



# Recent advances in childhood vitiligo

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**Abstract** Vitiligo is an autoimmune depigmentation disorder that is estimated to affect about .5% of the worldwide population. Half of all cases begin in childhood. A variety of advances occurred in the past two decades that have enhanced the management of childhood vitiligo. This contribution reviews recent advances in vitiligo, including a better understanding of the pathogenesis and autoimmune comorbidities, description of the psychological comorbidities, a broader range of therapeutic options. © 2014 Elsevier Inc. All rights reserved.

## Introduction

Vitiligo vulgaris is an acquired autoimmune form of pigment loss appearing as hypopigmentation or depigmentation. Vitiligo affects about 0.5% to 2% of the worldwide population.<sup>1–4</sup> The most recent population-based study from China assessing 17,345 inhabitants of six cities reported 0.56% of the population had vitiligo, with 0.71% in men and 0.45% in women. In the 0- to 9-year-old age group the prevalence was 0.1% and for ages 10 to 19 years 0.36%, demonstrating that 64% of all cases occur prior to the age of 20 years old in that region. Vitiligo in children occurred predominantly in females (prevalence for 10 to 19 years old was 0.23% in men and 0.52% in women).<sup>5</sup> This corroborates historic vitiligo data that stated that half of all vitiligo cases occur in childhood and that half of childhood disease is noted in females.<sup>6</sup>

A second population-based study of 2,194 children in the Sinai desert of Egypt noted that only 0.18% of children under the age of 18 years old had vitiligo.<sup>7</sup> The effects of population-based genetic differences and/or environmental factors, such as the intensity of incidental sun exposure, on vitiligo prevalence remains unknown.

The pathogenesis of vitiligo includes a combination of genetic propensity and environmental triggering. The leading

theory is that vitiligo is an autoimmune attack on melanocyte antigens, accompanied by oxidative destruction and/or metabolic alteration, which result in curtailment of pigment production and eventually in melanocyte cell death.<sup>8–10</sup>

This contribution is a review of recent literature pertaining to pediatric vitiligo. It is divided into the following groupings: (1) clinical presentation of vitiligo, (2) recent advances in understanding the pathogenesis of vitiligo, (3) recent advances in the understanding of comorbidities of vitiligo, (4) psychological comorbidity of vitiligo, and (5) recent treatment paradigms in children.

## The clinical presentation of vitiligo

Vitiligo generally appears as hypopigmentation or depigmentation in typical areas. Earlier onset vitiligo tends to be more focal in nature. Most segmental vitiligo cases occur in childhood, accounting for about one-fifth to one-third of pediatric vitiligo cases.<sup>11</sup> Segmental disease involves a broad pattern of Blaschko's lines, usually rapidly extending through the full segment involved and involving the hair follicles, resulting in poliosis and loss of pigmentary reservoir of melanocytes for repigmentation. Eighty seven percent of segmental cases will occur before the age of 30. Segmental disease is usually believed to be limited in nature, such that secondary autoimmunity is not likely to occur. In clinical case reviews in the United States, Serbia, Greece, and

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Italy, children with segmental vitiligo have not been reported to develop thyroid disease, whereas 10.7% to 26% of children with generalized vitiligo will have discernible thyroid abnormalities.<sup>12–15</sup> Thyroid disease, as measured by TSH, T3, and/or T4 and anti-TPO antibodies has been found to correlate with disease location on the upper extremities in one study, but this was not corroborated in a survey-based study of U.S. children. The upper extremities are an uncommon site of segmental disease, which is usually truncal, facial or located on the hip/lower extremities further supporting the idea that nonsegmental vitiligo, rather than segmental disease, is associated with thyroid autoimmunity.<sup>14,16</sup>

Generalized disease or nonsegmental vitiligo involves intertriginous areas, bony prominences or periorificial regions of the body. The latter may be called acrofacial disease or lip-tip involvement when hypopigmentation is limited to around orifices, fingertips, toes, and genitalia. Trichrome vitiligo is an unusual variant in which some of the skin is fully depigmented, some hypopigmented, and some is normal coloration.<sup>17</sup> Commonly involved sites that are underreported include the oral mucosa and the palms and soles. When these are involved disease can spread onto lips and periorificial skin, as well as dorsal hands and feet. In this author's experience, treating the margins of the lips, palms, and soles may prevent spread to the more visible sites when this is noted. The natural history of generalized disease is often slow extension in regions involved. Rarely, aggressive extension occurs resulting in universal depigmentation.<sup>18</sup>

