
HRVATSKO DRUŠTVO
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Hotel Sheraton,
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22.-25.10.2026.
JESENSKA AKADEMIJA
SUPLEMENTACIJE
U MEDICINI
PROMJENA SASTAVA CRIJEVNOG MIKROBIOMA POVEZANOG S IMUNOLOŠKIM ČIMBENICIMA U KRONIČNOJ URTIKARIJI - ŠTO JE POZNATO?
Liborija Lugović Mihić, KBC SM

PROMJENA SASTAVA CRIJEVNOG MIKROBIOMA POVEZANOG S IMUNOLOŠKIM ČIMBENICIMA U KRONIČNOJ URTIKARIJI - ŠTO JE POZNATO?

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↑ povećana relativna zastuplj **oportunističkih** bakterija
↓ smanjena relativna zastuplj **beneficijalnih** bakterija

Pomozite, molim vas...

BOLESNICI S KU

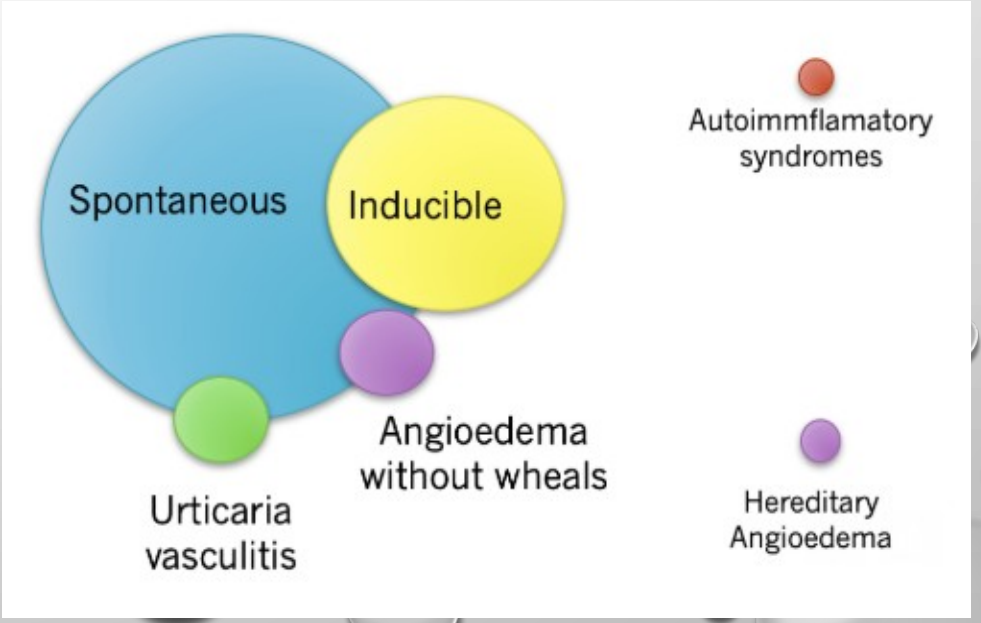




- **Kronična urtikarija (KU)** (spontana/KSU ili inducirana): recidivirajuće urtike sa svrbežom i mogućim angioedemom, duže od **6 tjedana**.

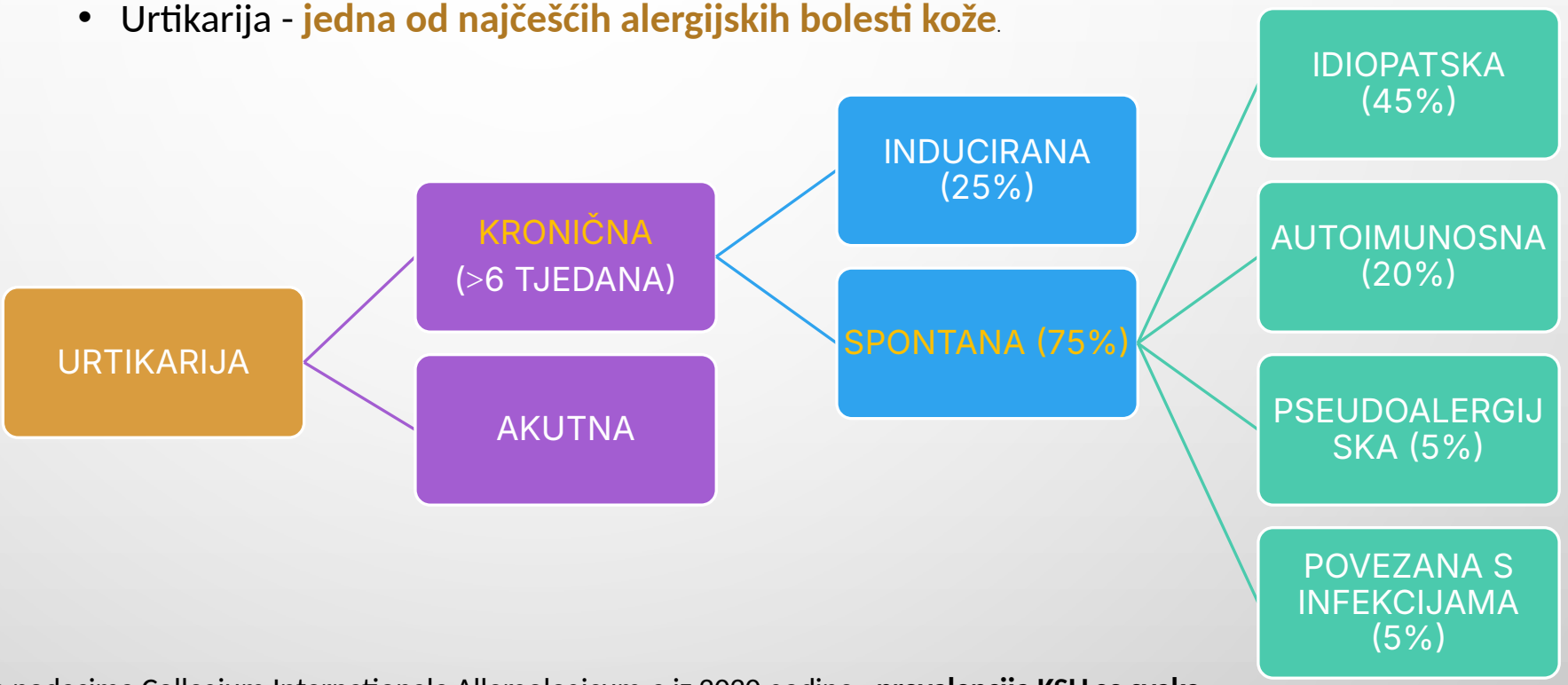
- Do 1% opće populacije oboli od KU nekad u životu; trend povećane prevalencije zadnjih godina.

- KSU (osobito angioedem) jako utječe na **kvalitetu života**, rad i učenje, mentalno zdravlje te nosi velik ekon.-socijalni teret za obitelj.



- Urtikarija - **jedna od najčešćih alergijskih bolesti kože**.



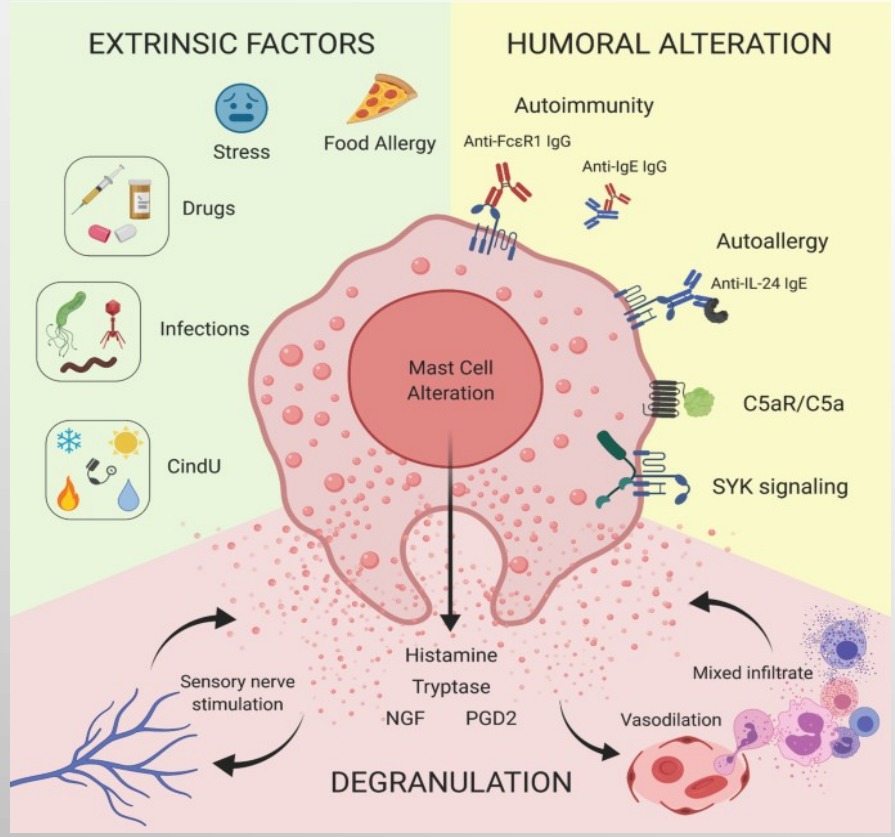


- Prema podacima Collegium Internationale Allergologicum-a iz 2020.godine: **prevalencija KSU se svake godine povećava** i pojavljuje se u svim dobnim skupinama.

- IZVOR: Maurer M, Eyerich K, Eyerich S, Ferrer M, Gutermuth J, Hartmann K, Jakob T, Kapp A, Kolkhir P, Larenas-linnemann D, Park HS, Pejler G, Sánchez-borges M, Schäkel K, Simon D, Simon HU, Weller K, Zuberbier T, Metz M. Urticaria: Collegium Internationale Allergologicum (CIA) Update 2020. Int Arch Allergy imunol. 2020;181(5):321-333

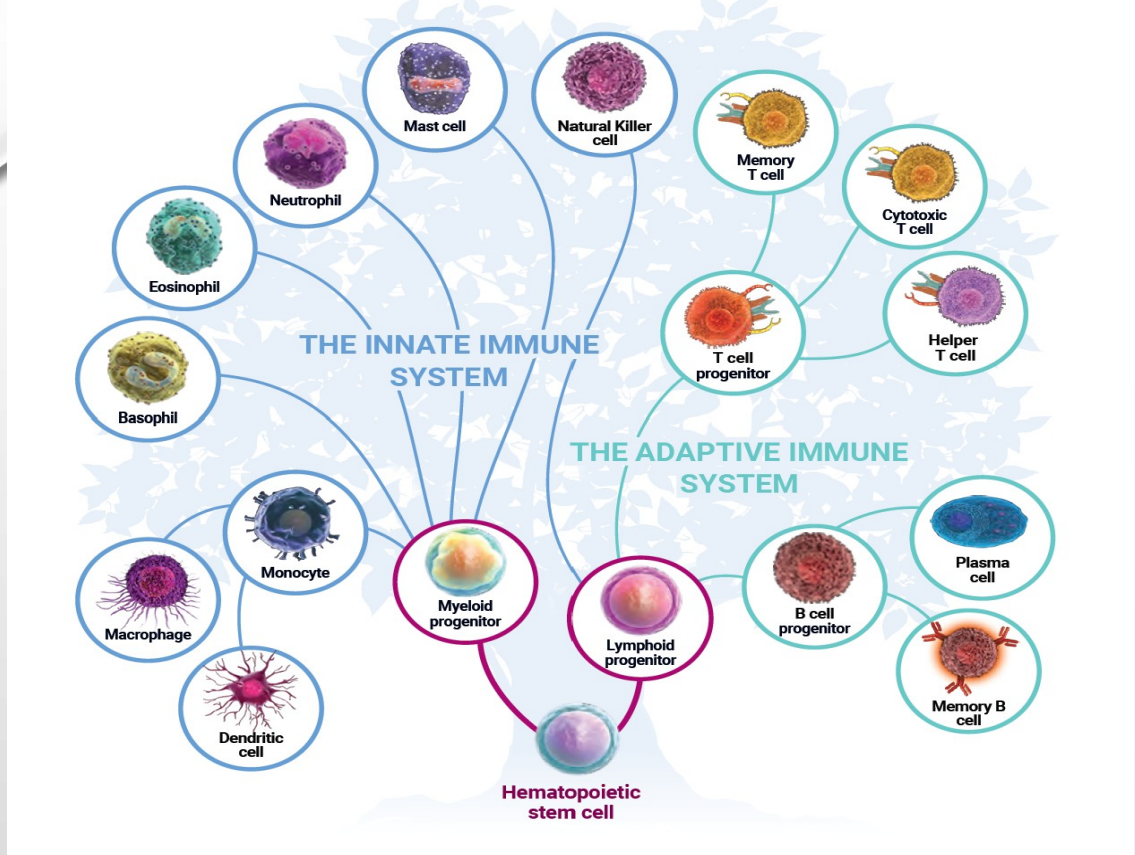
Prosječno **trajanje bolesti iznosi 2-5 godina,** u 10–25% pac. traje duže od **5 godina**.

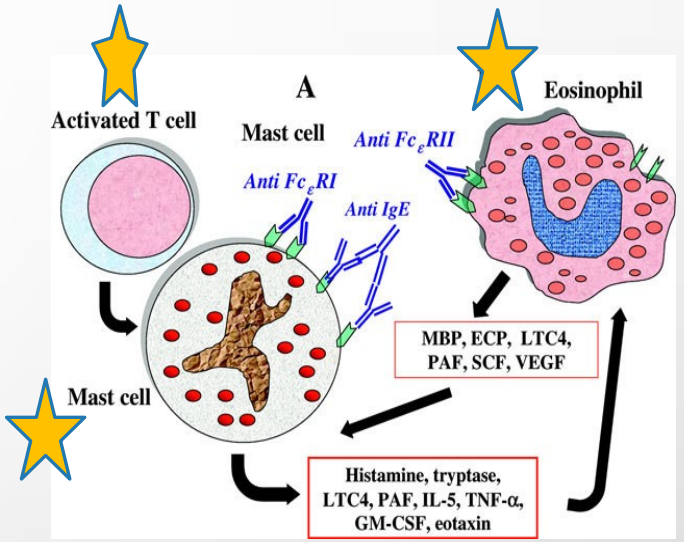
Imunopatogeneza KU i imunosne promjene u perif. krvi i koži pac.



- **Patogeneza** KU: slabo upoznata, osobito KSU, kod KSU česta autoimunosna etiologija.

- **Ključni patogenetski događaji** kod KSU: aktivacija **mastocita, bazofila, T-lc i eozinofila,** povećana vask permeabilnost i vazodilatacija, aktivacija koagulacijskih puteva i autoimunosnih procesa i oslob mastocitnih medijatora.



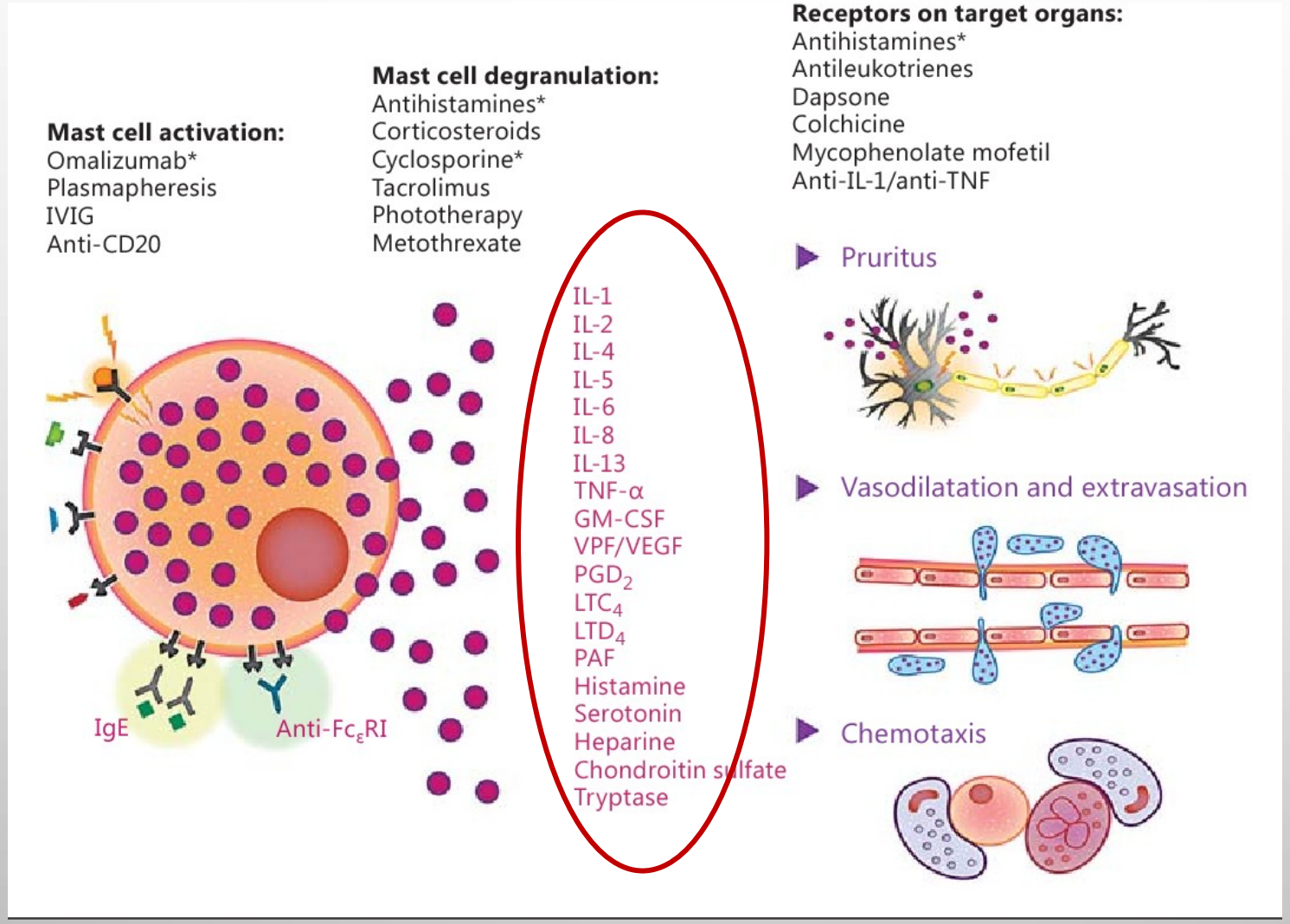


- KSU uključuje sudjelovanje obje imunosti:
- **Urođena imunost** (mastociti, bazofili, eozinofili, neutrofili, monociti, makrofagi, NK stanice, urođene limfoidne st/ILc, komp komplementa) i
- **Stečena imunost** (Th1, Th2 stanice, Th9 stanice, Th17 stanice, Treg stanice, B stanice + protutijela)

MASTOCITI POVEZUJU URO̊ĐENU I STEČENU IMUNOST, STAN. AKTIVACIJU I POLARIZACIJU.

