Vitiligo Treatment Update
Review article

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Introduction:

Vitiligo is an acquired, progressive depigmenting disorder of unknown etiology[1], in which melanocytes are selectively destroyed.[2] Vitiligo, is a disfiguring skin disease that affects 1% of the general population[3], mostly between the ages of 10 and 30 years.[4] Recent genetic and epidemiologic studies indicate that vitiligo affects men and women equally. The prevalence in the population is about one in 200.[5]

There are many hypotheses concerning the derivation of the word *vitiligo*. The word may have evolved from the Latin word *vitium*, meaning a defect, or *vitelius* signifying a calf's white patches. Documentation of the use of the word *vitiligo* occurred in the first century AD when the Roman physician Celsus wrote *De Medicina*. Vitiligo is cited in many ancient writings. In the Holy Quran, the word *baras*, meaning white skin, is used to describe a condition that Jesus cured.[6]

Clinical picture:

Vitiligo is a chronic cutaneous disorder characterized by irregular patches of pigment loss. It is characterized by cutaneous white macules that often develop in cosmetically important areas such as the face, the dorsal hands, and the arms.[7] Other sites which may be included are axillae, groin, umbilicus, genitalia, elbows, knees, and areas of trauma. Also the oral mucosa and the retina may be involved.[8] The course is usually progressive with periods of stability.[4] Hairs within patches of vitiligo often remain pigmented, but in older lesions the hairs also become amelanotic.

Trauma to the skin can also result in further depigmentation, i.e. the Koebner phenomenon.[8] Occupational vitiligo can occur too after contact with industrial chemicals such as substituted phenols. Sometimes it is confined to the areas of exposure, but is frequently more extensive, implying systemic exposure. Occupational vitiligo can be indistinguishable from the idiopathic variety.[9] Vitiligo in blacks may have a trichrome appearance i.e. lesions that have a tan zone of varying width between normal and totally depigmented skin, which exhibits an intermediate hue.[10] Some patients may develop inflammatory vitiligo in which there is an erythematous rim at the periphery of a patch of hypopigmented or depigmented skin.[11]

Classification of Vitiligo:

To date, a classification system describing vitiligo as generalized or localized type according to the distribution of lesions has been commonly used: [12]

Localized type (**Figure1**) is subdivided into focal and segmental and mucosal subtypes:

- o Focal - One or more macules in one area but not clearly in a segmental or zosteriform distribution
- o Segmental - One or more macules in a quasi-dermatomal pattern
- o Mucosal - Mucous membrane alone

- Generalized type (**Figure2**) is subdivided into acrofacial, vulgaris and universal subtypes:
  - o Acrofacial - Vitiligo of this type is characterized by depigmentation of the distal fingers and facial orifices - the latter in a circumferential pattern.
  - o Vulgaris - Scattered macules which may include any part of the body.
  - o Universal - This type of vitiligo is characterized by the loss of pigmentation over the entire body, but is rare.
- An overlap of various types is classified as mixed type.

Association:-

- Vitiligo is associated with autoimmune diseases such as autoimmune thyroiditis [13], primary hypothyroidism [14], alopecia areata[15], pernicious anaemia[16], Addison's disease[17], morphoea[18], myasthenia Gravis[19], lichen sclerosus[20], and polyglandular autoimmune endocrinopathy.[21]
- Vitiligo is associated with insulin-dependent diabetes but not with non-insulin-dependent diabetes. This gives further weight to the theory that vitiligo is an autoimmune disease. [22] Several clinical obser-

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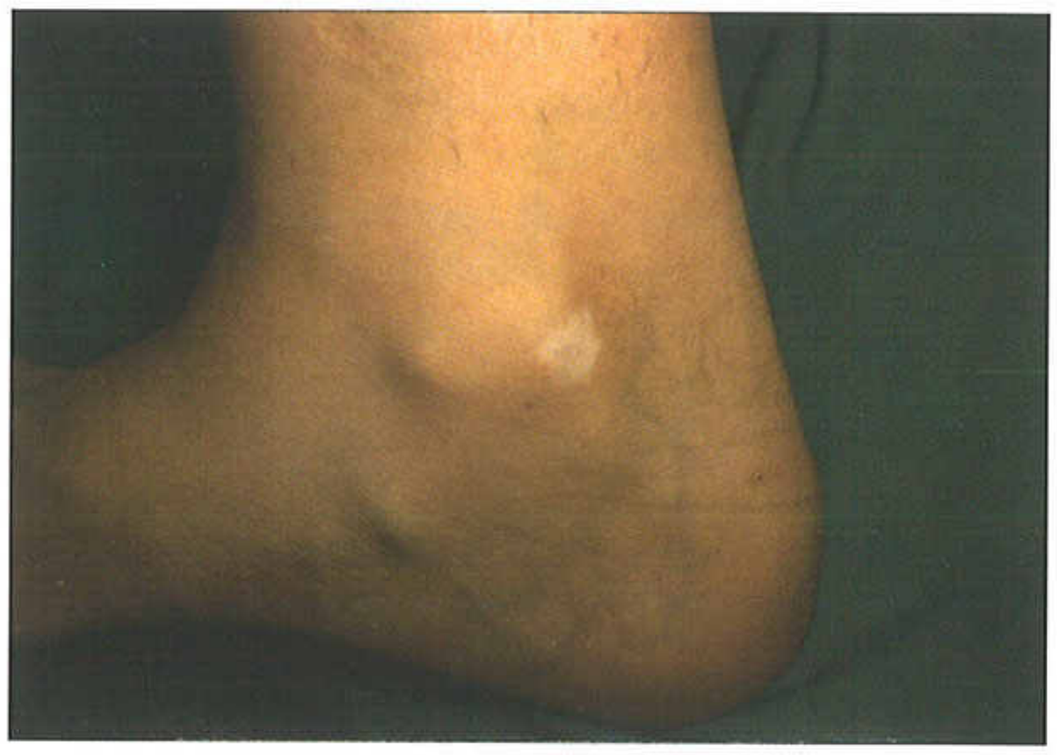

