

Proposal for Guidelines for the Treatment of Vitiligo in Croatia

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Abstract: Vitiligo, an acquired depigmentation disorder, because of its impressive clinical presentation has a large impact on psychosocial life of patients. Although the exact etiopathogenesis still remains uncertain, several therapeutic options are available for treatment of this condition. Unfortunately, patients are often confronted with difficulties regarding to receiving suitable therapy. Because of the fact that vitiligo is not contagious and not life-threatening disease, physicians usually do not recognize patients' problems and consider vitiligo as only a cosmetic problem, which should be treated only by camouflage and sun protection products. On the other hand, because of the lack of the accurate information for patients, a widely open market for different kind of alternative questionable therapies occurs so patients are often experimenting with different types of unproven medications. The need for widely accepted consensus concerning vitiligo treatment and establishment of the therapeutic guidelines exists worldwide. Our aim was to introduce for the first time vitiligo therapy guidelines in Republic of Croatia, based on the evidence-based accepted vitiligo therapy world recommendations and our experience. We present a review of therapy for vitiligo regarding to various vitiligo types and severity of lesions as well adequate therapeutic options. Also, our intention is to improve social component of patient's life through rising awareness of this condition which affects over 35 million people worldwide.

Keywords: Depigmentation, melanocytes, vitiligo, guidelines, Croatia.

INTRODUCTION

Vitiligo is an acquired, chronic disease characterized by an appearance of circumscribed depigmented macules and patches, which usually increase in size with time, anywhere on the human body due to a substantial loss of functioning epidermal and/or hair follicle melanocytes [1, 2]. Spontaneous repigmentation is rare and occurs in a perifollicular pattern. Vitiligo is generally slowly progressive disorder [3].

Vitiligo affects 0.5-2% of the general population worldwide, but varies based on region, without sex or racial differences. It affects all age groups [1].

Based on distribution, vitiligo is classified as: localized comprising unilateral depigmented macules following segmental (dermatomal) or focal (quasidermatomal) pattern; generalized comprising acrofacial pattern involving face and distal extremities, and vitiligo vulgaris with widespread, usually symmetrically distributed lesions; universal vitiligo with complete or nearly complete depigmentation, and mucosal vitiligo presenting with typical depigmented macules exclusively on mucosal surfaces [4].

Occurrence of vitiliginous lesions within the areas of physical trauma or friction, known as Koebner phenomenon in vitiligo patients has been well described in literature [5].

ETIOPATHOGENESIS

Vitiligo is a multifactorial disorder which involves complex interactions between genetic risk factors and

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environmental triggers. Therefore, several hypotheses regarding the etiopathogenesis of vitiligo exist.

The importance of genetic background is supported by studies demonstrating significantly higher (7-10 times) incidence of vitiligo among first degree relatives [6]. However, it seems that mode of inheritance is polygenic, non-Mendelian with incomplete penetrance and multiple susceptibility loci [7]. The study by Jin *et al.* confirmed a vitiligo susceptibility gene NALP1 on chromosome 17p13, which encodes NACHT leucine-rich-repeat protein 1 [8]. Mutations in NALP1 were detected in families with a variety of vitiligo-associated autoimmune and autoinflammatory diseases such as autoimmune thyroid disease, autoimmune diabetes mellitus, rheumatoid arthritis, psoriasis, pernicious anemia, and systemic lupus erythematosus [8, 9]. Certain HLA types have been frequently associated with vitiligo worldwide, primarily HLA A2, DR4, DR7 and Cw6 [1].

According to the autoimmune hypothesis, the loss of melanocytes in vitiligo is explained by defect in both cellular and humoral pathways. Namely, in the sera of vitiligo patients, autoantibodies directed against several melanocyte antigens such as tyrosinase and tyrosinase-related proteins 1 and 2 have been found as well as melanocyte-specific CD8+ T lymphocytes which also infiltrated the dermis [1]. This theory is also supported by the fact that approximately 20% of vitiligo patients also suffer from at least one autoimmune disease, among which systemic lupus erythematosus, diabetes mellitus type I, pernicious anemia, rheumatoid arthritis, and autoimmune thyroid disease are the most frequently reported [10]. Recent literature findings suggest an important role of inducible heat-shock protein 70 (HSP70i) in etiopathogenesis of vitiligo [11, 12]. In the presence of stress, melanocytes secrete antigen-bound HSP70i activating dendritic cells which are responsible for inducing immune response [12].

