Hiperpigmentacije – kako se (iz)boriti

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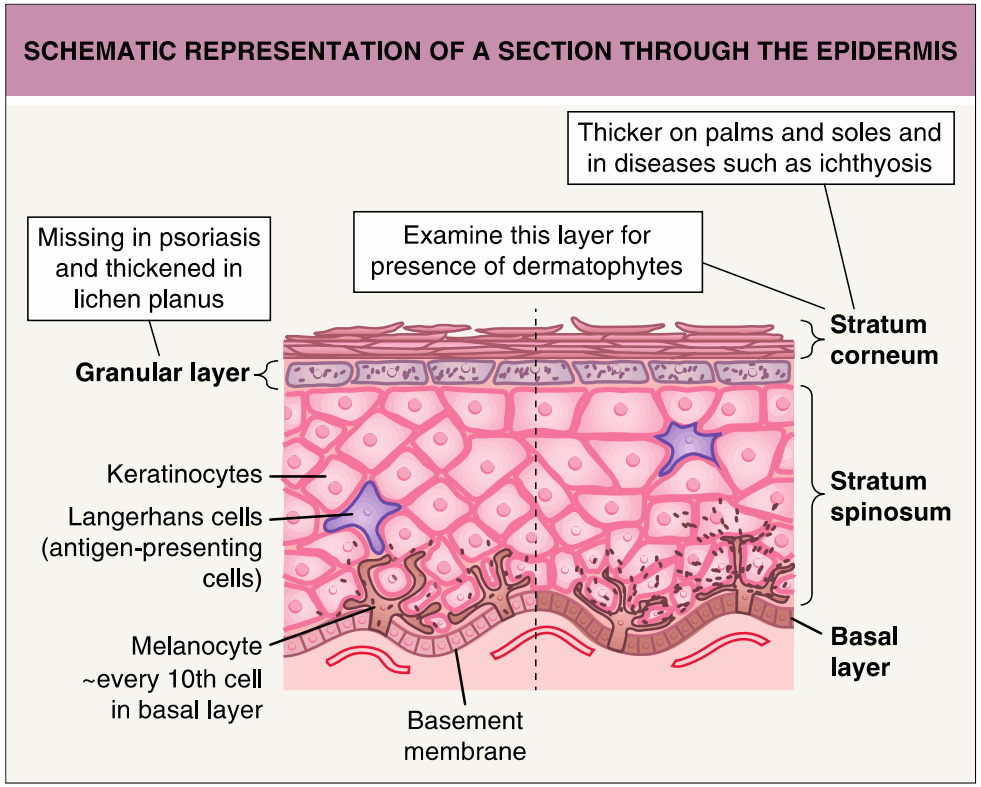
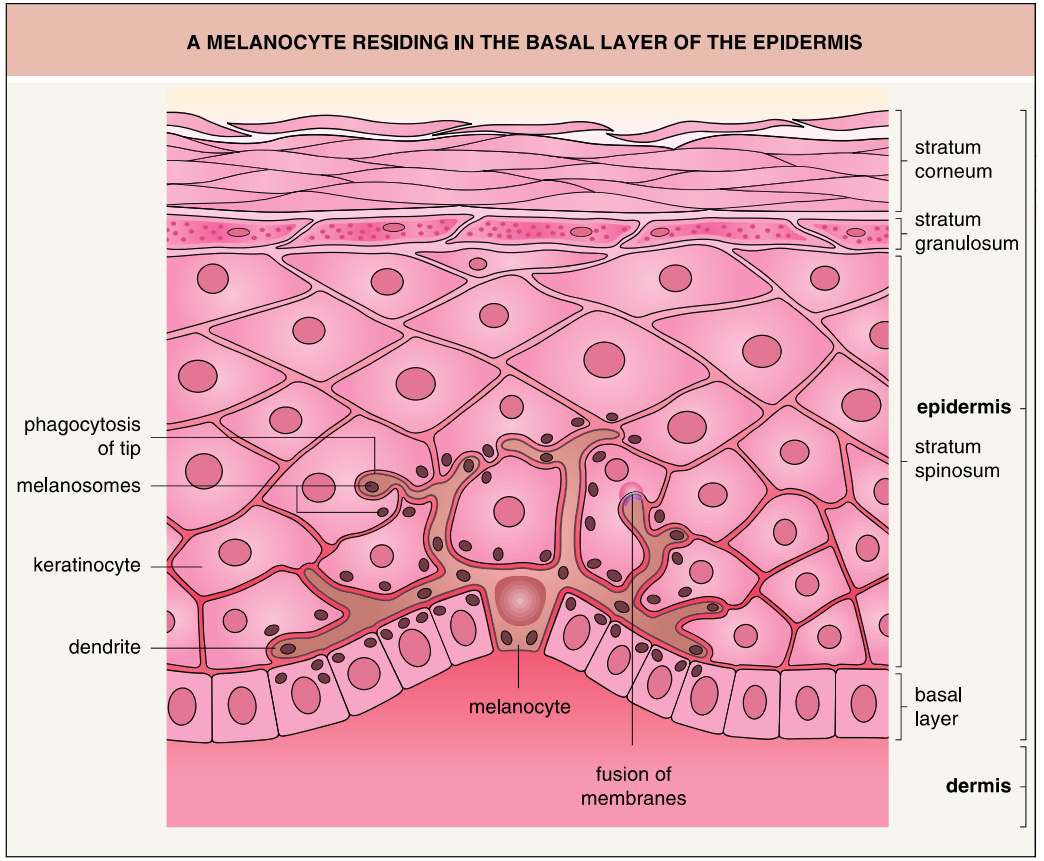
Melanociti

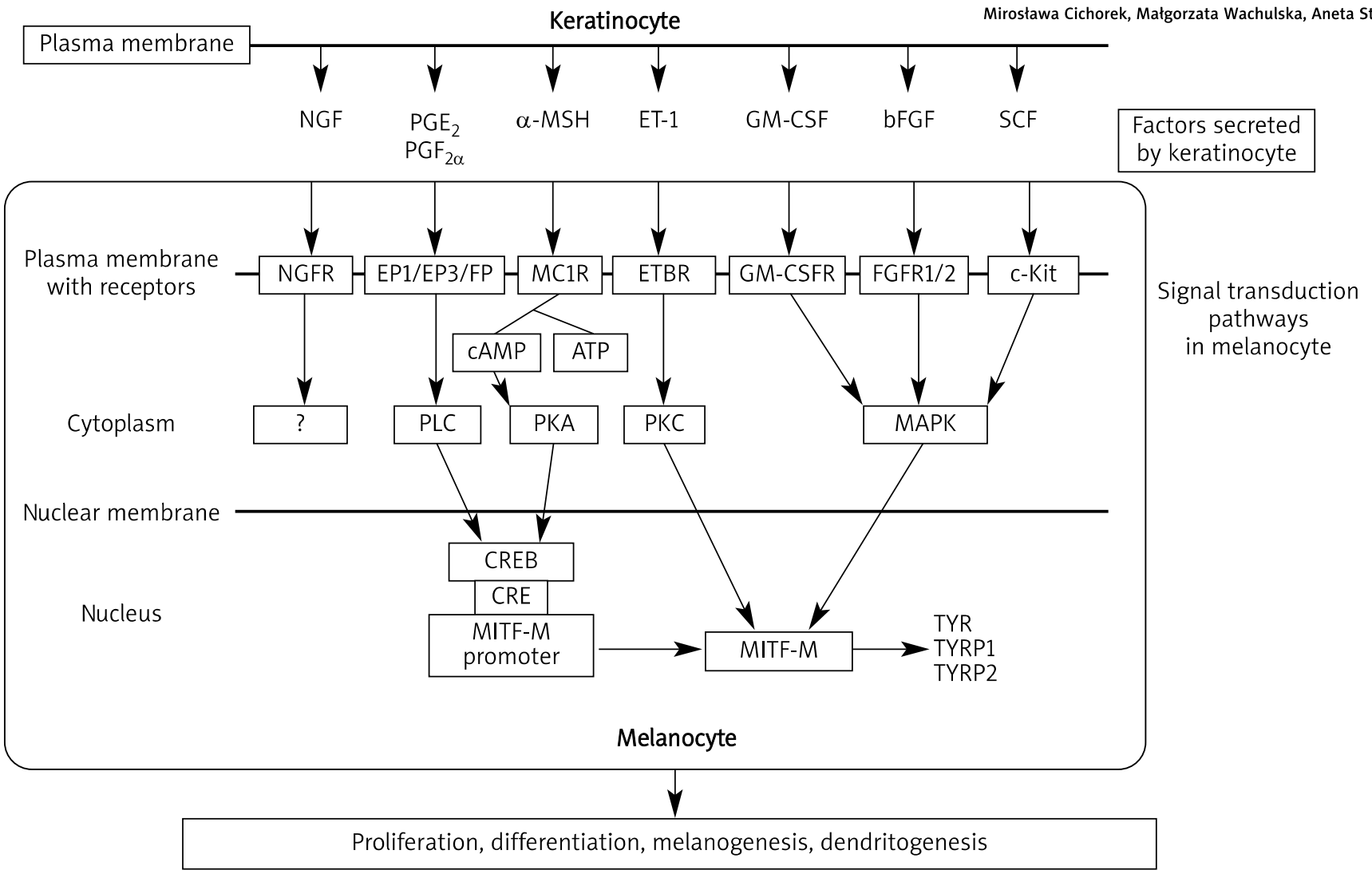

SCHEMATIC REPRESENTATION OF A SECTION THROUGH THE EPIDERMIS
Thicker on palms and soles and in diseases such as ichthyosis
Missing in psoriasis and thickened in lichen planus
Examine this layer for presence of dermatophytes
Stratum corneum
Granular layer
Keratinocytes
Langerhans cells (antigen-presenting cells)
Stratum spinosum
Melanocyte ~every 10th cell in basal layer
Basal layer
Basement membrane


A MELANOCYTE RESIDING IN THE BASAL LAYER OF THE EPIDERMIS
stratum corneum
stratum granulosum
epidermis
stratum spinosum
basal layer
dermis
phagocytosis of tip
melanosomes
keratinocyte
dendrite
melanocyte
fusion of membranes

Melanociti

Skin melanocytes: biology and development

Mirosława Cichorek, Małgorzata Wachulska, Aneta Stasiewicz, Agata Tymińska



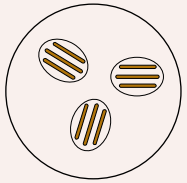
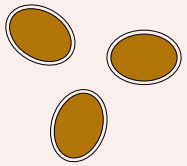
Postep Derm Allergol, 2013

Melanociti

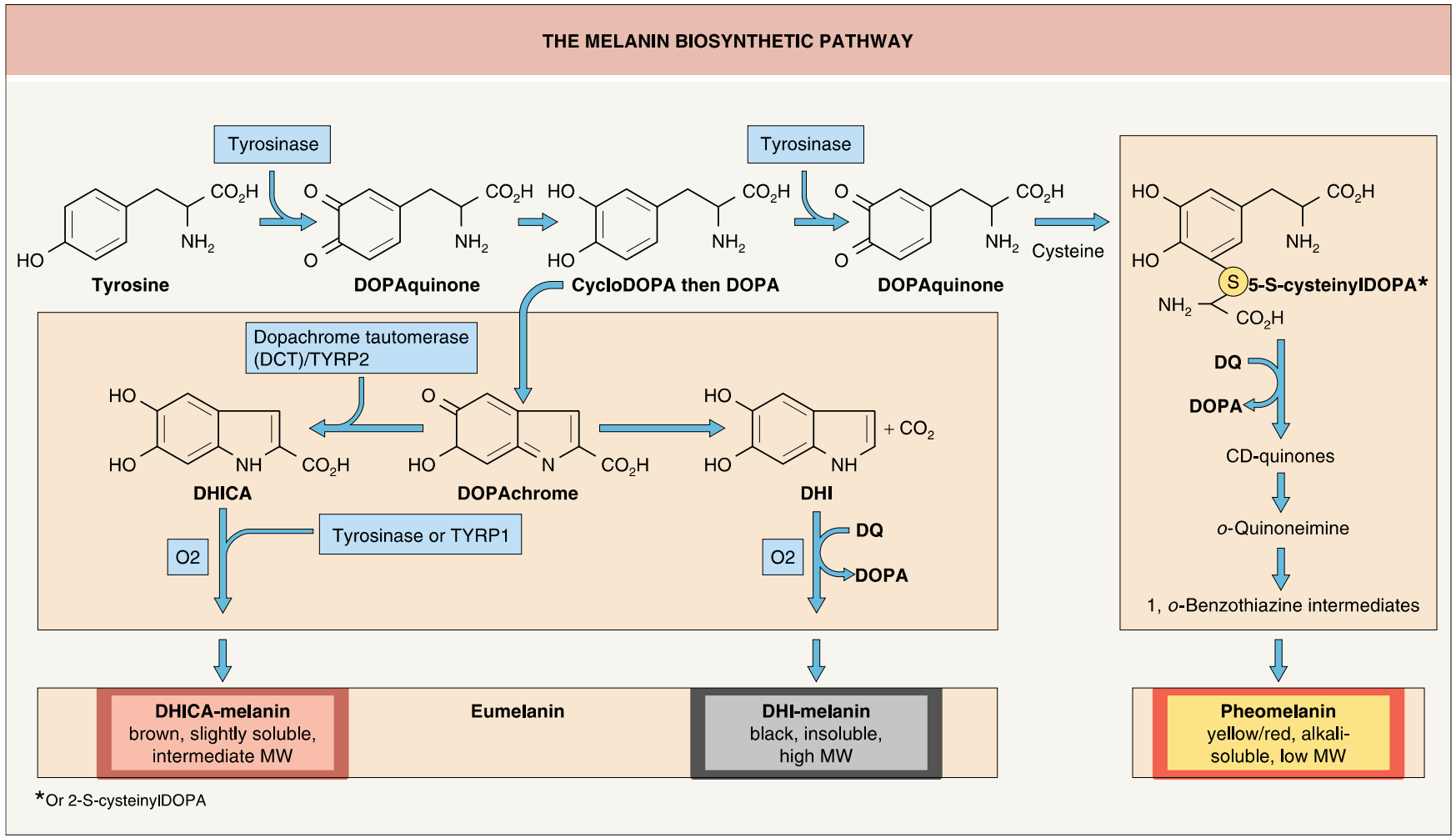
FOUR MAJOR STAGES OF EUMELANIN MELANOSOMES

Stage	Description	Electron micrographs
I	Spherical; no melanin deposition	
II	Oval; obvious matrix in the form of parallel longitudinal filaments; minimal deposition of melanin; high tyrosinase activity	
III	Oval; moderate deposition of melanin; high tyrosinase activity	
IV	Oval; heavy deposition of melanin; electron-opaque; minimum tyrosinase activity	

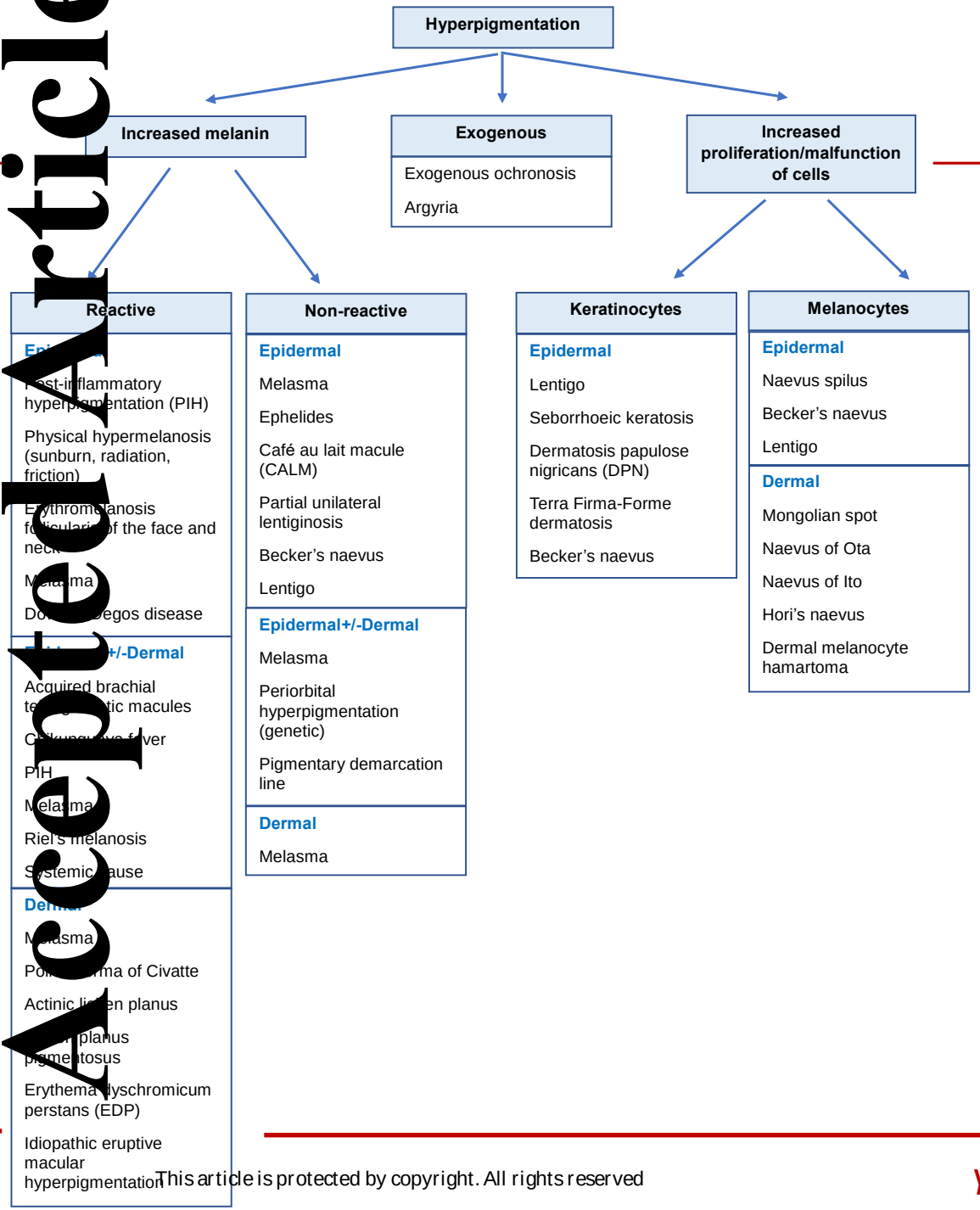
MELANOSOMES IN LIGHTLY PIGMENTED VERSUS DARKLY PIGMENTED SKIN

	Lightly pigmented skin	Darkly pigmented skin
Melanization	Stages II, III	Stage IV
Size (diameter)	0.3–0.5 microns	0.5–0.8 microns
Number per cell	<20	>200
Distribution of melanosomes within the lysosomes of keratinocytes	Groups of 2–10 	Single 
Degradation	Fast	Slow

Melanogeneza

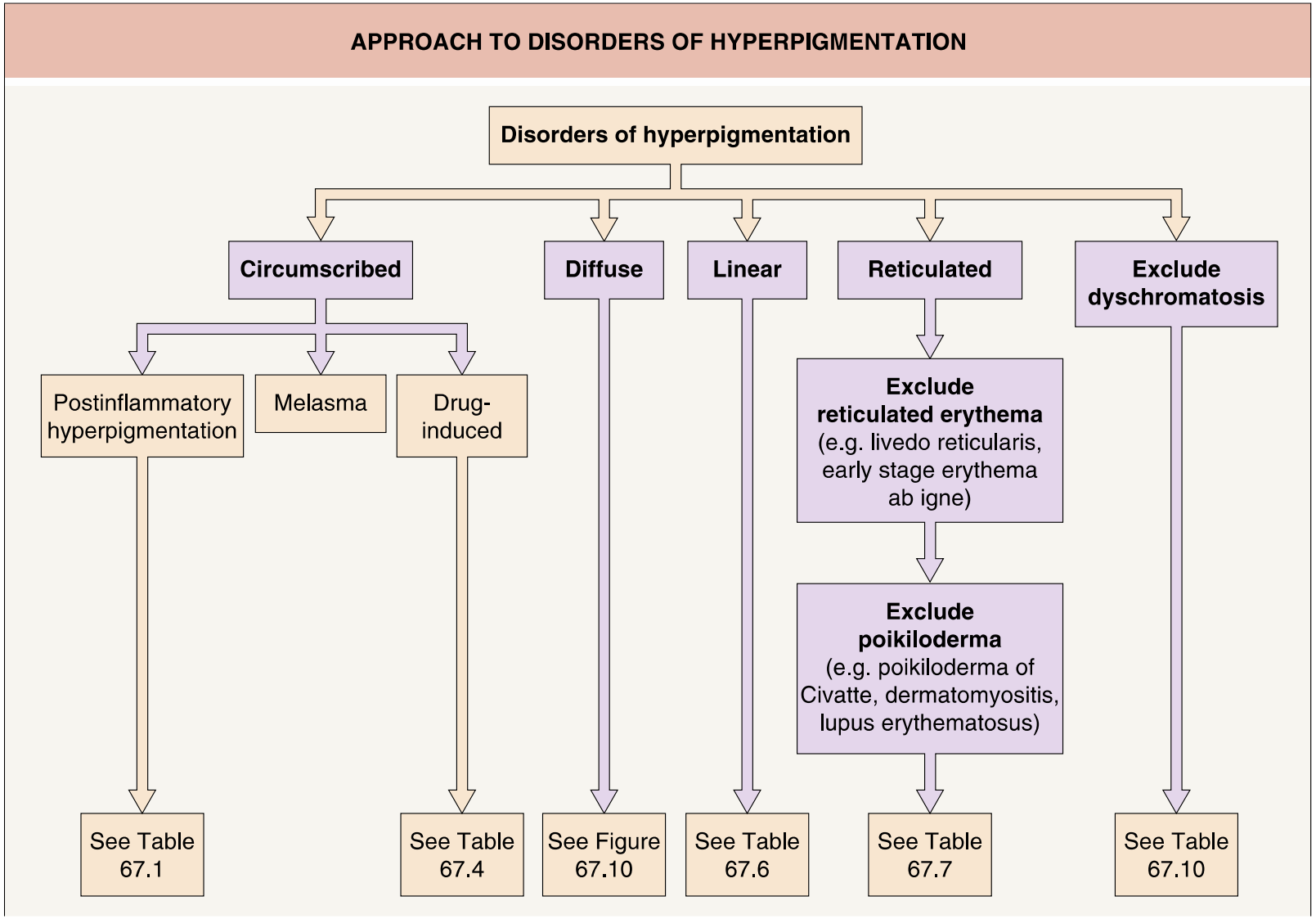


Podela hiperpigmentacija

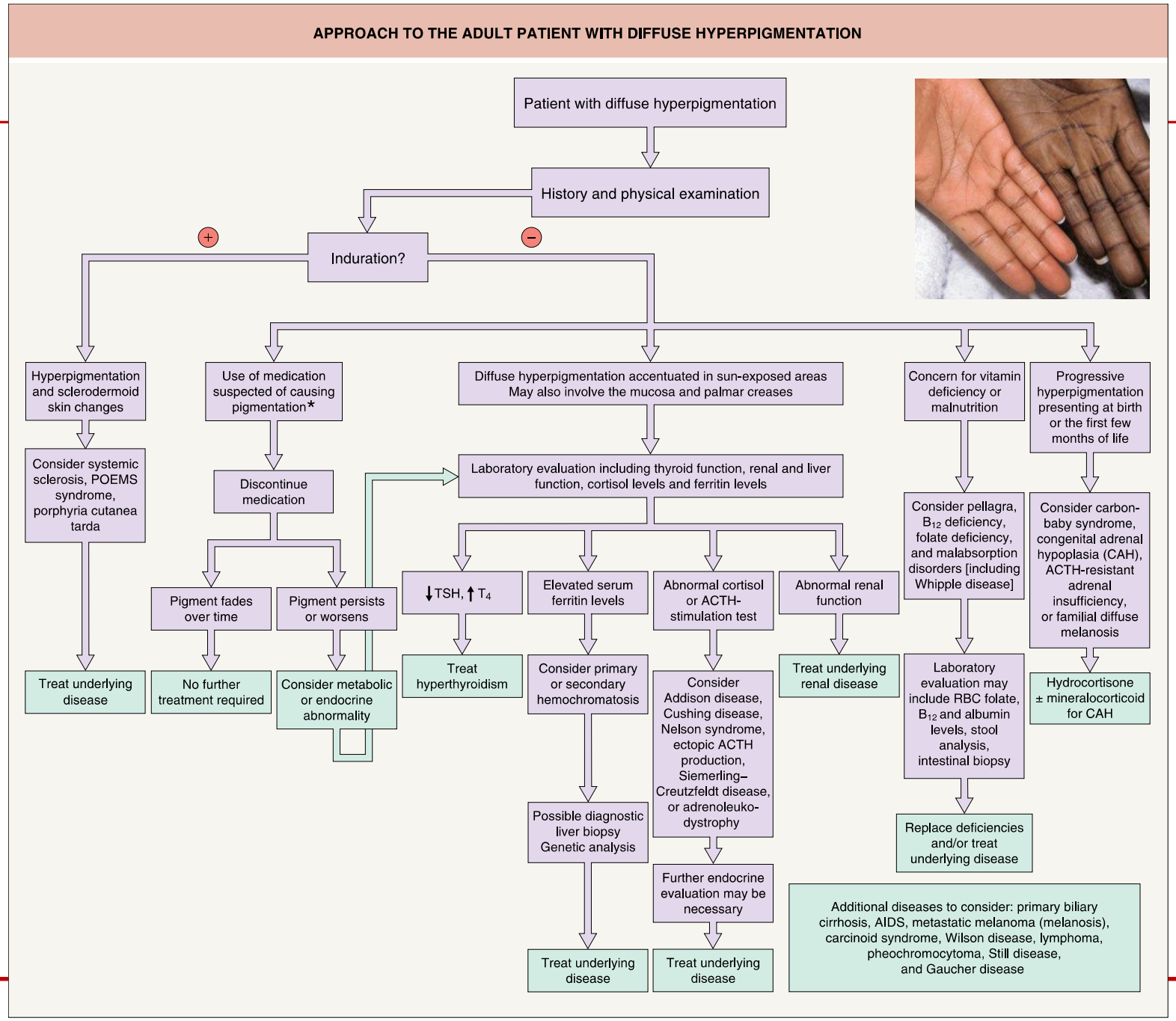


Yoo J. Clin Exp Dermatol, 2021

Podela hiperpigmentacija – dijagnostički algoritam



Podela


APPROACH TO THE ADULT PATIENT WITH DIFFUSE HYPERPIGMENTATION
Patient with diffuse hyperpigmentation
History and physical examination
Induration?
+
−
Hyperpigmentation and sclerodermoid skin changes
Consider systemic sclerosis, POEMS syndrome, porphyria cutanea tarda
Treat underlying disease
Use of medication suspected of causing pigmentation*
Discontinue medication
Pigment fades over time
No further treatment required
Pigment persists or worsens
Consider metabolic or endocrine abnormality
Diffuse hyperpigmentation accentuated in sun-exposed areas
May also involve the mucosa and palmar creases
Laboratory evaluation including thyroid function, renal and liver function, cortisol levels and ferritin levels
↓TSH, ↑T4
Treat hyperthyroidism
Elevated serum ferritin levels
Consider primary or secondary hemochromatosis
Possible diagnostic liver biopsy
Genetic analysis
Treat underlying disease
Abnormal cortisol or ACTH-stimulation test
Consider Addison disease, Cushing disease, Nelson syndrome, ectopic ACTH production, Siemerling–Creutzfeldt disease, or adrenoleuko-dystrophy
Further endocrine evaluation may be necessary
Treat underlying disease
Abnormal renal function
Treat underlying renal disease
Concern for vitamin deficiency or malnutrition
Consider pellagra, B12 deficiency, folate deficiency, and malabsorption disorders [including Whipple disease]
Laboratory evaluation may include RBC folate, B12 and albumin levels, stool analysis, intestinal biopsy
Replace deficiencies and/or treat underlying disease
Progressive hyperpigmentation presenting at birth or the first few months of life
Consider carbon-baby syndrome, congenital adrenal hypoplasia (CAH), ACTH-resistant adrenal insufficiency, or familial diffuse melanosis
Hydrocortisone ± mineralocorticoid for CAH
Additional diseases to consider: primary biliary cirrhosis, AIDS, metastatic melanoma (melanosis), carcinoid syndrome, Wilson disease, lymphoma, pheochromocytoma, Still disease, and Gaucher disease