A recent paper highlighted the fact that despite our understanding that segmental vitiligo is a limited type, some children with segmental vitiligo will go on to develop the generalized disease. The authors term this type a mixed form of vitiligo. This form of mixed type likely represents a twin spotting phenomenon in an individual with the genetic propensity for vitiligo.<sup>19</sup> This mixed form of vitiligo behaves as a generalized disease in terms of the propensity to autoimmune illnesses. Overlapping occurrence of localized vitiligo and generalized alopecia areata has been reported as well. While this too is segmental vitiligo, the fact that alopecia areata is not considered segmental confers the standard autoimmune comorbidity risks on such patients.<sup>20</sup>

While the entity of inflammatory vitiligo is sometimes discussed in childhood, symptoms of inflammation appear to be more common in childhood than previously believed. 30.1% of children report signs of itching or burning in their lesions.<sup>21</sup> This may correlate with self-consciousness, teasing, and bullying.<sup>20</sup> Screening children for symptomatology, therefore, may identify children who are susceptible to become bullied if they aren't already.

Halo nevi are often noted in children with vitiligo and represent form fruste of generalized vitiligo when not noted in segmental areas of disease. Halo nevi have recently been found to be associated with onset of vitiligo prior to the age of 18 years old and Fitzpatrick phototypes I-III as well as truncal involvement.<sup>22</sup> Halo nevi, as well as leukotrichia, are

markers of progression from segmental vitiligo to mixed type (mixed segmental and generalized vitiligo).<sup>23</sup>

## Recent advances in understanding the pathogenesis of vitiligo

Vitiligo is a polygenic or multifactorial disease.<sup>24</sup> Only 23% of identical twins will match on this illness.<sup>25</sup> The genetics of vitiligo have recently been elucidated in a multinational American and European genome-wide association study (Vit Gen), as well as in a Chinese regional genetic studies.<sup>26,27</sup> Vitiligo is an autoimmune condition; however, a succession of minute immunologic errors has to occur in order for vitiligo to be triggered. The ongoing Vit Gen study, as well as a number of genomic studies assessing vitiligo patients worldwide, identified over a dozen candidate genes for vitiligo. These include linkage to pigmentation gene variants (eg, TYR, OCA2 and its transcription down-regulator HERC2, MC1R) that may allow melanocytes to become the target of aberrant immune response, MHC genes presumed to promote antigen presentation of melanocyte self-antigens (HLA-A\*02:01),<sup>28</sup> augmentation of the aberrant self-immunity via aberrant T cells (autoreactive T cell-cytotoxicity),<sup>29</sup> and B cell (auto-antibody production and cellular adjuvants of T cells).<sup>30</sup> Genes involved in B and T cell development, activity and/or repression promoting immune response against melanocytes (CTLA4, BACH2, CD44, IKZF4, LNK).<sup>25</sup> Further exacerbation is noted due to augmentation of melanocyte destruction via exaggerated oxidative stress,<sup>31</sup> augmentation via innate immunity (eg, NLRP-1 formerly NALP-1), genes that affect apoptosis (CASP7) and polymorphisms in genes that regulate anti-inflammatory activity, including glutathione S transferase<sup>32</sup> and the vitamin D receptor, and final promotion of melanocyte cell death via keratinocytes,<sup>33,34</sup> ultimately resulting in melanocytorrhagy (poor cellular attachment of melanocytes resulting in extreme susceptibility to the Koebner phenomenon)<sup>35</sup> promoting cellular apoptosis or other forms of cellular death of the melanocyte.<sup>36</sup> HLA-A\*02:01 seems to be associated with vitiligo in all age groups suggesting that while environmental triggers may change, this is the final pathway to melanocyte antigen presentation.