Neural theory explains distribution of skin lesions, especially in segmental vitiligo, by the fact that melanocytes are in direct contact with nerve endings in depigmented lesions, whereas this has not been observed in normal skin [13].

Psychological stress is another well documented trigger of vitiligo in susceptible patients. Neurogenic factors influenced by mental stress, such as neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), catecholamines, and nerve growth factor (NGF), lead to melanocyte destruction [14]. Neurogenic

factors enhance migration, proliferation and the phagocytosis capabilities of antigen-presenting cell, lymphocytes, macrophages and polymorphonuclear leukocytes (PMNs). They can also stimulate the production of proinflammatory cytokines in lymphocytes and PMNs, such as interleukin (IL)-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, interferon- γ (IFN- γ), and tumor necrosis factor- α (TNF- α), skewing the immune response toward the Th1 pathway or Th2-type response [15].

Destruction of melanocytes explained by defective oxygen metabolism resulting in increased production and decreased degradation of reactive oxygen species (ROS) presents another hypothesis of etiopathogenesis of vitiligo which is supported by increasing amount of evidence [16]. ROS can cause direct cytotoxic effects of melanocytes, deactivation of enzymes such as catalase (converts hydrogen peroxide to oxygen and water), and formation of oxidative stress-mediated neoantigens (i.e. structurally modified tyrosinase (TYR), tyrosinase-related protein 2 (TYRP2) which triggers further specific adaptive immune response against melanocytes [14, 17-19].

Other theories aiming to elucidate the etiopathogenesis of vitiligo include defects in structure of melanocytes and their malfunction, decreased viability of melanocytes and dysregulation of apoptosis, defects in growth factors, and peroxidation of phospholipids in melanocyte membrane [1, 4, 20].

The convergent theory encompasses various elements of different hypotheses and relies much on future investigations that might help explain the sequence of particular events in the etiopathogenesis of vitiligo [1].

DIAGNOSIS

Vitiligo is usually diagnosed clinically following a complete history and physical examination. Despite straightforward clinical appearance of vitiligo in majority of cases, several additional diagnostic procedures may be needed for confirmation of diagnosis in some less clear cases.

Patients with vitiligo should be examined under both visible and ultraviolet light of about 365 nm wavelengths (i.e. Wood's lamp). While under visible light, the contrast between depigmented macules and surrounding skin is not striking in light-skinned individuals, with Wood's lamp examination more lesions may become apparent [21].

Excisional biopsy of perilesional skin should be performed. The most prominent histologic feature of vitiligo is loss of melanocytes of the basal layer of the epidermis.

Immunohistochemical stains such as HMB45, Mel-5 or S-100 reveal marked reduction of DOPA-positive epidermal melanocytes compared with normal skin which appear to be replaced by Langerhans` and dermal dendritic cells. Collagen and elastic fibers are not affected in vitiligo [22].

In patients with vitiligo, a complete blood count with differential and platelet count, blood glucose, antinuclear antibody, and thyroid-stimulating hormone (TSH) levels have to be evaluated. Additional laboratory findings include free T3 and free T4 levels, antithyroperoxidase, antithyroglobulin antibodies, and ultrasound imaging of the thyroid gland. These diagnostic procedures should be performed because of the fact that almost 20% of vitiligo patients suffer from several autoimmune diseases [10]. Due to the fact that calcium uptake in melanocytes is decreased in patients with vitiligo, serum levels of 25-hydroxy vitamin D, and calcium should also be checked [1].

Serology for *Borrelia burgdorferi*, *Cytomegalovirus* serology and *Epstein-Barr virus* specific serologies are also recommended in Croatia because several regions in the country have been known as endemic regions for Lyme borreliosis and also due to molecular mimicry, a possible etiopathogenetic factor [23].