- **Mastociti -** razne uloge: oni potiču i moduliraju T-lc akt:
  - stimuliraju B-lc na stvar IgE (kroz IL-4 i IL-13);
- stvaraju medijatore (npr. TNFα) koji poveć izražavanje vaskular endot. stanica i izraž adh. mol, što pomaže regrutaciju T-lc;
  - alergen-spec Th2 lc stimuliraju B-lc na stvaranje IgE, što stimulira/aktivira mastocite i bazofile.
-

Mehanizmi i ciljanje medijatora
kod kronične spontane urtikarije



Izvor: Deza G, Giménez-Arnau A, Itch in Urticaria Managenment, Curr Probl Dermatol.2016:50:77-85.



Liječenje KSU

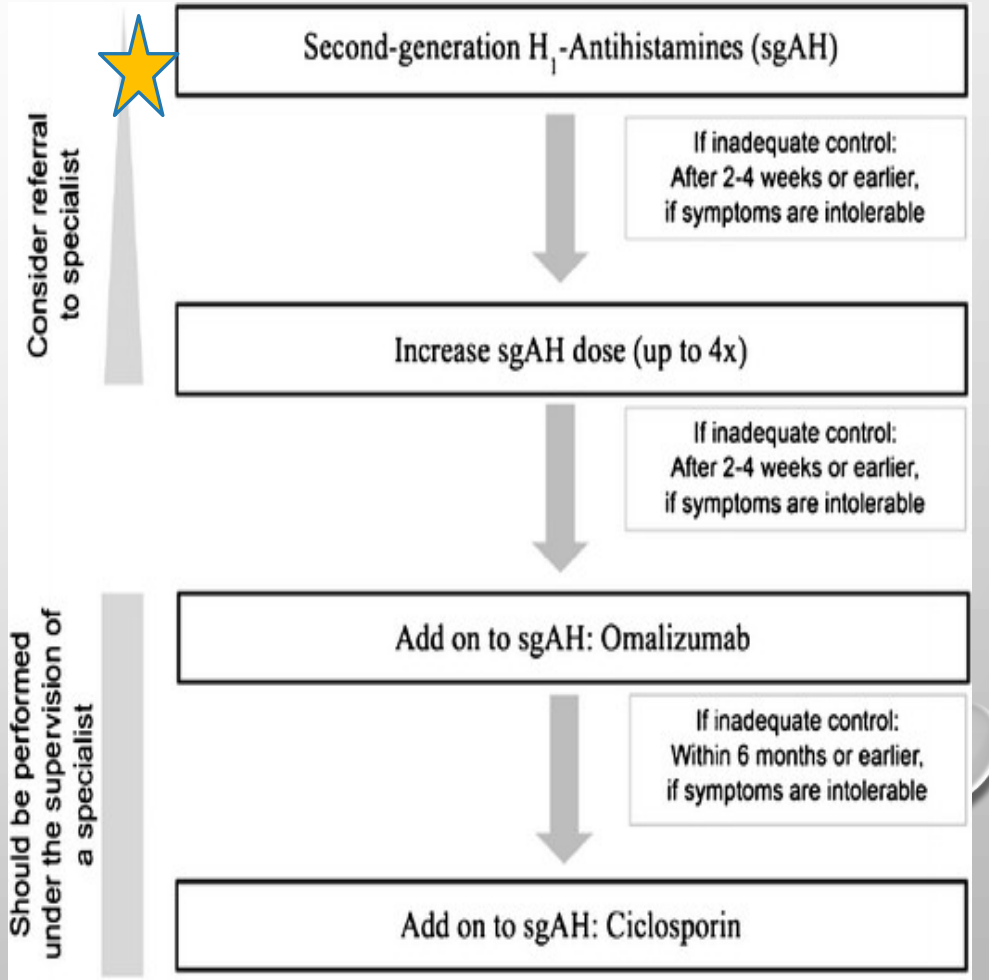


- **Liječenje KSU** često fokusirano na "**kontrolu simptoma**".

- Sadašnje **smjernice:** terapijske opcije za rKSU povećane doze (do 4-struke) **nsAH,** uz **kortikosteroide,** biološki lijek **omalizumab** (+ dupi, rembi) **i ciklosporin**, često s ograničenjima (moguće ozbiljne nuspojave, nereaktivnosti, visoka cijena, itd.) → potrebna učinkovitija terapija!

- U aktualnom liječenju KU najvažniji **nesedir. H1-AH** (nsAH), 2. gen.; **40–55% pac. je nereakt.** na konvenc. doze AH.

- Rezistantna KSU (rKSU)= **nereaktivnost** na nsAHs nakon 2-4 tjedna th u odobrenoj dozi.

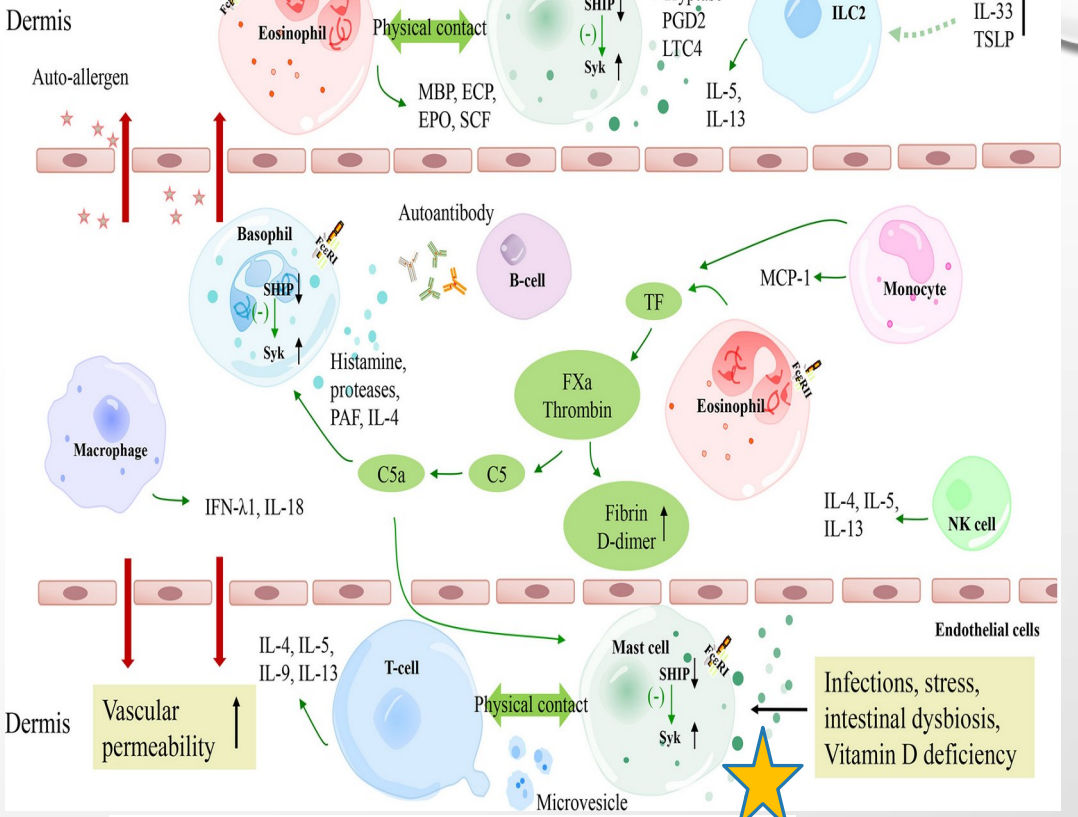


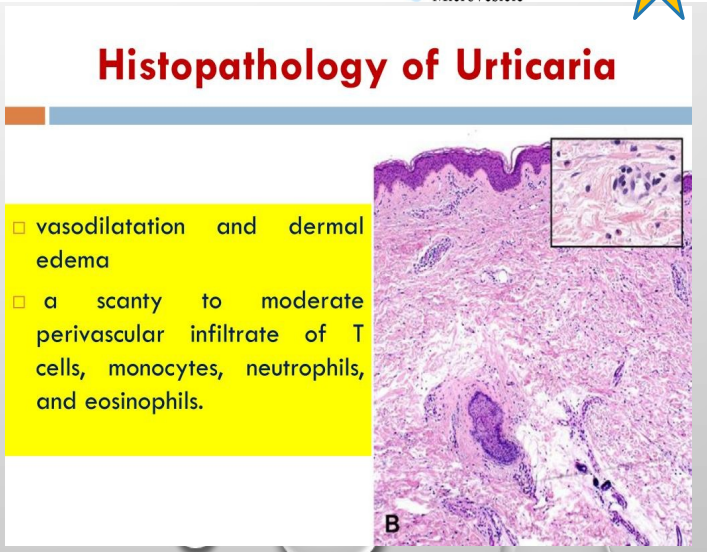

RESEARCH
ANALYSIS OF ACTION
the best

- U **KOŽI urtik. KSU promjena:** mastociti dominiraju, povećan broj bazofila, eozinofila, makrofaga, neutrofila i T-lc, uz veći broj Th17 stanica.

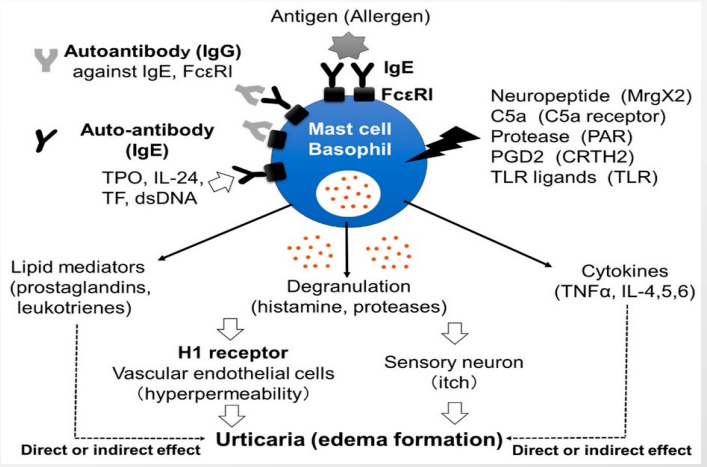
- Ključni faktori: pro-upalne **Th17 stanice** i **neravnoteža Th17 stanica/Treg stanica** **+** genetski faktori.

- U urtikama: poveć.izraž. **Th17-povezanih puteva**: IL-17 signaliziranje, Th17 stan diferencijacija uz signalne događaje posredovane IL-6 i IL-23 + veća izraženost **Th17-povez. genske ekspresije (npr. IL-6)**(vs Zd.os.).

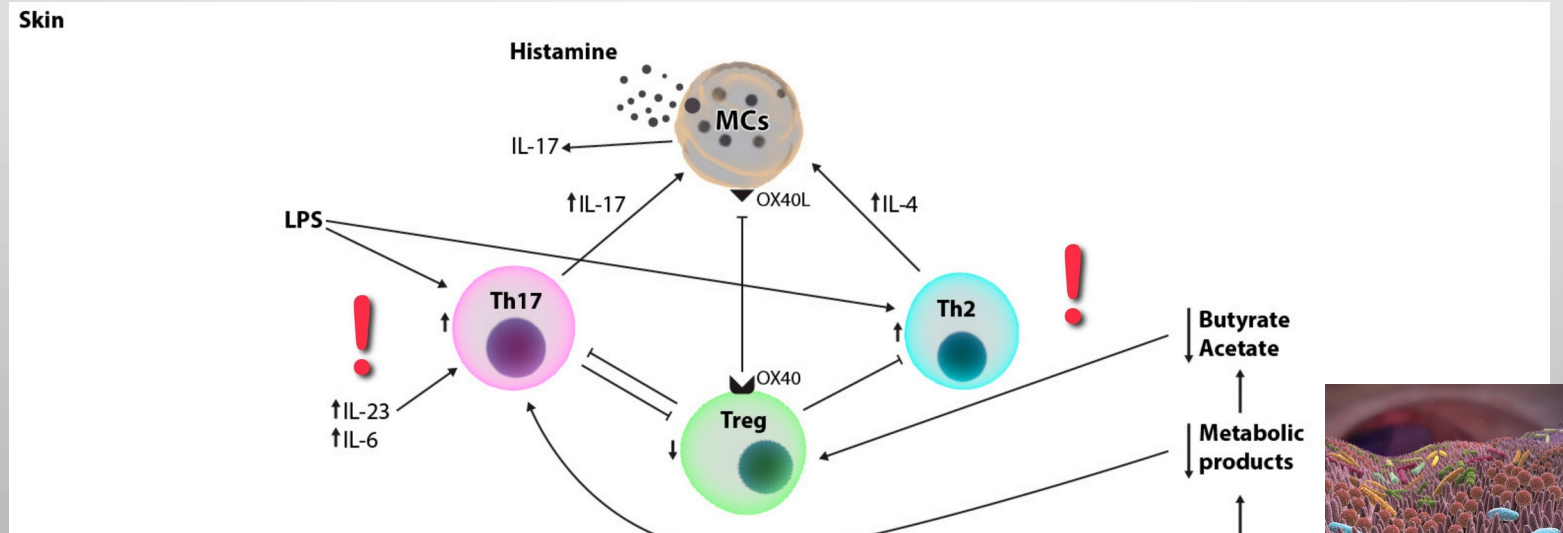




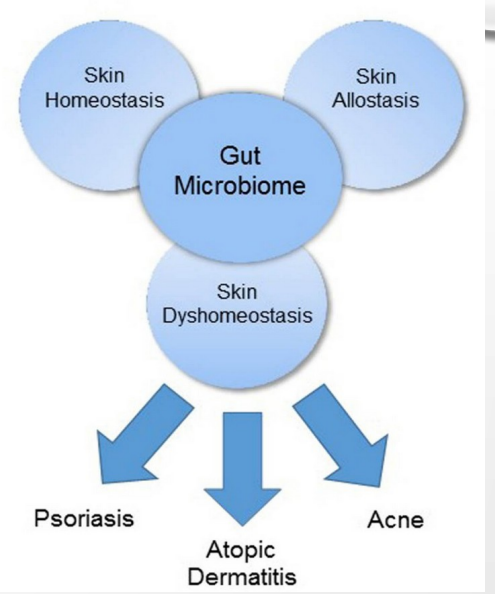
- U **zdravoj** koži (u usporebi s urtik.pr.): veći broj **Treg st** i mirujućih mastocita, tj. **Tregs mogu suprimirati mirujuće mastocite** (i inhib. stvaranje urtika).



- Kod **urtikarije**: suprimirani Treg (kod aktiviranih mastocita, dominantnije <u>Th2 st</u>. s više IL-6 i manjeg omjera Th1/Th2 citokina), što potiče Th17 odgovor.



HOMEOSTAZA **MIKROBIOTE I HUMANOG IMUNOG SUSTAVA**



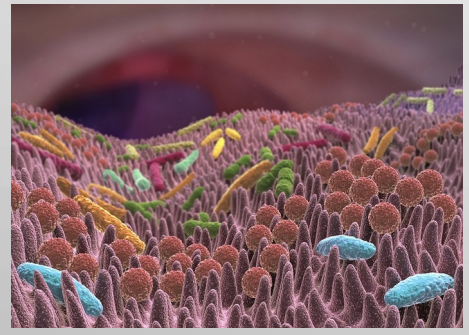
(novija istraž.)

- SASTAV **CRIJEVNOG MIKROBIOMA** povezan s **KU**

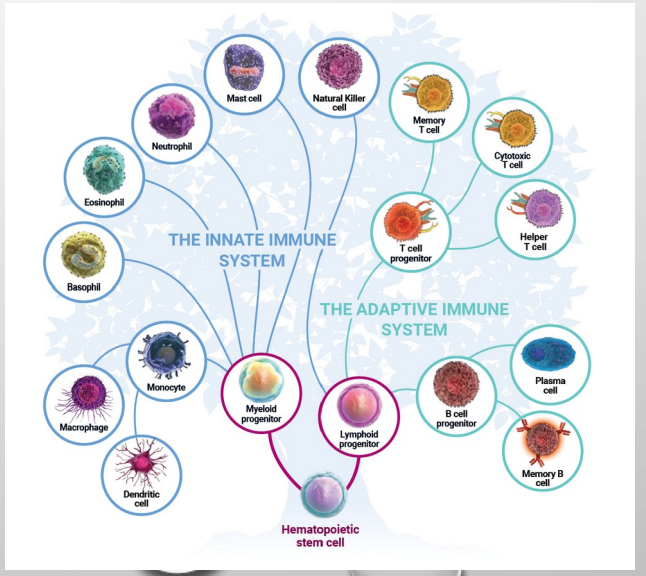
nepoznati mehanizmi odgovorni za ovu poveznicu.

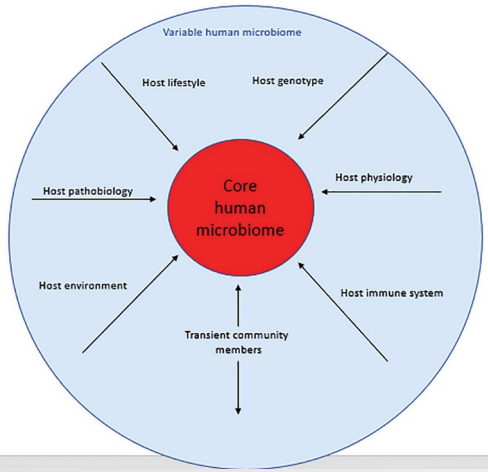
- **sastav mikrobioma regulira** funkcije **imunog** sustava →

promjene sastava mikrobiota (**disbioza**) mogu utjecati na **tijek KSU** (težinu bolesti, KŽ i ishod liječenja).