Vitamin D has been linked to more than 125 medical conditions, including lupus, multiple sclerosis, and diabetes mellitus.<sup>37–39</sup> While the mechanism by which vitamin D contributes to vitiligo is unknown, individuals with the Apa I-A variant genotype carriers have higher vitamin D levels and reduced risk of vitiligo, suggesting vitamin D may confer some protective benefit for some individuals.<sup>40</sup> Vitiligo patients with low vitamin D levels (25OH D < 15ng/dL) are more likely to develop polyautoimmunity.<sup>41</sup> This is noted in adult and pediatric patients usually more than 3 years of age.

Vitiligo can be exacerbated by chemical exposures, termed chemical vitiligo or chemical leukoderma, when vitiligo is absent. Although uncommon in childhood, teenagers with vitiligo should be counseled to avoid dyeing their hair, if possible, due to the risk of exacerbation of disease by chemicals in hair dyes such as para-phenylenediamine, by a combination of contact dermatitis and exacerbation of oxidative damage.<sup>42</sup> When chemicals are involved in the initiation of vitiliginous lesions, lesions will often be found on the scalp and face, the latter due to thin skin, and hands and feet due to high rates of exposure.

A recent paper identified a new pathway through which phenolic chemicals can initiate the process of vitiligo. The authors found that phenolic chemicals can initiate the unfolded protein response, resulting in production of IL-6 and IL-8.<sup>43</sup> The linkage between the unfolded protein response and vitiligo may be the linkage between oxidative damage and melanocyte destruction. Circulating IL-2 and IL-6 elevation have previously been reported to be elevated in vitiligo.<sup>44</sup>

Vitiligo has also been associated with tan/ brown and hazel/ green eye color,<sup>40</sup> suggesting that specific variants of pigmentation promote risk of vitiligo.

## Recent advances in the understanding of comorbidities of vitiligo

Because vitiligo is an autoimmune illness, patients with disease have the genetic and environmental features that select for development of other autoimmune conditions. Parents of children with vitiligo (8.4%) will report secondary autoimmunity. The most commonly reported secondary autoimmunity was thyroid disease at 5.4%, although studies assessing subclinical (presence of thyroid antibodies) and clinical thyroid disease suggest the number may be closer to 25%. Thyroid disease is more common in girls with vitiligo and hypothyroidism is six times as common as hyperthyroidism.<sup>12,13</sup> Rheumatoid arthritis (1.1%), psoriasis (1.1%), and alopecia areata (0.8%) were the three next most common in this U.S.-based survey.<sup>16</sup> Other reports outside the United States associated childhood vitiligo with celiac disease, Addison's disease, and pemphigus vulgaris.<sup>45</sup> The presence of alopecia areata and vitiligo overlapping may relate to attack of pigment antigens in the hair follicles causing concurrent vitiligo and alopecia areata. A case report of thyroid disease in a teenage male with overlapping alopecia areata and segmental vitiligo highlights that despite segmental disease, the presence of a systemic autoimmune condition like alopecia areata or mixed type vitiligo are associated with autoimmune thyroiditis. Vitamin D deficiency is not uncommon in the general population. Comorbid vitamin D deficiency in individuals with vitiligo, including both children and adults, seems to portend greater risk of secondary autoimmunity, especially thyroid disease. Patients

with vitamin D deficiency may have a typical appearance of confetti-like hypopigmentation.<sup>46</sup> This particular appearance has been termed vitiligo punctata (or speckled type) and can be associated with follicular depigmentation as well.<sup>47</sup>

The current data support screening children with vitiligo of a generalized nature for thyroid disease and 25 OH vitamin D levels. Deficient of the latter may signal the need for broader screening including diabetes, rheumatoid arthritis, pernicious anemia, and lupus.

## Psychological morbidity of vitiligo

Psychological impairment is not uncommon in children with vitiligo. Severe impairment affects 13% of children and adolescents with disease, but 10.7% of children with less than 25% BSA involvement will have moderate to severe deficits in their quality of life scores on CDLQI, and 51.1% of children will have reportable psychological impairment with their vitiligo.<sup>20</sup>

While children may not have reached the age of sexual maturity, adults with vitiligo are more likely to experience sexual dysfunction with larger surface areas or genital disease.<sup>48</sup> In one study of children 8 to 18 years of age, genital disease correlated with impaired quality of life for females with vitiligo.<sup>49</sup> A case has been reported of individuals developing obsessive compulsive disorder and interference with the sexual debut in an individual with segmental vitiligo of the penis<sup>50</sup>; therefore, special consideration of potential future effect on sexual function should be given to children with genital disease.

