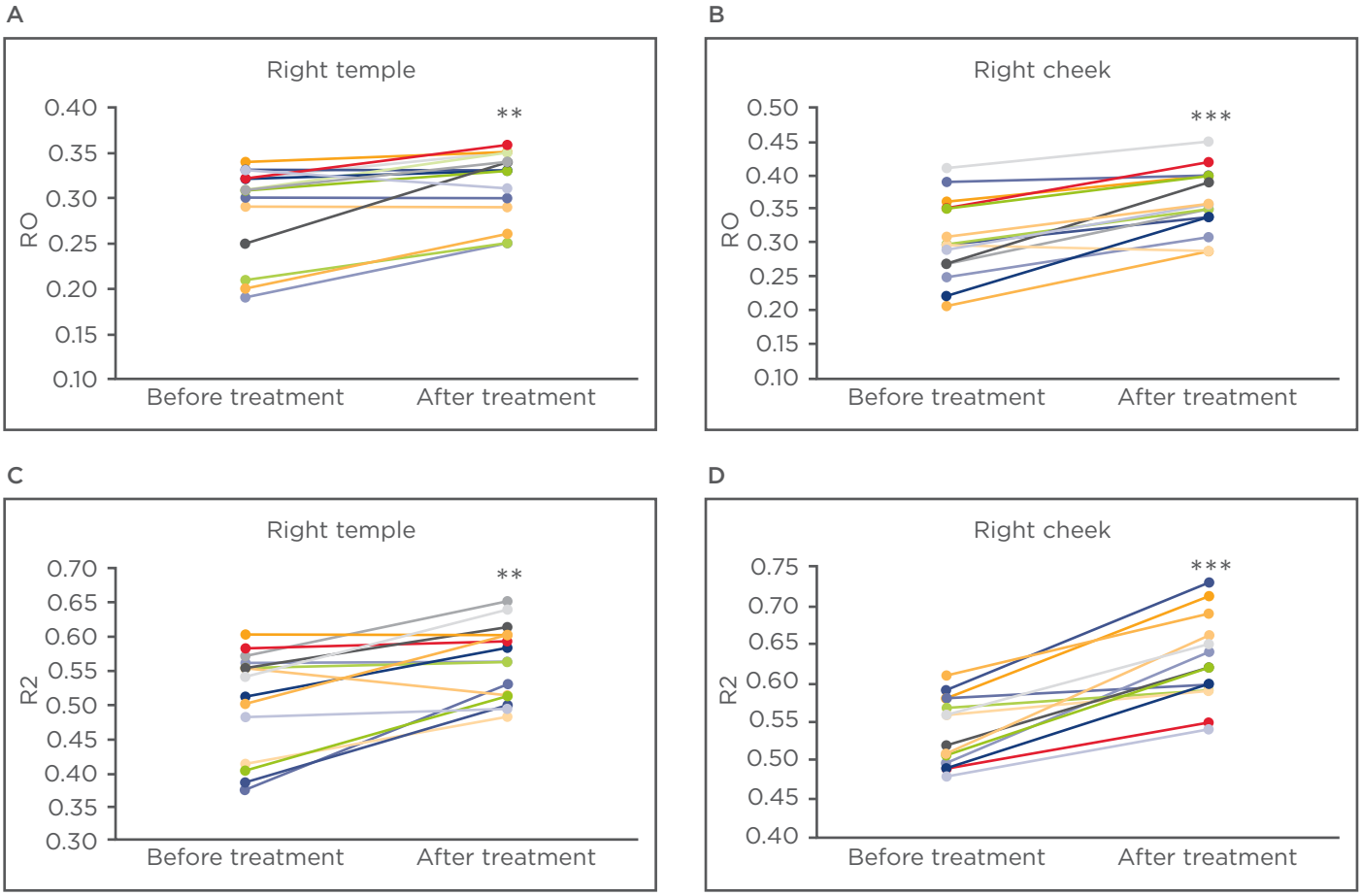


**Figure 1: The two parameters of skin elasticity, R0 and R2, both increased significantly after treatment.** A) R0 before and after treatment on the right temple; **p<0.01; B) R0 before and after treatment on the right cheek; ***p<0.001; C) R2 before and after treatment on the right temple; **p<0.01; D) R2 before and after treatment on the right cheek; ***p<0.001.

### Statistical Analysis

The data was analysed using Excel. A paired t-test was performed to determine significant changes.

## RESULTS

3D-MatrixLift is a new treatment regimen for skin rejuvenation that combines medical needling and the application of a stem cell and growth factor-rich solution with irradiation by LED light. To test the efficacy of this new treatment, 15 participants were enrolled in a single-centre, prospective pilot study. The 3D-MatrixLift was performed five times with 1-week intervals. Skin elasticity was measured prior to treatment and 10 days after the last treatment on the right temple and the right cheek with a CUTOMETER Dual MPA 580. The skin elasticity parameters R0 (passive behaviour of the skin to force) and R2 (gross elasticity) were determined.

All participants completed the study and no adverse effects were observed. Small dot-like bleedings were observed, although these were mainly limited to the forehead region and could be stopped rapidly with a swab drained in saline solution. A reddening of the facial skin similar to sunburn appeared after the treatment but faded after 3–6 hours.

### Skin Elasticity Measurements

The passive behaviour of the skin to force (R0) and the gross elasticity (R2) increased significantly on the right temple as well as on the right cheek after the treatment regimen (Figure 1). Some participants, however, responded more strongly to the treatment regimen than others.

## DISCUSSION

The present study confirms that 3D-MatrixLift, a combination of medical needling and application of a stem cell and growth factor-rich solution with LED light, is a safe and effective procedure to treat signs of ageing.

The passive behaviour of the skin in relation to force, represented by the value R0, increased significantly after treatment indicating that the skin was softened by the treatment regimen. This might be due to a reduction in stress between the stratum corneum and the underlying epidermis and dermis through remodelling of the collagen structures.

Gross elasticity, represented by the value R2, also increased significantly after treatment indicating that the ability of the skin to return to its original position after deformation increased. This effect is probably due to improved function of the elastic fibres of the skin and confirms the skin remodelling effect of the treatment.

However, a response to the treatment was not observed in all participants. It was noted that the participants who showed an observable response mainly included those with skin damage, for example due to chemotherapy. Participants who had seen a beautician at least once per month for longer than a year showed no improvement in elasticity parameters. These results confirm that regular skin care can reduce the signs of ageing.

In comparison with previous PRP preparations, the 3D-MatrixLift regimen includes a novel cell separation technique through differential centrifugation that allows the enrichment of the solution with mononuclear cells, mesenchymal stem cells, and platelets, which release growth factors and epigenetic factors for modulation of gene expression and cell cycle modification. NO, for example, is involved in the epigenetic regulation of proliferation and differentiation of skin cells. The production of NO in the skin is activated via nitrosated amino acid metabolism induced by LED light stimulation and promotes regeneration and wound healing of the skin. Following this pilot study, another study focussing on sun-damaged skin and inflammatory skin diseases is planned. This study will feature a higher number of participants.

In conclusion, this is the first study to demonstrate that 3D-MatrixLift, a combination of medical needling and the application of a stem cell and growth factor-rich solution with LED light, improves skin elasticity with no significant adverse effects.

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# ACNE AND SYSTEMIC DISEASES

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## ABSTRACT

Acne is a very common, multifactorial, complex, and chronic disease of the pilosebaceous unit that affects approximately 85% of adolescent patients and 3% of adult patients. The roles of sebaceous glands, androgens, follicular epithelial cells, *Propionibacterium acnes*, immune mediators, environmental factors, and genetic factors are well known in acne pathogenesis. Although it is not a life-threatening disease, it is closely associated with low quality of life and psychological depression. Moreover, acne can also be associated with hypovitaminosis, or may present as a part of systemic syndromes such as: congenital adrenal hyperplasia; seborrhoea-acne-hirsutism-androgenetic alopecia syndrome; polycystic ovary syndrome; hyperandrogenaemia, insulin resistance, and acanthosis nigricans syndrome; Apert syndrome; synovitis-acne-pustulosis-hyperostosis-osteitis syndrome; pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; metabolic syndromes; and Behçet's syndrome. These syndromes must be excluded in patients with severe and recalcitrant acne.

Keywords: Acne vulgaris, hyperandrogenaemia, insulin resistance, systemic diseases.

## INTRODUCTION

Acne is a very common multifactorial disease of the pilosebaceous unit. The roles of androgenic stimulation of sebaceous glands, hyperproliferation/hyperkeratosis of follicular infra-infundibulum, inflammation, and increased colonisation of *Propionibacterium acnes* are classically well known aetiological factors in acne pathogenesis.[1] Abnormalities in androgenic steroid metabolism, insulin resistance, cell–cell signalling pathways, and uncontrolled inflammation may result in different clinical symptoms, including acne vulgaris.[1,2] The role of dietary factors and some genetic mutations are also demonstrated in recent studies.[3] Acne affects approximately 85% of adolescent patients and 3% of adult patients between the ages of 35 and 44 years all over the world.[1] Although acne is not a life-threatening disease, it is associated with low self-esteem, low quality of life, and depression. Aside from these effects, it can also be a component of systemic disorders such as hypovitaminosis, systemic syndromes (congenital adrenal hyperplasia [CAH], seborrhoea-acne-hirsutism-androgenetic alopecia syndrome [SAHA], polycystic ovary syndrome [PCOS], hyperandrogenaemia, insulin resistance, and acanthosis nigricans syndrome [HAIR-An], Apert syndrome [AS], synovitis-acne-pustulosis-hyperostosis-osteitis syndrome [SAPHO], pyogenic arthritis, pyoderma gangrenosum, and acne syndrome [PAPA]), metabolic syndromes, and Behçet's syndrome.[4,5] These syndromes should be borne in mind when considering children or adolescents with severe and/or treatment-resistant acne, a female who has never had acne but who suddenly develops severe acne as a late-onset disorder, when there is failure to respond to conventional therapies, and in cases with acne and other signs of hyperandrogenism such as hirsutism, irregular menstruation periods, changes in voice, Cushingoid features, increased libido, development of acanthosis nigricans, resistance to insulin, or androgenetic alopecia. This review addresses the pathogenesis of acne and several systemic syndromes with genetic mutations.

## ACNE AND SYSTEMIC SYNDROMES

### Congenital Adrenal Hyperplasia and Acne

CAH is an autosomal recessive disorder that is usually related to 21-hydroxylase deficiency due to mutations in the *CYP21A2* gene. This mutation leads to decreased production of cortisol and mineralocorticoids, as well as excessive production of androgens.[6] CAH may be classified as one of two groups depending on whether there is a complete loss of enzyme function (as in the severe, classical form) or whether they present as milder, non-classical forms. Dermatological symptoms are usually associated with excessive androgen production and present in many different ways, such as rapid early childhood growth, advanced skeletal age, early appearance of facial, axillary, and pubic hair, premature adrenarche, acne, impaired fertility in both sexes, hirsutism, androgenetic alopecia, seborrhoea, and menstrual disorders in female patients.[7,8] These manifestations may be progressive with age. Severe recalcitrant cystic acne in the peripubertal-to-adult period may be associated with CAH, especially with non-classical CAH.[9] It can be difficult to differentiate CAH from PCOS clinically, and therefore serum concentrations of 17-OHP should be investigated after adrenocorticotropic hormone stimulation (17-OHP60) in women with persistent acne in adult life.[9] Treatment of CAH with oral glucocorticoids and fludrocortisone reduces increased androgen levels in patients.

### Seborrhoea-Acne-Hirsutism-Androgenetic Alopecia Syndrome and Acne

SAHA syndrome was first defined in 1982 and characterised by the tetrad: seborrhoea, acne, hirsutism, and androgenetic alopecia. It is classified as one of four groups according to the aetiopathogenesis: idiopathic, ovarian, adrenal, and hyperprolactinaemic types.[8,10,11] Hyperandrogenaemia or increased sensitivity of the pilosebaceous unit to normal circulating androgen levels may lead to skin manifestations. This syndrome is more common in middle-aged female patients and can be associated with PCOS, cystic mastitis, obesity, insulin resistance, and infertility.[11] Acne severity is usually not related to serum androgen levels and hormonal therapies such as oral contraceptives, antiandrogens, and insulin-sensitising medications are helpful in treatment.

### Polycystic Ovary Syndrome and Acne

PCOS is one of the most common endocrine disorders in females of reproductive age. It is clinically characterised by an accumulation of incompletely developed follicles in the ovaries due to anovulation and multisystemic symptoms such as irregular menses and other clinical signs of hyperandrogenism including acne, seborrhoea, hirsutism, infertility, and female-type androgenetic alopecia.[12] As reported in the Rotterdam criteria, the menstrual cycle and endocrine dysfunction with hyperandrogenism are more important for diagnosis than ultrasound findings. PCOS affects approximately 10% of women attending gynaecology clinics, but the prevalence in the population varies from 10–20%, depending on which diagnostic criteria are used.[12] PCOS is also associated with hirsutism, infertility, acne, weight gain, Type 2 diabetes, cardiovascular disease, and endometrial hyperplasia. Hyperandrogenaemia, altered gonadotropin secretion, insulin resistance, and vitamin D deficiency are the most important factors in PCOS pathogenesis.[8] More recently, PCOS has been considered to be a major risk factor for metabolic syndrome.

Increased circulating androgen levels are seen in 60–80% of patients, with serum free testosterone being the most sensitive biochemical marker. Adrenal function is usually normal. Acne is seen in approximately one-third of women with PCOS and these patients usually have severe, late-onset, persistent, and/or treatment-resistant acne vulgaris.

Lifestyle modification, insulin sensitisers, oral contraceptives, and vitamin D supplementation are the most common therapeutic agents for the management of PCOS.[12-14]

### Hyperandrogenaemia, Insulin Resistance, and Acanthosis Nigricans Syndrome and Acne

HAIR-An syndrome is widely accepted as a subphenotype of PCOS. Clinical manifestations in young women include irregular menses, hyperandrogenic symptoms such as oily skin, hirsutism, acne, androgenetic alopecia, deepening of voice, clitorimegaly and changes in muscle mass, and insulin resistance with diabetic symptoms.[15] Patients have elevated insulin levels, and elevated or high-normal levels of testosterone and androstenedione. Adrenal function is usually normal. Hyperinsulinaemia directly affects the androgen levels. Hyperinsulinaemia and hyperandrogenaemia stimulate epithelial proliferation and melanin

accumulation. Weight loss and antiandrogens such as spironolactone and flutamide are traditional treatment options for HAIR-An syndrome.[15,16] Insulin sensitisers, such as metformin, rosiglitazone, and pioglitazone, are very important components of the treatment of HAIR-An syndrome as they improve hyperandrogenism and ovulation. In recalcitrant cases, surgical biliopancreatic diversion or bilateral wedge resection of ovaries and hormonal gonadotropin suppression may be an effective treatment approach.