Podela

DISORDERS WITH LINEAR HYPERPIGMENTATION

Follows the lines of Blaschko

Inherited/early onset

- Linear and whorled nevoid hypermelanosis ("pigmentary mosaicism"*; see Fig. 67.15)
- Early or subtle epidermal nevus
- Third stage of incontinentia pigmenti** (see Fig. 67.19)
- X-linked reticulate pigmentary disorder**
- Focal dermal hypoplasia** (Goltz syndrome; hyperpigmented macules within linear streaks, along with cribriform dermal atrophy, fat "herniation", hypopigmentation, and/or telangiectasias)
- X-linked hypohidrotic ectodermal dysplasia**
- Conradi–Hünermann–Happle syndrome**
- Café-au-lait macules of McCune–Albright syndrome (more often broad bands or block-like)
- Chimerism (more often block-like or ill-defined pattern)

Acquired/often later onset

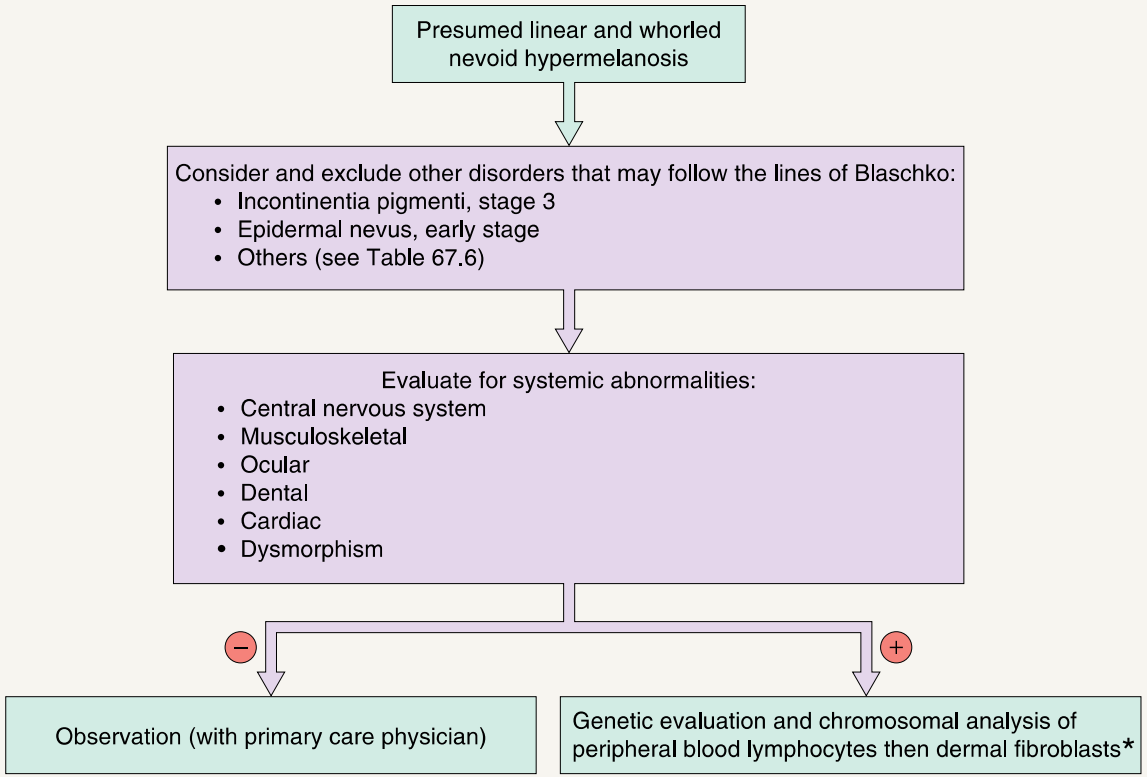
- Linear lichen planus, lichen planus pigmentosus, erythema dyschromicum perstans, or fixed drug eruption
- Linear atrophoderma of Moulin (see Fig. 67.17), possibly linear morphea
- Postinflammatory hyperpigmentation due to Blaschkitis
- Linear biphasic cutaneous amyloidosis‡

Does *not* follow the lines of Blaschko

- Pigmentary dermarcation lines (see Figs 67.11 & 67.12, Table 67.5)
- Linea nigra (see Fig. 27.11A)
- Phytophotodermatitis (see Fig. 67.13)
- Sock- or mitten-line hyperpigmentation
- Flagellate hyperpigmentation – e.g. from bleomycin (see Fig. 67.14), shiitake mushroom dermatitis, dermatomyositis, persistent plaques of Still disease
- Serpentine supravenous hyperpigmentation, e.g. from phlebitis, intravenous drug use, systemic sclerosis
- Additional causes of linear postinflammatory hyperpigmentation – excoriations, trauma/abuse, burns, allergic contact dermatitis (especially to plants), koebnerized lesions (e.g. psoriasis, lichen planus), coining

*Pigmentary mosaicism can also present with hyperpigmentation in a block-like pattern, referred to as segmental pigmentation disorder (see text).
**Primarily in female patients due to functional mosaicism (via lyonization) in these X-linked disorders; occasionally in male patients with somatic mosaicism or Klinefelter syndrome.
‡Single case.

APPROACH TO THE PATIENT WITH PRESUMED LINEAR AND WHORLED NEVOID HYPERMELANOSIS



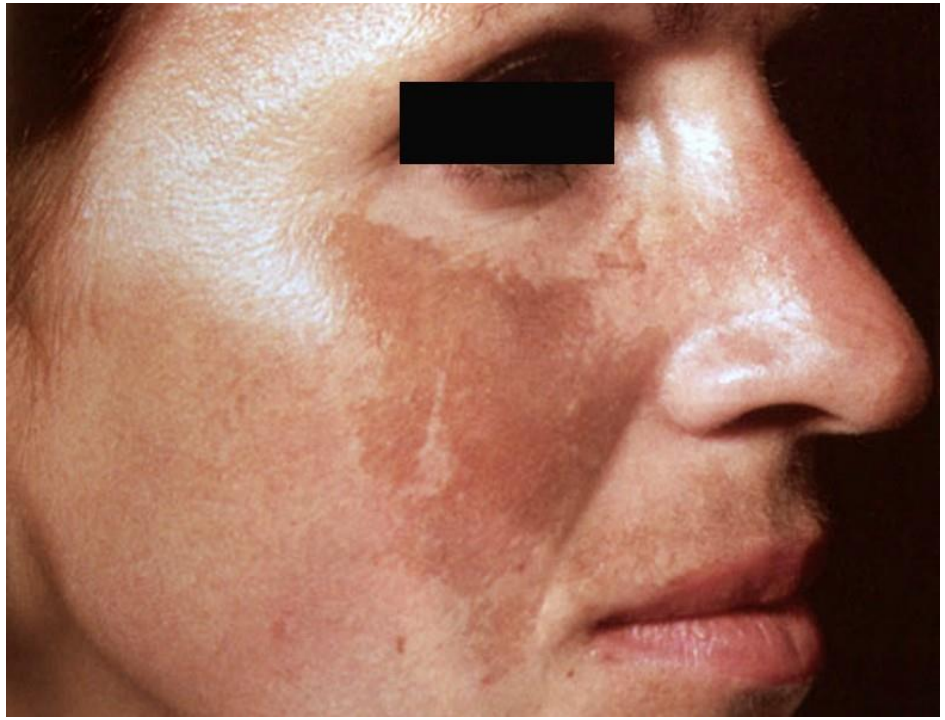
*Occasionally mosaicism only seen in keratinocytes

Podela

DISORDERS CHARACTERIZED BY RETICULATED PIGMENTATION	
Disorder	**Key features**
Confluent and reticulated papillomatosis	Elevated with rough texture; favors neck and upper trunk (see Fig. 67.20); responds well to minocycline
Erythema ab igne	Widely spaced net that corresponds to vascular pattern; due to heat injury (see Ch. 88)
Atopic dirty neck	Anterolateral neck
Prurigo pigmentosa	Typically young Japanese women; favors the back, neck, and chest; recurrent crops of pruritic papulovesicles that resolve with a reticulated pattern of hyperpigmentation
Dyskeratosis congenita*	XR > AD and AR forms (see Table 67.8); pterygium/nail dystrophy (see Fig. 67.23C), leukoplakia, pancytopenia; increased risk of mucosal squamous cell carcinoma and leukemia
Naegeli–Franceschetti–Jadassohn syndrome	AD due to *KRT14* mutations; fading reticulated hyperpigmentation, dental anomalies, hypohidrosis, palmoplantar keratoderma, hypoplastic dermatoglyphs, nail dystrophy
Dermatopathia pigmentosa reticularis	AD due to *KRT14* mutations; persistent reticulated hyperpigmentation (see Fig. 67.24), alopecia, nail dystrophy; palmoplantar keratoderma and hypoplastic dermatoglyphs in some patients
X-linked reticulate pigmentary disorder	XR due to *POLA1* mutations; generalized reticulated pigmentation in male patients (see Fig. 67.25); neonatal colitis, recurrent pneumonia, hypohidrosis, photophobia; amyloid deposits in adults
Dowling–Degos disease (DDD)	AD due to mutations in *KRT5*, *POFUT1*, and *POGLUT1* genes; reticulated hyperpigmentation favoring major flexures (see Fig. 67.26); may be composed of or admixed with discrete hyperpigmented macules and papules; variant associated with hidradenitis suppurativa due to *PSENEN* mutations
Galli–Galli disease	Acantholytic variant of DDD
Haber syndrome	Rosacea-like facial eruption plus the clinical features of DDD
Pigmentatio reticularis faciei et colli	Possible variant of DDD; hyperpigmentation of the face and neck plus multiple epidermoid cysts
Reticulate acropigmentation of Kitamura	AD due to *ADAM10* mutations; atrophic acral lentigo-like lesions, palmoplantar and dorsal phalangeal pitting
Epidermolysis bullosa simplex (EBS) with mottled pigmentation* and generalized severe EBS	AD due to *KRT5/14* mutations, with a specific P25L *KRT5* mutation usually underlying EBS with mottled pigmentation (see Ch. 32)
Mendes da Costa disease*	Traumatic bullae and hyperpigmentation, usually acral; dwarfism, atrichia
Cantu syndrome	Reticulated pigmentation of face, forearms and feet; palmoplantar keratoderma
Reticulate genital hyperpigmentation associated with localized vitiligo*	Congenital or acquired reticulate hyperpigmentation of the genitalia, followed by the development of vitiligo in the same region
Mitochondrial disorders	Sun-exposed areas (e.g. cheeks, dorsal aspects of the forearms and hands); additional cutaneous findings include hypertrichosis, hair shaft abnormalities and acrocyanosis (see Ch. 63)
Postinflammatory	Lichenoid dermatoses (e.g. lichen planus pigmentosus); contact dermatitis (e.g. due to benzoyl peroxide)
Drug-induced	Diltiazem (sun-exposed areas); chemotherapeutic agents such as 5-fluorouracil and bleomycin (see Table 67.4)
*Also dyschromatosis.	

Melazma

- Melasma (Chloasma)
- *Gr*. “melas” – crno
- Stečena hipermelanoza lica
- Mlade i žene srednjih godina
- Tamniji fototipovi



Melazma - patofiziologija

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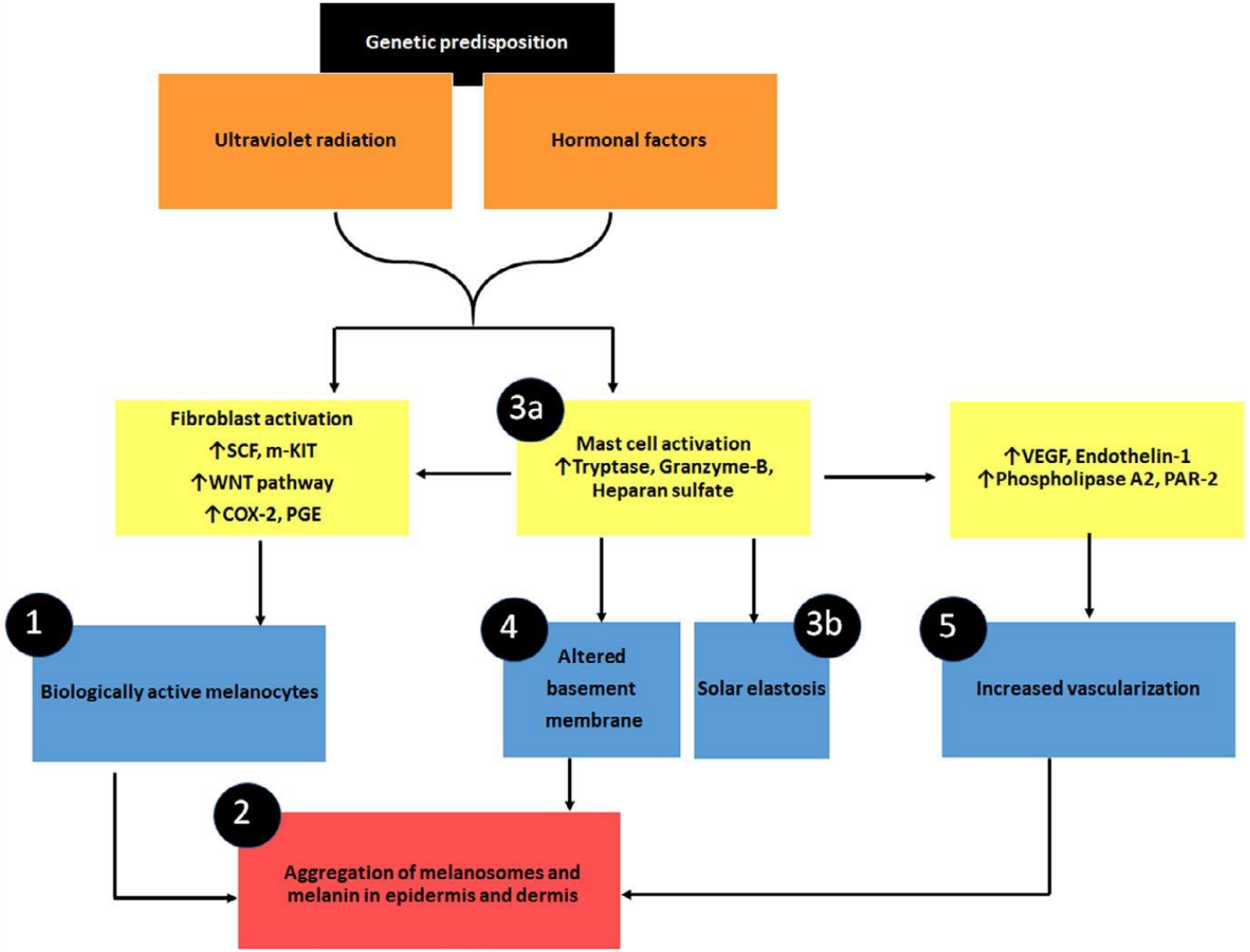
DOI: 10.1111/jocd.14382

JCD Journal of Cosmetic Dermatology WILE

REVIEW ARTICLES

The pathogenesis of melasma and implications for treatment

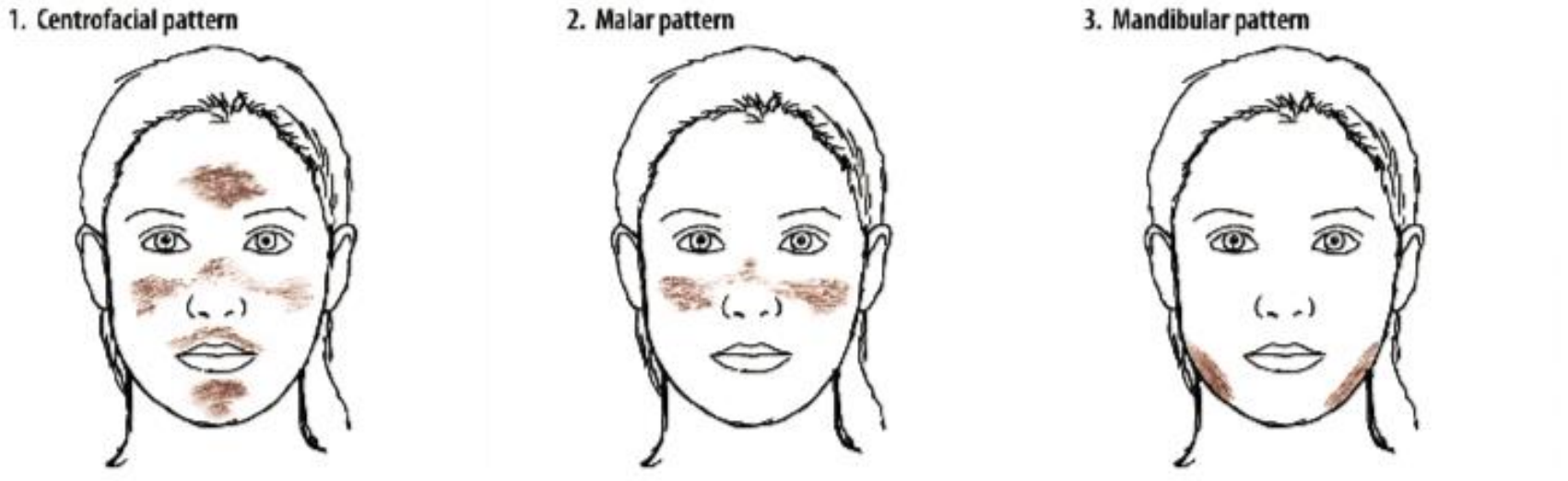
Ofir Artzi MD[1,2] | Tamir Horovitz MD[1,2] | Efrat Bar-Ilan MD[1,2] | Waseem Shehadeh MD[1,2] | Amir Koren MD[1,2] | Lior Zusmanovitch MD[1,2] | Joseph N. Mehrabi MD[2] | Fares Salameh MD[1,2] | Gila Isman Nelkenbaum MD[1,2] | Eyal Zur RPh[4] | Eli Sprecher MD, PhD[1,2] | Jacob Mashiah MD[1,2,3]



Artzi et al. JCD, 2021

Melazma – klinička slika

- **Lice**, dekolte, nadlaktice
- Klinički oblici: *centrofacijalni (65%), malarni (20%), mandibularni (15%)*

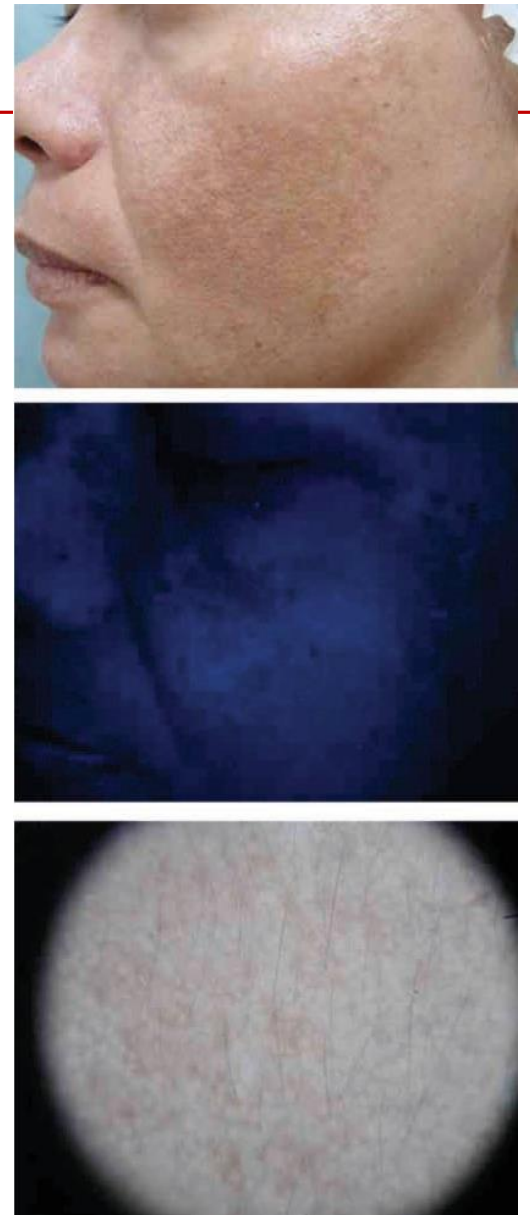


Melazma – klinička slika

Prema lokalizaciji pigmenta
Epidermalna
Dermalna
Mešovita
Inaparentna

- Wood-ova lampa

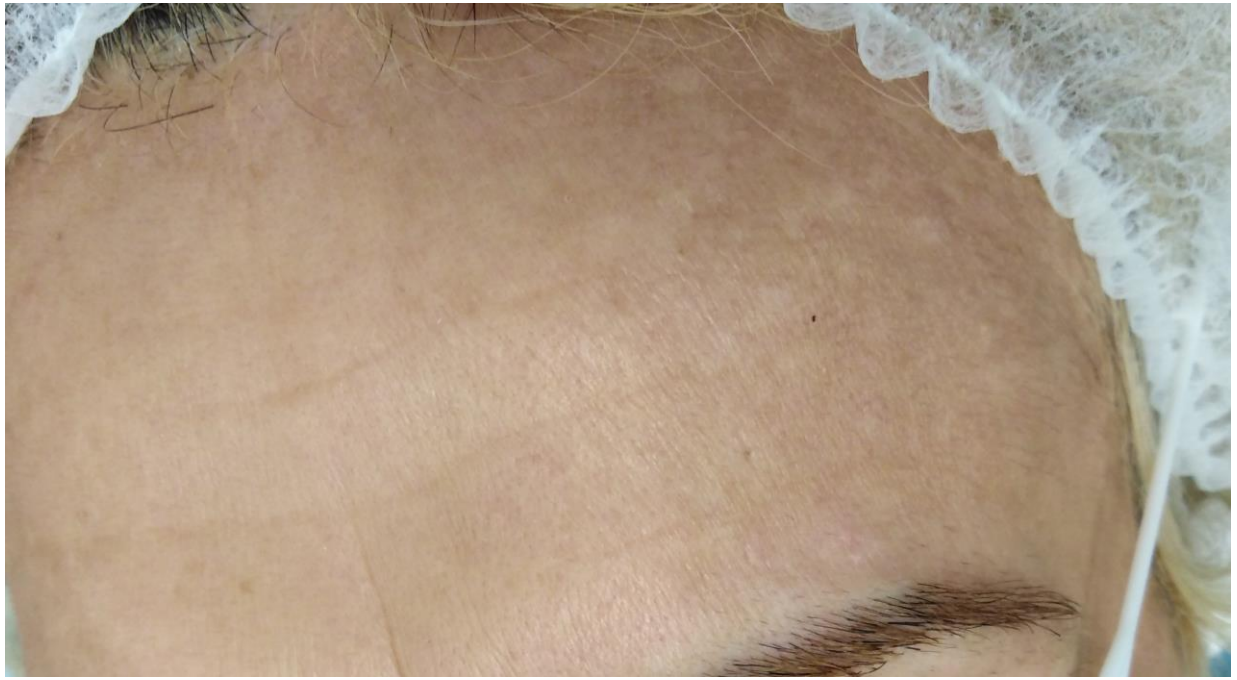
Epidermalna melazma



Dermalna melazma

Melazma – terapija

- Topikalna
- Oralna
- Proceduralna
- Kombinovana



Melazma – topikalna terapija

- Fotoprotekcija (UVA, UVB filteri, blokatori vidljive svetlosti)
- Depigmentacijski agensi
  - *Hidrokinon*
  - *Azelaična kiselina*
  - *Vitamin C*
- Retinoidi
  - *Tretinoin*
  - *Adapalen*
- Traneksamična kiselina