INTERNATIONAL UP-TO-DATE GUIDELINES FOR THE MANAGEMENT OF VITILIGO

Therapeutic modalities for the management of vitiligo are not widely known, possibly due to the fact that this condition is still considered as an orphan disease. Unfortunately, many physicians (including dermatologists) still consider vitiligo to be an incurable disease and only a few guidelines for the management of vitiligo are available. All of them emphasize the importance of accurate diagnosis. Nonsegmental type of vitiligo (NSV) is often associated with other autoimmune diseases, especially with autoimmune thyroid disease so the adequate diagnostic procedures such as TSH, T3, T4 levels, and antithyroid antibodies should be performed [24]. The following therapeutic options which are in use today are: topical corticosteroids, topical calcineurin inhibitors, topical vitamin D3 analogues, phototherapy (PUVA and NB-UVB), oral corticosteroids, antioxidants (e.g. catalase,

vitamin B6), laser and surgical therapy [4]. According to the literature, combination therapy is often recommended because of its better effectivity compared to monotherapy [24-27]. Further mentioned algorithms for vitiligo treatment were constituted from different working groups and organizations in the last few years [24, 26, 27]. A group of British authors from British Association of Dermatologists, Departments of Dermatology, The Vitiligo Society and Clinical Standards Department established algorithm for the management of vitiligo in adults and children by non-specialists in 2010 (Figure 1). The European Dermatology Forum Consensus presented algorithms for the management of patients with non-segmental or segmental vitiligo in 2013 (Figure 2), the same year when Japanese authors provided their proposal of the algorithm for the management of vitiligo in Japan (Figure 3).

AIMS

The aim of this work is to establish diagnostic and therapeutic procedures of vitiligo in Croatia by the members of the Croatian Vitiligo Working Group. Up until now, it summarizes evidence-based and expert-based recommendations.

CURRENT TREATMENT OPTIONS FOR VITILIGO IN CROATIA

First-line and the most prevalent treatment modality for vitiligo in Croatia are potent and mild potent topical corticosteroids-betamethasone esters and mometasone furoate. Topical immunomodulators, tacrolimus and pimecrolimus, are not used very often because their use in vitiligo treatment is not covered by Croatian public health insurance. Mini-pulse dosage of corticosteroids (prednisolone) is recommended in patients with generalized and fast-spreading vitiligo. The main reason for insufficient application of narrowband UVB, although present in all major hospitals and covered by Croatian public health insurance, is the lack of fluorescent lamps in the country and its prevalent usage amongst psoriasis patients. Taking into consideration that vitiligo is often neglected disease, narrowband UVB therapy in our country is not available for the most of the patients, so, although it is golden standard in vitiligo treatment, we have placed it as a second line of treatment. PUVA therapy is historically used for treating vitiligo; it is used in a few specialized institutions. Excimer laser and surgical therapy for vitiligo are still not available in Croatia.

