Vitiligo is an acquired depigmented disorder of the skin and mucosa caused by substantial loss of functioning melanocytes. It is characterized by well-circumscribed whitish macules and/or patches that can occur on any part of the body. Regardless of race and ethnic background, vitiligo affects around 1-2% of the population. Female preponderance has been reported in consequence of cosmetic concern. Vitiligo is one of the diseases that can significantly impair the quality of life since many patients feel distress, embarrassment and also have social and job discrimination.

Pathogenesis
The pathogenesis that involves melanocyte destruction in vitiligo is still inconclusive. Substantial hypotheses which include autoimmune, genetics, neurohumoral and autocytoxic, have been proposed. Among these, the autoimmune hypothesis has been the most supported by the medical literatures. Antimelanocytic antibodies and anti-organ antibodies have been detected in vitiligo patients. Furthermore CD8+ T cells, macrophages and langerhans cells have a role as well in melanocyte destruction. This hypothesis usually explains generalized vitiligo which is often related to autoimmune endocrinopathies. The genetics of vitiligo are inherited in a non-Mendelian, multifactorial and polygenic pattern. The NALP1 gene and PTPN22 gene have recently been found to be related to vitiligo with autoimmune disorders. The neurohumoral hypothesis is explained by the toxic substances released from peripheral nerve endings which destroy melanocytes. Segmental vitiligo is the most supported by this evidence. The autocytoxic theory is explained through the intrinsic defects of melanocytes and melanocytorrhagia which leads to melanocyte destruction.

Clinical manifestation
Vitiligo appears as chalky white macules and/or patches with sharp borders, smooth surface, surrounded by normal skin. The size of the lesions varies from few millimeters to centimeters. Poliosis (white hairs) can be seen in the lesions. The lesions usually occur on the face (periorificial), dorsal surface of hands and feet, axilla, umbilicus, inguinal/genital area and areas above the joint. Köebner phenomenon is commonly seen.

According to the extent of involvement and distribution, vitiligo is classified into 3 types: localized, generalized, and universal vitiligo. Localized vitiligo is divided into focal, segmental (Fig 1.) and mucosal type (Fig 2.). Generalized vitiligo is the most common type and divided into vulgaris (Fig 3.), lip-tip (Fig 4.) and mixed type. Lastly, universal vitiligo is defined as vitiligo lesions involving more than 80% of the body surface area. In addition, vitiligo can be divided into segmental (SV) type and nonsegmental (NSV) type from the distribution of the lesions (unilateral or bilateral) and pathogenesis. Segmental type usually occurs on face, and is distributed unilaterally which begins in childhood. Nonsegmental type has a progressive onset and is located bilaterally upon friction sites.

Associated conditions
Most of the vitiligo patients are healthy. However, vitiligo may be associated with autoimmune disorders. Thyroid disease (hyperthyroidism and hypothyroidism) are the most recognized. Frati et al., reported the prevalence of thyroid disease as 18.5% of 15,126 vitiligo patients. Other associations which are recognized include diabetes mellitus, addison disease, gonadal failure, pemicious anemia,
systemic lupus erythematosus, alopecia areata, lichen sclerosus and multiple endocrinopathy syndrome (MEN). Generalized vitiligo and universal vitiligo are more commonly associated with autoimmune conditions. In contrast, segmental type is less associated with autoimmune conditions. Therefore, screening for thyroid function and thyroid antibodies should be considered in every patient. Additional investigations related to autoimmune and endocrinopathie conditions should be concerned in those who have symptoms or positive family history.

Vitiligo can be associated with ophthalmie and auditory conditions. Vogt-Koyanagi-Harada (VKH) syndrome is a T-cell mediated autoimmune disorder. Vitiligo, uveitis, aseptic meningitis and dysacusia can be found. Alezzandrini syndrome is a rare condition present with facial vitiligo, and poliosis with ophthalmic symptoms in the similar side.