Melazma – topikalna terapija: najčešće kombinacije

Kligmanova i Willisova formula	**Pathakova formula**	**Westerhofova formula**	**Katsambasova formula**
5% hidrokinon, 0,1% tretionin, 0,1% deksametazon	2% hidrokinon, 0,05-0,1% tretionin	4,7% N-acetilcistein, 2% hidrokinon, 0,1% triamcinolon acetonid	4% hidrokinon, 0,05% tretionin, 1% hidrokortizon acetat

Melazma – terapija

- Hemijski pilinzi
  - Glikolna kiselina
  - Salicilna kiselina
  - Trihlorsirćetna kiselina

Oralna terapija

- Traneksemična kiselina

- Laseri i terapija svetlošću
  - Ablativni laseri: - CO2 laser
    - ER: YAG laser
  - Neablativni laseri: - Pikosekundni
    - QS-Nd:YAG !
  - 694 nm rubin frakcioni laser
  - Intenzivna pulsirajuća svetlost

Melazma – th opcije

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DOI: 10.1111/jocd.14382

JCD Journal of Cosmetic Dermatology WILEY

The pathogenesis of melasma and implications for treatment

Treatment modality	Treatment mechanism				
	Inhibiting biologically active melanocytes	Degrading melanosomes and melanocytes	Restoring changes in basement membrane	Reducing the vascular component	Reducing mast cell count and solar elastosis
QS laser		✓		✓	
PS laser		✓			
NAFL		✓			✓
FAL		✓	✓		✓
IPL		✓		✓	
Topical HQ	✓	✓			
Oral TXA	✓			✓	✓
Topical TXA	✓			✓	✓
Topical MET	✓				
Topical CYS	✓				
PBM	✓				
Pulsed RF microneedling			✓	✓	✓
Fractional RF			✓		✓
Heparanase inhibitors			✓		
PDL				✓	
Niacinamide	✓				✓
Medical plants	✓				✓
Topical Tacrolimus					✓
Topical steroids	✓	✓			✓

Artzi et al. JCD, 2021

PIH

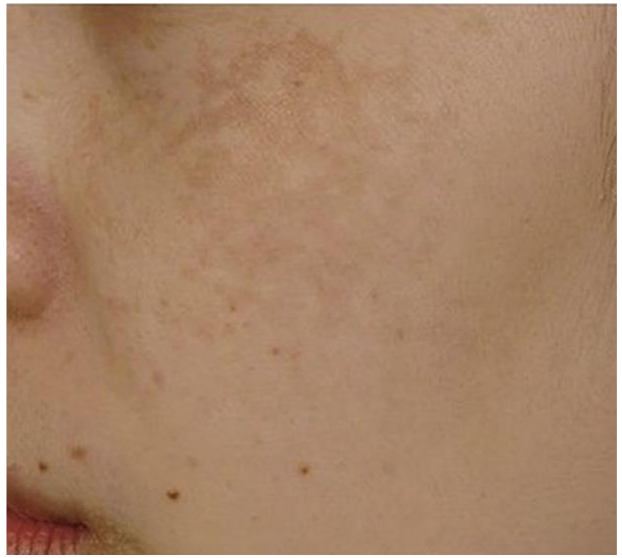
Postinflammatory hyperpigmentation: A comprehensive overview

Treatment options and prevention

Suteeraporn Chaowattanapanit, MD,[a,b] Narumol Silpa-archa, MD,[a,c] Indermeet Kohli, PhD,[a] Henry W. Lim, MD,[a] and Iltefat Hamzavi, MD[a]
Detroit, Michigan, and Khon Kaen and Bangkok, Thailand

Table I. Dermatologic conditions that can cause postinflammatory hyperpigmentation

Inflammatory dermatoses	Acne/acneiform eruption	Infections	Impetigo
	Pseudofolliculitis barbae		Viral exanthem
	Eczema		Chickenpox
	Atopic dermatitis		Herpes zoster
	Irritant contact dermatitis		Dermatophytosis
	Allergic contact dermatitis		Syphilis
	Pigmented contact dermatitis		Pinta
	Photoallergic contact dermatitis		Onchocerciasis
	Lichen simplex chronicus	Drug reactions	Phototoxic dermatitis
	Insect bites		Morbilliform eruption
	Papulosquamous disorders		Erythema multiforme
	Psoriasis		Fixed drug eruption
	Pityriasis rosea		Stevens-Johnson syndrome/toxic epidermal necrolysis
	Lichen planus/lichen planus pigmentosus		Lichenoid drug eruption
	Lichenoid dermatitis	Dermatologic procedures	Chemical peel
	Erythema dyschromicum perstans		Dermabrasion
	Connective tissue disease		Cryotherapy
	Lupus erythematosus		Laser treatment
	Vasculitis		Intense pulsed light treatment
	Morphea/scleroderma	Miscellaneous	Mycosis fungoides
	Atrophoderma of Pasini and Pierini		Neurotic excoriation
	Vesiculobullous disorders		Sunburn
	Pemphigus		Trauma
	Bullous pemphigoid		Friction
	Dermatitis herpetiformis		



JAAD, 2017

PIH – algoritam za dg i th

Postinflammatory hyperpigmentation: A comprehensive overview

Treatment options and prevention

Suteeraporn Chaowattanapanit, MD,[a,b] Narumol Silpa-archa, MD,[a,c] Indermeet Kohli, PhD,[a] Henry W. Lim, MD,[a] and Iltefat Hamzavi, MD[a]
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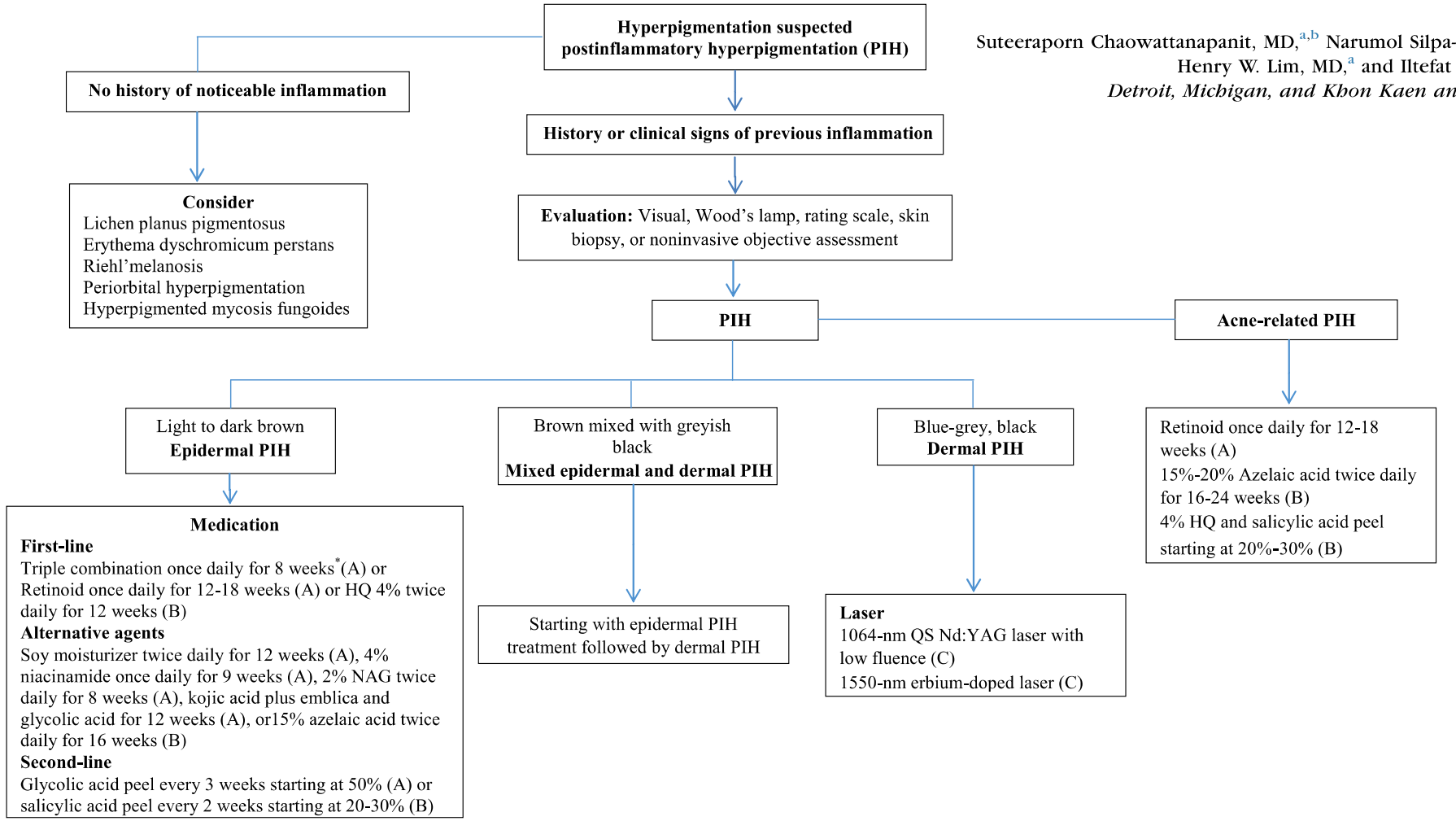

JAAD, 2017

PIH

Table I. Treatment options for hyperpigmentation and their proposed mechanisms of action

Treatment	Mechanism of action				
	Tyrosinase inhibition	Melanosome transfer inhibition	Increased epidermal turnover	Antioxidation	Other
Hydroquinone	●				
Mequinol	●				
Retinoic acid	●	●	●		
Azelaic acid	●				
Arbutin/deoxyarbutin	●				● Melanosome maturation inhibition
Licorice	●				
Kojic acid	● Interacts with copper				
Soy		● PAR-2			
Ascorbic acid (vitamin C)	● Interacts with copper			●	
Niacinamide		●			
N-acetyl glucosamine	●				
Aloesin	●				
Mulberry				●	
Rucinol	●				
Emblica	●			●	
Pycnogenol				●	
Mulberry	●			●	
Coffeeberry				●	
Green tea	●			●	
Silymarin	●			●	
Grape seed extract				●	
Orchid				●	
Belides		●		●	
Tranexamic acid				●	● Inhibits UV-induced plasmin activity in keratinocytes
Polypodium leucotomos				●	
Glutathione	●			●	
Chemical peel			●		
Dermabrasion			●		
Pigmented-specific laser					● Destroys melanin

Postinflammatory hyperpigmentation: A comprehensive overview

Treatment options and prevention

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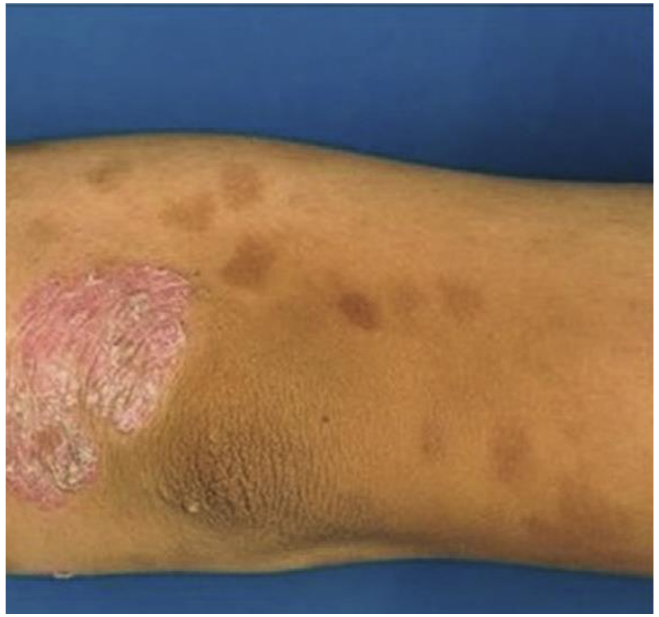


JAAD, 2017

Lekovi – pigmentacije

An Update on Drug-Induced Pigmentation

Amanda F. Nahhas[1,2] · Taylor L. Braunberger[2] · Iltefat H. Hamzavi[2]

- Oko 10% do 20% of stečenih hiperpigmentacija, kod pojedinih lekova i do 25% pacijenata koji ih primaju

- Pigmentacije i nokatnog aparata i sluzokoža

- Četiri mehanizma:
  1. Akumulacija melanina izazvana:
     (a) direktnom indukcijom melanocita na preteranu produkciju melanina
     (b) nespecifičnom kutanom inflamatornom reakcijom na lek
     (c) stvaranjem stabilnih kompleksa lek-melanin koji sprečavaju uklanjanje melanina od strane dermalnih melanofaga
  1. Akumulacija leka koji saturiše makrofage u dermu (koji onda ne mogu da ga eliminišu) ili akumulacija u vidu slobodno razbacanih granula u ekstracelularnom matriksu (nevezanih za melanin)
  2. Sinteza novog pigmenta pod uticajem leka, npr. lipofuscina
  3. Deponovanje gvožđa nakon oštećenja krvih sudova izazvanog lekom i ekstravazacije eritrocita i njihove lize

Am J Clin Dermatol, 2018

Lekovi – pigmentacije

Chemotherapeutic agents	
BCNU (carmustine)	• Hyperpigmentation at sites of topical application (not with parenteral administration)
Bleomycin (intravenous or intralesional)	• Linear, flagellate bands that favor the trunk and may be associated with minor trauma (see text) • Transverse melanonychia • Hyperpigmentation overlying joints/pressure points or localized to striae and palmar creases • Sclerodermoid changes
Busulfan	• Generalized hyperpigmentation resembling Addison disease; sometimes associated with drug-induced pulmonary fibrosis
Cyclophosphamide	• Diffuse hyperpigmentation of the skin and mucous membranes • Pigment localized to the nails (transverse, longitudinal, or diffuse melanonychia), palms and soles, or teeth
Dactinomycin	• Generalized hyperpigmentation, most prominent on the face
Daunorubicin	• Hyperpigmentation of sun-exposed areas • Transverse brown–black melanonychia
Doxorubicin	• Hyperpigmentation overlying the small joints of the hands and involving the palms (especially the creases), soles, and oral mucosa (buccal, tongue) • Transverse melanonychia
5-Fluorouracil	• Hyperpigmentation in sun-exposed areas (~5% of patients treated systemically; often follows an erythematous photosensitivity reaction) • Increased pigmentation of skin overlying veins in which the drug was infused • Other sites include the dorsal aspects of the hands, palms/soles, and radiation ports • Transverse or diffuse melanonychia; lunular pigmentation
Hydroxyurea	• Reversible hyperpigmentation over pressure points and on the back • Longitudinal, transverse or diffuse melanonychia; lunular pigmentation
Mechlorethamine (nitrogen mustard)	• Topical use for cutaneous T-cell lymphoma may result in generalized hyperpigmentation • More intense in lesional skin
Methotrexate	• Uniform hyperpigmentation in sun-exposed areas (occasionally follows an erythematous photosensitivity reaction)
Antimalarials	
Chloroquine, hydroxychloroquine, quinacrine	• Gray to blue–black pigment, usually pretibial, with (hydroxy)chloroquine; face, hard palate, sclerae, and subungual areas may be involved • Diffuse yellow to yellow–brown discoloration with quinacrine • Discoloration affects up to 25% of patients

Heavy metals	
Arsenic	• Areas of bronze hyperpigmentation ± superimposed "raindrops" of lightly pigmented skin; favors axillae, groin, palms, soles, nipples, and pressure points • Dyspigmentation appears 1–20 years after arsenic exposure, with a strong dose–response relationship • Palmoplantar keratoses and squamous cell carcinoma typically develop after dyspigmentation (see Ch. 88)
Bismuth	• Generalized blue–gray discoloration of the face, neck and dorsal hands • Oral mucosa and gingivae may be involved
Gold (chrysiasis)	• Permanent blue–gray discoloration in sun-exposed areas, particularly around the eyes
Iron	• Permanent brown pigment at injection sites or in areas of application of ferric subsulfate (Monsel's) solution as a hemostatic agent • Dermal hemosiderin deposits (due to lysis of extravasated red blood cells and release of their iron stores) are commonly observed in the setting of venous hypertension, in pigmented purpuric dermatoses, and as a side effect of sclerotherapy of superficial veins
Lead	• "Lead line" in gingival margin • Nail discoloration
Mercury	• Slate-gray discoloration, particularly in skin folds
Silver (argyria)	• Diffuse slate-gray discoloration (see Fig. 67.7A), increased in sun-exposed areas; occurs in settings of occupational exposure, alternative medications, or systemic absorption from use of silver sulfadiazine on extensive burns/wounds • The nail unit (diffuse or localized to the lunulae) and sclerae may also be affected • Sites of topical application, e.g. of silver sulfadiazine to burns or ulcers

Bolognia, 2018

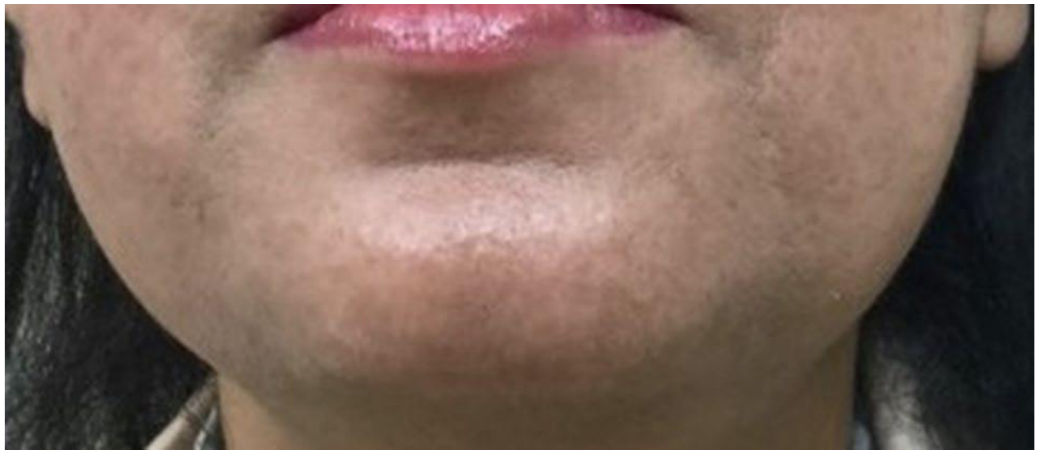
Lekovi – pigmentacije

Miscellaneous compounds	
Amiodarone	• Slate-gray to violaceous discoloration of sun-exposed skin, especially the face (less common than erythema from photosensitivity) • Fair-skinned patients after long-term, continuous therapy
Azidothymidine (zidovudine, AZT)	• Longitudinal > transverse and diffuse melanonychia (up to 10% of patients); blue lunulae • Mucocutaneous hyperpigmentation (e.g. widespread diffuse, acral, oral macules); most common in patients with darkly pigmented skin, and may be accentuated in areas of friction or sun exposure
Clofazimine	• Diffuse red to red–brown discoloration of skin, conjunctivae • Violet–brown to blue–gray discoloration, especially of lesional skin
Diltiazem (rarely amlodipine)	• Slate-gray to gray–brown discoloration of sun-exposed skin in patients with skin phototypes IV–VI; perifollicular accentuation and a reticular pattern may be observed
Dioxins	• Hyperpigmentation may occur in sun-exposed areas • Chloracne is a more common skin finding
Ezogabine	• Blue–gray discoloration, most often lips, face, nail beds, and hard palate • Black pigment deposits on conjunctivae
Hydroquinone	• Hyperpigmentation in areas of application due to irritant contact dermatitis (i.e. postinflammatory) or exogenous ochronosis; the latter may also result in small “caviar-like” papules
Imatinib (also dasatinib)	• Localized or diffuse hyperpigmentation (<5% of patients) • Diffuse melanonychia, repigmentation of gray hair, and pigmentation of the gingiva and teeth
Minocycline	• *Type I*: blue–black discoloration in sites of inflammation and scars, including those due to acne or ablative laser therapy (see Fig. 127.6A) • *Type II*: blue–gray macules/patches (1 mm–10 cm in size) within previously normal skin, most often on the shins (see Figs 67.9 & 127.6B–D); sometimes misdiagnosed as ecchymoses • *Type III*: diffuse “muddy brown” pigmentation that is most prominent in sun-exposed areas • Blue–black discoloration may also involve nails, sclerae, oral mucosa, bones, thyroid, and teeth
Psoralens	• Diffuse hyperpigmentation after exposure to UVA light following oral administration (PUVA) • Circumscribed or linear streaks of hyperpigmentation can be seen with topical exposure, e.g. topical PUVA or phytophotodermatitis (exposure to psoralen-containing plants plus sunlight)
Psychotropic drugs (chlorpromazine, thioridazine, imipramine, desipramine, amitriptyline)	• Slate-gray to brown (with amitriptyline) discoloration in sun-exposed areas

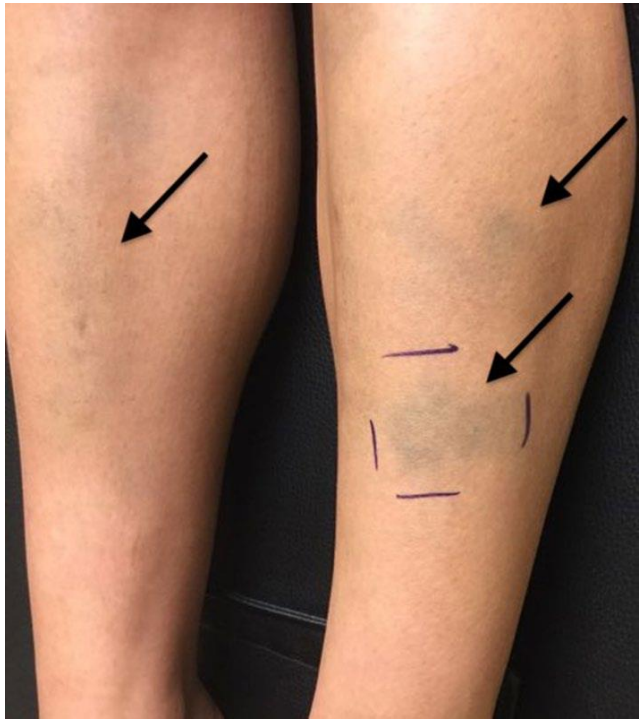
Lekovi – pigmentacije

An Update on Drug-Induced Pigmentation

Amanda F. Nahhas[1,2] · Taylor L. Braunberger[2] · Iltefat H. Hamzavi[2]



