INFEKCIJE PROBAVNOG SUSTAVA: NOVOSTI U EPIDEMIOLOGIJI, KLINIČKOJ SLICI, DIJAGNOSTICI, TERAPIJI I PREVENCIJI

Voditelji:

Voditelji:
Dragan Soldo, dr. med.
Prof. dr. sc. Goran Tešović, dr. med.
Prof. dr. sc. prim. Jasmina Vraneš, dr. med.
Izv. prof. dr. sc. prim. Mario Sviben, dr. med.
Izv. prof. dr. sc. Mirjana Balen Topić, dr. med.
Prof. dr. sc. prim. Sunčanica Ljubin Sternak, dr. med.
Izv. prof. dr. sc. Tajana Filipec Kanižaj, dr. med.
Prim. Tatjana Nemeth Blažić, dr. med.

Zagreb, 17. svibanj 2024.

KNJIGA SAŽETAKA

Poštovane kolegice, poštovane kolege

infekcije probavnog sustava jedan su od vodećih uzroka morbiditeta i mortaliteta u cijelome svijetu.
Zbog uglavnom kratke inkubacije, velikog broja uzročnika i načina prijenosa ove bolesti imaju i veliki društveno-gospodarski značaj.
Kao uzročnici ovih infekcija značajne su mnogobrojne bakterije, virusi, ali i paraziti i gljive.
Ovim multidisciplinarnim simpozijem u organizaciji najrelevantnijih stručnih društava i zdravstvenih ustanova iz područja probavnih infekcija želimo Vam prikazati novosti u epidemiologiji kao i praćenju najznačajnijih infekcija probavnog sustava; „nove“, emergentne probavne infekcije; značaj zdravog i raznolikog crijevnog mikrobioma u zdravlju probavnog sustava; osobitosti kliničkih slika pojedinih infekcija; novosti u dijagnostici te mogućnosti liječenja i prevencije s osobitim osvrtom na antimikrobnu otpornost i nova cjepiva.

Voditelji

7.00-7.45	Registracija polaznika
7.45-8.00	Otvaranje Simpozija
8.00-8.15	Prim. Tatjana Nemeth Blažić, dr.med; Iva Pem Novosel, dr.med. Epidemiologija infekcija probavnog sustava u zemlji i svijetu
8.15-8.30	Dragan Soldo, dr.med. Probavne infekcije u ordinaciji liječnika obiteljske medicine
8.30-8.45	Prof.dr.sc. prim. Sunčanica Ljubin Sternak ,dr.med. Uloga mikrobiote/mikrobioma probavnog sustava u zdravlju i bolesti
8.45-9.00	Prof.dr.sc. Goran Tešović , dr.med; Maja Vrdoljak Pažur, dr.med. Klinički aspekti i liječenje probavnih infekcija u djece
9.00-9.15	Izv.prof.dr.sc. Mirjana Balen Topić , dr.med. Antibiotici tijekom akutne crijevne infekcije-da ili ne?
9.15-9.30	Mini simpozij Abela Pharm Sanja Zember, dr.med. Prati li svaki antibiotik uspješan probiotik? Novosti u liječenju postantmikrobne dijareje
9.30-9.45 Pauza	Ivana Šimić, dipl. ing. preh. teh. - nutricionist Pravilna prehrana tijekom probavnih infekcija
10.15-10.30	Izv.prof.dr.sc. Tomislav Meštrović , dr.med. Uzimanje uzoraka, obrada i mikrobiološka dijagnostika probavnih infekcija-od smjernica do kliničke prakse
10.30-10.45	Prof.dr.sc. prim. Jasmina Vraneš, dr.med. Kada upotrijebiti i kako interpretirati rezultate molekularnog panela u dijagnostici gastroenteritisa
10.45-11.00	Doc.dr.sc. Irena Tabain, dr.med. Virusne infekcije probavnog sustava-pregled najčešćih uzročnika
11.00-11.15	Mini simpozij A&B Prof.dr.sc. prim. Jasmina Vraneš, dr.med. Usporedba konvencionalnih dijagnostičkih metoda i BioFire FilmArray gastrointestinalnog panela
11.15-11.30	Mini simpozij Kormedix Caden Hu, Master of Science in Microbiology Fudan University, Shanghai, China Application of MALDI-TOF MS in Rapid Diagnosis of Gastrointestinal Infections—Exploring the Role of MALDI-TOF MS Technology in Diagnosing Gastrointestinal Infections, Including Rapid Identification of Bacteria, Fungi, etc.
11.30-11.45	Doc.dr.sc. Miloš Lalovac, dr.med; Maja Mijić, dr.med. Klinički aspekti i novosti u liječenju virusnih hepatitisa
11.45-12.00	Dr.sc. Maja Bogdanić, dr.med; Izv.prof.dr.sc. prim. Tatjana Vilibić Čavlek,dr.med.-Trendovi seroprevalencije i molekularna epidemiologija hepatitisa E u Hrvatskoj

12.00-12.15	Mini simpozij Kemolab Prof.dr.sc. Anna Mrzljak, dr.med. Hepatitis E infekcija u imunokompromitiranih u Hrvatskoj
12.15-13.15 Pauza	
13.15-13.30	Izv.prof.dr.sc. Marija Santini , dr.med. Infekcije probavnog sustava kod bolesnika s HIV infekcijom
13.30-13.45	Vanja Romih Pintar, dr.med. Infekcije probavnog sustava u MSM populaciji
13.45-14.15	Mini simpozij GSK/ViiV Izv.prof.dr.sc. Marija Santini, dr.med. Živjeti zdravo s HIV infekcijom
14.15-14.30	Izv.prof.dr.sc.Tajana Filipec Kanižaj , dr.med. Klinički aspekti i liječenje *Helicobacter pylori* infekcije
14.30-14.45	Doc.dr.sc. Vladimir Krajinović, dr.med. *Clostridioides difficile*-klinički aspekti i novosti u liječenju
14.45-15.00	Mini simpozij Oktal pharma Izv.prof.dr.sc.Tajana Filipec Kanižaj, dr.med. Probiotici u smjernicama eradikacijske terapije bakterije *Helicobacter pylori*
15.00-15.15	Prim. Ana Gverić Grginić, dr.med. Trbušni tifus: etiopatogeneza, dijagnostika, terapija i prevencija
15.15-15.30	Mini simpozij Labomar Dr.Adem Nasraddin Innovative solutions for infection identification and management
15.30-15.45 Pauza	
15.45-16.00	Doc.dr.sc. Ljiljana Žmak, dr.med. Klinički aspekti i dijagnostika tuberkuloze probavnog sustava
16.00-16.15	Mini simpozij Biospectra Dr.Adem Nasraddin Advancing gastrointestinal health R-biopharm
16.15-16.30	Izv.prof. dr.sc. prim. Mario Sviben, dr.med. Helminti kao uzročnici probavnih infekcija
16.30-16.45	Izv.prof.dr.sc. Mirjana Balen Topić, dr.med. Pojava „lisičje trakavice“ – *Echinococcus multilocularis* infekcije u pacijenata u Hrvatskoj
16.45-17.00	Dr. sc. Ivančica Kovaček, dr.med. prof.v.s. Mikrobiološki nadzor hrane i alimentarne toksikoinfekcije
17.00-17.15	Prim. Silvija Šoprek Strugar, dr.med. Antimikrobna rezistencija crijevnih patogena
17.15-17.30	Vesna Višekruna Vučina, dr.med; Ivan Mlinarić, dr.med. Prevencija probavnih infekcija cijepljenjem
17.30-18.00	Diskusija. Zatvaranje Simpozija

Epidemiologija infekcija probavnog sustava u zemlji i svijetu

Prim. Iva Pem Novosel, dr. med.

Prim. Tatjana Nemeth, dr. med.

Simpozij Infekcije probavnog sustava: novosti u epidemiologiji, kliničkoj slici, dijagnostici, terapiji i prevenciji

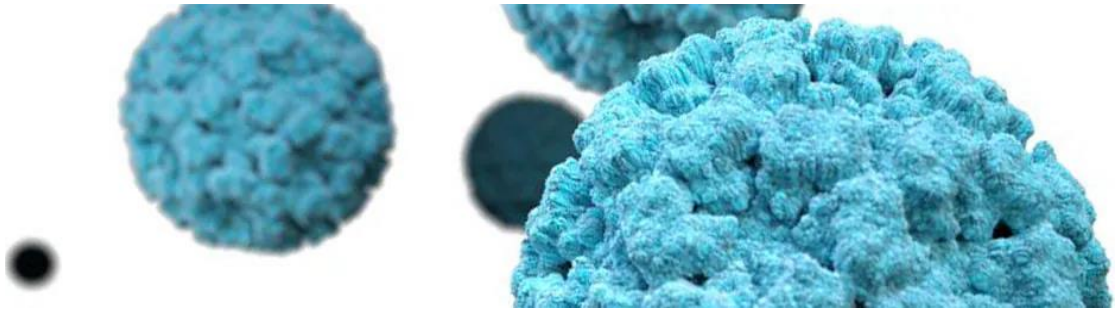
Zagreb, 17. svibnja 2024.

Trovanje hranom *ili alimentarna toksoinfekcija*

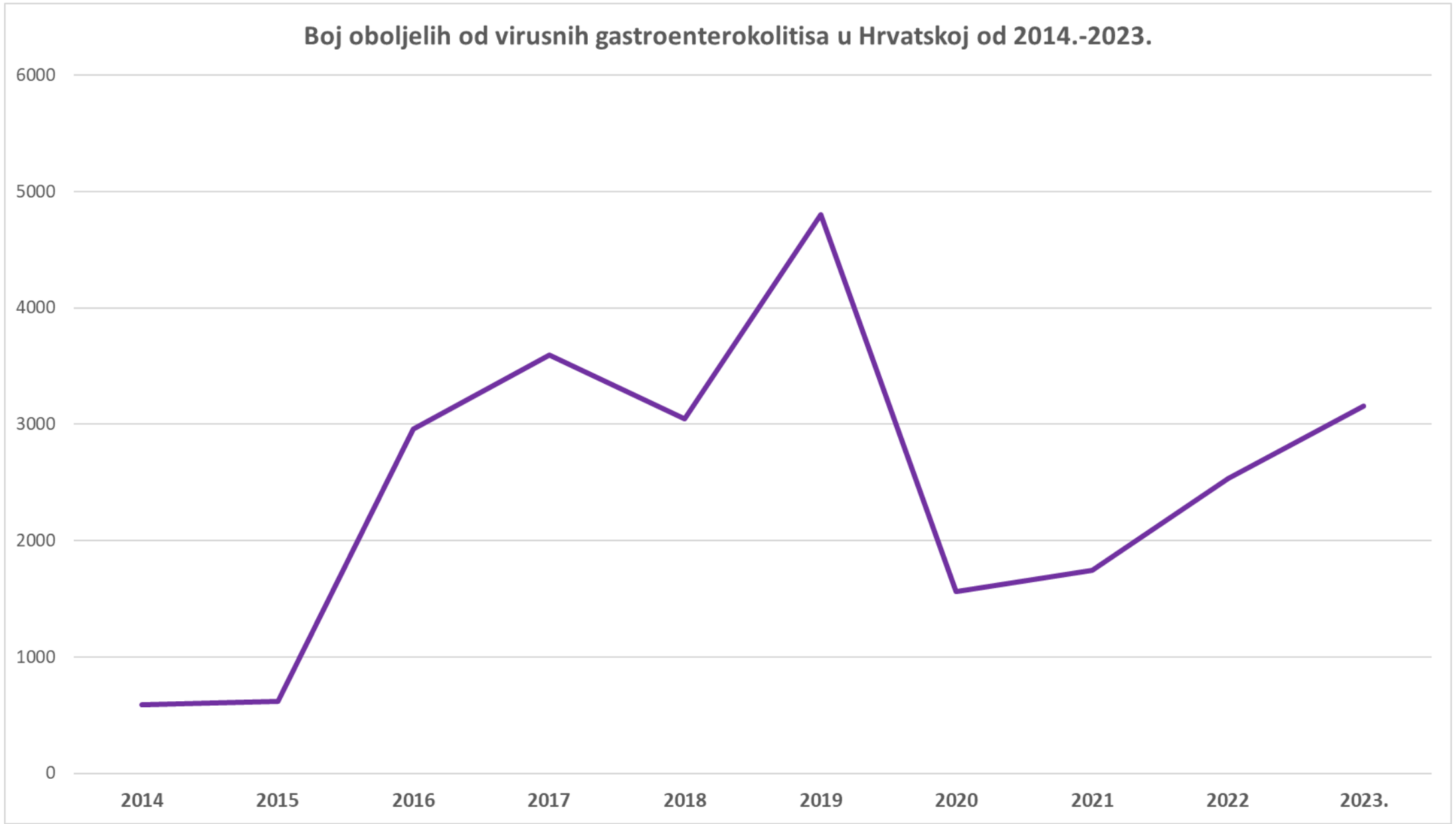
- **bakterije ili njihovi toksini** najčešća trovanja hranom ako se uslijed neprimjerene pripreme i pohrane namirnica nađu u hrani,
- **Salmonele** (*Salmonella enteritidis*),

- a česti su ***Staphylococcus aureus*** (na otvorenim ranicama kože ili u sluznici nosa ljudi koji pripremaju hranu. U hrani stvara toksin otporan na temperaturu, koji se kasnijom termičkom obradom ne može uništiti te unatoč kuhanju dovodi do obolijevanja (često pri konzumiranju sladoleda ili ohlađenog mesa odojka).
- ***Campylobacter, Clostridium perfringens***, ***Echerichia coli***, ***Clostridium botulinum***.
- **virusi** (norovirusi, enterovirusi, hepatitis A i dr.) - **kemikalije** (poput insekticida i herbicida)
- **metali (**kao što su olovo, živa i kadmij)
- **otrovne biljke (**kao što su velebilje i nejestive gljive), mikotoksini, ostaci veterinarskih lijekova itd.

Norovirusi



- Norovirus je vodeći uzrok povraćanja i proljeva te bolesti koje se prenose hranom u SAD.
- Vrlo lako i brzo širi, mogu se zaraziti i oboljeti ljudi svih životnih dobi.
- Norovirusnu bolest može se dobiti mnogo puta u životu jer postoji mnogo različitih vrsta norovirusa. Infekcija jednim tipom virusa možda neće zaštititi od drugih tipova.
- Moguće je razviti zaštitu protiv određenih vrsta. No, ne zna se koliko točno zaštita traje.
- Obično se razviju simptomi 12 do 48 sati nakon izlaganju norovirusu.
- Većina ljudi s norovirusnom bolešću ozdravi u roku od 1 do 3 dana, ali još uvijek mogu širiti virus nekoliko dana nakon toga.

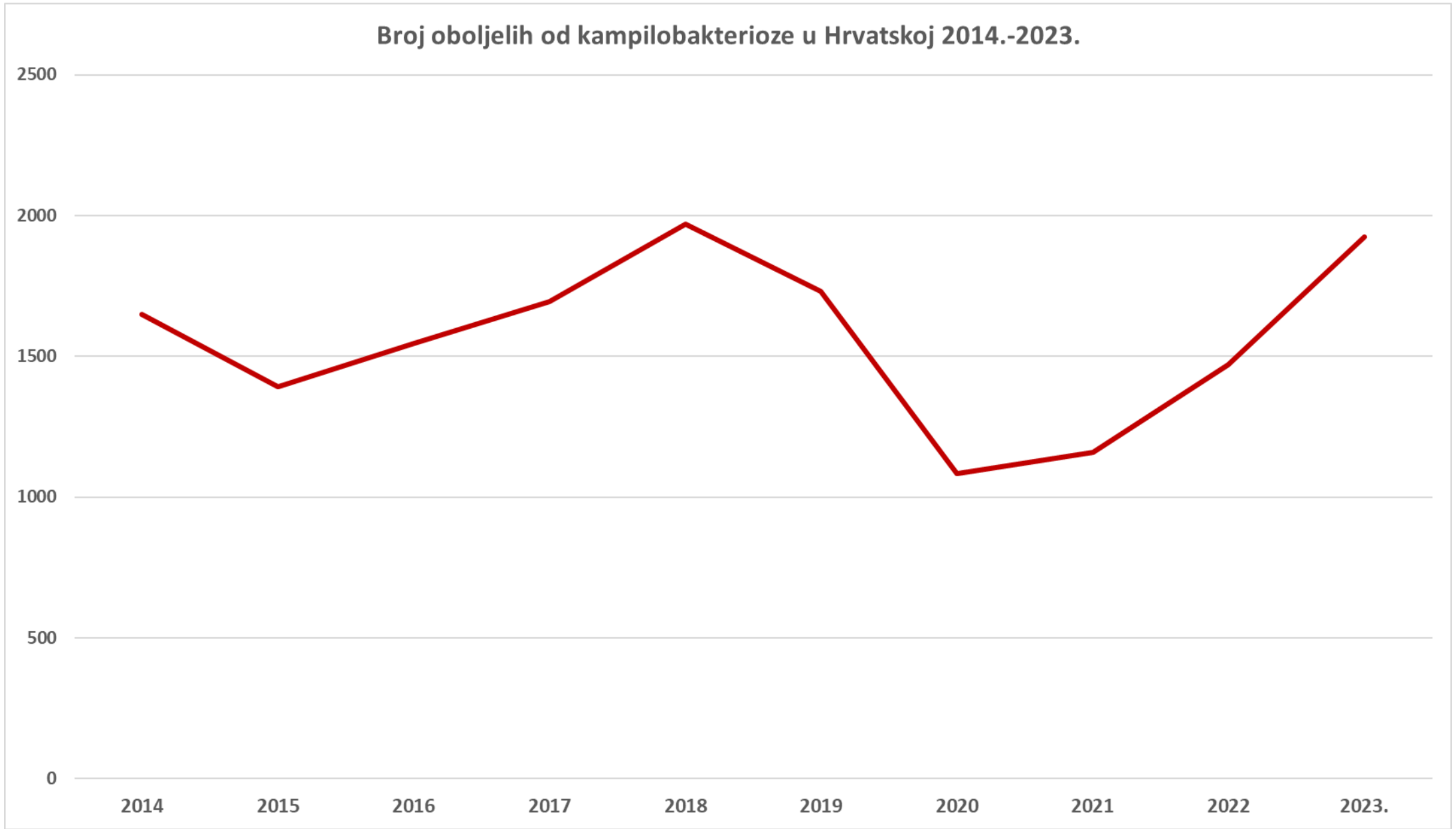

Boj oboljelih od virusnih gastroenterokolitisa u Hrvatskoj od 2014.-2023.
6000
5000
4000
3000
2000
1000
0
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023.

Kampilobakterioza

- Kampilobakteri su u obliku spirale, zakrivljene poput slova S.
- Najčešći uzročnici ove bolesti su *C. jejuni* i *C. coli*.
- Lako se uništava visokom temperaturom, a budući je hrana glavni put prijenosa, to znači da će dobra termička obrada hrane uništiti bakteriju.
- *Campylobacter* normalno naseljava probavni sustav većine toplokrvnih životinja kao što su divlje ptice, perad, svinje, goveda, ovce, psi i mačke, nalazi se i u školjkama, u kamenicama i dr.

Klinička slika:

- Vrijeme inkubacije: 2-5 dana nakon infekcije bakterijom, može varirati od 1 do 10 dana.
- Uobičajeni klinički simptomi ove bolesti su: proljev (često krvavi), bol u trbuhu, vrućica, glavobolja, mučnina i/ili povraćanje. Simptomi obično traju 3-6 dana.
- Postinfekcijske komplikacije mogu uključivati reaktivni artritis, sindrom iritabilnog crijeva i neurološke poremećaje kao Guillain-Barré sindrom (paralize mišića).


Broj oboljelih od kampilobakterioze u Hrvatskoj 2014.-2023.
2500
2000
1500
1000
500
0
2014
2015
2016
2017
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2019
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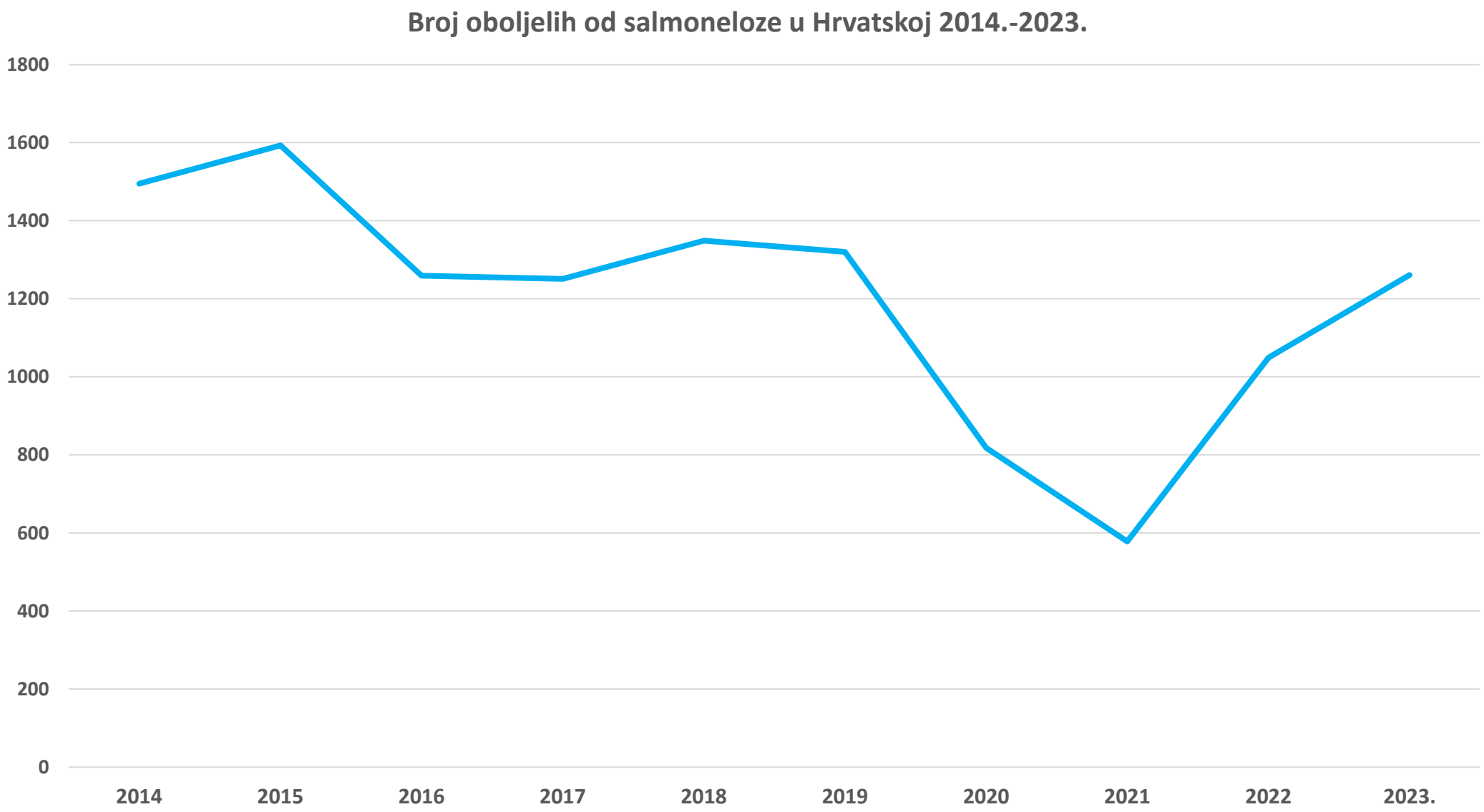
2021
2022
2023.

Salmoneloze

- Kad danas govorimo o salmonelozama, uglavnom mislimo na tzv. **netifusne salmoneloze** (koje nisu uzrokovane serotipom *Salmonella* Typhi koji dovodi do razvoja trbušnog tifusa)
- **Najčešći put prijenosa zaraze je konzumacija zaražene (tj. zagađene ili kontaminirane) hrane, koja uglavnom nema neuobičajen izgled ili miris.**
- Namirnice s najvišim rizikom za razvoj salmoneloze su sirovo meso (perad), jaja i mliječni proizvodi (kolači koji se prave od tih namirnica), no zabilježene su i epidemije salmoneloza podrijetlom iz povrća i voća.
- Salmoneloza, prvenstveno rezultira blagom do teškom bolešću proljeva, poznatom kao akutni gastroenteritis.

Klinička slika:

- iznenadna pojava proljeva (koji može biti krvav), grčevi u trbuhu, groznica (gotovo uvijek prisutna),
- mogu se javiti mučnina, povraćanje i glavobolja, ali rjeđe.


Broj oboljelih od salmoneloze u Hrvatskoj 2014.-2023.
1800
1600
1400
1200
1000
800
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200
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2016
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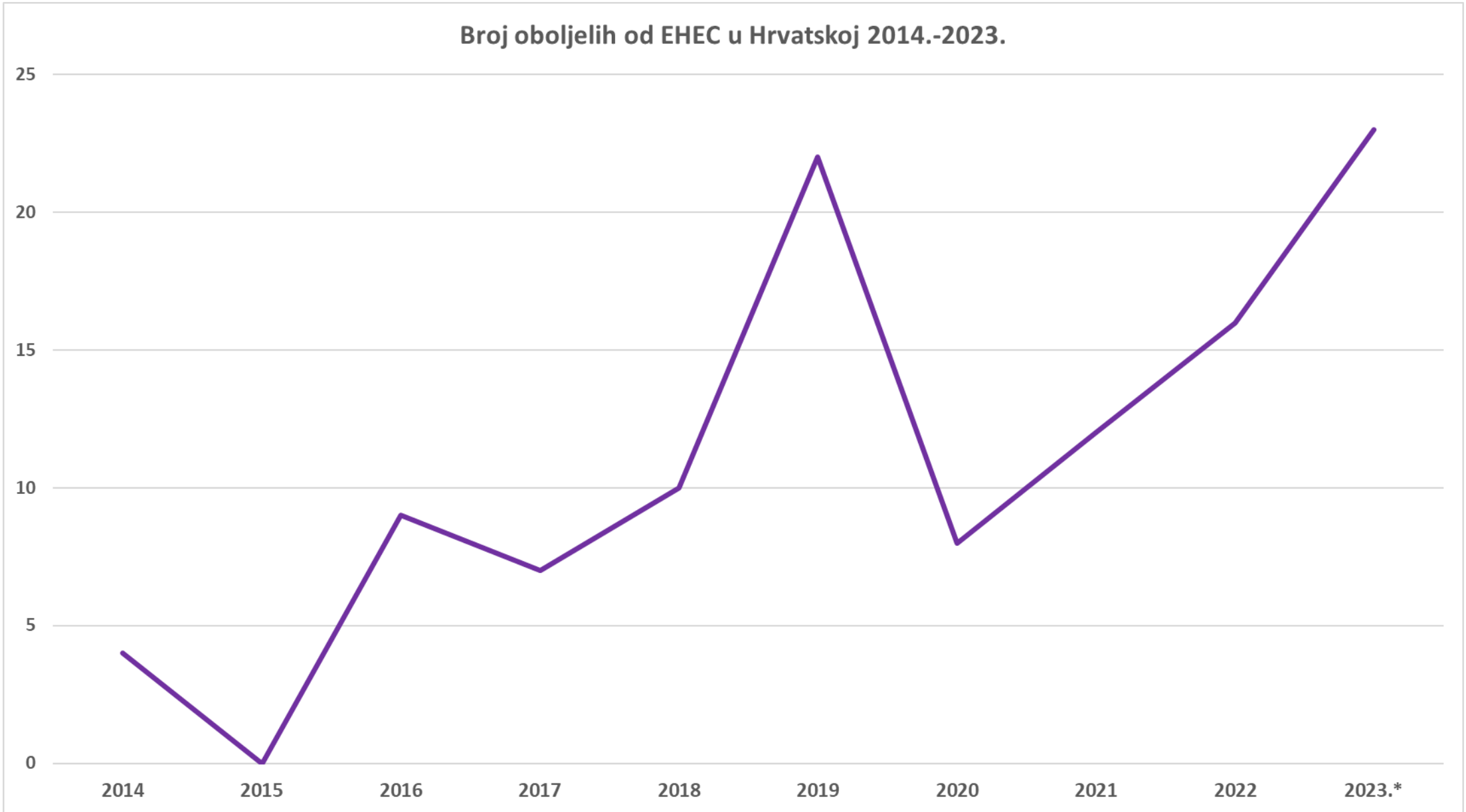
2021
2022
2023.

Salmoneloze

- Proljev može trajati nekoliko dana i dovesti do potencijalno teške dehidracije, osobito u dojenčadi i djece mlađe od 2 godine te u odraslih starijih od 65 godina.
- Većina ljudi se potpuno se oporavi, iako može proći nekoliko mjeseci prije nego što njihova stolica postane sasvim normalna. Salmonella se može se naći u stolici nekoliko tjedana (kliconoštvo), pa i do godine dana.
- Ponekad se infekcija može proširiti na urin, krv, kosti, zglobove, mozak ili živčani sustav, uzrokujući simptome povezane s tim sustavom. Neke od ovih izvancrijevnih infekcija mogu imati dugoročne posljedice, ovisno o tome koji je dio tijela zaražen.

Rizični čimbenici

- Infekcija salmonelom češća je u ljetnim mjesecima (lipanj, srpanj i kolovoz) nego zimi.
- Djeca mlađa od 5 godina najvjerojatnije će dobiti infekciju.
- Dojenčad koja nisu dojena imaju veću vjerojatnost za infekciju.
- Djeca od 5 godina i mlađa, odrasli stariji od 65 godina i osobe s oslabljenim imunološkim sustavom imaju najveću vjerojatnost za teške infekcije.
- Određeni lijekovi (na primjer, lijekovi za smanjenje želučane kiseline) mogu povećati rizik od infekcije.


Broj oboljelih od EHEC u Hrvatskoj 2014.-2023.
25
20
15
10
5
0
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023.*

Pridržavanje osnovih mjera za sprečavanje crijevnih infekcija:

- **redovito i temeljito pranje ruku toplom vodom i tekućim sapunom**
- **termička obrada hrane**
- **temeljito pranje voća i povrća**
- **izbjegavanje držanja hrane na sobnoj temperaturi i prigrijavanje hrane**
- **izbjegavanje konzumiranja nepasteriziranog mlijeka i higijenski sumnjive površinske vode.**
- Svaki slučaj infekcije salmonelom je obavezno prijaviti nadležnoj epidemiološkoj službi i pratiti kliconoše.

Prevencija crijevnih infekcija

Pridržavanje osnovih mjera za sprečavanje crijevnih infekcija:

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- Svaki slučaj infekcije salmonelom je obavezno prijaviti nadležnoj epidemiološkoj službi i pratiti kliconoše.

Pohranjivanje namirnica

- **Lako kvarljive namirnice pohraniti u hladnjak**.
- **Paziti na raspored namirnica u hladnjaku**.
- **Paziti na temperaturu čuvanja hrane**. Provjerite radi li hladnjak na optimalnoj temperaturi (ne smije biti viša od 4-5°C). Ne stavljati vruću hranu u hladnjak.
- **Paziti na prosječno vrijeme za pravilno uskladištenje namirnica u hladnjaku** *S mesom poseban oprez!* U normalnim uvjetima, svježa svinjetina, govedina, janjetina i teletina može se u hladnjaku čuvati max. do 4 dana, a mljeveno meso, perad i riba jedan do dva dana.
- **Namirnice koje se ne pohranjuju u hladnjak zaštititi od insekata i drugih životinja**. Držati ih na suhom u dobro zatvorenim posudama. Sadržaj otvorenih konzervi najbolje je odmah iskoristiti ili ga premjestiti u staklenku i spremiti u hladnjak.
- **Odvojiti hranu od sredstva za čišćenje i ostalih kemikalija**. Ne koristite ambalažu od hrane i pića za držanje kućnih kemijskih sredstava ili već korištene posude u druge svrhe!!!
- **Ne držite hranu na podu, jer to privlači štetočine** (miševe, mrave, žohare…) u smočnicu.
- **Održavati smočnicu suhom i ne pretoplom** (do 25 °C).

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

NASTAVNI ZAVOD ZA
JAVNO ZDRAVSTVO
DR. ANDRIJA ŠTAMPAR

Stvaramo zdraviju budućnost

Uloga mikrobiote/mikrobioma probavnog sustava u zdravlju i bolesti

Prof.dr.sc. Sunčanica Ljubin Sternak,
prim.dr.med.