**Diagnosis**

The diagnosis of vitiligo is usually straightforward based on a clinical examination. However, in the very early stage of vitiligo or in a fair skinned patient, Wood’s lamp, a portable ultraviolet device which emits long wave ultraviolet A (peak at 365 nm), can help to diagnose vitiligo. Upon examine of the lesion with Wood’s lamp in the dark room, the depigmented lesions will show enhancement since light absorption from melanocytes is limited. The histopathology of vitiligo shows melanocytes depletion. In the early stage of vitiligo, superficial perivascular infiltration with lymphocytes can be seen at the margin of the lesion. However, skin biopsy is not necessary for diagnosis in most cases.

**Differential diagnosis**

Several conditions can mimic vitiligo. These conditions include chemical leukoderma, postinflammatory depigmentation, pityriasis alba, tinea versicolor, idiopathic guttate hypomelanosis, nevus depigmentosus and Piebaldism.

**Treatment**

Vitiligo is usually asymptomatic, but has a dramatic psychological effect. At the first visit it is important to give counseling to the patients about the unpredictable course of the disease and guidelines of management. The patients with mucosal vitiligo, positive family history, Köebner phenomenon and nonsegmental type commonly progress without treatment. Fortunately, younger patients, patients who have lesions on their face and neck or have recent onset of disease and darker skin types have better prognosis. The lesions on the fingertips, hands and feet or lesions on hair-bearing skin in which terminal hairs are totally white are less responsive to therapies because of the absence of melanocyte reservoirs. Consequently, patients should manage how to live with chronic disease peacefully. At present, various treatment modalities include medical, phototherapy, laser, surgical, camouflage and alternative therapies which have been used. Unfortunately, there is no cure method. The aim of the treatment is to halt disease progression and increase repigmentation. The mechanism of the treatment is to stimulate the inactive melanocytes in the middle and/or lower parts of the outer root sheaths of hair follicles to proliferate, and migrate upward to the nearby epidermis. In universal vitiligo, patients lose pigment over the entire body surface area and are left with only isolated islands of normal pigmentation. It might be impossible to get all lesions repigmented. For cosmetic reasons, depigmentation of the normal skin might be the option.

**Medical treatment**

- **Corticosteroids**
  
  Topical corticosteroids are commonly used as the first line in localized vitiligo. If there is no repigmentation in three months, they should be discontinued to prevent side effects. Corticosteroids have immunosuppressive effects toward autoantibodies and complement mediated melanocyte destruction. It also induces melanocyte repopulation and melanin production in depigmented skin. In the study of 101 vitiligo children by Kwinter et al., the response rate of moderate to high potency corticosteroids was 64%. Head and neck lesions have the best response rates. The side effects include skin atrophy, telangiectasia, folliculitis, striae and systemic absorption. Systemic corticosteroid, administration of dexamethasone 10 mg intravenous 2 con-secutive days per week for a maximum of 24 weeks...
can halt disease progression as high as 88%, but can stimulate repigmentation in only 37.6% of cases.\textsuperscript{22} Copious side effects are usually found with this modality.\textsuperscript{22}

- Calcineurin inhibitors
  
  Tacrolimus and pimecrolimus are new immunosuppressive agents that act by inhibiting T-cell activation and cytokine release. Topical tacrolimus was first reported for treatment of vitiligo in 2002.\textsuperscript{23} The mechanism in vitiligo involves the promotion of melanocytes and melanoblasts as well as decreases the tumor necrosis factor-alpha (TNF-alpha).\textsuperscript{24} A double-blind randomized trial of 0.1% tacrolimus compared to 0.05% clobetasol for the treatment of vitiligo in children demonstrated higher efficacy in the clobetasol group. After 2 months, the mean percentage of repigmentation was 49.3% for clobetasol and 41.3% for tacrolimus. However, a few patients in the clobetasol group developed skin atrophy or telangiectasia, while the tacrolimus group was spared these adverse effects.\textsuperscript{25} From the authors’ experience in a vitiligo clinic, most of the patients with localized vitiligo responded well to topical tacrolimus. The lesions on the face have the best response. Common side effects are stinging and burning sensation.

