Vitiligo

Khaled Ezzedine, Viktoria Eleftheriadou, Maxine Whitton, Nanja van Geel

Vitiligo, an acquired pigmentary disorder of unknown origin, is the most frequent cause of depigmentation worldwide, with an estimated prevalence of 1%. The disorder can be psychologically devastating and stigmatising, especially in dark skinned individuals. Vitiligo is clinically characterised by the development of white macules due to the loss of functioning melanocytes in the skin or hair, or both. Two forms of the disease are well recognised: segmental and non-segmental vitiligo (the commonest form). To distinguish between these two forms is of prime importance because therapeutic options and prognosis are quite different. The importance of early treatment and understanding of the profound psychosocial effect of vitiligo will be emphasised throughout this Seminar.

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Department of Dermatology and Paediatric Dermatology, National Centre for Rare Skin disorders, Hôpital Pellegrin, Bordeaux, France, and Institut National de la Santé et de la Recherche Médicale. U1035, University of Bordeaux, Bordeaux, France
(K Ezzedine PhD)**; Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK**
(V Eleftheriadou PhD, M Whitton BA Hons)**; and Department of Dermatology, Ghent University Hospital, Ghent, Belgium**
(N van Geel PhD)

Correspondence to:
Dr Khaled Ezzedine, Department of Dermatology and Paediatric Dermatology, National Centre for Rare Skin Disorders, Hôpital St-André, rue Jean Burguet 33075, Bordeaux, France
khaled.ezzedine@chu-bordeaux.fr

Introduction

Vitiligo is an acquired chronic depigmenting disorder of the skin resulting from selective destruction of melanocytes. Celsus[1] was the first to use the term vitiligo in his Latin medical classic *De Medicina* during the second century BCE.[1,2] The name is believed to derive from the Latin *vitium*, meaning defect or blemish,[3] rather than *vitellus*, meaning calf.[4] Typical vitiligo lesions can be defined as milky white, non-scaly macules with distinct margins. According to a recent international consensus conference,[5] vitiligo can be classified into two major forms—namely, non-segmental vitiligo, also known as vitiligo, and segmental vitiligo. Non-segmental vitiligo, the commonest form of this unpredictable disease, is characterised by symmetrical and bilateral white patches. Different clinical subtypes have been described, including generalised, acrofacial, and universalis types, all with a bilateral distribution. Segmental vitiligo is less common than non-segmental vitiligo and usually has a unilateral distribution. Overall, progressive patchy loss of pigmentation from skin, overlying hair, and sometimes mucosa remains the basis of diagnosis of vitiligo.

Epidemiology

Vitiligo is the most common depigmenting disorder. The largest epidemiological study[6] was done in 1977 on the island of Bornholm in Denmark, where vitiligo was reported to affect 0·38% of the population. The prevalence of vitiligo is often referred to as 0·5–1% of the world's population,[5] although the exact prevalence is difficult to estimate, with rates as high as 8·8% in India.[7] This high value could be due to the inclusion of cases with chemically induced depigmentation,[8] or because these data referred to the prevalence of patients with vitiligo within one skin institute in Delhi.[7] On the other hand, estimated prevalence of vitiligo in the black population of the French West Indies is much the same as, or slightly less than, the accepted data for white people.[9] Overall, the highest incidence has been recorded in India (up to 8·8%), followed by Mexico (2·6–4%), and then Japan (1·68%).[8] The disparity between prevalence and incidence data could be due to high reporting of data; places where social and cultural stigma are common, forcing patients to seek early consultation, or where lesions are more prominent in dark skinned populations.[8]

Adults and children of both sexes are equally affected, although women and girls often present for treatment more frequently, possibly because of the greater negative social effects for affected women and girls than for men and boys[10,11] Non-segmental vitiligo develops at all ages, but usually occurs in young people between the ages of 10 years and 30 years.[8,10,12,13] However, findings from one epidemiological study[6] showed that almost 50% of people develop vitiligo after age 40 years. Almost half of patients are estimated to present before age 20 years, and nearly 70–80% before age 30 years.[8] Childhood-onset vitiligo (before age 12 years) is reported to be common and affects 32–37% of patients[13,14] compared with previously reported 25%.[15–17] Non-segmental vitiligo can occur at any age, whereas segmental vitiligo tends to occur at a young age,[14] before age 30 years in 87% of cases and before age 10 years in 41·3%. Segmental vitiligo accounts for 5–16% of overall vitiligo cases.[18,19] Findings from a study in Jordan[20] showed that vitiligo prevalence increases with age (0·45% <1 year old, 1% 1–5 years old, 2·1% 5–12 years old). Findings from a review of available studies[21] supported this notion because the prevalence of vitiligo was seen to range from 0·06% to 2·28% in the general population, and from 0% to 2·16% in child populations.

Classification

Segmental vitiligo lesions are characterised by their unilateral and segmental or band-shaped distribution, (figure 1) early involvement of the follicular melanocyte reservoir, early age of onset, and rapid stabilisation,[22] whereas non-segmental vitiligo lesions are typically bilaterally distributed in an acrofacial pattern, or scattered symmetrically over the entire body, evolving over time. Non-segmental vitiligo can initially have an

Search strategy and selection criteria

We searched PubMed with the terms "vitiligo", "autoimmunity", and "leucoderma". Our search covered articles published in English between Jan 1, 2000, and Jan 31, 2014. We identified additional reports that were judged the most relevant and recently published from the reference lists of selected articles. Some important older publications are cited either directly or indirectly through review articles.