Mikrobiota, eubioza i disbioza

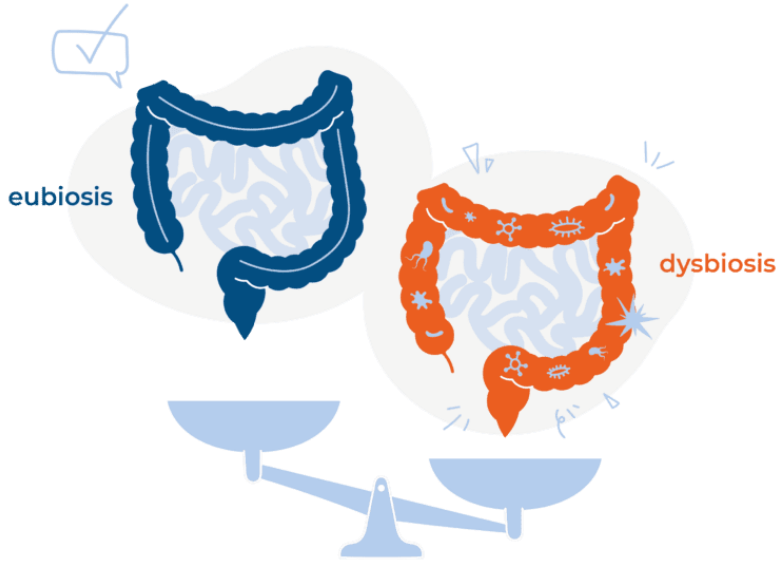
Ljudsko tijelo je nastanjeno ogromnim brojem mikroorganizama: bakterijama, arhejama, virusima i gljivama koje žive na površini tijela i u šupljinama koje komuniciraju sa okolinom - zbirka anatomskih niša s jedinstvenim mikrobiološkim potpisom

Populacije različitih mikroorganizama čine rezidentnu floru ili MIKROBIOTU-zbroj svih genoma mikrobiote predstavlja MIKROBIOM

Mikroorganizami koji nastanjuju probavni sustav su funkcionalni dio ljudskog organizma sudjelujući u brojnim fiziološkim procesima (rast i razvoj, imunitet, metabolički procesi i dr.) te su stoga jedan od važnih čimbenika u održavanju homestaze odnosno razvoju bolesti

EUBIOZA je stanje karakterizirano stabilnom mikrobnom zajednicom u stanju ravnoteže i obično se sastoji od mnoštva vrsta koje imaju komenzalan i mutualistički odnos s domaćinom

Poremećaj homeostaze mikrobiote (poremećaj u sastavu - smanjenje komenzala i povećanje oportunističkih mikroorganizama i funkciji mikrobiote) naziva se DISBIOZA



https://www.ab-biotics.com/dysbiosis-world-microbiome-day/

Normalna mikrobiota crijeva

Nema zlatnog standarda

Glavna karakteristika zdrave mikrobiote je raznolikost i elastičnost (sposobnost povratka u početno stanje nakon poremećaja)

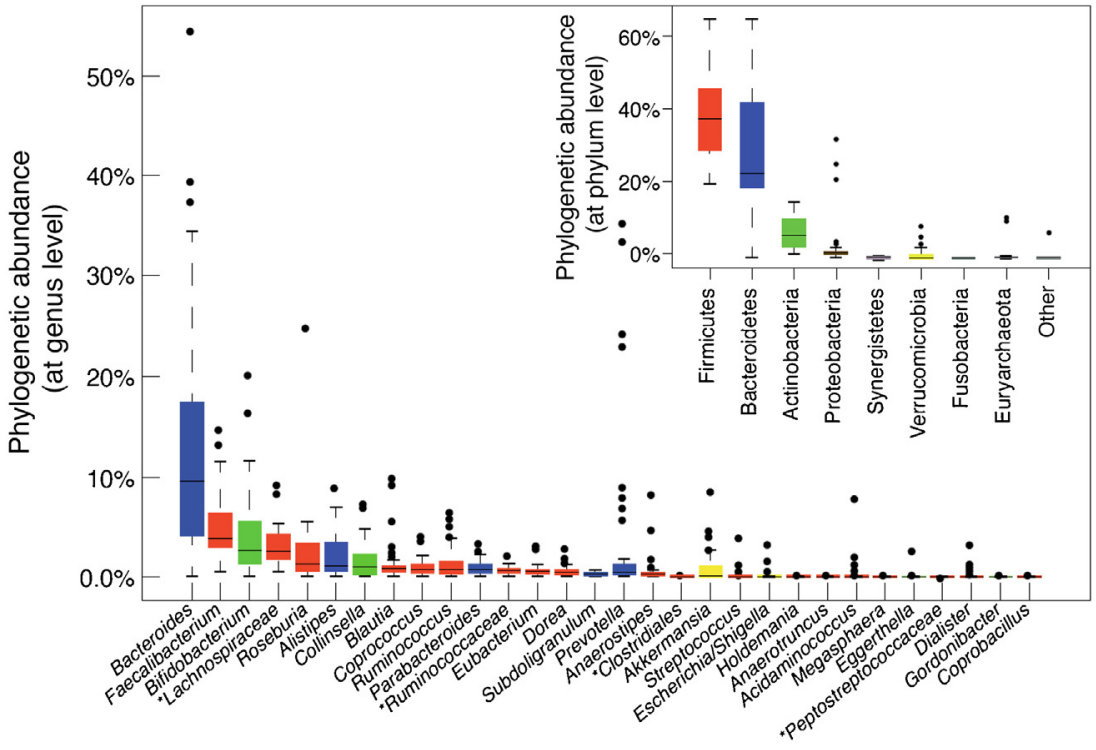
Velike razlike između pojedinaca, ovisi o stilu života, dobi, genteskoj predispoziciji i dr.

Tri glavna enterotipa s obzirom na rod koji prevaldava:

enterotip 1-*Bacteroides*

enterotip 2- *Prevotella*

enterotip 3- *Ruminococcus* ili *Bifidobacterium*



Bakterijski sastav crijevne mikrobiote (rodovi i koljena) dobiven sekvenciranjem nove generacija DNA ekstrahirane iz uzoraka stolice španjolskih i danskih ispitanika, Izvor: Alvarez et al. Gut microbes and health. Gastroenterologia y Hepatologia.2022.

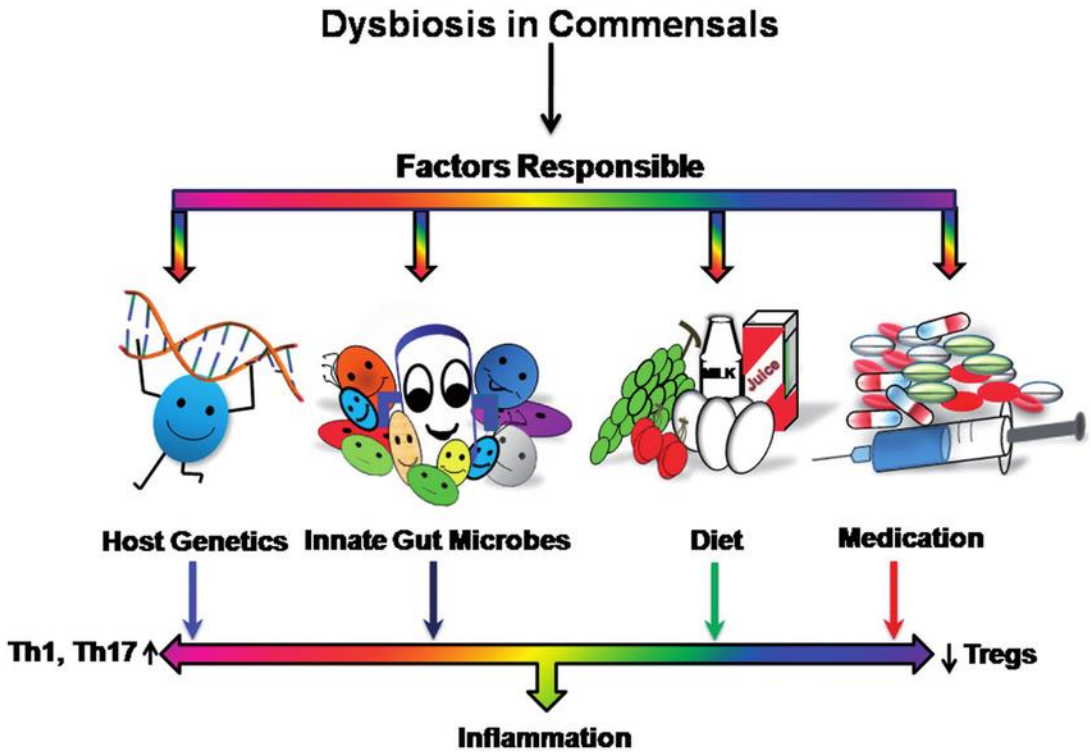
Disbioza mikrobiote crijeva

Disbiozu mogu uzrokovati ili doprinjeti nastanku mnogobrojni čimbenici:

Ako je neki od čimbenika dugo traje u značajnom opsegu može dovesti do upalnog procesa i razvoja kroničnih bolesti

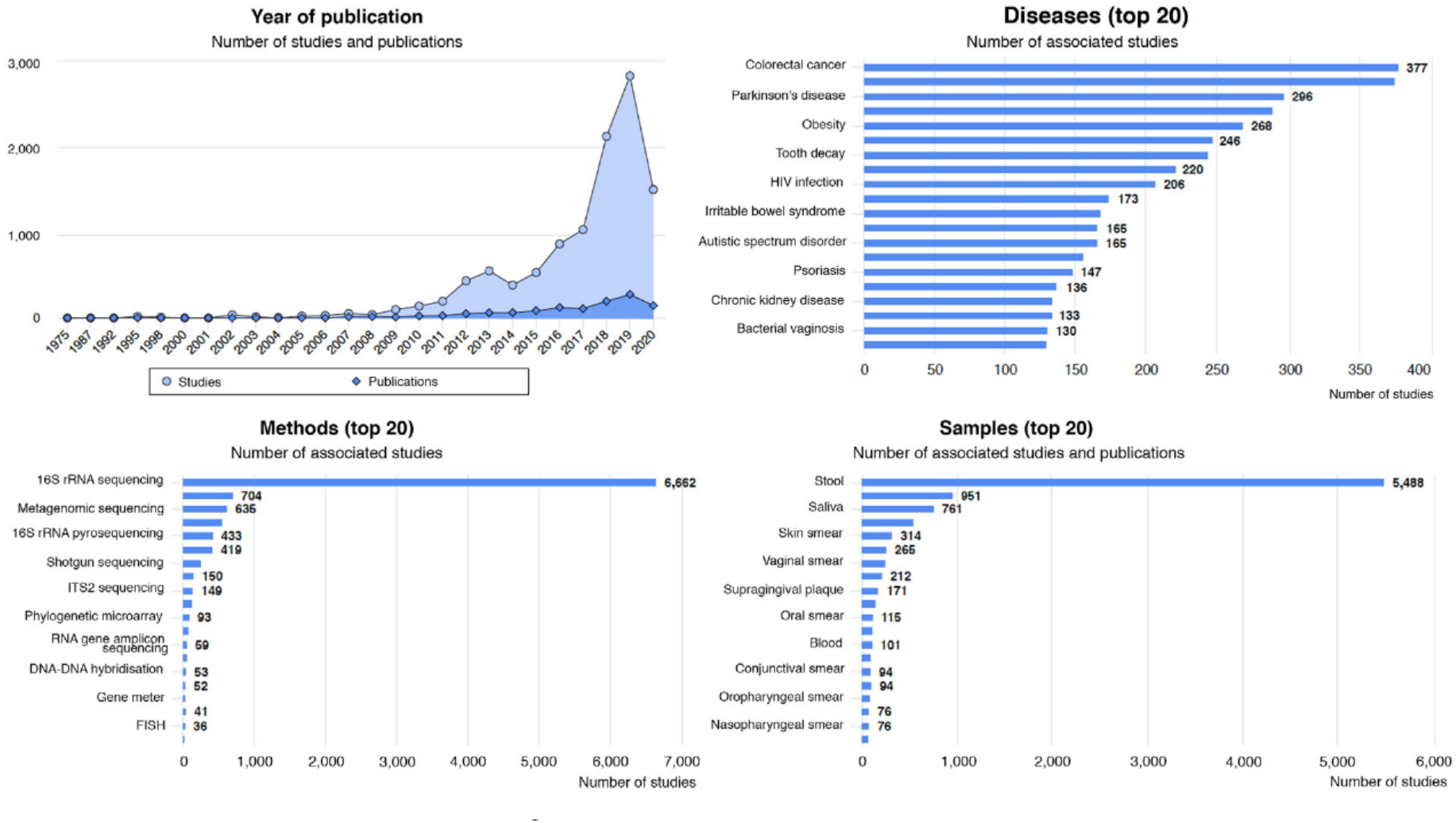
- Genetska predispozicija
- Stil života
- Liječenje antibioticima ali i drugim lijekovima
- Prehrana
- Stres

U ranom životu disbioza majke vertiklanim prijenosom može utjecati na inicijalnu akviziciju crijevne flore djeteta što može rezultirati dugotrajnim posljedicama za djetetovo zdravlje



Izvor: Sathyabama S, Khan N, Agrewala JN. Friendly pathogens: prevent or provoke autoimmunity. Crit Rev Microbiol. 2014

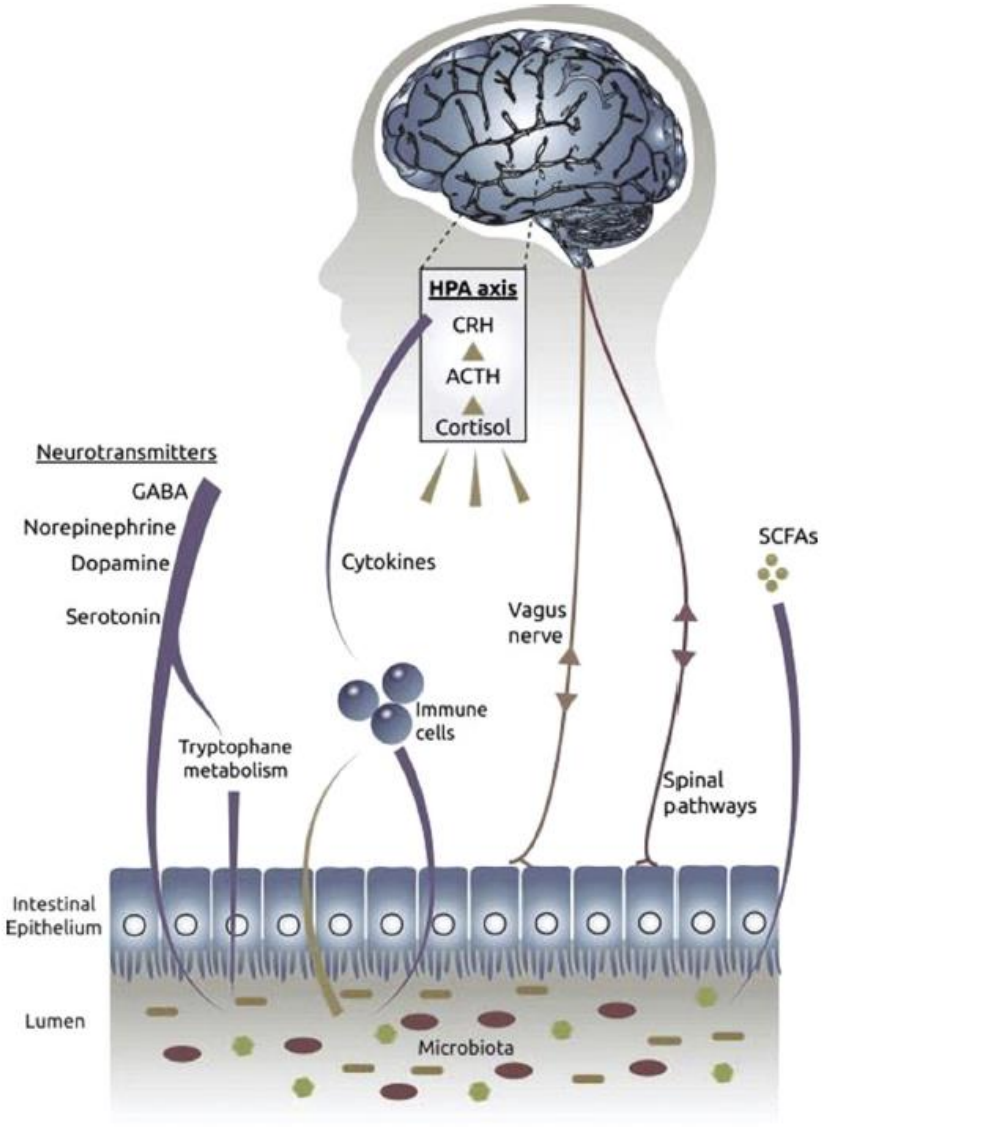
Disbioza mikrobiote crijeva i bolesti



Grafovi sa stranica Disbiom®, koja opisuje publikacije i studije koje povezuju promjene u mikrobioti sa bolestima. Izvor: Alvarez et al. Gut microbes and health. Gastroenterologia y Hepatologia.2022.

Mikrobiota crijeva i mozak

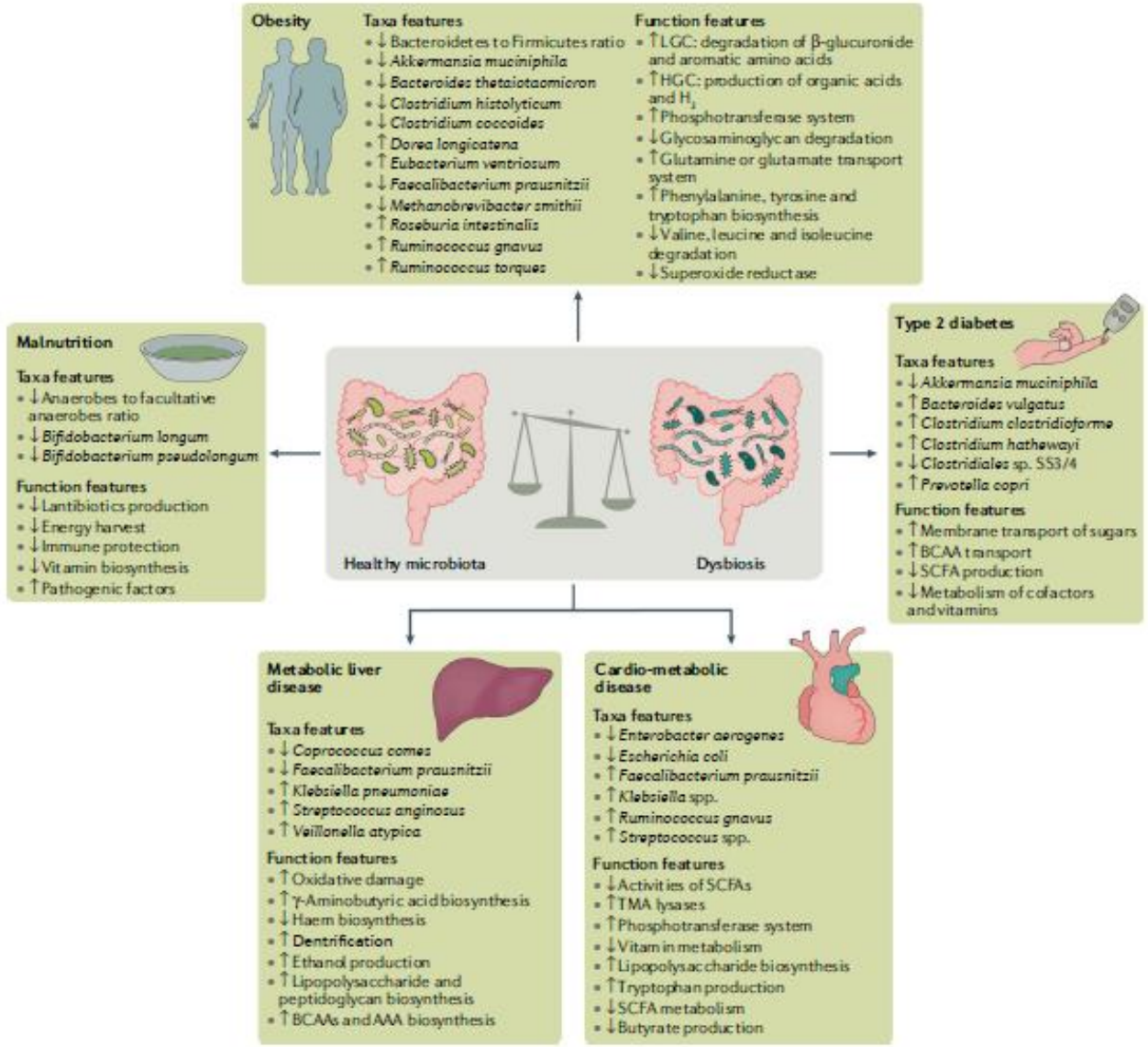
- Mikrobiota crijeva proizvodi mnoštvo neuroloških i endokrinih signala preko kojih komunicira sa drugim tkivima pa tako i mozgom s kojim komunicira putem vagusnog živca, ili putem kratkolančanih masnih kiselina, citokina i triptofana
- Os mozak-crijeva-mikrobiota predstavlja promjenu paradigme u neuroznanosti i pruža novi cilj za liječenje ne samo sindroma iritabilnog crijeva već i stanja, kao što su depresija, autizam i Parkinsonova bolest
- Psihobiotici - bakterije koje kada se unesu u dovoljnim količinama imaju pozitivan učinak na mentalno zdravlje



Izvor: Dinan et al. The Microbiome-Gut-Brain axis in health and disease. 2016.

Mikrobiota crijeva i metabolizam

- Mikrobiota crijeva ima ključnu uloga u probavi i regulaciji metabolizma
- Disbioza crijevne mikrobiote nalazimo u raznim metaboličkim poremećajima:
  - Pretilosti
  - Dijabetes tipa 2
  - Pothranjenost
  - Metaboličke bolesti jetre (masna jetra koja nije uzrokovana alkoholizmom)
  - Bolesti povezane sa krvožilnim sustavom i srcem (ateroskleroza)
- Disbioza se očituje na samo u promjeni u zastupljnosti određenih vrsta nego i kroz funkcionalne poremećaje kao što je smanjen ili povećan kapacitet raznih metaboličkih puteva(fermentacija, razgradnja AK, razni transportni i enzimatski sustavi)



Izvor: Fan Y and Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol 19, 55–71 (2021)

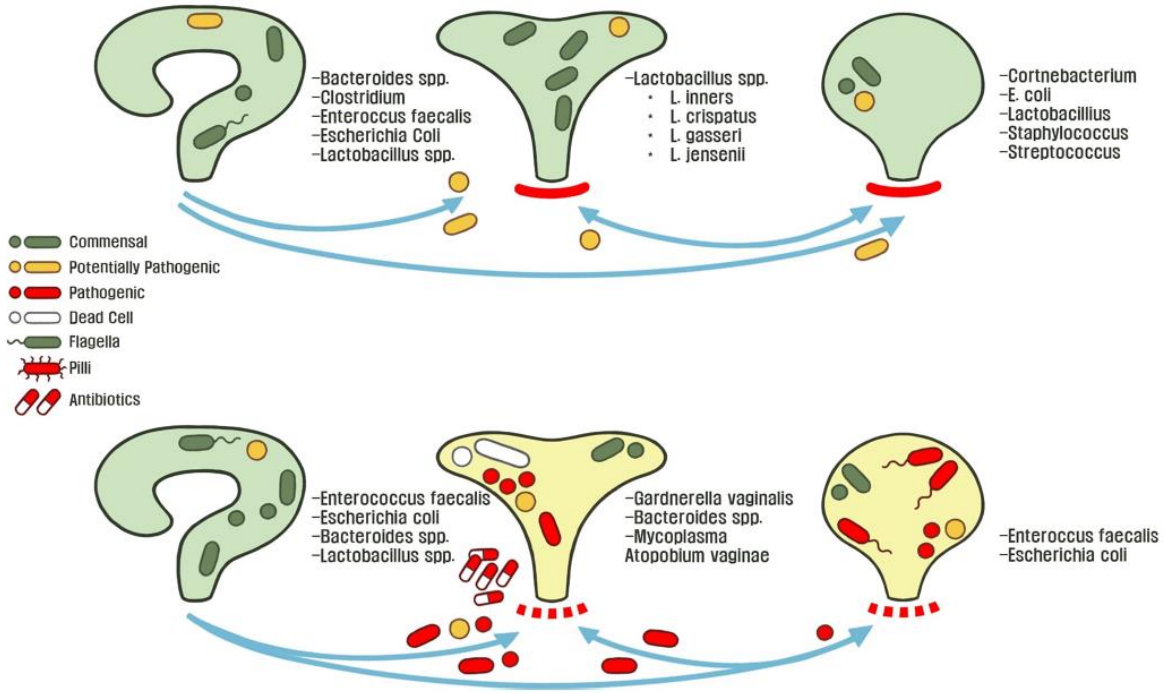
Mikrobiota crijeva i debljina

Prenosiva mikrobiota povezana s pretilošću može potaknuti debljanje kod mršavih miševa (2006.g.)

Mikrobiota crijeva u pretilih razlikuje se od mikrobiote crijeva mršavih ljudi

Mikrobiota u pretilih		Mikrobiota u mršavih
↑ Proizvođači kratkolančanih masnih kiselina • *Eubacterium ventriosum* • *Roseburia intestinalis*	≠	↑ Proizvođači maslačne kiseline i metana • *Oscillospira spp.* • *Methanobrevibacter smithii*
↓ Fermentori glutamata • *Bacteroides thetaiotaomicorm*		

Utjecaj mikrobiote crijeva i vagine na sastav urobioma i rekurentne IMS

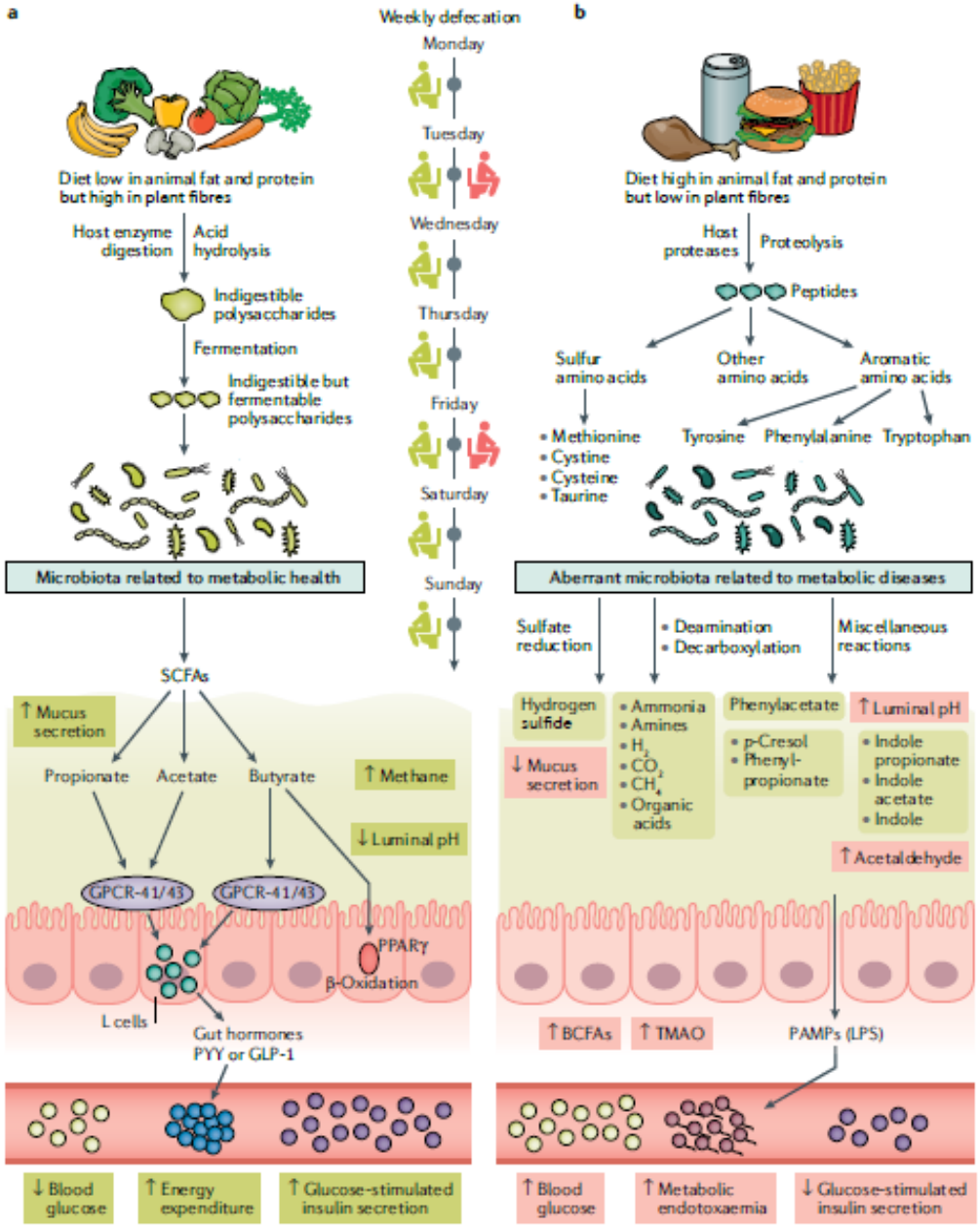


Komunikacija mikrobiote crijeva vagine i mokraćnog mjehura u homeostazi i disbiozi
Preuzeto iz:: Josephs-Spaulding J et al. Recurrent Urinary Tract Infections: Unraveling the Complicated Environment of Uncomplicated rUTIs. Front Cell Infect Microbiol. 2021

- zdravi mikrobiom crijeva, vagine i mokraćnog mjehura štiti svoju nišu od stranih patogena kontroliranjem abiotskih čimbenika i nadmašivanjem potencijalno invazivne mikrobiote
- nepovoljni vanjski čimbenici remete homeostazu i potiču nastanak disbioze različitim mehanizmima kao što su:
  - loša higijena,
  - metaboličke promjene (menopauza, metaboličke bolesti itd.),
  - Izloženost metalima iz okoliša
  - antibiotici
  - konzumacija patogena koji se prenose hranom.
- Prijenos mikrobiote perianalno-urogenitalnim putem oblikuje međusobno povezane mikrobiote, dolazi do neravnoteže-disbioza i predispozicije za razvoj IMS

Prehrana i mikrobiota crijeva

- Brojni su faktori koji utječu na ravnoteža između zdrave crijevne mikrobiote i disbioze (genteska predispozicija, fizička aktivnost, pušenje, lijekovi) a jedan od ključnih je i prehrana
- Metabolički zdrava mikrobiota cirjeva uglavnom je podržava prehranom koja uključuje manje životinjskih masti i proteina a više povrća bogatog vlaknima

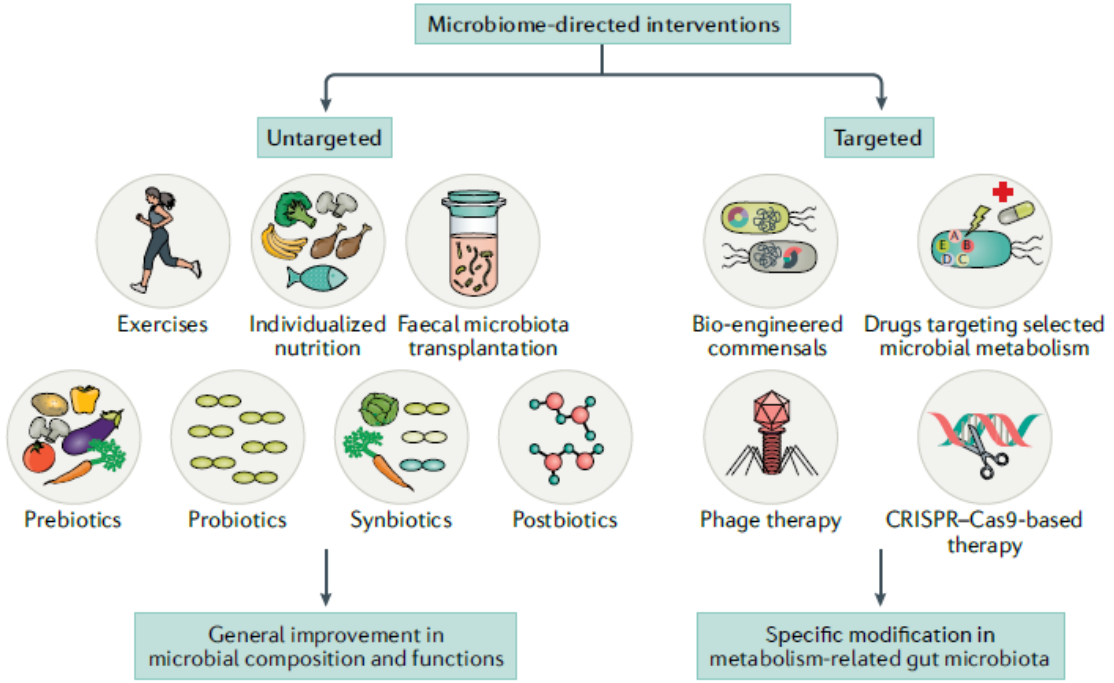


Izvor: Fan Y and Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol 19, 55–71 (2021)

Možemo li utjecati na mikrobiotu crijeva?