## Apert Syndrome and Acne

AS is a rare genetic and congenital disease characterised by craniosynostosis and syndactyly of fingers and toes. AS was first described by Wheaton in 1894 and then reviewed extensively by the French physician Apert in 1906. AS has a dominant inheritance pattern, but most of the cases are sporadic and exhibit a paternal effect. Dermatological manifestations of AS are hyperhidrosis, oily skin, resistant acne, interrupted eyebrows, excessive forehead wrinkling, lateral plantar hyperkeratosis, skin dimpling over joints, and oculocutaneous hypopigmentation.[17] The association between AS and acne vulgaris was first reported by Solomon et al. in 1970. A possible mechanism is end-organ hypersensitivity to circulating androgens.[18] More than 98% of AS cases are caused by *de novo* mutations (S252W and P253R) in the gene encoding fibroblast growth factor receptor 2 (FGFR2).[17] Increased FGFR2 signalling has a major pathogenic role in follicular hyperkeratinisation and sebaceous gland hypertrophy in acne, and effective anti-acne drugs increase FGFR2 signalling.[19] Increased FGFR2 signalling activity is seen in AS, which upregulates the activity of phosphoinositol-3-kinase/Akt and mitogen-activated protein kinase signal-transduction pathways. This results in a nuclear deficiency of the transcription factor forkhead box protein O1, which is thought to be a key transcription factor in the pathogenesis of acne vulgaris.[7]

## Synovitis-Acne-Pustulosis-Hyperostosis-Osteitis Syndrome and Acne

SAPHO syndrome is a rare multifactorial systemic syndrome that usually affects children and young adults, with a female predominancy.[20] This syndrome was first described in 1987 by Chamot et al.[20,21] The aetiology of SAPHO is unknown but may include genetic, infectious, and immunological abnormalities. *P. acnes* is one of the most highly suspected microorganisms with regard to the aetiology of SAPHO syndrome.[21] As suggested by the name of the syndrome, it is characterised clinically by chronic, recurrent multifocal osteomyelitis, acute or chronic sterile arthritis associated with pustular or palmoplantar psoriasis, or sterile osteitis in the presence of a skin manifestation such as severe acne. Presence of any of these is sufficient for a diagnosis of SAPHO syndrome. Arthritis is usually seronegative. Skin manifestations include Sweet's syndrome, Sneddon–Wilkinson disease, pyoderma gangrenosum (PG), palmoplantar pustulosis, acne, hidradenitis suppurativa, folliculitis, and psoriasis. Acne is usually seen in 25% of patients with SAPHO syndrome and may present as acne conglobata, acne fulminans, or hidradenitis suppurativa.[20,21] This syndrome may also be associated with ulcerative colitis.[22] Non-steroidal anti-inflammatory drugs are generally offered as the first-line therapy option, while systemic antimicrobial therapies such as doxycycline, azithromycin, sulfamethoxazole/trimethoprim, and clindamycin can be used with anti-inflammatory and immunomodulatory effects. Other treatment options include corticosteroids, photochemotherapy, retinoids, colchicine, bisphosphonates, and disease-modifying agents such as methotrexate, sulfasalazine, and anti-tumour necrosis factor (TNF) therapy.[21]

## Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne Syndrome

PAPA syndrome is an autosomal dominant hereditary disease that is associated with mutations in the *PSTPIP1/CD2BP1* gene on chromosome 15q.[23] It was first described in 1997 and classified in the group of auto-inflammatory disorders. The affected protein, CD2-binding protein 1 (encoded by *PSTPIP1*), is a cytoskeletal adaptor protein that interacts with a number of other intracellular and membrane proteins such as PTP-PEST, CD2, WASP, Fas ligand, and pyrin, and was first described in 2002.[24] Arthritis is generally the initial symptom of this syndrome, followed by acne and PG, although acne and PG may not be seen in all patients. Arthritis is classified as seronegative or aseptic arthritis and usually starts between the ages of 1 and 16 years. Acneiform lesions begin at puberty.[4] PG is usually the final symptom of this syndrome and seeing a child or adolescent patient with PG is an important finding of PAPA syndrome. Systemic corticosteroids, interleukin (IL)-1 receptor antagonist, anti-TNF agents, leflunomide, sulfasalazine, and dapsone are treatment options for PAPA syndrome.

## Vitaminosis and Acne

The role of diet is a very controversial topic in acne pathogenesis. Many nutrients have been incriminated in acne pathogenesis, including chocolate, sugar, multivitamins (or hypovitaminosis), dairy products, and oily and fatty foods with a high glycaemic index. Serum levels of vitamin A, vitamin E, vitamin D3, vitamin B12, folic acid, and minerals such as zinc and copper have been evaluated in patients with acne vulgaris.[25]

Vitamin A is a lipid-soluble vitamin that has a role in the keratinisation and immune regulation of the skin. Low levels of vitamin A in patients with acne vulgaris have been shown in a few studies in the literature.[25,26] Kligman et al.[27] reported that oral vitamin A (retinol) is effective in acne treatment when used in high doses (300,000 U daily for women, 400,000–500,000 U daily for men).

Vitamin E is another lipid-soluble vitamin that is an effective non-enzymatic antioxidant, protecting the skin from the adverse effects of oxidative stress. It also has a synergistic effect with vitamin A.[28] Reactive oxygen species produced by neutrophils have a role in the inflammatory process of acne.[27] Low levels of vitamin E in patients with acne vulgaris have also been reported in the literature.[25,26]

Vitamin B12 is an essential vitamin that has a role in cellular proliferation, infertility, and nerve damage. It works together with folic acid and iron. The role of this vitamin in acne pathogenesis was first reported in 1976 by Braun-Falco and Lincke.[29] They reported that with vitamin B12 therapies, patients were developing acne and/or acneiform eruptions. These lesions may appear after initial treatment as small papules or pustules on the face, back, chest, and upper arms. All age groups can be affected, with a predisposition for females. The aetiological and pathogenic mechanisms of this reaction are not well known. Several cases of an eruption resembling acne rosacea have been reported after ingestion of high-dose vitamin B supplements. The most important consideration is that the eruption does not respond to classical rosacea treatment, but resolves quickly after discontinuation of the vitamin supplement.[30] Aside from this side effect, Karadag et al.[29,31] reported vitamin B12 and folic acid deficiency after the treatment of acne vulgaris with systemic isotretinoin.

Vitamin D is the other lipid-soluble vitamin that is also identified as a prohormone steroid with endocrine, paracrine, and autocrine functions.[32] The endocrine effects of vitamin D mainly influence serum calcium homeostasis, but it has recently been discovered that it is essential for the proper function of nearly every tissue in the body including the brain, heart, muscles, immune system, and skin. The relationship between vitamin D and acne has long been theorised: Simpson et al.[33] reported the effect of vitamin D in the treatment of acne vulgaris in 1940. In a more recent study, Agak et al.[34] reported that *P. acnes* is a potent inducer of Th17 cells, and 1,25(OH)2D inhibits *P. acnes*-induced Th17 cell differentiation, which can be an effective option for modulating acne. In this study, sebocytes were identified as 1,25(OH)2D-responsive target cells; this effect may be an option in acne therapy. In another recent study, the expression of inflammatory biomarkers has been shown to be influenced by treatment with vitamin D in cultured sebocytes. Ekiz et al.[35] also reported that high serum levels of vitamin D in patients with rosacea may lead to remission.

Zinc is an essential element for the proper development and function of the human skin. Zinc supplement-induced remission of acne was first reported in the 1970s by Michaelsson and Fitzherbert. Patients with acne vulgaris have been reported to have low levels of serum zinc.[25] Zinc has a bacteriostatic effect on *P. acnes*, inhibits chemotaxis, and may decrease production of the inflammatory cytokine TNFα.[27]

## Metabolic Syndrome and Acne

Metabolic syndrome is a multiplex syndrome consisting of abdominal obesity (waist circumference >102 cm in men and >88 cm in women), hypertriglyceridaemia (≥150 mg/dL [1.69 mmol/L]), low high-density lipoprotein cholesterol (<40 mg/dL [1.04 mmol/L] in men and <50 mg/dL [1.29 mmol/L] in women), high blood pressure (≥130/85 mmHg), and high fasting glucose (≥110 mg/dL [≥6.1 mmol/L]), and which is a risk factor for coronary heart disease, as well as for diabetes, fatty liver, and several cancers. This syndrome arises from insulin resistance and abnormal adipose deposition and function.

Insulin/insulin-like growth factor 1 receptors can be expressed by epidermal keratinocytes, and hyperinsulinaemia may lead to increased proliferation of basal keratinocytes within the follicular sebaceous unit duct, inducing failure of terminal differentiation of follicular corneocytes and thus actively participating in acne pathogenesis.

Another mechanism linking insulin resistance and acne development is aggravation of the mammalian target of rapamycin complex 1 (mTORC1) signalling pathway.[36] Stimulation of the mTORC1 signalling pathway via a Western diet may be strongly associated with acne with increased body mass index, insulin resistance, and early onset of menarche.[37]

The role of insulin resistance is very well known in female patients with PCOS and acne vulgaris.[38] In addition, there are published studies that support the role of insulin resistance in male patients with acne vulgaris and in post-adolescent acne.[39,40]

These mechanisms should be kept in mind during the treatment of acne vulgaris. Stabile et al.[41] reported that insulin sensitisers not only improve the irregularity of menses and hirsutism in patients with PCOS, but also reduce insulin resistance as well as reducing the body's inflammatory response. Using insulin sensitisers in male patients with treatment-resistant acne vulgaris was supported by results of Fabbrocini et al.[42] These studies describe the importance of insulin resistance in acne vulgaris pathogenesis and underline the use of metformin and diet as a possible adjuvant therapy in this condition.

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# PYODERMA GANGRENOSUM: A MINI-REVIEW

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## ABSTRACT

Pyoderma gangrenosum (PG) is a rare, chronic neutrophilic dermatosis of unknown aetiology that usually presents with necrotising ulcers, although the evolution of the disease can be variable and is not always progressive. Its pathogenesis is poorly understood but an underlying immunological abnormality seems to be implicated in the genesis of the lesions. This hypothesis is supported by its frequent association with inflammatory bowel disease, malignancies, and rheumatological disorders. The diagnosis is challenging even for dermatologists as there are no specific tests or histological features. There are no clinical trials evaluating the efficacy of the different drugs used to treat the disease due to its rarity, and therefore there is no 'gold standard' therapy. In this mini-review we describe the main clinical aspects of PG, its pathophysiology, association with underlying diseases, diagnosis, treatment options, and prognosis.

Keywords: Pyoderma gangrenosum (PG), neutrophilic dermatoses (NDs), ulcer, treatments.

## INTRODUCTION

Pyoderma gangrenosum (PG) is a rare, chronic, recurrent, ulcerative dermatosis that is now included within the spectrum of the neutrophilic diseases. PG lesions are characterised by prominent neutrophilic infiltration of the skin in the absence of infectious cause or vasculitis, although they can show evidence of leukocytoclastic vasculitis.[1,2] The condition is potentially lethal and causes considerable morbidity. It goes unrecognised or is misdiagnosed in up to 30% of cases and can occur at any age, with a peak of incidence between 20–50 years of age. Women are slightly more susceptible to the disease than men.[3,4] Paediatric PG represents 4% of all cases.[5] It usually presents as a papule or pustule that develops into one or more painful ulcers with violaceous and undermined borders.[6,7] Several variants are recognised. Since there are no accepted consensus diagnostic criteria and the diagnosis is one of exclusion, identification of PG is often delayed and challenging. This is made more difficult by there being no clinical trials that have evaluated the efficacy of the different drugs used in the treatment of PG due to the rarity of the disease; therefore there is no 'gold standard' therapy.

## PATHOGENESIS

Both the aetiology and pathogenesis of PG are not yet completely understood. An abnormal immunological response to undefined triggers and factors may combine and be responsible for the clinical manifestations. The pathergy phenomenon, an aberrant exaggerated inflammatory response, is characteristically observed in up to 30% of PG cases.[3]

PG is frequently associated with inflammatory bowel disease (IBD). This supports the hypothesis of possible cross-reactivity between intestinal and cutaneous antigens.[8] Dysregulation of the normal T cell response also appears to be implicated. This is supported by the observation that PG lesions heal when treated with immunosuppressive drugs and tumour necrosis factor (TNF) inhibitors. Nevertheless, lesions may appear during treatment with etanercept or infliximab, although this is rare.[9-11]

PG is considered to be within the spectrum of the neutrophilic dermatoses (NDs). This group comprises a number of heterogeneous disorders characterised by inflammatory skin lesions that, observed histologically, show an intense

inflammatory infiltrate composed primarily of neutrophils, with no evidence of infection.[1,2] These entities probably share a common pathophysiological mechanism that involves an abnormal recruitment or haemostasis of polymorphonuclear neutrophils. An elevation of the cutaneous and/or circulating levels of pro-inflammatory cytokines and potent attracting chemokines, namely interleukin (IL)-6, chemokine (C-X-C motif) ligand (CXCL) 8, and CXCL1–3, are observed in PG ulcers.[12,13] An overexpression of matrix metalloproteinases (MMPs), namely MMP-2, 9, and 10, is also observed in PG and Sweet´s syndrome (SS) lesions. An increase in the neutrophil elastase inhibitor, elafin, as well as an intensification of the Fas/FasL system are contributing factors for ulcer formation and abnormal wound healing.[12-14] Some authors have suggested that PG during pregnancy and puerperium may be a consequence of high granulocyte-colony stimulating factor (G-CSF) levels and pathergy.[15] Levels of IL-17, IL-23, and Th17 cells have been found to be increased in PG cutaneous lesions.[16-19]

An abnormal genetic background is thought to play a role in the pathogenesis of PG. This is supported by the presence of PG lesions in patients with: PAPA syndrome (pyogenic sterile arthritis, PG, and acne); PAPASH syndrome (pyogenic sterile arthritis, PG, acne, and hidradenitis suppurativa); and PASH syndrome (PG, acne, and hidradenitis suppurativa). In these patients, several mutations, namely in the *PSTPIP1* gene on chromosome 15q25, result in an aberrant production of IL-1.[13,20,21] On the other hand, PG associated with IBD may show abnormalities in *IL8RA*, *TIMP3*, and *TRAF31P2* genes.[21] Due to recently acquired knowledge regarding its pathophysiology, it is now accepted that PG is a systemic immune-mediated inflammatory disease rather than a purely cutaneous disease.

## ASSOCIATED DISEASES

PG can be idiopathic, but most cases are associated with other diseases (50–80%): IBD (up to 41%), rheumatoid arthritis, seronegative arthritis, haematological malignancies, paraproteinaemia, and, rarely, solid tumours (single reports or small case series) (Table 1).[6-8,22] A recent study indicates that new-onset PG can herald a recurrence of a previously diagnosed solid organ malignancy, and recurrent PG can be associated with new-onset solid organ malignancy.[23] Furthermore, PG has been associated with hepatitis C virus infection, HIV infection, and other NDs, such as SS, subcorneal pustular dermatosis, aseptic abscesses syndrome, Behçet's disease, and Sjögren´s syndrome. It may also be drug-induced (interferon alpha 2b, G-CSF, gefitinib, pazopanib, sunitinib, imatinib, infliximab, rituximab, etanercept, and propylthiouracil).[2,9,11,24,25] Familial forms have been reported in the context of the PAPA, PAPASH, and PASH syndromes. Recently, a case of PG associated with common variable immunodeficiency has been reported.[26]

## CLINICAL FEATURES

Four major clinical variants of PG have been described: ulcerative (classic), pustular, bullous, and vegetative (superficial). In most cases only one form is seen, but more than one subtype can be observed simultaneously in the same patient. In addition, PG may present overlapping features of other NDs.[5,27] PG most commonly presents on the lower limbs, namely the pretibial area, but other skin areas (head, neck, breasts, genitalia, and upper extremities) can be involved.[5,28] Clinically, the classical form (ulcerative) is characterised by rapidly progressing, painful ulcers with well-defined, violaceous, undermined borders (Figure 1A). The base of the ulcers is usually granulation tissue, and is sometimes necrotic and covered with purulent exudates. There is also inflammation of the perilesional skin.[6,29]

The pustular type presents as multiple sterile pustules with a surrounding erythematous halo on the extensor surface of the extremities and upper trunk, and is commonly associated with IBD (Figure 1B).[30] It usually remits with the control of the digestive disease.[3,7]

Bullous PG is associated with haematological malignancies and has features that overlap with bullous SS (Figure 2A and 2B). In this type of PG, grouped vesicles typically coalesce to form large bullae that ultimately ulcerate. The dorsal aspect of the hands, extensor surface of the arms, and the face are the most common locations. The presence of PG in these patients is suggestive of a poor outcome.[31,32]

The vegetative (superficial) type is the most uncommon, most localised, and least aggressive variant of PG. It presents as a unique, erythematous, ulcerated plaque without the

characteristic undermined border. It is usually localised on the trunk and less associated with underlying disorders.[33,34] The pathergy phenomenon is observed in these cases, and therefore surgical procedures, such as breast surgery or caesarean section, may worsen or trigger the lesions. Peristomal PG (15% of PG) is a pathergy phenomenon and may be observed after any stomal creation, with most of the cases occurring in patients who underwent ileostomy or colostomy for the treatment of IBD (namely, Crohn's disease).[4,7] An average of 17.1 postoperative days has been reported for the development of the lesions.[35]

PG can be associated with systemic symptoms (due to IL-1β elevation) and, rarely, with extracutaneous neutrophilic infiltrates, namely in the lungs, heart, bones, and central nervous system. Eyes, oral mucosa, pharynx, larynx, and vulva may be affected in the form of aphthous lesions.[2,36] During the healing process, new epithelial growth connecting the ulcer bed to the surrounding normal skin is observed and referred to as 'Gulliver´s sign'.[37] The final stage of the process usually results in cribriform ('cigarette paper-like') scars. Adult and childhood PG have a similar clinical appearance, but in the latter the condition tends to involve the head, genital, and perianal areas.[2,7,11]

