EMJ EUROPEAN MEDICAL JOURNAL

# DERMATOLOGY

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## INSIDE

Review of

**EADV 2013**

Istanbul, Turkey

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ISSN 2054-6211 — December 2013 • emjreviews.com

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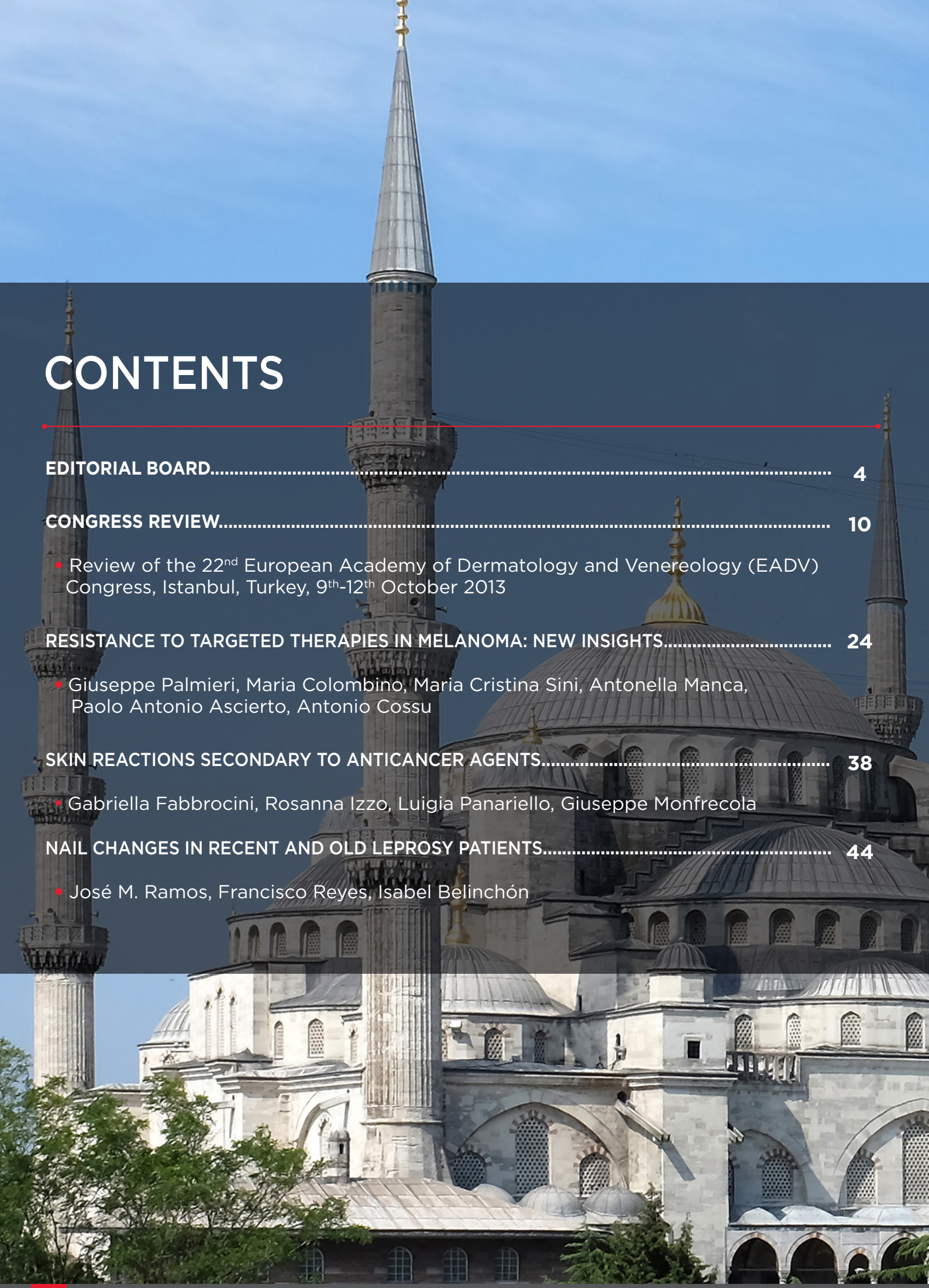

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# DERMATOLOGY

EMJ GORELY NEW MEDIA

*European Medical Journal*
Dermatology - December 2013



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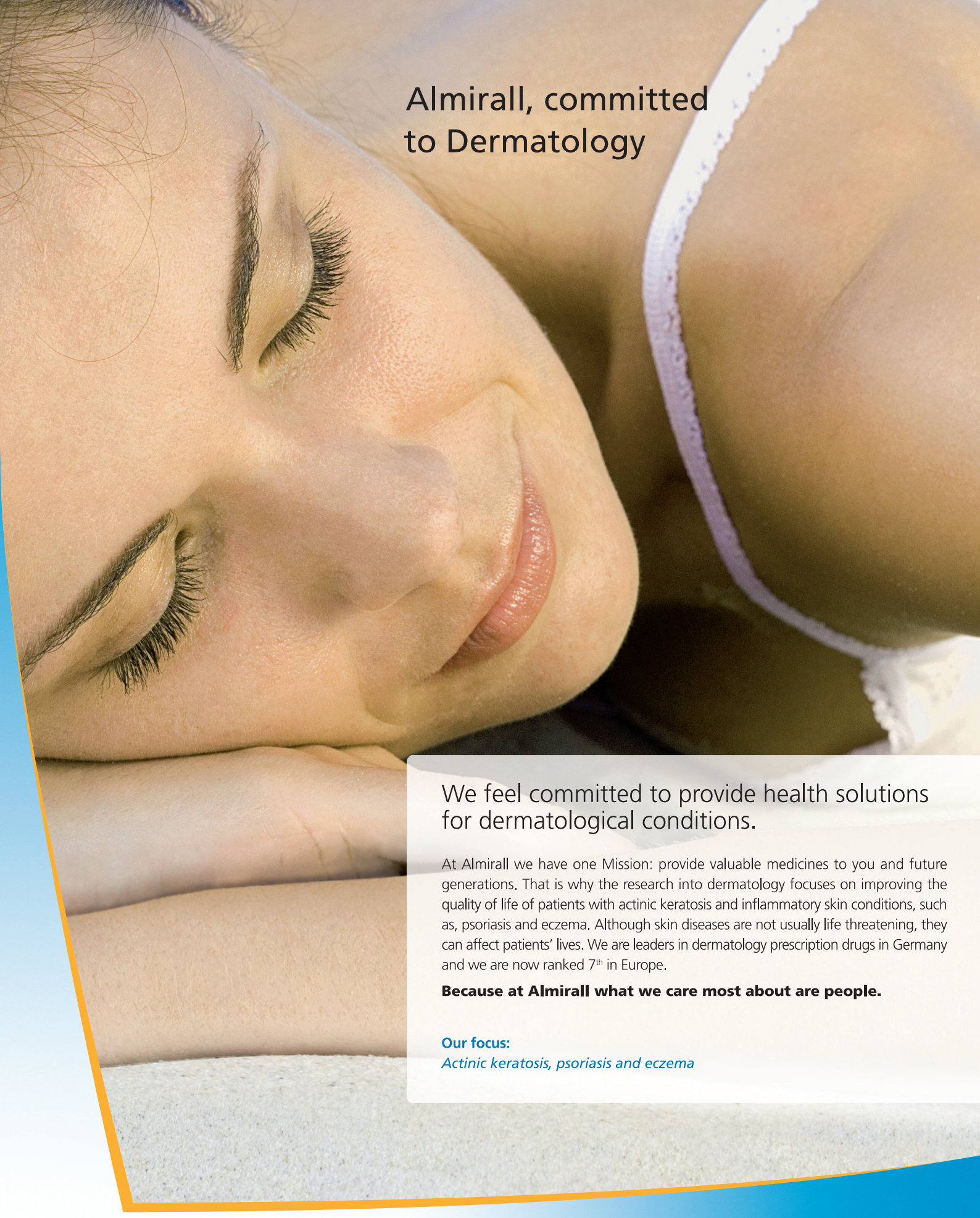

# Almirall, committed to Dermatology

## We feel committed to provide health solutions for dermatological conditions.

At Almirall we have one Mission: provide valuable medicines to you and future generations. That is why the research into dermatology focuses on improving the quality of life of patients with actinic keratosis and inflammatory skin conditions, such as, psoriasis and eczema. Although skin diseases are not usually life threatening, they can affect patients' lives. We are leaders in dermatology prescription drugs in Germany and we are now ranked 7th in Europe.

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# Welcome


## Kelly-Ann Lazarus

*Editor, European Medical Journal*


I would like to wish you a warm welcome to the inaugural edition of *EMJ – Dermatology*, featuring the latest updates on diagnosis and treatments for dermatological conditions, and a review of the EADV Congress 2013, held in Istanbul, Turkey.

This 22nd annual meeting hosted by the European Academy of Dermatology and Venereology focused on aesthetic dermatology and centred around the motto of 'dermatovenereology in a changing world'. Tattoos and ageing skin were popular topics of research over the past year. Tattoo complications have become a sub-specialty for dermatologists, with EADV and the European Society of Tattoo and Pigment Research joining together to address major problems and propose solutions to EU institutions, regulators and professionals. Dermatologists are now taking a more holistic approach to combat the signs of ageing skin by combining less invasive and systematic treatments, such as oral supplements.

New technologies were also showcased at the meeting, for example a new method developed to detect skin cancer - automated body mapping (ATBM) - only takes 3 minutes, is easy to use and produces images to support dermatologists as well as patients. Also the first non-surgical method for reduction of 'double chin' (unwanted submental fat) by use of ATX-101 was presented with results from patients who felt much happier with the results than those who underwent surgery.

An exciting collection of articles is also included in this publication; one example features an insight into the severe nail conditions that occur in leprosy, which are often omitted from dermatological assessments, but are very important in the diagnosis and treatment of the complex disease. Others include: information regarding the resistance to targeted therapies in melanoma, the association between psoriasis and severe comorbid conditions, and a review of the clinical challenges and open questions on cellulitis management.

A particularly interesting paper is included on the resistance to targeted therapies in melanoma, and this links with issues highlighted by other authors in skin toxic events caused by chemotherapeutic agents, and the need for cooperation between dermatologists and oncologists to improve compliance to treatment and quality of life of patients.

I hope that you enjoy this edition of *EMJ – Dermatology* and would like to express gratitude to our Editorial Board for their continued support, particularly to Anand Reddi and Prof Dellavalle for providing an insightful Foreword to this publication.


**Kelly-Ann Lazarus**

*Editor, European Medical Journal*



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Skinoren®/Finacea 15% Gel. Active substance: Azelaic acid. Qualitative and quantitative composition: 1 g Skinoren/Finacea Gel contains 150 mg (15 %) azelaic acid; Excipients: 1 mg benzoic acid /g gel, 0.12 g propylene glycol /g gel, lecithin, triglycerides (medium chain), polysorbate 80 (mixture of oleate esters of sorbitol and sorbitol anhydrides), carbomer 980, sodium hydroxide, disodium edentate, purified water. Therapeutic indications: Treatment of acne vulgaris, papulopustular rosacea. Contraindications: Hypersensitivity to the active substance or to any of the excipients of the gel. Undesirable effects. Only cutaneous treatment-related adverse events were reported in clinical studies. In the great majority of cases the symptoms were mild or moderate; the frequency of irritative symptoms gradually decreased during the course of therapy. In clinical studies, most frequently observed side effects included application site pruritus, application site burning, and application site pain. Frequencies of side effects observed in clinical studies are defined according to the MedDRA frequency convention: Acne: **Skin and subcutaneous tissue disorders**. Uncommon = 1/1000, < 1/100 Contact dermatitis; **General disorders and administration site conditions.** Very common = 1/10 Application site pruritus, Application site burning, Application site pain; Common = 1/100, < 1/10 Application site dryness, Application site rash, Application site paraesthesia; Uncommon = 1/1000, < 1/100 Application site erythema, Application site exfoliation, Application site warmth, Application site discolouration; Rosacea: **Skin and subcutaneous tissue disorders.** Uncommon = 1/1000, < 1/100 Acne, Contact dermatitis; **General disorders and administration site conditions:** Very common = 1/10 Application site burning, Application site pain, Application site pruritus; Common = 1/100, < 1/10 Application site paraesthesia, Application site dryness, Application site rash, Application site oedema; Uncommon = 1/1000, < 1/100 Application site discomfort, Application site erythema, Application site urticaria; Hypersensitivity has been reported rarely in post-marketing surveillance. Worsening of asthma in patients treated with azelaic acid has been reported rarely during post-marketing surveillance (the frequency is not known). **Pediatric population.** Treatment of acne vulgaris in adolescents 12-18 years of age: In 4 clinical phase II and II/III studies involving adolescents 12-17 years of age (120/383; 31%), the overall incidence of adverse events for Skinoren gel was similar for the groups aged 12-17 years (40%), aged 18 years (37%) and for the entire patient population (38%). This similarity also applied to the group aged 12-20 years (40%). Special warning: Keep out of the reach and sight of children. Prescription Only Medicine. Date of revision of the text: March 2010.Intendis GmbH, 10589. Berlin

Skinoren® 20% Cream. Active substance: Azelaic acid. Qualitative and quantitative composition: 1 g Skinoren Cream contains 200 mg (20 %) azelaic acid; Excipients: Arlatone 983 S (polyoxyethylene fatty acid ester), Cutina CBS (mixture of mono-diglycerides, fatty alcohols, triglycerides and wax esters), cetearyl octanoate, propylene glycol, glycerol 85%, benzoic acid, purified water. Therapeutic indications: Treatment of acne vulgaris, melasma. Contraindications: Hypersensitivity to the active substance or to any of the excipients of the cream. Undesirable effects. In clinical studies, most frequently observed side effects included application site burning, application site pruritus, and application site erythema. Frequencies of side effects observed in clinical studies are defined according to the MedDRA frequency convention: **Skin and subcutaneous tissue disorders**. Uncommon = 1/1000, < 1/100 seborrhea, acne, skin depigmentation; Rare = 1/10000 to <1/1000 cheilitis; **General disorders and administration site conditions.** Very common = 1/10 application site burning, application site pruritus, application site erythema; Common = 1/100, < 1/10 application site exfoliation, application site pain, application site dryness, application site discolouration, application site irritation; Uncommon = 1/1000, < 1/100 application site paraesthesia, application site dermatitis, application site discomfort, application site oedema; Rare = 1/10000 to <1/1000 application site vesicles, application site eczema, application site warmth, application site ulcer; **Immune system disorders.** Rare = 1/10000 to <1/1000 drug hypersensitivity; Generally, local skin irritation regresses in the course of treatment. Rash has been reported rarely in post-marketing surveillance. Worsening of asthma in patients treated with azelaic acid has been reported rarely during post-marketing surveillance (the frequency is not known). **Pediatric population.** In clinical studies involving adolescents 12-18 years of age (454/1336; 34%), the local tolerability of Skinoren cream was similar in pediatric and adult patients. Special warning: Keep out of the reach and sight of children. Prescription Only Medicine. Date of revision of the text: March 2010. Intendis GmbH, 10589. Berlin.

G.INT.11.2011.0040

# Foreword


## Anand Reddi and Prof. Robert P. Dellavalle

*Department of Dermatology, University of Colorado School Medicine*


Dear Colleagues,

Welcome to the inaugural issue of the *European Medical Journal - Dermatology*. A distinguishing feature of this journal is its focus on congress reviews as well as breaking news and analysis including perspectives from industry.

Dermatology is witnessing a renaissance. New technologies are interrogating the genomic *terra incognita* of skin disease. The torrent of data from these studies is giving rise to new-targeted treatments that take advantage of disease specific molecular targets.

Personalised medicine profiles an individual's molecular characteristics and exploits those genetic distinctions to increase diagnostic precision that ultimately leads to the use of a targeted therapy. Diseases are no longer viewed as homogenous entities but rather as diverse heterogeneous sub-types due to genomic differences.

It appears that personalised medicine in dermatology clinical practice is coming of age. For example, the inherited blistering disease epidermolysis bullosa, is due to a cadre of single gene mutations associated with the extracellular matrix. Recognition of these mutations is allowing for improved diagnosis and classification as well as heralding for the first time new gene, protein and cell based therapies. The identification of hedgehog pathway mutations in basal cell carcinoma, and activating mutations in BRAF in melanoma, has resulted in new classes of targeted cancer therapies. Genome wide expression profiling in patients with scleroderma reveals that patients with localised disease have an inflammatory expression signature whereas patients with diffuse disease have a fibrotic expression signature. Excitingly, these observations could result in new treatment profiles with anti-inflammatory or anti-fibrotic agents, depending on the presence of localised or diffuse disease.

The *European Medical Journal - Dermatology* will be uniquely poised to deliver to its readership the latest breakthroughs in dermatology including those involving personalised medicine.


## Anand Reddi and Prof. Robert P. Dellavalle



*Department of Dermatology, University of Colorado School Medicine and Veterans Administration Hospital, Denver, Colorado, USA*

# EADV CONGRESS 2013

## ICC ISTANBUL CONGRESS CENTER TAŞKIŞLA ISTANBUL, TURKEY

9TH-12TH OCTOBER 2013

# Welcome to the *European Medical Journal* review of the 22nd European Academy of Dermatology and Venereology (EADV) Congress 2013

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# **Welcome** to the *European Medical Journal* review of the 22nd European Academy of Dermatology and Venereology (EADV) Congress 2013

'DERMATOVENEREOLOGY in a changing world' was the theme of the 22nd European Academy of Dermatology and Venereology (EADV) Congress, held from the 9th–12th October 2013, in Istanbul, Turkey.

The study of dermatovenereology has become increasingly popular, especially among young doctors. The improvements within this area have contributed to cosmetic dermatology, the development of new drugs, new treatments, and new ways of diagnosing patients. For example, a new piece of innovative technology, an automated body mapping (ATBM) system, was presented at the Congress. ATBM saves the physician time, while also supporting the patient and reducing their worries.

With regards to cosmetic dermatology, a study was presented which focused on ageing skin. The study highlighted that when treating ageing skin, dermatologists take a holistic approach, combining both systemic and topical treatments, and tailoring the treatment to the individual.

Over the 4 days, the rich scientific programme provided updates and addressed important and relevant questions within the discipline. Prof Luca Borradori, Chairman of the EADV Scientific Programming Committee (SPC), said: "Our commitment to you is always the passage of practical, relevant knowledge and clear take-home messages, in a complete educational programme, compiled by an outstanding Faculty."

"Our commitment to you is always the passage of practical, relevant knowledge and clear take-home messages, in a complete educational programme, compiled by an outstanding Faculty."

*Prof Luca Borradori*
*Chairman,*
*EADV Scientific Programming Committee*




> "Let it be the city where great minds meet once again, looking for wisdom and excellence. Let it be the perfect setting in which to house our 22nd EADV Congress."
>
> *Prof Jana Hercogová*
> *President, EADV*

With over 150 first-class sessions, 10 courses, a number of peer-reviewed abstracts divided into nine different categories, all of which provided bulletins on continuing research and studies, a board of experts from five continents and 42 different countries, as well as the representation of all European schools - this year's EADV Congress did not disappoint.

The venue of the Congress - Istanbul, Turkey, provided an excellent backdrop, offering a balance of tradition and modernisation, with a distinctive blend of both the East and West. It is a city which embraces change while never losing its historic roots. Prof Jana Hercogová, EADV President 2012–2014, said: "With its new found sense of energy and innovation, Istanbul has in recent years become the world's hippest place."

New ideas and diverse points of view, were not only absorbed in the city itself but also throughout the Congress. As Prof Hercogová so eloquently summarised: "Let it be the city where great minds meet once again, looking for wisdom and excellence. Let it be the perfect setting in which to house our 22nd EADV Congress."




# Get inked and live with the consequences

TATTOOS are proving troublesome for dermatologists as people are experiencing complications or chronic reactions. It is estimated that around 120 million people are tattooed worldwide, but it is unknown just how many people experience an adverse reaction.

During the Congress, Prof Agustin Alomar, Institut Universitari Dexeus, Department of Dermatology, Barcelona, Spain, presented his abstract, 'Tattoo problems' (Abstract: WS24.2), which highlighted the need for legislation in this area because as the popularity of tattoos increases, the number of complications increase also. There is very little regulation in this field, the inks which are used during this process can spread many harmful infections.

It is estimated that 30% of individuals consider having their tattoo removed. Dr Nicolas Kluger, University of Helsinki and Helsinki University Hospital, Department of Skin and Allergic Diseases, Helsinki, Finland, highlighted in his abstract, 'Tattoo removal complications: the old, the classic and the new ones' (Abstract: WS24.6), while surgery and laser treatments remain the gold standard for tattoo removal, there are drawbacks to both procedures and they are both costly. For this reason, people are choosing cheaper, faster, and easier methods which can be performed by non-professional individuals or even by themselves.

As tattoo complications and reactions are becoming ever-more prevalent, it has now developed into a sub-speciality for dermatologists. The combined force of the EADV, and the European Society of Tattoo and Pigment Research (ESTP), will develop a database which will measure and monitor problems which need to be set up as top priorities, they will then outline and propose new policies to European Union institutions, regulators, and professionals.


# New system to detect skin cancer

A NEW procedure, Automated Total Body Mapping (ATBM), has been revealed for analysing the whole body's skin surface, saving dermatologists' time and reassuring patients.

In just 3 minutes, ATBM will record images of the skin's surface and monitor it for any changes. Patients at high-risk of developing skin cancer; those with numerous moles, or dysplastic nevus syndrome, will visit a dermatologist every 3 months, who will check for skin cancer. Previously, these examinations were a lengthy process: not anymore.

The FotoFinder bodystudio ATBM system controls the imaging process automatically, with photographs being taken from four sides. It has an automated camera in the perfect position for recording the skin surface from head to toe. The photographs are then compared automatically to previously saved photographs in the system. The Bodyscan ATBM then highlights both new and changed lesions on the body.

This new procedure integrates mole examinations with digital dermoscopy. Relevant nevi are noted on the body image and recorded with a full HD video dermatoscope, microscopically. The Moleanalyzer supports the system by giving a malignancy score using clinically-approved pattern recognition algorithms.

As it is easy to use, the system can be given to practice staff to perform. All images are reproducible in future examinations. Results of each consultation are available on the network to view on several workstations, ensuring the doctor can spend maximum time with the patient.

Mr Andreas Mayer, Managing Director of FotoFinder Systems stated: "Our skin is an extremely large organ that takes a long time to examine. The new ATBM procedure reduces the effort involved to a minimum. Thanks to the impressive total body photographs, doctors can spot any conspicuous features and changes at a glance. In this way, the system supports the medical expertise of the dermatologist and gives patients more security."

"The new ATBM procedure reduces the effort involved to a minimum. Thanks to the impressive total body photographs, doctors can spot any conspicuous features and changes at a glance."

*Andreas Mayer*
*Managing Director, FotoFinder Systems*

EADV CONGRESS 2013

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9TH-12TH OCTOBER 2013

# STELARA® approved for the treatment of active psoriatic arthritis

> "We believe STELARA® will play a critically important role in the treatment of this chronic disease moving forward."
>
> *Dr Jerome A. Boscia*
> *Vice President, Janssen Research and Development, LLC, USA*

STELARA® (ustekinumab) has been approved by the European Commission for active psoriatic arthritis in adults. It can be used exclusively on its own or in combination therapy with methotrexate. This therapy can benefit those that did not benefit from previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy.

Active psoriatic arthritis is a chronic autoimmune disease affecting joints and causing tissue inflammation, and it is associated with the development of psoriasis. The disease affects approximately 37 million people worldwide, and 4.2 million people across Europe. The cause is unknown but it is thought to be an immune-mediated inflammatory disease with genetic predispositions.

STELARA® is a monoclonal antibody that targets interleukin (IL)-12 and (IL)-23, which are both involved in immune-mediated inflammatory diseases. Data from the Phase III multicentre, randomised, double-bind, placebo-controlled trials of ustekinumab showed significant improvement in arthritis signs and symptoms at both primary and secondary endpoints.

Dr Jerome A. Boscia, Vice President, Head of Immunology Development, Janssen Research and Development, LLC, USA, said: "Data from the Phase III clinical programme, one of the largest conducted for a biologic to date in psoriatic arthritis, showed STELARA® effective in improving symptoms and signs of active psoriatic arthritis in anti-TNF-alpha naïve and experienced patients. We believe STELARA® will play a critically important role in the treatment of this chronic disease moving forward."


# Topical treatments for actinic keratosis improve patient outcomes

TOPICAL treatments used to treat actinic keratosis (AK) are the preferred treatment option for physicians; they are of a short duration with fast resolving skin responses and improve the patient's quality of life, while also preventing the patient from developing new lesions.

The number of patients with AK is rising, especially in Europe, the USA, and Australia. AK are rough skin lesions caused by cumulative exposure to the sun, and could lead to non-melanoma skin cancer (NMSC).

Prof Eggert Stockfleth, Skin Cancer Center Charité, Department of Dermatology, Charité University Medicine Berlin, Germany, said: "Actinic Keratosis is a chronic condition which can be considered a form of early-stage skin cancer. Therefore it is important that physicians identify treatment options that will lead to improved adherence and ultimately improved outcomes for their patients to ensure satisfaction for patients over the longer term. These findings from over 400 physicians across eight countries provide us with a great insight into AK management and enable us to develop recommendations for improved practice."

80% of physicians found that field therapy is the most effective treatment for AK. Ingenol mebutate gel - a novel topical, field-directed treatment - has had significant improvements in a patient's quality of life; it will not only clear obvious AK lesions but also subclinical lesions, reducing the risk of developing new lesions.

In the view of Prof Matthias Augustin, University Medical Center Hamburg-Eppendorf, Germany, said: "This study suggests that patients are satisfied with the short treatment duration and the effect associated with using ingenol mebutate gel. Even patients that were not completely cleared stated improved quality of life when using this treatment."

> "This study suggests that patients are satisfied with the short treatment duration and the effect associated with using ingenol mebutate gel."
>
> *Prof Matthias Augustin*
> *University Medical Canter Hamburg-Eppendorf, Germany*

# Dermatologists: making skin young and healthy

AGEING skin is unavoidable but as more people want the signs of skin ageing to be discrete, dermatologists are adopting a holistic approach, aiming to reduce, postpone, or even repair the effects of both genetically programmed ageing (endogenous), and the environmental injuries of the skin (exogenous).

As many people desire youthful and healthy looking skin, the demand for effective treatments of the ageing face is growing. In order to achieve these objectives, dermatologists combine both systemic and also topical treatments.

Systemic treatments include a number of different ingredients which target all levels of the intrinsic and extrinsic ageing process, and enhance the health and beauty of the skin. In this group 'beauty pills', or 'oral cosmetics', are included, these are oral supplements which deliver health benefits beyond a traditional vitamin tablet. Also included in this group are systemic antioxidants which possess anti-ageing properties and prevent various diseases associated with oxidative stress.

Topical antioxidants reduce the free radical damage that is implicated in both the intrinsic and extrinsic ageing process. The treatments are less invasive and often include creams and lotions that contain biologically active ingredients, which can improve the appearance of skin without altering its structure and function. The most popular products within this area include: moisturisers, exfoliating agents, and sunscreens.

To deliver the best results, dermatologists are tailoring the treatment for each individual patient, taking into account factors such as their age, lifestyle, skin type, wishes, and expectations.




# Extinction of the double chin with ATX-101

> "If an individual's self-image is suffering because of a double chin, this can have a negative impact on his or her psychological wellbeing."
>
> *Prof Berthhold Rzany*
> *Study Investigator,*
> *European ATX-101 Phase III Trial, Germany*

KYTHERA, in collaboration with Bayer Consumer Care, announced that there were favourable outcomes concerning ATX-101 in the reduction of unwanted submental fat (SMF), which is commonly known as a 'double chin'.

SMF can be due to a number of factors, including genetic predisposition or ageing. This unwanted fat can also be problematic since it is resistant to weight loss measures. The ATX-101 is a registered formulation of a purified synthetic version of deoxycholic acid (DCA), which is a naturally-occurring molecule in the body that aids in dietary fat catabolism. ATX-101 facilitates the disruption of the cell membrane of adipocytes (fat cells) and mediates adipocytolysis (destruction of fat cells). The destroyed fat cells are then naturally eliminated from the body.

"If an individual's self-image is suffering because of a double chin, this can have a negative impact on his or her psychological wellbeing," said Prof Berthhold Rzany, study investigator of the European ATX-101 Phase III trial, private practice for Dermatology and Aesthetic Medicine, Berlin, Germany. "Established surgical methods of SMF reduction are effective, but they are also invasive and may not be suitable for everyone. ATX-101 is the only non-surgical therapy to undergo comprehensive clinical evaluation for the reduction of unwanted SMF. The data presented indicate that the drug is not only effective and well-tolerated, but can also increase the satisfaction that treated individuals have with the outward appearance of their face and chin."

The clinical trial included patients in two European, randomised, double-blind, Phase III studies who received 1 or 2 mg/cm$^2$ of ATX-101 or placebo injected directly into their SMF. The treatment duration was 12 weeks with four visits spaced between 4 week separations. The reduction in SMF was assessed using the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) and the Subject Self-Rating Scale (SSRS).