Postupci koji utječu na sastav i funkcionalnost crijevne mikrobiote

- Nespecifični:
  - Vježbanje
  - individualizirana prehrana
  - fekalna transplantacija
- Specifični (većina još u pretkliničkim fazam istraživanja):
  - genetski modificirani komensali
  - lijekovi koji specifično djeluju na metabolizam mikroorganizma
  - bakteriofagi
  - CRISPR-Cas9 tehnologija

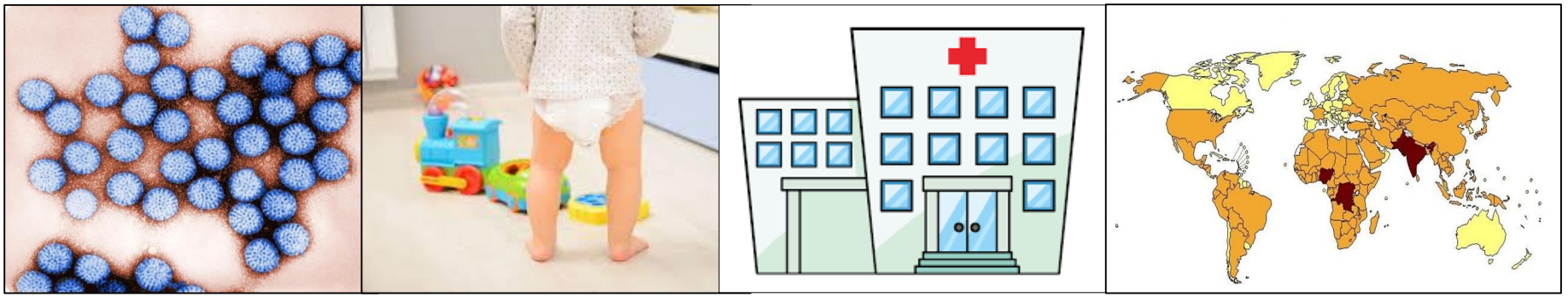


Izvor: Fan Y and Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol 19, 55–71 (2021)

Zaključak

Neke kronične nezarazne bolesti razvijenog društva (atopije, metabolički sindromi, upalne bolesti, rak i neki poremećaji ponašanja) povezani su s disbiozom crijeva

Treba poticati zdrave navike i način života koji omogućuje održavanje raznolikost i funkcionalnost crijevne mikrobiote sa ciljem promicanja zdravlja i prevencije bolesti



Klinički aspekti i liječenje probavnih infekcija u djece

Maja Vrdoljak Pažur

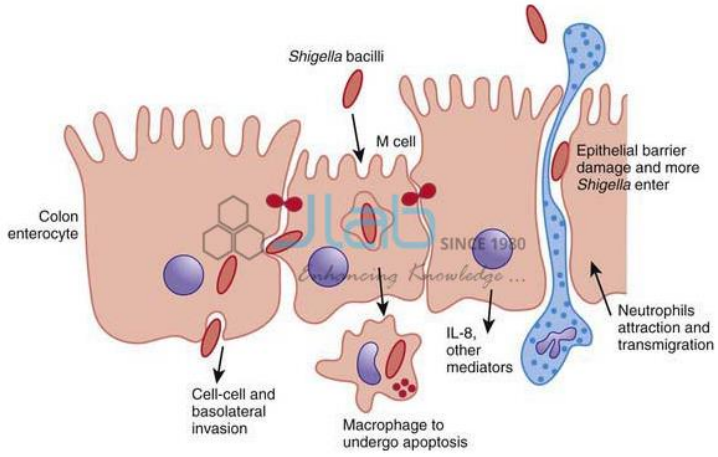
Goran Tešović

Zagreb, 17. svibnja 2024. g.

1. DEFINICIJA

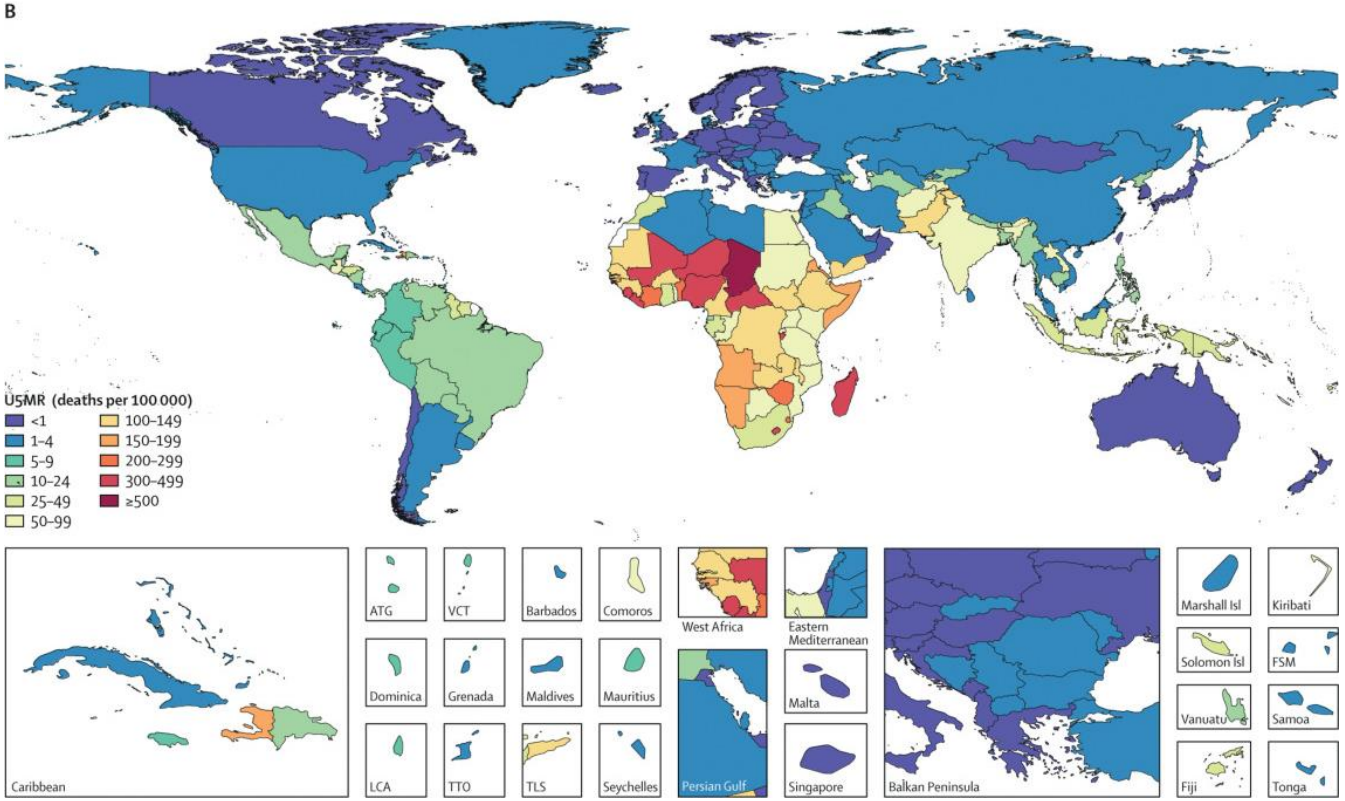
- promjena konzistencije stolice (mekša ili tekuća) i/ili povećanje broja stolica (tipično ≥3/24h) ± povraćanje ili vrućica.

- Gastro → ≥3 epizoda povraćanja
- Enteritis → obilne, vodenaste stolice; virusi i enterotoksini bakterija
- Kolitis → oskudne stolice, s primjesama krvi i sluzi, bolna defekacija, lažni pozivi, tenezmi; invazija bakterija i citotoksini



2. EPIDEMIOLOGIJA

- 2016. → AGE je bio 8. vodeći uzrok smrti u svim dobnim skupinama i 5. najčešći u djece <5 g. (gotovo 450 000 smrtnih slučajeva)
- Ukupna smrtnost 22.4/100 000, s većim stopama u djece <5 g. (70.6/100 000)
- Najviša smrtnost → subsaharska Afrika



GBD 2016 Diarrhoeal Disease Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis. 2018;18(11):1211-1228.

3. ETIOLOGIJA

AKUTNO POVRAĆANJE

AKUTNI VODENASTI PROLJEV

INVAZIVNI PROLJEV (DIZENTERIJA)

PERZISTENTNI PROLJEV

CRIJEVNA VRUĆICA

Bakterije	Bakterijski toksini	Virusi	Paraziti
Salmonella spp.	*Staphylococcus aureus*	Rotavirus (skupina A, B i C)	*Entamoeba histolytica*
Campylobacter spp.	*Bacillus cereus*	Norovirus	*Giardia lamblia*
Shigella spp.	*Clostridium perfringens* (tip A i C)	Adenovirus (tip 40, 41 i 31)	*Cryptosporidium spp.*
Dijarogena *E. coli*		Astrovirus	*Cyclospora*
Clostridium difficile			*Blastocystis hominis*
Yersinia enterocolitica			*Microsporidia*
Vibrio cholerae			*Strongyloides stercoralis*

- Rotavirus (RV) – najvažniji uzročnik akutnog gastroenteritisa (AGE) u djece < 5 g.
- **Prije uvođenja rotavirusnih cjepiva (2006.g.)**

<5 godina

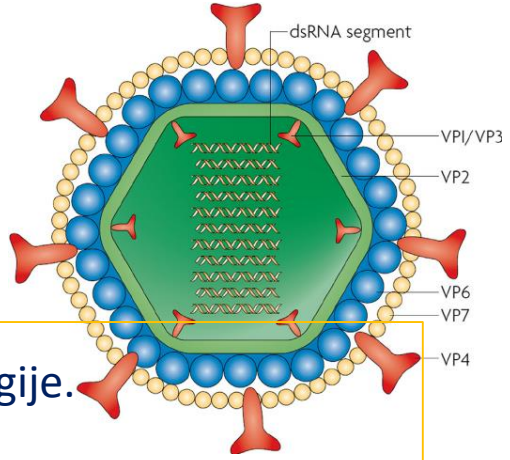
- 111 milijuna epizoda RVGE koje zahtijevaju kućnu skrb
- 25 milijuna posjeta bolnicama
- 2 milijuna hospitalizacija
- > 500 000 smrti

- Smrtnost je značajno pala (59-77%), no morbiditet i mortalitet i dalje su visoki.

Do 5. godine života, gotovo svako dijete imalo je barem jednu epizodu rotavirusnog gastroenteritisa!

- Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis 2003;9:565-72.
- Troeger C, Khalil IA, Rao PC, Cao S, Blacker BF, Ahmed T, i sur. Rotavirus Vaccination and the Global Burden of Rotavirus Diarrhea Among Children Younger Than 5 Years. JAMA Pediatr. 2018;172(10):958–65.

ZNAČAJKE RVGE



- Bolest je obično **težeg tijeka** u usporedbi s AGE druge etiologije.
- Infekcija je **univerzalna.**
- **Prva infekcija u dobi nakon tri mjeseca života → najveći rizik od težeg tijeka bolesti i dehidracije.**
- Bolest je **sezonska** u umjerenim klimama (vrhunac broja slučajeva u zimskim mjesecima), dok je u toplijim područjima tropskih regija bolest cjelogodišnja.

- Velázquez FR, Matson DO, Calva JJ, Guerrero L, Morrow AL, Carter-Campbell S, i sur. Rotavirus infection in infants as protection against subsequent infections. N Engl J Med. 1996;335(14):1022–8.
- Black RE, Brown KH, Becker S, Alim ARMA, Huq I. Longitudinal studies of infectious diseases and physical growth of children in rural Bangladesh. II. Incidence of diarrhea and association with known pathogens. Am J Epidemiol. 1982;115(3):315–24.
- Sanderson C, Clark A, Taylor D, Bolanos B. Global review of rotavirus morbidity and mortality data by age and region. Report to WHO/IVB, 2011.
- Cook SM, Glass RI, LeBaron CW, Ho MS. Global seasonality of rotavirus infections. Bull World Health Organ. 1990;68(2):171–7.

4. KLINIČKA SLIKA

- Virusni AGE – uglavnom nagli početak (povraćanje, vrućica, proljev)
- Virusna vrs. bakterijska etiologija? Ne može se sa sigurnošću razlikovati!
- U prilog virusne infekcije - izraženije povraćanje, respiratorni simptomi
- U prilog bakterijske infekcije – viša vrućica (>40 °C), krv u stolici, izraženija bol u trbuhu

ANAMNEZA

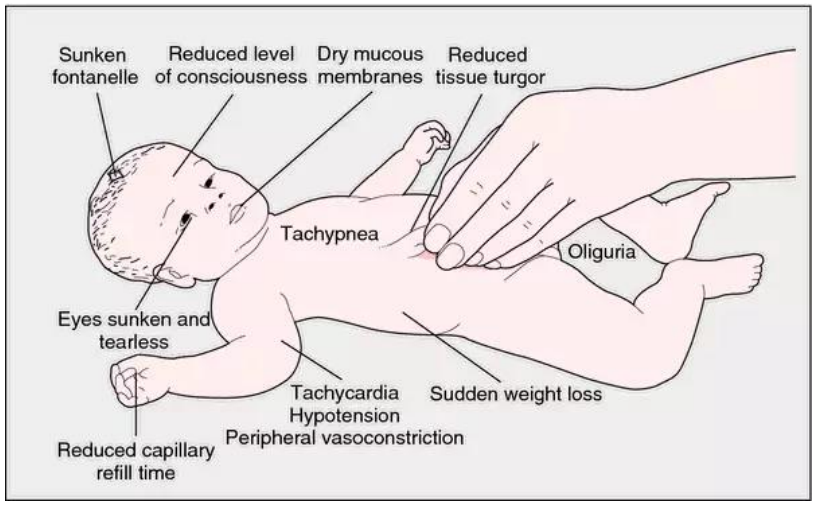
- broj povraćanja
- stolica – broj, krv, sluz
- bolovi u trbuhu
- peroralni unos
- mokrenje
- vrućica
- epidemiološki podaci – putovanja, izloženost kontaminiranoj hrani/vodi
- prethodno uzimanje antibiotika

KLINIČKA PROCJENA

- vitalni znakovi
- vrijeme kapilarne reperfuzije
- turgor kože
- ponašanje djeteta – iritabilnost, letargija, bljedilo
- tjelesna težina
- vlažnost sluznica
- pregled trbuha – distenzija, bolnost na palpaciju, defans

4. KLINIČKA SLIKA – procjena stupnja dehidracije

DEHIDRACIJA(% gubitak TT)	BLAGA (3-5%)	UMJERENA (6-10%)	TEŠKA >10%/ŠOK
Stanje svijesti	normalno	iritabilnost, nemir	letargija
Puls	normalan	ubrzan	ubrzan
Kvaliteta pulsa	normalan	normalan/oslabljen	oslabljen
Vrijeme kap. reperfuzije	normalno	produženo >3 s	produženo >3s
Arterijski tlak	normalan	normalan	normalan/snižen
Disanje	normalno	ubrzano	ubrzano
Oči	normalne	blago upale, manje suza	upale, nema suza
Fontanela	normalna	upala	upala
Mokrenje	normalno/smanjeno	smanjeno	oligurija/anurija



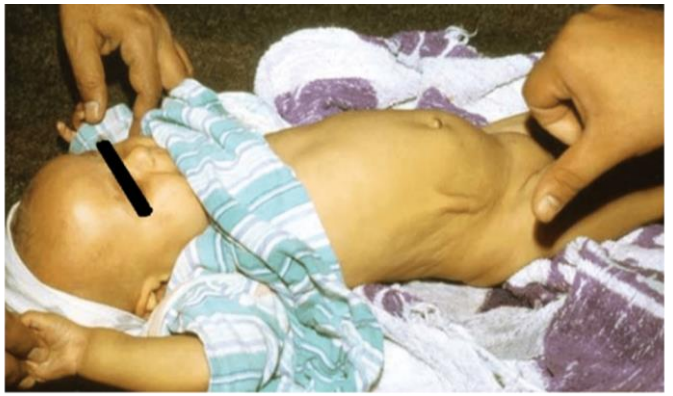
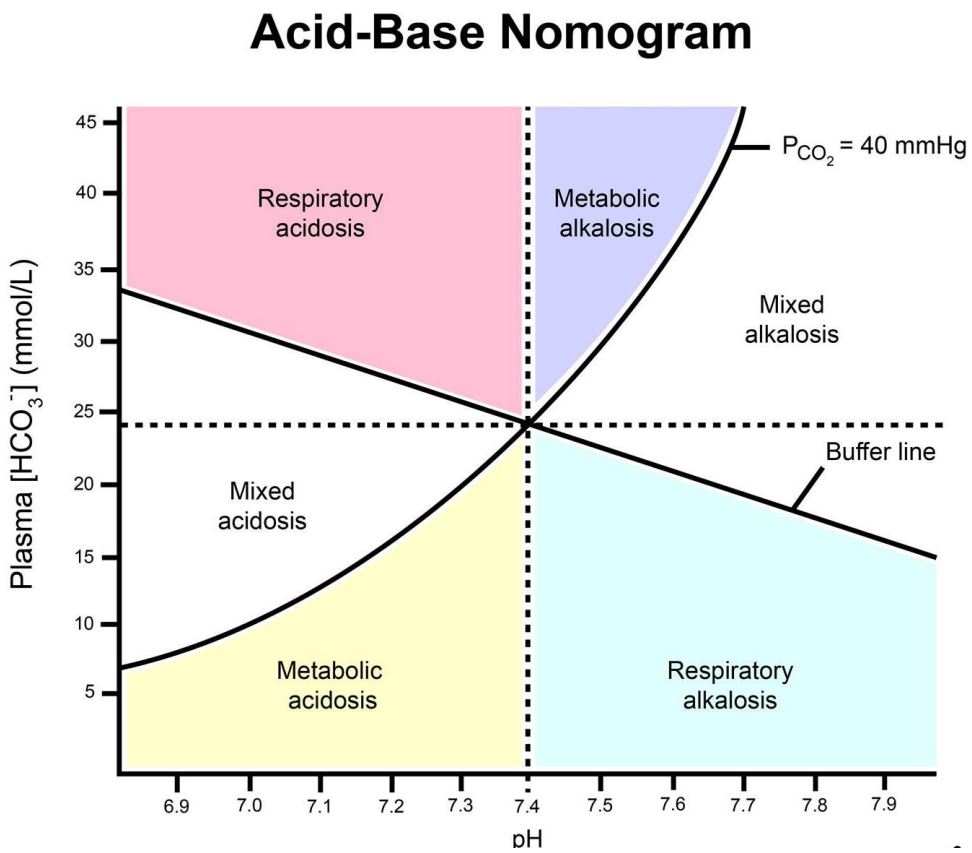


Figure 2: Reduced skin turgor of the abdominal skin. A red flag sign of dehydration

5. DIJAGNOSTIČKI POSTUPCI

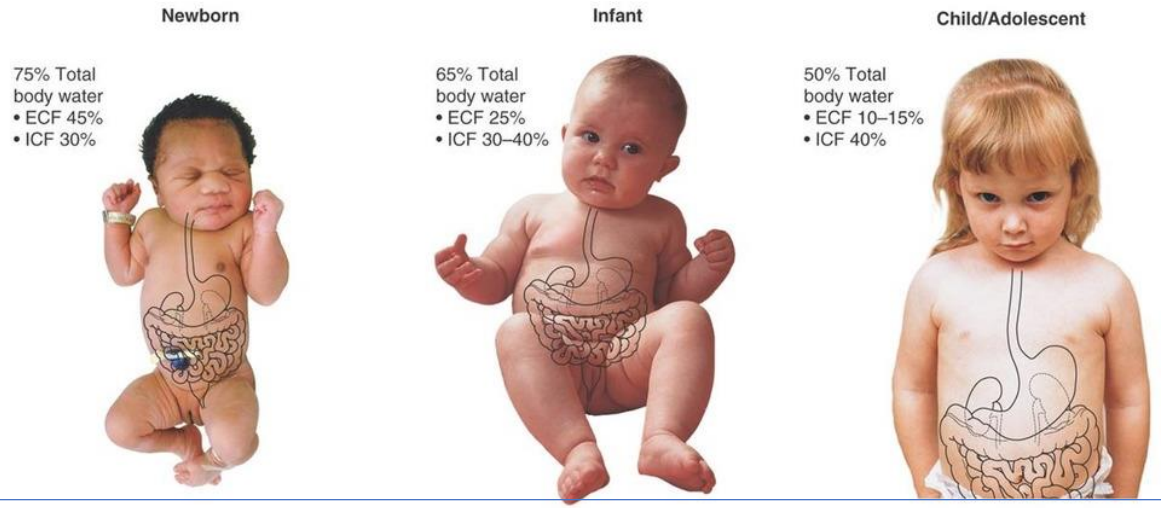
- U slučajevima blaže dehidracije uglavnom nisu potrebni!
- U slučajevima umjereno teške ili teške dehidracije**: ABS, GUK, elektroliti, Hgb, Htc**



6. LIJEČENJE – osnovni principi

- Uglavnom SIMPTOMATSKO
- Antimikrobno liječenje je rijetko indicirano

1. **Nadoknaditi sve *dosadašnje gubitke*, tj. postojeći manjak tekućine**
2. **Osigurati normalne *dnevne potrebe* organizma**
3. **Nadoknađivati *daljnje aktualne gubitke* (proljevi, povraćanje, febrilitet i sl.)**



- Guarino A, Ashkenazi S, Gendrel D, i sur. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. J Pediatr Gastroenterol Nutr. 2014;59(1):132-52.
- Richter D. i sur. Hitna pedijatrijska ambulanta. Zagreb. 2023.

6. LIJEČENJE – osnovni principi

- **Dva glavna načela liječenja AGE:**
- 1. inicijalna rehidracija u trajanju od **4-6 sati**, i zatim
- 2. postupna realimentacija uz nastavak nadoknade tekućih gubitaka

- U prvim satima prioritet je rehidracija, a ne prehrana.
- Ako je moguć peroralni unos, rehidracija se provodi otopinama oralnih rehidracijskih soli (ORS) – moguće u većini slučajeva **blage dehidracije**

- **ORS – hipotonična otopina (50-60 mmol/L Na)**
- **Odnos Na i glukoze mora biti 1:1 –** omogućuje kotransport Na i glukoze, što u stanicu uvlači vodu iz lumena crijeva.

- Guarino A, Ashkenazi S, Gendrel D, i sur. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. J Pediatr Gastroenterol Nutr. 2014;59(1):132-52.
- Richter D. i sur. Hitna pedijatrijska ambulanta. Zagreb. 2023.

6. LIJEČENJE

- **RACEKADOTRIL** – antisekretorni lijek; inhibitor enkefalinaze (endopeptidaze); antisekretorno i proapsorptivno djelovanje
- *There is some evidence that racecadotril is more effective than placebo or no intervention in reducing the duration of illness and stool output in children with acute diarrhoea.*
- **PROBIOTICI**
- Povoljno djelovanje dokazano jedino za *Saccharomyces boulardii* i *Lactobacillus rhamnosus*
- **ONDANSETRON**: 0.15 mg/kg i.v., jednokratno; OPREZ – produžuje QT interval, moguće aritmije

Gordon M, Akobeng A. Racecadotril for acute diarrhoea in children: systematic review and meta-analyses. Arch Dis Child. 2016 Mar;101(3):234-40.

7. CIJEPLJENJE

Najučinkovitiji način prevencije rotavirusne infekcije

Glavni cilj RV cjepiva → „oponašati" zaštitu stečenu nakon prirodne infekcije (simptomatske ili asimptomatske)

- Prevencija srednje teških i teških oblika infekcije, no ne nužno blažih oblika.
- Smanjenje mortaliteta u slabije razvijenim zemljama
- Smanjenje broja hospitalizacije zbog RVGE
- Smanjenje broj pregleda u hitnim ambulantama zbog AGE
- Smanjenje broja posjeta primarnom pedijatru

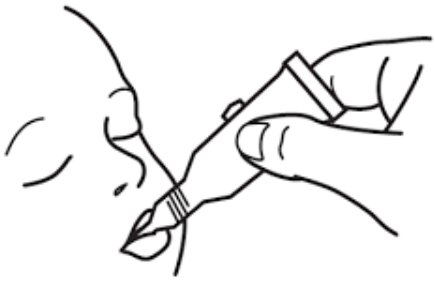
Dennehy PH. Rotavirus vaccines: an overview. Clin Microbiol Rev. 2008;21:198 –208.

Cjepivo	Godina	Sastav	Broj doza
SZO			
Rotarix, RV1 GSK Biologicals, Rixensart, Belgija	2009.	Monovalentno G1P[8] humano cjepivo	2
RotaTeq, RV5 Merck Sharp & Dohme Corp., Whitehouse Station, New Jersey, SAD	2008.	Peterovalentno (G1, G2, G3, G4, P[8]) humano-bovino reasortno cjepivo	3
Rotavac Bharat Biotech International Ltd., Indija	2018.	Monovalentno G9P[11]	3
Rotasiil Serum Institute of India Ltd., Indija	2018.	Peterovalentno (G1, G2, G3, G4, G9) humano-bovino reasortno cjepivo	3
NACIONALNO DOSTUPNA CJEPIVA			
Rotavin-M1 POLYVAC, Thành phố Hà Nội, Vijetnam	2008.	Monovalentno G1P[8] humano cjepivo	3
Lanzhou Lamb Lanzhou IBP, Kina	2000.	Monovalentno G10P[15] janjeće cjepivo	4

Glass RI, Tate JE, Jiang B, Parashar U. The Rotavirus Vaccine Story: From Discovery to the Eventual Control of Rotavirus Disease. J Infect Dis. 2021;224(Suppl 4):S331–42.

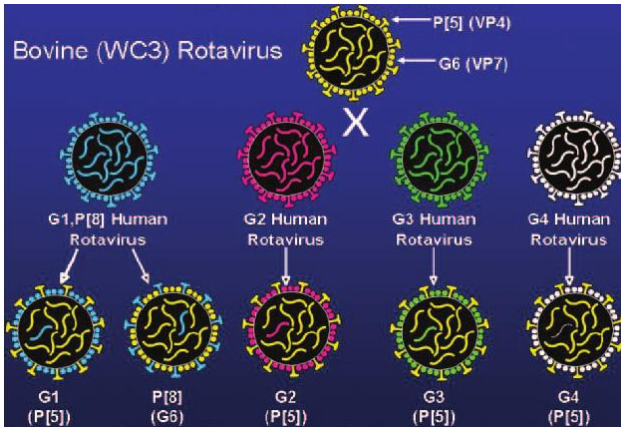
7. CIJEPLJENJE

- RV cjepiva u RH:
  - ➢ Nisu dio kalendara cijepljenja
  - ➢ Odobrena samo za rizične skupine



- **Rotarix®** (GlaxoSmithKline Biologicals) → RV1
  - ➢ sadržava the RIX4414 soj humanog RV G1P[8]
  - ➢ 2 oralne doze (2 mj. i 4. mj. starosti)

- **RotaTeq®** (Sanofi Pasteur MSD) → RV5
  - ➢ Humano-bovino reasortno cjepivo; Wistar Calf 3 (WC3) soj bovinog RV + geni humanih RV
  - ➢ 3 oralne doze (2, 4, 6 mj.)



- Bernstein DI, Smith VE, Sherwood JR, et al. Safety and immunogenicity of live, attenuated human rotavirus vaccine 89-12. Vaccine. 1998;16:381–387.
- Clark HF, Offit PA, Ellis RW, et al. The development of multivalent bovine rotavirus (strain WC3) reassortant vaccine for infants. J Infect Dis. 1996;174(Suppl 1):S73–S80.

8. ZAKLJUČCI

- AGE su vrlo česte, a najčešće je dovoljno simptomatsko liječenje!
- Pri kliničkom pregledu bolesnika važno je razmišljati o akutnoj kirurškoj ili ginekološkoj bolesti, procijeniti stupanj dehidracije te razmisliti o bolesnikovim komorbiditetima i etiološkoj dijagnozi.
- Koristiti oralne rehidracijske otopine za rehidraciju, a ne čistu vodu!
- Istraživanja su pokazala da samo LGG i *S. boulardii* imaju povoljan učinak u bolesnika s infektivnim proljevima.
- Primjena antisekretornih lijekova ima smisla u sekretornim proljevima.
- Izbjegavati primjenu antiperistaltičkih lijekova u bolesnika koji imaju infektivni proljev.
- Pri propisivanju antibiotika uzeti u obzir podatke o lokalnoj rezistenciji uzročnika.

Antibiotici za akutne infektivne proljeve – da ili ne?

Izv. prof. dr. sc. Mirjana Balen Topić, dr. med.
Odjel za gastrointestinalne infekcije
Klinika za infektivne bolesti "Dr.Fran Mihaljević"

Uzročnici dijarejalnih bolesti

Bakterije	Bakterijski toksini	Virusi	Paraziti
Salmonella spp.	*Staphylococcus aureus*	rotavirus (grupa A, B i C)	*Entamoeba histolytica*
Campylobacter spp.	*Bacillus cereus*	norovirus	*Giardia lamblia*
Shigella spp.	*Clostridium perfringens* (tip A i C)	adenovirus (tip 40, 41 i 31)	*Cryptosporidium* spp.
Dijareogene *Escherichia coli**		astrovirus	*Cyclospora*
Clostridium difficile			*Cystoisospora belli*
Klebsiella oxitoca			*Blastocystis hominis*
Yersinia enterocolitica			*microsporidia*
Listeria monocytogenes			*(Enterocytozoon bieneusi*
Vibrio cholerae *(O1 i non O1)*			*Septata intestinalis)*
Vibrio parahaemolyticus			*Strongyloides stercoralis*†
Aeromonas hydrophila			*Trichinella spiralis*
Plesiomonas shigelloides			
Edwardsiella			

Empirijsko antibiotsko liječenje AIP

- Pacijent je imunokompetentan, BEZ čimbenika rizika:

Febrilitet > 5 dana

Sumnja na bakterijemiju;
Trajanje TH: za vrijeme febriliteta
+ 7 afebrilnih dana

ciprofloksacin
ili
ceftriakson

Febrilitet + krvave stolice

Šok, klinički teška bolest

Prevencija komplikacija;
Trajanje TH: 4 dana

- Pacijent IMA čimbenike rizika ili je imunokompromitiran:

Dob < 3 mj. ili > 60 godina

Kronične bolesti
(DM, ciroza jetre, renalna lezija, maligne bolesti, LE, IBD, bolesti srčanih zalistaka)

Ugrađene endoproteze,
Operirani srčani zalisci

Operacije:
splenektomija, reseciran želudac, vagotomija ili antiulkusna terapija

Imunosupresivna ili sistemna kortikosteroidna terapija, imunodeficijencija

Trajanje TH:
za vrijeme febriliteta
+ 7 afebrilnih dana

ciprofloksacin
ili
ceftriakson

- Empirijsko liječenje febrilnog AIP u trudnica:

Trudnica

azitromicin
ili
betalaktam
(ceftriakson; amoksicilin ?)

- Pacijent IMA čimbenike rizika ili je imunokompromitiran:

Antimikrobna terapija u zadnja 4 tjedna

Sumnja na *C. difficile* infekciju

vankomicin p.o.
+/- metronidazol
fidaksomicin

Empirijska terapija AIP u odraslih (izvor: Up to date)

Antibiotik	**Vodenasti proljev BEZ krvi**	**Dizenterija (vidljiva krv ili sluz)**
azitromicin	1x500 mg tbl /3 dana ili 1x1000 mg (ili 2x500 mg)	1x500 mg tbl /3 dana
ciprofloksacin	2x500 mg / 3-5 dana ili 1x750 mg	2x500 mg / 3-5 dana
levofloksacin	1x500 mg / 3-5 dana ili 1x500 mg	1x500 mg / 3-5 dana

Ciljano antibiotsko liječenje AIP

Salmoneloza -
empirijska TH:
- kinoloni
- ceftriakson

Kampilobakterioza -
empirijska TH:
- makrolidi

- **C. difficile infekcija**

  OBAVEZNO liječiti:
  - vankomicin p.o.
  - metronidazol +/-
  - fidaksomicin

Šigeloza –
empirijska TH:
- kinoloni / 3 dana
- makrolidi

Jersinioza –
Nedefiniran optimum TH.
- enterokolitis: TH 4 dana
- sepsa: 2 - **3 tj.** (pa i duže...)

- kinoloni, doksiciklin, trimetoprim/sulfametoksazol, aminoglikozidi....