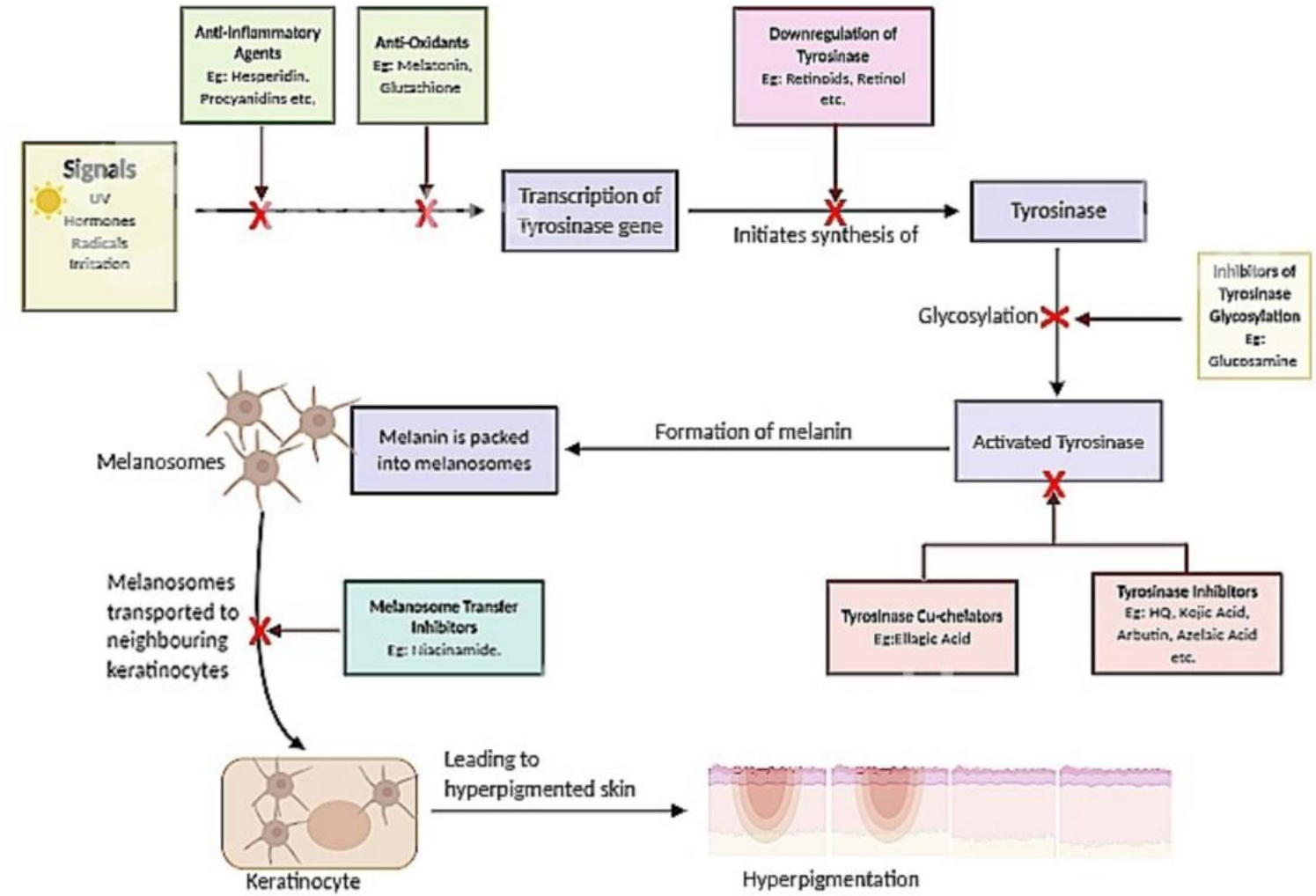
HHQ



Minociklin

Am J Clin Dermatol, 2018

Hiperpigmentacije – th opcije



Nautiyal A et al. Pigment Cell Melanoma Res, 2021

Aesthetic Dermatology
Editor: D.J. Goldberg
Vol. 5

Table 1. Topical skin-lightening agents

Ingredient	Pathway	Clinical trials
Reduction in melanin synthesis		
Hydroquinone	Inhibition of tyrosinase and melanin synthesis	Clinical studies in patients with melasma showed reduction of pigmentation [43]
Arbutin	Inhibition of tyrosinase and melanin production	Clinical trial showed overall skin lightness and improvement in solar lentigines after 12 weeks of treatment [12]
Licorice extract	Inhibits tyrosinase	Glabridin inhibited UVB-induced pigmentation and erythema in guinea pigs [16] Trial for melasma treatment using liquiritin cream showed good to excellent results in 90% of the patients [17]
Kojic acid	Chelates copper, thus inhibiting tyrosinase	A 12-week, split-face trial of Chinese women with melasma showed greater efficacy of 2% kojic acid cream when mixed with 10% glycolic acid/2% HQ cream [19]
Azelaic acid	Reversibly blocks tyrosinase Inhibits mitochondrial metabolism, DNA, and protein synthesis	Comparative study showed that 20% azelaic acid is more effective than 2% hydroquinone in patients with melasma [21]
Vitamin C	Inhibits tyrosinase	Randomized, double-blind study in Japan: areas applied with a pro-vitamin C cream after UV exposure showed significantly less UVB-induced skin hyperpigmentation compared with controls [22]
Vitamin E	Inhibits tyrosinase (works best when combined with vitamin C)	Double-blind study comparing a combination of vitamins E and C with single preparations of vitamins E and C in the treatment of melasma or pigmented contact dermatitis showed that the combination treatment resulted in a significantly better clinical improvement in both conditions
Cysteamine	Inhibits tyrosinase and peroxidase	Double-blind, randomized, placebo control of 5% cysteamine cream applied twice daily showed greater efficacy than placebo in the treatment of melasma at both 2 and 4 months [41]

Cosmeceuticals

Editors
J. Comstock
M.H. Gold

Basel: Carger, 2021

Aesthetic Dermatology
Editor: D.J. Goldberg
Vol. 5

Cosmeceuticals

Editors
J. Comstock
M.H. Gold

Reduction in melanocyte activation		
Tetrapeptide-30	Reduces keratinocyte-induced activation of melanocytes	A clinical study of women with melasma and post-inflammatory hyperpigmentation from acne showed a significant improvement after 4 weeks of topical tetrapeptide-30 compared to vehicle [24]
Undecylenoyl phenylalanine	α-MSH antagonist: inhibition of melanotropin and the activation of melanocytes	Double-blind, randomized, comparative study evaluated undecylenoyl phenylalanine 2% topical cream in female melasma patients where 85% had a statistically significant difference ($p < 0.001$) in efficacy between the active preparation and the vehicle [25]
Broad-spectrum sunscreen	Blocks UV-induced activation of melanocytes	Asian pregnant females who applied broad-spectrum sunscreen (SPF 50) for a 12-month period had a much lower incidence of developing melasma compared to their cohorts [26]
Inhibition of melanosome transfer		
Niacinamide	Inhibits melanosome transfer	A randomized, split-face study of 27 melasma patients compared niacinamide 4% cream with 4% hydroquinone cream and the colorimetric improvement was similar in both treatment arms at week 8 [28]
Soy	Inhibits melanin transfer by inhibiting the PAR-2 pathway via trypsin inhibitors	A 12-week study of females with hyperpigmentation secondary to photodamage who applied soy-containing daily moisturizer with sunscreen twice daily showed significant improvement in their hyperpigmentation, skin tone, and overall skin appearance [32]

Basel: Carger, 2021

Aesthetic Dermatology
Editor: D.J. Goldberg
Vol. 5

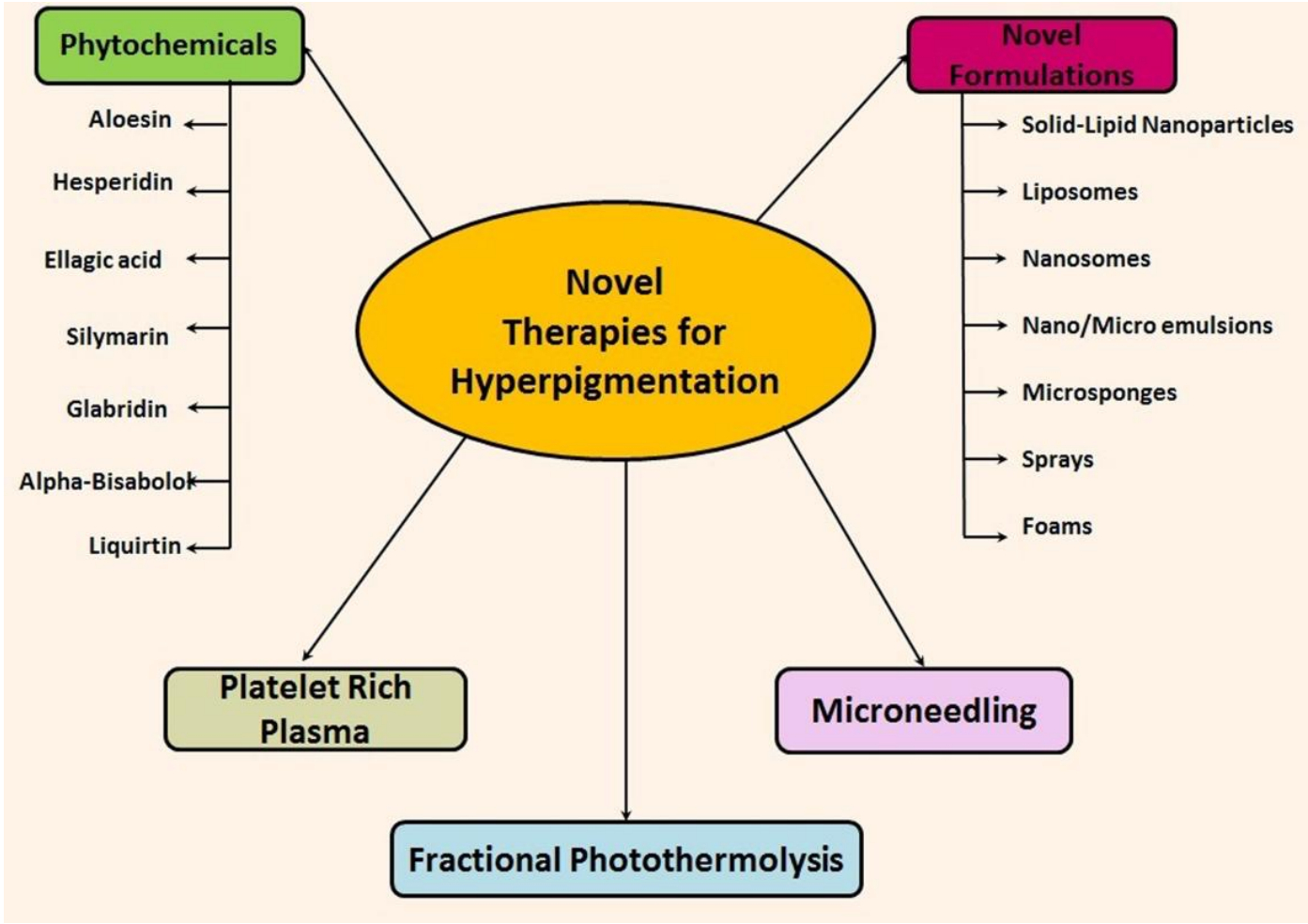
Cosmeceuticals

Editors
J. Comstock
M.H. Gold

Ingredient	Pathway	Clinical trials
Removal of epidermal pigment		
Alpha hydroxy acids	Chemically exfoliate	Study of refractory melasma in Japanese females was successfully treated and results maintained for 10 months by using a daily combination of a 20% glycolic acid chemical peels and 5% hydroquinone at home [44]
Linoleic acid	Increases cell turnover	When applied topically with alpha linoleic acid and oleic acid, linoleic acid was found to be efficacious in inhibiting UV-induced hyperpigmentation in the skin of brown guinea pigs [35]
Retinoids	Increases cell turnover Interferes with melanin dispersion Inhibits tyrosinase	Combination therapy of tretinoin 0.1%, hydroquinone 4%, and dexamethasone 0.1% cream synergistically treats patients faster with a favorable safety profile. Tretinoin was shown to reduce the atrophy of the corticosteroid and facilitated epidermal penetration and delivery of the hydroquinone [15, 37]

Basel: Carger, 2021

Hiperpigmentacije – nove th opcije



Nautiyal A et al. Pigment Cell Melanoma Res, 2021

Fotoprotekcija

- Krucijalna u terapiji i prevenciji hiperpigmentacija
- Fe oksid za vidljivu svetlost?
- Oralna i topikalna?

Fotoprotekcija

REVIEW

Photoprotection beyond ultraviolet radiation: A review of tinted sunscreens

Alexis B. Lyons, MD,[a] Carles Trullas, MSc,[b] Indermeet Kohli, PhD,[a] Iltefat H. Hamzavi, MD,[a] and Henry W. Lim, MD[a]
Detroit, Michigan; and Barcelona, Spain

Cutaneous Interaction with Visible Light: What Do We Know

Leah Cohen, BA, Merrick A. Brodsky, MD, Raheel Zubair, MD, MHS, Indermeet Kohli, PhD, Iltefat H. Hamzavi, MD, Mona Sadeghpour, MD

Capsule Summary

- We synthesize current evidence for the role of visible light in inducing pigmentary changes in patients with darker skin phototypes.
- For patients with disorders of hyperpigmentation, such as melasma and post-inflammatory hyperpigmentation, the use of sunscreens containing iron oxides can help prevent pigmentary changes caused by visible light.

CAPSULE SUMMARY

- Ultraviolet radiation and visible light both have biologic effects on the skin.
- Tinted sunscreens can provide photoprotection against visible light. Patients with hyperpigmentation disorders, including melasma, or those with visible light—induced photodermatoses can benefit from the use of tinted sunscreen.

Table I. Dermatoses aggravated or induced by visible light

Visible light-aggravated dermatoses
Melasma
Postinflammatory hyperpigmentation
Lichen planus pigmentosus (most likely)
Photodermatoses with action spectrum in the visible light range
Cutaneous porphyrias
Solar urticaria
Chronic actinic dermatitis (uncommon)

JAAD, 2020, 2021

Fotoprotekcija

REVIEW

Photoprotection beyond ultraviolet radiation: A review of tinted sunscreens

Alexis B. Lyons, MD,[a] Carles Trullas, MSc,[b] Indermeet Kohli, PhD,[a] Iltefat H. Hamzavi, MD,[a] and Henry W. Lim, MD[a]
Detroit, Michigan; and Barcelona, Spain

Table II. Chemical formulas of pigments used in tinted sunscreens

	Color			
Variable	**Iron oxide red**	**Iron oxide yellow**	**Iron oxide black**	**Pigmentary titanium dioxide**
Chemical formula	Fe_2O_3	$FeO(OH)\cdot H_2O$	$FeO\cdot Fe_2O_3$	TiO_2
INCI name	CI 77491*	CI 77492	CI 77499	CI 77891

INCI, International Nomenclature of Cosmetic Ingredients.
*Color index (*CI*), a universally accepted nomenclature for pigments and dyes.

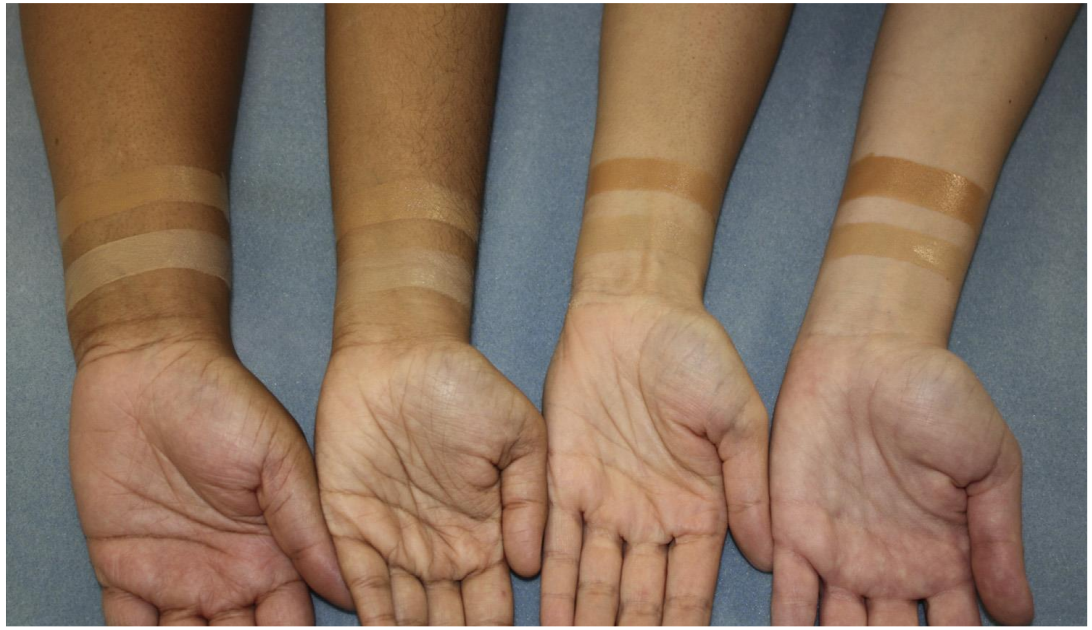


Fig 1. Two different shades of tinted sunscreens on various skin types.

JAAD, 2021

Hvala!

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Katedra dermatovenerologije, Medicinski fakultet, Univerzitet u Beogradu

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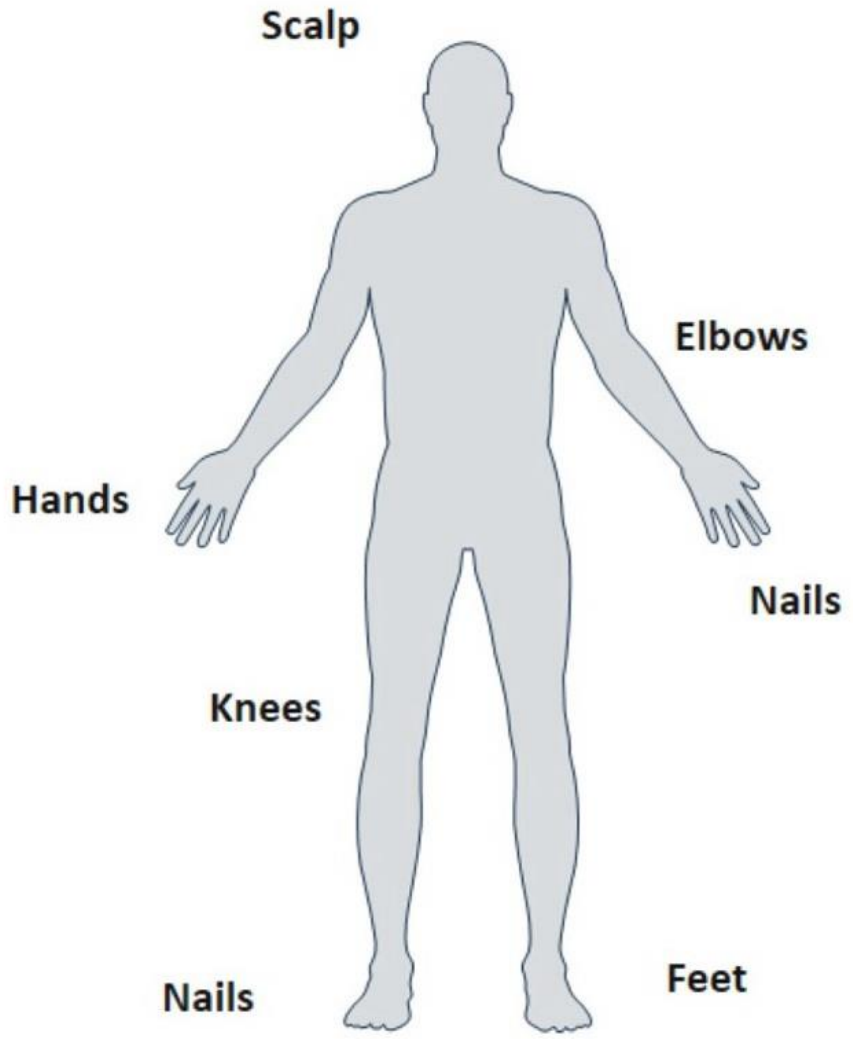
PSORIASIS VULGARIS REVIEW AND UPDATE

Prof. dr Danica Tiodorović
Klinika za dermatovenerologiju, UKC Niš
Medicinski Fakultet, Univerzitet u Nišu

PsO



Menter A, et al. *J Am Acad Dermatol*. 2008;58:826-850.

Hronična T-ćelijski posredovana bolest sa lokalizovanom hiperproliferacijom keratinocita i povišenim vrednostima Th1 i 17 T helper ćelijskih citokina (Th17)

20% pacijenata ima umereno do tešku psorijazu, koja zahvata najmanje **5%** površine tela

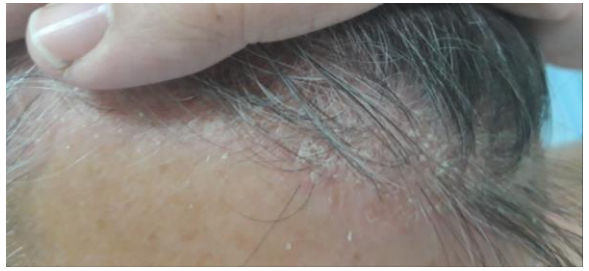
EPIDEMILOGIJA

- Veliko populaciono istraživanje "Multinational Assement of Psoriasis and Psoriatic Arthritis" (MAPP) -
  prevalenca psorijaze kreće se od 1,4% u Španiji do 3,3% u Kanadi
- Ukupna prevalenca - 1,9%
- Prevalenca u USA - 2,2%
- U Srbiji se procenjuje da 150.000 ljudi ima psorijazu

Starosna distribucija i genetska predispozicija

- Psorijaza se može javiti u bilo kom uzrastu

- Ipak, početak bolesti obično prati bimodalnu distribuciju
- 20-30 godine
- 50-60 godine

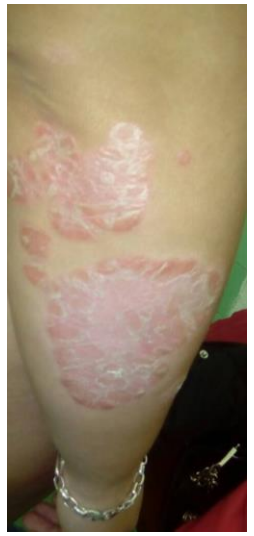


- Pozitivna porodična anamaneza je česta

- Oko 30% pacijenta imaju prvog srodnika sa psorijazom

Starosna distribucija i genetska predispozicija

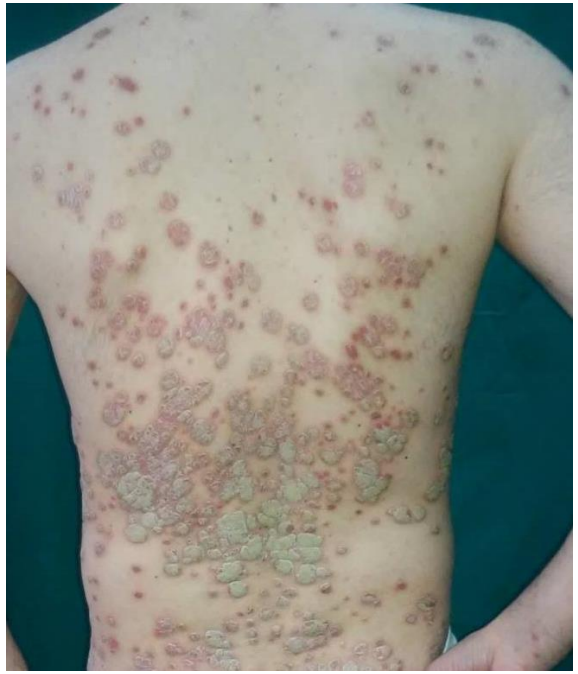
- Rizik za nastanak psorijaze povećava se sa brojem aficiranih rođaka
- Neke studije sugerišu da bimodalna distribucija predstavlja 2 različite forme psorijaze
- Pacijenti sa ranom pojavom psorijaze imaju težu formu psorijaze i mnogo veću verovatnoću za posedovanjem genetskog markera



Patogeneza

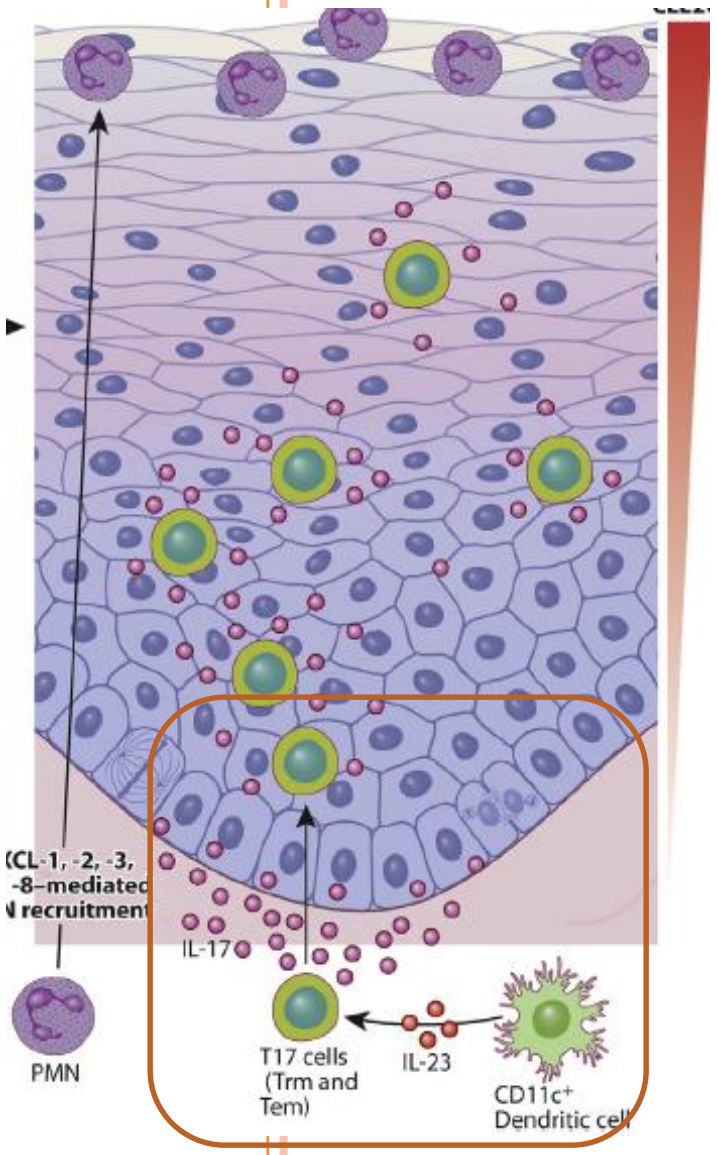
Kompleksna i tesno povezana sa:

- imunim sistemom
- psorijaza –asociranim lokusima
- autoantigenima
- brojinim faktorima spoljašnje sredine