- Calcipotriol

Calcipotriol is vitamin D analog with immunomodulatory effect via vitamin D receptor to enhance melanocytes development and melanin synthesis.\textsuperscript{26} As a monotherapy, the efficacy is inferior to topical corticosteroids. When combined with topical corticosteroids the repigmentation rate increases.\textsuperscript{27} It is usually used in localized vitiligo and the reported side effect is mild irritation.

**Phototherapy**

Ultraviolet (UV) light which includes UVA and UVB shows benefit in vitiligo. The mechanism involves both immunosuppression and melanocyte stimulation.

- Narrowband UVB (NB UVB) phototherapy

Narrowband UVB is the portion of the UV spectrum from 311-312 nm., It is currently the first line of treatment in generalized vitiligo. The mechanism is induction of the enzyme tyrosinase and increases HMB45 on the surface of the melanosomes.\textsuperscript{28} The patients are irradiated over their whole body two to three times per week in a duration which varies from 6 months to 2 years. The pattern of repigmentation is perifollicular or marginal. When used as a monotherapy, the rate of repigmentation varies from 41% to 100%.\textsuperscript{29} Compared to PUVA (psoralen plus UVA), NB UVB provides a higher rate of repigmentation and is more cosmetically acceptable.\textsuperscript{29} From the authors’ experience, most patients responded well to NB UVB phototherapy with a treatment duration which varies from 6 months to 2 years (Fig 5). Common side effects of NB UVB include skin erythema, dryness and itching. It can be combined with other topical treatments such as topical corticosteroids or calcineurin inhibitors to achieve better results.

- PUVA (Psoralen plus UVA) photochemotherapy

Psoralen is a photosensitizer derived from plants. It can be taken either oral or applied topically. When combined with UVA, a photochemical reaction occurs. The mechanism of PUVA in vitiligo is to stimulate melanocytes in hair follicles, induce melanocyte hypertrophy and hyperactive melanosomes.\textsuperscript{30} At present, PUVA is less commonly used in generalized vitiligo. As compared to narrowband UVB, the repigmentation from PUVA is darker than the normal skin which is less cosmetically acceptable. In addition, patients have to avoid the sun including wearing sunglasses for 24 hours after ingestion of psoralens. Common side effects include nausea, vomiting, skin erythema and pruritus. Patients should not receive PUVA more than 200 treatments since long term treatment may increase the risk of skin cancer.

**Targeted phototherapy**

This recent modality involves the application of light energy focused on the selective lesion. Targeted phototherapy includes different methods such as non laser (UVA, UVB) and laser therapy. The uninvolved areas are light sparing thus the side effects are minimized.

- Targeted UVA/UVB phototherapy

The machine can emit UVA, broadband UVB and NB UVB (311 nm). It can be used in localized vitiligo that has not responded to topical medication or segmental vitiligo. The mechanism and frequency of treatment are similar to conventional phototherapy. It is convenient to use in children that are unfamiliar to large cabinets. Asawanonda et al., reported the efficacy of target broadband UVB when using twice weekly for 12 weeks in 6 patients. Repigmentation occurs in all patients. Usually, acral lesions achieve the least improvement.\textsuperscript{31} Target broadband UVB and NB UVB show similar responses in nonsegmental vitiligo.\textsuperscript{32}

- 308-nm excimer laser

308-nm excimer laser produces a monochromatic wavelength and coherent beam of light. The FDA has approved this device for vitiligo. The frequency is one to three times a week for an initial course of 12 weeks. As with other treatments, the face and neck have better response than acral parts. Contrary to UV radiation, dark skin type patients have better responses.\textsuperscript{33} When excimer laser is combined with topical corticosteroids or topical tacrolimus, they have synergistic effects.\textsuperscript{34,35} Erythema and pruritus are reported as side effects.

**Surgical treatment**

The surgical method is an option for recalcitrant lesions that fail nonsurgical treatment. Stable disease (no progression of lesions for at least 2 years) and segmental type of vitiligo respond well to surgical intervention. At present, various methods have been reported and will be discussed below.

