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PEER-REVIEWED CONFERENCE REPORT

Melanoma: Surveillance and follow-up

Screening and follow-up protocols for melanoma remains a topic that stirs discussion among dermatologists in the Netherlands. Here, we review the standard of care, as well as new evidence.

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Eligibility and selection of JAK inhibitors for constitutional eczema

Three JAK inhibitors have become available for the treatment of constitutional eczema, in addition to biologics dupilumab and tralokinumab. What are the eligibility criteria for these newer agents?

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Life-threatening skin infections

How do life-threatening skin infections arise, and how can dermatologists recognise them?
Haemodynamic instability, infection spread leading to organ failure and shock, or pathogen toxin damage can be consequences.

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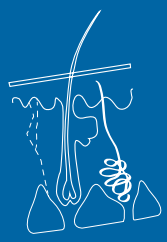

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Head Office
Medicom Medical Publishers
De Ruijterlaan 1-A
3742 AE Baarn
The Netherlands

Postal address
Medicom Medical Publishers
PO Box 90
3740 AB Baarn
The Netherlands

Telephone +31 85 4012 560
E-mail publishers@medicom-publishers.com

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Letter from the Editor

Dear colleagues,

From 09–10 March 2023, the Dutch Dermatology Days took place in Ermelo. A yearly event that means a lot to the Dutch dermatologist, from getting new information on dermatology, organisational aspects and just to see each other and enjoy the Dutch collegiality between dermatologists.

During the previous 20 years, biologics have innovated our therapeutical potential in psoriasis. Subsquently, hydradenitis chronica suppurativa was innovated by treatment with anti-TNFs. More recently, biologics became available for the treatment of atopic dermatitis. Another important development are small molecules, in particular Janus kinase inhibitors. Different small molecules became available for both psoriasis and atopic dermatitis, targeted at pathways relevant for the disease.
In this overview, we provide more information on Janus kinase inhibitors. A more recent development is the application of new targeted therapies in various inflammatory dermatoses of the skin. It is important to see that the whole field of inflammatory dermatoses is moving. The question is to what extent do we have the resources to pay for these innovations? It is important to realise that we have to look at the balance between value and cost. A dermatologist is creating value by prescribing the medications which are appropriate. "Costs are what you pay, and value is what you get."

In this review, we have selected aspects that matter in practice. With respect to dermato-oncology: the role of the surgeon in stage I-II melanomas was discussed, especially with reference to re-excisions, sentinel node procedures, and adjuvant therapy. The follow-up of patients with melanoma was presented, critically addressing the question "which of the 10,000 to 100,000 patients with multiple atypical naevi in the Netherlands should be screened and how frequently should we provide follow-up visitations for our patients with melanoma?" The association between nutrition and the skin was addressed with special attention for obesity.

The frequency of scabies is rising. Therefore, this topic was revisited around the question of "Therapy failure or resistance?" Life-threatening infections of the skin are a real threat and dermatologists should know about the infections and the mechanisms of how these are life-threatening.

Best regards,
Peter CM van de Kerkhof

Biography

Peter C.M. van de Kerkhof is emeritus Professor of Dermatology and immediate past chairman of the Department of Dermatology of Radboud University Nijmegen. He is currently the coordinating Medical Officer of the International Psoriasis Council and chair of the scientific advisory board of the Dutch burn association. He has been working for many years on the pathogenesis and treatment of psoriasis. He has published more than 700 publications in peer-reviewed journals and has given many presentations on invitation at international conferences. He has served as president of the ESDR, EDF, and the International Psoriasis Council, and was board member of various international societies. Current interests are pathogenesis and development of biomarkers for psoriasis; real clinical practice research; and personalised medicine.

Conflict of Interest Statement:
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Dermato-Oncology

The role of surgeons in stage I–II melanoma

"Invasive treatments should improve either overall survival, local control, or the quality of life of patients," stated Dr Dirk Grünhagen (Erasmus MC, the Netherlands). According to Dr Grünhagen, the role of the surgeon in the treatment of stage I–II melanoma has become largely redundant in recent years. However, in some instances, surgeons still play an important part in the management of these patients. He discussed the use of re-excisions, sentinel node procedures, and adjuvant therapy.

The purpose of re-excision

One purpose of re-excision is to avoid microsatellitosis. However, according to Dr Grünhagen, this occurs in less than 5% of patients [1]. "In thin melanoma, the incidence of microsatellitosis is even lower," he added. Re-excision is also not useful in improving overall survival. "Although local control will be slightly improved after re-excision, local relapse occurs in less than 5% of patients," which suggests that 95% of the re-excision procedures for patients with stage I–II melanoma are redundant. "Since the usefulness of re-excision is limited, decision-making by a melanoma surgeon is crucial," concluded Dr Grünhagen.

Sentinel node procedure and lymph node dissection

"Performing a sentinel node procedure plus complete lymph node dissection does not lead to an overall survival benefit for patients either," continued Dr Grünhagen. However, local control is slightly improved after complete lymph node dissection for sentinel node-positive melanoma. According to Dr Grünhagen, this effect is not very relevant, since these nodes can be monitored clinically, and one can perform a delayed lymph node dissection if the patient presents with swelling at a later moment. In terms of quality of life, Dr Grünhagen mentioned that 6% of the patients who undergo a sentinel node procedure experience lymph oedema compared with 24% of patients who had a complete lymph node dissection.