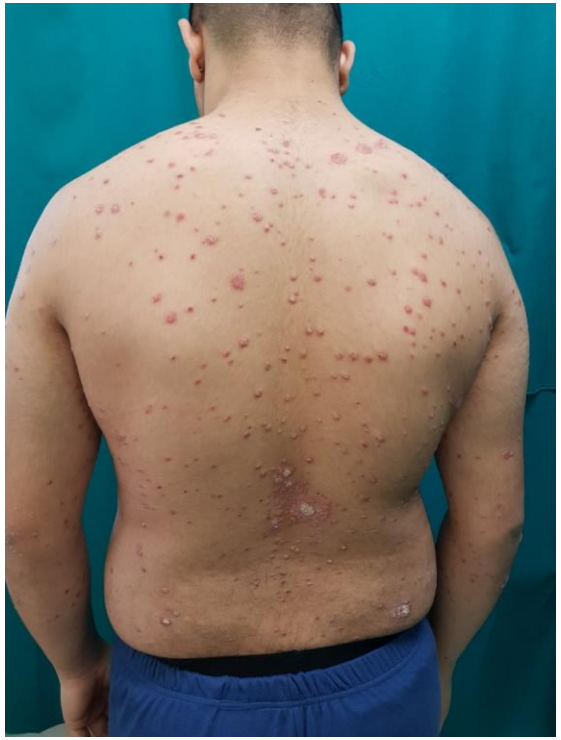
- IL23/17 osovina - predstavlja centralnu imunsku osnovu za razvoj psorijaze → povećane nivoe IL17

- Kao odgovor na IL23, patogene T17 ćelije produkuju visoke vrednosti IL17, koji ima širok inflamatorni efekat na keratinocite i brojne imunske ćelije u koži

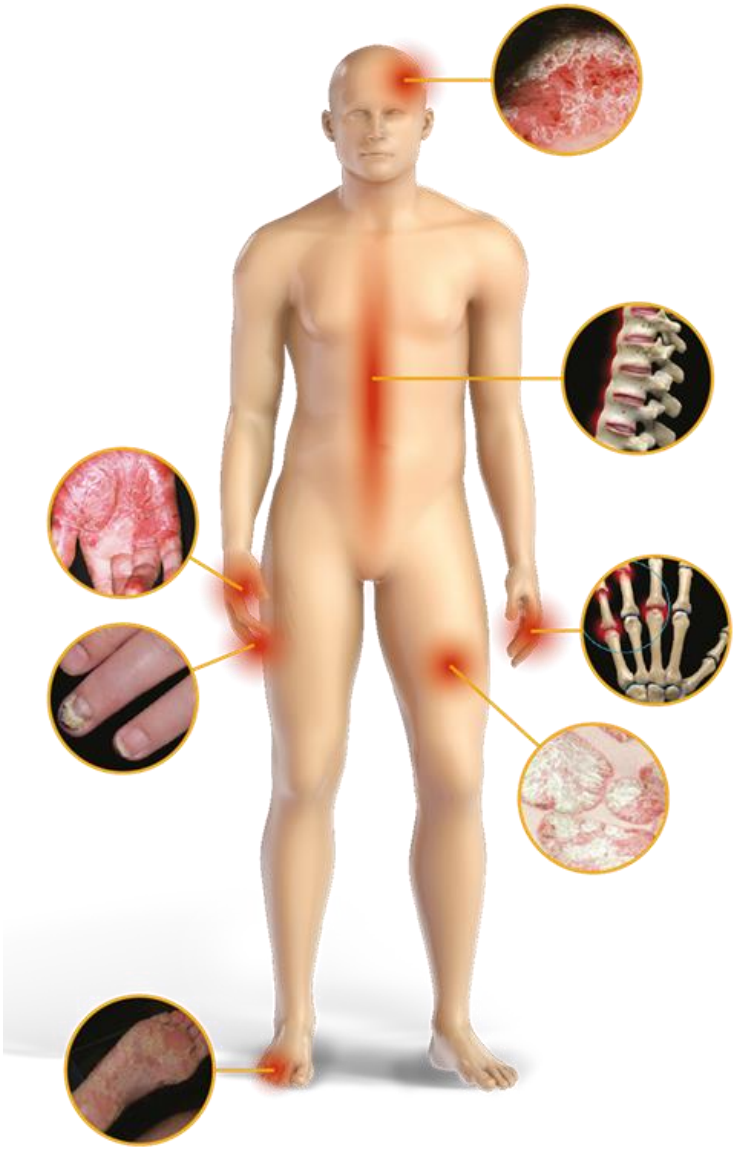


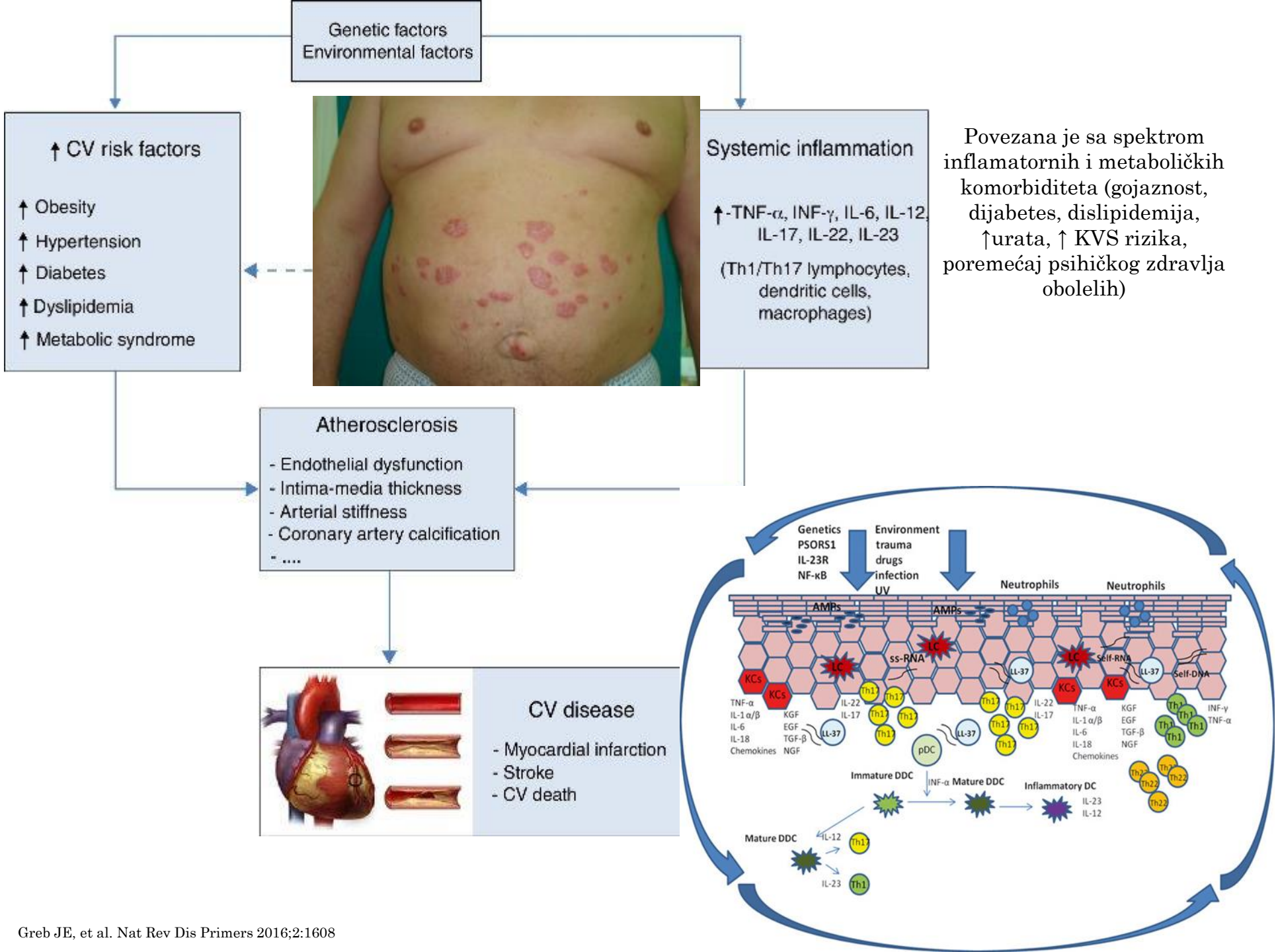
Klinički oblici

- hronična plak psorijaza
- gutatna (kapljičasta) forma
- psorijaza pregiba (inverzna)
- eritrodermijska psorijaza
- pustulozna (sa gnojanicama) psorijaza
- psorijaza dlanova i/ili tabana



Psorijaza znači više od bolesti kože





Povezana je sa spektrom inflamatornih i metaboličkih komorbiditeta (gojaznost, dijabetes, dislipidemija, ↑urata, ↑ KVS rizika, poremećaj psihičkog zdravlja obolelih)

Greb JE, et al. Nat Rev Dis Primers 2016;2:1608

Impact of systemic treatment of psoriasis on inflammatory parameters and markers of comorbidities and cardiovascular risk: results of a prospective longitudinal observational study

H. Montaudié,[1] C. Albert-Sabonnadière,[2] E. Acquacalda,[2] E. Fontas,[3] A. Danré,[2] C. Roux,[2] J.P. Ortonne,[1] J.P. Lacour,[1] L. Euller-Ziegler,[2] T. Passeron[1,4,*]

JEADV 2014, **28**, 1186–1191

Conclusions We observed a high frequency of disturbance of inflammatory parameters and markers of comorbidities and CV risk in a population with moderate to severe PsO and PsA, most of which were not detected before. A significant decrease in inflammatory parameters was noted after the introduction of systemic therapy, while other parameters remained unaffected by the treatment, except the weight that increased under biologics therapies.

Psoriasis is the independent factor for early atherosclerosis: A prospective study of cardiometabolic risk profile

Psorijaza jeste nezavisni faktor rane ateroskleroze – prospektivna studija kardiometaboličkog rizika

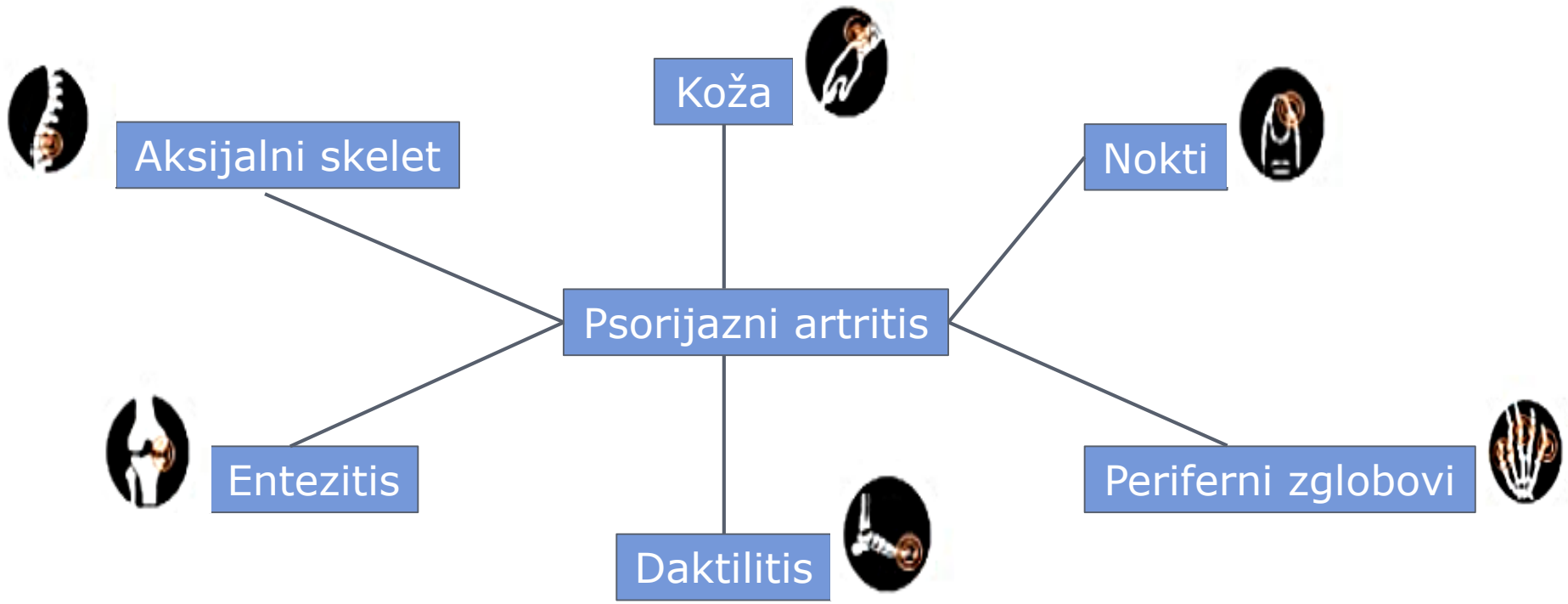
Miroslav Ž. Dinić*, Radoš D. Zečević*†, Zoran Hajduković†‡, Mirjana Mijušković†§, Predrag Djurić†‖, Zoran Jović†‖, Aleksandra Grdinić†‖, Mirjana Petrović†§, Brankica Terzić§, Janko Pejović†¶, Lidija Kandolf Sekulović*†

Zaključak. Kardiometabolički biomarkeri rizika i ultrasonografski znaci rane ateroskleroze u vezi su sa postojećom psorijazom

Vojnosanitetski pregled 2016, 73(12):1094-1101.

PSORIJAZA I PSORIJAZNI ARTRITIS

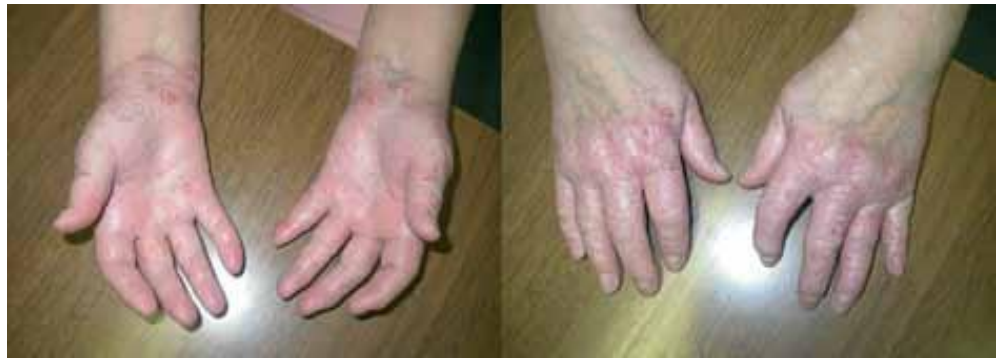
Približno 30% pacijenata sa psorijazom će razviti psorijazni artritis



Semin Arthritis Rheum. 2016 Dec;46(3):291-304. Clin Med (Lond). 2017 Feb;17(1):65-70.

Psorijazni artritis

- Kod oko 75% obolelih manifestuju se prvo promene na koži
- Kod oko 15% bolesnika pojava artritisa i promena na koži dešava se uporedo
- Kod oko 10% prvo se pojavljuje artritis, a potom promene na koži

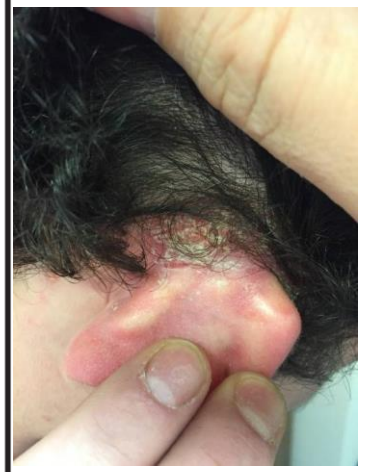


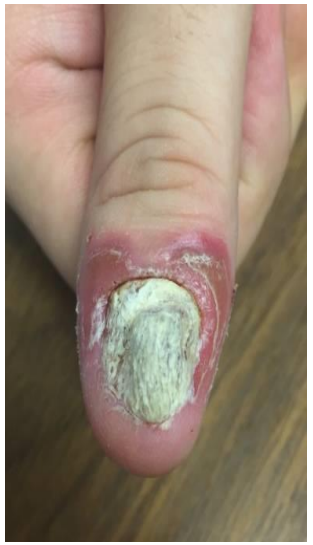
Reich K, et al. Br J Dermatol 2009;160:1040

Table 2. Predictors of psoriatic arthritis within the incidence cohort of psoriasis subjects*

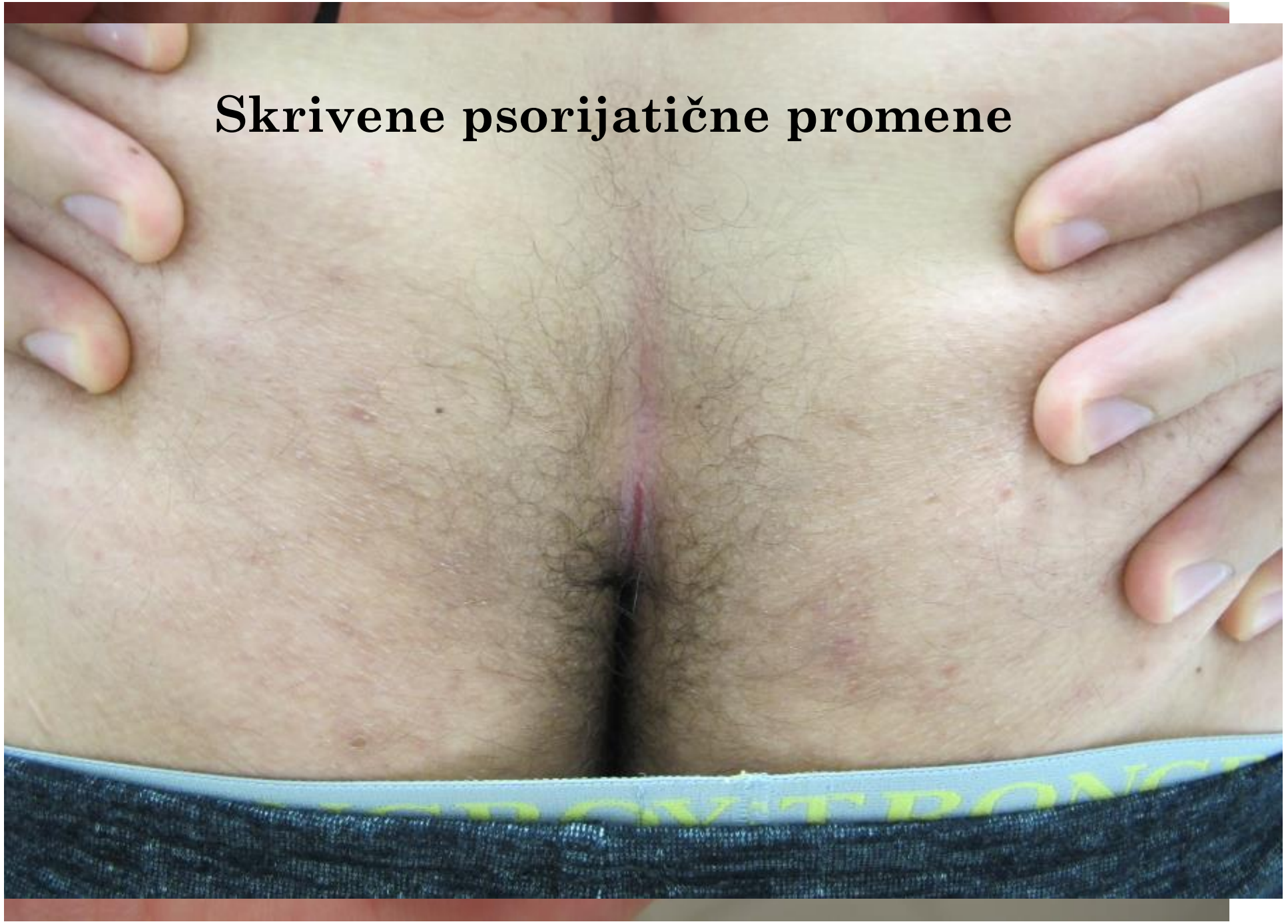
Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 61, No. 2, February 15, 2009, pp 233–239

	Univariate	Multivariate
Age, years†	0.91 (0.77–1.07)	0.92 (0.78–1.09)
Men (vs. women)	1.53 (0.90–2.59)	1.35 (0.78–2.33)
Calendar year†	0.78 (0.56–1.09)	0.76 (0.54–1.08)
Type of psoriasis		
Plaque	1.72 (0.81–3.63)	
Guttate	0.36 (0.09–1.48)	
Sebopsoriasis	1.96 (0.78–4.93)	
Pustular	–	
Unknown	0.82 (0.26–2.63)	
Site of psoriasis		
Scalp	3.89 (2.18–6.94)	3.75 (2.09–6.71)
Extremities	0.83 (0.47–1.45)	
Trunk	0.80 (0.40–1.58)	
Intergluteal/perianal	2.35 (1.32–4.19)	1.95 (1.07–3.56)
Face	1.15 (0.52–2.53)	
Palms and/or soles	0.20 (0.03–1.47)	
Axilla/groin	1.40 (0.44–4.48)	
Unknown	0.88 (0.32–2.44)	
No. of affected sites‡		
Unknown	1.06 (0.36–3.07)	
2 sites	0.77 (0.37–1.64)	
≥3 sites	2.24 (1.23–4.08)	
Nail dystrophy	2.93 (1.68–5.12)	2.24 (1.26–3.98)





Skrivene psorijatične promene



Quality of life issues in psoriasis

Jane Choi, MD, and John Y. M. Koo, MD
San Francisco, California

Psoriasis is associated with significant psychosocial morbidity and a decrease in health-related quality of life. It is important to view psoriasis as a serious disease and resist the tendency to underestimate its impact on overall patient well-being. The disability experienced by psoriasis sufferers is comparable to that of patients with other chronic illnesses such as heart disease, diabetes, cancer, and depression. Aggressive intervention is warranted in order to improve patient quality of life and decrease the potential for psychosocial sequelae. Health-related quality of life measures are becoming a necessary adjunct to traditional clinical assessments in the evaluation and treatment of psoriasis patients by the individual clinician. They also provide valuable information to government agencies and third party payers in the determination of resource allocation and reimbursement. (J Am Acad Dermatol 2003;49:S57-61).