**Table 1: Diagnostic criteria and systemic diseases associated with pyoderma gangrenosum.[29]**

| Diagnosis of classic ulcerative pyoderma gangrenosum requires two major and at least two minor criteria. | |
|---|---|
| **Major criteria**<br>✓ Rapid progression of a painful, necrolytic, cutaneous ulcer with an irregular, violaceous, and undermined border<br>✓ Exclusion of other causes of cutaneous ulceration | |
| **Minor criteria**<br>✓ History suggestive of pathergy<br>✓ Clinical finding of cribriform scarring<br>✓ Systemic diseases associated with pyoderma gangrenosum<br>✓ Histopathological findings (sterile dermal neutrophilic infiltration ± mixed inflammation ± lymphocytic vasculitis)<br>✓ Treatment response (rapid response to systemic steroid treatment) | |
| **Systemic diseases associated with pyoderma gangrenosum** | |
| Inflammatory bowel diseases | Ulcerative colitis, Crohn's disease |
| Arthritis | Seronegative arthritis, ankylosing spondylitis, rheumatoid arthritis,<br>PAPA and PAPASH syndromes |
| Hepatic disease | Autoimmune hepatitis |
| Infections | HIV, HCV |
| Malignancies | Myelodysplasia, acute myeloid leukaemia, Hodgkin disease, monoclonal gammopathy<br>Colon, prostate, and bladder carcinoma, glioblastoma multiforme |
| Drugs | Propylthiouracil, antipsychotic drugs, isotretinoin, pegfilgrastim, TNF inhibitors, gefitinib, pazopanib, rituximab, infliximab, G-CSF, interferon |
| Others | Hidradenitis suppurativa, PASH syndrome<br>Systemic lupus erythematous, Behçet's disease, sarcoidosis<br>Takayasu's arteritis<br>Autoimmune thyroid disease<br>Gastric and duodenal ulcer<br>Diabetes mellitus<br>Pregnancy<br>CVI |

PAPA: pyogenic sterile arthritis, pyoderma gangrenosum, and acne; PAPASH: pyogenic sterile arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa; HIV: human immunodeficiency virus; HCV: hepatitis C virus; G-CSF: granulocyte-colony stimulating factor; PASH: pyoderma gangrenosum, acne, and hidradenitis suppurativa; CVI: common variable immunodeficiency; TNF: tumour necrosis factor.

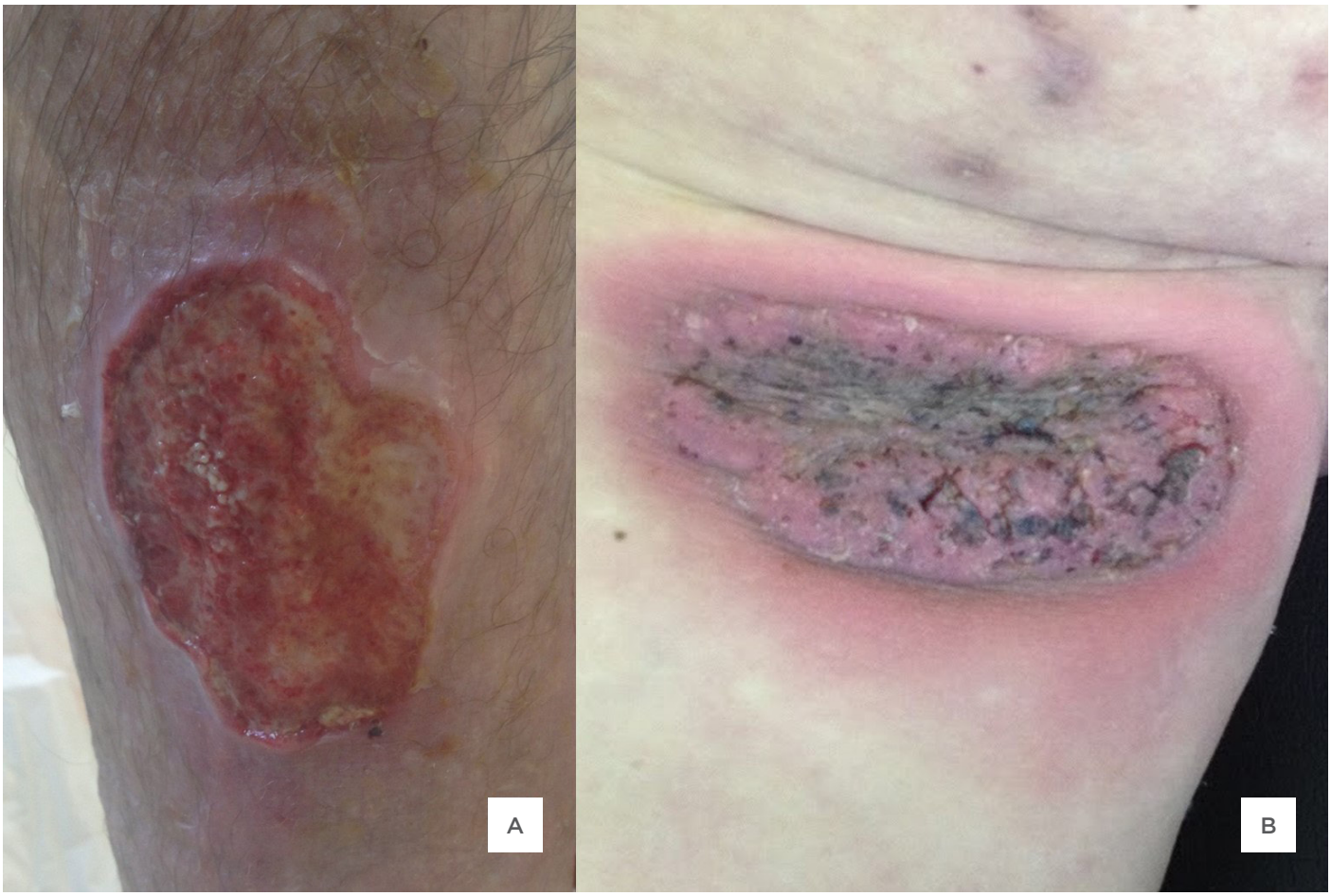


**Figure 1: Pyoderma gangrenosum with well-defined, violaceous, undermined borders (A). Cribriform inflammatory pyoderma gangrenosum ulcer in a patient with inflammatory bowel disease (B).**

## DIAGNOSIS

There are no specific, accepted tests or consensus diagnostic criteria for PG. Su et al.[29] proposed that diagnosis of PG could be made if two major and at least two minor criteria were present (Table 1). However, the diagnosis relies on clinical suspicion and requires exclusion of other causes of skin ulceration, namely: infections (ecthyma gangrenosum, deep mycoses, and infection with atypical mycobacteria), vascular diseases (venous or arterial insufficiency), vasculitis, factitia, other NDs, and neoplasms (Table 2).[6,38] Histopathology is useful to rule out other causes of ulcerations, and the histological findings vary depending on PG variant, the site, and the timing of the skin biopsy. Biopsy should include the ulcer's border and the adjacent skin, and a specimen should be sent for culture. In recent, actively expanding lesions, a dense neutrophilic dermal infiltrate with micro-abscesses, occasional vasculitis, and leukocytoclasia is observed. In older, fully developed lesions, tissue necrosis along with a surrounding mononuclear cell infiltrate is usually seen.[3] Analyses should include: a complete blood cell count, chemistry and liver function tests, erythrocyte sedimentation rate, C-reactive protein level, serum and urine protein electrophoresis, and anti-nuclear and anti-neutrophil cytoplasmic antibodies. Colonoscopy should also be performed to exclude IBD.

## TREATMENT

Prospective, randomised case–control studies that evaluate and compare treatment regimens are lacking in the literature due to the rarity of PG. Indeed, no randomised controlled trials have been performed. Therefore, there is no 'gold standard' therapy or therapeutic guidelines.[38,39] The treatment approach is mostly empirical or based upon expert recommendations, and tries to target the different immunological mediators that seem to be involved in its pathogenesis.

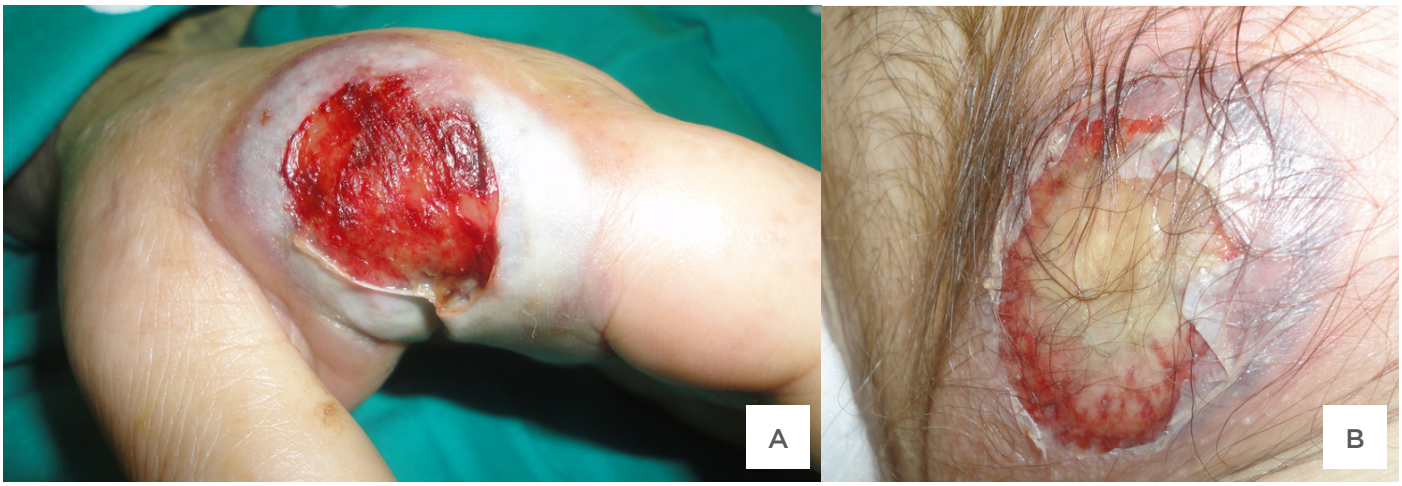


**Figure 2: Bullous pyoderma gangrenosum on the dorsal aspect of the hand (A) and genital area (B) of a patient with a myelodysplastic syndrome.**

**Table 2: Differential diagnoses of pyoderma gangrenosum.[6]**

| | |
|---|---|
| **Vascular diseases** | Arterial or venous insufficiency<br>Vascular occlusive diseases - livedoid vasculopathy, Dowling–Degos disease, ulcers of sickle cell disease, antiphospholipid antibody syndrome |
| **Malignancies** | Basal cell carcinoma<br>Squamous cell carcinoma<br>Cutaneous T cell lymphoma<br>Leukaemia cutis |
| **Infections** | *Bacterial*<br>Impetigo, ecthyma, necrotising fasciitis, anthrax, tuberculosis, atypical mycobacteria, Buruli ulcer, syphilitic gumma<br>*Viral*<br>Chronic herpes simplex, cytomegalovirus<br>*Protozoal*<br>Leishmaniasis, amoebiasis cutis<br>*Fungal*<br>Blastomycosis, histoplasmosis, sporotrichosis, cryptococcosis, aspergillosis, penicilliosis, zygomycosis |
| **Exogenous tissue injury** | Arthropod bite<br>Factitial ulcers<br>Drug-induced tissue injury<br>Halogenodermas (iododerma/bromoderma)<br>Calciphylaxis |
| **Neutrophilic dermatoses** | Sweet's syndrome<br>Subcorneal pustular dermatosis<br>Bullous lupus erythematosus |
| **Vasculitis** | Behçet's disease<br>Polyarteritis<br>ANCA-associated vasculitides<br>Cryoglobulinemic vasculitis |
| **Others** | Cutaneous Crohn's disease |

ANCA: anti-neutrophil cytoplasmic antibody.

Therapeutic choice is influenced by several factors: associated disease, extension, number and depth of the lesions, patient's performance status, and long-term side effects of the drugs.[3,7] Treatment of the underlying disease should be performed. PG may heal spontaneously, but most cases require local and systemic treatment.

## TOPICAL TREATMENT

A good response to topical treatments may occur in mild lesions, namely in the vegetative type.[7,11] Topical modalities include: dressings, topical agents, and intralesional injections. Topical corticosteroids (Class III and IV) or tacrolimus are the most frequently used. Topical sodium cromoglicate, 5-aminosalicylic acid, nitrogen mustards, benzoyl peroxide, and nicotine have been used with success.[7,40-42] Topical tacrolimus 0.3% seems to be more effective than clobetasol propionate 0.05% in the treatment of peristomal PG, namely in lesions larger than 2 cm.[43] Recently, two cases have been successfully treated with autologous platelet-rich plasma gel.[44] Collagenase ointment and timolol gel have also been used to treat idiopathic PG.[45] Infliximab gel has been used to improve refractory lesions in a patient with ulcerative colitis,[46] and crushed dapsone has been used in the treatment of peristomal PG.[47] Intralesional corticosteroids or cyclosporine administered on the edges may also control the disease. Recently, the use of a dermal injection of activated protein C has been described.[48] Ulcer debridement or stoma relocation is not recommended, as it can aggravate the lesions. The use of adequate wound dressing is important, namely for managing heavy exudates. It is important to note that topical treatments alone are usually inefficient.

## SYSTEMIC THERAPY

Systemic treatment is required in severe disease or rapidly progressive lesions. Corticosteroids and cyclosporine are widely accepted as first-line therapies, but Ormerod et al.[49] only recently published the first randomised controlled trial that compared prednisolone (0.75 mg/kg/day) and cyclosporine (4 mg/kg/day) in PG treatment. They concluded that both have comparable effectiveness, with ulcers healing in 47% of the patients after 6 months of treatment. It appears that starting with high doses (ranging from 0.5–2.0 mg/kg/day) of oral prednisone is an effective strategy. Disease stabilisation usually occurs within 24 hours. Tapering or discontinuation of the drug should only be recommended when the inflammatory component is absent or when the ulcer is healed, respectively.[28,40] The sulpha drugs, such as dapsone (50–200 mg/day), may be beneficial, but not all patients will have a favourable response. Sulfasalazine (4–6 g/day) is the most effective sulpha drug, especially in patients with associated ulcerative colitis and idiopathic forms of PG.[3,7] Other systemic drugs have been reported to successfully treat PG, or have been used as effective corticosteroid-sparing agents, namely: azathioprine (100–150 mg/day), clofazimine (200–400 mg/day), mycophenolate mofetil (2–4 g/day), thalidomide (400 mg/day), methotrexate, minocycline, cyclophosphamide, and intravenous immunoglobulin.[34,50-52] New therapeutics have emerged due to recently acquired knowledge regarding PG pathophysiology suggesting that PG represents the cutaneous manifestation of a generalised inflammation. Anti-TNF agents, adalimumab, etanercept, and infliximab seem to be effective, especially if there is associated IBD. Only one prospective, double-blind, placebo-controlled study has been performed in the treatment of PG with biologics (infliximab 5 mg/kg) to date.[39] Another alternative treatment is the human monoclonal antibody ustekinumab (anti-IL-12/IL-23).[53]

The literature shows that PG lesions associated with auto-inflammatory syndromes have successfully been treated with the recombinant human IL-1β receptor antagonist anakinra and the human monoclonal IL-1β antagonist canakinumab.[54,55] There have only been single case reports on the treatment of PG with the chimeric monoclonal anti-CD20 antibody rituximab.[56] Certolizumab pegol, a recombinant antigen-binding fragment of a humanised monoclonal antibody that selectively neutralises TNF may be an alternative therapy for the treatment of PG in cases of intolerance or ineffectiveness of other anti-TNF agents.[57] Multidrug regimens may be considered for refractory disease, namely systemic steroids in combination with cyclosporine. Other valid combinations include: methotrexate and infliximab; and cyclosporine, mycophenolate mofetil, and prednisone.[11]

## ADJUVANT THERAPY

Patients should receive local antimicrobial treatment if superinfection is clinically suspected. Pain management should be considered. Therefore, addition of osmotically active agents, such as macrogol, should be avoided. Morphine-containing hydrogel formulations can be used,[58] and oral narcotics may be required in severe cases.[2]

## PROGNOSIS

Some ulcers may heal spontaneously with cribriform scars, but PG usually has a chronic relapsing course (up to 70%).[59] PG patients have a risk of death that is three-times higher than the general population.[60] Proper management of any underlying systemic disease prevents rebound flares. Ulcerative and bullous variants have a worse prognosis. A rapid response to treatment suggests a good course for the disease.