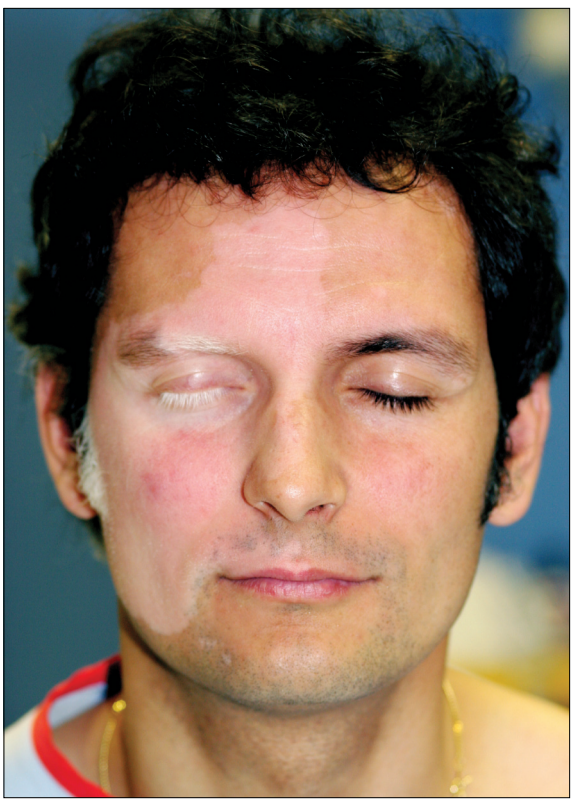

Figure 1: **Typical segmental vitiligo of the face with eyelash and eyebrow whitening**

acrofacial distribution, but can later progress to the generalised or universal form (figure 2). Most often, non-segmental vitiligo has a predilection for extensor surfaces (eg, posterior surface of the elbow), although some cases show a flexural surface distribution of the lesions (eg, anterior surface of the elbows), suggesting different triggers.[23,24] In a study of latent class analyses,[25] two phenotypes of non-segmental vitiligo have been distinguished; the first is of early onset (before the age of 12 years) and is often associated with halo naevus (figure 2) and a familial background of premature hair greying, whereas the second is of late onset and is most often associated with an acrofacial pattern. These two phenotypes are probably associated with distinct pathophysiology pathways and could help refine results from genetic studies. Moreover, according to a Vitiligo Global Issue Consensus Conference,[5] the term vitiligo can be used as an umbrella term for all non-segmental forms of vitiligo (including several variants: acrofacial, mucosal, generalised, universal, mixed, and rare). Mixed vitiligo (figure 2) has been defined as the coexistence of non-segmental and segmental vitiligo in one patient, and is classified as a subgroup of non-segmental vitiligo.[26]

Segmental vitiligo (figure 1) is further classified as unisegmental, bisegmental, or plurisegmental. On the basis of this latest consensus, the presence of focal lesions (small, isolated, depigmented lesions) that have not evolved into non-segmental or segmental vitiligo after 1–2 years is regarded as unclassifiable vitiligo. Rare variants have been reported in the revised classification proposed by a group of international experts, two of which are follicular vitiligo[27] and vitiligo minor.[5] Vitiligo minor (a subgroup of non-segmental vitiligo) seems to be limited to dark skinned individuals. The term minor refers to the incomplete defect in pigmentation with a pale skin colour compared with healthy skin. The relation of vitiligo minor to true vitiligo is supported by pathological examination and coexistence with conventional vitiligo chalk-white macules.[5]

Pathophysiology

Histological examination and immunohistochemical studies with a large panel of antibodies generally show an absence of melanocytes in lesional skin, although sometimes an occasional melanocyte can be seen.[28] However, the presence of a lymphocytic infiltrate has been described when biopsy specimens are taken from perilesional skin of actively spreading or inflammatory vitiligo (figure 3), in which there is a raised erythematous border. Various theories have been suggested for the cause of melanocyte loss in vitiligo; some have proposed that vitiligo is a multifactorial disease, with both genetic and environmental factors implicated in its initiation. The same causal mechanisms might not apply to all cases, and different pathogenetic mechanisms might work together (convergence or integrated theory), ultimately leading to the same clinical result.[28–30]

The autoimmune or autoinflammatory theory is the leading hypothesis for causation and is supported by strong evidence (figure 4). The hypothesis is mainly based on the clinical association of vitiligo with several other autoimmune disorders, such as thyroiditis.[31] An increased frequency of autoimmune diseases has been reported in relatives of vitiligo patients, supporting a genetic component of the disorder. Findings from an epidemiological survey in the UK and North America[32] showed that 19·4% of patients with vitiligo aged 20 years or older reported clinical history of autoimmune thyroid (most frequently hyperthyroid) disease compared with 2·39% of the overall white population of the same age. Many other studies[33–36] supported the associations of vitiligo with thyroid disorders and other associated autoimmune diseases, such as rheumatoid arthritis, psoriasis, adult-onset diabetes mellitus, Addison's disease, pernicious anaemia, alopecia areata, systemic lupus erythematosus, and atopic background, although the frequency varied. These differences could be attributable to the different ages, skin types, and races of the studied populations.[37]

The association between vitiligo and autoimmune diseases has not yet been fully explained, but genetic data have provided important insights. A shared underlying genetic susceptibility to autoimmune diseases has been

suggested. Genome-wide association analyses have identified several susceptibility loci for generalised vitiligo,[38] including the gene encoding tyrosinase, *TYR*.[39] Tyrosinase is a melanocyte enzyme that catalyses the rate-limiting steps of melanin biosynthesis,[40,41] and is a major autoantigen in generalised vitiligo.[42] A genome-wide association study[39] has identified a susceptibility variant for non-segmental vitiligo in *TYR* in European white people that is rarely seen in melanoma patients, suggesting a genetic dysregulation of immunosurveillance against the melanocytic system. Moreover, in the same study, nearly all the susceptibility genes that were identified encode components of the immune system, supporting the hypothesis of a deregulated immune response in vitiligo. Several of these loci (eg, *HLA* class I and II, *PTPN22*, *IL2R* α, *GZMB*, *FOXP3*, *BACH2*, *CD80*, and *CCR6*) suggest a role for adaptive immunity, and some of them are shared with other autoimmune disorders, such as type 1 diabetes, thyroid disease, and rheumatoid arthritis.[43–45] Other loci (eg, *NLRP1*, *IFIH1* [*MDA5*], *TRIF*, *CASP7*, and *C1QTNF6*) point to components of the innate immune system.[46] The association of *XPB1* with vitiligo supports a role for the unfolded protein response pathway in pathogenesis, which is associated with susceptibility to inflammatory bowel disease.[38,44,47]