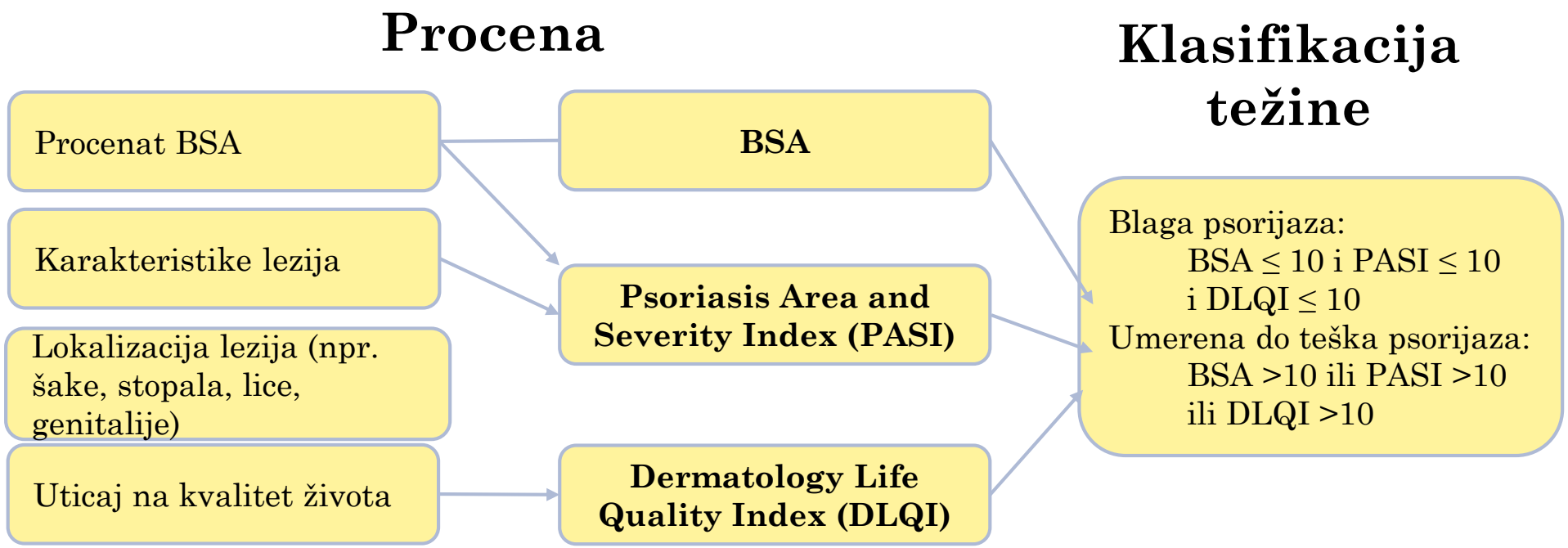
PSORIJAZA: PROCENA TEŽINE BOLESTI

- PASI (*Psoriasis Area and Severity Index*)
- BSA (*Body Surface Area*)
- DLQI (*Dermatological Quality of Life Index*)
- PGA (*Physician Global Assessment*)

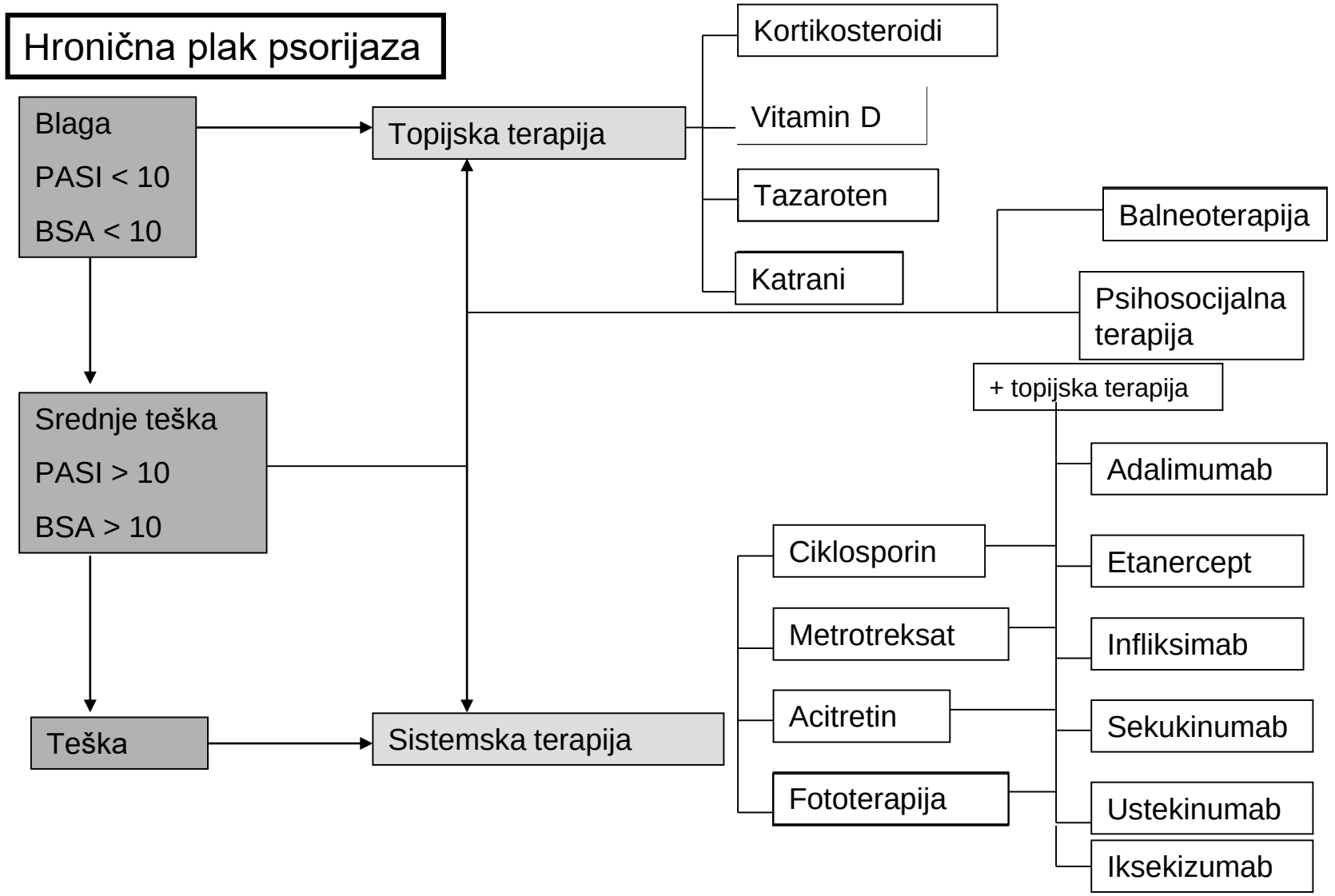
- *"Mean PASI and DLQI correlate predictably in patients with chronic moderate-to-severe plaque psoriasis undergoing treatment with biological agents. A reduction in PASI of at least 75% can translate to significant quality-of-life improvement in patients treated with these therapies."*

- Mattei L et al. *J Eur Acad Dermatol Venerol* 2014;28:333–337

PROCENA I KLASIFIKACIJA TEŽINE PSORIJAZE



Armstrong AW, et al. JAMA Dermatol 2013; 149: 1180-5.
Menter A, et al. J Am Acad Dermatol 2008; 58: 826-50.
Spuls PI, et al. J Invest Dermatol 2010; 130: 933-43.
Both H, et al. J Invest Dermatol 2007; 127: 2726-39.
Mrowietz U, et al. Arch Dermatol Res 2011; 303: 1-10.



GUIDELINES Serbian Journal of Dermatology and Venereology 2016; 8 (2): 61-78
DOI: 10.1515/sjdv-2016-0006

Serbian Association of Dermatovenereologists' Guidelines for the Diagnosis and Treatment of Psoriasis

Clinics in Dermatology (2008) 26, 580–586

ELSEVIER

Clinics in Dermatology

Emollients, moisturizers, and keratolytic agents in psoriasis

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[a]*Bioskin, Seydelstr. 18, D-10117 Berlin, Germany*
[b]*Department of Dermatology, San Gallicano Dermatological Institute, Via Chianesi 53, I-00144 Rome, Italy*

Abstract Emollients, moisturizers, and keratolytic agents are essential in the topical treatment of psoriasis. They are adjuvants for classic treatments and help to reduce the scale load of individual patients. The major role for emollients and moisturizers is the supportive role in normalizing hyperproliferation, differentiation, and apoptosis; furthermore, they exert anti-inflammatory effects, for example, through physiologic lipids. Subsequently, an improved barrier function and stratum corneum hydration makes the epidermis more resistant to external stressors and reduces the induction of Koebner phenomena. Most of the emollients are lipid-rich (sometimes oily). The keratolytic agents, especially salicylic acid, and higher concentration of urea should be used in the initial keratolytic phase, whereas moisturizing products and emollients are especially suitable in the intermediate phase and the chronic/remission phase of psoriasis. They should be combined with bath oils.

Article

Study of Skin Barrier Function in Psoriasis: The Impact of Emollients

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[2] Department of Dermatology at Hospital Universitario Virgen de las Nieves, 18012 Granada, Spain
[3] Instituto de Investigación Biosanitaria ibs.GRANADA, 18012 Granada, Spain
* Correspondence: tmontero@correo.ugr.es; Tel.: +34-958-023-422

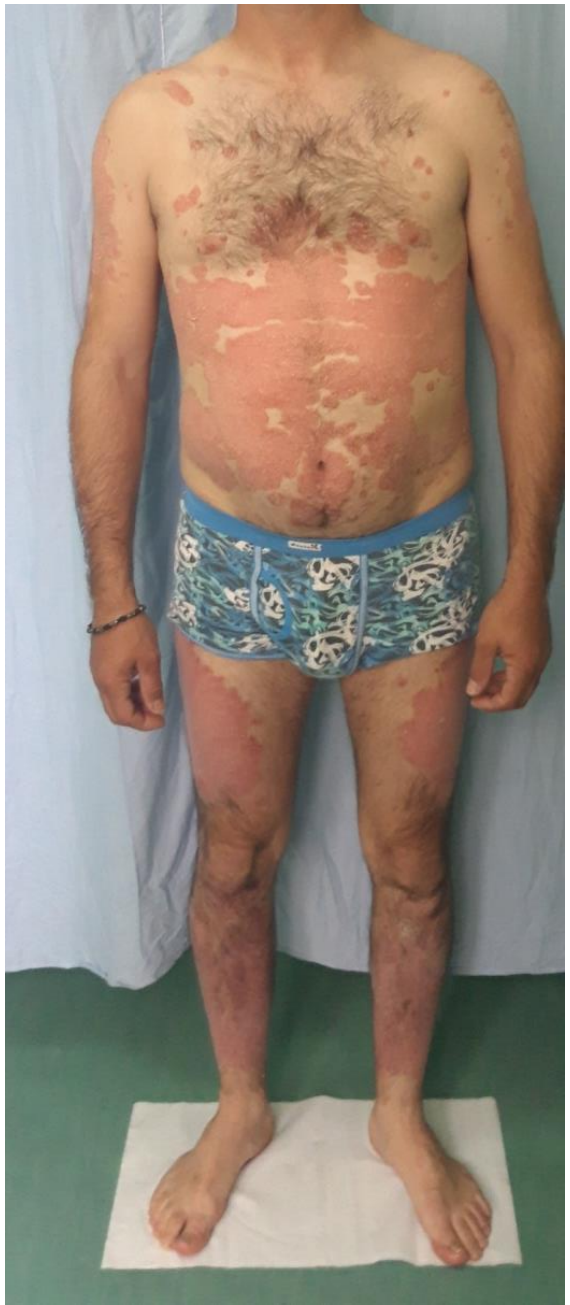
Abstract: Psoriasis is a chronic multi-systemic inflammatory disease that affects the epidermal barrier. Emollients can be used as a coadjutant therapy for psoriasis management, but little is known about how the epidermal barrier function in psoriatic patients is modified by moisturizers. The objective of this study is to evaluate the effect of Vaseline jelly and a water-based formula on epidermal barrier function in psoriatic patients. Thirty-one patients with plaque-type psoriasis and thirty-one gender and age-matched healthy controls were enrolled in the study. Temperature, transepidermal water loss (TEWL), stratum corneum hydration (SCH), pH, elasticity and the erythema index were measured using non-invasive tools before and after applying Vaseline jelly and a water-based formula. TEWL was higher in psoriatic plaques than uninvolved psoriatic skin (13.23 vs. 8.54 $g \cdot m^{-2} \cdot h^{-1}$; $p < 0.001$). SCH was lower in psoriatic plaques than uninvolved psoriatic skin and healthy skin (13.44 vs. 30.55 vs. 30.90 arbitrary units (AU), $p < 0.001$). In psoriatic plaques, TEWL decreased by 5.59 $g \cdot m^{-2} \cdot h^{-1}$ ($p = 0.001$) after applying Vaseline Jelly, while it increased by 3.60 $g \cdot m^{-2} \cdot h^{-1}$ ($p = 0.006$) after applying the water-based formula. SCH increased by 9.44 AU after applying the water-based formula ($p = 0.003$). The use of emollients may improve epidermal barrier function in psoriatic patients. TEWL is decreased by using Vaseline, and SCH is increased by using the water-based formula.

Figure 1. Changes in homeostasis parameters after using emollients.

UVOĐENJE SISTEMSKE TERAPIJE KOD BOLESNIKA SA PSORIJAZOM

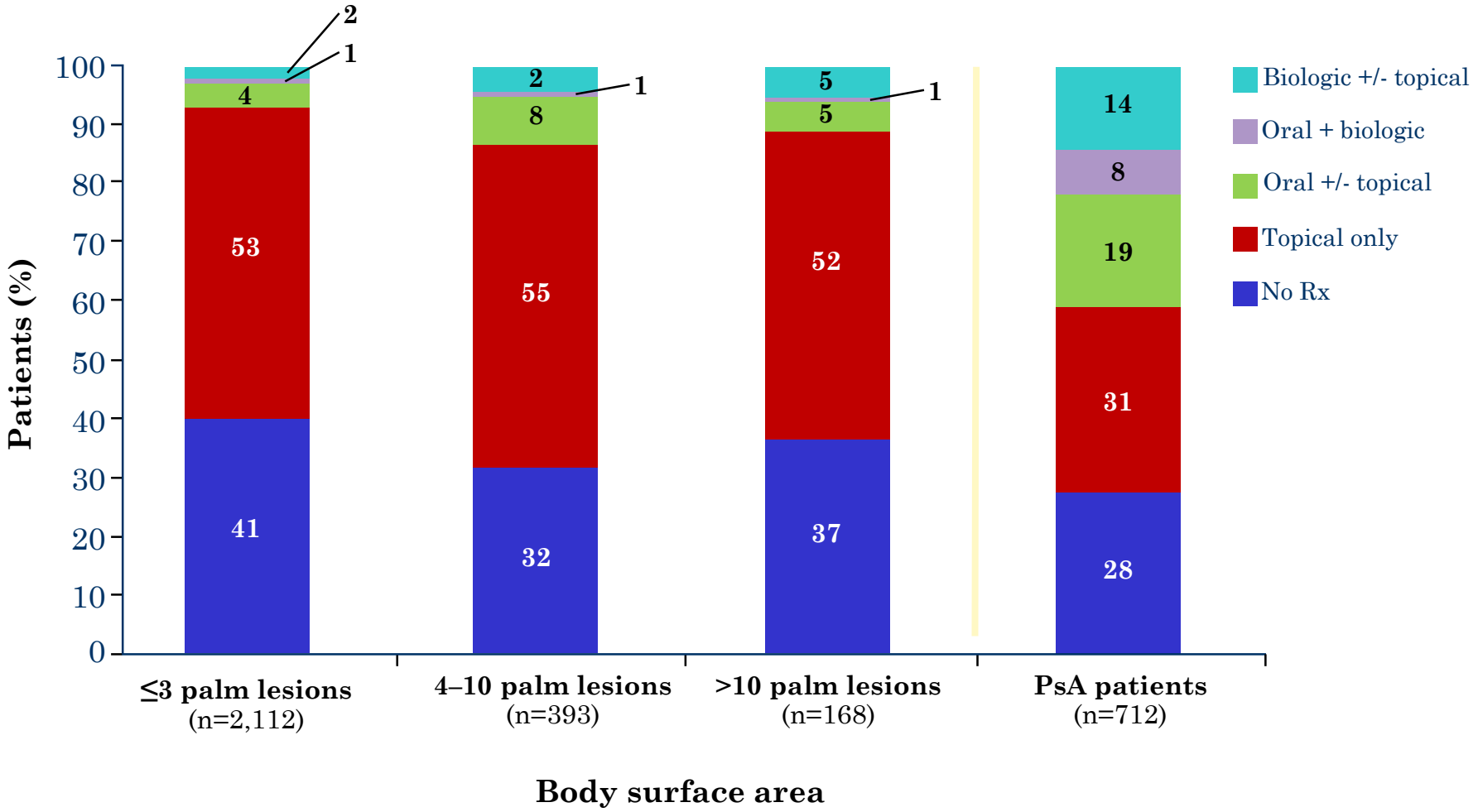
- Prospektivna studija
  - 142 bolesnika
  - PASI 18.5
  - DLQI 12
  - Odlaganje uvođenja sistemske terapije

3 godine



Maza A, et al. Br J Dermatol 2012: 167; 643–8.

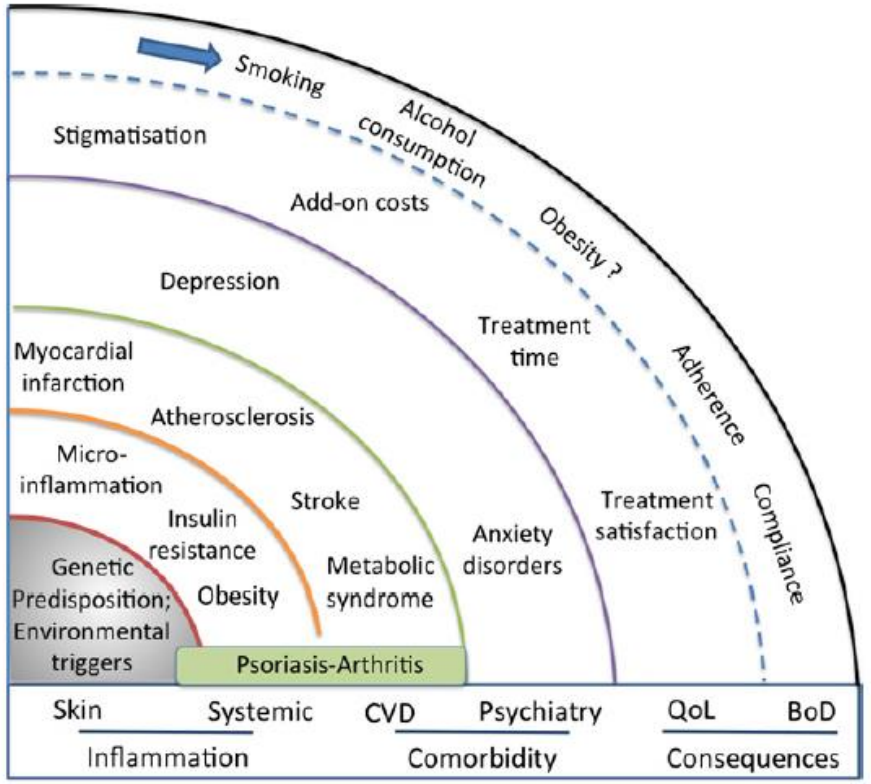
Oko 90% bolesnika sa BSA ≥10 se ne leči ili se leči topijskom terapijom



Lebwohl MG, et al. J Am Acad Dermatol 2014; 70: 871–81

Faktori koji utiču na terapijski izbor u lečenju psorijaze

- Godine starosti pacijenta
- Tip psorijaze
- Lokalizacija i stepen zahvaćeno
- Prethodno lečenje
- Pridružene bolesti
- Neželjeni efekti terapije
- Kontraindikacije
- Životni stil pacijenta
- Adherenca
- Terapijske preporuke



Mrowietz U, et al. Exp Dermatol 2014; 23: 705-9.

PASI90 i PASI100 povezani su sa boljim DLQI skorom

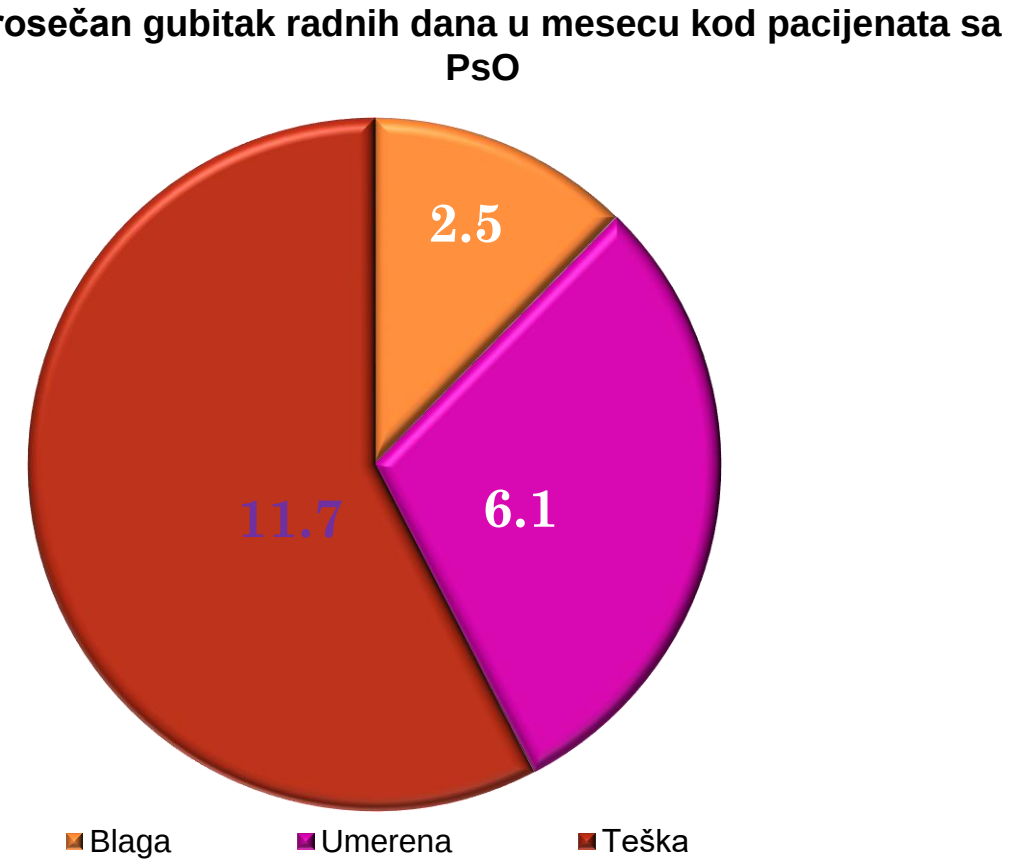
Percent of Patients With DLQI Total Score = 0 or 1 at Week 16 by PASI Response Category at Week 16

PASI Category	DLQI (0,1) Responders (%)
Group 1: <75 PASI (N=65)	12.7
Group 2: 75-<90 PASI (N=15)	33.3
Group 3: 90-<100 PASI (N=29)	79.3
Group 4: 100 PASI (N=32)	84.4

- Significant differences were observed between group 1 vs 3 (*P*<.0001); group 1 vs 4 (*P*<.0001); group 2 vs 3 (*P*<.01); and group 2 vs group 4 (*P*<.01)
- No significant differences were observed between group 1 vs 2 or between group 3 vs 4

Edson-Heredia E. et al. Invest Dermatol 2014;134:18-23

Društvo u celini podnosi značajan finansijski teret: visoka stopa izostajanja iz škole/posla zbog bolesti ili dugotrajnih tretmana, ograničen izbor karijere



Pacijenti sa teškom PsO propuštaju značajan broj radnih dana

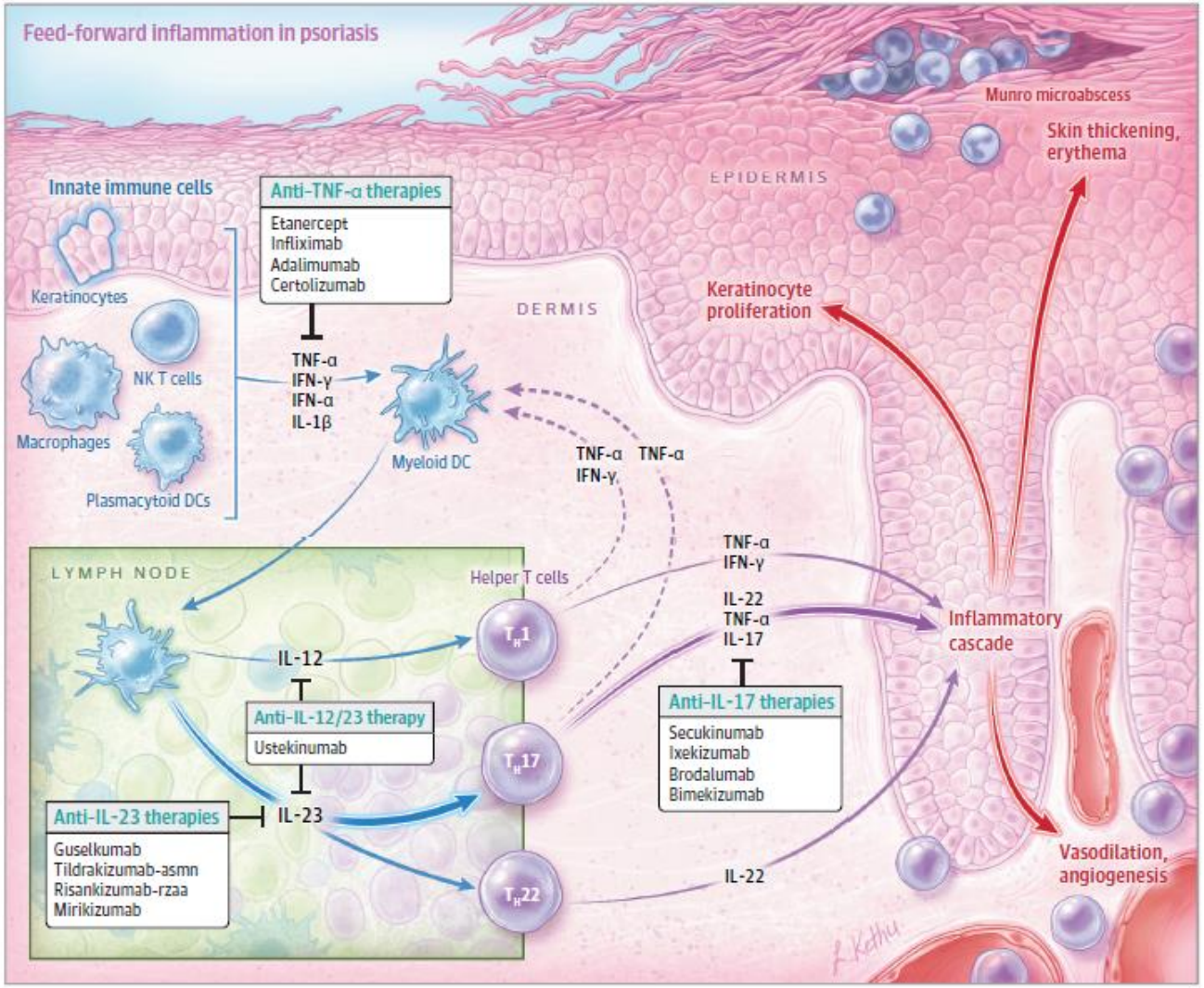
Augustin M et al. Dermatology 2008;216:366-72