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# QUALITY OF LIFE EVALUATION IN PSORIASIS PATIENTS STARTING A BIOLOGICAL TREATMENT: THE IMPORTANCE OF A MORE COMPREHENSIVE ASSESSMENT OF DISEASE BURDEN

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## ABSTRACT

Psoriasis is a chronic condition that has a significant negative impact on a patient's quality of life (QoL). Measures of the clinical severity of psoriasis alone may not reflect patients' perceptions of the impact of the disease on their lives. The aim of our study was to assess QoL in psoriasis patients who were candidates to receive one of the new biological treatments in order to obtain a more complete evaluation of the severity of the disease prior to treatment. A total of 180 patients were analysed, with all being affected by plaque-type psoriasis. The clinical severity of psoriasis was assessed by the Psoriasis Area and Severity Index, while QoL was assessed by three measures: the Dermatology Life Quality Index, the Skindex-29, and the Psoriasis Disability Index. Our results show how pervasive the impact of psoriasis is in patients who are candidates for the new biological treatments, and they further confirm the lack of a strong correlation between measures of clinical severity and QoL.

Keywords: Biological therapies, psoriasis, quality of life (QoL), questionnaire.

## INTRODUCTION

Psoriasis is a chronic disease that affects 1–3% of the world's population, with an equal gender distribution.[1,2] It has a substantial physical, functional, and psycho-social impact on everyday life for most of those affected.[3] Recent investigations have shown that patients with psoriasis suffer as much disability as people with severe medical conditions such as cancer, arthritis, heart disease, diabetes, and depression.[4-6] In addition to frequent symptoms,[7] such as itching and pain, some patients experience joint involvement that may cause severe physical disability.

Acting as an organ of sensation, sexuality, and social interaction, the condition of the skin affects body-image and self-esteem, as well as aspects of social life such as participation and interaction at work or at school. Social rejection is a common feeling experienced by people with psoriasis. Several studies have described common reactions to psoriasis as including embarrassment, impaired daily activities, anxiety, anger, and depression.[8-10] The presence of psoriasis has also been found to affect sexual activity. Patients with psoriasis, particularly women, have difficulty in starting sexual relationships. However, sexual problems have not been correlated with the extent of the skin disease or with its location in the genital area.[11-13]

Psoriasis is often associated with psychiatric problems, such as depression and anxiety,[14] that also have a negative effect on quality of life (QoL).[15,16] Patients with psoriasis attribute a significant negative effect on their QoL to their disease and/or its treatment. The classical treatments of psoriasis are often unsatisfactory for patients in being inconvenient, messy, and associated with side effects.[17-19]

The World Health Organization Quality of Life Group defined QoL as "an individual's perception of their position in life in the context of the culture and

value system in which they live and in relation to their goals, expectations, standards, and concerns".[20] This definition has deeply changed the concept of health, which is no longer considered to be the absence of illness but rather a state of suitable physical, psychological, and social wellbeing. Testa and Simonson,[21] beginning from the definition proposed by the World Health Organization, defined health-related QoL as "the aspects (or domains) of the physical–functional, psychological–emotional, and social health that are influenced by the experiences, beliefs, objectives, and expectations of the individuals".

The aim of this study was to investigate the QoL and clinical characteristics of patients with psoriasis referred to the dermatological clinic of the University of Rome Tor Vergata as candidates to receive one of the new biological treatments, in order to better manage the disease and the effect of treatment while also considering the patient's point of view.

## PATIENTS AND METHODS

### Patients

Consecutive patients with psoriasis who were referred to a dermatological reference centre as candidates for biological treatments were invited to participate in the study. To be eligible for treatment with a biological drug, patients had to demonstrate unresponsiveness to other systemic therapies, including methotrexate, cyclosporine, and psoralen ultraviolet A. Socio-demographic variables and clinical data were collected for each patient, with the clinical severity of psoriasis evaluated using the Psoriasis Area and Severity Index (PASI).

### Quality of Life Measurements

Three different measures were used to assess QoL: the Dermatology Life Quality Index (DLQI), the Skindex-29, and the Psoriasis Disability Index (PDI).

#### Dermatology Life Quality Index

The DLQI is the first dermatology-specific QoL questionnaire. Published in 1994, the questionnaire was designed to be used in adults over the age of 18 years, and consists of 10 questions concerning symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment; all questions relate to the previous week. Each question is scored from 0–3 and the total score can range from 0–30, with higher scores indicating greater disability. The DLQI has been shown to have good reliability and validity when used in a dermatological setting.[22]

#### Skindex-29

Skindex-29 is a reliable and valid instrument that has been specifically designed for measuring QoL in dermatological patients. Twenty-nine items are combined to form three scales assessing essential domains of QoL (burden of symptoms, social functioning, and emotional state). Patients are requested to answer the questions, referring to the previous 4-week period, using a 5-point scale ranging from 'Never' to 'All the time'. The scores from the three scales, and an overall or summary score, are calculated on a 100-point scale, with lower scores indicating a better QoL.[23]

#### Psoriasis Disability Index

The PDI is an appropriate method to give a rapid global measure of psoriasis disability. It considers the impact of psoriasis on daily activities, work, personal relationships, leisure, and treatment-related aspects. The questionnaire includes 15 questions that refer to the previous 4-week period, and which are answered using a 4-point linear scale ranging from 0 (no disability) to 3 (maximum level of disability).[24]

### Statistical Analysis

Data were entered into a computerised database and QoL scores were calculated for each QoL measure. All statistical analyses were performed using STATA 11.2 software (Statacorp LP Inc., College Station, Texas, USA).

## RESULTS

### Patient Characteristics

One hundred and eighty patients (104 males and 76 females) aged between 20 and 79 years, and affected by moderate-to-severe psoriasis were recruited to the study. At baseline, the mean PASI was 16.65 (range: 8–59) and the mean disease duration was 22.9 years (range: 5–65). A majority of the patients (80%) were refractory to at least two conventional therapies, and only 20% of patients showing comorbidities (i.e. hypertension, hyperlipidaemia, cardiovascular disease) were treated with only one conventional therapy.

**Table 1: Mean quality of life scores in 180 psoriasis patients starting a biological treatment.**

| Patient characteristic | | n (%) | DLQI | PDI | Skindex-29 | | |
|---|---|---|---|---|---|---|---|
| | | | | | Symptoms | Emotions | Functioning |
| Sex | Male | 104 (58) | 11.5 | 25.9 | 47.2 | 49.1 | 38.2 |
| | Female | 76 (42) | 12.8 | 28.8 | 47.0 | 53.5 | 36.7 |
| Age, years | <40 | 46 (31) | 12.0 | 25.3* | 43.5 | 46.5* | 33.6 |
| | 40–49 | 42 (28) | 13.3 | 33.1* | 52.1 | 58.4* | 43.7 |
| | >50 | 62 (41) | 11.0 | 24.0* | 46.5 | 48.4* | 36.6 |
| PASI | <10 | 54 (36) | 9.5* | 20.3* | 37.8* | 42.9* | 31.2* |
| | 10–19.9 | 61 (41) | 12.2* | 27.8* | 49.8* | 52.8* | 38.5* |
| | >20 | 35 (23) | 15.2* | 35.0* | 57.3* | 55.4* | 43.1* |
| Disease duration, years | <10 | 55 (37) | 12.8 | 27.8 | 47.8 | 51.5 | 36.2 |
| | >10 | 95 (63) | 11.6 | 26.6 | 47.0 | 50.2 | 38.4 |

*p<0.05.
DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index; PDI: Psoriasis Disability Index.

## Quality of Life

According to all of the scales that we utilised, mean QoL scores were invariably high, indicating a severe burden of disease (Table 1). The only statistically significant difference was observed in relation to PASI scores, with higher DLQI scores in higher PASI categories. Females had a mean score slightly higher than males, patients aged 40–49 years had slightly higher scores than younger and older patients, and patients with a shorter duration of disease had slightly higher scores than those with a longer disease history. Unsurprisingly given its high correlation with the DLQI,[25] the PDI scores showed exactly the same pattern.

For the different variables considered, the pattern of mean scores obtained using Skindex-29 was fairly consistent with those observed using the DLQI and the PDI, with only a few non-significant exceptions. However, patients with a longer duration of disease were slightly more affected on the 'Functioning' scale than those with a shorter duration. The observed differences were statistically significant for PASI on all three Skindex-29 scales, as well as for age on the 'Emotions' scale, with higher scores in the 40–49 years age group.

To estimate the independent role of sex, age, duration of disease, and PASI on the two dermatology-specific instruments (DLQI and Skindex-29), while simultaneously adjusting for all of the other variables, we created separate logistic regression models. The dependent variables were defined using a cut-off value of 10 for the DLQI, and cut-off values of 50, 50, and 33 for the 'Symptoms', 'Emotions', and 'Functioning' scales of the Skindex-29, respectively.[26] For DLQI, only PASI >20 was associated with scores >10, with an odds ratio (OR) of 6.3 versus PASI <10 (95% confidence interval [CI]: 2.1–19.4).

For the Skindex-29 'Symptoms' scale, in addition to PASI >20 (OR: 7.4, 95% CI: 2.5–22.4), age was associated with significant differences both for the 40–49 years (OR: 3.4, 95% CI: 1.2–9.2) and the >50 years (OR: 3.5, 95% CI: 1.4–8.9) age groups versus patients in the <40 years age group. For 'Functioning', significant ORs were observed for the 40–49 years age group (OR: 3.1, 95% CI: 1.2–8.2) and the >50 years age group (OR: 2.6, 95% CI: 1.1–6.3) versus the <40 years age group; and PASI >20 was significantly higher than PASI <10 (OR: 3.7, 95% CI: 1.3–10.3). Interestingly, for the 'Emotions' scale, in addition to the difference between the 40–49 years and <40 years age groups (OR: 3.2, 95% CI: 1.2–8.5), a statistically significant difference was observed for women versus men (OR: 2.5, 95% CI: 1.1–5.4).

## DISCUSSION

In this study we describe the QoL of a group of psoriasis patients selected for biological treatments, and show that the level of QoL impairment was extremely high, according to both dermatological instruments and questionnaires. Given that these treatments will be increasingly used in patients with psoriasis over the next few years, it is important to investigate the impact of the disease on QoL in order to better evaluate a patient's condition at the start of treatment and to monitor the course of the disease in relation to the effects of the therapy, both during the period of administration and after the end of treatment cycles.

A novelty of our study is that QoL was evaluated using different instruments. The use of dermatology-specific QoL questionnaires, such as the DLQI and the Skindex-29, can highlight specific problems due to skin involvement, while allowing comparisons with a wide range of dermatological conditions. Furthermore, disease-specific instruments, such as the PDI, are appropriate tools to explore disability due specifically to psoriasis. We observed that QoL, as measured by the different instruments, was fairly consistently associated with gender (women had a worse QoL than men), age (patients in the intermediate age group [i.e. 40–49 years] had a worse QoL), and clinical severity.

In our study we observed that women had a worse QoL than men. Gender differences with regard to the impact of psoriasis are an important issue to consider. Recent studies in several diseases have shown that women report more physical disability, a lower QoL, more pain, more symptoms, and more psychological problems compared with men.[27-29] Several studies have shown women to be more likely than men to report impairment of psoriasis-related QoL.[30,31] In our study, women had higher scores on the vast majority of scales used. This is almost certainly due to the cosmetic disfigurement caused by psoriasis, as recent studies have shown that women are more invested in their appearance and tend to be dissatisfied with their body-image.[32]

Multivariate analyses showed that the variables more associated with QoL were high PASI scores (in DLQI and the 'Symptoms' scale of Skindex-29) and the 40–49 years age group (for all Skindex-29 scales). Our results show that older patients with psoriasis had worse QoL: patients who were >40 years old had significantly lower mean QoL improvement than younger patients (≤40 years of age). It is important to note that no association between PASI and the psycho-social measures used in this study (e.g. 'Symptoms' and 'Functioning' scales of the Skindex-29) was observed.

In conclusion, our results show how pervasive the impact of psoriasis is in patients who are starting a biological treatment, and they further confirm the lack of a strong correlation between measures of clinical severity and QoL. Our findings stress the complexity of the factors that affect QoL in patients with moderate-to-severe psoriasis, and underline the need for a thorough assessment of QoL in these patients. If the primary success of healthcare for patients suffering from psoriasis is to maximise functioning in everyday life and achieve the highest possible level of QoL, then it will be difficult to show that these objectives are achieved if we fail to collect valid measurements that document the true extent of the changes induced by dermatological interventions.

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# *STAPHYLOCOCCUS AUREUS* AND ATOPIC DERMATITIS: WHICH CAME FIRST, THE CHICKEN OR THE EGG?

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## ABSTRACT

Atopic dermatitis (AD) is a highly pruritic, chronic inflammatory skin disease that affects up to 25% of children and 10% of adults. Approximately 90% of patients with AD are colonised by *Staphylococcus aureus*, compared with only 5–30% of non-atopic individuals. Th2 cytokines have a permissive effect on microbial invasion, the epidermal barrier, and cell-mediated immunity, which lowers the production of antimicrobial proteins. Superantigen-producing *S. aureus* colonisation is correlated with serum interleukin (IL)-4 levels. Up to 50–60% of the *S. aureus* found on patients with AD is toxin-producing.[1] *S. aureus* colonisation, infection, and production of toxins and superantigens is believed to drive, at least in part, the pathogenesis of AD. *S. aureus* mechanically disrupts epidermal integrity through protease activity, and also has the ability to be internalised by keratinocytes in which it activates the inflammasome and induces apoptosis. Some patients with AD produce specific immunoglobulin E (IgE) antibodies directed against staphylococcal superantigens to an extent that correlates with skin disease severity. IL-4 and IL-13 have also been reported to increase staphylococcal α-toxin-induced keratinocyte death via STAT6 signalling. The *S. aureus* superantigens staphylococcal enterotoxin B and toxic shock syndrome toxin 1 promote lymphocyte IL-31 production in patients with AD. IL-31 has, in turn, been shown to reduce filaggrin expression and mediate pro-inflammatory cytokine excretion, as well as induce toxin-specific IgE and basophilic activation. The ability of *S. aureus* to colonise skin affected by AD, and to activate and maintain a Th2 environment allowing, via the destruction of tight junctions, exposure to allergens and thus causing allergic sensitisation, makes it one of the main protagonists of the 'atopic march'.

Keywords: Atopic dermatitis (AD), *Staphylococcus aureus*, atopic march, immunoglobulin E (IgE) sensitisation, skin immunity.