It is especially important to consider that therapy early (before 5 years) is more effective in patients using tacrolimus<sup>51</sup> and likely most treatments. While many parents may wish to defer therapy because their child is not bothered by lesions, a recent study demonstrated that while 45.6% of children (0 to 6 years old) and 50% of children (7 to 14 years) are unbothered by their lesions only 4.1% of teenagers (15 to 18 years old) feel similarly; therefore, it is reasonable to initiate therapy in an effort to reduce self-consciousness at a later date. As facial and leg lesions seem to be most associated with self-consciousness, these sites should be addressed early.<sup>20</sup>

It is important to remember that children who are self-conscious may be more susceptible to teasing and bullying. Factors that correlated with being teased or bullied in children with vitiligo included body surface area greater than 25% and lesions on the face for children ages 4 to 16 years old. Facial lesions were previously associated with psychological impairment in multiple studies assessing children and adolescents with vitiligo. Decision on clothing is also strongly affected by presence of vitiligo, especially on the abdomen and legs.<sup>20,49,52</sup>

Offering cosmetic cover-up or camouflage for children who are psychologically bothered by their lesions may ultimately aid in daily function until therapy is successful.<sup>53</sup> Bleaching is

an option in motivated mature teenagers, but should be discouraged in children and preteens as the psychological implications of total color shift is not known in young children. Psychotherapy can also help children boost their self esteem.<sup>54</sup>

## Current treatment paradigms for vitiligo

A survey of dermatologists published by *Ongena* in 2004<sup>55</sup> suggested that only 36% of Belgian dermatologists offer therapy for vitiligo, that being an improvement over Njoo's cohort of dermatologists in the Netherlands reporting only 16% treated vitiligo in 1999.<sup>56</sup> Since then, therapies have improved dramatically and it cannot be stressed enough that most vitiligo patients can achieve some positive results (ie, repigmentation) using current treatments. Therapeutic choices may be influenced by the paucity of well-designed trials for agents used to treat vitiligo, particularly, trials noting long-term efficacy.<sup>57</sup> The current data on physician attitudes in the United States toward therapy are unavailable, but given the plethora of agents that generate reasonably good repigmentation, there should be virtually no cases of vitiligo in which therapy is not offered. In a recent survey of dermatologists and patients with vitiligo in Saudi Arabia, 69% of dermatologists reported encouragement of therapy to patients. It is unclear if there is a difference in therapy offered based on skin tone, ie, whether Caucasian populations are offered therapy less often than patients of color; however, the above data suggests this is the case.<sup>58</sup>

Current therapies work on a variety of principles, including rescue of damaged pigment cells, quelling of the autoimmune inflammatory process, reduction in oxidative damage, and repigmentation from the hair follicles, borders of lesions, dermal melanocytes or from grafts.

It is important to consider vitiligo an inflammatory dermatosis, although the inflammation is generally not visible to the naked eye. A recent position paper has highlighted that treatment of the silent inflammation and triggers of inflammation in vitiligo should be a priority.<sup>59</sup> This allows the practitioner, patient, and medical insurance carrier to conceptually understand why they are receiving prescriptions for medications and treatments that are otherwise indicated for steroid-responsive dermatoses and atopic dermatitis. Therapies for vitiligo may also involve movement of melanocytes into depigmented skin. The following is a brief review of recent literature pertaining to therapeutic options in children with vitiligo.