Several studies in animals support the role of the innate immune response. An overactive so-called danger signalling cascade in vitiligo lesions has been shown, with a possibly central role for inducible heat shock protein 70i and the inflammasome, a multiprotein complex producing proinflammatory signals.[48,49] These factors are implicated in damage-associated molecular patterns (DAMPs), which are self-derived so-called danger signalling patterns that occur after cell damage and are activated during sterile inflammation (not associated with pathogens as in pathogen-associated molecular patterns [PAMPs]).[30] The generation and release of DAMPs are likely to provide the initiating danger signal in vitiligo and act as ligands for innate pattern recognition receptors (eg, toll-like receptors and nucleotide oligomerisation domain-like receptors), with subsequent activation of the innate immune response (inflammation). Exosome (small microvesicle) secretion might provide the means by which melanocytes communicate stress to the innate immune system.[50] Findings from in-vitro studies have shown the release of exosomes from melanocytes after treatment with monobenzone.[51] These exosomes can contain, in addition to melanocyte antigens, miRNAs, heat-shock proteins, and other proteins that act as DAMPs.

Research into the pathogenesis of vitiligo additionally points to the importance of reactive oxygen species and therefore melanocyte-intrinsic abnormalities as possibly key inducers of the whole inflammatory cascade.[52,53] Melanocytes from patients with vitiligo have proved more susceptible to oxidative stress than those from unaffected individuals and more difficult to culture ex vivo than those from healthy controls.[52–54] This finding has been attributed to an inherited inability to manage stressors from normal cellular processes (eg, melanogenesis) or exposure to environmental factors (injury or chemicals). In response to stressors, reactive oxygen species are released from

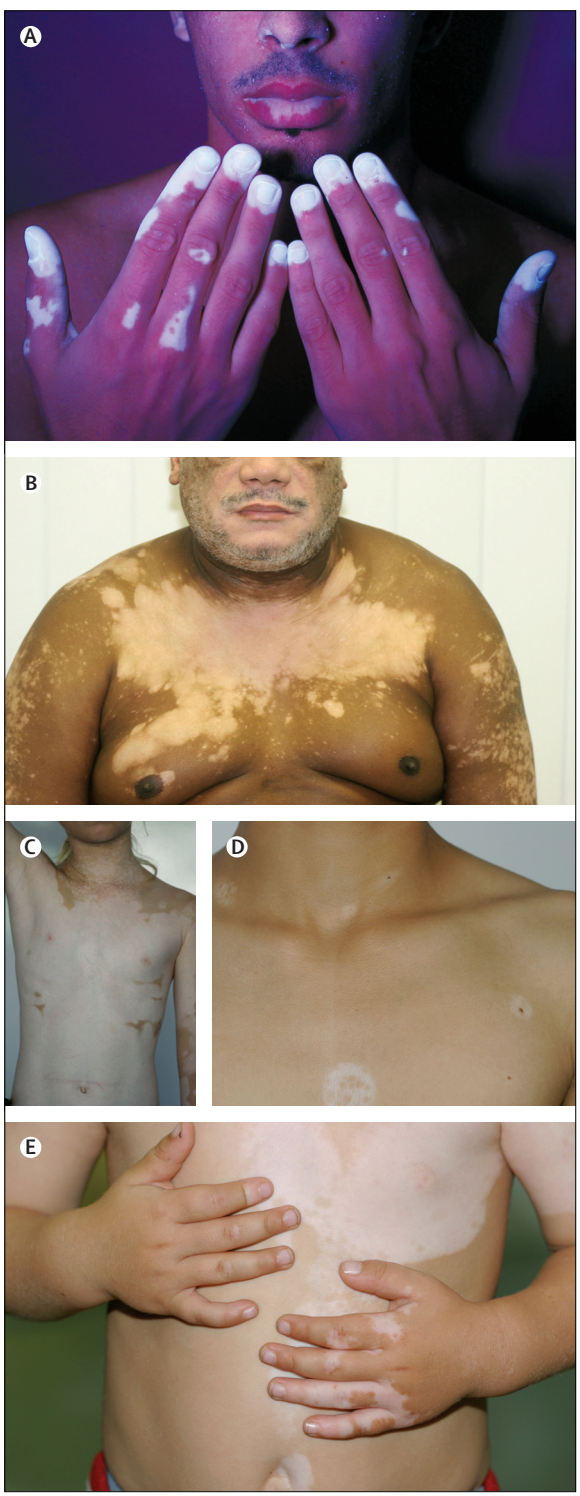

***Figure 2*: Non-segmental vitiligo**
(A) Acrofacial vitiligo under ultraviolet light. Note the typical involvement of hand associated with periorificial lesions. (B) Generalised vitiligo. This patient had a few acrofacial lesions for 10 years that evolved within 6 months into a generalised form, spreading to the trunk. (C) Universal vitiligo with an affected surface area of more than 60%. Note the residual islets of pigmentation. (D) Generalised form of vitiligo with associated halo naevi. (E) Mixed vitiligo with typical segmental lesions of the trunk associated with bilateral hand lesions.