## INTRODUCTION

Atopic dermatitis (AD) is a highly pruritic, chronic inflammatory skin disease that affects up to 25% of children and 10% of adults, and which is associated with significant morbidity as well as physical, psychological, and economic impairments to quality of life. The disease often begins in childhood, with approximately 60% of patients developing the disease prior to the age of 1 year, and its prevalence has markedly increased during the past three decades.[1-3] In many patients, the early onset of AD is the first clinical manifestation of allergic disease and often triggers the 'atopic march' (i.e. the subsequent development of food allergies, allergic rhinitis, and asthma), even if recent work suggests that only a small proportion of children (approximately 7%) follow a trajectory profile similar to that of the atopic march.[4] In addition, approximately 20% of patients do not have any evidence of immunoglobin E (IgE) sensitisation,[5] which suggests a degree of heterogeneity within the population. AD is a complex immunological disease based on a variety of genetic traits that cause susceptibility to environmental factors. It is characterised by reduced skin barrier function, intracutaneous and blood T-cell activation, and susceptibility to cutaneous microbial and viral

infections.[6] Mutations in filaggrin (FLG), an epidermal barrier protein, have been identified in approximately 30% of patients with AD.[7] They constitute the strongest known risk factor for AD and are associated with early onset, a more severe course, and higher prevalence of IgE-mediated sensitisation.[8] Levels of FLG are determined by genotype, but expression is also downregulated by Th2 cytokines in patients with AD[9] and FLG proteolysis is accelerated after exposure to either low ambient humidity[10] or skin irritants.[11] Therefore, levels of FLG and its degradation products are influenced not only by the individual's FLG genotype, but also by inflammation and exogenous stressors. A detailed characterisation of AD inflammation has revealed a biphasic cutaneous cytokine milieu with initial recruitment of interleukin (IL)-4-producing Th2 cells, followed by a mixed phenotype in the chronic phase.[12,13] The cutaneous barrier dysfunction also contributes to Th2 cell polarisation and the Th2 cell cytokine IL-4 further reduces the cutaneous barrier, forming a 'vicious circle'. In addition, IL-4 suppresses antimicrobial peptide production and immune function, allowing cutaneous microbes to expand and persist.[14,15] Approximately 90% of patients with AD are colonised by *Staphylococcus aureus*, while only 5–30% of nonatopic individuals are colonised by this bacterium.[16] *S. aureus* is usually recovered in densities of $10^5$ colony-forming units (CFU)/$cm^2$ from lesional atopic eczema sites, but can reach concentrations of up to $10^7$ CFU/$cm^2$, a density which is 1,000-times higher than on nonlesional skin.[17] In addition to higher rates of colonisation, up to 50–60% of the *S. aureus* found on patients with AD is toxin-producing.[18] *S. aureus* colonisation, infection, and production of toxins and superantigens are believed to drive, at least in part, the pathogenesis of AD. The severity of AD has been shown to correlate with the density of colonisation, with superantigen-secreting *S. aureus*[19] and *S. aureus* superantigen augmenting allergen-induced cutaneous inflammation in a murine model of skin inflammation.[20] Patients with AD also produce IgE antibodies directed against the superantigens found on their skin,[21] and the presence of IgE antibodies to the superantigens correlates with skin disease severity. *S. aureus* superantigens drive AD disease pathogenesis by inducing skin inflammation[22] and directly inducing T-cell proliferation.[23]

## *STAPHYLOCCOCUS AUREUS*: THE 'OPPORTUNIST'

*S. aureus* is an important human pathogen that causes a variety of infections ranging from localised skin and soft-tissue infections (SSTIs) to severe necrotising fasciitis and life-threatening disseminated infections. The ability of *S. aureus* to evoke these diverse clinical manifestations is attributed to its production of numerous exotoxins. One important mechanism promoting colonisation is adherence of *S. aureus* to surface components of the nasal epithelium or epidermal keratinocytes, such as fibrinogen, fibronectin, and cytokeratins. *S. aureus* utilises microbial surface components, such as fibrinogen-binding proteins A and B, iron-regulated surface determinant, and wall teichoic acid, to bind adhesive matrix molecules.[24,25] Interestingly, pH values between 7 and 8, which are usually found in AD after the disruption of the skin barrier (compared with the pH values of 4.2–5.6 found in normal skin), are more likely to support this adhesion process.[26] Furthermore, the expression of fibronectin is regulated by IL-4, the crucial Th2-promoting cytokine that is present in higher concentrations in AD patients.[27]

*S. aureus* is generally regarded as an extracellular microorganism, but there is ample evidence that it can be internalised by a variety of host cells[28] in a fibronectin-binding protein (FnBP)-dependent manner.[29] Strain-dependent, FnBP-independent invasion mechanisms have also been reported for primary human keratinocytes.[30] Intracellular *S. aureus* has been shown to escape the endosome and induce apoptosis in epithelial cells. Panton–Valentine leukocidin (PVL) is a two-component (LukS-PV and LukF-PV), pore-forming toxin that targets neutrophils and is a useful marker for *S. aureus* strains with the potential to cause severe infections. PVL promotes severe SSTIs by exerting toxic effects on host keratinocytes. PVL also allows bacteria to escape from endosomes and multiply. In fact, PVL-positive, community-acquired, methicillin-resistant *S. aureus* (CA-MRSA) is taken up by human keratinocytes and engulfed within endosomes before the PVL released from CA-MRSA is able to disrupt the endosomal membrane and facilitate the escape of the bacteria into the cytoplasm, where they are then able to replicate.[31] This process stimulates induction of the apoptotic cascade followed by the release of inflammatory cytokines, recruitment of leukocytes, and further cell damage. *S. aureus*

internalised by human keratinocytes can also be recognised by nucleotide-binding oligomerisation domain-like receptors and activate the cascade of the inflammasome. This promotes Th1 or Th17-mediated inflammation and may be important in acute forms of AD.[32] Recent evidence indicates that *S. aureus* secretes extracellular vesicles (EVs) as well as soluble α-toxins.[33] EVs derived from *S. aureus* are 20–200 nm vesicular structures that are membrane-enveloped spherical complexes containing about 90 proteins, DNA, RNA, and toxins. *S. aureus* EVs show potent immunogenicity and are related to AD pathogenesis.[34] α-haemolysin from *S. aureus* is also related to AD disease development and/or progression, with its production being significantly higher in the *S. aureus* present on the cutis of patients with severe AD compared with *S. aureus* from mild and moderate AD.[35] EV-associated α-haemolysin induces necrotic cell death by carrying α-haemolysin into the cytoplasm of keratinocytes, whereas soluble haemolysin induces keratinocyte death via apoptosis. EV-associated α-haemolysin induces IL-1β and IL-6 production in keratinocytes, dermal infiltration of inflammatory cells (particularly eosinophils), skin barrier disruption via keratinocyte cell death,[35] and consequently enhances penetration of high-molecular-weight allergens. In addition, EV-associated α-haemolysin induces epidermal thickening and eosinophilic inflammation in the dermis, whereas the soluble form induces only epidermal thickening.

Staphylococcal toxins are enzymes that injure the skin, resulting in activation and proliferation of epidermal keratinocytes that produce and release IL-18. IL-18 induces super Th1 cells to produce and secrete interferon (IFN)-γ and IL-13. IL-18 is presumed to be involved in the pathogenesis of AD because the serum levels of IL-18 in patients with AD significantly correlate with skin scores of AD lesions.[36] Furthermore, an increase of IL-18 production by epidermal cells was observed in AD mice models induced by subsequent topical application of *S. aureus* products,[37] and production of phenol-soluble modulins by *S. aureus* is necessary and sufficient to stimulate IL-18 release from keratinocytes.[38] The cutaneous application of *S. aureus* EVs induces skin inflammation characterised by infiltration of mast cells (MCs) and eosinophils. This inflammatory response is associated with enhanced production of not only Th1/Th17-type cytokines in the skin, but also Th2-type cytokines. Fibroblasts, smooth muscle cells, and MCs all have the potential to produce thymic stromal lymphopoietin (TSLP), and *in vitro* stimulation of fibroblasts with *S. aureus* EVs increases the secretion of Th2-type cytokines, such as TSLP, macrophage inflammatory protein 1α, IL-6, and eotaxin, with TSLP activating myeloid dendritic cells to create a Th2-permissive microenvironment. These *in vitro* findings demonstrate that Th2-type inflammation induced by *S. aureus* EVs is mediated by local production of Th2-type cytokines by dermal fibroblasts, and that *S. aureus*-derived EVs are a novel diagnostic and therapeutic target for the control of AD.[39] Finally, the *S. aureus* superantigens staphylococcal enterotoxin B (SEB) and toxic shock syndrome toxin 1 promote lymphocyte IL-31 production in patients with AD. IL-31, in turn, has been shown to reduce FLG expression, mediate pro-inflammatory cytokine excretion, and induce toxin-specific IgE and basophilic activation.[40]

## SKIN DEFENCE MECHANISMS AND THE TH2 ENVIRONMENT

Healthy skin is in direct contact with the external environment and is thus continuously exposed to large numbers of microorganisms. On the skin's surface, the presence of commensal microorganisms that occupy niches suitable for bacterial growth combined with a lower temperature and pH creates an environment that resists pathogen growth. To cope with substantial microbial exposure, the epithelial surface produces a diverse arsenal of antimicrobial proteins (AMPs) that directly kill or inhibit the growth of microorganisms. The most abundant AMPs produced by human keratinocytes are human β-defensin (HBD)-1, HBD-2, HBD-3, the cathelicidin IL-37, and the AMP ribonuclease 7. The aqueous and lipid components of the skin surface combine with AMPs produced by keratinocytes to enhance the barrier/protective function. The aqueous/lipid layer may serve a function that is similar to that of the intestinal mucus by trapping AMPs at the epithelial surface.[41] Resident bone marrow-derived cells in the dermis, such as MCs and Langerhans cells, provide essential additional AMPs after skin injury or in the early stages of infection. Many AMPs are involved in this defence, such as HBD-1, HBD-2, HBD-3, HBD-4, cathelicidin, dermicidin, ribonuclease 7, psoriasin, lactoferrin, lysozyme, secretory leukocyte protease inhibitor, elafin, α-melanocyte-stimulating hormone,

catestatin, and calprotectin. Inhibition of AMP expression in AD seems to be partially due to the excess production of the Th2 cell cytokines IL-4 and IL-13, which in turn induce the expression of SOCS1 and SOCS3 via STAT6.[42] Furthermore, the Th2 cytokines inhibit lamellar body production, which are organelles critical for epidermal barrier formation that normally occurs during keratinocyte differentiation. Lamellar bodies are also involved in the transport of acid sphingomyelinase, an enzyme that cleaves the α-toxin receptor sphingomyelin. The reduction in lamellar bodies may result in reduced surface acid sphingomyelinase, as well as reduced levels of ceramides. Staphylococcal α-toxin is one of the most prominent and destructive cytolytic toxins. This pore-forming toxin requires that the host expresses sphingomyelin on its cell surface; α-toxin specifically recognises the phosphocholine head group of sphingomyelin and, following binding, α-toxin heptamerises and becomes irreversibly inserted into the cell membrane. A Th2 cytokine milieu renders cells more sensitive to α-toxin-induced cell death. Therefore, the increased cell death in AD skin correlates with increased exposure to Th2 cytokines.[43] The ability of exogenous sphingomyelinase or phosphocholine to reverse α-toxin toxicity not only confirms the mechanism, but also provides a rationale for possible future therapeutics. Epidermal barrier protein FLG also plays an important role in protecting cells by mediating the secretion of sphingomyelinase. Sphingomyelinase is the primary enzyme responsible for producing ceramide, and levels of this enzyme are reported to be decreased in atopic skin. In addition, sphingomyelinase is an enzyme that reduces the number of α-toxin binding sites on the keratinocyte surface, and deficiency in FLG implies decreased sphingomyelinase enzyme activity and increased keratinocyte α-toxin-mediated cytotoxicity.[44]

IL-4 and IL-13 have also been shown to inhibit FLG expression,[9] and therefore a positive feedback pathway can be envisaged in which Th2 cytokines not only provide a permissive environment for *S. aureus*, but also enhance the effects of staphylococcal products. Among these, δ-toxin is a potent inducer of MC degranulation and promotes local inflammation by release of pro-inflammatory mediators by activating MCs. In addition, IgE enhanced δ-toxin-induced MC degranulation in the absence of antigens, and *S. aureus* isolates recovered from AD patients produced high levels of δ-toxin.[22] Staphylococcal superantigens may exacerbate AD by acting as a new group of allergens, since specific IgE to staphylococcal enterotoxin A and B could be detected in the sera of 57% of AD patients, most of whom were identified as carriers of toxigenic *S. aureus* strains.[17] The presence of IgE antibodies to SEB is associated with severe skin lesions quantified by the SCORAD score in adults. Therefore, staphylococcal exotoxins, especially SEB, may exacerbate skin lesions in AD not only in their function as superantigens, but also as a new group of allergens.[45] In patients with asthma and allergic rhinitis, significantly higher levels of blood eosinophils and specific IgE to indoor allergens have been observed, as have higher levels of total IgE in patients with high serum levels of IgE specific to staphylococcal superantigens. Eosinophilic inflammation and IgE production in response to indoor allergens are greater in patients with an IgE response to more than two staphylococcal superantigens. These findings suggest that IgE specific for staphylococcal superantigens may be a risk factor for eosinophilic inflammation and the development of an IgE response to indoor allergens.[46] The *S. aureus* strains from patients with steroid-resistant AD have shown the ability to produce large numbers of different superantigen types per organism. Each superantigen is known to activate only a subset of T cells expressing particular Vβ T cell receptor regions. The net effect of *S. aureus* strains producing a larger number of superantigen types would be to recruit larger numbers of T cells to produce pro-inflammatory cytokines and to induce a wider spectrum of T cells that fail to respond to the immunosuppressive effects of corticosteroids. This process could thus contribute to steroid-resistant AD in some patients.[47] *S. aureus* produces various molecules that can stimulate cells independently of IgE, such as peptidoglycan and lipoproteins.[48] The human innate immune system recognises bacterial lipoproteins through Toll-like receptor (TLR) 2, which forms a heterodimer with either TLR6 or TLR1 for the specific recognition of diacylated or triacylated lipoproteins/lipopeptides, respectively. The *S. aureus*-derived ligands for the TLR2–TLR6 heterodimer could induce expression of TSLP, the master switch for Th2 responses, in keratinocytes, leading to Th2 skewing in the sensitisation to environmental allergens and *S. aureus*-derived allergens through the skin, the exacerbation of AD, or both. Furthermore, TSLP induces invariant natural killer T cells to secrete

IL-4, IL-13, and additional IFN-γ when cocultured with dendritic cells. Therefore, TSLP represents a critical factor linking responses at the interfaces between the body and the environment with allergic Type 2 immune responses.[49]

## CONCLUSIONS

From the above observations it can be inferred that *S. aureus* is not only a coloniser of altered skin, which allows its survival due to genetic and local immunological factors, but is also capable of inducing the maintenance of an environment favourable to its survival via interactions with the cutaneous immune system,[50] e.g. maintaining a low level of AMPs and creating an ecosystem that is almost free from bacteria that could interfere with its growth, such as *S. epidermidis*.[51] Furthermore, the ability to form a biofilm, especially in terms of eccrine ducts due to the local presence of water and salts,[52] makes the eradication of *S. aureus* from the skin difficult. However, this is a necessary condition for breaking the vicious circle of *S. aureus* infection–inflammation–maintenance, and ameliorating the allergic environment leading to Th2 sensitisation. Considering the poor action of systemic antibiotic therapy due to the presence of MRSA, new therapeutic strategies to maintain a reduced cutaneous bacterial load as far as possible could also include, in addition to the constant application of skin barrier repair creams[53] alone or in combination with topical antibiotics,[54] the regular use of bleach baths[55] that reversibly inhibit the expression of CCL2 and superoxide dismutase 2, two NF-κB-dependent genes, in primary human keratinocytes.[56] The difficulty is that the skin is rapidly recolonised by *S. aureus*, the 'opportunist'.

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# NASAL VOLUMETRIC REMODELLING WITH THE AID OF A NEW, STABILISED HYALURONIC ACID DERMAL FILLER

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## ABSTRACT

Dermal fillers around the nose have become particularly popular among patients due to the minimally invasive aspect of these corrections. Nevertheless, the area of interest is particularly vascularised and prone to potentially devastating ischaemic complications. Therefore, technical details are crucial for achieving good aesthetic outcomes in safety. The author presents his experience with the use of a new, stabilised hyaluronic acid dermal filler (Decoria Essence, Bohus BioTech AB, Strömstad, Sweden), as well as the highlights and tips of his technique.

Keywords: Nasal augmentation, rhinofiller, medical rhinoplasty, hyaluronic acid, cannula, technique.

## INTRODUCTION

Medical rhinoplasty was first described by Braccini and Dohan Ehrenfest in 2008.[1] The concept, although highly polemic and refused by rhinoplasty surgeons at its onset, developed exponentially among aesthetic patients due to its minimally invasive characteristics, with minimal or no downtime and pleasing aesthetic improvements. The term 'medical rhinoplasty' or 'rhinofiller' is defined as the application of dermal fillers in the external or internal nasal area to modify or improve aesthetics or functionality. It is especially suitable for patients with minor aesthetic or functional concerns that are refractory to surgery.