## Topical therapies

Tacrolimus is a calcineurin inhibitor,<sup>58</sup> working to block phosphorylation of NF-AT (nuclear factor of activated T-cells) pathway as an antiinflammatory agent. Topical tacrolimus was approved for usage in moderate to severe atopic dermatitis. Tacrolimus is not atrophogenic and can,

therefore, be applied on the face, intertriginous regions, and genitalia, long-term without risk of atrophy. Usage for children with vitiligo has been described in the literature since 2003. The best results are often obtained with application of the medication on lesions of the head and neck. Results are often excellent for focal disease.<sup>59</sup>

A recent clinical trial of a mixture of children, teenagers, and adults comparing topical tacrolimus 0.1% and fluticasone 0.05% for segmental vitiligo indicated that there was only 15% versus 5% repigmentation with these agents at 6 months time.<sup>60</sup> Prior exclusively pediatric data (ages 5 to 15 years old) on topical tacrolimus had demonstrated a good response in segmental disease, suggesting that the medication may work better in children. In the 2004 series by Silverberg et al., 94% of head and neck segmental vitiligo demonstrated some repigmentation. There may be some relationship to racial/ethnic background as many of the segmental vitiligo cases in that series were Hispanic or Latino. Tacrolimus has previously been shown to be more effective in patients with Fitzpatrick Skin Types 3 to 4.<sup>61</sup> In a clinical trial of tacrolimus 0.1% in children versus adults, the authors concluded that children were nine times more likely to get a good response than adults with vitiligo. These authors also noted 76.92% response in segmental vitiligo and 56.25% in acrofacial variants.<sup>62</sup>

Treatment with tacrolimus topically should be initiated as soon as possible, as usage after 5 years of active disease reduces efficacy. This has been confirmed in both American mixed ethnic/racial and Thai cohorts.<sup>50,59</sup> Application of tacrolimus appears to be most effective for lesions of the head and neck. The Vitiligo European Task Force recommends that usage of this agent is for head and neck lesions.<sup>46</sup>

Response of vitiligo on the head and neck is generally superior to that of lesions on the body and extremities. Tacrolimus 0.1% has been shown to be as effective as clobetasol propionate 0.05% for head and neck vitiligo in children (ages 2 to 16 years old), with 58% achieving >50% repigmentation in both groups. On the body clobetasol propionate 0.05% was superior to tacrolimus 0.1% with 39% versus 23% achieving >50% repigmentation of lesions, versus 2.4% spontaneous repigmentation with placebo alone.<sup>63</sup> The addition of calcipotriene 0.005% ointment nightly to a topical corticosteroid regimen can also enhance corticosteroid results.<sup>64</sup> A stable, fixed-combination of betamethasone dipropionate 0.064% and calcipotriene 0.005% has been reported effective as a daily product for facial vitiligo of childhood. Response occurs within three months, but atrophy appears to be a risk with this therapy.<sup>65</sup>

Tacrolimus ointment may be more effective in vitiligo when applied under occlusion; however, the safety of long-term usage in this fashion is not established in young children.<sup>66</sup> Tacrolimus is more likely to produce response in the summer than in the winter (unpublished data). Adjunctively, topical tacrolimus enhances results of excimer laser.<sup>60</sup>

Systemic administration for individuals with allografts has been associated with EBV-associated lymphoma development.<sup>67</sup> Topical tacrolimus has a black box warning regarding avoidance of usage before 2 years of age and theoretical risk of malignancy.

Pimecrolimus 1% cream is a calcineurin inhibitor effective for mild to moderate atopic dermatitis symptoms. Similar to topical tacrolimus, pimecrolimus can be used on sensitive and thin skin without atrophy and bears a black box warning regarding age restrictions and theoretical risks of malignancy.

Pimecrolimus is somewhat beneficial at reducing lesions of vitiligo on the face, achieving results similar to those of a mid-potency topical corticosteroid. A Turkish cohort of children randomized with vitiligo to receive either mometasone 0.1% cream or pimecrolimus 1% cream. At three months, results were 65% and 42% repigmentation, respectively. Pimecrolimus had little to no effect on the body, while mometasone 0.1% cream (a Class IV corticosteroid) effected repigmentation on any part of the body.<sup>68</sup> The Vitiligo European Task Force recommended usage of potent (eg, mometasone) topical corticosteroids rather than super-potent corticosteroids topically for children with vitiligo as the optimal choice of corticosteroid in terms of risk of absorption and atrophy. Regimens that can be used to avoid atrophy with potent corticosteroid usage include application 15 days per month for six months.<sup>46</sup>