Adjuvant therapy

"Since the arrival of adjuvant immunotherapies for stage III melanoma in 2017, the sentinel procedure gained renewed attention," said Dr Grünhagen. Adjuvant immunotherapy has been shown to provide a disease-free survival benefit for patients with stage III [2,3]. "A sentinel node procedure can discriminate patients with stage I–II melanoma from those with stage III melanoma, and hence select patients eligible for adjuvant immunotherapy," Dr Grünhagen explained. However, after 5 more years of follow-up, an overall survival benefit of these adjuvant therapies has not yet been demonstrated.

"Adjuvant therapy can be administered in a later stage of the disease as well, with a similar effect for the patient. Therefore, the sentinel node procedure may not be as important as we thought for the selection of patients," he said. "Furthermore, 80% of the patients eligible for a sentinel node procedure test negative, making the procedure in retrospect unnecessary."

The way forward

To avoid unnecessary sentinel node procedures in the future, clinical parameters in combination with genetic testing could estimate the risk of a negative sentinel node. With these tools, low-risk patients could be discouraged to undergo a sentinel node procedure. This could help to reduce the number of negative sentinel node procedures.

"Finally, I plead for an individual risk classification with respect to selecting patients for adjuvant therapy. If you know the absolute risk of relapse or death of the patient, there is a larger potential effect of adjuvant therapy. I think, in future, the characteristics of the melanoma that are documented during the primary excision can help to further stratify patients into risk categories. The high-risk group will receive adjuvant therapy, the low-risk group will be monitored, and the intermediate-risk group may receive a sentinel node procedure to further clarify their risk profile."

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Melanoma: Surveillance and follow-up

Dr Remco van Doorn (Leiden University Medical Center, the Netherlands) talked about screening and follow-up for melanoma, a topic that stirs discussion among dermatologists. "In the Netherlands, the lifetime risk of

developing a melanoma is 1%," outlined Dr van Doorn [1]. "About 15% of these tumours are metastatic, whereas the other 85% are limited to the skin and therefore under the management of a dermatologist."

The risk for melanoma is affected by hereditary factors (5%), DNA replication errors (9%), but mostly environmental factors (86%), such as UV radiation. In addition, important clinical risk factors for developing sporadic melanoma are a history of skin cancer, having ≥100 naevi, ≥ 5 atypical naevi, and red hair (see Figure).

Figure: Clinical risk factors of sporadic melanoma [1]

	Relative risk
>100 naevi	7
>5 atypical naevi	6.4
Skin colour, light	2.1
Hair colour	
red	3.6
blonde	2.0
Eye colour, blue	1.5
Freckles	2.1
Actinic lentigines	2.0
History of skin cancer	4.3

Screening for sporadic melanoma

Individuals with ≥100 naevi or ≥5 atypical naevi are eligible for screening in the Netherlands. This screening includes a total body inspection, once a year, ideally with total body photography, applying dermatoscopy on suspected naevi and providing advice on self-inspection of the skin and sunbathing. "10,000 to 100,000 individuals in the Netherlands fulfil these criteria, but not all of them are screened regularly," said Dr van Doorn. In addition, a study followed 1,100 individuals who fitted the screening criteria and were screened for 5 consecutive years. The incidence of melanoma was 1.1% per surveillance year. Most melanomas were discovered by the dermatologist (78%), whereas the patients detected 17% of their melanoma.

"Another group that we screen are children with congenital naevi," continued Dr van Doorn. The screening and frequency of screening are based on the 'projected adult size' of these naevi, the number of congenital naevi, and whether there are satellites present. Then there is the group of individuals with hereditary melanoma, which comprises approximately 10% of all melanoma. The eligibility criterium for this screening is 3 melanoma within the family in at least 2 different first-degree family members.

Dr van Doorn added that individuals with *CDKN2A* mutations are at higher risk for melanoma, as well as for pancreas carcinoma and head/neck tumours. Similarly, those with BAP1-associated tumour predisposition syndrome have an increased risk for melanoma and several other tumours. "Patients with these kinds of mutations or other rare mutations need to receive a much broader screening, based on their gene deficiency," clarified Dr van Doorn. "A clinical genetical consultation will further inform the patient on screening options, DNA testing, and advice for other family members. For example, first-degree and second-degree relatives of patients who carry *CDKN2A* or *BAP1* mutations should be screened for melanoma and other cancers.

Follow-up

"Once we detect a melanoma in the screened population, we follow the patient based on the AJCC classification," explained Dr van Doorn. "There is, however, no clear consensus on the frequency of follow-up." He explained that the Leiden University Medical Center follows the follow-up protocol of the MELFO study [2]. This study showed that stage I–II patients with pT1b-pT2a tumours only need to be screened once a year, those with pT2b-pT3a tumours can be safely monitored with 2 screening per year in the first 2 years and yearly screenings in the subsequent 3 years, and that patients with pT3b-pT4b tumours should receive 3 screenings per year in the first 2 years, 2 screenings per year in the third year, and yearly screenings in the following 2 years. Furthermore, patients with stage III melanoma will primarily be followed by the surgeon but will receive yearly screenings by a dermatologist. Finally, patients with stage IV melanoma will primarily be followed by the oncologist and receive yearly screenings by a dermatologist.