There were significant results from the trial; ATX-101 patients saw definition in their faces after the treatment. Also, the psychological impact of SMF on these patients was elevated as they reported feeling happier and less embarrassed than their placebo counterparts. The side-effects of the drug were reported to be mild-to-moderate in intensity and was contained in the injection site.

More developments will continue and, if approved, ATX-101 will be the first non-surgical method for the reduction of SMF.



# HUMIRA® brings hope to hidradenitis suppurativa sufferers

DATA have shown that HUMIRA® prompts a significant response rate in adults under the therapy than their placebo counterparts. This was shown in a Phase II study which assessed HUMIRA® (adalimumab) for the treatment of moderate-to-severe hidradenitis suppurativa (HS) during a 16-week therapy period.

The hidradenitis suppurativa clinical response (HiSCR) endpoint was used to report the efficacy of the data gathered based on the reduction of total abscess and inflammatory nodule count from baseline.

HS is an inflammatory disorder that is characterised by inflamed areas, particularly localised around the armpits and groin. The inflamed area is composed mainly of lesions, nodules and boils, and usually occurs where many oil and sweat glands are located. It is more common in women than in men, and develops during early adulthood.

HUMIRA was evaluated under the HiSCR to measure the endpoint that requires at least a 50% reduction from baseline in total inflammatory nodule count, which also includes abscesses and draining fistulas. This was found to be a better tool in the analysis of HUMIRA, based on patients' clinical response rates instead of HS-physician-global assessment (PGA), which relies mainly on the clinician's observations with reference to a health scale.

> "We are excited that HiSCR has the potential to be a useful method to assess the efficacy of HS therapies in research and in clinical practice."
>
> *John Medich*
> *Vice President,*
> *Clinical Development, Immunology, AbbVie*

"AbbVie developed the HiSCR endpoint to help advance hidradenitis suppurativa research and address the need for a reliable and relatively simple measure of clinical response in HS," said Mr John Medich, Vice President, Clinical Development, Immunology, AbbVie. "We are excited that HiSCR has the potential to be a useful method to assess the efficacy of HS therapies in research and in clinical practice."

Future developments, including two Phase III clinical trials (PIONEER I and PIONEER II) will be ongoing in 2014, to evaluate HUMIRA in 600 patients.


# Correlation found between psoriasis severity and heart disease

> "Our findings underline the importance of regular evaluation and treatment of cardiovascular risk factors in patients with psoriasis."
>
> *Dr Usman Khalid*
> *Gentofte Hospital, Hellerup, Denmark*

PSORIASIS sufferers may be at higher risk of type 2 diabetes mellitus, and thus, heart failure according to new research. Experts suggest that they should be screened for heart disease.

Researchers investigated medical data on all adults in Denmark; they discovered that there was a distinct correlation between psoriasis and heart failure: where the severity of psoriasis increases, the risk of heart failure also rises.

Lead author Dr Usman Khalid, Gentofte Hospital, Hellerup, Denmark, stated: "Our findings underline the importance of regular evaluation and treatment of cardiovascular risk factors in patients with psoriasis."

This link may be due to chronic inflammation, which is a component of both psoriasis and heart failure, he added.

With psoriasis affecting 125 million people worldwide this could have an extensive impact on the health of vast numbers of individuals.

Dr Khalid suggests: "Psoriasis should be considered a systemic inflammatory disease that affects the whole body, rather than an isolated skin lesion."

Adding: "Clinicians should consider early screening and treatment of cardiovascular risk factors in patients with psoriasis – such as obesity, smoking and a sedentary lifestyle – in order to reduce the long-term risk of cardiovascular disease and death."

Researchers suggest educating patients with psoriasis about this connection could encourage them to modify their lifestyle; including diet and weight management.

Further studies are required to evaluate the impact of psoriasis treatment on the risk of major health issues, such as diabetes and cardiovascular disease.

> "Psoriasis should be considered a systemic inflammatory disease that affects the whole body, rather than an isolated skin lesion."
>
> *Dr Usman Khalid*
> *Gentofte Hospital, Hellerup, Denmark*



# Novartis reveals latest clinical results

> "The new Phase III results for secukinumab and omalizumab being presented at EADV show our potential to transform patient care in psoriasis and CSU, with the aim of helping patients to achieve clear skin."
>
> *David Epstein*
> *Division Head, Novartis Pharmaceuticals*

NOVARTIS announced results from their Phase III studies of secukinumab (IN457) for moderate-to-severe plaque psoriasis and omalizumab (Xolair®) for the relief of chronic spontaneous urticaria (CSU).

CSU is characterised by red, swollen, itchy, and sometimes painful hives or wheals on the skin. "The new Phase III results for secukinumab and omalizumab being presented at EADV show our potential to transform patient care in psoriasis and CSU, with the aim of helping patients to achieve clear skin," said Mr David Epstein, Division Head, Novartis Pharmaceuticals, Novartis AG. "Specialty dermatology is an emerging area of importance for Novartis, and we are on track to deliver an innovative approach to targeted therapies for people suffering from severe skin diseases in need of new treatment options."

IL-17A is involved in the development of psoriasis and is highly concentrated in affected skin. Secukinumab (AIN457) is a human monoclonal antibody that binds selectively to IL-17A, therefore neutralising the effect of the pro-inflammatory cytokine. Results from the Phase III FIXTURE study have shown that secukinmab is superior to Enbrel®, the current standard-of-care in anti-TNF medication approved to treat moderate-to-severe plaque psoriasis.

Xolair® (omalizumab) is a monoclonal antibody that targets immunoglobulin E (IgE) and affects mast-cell and basophil function. Data from ASTERIA I, were presented at the Congress detailing the three pivotal registration studies for omalizumab. Results from the studies will be released in 2013 and 2014 for moderate-to-severe plaque psoriasis. It should be noted that omalizumab is currently not approved for the treatment of CSU.

> "We are on track to deliver an innovative approach to targeted therapies for people suffering from severe skin diseases in need of new treatment options."
>
> *David Epstein*
> *Division Head, Novartis Pharmaceuticals*

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# RESISTANCE TO TARGETED THERAPIES IN MELANOMA: NEW INSIGHTS

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**Disclosure:** Paolo Antonio Ascierto is a consultant of Bristol Myers Squibb, MSD, and Roche-Genentech. He participated in the Advisory Board from Bristol Myers Squibb, MSD, Roche-Genentech, GSK, Amgen, Celgene, Medimmune, and Novartis. He received honoraria from Brystol Myers Squibb, MSD, and Roche-Genentech. All remaining authors declare the absence of any conflict of interest.
**Received:** 18.10.13 **Accepted:** 19.11.13
**Citation:** EMJ Dermatol. 2013;1:24-37.

## ABSTRACT

Several molecular mechanisms are involved in melanoma genesis and progression. Molecular targets for effective therapeutic intervention have been identified within the RAS-RAF-MEK-ERK and, to a less extent, PI3K-AKT pathways. The development of inhibitors of key effectors (mainly BRAF mutant, MEK, and KIT) into such pathways has significantly improved the treatment of patients with advanced melanoma. However, emerging data indicate that a large variety of acquired and intrinsic mechanisms may drive resistance to the main targeted inhibitors. All the evidence suggests that in melanoma, as probably in all types of cancer, it is unlikely that targeting a single component in pathogenetic signalling pathways could yield significant antitumour responses. Therefore, knowledge of the multiple altered signalling events involved in response and resistance to targeted treatments will allow for the development of more effective combination therapies, which may represent the next challenge for the management of patients with such a disease.

Keywords: Malignant melanoma, molecular pathogenesis, targeted therapy, BRAF/MEK/KIT inhibitors, drug resistance.

## INTRODUCTION

Complex molecular mechanisms are involved in the development, progression, and resistance-to-therapy of melanoma. Although the majority of such pathogenetic mechanisms are still largely unknown, several genes and cell-signalling pathways have been implicated.[1] Among them, the mitogen-activated protein kinase (MAPK; including the cascade of NRAS, BRAF, MEK1/2, and ERK1/2 proteins) - a major signalling pathway involved in the control of cell proliferation - has been reported to play a crucial role in melanoma pathogenesis.[2] Indeed, the ERK1/2 proteins have been found to be constitutively activated in melanoma, mostly as a consequence of mutations in upstream components of the pathway, and their increased activity has been implicated in rapid cell growth as well as enhanced cell survival and resistance to apoptosis.[2] About half of melanomas harbour a driver mutation in BRAF; whereas one-fifth of cases present an oncogenic mutation in NRAS.[3] Since BRAF and NRAS mutations have been found mutually exclusive,[4,5] about two-thirds of patients present a melanoma carrying a mutated BRAF or NRAS gene.

In the treatment of patients with advanced melanoma, the availability of either targeted T cell immunotherapy (the anti-CTLA4 agent ipilimumab and the anti-PD-1 and anti-PD-L1 agents [nivolumab, lambrolizumab, MPDL3280A]) or inhibitors of key effectors into the MAPK pathway (BRAF-mutant inhibitors [vemurafenib,

dabrafenib] MEK inhibitors [trametinib], and their combination) is allowing for the ineffectiveness of the conventional therapies to be overcome.[6] Vemurafenib and dabrafenib have been successfully introduced into the clinical practice and have been demonstrated to achieve rapid tumour shrinkage in the majority of cases.[7] Treatments with both these drugs improve response rates and progression-free survival (PFS), with a favourable impact on overall survival (OS).[7] Analogously, MEK inhibitors as well as the combination of a BRAF inhibitor along with a MEK inhibitor have been recently demonstrated to exert a similar clinical efficacy (in the latter case, with a reduced incidence of both keratoacanthomas and squamous cell carcinomas as cutaneous adverse effects).[8]

Although the vast majority (up to 80%) of melanoma patients carrying BRAF mutations show clinical and pathological response to therapy - with different rates of tumour reduction - when treated with either a BRAF inhibitor or a MEK inhibitor (this latter agent exerts a more limited antiproliferative effect in NRAS-mutated tumours),[7,8] most of them develop resistance within 6-8 months after treatment initiation as a consequence of reactivation of the MAPK pathway or activation of alternative signalling pathways.[9] Nevertheless, a fraction of them are primarily refractory due to an intrinsic resistance to such inhibitors.[9] Here we summarise the main results with inhibitors of the MAPK components in melanoma patients and present the known mechanisms of resistance to such targeted therapies.

## TARGETED THERAPIES AGAINST MAPK PATHWAY COMPONENTS

Despite the huge amount of knowledge implicating RAS in tumour initiation and promotion, RAS itself has not become a successful target of therapy.[10,11] The strategies used to develop drugs able to inhibit the RAS activity are aimed at preventing its interaction with several components of the upstream or downstream signalling pathways regulated by this protein.[11] In this sense, the block of prenylation (farnesylation) markedly impairs the functioning of active RAS protein.[12] While a good *in vitro* antitumour activity has been reported in human melanoma cell lines (with downregulation of ERK and/or AKT and induction of apoptosis),[12,13] farnesyltransferase inhibitors have always failed to be effective in melanoma patients (even if all cohorts treated with these agents were never selected for the RAS status).[14,15] A recently discovered farnesyltransferase inhibitor, lonafarnib, exhibited to enhance the antitumour activity of the pan-RAF inhibitor sorafenib by exerting downregulation of the antiapoptotic signals and inhibition of cell proliferation; however, this agent alone lacked any capability of inhibiting tumour growth.[16] Therefore, a combination of farnesyltransferase inhibitors with other pathway-targeted drugs or, alternatively, a more stringent selection of the patients' cohorts could be helpful to increase the clinical efficacy of such compounds. Therapeutic strategies have thus been focused on inhibiting downstream effectors of the RAS-driven pathways, MAPK and PI3K-AKT.

The first drug developed against BRAF was the BAY 43-9006 or sorafenib, which is however unspecific for mutated BRAF and suppresses activity of several different kinases (indeed, it is recognised as a multikinase inhibitor).[17] In advanced melanoma, the combination of sorafenib with the chemotherapeutic agents carboplatin and paclitaxel has failed to show any efficacy in terms of either PFS or OS compared to the same regimen plus an oral placebo in a Phase III trial,[18] despite an initial encouraging improvement in PFS by the addition of sorafenib to dacarbazine in a previous Phase II study.[19]

Thereafter, a second generation anti-BRAF compound (vemurafenib, also known as PLX4032 or RO5185426), which instead acts a potent and selective inhibitor of the mutated BRAF kinase, has been demonstrated to be highly effective in melanoma patients carrying the $^{V600E}$BRAF mutation.[20] A Phase III study comparing vemurafenib with dacarbazine in 675 previously untreated BRAF-mutant patients revealed OS to be 84% (95% CI: 78-89) in the vemurafenib group and 64% (95% CI: 56-73) in the dacarbazine group.[21] In this study, patients treated with vemurafenib presented a relative reduction of 63% in the risk of death and of 74% in the risk of either death or disease progression, as compared with those undergoing dacarbazine treatment.[21] An analogous clinical activity has been demonstrated for an additional BRAF inhibitor compound, dabrafenib (previously known as GSK2118436), which significantly improved PFS compared with dacarbazine.[22]

Interestingly, this molecule seems to be equally active on different mutations at codons 600 of the BRAF gene (V600E/K/D/R).[22-25]

In addition to the inhibitory activity in cells with a mutant BRAF (which is revealed by the decreased levels of phosphorylated ERK1/2 proteins and subsequent growth arrest), vemurafenib and dabrafenib also induce MAPK pathway activation in cells with a wild-type BRAF through RAF-mediated induction of ERK1/2 phosphorylation.[26,27] BRAF inhibitors seem to paradoxically stimulate ERK signalling through activating dimerisation of the different RAF isoforms (see below); such conformational effects may explain either the high frequency of keratoacanthomas and squamous cell carcinomas among patients treated with BRAF inhibitors or the development of an acquired resistance to these drugs.[26-28] Overall, a clinical benefit has been reported up to an unprecedented 80% rate of BRAF-mutated patients treated with vemurafenib or dabrafenib; response to each of these oral agents occurs within few days or weeks.[29] Since reactivation of the downstream MEK-ERK pathway seems to represent the main mechanism of resistance to BRAF inhibitors (see below), a promising strategy for overcoming such a limited persistence of the antiproliferative effects was to include new compounds blocking MEK1/2 proteins into the treatment options.

Several MEK inhibitors have been introduced in clinical trials. Unlike the BRAF inhibitors which are highly selective for the mutated protein, MEK inhibitors are targeted against the wild-type gene product. As single agents, these compounds (AS703026, AZD6244, E6201, GSK1120212, GDC0973, MEK162) have shown a markedly high activity in patients carrying tumours with constitutive activation of the RAS-BRAF-MEK-ERK signalling cascade. Detection of RAS mutations in primary tumours seems to represent the strongest marker for selecting patients with the highest chance to respond to MEK inhibitors; AS703026 and AZD6244 have activity in KRAS mutant colon cancer cell lines/xenografts in combination with cetuximab,[30,31] whereas GSK1120212 (also known as trametinib) has been found to be effective in NRAS-mutated melanoma.[32] In melanoma patients carrying BRAF mutations, the response to MEK inhibitors seems to be partially dependent on exposition to prior BRAF inhibitor therapy (for GSK1120212, a significant clinical activity was observed in BRAF inhibitor-naive patients only[33]) or status of the PI3K-AKT pathway (for selumetinib [previously known as AZD6244] and E6201, a significantly low responsiveness to MEK inhibitors was found in BRAF mutant melanomas expressing high levels of phosphorylated AKT[34] or presenting PTEN inactivation with subsequent stimulation of downstream PI3K signalling,[35] respectively). In other words, coexistence of an unaffected PI3K-AKT status may contribute to increased sensitivity to MEK inhibitors in melanomas whose MAPK pathway is activated through oncogenic mutations in BRAF gene. Finally, the MEK inhibition has been demonstrated to abrogate the CRAF-dependent activation of ERK in wild-type BRAF cells, contributing to reduce the chances of cutaneous adverse events.[36]

Current clinical investigations have shown great promise with the combination of targeted therapies as a new effective strategy of melanoma treatment. A combined treatment with MEK and BRAF inhibitors in BRAF mutated metastatic patients showed a significant improvement of the PFS rates,[37] providing further support to the hypothesis that this could be the way for a better management of such melanoma cases. Actually, a number of clinical trials of trametinib in combination with other targeted drugs, whose activity is somehow interfering with the MAPK-driven tumour growth, are underway and expected to show great promise. As an example, it has been recently demonstrated that MEK inhibitors may enhance the ability of histone deacetylase (HDAC) inhibitors to induce apoptosis in tumour cells with constitutive activation of the BRAF-MEK-ERK signalling cascade both *in vitro* and *in vivo*.[38]

Specific mutations within the kinase domain of the KIT gene may also cause an uncontrolled melanoma cell proliferation; such mutations are less frequent than those in BRAF/NRAS genes among cutaneous melanomas (overall, 2-3% of total cases; about 20% in acral lentiginous melanomas and 3-5% in melanomas from chronic sun-damaged skin).[39,40] Overall, 30% of melanomas with KIT mutations also show increased copy number/amplification of the gene; all KIT aberrations do not typically coexist with BRAF or NRAS mutations.[39,40] For the limited cohort of cutaneous melanomas carrying KIT mutations, several small tyrosine kinase inhibitors have been shown to induce cell cycle arrest and apoptosis

with significant inhibition of migration and invasion of melanoma cells. Promising results concerning the clinical responses have been registered for these compounds, though on limited subsets of melanoma patients harbouring KIT aberrations (mainly, those carrying some gene sequence variants - such as K642E and L576P - which are highly responsive).[41-45] In particular:

- imatinib, formerly known as STI571, has been demonstrated to be effective in patients with metastatic melanoma harbouring KIT mutations, but not in cases with KIT amplification only.[46] Therefore, the National Comprehensive Cancer Network (NCCN) guidelines have included imatinib as an effective treatment option for KIT-mutated tumours;[47]

- nilotinib (AMN107) inhibits both wild-type and mutant (in exons 11, 13, and 17) KIT as well as imatinib-resistant KIT mutant tumours.[48] This drug has been reported to present a very favourable toxicity profile with durable response in metastatic melanoma patients with KIT mutations;[49]

- dasatinib inhibits both wild-type and mutant KIT in a dose-dependent manner, causing inhibition of cell migration and invasion through reduction of the phosphorylation of either Src kinase or FAK pathway.[50] Dasatinib in combination with dacarbazine appears to be more active than either agent alone.[51]

## RESISTANCE TO MAPK-TARGETED THERAPIES

Intrinsic and acquired resistance to targeted therapy agents have been reported to play a role in the treatment of advanced melanoma patients. In this regard, it is to be underlined that the vast majority of data about such an issue are related to the resistance to BRAF inhibitors, since vemurafenib and dabrafenib have been the most extensively studied, both preclinically and clinically.

### Intrinsic Resistance

About one-fifth of patients treated with vemurafenib or dabrafenib are not responsive to the treatment from the beginning.[9] As shown in Figure 1, the molecular events underlying such an intrinsic resistance are various:

- loss of PTEN tumour suppressor protein, with increased basal levels of AKT signalling;[52]

- gene amplification and/or overexpression of cyclin D1, which contrasts the activity of the cyclin-dependent kinase inhibitor $p16^{CDKN2A}$ and stimulates the cyclin D1-RB pathway.[53] In this regard, inactivation of FBXO4, encoding an enzyme involved in cyclin D1 proteolysis, has been recently demonstrated to induce cyclin D1 accumulation in melanoma cells;[54]

- silencing of the NF1 gene,[55] which either promotes RAS activation or impairs the mechanisms regulating the senescence process and controlling the cell proliferation;

- increased activity of protein kinase D3 (PRKD3), with activation of the PI3K-AKT signalling in presence of a specific inhibition of the oncogenic BRAF.[56]

To better understand the reasons why all these apparently different molecular alterations are implicated in conferring resistance to BRAF or MEK inhibitors in melanoma cells, it is necessary to keep in mind the relationship between RAF-MEK-ERK activation and melanomagenesis. Oncogenic BRAF mutant strongly stimulates cell cycle progression by activation of the downstream MEK-ERK pathway. However, the BRAF-driven melanocytic proliferation needs the coexistence of alterations in additional cell-cycle factors (such as p53 deficiency, genetic or epigenetic inactivation of $p16^{CDKN2A}$ gene with subsequent preponderant activity of cyclin D1-CDK4/6-phospho-RB complex, increased levels of active AKT) in order to promote the melanoma growth and progression.[57] In a subset of melanomas, such additional pathogenetic alterations acquire a prevalent role, and tumour cell proliferation becomes independent or less dependent on activation of the BRAF-MEK-ERK pathway. In these cases, treatment with BRAF inhibitors may be ineffective due to existence of such alternative proliferation drivers.

The elevated intracellular concentration of cyclin D1 - often related to the amplification of the gene locus at chromosomal level - may represent a strong stimulus to cell proliferation, independently from the functional status of the RAF-MEK-ERK pathway, since it determines a marked increase in activating bind to the CDK4/6 kinases and, sequentially, in phosphorylation of the RB protein. As a confirmation of the role of cyclin D1 overexpression in promoting MAPK-independent cell proliferation, cytostatic effects

of BRAF (as well as MEK) inhibitors have always been associated with diminished levels of both cyclin D1 and phospho-Rb.[58,59] Analogously, activated AKT has been indicated to promote cell proliferation through the downregulation of the p27 cyclin-dependent kinase inhibitor and, mostly, the upregulation of cyclins E and D1.[60,61] Activation of AKT is almost entirely determined by an upstream PI3K activation, since activating mutations of AKT are nearly absent in melanoma (rare mutations in AKT1 and AKT3 genes have been reported in a limited number of melanomas and melanoma cell lines).[62,63]

The intracellular accumulation of active AKT does result in the suppression of apoptosis and induction of cell survival,[61] through inactivation of many pro-apoptotic proteins, such as BAD (Bcl-2 antagonist of cell death[64]) and MDM2 (that lead to increased p53 degradation[65,66]). A member of the Bcl-2 family, BCL2A1, has been recently found amplified in ~30% of melanomas and overexpression of the corresponding gene product associated with poorer clinical responses to BRAF inhibitors.[67] Moreover, silencing of PTEN and subsequent activation of the PI3K-AKT pathway participate, in conjunction with the activation of the BRAF-MEK-ERK pathway, in regulating the expression levels of the BIM protein, a pro-apoptotic member of the Bcl-2 protein family.[68] The presence of PTEN inactivation may therefore interfere with the BRAF inhibition by reducing the levels of BIM protein and, thus, the extent of apoptotic induction; as a confirmation of this, a simultaneous treatment with BRAF and PI3K inhibitors has been reported to enhance BIM expression and increase the level of apoptosis.[52] Alternatively, the PI3K signalling may be directly increased by the occurrence of activating mutations in its kinase domain.[69]

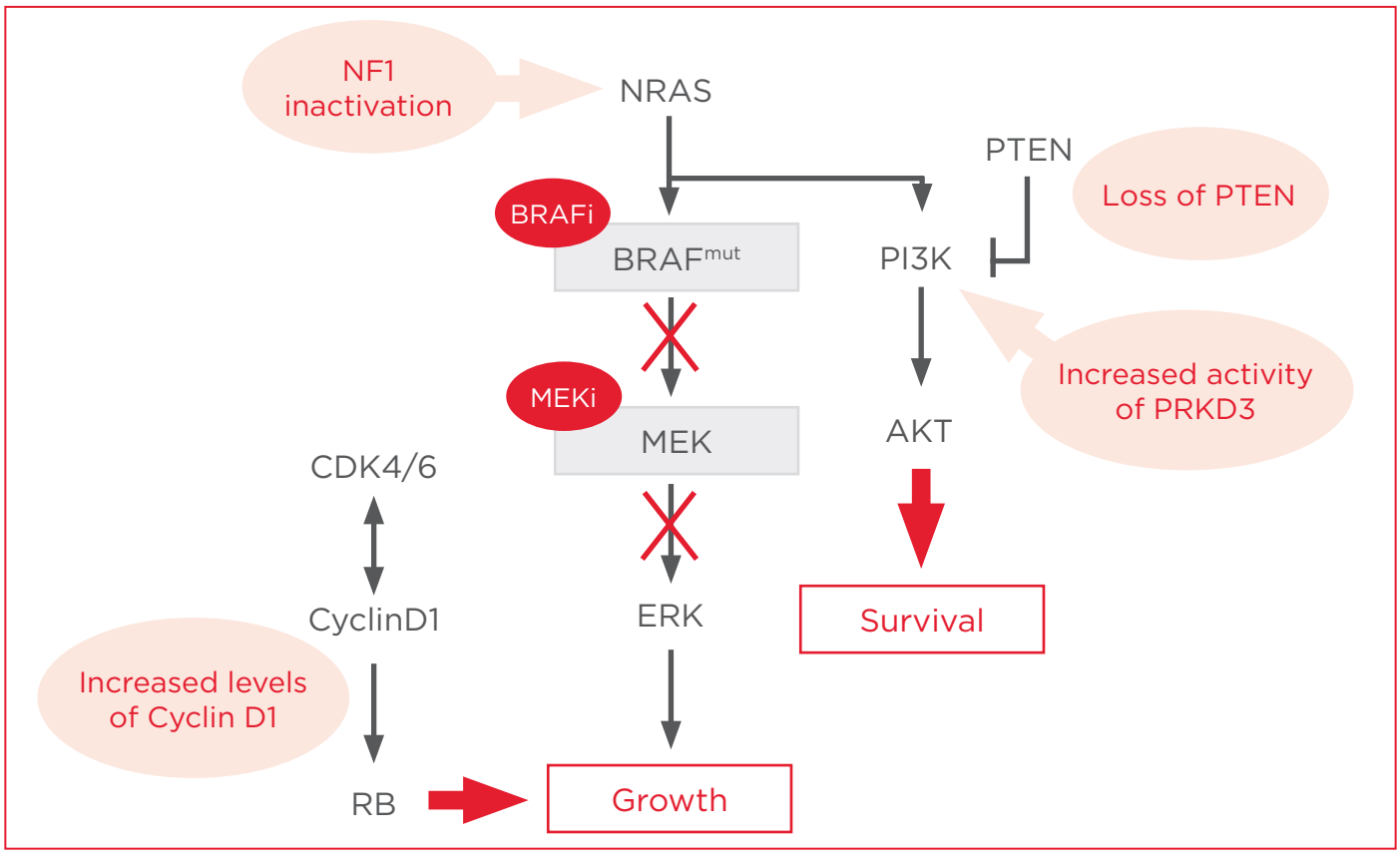


**Figure 1. Mechanisms of intrinsic resistance to BRAF-MEK inhibitors.**
Coexistent molecular features (pink balloons) are found to impair the antitumour activity of BRAF and/or MEK inhibitors by interfering with the key effectors of the two major pathways involved in melanoma pathogenesis. Arrows represent activating signals and interrupted lines represent inhibiting signals.
CDK: cyclin-dependent kinase; ERK: extracellular-related kinase; MEK: mitogen-activated protein kinase-extracellular-related kinase; PI3K: phosphatidylinositol 3 kinase; PTEN: phosphatase and tensin homologue are reported.

Hence, the occurrence of a p53 deficiency or, more generally, a status of apoptosis escape, with an unbalanced ratio between pro and anti-apoptotic effectors - all events found to cooperate with BRAF mutations in driving the melanoma progression[70,71] - may induce a MAPK-independent tumour growth.[72] Inactivation of AKT by targeting PI3K has also been demonstrated to effectively inhibit cell proliferation.[52,73] The combination of a BRAF or MEK inhibitor with a PI3K/mTOR inhibitor was found to enhance cell growth inhibition through achievement of ERK hypophosphorylation, reduced cyclin D1 levels, and increased p27 levels, overcoming the resistance encountered by the use of a single anti-BRAF or anti-MEK agent.[58,74] Amplification of cyclin D1, allelic deletions downregulating $p16^{CDKN2A}$, and alterations inactivating PTEN have all been associated with a poorer PFS after treatment with dabrafenib in patients with BRAF-mutant metastatic melanoma.[75]

Finally, loss of NF1 and activation of PRKD3 - the other two molecular events mentioned previously - contribute to the resistance to such target therapies by also stimulating the PI3K-AKT pathway directly (PRKD3) or indirectly, through activation of RAS (NF1).[55,56] Inactivation of NF1 by genetic or epigenetic impairments has been described in BRAF-mutant melanoma cells that are intrinsically resistant to BRAF inhibition as well as in melanomas developing resistance to vemurafenib.[55,76] For PRKD3, gene silencing has been reported to enhance cell growth arrest by BRAF and MEK inhibitors, and enforce cell sensitivity to these agents.[56] The NF1 loss and the PRKD3 activation can be considered as key mediators of both acquired and intrinsic BRAF inhibitor resistance (increased activity of PRKD3 seems to however confer resistance to RAF265 rather than approved BRAF inhibitors[56]).