The procedure is currently a frequent request in aesthetic practice, and many physicians perform it systematically. Nevertheless, it should be considered that it is an advanced technique and should only be attempted by expert practitioners due to the potential for devastating vascular complications. Local anatomical knowledge and advanced technical skills are required to achieve successful and safe corrections.

## MATERIALS AND METHODS

Private aesthetic patients requesting medical rhinoplasty were recruited on a first-come basis between September 2014 and July 2015. Exclusion criteria included severe nasal airway impairment, permanent filler in the area, history of ischaemic/thrombotic events or known hypercoagulability, local infection, or recent trauma. Nasal analysis was performed clinically and photographically. Areas of potential correction included aesthetic dorsal lines, dorsum, minor hump camouflage, radix enhancement, tip rotation and projection, and base augmentation (Figure 1).

In each case, a morphing simulation was created using a computer program (Crisalix Virtual Aesthetics, 3D software, Swiss Federal Institute of Technology, Lausanne, Switzerland) before treatment in order to give the patients an indication of the post-treatment outcomes, explain the procedure, and establish common goals. In addition, specific, informed consent was properly discussed and obtained.

A new, stabilised hyaluronic acid (HA) filler (Decoria Essence, Bohus BioTech AB, Strömstad, Sweden)

was used for corrections. This new Decoria Proprietary Spherification technology dermal filler enhances performance by combining spherically shaped particles with low levels of crosslinking, in contrast to other HA fillers which are normally composed of rhombus-shaped particles with a high level of crosslinking. The spheres result in a smooth product with high biocompatibility compared with traditional products composed of rhombus-shaped particles. All other parameters are equal, which makes Decoria easy to inject and provides an even result with low levels of immediate reactions and long-term adverse events (AEs), and no oedema which is particularly important in the nasal region. Due to the controlled and narrow size distribution of the particles, Decoria is also a more cohesive product that stays in place compared with so-called 'monophasic' products. The particles are tissue-customised, which means that a specific Decoria product is available for a specific skin depth and indication type.

Treatments were performed under local anaesthetic (lidocaine intradermal vesicles applied using a 0.3 mL syringe with a 32 G needle) with the aid of a 25 G (0.5 mm) × 4 cm blunt-tip, disposable cannula, Tulip GEMS™ SuperLuerLok Injector (Tulip Medical, CA, USA). The cannulae were manually bent, maintaining sterility at all times, in order to obtain a better compliance of shapes and silhouette within the nasal area. The distribution of material was performed as required to follow the treatment plan. Refinements were carried out sporadically in the tip through needle infiltration and with extreme care. The specific pattern of anaesthetic peripheral blocks and filler infiltration is shown in Figure 2.

A satisfaction questionnaire with a 5-point scale was applied at follow-up visits in order to objectivise the outcome and grade it as either: Unsatisfactory, Poor, Average, Satisfactory, or Outstanding.

## RESULTS

A total of 58 patients (38 females and 20 males) were treated between September 2014 and July 2015 in a private-practice setting on a first-come basis. The mean age of patients undergoing correction was 35 years (range: 25–53). A previous rhinoplasty had been performed in 30% of the patients, with the remaining 70% undergoing a primary correction. The aesthetic concerns of the patients undergoing a primary correction were: minor hump and base hypoprojection (65%), asymmetrical dorsal aesthetic lines (15%), nasal anti-ageing (10%), tip correction (5%), and 'other' (5%). The aesthetic concerns of the patients who had a previous rhinoplasty were: dorsum unevenness (40%), dorsum asymmetry (30%), tip defects (20%), and 'other' (10%). The mean product volume used was 0.8 mL (range: 0.6–2.0 mL). A maximum of 1 mL was established per session.

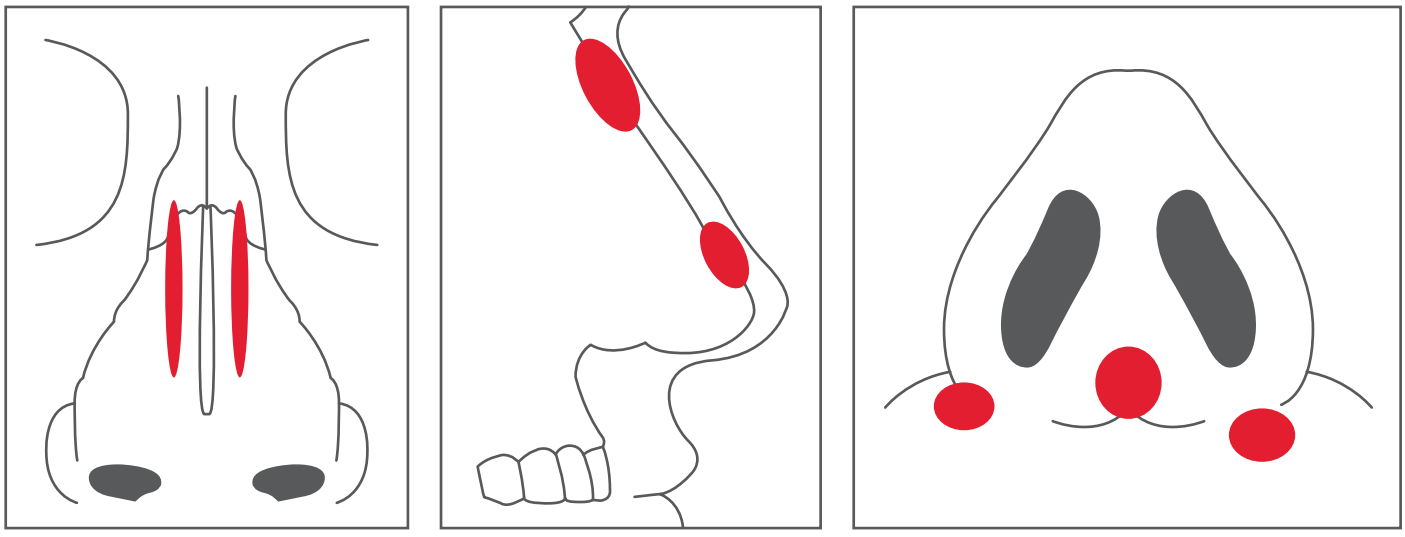


**Figure 1: Nasal areas for potential correction with fillers.**
*Modified from Rohrich RJ et al. (eds.), Dallas Rhinoplasty: Nasal Surgery by the Masters (2014) 3rd edition, Boca Raton: CRC press.*

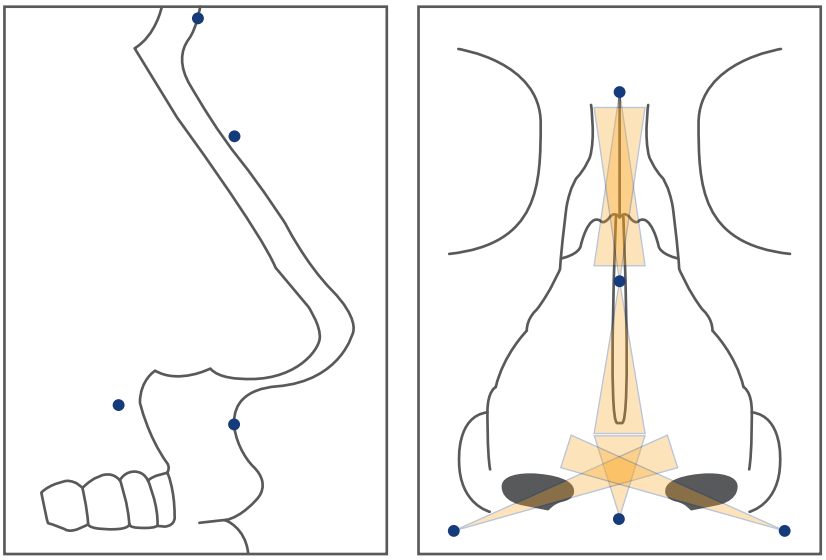

**Figure 2: Anaesthetic peri-spheral vesicles (blue dots) and infiltration patterns (orange triangles).**

If the expected correction was not achieved after one session, further retouches were delayed until a follow-up visit after 15 days.

Objective reduction in dorsal hump, increase in tip projection, and columella labial angle (CLA) was improved in >85% of cases. The mean increase in CLA was 10° (range: 5–15). Follow-up was carried out up to 11 months (range: 3–11). Fewer than 5% of cases required successive corrections in order to maintain aesthetic improvements during the study period. An example of the aesthetic improvement is shown in Figure 3.

The complication rate was low and included haematoma (2%), under-correction (15%), and minor swelling and bruising (10%). The dermal filler showed excellent biocompatibility, with scarce recruitment of fluid after treatments. This fact may be of fundamental importance to avoid indirect vascular compromise and mechanical obstruction. No vascular complications were observed. According to the follow-up evaluation forms, 97% of the patients found the result of their treatment to be either 'Satisfactory' or 'Outstanding'.

## DISCUSSION AND CONCLUSIONS

Rhinofiller is an infiltration of a dermal filler to modify external or internal nasal structures for aesthetic or functional purposes. Since its appearance in 2008,[1] many different temporary[2-5] or permanent[6] substances have been used to achieve the desired corrections. Successful application presupposes an adequate anatomical knowledge of the related structures. The nasal area is comprised of different, interacting tissues, such as the skin, subcutaneous tissues, muscle, bone, cartilage, and mucosa, which come together to form a normal, functional, and aesthetically pleasing nose. To make things more complicated, there is also a vascular anatomy formed by two main circuits: the supratrochlear and dorsal arteries and the facial circuit that includes the superior labial and angular artery, all of which must be anastomosed in the tip. This has been the subject of recent interest and study because it is believed that a proper technique and anatomical knowledge is of prime importance in order to avoid vascular complications.[7-9]

Facial vascular complications were first described in 1991 after collagen injections in the glabellar area.[10] The reported incidence of 'Nicolau syndrome' or embolia cutis medicamentosa (ECM) following glabellar treatments is 9/10,000 procedures (0.09%). The known risk factors associated with this catastrophic event are: a high syringe-piston pressure, a highly vascularised territory, and previously traumatised tissue. The first of these factors can be mitigated using fluid materials with low viscosity. Unfortunately, the entire facial region, and especially the nasal area, is considered highly vascularised and many reports of paranasal vascular complications have been published, which vary from mild symptoms of pain and skin-colour changes to necrosis and even bilateral blindness.[11-19] The pathophysiology of

ECM is an intravascular injection that advances in a retrograde mode to a distant area and, through changes in blood pressure, arrives at a distant vessel and causes a vascular complication. The resulting symptoms vary according to the physiology of the vessel that is compromised: affliction of arteries leads to pallor whereas occlusion of veins manifests as livedo reticularis.

According to the author's experience, there is a second mechanism of vascular compromise in the nose known as 'compartmental syndrome'. Due to the low elasticity of the nasal skin (especially after surgical rhinoplasty), there is a chance of producing indirect vascular compromise due to mechanical obstruction when large amounts of filler are positioned, even in the absence of intravascular injection. The former, together with the altered anatomy and possible iatrogenic vascular damage, make these corrections particularly tricky in this patient setting.

Vascular complications can range from mild to severe and therefore prompt recognition and treatment are crucial. Oral aspirin, nitrate creams 2%, heat, massages, and intralesional hyaluronidase have all been proven to be beneficial.[20] The author has also used intralesional heparin mesotherapy with good results (unpublished observations). In severe, unresponsive cases, prostaglandin E1 (alprostadil) treatment can sometimes limit the extent of the damage.[21] For remaining scar tissue, occasionally complex reconstruction procedures are necessary,[22,23] although the recent use of stem cells has shown promising results.[24]

All of the above have determined nasal augmentation with dermal fillers to be particularly challenging, and mastery of the correct technique is of the utmost importance in order to achieve good results and reduce the incidence of adverse reactions. Important factors to consider include:

- Patient selection: proper patient selection is vital in order to achieve a good outcome. Rule out individuals with unrealistic expectations and treat post-rhinoplasty patients with extreme care.
- Material: a good technique begins with selection of the correct material. Only temporary or autologous materials (fat) should be used in the nose. Among temporary materials, HA is the best option because it causes no fibrotic changes in the subcutaneous tissue, such as those which can occur with calcium hydroxyapatite. Moderate-viscosity HA is preferred due to a lower piston pressure in the syringe. In the present study, Decoria Essence proved to be a good product for nasal augmentation in terms of aesthetic improvement, patient compliance, biocompatibility, and durability.

**Figure 3: Lateral view before and after treatment.**

- Correct amount of material: never exceed the correct quantity of filler used in the nose. It is always better to under-correct and then repeat as needed. A good safety measure is to stay within 1 mL of filler per session. Remember that the pressure of the material can induce vascular problems even without being intravascular. Place the fingers to position and maintain the product in the target area to avoid migration. Small amounts of material should be placed using low infiltrative pressure and few passes in a retrograde infiltration mode.
- Cryotherapy: it is always wise to favour vasoconstriction in order to limit bruising and oedema and reduce intravascular compromise.
- Cannulae, manually curved. The use of atraumatic cannulae permits gentle dissection of the tissues, reduces the trauma and risks of intravascular injection, and delivers the material through a laminar flux that guarantees evenness. The manually curved feature allows for perfect shape compatibility with the nose dorsum. The use of local anaesthetic vesicles and needle skin penetration prior to cannula entry limits pain, trauma, and vascular compromise.
- Needles: extreme caution should be used when injecting with needles around the nose; their use should be limited to retouches or refinements and only by very experienced physicians. Perform tunnels (visible entry and exit points created with the needle being used) and allow material exit if needed. The most risky areas are the tip, glabella, canine fossa, and columellar base. Avoid bolus techniques in these regions and inject only when 'coming out'. It is preferable to use medium-sized needles and inject into the deep or intermediate plane. Prior aspiration is not useful.
- Improve, do not cancel or attempt a perfect outcome: this technique should be considered part of the armamentarium of every aesthetic surgeon, but not used as a single instrument. Whenever we want to completely correct a surgical deformity with fillers we get into excess and possible complications.
- Planning and discussion of potential complications is essential (proper informed consent): very frequently, patients are ill-informed about this procedure and have often read that it is extremely easy and free of risks. Establish a good relationship based on truth and trust with your patient. Morphing software can be of great help in this phase to help communicate with patients and establish common goals. Under-promise and over-deliver.
- Analyse CLA: analysis of this feature allows objectivisation of the outcome and even the most critical patients will potentially be able to appreciate the improvement.
- Available kit for potential ECM: If you intend to treat the nose with dermal fillers, you should be prepared to handle the complications as well.

The use of dermal fillers around the nose, although an advanced technique with potentially severe AEs, is a powerful tool that can be used with a great deal of satisfaction and safety for the benefit of patients who wish to achieve aesthetic or functional improvements without a surgical procedure. The risks and benefits should always be considered and discussed, and complications should be prevented and promptly treated if necessary.

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# NEW DERMATOLOGICAL INDICATIONS FOR PULSED DYE LASERS

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## ABSTRACT

Laser therapy has been classically focussed on three different chromophores: haemoglobin, melanin, and water, based on selective photothermolysis theory. Despite the fact that therapy is evolving with the introduction of multiple new wavelengths and the description of more therapeutic targets, some laser devices, such as the pulsed dye laser (PDL), are still relevant in our clinical practice. Based on a redefined concept of selective photothermolysis, PDL seems to be a promising tool for the treatment of skin conditions different to vascular lesions. Its role in viral infections, inflammatory diseases (such as acne or systemic lupus erythematosus), scars, and basal cell carcinoma is reviewed in this paper.

Keywords: Selective photothermolysis, pulsed dye laser (PDL), vascular laser, chromophore.

## INTRODUCTION

For years, dermatological laser therapy has targeted three classical chromophores (haemoglobin, melanin, and water) that have allowed the removal of hair follicles as well as the successful treatment of acne scars, some signs of skin ageing, and various vascular and pigmented lesions.[1] Although therapy is evolving with the acquisition of multiple new wavelengths and the description of further therapeutic targets, laser devices such as the pulsed dye laser (PDL) are still present in our clinical practice. Moreover, their role is even more relevant due to the increase in therapeutic indications.