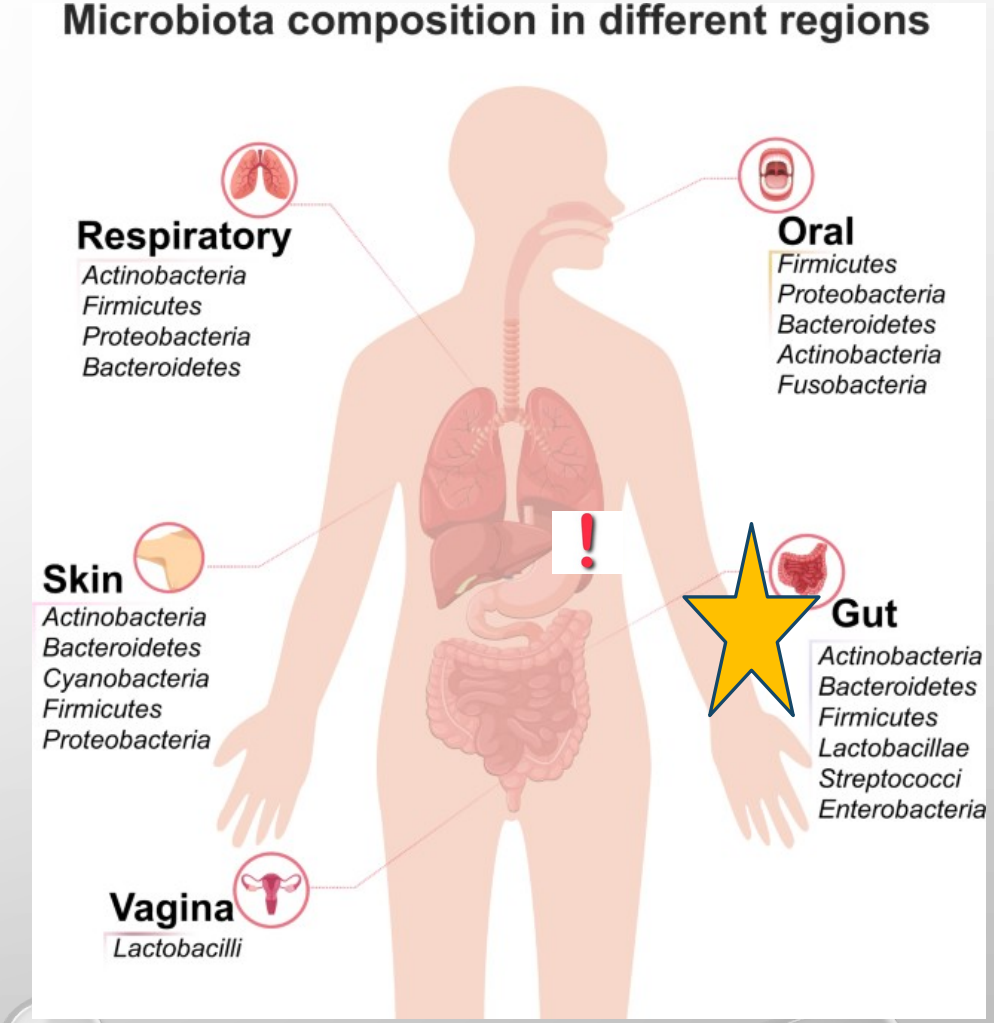


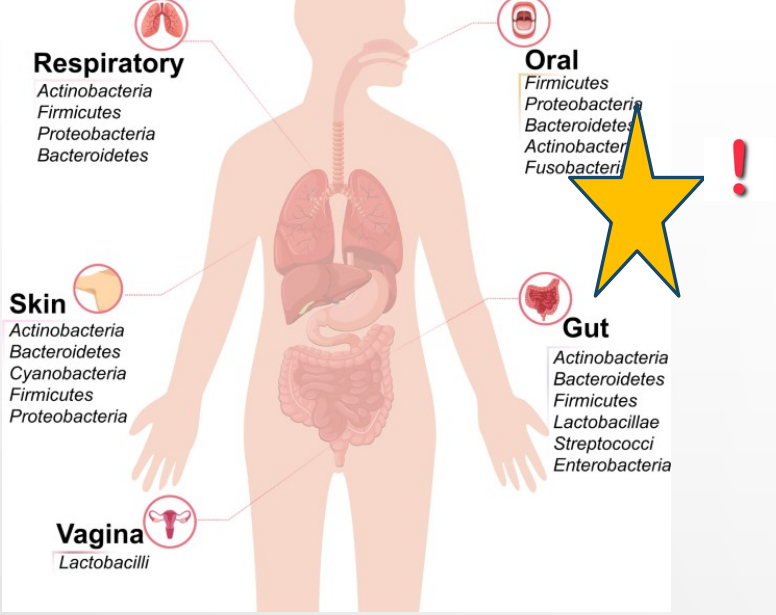


Obilježja crijevnog mikrobioma zdravih osoba

- **Ljudska mikrobiota =** brojne bakterije i drugi mikroorganizmi (archaea, gljive, virusi i protozoa) u/na tijelu, uključujući genomski sadržaj organizama naseljenih na pojedinom mjestu.

- **<u>Crijevni</u> mikrobiom** odraslih**:** ugl naseljen bakterijama iz **3 glavna koljena: *Actinobacteria*, *Bacteroidetes* i *Firmicutes***
(zajedno >90% ukupnih crijevnih bakterija).





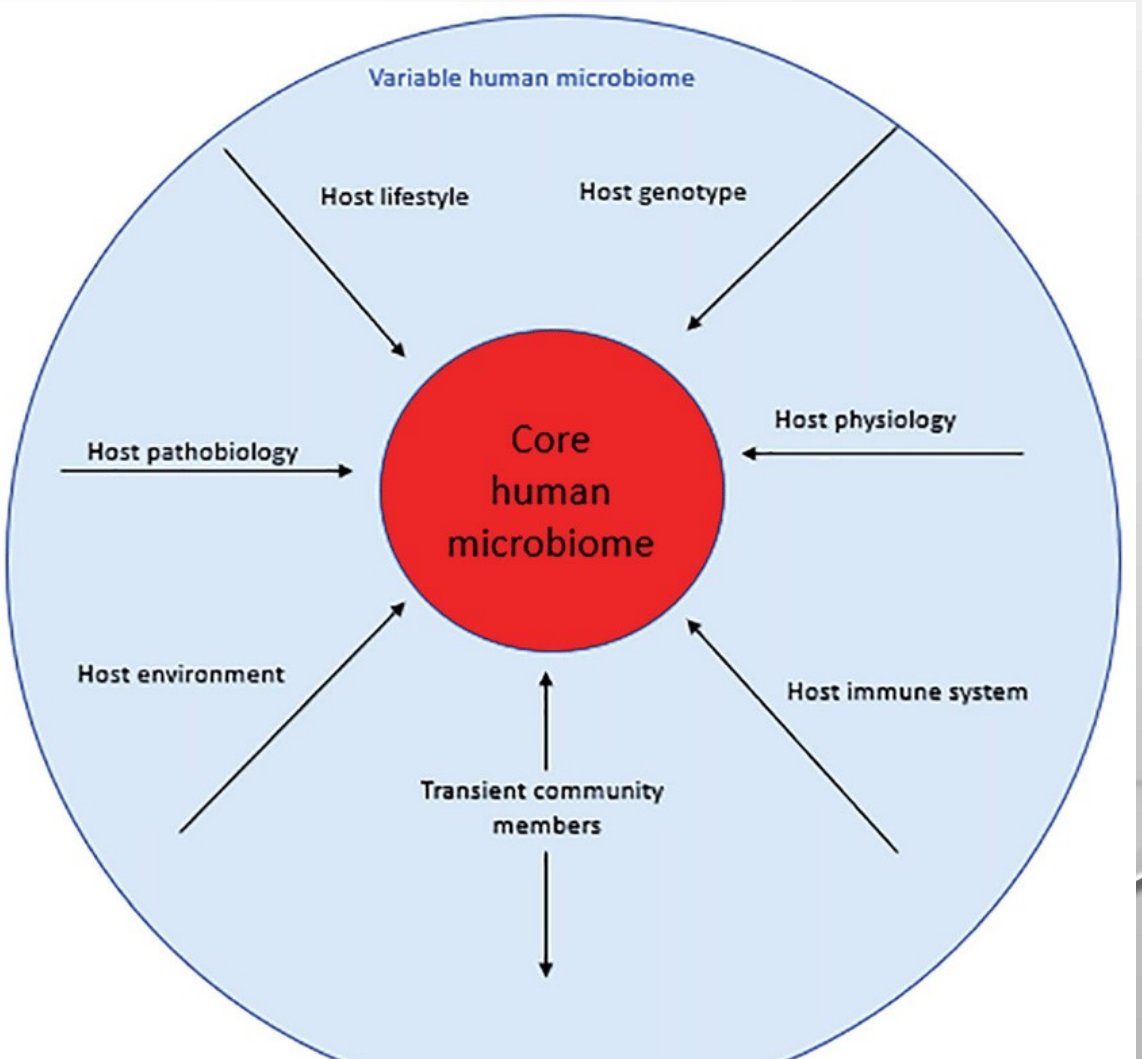
Obilježja crijevnog mikrobioma zdravih osoba

-

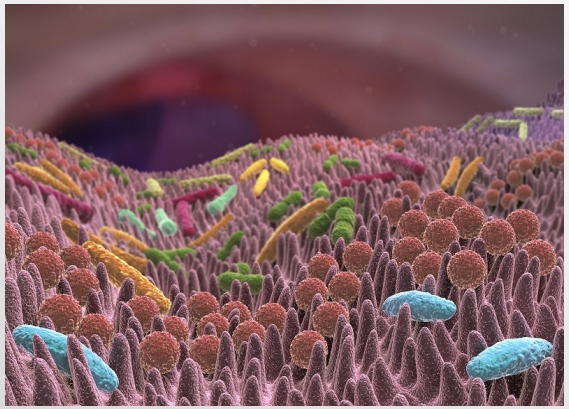
- Crijevni mikrobiom čovjeka sadrži

- (1.) **osnovni** (core) **mikrobiom** (sličan u većine osoba) i

- (2.) **varijabilni** **mikrobiom** (jedinstven za podgrupe osoba, ovisno o lifestyle-u i fiziološkim razlikama).

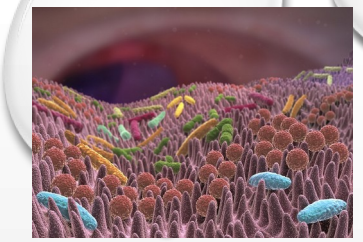


NAJČEŠĆE BAKTERIJE U DEBELOM CRIJEVU ČOVJEKA



Bakterija	Incidencija (%)
Bacteroides fragilis	**100**
Bacteroides ***melaninogenicus***	**100**
Bacteroides ***oralis***	**100**
Enterococcus faecalis	**100**
Escherichia coli	**100**
Enterobacter sp.	40–80
Klebsiella sp.	40–80
Bifidobacterium bifidum	30–70
Staphylococcus aureus	30–50
Lactobacillus	20–60
Clostridium perfringens	25–35
Proteus mirabilis	5–55
Clostridium tetani	1–35
Clostridium septicum	5–25
Pseudomonas aeruginosa	3–11
Salmonella enterica	3–7
Faecalibacterium prausnitzii	?common
Peptostreptococcus sp.	?common
Peptococcus sp.	?common

Izbor: https://en.wikipedia.org/wiki/Gut_microbiota
Todar, Kenneth (2012). "The Normal Bacterial Flora of Humans" Todar's Online Textbook of Bacteriology. Retrieved June 25, 2016.



Crijevni mikrobiom i imunost zdravih osoba

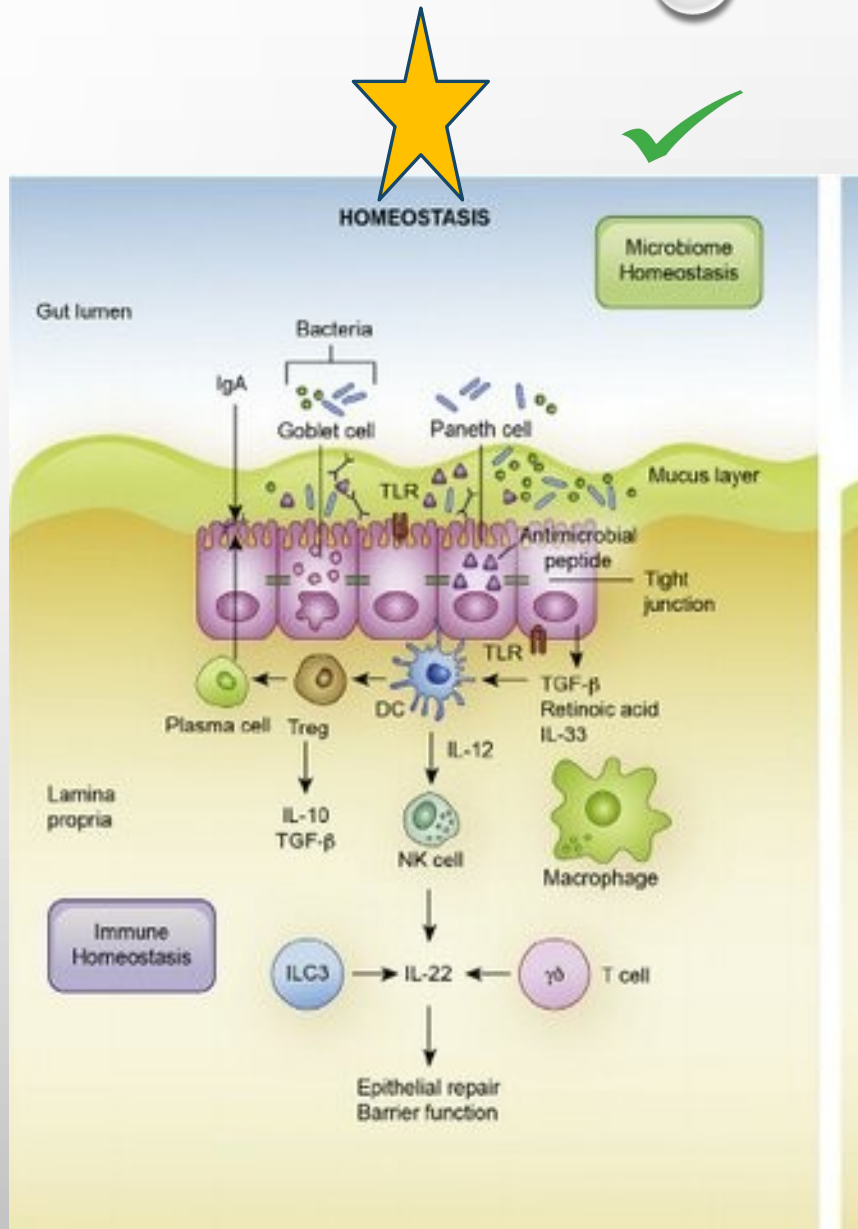
- **Crijevna mikrobiota** - najveći i najraznovrsniji rezervoar mikroorganizama u ljudi, sadrži oko 10^{13}–10^{14} bakterija

- **Uloge crijevne mikrobiote:**

  sudjeluje u probavi i metaboličkim procesima, održavanju cjelovitosti crijevnog epitela, sintezi vitamina, zaštiti od patogena, modulaciji i održavanju ravnoteže imun. sustava

  - **Humana mikrobiota značajna za imunosni** sustav; potrebna za razvoj/regulaciju nekih imunosnih faktora.

- U crijevima: **70-80% stanica imunosnog** sustava.



Povezanost crijevne mikrobiote i imunosti

- u održavanju **PRIROĐENE IMUNOSTI:** granulociti, makrofagi, NK stanice, GALT (*Gut Associated Lymphoid Tissue*, limfatično tkivo pridruženo crijevnoj sluznici), sluznički IgA… ; stanice crijevnog epitela luče **AMP** (s protuupalnim i baktericidnim djel.)

-povezana sa **STEČENOM IMUNOSTI**: mikrobiota GI trakta utječe na usmjerenje populacija **T-lc** u različite subpopulacije **Th** stanica (uz regul. aktivnosti **neutrofil**a)

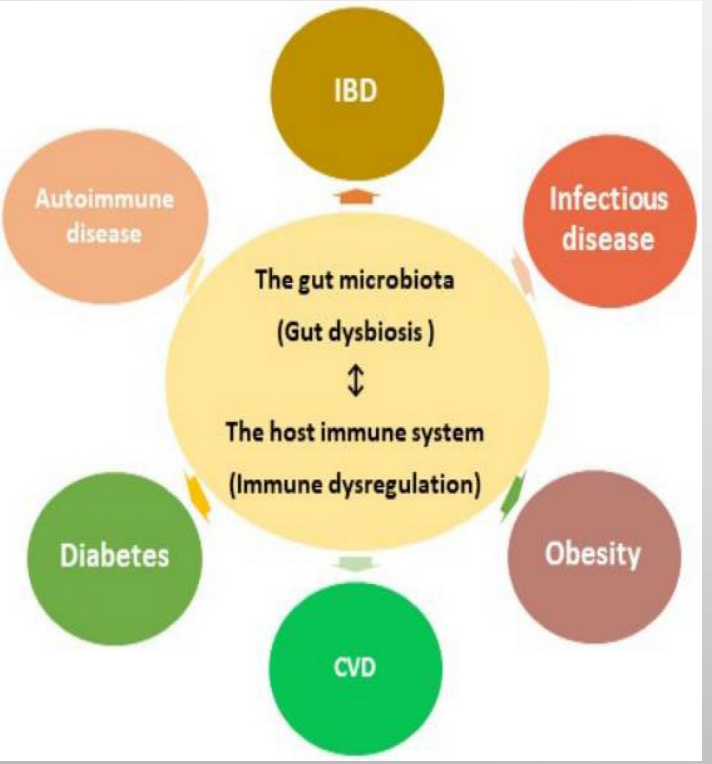
- **Crijevne bakterije proizvode klMK (<6 ugljik. atoma) (butirat, propionat i acetat…)** - klMK sudjeluju u **modulaciji crij. imunosustava** i održavanju ravnoteže protuupalnih-upalnih procesa (TLR receptori - važni posrednici upalnih puteva u crijevu, veza urođene i stečene imunosti)

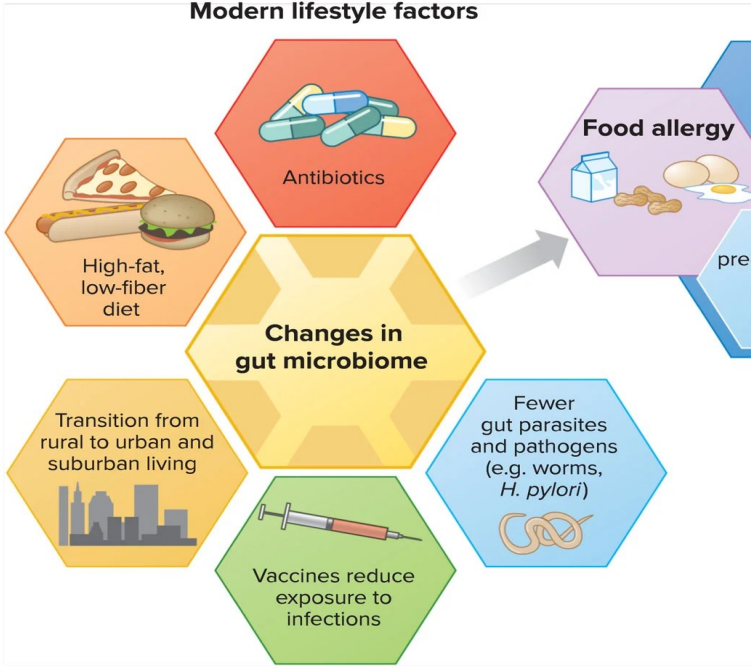
Neravnoteža mikrobiote….