Kolera –
Antibiotik JEDNOKRATNO:
- doksiciklin 1x300 mg
- ciprofloksacin 1x1000 mg
- azitromicin....

Crijevno patogene *E. coli* –

NE liječiti antibiotikom

Preporuke liječenja putničke dijareje

- Blaga bolest: ORS, loperamid, bizmut
- Blaga do umjerena bolest: dodati **ciprofloksacin**, ili **azitromicin**
- Dizenterički sindrom, krvave stolice: dodati **metronidazol** ili tinidazol
- **Ako nema poboljšanja za 48 h:** kultivacija stolice, pregled na jajašca i ciste parazita, acidorezistentno bojenje za *Cryptosporidium* i *Cyclospora*

Antibiotici za akutne infektivne proljeve – DA ili NE?

Većinom NE.

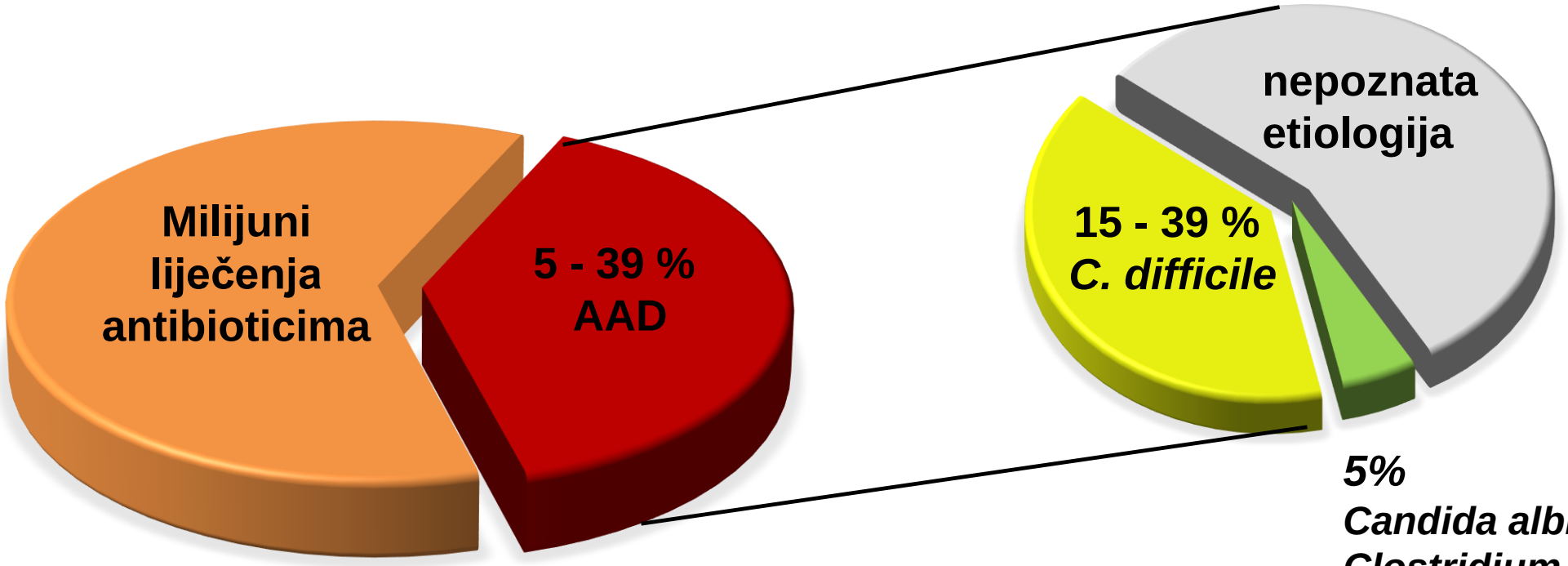
Ali... treba znati prepoznati indikacije kada DA.

PRATI LI SVAKI ANTIBIOTIK USPJEŠAN PROBIOTIK?

NOVOSTI U LIJEČENJU POSTANTIMIKROBNE DIJAREJE (AAD)

Sanja Zember, dr. med. spec. infektolog

AAD - Antibiotic-associated diarrhoea
CDAD - *C.difficile*-associated diarrhoea



Fighting antibiotic-associated diarrhoea and antibiotic resistance
https://hospitalpharmacyeurope.com/news/editors-pick/fighting-antibiotic-associated-diarrhoea-and-antibiotic-resistance/

CDI - *Clostridioides difficile* infekcija

RIZIČNI ČIMBENICI ZA CDI:

INICIJALNA EPIZODA CDI
izloženost antibioticima
starija životna dob (≥ 65 godina)
hospitalizacija (osobito dugotrajna) ili boravak u ustanovi za dugotrajnu zdravstvenu skrb i njegu
terapija koja suprimira lučenje želučane kiseline
abdominalna operacija / NG sonda
diabetes mellitus
terminalni stadij bubrežne bolesti
IBD

REKURENTNA EPIZODA CDI
izloženost antibioticima nakon prethodne epizode CDI
starija životna dob (≥ 65 godina)
produžen ili recentni boravak u ustanovi za dugotrajnu zdravstvenu skrb i njegu
terapija koja suprimira lučenje želučane kiseline
infekcija hipervirulentnim sojem
prethodna epizoda CDI

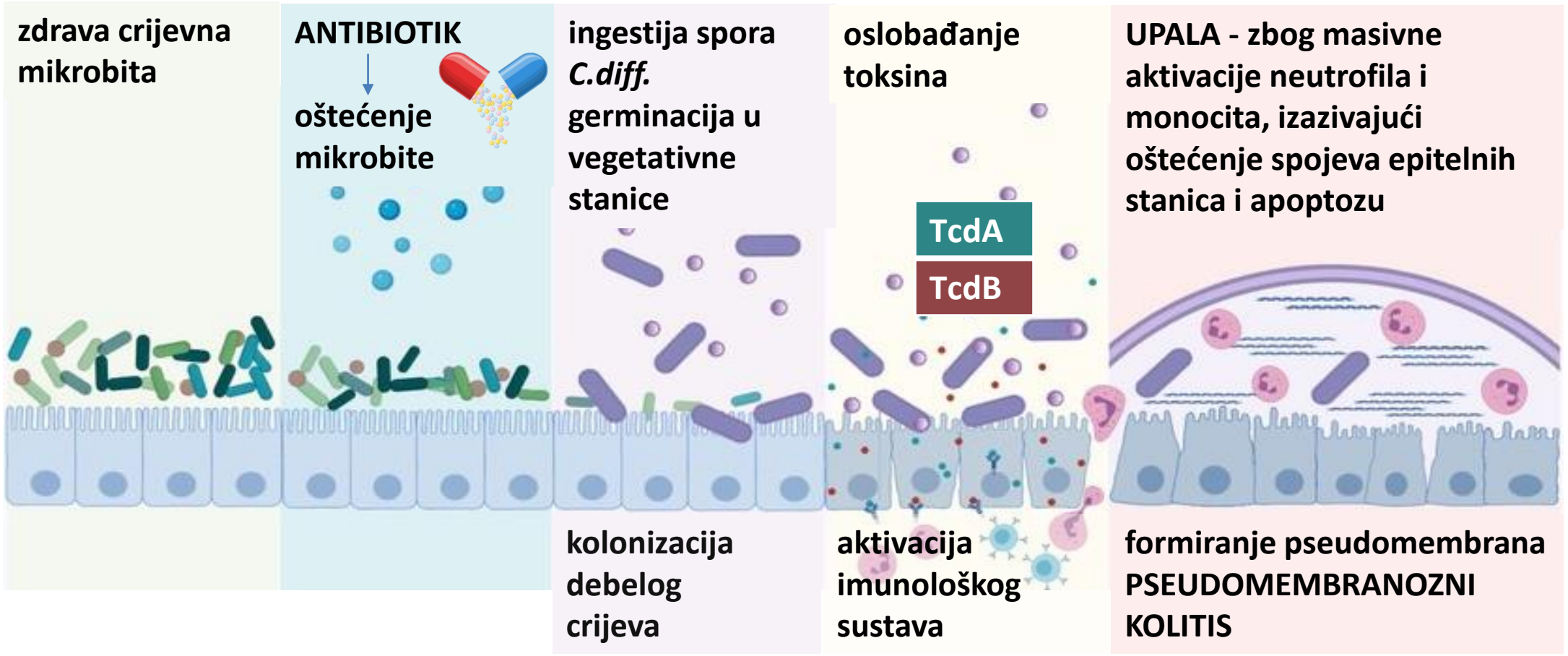
Updated Clinical Practice Guidelines for C difficile Infection in Adults

CDI - *Clostridioides difficile* infekcija

RIZIČNI ČIMBENICI ZA CDI:

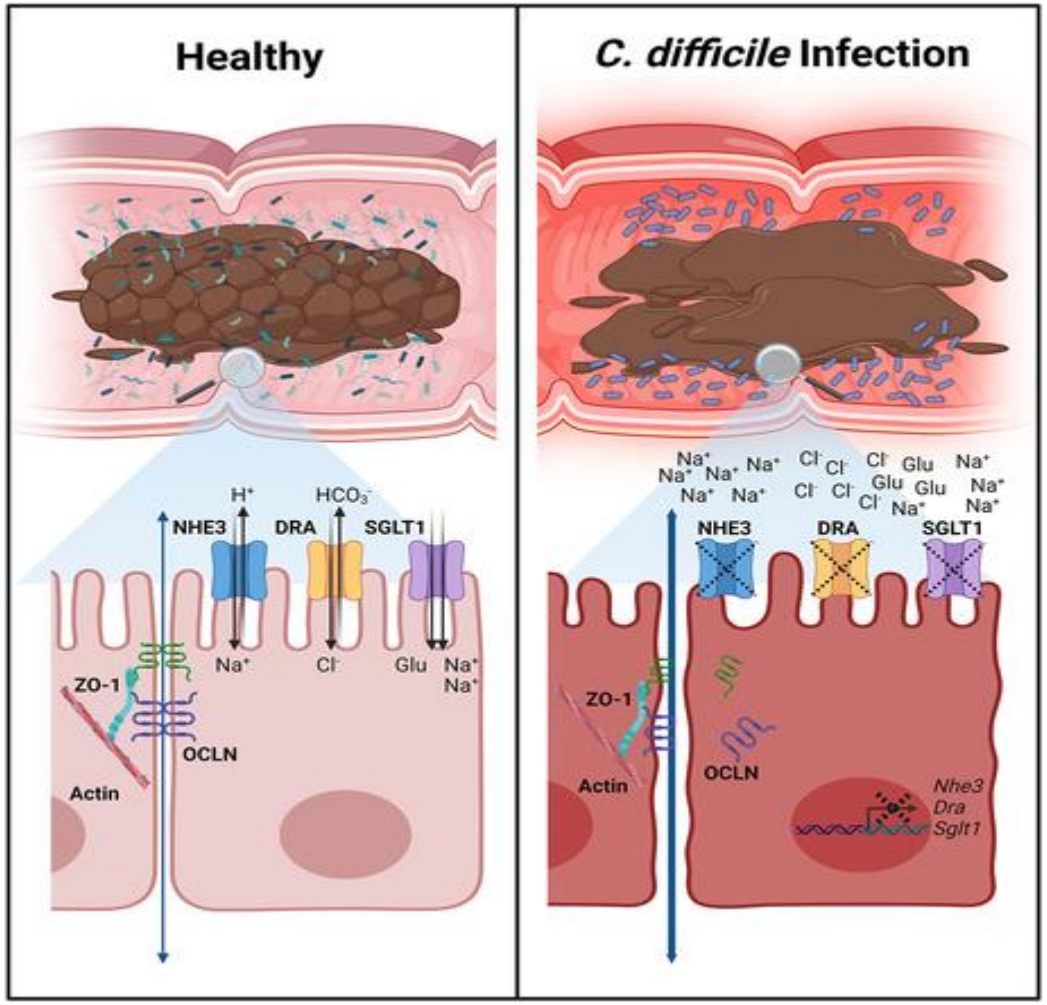
uporaba antibiotika koji mijenjaju crijevnu mikrobiotu
KARBAPENEMI
KLINDAMICIN
FLUOROKINOLONI
PIPERACILLIN-TAZOBACTAM
TREĆA I ČETVRTA GENERACIJA CEFALOSPORINA

CDI patogeneza



Morales-Olvera Claudia; Lanz-Zubiría Lorena; Aguilar-Zamora Emmanuel; Camorlinga-Ponce Margarita; Aparicio-Ozores Gerardo; Aguilar-Zapata Daniel; Chavez-Tapia Norberto; Uribe Misael; Barbero-Becerra Varenka; Juárez-Hernández Eva: Clostridioides Difficile in Latin America: An Epidemiological Overview; Current Microbiology; 2023/09/28 DO - 10.1007/s00284-023-03475-x

CDI patogeneza



CDI

- povećana je propusnost crijeva
- smanjuje se apikalno obilje ionskih transportera: NHE3, SGLT1 i DRA
- nefunkcionalna apsorpcija vode i otopljenih tvari u debelom crijevu uzrokuje **OSMOTSKI PROLJEV**

F. Christopher Peritore-Galve, Izumi Kaji, Anna Smith, Lauren M. Walker, John A. Shupe, M. Kay Washington, Holly M. Scott Algood, Pradeep K. Dudeja, James R. Goldenring & D. Borden Lacy (2023) Increased intestinal permeability and downregulation of absorptive ion transporters Nhe3, Dra, and Sglt1 contribute to diarrhea during Clostridioides difficile infection, Gut Microbes, 15:1, DOI: 10.1080/19490976.2023.2225841

KLINIČKE MANIFESTACIJE CDI

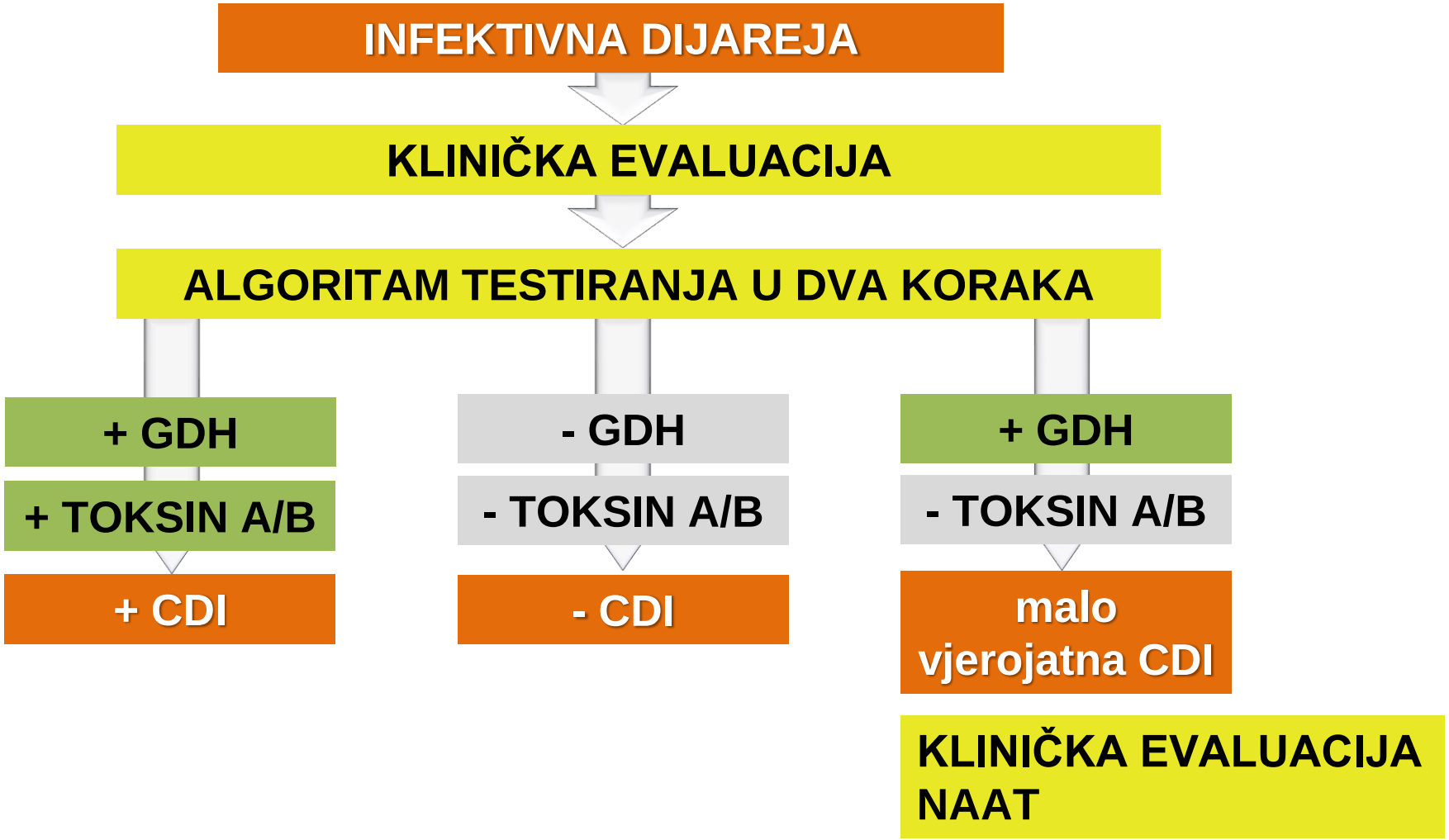
Kliničke manifestacije CDI su:

- **asimptomatsko nosilaštvo**
- **blagi ili umjereno teški, akutni vodenasti proljev**
- **teški kolitis - pseudomembranozni kolitis**
- **opasne komplikacije: sepsa, zatajenje bubrega, toksični megakolon, perforacija crijeva**

Rizik za razvoj CDI prisutan je:

- tijekom antimikrobne terapije
- unutar prvog mjeseca nakon prekida antimikrobne terapije
- 3 mjeseca nakon završetka antimikrobne terapije

ESCMID smjernica: algoritam testiranja CDI u dva koraka



PREPORUKE ZA LIJEČENJE CDI

	IDSA/SHEA 2021	ESCMID 2021	ASID 2016
INICIJALNA EPIZODA - blaži oblik	**FIDAXOMICIN** STD ili **VANKOMICIN** 4x125 mg po. 10 d Ako nisu dostupni: **METRONIDAZOL** 3x500 mg po. 10-14 d	**FIDAXOMICIN** STD ili **VANKOMICIN** 4x125 mg po. 10 d Ako nisu dostupni: **METRONIDAZOL** 3x500 mg po. 10-14 d Ako postoji visok rizik od recidiva, osobito kod starijih hospitaliziranih pacijenata, razmotriti EPFX ili dodati **BEZLOTOKSUMAB** ako fidaksomicin nije dostupan	**METRONIDAZOL** 3x400 mg po. 10 dana

Indikacija HZZO-a:
Kod rekurirajućeg kolitisa uzrokovanog *C. difficile* (**više od 2 recidiva**) kod kojeg je prethodno provedena terapija peroralnim metronidazolom i/ili peroralnim vankomicinom. Propisuje se kao rezervni antibiotik.

FIDAXOMICIN

- **STD:** 2x200 mg po. 10 dana;
- **EPFX** 2x200 mg po.- 5 dana potom 200 mg po. svaki drugi dan- 20 dana

VANKOMICIN

- pulsni režim: 4x125 mg- 10-14 dana, 2x125mg- 7 dana, 1x125mg- 7 dana, a zatim svaka 2-3 dana tijekom 2-8 tjedana

IDSA-SHEA: Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America
ESCMID: European Society of Clinical Microbiology and Infectious Diseases
ASID-Australasian Society for Infectious Diseases

Bishop EJ, Tiruvoipati R. Management of Clostridioides difficile infection in adults and challenges in clinical practice: review and comparison of current IDSA/SHEA, ESCMID and ASID guidelines. J Antimicrob Chemother. 2022 Dec 23;78(1):21-30. doi: 10.1093/jac/dkac404. PMID: 36441203; PMCID: PMC9780550.

PREPORUKE ZA LIJEČENJE CDI

	IDSA/SHEA 2021	ESCMID 2021	ASID 2016
PRVI RECIDIV blaži oblik	**FIDAKSOMICIN** STD ili EPFX ili **VANKOMICIN** - pulsni režim ili 4x125 mg po. 10 dana i kao dodatak **BEZLOTOKSUMABU** ako je prethodna epizoda bila unutar 6 mjeseci	**FIDAKSOMICIN** STD (ako se fidaksomicin ne koristi za inicijalnu epizodu CDI) ili **FIDAKSOMICIN** STD ili **VANKOMICIN** 4x125 mg po. 10 dana s **BEZLOTOKSUMABOM** ili **VANKOMICIN** pulsni režim	**VANKOMICIN** 4x125 mg po. tijekom 10 dana
DRUGI ILI SLJEDEĆI RECIDIV blaži oblik	**FIDAKSOMICIN** STD ili EPFX ili **VANKOMICIN** - pulsni režim ili 4x125 mg po. 10 dana nakon čega slijedi **RIFAKSIMIN** 3x400 mg po. 20 dana i **BEZLOTOKSUMAB** ako je prethodna epizoda bila unutar 6 mjeseci **FMT**: potrebno je pokušati s antibiotskim liječenjem za najmanje dva recidiva (tj. tri epizode CDI) prije FMT	**FMT**: nakon **FIDAKSOMICINA** STD ili **VANKOMICINA** 4x125 mg po.,10 d ili **FIDAKSOMICINA** STD ili **VANKOMICINA** 4x125 mg po., 10 d s dodatnim **BEZLOTOKSUMABOM** ili **VANKOMICIN** pulsni režim prihvatljiva je alternativa ako druge opcije nisu dostupne	**VANKOMICIN** 4x125 mg po. 14 dana ± pulsni režim ili **FIDAKSOMICIN** STD ili **FMT** ako je dostupna ili **VANKOMICIN** 4x125 mg po. 10 dana nakon čega slijedi **RIFAKSIMIN** 3x400 mg po. 20 d

PREPORUKE ZA LIJEČENJE CDI

	IDSA/SHEA 2021	ESCMID 2021	ASID 2016
TEŠKI CDI	**FIDAKSOMICIN** STD ili **VANKOMICIN** 4x125 mg po., 10 dana + **BEZLOTOKSUMAB** za inicijalni CDI ako postoje drugi čimbenici rizika za recidiv (dob ≥65 godina, IK domaćin) ili ako je bila epizoda u prethodnih 6 mj.	**FIDAXOMICIN** STD ili **VANKOMICIN** 4x125 mg po. 10 d	**VANKOMICIN** 4x125 mg po. 10 d Ako pacijent ne podnosi oralnu terapiju - primjena **VANKOMICINA** NG sondom + **METRONIDAZOL** 3x500 mg iv. ± **VANKOMICIN** rektalno
TEŠKI CDI- kompliciran 'fulminantni'	**VANKOMICIN** 4x500 mg po. ili nazogastričnom sondom + **METRONIDAZOL** 3x500 mg iv. razmisliti o **VANKOMICINU** rektalno ako je prisutan ileus	**FIDAXOMICIN** STD ili **VANKOMICIN** 4x125 mg po. 10 d - razmotriti **TIGECIKLIN** 100 mg iv., zatim 2x50 mg Savjetovati se s kirurgom!	**VANKOMICIN** 4x500 mg po. ili NG sondom ± **VANKOMICIN** rektalno + **METRONIDAZOL** 3x500 mg iv. Savjetovati se s kirurgom!
TEŠKI CDI- kompliciran 'fulminantni' refraktorni	Nema komentara	Upućivanje na operaciju ili razmisliti o **FMT** ako pacijent nije prihvatljiv za operaciju	Razmotriti monoterapiju **TIGECIKLINOM** ili **FMT** i razmotriti mogućnost operacije

WGO smjernice

Popis randomiziranih kontroliranih ispitivanja s probioticima i/ili prebioticima u gastroenterologiji (indikacije za odrasle)

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	Comments
Prevention of *C.difficile*–associated diarrhea (or prevention of recurrence)	***Lactobacillus acidophilus* CL1285 and *L. casei* LBC80R**	≥ 10e10 cfu, once daily	2	Primary prevention
	Yogurt with *L. casei* DN114 and *L. bulgaricus* and *Streptococcus thermophilus*	10e7–10e8 cfu twice daily	3	Primary prevention
	***Saccharomyces boulardii* CNCM I-745**	10e9 cfu or 250 mg, twice daily	2	Primary prevention
	***Lactobacillus acidophilus* NCFM, *L. paracasei* Lpc-37, *Bifidobacterium lactis* Bi-07, *B. lactis* Bl-04**	1.7 × 10e10 cfu, once daily	3	Primary prevention
	***Lactobacillus acidophilus + Bifidobacterium bifidum* (Cultech strains)**	2 × 10e10 cfu, once daily	3	Primary prevention
	Oligofructose	4 g, three times daily	3	Prevention of recurrence

World Gastroenterology Organisation; Global Guidelines; Probiotics and prebiotics; February 2023
https://www.worldgastroenterology.org/guidelines/probiotics-and-prebiotics/probiotics-and-prebiotics-english

BULARDI® „zlatni standard”

kapsula sadrži:

- **do 10x10^9 živih stanica *S. boulardii,* do kraja roka valjanosti**

„aTECH tehnologija pakiranja”

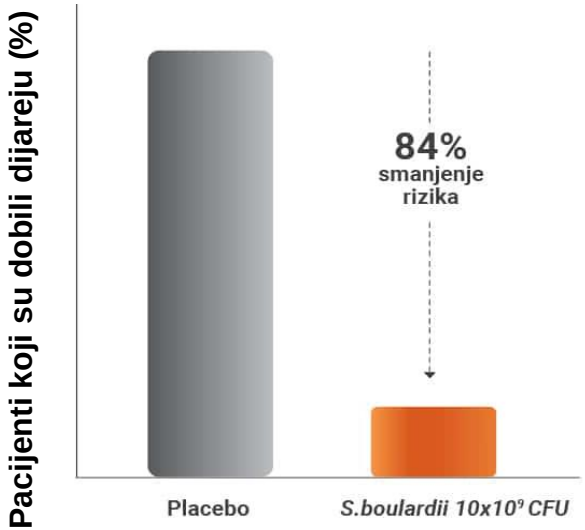
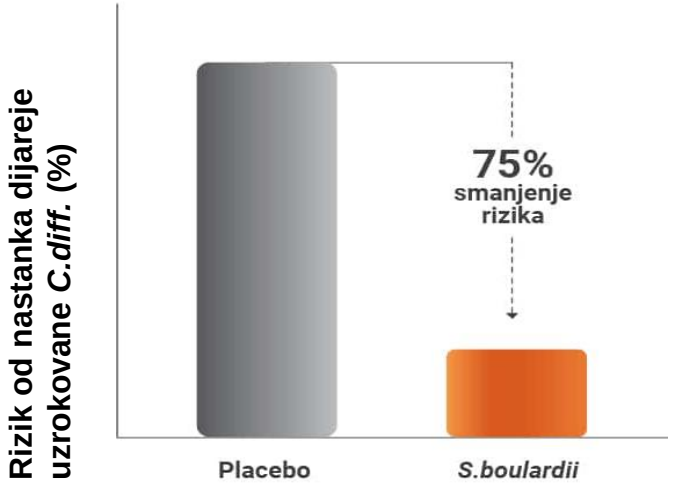
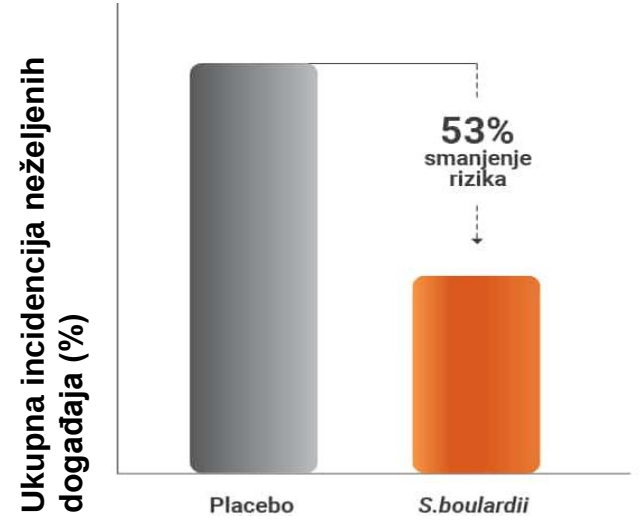
- vrećica ispunjena **dušikom**
- blister od višeslojne PVdC folije (PVC/PVdC/PE)
- omogućuje zaštitu od vlažnosti, UV-a i kisika
- preživljavanje stanica *S. boulardii* preko **64%** u trajanju do 2 godine

AbelaPharm *S. boulardii* proizvodi su u rangu „zlatnog standarda” zbog visoke kakvoće aktivne tvari i optimiziranog tehnološkog procesa proizvodnje i pakiranja probiotičkih pripravaka **(Korčok et al., 2021.)**

BULARDI® - kliničke studije

Probiotic Excellence Center®

Croatia AbelaPharm

UČINKOVITO DOPRINOSI SMANJENJU POJAVE ANTIBIOTSKE DIJAREJE	UČINKOVITO DOPRINOSI SMANJENJU RIZIKA OD *C.difficile* DIJAREJE	DOPRINOSI SMANJENJU NEGATIVNIH UČINAKA ERADIKACIJE *H.pylori*
		

1. Prophylactic Saccharomyces boulardii in the prevention of ADD, A prospective study.Can et al. Med Sci Monit. 2016; 12(4):
2. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of Clostridium difficile disease, Am J Gastroenterol, 2006 Apr;101(4):812-22
3. Saccharomyces boulardii as an adjuvant therapy for Helicobacter pylori eradication: A systematic review and meta-analysis with trial sequential analysis, Ben-Gang Zhou, Ling-Xiao Chen, Bo Li, Lin-Yan Wan, Yao-Wei Ai, PubMed, 2019 Oct;24(5):e12651.

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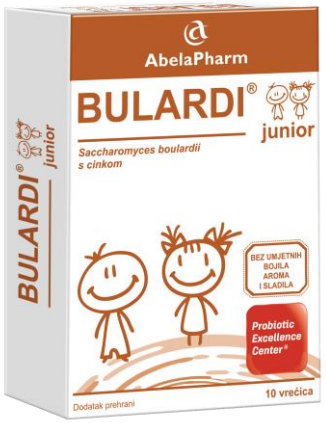
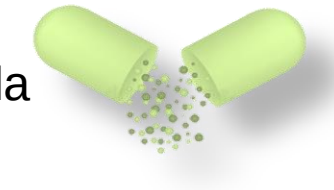
Probiotic Excellence Center®

Croatia AbelaPharm

ODRASLI DJECA od 3. godine	ODRASLI I DJECA od 1.g. DJECA od 2. mj. do 1.g.	DOJENČAD od 2. mjeseca do 1. godine
		 
Saccharomyces boulardii **500 mg** **+ vitamin D3 1000 I.J.**	***Saccharomyces boulardii*** **250 mg**	***Saccharomyces boulardii*** **250 mg (kapsule / vrećice)** **+ cink 5 mg**

pakiranje:
10 i 30 kapsula



kapsula se može otvoriti, sadržaj ispraznuti u žličicu s malo tekućine i odmah otopiti

cink potiče regeneraciju crijevnog epitela, jača imunitet crijeva, ublažava simptome i skraćuje vrijeme trajanja dijareje

BULARDI®

SVAKI ANTIBIOTIK PRATI USPJEŠAN PROBIOTIK!

Probiotic Excellence Center®

Pravilna prehrana tijekom probavnih infekcija

Ivana Šimić, dipl. ing. preh. teh.
Služba za promicanje zdravlja
Hrvatski zavod za javno zdravstvo

Virusne infekcije

Bakterijske infekcije

Gljivične infekcije

Uobičajeni simptomi:

- mučnina i povraćanje
- grčevi u trbuhu, proljev
- povišena temperatura (ponekad)
- glavobolja i opća slabost
- nedostatak apetita

1

nadoknada izgubljene tekućine (i elektrolita)

2

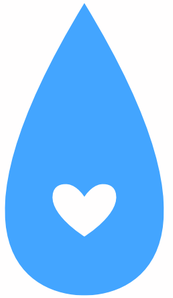
konzumacija lakoprobavljive hrane koja povoljno djeluje na simptome

3

mirovanje i odmor

konzumacija uravnotežene prehrane

Nadoknada izgubljene tekućine i elektrolita



DA

- voda
- nezaslađen ili blago zaslađen šipkov čaj
- bistre juha
- za djecu: oralna rehidracijska otopina
- za dojenčad: potaknuti majku da nastavi dojiti

*kokosova voda, čaj od đumbira i paprene metvice

NE

- pića s visokim udjelom šećera (pr. gazirana pića ili sportski napitci)
- čajevi (pr.crni)
- kofein
- alkohol

Dojenčad, mala djeca, starije osobe, osobe s oslabljenim imunološkim sustavim posebno su osjetljive na dehidraciju.