The classical concept of selective photothermolysis[2] establishes the relationship between one tissue target and a fixed wavelength and pulse duration. This theory implies a single correspondence between a laser device and a medical indication. The tissue effect of lasers is well understood. On the one hand, the specific thermal effect on the target chromophore allows for the treatment of vascular lesions with PDL, or achieves hair removal with melanin-absorbed long pulsed lasers. On the other hand, lasers with very short pulses and high energy reach a specific mechanical effect on the target, such as Q-switched lasers for tattoo removal.[3]

Nowadays, the classical theory of selective photothermolysis has been redefined, because one laser target can be applied in multiple indications.[1] Pulse durations are changing, and longer pulses are used in order to target larger structures and to preserve the epidermis. The multi-pass technique (also called 'pulse stacking')[4] enables a greater target destruction, thus preserving laser selectivity. With pulse stacking, two or three pulses are applied to the same cutaneous area immediately after the preceding pulse. Cumulative heating may result in greater overall capillary heating and vessel damage than is achievable from a single high-energy pulse. Epidermis thermal relaxation time is shorter than that of dermal capillaries, and pulse stacking is able to apply cumulative heating to the dermal capillaries, allowing epidermal cooling between pulses.[5]

Larger spot diameters are also available, thus allowing deeper penetration and less scattering. Cooling systems play an important role in our daily practice because they are essential in protecting the epidermis during laser treatment.[6] It is also interesting to highlight the photoinduced modulation of biological functions triggered by lasers: cytokine activation, collagen remodelling, growth factor release, activation of

inflammatory cells, and effects on microvasculature and angiogenesis.[7]

In 1966, Fritz P. Schäfer discovered the dye laser.[3] Since then, PDLs are routinely used in dermatology for the treatment of vascular malformations due to their high haemoglobin absorption.[8] Over time, and according to the redefined concept of selective photothermolysis, the number of PDL indications has grown in a noteworthy manner.[9]

## PULSED DYE LASER IN NON-VASCULAR LESIONS

### Viral Infections

In the case of viral warts, the PDL mechanism of action is based on laser interaction with wart vasculature and the thermal injury to human papillomavirus.[9-11] It has also been postulated that the resulting tissue damage is followed by a cell-mediated immune response with upregulation of lesional interleukins 2 and 4. It is well known that both play a role in the fight against viral infections.[11]

There are numerous reports in the literature of different treatment protocols and a variable rate of success.[9] In 2008, Park and Choi[10] described a case series of 120 patients with viral warts treated with PDL. Fluences between 9 and 9.5 J/cm$^2$ and short pulses were used. The treatment was performed every 2 weeks with an overall clearance rate of 49.5% and a better response in flat and periungual warts. Most patients experienced tolerable, minimal-to-mild pain, whereas crusting, scarring, or pigment changes were not significant. A recent article from Sparreboom et al.[11] evaluated the effect of PDL at higher fluences (12.5–15.0 J/cm$^2$). A retrospective study of 227 patients was performed, which represents the largest report available in the literature with respect to PDL treatment for recalcitrant viral warts. Despite its retrospective nature, the overall efficacy reported in the study was 86%. The authors conclude that PDL therapy is an effective and safe second-line treatment for recalcitrant viral warts.

In our experience, PDL represents an excellent treatment option for recalcitrant warts, and we employ high fluences as has been previously described (Figure 1).

Facial flat warts have also shown a good clinical response to PDL treatment. They are not only a contagious viral disease, but also a cause of distressing cosmetic problems. Their management can represent a therapeutic challenge because no monotherapy has been proven to achieve complete remission in every case. In our experience, treatment with PDL seems to be a promising therapeutic option. We performed a prospective study in 32 patients who were treated with PDL at a wavelength of 595 nm, a laser energy density of 9 or 14 J/cm$^2$ with a spot size of 7 or 5 mm, respectively, with a pre-cooled airflow skin cooling system at its highest setting and a pulse duration of 0.5 milliseconds. A complete response was noted in 44% of patients and an excellent response was observed in 56% of cases with 1-year follow-up. Only four cases of recurrence were observed. No significant side effects were reported, except intense temporary purpuric response.[12]

In the case of molluscum contagiosum,[9,13,14] this poxvirus infection has also been treated with PDL in a satisfactory way. Although spontaneous regression of this condition has led to proposals to leave lesions to spontaneous resolution, sometimes the infection is recurrent and widespread. The mechanism of action is attributed to vascular damage and a nonspecific thermal effect, with an increase in mast cells and T lymphocytes also involved. Isolated case reports in immunosuppressed patients are described in the literature, and the largest case series to date includes 76 patients.[14] The authors employed 585 nm collagen remodelling, double flashlamp excited pumped dye laser (ED2000®, Deka MELA, Calenzano, Italy) with the following parameters: spot size 5 mm, fluence 2–4 J/cm$^2$, with a short pulse duration of 250 microseconds in all cases. At higher fluences (3.5–4.0 J/cm$^2$), the success rate reached 98%. This response was seen with one or two treatments and no relevant adverse events were described (in most cases transient hyperpigmentation was present after treatment). PDL collagen remodelling was used due to better tolerance (due to a shorter pulse duration) and because it uses lower fluences, thus enabling the treatment of paediatric patients with a large number of lesions.

In our practice, conventional PDL treatment is also effective in treating molluscum contagiosum infection. Although it is more expensive than conventional treatments, it is a good alternative for the management of difficult areas, such as the periocular region (Figure 2).

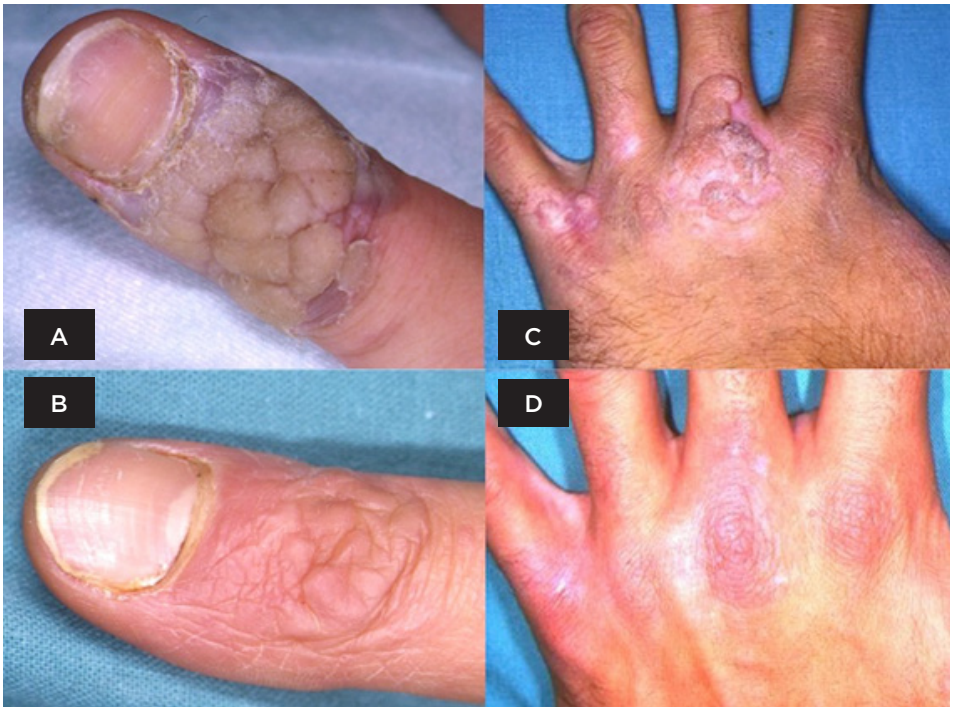


**Figure 1: Pulsed dye laser (PDL) treatment for recalcitrant viral warts.**
A) Pre-treatment image: a 25-year-old man presented with periungual viral warts resistant to multiple topical treatments. B) Complete resolution after three treatments with PDL (fluence: 12 J/cm$^2$, pulse duration: 1.5 ms, pulse diameter: 7 mm, pulse stacking: 3). C) Pre-treatment image: a 30-year-old man presented with painful and recalcitrant viral warts on the dorsal aspect of left hand. D) Complete resolution after two treatments with PDL (fluence: 13 J/cm$^2$, pulse duration: 1.5 ms, pulse diameter: 7 mm, pulse stacking: 5).

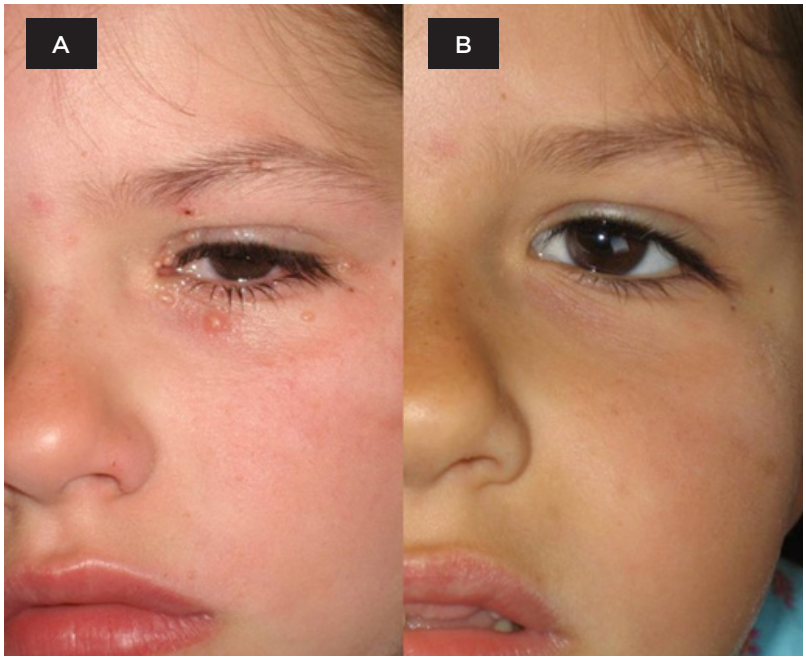


**Figure 2: Molluscum contagiosum treated with pulsed dye laser (PDL).**
A) Pre-treatment image: a 4-year-old boy presented with multiple palpebral molluscum contagiosum. B) Excellent cosmetic result after one treatment with PDL (fluence: 7 J/cm$^2$, pulse duration: 0.5 ms, pulse diameter: 7 mm) associated with ocular protection.

## Acne Vulgaris

Acne is one of the most prevalent human skin conditions. Conventional topical treatments (retinoids, antimicrobials, and anti-inflammatory agents) are sometimes associated with skin irritation, and conventional oral medications (oral contraceptives, antibiotics, and retinoids) may be associated with adverse effects such as gastrointestinal discomfort, antibiotic resistance, birth defects, and thromboembolic events.[15] Therefore, physical approaches are sometimes applied.[9,15,16] Although recent, prospective randomised trials have shown satisfactory results in acne treatment based on selective photothermolysis of sebaceous follicles and topical gold microparticles,[17] conventional PDL may also be employed with promising results.[9,15,16] Although PDL effectiveness has been associated with *Propionibacterium acnes* selectivity,[15,16] upregulation of transforming growth factor-beta may explain the highly potent immunosuppressive response in acne.[18] As subpurpuric doses are employed, it is well tolerated with mildly adverse effects. Combined physical treatments have demonstrated better results than employing PDL alone.[15,16] Both PDL and 1450 nm diode lasers have shown improvements with no significant adverse events in mild-to-moderate inflammatory acne.[16] Moreover, PDL-assisted photodynamic therapy with methyl aminolevulinic acid is slightly superior to PDL for the treatment of inflammatory acne. Non-inflammatory lesions show a similar reduction with both treatment options.[15]

## Systemic Lupus Erythematosus

Although systemic lupus erythematosus (SLE) is associated with cutaneous photosensitivity, the pathogenesis may be linked to ultraviolet-mediated cell apoptosis and chemokine, cytokine, and cellular adhesion molecule-dependent events.[19] There have been no reports to date of the use of lasers in the ultraviolet A or B spectra, due to their recognised photosensitising effect in SLE. However, there are 14 reports of the use of lasers with wavelengths in the visible light spectrum (PDL, argon, and intense pulsed light), with good tolerance. This supports the hypothesis that monochromatic laser light is unlikely to be photosensitising in SLE and may be a safe and effective treatment option in some patients, as suggested by various groups.[19-23]

To date, PDL has been used in eight studies with varying degrees of improvement and no remarkable permanent adverse events.[20] In a retrospective study by our group,[21] 14 patients with different forms of SLE were treated with a dye laser and obtained a clearance rate of >60%. The telangiectasic component related to SLE showed an excellent improvement (Figures 3a and 3b). We also obtained good results with the erythematosus component in discoid SLE (Figures 3c and 3d). Telangiectasias and chronic erythema improvement is based on the selective photothermolytic ablation of the dilated capillaries and venules. Ten lupus tumidus patients were also treated with PDL in a prospective study with excellent response.[22] Post-laser purpura seems to be necessary in order to achieve clinical improvement. However, PDL treatment does not prevent recurrences. The aforementioned improvement is also accompanied by a reduction of the dermal lymphocytic infiltrate and disappearance of mucin deposition. Post-laser immunohistological changes of cutaneous SLE have been described in another prospective study by our group.[23]

## Psoriasis

Laser treatment for psoriasis has been studied since the 1980s, with the carbon dioxide ablative laser, the helium–neon laser, and red light photodynamic therapy.[24] Vascular lasers could be effective in psoriasis treatment by targeting the papillary dermal vasculature and allowing a reduction in epidermal thickness.[25] Although the excimer laser seems to be more effective in localised chronic plaque psoriasis treatment,[24] Grade B[26] recommendation has been proposed based on several studies. No solid conclusion could be drawn for the treatment of nail psoriasis with PDL.[27]

## Hypertrophic Scars and Keloids

Hypertrophic scars and keloids develop as a result of an exaggerated proliferation of dermal fibroblasts and an excess accumulation of collagen following skin injury. Consensus literature is absent regarding the best treatment approach.[28]

Several studies have demonstrated PDL effectiveness in improving the colour, vascularity, height, texture, and pliability of scars.[29] The mechanism by which PDL improves hypertrophic and keloid scars is not yet known. Selective destruction of small vessels, either directly through heat collagenolysis or indirectly through impaired cellular function, has been proposed.[30] Early treatment, starting at the date of suture

removal, has demonstrated improvement in scar appearance.[29] A recently published prospective study by Gladsjo and Jiang[30] concluded that non-purpuric PDL settings lead to significant improvement in the appearance of fresh surgical scars in terms of vascularity, pliability, and Vancouver Scar Scale total scores. This assessment differs from that of many clinicians, who believe that inducing purpura results in better and quicker scar improvement.