## Acquired Resistance

In the vast majority of patients with BRAF-mutated melanomas, response to BRAF inhibitors is not durable and resistance to treatment develops in 6-8 months from the initiation of therapy. The mechanisms for this acquired resistance have proven to be highly heterogeneous.[77] Figure 2 summarises the different events involved in such a drug resistance. At a glance, two separate scenarios may be depicted.

The first scenario includes mechanisms underlying reactivation of the RAS-RAF-MEK-ERK pathway through induced alterations in components of this signalling cascade: activation of RAS signalling,[78] activating mutations in MAP2K1 (encoding MEK1 protein) or MAP2K2 (encoding MEK2 protein) genes,[79,80] activation of MAPK pathway agonists such as COT kinase,[81] occurrence of alternative splicing of the mutated BRAF mRNA,[82] BRAF-mutated gene amplification.[83] In this case, the cell proliferation/tumour growth is still depending on RAS-BRAF-MEK-ERK cascade activity and BRAF inhibition is overcome with alternative changes within this same pathway (real failure of BRAF inhibitors).

The second scenario is represented by reactivation of the suppressed ERK signalling through induced alterations in components of cell proliferation-controlling pathways different from the BRAF-MEK-ERK one: upregulation of the receptor tyrosine kinase (RTK) effectors - such as the platelet-derived growth factor receptor β (PDGFRβ),[84] activation of the MET-HGF system,[85] amplification of the CCND1/cyclin D1 gene or lack of PTEN function with subsequent activation of the PI3K-AKT pathway,[59] enhancement of the IGF-1R/PI3K signalling,[86] upregulation of the signal transducer and activator of transcription 3 (STAT3)-paired box homeotic gene 3 (PAX3)-signalling pathway.[87,88] In this case, BRAF inhibition is still effective, but the tumour is not dependent upon RAF-MEK-ERK signalling for growth and survival (paradoxical failure of BRAF inhibitors).

## Activation of RAS

Inibition of mutated BRAF leads to ERK hypophosphorylation; thus, ERK signalling is temporarily turned down after BRAF inhibition with subsequent relief of the physiological negative feedback on RAS (Figure 2). In melanoma with mutated BRAF, activation of the downstream MEK-ERK pathway is independent on the RAS-ligand activity, and BRAF mutant transmits continuous proliferation signals acting as a RAF-inhibitor-sensitive monomer. Vemurafenib and dabrafenib potently inhibit such BRAF mutant monomers, causing markedly decreased levels of ERK phosphorylation.[89] As a consequence, the ERK-dependent feedback is progressively turned off, RAS-driven signal transduction is restored with increasing levels of active RAS-GTP, and RAF-inhibitor-resistant RAF dimers are generated (Figure 3).

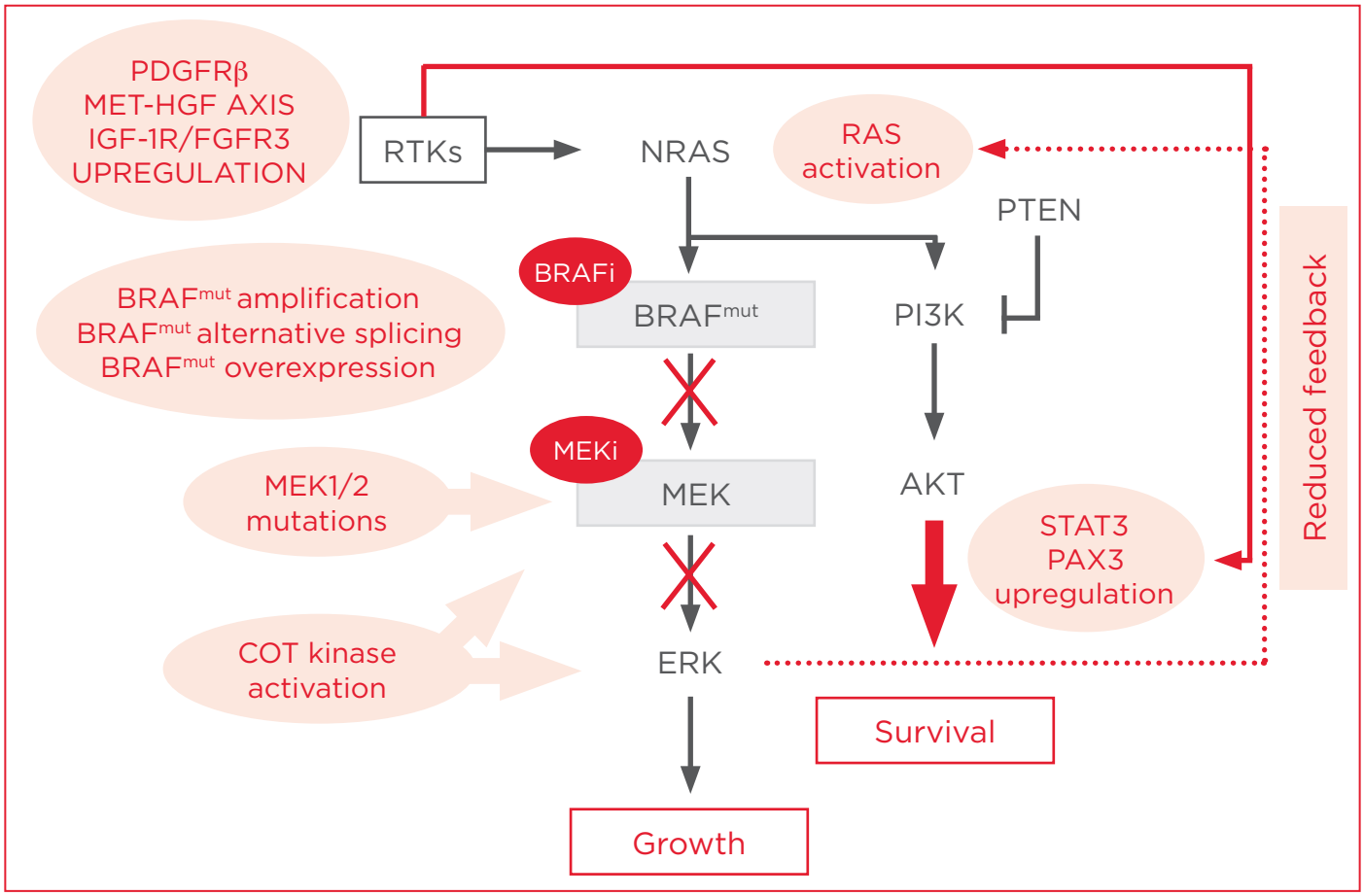


**Figure 2. Mechanisms of acquired resistance to BRAF-MEK inhibitors.**
Multiple acquired mechanisms (pink balloons) are involved in reactivation of components of the MAPK pathway or activation of alternative cell proliferation-controlling pathways. Arrows represent activating signals and interrupted lines represent inhibiting signals.
PDGFRβ: platelet derived growth factor receptor-beta; MET: MNNG HOS transforming gene; HGF: hepatocyte growth factor; IGF-1R: insulin like growth factor-1 receptor; FGFR3: fibroblast growth factor receptor 3; RTK: receptor tyrosine kinase; COT: cancer Osaka thyroid; STAT3: signal transducer and activator of transcription 3; PAX3: paired box homeotic gene 3.

The RAF homodimers (CRAF-CRAF) or heterodimers (BRAF mutant-CRAF) are able to restimulate the MEK-ERK pathway, resulting in an increased activity of the ERK1/2 proteins.[84,90] In preclinical models, increased CRAF activity was firstly identified in drug-resistant clones derived from cell lines undergoing BRAF inhibition.[91] Occurrence of CRAF mutations has been also reported to contribute to reactivate the MEK-ERK axis - again, in a dimerisation-dependent manner - following exposure to RAF inhibitors.[92] Alternatively, an enhanced activation of fibroblast growth factor receptor 3 (FGFR3) has been found to promote the RAS-driven signal transduction and confer resistance to vemurafenib in $BRAF^{V600E}$ melanoma cells (*in vitro* inhibition of the FGFR3/RAS axis indeed restores the sensitivity of vemurafenib-resistant cells to vemurafenib).[93]

Enhanced RAS-dependent RAF dimerisation has also been involved into the pathogenesis of squamous cell carcinomas, as a side-effect in subsets of patients treated with RAF inhibitors.[94-96] These agents have been demonstrated to indeed activate MAPK pathway by inducing RAF dimerisation in cells lacking BRAF mutations[26,28,82,97] leading to increased keratinocyte proliferation. In addition to the important role played by the intracellular levels of RAS-GTP, activating mutations in NRAS have been described to be acquired after treatment with BRAF inhibitors.[84,89,98] Again, such oncogenic mutations

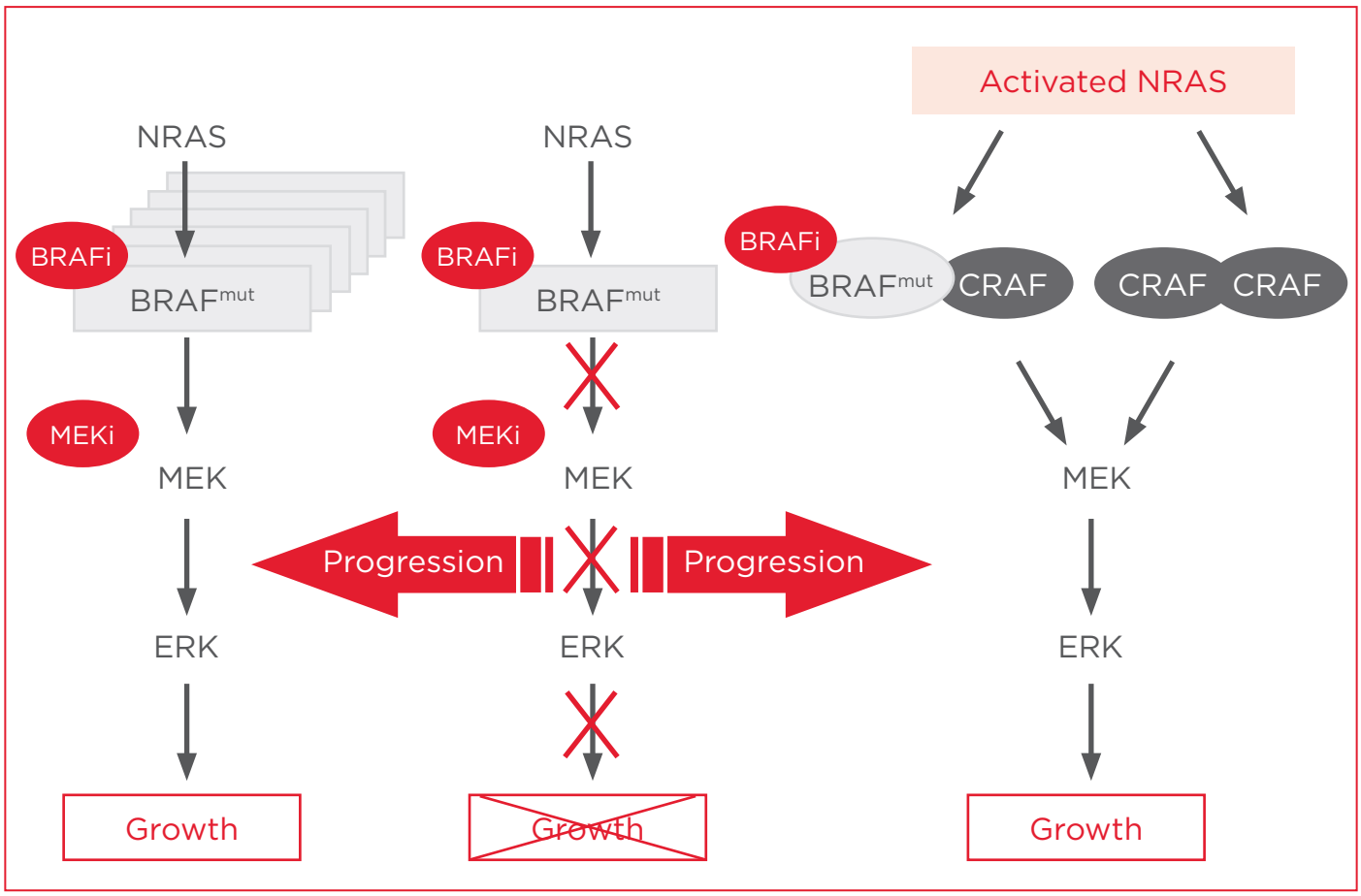


**Figure 3. BRAF inhibitor resistance by qualitative and quantitative alterations of the target.**
Mechanisms of acquired resistance to BRAF inhibition based on either generation of resistant RAF dimers or amplification of the BRAF-mutant monomers have been reported.

(usually, affecting the codon 61 of the NRAS gene) lead to activation of the RAS-dependent pathways: the MEK-ERK signalling, through dimerisation of RAF proteins and trans-activations of the RAF dimers, and the AKT signalling, through direct stimulation of the PI3K protein. Mutations in any of the three isoforms of RAS (with preponderance of those occurring in HRAS gene) may also contribute to the development of squamous cell carcinomas as adverse events during the treatment with BRAF inhibitors.[74,84]

## Quantitative and Qualitative Changes in BRAF

Resistance to either BRAF or MEK inhibitors has been reported in melanomas showing an increased copy number of the BRAF-mutant allele in a subset of melanomas[83,99] (Figure 3). Gene mutations and copy number gains may occur independently of each other, since they are determined from different pathogenetic mechanisms: alterations affecting the molecular machinery that monitor the proper progression of the cell cycle seem to be responsible for the presence of gross genomic anomalies during the malignant progression (indeed, copy number gains are often the consequence of random genomic instability), whereas mutations usually occur in diploid karyotypes with few structural abnormalities during the initial phases of evolution of malignancies.[100] However, in some cases gene amplifications tend to occur in the same cancers presenting oncogenic mutations as reported for EGFR in NSCLC or BRAF in colorectal carcinoma.[101,102] In melanoma, BRAF amplification has been poorly detected as a pre-existing alteration in cell clones prior to BRAF or MEK inhibitor treatment, suggesting that it might be mostly an acquired phenomenon in response to target therapy.[103]

A peculiar, qualitative mechanism of resistance is represented by the intracellular accumulation of a splice variant of the mutated BRAF mRNA.

A subset of melanoma cells resistant to BRAF inhibitors expresses a truncated form of $BRAF^{V600E}$, $p61BRAF^{V600E}$, which lacks a region that encompasses the RAS-binding domain. This leads to enhanced dimerisation of the truncated BRAF mutant, whose kinase remains constitutively activated. The final effect of such an alteration is a transactivation of the MEK-ERK pathways, with ERK signalling being resistant to the RAF inhibitors.[28,82] Moreover, the vemurafenib-resistant melanomas presenting an enhanced transcription and translation of the mutated BRAF kinase may develop a drug dependency for their continued proliferation, such that cessation of BRAF inhibitor administration may lead to regression of non-lethal drug-resistant tumours.[104] This evidence has suggested that a discontinued treatment with these agents may somehow prevent the emergence of lethal drug-resistant cell clones.[104]

## ERK Activation Via Alternative Kinases

In a fraction of BRAF-mutant melanoma cells resistant to BRAF inhibitors, resistance has been demonstrated to be maintained after downregulation of the kinase activities inducing RAF dimerisation, as a consequence of an alternative way of stimulation of the ERK signalling (Figure 2). In some of these cases, amplification of the receptor tyrosine kinase (RTK) MET as well as increased levels of the hepatocyte growth factor (HGF), which is the main ligand of the MET receptor, have been reported.[85,105,106] HGF acts as a soluble factor which may be overexpressed by stromal cells of the tumour microenvironment and stimulates MET receptor in a paracrine manner.[107] The HGF-MET interaction promotes transduction of the signals to the downstream PI3K effector with subsequent enhancement of the AKT activity.[106] Hyperstimulation of MET by HGF seems to be involved in both intrinsic and acquired resistance to BRAF inhibition; consistently, simultaneous administration of BRAF and HGF or MET inhibitors has been found to reverse drug resistance to the BRAF inhibitor alone.[85]

Activation of other RTKs has been proposed as contributing to anti-BRAF drug resistance, including IGF-1R-mediated mechanisms. The IGF-1R signalling cooperates with the MAPK pathway in regulating progression from benign nevi to malignant melanoma through sustainment of cell survival and dissemination.[108] Interruption of IGF-1R signalling has been shown to inhibit tumour growth and block metastasis formation in a wide variety of tumour models.[86] The main target of the increased expression of IGF-1R is again the PI3K-AKT pathway, whose activation is responsible for the development of resistance to BRAF inhibitors.[108] Dual inhibition of IGF-1R and MEK inhibitors has been demonstrated to induce growth arrest in BRAF inhibitor-resistant cells.[86]

An additional RTK protein involved in resistance to both BRAF and MEK inhibitors is represented by the PDGFRβ receptor, whose upregulation improves cell survival and invasiveness in a manner that is independent of the activation of the MAPK pathway.[84] In the presence of BRAF or MEK inhibition, the increased activity of PDGFRβ has been indicated to induce overexpression of the transcriptional activation factors STAT3 or PAX3 through stimulation of the Src/FAK signal transducers.[88,109] Indeed, silencing of one or both of these two genes may resume tumour growth arrest in BRAF-mutated melanoma cells with acquired resistance to vemurafenib.[87] Recent data have indicated that STAT3 protein can be activated by mutated BRAF and involved in stabilisation of the anti-apoptotic protein Mcl-1.[110] Downregulation of STAT3 - induced by BRAF-MEK inhibition - is able to impair the Mcl-1 activity and reduce melanoma cell survival.[110] Conversely, upregulation of STAT3 - exerted by increased levels of RTK activation - allows cells to become independent of the activity of the BRAF-MEK pathway and contribute to resistance to BRAF and MEK inhibitors (STAT3 expression is strongly enhanced in BRAF/MEK-inhibitor-resistant cells).[87,88,111]

Nearly all results about the role of the RTK effectors in resistance to such targeted treatments have been obtained in studies on melanoma cell lines; therefore, significant data from analysis of clinical samples are not yet available.

## Reactivation of MEK-ERK Pathway

Preclinical models have indicated that an increased expression of the COT kinase may strongly stimulate MEK and subsequently activate ERK signalling or directly promote the ERK activity, independently of the status of the upstream BRAF kinase.[81] The overexpression of the COT kinase, which is encoded by the MAP3K8 gene, is induced by the treatment with BRAF or

MEK inhibitors in both melanoma cells and tissues, acting as an agonist of the MAPK pathway and leading to resistance to BRAF-MEK inhibition.[81]

Another mechanism of resistance to BRAF of MEK inhibitors in BRAF-mutated melanoma is represented by the occurrence of activating mutations in either MAP2K1 (encoding MEK1 protein) or MAP2K2 (encoding MEK2 protein) genes.[112] *In vitro* models indicated that specific mutations in MAP2K1 (P124L and Q56P) may contribute to modify the allosteric pocket of MEK1 or disrupt the helix A conformation; such changes are able to make MEK1 protein either independent of stimulation by upstream oncogenic BRAF or insensitive to MEK inhibitors (through a block of their bind to the kinase).[79]

Most of the previously presented data are referred to mechanisms of resistance to inhibitors of mutated BRAF. Among them, several alterations are also involved in the acquired resistance to MEK inhibitors, including: amplification of BRAF mutant,[102] upregulation of the STAT3 transcription activator,[111] and driver mutations in MAP2K1 or MAP2K2 genes constitutively inducing the kinase activity of the MEK protein or the allosteric block of the binding of anti-MEK agents.[79,113] Melanoma cells chronically exposed to a MEK inhibitor have been recently reported to show both MAP2K2 mutations and BRAF-mutant amplification, with a subsequent acquired resistance to BRAF-MEK inhibition.[98] In preclinical studies, resistance to MEK inhibitors in BRAF-mutated melanomas has been correlated to activation of AKT; conversely, sensitive cell lines show upregulation of the PTEN tumour suppressor gene.[114,115]

For KIT, presence of some specific sequence variants within the coding regions of the gene have been found to render melanoma cells sensitive to KIT inhibition (see above). Acquisition of secondary mutations able to resume the gene signalling represents the main mechanism of resistance to KIT inhibitors (imatinib, nilotinib, dasatinib, sunitinib); different types of mutations have been reported to suppress the inhibitory activity of some or all of these agents.[116] Moreover, NRAS mutations and KIT amplifications may cause resistance to imatinib in KIT mutant melanoma.[46] In KIT-inhibitor resistant cells, simultaneous inhibition of the BRAF-MEK or PI3K-AKT pathways has been reported to induce apoptosis and growth arrest, suggesting that resistance is mediated by activation of these functional cascades.[46,117]

## FUTURE PERSPECTIVES

Considering all the above-described molecular mechanisms underlying resistance to BRAF, MEK, and KIT inhibitors, it is evident that a crucial role in determining such a phenomenon is played by the increased activity of ERK or AKT signalling. In most cases, the addition of a compound directed against one of these latter activated effectors to the treatment with a targeted agent may contribute to overcoming resistance to single inhibitors.

Activation of the ERK1/2 proteins and, therefore, of the ERK-dependent nuclear transcription has been largely reported to significantly drive either the development of an acquired drug resistance or the occurrence of most of the side-effects in melanoma patients. In preclinical models, a selective, ATP-competitive inhibitor of ERK1/2 kinases has been described to resume growth suppression in melanoma cells whose resistance was determined by ERK reactivation.[118] Moreover, discovery of a new RAF inhibitor, able to both inhibit ERK activity and protect ERK1/2 kinases from NRAS-driven reactivation in vemurafenib-resistant cells, further supports the hypothesis that a more efficient inhibition of ERK signalling in patients with activated MAPK pathway might represent a treatment option for avoiding or delaying the development of drug resistance.[119] Similar results have been described for a combined inhibition of BRAF mutant and MEK, with enhanced suppression of ERK activity, increased levels of apoptosis, and sustained antiproliferative effects.[120] A combination therapy based on the simultaneous use of MEK and BRAF inhibitors - therefore, targeting two effectors of the same pathway - has also been reported to achieve a clinical benefit.[37]

Nevertheless, preclinical data for the combination of MAPK signalling inhibitors and PI3K-AKT pathway inhibitors seem to suggest that such a treatment may become a winning therapeutic strategy to exert an effective antitumour outcome in melanoma patients. In this sense, combined treatment based on inhibition of BRAF and silencing of AKT3 was found to significantly increase suppression of tumour growth as compared to the result obtained by single agent

administration.[74,121,122] Similarly, the synergistic use of MEK and PI3K inhibitors[59,123,124] as well as the combinations of MEK inhibitors with agents inhibiting mTOR (the downstream effector of the PI3K-AKT pathway)[58,125,126] have been reported to exert an effective antitumour response. In other words, suppression of AKT activity by inhibition of either upstream (PI3K) or downstream (mTOR) effectors of this signalling cascade may enhance the antitumour effectiveness of the MAPK-targeted therapies. Finally, combination of MEK inhibitors with CDK4/6 inhibitors is under investigation, particularly in NRAS mutant melanomas.[127] Future efforts will be aimed at assessing composition and schedules of administration for such combined therapies in melanoma patients.


## Acknowledgements

The authors are writing on behalf of the Italian Melanoma Intergroup (IMI). Work was partially supported by the Italian Ministry of Health 'Progetto Ricerca Finalizzata' and Sardinia Regional Government (Regione Autonoma della Sardegna).


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# SKIN REACTIONS SECONDARY TO ANTICANCER AGENTS

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**Disclosure:** No potential conflict of interest.
**Received:** 17.09.13 **Accepted:** 11.11.13
**Citation:** EMJ Dermatol. 2013;1:38-43.

## ABSTRACT

In recent decades, new chemotherapeutic agents have been introduced in cancer therapy. The skin is often the target for the toxicity of these drugs. Skin side-effects may decrease the compliance and the quality of life of these patients. To cure and to prevent these side-effects dermatologists can cooperate with oncologists. In this paper we propose a brief review of the main toxic skin events caused by chemotherapeutic agents, in particular linked to the epidermal growth factor receptor (EGF-R) inhibitor.

Keywords: Skin reaction, chemotherapy, EGF-R inhibitors, radiodermatitis.

## INTRODUCTION

### New Antineoplastic Agents and Skin Toxicities

In recent decades, new chemotherapeutic agents have been introduced for cancer treatments, with various different side-effects: in particular the use of molecular target therapy has shown evidence of significant skin side-effects.[1] New drugs and new therapeutic schedules have brought many malignancies to a better prognosis and a longer survival. But sometimes many side-effects occur, reducing the compliance of the patients and decreasing their quality of life.[2,3] Sometimes it is necessary to interrupt the therapy. The aim of the dermatological research is to identify the correct prevention and therapy of these skin reactions. Common skin reactions undergoing chemotherapy include alopecia, papulopustular rash, hand-foot syndrome, paronychia and mucositis.[4] Alopecia and mucositis are very well-known side-effects of chemotherapy. No data will be presented in this review. Additional information on papulopustular follicular rash, hand-foot syndrome and paronychia are described below.

## EGFR INHIBITORS AND THE PAPULOPUSTULAR FOLLICULAR RASH

Among the innovative therapeutic strategies in chemotherapy, the epidermal growth factor receptor (EGFR) inhibitors (cetuximab, panitumumab, erlotinib, gefitinib) approved for lung and colon-rectum tumours showed an increasing skin toxicity, causing widespread skin dryness (in >90% of patients) and a papulopustular follicular rash which can be complicated by pruritus, pain and infections.[3,5] The papulopustular follicular rash, very often involves the seborrhoeic areas, scalp and chest, and less frequently, the extremities and the back, with papule and pustules. For these reasons it is also defined as an acneiform rash but the pathogenesis and histology is completely different from acne.[6] Its peculiar characteristic is the association of a typical sebaceous gland disease with a marked xerosis, suggesting

the keratinocyte itself is involved in the pathogenesis.[1] EGFR is expressed in epidermal keratinocytes, in hair follicle epithelium and in the sweat glands. Its activation plays a crucial role in keratinocyte proliferation and differentiation.[7] Its inhibition induces growth arrest and apoptosis, decreasing cell migration, increasing cell attachment and differentiation, and stimulating inflammation.[8]

Although the rash has been defined as 'acneiform,' distinctions should be done. The EGFRI (EGFR-inhibitor)-induced papulopustular eruption does not present comedones. In acne, the primary process is sebaceous hyperplasia and lipid release into the follicular lumen; it leads to comedo formation and overgrowth of *Propionibacterium acnes* that result in follicular wall rupture, stimulating neutrophil chemotaxis and pustule formation. On the other hand, in EGFRI rash the primary event is the damage of sebaceous glands and follicular epithelium, which leads to alteration in keratinocytes growth and differentiation. This causes the release of cytokines and the infiltration of mononuclear leucocytes ('sterile folliculitis').[9] The severity of the papulopustular rash is dose-dependent and correlates with an improved tumour response and survival.[8] The incidence of papulopustolar rash varies from 12-35%[8,10] and it often represents one of the cutaneous aspects persistently influencing the patient's quality of life. Gutzmer et al.[11] described cutaneous adverse reaction by targeted therapies (Table 1) and the classification of severity cutaneous adverse events during therapy with various EGFRI (Table 1 and 2).