- **Disbioza** – neravnoteža u sastavu ljudske mikrobiote.

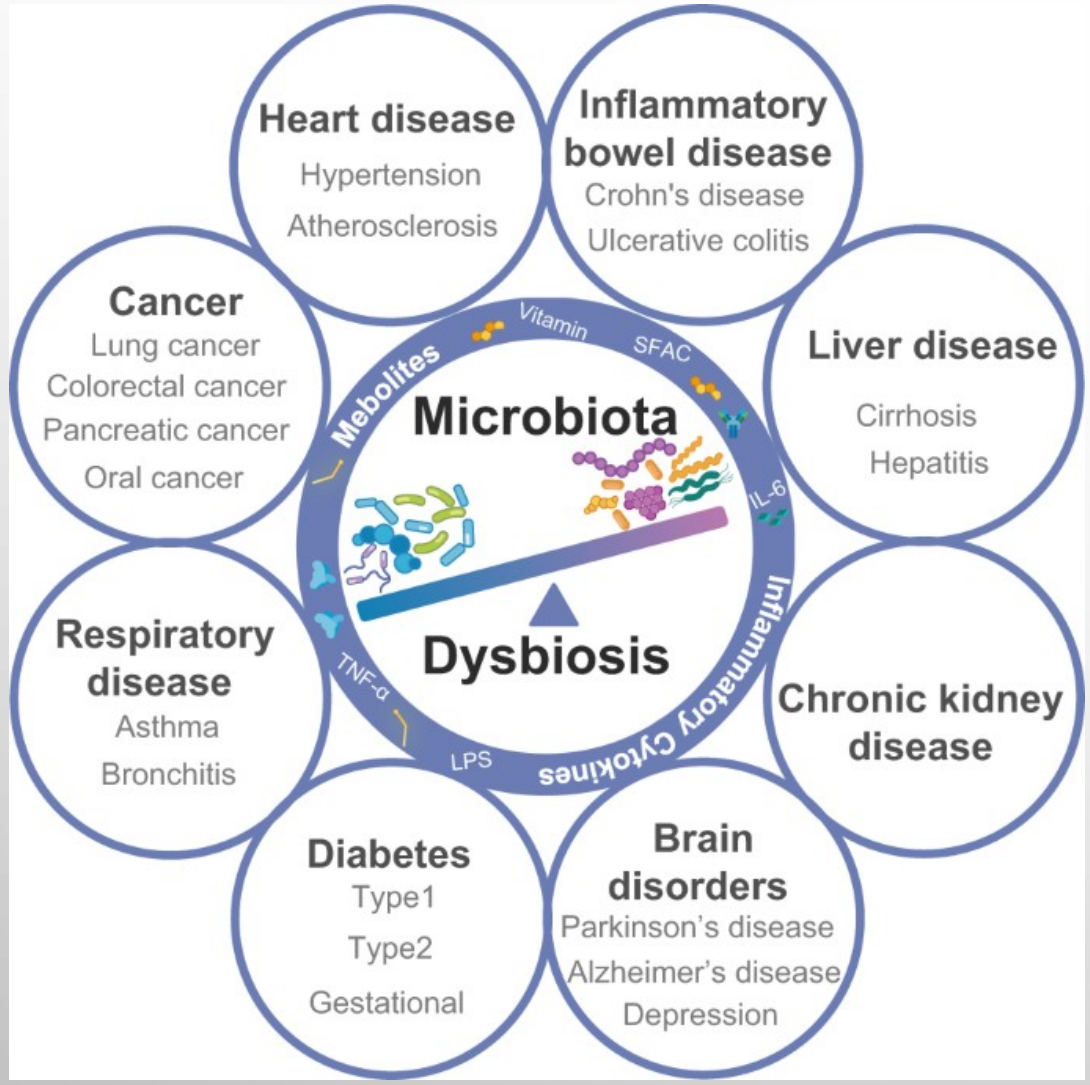
- Različiti **faktori** mogu biti uključeni u **bakterijsku neravnotežu**, uklj. psihosocijalni stres, (ne)zdrave navike, ishrana, socijalni odnosi, okolišni faktori, pušenje i unos alkohola i korištenje lijekova (npr. antibiotici ili probiotici).

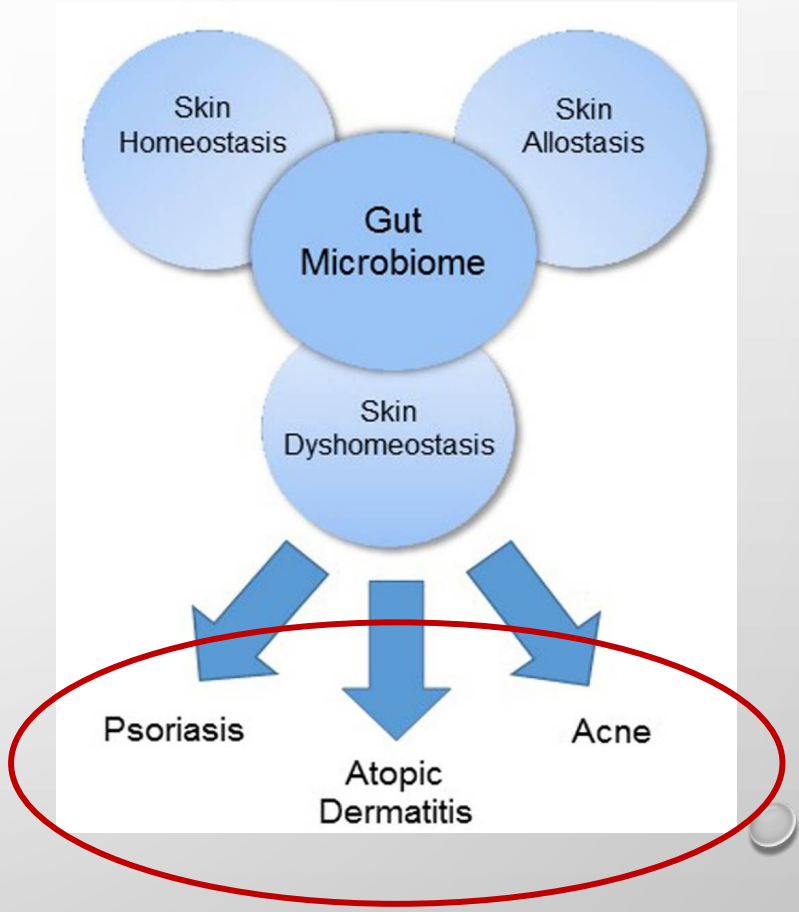
- **Promjene sastava** mikrobioma su povezane s patogenezom psihijatr. bolesti, imunosnih crijevnih bolesti, kardiovaskularnih i neuroloških bolesti, alergijskih bolesti, karcinoma, dijabetesa, reumatoidnog artritisa, metaboličkog sindroma, bolesti jetre, debljine i kwashiorkora.

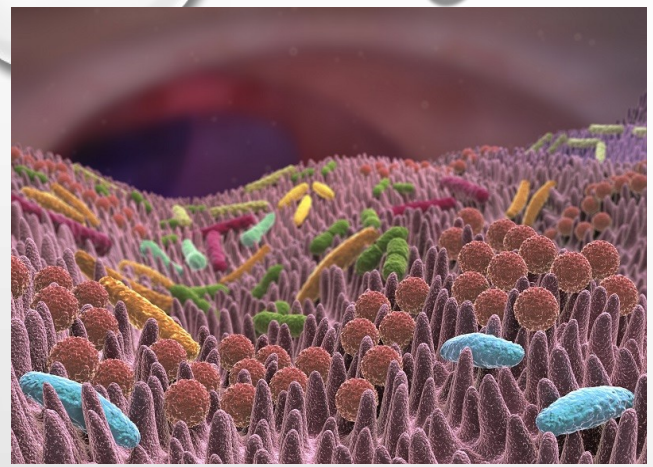


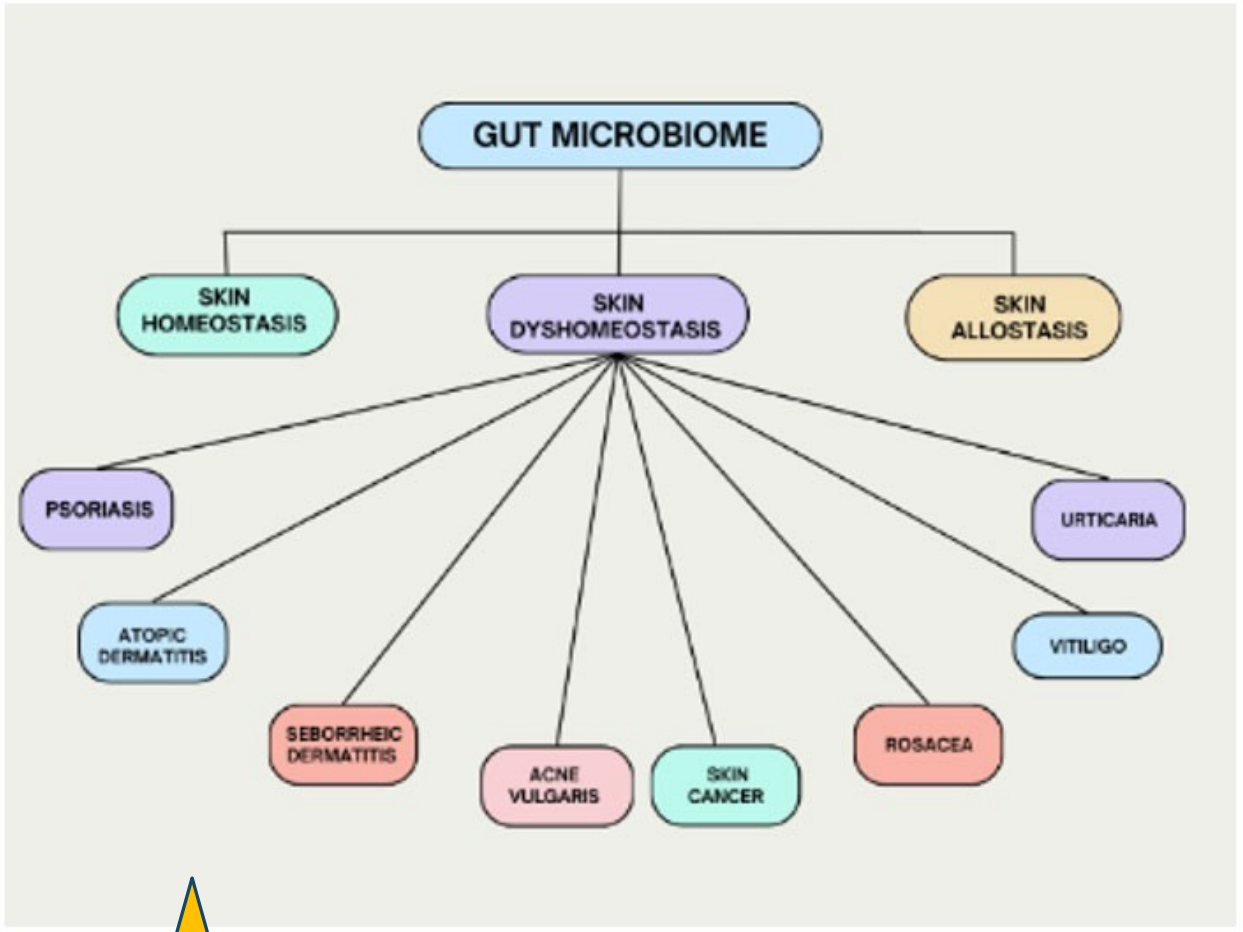


SOURCE: O.I. IWEALA & C.R. NAGLER / *AR IMMUNOLOGY* 2019


Heart disease
Hypertension
Atherosclerosis
Inflammatory bowel disease
Crohn's disease
Ulcerative colitis
Cancer
Lung cancer
Colorectal cancer
Pancreatic cancer
Oral cancer
Liver disease
Cirrhosis
Hepatitis
Microbiota
Dysbiosis
Mebolites
Vitamin
SFAC
IL-6
Inflammatory Cytokines
TNF-α
LPS
Respiratory disease
Asthma
Bronchitis
Chronic kidney disease
Diabetes
Type1
Type2
Gestational
Brain disorders
Parkinson's disease
Alzheimer's disease
Depression

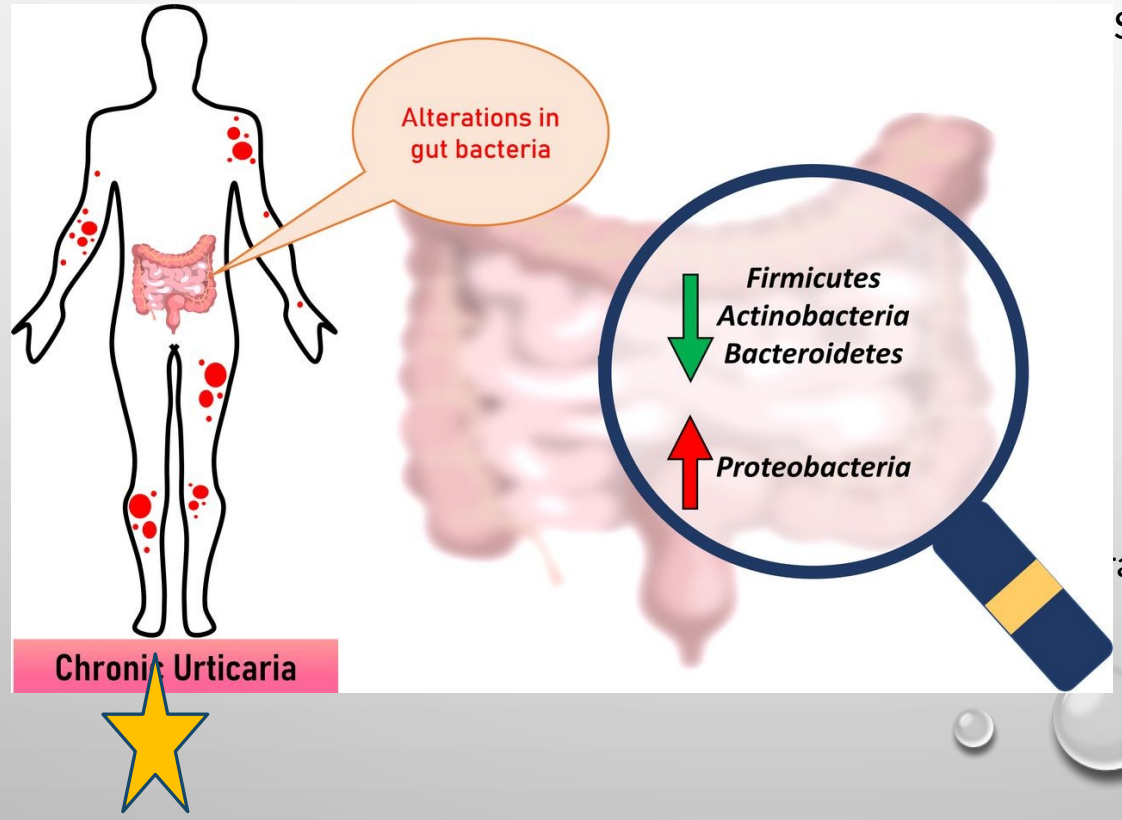

Skin Homeostasis
Skin Allostasis
Gut Microbiome
Skin Dyshomeostasis
Psoriasis
Atopic Dermatitis
Acne





Effect of gut microbiome on skin dyshomeostasis

Crijevni mikrobiom odraslih je ugl. naseljen bakterijama iz **3 glavna koljena**: ***Actinobacteria***, ***Bacteroidetes*** i ***Firmicutes***, koji zajedno čine >90% ukupnih crij. bakterija.



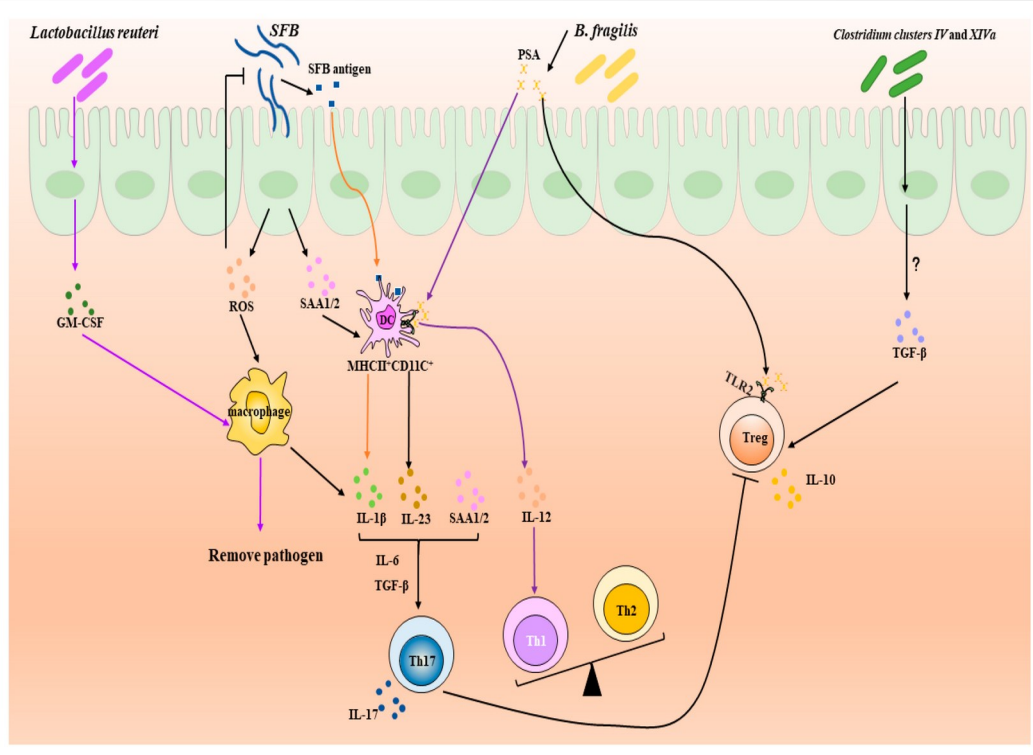
- Novije studije: **u pac. s KSU** promijenjen sastav crijevnog mikrobioma**.**

Spoznaja: **promjene crijevnog mikrobioma uzrokuju pro-upalne odgovore** posredovane **neravnotežom Th1/Th2/Th17 citokina**, što može doprinijeti KSU patogenezi.