Figure1: *Localized depigmented patch on the foot*

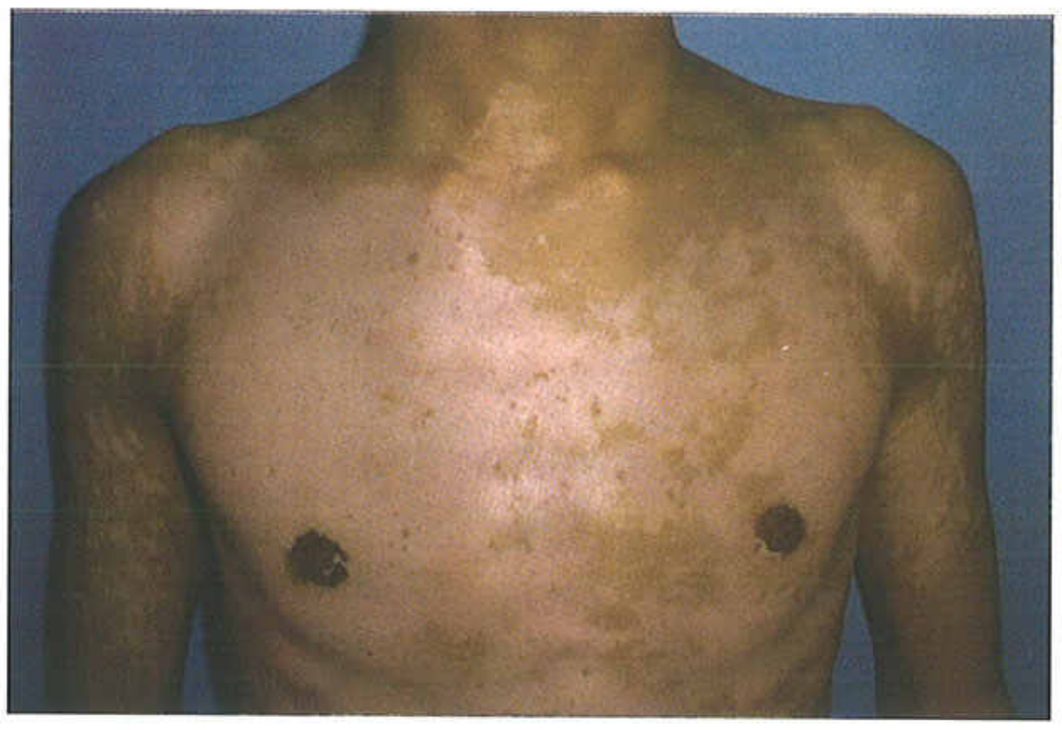

Figure2: *Generalized vitiligo. It is characterized by a bilateral, symmetrical depigmentation with a widespread distribution of many macules in a random pattern.*

vations suggest that there is a link between vitiligo and melanoma. Most patients with melanoma or with vitiligo develop antibodies to similar antigens that are present both on melanocytes and on melanoma cells. These findings support the hypothesis that the clinical link between the two diseases results from immune responses to antigens shared by normal and malignant pigment cells. [23]

Aetiology:

- The destruction of melanocytes is the cause of depigmented maculae that clinically represent the disease vitiligo.
- Although the cause is unknown, various theories such as the autoimmune, autocytotoxic [self-destruction theory], and neural hypotheses have been proposed [6]:
- The autoimmune theory stems from the association with autoimmune disorders, and the finding of antimelanocyte autoantibodies in some individuals. [26] As circulating antibodies and T lymphocytes, which react against melanocyte antigens, are present in the sera of a significant proportion of vitiligo patients compared with healthy individuals. Immunosuppressive therapies which are reasonably effective in treating the condition, well-studied animal models of the disease as well as the association of vitiligo with MHC antigens, all add credence to the hypothesis that immune mechanisms play a role in the development of vitiligo. [24]
- In the self-destruction theory it is proposed that melanocytes destroy themselves due to a defect in the natural protective mechanism that removes toxic melanin precursors[25], or they may be destroyed by surrounding keratinocytes that liberate chemicals that cause oxidative stresses. In normal melanocytes there is some defense or scavenging mechanism against these cytotoxic melanin precursors or chemicals generating oxidative stresses, but there is a defect in this defense mechanism in vitiligo melanocytes. [26]
- In the neuronal theory, it is suggested that dermal nerve endings release a chemical, which is toxic to the melanocytes[27], and destroys the melanocytes or inhibits the production of melanin pigments.

Due to the observed variation in clinical manifestations of the disease, it seems likely that the etiology of vitiligo may differ among patients. Therefore several theories on vitiligo etiopathogenesis have been combined to formulate a convergence theory for vitiligo. Stress, accumulation of toxic compounds, infection, autoimmunity, mutations, altered cellular environment and impaired melanocyte migration and/or proliferation can all contribute to vitiligo etiopathogenesis in varying proportions.28 It is likely that the loss of epidermal and follicular melanocytes in vitiligo may be the result of several different pathogenetic mechanisms. [29]

Familial cases of vitiligo are common and a family history is found in 6-38% of cases. [30] Abnormalities of the C4B gene and certain HLA associations may be risk factors for vitiligo[31-32]Of 131 patients with