**Table 1. Cutaneous adverse events by targeted therapies.**

| Target structure (reference) | Main indications | Substances | Cutaneous adverse events | Frequency |
|---|---|---|---|---|
| EGFR inhibitors | Carcinomas of lung, pancreas, gastrointestinal tract, breast; squamous cell carcinomas of the head and neck | Erlotinib, gefitinib, lapatinib, cetuximab, panitumumab | Papulopustular rash,<br>perifollicular xanthoma,<br>xerosis cutis/prunitus,<br>eczema craquele,<br>fissures/rhagades,<br>paronychia,<br>hypertrichosis,<br>hair follicle abnormalities | ++<br>+/-<br>++<br>+<br>++<br>++<br>+<br>+ |
| Multikinase inhibitors | Renal cell carcinoma, hepatocellular carcinoma | Sorafenib, sunitinib, pazopanib | Maculo-papular rash,<br>hand-foot syndrome,<br>hair discoloration,<br>skin discoloration,<br>xerosis cutis/prunitus,<br>facial erythema,<br>alopecia,<br>epithelial skin tumours,<br>subungual splinter haemorrhages | ++<br>++/pazopanib +<br>++/sorafenib -<br>++ (only sunitinib)<br>+<br>+<br>+<br>+ (only sorafenib)<br>+ |
| BCR/ABL<br>0-kit | Certain leukaemia entities, gastrointestinal stomal tumour | Imatinib, nilotinib, dasatinib | Maculo-papular rash,<br>periorbital oedema,<br>xerosis cutis/prunitus,<br>light sensitivity,<br>alopecia,<br>pigmentation disorders,<br>pustules/folliculitis | ++<br>++ (only imatinib)<br>+<br>+<br>+<br>+<br>+/- |
| Mutated BRAF | In clinical trials, with focus on melanoma | Vemurafenib (PLX4032, RG7204, RO5185426), GSK2118436 | Maculo-papular rash,<br>light sensitivity,<br>epithelial skin tumours,<br>alopecia,<br>hand-foot syndrome | ++<br>++(only vernurafenib)<br>++<br>+<br>+ |
| MEK | In clinical trials, with focus on melanoma | Selumetinib (AZD6244) GSK1120212 CI-1040 (PD184352) | Papulopustular rash,<br>xerosis/prunitus,<br>paronychia,<br>fissures/rhagades | ++<br>+<br>+<br>+ |

(++ very frequent [≥10%], + frequent [≥1%], +/- occasionally [≥0.1%], - seldom/never [<0.1%])
*Adapted from Gutzmer et al.*[11]

**Table 2. Classification of severity of cutaneous adverse events (as defined by the National Cancer Institute Common Toxicity Criteria, version 4.03).**

| | Papulopustular (acneiform) rash | Maculo-papular rash | Hand-foot syndrome |
|---|---|---|---|
| Grade 1 | <10% body-surface area, with or without symptoms of pruritus or tenderness | <10% body-surface area, with or without symptoms (e.g. pruritus, tightness, or burning) | Minimal skin changes (e.g., erythema, oedema, or hyperkeratosis) without pain |
| Grade 2 | 10-30% body-surface area, with or without symptoms of pruritus or tenderness; with psychosocial impact; limiting instrumental activities of daily living | 10-30% body-surface area, with or without symptoms (e.g. pruritus, tightness, or burning), limiting instrumental activities of daily living | Skin changes (e.g., peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain; limiting practical activities |
| Grade 3 | >30% body-surface area, with or without symptoms of pruritus or tenderness; limiting self-care activities of daily living: associated with local super-infection with oral antibiotics indicated | >30% body-surface area, with or without associated symptoms; limiting self-care activities of daily living | Severe skin changes (e.g.,peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain; limiting self-care activities |
| Grade 4 | Covering any percent of the body-surface area; with or without symptoms of pruritus or tenderness; associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences | | |
| Grade 5 | Death | | |

*Adapted from Gutzmer et al.*[11]

Recently, Curry et al.[12] divided skin reactions into two groups: cutaneous inflammations and cutaneous epithelial proliferations, but the classification of Gutzmer fits the aim of the investigation better. EGFRI (such as cetuximab) and MEK inhibitors (such as selumetinib and trametinib) showed papulopustular rash with a suppurative folliculitis in 83%, 93%, and 80% of the patients on therapy, respectively.[12]

## HAND-FOOT SYNDROME AND MULTIKINASE INHIBITORS

Hand-foot syndrome (HFSR) is one of the most common skin reactions, occurring in 30-60% of patients in therapy with EGFRI erlotinib and tyrosine kinase inhibitor sorafenib.[12-14] The HFSR often requires cessation or reduction of the dose of sorafenib therapy. Although the specific mechanisms underlying the sorafenib-induced HFSR are unknown, vascular endothelial growth factor receptor (VEGFR) was reported to be primarily responsible for this side-effect.[13-17] Sunitinib, like sorafenib, is a multikinase inhibitor used for kidney and liver cancers: it is associated with bullous manifestation and HFSR, which can also be used as a marker of drug efficacy;[18] inflammatory actinic keratosis has also been observed with these two drugs.[18,19] Other multikinase inhibitors in addition to HFSR also induce skin changes, such as facial erythema and subungual splinter haemorrhages.[20] RAF inhibitors such as vemurafenib were also associated with a variety of cutaneous epithelial proliferations (keratosis pilaris, seborrheic keratosis, verruca vulgaris, actinic keratosis, keratoacanthoma, and squamous cell carcinoma).[12]

BRAF inhibitors can lead to the development of rashes and cutaneous keratinocytic neoplasms, for which patients should be closely monitored. Finally, MEK/ERK inhibitors induce similar skin toxicities to EGFRI, such as papulopustular rashes, skin xerosis and paronychia.[19-21] Multikinase inhibitors used in haematology, such as imatinib,

dasatinib and nilotinib, frequently cause skin toxicity, such as exfoliative dermatitis, associated with fever[18] and frequently with oedema. The phosphoinositide 3-kinase (PI3K)/serine-threonine protein kinase Akt pathway is a vital transduction cascade that is connected with many essential cellular activities, such as growth and survival. PI3K inhibitor BKM120 and AKT inhibitor MK2206, used in patients with ovarian cancer, produced maculopapular eruptions.[12]

## NAIL DAMAGE AND EGFR

Paronychia and periungual pyogenic granuloma-like lesions are observed in 10-30% of patients receiving EGFRI therapy, developing after 2 or more months of drug exposure. Paronychia is characterised by oedematous inflammation of the nail folds and usually affects the first digits. Periungual pyogenic granuloma-like lesions are characterised by easily bleeding, friable vascular tissue overgrowth on lateral nail folds.[22] The pathogenesis of paronychia is due to the traumatic conflict between the thin tissues around the nail and the nail itself. In fact, changes in growth and differentiation of the nail are responsible for the retention of squama in the nail folds, which act as foreign bodies, causing an inflammatory reaction.[23]

## RADIATION THERAPY AND SKIN REACTION

Up to 60% of patients with cancer receive radiotherapy treatment. One of the main side-effects of this treatment is an acute skin reaction, which may range in severity from a mild erythema to very severe radiodermatitis. Different treatments are proposed.[24-28] Skin radiotherapy (RT) reactions can be divided into acute and chronic. Radiation-induced acute skin reactions are traditionally assessed using the Radiation Therapy Oncology Group (RTOG) toxicity criteria.[24-31] To treat severe acute radiation skin reactions (ARSR) such as radiodermatitis, the data show that, among the topical products analysed, calendula, corticosteroids, topical sodium hyaluronate, urea, and allantoin have shown significant protective effects.[25] In the expert opinion from the Cancer Care Ontario's Supportive Care Guidelines Group (SCGG) the use of a plain, non-scented, lanolin-free hydrophilic cream may be helpful in preventing radiation skin reactions. In addition, a low dose (i.e. 1%) corticosteroid cream may be beneficial in the reduction of itching and irritation.[32] To reduce the risk of severe acute radiation skin reaction some authors suggest that it can be useful to stop smoking during RT because smoking is an independent risk factor for ARSR.[24]

Among the skin reactions it can be useful to signal the Erythema Multiforme associated with Phenytoin and Cranial radiation Therapy (EMPACT) syndrome. Phenytoin is commonly used as an antiepileptic medication for seizure prophylaxis in patients with brain metastases;[33] it can, rarely, cause side-effects when associated with radiotherapy. The EMPACT syndrome is characterised by erythematous macular eruption on the scalp within the radiation field in patients under phenytoin therapy; that usually dramatically extends after a few days to involve extensive areas of the face, trunk and extremities. Significant mucocutaneous blistering and desquamation with conjunctival suffusion can also develop.[33] The pathogenesis of the EMPACT syndrome is still unclear. Studies in mice have shown that brain radiation can induce the increase of TNF-α, TNF-β, ICAM-1, and cytokines that could induce cellular autoimmunity. Moreover, radiation can alter the metabolism of phenytoin and anticonvulsant drugs. Normally, phenytoin and other anticonvulsants induce microsomal cytochrome P450 3A (CYP3A) and produce oxidative intermediates that are later detoxified by epoxide hydrolase. In the case of therapy with phenytoin/phenobarbital and radiation therapy, a deficiency of this enzyme can develop. Oxidative intermediates, which cannot be metabolised, have direct toxicity for cells, and/or they can bind cell macromolecules and behave as haptens. These mechanisms can stimulate a new immune response and be responsible for skin manifestations. Fabbrocini et al.[33] described two interesting cases of EMPACT syndrome, caused by the combination of phenobarbital and cranial radiotherapy.

## CONCLUSIONS

In these last years, new cancer therapies have led to the increase of anticancer therapy success, but several skin reactions have emerged. These negatively impact on the quality of life of these patients. The dermatologist plays a critical role in the management of these adverse effects. A strong relationship between dermatologists and oncologists is important to make the best

decisions for patients and to choose anti-toxicity interventions with minimal side-effects. During and after radiation therapy it is particularly necessary to have a close follow-up in order to identify and monitor precancerous lesions occurring in these patients.

## Take-Home Messages:

• New chemotherapeutic agents increase survival, but can lead to several skin reactions, worsening the quality of life of patients.

• The EGFRI (such as cetuximab, panitumumab, erlotinib, and gefitinib) showed increasing skin toxicity, causing widespread skin dryness and the papulopustular follicular rash.

• HFSR occurred in 30-60% of patients in therapy with EGFRIs erlotinib and sorafenib.

• Paronychia and periungual pyogenic granuloma-like lesions could be observed in patients receiving EGFRI therapy.

• It is necessary to pay attention to cranial radiation therapy and neuroleptic drugs such as phenobarbital and phenytoin that can cause skin reaction such as EMPACT syndrome.

• Hydration, antimicrobial, sterile tissue, protective ointment, and specific dermocosmetological treatments can reduce the side-effects of chemo and radiotherapy.

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# NAIL CHANGES IN RECENT AND OLD LEPROSY PATIENTS

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**Disclosure:** No potential conflict of interest.
**Received:** 27.09.13 **Accepted:** 21.10.13
**Citation:** EMJ Dermatol. 2013;1:44-52.

## ABSTRACT

Nails are elements of skin that can often be omitted from the dermatological assessment of leprosy. However, there are common nail conditions that require special management. This article considers nail presentations in leprosy patients. General and specific conditions will be discussed. It also considers the common nail conditions seen in leprosy patients and provides a guide to diagnosis and management.

Keywords: Leprosy, nails, neuropathy, multibacillary leprosy, paucibacillary leprosy, acro-osteolysis, bone atrophy, type 2 lepra reaction, anonychia, clofazimine, dapsone.

## INTRODUCTION

Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae*, known since ancient times and with great historical connotations.[1] This infection is not fatal but affects the skin and peripheral nerves. The disease causes cutaneous lesions, skin lesions, and neuropathy, with secondary complications potentially resulting in deformity and disability. In fact, leprosy remains a stigmatising disease. In many parts of the world the prevalence of the disease is very low, while in others it is a major public health issue.[2] Since the generalisation of multidrug therapy (MDT) (or combination of fixed-dose drug treatments with a shorter duration) and early diagnosis of leprosy, there has been an observed decrease not only in prevalence across the world, but also in mortality and morbidity and functional damage.[2-12] The number of new cases of leprosy declared by the World Health Organization (WHO) has decreased from 620,000 in 2002, to 182,000 in 2012. Most cases occur in Southeast Asia, America and Africa, and particularly in India, Brazil, Indonesia, Bangladesh, Democratic Republic of the Congo, Ethiopia, Nepal, and Myanmar.[2,13]

Leprosy can cause damage to the nails, generally indirectly. There are few reviews about the affectation of the nails due to leprosy. Nails are keratin-based elements of the skin structure that are often omitted from the dermatological assessment of leprosy. However, there are common nail conditions that require diagnosis and management. Therefore, we considered it interesting to show our experience obtained in a rural hospital in the southern region of Ethiopia.[7,14-16] The Gambo General Rural Hospital is a referral institution in Ethiopia's Programme of Leprosy Care according to its Ministry of Health's guidelines for the Tuberculosis and Leprosy Prevention and Control Programme.[17] It is located in the West Arsi zone, 250 km south of Addis Ababa. In 1960, the Leprosy Centre in Gambo was erected and, until 1986, it supervised 20 leprosy care stations in the Arsi Region. After that, it was transformed into the Gambo General Hospital where, in addition to leprosy, they also attend to other general medical conditions. During this period a leper village was built around the hospital. This hospital is a reference centre for the treatment of patients with leprosy.[7,15,16]

## PREVALENCE OF NAIL CHANGES IN LEPROSY

Limited studies have examined the prevalence of nail changes in leprosy patients. In the first study conducted in 1991 in India, Patki and Baran[17] found a prevalence of nail changes of 64% among the 357 patients studied. Years later, Kaur et al.[18] in a study conducted in 2003 with 300 patients with leprosy in India, found a prevalence of 77.3% overall, 56% in paucibacillary (PB) leprosy, 87.3% in the multibacillary (MB) leprosy, and 96% in former lepers living in the surrounding leper village. More recently in the study of El-Darouti et al.[19] involving 115 leprosy patients in Turkey, the prevalence of nail changes found was 86% in both MB and PB leprosy. There are several reviews about nail problems in leprosy patients.[18-20]

## CAUSES OF NAIL DAMAGE

In leprosy nails can be affected in up to three out of four patients with the disease. Associated factors are many and they include repeated trauma, neuropathy, vascular insufficiency, infections, or drugs used in leprosy treatment.[17-19,21] In Table 1 the causes involved in nail damage in leprosy can be observed.

**Table 1. Causes of nail changes and nail pathology in leprosy patients.**

| Cause | Nail problem |
|---|---|
| Neuropathy (sensitive, motor, autonomic) | Subungual haemorrhage<br>Onycholysis<br>Onychauxis<br>Onychogryphosis<br>Pterygium unguis<br>Onychoheterotopia |
| Injury (acute or chronic injury) | |
| Vasculopathy | Pterygium unguis<br>Flag sign<br>Pallor of nail |
| Acro-osteolysis | Brachyonychia<br>Pseudoclubbing or Racket nail<br>Anonychia |
| Infection (ulcer, osteomyelitis) | Onychomycosis<br>Paronychia |
| Type 2 lepra reaction | Pterygium unguis |
| Drugs (clofazimine, dapsone) | Beau's lines<br>Subungual hyperkeratosis<br>Onycholysis |
| Multifactorial | Longitudinal melanonychia<br>Pitting nails<br>Pseudomacrolunula<br>True leukonychia<br>Hapalonychia<br>Pallor of nail<br>Terry's nails<br>Flag Sign |

## Neuropathy

The main factor is neuropathy, which also facilitates the negative action of all other causes.[17-19] In this context it can be assumed that, since one of the main causes is peripheral neuropathy, these changes would be similar to those seen in patients with diabetic neuropathy. But this is not so, and we have seen that nail pathology is more frequent and more florid in leprosy patients than in diabetic patients.[19] As a result of neurological damage, there can be a loss of sensitivity and a deformity of the fingers and toes, and from autonomic neuropathy with anhidrotics, dryness and cracking of the skin, particularly of the hands and feet can be observed. Due to anaesthesia of distal areas of the fingers, as well as deformity thereof, any small thermal or mechanical trauma, especially if recurrent, is predisposed to wound or burn with repeated infections of the area, leading to osteolysis of the last phalanx with the tapering and the loss of the tips of the fingers and toes, and therefore of the nails.[5,6,22]

## Acro-Osteolysis

Acro-osteolysis refers to bony resorption of the terminal digital tuft. It is a well-recognised condition in leprosy patients. It is common in advanced stages and appears as a result of nerve disorders (motor, sensory and vase-motors).[23,24] Acro-osteolysis also is facilitated by: 1) repeated trauma, 2) ischaemia occurring at type 2 lepra reaction endarteritis, 3) diffuse osteoporosis associated with testicular atrophy presenting in leprosy, and 4) bone damage granulomas due to direct specific lepromatous leprosy. Moreover, osteomyelitis can contribute to acro-osteolysis.[23,24] During bone resorption, osteoclasts break down bone, release minerals, and transfer calcium from the bone fluid to the blood. Absorption of the trabecular (or spongy) bone and the development of bone atrophy (loss of bone density) are associated with impaired nerve function, male sex, grade of disability at diagnosis, and the occurrence of four or more leprosy reactions. The initial changes in the radiograph of the fingers are transverse lytic bands in the distal phalanx, and when damage evolves, this resorption can reach the terminal phalanges with deform destructive osteolytic changes causing dystrophic nails.[18] These nail changes support Baran and Juhlin's hypothesis,[25] indicating that the evolution of the nail depends on underlying bone, therefore hyponychia and anonychia occur when the bone is hypoplastic or absent. In fact in leprosy, nail changes usually occur secondary to distal reabsorption of the phalanges.[17]

## Leprosy Reactions

Another circumstance that has consequences for the nails is the presence of vasculitis, which occurs during type 2 lepra reaction (erythema nodosum leprosum (ENL) reaction). Type 2 lepra reaction is involved with the consequent production of immune complex.[12] Usually it is presented as erythematous subcutaneous nodules, neuronal damage and multi-organ involvement. In this process iridocyclitis, orchitis and other systemic manifestations such as fever, arthritis, lymphadenitis, neuritis or nephritis may appear.[26] In this leprosy reaction, peripheral vasculature is affected, precipitating distal tissue loss, sometimes including nails.[27] The type 2 lepra reaction may appear before the diagnosis of leprosy during treatment or at the end of treatment.[4,5]

## Drugs

Medications used in the treatment of leprosy, such as clofazimine and dapsone, have also been implicated in various nail changes such as Beau's lines, subungual hyperkeratosis and onycholysis as it is explained after.[17-19]

# NAIL CHANGES IN LEPROSY

Nail changes are not specific to leprosy and may be observed in other peripheral neuropathies such as diabetes mellitus[28] as we have previously indicated. In leprosy patients, the sheet, the matrix, the bed and periungual folds of the nail can all be affected. The alterations may be varied, affecting the shape, size, thickness, surface area, consistency, colour, and relative bed, that is to say the sheet nail tissue in general. In Table 1, we can see the type of nail changes in leprosy patients, proposed by Patki and Baran,[17] according to cause of nail damage.

## Anonychia

The absence of nail or anonychia (Figure 1) is usually the result of disease progression and may be associated with the loss of the terminal

phalange. During this process the nails dry, gradually tarnish, and shrivel before disappearing.[29] The anonychia usually affects all nails. At this stage of mutilation with absence of phalanges and anonychia, sometimes the hand resembles the fins of the fish (Figure 1).

## Beau's Lines or Transverse Lines

Beau's lines are transverse depressions in the nail plate that occur as a result of a temporary cessation in nail growth (Figure 2). The causes include trauma, nutritional disorders (especially minerals such as zinc and iron), febrile illness, and drug sensitivity.[30] In patients with leprosy, they appear after trauma or severe episodes of leprosy reaction or as the side-effect of treatment with dapsone and/or clofazimine.[31,32]

## Brachyonychia

The brachyoychia consist of micronychia (abnormal smallness of the fingernails or toenails) or decreasing the length of the nail, and in leprosy usually appear following the acro-osteolysis and subsequent tissue pad of the fingers (Figure 3).[33]

## Diffuse Lunula or Pseudomacrolunula

Diffuse leukonychia or pseudomacrolunula was described by Pardo-Castello as an early change in leprosy.[34] It produces a distal advancement of the lunula, giving a white appearance to the nail, so it is also known as apparent leukonychia. In these cases it holds the transparency of the sheet, being the matrix and the normal film (Figure 3). This alteration was more frequently found in the study of 118 patients by El-Darouti et al.[19] than in others studies.[17,18]

## Flag Sign

Flag sign is the alternating transverse bands of pseudo-whitish and pinkish discoloration of the nail plate in the fingernail. This sign can be ascribed to peripheral vascular changes that are expected to occur more commonly in MB leprosy patients. It has been described recently in the study of El- Darouti et al.[19] in 15% of patients with leprosy and in 5% of diabetic patients studied.[19]

## Hapalonychia and Onychorrhexis

Hapalonychia (softened nails) and onychorrhexis (brittle nails) (Figure 4) are characterised by

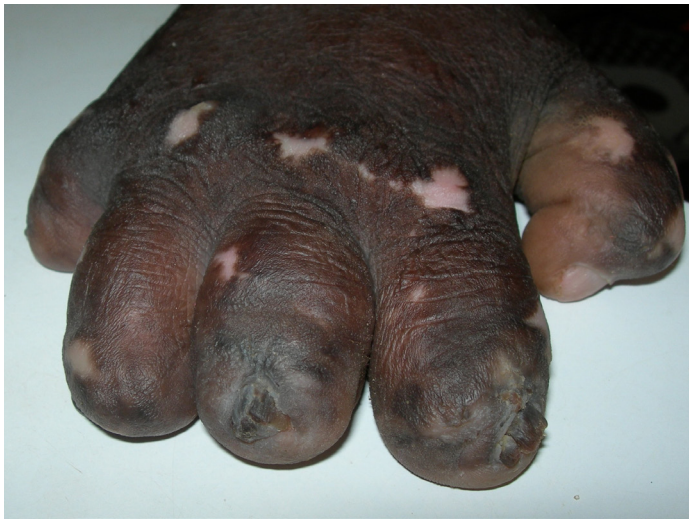

**Figure 1. Hand with absence of phalanges and anonychia, resembles the fins of a fish and also onychoheterotopia.**

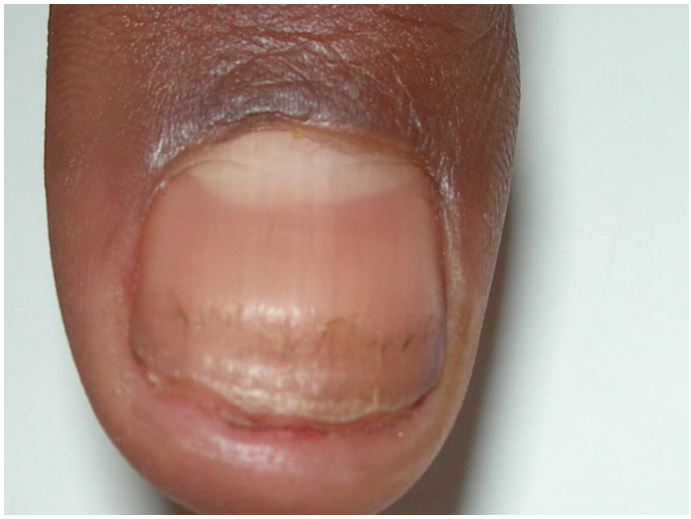

**Figure 2. Nail with Beau's line with transverse depressions in the nail plate.**

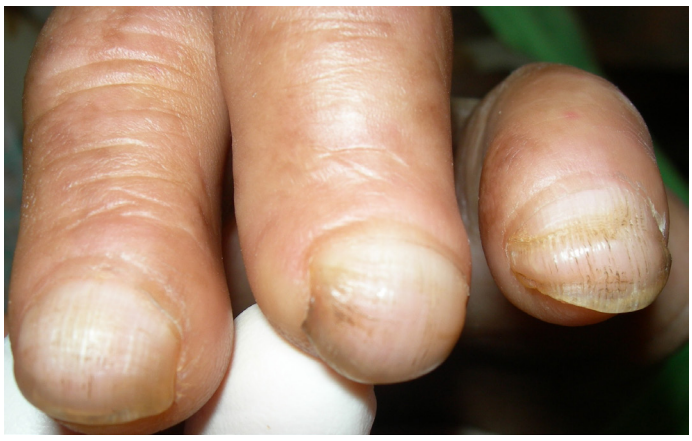

**Figure 3. Nails of three fingers of hand with brachyonychia, diffuse leukonychia or pseudo-macrolunula and splinter haemorrhage.**

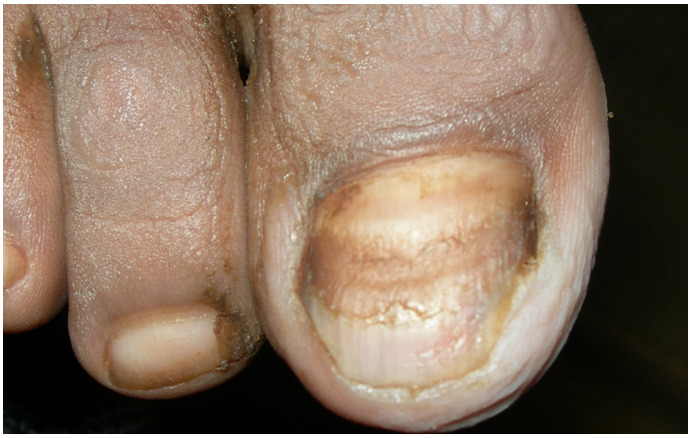

Figure 4. Nail of foot with onychorrhexis.

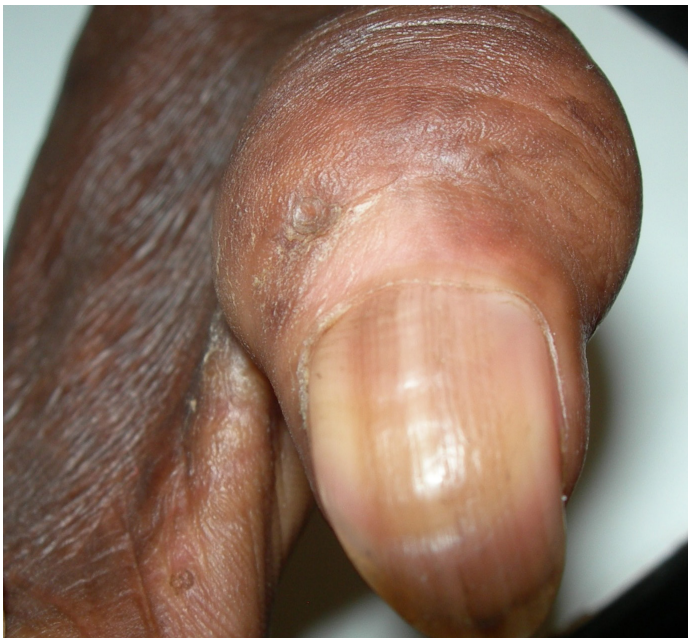

Figure 5. Nail with longitudinal melanonychia and pseudoclubbing with the preservation of the nail-fold angle.

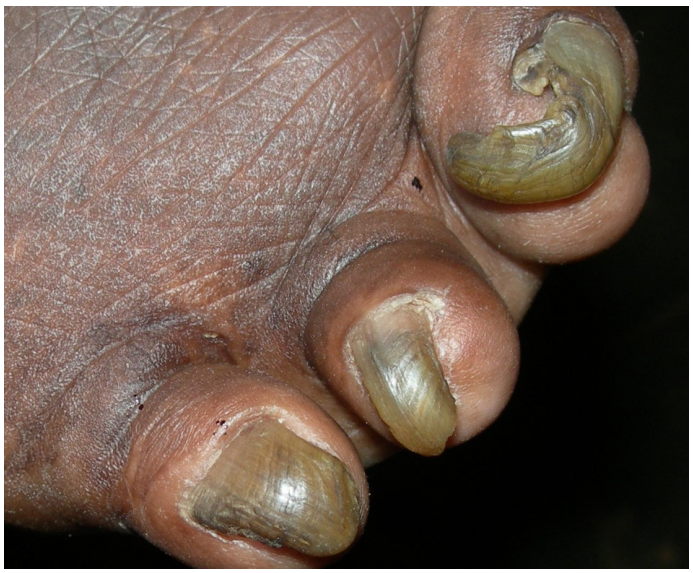

Figure 6. Nails of three toes with onychogryphosis.

softened nails resulting from a defect in the matrix that makes the nails thin and soft so that they can be easily bent. They occur in old leprosy patients[33] and are more frequent in the advanced stages of the disease, especially in the 'crow hand'.[17,35,36]

## Longitudinal Melanonychia

Longitudinal melanonychia is characterised by the presence of longitudinal brown or black lines in the nail plate as a result of increased melanin deposits (Figure 5). They originate in the nail matrix and are the result of an increased production of melanin by matrix melanocytes or an increased number of melanocytes in the nail matrix.[17] It has been associated with a range of drugs, especially hydroxyurea, doxorubicin or zidovudine.[37] The prevalence of melanonychia in the general population has been estimated to be 1%, increasing to 12% in hospitalised patients.[38] The longitudinal melanonychia is the most common nail manifestation in the study of Kaur et al.[18] and also ranks second in the series of El-Darouti et al.[19]

## Onychauxis

Onychauxis (localised hypertrophy of the nail plate) manifests as hyperkeratosis, discoloration, and loss of translucency of the nail plate, with or without subungual hyperkeratosis.[21] It is often part of the nail dystrophy in patients with leprosy.[18,19]

## Onychoheterotopia

Onychoheterotopia (Figure 1) is a growth of nail tissue in any site other than the classical nail unit areas. It develops either after a single overwhelming trauma or after chronic repetitive injuries, which lead to both splitting and implantation of the germinal matrix or heterotopic inoculation of the oncocytes (nail bed cells). Osseous defects may occur from the contact of the ectopic matrix with the underlying bone. Such cases occur predominantly over the dorsal aspect of the hand.[39] It is a very rare entity in patients with leprosy[39] resulting in continued trauma, and it can be seen in patients with long-standing neuropathic damage.[18,19]

## Onychogryphosis

Onychogryphosis (Figure 6) refers to nail plate thickening with gross hyperkeratosis and

increased curvature of the nail plate, either downward (oyster-like onychogryphosis) or upward (known as ram's horn dystrophy).[21] It usually occurs as a result of repeated minor injury to the nails as in the onychauxis. It is more common in toenails than in fingernails,[40] as it can be associated with poorly fitting footwear. In a series of 20 patients who recovered from leprosy in Japan, onychogryphosis was the most common nail disorder.[33] In patients with leprosy treatment, there was speculation about the possible involvement of clofazimine in its development.[41]

## Onycholysis

Onycholysis is distal separation of the nail plate from the underlying nail bed and leads to a space where it accumulates subungual keratin and impurities.[21] Nails with onycholysis are usually smooth, firm, and without nail bed inflammation. It is not a disease of the nail matrix, though nail discoloration may appear underneath the nail as a result of secondary infection, both bacterial and fungal.[42] Onycholysis is associated with many systemic conditions, not only leprosy, although it is a common disorder in lepers.[17-19] It is worth noting the so-called green nail, which shows a green colouration of the nail due to pyocyanin and pyoverdin pigment produced by *Pseudomonas aeruginosa* infection that often occur when onycholysis and humidity are present in leprosy nails.[43]

## Onychomycosis

Onychomycosis is a fungal infection of the nail. It has been observed in 20-30% of patients with leprosy as recorded by Pardo-Castello and Pardo,[34] however, in more recent series the prevalence was found to be <5%.[18,19] In the general population the prevalence of onychomycosis is about 2%,[44] which means it is more common in patients with leprosy.[45,46] The nail can be affected in the context of tinea corporis and results in tinea unguium caused by dermatophytes (*Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, etc.), and at other times by *Candida albicans* ('thrush nail').[44,46] This condition is characterised by asymmetrical nail discolouration and nail thickening with subungual hyperkeratosis. Infection may be superficial, proximal or distal and sampling for microscopy and/or culture may involve nail plate scraping, punch biopsy or collection of subungual debris.