Pimecrolimus 1% cream may be significantly more effective when paired with either microdermabrasion preceding the pimecrolimus application or excimer laser adjunctively. A study of sixty-five Iranian children treated three lesions randomizing pimecrolimus 1% cream, pimecrolimus 1% cream with microdermabrasion, and/or microdermabrasion without creams. After three months, more than 50% repigmentation was noted in 32.1%, 60.4%, and 1.7% of lesions, respectively.<sup>69</sup> Excimer laser twice weekly over sites of pimecrolimus application statistically improves the repigmentation.<sup>70</sup>

## Phototherapy and surgical therapies

Grafting is an alternative therapy for individuals with stable vitiligo. Grafting can be done with 1-mm mini-grafts,<sup>71</sup> epidermal cell transplantation from the foreskin,<sup>72</sup> autologous cultured melanocytes<sup>73</sup> or split thickness grafting. Results tend to promote repigmentation with some side effects, such as pebbling, scarring, and mottling of color. Repigmentation appears to take place more rapidly in children under the age of 15 years and with segmental disease.<sup>64</sup> Enhanced results are noted with addition of ultraviolet light to promote melanocyte migration and pigmentation, with excimer laser being the preferred repigmentation modality over Narrowband UVB, due to overall lower exposure to UV light with excimer.<sup>74,75</sup>

Although there are reports of usage of these techniques in children, the long-term safety (eg, risk of skin cancer in the scar) and efficacy (eg, hardness of the pigmentation after three decades) is unknown, but is felt to be good anecdotally.<sup>71,76</sup> Sahni et al. reported on 13 children and adolescents who were transplanted with epidermal suspension grafts in 19 lesions, with >90% repigmentation noted in 79% of lesions at one year and 75% to 90% in the remaining four lesions.<sup>74</sup> Epidermal suspension grafts can be used in stable lesions that have no melanocyte reservoir, such as segmental vitiligo with poliosis or fingertip lesions. Narrowband UVB has been used for more than a decade in children with vitiligo to both stabilize illness (stability achieved in 80% of children at one year of therapy is done twice weekly) as well as effect repigmentation.<sup>77</sup> Another study recommended that treatment be discontinued at 6 months if no improvement is noted.<sup>78</sup> In my experience, a topical therapy can be added to improve results if limited improvement is noted in 3 months. Repigmentation can be sped up by the addition of tacrolimus, but given the black box label, this is undertaken with caution.<sup>79</sup> Alternatively, low potency topical corticosteroids can be used locally to enhance speed of repigmentation and reduce cumulative UVB exposure. Further enhancement of results can be noted in adults with the addition of laser dermabrasion to the sites.<sup>80</sup> This is akin to the enhancement of results when using microdermabrasion in addition to pimecrolimus; however, the usage of laser dermabrasion is not approved in children.<sup>67</sup> The addition of topical calcipotriol in a cohort of adults and adolescents undergoing NB UVB phototherapy were similar with and without the additional calcipotriol, suggesting that this would not be an ideal therapy to add onto narrowband UVB.<sup>81</sup> Calcipotriol has previously been tested as a supplement to the excimer laser and found to similarly not enhance therapeutic response.<sup>82</sup>

Usage of therapies and choice of therapy has to be discussed in concert with parents and in light of potential side effects. Cosmetic notability should be considered in the usage of therapies, particularly since such sites of disease involvement may engender teasing or bullying. Feasibility of therapy in childhood may also play a role, ie, children with complex school schedules would not necessarily be good candidates for frequent in-office therapy.

Early vitiligo and limited disease should be amenable to topical therapies, regimens to include topical tacrolimus/pimecrolimus (especially for head and neck) or topical corticosteroids with or without calcipotriene. Cycling of medications every 6 months ensures limitation of side effects and maximization of potential repigmentation. Usage of adjunctive microdermabrasion, phototherapy (NB UVB), excimer laser or grafting in stable cases (eg, segmental vitiligo that hasn't repigmented or advanced in more than 5 years). Review of general health including assessment of vitamin D status and screening for comorbid autoimmune diseases can improve the patients overall health.

## Conclusions

Vitiligo is a complex autoimmune disorder whose genetic basis and process of autoimmune development is just being understood. Offering therapy to parents and children is essential in the process of disease control and sense of well-being. Choice of therapies is limited with reasonable results. There is no specific test to indicate which therapies are most effective in which patients; therefore, cycling of therapies is advisable.

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