Istraž.: Kod KSU, poznavanje humanog **metaboloma** (malih molekula nastalih od mikroorg.) i **crijevne disbakterioze** (usporedba s Zd.os.)→ bolje razumijevanje potenc. uzroka upale i potenc. novi pristup KSU.

- **Crijevne bakterije** u interakciji s **dendr. stanicama** intest. epitela → aktiviraju signalne puteve **imunosnih efektornih stanica** (makrofazi, B-lc, NK stanica i T-lc).

- **Crijevna lamina propria** sadrži velik broj **Th17** stanica i **Treg stanica** → **komenzalna mikrobiota** potiče **Th17 stanični odgovor.-**



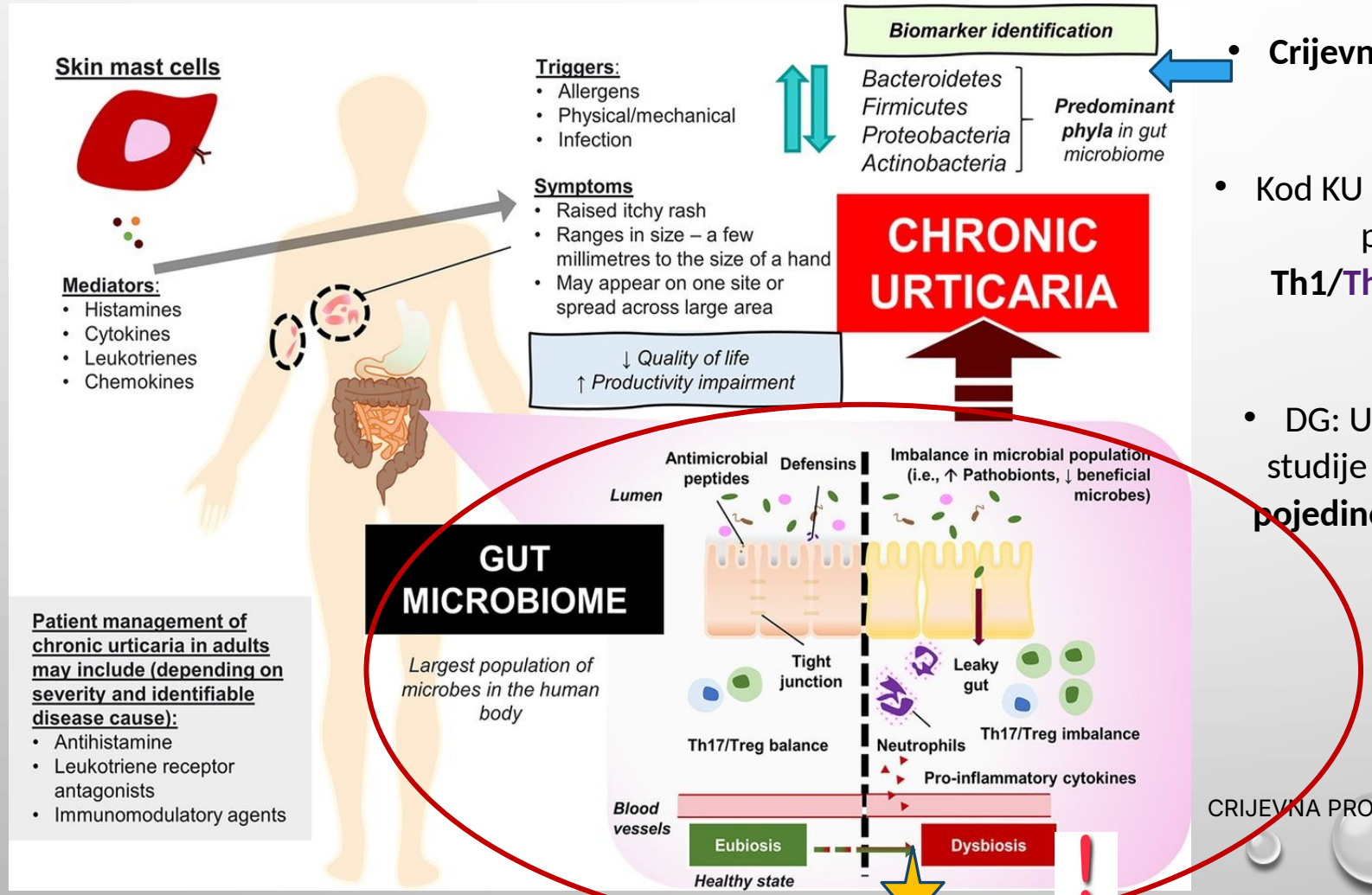
- **Treg stanice** održavaju imunosnu homeostazu i pomažu imunosnu toleranciju alergena

→ U pac. s KU je **smanjen broj/funkcija Treg stanice** → pretpostavka: **smanj nekih bakterija** može remetiti **ulogu Treg stanice** u imun odgovoru (putem **induc. Toll-like receptora**) vodeći ka KSU (pojavi,perzistiranju).

(TL receptori - važni medijator upalnih puteva u crijevu, veza urođene i stečene imunosti)

Crijevni mikrobiom pac. s KSU

Crijevni mikrobiom odraslih je ugl naseljen bakterijama iz **3 glavna koljena: *Actinobacteria*, *Bacteroidetes*** i ***Firmicutes*,** koji zajedno čine više od 90% ukupnih crijev bakterija.



- **Crijevni mikrobiom <u>pac. s KSU</u>** se razlikuje od onog zdravih; poremećen sastav crijevnog mikrobioma

- Kod KU su **upalne/imun. promjene povez.** s **crij. disbiozom** - promijenjen imunosni odgovor uz **neravnotežu Th1/Th2/Th17 citokina** može doprinijeti KSU (slično astmi i atopijskom dermatitisu).

- DG: U pac. s KSU/Zd.os u identifikaciji vrsta i roda mnoge studije **koristile 16s rRNA sekvencioniranje** te usporedbu, a **pojedine putem qPCR uspoređivale** specif. vrste u 2 skupine.

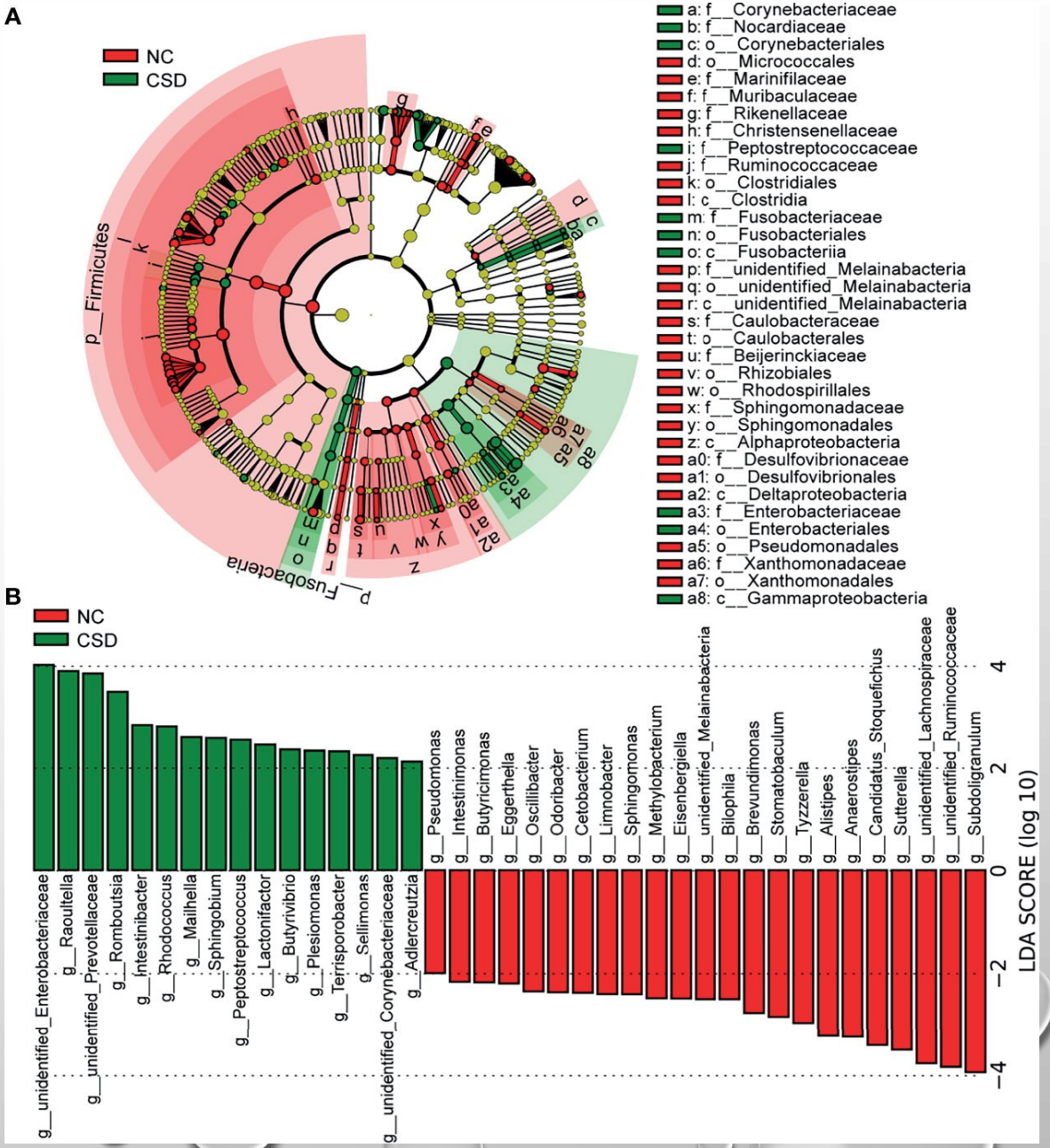
CRIJEVNA PROPUSNOST!

- DG: Upoznavanje interakcija crij. mikrobioma i domaćina važna za upozn. promjena mikrobioma udruženih s KSU (pojava,perzist)

- Dva glavna pristupa **sekvencioniranju mikrobiota**:
  targeted 16s rRNA sekvencioniranje i
  non-targeted sekvencioniranje cijelog genetskog materijala (shotgun mehoda)
  metagenomika (analiza strukture i funkcija svih nukleotidnih sekvenci).

- METABOLITI: **Mikroorganizmi crijevnog mikrobioma** vrše i važne metaboličke funkcije (sintezu aminokis., stvaranje kratkolanč MK, biotransformaciju žučnih kiselina).

- Analiza crijevnog metaboloma: **nove tehnologije,**
  npr. ***mass spektrometrija*** i ***NMR spektroskopija*** postale korisna sredstva (razl biološki uzorci, najčešće feces).

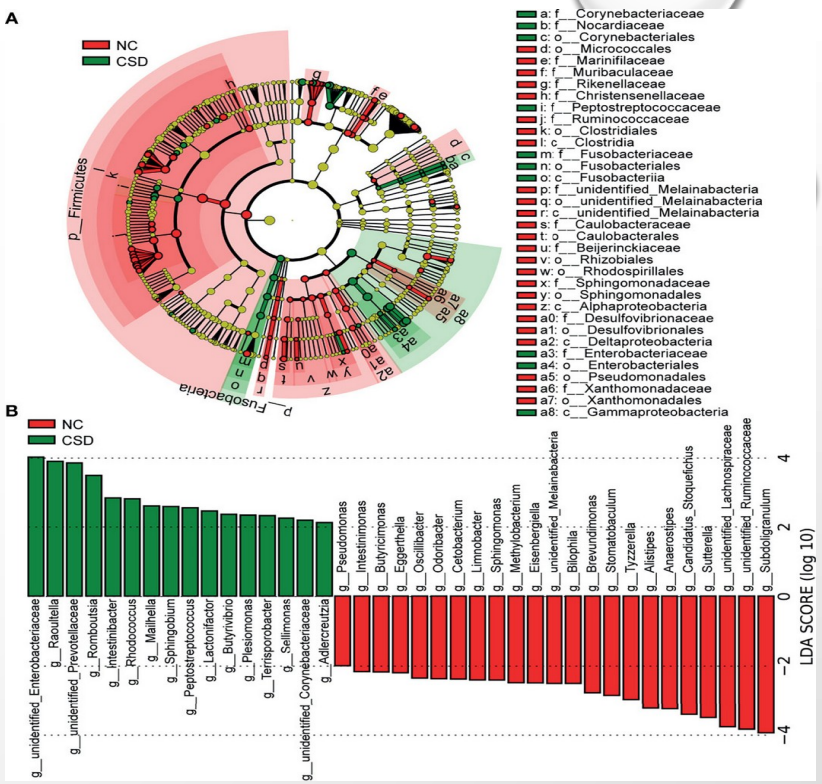


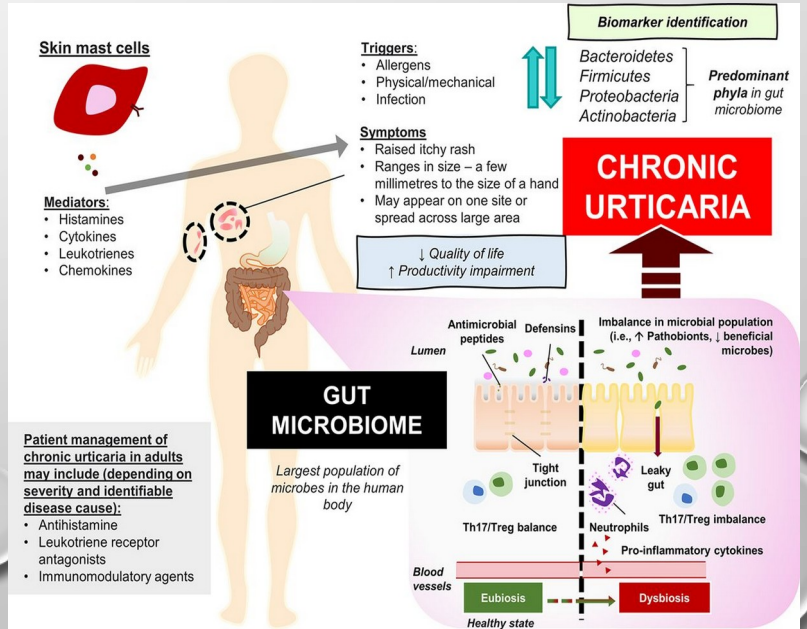
Analiza crijevnog mikrobioma

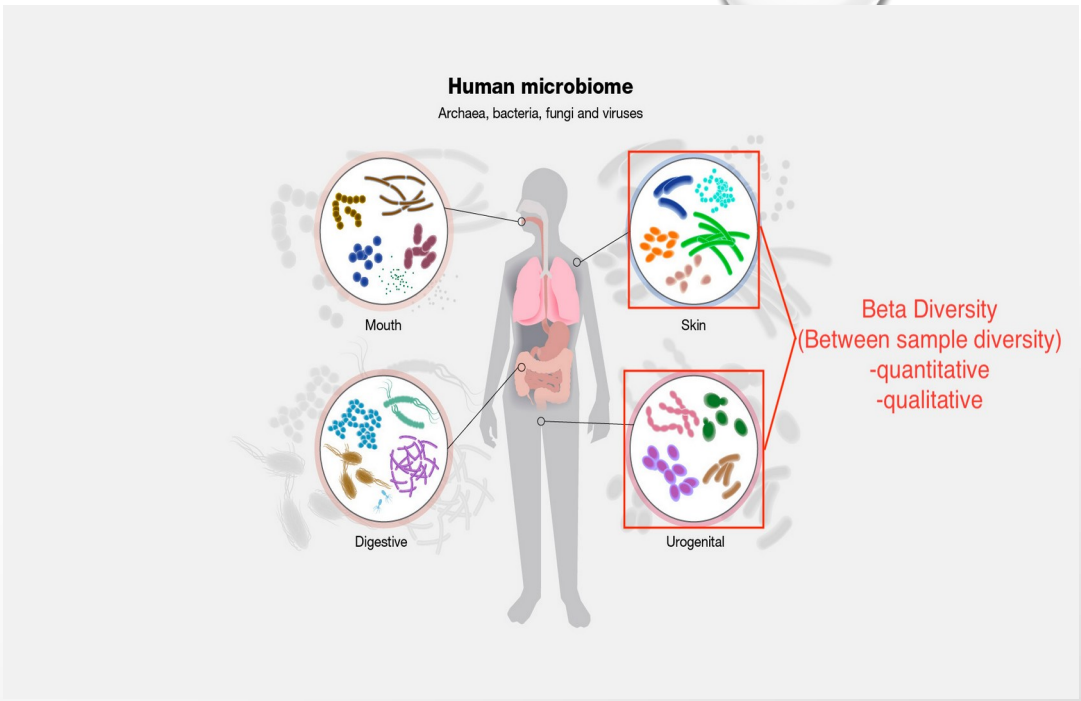
- **Napredne tehnologije** su doprinijela razumijevanju uloge mikrobioma u patogenezi nekoliko **autoimunosnih** bolesti (SLE, reumatoidni artritis, Sjögrenov sy, Crohnova bolest, Behcetova bolest, dijabetes tipa I, psorijaza i psorijatički artritis…) + **alergijske bolesti** (alergije na hranu, atopijski dermatitis, astma…).

- Razvoj **molekularne biologije/bioinformatike + smanjenje cijene sekvencioniranja** doprinio upoznavanju mikrobioma, detekciji mikroorganizama i funkcij. gena (porast istraž promjena mikrobioma kod autoimunosnih/imunosnih bolesti).

- Promjene **ishrane/dijeta, nezdrav lifestyle ili promj. crij. epitelnih stanica** → mogu **potaknuti proupalne citokine**/medijatore, što utječe na luminalni mikrookoliš → moguća crijevna **disbioza** i različite bolesti (kao KSU).







- Za uvid u **specifična obilježja crijevnog mikrobioma** (mikroorganizmi, bakterijski sastav), važni **podaci o alfa i beta** raznolikosti kod spec. bolesti.

- **Alfa** raznolikost **=** **u pojedinom uzorku** procjena vrste (izražene putem metoda: **Chao1 value, ACE value i Shannon index**, itd).