"Although I have outlined the current state of affairs with regard to the surveillance and follow-up of patients with melanoma, it is still not completely established which of the 10,000 to 100,000 patients with multiple atypical naevi in the Netherlands should be screened and how frequently we should provide follow-up visitations for our patients with melanoma," concluded Dr van Doorn.

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2. Deckers EA, et al. Ann Surg Oncol. 2020;27(5):1407–1417.

When to screen for anal intraepithelial neoplasia?

"Cervical cancers and anal cancers are human papillomavirus (HPV)-related diseases," explained Prof. Henry de Vries (Amsterdam UMC, the Netherlands) [1].

"And HPV16 is the most important variant for anal cancers." HPV-related cancers typically develop in the transitional epithelium. "Fortunately, both types of cancer have treatable preliminary stages," he said. In the case of anal cancer, this preliminary stage is called anal intraepithelial neoplasia (AIN).

Low-grade squamous intra-epithelial lesions (i.e. AIN grade 1) will mostly be processed by the body. For high-grade lesions (i.e.AIN grade 2 or 3), there is an increased risk for transformation to anal cancer.

Risk groups

"The past 30 years, the incidence of anal cancer in the Netherlands has increased," continued Prof. de Vries. "However, the absolute incidence is still low, with 1.3 cases per 100,000 person-years." Certain subgroups have an increased risk for anal cancer. Homosexual men, especially those who are HIV positive and above 30 years of age, have the highest risk for this type of cancer. For HIV-positive homosexual men 60 years or older, the incidence is 100 per 100,000 person-years. Other individuals with an increased risk for anal cancer are HIV-positive women, HIV-positive heterosexual men, women with a history of gynaecological cancer, and non-HIV immunosuppressed women.

Is screening for anal cancer useful?

"The screening procedure is not easy," emphasised Prof. de Vries. "The learning curve only flattens after approximately 200 screening procedures." To assess whether screening for anal cancer can be useful, the ANCHOR study included 4,446 individuals above 35 years of age with high-grade squamous intra-epithelial lesions, without anal cancer [2]. The participants were either treated or followed a wait-and-see approach and the primary outcome was the progression to anal cancer. This study was aborted because a large effect was found, and it was unethical to continue. After 48 months, participants in the wait-and-see group had a 57% increased risk to progress to anal cancer compared with participants who received treatment (P=0.03).

Prof. de Vries noted that screening for anal cancer may be effective but nonetheless suboptimal: "Anal cytology is unreliable, high-resolution anoscopy is difficult, expensive, and burdensome for the patient, and ablative treatment has a limited success rate." Furthermore, only 10% of the patients with high-grade lesions progress to cancer and about one-third of the patients with these lesions actually regress [3]. Clearly, there is a need to further select eligible patients for screening and treatment.

Host cell DNA (hyper)methylation at tumour suppressor gene promoters is a promising biomarker to discriminate patients who would benefit from frequent screening and treatment and those that can be managed with a wait-and-see approach [4,5]. "Ideally, we would use anal swabs to collect this biomarker, but the studies that have been conducted used biopsies," added Prof. de Vries.

Prof. de Vries concluded his presentation by stressing that there is a need for well-trained professionals to perform high-resolution anoscopies in patients who would benefit from this procedure.

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JAK Inhibitors

Eligibility and selection of JAK inhibitors for constitutional eczema

"In recent years, 3 JAK inhibitors, baricitinib, upadacitinib, and abrocitinib, have become available for the treatment of constitutional eczema," said Dr Dirk Jan Hijnen (Erasmus MC, the Netherlands) [1]. "Other targeted therapies available to treat this condition are the biologic therapies dupilumab and tralokinumab." According to Dr Hijnen, dupilumab is the most frequently prescribed first-line targeted therapy, since clinicians have the longest experience with this agent. During his presentation, Dr Hijnen discussed eligibility for these newer agents and the selection process for each of them.

When to choose a JAK inhibitor?

The Dutch guidelines dictate that patients should first receive intensive local therapy to treat their constitutional eczema [2]. If this treatment does not lead to the intended treatment result, a 'classic' systemic therapy should be prescribed, being either methotrexate, cyclosporin A, azathioprine, or enteric-coated mycophenolate sodium. If this first systemic therapy fails after 16 weeks, 1 of the available biologic therapies or JAK inhibitors should be considered.

"How does one choose between the various available targeted therapies?" asked Dr Hijnen. "First, women who wish to have children should receive either cyclosporin A or azathioprine. Second, patients over 65 years of age, patients who have a history of cancer, those with high risk for thromboembolic events, or patients who have a long history of smoking cigarettes, should preferably receive 1 of the biologic therapies, in my opinion. If all these criteria are not applicable, either a JAK inhibitor or a biologic therapy could be selected."

Dr Hijnen added that biologics are injected therapies, which may be less convenient for the patients than the orally administered JAK inhibitors. On the other hand, JAK inhibitors require lab testing and screening, which slows down the initiation of the therapy. "Patients with concurrent asthma may experience alleviation of both eczema and asthma from biologics, whereas patients with concomitant conjunctivitis may benefit more from JAK inhibitors," explained Dr Hijnen. Finally, JAK inhibitors usually result in a swift reduction of itching of the skin, whereas the effect of biologics takes weeks or months to kick in. When opting for a JAK inhibitor, several considerations should be made to select the right JAK inhibitor for the right patient.