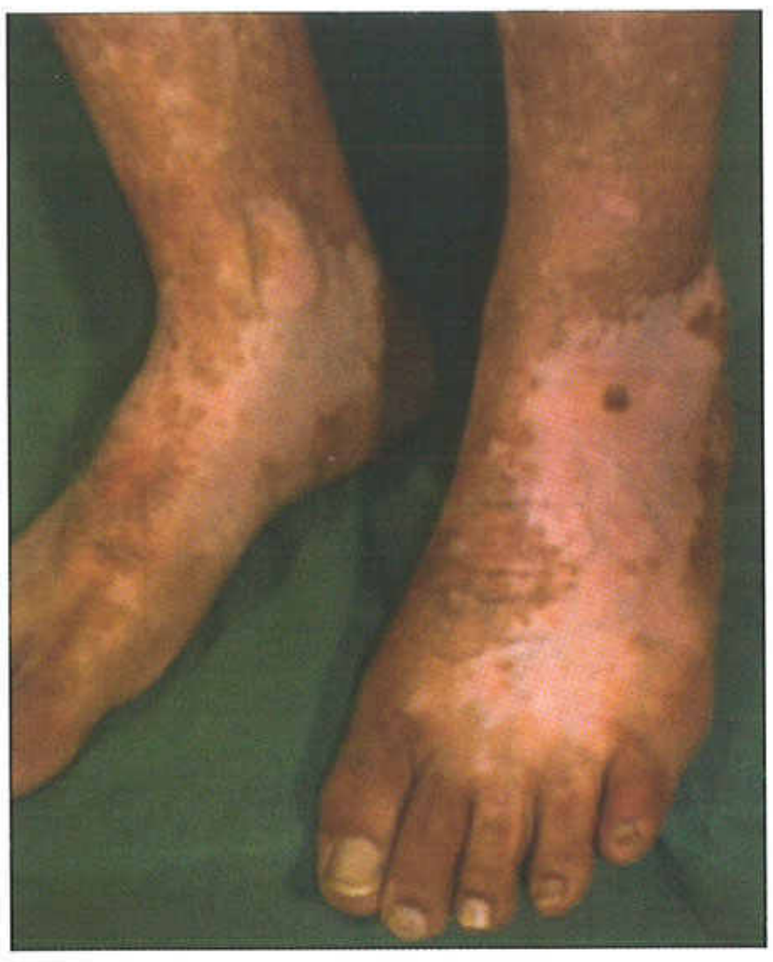

Figure3: *Erythema with areas of repigmentation during PUVA therapy*

non-segmental vitiligo studied, [29] (22%) had a family history of this disorder. The clinical features and HLA antigens were assessed, and a comparison made between patients with familial and those with non-familial, non-segmental vitiligo. Familial patients developed skin lesions significantly earlier than non-familial patients. There was a significant association between HLA-B46 and familial non-segmental vitiligo, whereas HLA-A31 and CW4 were found in non-familial patients. The differences in clinical features and HLA phenotypes suggest heterogeneity in the pathogenic process between familial and non-familial vitiligo patients. [33]

Treatment:

Despite the inherent difficulties in stimulating melanocytes to repigment vitiliginous lesions, a variety of medical, surgical, and adjunctive/alternative therapies benefit innumerable patients with vitiligo. These treatments may be used as monotherapies or combination therapies to achieve optimal results.[34] Although there is as yet no definitive cure, many patients have obtained respectable repigmentation by the use of topical or oral psoralen plus ultraviolet light. When large areas of skin are involved or when the patient is unresponsive to therapy, serious consideration should be given to depigmentation therapy.[7]

The various medical therapeutic options available today are able to give 60-90% results either singly or in combination. They can be broadly divided as seen in table 1:

Phototherapy:

- **PUVA Photochemotherapy:**

Performing photochemotherapy with a topical or systemic psoralen was the main method of repigmenting vitiliginous skin lesions.[35]

Historically, photochemotherapy of vitiligo can be traced back as far as 3000 B.C. in Egypt and India.[36] Modern photochemotherapy of vitiligo with psoralen and ultraviolet A (PUVA) was introduced in 1948 by El Mofty in Egypt.[37]He showed that 8-methoxypsoralen [8-MOP], Oxsoralen isolated from the powder of Ammi majus Linnaeus is effective in the treatment of vitiligo. A high energy UVA long-wave lamp was developed and found to be effective in introducing new melanin pigmentation in 1974. The combination of this high energy UVA lamp and oral or topical 8-MOP has been applied for the treatment of vitiligo.[38] A number of adverse reactions are associated with this drug. These include gastrointestinal side effects, such as nausea and vomiting. Other adverse effects include pruritus and erythema (**Figure3**). Skin cancer has been reported infrequently as a consequence of PUVA therapy for vitiligo.[39] For phototherapy of vitiligo, use of 5-methoxypsoralen (5-MOP) can replace 8-MOP. The incidence and severity of adverse events such as nausea and vomiting, pruritus, and erythema is 2 to 11 times more frequent with 8-MOP than with 5-MOP. Contraindications for the use of 5-MOP are similar to those for 8-MOP, including renal or hepatic disease, photosensitive skin diseases, cataracts, glaucoma, and skin cancer. It is also contraindicated for infants, pregnant women, and lactating mothers.[40]

Mechanism of PUVA therapy:

The reservoir for melanocytes that migrate into the depigmented skin comes from contiguous pigmented skin (melanocytes migrate about 2 to 3 mm into the depigmented skin) and from the hair follicle, the most important reservoir. Because of the absence of reservoirs, hair-bearing skin such as that on the forearms or legs in which the terminal (not vellus) hairs are totally depigmented are less likely to respond to medical treatments, as is glabrous skin such as that

on the palms, fingertips, and dorsum of the feet.[41] It has been determined that this repigmentation occurs through the action of immune cytokines and inflammatory mediators released in the skin, particularly by keratinocytes, as a consequence of PUVA therapy.[42] These cytokines and mediators act as signals for melanocyte migration from the hair follicles.

Topical PUVA:

For patients with limited vitiligo, topical PUVAsol (topical PUVA + sunlight) remains a popular, practical, and efficacious therapeutic option. This regimen, used extensively with children and adults who have limited vitiligo.[35] In brief, 1% methoxsalen lotion (Oxsoralen) is diluted to a concentration of 0.001%. Patients are instructed to apply a thin film of the diluted lotion to affected areas and, after 30 minutes, to expose themselves to titrating doses (5-30 minutes) of sunlight.