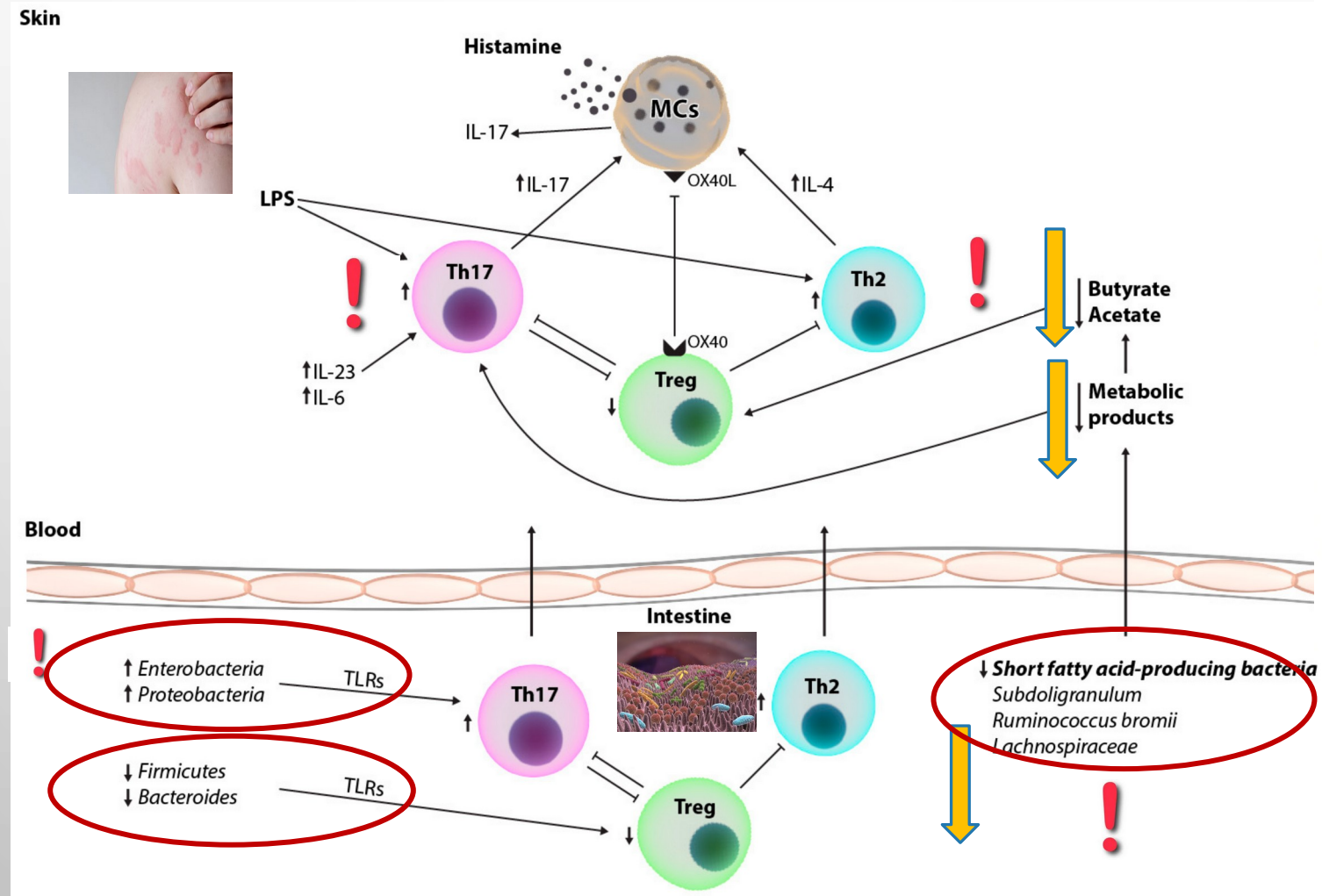
- **Beta** raznolikost **=** (usporedba grupa) **omjer svih** *Operational Taxonomic Units* (OTUS) - identifikacija diferencijacija **između grupa** analizom čestih OTUS.

CSU:



- Lu i Wang: u pac. s KSU **smanjena alfa raznolikost crijevnog mikrobioma**→ promjene sastava crijevnog mikrobioma.

- Zhang: **beta analizom** utvrđena značajna razlika u nalazu clustering/grupiranja između pac. s KSU. vs Zd.os., tj. razlikovanje **sastava crijevnog mikrobioma** između dvije grupe.



↑ povećana relativna zastuplj **oportunističkih** bakterija

↓ smanjena relativna zastuplj **beneficijalnih** bakterija

life

Review

Gut Microbiome Composition in Patients with Chronic Urticaria: A Review of Current Evidence and Data

Mirela Krišto [1], Liborija Lugović-Mihić [1,2,*], Melba Muñoz [3,4], Maja Rupnik [5,6], Aleksander Mahni, Petar Ozretić [7], Morana Jaganjac [8], Diana Česić [1] and Matea Kuna [1]

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Abstract: Recent studies have linked gut microorganism composition and chronic urti however, the underlying mechanisms responsible for this connection are unknown. Since immune system is in homeostasis with microbiota, and the composition of the microbiom the development and function of the immune system, it is likely that an alteration of components (a dysbiosis) could influence the course of chronic spontaneous urticaria (CSU disease severity, patient quality of life and treatment outcome. To date, several studies hav changes in the gut microbiota composition of patients with CSU, though only a few hav metabolic abnormalities associated with gut dysbiosis. The studies on CSU patients pro showed that the relative abundance of beneficial bacteria was decreased (*Firmicutes* and while that of opportunistic bacteria was increased (*Enterobacteria* and *Proteobacteria*). serum metabolome analysis revealed that gut microbiota-associated alterations in unsatu acids and the butanoate metabolism pathway may play a role in CSU. These findings are associated with inflammation mediated by the imbalance of Th1/Th2/Th17 cytokines, w contribute to CSU pathogenesis. Further research in this field could improve clinical, and therapeutic approaches to patients with CSU. By applying new knowledge on gu communities and metabolomics, future CSU therapies could modify the microbiota c using agents such as probiotics or other similar agents, which, in combination with curre therapies, could hopefully lead to a reduction in symptoms and an improved quality CSU patients.

Keywords: gut microbiome; intestinal microbiome composition; chronic spontaneou dysbiosis; metabolome

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Citation: Krišto, M.; Lugović-Mihić, L.; Muñoz, M.; Rupnik, M.; Mahnic, A.; Ozretić, P.; Jaganjac, M.; Česić, D.; Kuna, M. Gut Microbiome Composition in Patients with Chronic Urticaria: A Review of Current Evidence and Data. *Life* **2023**, *13*, 152. https://doi.org/10.3390/life13010152

Academic Editor: Ron Kohen

Received: 10 November 2022
Revised: 21 December 2022
Accepted: 25 December 2022
Published: 4 January 2023

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1. Introduction

Chronic urticaria (CU), whether spontaneous or inducible, is characteri current episodes of pruritic wheals, with or without associated angioedema longer than 6 weeks [1,2]. Globally, up to 1% of the general population suffers at some point in life, and a trend of increasing prevalence has been observed years [3]. Chronic spontaneous urticaria (CSU), especially concomitant angioeder

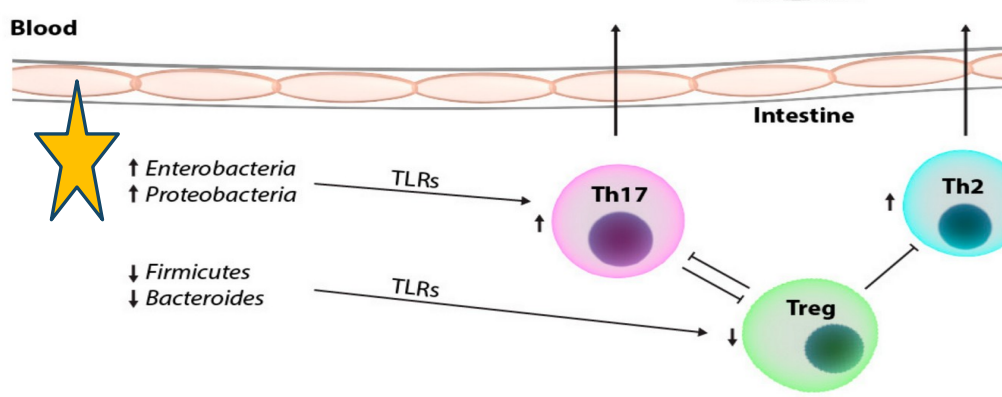
PROMIJENJEN SASTAV CRIJEVNOG MIKROBIOMA U BOLESNIKA S KSU

(Toll-like/TLR receptori - važni medijator upalnih puteva u crijevu, veza urođene i stečene imunosti)

(1.) **OPORTUNISTIČKA** bakterija ↑

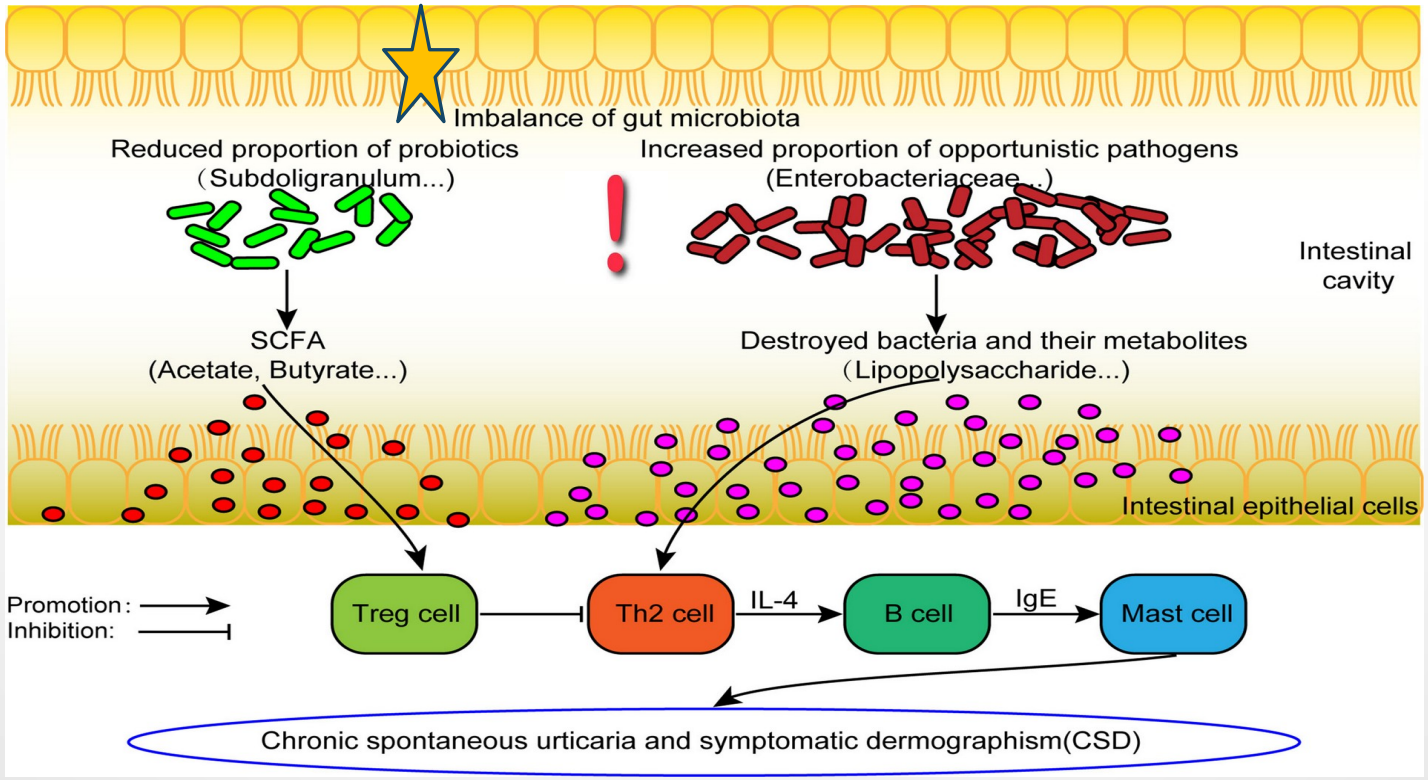
↑ povećana relativna zastuplj **oportunističkih** bakterija

↓ smanjena relativna zastuplj **beneficijalnih** bakterija



- **Zhang** i sur: sastav **crijevnog mikrobioma bol s KSU** značajno **različit od Zd.os.**:
  Proteobacteria („phylum" razina) ↑, ***bacilli*** („class" razina), ***Enterobacterales*** („order" razina), ***Enterobacteriaceae*** („family" razina) ↑, ***Megamonas, Dialister i Megasphaera*** („genus" razina). ❗
- → u pac. s KSU značajno veća relativna raznolikost *Proteobacteria* ↑ (**promjene njihove relat zastupljenosti** može uzrokovati disbiozu i biti **povezane s nekim bolestima** /=u astmatičara i alergičara).
- **Wang** i sur: **u pac. s KSU** (vs Zd.os.) **povećanje** neidentificiranih *Enterobacteriaceae* ↑; značajno **smanjena** zastup *Firmicutes* ↓, *Bacteroides*, *Faecalibacterium*, *Bifidobacterium* i neidentif. *Ruminococcaceae*.
- **Lu i sur**: u KU pac. znač. ↓**zastuplj** *Bacteroidetes*; ↑*Actinobacteria i Proteobacteria*.

•**Patogene bakterije npr. *Enterobacteriaceae* stvaraju lipopolisaharide, što <u>promovira Th2 stan</u> diferencijaciju** i stvaranje IL-4. Pretpostavka: povećana zastup *Enterobacteriaceae* aktivira mastocite i potiče oslobađanje histamina → manif urtikarije

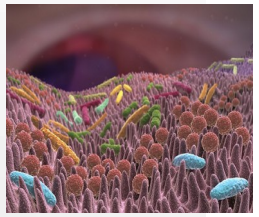


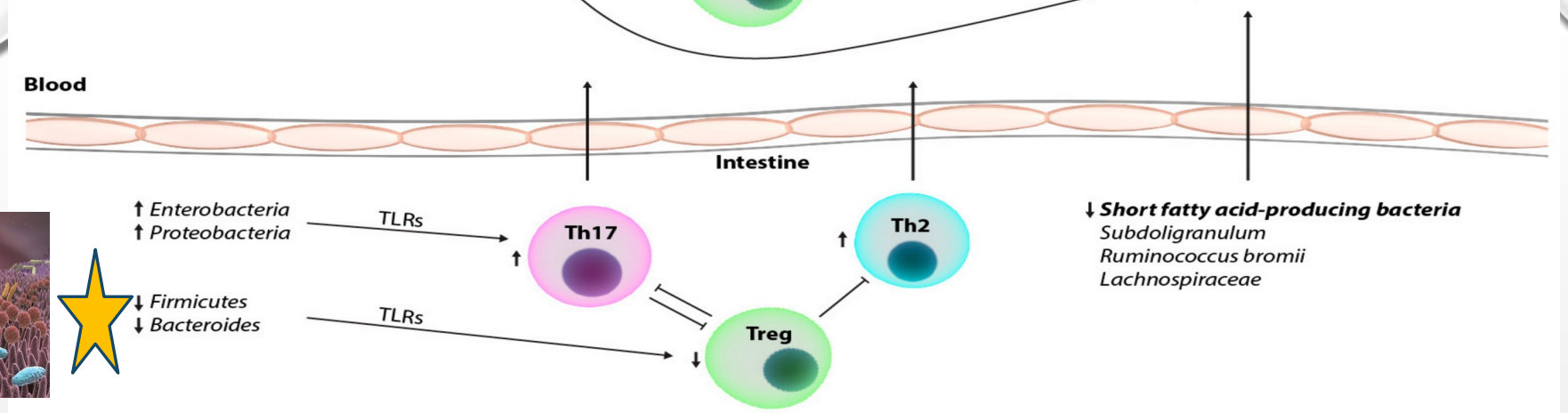
- Pretpostavka: **crijevna disbioza** je inicijalni događaj (prvenst. kod autoimune KSU) pa smanjenje **nekih bakterija** može **modulirati imunosne funkcije Treg** stanice (putem poticanja Toll-like receptora intestinalnih APCs).

- Povezanost između **crijevne disbioze i metaboličkih odstupanja** (osobito promjene nezas. MK i puteva metabolizma butanoata) doprinosi **neravnoteži Th17/Treg** putem **inaktivacije Treg st i pov izraženosti Th17-povezanih gena → korekcija Th17/Treg neravnoteže** moguć pristup KSU kroz modif crij. mikrobioma.

↑ povećana relativna zastuplj **oportunističkih** bakterija

↓ smanjena relativna zastuplj **beneficijalnih** bakterija



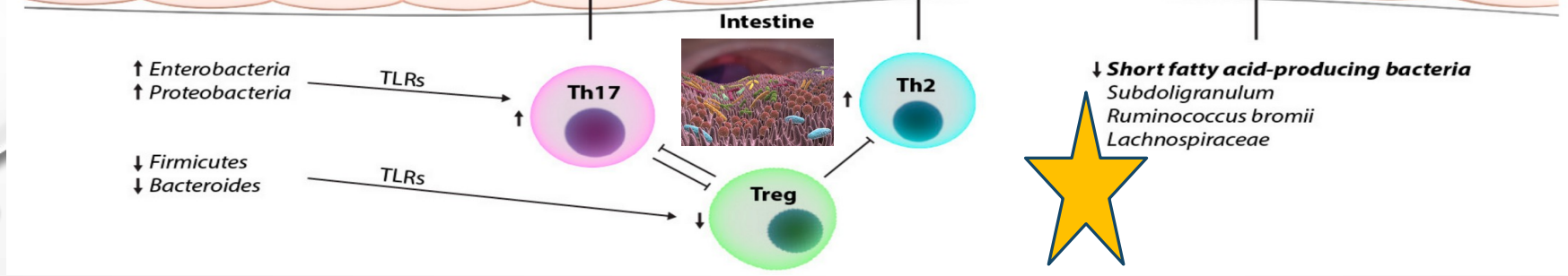


- (2.) Od **BENEFICIJALNIH/komenzalnih bakterija,**
  u ljudi >90% ***Firmicutes i Bacteroidetes***.

Firmicutes **- razgrađuju netopiva vlakna iz hrane,** oslobađaju hranjive tvari i pomažu rast drugih crijevnih bakterijskih vrsta **(u KU ↓)**

Bacteroides - doprinosi **regulaciji imunosnog sustava**, u interakciji je s drugim mikroorganizmima, pomažući raznolikosti intestinalne flore **(u KU ↓)**

- Lu: u KU pac., **manja** zastuplj **(↓)** ***Bacteroides*** sp., ***Faecalibacterium Prausnitzii***, *i* ***Prevotella Copri***, ***a*** **veća** zastup **(↑)** *Escherichia coli*.