Selecting the right JAK inhibitor for the right patient

"In my opinion, the largest difference between baricitinib on the one side and upadacitinib and abrocitinib on the other side is the displayed efficacy in clinical trials, favouring upadacitinib and abrocitinib over baricitinib," stated Dr Hijnen. He added that baricitinib may be more effective in patients over 60 years compared with younger patients because it inhibits a relatively broad range of cytokines. "In young patients with severe eczema, I prefer to initiate with a high dose of either upadacitinib (30 m daily) or abrocitinib (200 mg daily) and reduce these doses to 15 mg and 100 mg when the clinical situation allows these reductions."

For patients >65 years or those with risk factors such as obesity or a history of smoking, Dr Hijnen would start with a lower dose of 1 of these agents. Furthermore, he said that screening for latent tuberculosis should be done before the initiation of therapy with JAK inhibitors, because the re-activation of tuberculosis may be atypical while being treated with JAK inhibitors. He also explained that patients with herpes zoster or herpes simplex should interrupt their intake of JAK inhibitors, possibly start therapy with valaciclovir, and re-start JAK inhibitor therapy when the patient does not show new symptoms, which is generally within 1 to 2 weeks.

Another consideration is acne, which is a possible side effect of JAK inhibitors. "There is no one-size-fits-all therapy for this JAK inhibitor-induced acne," mentioned Dr Hijnen. "Normally, we follow standard acne therapies. However, I would recommend having at least 2 different JAK inhibitors in the therapeutical arsenal, so one has the option to switch if these kinds of side effects occur. In practice, I see that the selectivity of upadacitinib and abrocitinib is relative and that patients respond differently to these agents." Dr Hijnen concluded that there are currently no known absolute contra-indications to JAK inhibitors in the dermatological populations.

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The rise of JAK inhibitors for alopecia areata

"In 2010, the treatment landscape for patients with alopecia areata (AA) included the use of intralesional and topical corticosteroids, topical minoxidil, and topical immunotherapy," said Dr Brett King (Yale University, CT, USA) [1]. "For patients with severe disease, we had methotrexate, cyclosporine, and systemic corticosteroids. These agents address lymphocytes in a broad way and are relatively non-specific." According to Dr King, more specific agents are needed to target hair loss in these patients, and JAK inhibitors are stepping up to the plate.

A 2014 study taught the community much about the pathogenesis of AA, showing that the disease is driven by cytotoxic T lymphocytes and reversed by JAK inhibition [2]. "Since then, various studies have been conducted to assess the safety and efficacy of JAK inhibitors in the treatment of AA, including 5 randomised clinical trials."

In a phase 2 study, ruxolitinib 1.5% cream failed in a population of patients with severe AA [3]. Similarly, a delgocitinib ointment was ineffective in a population of patients with AA [4]. Treatment with deuruxolitinib did result in a SALT score ≤20 in 30–42% of the patients after 24 weeks of therapy, meeting the primary endpoint of a phase 3 trial (NCT04518995) [5]. Likewise, long-term data of the phase 3 ALLEGRO-LT study investigating ritlecitinib showed that 30–40% of the patients achieved a SALT score ≤20 after 48 weeks of therapy (NCT04006457) [6]. Dr King added that the efficacy rates continued to improve after 24 weeks, indicating that it takes time to regrow hair in patients with AA. Finally, treatment with baricitinib resulted in an efficacy rate of 20–34% after 36 weeks of therapy, which rose further to 23–39% after 52 weeks of treatment in the BRAVE-AA1 and BRAVE-AA2 trials [7,8]. "In all these clinical trials, the vast majority of patients who achieved a SALT score ≤20 also achieved a SALT score ≤ 10," mentioned Dr King.

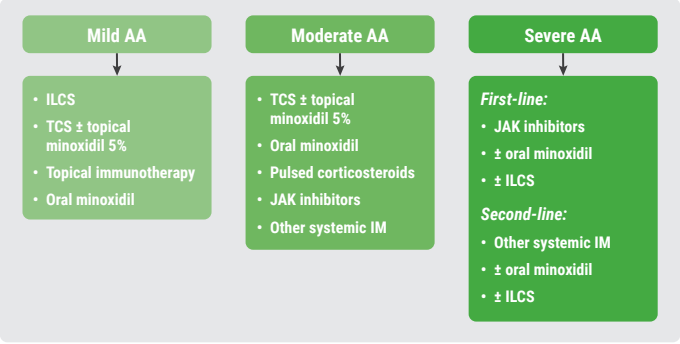
Importantly, the trials showed that JAK inhibitors are less effective in patients with baseline SALT scores between 95 to 100 (10–20% efficacy) than in patients with baseline SALT scores between 50 and 94 (33–48% efficacy) [9]. Next, the duration of the current episode of severe disease influences the efficacy of JAK inhibition, with longer periods of hair loss (>4 years) resulting in reduced efficacy of JAK inhibitors compared with a shorter duration of the current episode of hair loss (≤4 years) [1]. "Thus, treating early appears to be very important," added Dr King.