JAMA | Review

Pathophysiology, Clinical Presentation, and Treatment of Psoriasis
A Review

April W. Armstrong, MD, MPH; Charlotte R

Figure 1. Pathophysiology of Psoriasis



Novi molekuli ciljaju ključna mesta u patofiziologiji psorijaze

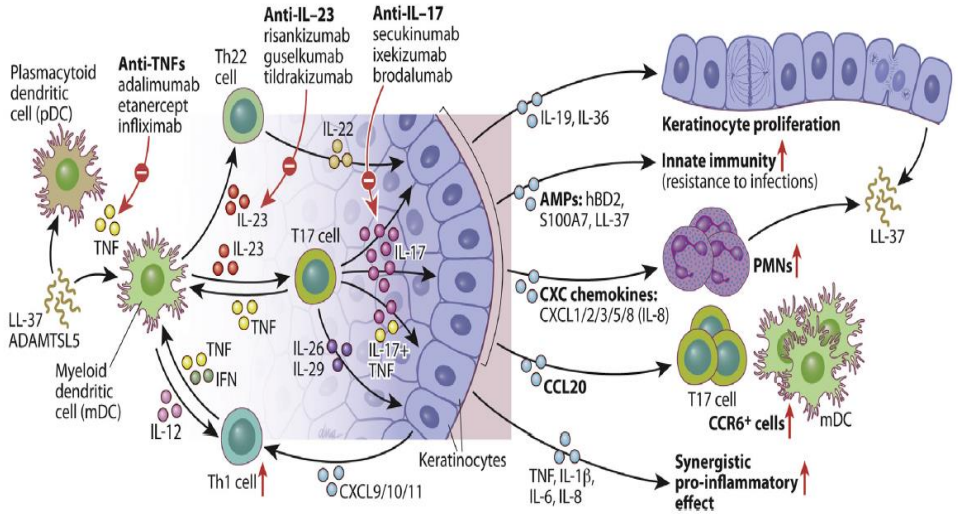
TNFα

IL-12/23

PDE4

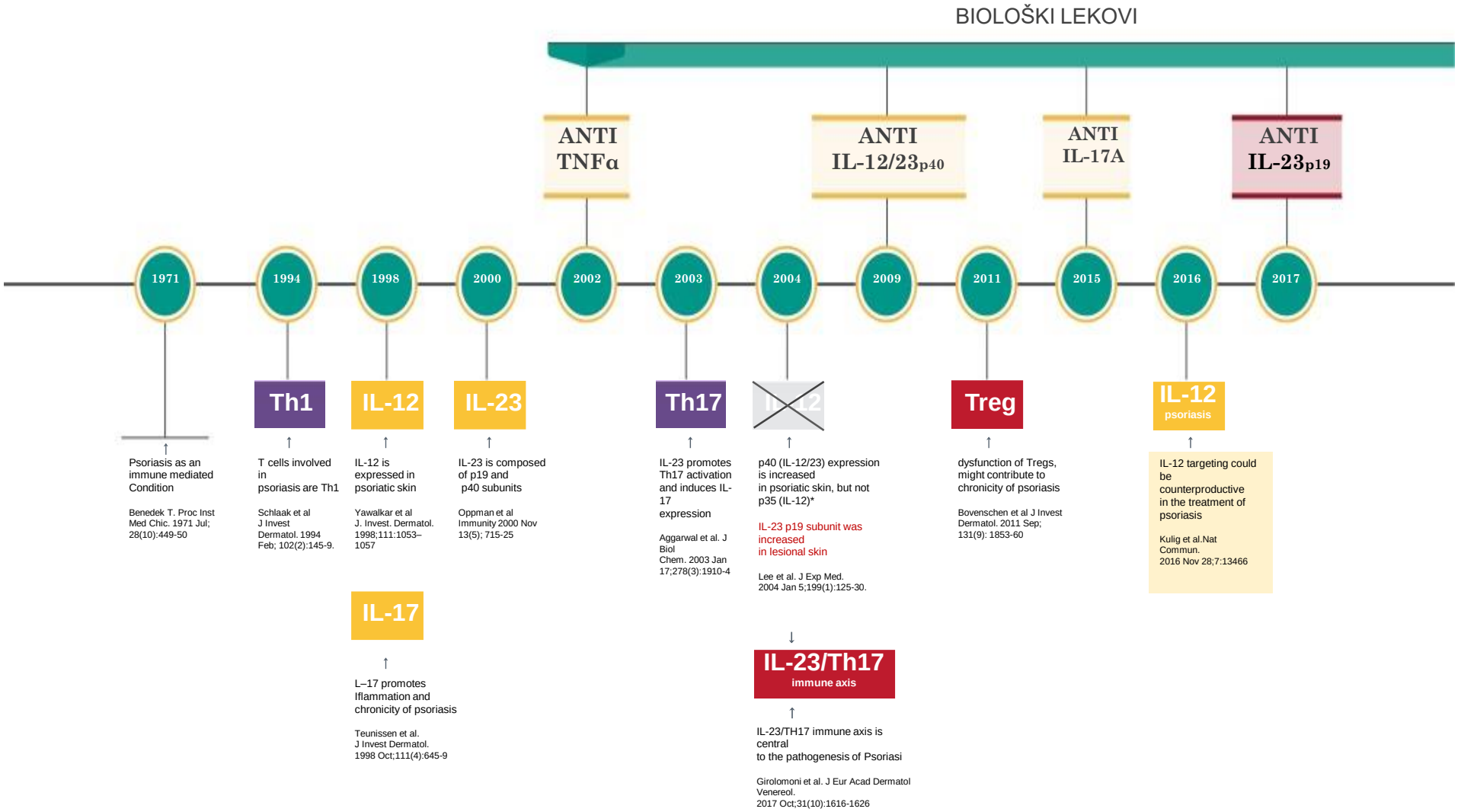
IL-17

IL-23



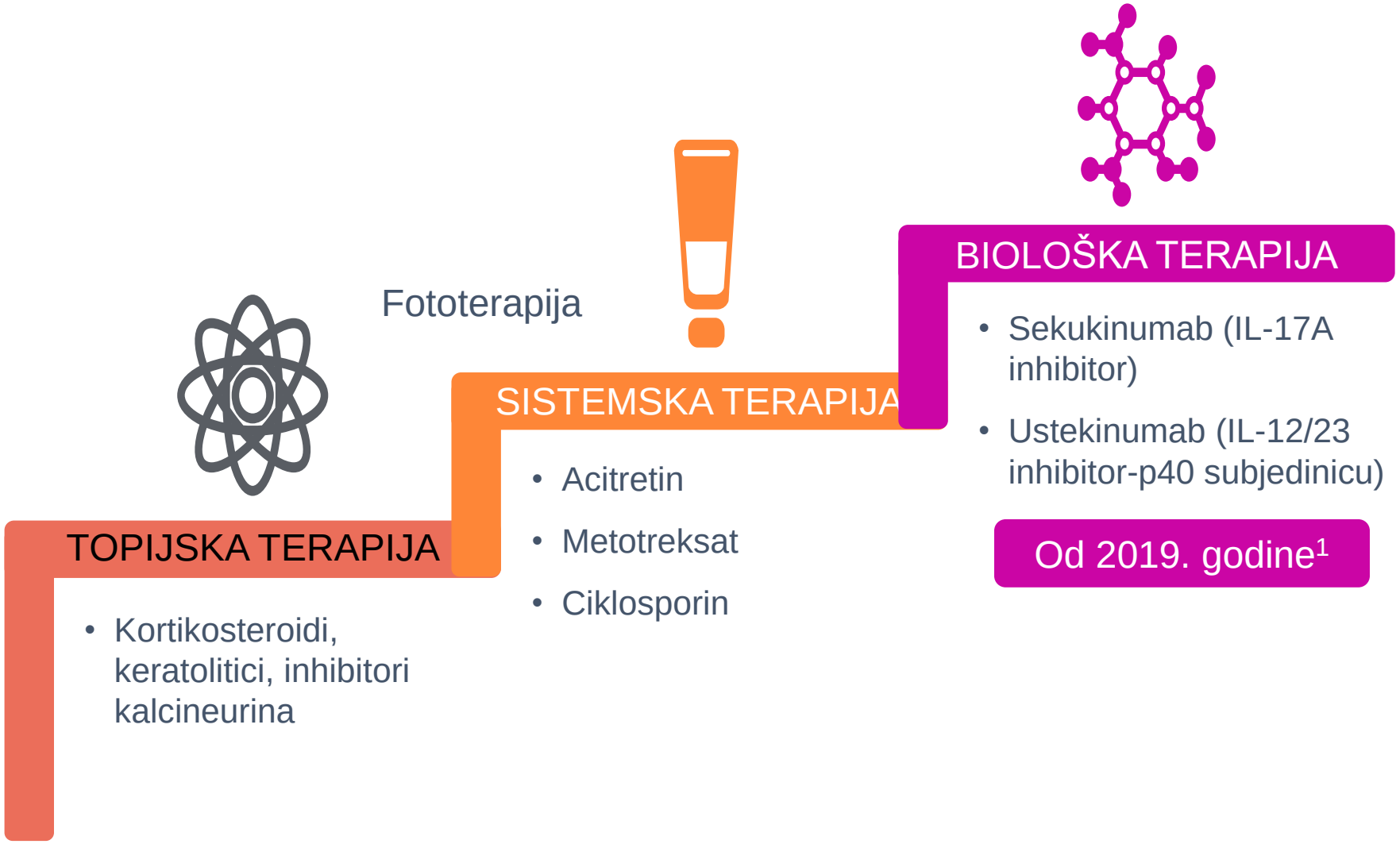
J Allergy Clin Immunol 2017;140(3):645-53.

Najnovija otkrića u patogenezi PsO praćena su dostupnošću novih terapijskih opcija



Deodhar A, Gottlieb AB, Boehncke W-H, et al. *Lancet* 2018; **391:** 2213–24.

Terapijske opcije u Srbiji danas



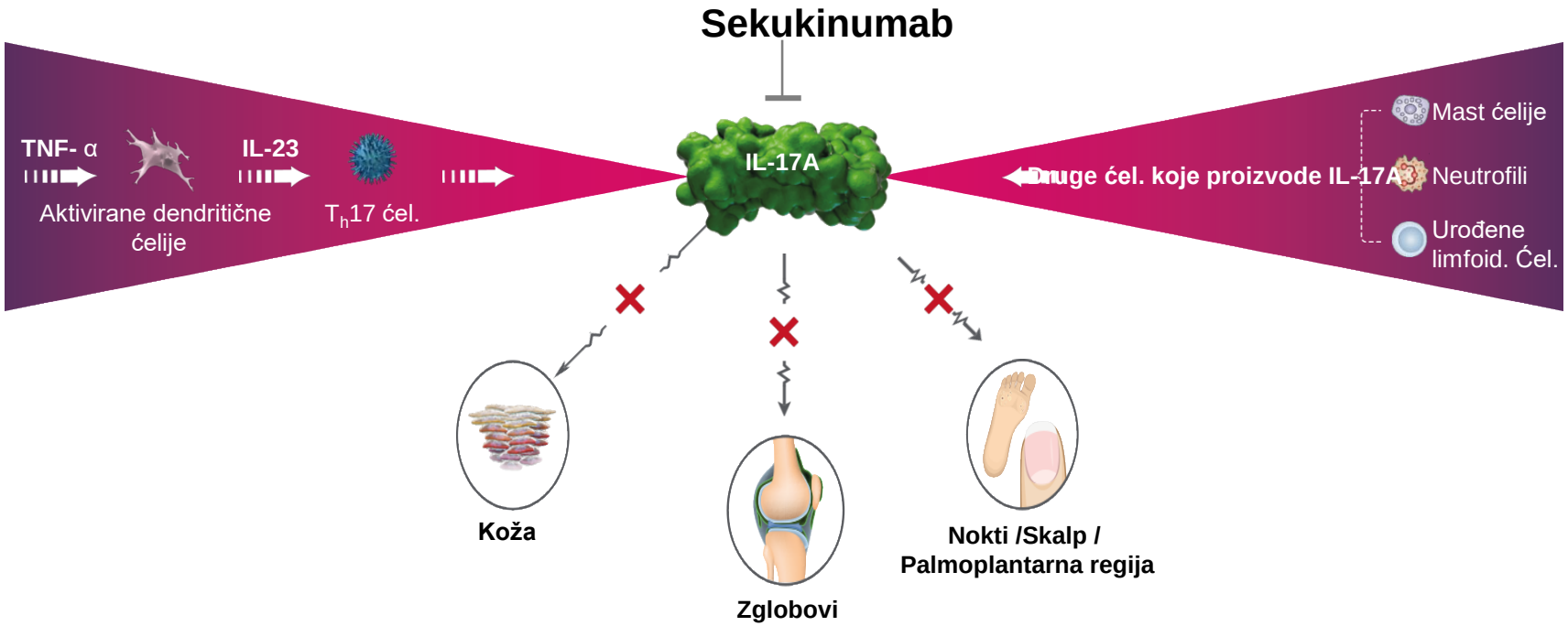
1. Sl.glasnik 31. januar 2019. Godina LXXV – broj 5

KO SU KANDIDATI ZA BIOLOŠKU TERAPIJU?

1. Lek je indikovan za terapiju umerene do teške plak psorijaze (PASI≥10 i/ili BSA≥10 i/ili DLQI≥10) (Psoriasis Area and Severity Index, Body Surface Area, Dermatological Quality of Life Index) ili psorijazu sa lokalizacijom na licu ili šakama/stopalima, kod odraslih osoba kod kojih nije bilo odgovora na drugu sistemsku terapiju ili kod kojih je primena sistemske terapije bila kontraindikovana ili koji ne podnose drugu sistemsku terapiju, uključujući acitretin, metotreksat ili PUVA fototerapiju (L40.0-L40.3; L40.5-L40.9). 2. Teška forma hronične plak psorijaze (PASI (Psoriais Area and Severity Index) ≥ 10 i/ili BSA (Body Surface Area) ≥ 10 i/ili indeks kvaliteta života DLQI ≥ 10) kod adolescenata uzrasta 12 i više godina, koji nisu odgovorili, ili ne podnose, ili imaju kontraindikacije na najmanje dva različita ranije primenjena konvencionalna leka, uključujući fototerapiju, retinoide, metotreksat i ciklosporin (L40.0-L40.3; L40.5-L40.9).	Lek se uvodi u terapiju na osnovu mišljenja Komisije RFZO.

Sekukinumab - IL-17A inhibitor

- Kompletno humano monoklonsko antitelo koje se selektivno vezuje i inhibiše IL-17A.
- Blokira biološku aktivnost IL-17A na target ćelijama koje su uključene u patofiziologiju PsO, bez obzira na poreklo IL-17A.[1,2]



1. Miossec P, et al. *N Engl J Med.* 2009;361:888–898.
2. Cosentyx SmPC Januar 2018.

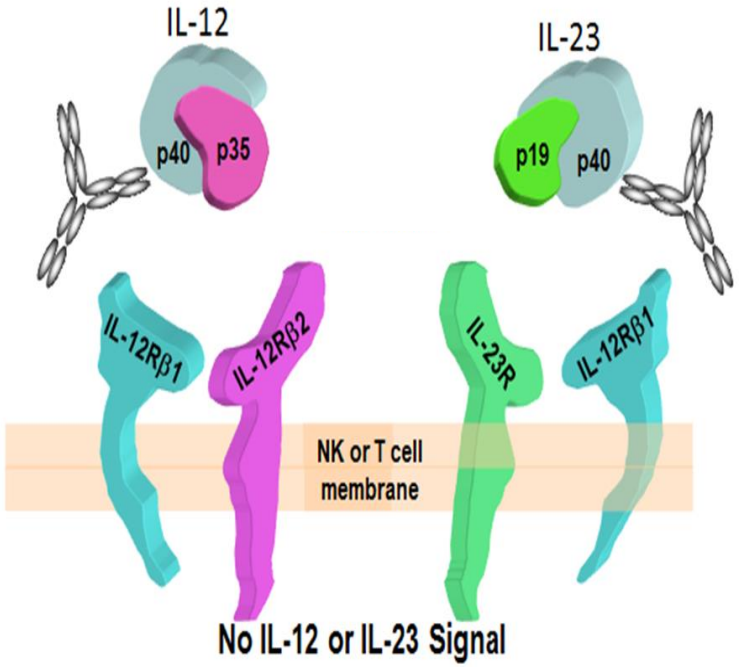
Registracione studije faze[1,2]

ERASURE FIXTURE	Plak PsO	Pivotal Phase 3 trials Comparing the Efficacy and Safety of Secukinumab vs. Placebo and Etanercept in Moderate-to-Severe Plaque PsO

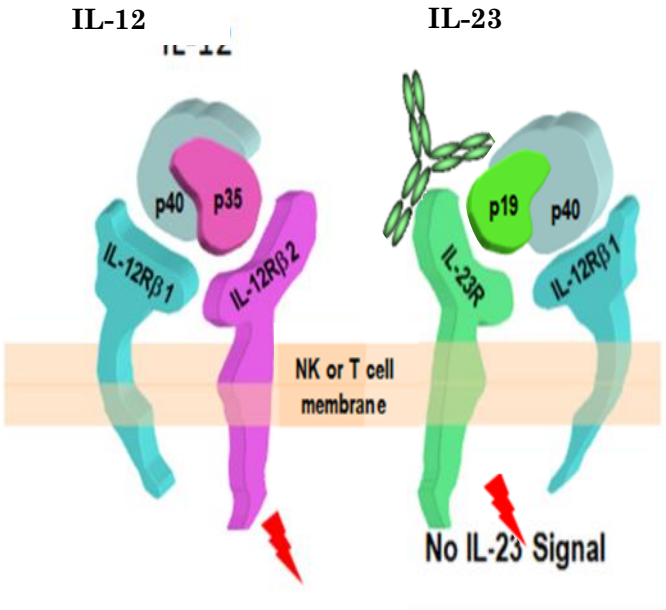
1. Langley RG, et al. NEJM 2014;371:326
2. Blauvelt A et al. AAD 2015
3. Thaçi D, et al. JAAD. 2015;73:400; Blauvelt A, et al. JAAD. 2017;76:60
4. Blauvelt A, et al. JAAD 2017;76:60
5. Reich K, et al. *EADV* 2016; Vienna, Austria (Poster 2095)
6. Bagel J, et al. JAAD. 2017 Oct;77(4):667-674
7. Gottlieb A, et al. PGC 2017; London, UK (Poster 026)

CLEAR	Plak PsO	Secukinumab vs. Ustekinumab in Patients With Moderate-to-Severe Plaque PsO
GESTURE	Palmoplantarna PsO	Efficacy and Safety of Secukinumab in Patients with Moderate-to-Severe Palmoplantar PsO
TRANSFIGURE	PsO noktiju	Efficacy, Safety, and Tolerability of Secukinumab in Patients with Moderate-to-Severe Nail PsO
SCALP	PsO poglavine	Efficacy and Safety of Secukinumab in Patients with Moderate-to-Severe Scalp PsO

Ustekinumab deluje na p40 subjedinicu IL-12 i IL-23



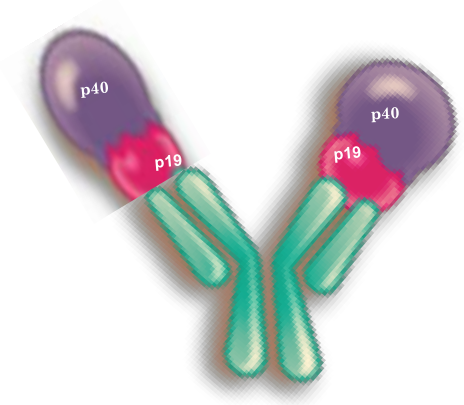
Guselkumab deluje na p19 subjedinicu samo IL-23



IL, interleukin; NK, natural killer [cell].

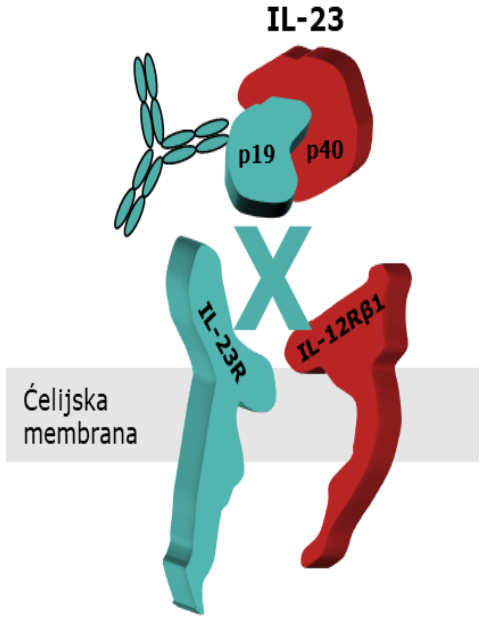
Figure adapted from: 1. Langley RG, et al. *Br J Dermatol* 2018 ;178:114-123; 2. Langley RG, et al. P4915. Presented at 2017 American Academy of Dermatology Annual Meeting, 3–7 March 2017, Orlando, FL, USA.

GUSELKUMAB JE PRVI SELEKTIVNI INHIBITOR IL-23



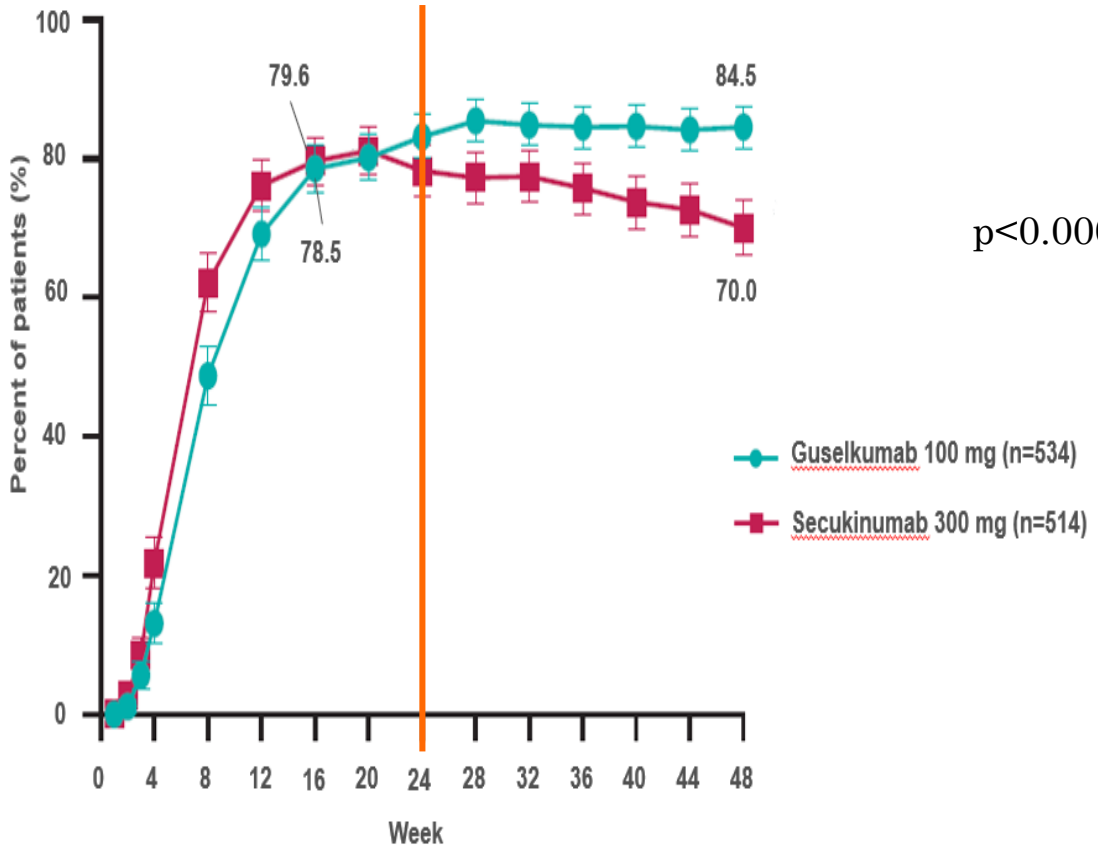
- Potpuno humano IgG1 lambda monoklonsko antitelo
- Vezuje sa za p19 subjedinicu IL-23, deluje ushodno u patogenetskom mehanizmu psorijaze i inhibicijom IL-23 sprečava intracelularnu i nishodnu signalizaciju IL-23 [1]

Guselkumab ima nizak K_D (3.3 pM) zbog čega ima visok afinitet,[2] koji je neophodan da se prevaziđe visok afinitet IL-23 za receptor[3]



1. Gordon KB, et al. *N Engl J Med* 2015; 373: 136–144; 2. US FDA Center for Drug Evaluation and Research. Available at: www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761061Orig1s000MultidisciplineR.pdf. Last accessed January 2020; 3. Singh S, et al. *mAbs* 2015;7:778–791;

Guselkumab je IL23 inhibitor (p19 subjedinicu) pokazao superiorniju dugoročnu efikasnost vs. sekukinumab



p<0.0001

PASI90 odgovor postignut sa guselkumabom oko 24. nedelje se i dalje održava, dok odgovor sekukinumaba opada[1]*

*Total ECLIPSE population with moderate to severe plaque psoriasis (p<0.0001 ±95% CI). Non-responder imputation was used for missing data.