- prema potrebi nadomjestiti tekućinu i elektrolite infuzijom

Prehrana

Hrana koja se lako probavlja, ima malo vlakana i bogata je hranjivim tvarima.

- lakoprobavljiva hrana, u trajanju od 2 do 3 dana
- priprema obroka kuhanjem i pirjanjem te pečenjem u pećnici bez dodataka masnoće

  bez prženja i pohanja u dubokoj masnoći
- izbjegavanje jakih i nadražujućih začina
- izbjegavanje hrane intenzivnih okusa i mirisa

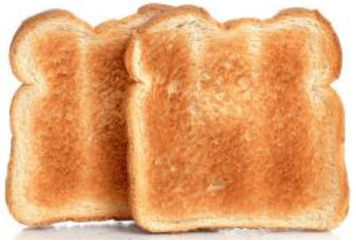
Prehrana

B R A T
(engl. banana, rice,apple, toast)
iz 1920-ih

BRATY : + jogurt
BRATT: + čaj

banana, riža, ribana jabuka ili pire od jabuke i tost ili dvopek

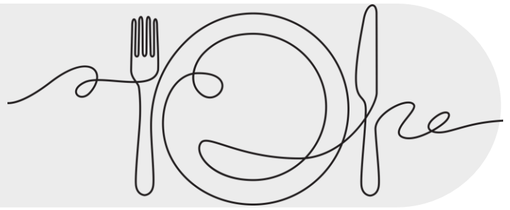
lako probavljiva hrana koje neće nadražiti iscrpljeni probavni sustav



relativna korist u odnosu na druge dijete nije dokazana

ne osigurava sve hranjive tvari koje bi pomogle bržem oporavku

Prehrana



- žitarice (riža)
- krumpir, batat, bundeva
- kuhano povrće (mrkva, cikla)
- nemasni mliječni proizvodi (svježi sir, jogurt s probiotikom, kefir) ili biljne zamjene
- nemasno meso (piletina, puretina)
- banane, ribane jabuke

- masne juhe i jela
- masne i slatke slastičarske proizvode i industrijske deserte
- povrće koje uzrokuje nadimanje (kupusnjače)
- mahunarke
- punomasni mliječni proizvodi
- nezrelo voće, voćni sokovi s dodanim šećerom
- kofein, alkohol
- hrana koja sadrži sorbitol i druge šećerne alkohole

Namirnice koje je preporučeno konzumirati kod dugotrajnih proljeva i primjer jelovnika

Doručak	Užina 1	Ručak	Užina 2	Večera
Čaj od šipka *(1 šalica - 250 mL)* **Zobene pahuljice na rižinom napitku s bananom i cimetom** *(zobene pahuljice 60 g, rižin napitak 250 mL, banana 180 g, cimet)*	**Jogurt probiotik** *(150 g)* **Dvopek** *6 kom*	**Juha od bundeve** *(bundeva 200 g, korijen celera 10 g, mrkva 10 g, koraba 10 g, bučino ulje 3 g, sol 0,5 g)* **Pureći file pirjan u povrću** *(pureći file 120 g, mrkva 30 g, celer 20 g, maslinovo ulje 5 g, peršinov list 1 g, sol 0,5 g)* **Riža s mrkvom** *(riža 70 g, mrkva 100 g, celer 10 g, maslinovo ulje 5 g, sol 0,5 g)* **Salata od cikle** *(cikla 200 g, limunov sok 7 g, maslinovo ulje 3 g, sol 0,5 g)*	**Puding na kompotu** *(puding 30 g, kompot od jabuke 160 g)*	**Kuhani juneći but** *(junetina 120 g, sol 0,5 g)* **Pire-krumpir** *(krumpir 300 g, rižin napitak 50 g, sol 0,5 g)* **Umak od špinata** *(špinat 100 g, rižin napitak 50 g, gustin 5 g, sol 0,5 g)*
Energetska vrijednost (kcal): 2027; Bjelančevine (g): 87; Masti (g): 45; Ugljikohidrati (g): 327				

(preuzeto iz Bolničkih prehrambenih smjernica, KBC Rijeka)

Skupina namirnica	Preporučuje se	U malim količinama	Ne preporučuje se
Žitarice i proizvodi od žitarica	odstajali bijeli kruh, dvopek, tost, tjestenina, riža, kukuruzna i pšenična krupica	kuhani ječam, proso, zob	vrući i svježi kruh i peciva, dizana pržena tijesta, okruglice, kruh sa sjemenkama, masni i slatki pekarski proizvodi, integralne žitarice (heljda, kvinoja)
Mlijeko i mliječni proizvodi	nezašećerene biljne zamjene za mlijeko (kokosovo, bademovo, zobeno i sl.), mlijeko bez laktoze	svježi posni sir, jogurt, jogurti s probiotičkim kulturama, skuta, mlaćenica	mlijeko, masni i dimljeni sirevi, slatko i kiselo vrhnje
Povrće	kuhano ili pirjano: krumpir, mrkva, tikvica, cikla, celer, špinat, blitva, bundeva	cvjetača	sirovo povrće, ukiseljeno povrće, mahunarke, kupus, kelj, prokulica, brokula, krastavac, paprika, luk, češnjak
Voće	kompot, pečena jabuka, pire od voća, banana	svježe cijeđeni voćni sokovi razrijeđeni s vodom, oguljeno voće (marelica, breskva, ribana jabuka)	svježe voće, orašasto voće, suho voće
Meso, jaja, riba	nemasno meso kuhano ili pirjano u vlastitom soku (perad bez kože, teletina, junetina), kuhana nemasna bijela riba, tvrdo kuhana jaja		mesa s vidljivom masnoćom, svinjetina, pohana mesa, mesne konzerve, paštete, pohana i pržena riba, masna riba, omleti i pečena jaja
Pića, napitci i juhe	voda, čajevi bez šećera ili s vrlo malo šećera, obrane juhe, prežgana juha		voćni sokovi, zaslađeni i gazirani napitci, alkoholna pića, instant-juhe
Masti i ulja		maslinovo, bučino, laneno, suncokretovo ulje, ulje uljane repice	maslac, margarin, majoneza, svinjska mast
Deserti	suhi keksi (*petit beurre*), slani štapići, krekeri od riže, tamna čokolada, kakao na vodi	lagani biskvit, riža ili griz na kompotu ili biljnoj zamjeni za mlijeko, palačinke s malo masnoće	masni kolači, kolači s kremom, kolači od dizanog tijesta, med, marmelada
Začini	limunov sok	sol	konzumni šećer, alkoholni ocat, senf, mljevena paprika, papar, dodaci jelima od sušenog povrća sa soli

Vrdoljak I, Kozina Loje M, Ferk K, Šanko K.Bolničke prehrambne smjernice. Rijeka: Klinički bolnički centar; 2022.

1 DAN

Piti što više tekućine

*blago zaslađeni ili nezaslađeni čaj
*voda
*obrana juha
*oralna rehidracijska otopina

Hrana koja se preporučuje

*kuhana slana riža s rižinom sluzi
*dvopek, krekeri, slani štapići, suhi keksi
*banana: žuta, manje zrela

2 i 3 DAN

preporuke od 1. dana
+
*juha od mrkve ili obrana juha s griz-knedlama ili tjesteninom
*kompot od jabuke, ribana jabuka
*kuhana piletina, teletina ili bijela riba
*kuhana tjestenina i odstajali kruh
*kuhana mrkva ili cikla

4 DAN

*konzumirati lakoprobavljivu kuhanu hranu, bez masnoća
*osigurati dovoljan unos tekućine, minimalno 2 litre dnevno
* jela pripremati kuhanjem ili pirjanjem bez dodatka masnoće, a izbaciti prženu i pohanu hranu te jela sa zaprškom
*ograničiti unos prehrambenih vlakana (svježe voće i povrće, mahunarke, orašasti plodovi i sjemenke, int. žitarice)
*nakon nestanka simptoma (idućih nekoliko dana) postupno uvoditi u prehranu namirnice bogate preh. vlaknima

Čim je moguće vratiti se uravnoteženoj prehrani

PREHRAMBENA VLAKNA

	No Water-Holding Capacity			Water-Holding Capacity			
	Insoluble	Soluble, Nonviscous		Soluble Viscous	Soluble Viscous/Gel Forming		
	Wheat Bran	Wheat Dextrin	Inulin	Methylcellulose	Partially Hydrolyzed Guar Gum	β-Glucan	Psyllium
Source	Wheat	Heat/acid treated wheat	Chicory root	Chemically treated wood pulp	Guar beans	Oats, barley	Seed husk, *Plantago ovata*
Degree of fermentation	Poorly fermented	Readily fermented	Readily fermented	Nonfermented	Readily fermented	Readily fermented	Nonfermented
Cholesterol lowering					+/−[a]	+[b]	+
Improved glycemic control					+/−[a]	+[b]	+
Satiety						+[b]	+
Weight loss							+/−[c]
Constipation/ stool softener	+[d]			+/−[e]			+
Diarrhea/stool normalizer							+
Irritable bowel syndrome							+[f]

Blank cells indicate a totality of negative clinical data or a lack of clinical data supporting the health benefit.

[a]The efficacy of partially hydrolyzed guar gum depends on the degree to which it has been hydrolyzed. If a marketed product has little/no viscosity when mixed with water (as described above), then it will not exhibit significant gel-dependent health benefits.

[b]Oat products are typically marketed in fiber bars or cereals, requiring pressure and/or heat to make the final product, potentially reducing gel-forming capacity.

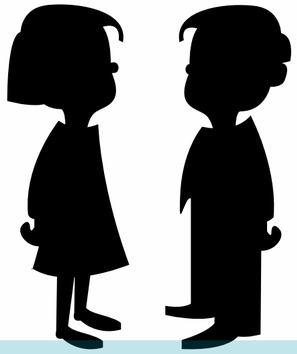
[c]The criteria for ''clinically demonstrated'' was publication of at least 2 well-controlled clinical studies. Sustained weight loss for psyllium was assessed in only 1 clinical study,[60] so a designation of +/− was deemed most appropriate.

[d]Insoluble fiber can have a significant laxative effect if the particle size is sufficiently large/coarse.

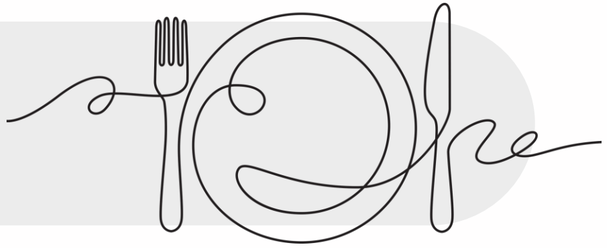
[e]Methylcellulose has an over-the-counter (OTC) indication for treatment of occasional constipation, but the American College of Gastroenterology determined that methylcelluose had insufficient clinical data to recommend it for treatment of chronic constipation.[42]

[f]A recent comprehensive review published in the *American Journal of Gastroenterology* determined that ''When fiber is recommended for functional bowel disease, use of a soluble supplement such as ispaghula/psyllium is best supported by the available evidence.''[9]

McRorie JW Jr. Evidence-Based Approach to Fiber Supplements and Clinically Meaningful Health Benefits, Part 2: What to Look for and How to Recommend an Effective Fiber Therapy. Nutr Today. 2015.



Djeca



Rehidracija

ORS - hipoosmolarna rehidracijska otopina 50-60 mmol/L Na (ESPGHAN)

- *smanjuje učestalost povraćanja, poboljšava učinkovitost rehidracije i nema povećanog rizika od nastanka hiponatrijemije*

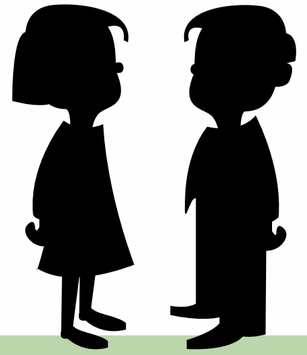
Probiotici

Upotreba probiotskih sojeva S. boulardii, L. reuteri and L. rhamnosus te simbiotički proizvodi koji sadrže barem jedan od ova tri soja može pomoći kod smanjenja intenziteta i trajanja proljeva.

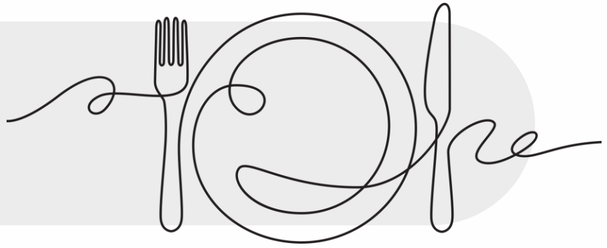
Bifidobacterium animalis subsp. lactis - kraće trajanjem proljeva, brže poboljšanjem konzistencije fecesa i promjene u crijevnom mikrobiomu.

Săsăran, M.O.; Mărginean, C.O.; Adumitrăchioaiei, H.; Meliț, L.E. Pathogen-Specific Benefits of Probiotic and Synbiotic Use in Childhood Acute Gastroenteritis: An Updated Review of the Literature. Nutrients. 2023

Chen, K., Jin, S., Ma, Y. et al. Adjudicative efficacy of Bifidobacterium animalis subsp. lactis BLa80 in treating acute diarrhea in children: a randomized, double-blinded, placebo-controlled study. Eur J Clin Nutr. 2024.



Djeca



- ne odgađati hranjenje
- dojenje nastaviti nepromijenjenom dinamikom
- nastavak prehrane onim mliječnim pripravkom koje je dijete konzumiralo, bez razrjeđivanja
- prelazak na formulu bez laktoze ili na bazi soje obično nije potrebno
- samo u rijetkim slučajevima opravdana je prehranu bez laktoze ili mlijeka

- promicanje raznovrsne djetetu poznate/uobičajene prehrane
- ne preporučuje se stroga dijeta
- nema dijetalnih ograničenja, osim izostavljanja rafiniranih šećera
- mliječne proizvode izbjegavati samo ako pogoršavaju simptome
- nema potrebe za većim ograničenjem masnoća
- ograničiti hiperosmolarne napitke s visokim udjelom šećera (pr.voćni i gazirani sokovi)

Guarino A et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. Journal of pediatric gastroenterology and nutrition 2014; 59:132-152.

Lo Vecchio et al. Comparison of Recommendations in Clinical Practice Guidelines for Acute Gastroenteritis in Children. J Pediatr Gastroenterol Nutr 2016; 63:226–235.

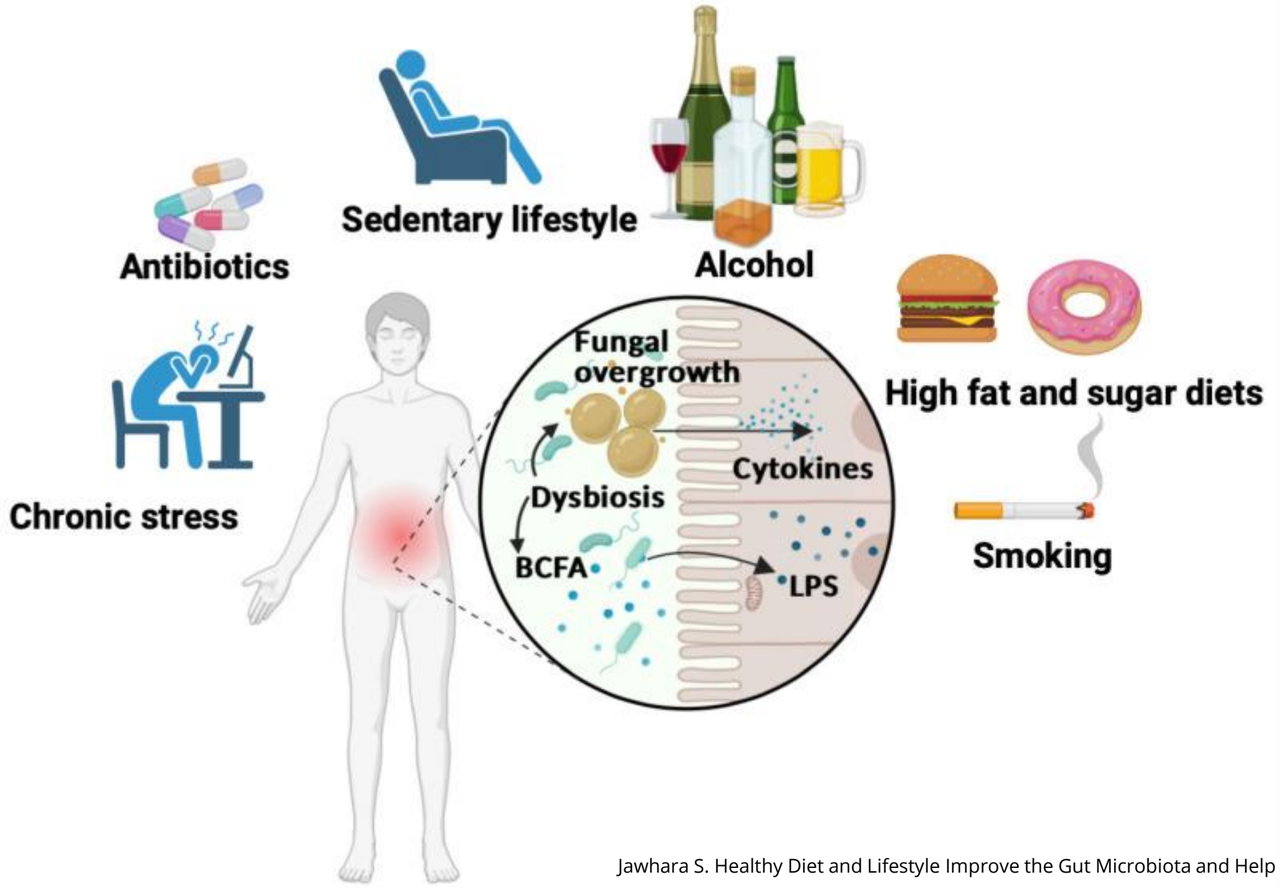
Kolaček S, Hosjak I, Niseteo T. Prehrana u općoj i kliničkoj pedijatriji. Zagreb: Medicinska naklada; 2017.

Virusne infekcije

Bakterijske infekcije

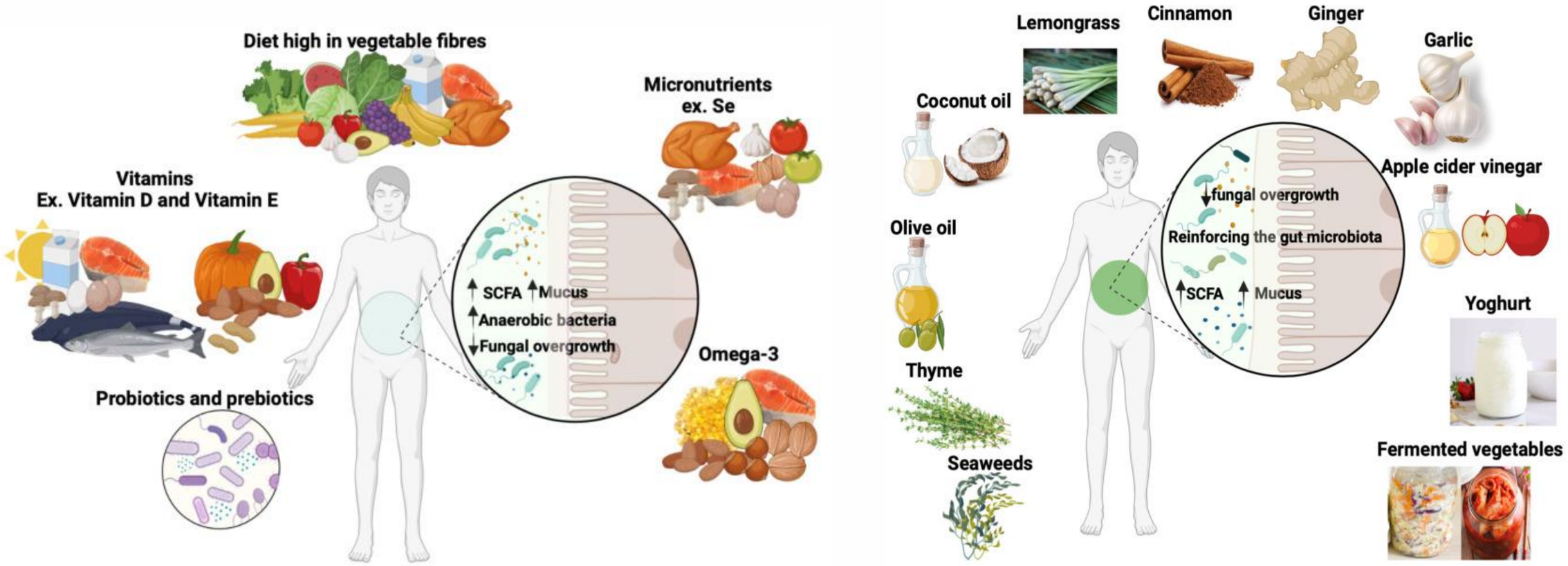
Gljivične infekcije

Čimbenici rizika



Jawhara S. Healthy Diet and Lifestyle Improve the Gut Microbiota and Help Combat Fungal Infection. Microorganisms. 2023.

Prehrana



Jawhara S. Healthy Diet and Lifestyle Improve the Gut Microbiota and Help Combat Fungal Infection. Microorganisms. 2023.

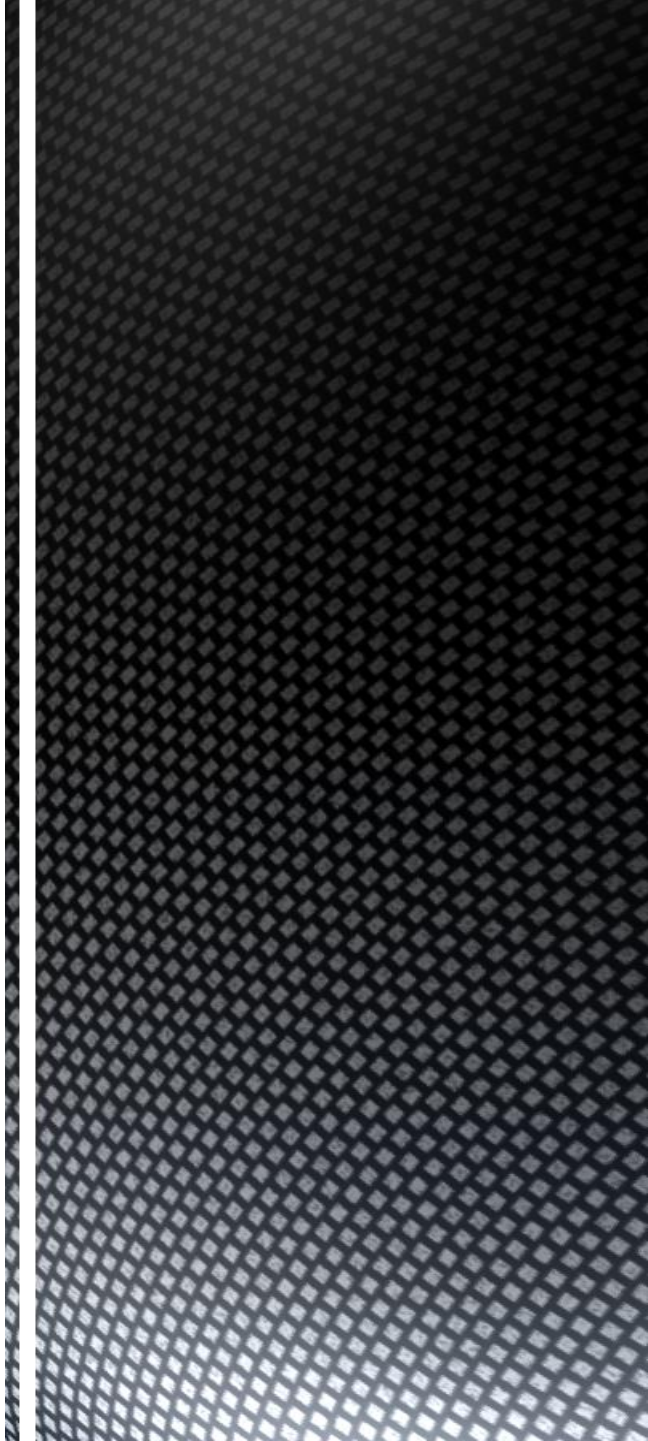
Infekcije probavnog sustava: novosti u epidemiologiji kliničkoj slici, dijagnostici, terapiji i prevenciji

Stručni simpozij

Zagreb, 17. svibnja 2024. g.

Uzimanje uzoraka, obrada i mikrobiološka dijagnostika probavnih infekcija – od smjernica do kliničke prakse

TOMISLAV MEŠTROVIĆ



Dijagnostika probavnih infekcija

- **Točna identifikacija** dobiva na značaju usporedno s povećanjem težine kliničke slike i epidemijskog potencijala
- **Prije započinjanja dijagnostike** u obzir treba uzeti kliničku prezentaciju bolesti, zdravstvene informacije, epidemiološke podatke i sociodemografske značajke pacijenta
- **Faze pretrage** – 1) predanalitička faza; 2) postavljanje indikacije; 3) uzimanje i transport uzorka; 4) analitička faza; 5) postanalitička faza; 6) izdavanje i interpretacija nalaza

Smjernice kao orijentir

- Vuković D, Antolović Požgain A, Roksandić Križan I, Ružman N, Zujić Atalić V, Bogdan M, Drenjančević D. ***Smjernice za mikrobiološku dijagnostiku infekcija probavnog sustava: smjernice za mikrobiološku dijagnostiku Hrvatskog društva za kliničku mikrobiologiju Hrvatskog liječničkog zbora.*** Zagreb: HLZ, Hrvatsko društvo za kliničku mikrobiologiju; 2021.

- Trenutno važeće smjernice

- Dostupne na stranicama **Hrvatskog društva za kliničku mikrobiologiju (HDKM)**

hdkm Hrvatsko društvo za kliničku mikrobiologiju Hrvatskog liječničkog zbora
Croatian Society of Clinical Microbiology of the Croatian Medical Association

Sve započinje s pravilno uzetim uzorkom

BJGP British Journal of General Practice

Br J Gen Pract. 2014 Nov; 64(628): e684–e693. PMCID: PMC4220220
Published online 2014 Oct 27. doi: 10.3399/bjgp14X682261 PMID: 25348992

Patients' perspectives on providing a stool sample to their GP: a qualitative study

Donna M Lecky, PhD, Project manager

Public Health England Primary Care Unit, Gloucester.

Meredith KD Hawking, MPH, Research assistant

Public Health England Primary Care Unit, Gloucester.

Cliodna AM McNulty, FRCPath, Head of Primary Care Unit and consultant microbiologist, on behalf of the ESBL steering group

Cliodna AM McNulty, Public Health England Primary Care Unit, Gloucester.

How this fits in

Stool specimen collection is needed to inform the management of many gastrointestinal diseases and infections, but returns by patients are generally <60%. Through interviews based on the theory of planned behaviour with patients who had and had not submitted stool specimens, it was found that personal attitudes, subjective norms, and perceived behavioural controls all influenced specimen return. Patients perceived that handling stools was dirty and embarrassing, and it was found that a lack of information about why patients were collecting the stool, how to do it, receptionist involvement, privacy during returning specimens, and fear of results were all barriers to collection. Stool specimen returns may be increased through greater explanation about the reason for collection by the GP, providing the patient with plastic gloves (or telling them where to get them), and giving the patient Public Health England's patient information leaflet on stool collection, which includes diagrams and opaque bags for return.

Uzorkovanje za istraživanje crijevnog mikrobioma

Article | Open access | Published: 07 July 2021

Fecal sample collection methods and time of day impact microbiome composition and short chain fatty acid concentrations

Jacquelyn Jones, Stacey N Reinke, Alishum Ali, Debra J Palmer & Claus T. Christophersen

Scientific Reports **11**, Article number: 13964 (2021) | Cite this article

Journal of the Formosan Medical Association

Volume 118, Issue 2, February 2019, Pages 545-555

open access

Review Article

Optimization of fecal sample processing for microbiome study — The journey from bathroom to bench

Wei-Kai Wu [a, b], Chieh-Chang Chen [c], Suraphan Panyod [b, d], Rou-An Chen [b], Ming-Shiang Wu [c, d], Lee-Yan Sheen [b], Shan-Chwen Chang [c, d]

› Res Rev J Microbiol Biotechnol. 2023 Mar;12(1):33-47. Epub 2023 Apr 3.

Accelerating Gut Microbiome Research with Robust Sample Collection

Zoe J Zreloff [1], Danielle Lange [1], Suzanne D Vernon [1], Martha R Carlin [1], Raul J Cano [1]

Postulati pravilnog uzorkovanja

- Uzorkovanje je optimalno provesti u inicijalna **72 sata od početka simptoma bolesti** → idealno čim prije

- U odraslih jedna stolica generalno dovoljna za detekciju većine bakterijskih patogena (drugi uzorak povećava osjetljivost za 20%) → **dodatni uzorci se moraju uzeti u različite dane**

- **Kod djece** se već u prvom uzorku stolice detektira 98% enteropatogenih bakterijskih uzročnika bolesti

Postulati pravilnog uzorkovanja

- **Kod virološke obrade** idealni uzorci stolice unutar 48 sati od nastanka simptoma → **najveća ekskrecija virusa**

- **Kod parazitološke obrade** tri uzorka stolice u razmaku od sedam dana (dokaz infekcije s *E. histolytica* i *G. lamblia* zahtijevaju i do šest uzoraka stolice); kod izolirane epizode proljeva ne treba ponavljati uzorke stolice

- **Ključan brzi transport do mikrobiološkog laboratorija!**

Postulati pravilnog uzorkovanja

- **Skladištenje za virološku obradu:** 2-3 tjedna na 4 °C
- U adekvatno zamrznutom uzorku **norovirus** je moguće detektirati praktički i <u>nakon jednog desetljeća</u>

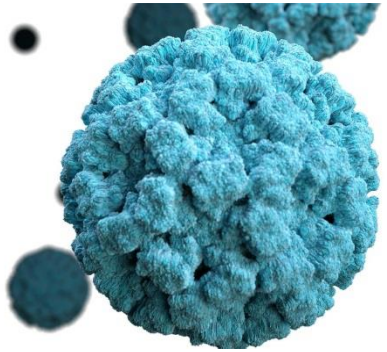
ELSEVIER

Journal of Virological Methods

Volume 267, May 2019, Pages 35-41

Impact of long-term storage of clinical samples collected from 1996 to 2017 on RT-PCR detection of norovirus

Jennifer L. Cannon [a], Marian Baker [b], Leslie Barclay [b], Jan Vinjé [b]



Postulati pravilnog uzorkovanja

- **Potrebna količina:** minimalno 5 ml proljevaste stolice ili 1-2 grama (veličine lješnjaka)
- Uzorak se smatra neadekvatnim ako u posudi ima ostatka dezinficijensa, sapuna ili deterdženta
- **Valja izbjegavati korištenje WC-papira** za uzimanje stolice zbog barijevih soli ⟶ inhibicija rasta pojedinih uzročnika
- Transport i obrada **u najkraćem mogućem roku** (po potrebi korištenje transportnog medija i transportnih sustava)

Vrijednost transportnih medija

J Microbiol Methods. 2018 Jun;149:53-54. doi: 10.1016/j.mimet.2018.05.001. Epub 2018 May 4.

Enhanced culture recovery of Campylobacter with modified Cary-Blair medium: A practical field experience.

Massip C[1], Guet-Revillet H[1], Grare M[1], Sommet A[2], Dubois D[3].

Diagn Microbiol Infect Dis. 2018 Dec 11. pii: S0732-8893(18)30675-8. doi: 10.1016/j.diagmicrobio.2018.11.020. [Epub ahead of print]

Evaluating the preservation and isolation of stool pathogens using the COPAN FecalSwab™ Transport System and Walk-Away Specimen Processor.

Goneau LW[1], Mazzulli A[2], Trimi X[2], Cabrera A[2], Lo P[2], Mazzulli T[2].