New treatment algorithm and oral minoxidil for AA

Dr King also drew attention to a forgotten agent. "Although the data is not as strong as the emerging data for JAK inhibitors, oral minoxidil demonstrated in 1987 to regrow hair in approximately 20% of patients with AA; yet, we have not been using this agent," he said. Combining minoxidil with a JAK inhibitor may result in greater efficacy than either one of the agents as monotherapy, retrospective data suggests [10].

Finally, Dr King introduced a treatment algorithm for AA, discriminating between mild, moderate, and severe AA (see Figure). "JAK inhibitors won't be changing the treatment for patients with mild AA, but JAK inhibitors are inarguably the first-line therapy for patients with severe disease," he concluded.

Figure: Proposed treatment algorithm for alopecia areata [1]



AA, alopecia areata; ILCS, intralesional corticosteroids; IM, immunosuppressive drugs; TCS, topical corticosteroids

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Nutrition and the Skin

Obesity and the skin: state of affairs

"Body fat is an organ that is disturbed when people have obesity," said Dr Mariëtte Boon (Leiden University Medical Center, the Netherlands) [1]. "Hormonal and metabolic changes, inflammatory processes, and mechanical stress have widespread effects throughout the body." This is why obesity is linked to 200 different diseases, including various skin conditions.

Approximately 60–70% of patients with obesity have significant skin changes [2].

Skin issues in patients with obesity are mostly related to mechanical stress (e.g. striae, hyperkeratosis of the heel), insulin resistance (e.g. acanthosis nigricans, skin tags), infections (e.g. increased risk of severe disease course with viral or bacterial infections, cellulitis), and the link between

obesity and autoinflammatory skin diseases such as psoriasis, atopic dermatitis, and hidradenitis suppurativa.

The first available treatment option for obesity is a lifestyle intervention. In the Netherlands, this entails a 2-year programme including interventions directed at diet, physical activity, and sustainable behavioural changes, with a specific focus on the underlying causes of the disease. "Research assessing the efficacy of these interventions is ongoing, but it is clear that healthcare professionals need to keep monitoring patients with obesity undergoing lifestyle interventions strictly," added Dr Boon. If this intervention fails, pharmacological options can be considered. The 2 agents that are currently approved for the treatment of obesity target the feeling of satiety.

Naltrexone/bupropion decreases appetite and increases the 'feeling of reward'. This agent can be prescribed to patients with a BMI of >30 kg/m^2 or patients with a BMI >27 kg/m^2 with at least 1 complication, such as type 2 diabetes or hypertension. This intervention is continued for 3 months after which a patient must have lost at least 5% of body weight. If this is not the case, the intervention will be stopped. A randomised controlled trial showed that patients lose on average 8% weight in 56 weeks of therapy [3].

Liraglutide is a second approved agent for the treatment of obesity. On top of a lifestyle intervention, this agent led to an average body weight loss of 10% after 56 weeks of therapy [4]. If a 1-year lifestyle intervention did not result in significant weight loss, this agent can be prescribed to patients with a BMI >40 kg/m^2 or to patients with a BMI >35 kg/m^2 who have at least 1 complication. If liraglutide does not show a clear benefit after 12 weeks of therapy, the treatment should be stopped.

Additionally, Dr Boon showed data from a meta-analysis that demonstrated that treatment with liraglutide improves psoriasis in patients with type 2 diabetes [5]. This effect could be explained by weight loss, but it is suspected that there is a direct anti-inflammatory effect of this agent as well, improving symptoms of autoinflammatory skin diseases.

"Another agent in the pipeline is semaglutide, which displayed an average 17% reduction in body weight in patients who were treated with this agent on top of a lifestyle intervention," mentioned Dr Boon [6]. If pharmacological therapies fail, bariatric surgery is the final option to deal with obesity.

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Skin diseases and nutrition

Prof. Reinhart Speeckaert (UZ Gent, Belgium) discussed the associations between skin diseases and nutrition. In the first part of his presentation, he talked about the effects of various nutrients on skin diseases. The second part of his talk was dedicated to specific nutritional deficiencies.

Nutrition and atopic dermatitis

"About 70% of the patients with atopic dermatitis will avoid specific foods to improve their disease," said Prof. Speeckaert [1]. "However, there is no evidence that this actually works, and it appears that non-allergic mechanisms do not play an important role in the course of the disease." He pointed out that flares of atopic dermatitis without other allergic symptoms are unlikely to be caused by food allergies. "Atopic dermatitis usually develops before food allergies develop. Therefore, it is unlikely that food allergies have an impact on eczema," clarified Prof. Speeckaert [1,2].

Prof. Speeckaert stressed that strict elimination of diet or calories is discouraged, but that excluding egg and cow's milk may have a positive effect on atopic dermatitis in children. Although excluding specific foods does not improve atopic dermatitis in most cases, certain diets have demonstrated a beneficial effect on eczema. Moreover, a powerful placebo effect of dietary change is seen in many conditions, including skin diseases. The best effects of diet change on atopic dermatitis were reported for a dairy-free diet, a paleo diet, and a gluten-free diet [3]. According to Prof. Speeckaert, oolong tea, L-histidine, and hempseed oil have displayed positive effects on atopic dermatitis as well. However, the results of the studies showing these effects have not been confirmed and should be interpreted with caution [4].