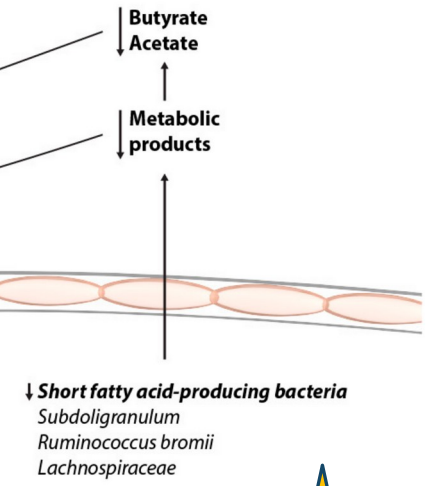


- U KU pac. značajno smanjene (3.) **BAKTERIJE KOJE STVARAJU KRATKOLANČ. MASNE KIS./klMK** (osnovna/core mikrobiota), uklj. ***Subdoligranulum*** (obligatni anaerob koji može stvarati butirat).

- **Stvaranje klMK ↑** poboljšava **funkciju Treg st. ↑ (Treg st suprimiraju** upalne T-lc odgovore, uključ Th2 i drugih subpop.) (↓)

- Liu i sur.:

  manja rel. zastup. bakterija iz *Ruminococceae* obitelji (uklj. *Butyricoccus* i *Faecalibacterium*) i veća relativna zastuplj subklasa *Enterobacteriaceae* obitelji → **oštećena Treg st funkcija** može **povećati broj Th2 st** (stvar IL-4)**, stvaranje IgE i mastocitnu aktivaciju/**Th2 citokini (IL-4, IL-5, i IL-13) potiču stvaranje IgE prema autoAg, što može aktiv. mastocite/bazofile.



Smanjenje bakterija koje stvaraju klMK

- **Smanjenje zastuplj (3.) <u>bakterija koje stvar klMK</u>** (***Subdoligranulum i Ruminococcus bromii***) može stimulirati **mastocitnu aktivaciju/degranulaciju**, vodeći ka KSU

- Kod KU, smanjena zastupljenost i ***Subdoligranulum*** i ***Ruminococcus bromii***

(remete diferencijaciju **Treg stanica** preko različitih puteva i smanjuju njihov broj/ošteć. funkcija).

- U pac. s KSU: smanjene **bakterija iz *Lachnonspiraceae*** obitelji (npr. *Anaerostipes*, *Blautia*, *Lachnospira)* → manje stvaraju (anti-upalnih) klMK (butirate i acetate) → → stanična neravnoteža (Treg/Th2) koja vodi jačim upalnim odgovorima.

→ u **respondera na AH** smanj. zastupljenost *Lachnospira* u usporedbi s neresponderima→ ***Lachnospira*** potencijalni **biomarker predviđanja učink. AH kod** KSU.

Beta raznolikost utvrdila značajno razlikovanje između CSU pac i Zdr.
U CSU grupi je bila znač smanjena alfa raznolikost prema *Evenness index*.
U CSU pac. uvrđeno je i signif smanjenje *Lachnospiraceae* obitelji putem *Linear discriminant analysis effect size (LEfSe)*

Life 2023, 13, 1280. https://doi.org/10.3390/life13061280 https://www.mdpi.com/journal/life

Article

Association of Gut *Lachnospiraceae* and Chronic Spontaneous Urticaria

Diana Ćesić [1,2,*], Liborija Lugović Mihić [2,3], Petar Ozretić [4], Ivana Lojkić [5], Marija Buljan [2,3], Mirna Šitum [2,3], Mario Zovak [2,6], Dinko Vidović [2,6], August Mijić [2,6], Nada Galić [2] and Arjana Tambić Andrašević [2,7]

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Abstract: (1) Background: Chronic spontaneous urticaria (CSU) has been linked to the dysbiosis of the gut microbiota. Furthermore, various studies have highlighted the anti-inflammatory properties of short-chain fatty acids (SCFAs), whose production is primarily regulated by the gut microbiota. However, only a few studies have investigated the role of major SCFA producers, such as *Lachnospiraceae*, in skin inflammatory diseases. (2) Goal: This study aimed to compare the abundance of *Lachnospiraceae* between CSU patients and healthy controls (HCs). (3) Material and methods: In this case–control study, 16S rRNA sequencing was performed to compare the composition of the gut microbiome between 22 CSU patients and 23 HCs. (4) Results: Beta-diversity revealed significant clustering ($p < 0.05$) between the CSU patients and HCs. Alpha diversity in the CSU group was significantly decreased according to the Evenness index ($p < 0.05$). The linear discriminant analysis effect size (LEfSe) identified the significant depletion of the *Lachnospiraceae* family in CSU patients. (5) Conclusion: Our study revealed the dysbiosis of the gut microbiota in CSU patients, including decreased levels of *Lachnospiraceae* members, responsible for SCFA production, suggesting that SCFAs may contribute to immune dysfunction in the pathogenesis of CSU. We speculate that the modulation of SCFAs could serve as a prospective additional option in CSU treatment.

Keywords: chronic spontaneous urticaria; gut microbiota; *Lachnospiraceae*; short-chain fatty acids

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Citation: Ćesić, D.; Lugović Mihić, L.; Ozretić, P.; Lojkić, I.; Buljan, M.; Šitum, M.; Zovak, M.; Vidović, D.; Mijić, A.; Galić, N.; et al. Association of Gut *Lachnospiraceae* and Chronic Spontaneous Urticaria. *Life* **2023**, *13*, 1280. https://doi.org/10.3390/life13061280

Academic Editor: Jacek C. Szepietowski

Received: 4 May 2023
Revised: 25 May 2023
Accepted: 26 May 2023
Published: 30 May 2023

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1. Introduction

Chronic spontaneous urticaria (CSU) is defined as the presence of urticaria, angioedema, or both, for a period of at least 6 weeks, without identifiable specific triggers [1]. It is characterized by daily or almost daily signs and symptoms or an intermittent course [1]. CSU affects about 1% of the general population and there has been a noticeable increase in the prevalence of this condition in recent years [2]. It is more frequently observed in young and middle-aged adults, affecting women two times more often than men [3]. However, children can be affected in the same proportion too [4]. The average duration of CSU is commonly around 5 years [5], although, in 10–25% of patients, it persists for more than 5 years [6]. The treatment of CSU is focused on "symptom control", targeting mast cell mediators and activators such as histamine and autoantibodies. Second-generation non-sedating H1 antihistamines are recommended as the initial treatment (up to four-fold dose),

U CSU pac je bila signif smanjena alfa raznolikost salivarne microbiote u usporedbi s Zdr, rezultirajući u promjeni sastava zajednice.
U pac s CSU znatno smanjeno bogatstvo vrsta/species (utvrđeno putem Shannon indeksa).

Life 2021, 11, 1329. https://doi.org/10.3390/life11121329 https://www.mdpi.com/journal/life

Article

Salivary Microbiota Is Significantly Less Diverse in Patients with Chronic Spontaneous Urticaria Compared to Healthy Controls: Preliminary Results

Diana Ćesić [1,2,*], Liborija Lugović-Mihić [1,2], Iva Ferček [3], Ana Gverić Grginić [4], Marko Jelić [5], Iva Bešlić [1,2] and Arjana Tambić Andrašević [2,5]

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Abstract: Background: Because of the important role in regulating the immune system, increasing evidence suggests a possible implication of gut microbiota in Chronic spontaneous urticaria (CSU). Although the oral cavity is the first site of contact between microbiota and the immune system, the association between salivary microbiota and CSU has not yet been reported. Objective: This case-control study aimed to compare differences in salivary microbiota between CSU patients and healthy controls (HC). Twenty-three participants—13 patients with CSU and 10 HC were enrolled; salivary microbiota was determined by molecular approach targeting 16S ribosomal RNA. Terminal restriction fragment length polymorphism (T-RFLP) analysis was performed. Results: Alpha diversity of salivary microbiota in CSU patients was significantly reduced compared to HC, resulting in alteration of the community composition. Species richness determined via the Shannon index was significantly reduced in the CSU group. Conclusion: Dysbiosis of salivary microbiota may contribute to a dysregulated immune system in the development of CSU. To our knowledge, this was the first study that reported an alteration in salivary microbiota composition in CSU patients.

Keywords: salivary microbiota; urticaria; chronic spontaneous urticaria; 16S rRNA gene; biodiversity; oral-gut axis; saliva

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Citation: Ćesić, D.; Lugović-Mihić, L.; Ferček, I.; Grginić, A.G.; Jelić, M.; Bešlić, I.; Tambić Andrašević, A. Salivary Microbiota Is Significantly Less Diverse in Patients with Chronic Spontaneous Urticaria Compared to Healthy Controls: Preliminary Results. *Life* **2021**, *11*, 1329. https://doi.org/10.3390/life11121329

Academic Editor: Annunziata Raimondo

Received: 2 November 2021
Accepted: 29 November 2021
Published: 1 December 2021

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1. Introduction

Chronic urticaria (CU) is defined as a continuous or intermittent occurrence of wheals, angioedema, or both for more than 6 weeks [1]. The prevalence of CU is increasing worldwide, with an overall point prevalence of 0.7%, ranging from 0.1% to 1.5% in adults [2,3]. Children population is affected in a similar proportion, with prevalence ranging from 0.1% to 3% [4]. Women are affected nearly twice as often as men, with the peak age between 20 and 40 years [5].

Based on the relevance of triggering factors, CU is classified into two categories–chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CInd) [1]. Approximately 80% of CU cases are CSU with no identified triggering stimuli or specific allergens [6]. Debilitating symptoms and often unsuccessful treatment affect patients' performance at work and school and significantly impair quality of life [2]. The course of the disease can be self-limiting, although, in 10–25% of patients, it lasts longer than 5 years [7].

↑ povećana relativna zastupljenost **oportunističkih** bakterija -*Entero, Proteo*

↓ smanjena relativna zastupljenost **beneficijalnih** bakterija - *Firm, Bact*

PROMIJENJEN SASTAV CRIJEVNOG MIKROBIOMA U PAC. S KSU

life

Review

Gut Microbiome Composition in Patients with Chronic Urticaria: A Review of Current Evidence and Data

Mirela Krišto [1], Liborija Lugović-Mihić [1,2,*], Melba Muñoz [3,4], Maja Rupnik [5,6], Aleksander Mahni
Petar Ozretić [7], Morana Jaganjac [8], Diana Ćesić [1] and Matea Kuna [1]

Table 1. A summary of the evidence on the association between gut microbiome composition and chronic urticaria.

Examinees	Methods	Key Results	CU Patients Versus Healthy Controls (HCs)		Limitations	References
			Increase	Decrease		
20 CU patients compared to 20 age- and sex-matched HCs	Bacterial genomic DNA extracted from stool samples and sequenced by PCR; bacterial amounts determined by qPCR.	The frequency and relative amounts of *A. muciniphila*, *C. leptum*, and *F. prausnitzii* were significantly higher in HCs than in those with CU.	Family *Enterobacteriaceae*	Species *Akkermansia muciniphila*, *Clostridium leptum*, *Faecalibacterium prausnitzii* ($p < 0.001$, $p < 0.01$, and $p < 0.05$)	Small number of examinees, more sophisticated analysing methods not included	[12] Nabizadeh et al., 2017.
20 CU patients compared to 20 age- and sex-matched HCs	Fecal samples analysed by PCR for frequency and bacterial load of Lactobacillus and Bifidobacterium genera.	The relative amounts of *Lactobacillus* and *Bifidobacterium* were significantly higher in fecal samples from HCs compared to CU patients.		Genus *Lactobacillus*, *Bifidobacterium* ($p = 0.038$ and 0.039)	Small number of examinees, more sophisticated analysing methods not included	[57] Rezazadeh et al. 2018.
10 CU patients compared to 10 HCs	Intestinal microbiome was analysed using 16S rRNA sequencing.	Significantly different microbial composition was observed between CU patients and HCs at the genus level.	Phylum *Proteobacteria*, *Actinobacteria* Order *Enterobacteriales*, *Lactobacillales*, *Pseudomonadales*; Genus *Veillonella*, *Sutterella*, *Streptococcus*, *Clostridium*, and *Escherichia*; Species *E.coli*	Phylum *Bacteroidetes* Genus *Faecalibacterium*, *Prevotella*, *Lachnobacterium*; Species *Faecalibacterium prausnitzii*, *Prevotella copri*, *Bacteroides fragilis*, *Bacteroides plebeius*	Very small number of examinees	[11] Lu et al., 2019.
100 CSU patients compared to 100 HCs	Fecal and blood samples were analysed using 16S rRNA gene sequencing and untargeted metabolomics, respectively.	The CSU group exhibited differences at the phyla and genera levels with decreased alpha diversity. The serum metabolome analysis revealed changes in unsaturated fatty acids and the butanoate metabolism pathway.	Family *Enterobacteriaceae*	Phylum *Firmicutes*; *Genus Bacteroides*, *Faecalibacterium*, *Bifidobacterium*, *Lactobacillus*, *Ruminococcaceae*	Small number of examinees	[13] Wang et al., 2020.

39 CSU patients compared to 40 HCs	Fecal samples were analysed using 16S rRNA gene sequencing and untargeted metabolomics.	A significant difference in beta diversity with no significant differences in alpha diversity between CSU patients and HCs ($p < 0.05$). Gut metabolomics showed decreased isobutyric acid in CSU patients.	Phylum *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria* Genus *Lactobacillus, Turicibacter, Lachnobacterium*	Genus *Phascolarctobacterium*	Single-center study, small number of examinees, confounding factors (age and diet) not taken into account	**[17]** Wang et al., 2021.
20 CSU patients compared to 20 age- and sex-matched HCs	Fecal microbial composition was analysed using 16S rRNA sequencing.	Beta diversity significantly differed between the two groups while alpha diversity did not.	Phylum *Firmicutes, Bacteroidetes, Proteobacteria* ($p = 0.03$), *Verrucomicrobia* Class *Bacilli* ($p = 0.04$) Order *Enterobacterales* ($p = 0.03$) Family *Enterobacteriaceae* ($p = 0.03$)	Genus *Megamonas, Megasphaera, Dialister* (all $p < 0.05$)	Small number of examinees	**[44]** Zhang et al., 2021.
↑ povećana relativna zastuplj **oportunističkih** bakterija- *Entero, Proteo* ↓ smanjena relativna zastuplj **beneficijalnih** bakterija- *Firm, Bact* 25 CSD patients compared to 25 age- and sex-matched HCs	Fecal samples were analysed by 16S rRNA sequencing, additionally verified by qPCR.	There were significant differences in both alpha and beta diversity in different indices with *Subdoligranulum* and *Ruminococcus bromii* (short chain fatty acid producing bacteria) as the gut microbiota biomarkers in CSD.	Phylum *Fusobacteria* Class *Gammaproteobacteria, Fusobacteria* *Order Enterobacteria, Fusobacteria* Family *Enterobacteriaceae, Fusobacteraceae, Peptostreptococcaceae, Streptococcaceae* Genus *Klebsiella*	Phylum *Firmicutes* Class *Clostridia, Alphaproteobacterial, Deltaproteobacteria* Order *Clostridiales, Rhodospirillales, Caulobacterales, Desulfovibrionales* Family *Ruminococceae, Rikenellaceae, Muribaculaceae, Christensenellaceae, Caulobacteraceae* *Genus/species Subdoligranulum, Ruminococcus bromii*	Small number of examinees	**[56]** Liu et al., 2021.
25 CSU patients with nsAH resistance, 19 CSU patients without nsAH resistance and 19 HCs	16S rRNA sequencing of the intestinal microbiome.	Much lower alpha diversity and evenness was observed in CSU patients with nsAH resistance than in those without ($p < 0.05$), who together with HCs showed almost no change in genera bacterium.	Genus *Prevotella, Megamonas, Escherichia, Succinivibrio, Klebsiella, Colidextribacter* (all $p < 0.05$) (in nsAH-resistant patients)	Genus *Blautia, Alistipes, Anaerostipes, Lachnospira* (all $p < 0.05$) (in nsAH-resistant patients)	Single-center study, small number of examinees, nsAHs other than levocetirizine not included	**[58]** Song et al., 2022.

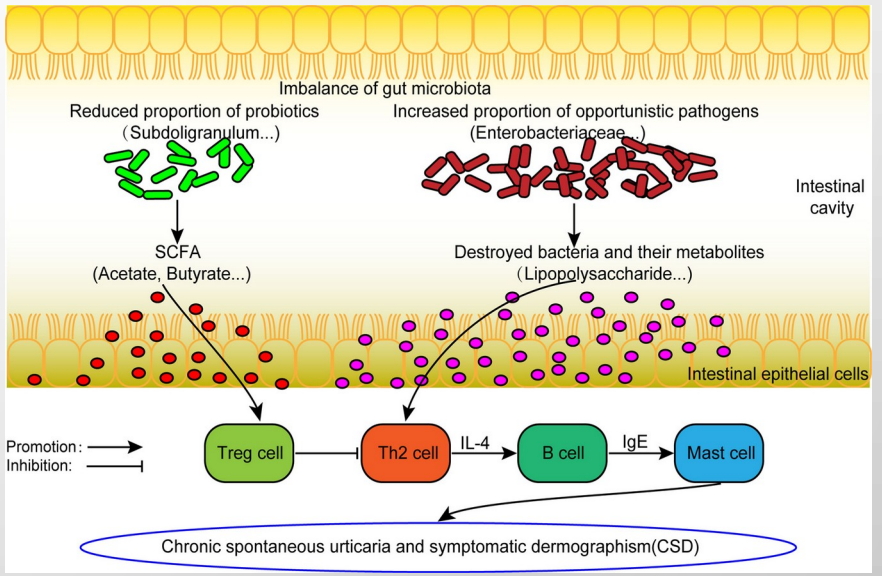
Terapijske implikacije

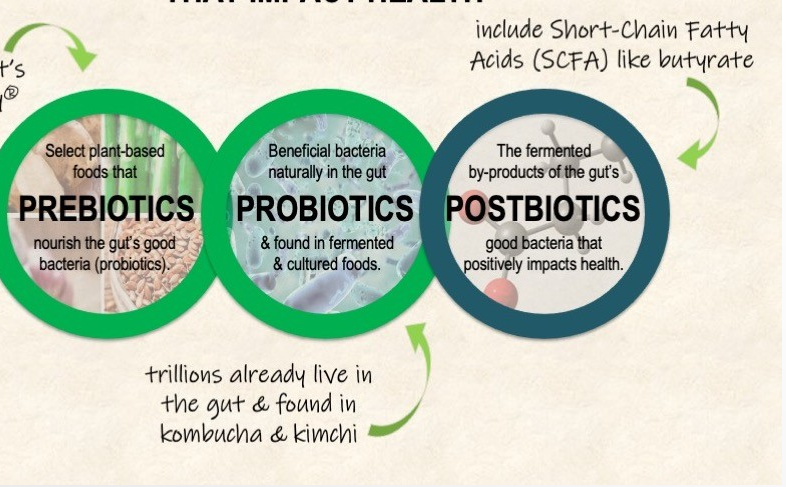
- Zbog česte neučinkovitosti AH u ovih pac., potrebna **učinkovitija terapijska opcija** (npr. dijetne strategije i suplementacija).