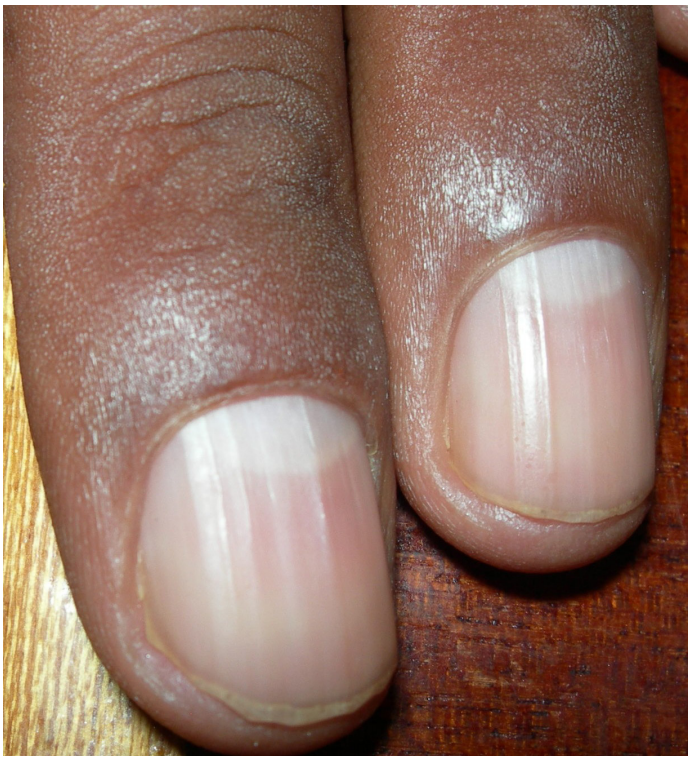

**Figure 7. Nails pallor with longitudinal striae.**

## Pallor of Nails

It may occur in leprosy patients, as the result of the anaemia associated to chronic disease or to haemolysis caused by dapsone (haemoglobinopathy), or vascular insufficiency (Figure 7).[18,19]

## Paronychia

Paronychia, consisting of infection of the nail folds, presents in both acute and chronic leprosy forms. The former usually has a bacterial cause (often *Staphylococcus aureus* and/or *Streptococcus pyogenes*) secondary to injury. Patients will often present with a solitary painful distal finger. There may be pus evident on tender, brilliant erythematous nail folds. An important differential diagnosis is herpetic whitlow.[37] These repeated bacterial infections cause destruction of the nail matrix, loss of the sheet and finally scarring of the nail bed.[47]

## Pitted Nails

Pitted nails are described as pinpoint (or larger) depressions in an otherwise normal nail.

The pittings are staking shaped defects on the surface of the nail plate, which appear due to the presence of parakeratosis in the proximal matrix. Pitting is usually associated with psoriasis and affects 10-15% of patients with the disorder, and it has also been reported in patients with Reiter's syndrome, sarcoidosis, pemphigus, alopecia areata, and incontinentia pigmenti.[21] In leprosy, it can appear up to 4% of the patients.[18]

## Pterygium Unguis

Pterygium unguis appears as an extension of the skin of the proximal nail fold that expands distally to adhere to the nail bed. Although lichen planus is the most common cause of pterygium unguis, the lesion may be a consequence of nail matrix destruction caused by other conditions, such as trauma, digital ischaemia, and bullous disorders.[48] In leprosy it is related to injuries and/or vascular ischaemia in the nail matrix that occur in endarteritis obliterans of type 2 lepra reaction.[48-50] No cases were reported in the study by El Darouti et al.[19] but it was common in the study by Patki and Baran.[17]

## Pseudoclubbing or Racket Nail

The pseudoclubbing or racket nail (Figure 5) appears due to the progressive regression of the pad of the finger with severe bone erosions of the terminal phalanges (brachyphalangia), which lead to the shortening and widening of the nail. Pseudoclubbing may be distinguished clinically from clubbing by the preservation of the nail-fold angle and bony erosion of the terminal phalanges on radiograph. The brachyonychia and pseudoclubbing are common in brachy-dactilias and support Baran and Juhlin's[25] hypothesis indicating that the evolution of the nail depends on subjacent bone.

## Splinter Haemorrhage and Subungual Haemorrhage

Splinter haemorrhages are extravasations of blood from the longitudinally oriented vessels of the nail bed (Figure 3). These haemorrhages do not blanch with pressure. They are formed as a result of the nail plate-dermis structural relationship and tend to be seen in older patients. They are seen as a grey area and even blue-black through the nail. Trauma is the most common cause, and they may also occur in psoriatic nails or with fungal infection. In leprosy patients, they occur after trauma, and the patient generally does not perceive them. They may be an early change and are usually followed by reabsorption or detachment of part or the whole nail, even to loss of the sheet. Interestingly, diseases which are similar in appearance, such as subungual nevi or melanoma, can also occur in patients with leprosy, and in these cases dermatoscopy could be very helpful.[51]

## Terry's Nails

Terry's nails are a special type of macrolunula, yielding a white and opaque colour that reaches 1-2 mm from the distal edge, the distal region being pink or brown.[21] Most of the nail plate is white, with a narrow pink distal band. All nails tend to be uniformly affected, with an appearance of ground glass. Terry[52] described it in 1954 in a patient with liver cirrhosis, and it has been found in 80% of patients with liver cirrhosis. In 1987 in India, Singh et al.[53] reported Terry's nails in leprosy patients. In the study of El Darouti et al.[19] up to 17% of patients with leprosy had this nail disorder.

## True Leukonychia

In the true leukonychia the nails are strikingly white, opaque with smooth surface and normal strength. The nail beds, folds and edges were normal. The origin of the white nail plate is in the matrix. True leukonychia may be total or subtotal, temporary or permanent. Partial leukonychia can be punctate, transverse and distal. The common causes of these disorders of keratinisation of distal nail matrix include: local trauma, exposure to extreme cold, disturbed nutrition and hepatic cirrhosis.[21]

# PERSONAL EXPERIENCE OF NAIL CHANGES IN OLD LEPROSY PATIENTS

A cross-sectional study was conducted in June 2011 in the Gambo General Rural Hospital.[14] patients were collected from the 45 admitted to the hospital. Four patients were excluded because they were admitted for treatment of leprosy or they were diagnosed less than 2 years previously. From 10 patients, 5 cases were women; the median age was 50.5 years (range: 33-65) and the time to diagnosis was 20 years (range: 2-40). 20 hands and 15 feet were assessed (5 feet had been amputated); also, 3 fingers were amputees.

**Table 2. Fingernail and toenail changes in 10 old leprosy cases.**

| | Percentage |
|---|---|
| **Fingernails** | |
| Any change | 94.0 |
| Longitudinal striatal | 46.6 |
| Pseudoclubbing or Racket nails | 25.8 |
| Longitudinal melanonychia | 24.7 |
| Brachyonychia | 20.6 |
| Pallor of nails | 20.6 |
| Onychauxis | 18.6 |
| Hapalonychia | 11.3 |
| Beau's lines | 10.3 |
| Onychorrhexis | 8.2 |
| True leukonychia | 8.2 |
| Ectopic nail | 7.2 |
| Terry's nails | 7.2 |
| Onychogryphosis | 5.2 |
| Pterygium unguis, | 2.1 |
| Anonychia, | 2.1 |
| Pterygium unguis | 2.1 |
| Flag sign | 1.0 |
| Subungual haemorrhage | 1.0 |
| | |
| **Toenails** | |
| Any change | 94.0 |
| Onycholysis | 49.3 |
| Brachyonychia | 49.3 |
| Onychauxis | 47.9 |
| Pseudoclubbing or Racket nails | 36.6 |
| Onychogryphosis | 22.5 |
| Longitudinal striatal | 19.7 |
| Onychorrhexis | 16.9 |
| Anonychia | 12.7 |
| Ectopic nails | 8.5 |
| Beau's line | 4.2 |
| Longitudinal melanonychia | 2.8 |
| Onychomycosis | 1.4 |

Three patients had ulcers on their feet, and one hand was fin-shaped due to a severe acro-osteolysis. All patients had nail changes in the hands and/or feet. 94% of the fingernails and 95% of the toenails showed alterations. Changes in the fingernails and toenails are recorded in Table 2. The main changes in the fingernails were longitudinal striae, pseudoclubbing and longitudinal melanonychia, however the main changes in the toenails were onycholysis, brachyonychia and onychauxis.

## TREATMENT OF NAIL PROBLEMS

The main focus for treating leprosy is in the early diagnosis, which allows the prevention of subsequent disabilities. Delay in the diagnosis is the main factor for a neuropathy, and peripheral neuropathy is the main cause of nail problems in these patients. Moreover, in the management of these patients it is important to adhere to correct hygiene of the hands and feet. A proper cleaning of hands and fingers with water and soap may prevent small injuries, and the use of petroleum jelly on the hands and feet may prevent friction and small lesions on the nails. Finally, proper rehabilitation of the disabilities on the hands and feet may reduce the prevalence of nail changes.

## CONCLUSIONS

In conclusion, nail changes in leprosy are multifactorial and could be related to one or more of the following factors: neuropathy, endarteritis, trauma, drugs, or superimposed infections. Several diverse nail changes are known to occur in leprosy. Therefore it is necessary to consider the pathology of the nails as an important part of leprosy for a proper diagnosis and treatment of such a complex disease.

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# XERODERMA PIGMENTOSUM: A MULTIDISCIPLINARY APPROACH

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**Disclosure:** No potential conflict of interest.
**Received:** 01.10.2013 **Accepted:** 06.11.13
**Citation:** EMJ Dermatol. 2013;1:54-63.

## ABSTRACT

Xeroderma pigmentosum (XP) is a rare, autosomal recessive disorder of DNA repair. Affected individuals are unable to repair ultraviolet radiation (UVR)-induced DNA damage, leading to a variety of clinical manifestations: a dramatic increase in mucocutaneous malignancies, increased lentigines, extreme photosensitivity (in approximately 50% of cases), and neurodegeneration (in approximately 30% of affected individuals). Incidence in Western Europe is recorded as 2.3 per million live births. There are eight different complementation groups, XP-A to XP-G, and XP-variant (XP-V) corresponding to the eight affected genes. Classically, XP patients were identified by clinicians for their tendency to develop severe and exaggerated sunburn on minimal sun exposure, however recently it has been shown that XP-C, XP-E and XP-V patients have normal sunburn reactions for skin type compared to the other groups, who suffer not only with severe, exaggerated sunburn, but also have an increased incidence of neurodegeneration.

A diagnosis of XP should be considered in a child with either severe sunburn, increasing lentigines at exposed sites, or development of multiple skin cancers at an early age. Skin biopsy and subsequent testing in cell cultures for defective DNA repair, confirms or excludes the diagnosis. Mean life expectancy is reduced; the two main causes of mortality are skin cancer and neurodegeneration. These clinical features distinguish XP from other disorders of DNA repair, namely Trichothiodystrophy and Cockayne syndrome, although overlapping syndromes do occur. Instigation of meticulous photoprotection for all XP patients has been shown to reduce both the lentigines and number of skin cancers dramatically and would be presumed to increase life expectancy. Compliance with photoprotection is a recognised problem amongst XP patients, particularly in those without easy sunburn. This is further accentuated by lack of social acceptance for people who wear UVR-protective visors. Increased awareness of XP, both within the medical and media spheres will benefit current and future XP patients; this will aid earlier diagnosis and timely photoprotection, with better compliance, and therefore, result in an improved prognosis.

Keywords: Xeroderma pigmentosum, DNA repair, sunburn, skin cancer, neurodegeneration, ultraviolet radiation DNA damage.

## INTRODUCTION

Nearly 140 years ago, the term 'xeroderma' was first used by Moritz Kaposi[1] for patients with dry, wrinkled, parchment-like skin, to characterise a rare disease he had noted in two patients; one with severely pigmented skin in predominantly sun-exposed areas (face, neck, shoulders, and arms), the other, aged 10 years, also had dry, thin skin, without the noted pigmentation, but within 1 year developed a fissured tumour on the nose. Kaposi described xeroderma pigmentosum (XP) as a condition existing from childhood that never improved either spontaneously or as a result of any treatment.

In 1883, Albert Neisser made the link between XP and neurodegeneration and in 1932, two Italian physicians, De Sanctis and Cacchione,[2] reported a 'xerodermic idiomacy' in which three XP patients also had neurological and other physical abnormalities: microcephaly with progressive mental deficiency, retarded growth and sexual development, hearing loss, choreoathetosis, ataxia, and eventual quadriparesis with Achilles-tendon shortening. Until recently, the term 'De Sanctis-Cacchione syndrome' was used to describe XP patients with severe neurodegeneration, but the term is no longer in use. In 1965, Reed et al.[3] described XP with choreoathetoid neurological complications. Cerebral and olivopontocerebellar atrophy were found at autopsy of two further XP cases.[4,5] A review, at National Institute of Health (NIH), described all the neurological abnormalities identified in XP patients and commented that the type of neurodegeneration detected can be found in many degenerative and hereditary disorders of the nervous system of non-XP patients, and usually correlates to distinctive pathological findings; however, postmortem cerebral examination of XP patients had failed to reveal any unique morphological or cellular abnormality, other than neuronal cell loss.[5,6]

Exposure of skin cells to ultraviolet radiation (UVR) causes the formation of cyclobutane pyrimidine dimers (CPDs)[7] and pyrimidine (6-4) pyrimidone photoproducts (6-4 PPs)[8] by crosslinking of adjacent pyrimidines in DNA. These photoproducts are removed by the nucleotide excision repair (NER) pathway. In 1968, Cleaver[9] showed that whereas fibroblasts from normal adult skin were able to repair damage induced by UVR, cultured fibroblasts from XP patients had a marked reduction in, or absence of, repair. Epstein et al.[10] confirmed this *in vivo* in 1970.

In 1971-2, the spectrum of clinical symptoms in XP prompted studies into the genetic heterogeneity using XP fibroblast cell fusion techniques. Each XP fibroblast was known to be deficient in repairing UVR-induced DNA damage. Fusing two XP fibroblasts from two separate donors enabled a heterokaryon to be formed (a cell containing nuclei from different donors in a common cytoplasm). This heterokaryon was found to exhibit normal DNA repair, implying that separately each cell supplied what the other lacked and therefore the defects in each cell were genetically different. This ultimately led to identification of seven separate XP 'complementation groups' deficient in NER, designated XP-A to XP-G.[11-16]

A separate group of XP patients with normal DNA excision repair in lymphocytes[17] and in fibroblasts[18] was reported by Burk et al. in 1971, and later these patients were designated 'XP-variant' (XP-V). Their cells showed normal levels of DNA repair after UVR exposure and it was assumed that the defect must lie elsewhere. Indeed, in 1975 Lehmann et al.[19] discovered that XP-V patients have a defect in the DNA post-replication repair pathway.

There have been several reviews of XP over the last 40 years,[20-24] but with the ever-expanding research into cellular mechanisms of DNA repair pathways, our understanding of XP as a whole continues to develop.

## EPIDEMIOLOGY

XP has been reported to occur in all ethnic groups worldwide and affects men and women in equal ratio. Amid Indian and Middle Eastern areas, incidence is quoted at 1:10,000-30,000.[25-28] In Japan, incidence is reported as 1:20,000–100,000,[29,30] and in Western Europe it has been estimated at 2.3 per million live births.[31] The incidence of XP in Japan appears 10-times higher than in Western countries, and approximately 60% of XP patients in Japan belong to the XP-A complementation group, twice the proportion seen in other countries.[22] 90% of patients are homozygous for the XP-A founder mutation, carried by 1% of the Japanese population.[28] In 2010, Soufir et al.[32] reported that 85% of XP families in the Maghreb region (Algeria, Tunisia and Morocco) carried a founder mutation in the XP-C gene. More recently, it has been reported that 1 in 5,000 individuals of the black Mahori population in the Comoro Islands have XP-C. This is linked to another founder mutation.[33] In the latter regions, consanguineous marriages are quite common, resulting in higher frequencies of homozygous mutations in genes corresponding to rare genetic disorders.

## AETIOLOGY AND GENETICS

XP is an autosomal recessive disorder that arises from mutations in the genes encoding for proteins that are integral to NER, a pathway that

repairs many types of DNA damage including those produced by UVR (CPDs/6-4PPs).[34-37] Patients have mutations in one of seven different XP genes (XP-A to XP-G) resulting in impaired NER. XP-V patients have normal NER, but mutations in DNA polymerase η (POLH) cause a defect in the ability to replicate DNA containing unrepaired damage.

NER consists of two sub-pathways that differ at the initial recognition step; global nucleotide excision repair (GG-NER) and transcription-coupled nucleotide excision repair (TC-NER), (Figure 1). GG-NER is a relatively slow, scanning of the entire genome; XP-E (with its partner protein DDB1) binds to the photoproduct,[38] and recruits XP-C, which recognises and binds to the distortion affecting the strand opposite the photoproduct.[39] GG-NER is responsible for repair of both strands of actively and non-actively transcribed genes. TC-NER identifies and rapidly repairs damage, specifically on the transcribed strand of actively transcribing DNA. RNA polymerase II stalls at the site of the photoproducts; recognition of this and recruitment of subsequent NER proteins is mediated by the CSA and CSB proteins. Defects in either of these proteins result in Cockayne syndrome rather than XP.

The two NER sub-pathways then converge to form the common stem where TFIIH (a complex containing 10 polypeptides including the helicases, XP-B and XP-D) is recruited to open up DNA around the site of the photoproduct. XP-A binds to verify that all the proteins are in the correct position. The heterodimeric nucleases ERCC1/XP-F and XP-G cleave the damaged

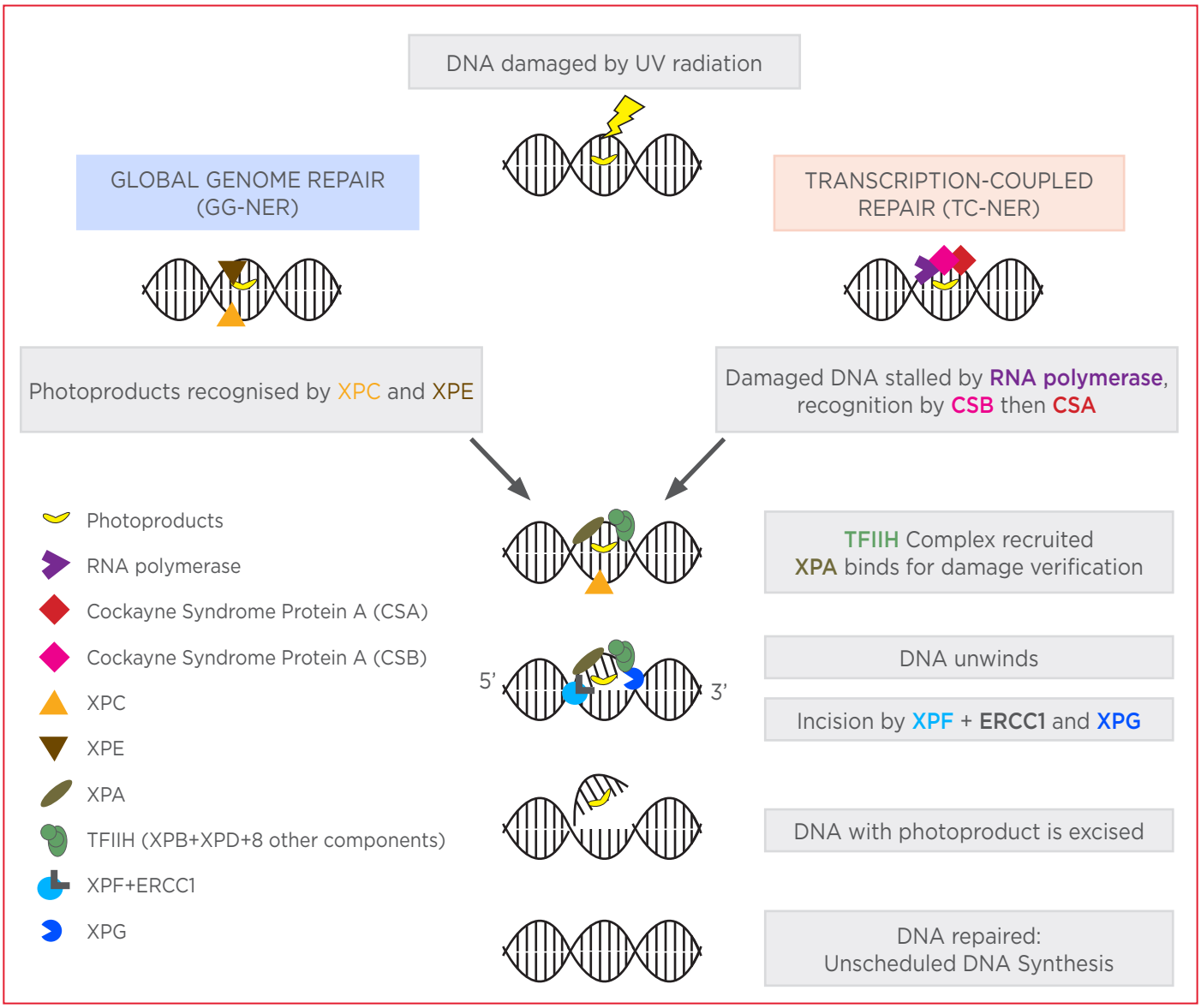


**Figure 1. A model for NER of UVR-induced DNA damage.**

DNA strand 5' and 3' to repair the damage respectively. An approximately 30-nucleotide fragment containing the damaged nucleotides is then excised and the resulting gap filled in using the undamaged strand as template. The DNA polymerisation that fills in the gap is known as unscheduled DNA synthesis (UDS). Mutations in XP-A, XP-B, XP-D, XP-F, and XP-G genes result in the impairment of both GG-NER and TC-NER. However, mutations in XP-C and XP-E genes affect only GG-NER, and therefore there is some preservation of NER via the TC-NER pathway.

NER is fully functional in XP-V patients. The defect is in the process of translesion synthesis, which is carried out by a specialised DNA polymerase, polη, that is able to replicate DNA past unrepaired photoproducts.[19,40]

The inability of XP patients to repair UVR-induced DNA damage explains the skin changes in these patients (lentigines and skin cancers). The neurodegeneration seen in only 30% of patients is harder to explain. It is likely to be related to the DNA repair defect and an efficient DNA repair mechanism is required to maintain the functional integrity of neuronal cells.[19] Brooks et al.[41] showed that DNA from neuronal cells that are exposed to endogenous oxygen radicals, produce oxidative DNA lesions called cyclopurines (cPu) (cyclo-2-deoxyadenosine and (5 S)-8,5'-cyclo-2'-deoxyguanosine). cPus requires removal from DNA, specifically via NER.[42] In XP-A cells (without functioning NER), the presence of a single cPu lesion on a transcribed DNA strand of a reporter gene strongly reduced gene expression. It was demonstrated that neuronal death resulted from accumulation of these unrepaired cPus. Later cPus were re-named as 8,5-cyclopurine-2-deoxynucleosides or 'cyPudNs'.[42] The biological properties of cyPudNs are very similar to other substrates of NER such as UVR-induced thymidine dimers. cyPudNs have been shown to block gene expression in XP cells, a biological effect that is compatible with causing neurodegeneration.[43,44]

## CLINICAL MANIFESTATIONS AND ASSOCIATIONS

Cutaneous clinical features of XP patients are largely determined by the cumulative amount of UVR exposure at sun-exposed sites (skin and eyes) and therefore also by age of the patient at diagnosis and timing of photoprotection initiation. XP includes a clinically heterogeneous group of patients with some genotype-phenotype correlations, both between and within different complementation groups.

The main recognised clinical manifestations are: photosensitivity, leading to severe and exaggerated sunburn reactions, increased lentigines, and pigmentary change, an overwhelming increase in skin cancer frequency, ocular abnormalities, and neurodegeneration.

### Sunburn

Sunburn is a normal response to UVR exposure. The confluent and well-demarcated, erythematous, oedematous, and tender reaction is caused by vasodilation and inflammation. Apoptotic keratinocytes are present in histological analysis.[45] The sunburn response is probably triggered by UVR-induced DNA damage. Patients with XP suffer with severe and prolonged sunburn. Their increased susceptibility to severe sunburn may relate to the persistence of UVR photoproducts in the DNA.[46]

Acute severe sunburn on minimal sun exposure was once considered a cardinal presenting feature of XP. However, with increasing research and analysis of larger groups of XP patients, it has been shown that only 50% of XP patients will suffer from severe and prolonged sunburn reactions.[21,47,48] The remaining 50% have sunburn reactions that are normal for their skin type and present with lentigines at sun-exposed sites, (together with an early onset of skin cancer). Our recent study, within a cohort of patients in the UK National XP service, has shown that patients in complementation groups XP-A, XP-D, XP-F, and XP-G have been shown to suffer from severe sunburn reactions; whereas, those in groups XP-C, XP-E and XP-V have normal sunburn reactions, consistent with similar findings of Kraemer and colleagues at the NIH.[47,48] XP-A, XP-B, XP-D, XP-F, and XP-G proteins are all required for the common stem of NER whereas XP-C and XP-E proteins are only required for GG-NER. In XP-C and XP-E, TC-NER is preserved. XP-V patients with mutations affecting DNA polymerase η, also have normal functioning TC-NER (and GG-NER). It is therefore hypothesised that normal sunburn reactions in approximately half of the XP patients relate to preservation of TC-NER.[49]

## Skin Cancers

XP patients have a >10,000-fold increased risk of developing non-melanoma and a 2,000-fold increased risk of melanoma skin cancer in patients under 20 years of age. The median age at diagnosis of first non-melanoma skin cancer (NMSC) is between 8 and 9 years,[21,50] significantly younger than the median age at diagnosis of first melanoma, at age 22 years. This is an inverse pattern to what is observed in the general population, where younger patients are more likely to present with melanoma and older patients with non-melanoma skin cancers.[51] UVR exposure to the oral cavity in XP patients can result in mucocutaneous malignancy, most commonly seen as squamous cell carcinoma of the tip of the tongue.[52]

Studies on UVR-induced mutagenesis in cultured cells have indicated a 'UVR-signature mutation', namely C to T transitions and CC to TT tandem mutations. The latter, in particular, are rarely found after exposure to any mutagenic agent other than UVR. Analysis of the p53 gene in skin tumours from XP patients has revealed these classical UVR-induced 'signature' mutations in the DNA,[53] indicating that the high level of p53 mutations found in the tumours is directly caused by unrepaired UVR-induced DNA photoproducts.[54] There is a significantly higher level of the UVR signature mutations in XP skin tumours compared to those found in non-XP, sporadic skin cancers.[55]

The XP patients in complementation groups that have severe sunburn reactions (XP-A, XP-B, XP-D, XP-F, XP-G) have lower rates of skin cancer than those patients with sunburn reactions that are normal for skin type (XP-C, XP-E, XP-V). This may be due to severe sunburn reactions prompting earlier diagnosis of XP and earlier age of initiating more rigorous photoprotection.[47]

In addition to skin cancer, the XP-C patient group seems to be at greater risk of developing other forms of malignancy, particularly neurological cancers.[56,57] This patient group has also been reported to occasionally develop pyogenic granulomas and multinodular thyroid carcinomas.[58]

## Ocular

There are three ways in which the eyes can be affected in XP; (1) UVR exposure resulting in DNA damage of the eyelids and periocular skin; (2) UVR exposure resulting in DNA damage of the ocular surface, and (3) the ocular manifestations of neurodegeneration. Even patients with few ophthalmic signs commonly describe photophobia, which is the earliest presenting ophthalmic symptom of XP.[21]

Damage to the eyelids and periocular skin can result in the development of cicatricial skin changes as well as skin cancers, which require excision.[59] The ocular surface (conjunctiva and cornea) can develop UVR-related damage including dry eye, conjunctival injection, and inflammation (without infection), as well as development of premature pingueculae and pterygia. Prolonged corneal exposure can result in corneal scarring and visual impairment. Ocular surface cancers, mainly squamous cell carcinomas, have also been reported in patients with significant UVR exposure and poor ocular photoprotection.[60]

Patients with XP-related neurodegeneration may also develop neuro-ophthalmological features, including sluggish pupils, nystagmus, and strabismus. (S. Morley, UK National XP Clinic ophthalmologist, personal communication).