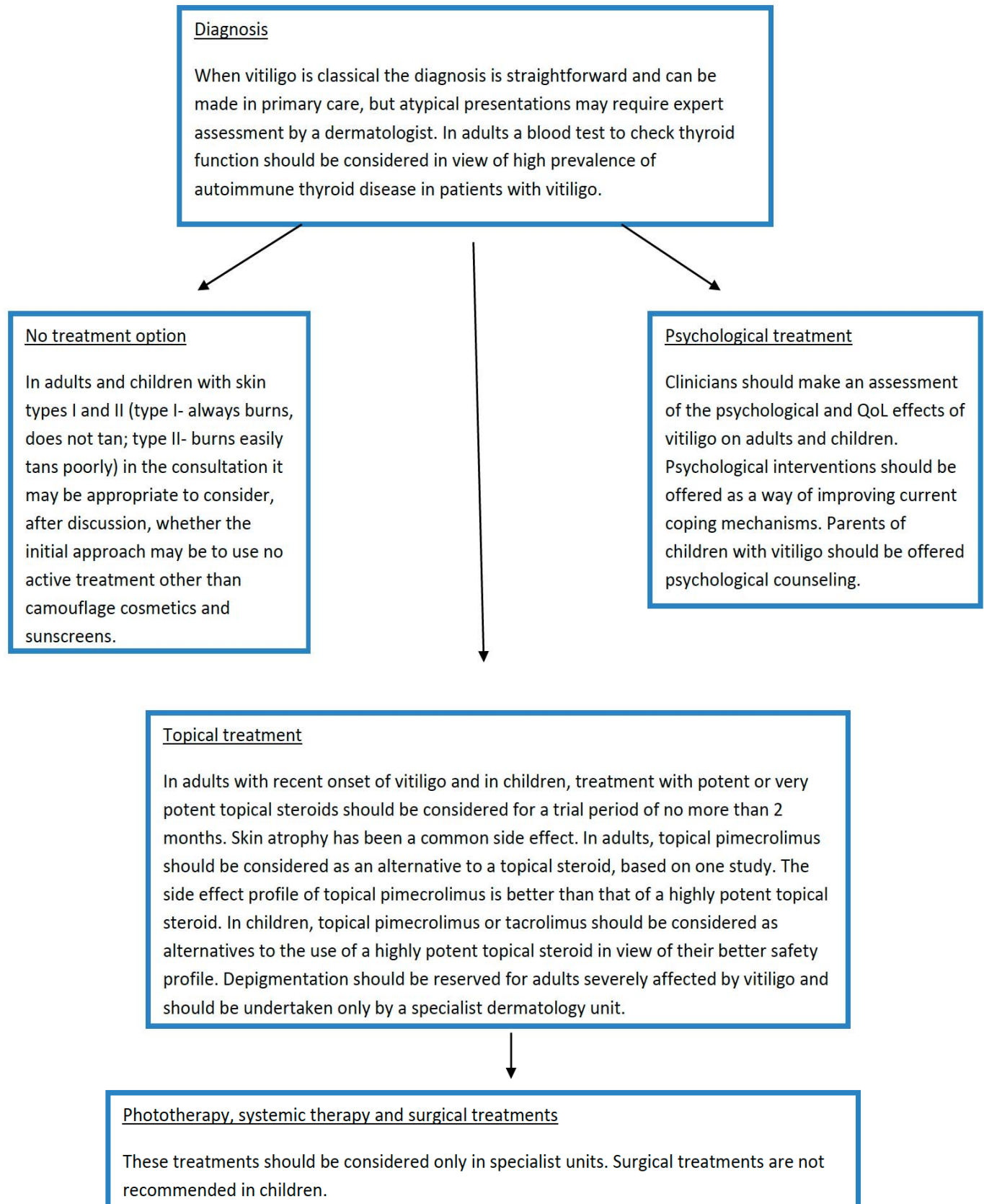


Figure 1: Algorithm for the management of vitiligo in adults and children by non-specialists in UK. (Gawkrodger DJ, et al. Modified from source: Postgrad Med J 2010; 86: 466-71).