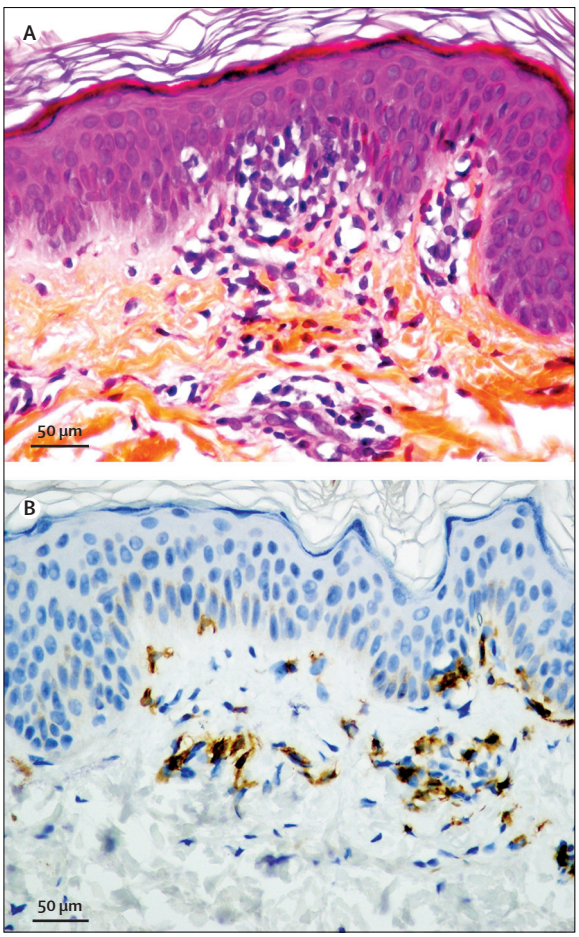

Figure 3: **Histology of perilesional skin of actively spreading vitiligo**
(A) Dermoepidermal lymphocytic infiltrate with a lichenoid alteration pattern. Haematoxylin-eosin-saffron staining. (B) Lymphocytic cytotoxic attack with a dense CD8+ T-lymphocytic infiltrate in both the dermis and epidermis CD8 antibody immunostaining.

melanocytes. This release increases NACHT, LRR, and PYD domains-containing protein signalling, causing caspases to be activated. This activation ultimately leads to release of interleukins 1β and 18 into the extracellular environment, with subsequent activation of innate immune cells (eg, natural killer cells and inflammatory dendritic cells. On the other hand, reactive oxygen species can also initiate a signalling cascade through unfolded protein response activation, ultimately leading to production of heat shock protein 70i, thereby increasing proinflammatory signalling after binding to toll-like receptors, as described above. Induction of the unfolded protein response can result in the direct release of proinflammatory cytokines (interleukins 6 and 8) from melanocytes, which can antagonise the suppressor function of regulatory T cells.[30]

Vitiligo is likely to have a second step in which the innate immune system subsequently triggers the adaptive immune system by activating dendritic cells, thereby facilitating targeted autoimmune destruction of melanocytes.[55] For example, evidence supports a role of melanocyte-specific cytotoxic T cells in progressive vitiligo.[56] Tetramer-positive CD8+ T cells were isolated from lesional skin and the blood of vitiligo patients, which proved capable of killing melanocytes in vitro.[56] This theory is supported by the fact that various effective treatment options in vitiligo (eg, local steroids and topical immunomodulators) have an immunosuppressive effect on the activation and maturation of T cells. So far, some antigenic proteins have been identified in vitiligo, consisting of gp100, MART1, tyrosinase, and tyrosinase-related proteins 1 and 2. The role of CD4+ T cells in the pathogenesis of the disease is still unclear, although a possible role of dysregulated regulatory T cells has been suggested.[57,58] This dysregulation leads to a decreased capacity to dampen active inflammatory processes and therefore a reduced threshold to develop autoimmune disorders.[59]

Many other hypotheses have been put forward in the past. Antibodies to normal human melanocytes have been detected with a specific immunoprecipitation assay,[60–62] and have a cytolytic effect on melanocytes.[63] The presence of these melanocyte antibodies has been linked to disease activity.[64] However, whether these antibodies play an initiating part in the development of vitiligo or are a secondary result of the disease is unclear.[65] Kroll and colleagues[66] postulate that extracellular matrix molecules that inhibit the adhesion of melanocytes to fibronectin could contribute to the loss of pigment cells in vitiligo. Repeated friction to perilesional skin in non-segmental vitiligo in vivo induces detachment and death of melanocytes, termed melanocytorrhagy.[67,68] Defective keratinocyte metabolism could have a major role in vitiligo, with low catalase concentrations in the epidermis of patients.[69] Catalase is the principal enzyme implicated in H_2O_2 removal, which is important in the management of oxidative stress. Furthermore, in the same context, defective tetrahydrobiopterin and catecholamine biosynthesis could explain the pathogenesis of the disease.[70]

We need to know whether a primary defect in pathogenesis should be sought for an increased susceptibility of melanocytes to oxidative stress, an overactive innate immune response to skin trauma, or recruitment of antigen-specific T cells (adaptive immune response), and how these pathways work together to maintain disease activity in vitiligo.

Management

Before management is discussed with the patient, the extent of the disease should be assessed with natural and Wood's lamp examination. The Vitiligo European Task Force[23] has developed an assessment form summarising the results of the personal and family history of the patient and clinical examination items. Skin phototype and disease duration, extent, and activity are important elements that will help to guide therapeutic management.

Additionally, the patient's psychological profile and way of coping with the disease should be carefully looked at. In non-segmental vitiligo, the course of the disease is unpredictable and, in some patients, a so-called acceleration phase with rapid disease progression in a few weeks or months needs urgent intervention, usually minipulse therapy.