## Superficial Pigmented Lesions (Lentigines)

Q-switched Alexandrite is the standard laser treatment for superficial pigmented lesions due to its mechanical effect. Although wavelength of 595 nm has been the standard of treatment for many vascular lesions, it is also well absorbed by melanin.[31-33] This feature can be employed to treat pigmented lesions with PDL when other laser devices are not available. Garden et al.[31] designed a prospective study using a modified PDL device with a compression handpiece and no epidermal cooling. Clearance of up to 79% was observed after four monthly treatments. The meniscus compression element displaces the blood away from the irradiated field, resulting in elimination of postprocedural purpura. It is therefore possible to avoid purpura if PDL is used with compression. Similar results have been described in the literature.[31,32]

## Basal Cell Carcinoma

Several reports have shown the effectiveness of PDL for the treatment of basal cell carcinoma.[34-39]

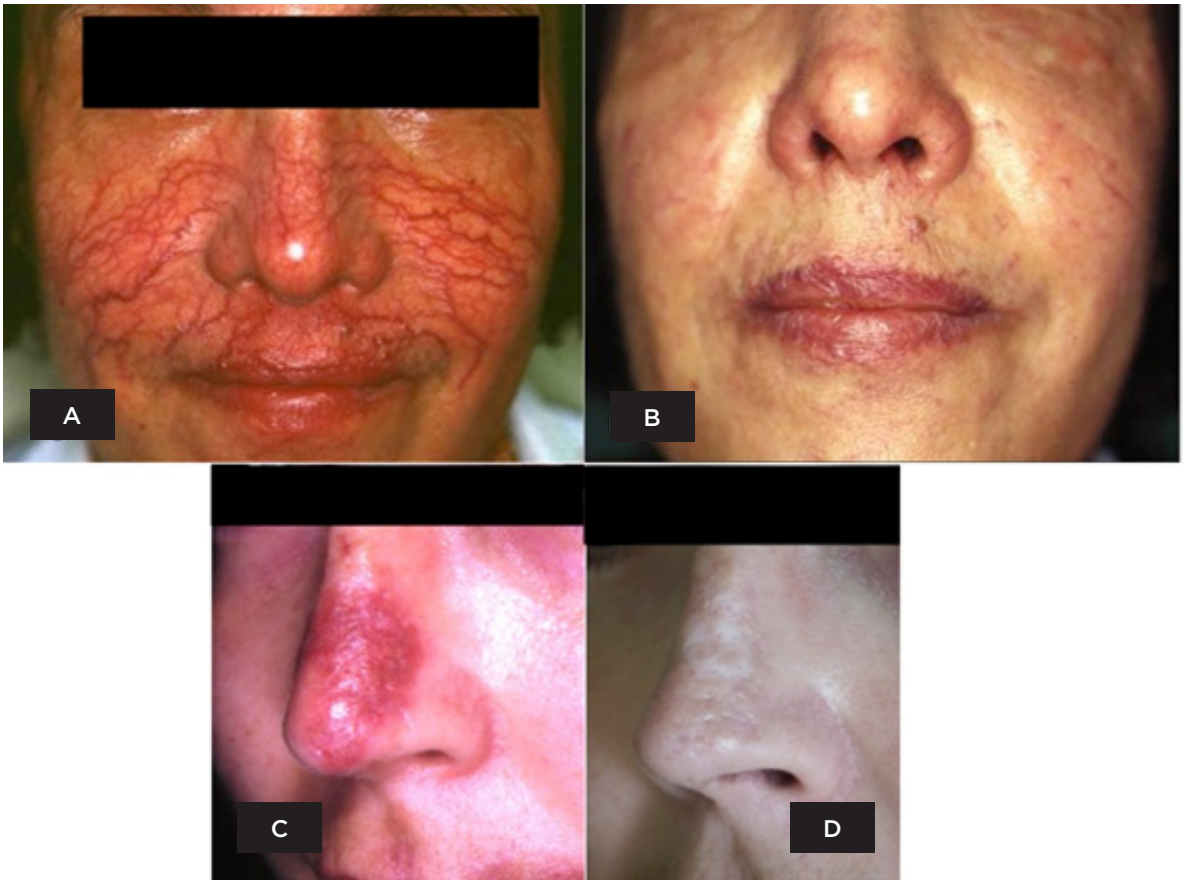


**Figure 3: Pulsed dye laser (PDL) treatment for systemic lupus erythematosus.**
A) Pre-treatment image: a 62-year-old woman with telangiectatic and erythematous facial lesions due to systemic lupus erythematosus. B) Good response after four treatments with PDL (fluence: 7 J/cm$^2$, pulse duration: 0.5 ms, pulse diameter: 7 mm). Throughout the treatment, a pre-cooled airflow skin cooling system (Cryo5©, Zimmer Medizinsysteme GmbH, Neu-Ulm, Germany) was used at its highest setting. C) Pre-treatment image: a 36-year-old woman presented with systemic lupus erythematosus nasal plaque resistant to topical steroids. D) Complete response and discrete hypopigmentation after three sessions of PDL (fluence: 8 J/cm$^2$, pulse duration: 0.5 ms, pulse diameter: 7 mm). The patient reported a high satisfaction.

Most studies have included low-risk basal cell carcinomas (BCCs) and an important limitation has been the lack of histological confirmation of the treatment results.[34,36] Although the exact mechanism of action of using PDL to treat BCC is unclear, the main hypothesis is that PDL has an antiangiogenic effect.[37] BCCs have been shown to utilise a specialised tumour-associated microvasculature for growth.[39] A prospective study developed by our group was performed in order to assess the effectiveness of PDL in high-risk BCCs with complete histological evaluation with Mohs micrographic surgery (MMS).[37] Seven patients with high-risk BCCs located on the face were included. All tumours were treated with three sessions of PDL at 4-week intervals. Apparent complete clinical response was achieved in five of the seven patients. Finally, MMS was performed in six patients, and clear margins were achieved after one stage of MMS. The histological evaluation of the tumour debulking specimens showed complete clearance in four of six cases. One patient who did not undergo MMS showed a recurrence after 14 months. This study demonstrates that PDL can be effective for the treatment of high-risk BCCs. Nevertheless, until further scientific evidence is available, treatment of high-risk BCCs should include histological confirmation of clearance. Although more evidence is needed, PDL treatment of BCC could be an interesting therapeutic option in older patients who are not able to undergo surgery.

Others conditions such as sarcoidosis,[40] dermatomyositis,[41] keratosis pilaris atrophicans,[42] sebaceous hyperplasia,[43] and angiolymphoid hyperplasia with eosinophilia[44] have also been treated with PDL in case reports and small case series, achieving promising results.

## CONCLUSION

Scientific and technical advances in laser therapy are gradually making their way into the routine practice of dermatologists. New wavelengths and therapeutic targets are promising tools for the treatment of challenging diseases. Nevertheless, PDL is still present in our clinical practice. Due to the redefined concept of selective photothermolysis, PDL seems to be a promising tool in the treatment of skin conditions different to vascular lesions: viral infections, inflammatory diseases, and tumoural diseases. Prospective studies with a large number of cases are needed in order to establish which are the optimal laser parameters.

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# ACNE TREATMENTS
# ACNELAN: AN ACNE SOLUTION BY MESOESTETIC®.
## A NON-INVASIVE ALTERNATIVE WITH PROVEN EFFICACY TO TOPICAL MEDICATIONS, ORAL ANTIBIOTICS AND CONTRACEPTIVES


Acne usually begins in adolescence, but the condition is not limited to any age group. According to an article in BMJ (*British Medical Journal*), nearly 90% of teenagers are affected by acne and approximately 50% of them continue to experience symptoms as adults.

Nowadays acne is often treated with topical application of medications, oral antibiotics, retinoids, benzoyl peroxide or oral contraceptives, which tend to have side effects.

mesoestetic Pharma Group, one of the leading pharmaceutical laboratories specialising in the field of dermatology and cosmetic medicine, has launched **acnelan**, an effective and innovative alternative for medical use in the treatment of acne-prone and seborrhoeic skin.

Ever since it was created in 1984, mesoestetic Pharma Group has been committed to applying innovative technology and ongoing efforts in R&D to provide effective solutions to patients' needs, with a particular focus on projects for the prevention and treatment of dermatological diseases. The fruit of this firm commitment is the development of **acnelan** in collaboration with a leading group of dermatologists who participated in the selection of active substances, the design and validation of application guidelines, and who carried out experimental studies on the formulations. This is a successful joint project that guarantees the highest efficacy, safety, and quality of the line.

### A Global Method: Intensive Professional Treatment Combined with a Home Maintenance Line

Given the different aetiology of acne-prone skin as well as its physical and emotional implications,

perseverance through treatment is extremely important. Therefore mesoestetic has developed an topical method that combines an intensive professional treatment and a comprehensive range of home maintenance products. The homecare line has been specifically designed as a convenient and efficient way of maintaining the effects of the professional treatment and includes: A daily cleansing foam, a daily cream with an overall multifocal effect and a purifying, descaling face mask for weekly use. A topical focal treatment will shortly be added to the range.

## Multifactorial Control

There is a clear unmet need for acne patients. The hormonal origin and multifactorial aetiology base of this condition hinders optimal control of its manifestations. This is why a cross-cutting approach is considered essential to therapeutic success. Reducing its manifestations can have exceptionally positive emotional consequences for sufferers, particularly adolescents, and can prevent permanent damage caused by the disease.

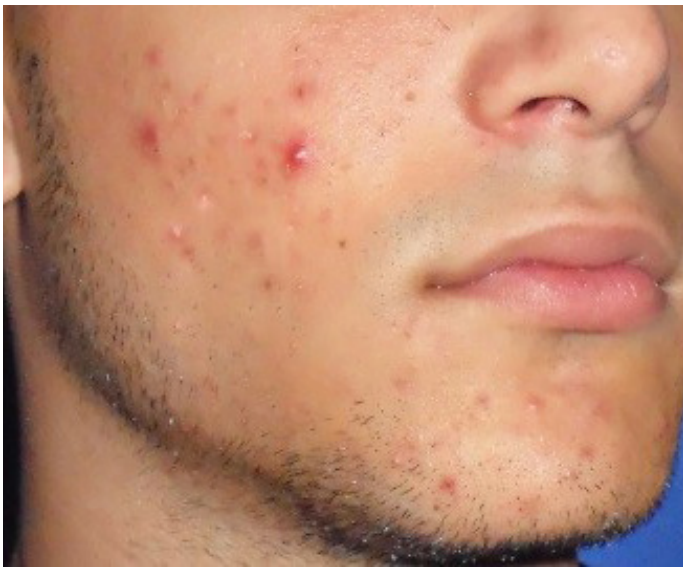
Acne solution by mesoestetic is a multifocal treatment that addresses the different factors that affect acne-prone skin simultaneously. At the heart of **acnelan** formulation is m.acne complex™, a unique combination of active ingredients selected specifically for their complementary properties. These include salicylic acid, mandelic acid, shikimic acid and sodium lepargylate which, in combination with the exclusive bexaretinyl complex, perfectly cleanse and renew acne-prone and seborrhoeic skin.

## Proven Efficacy Demonstrated by Clinic Studies

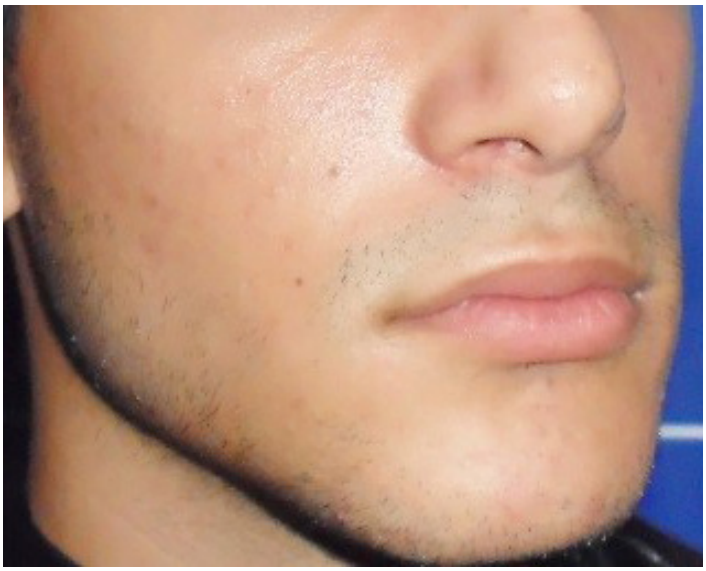
Between July 2014 and May 2015, clinical studies were conducted to demonstrate the efficiency and safety of the method. The clinical studies have been conducted in multiple centres on volunteers with acne-prone skin, who were treated with the intensive professional treatment in combination with the home care products.

Dr Manuel Asín, president of one of the cosmetic dermatology centres that participated in the study, and a member of the American Academy of Dermatology (AAD) declared: "*This new method provided 'good' to 'excellent' progressive and long lasting results in most of the different types of acne treated.*"

To see the study's results **click here** or on the pictures below:



BEFORE



AFTER

Pictures taken before and after 3 sessions with the acnelan method.

# Buyer's Guide

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- ADAMO SRL
- ADVALIGHT
- ALMA LASERS
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- ASCLEPION LASER TECHNOLOGIES
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- DAEJU MEDITECH ENGINEERING - INFILUX
- DANA
- DEKA
- DELEO
- DERMA MEDICAL SYSTEMS
- DERMACEUTIC
- DERMALUMICS S.L.
- DERMAPENWORLD-EQUIPMED
- DERMOFARM
- DERMOSCAN GMBH
- DINO-LITE EUROPE
- DR. HOENLE MEDIZINTECHNIK GMBH
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- ELI LILLY
- ELLIPSE A/S
- ENERGIST MEDICAL GROUP
- EPGONLINE.ORG
- EUNSUNG GLOBAL CORP.
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- FOTOFINDER SYSTEMS GMBH
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- GCT GMBH
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- GLOBAL MEDICS
- GME GMBH
- GUNA S.P.A.
- H&O EQUIPMENTS SA
- HEINE OPTOTECHNIK GMBH & CO., KG
- HIRONIC
- HYDRAFACIAL MD-EDGE SYSTEMS
- IFC GROUP
- ILOODA
- INTERNATIONAL PSORIASIS COUNCIL

# Dermatology

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- ISISPHARMA
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- VISIOMED AG
- WALDMANN - MEDICAL DIVISION
- ZELTIQ
- ZIMMER AESTHETIC DIVISION

# UPCOMING EVENTS

## German Society of Dermatology (DDG) Compact 2016

*26th–27th February 2016*

*Leipzig, Germany*

Continuing the concept of a time-saving way to exchange knowledge, the German Society of Dermatology's 'compact' meeting is returning this year with the theme: 'Skin in Old Age'. A plethora of topics will be discussed, from non-dermatological issues about the psychology and societal effects of ageing, to specialist topics in dermatology, such as aesthetics of ageing skin, UV protection, and oncology in older people.

## American Academy of Dermatology 74th Annual Meeting

*4th–8th March 2016*

*Washington, D.C., USA*

As the world's largest dermatology meeting, this is an unrivalled event. Offering exciting educational sessions on the latest news in dermatology, each attendee will be able to expand their knowledge and refine their skills. Acne, dermatitis, melanoma, and pigmentary disorders are just a few of the many topics that will be discussed. Hundreds of exhibitors will also be displaying their most up-to-date products and services on the exhaustive exhibit floor.

## 13th EADV Spring Symposium

*19th–22nd May 2016*

*Athens, Greece*

Athens, the most ancient of academic cities, will play host to the EADV Spring Symposium in 2016. Covering all areas of dermatology and venereology, the scientific programme will be presented by prominent experts in the field and promises to include the most topical treatment modalities developed in accordance with rapidly evolving medical technologies. From reviews and updates to training and education forums, this will be a comprehensive and rewarding event.

## 13th Congress of the European Society for Pediatric Dermatology

*26th–28th May 2016*

*Paris, France*

This congress aims to foster a diverse and rich environment in which a wide range of highly qualified dermatological and paediatric specialists, researchers, and paramedics will partake in and contribute to the exchange of knowledge and expertise. All of the basic and clinical research advances in paediatric dermatology will be discussed, with the practical benefits for patients and their families forming the focus of the meeting.

## 96th Annual Meeting of the British Association of Dermatologists

*5th–7th July 2016*

*Birmingham, UK*

The British Association of Dermatologists promotes 'healthy skin for all', and their historic annual meeting will be an event to help further this ambition. Alongside a varied scientific programme including poster presentations and guest lectures from international experts, there is a warm social programme to facilitate networking. This will include the Annual Dinner, a magnificent affair to welcome members and non-members alike.

## 16th World Congress on Cancers of the Skin® and 12th Congress of the European Association of Dermato-Oncology

*31st August–3rd September 2016*

*Vienna, Austria*

For scientists and clinicians working in the fields of melanoma and non-melanoma skin cancer, as well as lymphoma and rare skin tumours, this is considered to be one of the most important events of the year. The unique joint meeting will be comprised of talks on the prevention, recognition, and treatment of cutaneous malignancies in these specified areas, and will be presented by leading investigators in this challenging yet critical area of medicine.

## 13th Congress of the European Society of Contact Dermatitis

*14th–17th September 2016*

*Manchester, UK*

On top of inspiring lectures and presentations on the topic of contact dermatitis, there are several valuable awards available at this congress. The coveted Jan Wahlberg Prize will be presented to a young researcher in the field who provides work that has been published, or submitted for publishing, in the last 2 years. Five travel grants are also available for junior researchers who submit an abstract to the congress.

## 25th EADV Congress 2016

*28th September–2nd October 2016*

*Vienna, Austria*

Following the outstanding 24th EADV Congress, which brought a wealth of groundbreaking news and updates to the field, we at EMJ are already looking forward to 2016's meeting. This time held in Vienna, the stunning capital of Austria, the congress is fully expected to be a comprehensive event that will yet again offer the most up-to-date advancements in the world of dermatology and venereology. The extensive programme, which includes plenary lectures, educational classes, review and update sessions, and much more, has already been planned by the meticulous organisers, and the call for abstracts is imminent. This illustrious occasion to learn, share knowledge, and network is certainly not one to be missed by anyone involved in this expanding field of medicine.