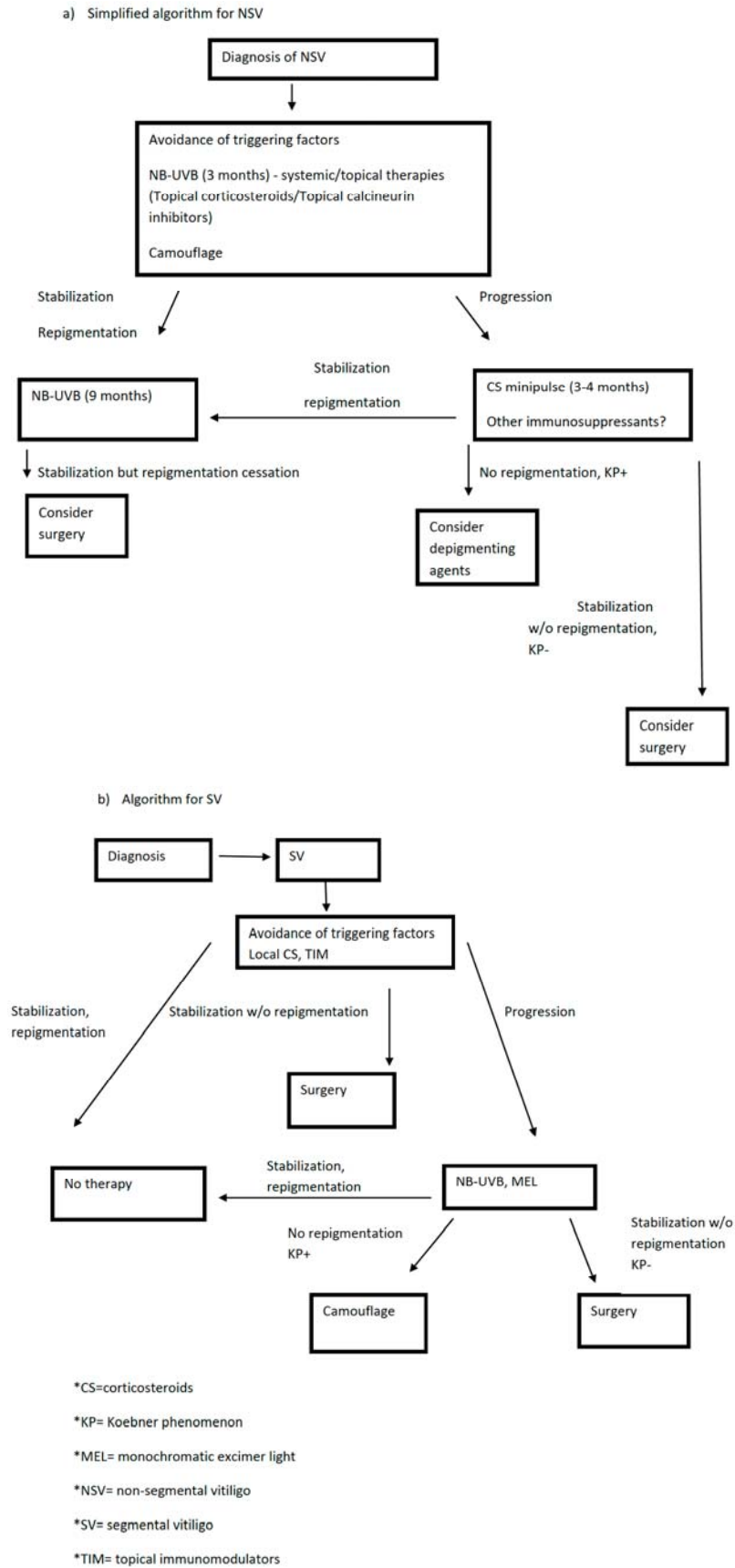


Figure 2: Guidelines for the management of vitiligo: the European Dermatology Forum Consensus. (Taieb A, *et al.* Modified from source: Br J Dermatol 2013; 168: 5-19).