Oral PUVA:

A single dose of 0.6 mg/kg of 8-methoxypsoralen taken 2 hours before exposure to artificial fluorescent UVA lamps (315 - 400 nm). Two or three times a week. Re-pigmentation may occur gradually in a perifollicular fashion, although sometimes it may develop over the whole area. If there is no response within 3 months, treatment should be stopped; otherwise treatment may be continued for a year or so as the pigmentation gradually expands; marked repigmentation occurs in up to 30% of patients. Relapse may then begin in up to 75% within 1-2 years.[39]

For oral PUVA to be successful in the treatment of vitiligo, the following requirements must be fulfilled:

1) Patients must be well informed about the different aspects of PUVA treatment, particularly length of therapy, side effects, and chances for success.
2) Only reliable and highly motivated patients should be treated with PUVA.
3) Close supervision by the treating physician is indispensable; this entails accurate and detailed documentation of all aspects of treatment.[43]

There is no correlation between improvement and with the extent of involvement at initiation of therapy, duration of vitiligo, skin phototype, age or sex of the patient. It also appears that the extent of repigmentation was not influenced by disease stability, use of adjuvant topical corticosteroids, or a positive family history of vitiligo.[39] The single most important factor in determining the response of vitiligo to PUVA therapy is the total number of treatments.[40] The recommended upper limit for the total number of treatments is 100-150, with a cumulative dose of 1000-1500 J/cm2 for white-skinned individuals.[41] If nausea, pruritus or erythema are problematic, 5-methoxy-psoralen (dose 1.2 mg/kg) may be used; it has fewer side-effects and gives a similar chance of repigmentation.[43]

- **Narrow-band UVB (311 nm) phototherapy:**
  Treating 78 patients with vitiligo twice weekly, Westerhof and Nievweboer[44] were the first to compare the efficacy of topical psoralen photochemo-therapy with that of NB-UVB (311 nm) phototherapy. In patients with extensive, generalized vitiligo, 311-nm UV-B therapy was more effective (67% response rate) than topical UV-A therapy (46% response rate). NB-UVB phototherapy offers several advantages over systemic psoralen photochemotherapy (psoralen + ultraviolet A [PUVA]), including ease of treatment, lack of need for post-treatment ocular protection, lack of side effects (eg, nausea, headaches) related to use of oral methoxsalen, and minimal phototoxic reactions. Furthermore, NB-UVB phototherapy can be used to treat young children who have extensive, progressive vitiligo. Disadvantages include the need for more treatments for maximal efficacy (3/wk for NB-UVB phototherapy vs. 2/wk for PUVA) and the lack of data concerning any possible long-term carcinogenic effects of NB-UVB phototherapy.[35] The mechanism whereby UV-B therapy repigments vitiligo is probably related to release of cytokines and inflammatory mediators in the skin that stimulate melanocyte migration and proliferation.[45] Some areas responded better than others. The face and neck showed the best results, whereas the trunk and proximal extremities had moderate repigmentation. In contrast, acral sites (fingers, feet) and areas of bony prominences and lower hair growth density (wrists, ankles, and joints) hardly repigmented.[46] Potential limitations of narrow-band UVB phototherapy are the scheduling difficulties and time commitment.[47] Narrow-band UVB therapy should not be applied longer than 12 months in children. If, no response is observed after 6 months, further therapy should

be discouraged. If in responding cases, parents or patients insist on continuing treatment after 1 year, only limited areas should be exposed to narrow-band UVB radiation.[46]

- **Khellin and UVA Therapy (KUVA):**
  Khellin, a furanochromone is being used for the treatment of vitiligo. Khellin and UVA have been reported to be as effective as PUVA in the treatment of vitiligo.[48] KUVA reportedly does not lead to the phototoxic erythema seen with PUVA. According to Ortel et al[49] 41% of their patients who received 100 to 200 treatments with KUVA obtained 70% or more repigmentation of their hypopigmented macules. An unexpected complication of the KUVA therapy was a temporary increase in transaminase levels in one-third of their study patients.
- **Topical application of pseudocatalase and calcium in combination with short-term UVB exposure:**
  The involved epidermis in vitiligo patient produces hydrogen peroxide due to increased monoamine oxidase A activity, where catalase is inactivated. In addition, calcium homeostasis is perturbed in the affected skin.[47] The substitution for insufficient catalase by pseudocatalase together with calcium and UVB exposure leads to effective repigmentation. Schallreuter et al[50], reported successful treatment of vitiligo depigmentation with topical application of pseudocatalase and calcium followed by short-term UVB light exposure. According to their study, repigmentation occurred in the majority of cases after 2 to 4 months treatment. Complete repigmentation of face and dorsum of hands appeared in as many as 90% of the treated group. In all patients, active depigmentation was arrested. None of the patients developed new lesions during treatment. No recurrence of the disease was observed during 2-year follow up. Schallreuter et al[51], showed rapid initiation of repigmentation in vitiligo with Dead Sea climatotherapy in combination with pseudocatalase. The results of this study show a significantly faster initiation of repigmentation in vitiligo after a combination of short-term climatotherapy (21 days) at the Dead Sea in combination with a pseudocatalase cream (PC-KUS) compared to either conventional climatotherapy at the Dead Sea alone or with placebo cream in combination with climatotherapy. This combined therapy is significantly faster in repigmentation than narrowband UVB activated pseudocatalase cream (PC-KUS) treatment alone. The results of this study support the necessity of epidermal H_2O_2 removal as well as the influence of solar UV-light in the successful treatment of vitiligo.
- **Phenylalanine and UVA Therapy:**
  L-Phenylalanine is a precursor of tyrosine, a substrate for melanin synthesis in the presence of tyrosinase. Cormane et al[52] reported a complete to partial response in 26.3% and partial to minimal response in 68.4%. Contraindications to this therapy include phenylketonuria, impaired liver and kidney function, malignant skin diseases, pregnancy, breast-feeding, history of using arsenates, radiotherapy, and autoimmune disorder.
- **The 308-nm xenon-chloride excimer laser:**
  On the basis of data that support narrowband UVB phototherapy as an efficacious and safe treatment modality for vitiligo, Spencer et al[53], embarked on a study of targeted phototherapy using a single-wavelength 308-nm UVB laser to treat focal areas of vitiligo. When compared with standard phototherapy, the 308-nm xenon-chloride excimer laser has the advantage of having increased precision and the ability to deliver higher energy fluencies to the target tissue in less time. It is possible that UVB radiation delivered in the form of laser light has a different light-tissue interaction, which may increase efficacy. A limitation of this therapy is that the laser has a 2 ∞ 2-cm spot size, making total-body treatments difficult. Targeted phototherapy with the 308-nm excimer laser delivers UV radiation to only the affected area. Uninvolved skin is not exposed. This limits total skin exposure to UV radiation and therefore may decrease the risk of skin cancer. Furthermore, if indeed the laser provides a faster therapeutic effect and fewer total treatments are necessary, it also limits cumulative exposure to UV radiation.