Evaluation of the FecalSwab for Stool Specimen Storage and Molecular Detection of Enteropathogens on the BD Max System

Melissa Richard-Greenblatt,[a,b] Candy Rutherford,[b] Kathy Luinstra,[b] Ana María Cárdenas,[c,d] Xiaoli Lilly Pang,[e,f] Padman Jayaratne,[a,b] Marek Smieja[a,b]

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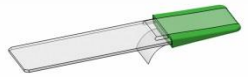
Drugi tipovi uzoraka

- **Rektalni bris** → iznimno kad nema mogućnosti uzorkovanja stolice (2,5 cm iza analnog sfinktera)

- **Perianalni otisak** → metoda po Grahamu



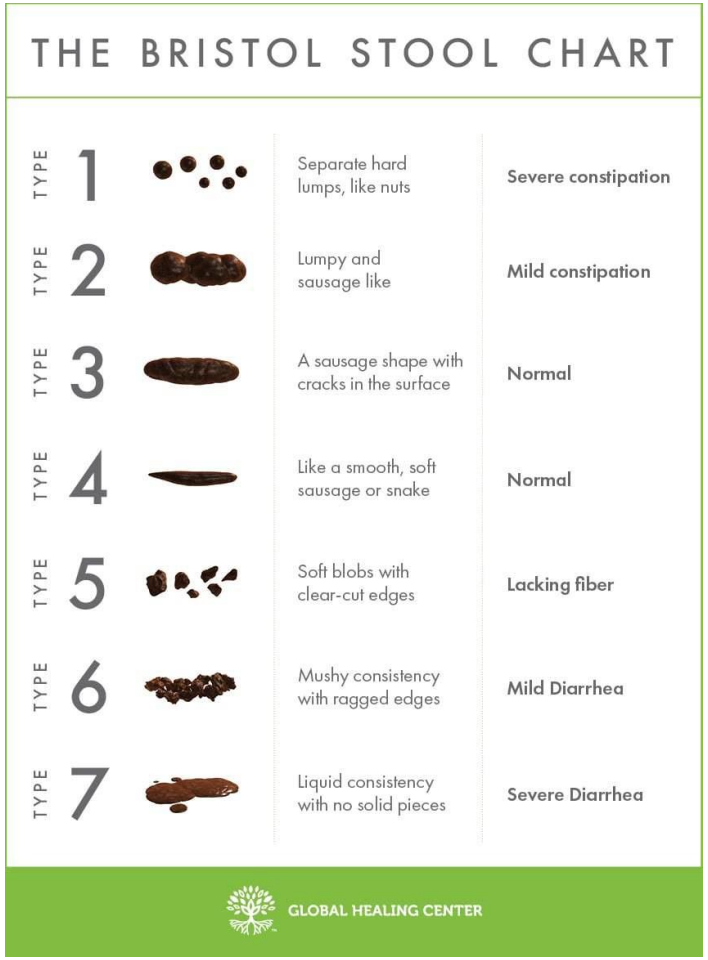
- **Sadržaj duodenuma, kolostome ili ileostome**
  → koristi se sterilni spremnik s čepom na navoj

Kriteriji za odbacivanje uzoraka

- Uzorak u transportnom mediju **stariji od 3 dana na 4°C ili više od 24 sata na 25°C**
- Odbaciti rutinsko testiranje pacijenata koji je **hospitaliziran više od 3 dana** (osim u slučaju HIV-a ili bolničke infekcije)
- Prepunjena posudica, izrazito čvrste stolice zbog otežane inokulacije, stolice s barijem, suhi brisevi

Koraci prije mikrobiološke dijagnostike

- **Makroskopski pregled** svakog uzorka koji dolazi u laboratorij (količina, priustnost krvi, sluzi, gnoja)
- Konzistencija uzorka stolice procjenjuje sukladno **Bristol Stool Scale** → **7 tipova** (tip 6 i 7 predstavljaju proljevastu stolicu)
- Detekcija **fekalnih leukocita** i **laktoferina** u stolici → zasad ograničene dijagnostičke vrijednosti



Nasađivanje uzoraka

- **Štapićem/pipetom** nanijeti dio/kap fekalnog materijala na 1/3 ili 1/4 površine hranilišta, a zatim raširiti sterilnom ezom

- Alternativno se mogu rabiti automatizirani sustavi za nasađivanje (**plate streaker**)

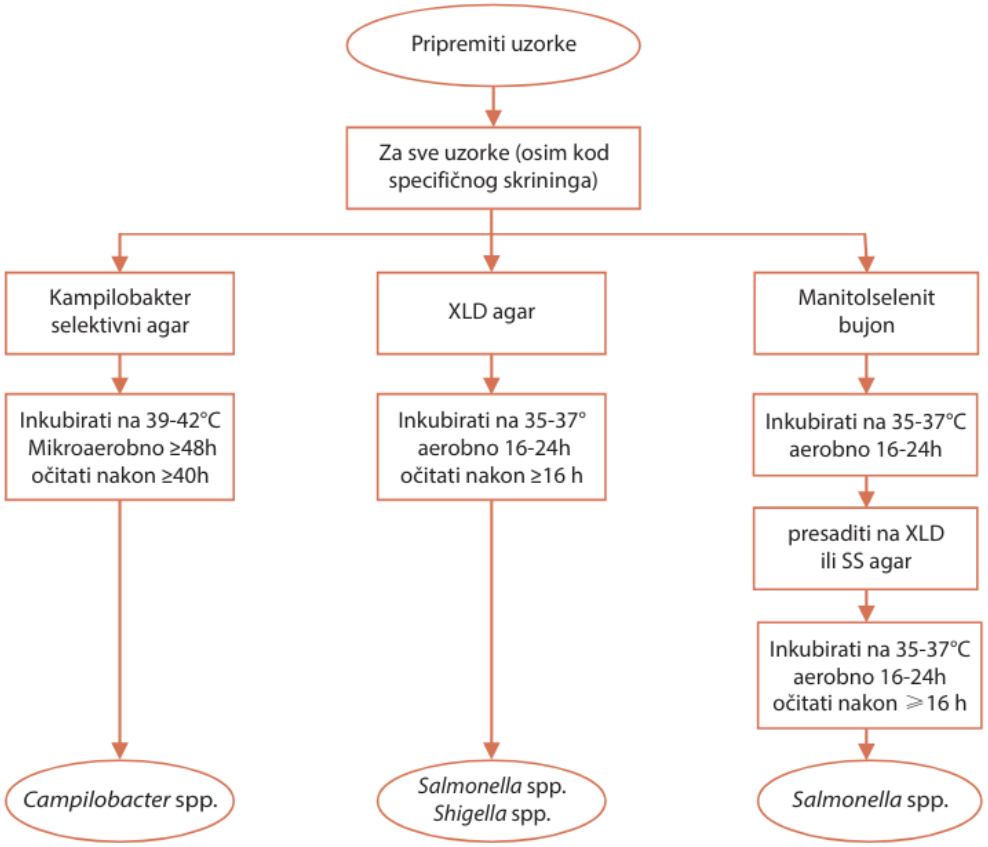
- Ako se koristi **tekuća podloga za obogaćivanje**, u nju se nasađuje uzorak veličine graška ili par kapi fekalnog materijala → nakon inkubacije se subkultivira na odgovarajuće podloge

Bakteriološka dijagnostička obrada

- **Osnovna bakteriološka obrada** predstavlja **minimalni standard** za najčešće uzročnike (rutinska dijagnostika) → *Salmonella* spp., *Shigella* spp. i *Campylobacter* spp.

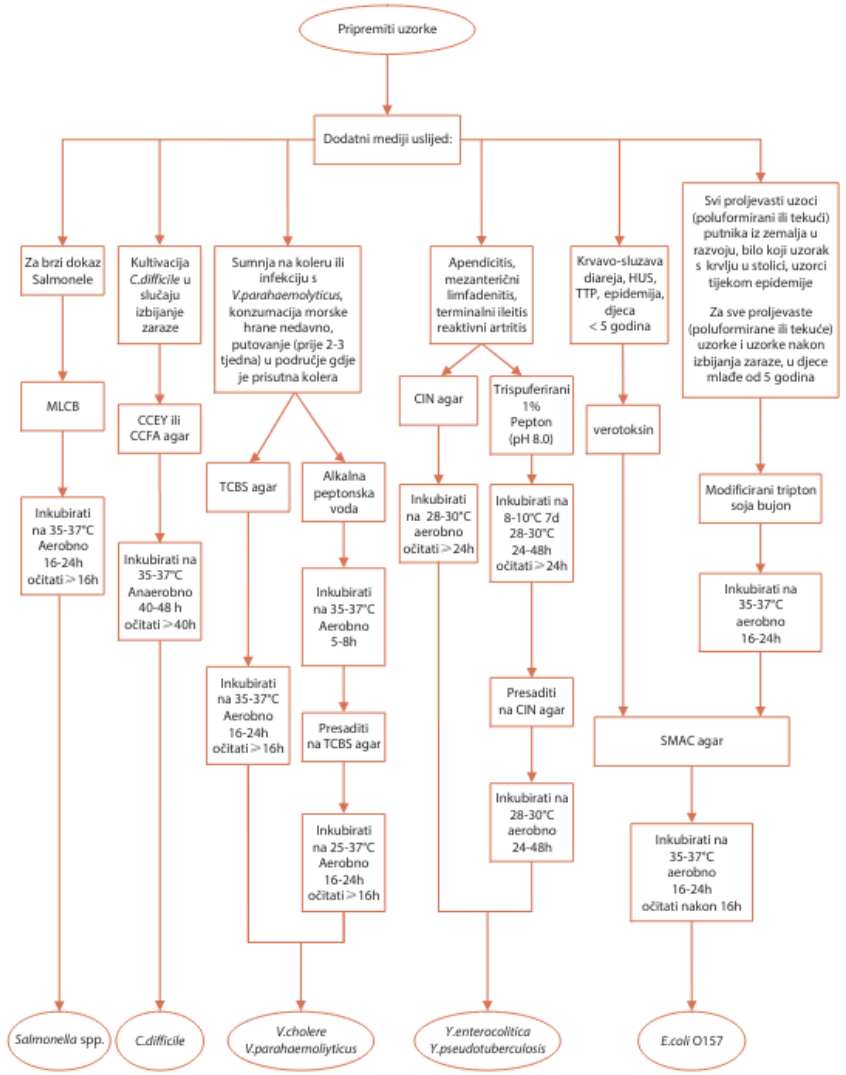
- **Dodatne pretrage** na **zahtjev kliničara ili mikrobiologa** → EHEC (krvavo-sluzavi proljev, HUS, TTP, putnički proljev u djece < 5 godina); *Vibrio* spp. (profuzni proljevi poput rižine vode); *Yersinia* spp. (perzistentni abdominalni bolovi); *Clostridioides difficile* (postantibiotski, bolnički i perzistentni proljevi)

Rutinska dijagnostika bakterijskih probavnih infekcija



Izvor: Vuković D, Antolović Požgain A, Roksandić Križan I, Ružman N, Zujić Atalić V, Bogdan M, Drenjančević D. *Smjernice za mikrobiološku dijagnostiku infekcija probavnog sustava: smjernice za mikrobiološku dijagnostiku Hrvatskog društva za kliničku mikrobiologiju Hrvatskog liječničkog zbora.* Zagreb: HLZ, Hrvatsko društvo za kliničku mikrobiologiju; 2021.

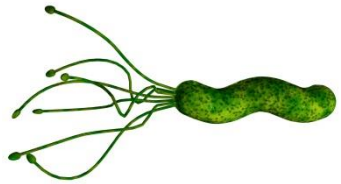
Dodatna dijagnostika bakterijskih probavnih infekcija



Izvor: Vuković D, Antolović Požgain A, Roksandić Križan I, Ružman N, Zujić Atalić V, Bogdan M, Drenjančević D. *Smjernice za mikrobiološku dijagnostiku infekcija probavnog sustava: smjernice za mikrobiološku dijagnostiku Hrvatskog društva za kliničku mikrobiologiju Hrvatskog liječničkog zbora.* Zagreb: HLZ, Hrvatsko društvo za kliničku mikrobiologiju; 2021.

Posebni bakterijski uzročnici

- Za ***Helicobacter pylori*** dostupna paleta dijagnostičkih opcija
- **Invazivni postupci:** kultivacija bioptata na neselektivna i selektivna hranilišta, antibiogram prema AMZH i EUCAST-u
- **Neinvazivni postupci:** detekcija antigena u stolici, urea izdisajni test, detekcija protutijela u serumu



Dijagnostika virusnih probavnih infekcija

- **Osnovne pretrage:** rotavirus i adenovirus (dokaz antigena EIA/ICT testovima)
- **Proširene pretrage:** norovirus i astrovirus (real time RT-PCR) sukladno epidemiološkoj i kliničkoj indikaciji
- Dokaz serumskih protutijela neadekvatan za dijagnostiku akutnih stanja
- **Epidemijske izolate** potvrditi u javnozdravstvenom laboratoriju i/ili Nacionalnom referentnom centru te arhivirati

Dijagnostika parazitarnih probavnih infekcija

- **Minimalne metode** koje laboratorij mora moći izvesti: nativni preparat i MIFC
- Druge metode koncentracije: sedimentacija, flotacija
- **Specifična bojenja** za izradu trajnih preparata te identifikaciju oocista intestinalnih kokcidija *Cryptosporidium* spp., *Cystoisospora belli* i *Cyclospora* spp.

Dijagnostika trovanja hranom

- Uzročnici alimentarne intoksikacije i njihovi toksini dokazuju se **prvenstveno u uzorcima hrane!**

- Dokazivanje uzročnika u bolesničkim uzorcima nije standardizirano – upitna vrijednost mikrobiološkog nalaza

- U nadležnosti **specijaliziranih laboratorija** akreditiranih za analizu hrane

Izdavanje nalaza

- Preporučljivo izdati napomenu **je li ili nije izoliran traženi mikroorganizam**; usmeno obavještavanje

- **Izdavanje antibiograma samo u posebnim situacijama**, te na zahtjev infektologa ili drugog nadležnog liječnika

- U slučaju neadkevatnog uzorka kad ponovno uzimanje nije moguće, a ordinarijus inzistira da se uzorak obradi, u nalazu obavezno izdati napomenu o tome

Zaključak

- Za pravilno uzorkovanje važna **suradnja** liječnika (i drugog medicinskog osoblja) **s mikrobiološkim laboratorijem**
- Slijediti upute/smjernice o **pravilnom odabiru, uzimanju i transportu te obradi** uzoraka za dijagnostiku probavnih bolesti
- Procjena adekvatnosti uzoraka prije mikrobiološke obrade
- **Odabir pretraga ovisno o širini dijagnostičke obrade** → ponekad potreba za spec. laboratorijima i epidemiološkim nadzorom

Simpozij: *„Infekcije probavnog sustava: novosti u epidemiologiji, kliničkoj slici, dijagnostici, terapiji i prevenciji”* , Zagreb 17. svibanj 2024., Hotel Dubrovnik

Kada upotrijebiti i kako interpretirati rezultate molekularnog panela u dijagnostici gastroenteritisa?

Prof. dr. sc. Jasmina Vraneš, prim. dr. med.
Zavod za javno zdravstvo “Dr. Andrija Štampar” &
Medicinski fakultet Sveučilišta u Zagrebu
jasmna.vranes@stampar.hr

Godišnji trošak 14 milijardi US dolara!

Diarrheal Diseases in the United States

Infectious disease mortality in the United States has generally decreased[a]

- However, diarrheal disease mortality increased from 1980 to 2014

About 179 million infections/year[b]

- Resulting in ~600,000 hospitalizations[b]

From 1999 to 2007, deaths increased from ~7000 to > 17,000 annually[c]

a. El Bcheraoui C, et al. JAMA. 2018;319:1248-1260; b. Hall AJ, et al. Emerg Infect Dis. 2011;17:1381-1388. c. CDC Division of News and Electronic Media. News release. March 14, 2012. Accessed November 24, 2021. https://www.cdc.gov/media/releases/2012/p0314_gastroenteritis.html

Causes of Acute Diarrheal Disease

Bacteria

- *Campylobacter* spp[a]
- Diarrheagenic *Escherichia coli*[a]
- *Salmonella* spp[a]
- *Vibrio* spp[a]
- *Plesiomonas* spp[b]
- *Clostridioides* difficile[a]
- *Yersinia* spp[a]

Viruses

- Adenovirus[a]
- Astrovirus[a]
- Norovirus[b]
- Rotavirus[a]
- Sapovirus[b]

Parasites

- *Cryptosporidium* spp[a]
- *Cyclospora* spp[a]
- *Entamoeba histolytica*[b]

"A multiplex panel can allow clinicians to quickly make a diagnosis without having to resort to time consuming and complex testing algorithms" - Ferric C Fang, MD

a. El Bcheraoui C, et al. JAMA. 2018;319:1248-1260; b. Cybulski RJ Jr, et al. Clin Infect Dis. 2018;67:1688-1696.

Diarrheal Pathogens Have Similar Presentations

	Campylobacter, *Salmonella*, and *Shigella* (n = 128)	Diarrheagenic *E coli* (n = 180)	*P* Value
Mean number of symptoms per patient (range)	3.7 (0-8)	3 (0-8)	NS
Patients with abdominal pain, n (%)	**93 (71)**	**128 (67)**	**NS**
Patients with nausea, n (%)	**55 (42)**	**55 (29)**	**NS**
Patients with diarrhea, n (%)	121 (92)	163 (85)	NS
Patients with watery diarrhea, n (%)	**69 (53)**	**71 (37)**	**NS**
Patients with blood in stool, n (%)	**22 (17)**	**25 (13)**	**NS**
Patients with fever, n (%)	27/126 (21)	13/172 (8)	.0005
Median duration of symptoms at presentation, days (range)	13.2 (1-240)	26 (1-365)	.0139

NS, not significant.

Cybulski RJ Jr, et al. Clin Infect Dis. 2018;67:1688-1696.

Challenges With Traditional Diagnostic Methods
Expert Experience

- Specific culture media required for some pathogens
- Some pathogens do not survive well in transport media
- Time-consuming culture and organism identification
- Molecular/immunologic assays to detect toxins may be needed
- Certain bacteria have contraindications for antibiotic treatment
- Viral and parasitic organisms cannot be cultured from stool samples using routine clinical methods

Chang LJ, et al. BMJ Open Gasterol. 2021;8:e000553; Connor BA, Am J Gastroenterol. 2020;115:1553-1555; Axelrad JE, J Clin Microbiol. 2019;57:e01775-18.

Multipleks PCR u odnosu na konvencionalnu dijagnostiku rezultira značajnim skraćenjem vremena do rezultata (TAT)

Impact of Multiplex PCR Testing in Patients With Acute Gastroenteritis
Shorter Turnaround Times

	2016 Stool Culture (n = 83)	2017 Multiplex PCR (n = 496)	*P* Value
Median time collection to first report (hours)	47	18	< .0001
Median time collection to antimicrobials (hours)	72	26	< .0001

Cybulski RJ Jr, et al. Clin Infect Dis. 2018;67:1688-1696.

Multiplex PCR May Reduce Unnecessary Diagnostic Testing and Treatment

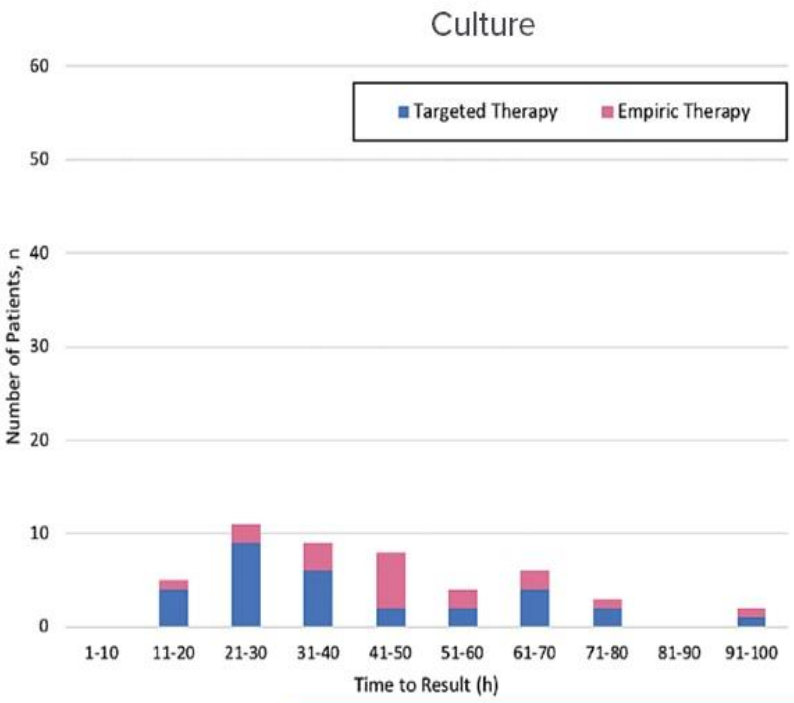
Study findings with the use of GI multiplex PCR (vs conventional methods):

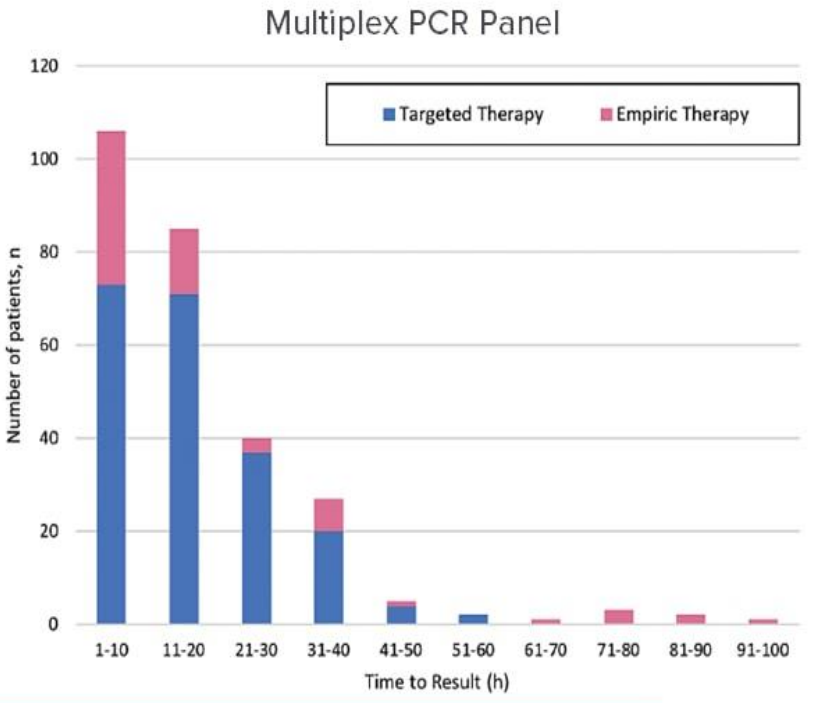
Fewer:

- Additional stool tests[a]
- Days on antibiotics[a,b]
- Imaging studies[a,b]
- Endoscopies[b]

a. Beal SG, et al. J Clin Microbiol. 2018;56:e01457-17; b. Axelrad JE, et al. J Clin Microbiol. 2019;57:e01775-18.

Multiplex PCR Facilitates Targeted Therapy





Rapid and targeted antimicrobial therapy were greater with multiplex PCR Panel

Cybulski R, et al. Clin Infect Dis. 2018;67:1688-1696.

Nedostatci multipleks PCR-a

- Cijena **POC** (engl. *point of care*) PCR testa po uzorku je vrlo visoka (za jeftinije multipleksiranje neophodan molekularni lab i ekspertiza).
- Neophodna je refleksna kultivacija kod detekcije salmonela, šigela, kampilobaktera i STEC-a.
- Ne razlikuje mrtve od živih patogena.
- PCR je vrlo osjetljiv pa se detektiraju i patogeni koji su u vrlo maloj količini prisutni u stolici, te nepotpune virusne čestice.
- Često se detektira dva i više patogena pa interpretacija nalaza vrlo važna!

Zaključak

- *Liječiti pacijenta a ne nalaz!* Refleksna kultivacija kod upotrebe multipleks PCR testa (*Salmonella*, *Shigella*, *Campylobacter* i *E.coli*).

- Indikacije ustanove (NZJZ AŠ) za **multipleks PCR**:
  - djeca do pet godina s jače izraženim simptomima te
  - imunokompromitirane osobe;
  - krv i sluz u stolici, i
  - dijareja u trajanju > 7 dana;
  - te epidemiološka indikacija, tj. mogućnost širenja (epidemija u kolektivu, putnici/migranti).

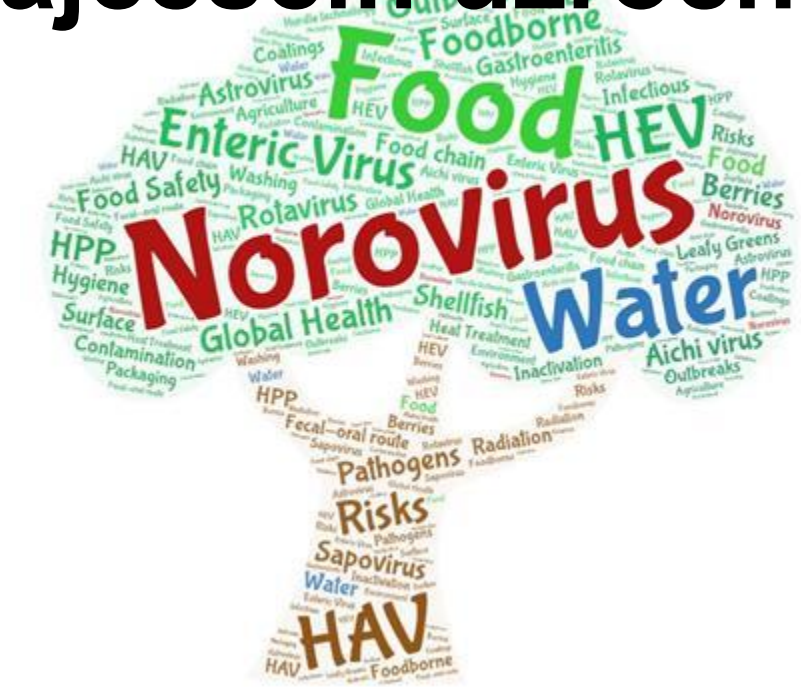
- TAT značajno skraćen s tri dana na jedan dan, a izbjegnuta potreba za ponovnim uzorkovanjem te endoskopskim i drugim pretragama.

- Izbjegnuto nepotrebno davanje antibiotika, u slučaju potrebe daju se ciljano.

Nastavni zavod za javno zdravstvo „Dr. Andrija Štampar”

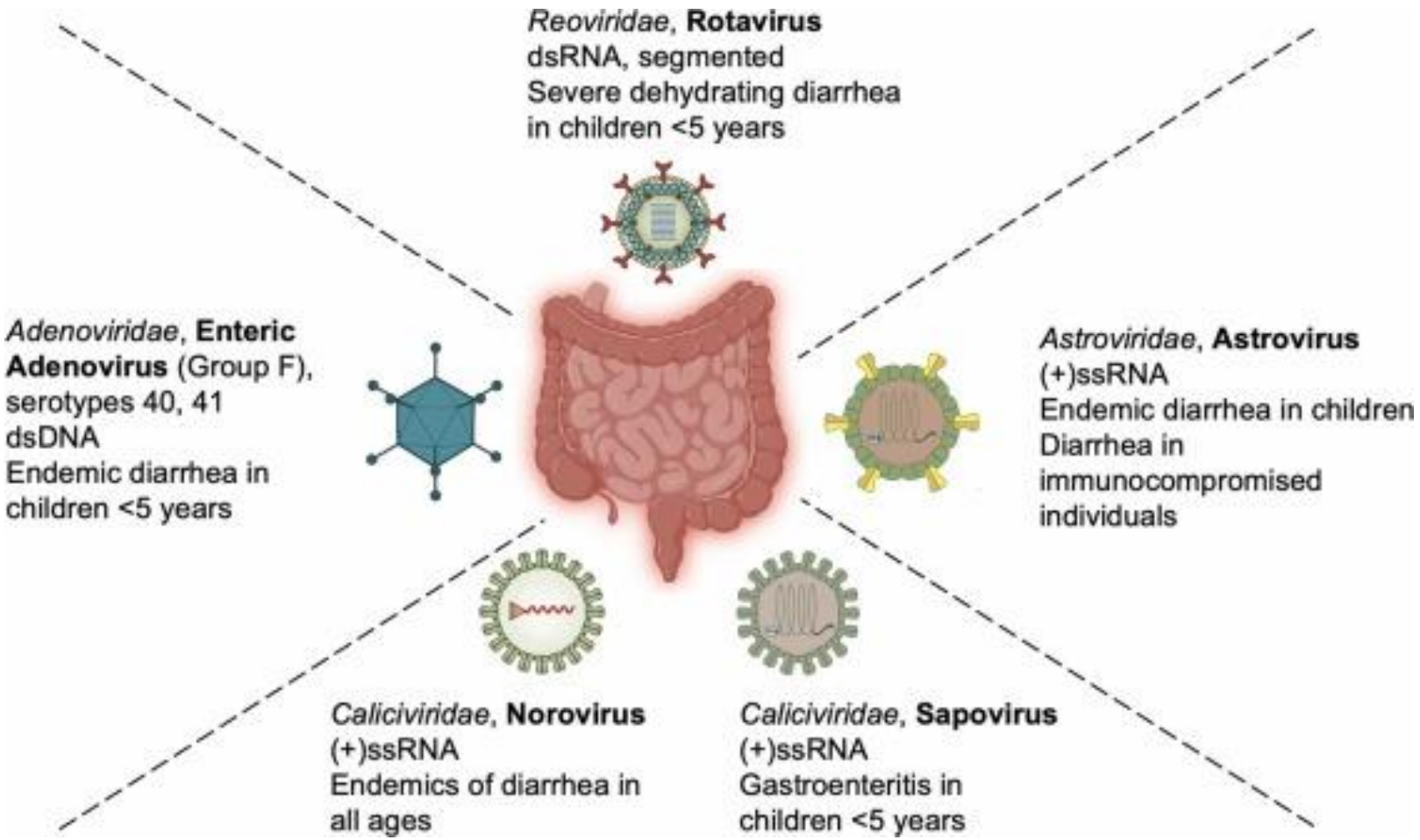
SURADNICI: prof. dr. sc. Sunčanica Ljubin Sternak, prim. mr. sc. Tatjana Marijan, Odjel za molekularnu mikrobiologiju & dr. Nada Pražić i dr. Ružica Cipriš, Odjel za dijagnostiku infekcija probavnog sustava

Virusne infekcije probavnog sustava-pregled najčešćih uzročnika

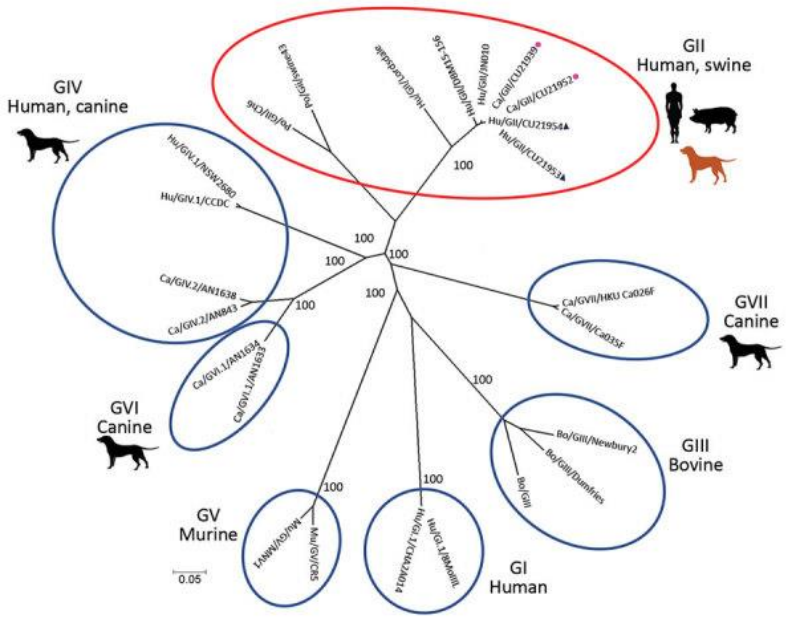


doc. dr. sc. Irena Tabain, dr. med.
RC MZ za virološku dijagnostiku infekcija dišnog i probavnog sustava
Hrvatski zavod za javno zdravstvo

Najznačajniji uzročnici



Norovirus-Epidemiologija



Norovirus klasifikacija

- **mala infektivna doza (svega 10-100 virusnih čestica)**
- **30x10^6** virusnih čestica/ povraćenom sadržaju
- **10^6** virusnih čestica/g stolice
- relativna postojanost u okolišu
- preživljavaju grijanje do 60°C
- fekalno-oralni put širenja
- zadržavaju se u kamenicama kuhanim na pari
- Hrana iz uzgoja, šunka, dagnje, površine (kvake, daske za rezanje)-7-56 dana
- Inaktivacija UV-om

Norovirus
- prijenos, dijagnostika, liječenje

Metode detekcije:

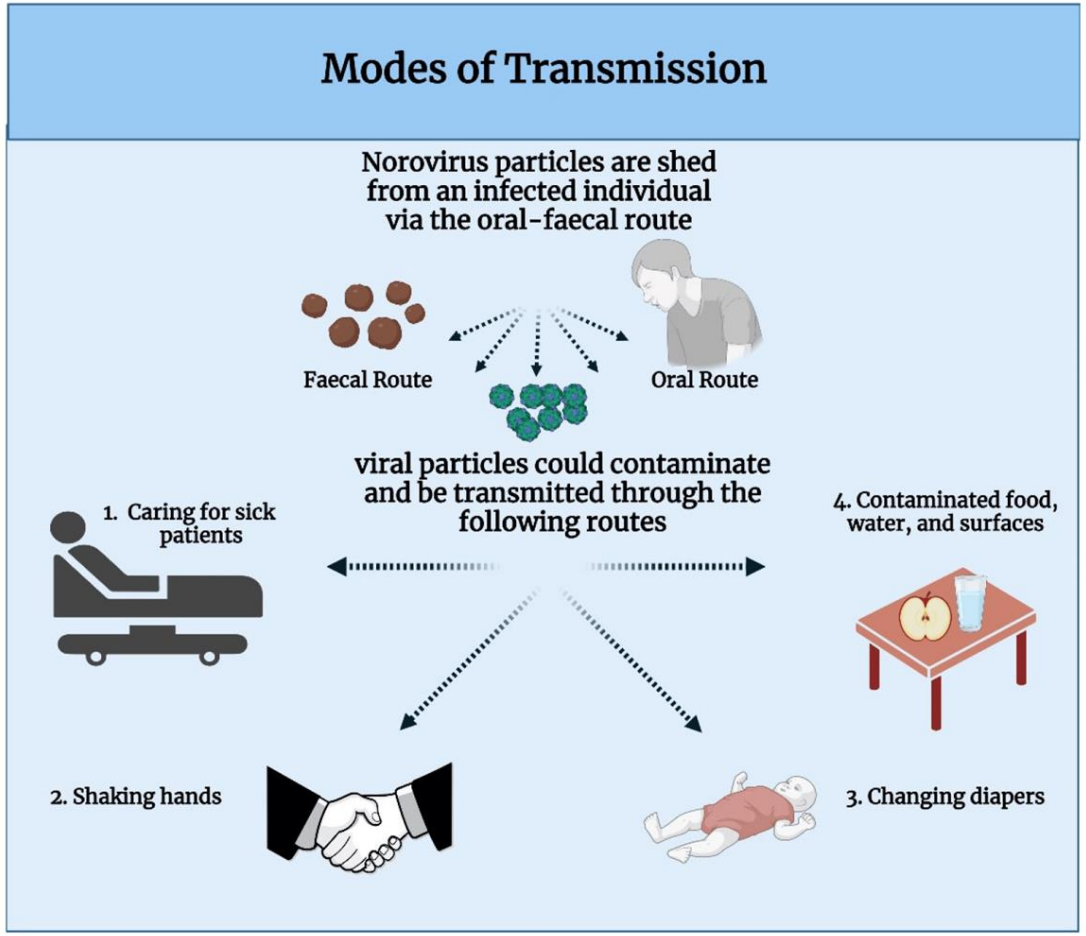
- EIA
- imunokromatografski testovi
- RT-PCR

Detekcija u hrani:

standardizirana metoda (norma: 15216:2013)

Terapija:

- simptomatska



Rotavirus

- Primarno: fekalno-oralni put
- kontaminirani predmeti
- infektivna doza: 1-10 (100) virusnih čestica
- 10^{11} virusnih čestica/stolici
- izlučivanje oko 4 dana (>30 dana)
- Inkubacija: 1-2 (4) dana

Fever

Severe watery diarrhoea

Vomiting

Detekcija, liječenje i prevencija

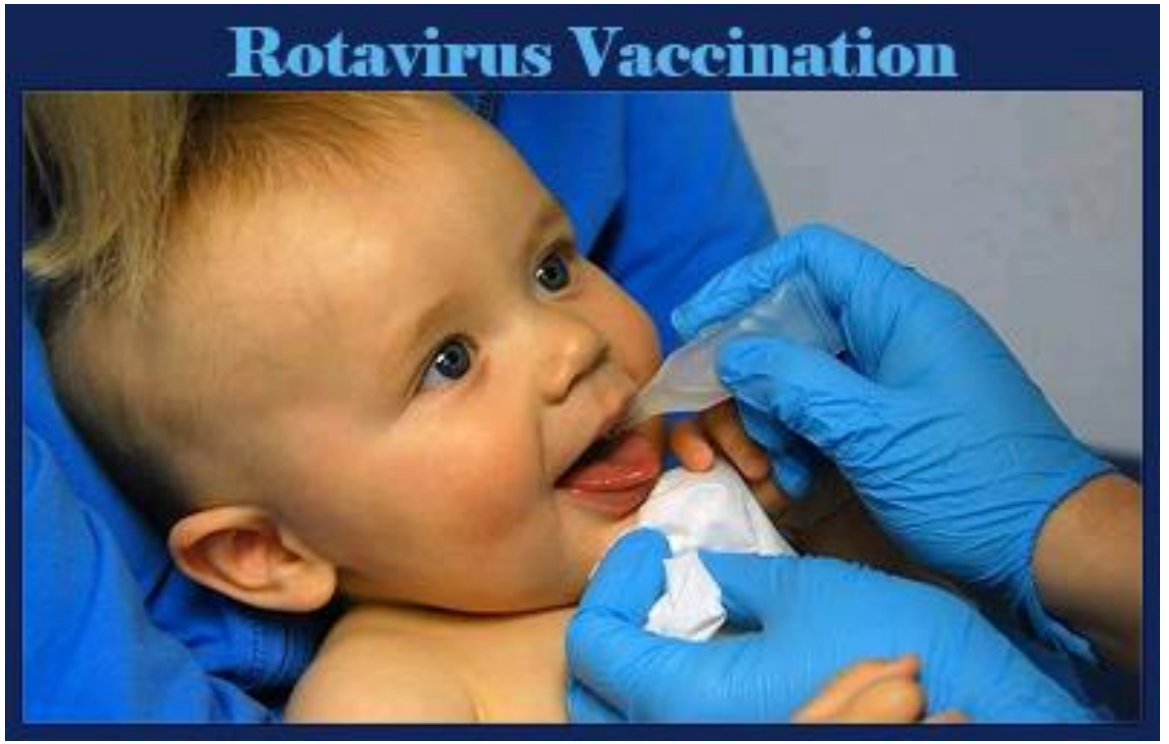
Laboratorijska dijagnostika:

- EIA
- IK
- RT-PCR

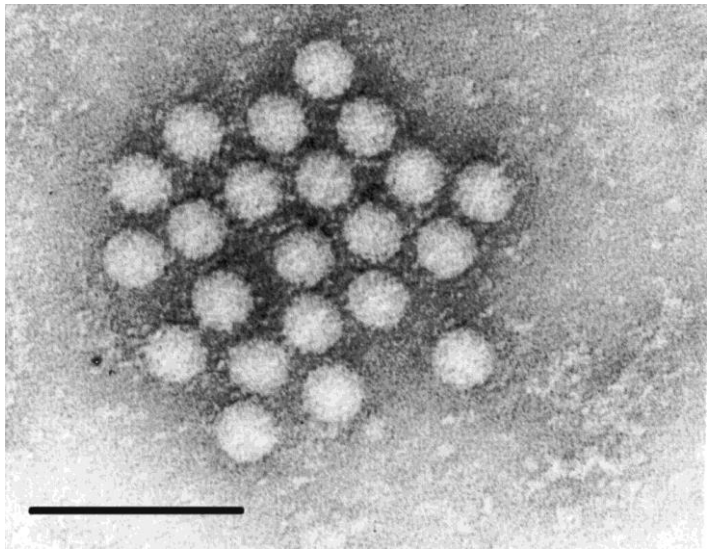
Terapija:

- Simptomatska

Prevencija: cijepljenje



Astroviridae



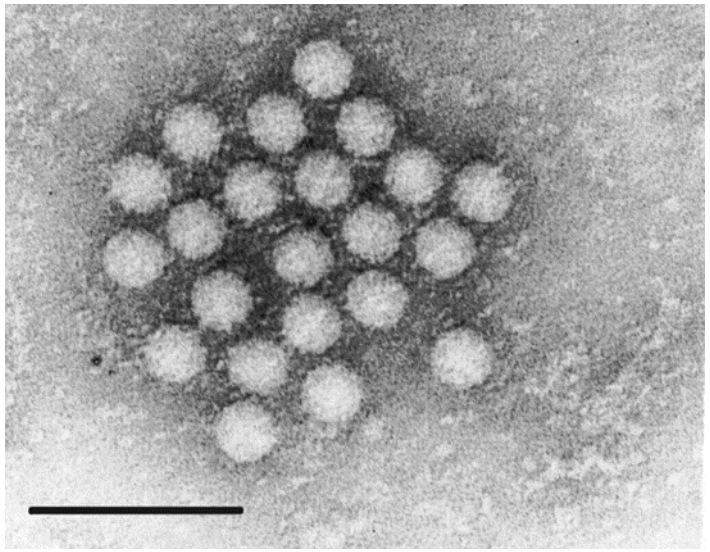
Rod

- *Mamastrovirus*

Karakteristike:

- 4°C/ 60-90 dana
- preživljava u vodi za piće, slatkoj i slanoj vodi, ali kloriranje smanjuje vijabilnost

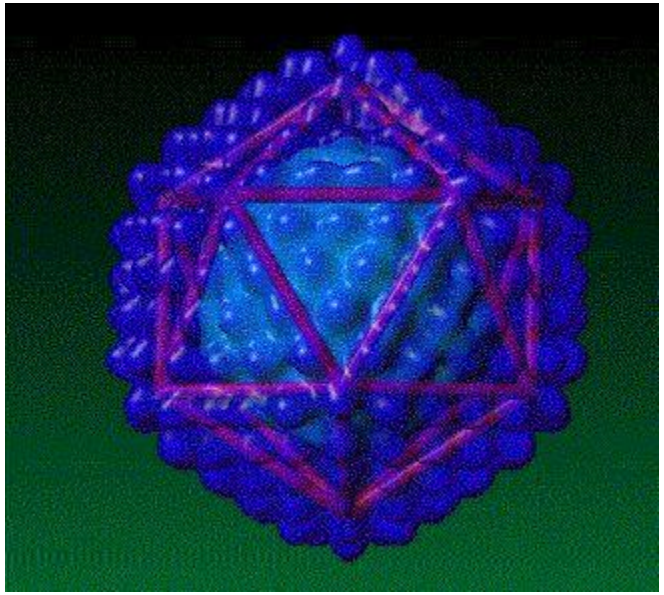
Astrovirusi



➢4°C/ 60-90 dana

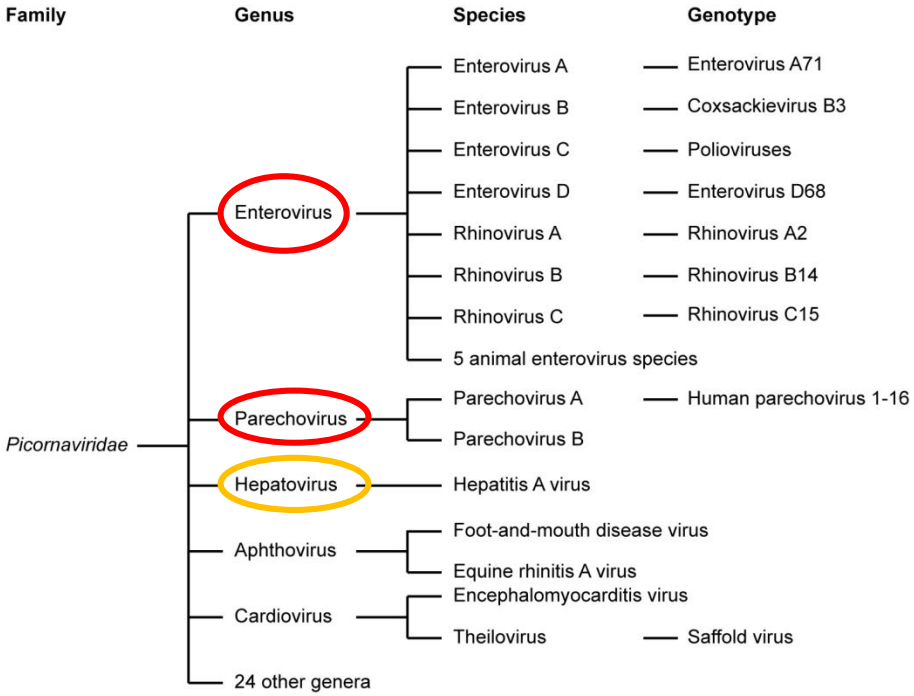
- Dojenčad i mala djeca (<7 godina)-najčešće
- Inkubacija: 1-4 dana
- mučnina, povraćanje, grčevi u trbuhu i proljev
- Praćeno temperaturom i glavoboljom

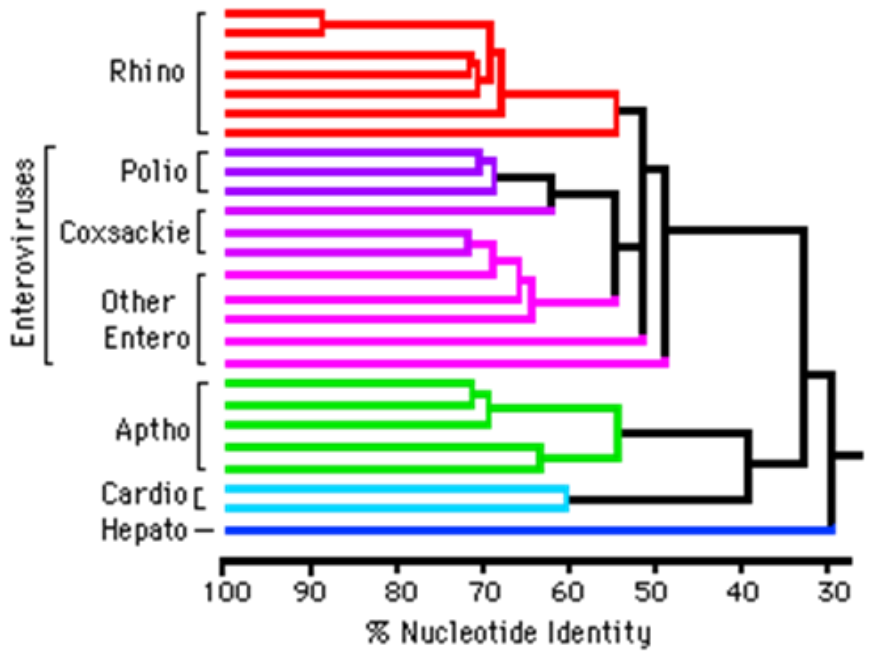
Adenovirusi



- *Mastadenovirus*
- Humani adv tipovi 40 i 41
- U stanicama crijeva
- prisutni u stolici
- 5-15% virusnih gastroenteritisa u djece u prvim godinama života
- Dg. Imunokromatografski testovi, EIA, PCR

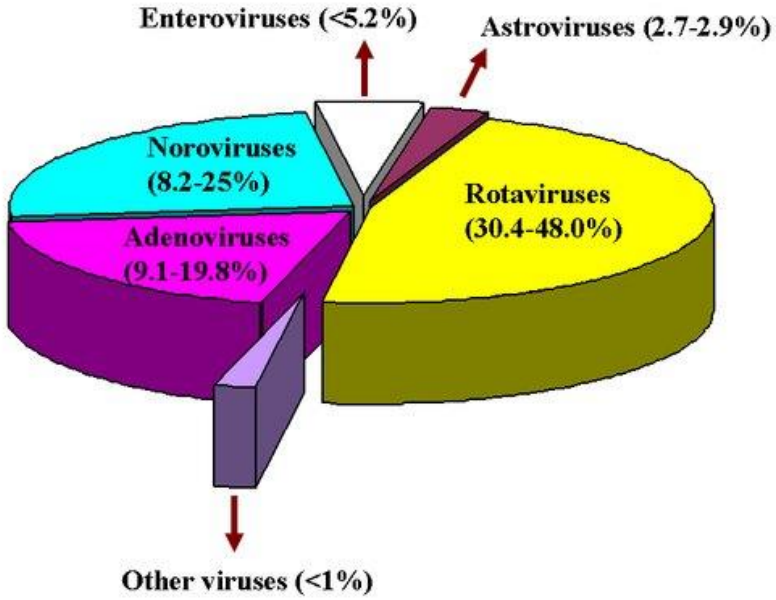
PICORNAVIRIDAE





Fizikalno-kemijske karakteristike enterovirusi i parechovirusi

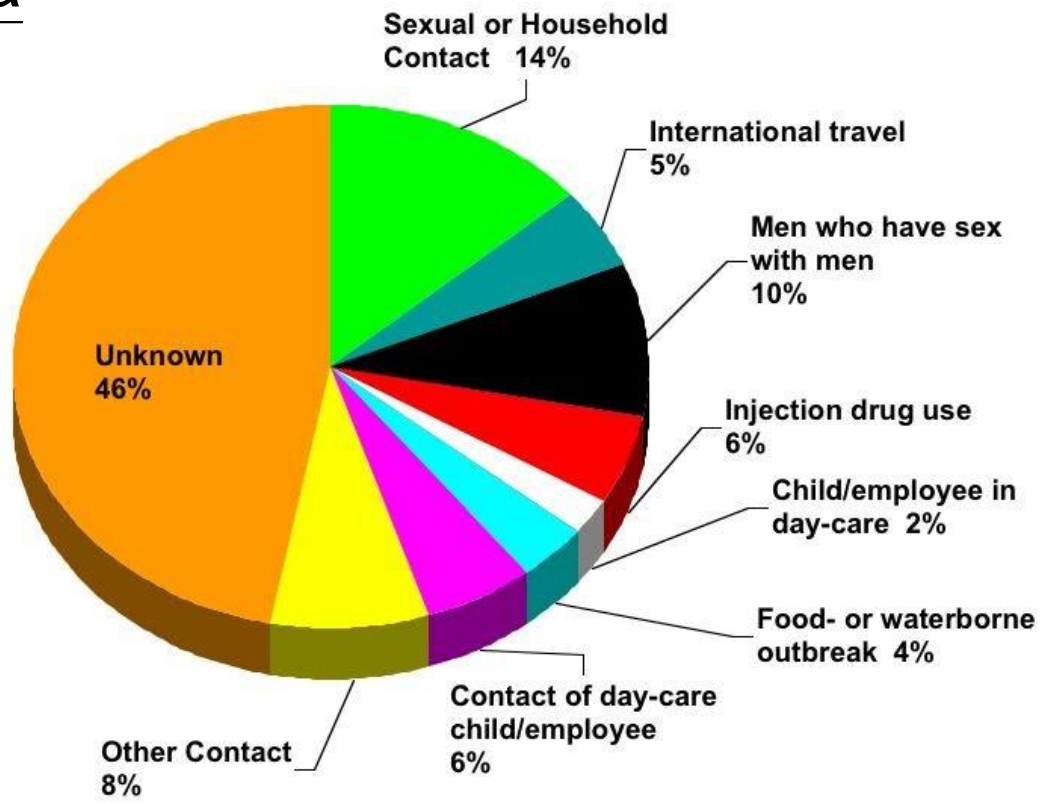
- Otporni na: eter, kloroform, 70% alkohol, ionske detergente, pH 3-9 (želudac!)
- Osjetljivi na: UV i isušivanje, natrij-hipoklorit, formaldehid, beta-propionolakton, zagrijavanje
- Tjednima +4°C
- godinama se mogu čuvati na -20˚C
- Tradicionalno: prijenos vodom



Uzročnici gastroenteritisa (Tsong-Ming L, et al. Open Infectious Diseases Journal, 2009;3:37-43)

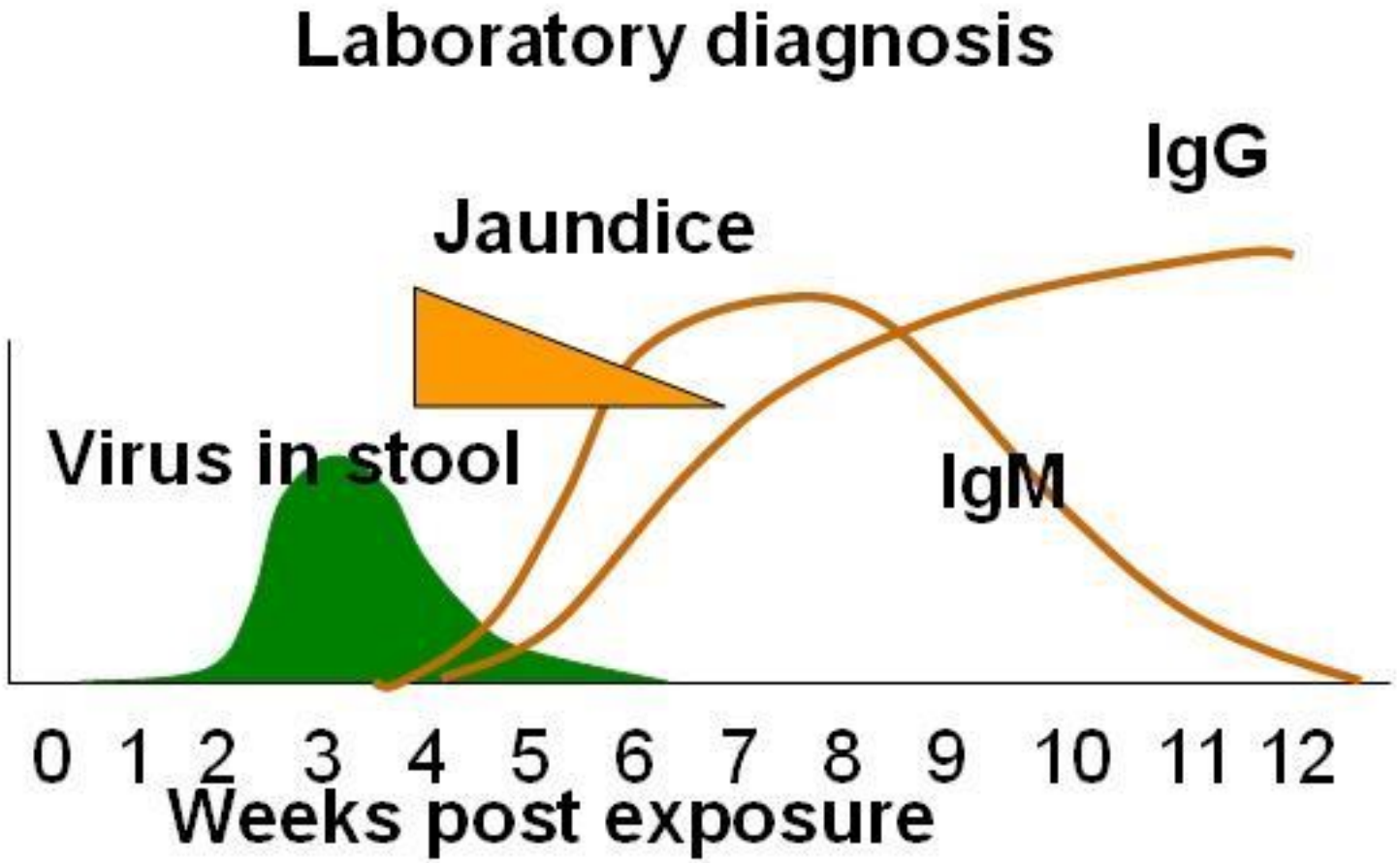
Virus hepatitisa A - epidemiologija

- **10-100** virusnih čestica
- fekalno-oralnim putem
  - kontaminirana voda, hrana (školjke - dagnje, kamenice)
- bliski osobni kontakt s oboljelom osobom
- kontakt sa zaraženom krvi (vrlo rijetko)



http://www.cdc.gov/ncidod/diseases/hepatitis/index.htm

HAV u stolici prije simptoma



U zaključku

- najvažnije su preventivne mjere
- bolji sustav praćenja
- na vrijeme detektirali oboljeli
- kontrola širenja virusa/bolesti
- metode molekularne epidemiologije

Mini simpozij A&B: *„Infekcije probavnog sustava: novosti u epidemiologiji, kliničkoj slici, dijagnostici, terapiji i prevenciji”*, Zagreb 17. svibanj 2024., Hotel Dubrovnik

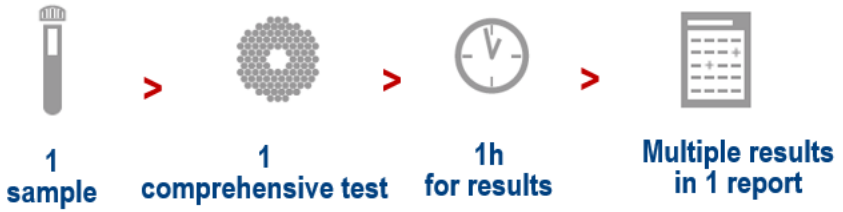
Usporedba konvencionalnih dijagnostičkih metoda i BioFire FilmArray gastro-intestinalnog (GI) panela

Prof. dr. sc. Jasmina Vraneš, prim. dr. med.
Zavod za javno zdravstvo “Dr. Andrija Štampar” &
Medicinski fakultet Sveučilišta u Zagrebu
jasmna.vranes@stampar.hr

Prednosti sindromskog testiranja

SYNDROMIC TESTING

A symptom-driven broad grouping of probable pathogens and mechanisms of resistance into one, rapid test that **maximizes the chance of getting the right therapy in a clinically relevant timeframe.**

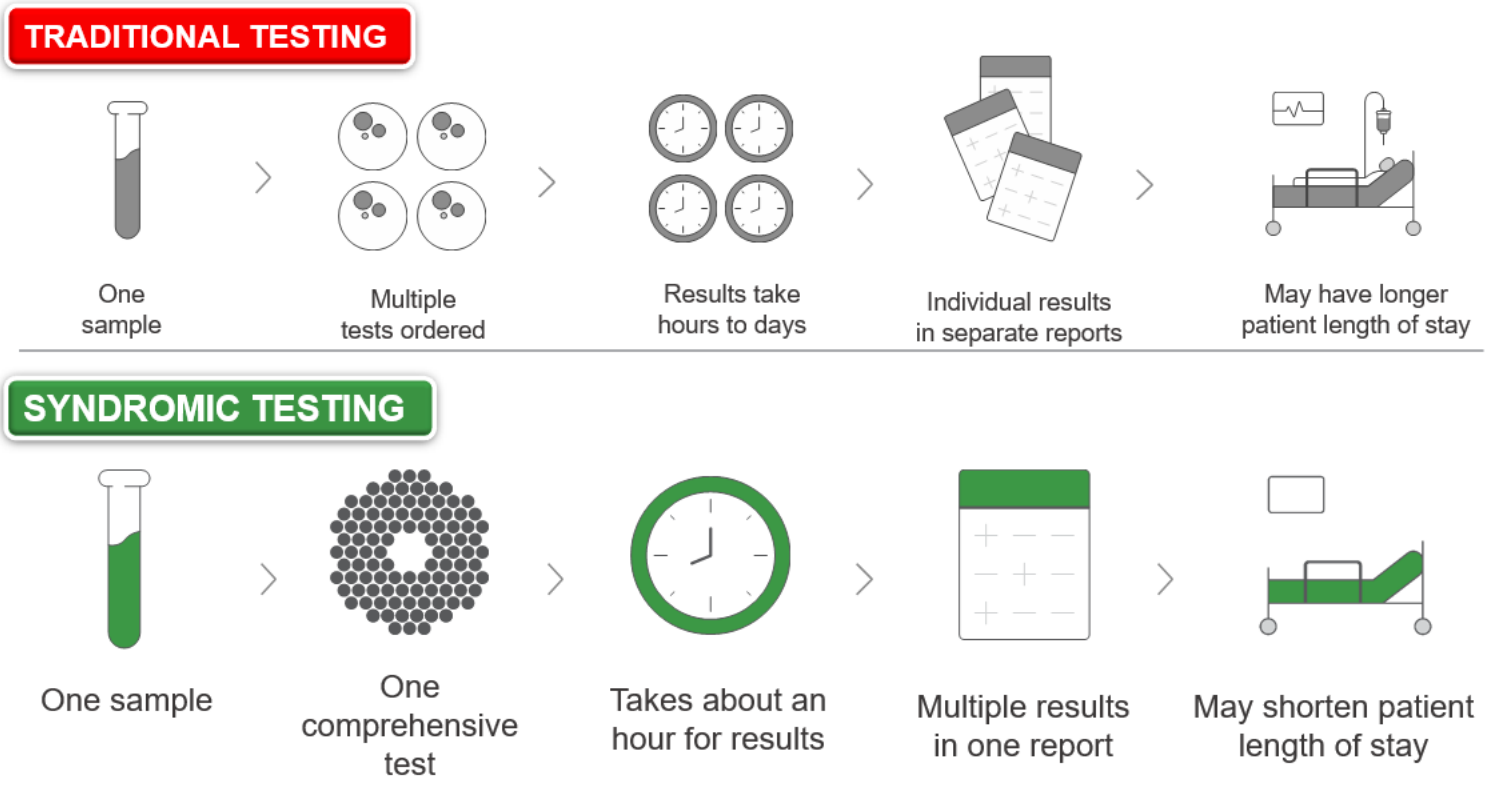


Meningitis / Encephalitis Panel	Gastrointestinal Panel	Respiratory 2.1 *plus* Panel	Pneumonia *plus* Panel	Blood Culture Identification 2 Panel	Joint Infection Panel
436	61	806	149	72	8

approx peer-reviewed papers (as of Aug 2023)

Cost benefit to the hospital

Usporedba konvencionalnog i sindromskog testiranja



Panel obuhvaća 22 patogena a rezultat je dostupan za jedan sat!

BIOFIRE® FILMARRAY®

GASTROINTESTINAL (GI) PANEL

1 Test. 22 Targets. ~1 Hour.

BACTERIA

Campylobacter (C. jejuni/C. coli/C. upsaliensis)
Clostridioides (Clostridium) difficile (toxin A/B)*
Plesiomonas shigelloides
Salmonella
Vibrio (V. parahaemolyticus/V. vulnificus/V. cholerae)
Vibrio cholerae
Yersinia enterocolitica
Diarrheagenic *Escherichia coli/Shigella*
Enteroaggregative *E. coli* (EAEC)
Enteropathogenic *E. coli* (EPEC)
Enterotoxigenic *E. coli* (ETEC) *lt/st*
Shiga-like toxin-producing *E. coli* (STEC) *stx1/stx2*
E. coli O157
Shigella/Enteroinvasive *E. coli* (EIEC)

*Selective reporting available for *C. diff*

VIRUSES

Adenovirus F40/41
Astrovirus
Norovirus GI/GII
Rotavirus A
Sapovirus (I, II, IV, and V)

PARASITES

Cryptosporidium
Cyclospora cayetanensis
Entamoeba histolytica
Giardia lamblia

Type of Detection: Qualitative

Results: about 1 Hour

Sample Type: stool in Cary Blair (200 µL)

Overall Performance: 98.5% sensitivity, 99.2% specificity[1]

FDA cleared | CE 2797

BIOMÉRIEUX

1. The stated performance is the aggregate of the prospective, archived, and seeded data from the clinical studies. Data on File. BIOFIRE Diagnostics.

BioFire® FilmArray®
Gastrointestinal Panel

GASTROINTESTINAL PANEL – PEER-REVIEWED EVIDENCE SUMMARY

Clinical Value

Time To Results

Decrease in turnaround time [1-7]
- 45 hours / - 69,3%

Shorter time to optimal therapy [3,19]
-57%

Impact on treatment decisions

Increase appropriate ABX use [19]
+ 26,7%

Decrease empiric treatment [3,7]
-10,4%

Decrease ABX days [2,5]
-1,5d

Increase ruling in/out infection causes [8,]

Impact on infection control

Increase correct isolation [20]
+60%

Increase correct de-isolation [5]
+25%

Strength of clinical evidence

> 160 studies

> 78 000 patients in **43** clinical utility studies with more than 100 cases

> 45 500 pts clinical outcomes in **24** studies

Performance of the test

Improved diagnostic Yield [2,3,6, 8-18]
+ 26,25%

Co-infection detection [2,3,6,9,18,20]
+ 12,9%

98,5% PPA (Se)
99.2% NPA (Sp)

Economic Value

Cost-effectiveness of testing

Reduced additional stool tests [2,7,10,18]
- 66,4%

Reduced downstream procedures [2,7]
- 53,8% for imaging,
- 2.3% for radiology,
- 1.2% for endoscopy

Difference in total health care costs [2]
-6,3%

Potential for cost-savings

Increase discharged Without ABX [19]
+ 9,1%

Reduced Hospital Length of Stay (LOS) [2, 19]
- 2,5 days

Decrease admission [19]
- 25%

Reduction of cost associated with hospital stay [2]
- 8,8%

1. Murphy C., et al. Eur J of Clin Microbiol Infect Dis. 2017
2. Beal S., et al. J Clin Microbiol. 2017
3. Cybulski RJ, Jr., Clin Infect Dis 2018
4. Malachira A., et al., 1717. Open Forum Infect Dis. 2018
5. Machiels JD., et al. PloS one. 2020
6. Ramakrishnan B., et al. Indian J Gastroentero. 2018
7. Sobczyk J., et al. Open Forum Infect Dis. 2020
8. Alejo-Cancho I., et al. PloS one. 2017
9. Ahmad W., et al. Dig Dis Sci. 2019
10. Rogers WS., et al. Clin Infect Dis. 2020
11. Otto C., et al. Eur J Clin Microbiol Infect Dis. 2017
12. Calderaro A., et al. Int J Med Microbiol. 2018
13. Pouletty M., et al. Arch Dis Child. 2019
14. Spina A., et al. Clin Microbiol Infect. 2015
15. Meyer J., et al. Scand J Gastroenterol. 2020
16. Stockmann C., et al. Clin Microbiol Infect. 2015
17. Axelrad JE., et al. J Clin Microbiol. 2019
18. Khare R., et al. J Clin Microbiol. 2014
19. Torres-Miranda D., et al. BMC Gastroenterol. 2020
20. Rand K., et al. Diagn Microbiol Infect Dis. 2015

Zaključak I
Kada upotrijebiti?