Nutrition and vitiligo

"Patients with vitiligo are generally very interested in food and vitamins," continued Prof. Speeckaert. With respect to food interventions, polypodium leucotomos in combination with phototherapy has the most profound effect on repigmentation [5]. "Ginkgo biloba is another plant extract that has demonstrated a positive effect on vitiligo," added Prof. Speeckaert [6]. "Online,

several sun-protection products are available that contain polypodium leucotomos or ginkgo biloba that dermatologists can recommend to their patients." Finally, a study assessing oral gliadin-protected superoxide dismutase in addition to phototherapy showed promising efficacy of this agent on patients with non-segmental vitiligo [7].

Nutrition and acne and hair loss

Prof. Speeckaert briefly described the effects of certain foods on acne. "Products with a high glycaemic index score, skim milk, whey proteins, fat food, and vitamin B12 are known to worsen acne, whereas omega 3 fatty acids, fruit, and vegetables improve this skin condition," he said. Next, he spoke about nutrition and hair. "In patients with alopecia areata and coeliac disease, a gluten-free diet reduces hair loss [8]. Furthermore, supplementing ferritin >50 µg/L in case of telogen effluvium is recommended in pre-menopausal women or individuals with nutritional deficiencies. "Finally, patients with hair loss should avoid biotin, since this supplement may interfere with laboratory tests," emphasised Prof. Speeckaert.

Nutritional dermatoses in patients hospitalised or with cancer

Evidence shows that 30–90% of the hospitalised patients or cancer patients suffer from malnutrition, mostly comprising mixed nutrient deficiencies [9]. "This is an underrecognised problem," according to Prof. Speeckaert. He explained that patients with persistent chemotherapy-related alopecia should be checked for ferritin, TSH, vitamin D, zinc, and proteins. If laboratory tests show a deficiency, supplementing these elements can improve the regrow of hair. Similarly, patients with therapy-resistant papulopustular dermatitis who receive EGFR inhibitors may have zinc deficiencies. Zinc supplementation may improve symptoms by approximately 25%. "Furthermore, protein deficiencies are mostly relevant in non-healing ulcers," explained Prof. Speeckaert. "Proteins are lost through wound exudate and crucial for all stages of wound healing." Protein shakes may offer a solution.

Nutrition deficiency disorders

Finally, Prof. Speeckaert discussed a broad spectrum of nutrition deficiencies that may be relevant to dermatologists. "Vitamin deficiencies are often hard to recognise," said Prof. Speeckaert. "Although this issue does not frequently occur in Western countries, we may encounter vitamin deficiencies in people with a decreased intake, such as homeless people, alcoholics, drug addicts, and individuals with eating disorders, or in individuals with increased use, such as patients with chronic diseases or patients with malabsorptive conditions.

At the end of his presentation, Prof. Speeckaert mentioned 6 entities that dermatologists should particularly be aware of: phrynoderma, vitamin C deficiency, vitamin K deficiency, pellagra, acrodermatitis enteropathica, and visual deficits. He provided an overview of the various nutrient deficiencies and the accompanying symptoms (see Figure).

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Figure: Nutrient deficiency and symptoms [1]

	Xerosis	Scales	Hair abnormalities	Nail abnormalities	Fissures/erosions	Oedema	Erythema	Pupura/ecchymoses	Visual impairment	Glossitis	Angular stomatitis	Seborrheic dermatitis	Hyperpigmentation	Phrynoderma
Marasmus	X		X	X										X
Kwashiorkor	X	X	X	X	X	X	X							X
Essential fatty acids	X	X	X	X	X		X	X						X
Vitamin A	X	X							X					X
Vitamin D			X											
Vitamin E									X					X
Vitamin K								X						
Vitamin B1 (thiamine)						X				X				X
Vitamin B2 (riboflavin)	X	X			X		X			X	X	X		X
Vitamin B3 (niacin)	X	X			X		X				X	X	X	X
Vitamin B6 (pyridoxine)							X		X	X	X	X		X
Vitamin B9 (folic acid)										X	X	X	X	X
Vitamin B12 (cobalamin)			X							X	X		X	X
Vitamin C (absorbic acid)			X		X	X	X	X					X	X
Biotin	X	X	X				X		X	X	X	X		
Iron			X	X						X	X			
Zinc	X		X		X			X	X	X	X	X		
Copper			X						X					
Selenium	X		X	X		X	X							

What's New?

The importance of anti-microbial proteins in the skin

Various studies have been conducted in recent years to assess *late cornified envelope* (*LCE*) genes and proteins and their protective role against bacteria, fungi, parasites, and other harmful agents. A complex network of anti-microbial proteins has been revealed, providing insights into the crucial barrier function of the skin. Dr Hanna Niehues (Radboud University Medical Center, the Netherlands) discussed the importance of LCE proteins with regard to the anti-microbial barrier function of the skin.

"The skin is the most important barrier of the body," Dr Niehues began her talk [1]. It prevents dehydration and protects against the penetration of microbes, allergens, and chemicals. According to Dr Niehues, the stratum granulosum has an important role in the protection against harmful infiltrators. "The keratinocytes that are present in this layer of the skin produce anti-microbial proteins."

The inflammatory skin diseases psoriasis and atopic dermatitis display the importance of these proteins since the barrier function of the skin is affected in patients with these conditions. Interestingly, psoriasis is characterised by sterile lesions, whereas bacterial infections of the skin are common in eczema. According to Dr Niehues, a strong correlation exists between the presence of anti-microbial proteins in the skin, which is lowered in patients with eczema and elevated in patients with psoriasis, and the type of lesions that are typical for these 2 conditions.