Calcipotriol:

Recent advances in the pathophysiology of vitiligo have demonstrated defective calcium homeostasis in depigmented skin. 1, 25-Dihydroxyvitamin D3 may be involved in the regulation of melanin synthesis, and receptors for 1, 25-dihydroxyvitamin D3 have been

demonstrated on melanocytes.[54]Also, development of hyperpigmentation in patients with psoriasis receiving treatment with PUVA and calcipotriol has been observed.[55] Twenty-one patients age 5 to 17 years with vitiligo were enrolled in a study by Parsad et al.[55] The children were advised to apply calcipotriol 50 microg/g in the evening and expose themselves to sunlight the next day for 10 to 15 minutes. Initial repigmentation occurred in the majority of children after 6 to 12 weeks of treatment. Marked to complete repigmentation was seen in 10 of 18 patients. The repigmentation was cosmetically excellent in the majority of children. All patients tolerated the calcipotriol well except for three patients who complained of mild irritation on application. A study by Ameen et al[54], about Topical calcipotriol as monotherapy and in combination with psoralen plus ultraviolet A in the treatment of vitiligo, showed that Topical calcipotriol appears to be an effective and well-tolerated treatment for vitiligo and can be safely used in conjunction with PUVA.[54] Twenty-one patients with vitiligo refractory to previous PUVA therapy were studied.[56] Patients received 60 sessions of PUVA 3 times a week and 0.005% topical calcipotriol twice daily. Patients were monitored for repigmentation overall and on the trunk, extremities, and acral regions. Starting at the median of the 17th treatment session, some degree of repigmentation was observed in 71.5% of the patients. After treatment, cosmetically acceptable overall repigmentation was observed in 29% of patients; repigmentation of lesions on the trunk, extremities, and acral region was noted in 36%, 58%, and 0% of patients, respectively. Adverse reactions were mild and tolerable. All responses were observed within the first 30 sessions (median 17 sessions). This finding indicates that the combination of PUVA with calcipotriol may shorten the duration of UVA exposure, leading to decreases in the dose-dependent side effects typically associated with PUVA treatment.

Corticosteroids:

Topical, intralesional, intramuscular, and oral steroids have been used with varying results.

- **Topical steroids** are used to repigment vitiliginous lesions. Corticosteroid preparations probably alter aberrant immunologic responses among patients with vitiligo.[35] Topical steroids are most useful on small patches of recent onset. A potent topical agent such as 0.1% betamethasone valerate (Betnovate) may be used on the face, and a superpotent agent such as 0.05% clobetasol propionate (Dermovate) on the body.[39] A study by Westerhof et al.[57] demonstrating that a combination of fluticasone propionate (FP) and UVA was three times more effective than either UVA or FP treatment alone has re enforced the belief in the use of sunlight as a adjunct to topical steroids. Topical steroid side effects include atrophy, telangiectasia, hypertrichosis, and steroid acne. In light of such side effects, particularly with high-potency or class I steroids, preparations should be used for 1 or 2 months and then stopped for 1 month or tapered to a low-potency preparation. Topical retinoids and steroid preparations can be used in combination to minimize atrophy.[35]
- **Intralesional tniamcinolone acetonide** given for 5 weeks produced 90% repigmentation in 30 of 52 depigmented macules, but caused skin atrophy in 26 of 52 macules treated.[58]
- Imamura et a1[59] reported successful treatment of vitiligo with **oral corticosteroids**. For adults, vitiligo is often stabilized with a series of up to 3 injections of triamcinolone acetonide 40 mg (1 injection every 4 to 6 weeks). Prolonged use of systemic steroids is associated with weight gain, fluid retention, and other side effects. Hence, long-term use of steroids is not indicated for patients with vitiligo.[35]

Oral dexamethasone pulse treatment for vitiligo were given for a maximum of 24 weeks.[60] A weekly pulse consisted of 10 mg dexamethasone taken as a single oral dose after breakfast on 2 consecutive days followed by 5 days without treatment. Side effects were common. Twenty patients (69%) reported one or more side effects such as weight gain, insomnia, acne, agitation, menstrual disturbance, and hypertrichosis. In general, these side effects were mild to moderate and completely subsided after discontinuation of therapy. Findings indicate that oral corticosteroid pulse therapy for vitiligo is an effective means to arrest active disease; however, it only has low potential to induce substantial repigmentation when given for a period of up to 24 weeks. Oral dexamethasone pulse treatment is effective in arresting progression of vitiligo but has a limited capacity to induce cosmetically acceptable repigmentation when given as monotherapy.

- Oral administration of a **sex steroid-thyroid hormone** (Metharmon-F) was tried as an alternative therapy to systemic corticosteroids for the treatment of vitiligo.[61] This treatment modality, al-

though based upon only four Japanese cases, showed the development of repigmentation of vitiligo skin with increased numbers of melanocytes and melanin granules in the keratinocytes.