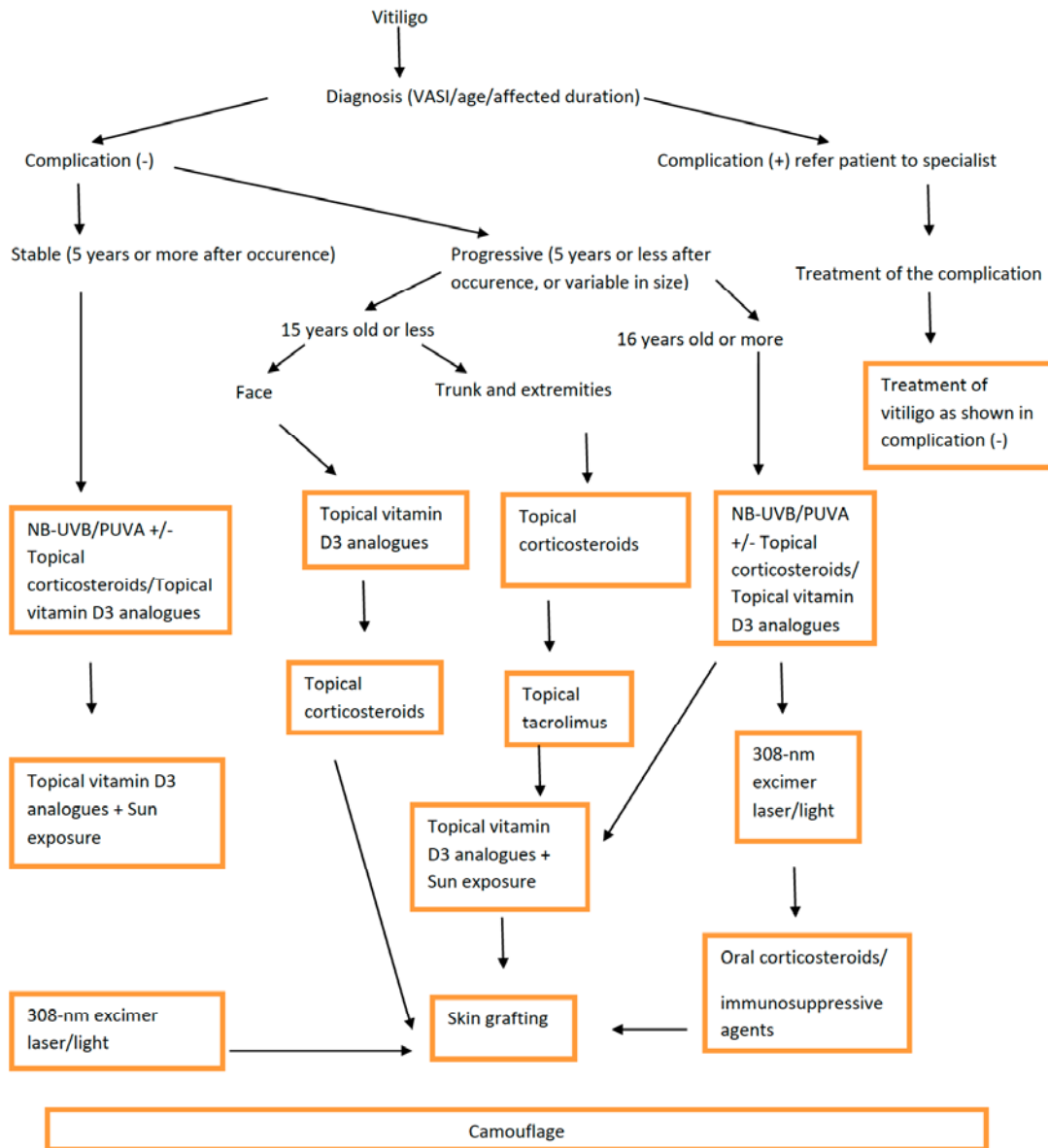


Figure 3: Proposed algorithm for the management of vitiligo in Japan. (Oiso N, *et al.* Modified from source: J Dermatol 2013; 40: 344-54).

PROPOSAL OF GUIDELINES FOR THE MANAGEMENT OF VITILIGO IN CROATIA

Considering available guidelines for the management of vitiligo, both available and unavailable therapeutic options in Croatia, and our clinical experience we have established our proposal for guidelines for the management of vitiligo in Croatia (Figure 4). This proposal and selection of specific therapeutic options in several lines are based on international up-to-date guidelines in accordance with evidence based medicine [24, 26, 27]. Of course, we have some specific approaches, i.e. that we put UVB 311 nm phototherapy as a second line of treatment (although it is a golden standard in vitiligo treatment) due to low availability in the country and prevalent

usage amongst psoriasis patients. Also, narrowband UVB devices for home use are available in Croatia, but not very often in use regarding to financial status of the majority of patients. Also, we still consider PUVA phototherapy as a third line of therapy for the similar reasons (still better availability and most commonly used therapy with more experience in specialized centers in comparison to UVB and successful therapy in patients with wider and resistant areas affected) [28-30].