Next, Dr Niehues zoomed in on specific anti-microbial proteins and the insights gained in recent years into their protective role. A study published in 2017 showed that deletion of *LCE 3B/C* genes, belonging to the LCE gene family, located on chromosome 1 of the epidermal differentiation complex, is associated with psoriasis. It has also been discovered that LCE proteins, and LCE 3 proteins in particular, are strongly anti-microbial. Furthermore, participants with *LCE 3B/C* deletion had significantly higher concentrations of LCE 3A in the skin, illustrating the interindividual variability of the presence of these proteins in the skin [2].

Another study analysed the impact of these LCE proteins on several bacteria by observing the process with a transmission electron microscope and showed that LCE proteins attack the cell membrane of the bacteria, resulting in the disintegration of the bacteria in several minutes. This effect was confirmed in an ex vivo experiment, demonstrating that LCE proteins affect the composition of the microbiome of the skin. Bacterial growth was strongly reduced due to the activity of LCE proteins.

Furthermore, it was demonstrated that the microbiome of the skin and mouth but not that of the gut were drastically changed in patients with *LCE 3B/C* deletion, harbouring a higher number and a greater diversity of bacteria [3]. Finally, the cysteine-rich tail (CYSRT1) protein, which also has an anti-microbial, showed interaction with all LCE proteins, and LCE proteins interacted with one another, indicating that a complex network of anti-microbial proteins regulates the barrier function of the skin [4].

Thus, Dr Niehues showed the importance and complexity of anti-microbial proteins in the skin and their protective role against harmful agents and organisms.

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OCT non-inferior to biopsy in basal cell carcinoma

Optical coherence tomography (OCT) could offer a non-invasive alternative to biopsy for diagnosing and treating patients with basal cell carcinoma (BCC). A randomised trial showed that OCT was non-inferior to punch biopsy.

"BCC is a common type of skin cancer and punch biopsy is the gold standard for diagnosing this malignancy," said Dr Tom Wolswijk (Maastricht UMC, the Netherlands) [1]. "Pain, infection, bleeding risk, and the 1–2 week waiting period until the results are available are, however, disadvantages of this method." Thus, a team of researchers aimed to investigate whether OCT is non-inferior to punch biopsy for diagnosing and treating patients with suspected BCC. The researchers

randomised 598 participants 1:1 to OCT or biopsy. If the diagnostic results of OCT were unclear, the patient was further treated based on biopsy results. The primary outcome was the proportion of patients with relapse-free survival (RFS) after 12 months of treatment. The results were recently published in the Lancet Oncology [2].

The modified intention-to-treat analysis showed that OCT was non-inferior to biopsy in terms of the proportion of patients who displayed RFS after 12 months of therapy (94% vs 93%; 95% CI -5.06 to 2.93). The results of the per-protocol analysis were comparable, with RFS rates of 95% and 94% for the respective study arms. Furthermore, for patients who had a clear OCT diagnosis, the sensitivity and specificity were 85.3% and 94.6%, respectively. Dr Wolswijk added that, in this study population with a BCC prevalence of 75%, a biopsy could be omitted in 66% of the patients. Finally, the study showed that OCT-based diagnostics and treatment were less costly than biopsy-based diagnostics and treatment (€ 689 vs € 758). However, purchasing an OCT instrument is an expensive matter.

Building on the results of this study, the research team is currently working on the refinement of OCT-driven diagnostics and treatment for patients with BCC by enhancing this technology with artificial intelligence.

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Infections

Scabies: Therapy failure and tips for the clinic

The incidence of scabies is on the rise. "Thus," argued Dr Robert Vodegel (Medical Center Leeuwarden, the Netherlands), "it is important that we focus on this condition and see how we can improve the current management of scabies" [1]. He delved into the treatment, treatment failure, and future directions to curb the rising incidence of this condition.

The treatment for scabies

According to the current IUSTI guidelines, the standard therapies to treat scabies are permethrin 5% cream (can be repeated once after 7–14 days), oral ivermectin 200 µg/kg (repeat after 7 days), or benzyl benzoate lotion 10–25% (on days 1, 2 and repeat after 7 days) [2]. Dr Vodegel added that this last treatment is mostly for pregnant patients and that the second treatment with ivermectin should preferably be administered within 7 to 10 days; a waiting period of 14 days is arguably too long when the lifespan of the mite is considered.

"Also, topical treatments need to be applied to all skin regions at night and left in place for 8–12 hours. The most frequently missed skin areas are the ankles, the hamstrings, toes and feet, the nails, and the armpits," explained Dr Vodegel. Therefore, it is important to inform the patient that the nails need to be clipped before applying topical treatments, the hands need to be re-treated after washing the hands, and other members of the household need to be treated simultaneously, including babies. Then there are hygienic measurements that need to be taken, such as washing, dry cleaning, and sealing clothes. Dr Vodegel stressed that the current IUSTI guideline did not offer recommendations on the treatment of persons who were in close contact with the patient. "This could be a major reason for therapy failure," he said.

Therapy failure or resistance

According to Dr Vodegel, causes of therapy failure include:

1. a wrong diagnosis,
2. local skin reactions because of the applied cream,
3. hypersensitivity reaction,
4. not strictly following hygiene protocol,
5. not treating relatives and other contacts,
6. non-compliance to therapy, and
7. possibly therapy resistance.