1. Reich et al. *Lancet* 2019; 394(10201):831-839.

POSITION STATEMENT

Practical recommendations for systemic treatment in psoriasis in case of coexisting inflammatory, neurologic, infectious or malignant disorders (BETA-PSO: Belgian Evidence-based Treatment Advice in Psoriasis; part 2)

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[1]Department of Dermatology, Ghent University Hospital, Ghent, Belgium
[2]Private Practice, Tremelo, Belgium
[3]Dermatology, Cliniques Saint-Luc, Université Catholique de Louvain, Brussels, Belgium
[4]Dermatology, University Hospital Leuven, Leuven, Belgium
[5]Dermatology, Centre Hospitalier Universitaire de Liège, Liège, Belgium
[6]Dermatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
[7]Dermatology, University Hospital of Antwerp, Antwerp, Belgium
*Correspondence: J.L.W. Lambert. E-mail: jo.lambert@uzgent.be

Table 3 Evidence of systemic treatments for psoriasis in different clinical conditions

	ACITR	CYCLO	MTX	FUM	APR	IFX	ETA	ADA	CERT	USTE	GUS	RIS	TIL	SECU	IXE	BROD
PsA peripheral	B	A	A	C	A	A	A	A	A	A	A	A	B	A	A	A
PsA spine	B	A	A	NA	A	A	A	A	A	A	A	A	NA	A	A	A
PsA enthesitis/dactylitis	B	A	A	NA	A	A	A	A	A	A	A	A	B	A	A	A
Inactive IBD	C	C	A	C	C	A	C	A	A	A	C	A	C	C	C	C
Active IBD	C	C	A	NA	C	A	A	A	A	A	C	A	C	A	A	A
HIV active	B	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
HIV non-active	B	B	B	A	B	B	B	B	B	B	B	B	B	B	B	B
Chronic Hep C	C	B	B	C	C	B	B	B	B	C	C	C	C	C	C	C
Chronic Hep B	B	B	A	NA	B	B	B	B	B	B	NA	NA	NA	B	C	C
Latent TB	B	C	C	NA	A	A	A	A	A	C	C	C	C	C	C	C
Demyelinating disease	C	B	B	A	NA	A	A	A	A	A	NA	NA	NA	C	NA	NA
Cancer	C	A	B	NA	C	B	B	B	B	B	NA	NA	NA	NA	NA	NA

KOJI JE KRAJNJI CILJ LEČENJA PSORIJAZE?

- Remisija bolesti (PASI 100, BSA 0, PGA 0, DLQI 0) PASI 75/90 DLQI 1-2

- **Kontrola bolesti – sprečiti pogoršanja**
  - PASI, BSA, PGA
  - izborom terapije uticati na komorbiditete

ŽIVOT BEZ PSORIJAZE

- Poboljšati zadovoljstvo bolesnika (HRQoL)
  - optimalan izbor terapije prema težini bolesti i željama bolesnika
  - DLQI

- Bolja saradnja lekara i pacijenta

Hvala na pažnji

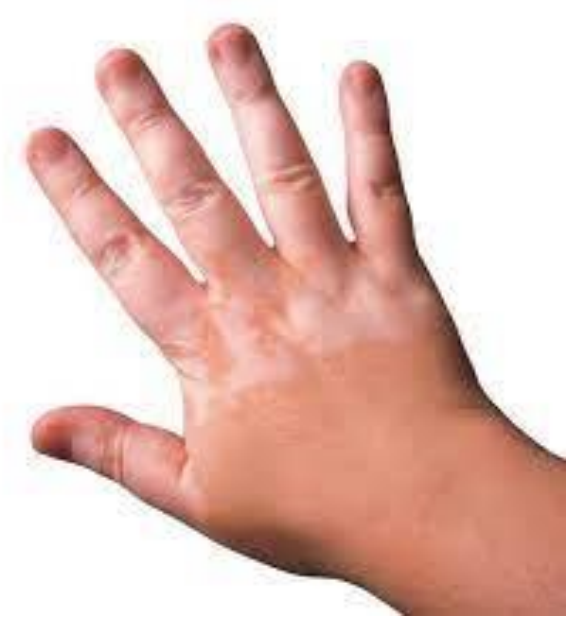
VITILIGO

Prof. dr Zoran Golušin

Medicinski fakultet Novi Sad

Klinika za kožno-venerične bolesti KCV, Novi Sad

Stečeni, autoimunski poremećaj, često sa jasnom naslednom komponentom, sa destrukcijom melanocita i gubitkom pigmenta

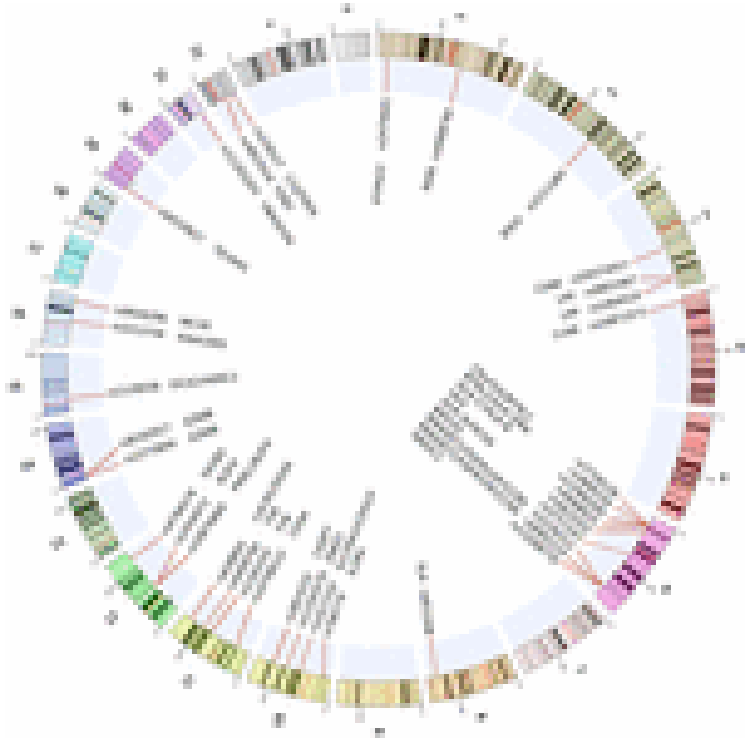


VITILIGO-EPIDEMIOLOGIJA

- Jedna od najčešćih dermatoloških bolesti, među najčešćim autoimunskim oboljenjima
- Među svim rasama i na svim podnebljima
- Prevalencija iznosi 0,5-1%
- Najveća prevalencija zabeležena u Indiji (oko 8%), Meksiku (oko 3%) i Japanu (oko 1,5%)
- Kod polovine obolelih javlja se pre 20. godine života, a kod 70-80% pre 30. godine

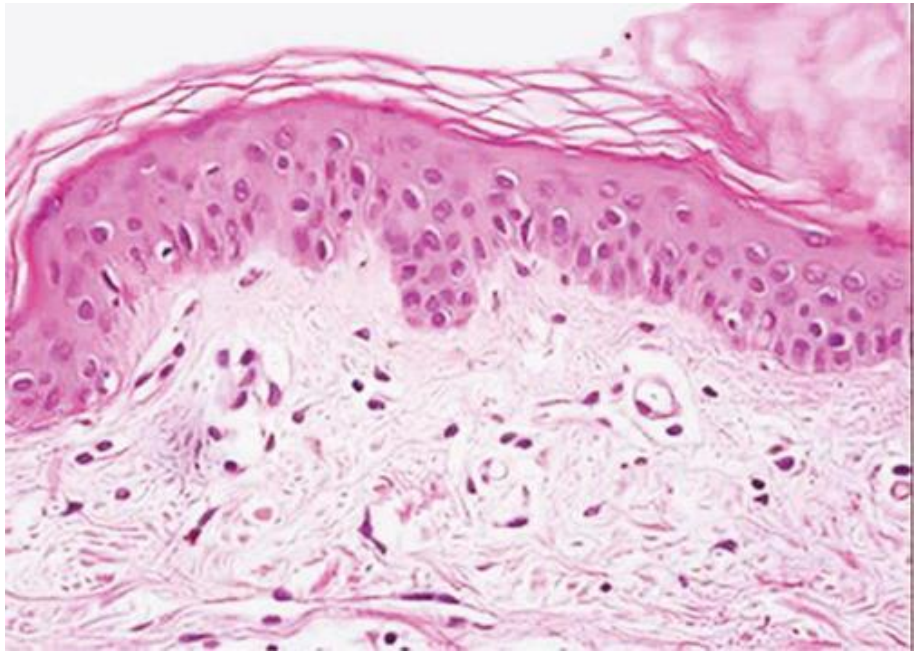
VITILIGO-ETIOPATOGENEZA

- Genetski faktori: poligenski, multifaktorski način nasleđivanja; rizik za srodnike u prvom kolenu je 6-18 puta povećan u odnosu na ostale; oko 40 genskih lokusa povezano sa vitiligom



VITILIGO-ETIOPATOGENEZA

- Autoimunski poremećaj: više od 80% obolelih ima antitela prema antigenima melanocita; antitela usmerena protiv tirozinaze i tirozinaza proteina TRP-2; u oboleloj koži prisustvo aktivisanih T limfocita sa predominacijom CD8 ćelija



VITILIGO-ETIOPATOGENEZA

- Oksidativni stres: deficit antioksidativnih enzima; smanjene koncentracije lipofilnih antioksidanasa; oksidativno oštećenje ćelija; autodestrukcija melanocita zbog proinflamatornih citokina koje oni sami proizvode
- Melanociti postaju nesposobni da neutrališu povećan broj reaktivnih vrsta kiseonika (ROS) koji nastaju prilikom stresa, UV zračenja, izloženosti hemikalijama...
- *In vitro* postoje dokazi o markerima za oksidativni stres u etiopatogenezi vitiliga, ali je njihova uloga još uvek nedovoljno dokazana

VITILIGO-ETIOPATOGENEZA

- Početni okidač mogu biti različite vrste oštećenja kože, UV zračenje ili mikroinfekcije
- Aktivisane dendritične ćelije prezentuju melanocitne antigene limfocitima, dolazi do uništavanja melanocita i depigmentacije kože
- U tipičnoj apigmentovanoj makuli na koži nađeno je potpuno odsustvo melanocita, dok melanociti na ivicama lezije ispoljavaju znakove degeneracije, a ponekad su prisutne i zapaljenske promene sa limfocitnim i makrofagnim infiltratom

Možemo li znati ko ima veći rizik za nastanak vitiliga?

Pigmentation Traits, Sun Exposure, and Risk of Incident Vitiligo in Women

Rachel Dunlap[1,6], Shaowei Wu[2,3,6], Erin Wilmer[1], Eunyoung Cho[1,4,5], Wen-Qing Li[1,4], Newsha Lajevardi[1] and Abrar Qureshi[1,4,5]

Journal of Investigative Dermatology (2017) **137**, 1234–1239

Veći rizik imaju žene sa najmanje jednim nevusom većim od 3 mm na gornjim ekstremitetima (povećana patološka aktivnost tirozinaze što dovodi do antimelanocitnog efekta), one koje dobijaju preplanuli ten posle dva sata izloženosti suncu (tirozinaza) i one sa anamnestičkim podatkom o opekotinama sa stvaranjem bula posle dva sata izloženosti suncu (UV oštećenje-stres-ekspresija činilaca koji automunskim putem dovode do depigmentacije).

Možemo li znati ko ima veći rizik za nastanak vitiliga?

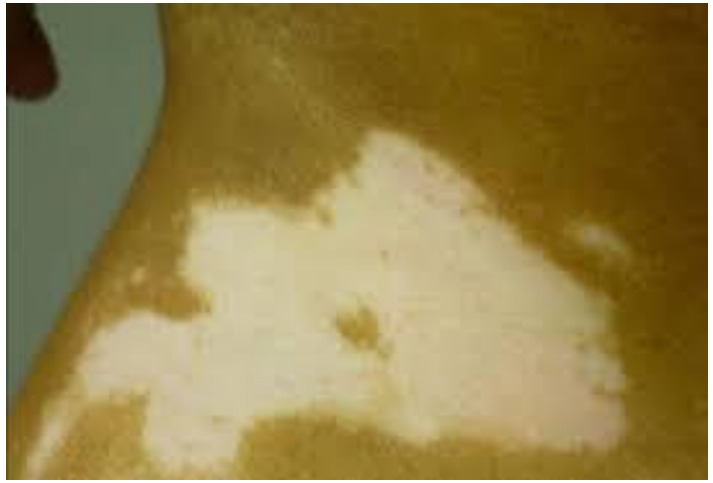
1. van Geel N, Speeckaert R, Lambert J,Mollet I, De Keyser S, De Schepper S, et al. Halo naevi with associated vitiligo-like depigmentations: pathogenetic hypothesis. J Eur Acad Dermatol Venereol 2012;26:55-61.

2. Ezzedine K, Diallo A, Leaute-Labreze C, Seneschal J, Mossalayi D, AlGhamdi K, et al. Halo nevi association in nonsegmental vitiligo affects age at onset and depigmentation pattern. Arch Dermatol 2012;148:497-502.

Halo melanocitni nevus je, uz alopeciju areatu i lichen sclerosus, autoimunsko oboljenje koje može biti udruženo sa vitiligom

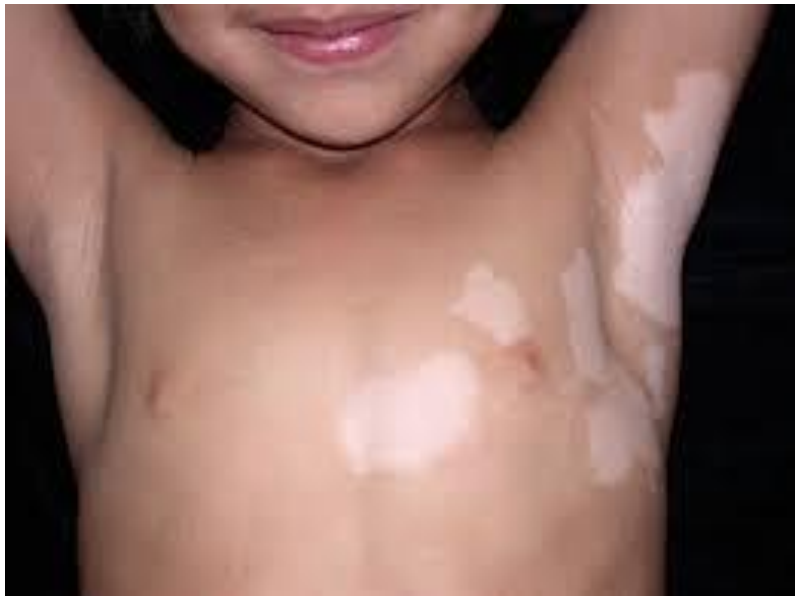
VITILIGO-PODTIPOVI

- Fokalni vitiligo: jedna makula u nedermatomskom rasporedu koja se najmanje dve godine ne razvija u nesegmentni vitiligo; ima bolju prognozu u odnosu na druge podtipove



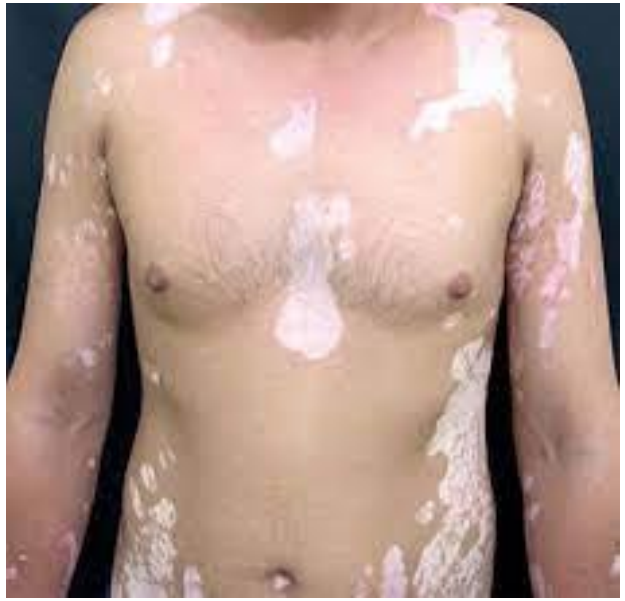
VITILIGO-PODTIPOVI

- Segmentni vitiligo: asimetričan dermatomski raspored; jednostrano lokalizovan



VITILIGO-PODTIPOVI

- Nesegmentni vitiligo: najčešći u populaciji; može biti generalizovani, akrofacijalni, univerzalni, sluznični, mešoviti (segmentni i nesegmentni)



TOK BOLESTI

- Najčešće počinje na koži izloženoj suncu
- Progresivan tok; stepen širenja najveći ako su početne promene na leđima, šakama i stopalima
- Pridruženost autoimunskih poremećaja štitaste žlezde, perniciozne anemije, sistemskog lupusa, dijabetesa...
- Spontana repigmentacija je retka, neujednačena i nepotpuna
- Treba pokrenuti melanocite pomoću melanocitnih prekursora u spoljašnjem omotaču dlake; repigmentacija uglavnom počinje u području folikula dlake

TERAPIJA

- Cilj lečenja: zaustaviti napredovanje bolesti, stimulisati pigmentaciju i održati repigmentaciju
- Opšte mere: zaštita od sunca sa SPF 50 i UVA filtere

Risk of skin cancer in patients with vitiligo in Denmark: A nationwide cohort study

Mads Gustaf Jørgensen, MD,[a,b,c] Navid Mohamadpour Toyserkani, MD, PhD,[d]
Alexander Egeberg, MD, PhD,[c] and Jens Ahm Sørensen, MD, PhD[a,b]
Odense, Region of Southern Denmark, Rigshospitalet, and Copenhagen, Denmark

JAAD Int 2020;1:31-8.

Istraživanje obuhvatilo preko 2.300 pacijenata sa vitiligom (oboleli od 1994. do 2017. godine) i preko 23.000 u kontrolnoj grupi bez vitiliga.
Faktori rizika za pojavu karcinoma kože bili su starost i muški pol.
Fototerapija nije povećala rizik za nastanak karcinoma kože i melanoma.
Nije primećena veća incidencija karcinoma kože kod osoba sa vitiligom.

Ako je autoimunski odgovor činilac nastanka vitiliga, onda bi on mogao da bude zaštitni faktor za nastanak i progresiju melanoma.
Sa druge strane, smanjena sinteza melanina može povećati fotooštećenje kože i povećati rizik za karcinom kože.

Br J Dermatol. 2020 Apr;182(4):907-915. doi: 10.1111/bjd.18247. Epub 2019 Sep 18.

The incidence and survival of melanoma and nonmelanoma skin cancer in patients with vitiligo: a nationwide population-based matched cohort study in Korea

H S Kim [1 2], H J Kim [3], E S Hong [1], K B Kim [3], J D Lee [1], T U Kang [4], H S Ahn [3]

Istraživanje obuhvatilo preko 130.000 pacijenata sa vitiligom i preko 2 miliona u kontrolnoj grupi bez vitiliga; pacijenti praćeni 6 godina.
Povećan rizik za nastanak karcinoma kože i melanoma kod osoba sa vitiligom.
Rizik veći kod žute rase u odnosu na belce?
U azijskoj opštoj populaciji učestalost melanoma je niža nego kod bele rase.

TERAPIJA

- Topikalni kortikosteroidi su prva linija terapije za ograničene oblike vitiliga (repigmentacija se postiže kod 75% pacijenata sa tamnijom kožom, kod nedavno nastalih lezija i kod lezija izloženih suncu).
- Potentniji kortikosteroidi oko 2 meseca (ili 15 dana mesečno tokom 6 meseci), zatim se prelazi na slabije preparate; najlošije reaguje segmentni vitiligo; neželjeni efekti ograničavaju dužu upotrebu posebno kod dece.

TERAPIJA

- Topikalni inhibitori kalcineurina: takrolimus ili pimekrolimus na delovima kože gde je je duža upotreba kortikosteroida neprimerena (lice, vrat, genitalna regija); dva puta dnevno 6 meseci; može se kombinovati sa kortikosteroidima ili sa UVB fototerapijom.
- Smanjuju infiltraciju CD4+ i CD8+ T limfocita, pa je u jednom istraživanju kod dece 0,1% takrolimus posle godinu dana terapije (2xdnevno) doveo do repigmentacije lezija na licu kod 81% pacijenata, dok je na ekstremitetima repigmentacija bila minimalna.
- Terapija održavanja kod repigmentovanih lezija

Kanwar AJ, Dogra S, Parsad D. Topical tacrolimus for treat-ment of childhood vitiligo in Asians. Clin Exp Dermatol.2004;29:589-92

TERAPIJA

- UVB fototerapija: uskotalasna 311 nm; počinje sa dozom od 0,2 J/cm^2 dva do tri puta nedeljno sa postepenih povećanjem od 20% prilikom svakog sledećeg zračenja dok se ne postigne minimalna eritemska doza; najčešće je potrebno 6-9 meseci lečenja.
- Kombinacija lokalne i fototerapije primenjuje se kada je zahvaćeno više od 15-20% kože
- Eksimerni laseri talasne dužine 308 nm kod lezija manje površine

TERAPIJA

- Oralni kortikosteroidi: kod brzonapredujućeg vitiliga; 2,5-10 mg deksametazona dnevno dva uzastopna dana nedeljno tokom 3-6 meseci; primarni cilj je zaustaviti progresiju bolesti.
- Metotreksat: kada su oralni kortikosteroidi kontraindikovani; cilj je zaustaviti progresiju bolesti; doza 10-15 mg nedeljno.
- Azatioprin 2x50 mg dnevno tokom 6 meseci zaustavlja progresiju bolesti kod 77,8% obolelih, ali je slab uticaj na repigmentaciju.

Patra S, Khaitan BK, Sharma VK, Khanna N. A randomized comparative study of the effect of betamethasone oral mini-pulse therapy versus oral azathioprine in progressive non-segmental vitiligo. J Am Acad Dermatol 2021;85:728–9.

TERAPIJA

- Hirurško lečenje: presađivanje minitransplantata na leukodermično područje samo kod stabilnog vitiliga (bez kliničke aktivnosti i bez Koebnerovog fenomena tokom 12 meseci); neželjeni efekti: ožiljci, dispigmentacija.
- Primena *in vitro* kultivisanih ćelija epidermisa

TERAPIJA

- Topikalni kalcipotriol: imunomodulator i korektor sniženog kalcijuma u melanocitima
- Oralni antioksidansi: u istraživanjima mali broj pacijenata, a širok spektar jedinjenja pa se ne može izvesti meta-analiza; često se kombinuju sa fototerapijom.
- Levamizol (antiparazitni lek): imunomodulatorno delovanje, pojačava funkciju limfocita i makrofaga; prestanak razvoja novih lezija posle 2-4 meseca terapije kod 94% lečenih.
- Depigmentacija preostalih pigmentovanih regija kako bi se boja kože ujednačila; monobenzil etar hidrohinon; laser.

Pasricha JS, Khera V. Effect of prolonged treatment with levamisole on vitiligo with limited and slow-spreading disease. Int J Dermatol 1994;33:584–7.

TERAPIJA

- Razvoj novih lekova zasnovan na boljem razumevanju intracelularnih molekula i signalnih puteva
- Topikalni analozi prostaglandina: indukcija tirozinaze i regulacija melanocitne proliferacije; postižu dobre efekte u repigmentaciji lezija na licu i repigmentaciji kod dece.
- Mikofenol mofetil 15% dva puta dnevno tri meseca
- Metotreksat 1% gel dva puta dnevno tri meseca
- Afamelatonid (analog alfa melanocitnog stimulirajućeg hormona): subkutano 16 mg mesecno tokom 4 meseca stimuliše melanogenezu; u kombinaciji sa fototerapijom daje bolje efekte nego samo primena fototerapije.

Jha AK, Prasad S, Sinha R. Bimatoprost ophthalmic solution in facial vitiligo. J Cosmet Dermatol 2018;17:437–40.

Lim HW, Grimes PE, Agbai O, et al. Afamelanotide and narrowband UV-B phototherapy for the treatment of vitiligo: a randomized multicenter trial. JAMA Dermatol 2015;151:42–50.

KOZMETIČKA SREDSTVA

- Samotamneći agensi daju koži smeđu boju; trajanje 3-5 dana; mogu da se koriste tokom cele godine; vodootporni.
- Pigmentni pokrivni kremovi

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Serum level of antioxidant vitamins and minerals in patients with vitiligo, a systematic review and meta-analysis

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[a] Department of Dermatology and Venereal Diseases, Dezhou People's Hospital, Dezhou, China
[b] Department of Dermatology and Venereal Diseases, Jinan City People's Hospital, Jinan, China
[c] Department of Endocrinology, Dezhou People's Hospital, Dezhou, China

- Obrađeno 13 istraživanja
- Analizirani nivoi vitamina A,C,E, selena, cinka i bakra u serumu pacijenata sa vitiligom (570 ispitanika) i bez vitiliga (580)
- Utvrđen niži nivo cinka (preventivno dejstvo) i viši nivo selena (?) kod obolelih od vitiliga
- Selen ima depigmentujuće dejstvo; inhibiše tirozinazu

Actas Dermosifiliogr. 2017;108(7):637–642

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www.actasdermo.org

ORIGINAL ARTICLE

Impact of Vitiligo on Quality of Life☆

M.A. Morales-Sánchez,* M. Vargas-Salinas, M.L. Peralta-Pedrero, M.G. Olguín-García, F. Jurado-Santa Cruz

Centro Dermatológico Dr. Ladislao de la Pascua, Secretaría de Salud de la Ciudad de México, Ciudad de México, Mexico

U nekim istraživanjima depresija je ustanovljena kod čak 59% obolelih od vitiliga.
Čak 24% ljudi ne bi se rukovali sa obolelima od vitiliga iz straha od zaraze, 25% ne bi sedeli za istim stolom, a 43% ne bi ušli u brak sa obolelima od vitiliga.

VITILIGO-ZAKLJUČAK

- Najbolji rezultati lečenja se primećuju na licu, dok akralne lezije slabo reaguju
- Sveže promene bolje reaguju na terapiju nego stare, pa je važno što pre započeti lečenje
- Kvalitet života ozbiljno narušen kod više od 50% obolelih
- Stid, depresija, anksioznost; društvena izoloacija
- Kod dece posledice mogu biti još veće; psihičke traume, nizak stepen samopoštovanja, izbegavanje sportskih aktivnosti...
- Psihološka podrška

HVALA NA PAŽNJI