Immunomodulators

- **Topical tacrolimus and pimecrolimus (New option for vitiligo treatment):** Tacrolimus inhibits T-cell activation by down-regulating the transcription of genes encoding proinflammatory cytokines, namely interleukins (IL) IL-2, IL-3, IL-4, IL-5; interferon gamma; tumor necrosis factor α; and granulocyte-macrophage colony-stimulating factor in T cells.[62] The efficacy of twice-daily application of topical tacrolimus in 6 patients with generalized vitiligo involving less than 20% body surface area was evaluated.[63] Various degrees of repigmentation were achieved in all patients: excellent in 1 patient, moderate in 4 patients, and mild in 1 patient. Minimal burning and stinging of the skin occurred in all our patients at the initiation of treatment with tacrolimus ointment. No cutaneous atrophy even in the thin areas of skin was encountered. Tacrolimus ointment was also well tolerated in the periocular areas. Tacrolimus ointment may be a rapidly efficacious and safe option for the treatment of vitiligo. The ease of topical self-administration with minimal side effects makes this novel immunomodulatory agent a promising addition to the therapeutic armamentarium for vitiligo.[63]

  A topical immunomoduIatoin pimecrolimus cream 1 % also shows promise. This cream formulation may be more cosmetically acceptable for some patients.[35]

- **Levamisole:** The efficacy of levamisole which acts as an immunomodulator has been studied for treating vitiligo, and it seems to be a safe and fairly effective modality for vitiligo patients who have limited and slow-spreading disease.[64]

Vitamin supplementation:

Juhlin and Olsson, [65] performed a 2-year study to test the hypothesis that folic acid, vitamin B12, and sun exposure could be helpful in treating vitiligo. A total of 100 patients were treated with oral folic acid, 5 mg twice a day, and vitamin B12, 1 mg twice a day, after being informed that sun exposure might enhance repigmentation and were asked to keep a record of sun exposure in summer and UVB irradiation in winter. Repigmentation was most evident on sun-exposed areas, and progression of the vitiligo stopped in 64% of the patients. Complete repigmentation was seen in 6 patients, and 52 patients improved. The authors found that folic acid and vitamin B12 supplementation combined with sun exposure can induce repigmentation better than either the vitamins or sun exposure alone. Treatment should continue as long as the white areas continue to repigment.

Depigmentation therapy:

Depigmentation therapy is a treatment option for patients with widespread, treatment-resistant vitiligo. The most commonly employed technique is the application of monobenzylether of hydroquinone (MBEH), also known as monobenzone, to areas with residual pigment. Prior to instituting therapy, the patient must be aware of the cost, treatment time course, risk of distant sites of depigmentation, probable permanency of depigmentation, side effects such as contact dermatitis, and the potential for repigmentation via follicular melanocytes. The social ramifications of depigmentation therapy also must be discussed, especially for patients with skin types IV and V.[66]

The sequential use of 4-methoxyphenol and Q-switched ruby laser also has been reported as a successful form of depigmentation therapy.[67] On the basis of the findings of this study Njoo et al concluded that depigmentation therapy using a 4-MP cream and/or QSR laser is an effective and safe method to remove disfiguring residual pigment in patients with vitiligo universalis. This combined therapy takes into account patients' preferences for the most convenient treatment. However, even after total depigmentation has been achieved, patients should be warned that perifollicular repigmentation may occur, especially on sun-exposed areas.

Because of the relatively high sensitivity of melanocytes to cryotherapy and the possibility of isomorphic phenomenon in vitiligo patients, removal of the remaining normally pigmented patches was attempted in patients with universal vitiligo using cryotherapy. In a study by Mohammed R A[68], all pigmented areas were treated to 1-3 sessions of cryotherapy using a closed contact CO_2 cryogun, with 4-6-week intervals. Complete and permanent depigmentation was achieved in all five patients with excellent cosmetic results and no complications or scarring. He concluded that Cryotherapy is a cost effective, non-complicating, easily

available procedure, which can be used for depigmentation of normally pigmented patches in patients with universal vitiligo. [68]

Surgical treatment:

The criteria for the selection of cases for Surgery are summarized in table 2:

Surgical treatment is contraindicated in patients with active vitiligo, where the existing lesions are increasing in size, and/or where there is a development of new lesions, as Koebnerization following surgical treatment is well known in such cases. Before undertaking any surgical method it is essential to perform a minigrafting test. To select stable vitiligo patients, a careful history and long-term evaluation of vitiligo activity is necessary before any surgical treatment is attempted.[69]

Several surgical modalities have been reported for treating stable patches of vitiligo:

- **Epidermal tissue grafts:**

  - **Epidermal suction blister grafts**: Falabella et al[70] were the first to report the application of epidermal blister grafts in the treatment of achromic and granulating areas. Separation of a viable donor epidermis from dermis can be accomplished through the production of suction blisters at 200 mm Hg negative pressure in 3 to 4 hours. The medial aspect of the arm or forearm, the buttock, and the medial aspect of the thigh are some of the preferred donor sites. The mechanical split created is exactly at the dermoepidermal junction, so grafts are purely epidermal and very thin.[71] Pigmented epidermis is harvested by this technique and is used to cover achromic areas in the recipient that have been prepared by denuding them with liquid nitrogen blisters or dermabrasion.[72] Although liquid nitrogen is more convenient than the suction pump at recipient sites, it can cause inflammation and subsequent hypertrophic scarring with postinflammatory hyperpigmentation.[73] Repigmentation can be seen in 1 to 2 weeks, and total repigmentation can occur within 1 to 3 months. An advantage of suction-blister grafts is that scarring is minimal.[6] Epidermal grafting by suction has proven to be an easy, safe, inexpensive, and effective treatment modality for stable localized vitiligo.[69] A disadvantage is that there may be achromic fissures between grafts in the recipient areas and that this technique is time consuming. It requires a minimum of 90 minutes for separation of the epidermis.[69] Hatchome, et al[73] treated 18 patients with vitiligo by means of epidermal grafting with the roof of a suction blister. Repigmentation appeared successfully in all patients, but no pigmentation could be achieved at recipient sites in 4 patients with generalized vitiligo in whom the Koebner phenomenon occurred at donor sites. Skouge and Morison[74] reported that a patient with progressive vitiligo was successfully treated with epidermal autograft in combination with PUVA therapy. They also reported that epidermal grafting combined with PUVA treatment for progressive vitiligo is effective and is not associated with the Koebner phenomenon in donor sites. Keun et al[75] evaluated the effectiveness and safety of a suction epidermal grafting method after the removal of the epidermis by the use of the Ultrapulse CO_2 laser with a computerized pattern generator. Eleven patients with 34 lesions of refractory stable vitiligo were studied. Of the 34 lesion sites, excellent repigmentation was seen in 30 and the other 4 had good repigmentation. No complications occurred. So they Concluded That Ultrapulse CO_2 laser is particularly well suited for deepithelialization in vitiligo surgery.