Other useful clinical history items consist of previous episodes of repigmentation and type, duration, and effectiveness of previous treatments. Analysis of Koebner's phenomenon (defined as "development of lesions at sites of specifically traumatised uninvolved skin of patients with cutaneous diseases")[71] is of particular interest for prevention of the disease.[72,73] A scoring of the probability of Koebner's phenomenon has been proposed.[74] Clinical evidence suggests that in vitiligo, some areas of the body related to daily life habits (eg, hygiene or clothing) and occupations (eg, construction workers or gardeners) are more susceptible to Koebner's phenomenon (figure 5). Finally, an overall quality of life assessment is suitable because a patient's personality and perceived severity of the disease are predictors of quality of life impairment, and will guide management options.[75] A vitiligo-specific quality-of-life instrument has been developed and can be used to assess the effect of the disease on daily life.[76] However, we need improved patient-reported outcome instruments that take into account patients' characteristics and help to assess the burden of disease in terms of coping and living with vitiligo.

Because of the frequent association of non-segmental vitiligo with autoimmune thyroid disease, especially Hashimoto's thyroiditis, regular measurement of thyrotropin concentration is recommended in patients with antibodies to thyroid peroxidase, which can precede overt thyroiditis. One should keep in mind that associated autoimmune disease frequencies are dependent on ethnic background and family history of autoimmune diseases, both of which make appropriate management difficult. Any symptoms suggestive of organ-specific autoimmune diseases and a personal or family history of autoimmune or autoinflammatory disorders should prompt appropriate investigation, and specialist advice can be helpful.

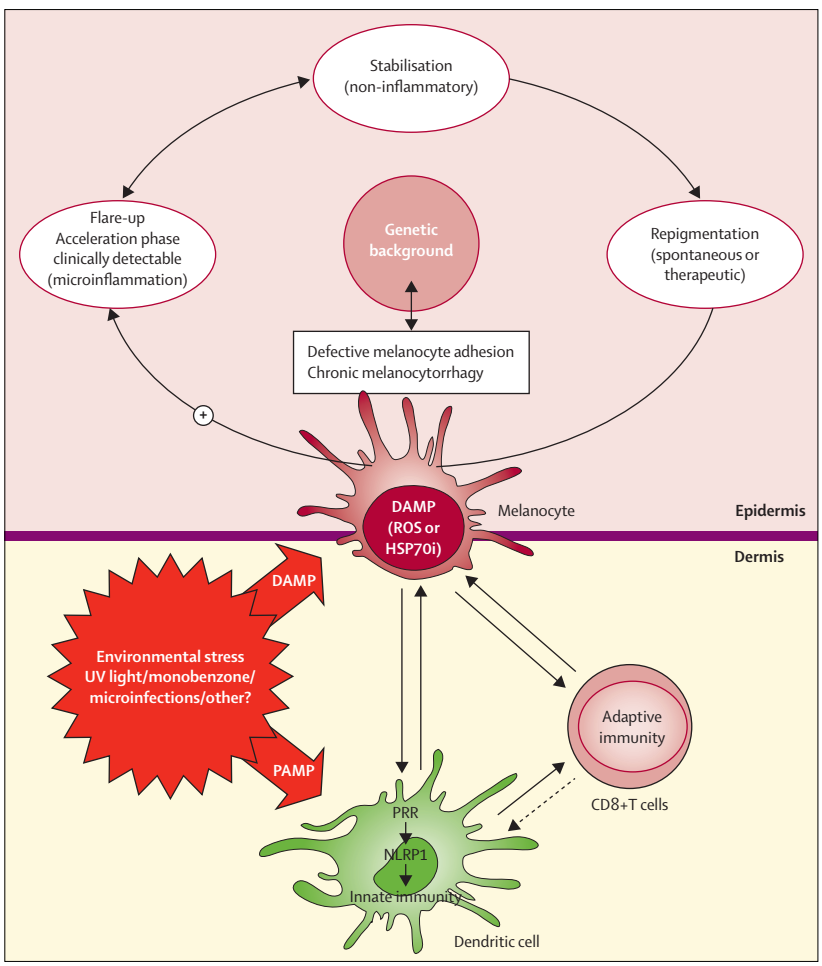

Figure 4: **Vitiligo pathogenesis**
The natural history of vitiligo is both chronic melanocytorrhagy and successive cycles, consisting of flare-up, stabilisation, and repigmentation phases in genetically predisposed individuals. Each flare-up is triggered by environmental factors, such as exposure to UV light or chemical (monobenzone), or microinfections. These triggers will induce the production of PAMPs or DAMPs, which will interact with NLRP1 in the cytoplasm of dendritic cells and initiate innate immunity, ultimately leading to adaptive immune response and melanocyte disappearance. The dashed arrow represents the passage of one phase to another. The arrow with a plus symbol represents triggering of flare-up by environmental stress, which induces a new cycle. DAMP=damage-associated molecular pattern. HSP70i=heat shock protein 70i. NLRP1=NACHT, LRR, and PYD domains-containing protein 1. PAMP=pathogen-associated molecular pattern. PRR=pattern recognition receptor. ROS=reactive oxygen species. UV=ultraviolet.

British Association of Dermatologists clinical guidelines[77] for the diagnosis and management of vitiligo recommend narrow band (NB) ultraviolet (UV) B, tacrolimus, and topical steroids. This user-friendly guideline was created on the basis of evidence from a 2006 Cochrane systematic review[78] and expert consensus taking into account patient choice and clinical expertise.[79] Whitton and colleagues in the 2010 updated Cochrane systematic review[80] concluded that no cure or way of restricting the spread of the disease have been reported so far. This review identified 57 randomised controlled studies published between 1966 and 2009, with 3139 participants and assessment of 82 interventions. These interventions included topical therapies (eg, glucocorticosteroids, cacineurin inhibitors, melagenina, and vitamin D), phototherapies (eg, NB-UVB, UVA, and xenon-chloride excimer laser), oral treatments (eg, zengse pills, *Ginkgo biloba*, and *Polypodium leucotomos*), surgical treatments (eg, skin grafts and melanocyte transplantation), and other interventions, such as psychological treatments. However, most of the trials, which covered a wide range of interventions, had fewer than 50 participants. The conclusion of the review was that no firm clinical recommendations for the treatment of vitiligo can be made, mainly because of heterogeneity in the design of trials and often small numbers of participants.[80] A new guideline for vitiligo was developed by the Vitiligo Guideline Subcommittee of the European Dermatology Forum[81] and brought several changes into the previously proposed management of vitiligo. This new European