- Suction blister epidermal graft

The viable epidermis is separated from the dermis by suction device. The depigmented areas (recipient sites) are

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**Fig 5.** Generalized vitiligo received narrowband UVB 5 months. A= before, B= after.
prepared by laser ablation or liquid nitrogen. The blister grafts are unroofed and removed to cover depigmented areas. Repigmentation spreads peripherally from the grafts and usually develops in 3 to 6 months. In a study of 45 patients with segmental and nonsegmental vitiligo, reepithelialization was detected in an average of 2 weeks and the skin color of the recipient site became normal in approximately 6 months. The advantage is less scarring in both donor and recipient sites.

- Split-thickness skin graft
  This technique uses a mechanical dermatome or scalpel to remove epidermis from donor areas. Large depigmented areas can be done in a single procedure. However, the donor and recipient sites usually heal with hyperpigmentation and scars. Agrawal et al., reported 68% of 32 vitiligo lesions achieved 100% repigmentation. The average time to get full color matching is 6.3 months.36
- Mini-Punch graft
  This technique is commonly used due to good repigmentation. The side effect includes cobblestoning appearance at the recipient site. In the largest trial performed in 1,000 patients, 74.5% of patients using this technique have 90-100% repigmentation.38
- Autologous melanocyte suspension transplant
  Tissue from the donor site that has melanocytes is harvested and cultured, followed by transplantation to the de-epithelialized recipient sites. This procedure can be done in large areas. By the reason of the complexity and time-consumed, few academic centers use this procedure.

Depigmentation

In patients that have extensive recalcitrant vitiligo or universal vitiligo, depigmentation of the normal skin might be the option. Topical, monobenzyl ether of hydri-quinone (MBEH) is a strong bleaching agent that can lead to melanocyte death. Side effects include itching, burning and erythema. The pigment-targeted lasers such as Q-switch ruby laser and Q-switched alexandrite laser have been reported as effective in depigmentation.39 Nevertheless, the depigmentation may not be permanent.

Alternative treatment

- Cosmetic camouflage
  The vitiligo lesions on face, neck and acral areas usually affect the psychological status. Camouflage may improve a patient’s self-confidence. This group contains makeup, self-tanning agents and tattoos. Self-tanning agents, such as dihydroxyacetone (DHA) can stain for 10 days after application. A tattoo is useful in mucosal lesions which are difficult to cover from cosmetics. The side effects are allergic reaction to tattoo, unsatisfactory color matching and Köeblner phenomenon.
- Antioxidants
  Oxidative stress has been referred to in the pathogenesis of vitiligo. Therefore, antioxidants may have a role in melanocytes protection from reactive oxygen species (ROS). Various studies of antioxidants for vitiligo have been reported, but still have inconclusive results.40 Antioxidants for vitiligo include vitamin E, vitamin C, alphalipoic acid, poly podium leucotomos, topical catalase and superoxide dismutase.
  Besides the treatments mentioned above, all vitiligo patients should be recommended to carry out adequate photo-protection since vitiligo lesions can get burnt easily and probably are a risk to skin cancers. Vitiligo patients should avoid the sun at peak periods, wear protective clothing and regularly apply broad-spectrum sunscreen when going out.

CONCLUSION

Vitiligo is a chronic pigmentation disorder that affects psychological status. The clinical course is sometimes unpredictable. Even though several options of treatment are now available, the management of this condition is still problematic. Each patient should be assessed and counseled individually for the plan of treatment. Besides appropriate treatments, encouragement of the patients together with using cosmetic camouflage will help patients to better cope with this condition.

REFERENCES

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Practical management in vitiligo

Vitiligo

Children < 12 years

No

Type of vitiligo

Localized

Lip-oral

Generalized

Universal

Systemic treatment

Topical antitumour necrosis factor inhibitors, calcipotriol

Not response

Phototherapy (NB-UVB or PUVA) or combination therapy

Not response

Depigmentation

Topical antitumour necrosis factor inhibitors, calcipotriol

Not response

Targeted phototherapy

NB-UVB, Narrowband UVB; PUVA, Psoralen plus UVA