  - **Thin Thiersch's Split-thickness grafts**: Thiersch was the first to use larger sheets of split' thickness skin grafts in 1886, for treating patients with cutaneous defects.[76] Behl in 1964 first reported the use of thin Thiersch's skin grafts to treat stable vitiligo.[77] Thin split-thickness Thiersch grafts obtained using a scalpel or dermatome are emplaced on recipient sites prepared by a process similar to dermabrasion. Recently, the use of the mechanical dermatome to harvest thin split-thickness grafts has shown excellent results. This is the best method to cover multiple lesions and large areas at one time, especially over the extremities, giving immediate results. Split-thickness grafts are not suitable for depigmentation caused by burns, as they may result in hypertrophic and hyperpigmented scars.[78] Ozdemir et al[79] compared the efficacy and side-effects of two surgical methods (suction blister

vs. thin split-thickness graft technique) for the treatment of vitiligo. Repigmentation rates were 25-65% in the suction blister technique and 90% in the thin split-thickness graft technique. They concluded that the thin split-thickness graft technique is superior to the suction blister technique in treating vitiligo.

- **Miniature full-thickness punch grafts**: The actual technique involves the harvesting of 1.2- to 2.0-mm punch grafts from the pigmented donor site, usually areas on the lower back below the waistline. These punch grafts can be harvested virtually next to each other. An area 2 by 2 cm can yield as many as 100 minigrafts. The grafts are emplaced 3 to 4 mm apart on the recipient site that has been prepared by defects made with the same-sized punch. The grafts are embedded by manual compression with saline-soaked gauze and are held in place by cover strips, which are removed after 7 days. After autologous minigrafting, PUVA therapy can hasten the repigmentation process. A test to assess the therapeutic effect is essential before undertaking the surgical procedure. Five to ten autologous minigrafts are implanted into the achromic area. If these implanted grafts repigment and signs of pigment spread are seen within 3-4 months, activity is ruled out and the stable nature of the vitiligo is confirmed. On the other hand, if the implanted grafts do not show any sign of pigment spread or they themselves become depigmented, it indicates that vitiligo is still active and no surgical intervention should be undertaken.[76] Histological studies have shown that the pigmentation that develops around either epidermal or punch grafts has normal melanin content and consists of functional melanocytes.[80] With full-thickness grafts, a larger number of melanocytes are available for transplantation as compared to epidermal or split-thickness grafts. This seems to be the best method to start with for a beginner.

- **Cellular grafts:**
  - **Transplantation of Autologous Cultured Melanocytes:**
    This technique involves harvesting melanocytes from a shave biopsy of the normally pigmented skin of the patient and expansion of the melanocyte population by cell culture. The cultured cells are transplanted into vitiliginous skin. Lerner et al[81] first introduced this technique. They reported a technique of autologous cultured melanocyte grafting that involves selectively growing melanocytes in 12-O tetradecanoyl-phorbol-13-acetate (TPA), cholera toxin, and isobutylmethyl xanthine. The melanocytes were cultured for 1 month and then injected into suction blisters produced on lesional skin. Puri et al[82] noted that unlike normal melanocytes, melanocytes from patients with vitiligo did not grow well in media containing TPA. TPA is also a potent tumor promoter and therefore poses long-term risks.[83] Chen et al[84] had studied the growth regulation of melanocytes in vitro and found that basic fibroblast growth factor can be a substitute for TPA. It is a safe natural substance and causes a significantly greater increase in cell growth than TPA. Many melanocytes can be obtained with the use of this modified culture medium, enabling transplantation to larger areas than are possible with epidermal grafting methods. They used the CO_2 laser to rapidly create an uncomplicated superficial epidermal ablation, which appears to be a fertile growth surface for transplanted melanocytes. CO_2 laser abrasion can create a more homogeneous dermabrasion than traditional dermabrasion procedures even in an uneven skin surface. Clinical repigmentation gradually took place within 4 weeks after each treatment. After 6 months, the treated areas had acquired a color similar to the surrounding skin, and this appearance remained unchanged at 10 months' follow-up. The repigmented portion amounted to 95% of the total treated areas. Although the culture of melanocytes is time-consuming, the encouraging results obtained indicate that the procedure can be a valuable treatment for large segmental vitiligo.[84]
  - **Transplantation of Autologous Melanocyte and Keratinocyte Co-cultures:** Melanocytes can be cultured in the presence of keratinocytes, and such cultures can be used to repigment areas of vitiligo. After confluence and differen-

tiation of the culture is reached in about 21 days, the sheet of cells is detached from the culture flask, transferred to a layer of petrolatum gauze, and grafted onto recipient sites previously denuded with liquid nitrogen. With subsequent pigment spread, satisfactory repigmentation and color match have been achieved. Although only primary cultures have been used for grafting, each of these cultures yielded a sheet of cells that was estimated to be 10 times the size of the original donor specimen. Olsson et al[85] collected 100 patients with vitiligo who were treated by transplantation of cultured autologous melanocytes to the depigmented areas, after removal of the epidermis at the recipient site by dermabrasion. The repigmented portion of the total treated area reached to 95% to 100% in 40 patients, 65% to 94% in 32, 20% to 64% in 22, and 0% to 19% in 6. It was more difficult to achieve complete repigmentation on the acral parts of fingers, elbows, and knees after 6 to 8 months posttransplantation. No scarring or other side effects occurred. The donor site had repigmented after 3 to 6 months in all but 2 patients. They indicated that, whereas the method is timeconsuming, the procedure would be valuable in motivated patients, when the extent of their vitiligo does not exceed 30% of the total body area, and when the areas of their treatment are not actively extending.