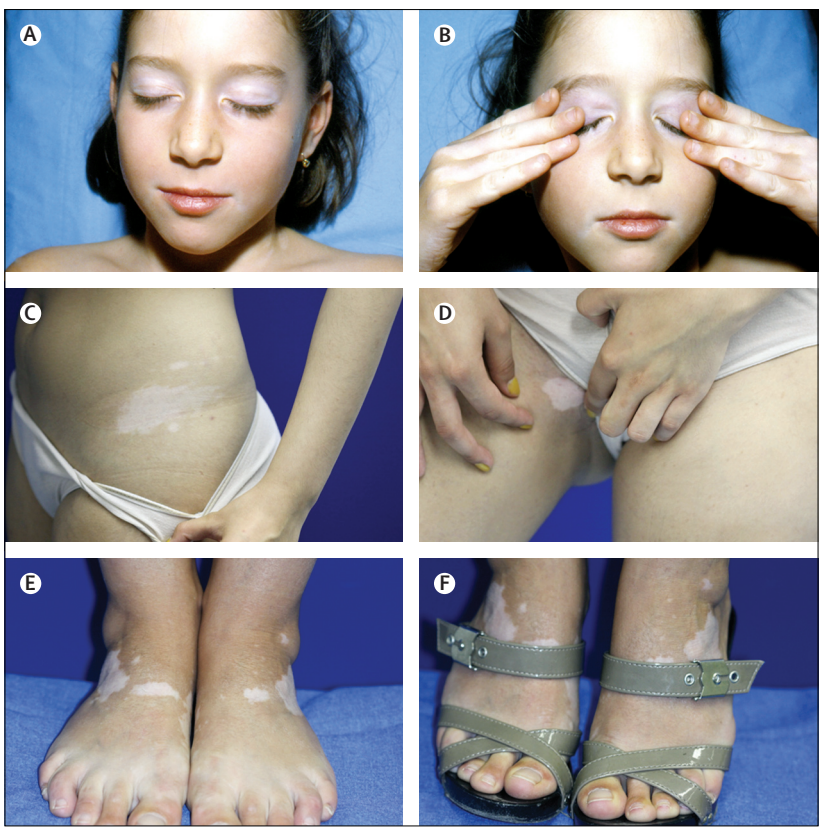

Figure 5: **Koebner's phenomenon in relation to daily living activities**
(A), (B) Eye rubbing. (C), (D) Underwear print. (E), (F) Shoe print.

Guideline aims to bring clarity to treatment options available for various types of vitiligo, ranging from first-line to fourth-line therapies (figure 6). Recommendations are based on best available evidence combined with expert opinion.

First-line treatments consist of topical treatments (corticosteroids and calcineurin inhibitors). Once daily application of potent topical corticosteroid preparations (eg, 0·10% betamethasone valerate and 0·05% clobetasol propionate) is recommended, but should preferably be applied in a discontinuous scheme (eg, 15 days per month for 6 months) to avoid local side-effects (skin atrophy, teleangiectasia, hypertrichosis, acneiform eruptions, and striae). The use of topical calcineurin inhibitors (pimecrolimus or tacrolimus) mainly for the facial and neck area is an alternative to topical steroids. Twice daily applications are recommended, initially for 6 months.[81]

Second-line treatments consist of phototherapy (NB-UVB and psoralen and UVA [PUVA]) and systemic steroid treatment. Treatment with phototherapy is effective in some cases. NB-UVB (311 nm) phototherapy is at least equally effective as PUVA, with fewer side-effects because of intake of psoralens.[81,82] UVB treatment can be used selectively and localised with targeted phototherapy devices (eg, excimer lamps or lasers; at 308 nm peak). No consensus exists as to the optimum duration of phototherapy, and practice varies widely. Irradiation will most often be stopped if no repigmentation occurs within the first 3 months of treatment, although repigmentation sometimes starts later on. Oral minipulse of moderate doses of betamethasone or dexamethasone for 3–6 months can be considered in fast spreading vitiligo to stop progression.[83] Third-line treatments consist of surgical grafting techniques and depigmenting treatments.

Surgical methods are proposed as a therapeutic option in patients with segmental vitiligo and those with non-segmental vitiligo with stable disease for at least 1 year after documented non-response of medical interventions and absence of Koebner's phenomenon. Only a few patients are therefore suitable for these interventions. The surgical techniques that are mentioned in the European guidelines[81] consist of tissue grafts (full-thickness punch, split-thickness, and suction-blister grafts) and cellular grafts (cultured melanocytes and non-cultured epidermal cellular grafts). The three tissue grafting methods seem to have much the same success rates of repigmentation. Moreover, cellular grafting techniques were, in general, equally effective, although the percentages of repigmentation were slightly inferior to the tissue grafts.[77,81,84] However, important advantages of cellular grafting are the possibility of treating large areas and better cosmetic results than with tissue grafts.[85,86] Furthermore, adverse events seem to be less frequently associated with cellular grafts than with punch grafting, followed by split-thickness grafting.[87]

Depigmenting treatment of residual areas of pigmentation should only be considered in widespread (>50% body surface area), refractory, and disfiguring vitiligo, or highly visible recalcitrant facial or hand vitiligo. Skin-bleaching methods reported are monobenzone ethyl ester or 4-methoxyphenol,[88,89] laser treatment (eg, 755 nm Q-switched alexandrite or 694 nm Q-switched ruby),[90] and cryotherapy.[91,92]