## Neurodegeneration

Neurological manifestations of XP typically follow skin symptoms in the natural history of the disease and do not arise before 2 years of age.[61] Parents notice mild cognitive impairment first, usually when the child is starting school; EEG studies confirm a spectrum of encephalopathy from mild-to-severe. Cerebellar signs manifest usually between age 4 and 16 years, usually dysarthria and difficulties with balance. Ataxia and areflexia follow suit; EMG studies show evidence of axonal sensory and motor neuropathy although this is not usually seen before the second decade of life. Some patients will also exhibit choreoathetoid involuntary movements in the upper limbs.[3] Most XP patients with neurological abnormalities will develop sensorineural deafness, and the degree of hearing loss has been shown to predict future neurological involvement.[48] Involvement of the corticospinal tract can result in tetraplegia, becoming wheelchair-bound and eventually bed-bound, a few years before death.[61]

Approximately 30% of XP patients will develop neurodegeneration; patients with mutations causing lack of XP-A, XP-D, XP-F, and XP-G

proteins have an increased susceptibility.[23,47,48,50] This is most likely due to the requirement for these proteins to deal with oxidative damage such as cyPudNs, which accumulate in DNA in neuronal cells.[44]

XP-C and XP-E patients classically do not develop clinically detectable neurodegeneration; however there have been reports of late-onset asymptomatic neurological disease in XP-C patients.[62] In one report, post-mortem analysis of an XP-C patient provided evidence of neurodegeration with neuronal loss in dorsal root ganglia.[63] A conceivable explanation for this was proposed by Nouspikel, who suggested a role for XP-C in domain-associated repair (DAR) (repair of both the transcribed and non-transcribed strand of active genes). As the non-transcribed strand of DNA serves as a template for repair, failure to repair the non-transcribed strand will eventually impact repair of the transcribed strand. XP-C is required for DAR so therefore lack of XP-C may result in lack of DAR and therefore gradual onset of neurodegeneration.[44]

### Psychological

Although not a presenting feature of XP, the social isolation and clothing restrictions of the disease can inevitably predispose these patients to depression. In patients with XP, adherence to a very restrictive photoprotection regime (including wearing a UVR-protective visor), which is highly visible to other people, causes poor health-related quality of life in terms of mental health (low mood, anxiety) and social isolation. There is a potential for bullying for school-age children, and concerns for job-security in adults at work should they disclose XP. A 20-year observational study of XP patients in Finland reported the symptom of increased fear and tendency to weep amongst 8/11 adults.[61]

Compliance is an issue; for children at school there is an impact on behaviour with tantrums and outbursts, due to the frustration of having to photoprotect, restrictions on outdoor activities, and being treated differently. This may create a barrier to successful learning at school, potentially limiting academic progress and impacting on social relationships (observations from the UK National XP clinic). In teenage years the necessity for photoprotection links more widely to patients' understanding and acceptance of XP.

Other psychological issues include potential for developing anxiety and depression from ongoing surgical procedures, many focused on the face, with potential for facial disfigurement or developing fatal skin cancers. Many patients are also anxious about the possibility of neurodegeneration, with loss of memory and early onset dementias as well as physical disabilities (J. Baulcomb, UK National XP clinic educational psychologist, personal communication).

## DIAGNOSIS

Initially the diagnosis is predominantly clinical: a young child may be brought to the paediatric department with bright, confluent erythema over all sun-exposed sites, or with lentigines at an unusually early age in sun-exposed areas. In the former case, the clinician assessing the child may suspect a skin allergy, drug reaction or even in some cases sunburn caused by parental neglect. After all differentials are excluded, the clinician would then request cellular tests to assess for defective DNA repair. This requires a 4 mm punch biopsy of the skin taken from an unexposed site (e.g. buttock area). This specimen is used to culture fibroblasts followed by UVR exposure and subsequent measurement of unscheduled DNA synthesis (UDS), (Figure 1). UDS refers to the newly synthesised DNA, which is formed when the damaged DNA is excised. UDS can be measured as incorporation of nucleotides into DNA of the irradiated cells by autoradiography,[64] liquid scintillation counting,[65] or fluorescence assay.[66] Typically a reduced level of UDS confirms diagnosis of XP. Mutational analysis to assign complementation group and define pathogenic mutation(s) in the affected gene(s) is then performed. Using next-generation sequencing techniques, a platform of DNA repair genes can be used for rapid identification of both complementation group and mutation analysis.

Diagnosis of XP-V is different as XP-V cells have normal levels of UDS. However, UVR-exposed XP-V cells show an exquisite sensitivity to caffeine, which impairs their survival.[67,68] Therefore, if XP-V is suspected, cultured fibroblasts are incubated in caffeine for a few days and their viability compared to that of normal cells. If UDS is normal and post-UV sensitivity to caffeine is detected, a diagnosis of XP-V is confirmed.[69]

Of the eight genes implicated in XP, mutations in the XP-C gene count for a substantial proportion in most but not all populations.[47,48,50,70] Immunohistochemistry staining with an antibody for XP-C protein has recently been shown to be a new rapid and cost-effective method for both diagnosis and potentially as a screening tool in suspected XP-C patients. UVR-protected, tumour-free skin of XP-C patients will show negative expression of the XP-C protein compared to normal controls.[71] In principle, use of antibodies to other XP proteins can be used to also look at deficiencies in other XP complementation groups. However, although this procedure is a rapid method of identifying reductions or absence of protein, as is the case for most XP-C and XP-V patients, immunohistochemistry cannot be used as a diagnostic tool in many other complementation groups because pathogenic missense mutations result in production of a defective XP protein present in normal quantity.

All the diagnostic procedures require specialised laboratories and technical skills and are therefore often not available in poorer countries, in which there may be high incidences of XP.

## GENETIC COUNSELLING AND PRENATAL DIAGNOSIS

As XP is an autosomal recessive disorder with 100% penetrance, it is only possible to offer prenatal diagnostic testing for XP in a family where parents already have an affected child.[72] Counselling and psychological support is of paramount importance in families at reproductive risk. These families can have prenatal diagnosis by mutational analysis or DNA repair testing on chorionic villus sampling at 10-12 weeks gestation.[73-76] In principle pre-implantation genetic diagnosis can also be carried out, if the pathogenic mutations are known and the carrier status of both parents confirmed, although to our knowledge this has not yet been done for XP.

## MANAGEMENT

Patients with XP require a multidisciplinary team approach to their care with involvement from dermatologists, specialist nurses, clinical psychologists, neurologists, and ophthalmologists. Particularly in childhood, if there is recognised early cognitive impairment, XP children require support from special schools and community mental health teams. Towards the end of their life, XP patients with severe neurodegeneration will require maximal assistance with all activities of daily living, and careful planning with all members of a multidisciplinary team is required.

As soon as the diagnosis of XP is confirmed, the most crucial aspect of their care is the instigation of meticulous photoprotection. This includes the application of sunscreen to all exposed areas of skin (20 minutes before UVR exposure), thickly woven clothing, gloves, and a UVR-protective visor. Some patients choose not to wear a visor and instead wear broad-brimmed hats, hoodies and UVR-protective wrap-round glasses. All windows in the home, car, and school should be covered with UVR-protective film, which is commercially available. Hospital theatre lights, halogen lights, metal halide lamps, and some fluorescent lights need to be avoided or covered. In addition, educational support from specialist XP nurses in the community has been shown to dramatically improve both adherence to and social acceptance of photoprotection (our unpublished audit data from the UK National XP clinic).

XP patients complying with good photoprotection are inevitably vitamin D deficient. Long-term supplementation of vitamin D in tablet, spray or in severe cases intramuscular form, should be administered and regular serum vitamin D levels checked at outpatient follow-up to ensure optimum levels are maintained.

Avoidance of cigarette smoke and environmental carcinogens are recommended. Carcinogens in cigarette smoke also cause DNA damage requiring NER, so XP patients are at higher risk of developing further lung cancer-promoting mutations.[77] It may be suggested that excess levels of caffeine are not recommended in XP-V patients because of cellular sensitivity to UVR in the presence of caffeine, although there is no definitive evidence to support this guidance.

The UK National XP Service was launched in April 2010 at St. John's Institute of Dermatology, Guy's and St. Thomas' NHS Trust, London, serving the current UK XP population (approximately 70 patients) and can also offer services to XP patients worldwide. Patients are invited to attend a one-stop clinic with assessments from the entire multidisciplinary team. This allows regular skin checks to assess and remove precancerous and

cancerous lesions, photographic monitoring of indeterminate lesions, as well as reviews from clinical psychology, clinical genetics, neuropsychology, neurology, and ophthalmology. Diagnostic services for XP patients, of which we are aware, are also available in the USA,[78] France,[79] Germany,[80] Italy,[81] the Netherlands,[82] and Japan.[83]

## FUTURE PROSPECTS

XP is a monogenic disorder and therefore although the future invites the possibility of protein or gene therapy, as yet there is no cure. Exciting work using retroviral-mediated XP-C gene transfer into deficient stem cell keratinocytes (from XP-C patients) has given hope that corrective therapy is not far away. However, this therapy has yet to be carried out in humans and still carries with it the risk of retroviral-mediated mutagenesis and oncogenic activation.[84]

Median age of death reported by the NIH is 32 years with two main causes identified as skin cancer in 34% and neurodegeneration in 31% of XP patients.[50] Better understanding, identification of milder phenotypes, with earlier diagnosis and improved photoprotection in recent years has resulted in an increase in median age of death. We anticipate improved survival in those without neurodegeneration who maintain lifelong vigorous photoprotection.

## CONCLUSIONS

The diagnosis of XP has a profound consequence on patients, particularly as their lifestyle measures require rigorous photoprotection. That said, there is a dramatic reduction in the number of skin cancers and improvement in life expectancy observed with photoprotective-compliant XP patients. Unfortunately the manifestation of neurodegeneration signifies a poor prognosis. A multidisciplinary team approach is crucial for all XP patients.

With the advances in medicine and genetics over the last half-century, the spectrum of XP as a disease has become increasingly acknowledged. From the first two patients described by Moritz Kaposi,[1] to several thousand patients diagnosed worldwide, the field of XP requires further research, particularly to identify mechanistic links behind sunburn reactions and neurodegeneration. Most importantly, it is to be hoped that the recent rapid advances in genetics may ultimately result in a cure for this severe disorder.


### Acknowledgements

The authors are indebted to Susie Morley, Consultant Ophthalmologist and Oculoplastic Surgeon, Guy's & St Thomas' NHS Foundation Trust; Jennifer Baulcomb, Educational Psychologist, Evelina Children's Hospital; Sally Turner, XP Clinical Nurse Specialist, Guy's & St Thomas' NHS Foundation Trust for helpful comments and advice.


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# NEW TRENDS IN CELLULITIS


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**Disclosure:** No potential conflict of interest.
**Received:** 21.08.13 **Accepted:** 25.10.13
**Citation:** EMJ Dermatol. 2013;1:64-76.



## ABSTRACT

Cellulitis is a severe infection of the soft tissues, with a variable aetiology from Gram-positive to Gram-negative bacteria and deep fungal infections, whose early recognition is mandatory to avoid potentially life threatening complications. Some pathogens might cause very similar clinical entities, and cellulitis differentiation at presentation towards abscess, necrotising fasciitis, and gangrene, requires expertise. Many mimics are also to be excluded, conditioning the treatment and patient's prognosis. The dermatologist is in a lead position to avoid misdiagnosis, to evaluate the type of assessment, and address initial treatment. Besides, skin and soft tissue infections are a common reason for emergency room visits and hospital admission, lacking precise clinical definition and managed with empirical antibiotic treatments. History, physical examination and laboratory data can help characterise the severity of the disease, and the probability of complications development, mainly necrotising fasciitis. Several admittance scores have been proposed to address the emergency decisions, and guidelines for treatment proposed. The present review will focus on clinical challenges and actual open questions on cellulitis management.



Keywords: Cellulitis, skin and soft tissue infections, erysipelas, emerging pathogens, cellulitis mimics.


## INTRODUCTION

### Maintained Criteria for Diagnosis

Cellulitis is a severe inflammation of the dermis and hypodermis sparing the fascial planes due to an infective, generally bacterial cause.[1-5] The course is usually acute, but subacute, or chronic inflammation is also possible.[6] Presentation is common to any aetiology, characterised by an expanding area of erythema, where all signs of inflammation are expressed: redness, warmth, tenderness, and swelling. Borders are ill-defined in true cellulitis, with a typical dusky hue that might be mistaken for an accidental injury, especially when the superior maxillary region is involved (the 'bruised cheek' sign).[7,8] The surface breaks in some points with vesicles (Figure 1) and/or pustules appearance (Figure 2), which progress to haemorrhagic bullae and necrotic tissue discharge, or adherent crusts and slough formation (escara) (Figure 3). Ascending lymphangitis might be seldom visible, especially on the internal leg surface directing towards mid-thigh (Figure 4).

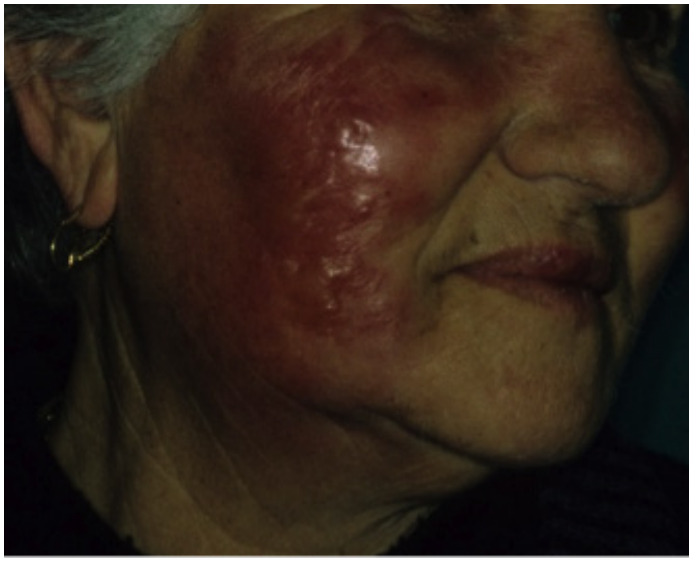

**Figure 1. Facial cellulitis with involvement of the superior maxillary region.**
The erythematous edematous surface is partially covered with vesicles and small bullae. Margin are ill-defined.

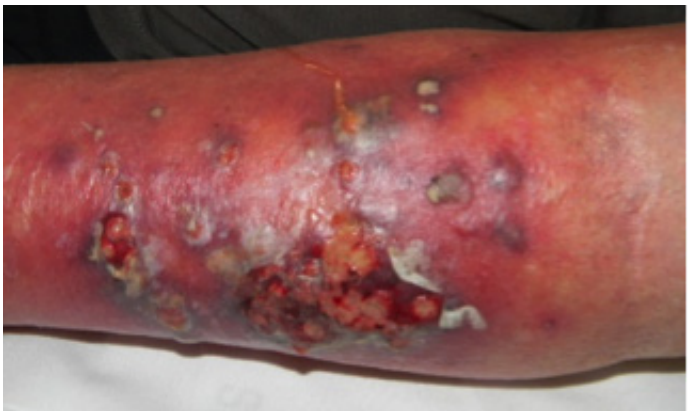

**Figure 2. Severe leg cellulitis with vesicles and pustules, discharging haemorrhagic and necrotic material.**

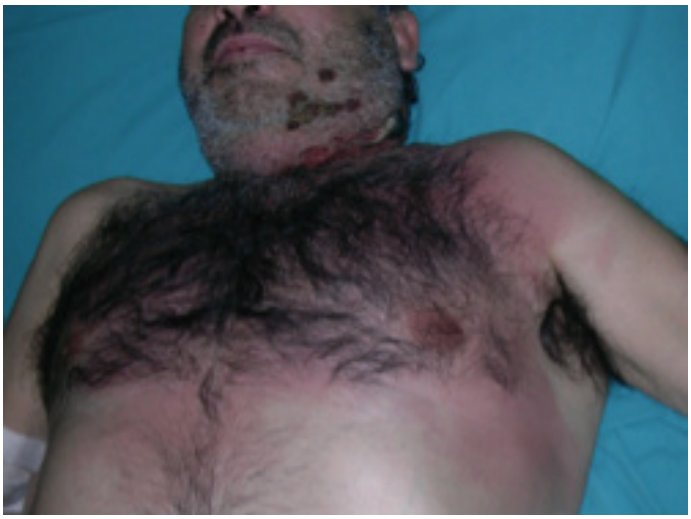

**Figure 3. Rapidly progressive neck cellulitis, extending to the trunk, with crusts and slough formation (escara) in the site of primary involvement.**

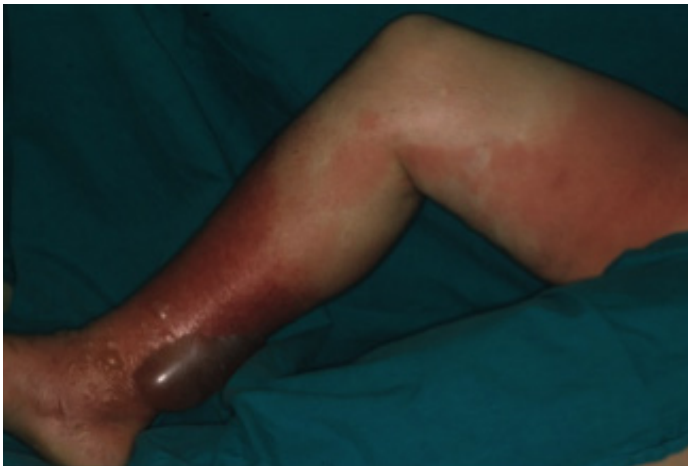

**Figure 4. Leg cellulitis with large bullous lesions and visible lymphangitis.**

Regional lymphadenopathy is usually constant, from mild to severe. Systemic symptoms, such as fever with chills, general malaise, usually precede the eruption and accompany the full development of the disease, which can take hours, up to a few days. Patients suffer heavy pain, with higher peripheral sensibility, and frequent paraesthesia. On the contrary, hypoaesthesia is an alarming sign of a deeper nerve involvement, which is a characteristic of necrotising fasciitis (NF) (also known as flesh-eating bacteria syndrome).[9,10]

The origin of the infection is sometimes difficult to establish, and microbiology tests are positive in approximately a quarter of patients,[3,11] because inflammation usually prevails on bacterial invasion and proliferation. Even a small amount of fragmented bacterial antigens released, amplified by the cytokines and lymphokines, are responsible for the massive neutrophils chemotaxis and skin infiltration. Moreover, the responsible pathogens are typically able to produce rising titres of several enzymes, such as streptolysin, deoxyribonuclease B, hyaluronidase, neuraminidase, phospholipase, which directly delivered in the deeper compartments induce degradation of the connective tissue core components, and cytoskeleton, thus, facilitating the spreading. In more aggressive forms, the release of bacterial toxins (pyrogenic exotoxin A or B) as well as synergistic effects of different bacterial species, such as *S. aureus* and anaerobes, is to be suspected. Massive lipopolysaccharide release from destroyed Gram-negative bacteria might result in severe vascular injury and keratinocytes necrosis, sometimes indicated by the term haemorrhagic cellulitis.[12]

A distinction in three stages has been proposed:[13] the serous stage is the initial inflammatory process, which may resolve on its own or after appropriate treatment. However, this frequently develops into a suppurative phase, in which pus formation might be detected by palpation, producing the sign of fluctuation. Imaging studies are useful to reveal deep gathered abscess before clinical evidence, especially when dealing with facial and neck compartments.[14-18] Once the pus is formed, resolution of the condition requires drainage, spontaneously through a fistulisation phase, or by means of surgical procedure.

Classification on the base of area involvement is useful, as common localised forms tend to be less severe than very diffuse forms.

A well-known diffuse and life-threatening condition for the imminent asphyxia risk is Ludwig's angina.[19,20]

Additional signs and symptoms may vary depending on the site of involvement. Facial cellulitis frequently occurs on the orbit, where an accurate assessment reveals impaired painful ocular movements, ptosis and proptosis of the eyelid, raised intraocular pressure, reduced or complete loss of trigeminal nerve sensation.[21] In the oropharyngeal area, other alert signs suggestive of spread into cervical spaces are: altered levels of consciousness, speech alteration, difficulty breathing, dysphagia, and intense lockjaw.[13]

## Laboratory Findings

Laboratory findings usually support the infective origin, demonstrating a slight leukocytosis with neutrophilia, and augmentation of inflammatory indexes. A sudden decrease in blood count might precede a shock reaction to lipopolysaccharide release in Gram-negative infections. Exudates cultures by needle aspiration or swab are not routinely performed in logical, cost-effective management.[1-5] Identification of pathogen and testing sensitivity to antibiotics is mandatory to adjust the treatment in those patients who fail to respond to treatment within 48 hours, and the further delay of performing culture at that moment might negatively affect the patient's prognosis. Blood culture is of limited use because it is positive in a minority of cases and the isolates are usually the same as in the skin lesions.[6,11,22] Swab culture of the nasopharynx is advisable to isolate occult aetiologic pathogens.[23]

## Radiologic Examination

Radiologic examination is advisable when the leg is involved to exclude subjacent osteomyelitis, and/or gas presence.[16] In facial cellulitis, radiology might be useful to rule out dental pathologies, thickening of prevertebral soft tissue, displacement of the airways, or an eventual gas presence. A computed tomography (CT) scan and magnetic resonance imaging (MRI) scan provide assessment of the extent of the involvement, topographical limits, detection of abscesses, and presence of air within tissues.[14-17,24-26] CT combines fast image acquisition with precise anatomical information, representing the most reliable technique for the evaluation of deep and multi-compartment lesions, detecting progression towards fasciitis, mediastinal and intracranial complications, as well as vascular complications with the contrast agent administration.[15,17] MRI is time-consuming, and the main advantage over CT is the multiplanar capability, useful to better investigate the retropharyngeal space, the epidural space, infections reaching the skull base, pre and paravertebral spaces, but also complements CT in the evaluation of osteomyelitis.[14,15,24] Ultrasonography is the first step of imaging a paediatric patient,[27] but in adults the hypodermis infiltration blocks ultrasound transmission,[25] as well as the field-of-view limitation and poor anatomical information confines its use to superficial lesions, detecting the subcutaneous accumulation of pus and guiding aspiration or drainage.[15,16,27] Invasive assessment, such as biopsy, is only seldom performed but the main histological features are: superficial and deep dermal oedema, diffuse heavy neutrophils infiltration, and vascular and lymphatic dilatation.[28,29] Large numbers of bacteria are usually present and identifiable with special stains. Necrosis of epidermal keratinocytes, and red cell extravasation are variable features, while in later stages, lymphocytes and histiocytes might prevail, eventually with granulation tissue formation.

## Mortality

Mortality of untreated patients has been recorded in 11%,[30] and might occur in neglected cases, when highly virulent organisms are involved or complications arise, mainly for shock, and multiple organ failure.[31] Possible systemic complications include septicaemia, pneumonia, toxic syndrome, and for the head and neck compartments, also descending mediastinitis, upper airway obstruction, thrombosis of the cavernous sinus, cerebral abscess, and meningitis.[15,19,53] Recurrent episodes of cellulitis are a major concern,[32,33] but a population-based cohort study suggest that only 11% of patients develops a recurrence within 1 year.[34] Long-term sequelae consist of scars, persistent lymphoedema, venous ulcers, and neurological alterations.

# CONSIDERATION ON EPIDEMIOLOGY AND PREDISPOSING FACTORS

Cellulitis affects individuals of any ethnicity rather than producing epidemics, occurring in apparent healthy patients,[1-6,35] facts indirectly attesting the role of predisposing individual conditions in the

development of the disease. The precise incidence of the disease is uncertain, but some American studies rated 24.6 cases per 1,000 person/year might be affected with cellulitis,[34] covering the 37.3% of the hospitalised population.[36]

Considering the site of involvement, lower extremities are the most frequently affected in adults,[36-38] while the head and neck district is typically involved in children,[7,27,39] and the umbilical region in neonates.[40] Children are affected at a very young age: 7-10 months, and a history of infections is often reported in the weeks before, especially otitis media.[39]

Research data on risk factors can be divided into two groups: factors predisposing to the development of cellulitis, and conditions influencing the severity of the disease (Table 1). In an attempt to give priority criteria, a port of entry is the first thing to search, as confirmed by published cohort and case-control studies.[32,33,41-46] Complications following surgery is a major concern,[3,47,50] especially in chronically immune-suppressed patients, in course of rheumatoid arthritis or lupus erythematosus.[48,51] Concerning leg cellulitis, injuries by foreign body, puncture wound, venous insufficiency, lymphoedema, venous or pressure ulcers, bacterial intertrigo and tinea pedis, are the most frequent conditions. Occurrence in course of dental pathology[13] is one of the most relevant causes of facial cellulitis, followed by major procedures on the head and neck, especially after traumatic, vascular, or neoplastic intervention. Previous varicella-zoster infections might provide portal of entry,[52-55] as well as tattooing and body piercing.[56,57] Infections can also spread from distant sites following the bloodstream and/or the lymphatic system.[58] Being overweight is an additional risk factor,[1-3,32,47] while the role of alcohol misuse, intravenous drug abuse, or smoking remain anecdotal, these are not confirmed in large series. Case-control and cohort studies have examined main recurrence associated factors, which again included venous insufficiency, local injury, obesity, lymphoedema, tinea pedis, and smoking.[32,34,42,45]

Bad prognosis risk factors have not been clearly investigated in controlled studies.[3] Observational retrospective studies suggest the role of chronic illness and bad nutritional status as risk factors for complications and mortality in skin and soft tissue infections (SSTIs).[31,59] Immunodeficiency should always be suspected, either as a primary cause (HIV) or as a consequence of systemic treatment, such as corticosteroids, and cytostatics. The potentially harmful role of oral non-steroidal anti-inflammatory drugs (NSAID) is controversial as some studies suggest an increased risk of complications, inducing a relief of nonspecific symptoms, which are alarm signals of the progression from cellulitis to NF.[60,61] The risk is particularly reported in children with varicella-zoster infections,[62] for an impairment of neutrophil blood cell function induced by NSAIDs. On the contrary, another study assesses the beneficial effects of combining the antibiotic treatment with anti-inflammatory drugs, shortening the time to recover, and hospital dismissal, and accounting for an increased number of complete resolution in

**Table 1. Predisposing factors.**

| | |
|---|---|
| Predisposing to cellulitis development | Providing a port of entry:<br>• Wounds, both accidental, voluntary (tattoo, piercing) or surgical<br>• Superficial or localised infections<br>• Eczematous dermatitis |
| Influencing the severity of the disease | • Infections - Sepsis<br>• Immunodeficiency (HIV) and immune-suppression (systemic treatments, ageing)<br>• Vascular damage (Ischemia; venous insufficiency; lymphatic stasis)<br>• Chronic illness (malignancies, kidney and liver insufficiency)<br>• Obesity<br>• Diabetes<br>• Malnutrition, vitamins deficiency, calamities, and war conditions |
| Controversial conditions | • Alcohol misuse<br>• Intravenous drugs abuse<br>• Tobacco smoking |

respect to patients treated with antibiotics alone. The rationale of the supplemental use of anti-inflammatory therapy refers to the role of the host inflammatory response on the amplification of the infectious tissue damage and cellulitis clinical manifestations development.[63] By contrast compromised host's defence and tissue functional deterioration are complications predisposing conditions frequent in diabetes, kidney and liver insufficiency, malnutrition, vitamin deficiency, as well as in course of malignancies, especially in patients exposed to chemotherapy and radiation regimen. War is an old but ever actual condition in which cellulitis might rapidly develop from wounds, but also from occult nasal infections.[24]

## THE PROBLEM OF DEFINITIONS

Cellulitis is part of a major spectrum of diseases, clustered under the common category of SSTIs, as the same pathogens are often the cause. The unpredictable course of such infections at presentation has led to 'unproven clinical practice', which relies on hospital admission to close clinical monitoring, and empirical broad spectrum intravenous antibiotic treatment.[2,3,64-66] In recent large observational studies, around 3% of emergency medical consultations at a UK district general hospital were due to cellulitis,[2] 27% of the patients were hospitalised in a larger collection of cases from 56 US hospitals,[67] and from a similar Scottish experience, about 70% of the cases could have been managed in the community.[68] Moreover, an extraordinary variation in antibiotic regimens are prescribed worldwide, from 46 in the US[69] to 35 in the Scottish experience,[68] and 25 initial regimens from a computerised provincial charts audit of five Canadian Emergency Departments.[65] Although there is clinical concern for rapid development of life-threatening conditions, careful history and clinical examination at presentation are usually sufficient to distinguish between severe and complicated conditions that require emergency admittance and uncomplicated patients who could be successfully treated as outpatients. Therefore, criteria definition update and constant clinical training improvement is to be promoted, both in primary and tertiary cares.