- **Camouflage Tattooing (Micropigmentation):**

Halder et al were the first to apply tattooing for treatment of vitiligo using nonallergenic iron oxide pigments.[86] Tattooing or Micropigmentation is one of the surgical methods used to treat stable vitiligo by permanent camouflage. Tattooing or micropigmentation is defined as uniform implantation of minute inert pigment granules into the dermis so as to artistically create a permanent cosmetic camouflage.[87] The sites referred for tattooing are lips, eyebrows, hands, fingers feet and toes. However, any part of the body (including elbows, knees, breasts and penis) can be treated by micropigmentation, when the patient is psychologically in need of a dramatic response. The initial result is impressive but subsequent fading and colour mismatch are the main drawbacks. Mahajan, et al[88] selected thirty patients with localised stable vitiligo for cosmetic tattooing. Of them, 19 cases (63.3%) had skin patches, 9 cases (30%) had mucosal patches, and 2 cases (6.7%) had both skin and mucosal involvement. After complete clinical evaluation, cosmetic tattooing was performed on these patients, and they were followed up for 6 months. As results, 23 cases (76.7%) had excellent color matching, 2 cases (6.7%) had good color matching, and 5 cases (16.6%) had pigment shedding. Excellent results were seen in all mucosal patches. Dark complexion cases showed better results than fair complexion ones. The most common complication of tattooing of the lips is herpes simplex infection. This infection can be prevented by prophylactic treatment with acyclovir.

Suga et al[89] used DHA which is a well-known cosmetic tanning product whose active ingredients cause the skin to turn brown by polymerizing the amino acids and amino groups in the skin to treat the depigmented areas of skin in 10 patients with segmental vitiligo or piebaldism. A sponge swab was used to apply the solution to the depigmented areas while avoiding streaking and contact with the eyes and mouth. The desired results normally appeared after a reaction time of approximately 6 hours. The benefit of using DHA lotion is that the resulting pigmentation cannot either be rubbed off on clothes or be removed by washing and remains for about 3 to 4 days. After 5 to 6 days the color gradually fades with the shedding of the skin surface because most of the chemical activity of DHA is confined to the dead outer layer of the stratum corneum. To obtain homogeneous and desirable brown coloration in the affected areas, we recommended additional application of the lotion on the second day after the initial application. To avoid the reaction of DHA with other substances, the patients were asked to avoid using any other topical application on the lesion. Seven of the 10 patients were moderately satisfied with the results of the treatment. However, 3 of the patients treated were unsatisfied with the results, claiming that the affected areas were not homogeneous with the surrounding skin. No patients reported contact dermatitis. A tanning product like the one mentioned can provide a safe and reasonable means for the cosmetically conscious patient to mask some of the disfiguration caused by segmented vitiligo or piebaldism.

- **Excision:**
  Small macules of vitiligo involving body folds, scrotum, or labia can be easily excised, as ample loose skin is available for wound closure. [69]

Conclusion:

The treatment ofPlate 3. Almost complete resolution of vitiligo lesion.Figure 4. Patient with moderate improvement vitiligo has improved during the last decade. However, the therapy is still not satisfying for many patients, which may due to the fact that the aetiopathogenesis is unknown. Several treatment modalities, such as PUVA, UVB and local corticosteroids are currently used in the treatment of active vitiligo. These treatments usually induce incomplete repigmentation. Because these treatments are slow or ineffective in some patients, and usually induce incomplete repigmentation, various surgical treatments have been tried, which intended to repigment vitiligo if patients have stable disease. Two types of surgical techniques are available: tissue grafts and cellular grafts. Tissue grafts are full-thickness punch grafts, split-thickness grafts and suction blister grafts. With tissue grafts, only a limited surface area can be treated but with good results in the majority of cases. Cellular grafts include non-cultured keratinocytes/melanocytes and cultured melanocytes. Starting from autologous cellular suspensions, epithelial grafts of various compositions can be cultured in vitro. They can be used for larger areas. A new and novel therapeutic option for the treatment of vitiligo is the use of topical tacrolimus and pimecrolimus, the immunomodulator drugs, which proved to be safe and effective.

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Table 1: Therapeutic options for vitiligo

1- Medical repigmentation Therapy.

- Topical medical repigmentation therapy includes:
  - Topical PUVA
  - Steroids
  - 5-Fluorouracil
  - Placental extract
  - Minoxidil with UVB
  - Melagenina
  - Coal tar
  - Pseudocatalase and calcium with UVB
  - Sunscreens
- Systemic medical repigmentation therapy includes:
  - Psoralens
  - Corticosteroids
  - Khellin
  - Phenylalanine
  - Placental extract
  - Nutritional agents
  - Immunomodulators

2- Medical depigmentation Therapy:

- Applying a 20% cream of monobenzylether of hydroquinone

3- Surgical management:

- Autologous punch grafts
- Autologous epidermal grafts
- Autalogous melanocyte grafts
- Thiersch grafts
- Micropigmentation, (tattooing)
- Dermabrasion / 5-fluorouracil

Table 2: Criteria for the Selection of Cases for Surgery

- No signs of activity = stable vitiligo
  - Size of the macule or patch should be stationary for more than 3 years
  - No recent development of new lesions
- Minigrafting test is negative for activity
- Lesions are refractory to medical treatment
- Stable segmental vitiligo with leukotrichia
- Skin over the lesion should not be thickened / lichenified

Source: Mutalik S, Ginzburg A. Surgical Management of Stable Vitiligo: A Review with Personal Experience. Derm Surg2000; 26(3): 248-254.