Effects on people

So far, there is no cure for vitiligo. Current treatment results vary between individuals and are often unsatisfactory. Best results are generally reported for the face, whereas acral lesions respond poorly. Moreover, treatment is more efficient in recently developed lesions compared with older lesions, which argues for early therapeutic intervention.[93] Patients with a fair complexion should be advised, after discussion, that no treatment can be offered because of an expected poor response and that they are best advised to seek effective cosmetic camouflage and sunscreen for lesions on exposed skin. Additionally, special recommendations to prevent triggering factors (Koebner's phenomenon) during daily activities can be recommended.[72,73] The psychosocial effect of vitiligo is

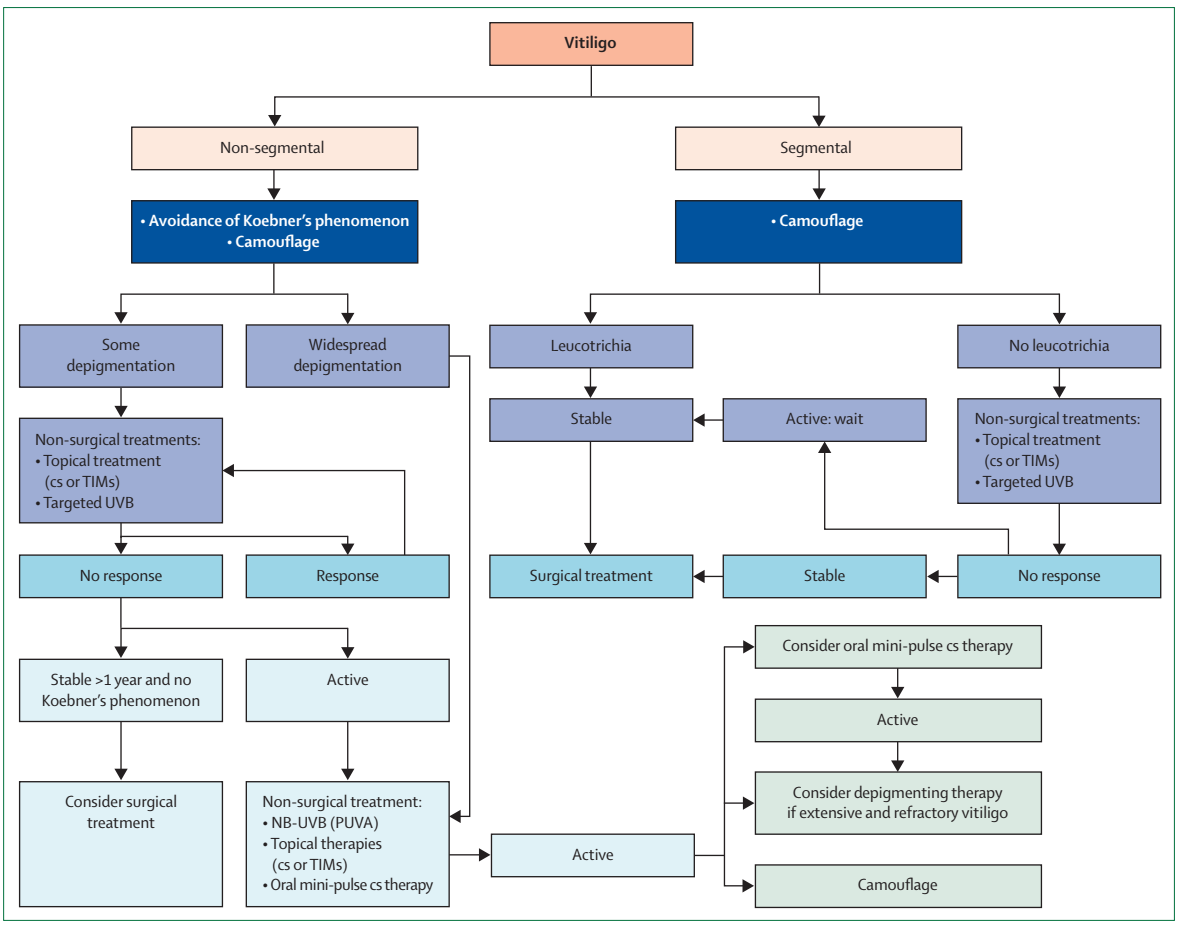

Figure 6: **Therapeutic algorithm of vitiligo**
cs=corticosteroids. NB=narrow band. PUVA=psoralen and UVA. TIM=topical immunomodulator. UV=ultraviolet.

important and well recognised. Provision should therefore be made for all patients with any form of the disease undergoing any type of treatment to be offered psychological support and counselling if at all possible.[94]

In a discussion with the UK Vitiligo Society, the manager mentioned that the Society had been contacted by a 25-year-old male student from Pakistan. This man had developed vitiligo while in England, mainly on his right hand and forearm, and was seeking advice about how he could have his right forearm amputated before returning to his country of origin. He said "I will surely be rejected by my family if they see my forearm". Vitiligo was recognised in ancient times and is still confused with leprosy in some countries. Hippocrates included lichen, leprosy, and vitiligo in the same category. The confusion with leprosy is an important cause of the social stigma attached to the white spots in some countries. Since ancient times, men and women with white patches of skin were often outcasts or disqualified from marriage, or if spots occurred during marriage, they provided a reason for divorce.[11] Porter and colleagues[95] reported that vitiligo has a major effect on the quality of life of patients and negatively affects sexual relations.[95–97] Many people are generally frightened and embarrassed by vitiligo. Patients often experience discrimination and believe that they do not receive adequate support from their doctors,[96–98] friends, and family.[98] Patients with vitiligo often have several psychological difficulties, such as shame, depression, and anxiety, which can lead to low self-esteem and social isolation.[75,95]