Current trends are to consider erysipelas (from the Greek ἐρυσίπελας—red skin) as a milder form of cellulitis rather than a distinct entity,[2-4,70] although the term is widely accepted and well describes the peculiar presentation of this very superficial dermis infection, which consists of a bright red swelling patch, sharply demarcated from the adjacent unaffected skin. Italian literature named 'step sign' this typical raised border, of non-pitting oedema absent in frank cellulitis, where the soft tissue inflammation is deeper and wide-spread from the very beginning. The erysipelas histology hallmark involvement is confined to the superficial dermis and lymphatic, which depends on a characteristic pyogenes tropism towards lymphatics, especially the Group A Beta-haemolytic streptococcus (GAS).[70] Nevertheless, the lymphatic involvement is also severe in all forms of cellulitis, and inflammation arising superficially might extend deeply within hours. From an anatomical point of view, dermis and subcutaneous tissues are intercommunicating spaces, the main first anatomical barrier being deep septa and fascial planes, confining the inflammation for a certain period of time, and differentiating cellulitis from NF and gangrene.[1-5,9,10]

Clinical attempts to stratify SSTIs cases and provide early identification of high-risks patients include:

- Extension and Site of primary infection,[71] distinguishing among head and hand involvement from inferior limb localisation, and a body area involvement >9% following the rule of nines. The face involvement has a higher risk of complications due to the abundance of sensitive anatomical structure.

- Eron's Clinical Classification, adopted from the CREST guidelines,[2,72] considers four classes of patients with different prognosis and management:

    - Class I: no signs of systemic toxicity, no uncontrolled comorbidities. The patient can usually be managed with oral antimicrobials on an outpatient basis.

    - Class II: history of comorbidity which may complicate or delay resolution of the infection (such as peripheral vascular disease or obesity). The patient is suitable for short-term (up to 48 hours) hospitalisation and discharge on outpatient parenteral antimicrobial therapy (OPAT), where this service is available.

    - Class III: significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension or unstable comorbidities that may

interfere with a response to therapy or limb threatening infection due to vascular compromise.

o Class IV: patients with sepsis syndrome or severe life threatening conditions.

• Clinical severity charts adopted to predict in-hospital mortality and length of stay, such as the standardised early warning score (SEWS), based on the assessment of several parameters:[73,74] respiratory rate, oxygen saturation, temperature, systolic blood pressure, heart rate, and level of consciousness. A score of ≥4 requires urgent medical assistance.

The recent Scottish retrospective study pointed out the doubtful prognostic significance of co-morbidity in otherwise healthy patients (SEWS<4), and suggests that Class I and II of the CREST guidelines can be merged, indicating less severe cases, safely managed as outpatients.[68] On the contrary, sepsis is a puzzling condition, worsening the patient's prognosis although the vital signs are not alarming (SEWS<4), and without comorbidity. Other international experiences confirm that sepsis is the major risk factor for mortality.[31,59,69]

## DIFFERENTIAL DIAGNOSIS

As specific criteria for the diagnosis of cellulitis are lacking, physician's experience is critical to point out cellulitis from the many mimics.[66,75,77] A study conducted in an infectious disease service suggests that more than 10% of the urgent referrals for cellulitis had a final alternative diagnosis.[78] Consultation with a dermatologist is recommended,[75] for their visual ability in recognising different conditions, evaluating the weight of each, favouring pre-existing conditions and determining if a biopsy is necessary. A first distinction should be made among clinical conditions representing possible complications of cellulitis, usually clustered in the same SSTIs spectrum, and the many imitators of cellulitis, whose assessment and treatment might differ greatly from antibiotics (Table 2 and 3).

**Table 2. Cellulitis differential diagnosis in the spectrum of the skin and soft tissue infections.**

| Entity | Definition | Clinical presentation |
|---|---|---|
| Abscess | An enclosed collection of necrotic tissue, bacteria and inflammatory cells, surrounded by a reactive capsule and a cell wall from nearby healthy tissues. | An erythematous painful swelling area with fluctuation and trophic alteration. A thick yellowish pus escapes from the abscess naturally by fistulisation or through medical intervention. |
| Necrotising fasciitis | Rapidly progressive necrosis of subcutaneous fat and fascia, also known as "flesh-eating syndrome". The patient is toxic, with fever, chills, tachycardia, malaise, and altered levels of consciousness.<br><br>Type I: mixed infection of anaerobes plus facultative species such as *streptococci* or *Enterobacteriaceae*.<br>Type II: infection with group *A streptococci* | An ill-defined red-purple to grey shiny patch, with violaceous bullae, ulcers and areas of shiny watery malodorous fluid discharge, due to fat necrosis. Deep palpation reveals a wood hardness. The presence of hypo- or anaesthesia suggests deeper nerve involvement. |
| Gangrene | Necrosis of deep soft tissue primarily due to a loss of blood supply, sometimes permitting invasion and proliferation of bacteria, especially those able to survive with little or no oxygen, such as the Clostridium family. It often has an abrupt onset following a deep penetrating wound. | Tender, dark yellow or brown discolouration of the skin, with sera-haematic bullae and patches of necrosis. A mousy smelling is common. Crepitus at palpation support the diagnosis of gas producing bacteria (Gas gangrene). |
| Erysipeloid | An occupational disease, caused by the *Erysipelotrix rhusiopathiae*, a Gram-positive rod contaminating dead matter of animal or fish origin. Veterinarians, meat packers, fishermen are frequently exposed to minimal trauma while handling the contaminated material. | Clinical features are common to erysipelas and other bacterial cellulitis, but it is usually milder and tends to self-limitation. |

**Table 3. Cellulitis mimickers.**

| Site of involvement | Clinical conditions | Differential criteria |
|---|---|---|
| Extremities | • Deep wounds<br>• Superficial infections, especially candidal intertrigo on hands, bacterial foot intertrigo, and tinea pedis.<br>• Diabetic and gangrenous foot.<br>• Acute gout attack and septic arthritis.<br>• Stasis dermatitis, chronic lymphoedema, venous insufficiency.<br>• Pyoderma gangrenosum. | • Long-standing manifestations, with initial indolent course and sudden worsening.<br>• Presence of minimal bilateral or pre-existing changes, such as pitting oedema, superficial scaling or *xerosis*, hyperpigmentation, varicosities and scars.<br>• Bound-down plaques or inverted champagne bottle appearance.<br>• Comorbidity: Obesity, diabetes, and bad nutritional state. |
| Cephalic involvement | • Recent surgical procedures on the head and neck.<br>• Herpes infections, especially H. Zoster ophthalmicus.<br>• Chronic sinusitis, otitis, and per-orbital inflammation, dental abscesses.<br>• Urticaria angioedema.<br>• Contact dermatitis.<br>• Carcinoma erysipeloides. | • Manifestations are usually milder, simulating a very initial inflammation.<br>• Allergic manifestations tend to be itching rather than painful.<br>• History of previous infections, allergy, and malignancy is often evocative.<br>• Systemic upset and fever are usually absent in all these conditions. |
| Any or multiple sites | • Insect bites<br>• Major surgical procedures<br>• Sweet Syndrome<br>• Well's cellulitis | • History of recent change in lifestyle, outdoor excursions or travel.<br>• Malignancies, and/or immune suppression are to be considered.<br>• More generalised lesions with fever and malaise are suspect for a systemic inflammatory disease. |

## A: Cellulitis Differential Diagnosis in the Spectrum of SSTIs

Considering erysipelas as a mild form of cellulitis, the main common entity that should differentiate from cellulitis is the abscess, which is defined as an enclosed collection of necrotic tissue, bacteria, and inflammatory cells (pus). Nevertheless, abscess formation and fistulisation is a frequent evolution of cellulitis, especially when not adequately treated (suppurative stage). Skin necrosis may complicate conventional cellulitis, extending through the subcutaneous fat and fascial planes or may occur with distinctive clinical features, configuring the NF. The distinction is not purely anatomical, as NF represents a more severe and extensive infection that poorly responds to wide spectrum antibiotics and requires aggressive surgical treatment (fasciotomy). Cellulitis evolution towards NF might progress at a very alarming rate, usually announced by a change in skin colour from red-purple or bluish to grey, with occurrence of violaceous bullae, and areas of shiny watery malodorous fluid discharge, due to fat necrosis, while consistency becomes hard as wood on deep palpation.[9,10,79] The term gangrene is also frequently used in association with cellulitis, especially in the form of gas gangrene which is synonymous with anaerobic cellulitis. Gangrene occurs primarily due to loss of blood supply, rapidly evolving to necrosis of soft tissue, muscles, and eventually bones. The infective form is usually due to a deep penetrating wound, allowing invasion and proliferation of those bacteria able to survive with little or no oxygen, such as the *Clostridium* family. These ubiquitous Gram-positive bacilli found in soil and bowel flora generate gas, whose presence is advised by soft tissue crepitating at palpation.[80-82]

There is another peculiar disease in the spectrum of cellulitis, called erysipeloid, from the causative Gram-positive rod *Erysipelothrix rhusiopathiae*.[83]

It is an unusual pathology, due to the exposure to contaminated materials derived from animals or fish, configuring an occupational disease in veterinarians, meat packers, and fisherman. Clinical features are common to other bacterial cellulitis, and a biopsy at the advancing edge of the lesion, extending through the entire dermis thickness, might be performed to assess the diagnosis, stating the usually milder, self-limited course.

### B: Cellulitis Mimickers

In distinguishing cellulitis from other clinical conditions one should consider the site of involvement and extension, as lower extremities and the head/neck region recognise different alternate diagnosis, while more rare entities, which include several inflammatory non-infective diseases, usually diffuse, occurring in any site of the body. Some concepts applied to all conditions: cellulitis is rarely bilateral, is rapidly progressive, with smooth, indistinctive borders, accompanied by systemic symptoms.

Trauma, insect bites, surgical procedures, allergies, and contact dermatitis are common at any age, while diabetic and gangrenous foot, gout, septic arthritis, and stasis dermatitis are elderly conditions. Patients with insect bites or allergies usually complain of intense itching rather than pain, and careful anamnesis usually helps to find a recent change in lifestyle, such as outdoor excursions or travel, hobbies, previous cutaneous allergies, or recent medications. The most common reported mimickers of leg cellulitis in adults are stasis dermatitis and chronic lymphoedema, both presenting ill-defined areas of erythema and not-pitting induration, with sudden worsening and serous drainage. Patient history usually reveals a long-standing process, and although one leg is usually more affected during flares, careful observation usually depicts bilateral involvement, superficial scaling areas, pigmentation alterations, varicosities, and scars from previous ulcerative lesions, with bound-down plaques appearance.[75] Patients are often obese, diabetic, or have a history of major trauma or surgery, such as radical lymphadenectomy for melanoma, or breast cancer when the arm is affected. Advanced skin changes, due to vascular and lymphatic compromise, cause lipodermatosclerosis, whose sudden worsening, with painful evidence of ill-defined warm erythematous-oedematous plaques is difficult to differentiate from cellulitis, which in turn might also complicate the disease at any moment. Leg observation usually reveals dark pigmentation, hyperkeratosis with wart-like buttons, and underlying sclerosing panniculitis, giving the features of an 'inverted champagne bottle' or 'inverted bowling pin'.[84-86] Herpes zoster is usually recognisable for its single dermatome disposition. Chronic sinusitis, otitis and per-orbital inflammation, especially in young patients, can cause mild-to-moderate swelling of the cheek, nose, and eyelid which can be difficult to distinguish from initial signs of cellulitis.[87] Carcinoma erysipeloides is sometimes confused with cellulitis at presentation, especially when metastasis involves the sphenoid and posterior wall of the orbit.[88-90] Breast cancer is usually the primary tumour, followed by prostate, lung, and the gastrointestinal tract. Absence of fever, and a slower, more indolent course than cellulitis are distinctive features of carcinoma erysipeloides.

Diffuse not-infective cellulitis mimickers include Sweet's syndrome (acute febrile neutrophilic dermatosis), in its acute presentation, with painful tender erythematous pseudo-vesicular plaques, accompanied by fever, general malaise, and neutrophilic leucocytosis.[91-94] Pyoderma gangrenosum might also simulate cellulitis, with acute often isolated lesions starting in the subcutaneous fat, with rapid necrotic evolution or superficial diffuse lesions, on erythematous-oedematous enlarging plaques.[95-97] Wells' eosinophilic cellulitis is another great simulator, which progresses slowly with erythematous oedematous lesions with sharp borders, a green hue and central clearing.[98-100] All these immune-mediated entities are corticosteroid-sensitive, and broad spectrum antibiotics will not modify progression.

## EMERGING PATHOGENS AND IMPLICATION FOR TREATMENT

The vast majority of cellulitis recognised the same causative agents, responding to common wide spectrum antibiotics,[1-5] but Gram-negative and polymicrobial infections[12,102] as well as widespread resistance to antimicrobial agents, especially methicillin-resistant *S. aureus* (MRSA)[103-110] have generated an increasing defensive attitude towards hospitalisation and overtreatment.

Major causative pathogens are *Staphylococcus aureus* and *Streptococcus pyogenes* (especially Group A beta-haemolytic *S. Pyogenes* (GAS). Sporadic cases due to other Gram-positive are reported: group G, B, C, and D Streptococci. In children *S. Pneumonia*[107] and *Haemophilus influenzae* are responsible of very severe cases.[7,8,112,113] Gram-negative *Neisseria meningitidis*, *Klebsiella pneumonia*, *Yersinia enterocolitis*, *Pseudomonas aeruginosa*, *Pastorella multicida* are increasingly reported,[114,116] together with mixture of Gram-positive and Gram-negative bacteria, aerobes and anaerobes, especially after surgical procedures and dental pathologies.[37] An endodontic origin is evoked in facial *Candida albicans* cellulitis, as well as deep contamination of other body sites through incisions, drainage, and percutaneous endoscopic procedures, especially in diabetic patients.[117-119] Among the rarest causes of cellulitis, *Nocardia* species and *Cryptococcus neoformans*, should be considered, both as consequence of a disseminated form or when an accidental port of entry have caused a primary skin infection.[120-128] Histoplasmosis and mucormycosis might manifest with cellulitis in those countries where the infections are prevalent.[129,130]

Inadequate treatment, for example in course of fungal cellulitis and selection of methicillin-resistant strains should be suspected in patients with a history of previous general antibiotic regimen, chronically immune-suppressed patients, among intravenous drug users, prisoners, male homosexuals, and HIV infected patients.[1-5,100-104,131] Military trainees and athletes are other apparently healthy categories in which increasing MRSA infections have been reported.[132-136]

Considering microbiologic variability and clinical difficulties, it is not surprising that 'gold standard' treatment for cellulitis has not been achieved,[1-5] and final choice remains empirical, based on expert consensus rather than evidence. European guidelines recommended penicillin as the initial standard treatment for simple community-acquired erysipelas and cellulitis,[3] while coverage for MRSA should be considered in peculiar settings.[5] CREST guidelines recommend oral antibiotics for Class I severity infections and intravenous antibiotics for any other classes, with an initial 24-36 hours in-hospital monitoring and the opportunity to continue the therapy as outpatients, in Class II and III patients. A randomised trial comparing oral to intravenous therapy showed no outcome differences in patients without complications.[73] Besides, the majority of studies are conducted in emergency settings, and suggest wide coverage of Streptococcus strains and *Staphylococcus aureus*, usually with combination of intravenous benzyl penicillin and flucloxacillin.[72,137,138] Cephalosporins are often used alone or in association, especially intramuscular ceftriaxone.[139,140] Other penicillase-resistant betalactams include dicloxacillin, nafticillin, betalactam/clavulanic acid, piperacillin/tazobactam.

For penicillin-allergic patients macrolides are recommended, mainly oral erythromycin or clindamycin, although there are no comparative data and oral azithromycin might be as well efficacious.[2,3,141] Concomitant therapy with ciprofloxacin and metronidazole is prescribed for polimicrobial infections.[98]

Very resistant infections are firstly treated with vancomycin, or teicoplanin, although susceptibility is decreasing for both drugs.[142,143] New antibiotics includes linezolide[144-146] quinupristin-dalfopristin[147,148] daptomycin,[153-155] ertapenem.[156] Initial short course of intravenous antibiotics in hospital settings and prosecution with several infusion devices and dosage adjustment as outpatient parenteral antibiotic therapy (OPAT) is an actual trend to reduce bad pressure and costs.[139,148,157,159] Old (ceftrixone, teicoplanin) and new drugs (quinupristin-dalfopristin, daptomycin, ertapenem) are under evaluation.[158]

Persistent inflammation rather than infection might be responsible for residual symptoms, mainly fever and pain, and slow skin healing, as suggested from a study showing the same results from 5-10 days treatments,[160] and other experiences using corticosteroids and other anti-inflammatories to improve response.[72,161,164] Concern relies on progression to NF, sepsis and metabolic aggravation, whose signs and symptoms might be masked by anti-inflammatory and analgesics.[164] Hyperbaric oxygen therapy has been proposed in severe cases as adjuvant measure.[165-167] Treatment of predisposing condition is otherwise mandatory, from metabolic compensations to chronic infections and nutritional state control.

Prophylaxis therapy in patients with more than two cellulitis episodes has not be validated, but daily oral penicillin is suggested.[5,168,169]

## CONCLUSION

Cellulitis is an emergency condition that must be handled early in any medical setting, from primary to tertiary cares. Any age can be affected, suddenly in otherwise healthy patients, although several local and general predisposing conditions might favour the occurrence. Acute complications are fortunately rare, but life-threatening. Long-term complications are recurrences and persistent lymphoedema, which further favour aggravation. Specific types of cellulitis might be tailored to microbiological findings based on cultures and drug sensitivities. Most patients recover completely after timely antibiotics, but guideline recommendations and severity evaluation are cumbersome, so that hospitalisation and overtreatment is a current issue. Clinical training is the clue to correct assessment and management of such challenging conditions.

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# PSORIASIS AND COMORBIDITIES

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**Disclosure:** No potential conflict of interest.
**Received:** 20.08.13 **Accepted:** 25.10.13
**Citation:** EMJ Dermatol. 2013;1:78-85.

## ABSTRACT

Psoriasis is a chronic inflammatory disease which is a result of complex interactions between genetic, environmental, and immunological factors. Psoriasis is now accepted as a systemic disorder accompanied by comorbidities rather than simply a cutaneous disease. Psoriasis has been associated with a number of systemic diseases such as diabetes mellitus, obesity, hypertension, metabolic syndrome, cardiovascular mortality, psoriatic arthritis, Crohn's disease, ulcerative colitis, pulmonary disease, psychiatric disorders, and malignancies referred to as comorbidities. Although the causal relationship between comorbidities and psoriasis has not been completely clarified yet, it seems that shared genetic susceptibility, common environmental factors, and/or overlapping inflammatory pathways may be potential biological links underlying this association. The presence of comorbid diseases is important since it is associated with a significantly reduced life span and a significant deterioration in life quality. It is also important to keep in mind that the comorbidities and drugs used to treat them have an impact on the choice of antipsoriatic treatment. Besides, systemic treatment of psoriasis with certain drugs may impact the comorbid conditions. Therefore, it is necessary for physicians to recognise these concomitant diseases early and to arrange management options. In this article, the current literature about psoriasis-associated comorbidities and treatment approaches will be discussed.

Keywords: Psoriasis, obesity, metabolic syndrome, comorbidity.

## INTRODUCTION

Psoriasis is a chronic, hyperproliferative, immune-mediated, and inflammatory skin disease affecting approximately 1-3% of the population worldwide.[1,2] Chronic plaque psoriasis, the most common form of psoriasis vulgaris, is characterised by sharply demarcated erythematous papules and plaques with scales and with various distribution, severity and course.[1-3] Today there is increasing evidence to substantiate that psoriasis is not just a disease of the skin but a systemic inflammatory disease.[4-8]

Psoriasis results from interaction between an individual's genetic susceptibility, specific environmental factors, and immune mechanisms.[1,8-12] T cells, dendritic antigen-presenting cells, and cytokine networks are recognised as playing a major role in the pathogenesis of psoriasis.[11] The majority of T cells infiltrating in psoriasis were assumed to belong to the T-helper cell (Th)1 subset. Recently, not only has aberrant activation of dendritic cells in skin been found to play a critical role but evidence also points to a role for both Th1 and Th17 cells in the pathogenesis of psoriasis due to elevated levels of many specific inflammatory cytokines.[9,11,12] In particular, Th1 and Th17 cells are expanded and stimulated to release inflammatory cytokines, including tumour necrosis factor alpha (TNF-α), interferon (IFN)-gamma, interleukin (IL)-17 and IL-22. These cytokines contribute to changes that enhance and perpetuate psoriasis. The continuous inflammation proceeds step-by-step inducing systemic inflammation cascade. Sustained skin inflammation is sufficient to induce secretion of other cytokines from subcutaneous fat cells, endothelial cells and other inflammatory cells, leading to endothelial dysfunction, vascular

inflammation, thrombosis and systemic inflammation[10,12,13] (Figure 1). 'Psoriatic march' is a recently defined term and has been used to describe this process developing in a step-wise manner.[8,10]

As demonstrated in many studies, psoriasis is described as an immune mediated inflammatory disease that is connected with a range of comorbidities.[6,8,11,14,15] Numerous studies have evaluated the increased prevalence of comorbid diseases in psoriatic patients, including obesity, diabetes mellitus, metabolic syndrome, cardiovascular disease (CVD), Crohn's disease, ulcerative colitis, non-alcoholic fatty liver disease, psychiatric illness, sleep apnoea, chronic obstructive pulmonary disease (COPD), and malignancy.[4,5,7,9,11,15-21] Below, we will overview these comorbidities briefly.

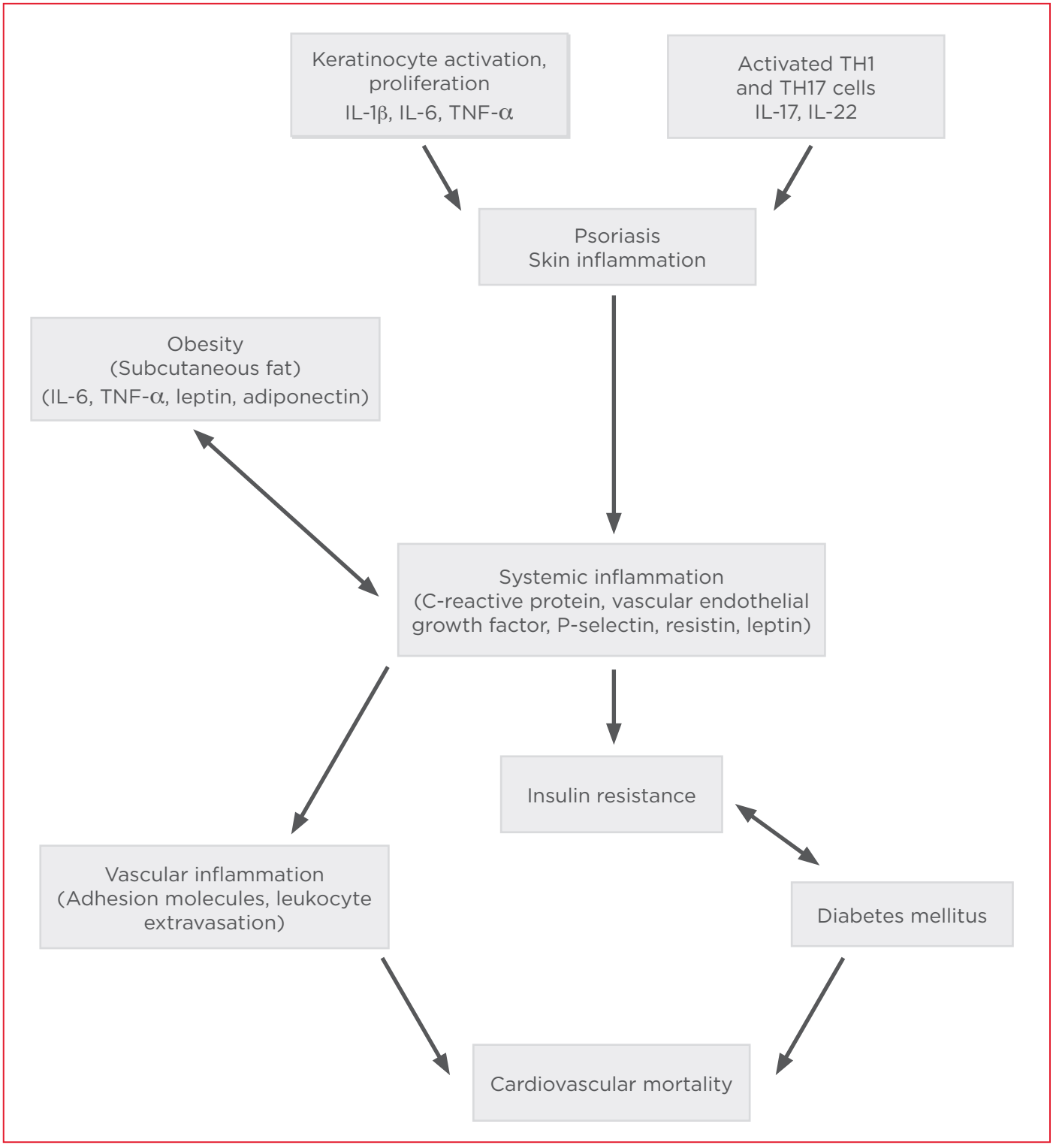


**Figure 1. Simplified mechanism of systemic inflammation and consequent events.**

## OBESITY AND METABOLIC SYNDROME

Recently, a strong association between increased adiposity, obesity, and psoriasis has emerged.[4,5,8] Several studies have shown a significant association between increased body mass index (BMI) and psoriasis.[22-25] In addition to obesity, patients with psoriasis are more likely to have metabolic syndrome.[4-7,15-17]

It is now clear that intra-abdominal fat is not merely an inert mass but an active metabolic and endocrine organ, secreting adipocytokines, promoting inflammation, and affecting glucose metabolism and vascular endothelial biology.[26,27] Subcutaneous fat cells (adipocytes) produce proinflammatory cytokines under the influence of inflammatory mediators such as TNF-α that is produced by the skin. Primary cytokines that are produced by adipocytes include IL-6, TNF-α, plasminogen activator inhibitor type 1 (PAI-1), leptin and adiponectin, each of which plays multiple roles in inflammation, metabolism and endothelial cell function.[26,27] Besides, adipocytes bear Toll-like receptors that behave as a component of innate immunity and allow an immediate response to foreign pathogens and release cytokines.[27] As systemic inflammation continues and with increasing BMI, adiponectin is downregulated while leptin and resistin are upregulated, which induces insulin resistance and causes endothelial cells to produce adhesion molecules, promoting a hepatic release of both fibrinogen and C-reactive protein, and augmenting the procoagulant effects on platelets.[8,17,26,27] These drive the process with consequences of metabolic syndrome.

Several studies have shown that psoriasis may be linked to obesity, however, controversy still exists as to whether obesity is a result or a causative factor of psoriasis.[6,11,16] Either way, this strong association makes psoriasis an important healthcare issue.

### Insulin Resistance/Diabetes Mellitus

Psoriatic patients have been found to be more insulin-resistant and to have impaired glucose tolerance and higher fasting insulin levels than healthy ones.[28-33] A large observational study by Brauchli et al.[31] demonstrated an increased risk of incident diabetes mellitus in patients with psoriasis when compared with a psoriasis-free study group. Among 1,061 incident cases of diabetes mellitus, 59% had a history of psoriasis. Also, they indicated that the risk was higher for patients with a longer psoriasis history.

Coto-Segura et al.[30] reported a recent study involving observational studies assessing the relationship between psoriasis or psoriatic arthritis and type 2 diabetes mellitus; their findings supported the association between psoriasis, psoriatic arthritis and type 2 diabetes mellitus. Another study reported by Armstrong et al.[32] recently demonstrated an increased prevalence and incidence of diabetes and indicated that this association is stronger among patients with severe psoriasis.

A study by Cohen et al.[33] supported previous reports of an association between psoriasis and diabetes mellitus. The age-adjusted proportion of diabetes was found to be significantly higher in psoriasis patients as compared to the control group. A possible explanation for the association between psoriasis and diabetes is the presence of chronic inflammation that occurs due to secretion of TNF-α and other proinflammatory cytokines such as IL-1 and IL-6, which precipitate both psoriasis and diabetes.