"It is still unclear whether therapy resistance is a real issue, or that infections persist because patients did not follow

the hygienic measurements strictly," added Dr Vodegel. "Perhaps the information we provide to our patients is more important than actual therapy resistance." If a therapy is not effective, the options are to repeat the current therapy, switch to another therapy, or combine ivermectin with permethrin. It must be noted that patients should not eat 2 hours before or after taking ivermectin. Furthermore, the scalp should be treated in children younger than 12 years, fragile elderly patients, and other vulnerable groups if they receive a permethrin treatment.

Future directions

Dr Vodegel ended his presentation by proposing actions that may counter the rising incidence of scabies in the Netherlands. According to Dr Vodegel, the Dutch guideline for the management of scabies is being revised at the moment and the concept version of the chapter related to the treatment has already been completed. This update includes recommendations on treating symptom-free relatives and other contacts, and renewed advice concerning the second treatment with permethrin. "It is important to recognise that the policy and possibilities with respect to managing scabies vary between regions. Also, educating general practitioners and developing a protocol for scabies outbreaks in institutions such as nursing homes and daycare centres would be improvements to our current management of scabies. Finally, we need prospective studies to gain more insight into why therapies fail in patients with scabies," concluded Dr Vodegel.

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Life-threatening skin infections

Dr Sandra Arend (Leiden UMC, the Netherlands) talked about life-threatening skin infections, how they arise, and how dermatologists can recognise them. "Skin infections can become life-threatening through haemodynamic instability, leading to organ failure and shock, or because the infection expands to vital organs," explained Dr Arend [1]. The mechanisms behind these events are either local extension of the infection, haematogenous spreading of the disease, or through toxin production of the pathogen."

The usual suspects

Streptococcus pyogenes A and *Staphylococcus aureus* are the usual suspects for skin infections. Since these bacteria are sensitive to antibiotics, infections with these pathogens are usually easy to treat. Yet, in some cases, infections with one of these bacteria can lead to life-threatening situations.

"Impetigo and erysipelas rarely lead to haemodynamic issues," continued Dr Arend. "The same is true for folliculitis. However, if a folliculitis turns into a boil, haematogenic spread may occur, especially if the boil is manipulated by the patient." Special attention needs to be given to a boil on the tip of the nose. If this infection spreads to the sinus cavernosus, the mortality rate is high. "The skin of the tip of the nose has a venous connection to the sinus cavernosus and the risk of spreading is, therefore, profound," added Dr Arend.

Then there is cellulitis, which will usually not lead to severe complications or life-threating situations, according to Dr Arend. "The first potentially life-threatening skin infection I would like to discuss is necrotising cellulitis," said Dr Arend. This condition often arises from a combined infection with anaerobic bacteria and gram-negative *streptococcus pyogenes* in patients with vascular diseases or diabetes. However, a mono-infection with *streptococcus pyogenes* may also lead to necrotising cellulitis. It can easily spread through the vascular system, leading to sepsis.

Finally, there is necrotising fasciitis, often involving the same pathogens as those that cause necrotising cellulitis. Necrotising fasciitis is characterised by excruciating pain and high fever. "Discriminating between these 2 life-threatening skin infections is relevant because immediate surgery is necessary to prevent further deterioration of the fascia in case of necrotising fasciitis. Dermatologists should pay attention to the absence of capillary refill, purple, brown, bronze, or white discolourations, loss of sensibility, crepitations, and bullae, which are symptoms of necrotising skin infections."

Unusual suspects

Dr Arend also discussed some unusual pathogens that may lead to severe skin infections. She mentioned that an infection with *capnocytophaga canimorsus* may lead to necrotising fasciitis. "Severe cases may arise after a dog bite in a patient with immunosuppression," said Dr Arend. Similarly, *pasteurella multocida* infections, which are caused by a cat bite, could lead to necrotising fasciitis. Another unusual suspect for the development of necrotising fasciitis is *vibrio vulnificus*. Working with oysters is a risk factor for infection.

Toxin-mediated diseases

Dr Arend also highlighted 3 toxin-mediated diseases that may lead to life-threatening skin infections. *Staphylococcus-scalded* skin syndrome is seen in small children with, for example, an infected nail. The exfoliating toxin may spread systemically. "Fortunately, the expansion is usually superficial, and the mortality rate is 'only' 5%," mentioned Dr Arend. If this syndrome occurs in adults, which is uncommon, the mortality rate is 50%.

Another toxin-mediated disease is scarlet fever. It usually starts with a throat infection and typical clinical signs of this condition are the so-called 'strawberry tongue' and the rash-free zone around the mouth and nose. "The scarlet rash that individuals with this disease develop is toxin-mediated," clarified Dr Arend.

Finally, toxic shock syndrome is life-threatening if it is caused by *streptococcus pyogenes*, whereas an underlying infection with *staphylococcus aureus* mostly leads to a less severe disease course.

Dr Arend also named some life-threatening infections with clear skin manifestations that dermatologists should be aware of. These include meningococcal sepsis, staphylococcal sepsis, endocarditis, typhoid fever, and viral haemorrhagic fever. Her last remark to the audience was not to forget to consider atypical mycobacteria in immunosuppressed patients.

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