Additionally, the unpredictable nature of vitiligo is associated with negative emotions, such as fear of vitiliginous lesion spreading, shame, insecurity, and sadness.[99] Perhaps unsurprisingly, patients with visible lesions have a higher level of stigmatisation than those whose lesions are hidden.[100] A survey done by the UK Vitiligo Society of their members showed that over half (57%) of respondents said that vitiligo moderately or severely affected their quality of life. Most respondents obtain information about their disease from non-medical sources, such as the internet.[101] Self-image of patients is greatly impaired, and mood disturbances are common, particularly in teenagers. Vitiligo that begins in childhood can be associated with severe psychological trauma, which can have a long-lasting effect on self-esteem. Children usually avoid or restrict sporting activities, and

often lose crucial days in school.[96] Findings from a study in the Netherlands on the effect of childhood vitiligo on adult life[102] showed that psychosexual development of young adults with childhood disease seems to be like that of healthy controls. However, patients with negative experiences of their vitiligo during childhood reported substantially more difficulties in social development. Furthermore, a small study[103] suggested that female Muslim patients in Iran have greater quality of life impairment than have men. Little research has been done into the psychological effect of the disease, and the effectiveness of psychological treatment is not fully understood.[104,105] Papadopoulos and colleagues[104] provided preliminary evidence that cognitive behavioural treatment could provide benefit to patients coping and living with vitiligo, and that psychological treatment itself could have a positive effect on progression of the disease.

Future directions

Whitton and colleagues[80] pointed out that there is no consensus about the classification and definition of the disorder or about methods of assessment and outcome measures used in trials, and noted heterogeneity of interventions used to treat vitiligo.[106,107] These issues have been recognised by international experts worldwide as a priority for research. Efforts have been made to resolve these issues by the creation of consensus,[5] identification and definition of priorities for research,[108] and raising of awareness about this devastating and neglected disease.[106] Patients and health-care professionals have an increasingly recognised key part to play in the identification of important areas for research. The pharmaceutical and medical technology industries and researchers are essential for the development of new treatments. However, the priorities of industry and researchers are not necessarily the same as those of patients and clinicians. For this reason, many areas of potentially valuable research are neglected.[109] A vitiligo priority setting partnership[94] has been established with the aim of helping to identify which interventions should be assessed in future clinical trials and which are the most important research topics to patients and clinicians. The partnership is an initiative of the James Lind Alliance and is the first priority setting partnership in the discipline of dermatology.

For the **HI-Light Vitligo Trial** see http://www.vitiligostudy.org.uk

For the **James Lind Alliance** see http://www.lindalliance.org

The ten most important unanswered questions in relation to vitiligo treatment have been identified through a process of questionnaires sent to both patients and health professionals, and a day-long workshop with patients, carers, and clinicians, to help to steer research agendas towards the investigation of topics and interventions of importance to patients and health-care professionals.[94] Questions of interest were effectiveness of systemic immunosuppressants, phototherapy in combination with topical agents in treatment of vitiligo, and psychological interventions for the management of the disorder. The roles of gene therapy and afamelanotide were deemed to be of great interest to patients and clinicians. Improved assessment of widely used treatments, such as topical corticosteroids and calcineurin inhibitors, was recommended. Also, psychological interventions and camouflage are of great importance. So far, the use of cosmetic camouflage is not being investigated, but one randomised trial[110] of psychological interventions for vitiligo is underway. One feasibility study[111] has received funding from the UK Dermatology Clinical Trials Network based in Nottingham, which aims to establish which psychological interventions patients would find useful for coping with their disease, with the aim of a full scale trial. This trial would investigate the effect of psychological intervention in conjunction with standard treatment compared with the intervention alone on quality of life.

The Centre of Evidence Based Dermatology in Nottingham (UK) has just completed a 5 year programme grant entitled Setting Priorities and Reducing Uncertainties in Skin Disease.[112] The 2010 updated Cochrane Review[80] was needed for this programme grant because it showed gaps in research. It also helped to inform the Priority Setting Partnership exercise, which led to development of a pilot randomised controlled trial to assess the use of handheld NB-UVB units for treatment of early onset vitiligo.[113] This pilot feasibility trial[111] of handheld NB-UVB devices at home for early onset vitiligo has led to the production of resources[114] consisting of treatment protocols for various skin types, a training programme with an educational DVD, and a treatment diary for patients, enabling them to treat their vitiligo at home with medical supervision. This work has provided the foundation for a large multicentre trial of the devices, which is currently being developed. The programme grant has included work to help to develop a patient-rated outcome measure[115] to be used in future trials. This work showed that people with vitiligo think that treatment success should be based on how noticeable their vitiligo is after treatment. Further work[115] to establish construct validity of this measure is underway.

One of the major challenges is how to combine halting of disease spread and repigmentation of existing lesions because these two goals need distinct mechanisms. Insights into pathogenesis have highlighted the role of the innate immune response. An overactive so-called danger signalling cascade in vitiligo lesions has been shown, with a possibly central role for inducible heat shock protein 70 in the development of vitiligo lesions.[48,49] Finally, the development of systemic biological therapies that target cytokines in the discipline of autoinflammatory skin diseases such as psoriasis suggests that a similar approach might be successfully used in vitiligo. In that sense, the report that the interferon γ–chemokine axis might be important in the pathogenesis of vitiligo supports a strategy of targeting this axis for the development of new vitiligo-specific treatments.[116–118] Thus, the cause and pathogenesis of vitiligo remain unclear. What causes the destruction of melanocytes is still not understood,[119] and uncertainties remain about the natural history and epidemiology of the disease.

Contributors
KE performed the literature search, designed the study, participated in the drafting of all manuscript sections, drafted figures 1, 2B–E, and 3–5, and was responsible for overall management of writing of the manuscript. VE participated in the drafting of the effects on people and future directions sections. MW participated in the drafting of the effects on people section. NvG participated in the drafting of the classification, pathophysiology, and management sections, and drafted figures 2A and 6. All authors reviewed and approved the final manuscript.

Declaration of interests
We declare no competing interests.

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