### Metabolic Syndrome

Metabolic syndrome is a combination of central obesity, dyslipidaemia, insulin resistance, and elevated blood pressure, which has been associated with an increased risk of CVD beyond traditional risk factors.[4,5,7] The metabolic syndrome is an important driver of adverse cardiovascular outcomes.[34,35] Although the pathophysiology of all components of metabolic syndrome has not been clarified completely, it is accepted to be a heterogeneous and a complex disorder, developing on the basis of insulin resistance which is due, in large part, to the action of increased levels of proinflammatory factors, such as TNF-α, that are central to the pathogenesis of psoriasis.[9,17,19,26]

Multiple epidemiologic studies have consistently demonstrated higher prevalence of metabolic syndrome in patients with psoriasis.[4,5,9,18-21] This association is valid for mild severity psoriasis and it is independent from the tendency of psoriatic patients to be obese.[4] Dose-response relationships between more severe psoriasis and higher prevalence of metabolic syndrome components were recently established.[5]

The underlying pathophysiology linking psoriasis and metabolic syndrome may involve overlapping inflammatory pathways and genetic predisposition. Chronic inflammation and dysregulation of cytokines not only promotes epidermal hyperplasia in psoriasis, but may also antagonise insulin signalling, alter adipokine expression, and mediate insulin resistance and obesity.[36]

Abdominal obesity and insulin resistance are considered underlying risk factors for the development of metabolic syndrome.[5,11,33]

## Non-Alcoholic Fatty Liver Disease

The relationship between non-alcoholic fatty liver disease (NAFLD) and psoriasis severity has been established. NAFLD is found to be highly prevalent among psoriasis patients, where it is closely associated with obesity and metabolic syndrome.[37-41] Gisondi et al.[39] have demonstrated a higher frequency of NAFLD in 130 patients with plaque psoriasis when compared with the control group (47% versus 28%). Patients with psoriasis and NAFLD also had higher serum C-reactive protein concentrations, greater severity of psoriasis, and revealed a higher frequency of metabolic syndrome than those with psoriasis alone. Miele and coworkers[37] prospectively examined the prevalence and characteristics of NAFLD in 142 patients with psoriasis and found NAFLD in 59.2% of the patients. The study revealed that NAFLD in psoriasis patients was significantly correlated with metabolic syndrome.

The proposed mechanism underlying these two disorders may involve common pathways. As NAFLD is thought to be an expression of metabolic syndrome in the liver, a degree of persistent inflammation with secretion of cytokines (TNF-α, IL-17/23) which induces the development of insulin resistance and metabolic syndrome is also implicated in the development of NAFLD.[40-42]

## Cardiovascular Diseases

Psoriasis is now thought to be an independent risk factor for coronary artery disease and acute myocardial infarction (MI).[43] The risk of developing ischaemic heart disease and cerebrovascular disease has been reported to be higher in patients with moderate-to-severe psoriasis than in the general population.[43-45]

Several factors are associated with a higher risk of CVD, such as age, high blood pressure, obesity, smoking, dyslipidaemia, physical inactivity, and psychological stress. Many of these factors are also prevalent in psoriatic patients, which effects the severity of psoriasis.[8,11,16,18,44,46-48] Several studies demonstrated higher prevalence of CVD such as MI, thrombophlebitis, pulmonary embolism, and cerebrovascular disease in patients with psoriasis, and an increased mortality.[43-53] Furthermore, it has been pointed out that the presence of psoriasis as an independent risk factor for the development of atherosclerosis[5] and MI, after controlling for different variables and risk, was found to be higher in young patients with severe psoriasis.[43,44]

Kimball and coworkers[45] estimated the 10-year risk of coronary heart disease and stroke in 1,591 patients with psoriasis and found a significantly higher cardiovascular risk in patients with psoriasis when compared with general population, with a risk that was 28% greater for coronary heart disease and 11.8% greater for stroke.

Gelfand et al.[43] examined the incidence of MI among patients with and without psoriasis. They identified 130,976 patients with psoriasis and 556,995 in the corresponding control group, followed-up for a mean of 5.4 years. The authors showed that patients with psoriasis had a higher incidence of MI compared with control patients, and that patients who had severe psoriasis had the highest rate.

The mechanistic link between psoriasis and this observed increase in cardiovascular comorbidities has not been fully defined. However, it is clear that the chronic inflammation plays an important part in the pathogenesis of many metabolic and vascular diseases.[8,11,13] An increased risk of atherosclerosis in patients with inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis has been demonstrated.[54,55] Inflammation was shown to be a key factor in atherogenesis, providing a unifying mechanism for explaining the association between atherosclerosis.[8,10,21]

Shared inflammatory pathways, including Th1-mediated inflammation, alterations in angiogenesis and endothelial dysfunction, may link the pathogenesis of psoriasis with the development of atherosclerosis and CVD.[13,23,43,44]

## Crohn's Disease and Ulcerative Colitis

Crohn's disease and ulcerative colitis have been demonstrated to be significantly higher in patients with psoriasis than in the normal population, suggesting the possibility of a genetic link and chronic inflammation.[56-58] Cohen et al.[56] examined the prevalence of inflammatory bowel disease in 12,502 patients with psoriasis and 24,287 age and sex matched control group members. They found a significantly higher prevalence of both Crohn's disease and ulcerative colitis in psoriasis patient group compared with the control group. These associations are biologically plausible, as systemic inflammation and TNF-α plays an important role in all three diseases.[56]

## Psychiatric Diseases

Psoriasis is a physically, socially, and psychologically disabling disease that negatively impacts quality of life.[3,59-67] Psoriasis impairs ability in daily activities that require the use of hands, walking, sitting and standing for long periods of time, occupational performance, sexual activities, and sleep; many also experience rejection which causes a feeling of stigmatisation.[62,63]

Psoriasis patients reported significantly higher degrees of depression and more body cathexis problems. In addition, the risk for developing psoriasis increased significantly in patients with moderate and severe depression. There is also a relationship between symptom severity and low affective expression.[63,65]

Krueger and coworkers[59] assessed patients' perspectives on the impact of psoriasis and a self-administered questionnaire was applied to patients. 79% of the patients reported that psoriasis had a negative impact on their lives and 40% felt frustrated with the ineffectiveness of their current therapies.[59] The study by Sampogna et al.[66] included 936 patients with psoriasis. The problems most frequently experienced by the patients were shame, anger, worry, and difficulties in social life. Dominguez and coworkers' study[67] included 86,880 females and the participants reported anti-depressant use and completed a scale. They found that depression was associated with an increased risk of incident psoriasis. Compared to women in the non-depressed group, women who reported either having high depressive symptomatology or who were on anti-depressants had 1.59 times relative risk of developing subsequent psoriasis. Sleep quality is also disturbed in patients with psoriasis due to itching and problems with depression and mood status.[68] Therefore, evaluation and treatment of psoriasis must include psychosomatic approaches in clinical practice.

## Chronic Obstructive Pulmonary Disease

Dreiher et al.[69] compared 12,502 psoriatic patients with 24,287 healthy controls, in terms of presence of COPD, and demonstrated a higher prevalence of COPD in patients with psoriasis. A multivariate logistic regression model demonstrated that psoriasis was significantly associated with COPD, after controlling for confounders including age, sex, socioeconomic status, smoking, and obesity.[69] Another recently performed study from Taiwan supported similar results that psoriasis patients were at a greater risk of developing COPD with significantly lower COPD-free survival rates than the comparison cohort.[70]

## Obstructive Sleep Apnoea Syndrome

Keeping in mind that psoriasis is associated with obesity and CVD, it is likely that psoriasis can be related to obstructive sleep apnoea syndrome (OSAS). Recent studies have reported that the frequency of OSAS was found to be higher in patients with psoriasis than the normal population.[71,72] Karaca et al.[71] demonstrated OSAS in 54.5% of patients with psoriasis. They also found higher psoriasis area severity index (PASI) in the OSAS group than in the non-OSAS group. Papadavid et al.[72] explored the association between OSAS and psoriasis in their study and found that psoriasis patients with OSAS presented more frequent snoring and had lower sleep quality compared with those without OSAS. They also reported that OSAS was associated with increased BMI and hypertension in psoriasis patients.

## Malignancy

The relationship between psoriasis and increased cancer risk is still debated. Gelfand et al.[73] reported a study of 2,718 patients and their results indicated that patients with psoriasis are at increased risk for developing lymphoma. The limitations of this study were that 10% of the population studied was above 65 years old and the rate of lymphoma included the patients treated with methotrexate. A recently reported meta-analysis of epidemiological studies, including

1,080 articles, indicated that there may be an increased risk of some solid cancers such as lung, in psoriasis, especially in smokers and alcohol users; however, the large heterogeneity between these studies regarding study population and follow-up constitute the limitation of this report.[74] Chen et al.[75] investigated 3,686 patients with psoriasis and found that 116 had incident cancers. The 7-year cumulative incidence of cancer among psoriasis patients was 4.8%. Certain cancers including urinary bladder, oropharynx/larynx, liver/gallbladder, and colon/rectum were found to be significantly associated with psoriasis. The limitation of this study is that it does not contain information regarding severity of psoriasis, status of smoking, and alcohol use. Another study of Prizment and coworkers[76] revealed that with age-adjustment, psoriasis was associated with increased risk of lung, colon, and total cancer. After adjustment for smoking, only the association for colon cancer remained statistically significant.

### Other Diseases

Although it has not been clarified whether the association of autoimmune diseases with psoriasis is a simple coincidence or is a pathogenic relationship, there have been several reports that indicate this co-occurrence. Bullous pemphigoid, systemic lupus erythematosus, myasthenia gravis, multiple sclerosis, Sjögren's syndrome, Hashimoto's thyroiditis, parkinsonism, dermatitis herpetiformis, pemphigus vulgaris, linear immunoglobulin A dermatosis, and vitiligo have been reported.[77-82] Recent data suggest that Th17 cells play an important role in the pathogenesis of a diverse group of immune-mediated diseases.[12]

## MANAGEMENT OF A PSORIATIC PATIENT

The presence of comorbidities has important implications in the approach to patients with psoriasis. Systemic anti-psoriatic agents such as cyclosporine could negatively affect cardio-metabolic comorbidities such as hyperlipidaemia, hypertension and hyperhomocysteinaemia and may have important interactions with drugs commonly used by psoriatic patients.[4,11,22,25] TNF-α seems to be a particularly attractive target as it is known to induce endothelial cell dysfunction, insulin resistance and atherosclerosis.[8,10] Biological agents targeting TNF-α constitute a relatively new and efficient approach to psoriasis. The recent findings that the risk of MI is reduced in patients with rheumatoid arthritis who respond to anti-TNF-α therapy compared to non-responders, support the hypothesis that the anti-inflammatory effect of TNF-α blockers might reduce the cardiovascular risk potentially also in psoriasis patients.[11,83,84] Use of TNF-α inhibitors for psoriasis was associated with a significant reduction in MI risk and was associated with non-statistically significant lower MI incident rate compared with treatment with oral agents/phototherapy.[85] Therapeutic intervention by use of anti-inflammatory drugs including methotrexate and TNF-α antagonists seem to diminish the risk.[5,9] Torres et al.[18] reported three cases of psoriasis with metabolic syndrome that improved without using any systemic and/or topical antipsoriatic treatments, just by strict diet, antihypertensive-anti-lipid and anti-diabetic treatments. These data also suggest that the treatments of these patients not only improve the skin lesions but also control the inflammation associated with the psoriasis. Therefore, it is important that the dermatologist systematically seeks these concomitant pathologies among psoriatic patients and discontinuation of smoking and alcohol consumption should be encouraged.

## CONCLUSION

Psoriasis is considered as a chronic, immune-modulated inflammatory disease. In this article, not only a summary of the evidence for a link between psoriasis and comorbidities is presented but also the main concepts regarding psoriasis are discussed. As mentioned during this article, recent literature brings a new point of view to psoriasis, which is a chronic recurrent disease with inflammatory state, including its association with severe comorbid conditions. This association has important clinical implications for the management of psoriasis: patients with psoriasis should be routinely screened for metabolic syndrome in a multidisciplinary manner and treated promptly and effectively, while clinicians should also monitor treatment efficacy and safety in patients with comorbid psoriasis and metabolic syndrome. Finally, patients should be encouraged to correct their cardiovascular risk factors, in particular obesity and smoking habits. Further research will be necessary to establish the directionality of this association and to demonstrate the effect of treatment on these comorbid diseases.

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# Simple blood test for a better outcome

BLOOD tests could be used to identify patients whose skin cancer has spread. As melanoma is difficult to treat once it spreads, measuring the levels of the gene TFP 12 in DNA in the blood could potentially be the key to early identification of the disease.

Prof Charlotte Proby, a Dermatologist based at the University of Dundee, UK, said: "Using blood tests to assess the landscape of our DNA is a simple way to learn more about what's going on under the skin."

Previously, detecting if melanoma had spread was difficult; these findings could mean that a faster diagnosis will be possible, and in turn, new treatments could be developed.

Dr Tim Crook, study author, Consultant Medical Oncologist, University of Dundee, said: "By using a blood test, we have the basis of a simple and accurate way of discovering how advanced the disease is, as well as an early warning sign of whether it has started to spread. This would give doctors and patients important information much sooner than is possible at the moment."

New treatments have been effective in the early stages, but identifying the patients whose cancer has just spread would significantly improve their chances. Although more than 8 in 10 patients now survive melanoma for at least 10 years, more can be done for these patients.

Dr Harpal Kumar, Chief Executive of Cancer Research UK, Chair of the National Cancer Research Institute, said: "This work could lead to quicker diagnosis and potentially new treatments giving patients and doctors an even better chance of beating the disease."

The next step is to develop a panel of similar biomarkers which will detect patients who need further treatment to fight their melanoma.

> "Using blood tests to assess the landscape of our DNA is a simple way to learn more about what's going on under the skin."
>
> *Prof Charlotte Proby, University of Dundee, UK*

# 33-year-old's skin cancer missed 2 years before her death

PARENTS of a young woman who died from skin cancer, thought to have been caused by frequent sunbed use, have expressed their anguish over how doctors failed to detect the disease earlier.

33-year-old Lianne Gosling visited her GP and was misdiagnosed with malignant melanoma in a mole above her eyebrow. She was also told the mole was normal and only to return if it bled or became itchy.

When she visited another GP about a separate issue, her mole was noticed and she was instructed to go for further examinations.

The mole was extracted and it was expected she would make a full recovery. However, following observations indicated metastasis which had spread to several of her major organs, including her lungs and liver.

Approximately 13,000 people are diagnosed with skin cancer per year, which has doubled in the last decade, and causes around 2,800 deaths. It is believed that sunbeds were the primary cause of the skin cancer and Lianne Gosling's parents now want to warn others of the risk posed by frequent sunbed usage.

Research indicated those who have used a sunbed are 20% more likely to develop melanoma later in life, compared to those who have never used one. Individuals who use sunbeds before the age of 35 were found to be 87% more likely to develop skin cancer than those who have never used a sunbed.


Clinicians in the USA have released details that could potentially save 50% of skin cancer sufferers with advanced cases, involving a combination of drugs; Yervoy and Nivolumab. This revolutionary discovery could fight and suppress the cancer simultaneously and prevent thousands of deaths throughout the UK.

# Stricter sunbed regulations needed

"This latest research, showing a link between sunbeds and the other, more common types of skin cancer provides yet more reason to enforce stronger regulation of the industry."

*Nina Goad*
*Spokeswoman,*
*British Association of Dermatologists*

SUNBED use is associated with both malignant melanoma and also non-melanoma skin cancers, and as a result of these findings there are demands for stricter sunbed regulations, especially where minors are concerned.

A number of Member States within the European Union, such as the UK, France, Spain, Portugal, Germany, Austria, and Belgium, do not allow people under 18-years of age to use sunbeds, however, not all of these countries are enforcing these regulations.

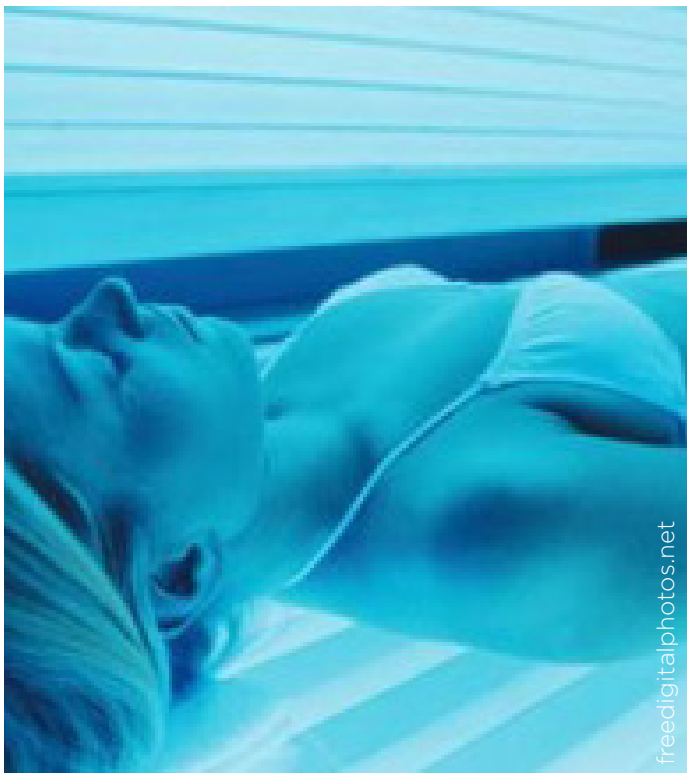
"These regulations must be tethered to warnings by health professions and educators about the risks of indoor tanning. Young people in particular should be made aware that the use of sunbeds for short-term cosmetic tanning carries the long-term price of an increased risk of skin cancer," said the researchers from the University of California in San Francisco, USA.

According to the study, sunbed users, compared to non-users, have a 67% higher risk of developing squamous skin cell cancer, combined with a 29% increased risk of developing basal cell carcinoma.

"We hope that these findings can support public health campaigns and motivate increased regulation to reduce exposure to this carcinogen, especially during early life," stated the authors.

Spokeswoman for the British Association of Dermatologists, Ms Nina Goad, said: "This latest research, showing a link between sunbeds and the other, more common types of skin cancer provides yet more reason to enforce stronger regulation of the industry. In particular, we need a total ban on coin-operated sunbeds as we know that these can be easily accessed by children."

Ms Goad also added that more information concerning the health risks needs to be available to users, this however, is not always done. She has suggested: "A UK-wide licensing system would make regulation of the industry more achievable."



# Combination laser therapy: the answer to angiofibroma

ANGIOFIBROMAS could be treated with a new laser technology and a new topical therapy. Patients with tuberous sclerosis, a genetic condition causing mostly benign tumours to develop in various areas of the body, tend to suffer from angiofibromas.

Researchers used electrosurgery, pulsed dye laser treatment, and ablative fractional resurfacing. They also used topical sirolimus, a new targeted treatment which works alongside laser surgery, prolonging the effects of treatment.

Dr Roy G. Geronemus, Director of the Laser and Skin Surgery Center of New York, USA, and analyst of the study stated: "The most significant finding was the enhanced effect of laser surgery by adding a novel targeted topical medical therapy, sirolimus." He added: "Utilising laser technology and medical innovation, treating patients with the angiofibromas of tuberous sclerosis is now easier and far more effective than we once thought possible."

The authors, Dr Geronemus and Dr Yoon-Soo Cindy Bae-Harboe, made reference to an angiofibromas patient who had experienced CO2 laser treatment 10 years before; a Caucasian female who had not been treated with topical sirolimus previously. Papular fibrotic lesions were treated with electrosurgery and subsequently had topical sirolimus, 0.2% ointment applied to these areas. The patient was also then advised to apply a small amount of topical sirolimus on the treated regions of the body.

Clinical results indicated no complications and vast improvements. The authors suggested: "They indicate that topical treatment may be an effective adjuvant therapy to laser surgery," when analysing reports investigating the safety of topical sirolimus.

It was concluded that using lasers and topical sirolimus as a combination approach to treating popular fibrotic angiofibroma will be the most effective technique.

# Laser lawsuits on the rise

LAWSUITS related to laser procedures are on the rise. In order to meet demand, more and more of the procedures are being performed by non-physicians, e.g. nurse practitioners, registered nurses, medical assistants, electrologists, and aestheticians.

"This does not shock me," said Dr Robert Murphy, President of the American Society of Plastic Surgeons. "We encourage the consumer to know who their physician is and know what their qualifications are as a basic requirement for entering into any treatment."

Using an online national database, the research team, led by Dr Hrak Ray Jalian, clinical instructor of medicine, Dermatology Division, David Geffen School of Medicine, University of California, Los Angeles, USA, charted the frequency of liability claims concerned with laser surgeries.

175 cases were identified from 1999 to 2012 that resulted in injury from the surgeries, and of these, 75 cases (42.9%) involved a laser procedure which was performed by a non-physician.

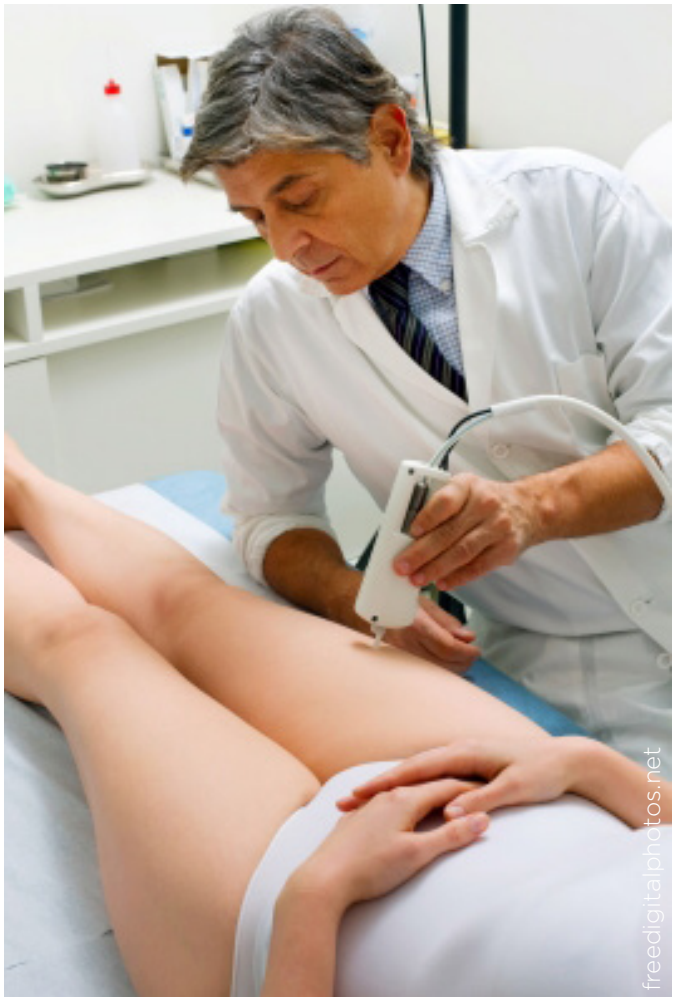
The number of procedures involving a non-physician increased from 36.3% in 2008, to 77.8% in 2011. Dr Jalian said: "Procedures performed by untrained individuals, particularly in non-medical settings, are more likely to result in litigation." He added: "Consumers should be aware that laser treatments are medical procedures and should verify the training, certification, and experience of the person performing the procedure."

Skin-related laser procedures are becoming increasingly popular. The most common of these is hair removal for which, between 2004 and 2012, 75.5% of cases involved a non-physician; this percentage rose to 85.7% during 2008 and 2012.

Dr Jalian has pointed out that the use of non-physician operators can be safe and effective as long as correct supervision and training is given. However, those who operate lasers should know the laws regarding physician supervision and non-physician laser operators.

"Procedures performed by untrained individuals, particularly in non-medical settings, are more likely to result in litigation."

*Dr Hrak Ray Jalian*
*David Geffen School of Medicine, University of California, USA*



# Radical new therapy involving mice may cure the baldness epidemic

HUMAN hairs were successfully grown from dermal papilla cells taken from donor hair follicles. Researchers from Columbia University Medical Centre, USA, and Durham University, UK, declared that this technique involved the generation of new human hair growth.

The current treatment of hair transplantation involves the redistribution the hair follicles from one section of the scalp to the other. But this method is time-consuming and leaves a large scar.

When human dermal papillae are cultured they lose their ability to form hair follicles. This problem is overcome as rodents' dermal skin papillae has the ability to proliferate and create a micro environment, allowing growth signals to target hair follicles.

This approach to fighting baldness included the harvesting of dermal papillae from human donors, which were cultured and injected into human skin, and then grafted onto the mice. The hair growth lasted around 6 weeks and genetic tests were carried out to ensure they were a match to the donor.

Dr Angela M. Christiano, lead study author, Professor of Dermatology and Professor of Genetics and Development, Columbia University Medical Center, New York, USA, said: "This method offers the possibility of inducing large numbers of hair follicles or rejuvenating existing hair follicles, starting with cells grown from just a few hundred donor hairs. It could make hair transplantation available to individuals with a limited number of follicles, including those with female-pattern hair loss, scarring alopecia, and hair loss due to burns."

# Breakthrough for skin regeneration

NEW multimodal optical microscopy technology combined with advanced image co-registration can visualise cellular-level structural, functional, and biomechanical data and provide insights into living tissue, particularly the skin. This technology was the brain-storm of a team of researchers from the Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, USA.

This remarkable technology can unlock key mysteries into the dynamics of skin regeneration and repair, incorporation of engineered skin constructs and the monitoring of new therapies, and also cosmetic applications.

"This is a remarkable combination of optical hardware and software technology that provides not only beautiful and fascinating images of dynamic microscopic processes, but also opens the door for future clinical application," said Dr Stephen Boppart, University of Illinois at Urbana-Champaign, USA, and senior author. He added: "Multimodal imaging and the ability to track cell and tissue dynamics over many months will yield enormous volumes of data that will undoubtedly provide clues into many complex processes in skin."

The team are planning to use this technology in clinical applications for cell and tissue investigation for a short and long-term duration in skin regeneration, in both normal and diabetic models. They are also hoping to discover new biomarkers in the disease mechanism.

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IFPA, International Federation of Psoriasis Associations

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## 13th Annual Caribbean Dermatology Symposium

*21st-25th Jan 2014*

*Radisson Aruba Resort, Aruba*

The Caribbean Dermatology Symposium is dedicated to providing high quality programmes for physicians and other healthcare professionals. During the symposium participants will be able to apply the most current treatments for common skin diseases, identify potential adverse effects of dermatologic treatments, and interpret various diagnostic tests for skin diseases.

## 5th International Congress in Aesthetic Dermatology

*23rd–24th Jan 2014*

*Bangkok, Thailand*

This congress promises a stimulating experience, providing knowledge on the latest techniques in anti-ageing and aesthetics, with updates in dermatology, for a practical and interactive experience for physicians, presenting them with information of where to effectively apply these techniques in daily practice. Workshops will also be available for physicians and they will have the opportunity to engage with other specialists within the area.

## European Workshop on Skin Immune Mediated Inflammatory Diseases (SIMID)

*24th–26th April 2014*

*Verona, Italy*

This innovative, discussion-driven congress will emphasise new research where SIMID are comprehensively examined from the perspective of basic mechanism to therapy. It will concentrate on inflammatory and immune-mediated diseases relevant to dermatology and medicine with new treatment options and with translational and clinical research being provided.

## 11th EADV Spring Symposium

*22nd–25th May 2014*

*Belgrade, Serbia*

Dermatologists and venereologists are urged to attend this congress in Serbia, with more relevant topics and specially selected areas than previous years, to allow for more in-depth discussions and more interaction. The programme includes hot topics from previous congresses, formed from evaluation forms. Topics will include dermatology and internal medicine, paediatric dermatology, nail and hair diseases, sexually transmitted diseases, and dermatological surgery.

## European Society for Pediatric Dermatology

*12th–14th Jun 2014*

*Kiel, Germany*

This interactive congress will include the latest developments in clinical and experimental paediatric dermatology through plenary lectures, industry symposia, sessions and courses, with opportunities to discuss with the leading experts in this field. It is ideal for practicing dermatologists, rheumatologists, and paediatric dermatologists.

## 94th Annual Meeting of the British Association of Dermatologists

*1st–3rd Jul 2014*

*Glasgow, Scotland*

Held by the British Association of Dermatologists, this will promote information about new developments in this therapeutic area. It will concentrate on dermatology, venereal diseases, and mycology. Dermatologists and general practitioners are encouraged to attend.

## 15th World Congress on Cancers of the Skin (WCCS2014)

*3rd–6th Sep 2014*

*Edinburgh, Scotland*

This interesting congress will explore various different forms of skin cancer and will also cover factors such as skin cancer burden and prevention. The 3-day event will also provide opportunities to network and exchange ideas between others attending. Dermatologists and oncologists specialising in dermatology may find this congress interesting.

## 23rd Congress of the European Academy of Dermatology & Venerology (EADV) 2014

*8th–12th Oct 2014*

*Amsterdam, the Netherlands*

This multidisciplinary conference will explore new developments and drugs for treating many diseases in the field of dermatology and venereology, such as psoriasis, disorders of pigmentations, collagen diseases, genodermatosis, and many more. This popular Congress usually has around 8,000 attendants and is ideal for dermatologists, venereologists and allied medical professionals, researchers, and students.