  - **Probiotici -** održivi mikroorganizmi s korisnim učincima (i sigurni kod odgov. primjene) koji moduliraju intest. mikrobiota i imunosni sustav, pa poboljš probavu i potencij. moduliraju IgE odgovor na alergene.

- Korist **regulacije mikrobiota (probioticima, prebioticima, i simbioticima)** u različitim medic. granama, uključ. dermatologiju.

  - Kod **promjene sastava mikrobioma** (npr. zbog modernog lifestyle-a), probiotska **suplementacija** može se suprotstaviti Th2 stan aktivnosti (**poticanjem stvaranja Th1 citokina** i smanjenjem **stvaranja IgE** npr. putem inhib IL-4 i IL-5).





- Dosad provedene **pojedine studije** o suplementaciji probioticima u pac. s KU (ugl na malom broju pac. s rKSU).

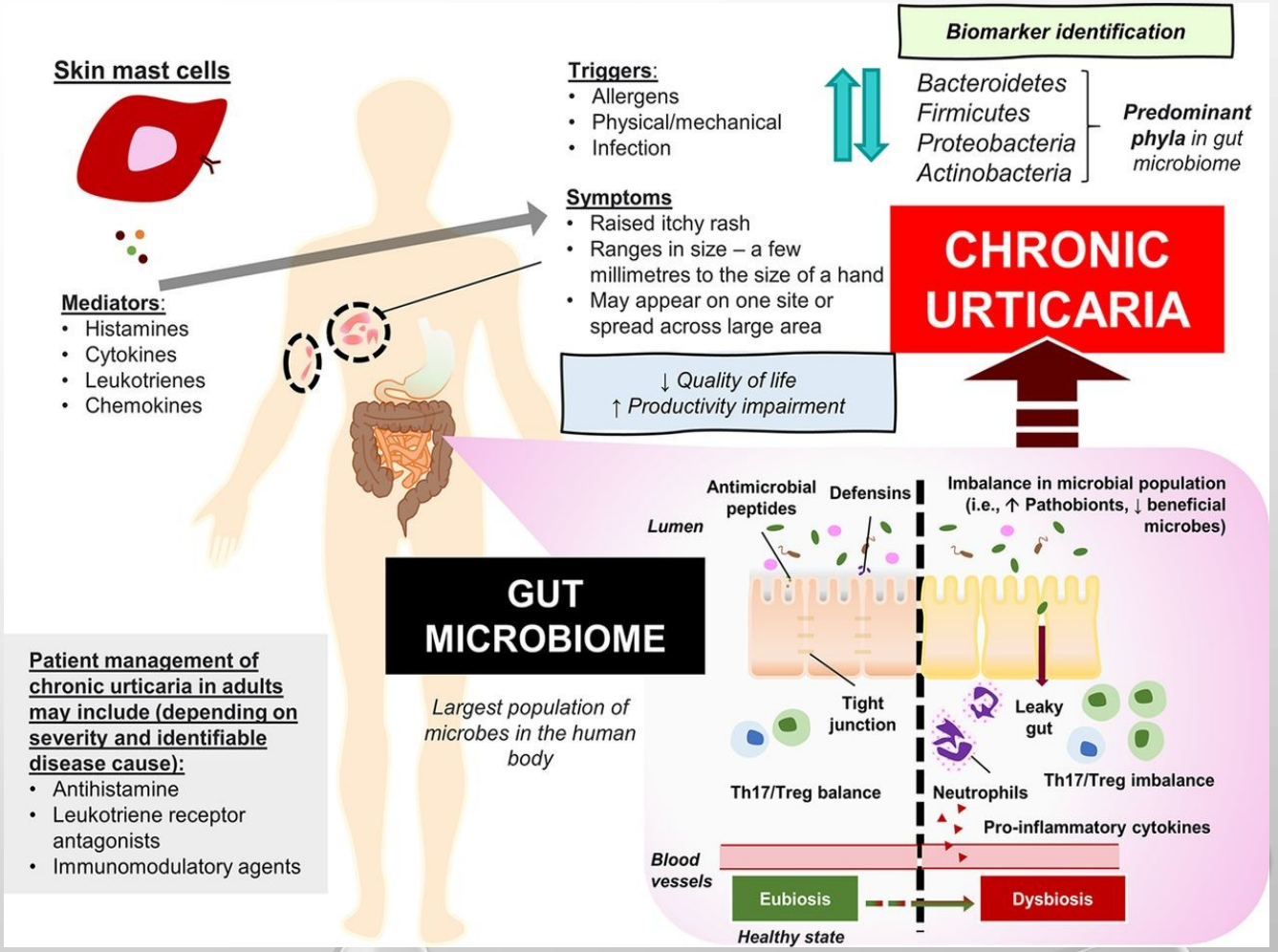
  - U studiji Nettis i sur., **kombinacija dva probiotika** (*Lactobacillus salivarius ls01 + Bifidobacterium breve br03)* davana pac. s KSU 8 tjedana (2xdnevno) → u dijela pac. smanjenje KSU simptoma → smanjenje oslobađ. pro-Th2 citokina (poboljšanje Th1/Th2 odnosa).

  - Neke ***Bifidobacterium* species** (probiotici) imaju korisne **anti-inflamatorne** učinke, poboljšavaju disbiozu i smanjuju upalni odgovor (npr. indukcijom Treg stanica i anti-upalnih medijatora).

- U pac. s KSU: **kombin. analiza** (crijevni mikrobiom + serum metabolom) i pokaz.metabolitičkih puteva **nezasićenih masnih kis** i **butanoata** s **crijevnim mikrobiomom** → uloga u patogenezi KSU.

- Metabolomika - perspektivno područje područje **proučav. malih molekula** (metabolita) koje čine individualni metabolom (metabolitske biokemijske funkcije su važne za međuodnos crijevni mikrobiom-domaćin).

- Crijevni mikrobiom modulira human fenotip – što objašnjava <58% varijacija individualnih plazmatskih metabolita.



Serumski metaboliti u bolesnika s kroničnom urtikarijom i atopijskim dermatitisom u odnosu na psihoneuroimunološke čimbenike u slini i serumu

MetaboloPsihoSalivaDerma

Financira Europska unija - NextGenerationEU

Trajanje: 48 mjeseci (10/2025 - 10/2029)

Interdisciplinarni translacijski projekt koji povezuje biokemijske, imunološke i psihičke parametre te uključuje salivarnu dijagnostiku u dermatovenerologiji.

O PROJEKTU

MetaboloPsihoSalivaDerma integrira biokemijske, imunološke i psihičke/psihološke parametre u cilju razumijevanja patofizioloških mehanizama bolesnika s kroničnom urtikarijom i atopijskim dermatitisom. Fokus je na upoznavanja obilježja serumskih metabolita (kao biokemijskih pokazatelja) u bolesnika s kroničnom urtikarijom i atopijskim dermatitisom i istraživanju psihoneuroimunoloških čimbenika kod tih bolesti te na neinvazivnoj salivarnoj dijagnostici, s ciljem razvoju kliničkih pristupa koja povezuju laboratorijsku analizu i kliničku praksu.

Projekt je, u konačnici, usmjeren na osmišljavanje razvoj personalizirane dijagnostike i terapije kroz integraciju različitih multidisciplinarnih čimbenika koji sudjeluju u razvoju kronične urtikarije i atopijskog dermatitisa.

ISTRAŽIVAČKI TIM

Voditeljica projekta: Liborija Lugović Mihić, KBCSM i sur. (dr. sc. Morana Jaganjac, Institut Ruđer Bošković (RBI), Laboratorij za oksidacijski stres na Institutu Ruđer Bošković (RBI) i drugi.)

ISTRAŽIVAČKE CJELINE (određivane kod kronične urtikarije, atopijskog dermatitisa i zdravih osoba)

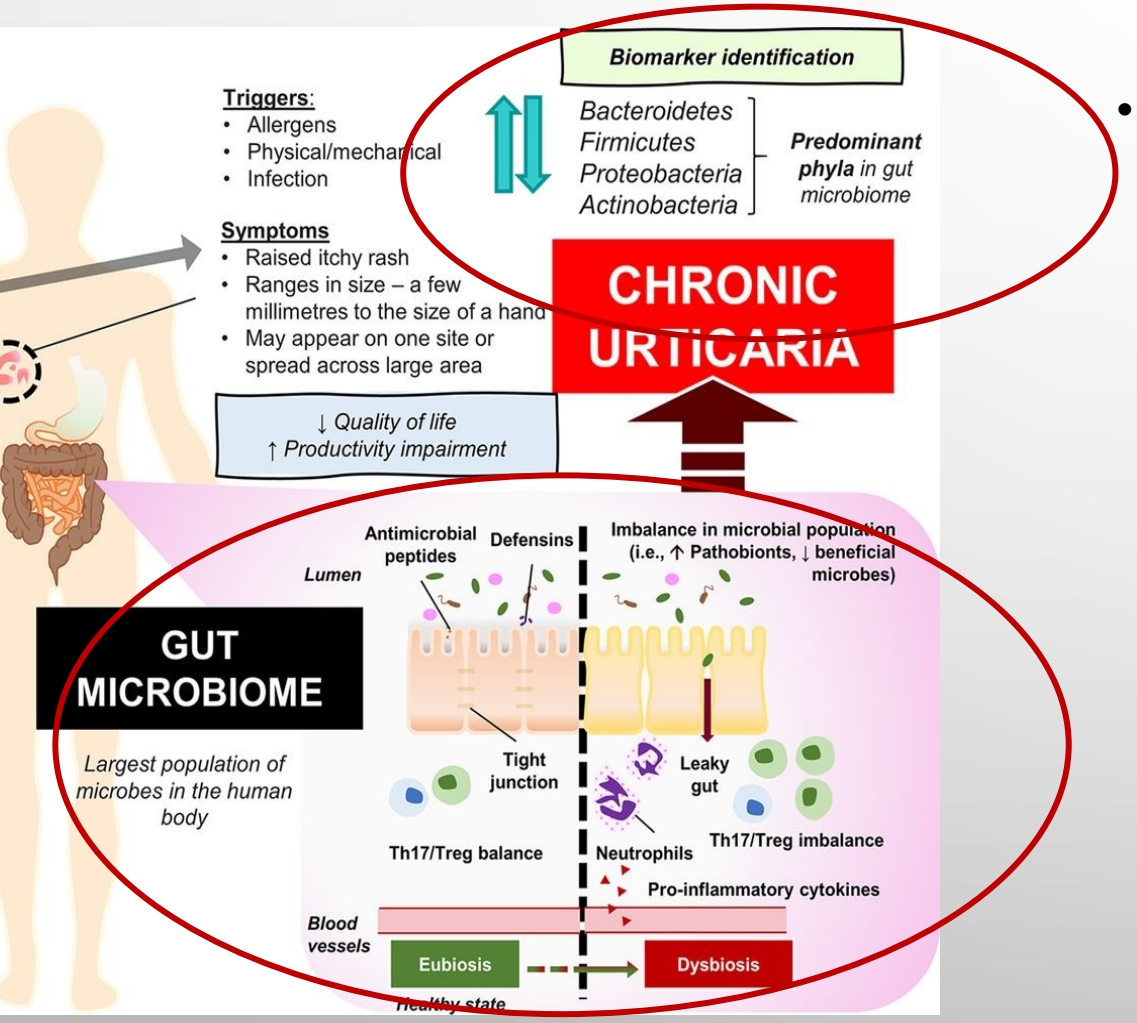
- METABOLOMSKA OBILJEŽJA (serumski metaboliti)
- IMUNOSNI ČIMBENICI (imunosne stanice, citokini, itd.)
- PSIHIČKA / PSIHOLOŠKA OBILJEŽJA (validirani psihološki upitnici, itd.)
- ENDOKRINI / HORMONSKI ČIMBENICI (razine hormona u slini i serumu, itd.)
- KLINIČKI ČIMBENICI KOD BOLESTI

Financira Europska unija
NextGenerationEU

REZULTATI I POKAZATELJI:

- uspostavu podataka koji mogu biti temelj za dijagnostičko-terapijsko planiranje kod navedenih bolesti, kao i personalizirani pristup liječenju
- razvoj digitalne baze podataka o ispitivanim čimbenicima
- kongresna priopćenja
- predavanja i edukativne aktivnosti

↑poveć. Raznol **opportunistic** bakterija ENTEROB, PROTEOB
↓smanj. Relativne **razn** of beneficial bakteria BACT, FIRMI



Perspektive…

- Nekoliko studija identificiralo sastav crijev mikrobioma pac. s KSU; uočena **metabolitska odstupanja** udružena s crijevnom disbiozom
- Wang: u pac. s KSU korelacija između crijevne mikrobiote i metabolita (pozitivna korelacija *Lachnobacterium* i α-mangostina), ↑ α-mangostin i glicirizinska kis. te ↓3-indol propionska kis., ksantin i isobutirična kis.
- (u KSU): promjene serum. metaboloma povezane s **crij. mikrobiomom+**pridružene promjene nezas. masnih kis. i puteva butanoatnog metabolizma → potencijalna **povezanost s upalom posred. neravnotežom Th1/Th2/Th17 citokina**, što doprinosi KSU patogenezi.

ZAKLJUČAK

- Prema većini studija, **pac. s KSU gube raznolikosti crijevnog mikrobioma,** udruženu s **narušenom regulacijom imunosnog sustava**.

- Prema spoznajama, crijevni **bakterijski produkti potiču** neravnotežu (pro/anti) imunosnih T-st subpopul, što usmjerava k upalnom **fenotipu**. Kod KSU, **proupalni odgovor** odgovoran za **mastocitnu aktivaciju** i teže manifestacije KSU.

- Analiza sastava mikrobioma pac. s KSU važna je za **otkrivanje potencijalnih biomarkera i terapijskih ciljeva za KSU**.

- **Dijetne intervencije i funkcionalna hrana** (npr. probiotici i prebiotici) mogu biti **korisne** za pac. s KSU te autoimunosnim/imunosnim bolestima. Potrebne su daljnje studije za potporu ovog zapažanja.



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Review

Gut Microbiome Composition in Patients with Chronic Urticaria: A Review of Current Evidence and Data

Mirela Krišto [1], Liborija Lugović-Mihić [1,2,*], Melba Muñoz [3,4], Maja Rupnik [5,6], Aleksander Mahnic [5], Petar Ozretić [7], Morana Jaganjac [8], Diana Ćesić [1] and Matea Kuna [1]

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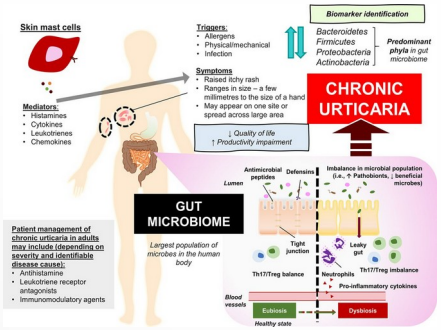
Abstract: Recent studies have linked gut microorganism composition and chronic urticaria (CU); however, the underlying mechanisms responsible for this connection are unknown. Since the human immune system is in homeostasis with microbiota, and the composition of the microbiome regulates the development and function of the immune system, it is likely that an alteration of microbiota components (a dysbiosis) could influence the course of chronic spontaneous urticaria (CSU), including disease severity, patient quality of life and treatment outcome. To date, several studies have identified changes in the gut microbiota composition of patients with CSU, though only a few have exhibited metabolic abnormalities associated with gut dysbiosis. The studies on CSU patients predominantly showed that the relative abundance of beneficial bacteria was decreased (*Firmicutes* and *Bacteroides*), while that of opportunistic bacteria was increased (*Enterobacteria* and *Proteobacteria*). In addition, serum metabolome analysis revealed that gut microbiota-associated alterations in unsaturated fatty acids and the butanoate metabolism pathway may play a role in CSU. These findings are potentially associated with inflammation mediated by the imbalance of Th1/Th2/Th17 cytokines, which might contribute to CSU pathogenesis. Further research in this field could improve clinical, diagnostic, and therapeutic approaches to patients with CSU. By applying new knowledge on gut microbial communities and metabolomics, future CSU therapies could modify the microbiota composition using agents such as probiotics or other similar agents, which, in combination with current standard therapies, could hopefully lead to a reduction in symptoms and an improved quality of life for CSU patients.

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Citation: Krišto, M.; Lugović-Mihić, L.; Muñoz, M.; Rupnik, M.; Mahnic, A.; Ozretić, P.; Jaganjac, M.; Ćesić, D.; Kuna, M. Gut Microbiome Composition in Patients with Chronic Urticaria: A Review of Current Evidence and Data. *Life* **2023**, *13*, 152. https://doi.org/10.3390/life13010152

Academic Editor: Ron Kohen

Received: 10 November 2022


Skin mast cells
Mediators:
• Histamines
• Cytokines
• Leukotrienes
• Chemokines
Triggers:
• Allergens
• Physical/mechanical
• Infection
Symptoms
• Raised itchy rash
• Ranges in size – a few millimetres to the size of a hand
• May appear on one site or spread across large area
↓ Quality of life
↑ Productivity impairment
Biomarker identification
Bacteroidetes
Firmicutes
Proteobacteria
Actinobacteria
Predominant phyla in gut microbiome
CHRONIC URTICARIA
GUT MICROBIOME
Largest population of microbes in the human body
Patient management of chronic urticaria in adults may include (depending on severity and identifiable disease cause):
• Antihistamine
• Leukotriene receptor antagonists
• Immunomodulatory agents
Lumen
Antimicrobial peptides
Defensins
Imbalance in microbial population (i.e., ↑ Pathobionts, ↓ beneficial microbes)
Tight junction
Leaky gut
Th17/Treg balance
Neutrophils
Th17/Treg imbalance
Pro-inflammatory cytokines
Blood vessels
Eubiosis
Dysbiosis
Healthy state


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