CONCLUSION

A universal treatment for vitiligo remains to be discovered. Each treatment should be individualized

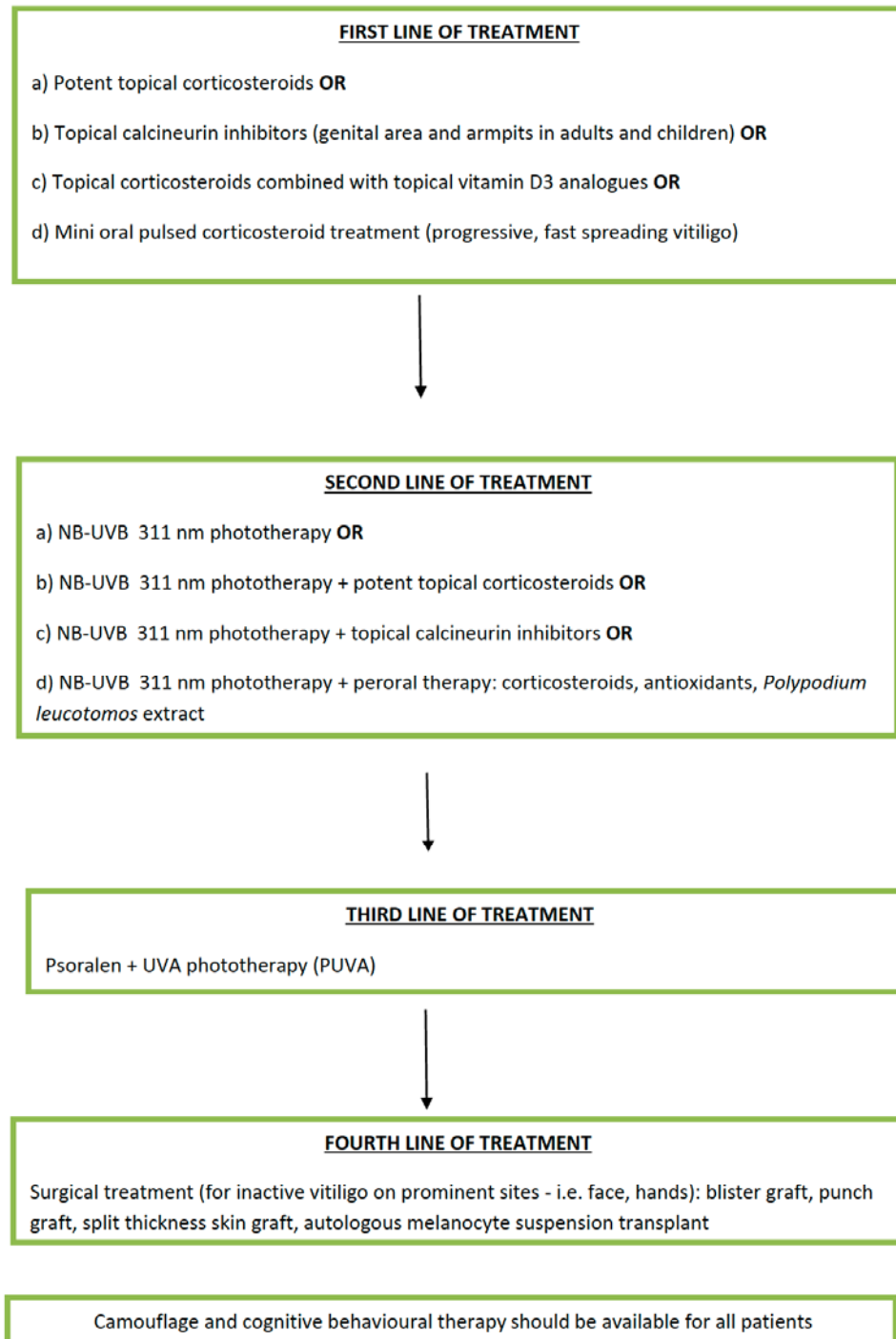


Figure 4: Proposed algorithm for the management of vitiligo in Croatia.

and several treatment modalities should be applied simultaneously. We have to try to establish adequate evidence-based and efficacious treatment modalities and to propose guideline for vitiligo treatment in Croatia.

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Received on 05-12-2013

Accepted on 19-12-2013

Published on 05-03-2014

DOI: <http://dx.doi.org/10.12970/2310-998X.2014.02.01.4>© 2014 Stanimirović *et al.*; Licensee Synergy Publishers.

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