- Community-acquired diarrhea ≥ 7 days duration
- Travel-related diarrhea
- Diarrhea with warning signs (*e.g.* blood in stools) or risk factors for severe disease
- Immunocompromised patients

POSITIONING

Zaključak II
Usporedba s konvencionalnim testovima

- Usporedba provedena u 274 pacijenta s uputnom dijagnozom gastroenteritisa i dijarejom u razdoblju od 18 mjeseci u NZJZ „Dr. Andrija Štampar" u Zagrebu pokazala je da je u 25 % testiranih pacijenata etiologija infekcije utvrđena jedino upotrebom GI panela (ali ne i konvencionalnim dijagnostičkim metodama).

- FilmArray GI panel bio je jednako uspješan u detekciji bakterijskih patogena kao i klasične metode bazirane na kultivaciji, ali je bio izrazito superioran u usporedbi s detekcijom virusnih patogena uz pomoć imunokromatografskih (IC) testova, te u usporedbi s detekcijom parazita uz pomoć klasičnih parazitoloških metoda detekcije.

- Upotrijebljeni brzi IC testovi za detekciju virusa u stolici bili su u 9 % lažno negativni, te u čak 49 % slučajeva lažno pozitivni!

Nastavni zavod za javno zdravstvo „Dr. Andrija Štampar”

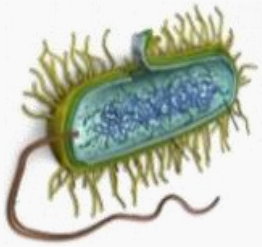
SURADNICI: prof. dr. Sunčanica Ljubin Sternak, prim. mr. sc. Tatjana Marijan, Odjel za molekularnu mikrobiologiju & dr. Nada Pražić i dr. Ružica Cipriš, Odjel za dijagnostiku infekcija probavnog sustava

Exploring the Role of MALDI-TOF MS Technology in Diagnosing Gastrointestinal Infections

Zybio Inc.

MALDI-TOF MS Principle

Plate with colonies



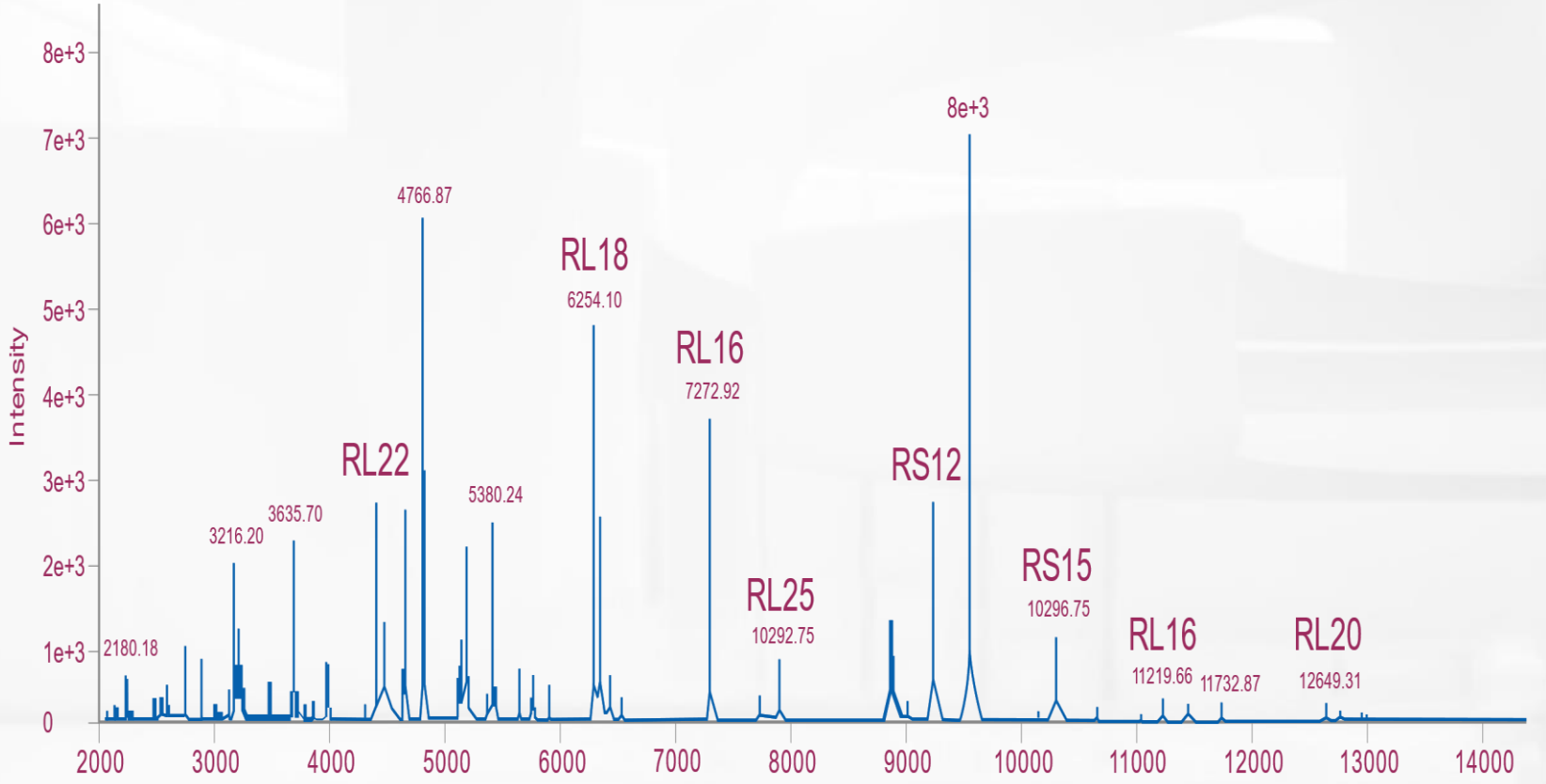
Bacterial shape

Ribosome

RL: Ribosomal Protein Large

PC: Polypeptide Chain

RS: Ribosomal Protein Small



Fingerprinting Technology for Whole Bacterial Ribosomal Protein

Local database capacity： > 4,051 species, 15,000 strains

zybio

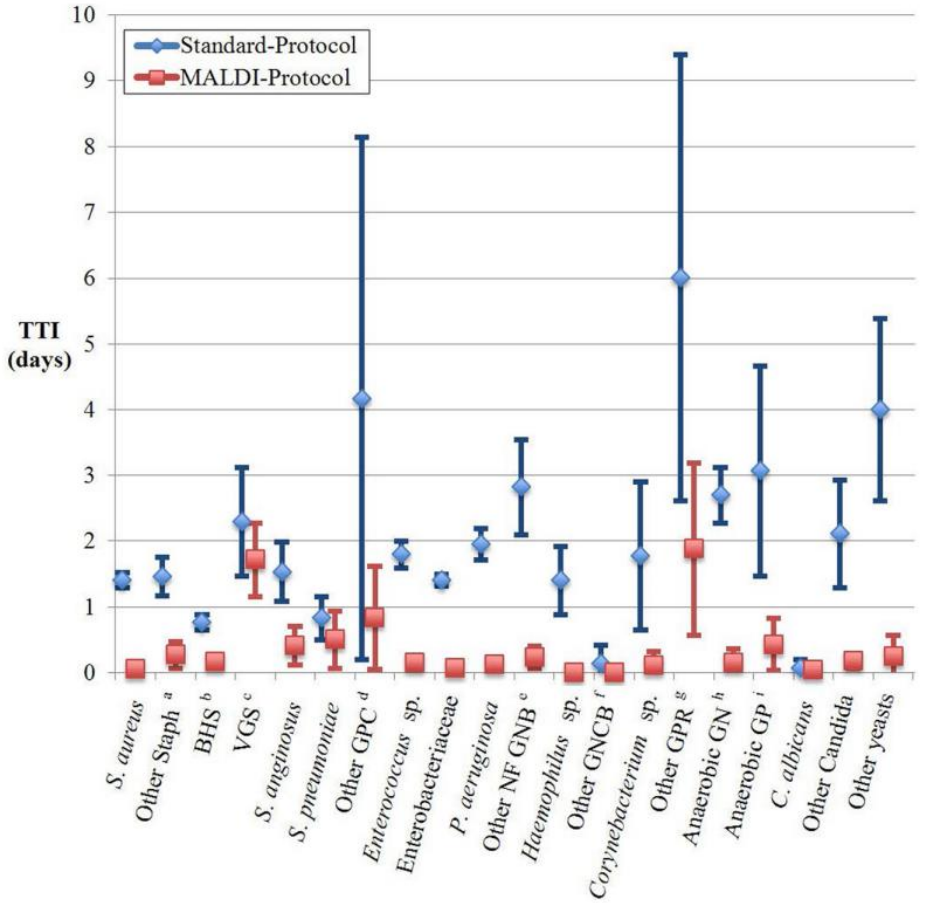
- **MALDI-TOF MS**

Prospective Evaluation of a Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry System in a Hospital Clinical Microbiology Laboratory for Identification of Bacteria and Yeasts: a Bench-by-Bench Study for Assessing the Impact on Time to Identification and Cost-Effectiveness

K. E. Tan,[a] B. C. Ellis,[b] R. Lee,[b] P. D. Stamper,[a] S. X. Zhang,[a,b] and K. C. Carroll[a,b]

Division of Medical Microbiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA,[a] and Microbiology Laboratory, Johns Hopkins Hospital, Baltimore, Maryland, USA[b]

Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) has been found to be an accurate, rapid, and inexpensive method for the identification of bacteria and yeasts. Previous evaluations have compared the accuracy, time to identification, and costs of the MALDI-TOF MS method against standard identification systems or commercial panels. In this prospective study, we compared a protocol incorporating MALDI-TOF MS (MALDI protocol) with the current standard identification protocols (standard protocol) to determine the performance in actual practice using a specimen-based, bench-by-bench approach. The potential impact on time to identification (TTI) and costs had MALDI-TOF MS been the first-line identification method was quantitated. The MALDI protocol includes supplementary tests, notably for *Streptococcus pneumoniae* and *Shigella*, and indications for repeat MALDI-TOF MS attempts, often not measured in previous studies. A total of 952 isolates (824 bacterial isolates and 128 yeast isolates) recovered from 2,214 specimens were assessed using the MALDI protocol. Compared with standard protocols, the MALDI protocol provided identifications 1.45 days earlier on average ($P < 0.001$). In our laboratory, we anticipate that the incorporation of the MALDI protocol can reduce reagent and labor costs of identification by $102,424 or 56.9% within 12 months. The model included the fixed annual costs of the MALDI-TOF MS, such as the cost of protein standards and instrument maintenance, and the annual prevalence of organisms encountered in our laboratory. This comprehensive cost analysis model can be generalized to other moderate- to high-volume laboratories.



Reduce **$102,424/56.9%** within 12 months

1.45 days earlier on average

Overall healthcare savings associated with rapid pathogen identification

S. Das et al. / Journal of Microbiological Methods 103 (2014) 80–100

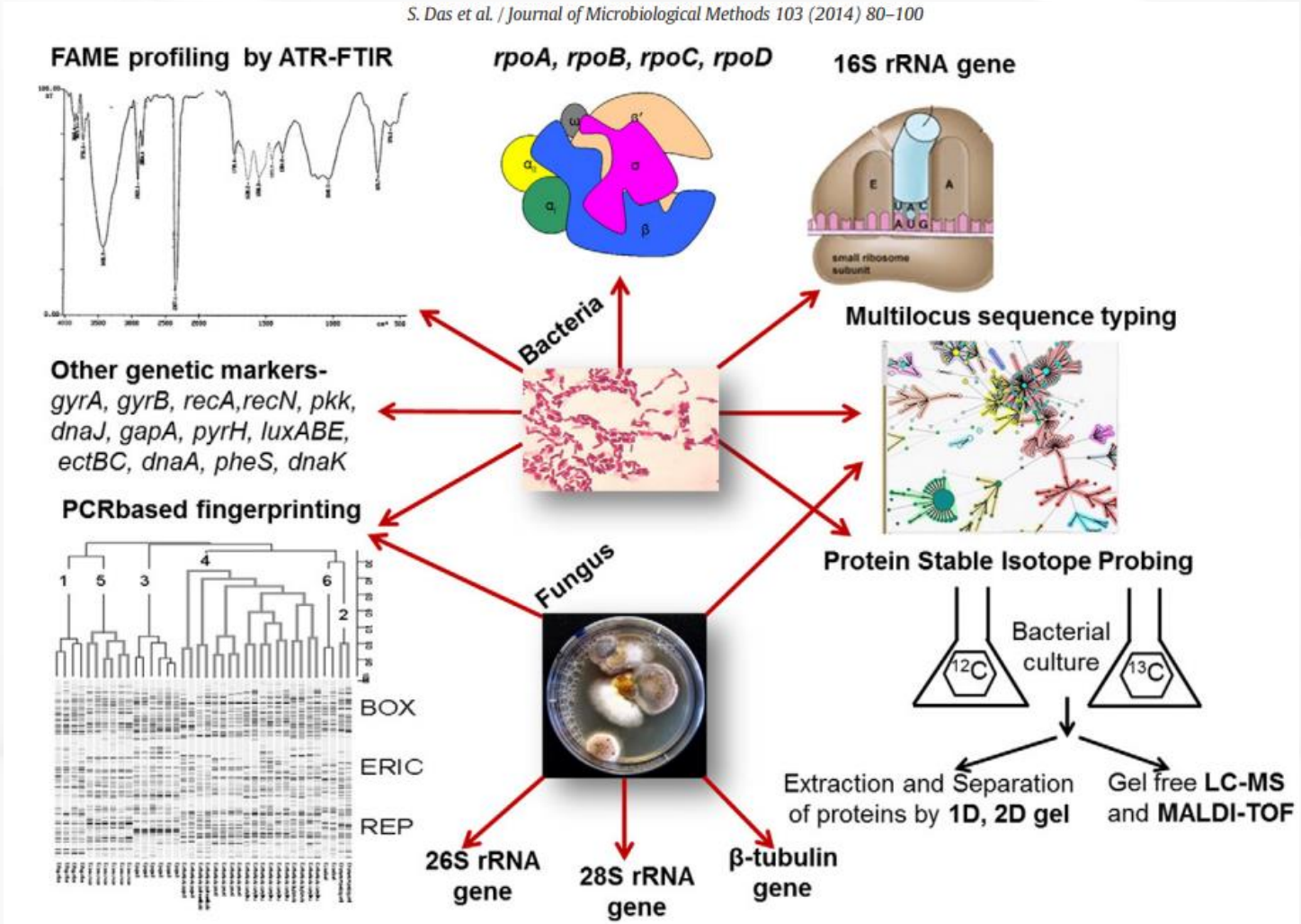


Fig. 1. Catalogue of gene targets for molecular identification of bacteria and fungi.

Paper: Understanding molecular identification and polyphasic taxonomic approaches for genetic relatedness and phylogenetic relationships of microorganisms

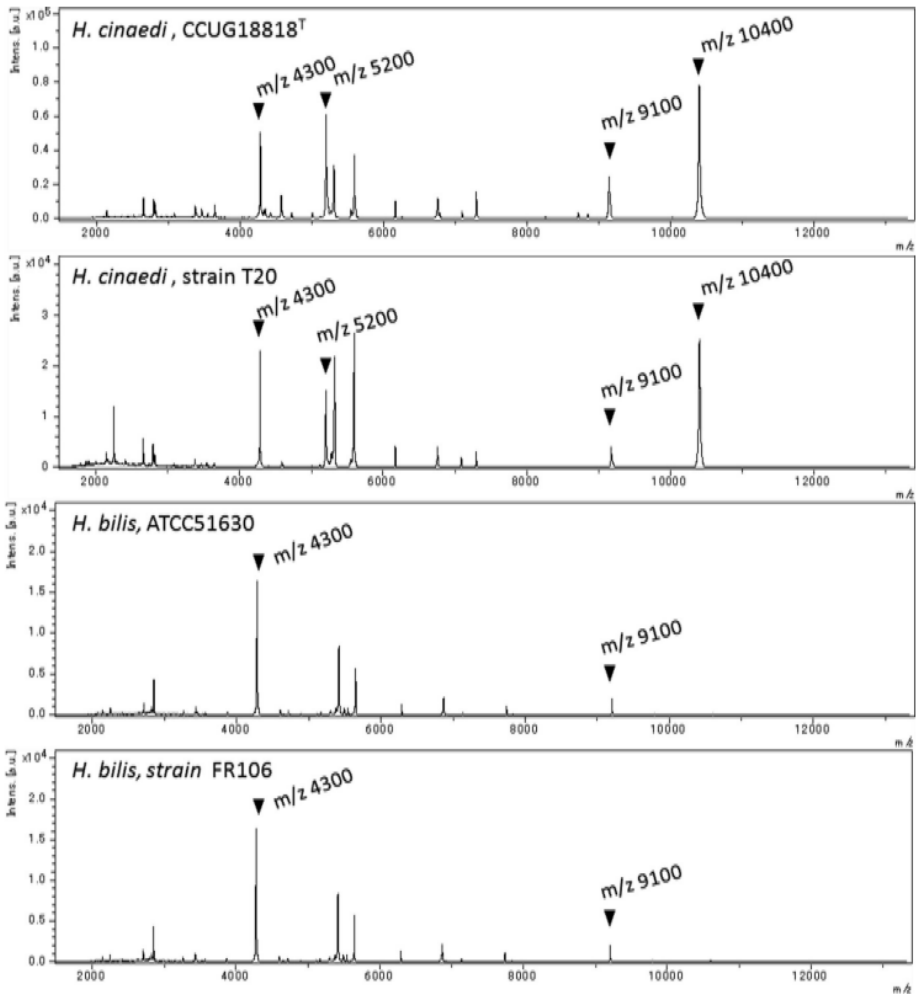


FIG 1 ICMS profiles obtained from analysis of *H. cinaedi* and *H. bilis* using MALDI-TOF MS. The relative intensities of the ions (in arbitrary units) are shown on the *y* axis, and *m/z* values, with the masses in Da, of the ions are shown on the *x* axis. For a single positive charge, *m/z* corresponds to the molecular mass of the protein. The arrows represent the peaks with *m/z* 4,300, 5,200, 9,100, and 1,0400.

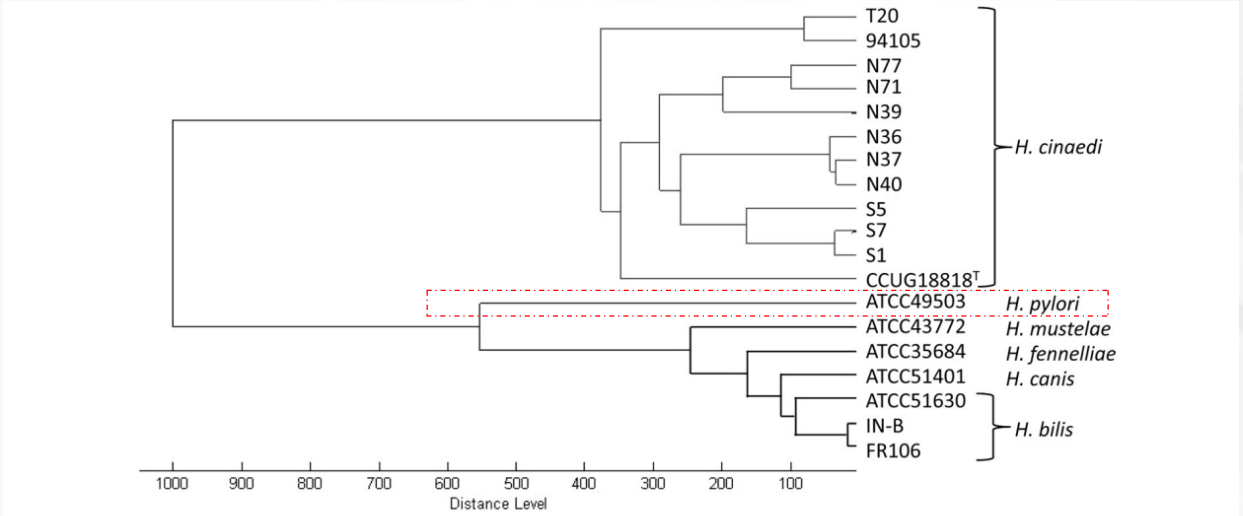


FIG 2 Dendrogram derived from numerical analysis of the ICMS of closely related helicobacters. Distances are displayed in relative units.

Paper: Rapid Identification and Subtyping of Helicobacter cinaedi Strains by Intact-Cell Mass Spectrometry Profiling with the Use of MALDI-TOF MS

The infestation mechanism of *H.pylori* to Human body

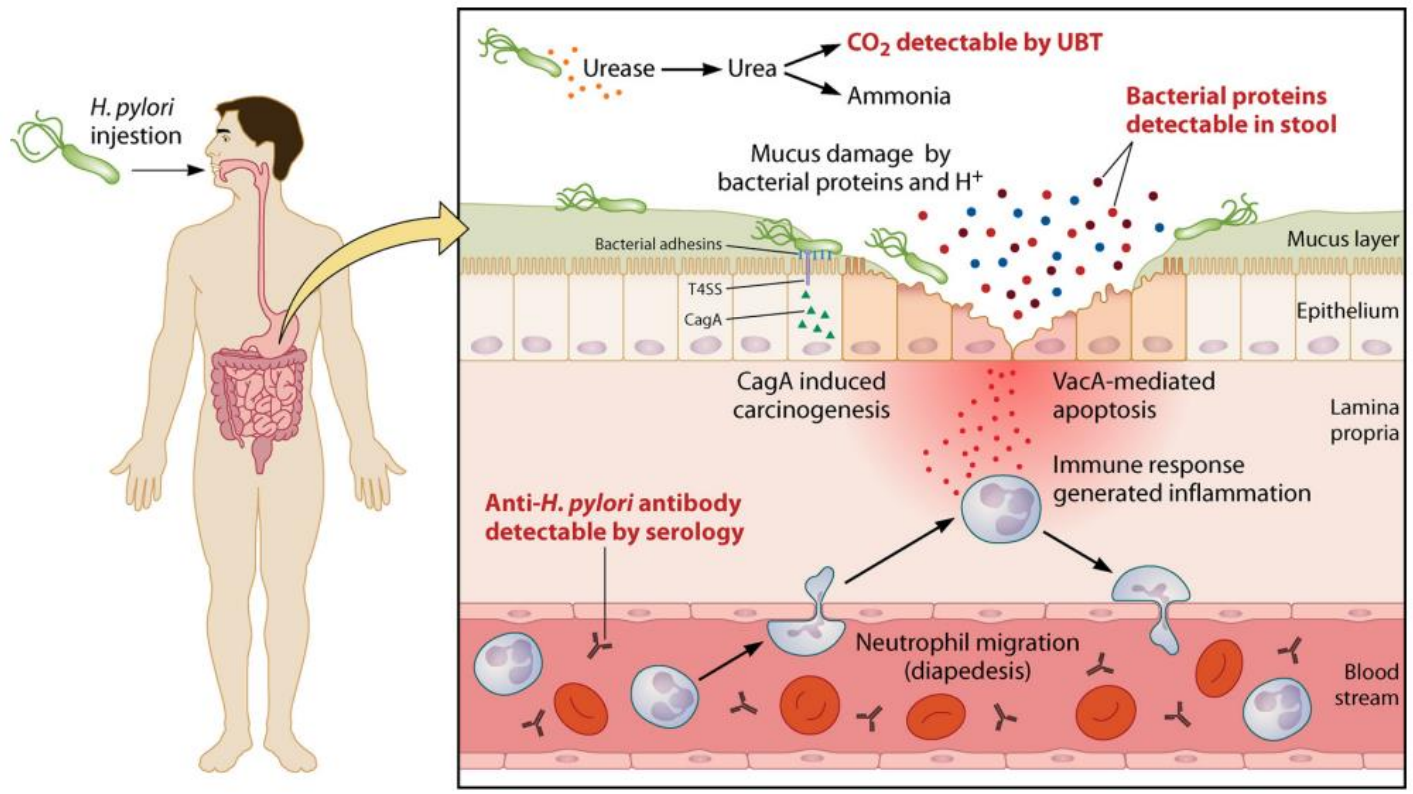


FIG 1 *H. pylori*-associated pathogenicity. After ingestion, *H. pylori* enters the stomach, and the urease produced by the bacteria hydrolyzes the urea, thereby generating CO_2, which can be detected by the urea breath test (UBT), and ammonia. Ammonia neutralizes the acidic pH, creating an almost neutral microenvironment around bacterial cells that enables the bacteria to survive under adverse gastric conditions. Later, the bacteria find their way into the mucus layer owing to multifactorial mechanisms such as their helical shape, the presence of flagella, and chemotaxis. Several proteins (such as BabA, SabA, and OipA) produced by bacteria help in the colonization and persistence of infection. Moreover, these proteins are detected in stool specimens of infected patients by stool antigen tests (SATs). The immune response targeting numerous immunogenic proteins is evaluated by identifying antibodies using serological tests. The protein CagA is directly translocated into the gastric epithelium, and CagA-mediated carcinogenesis is triggered, whereas the VacA protein contributes to apoptosis and epithelial cell death.

Paper: Helicobacter pylori Infection, Its Laboratory Diagnosis, and Antimicrobial Resistance: a Perspective of Clinical Relevance

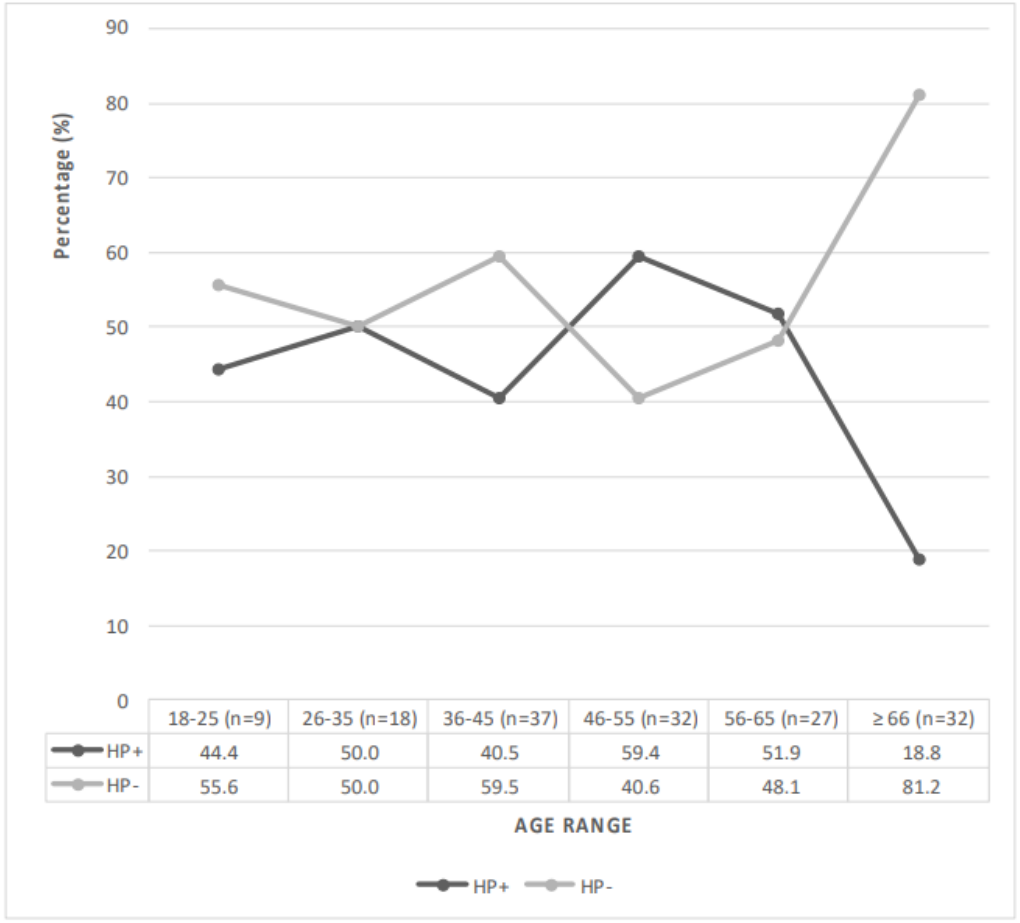


Figure 1. *H. pylori* infection dynamics according to age range. Distribution of patients colonized and not colonized by *H. pylori* according to age and expressed in years.

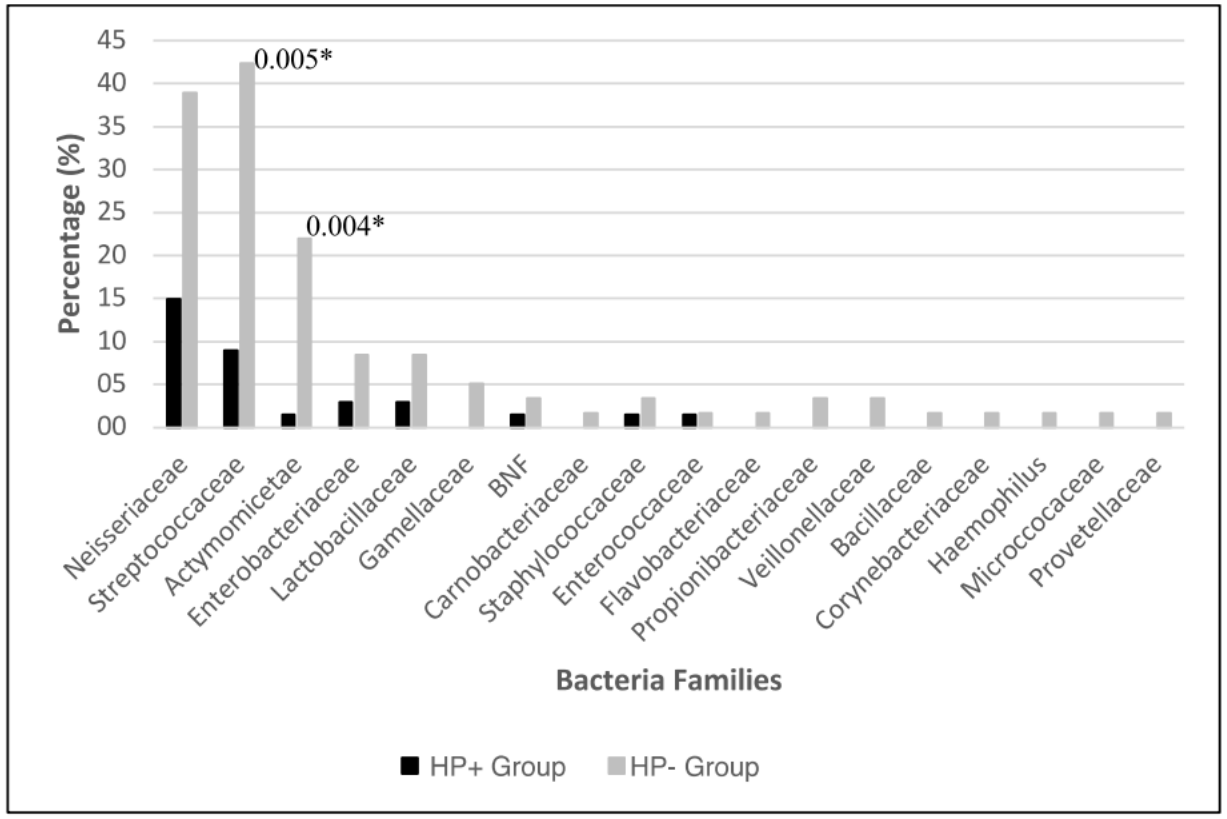
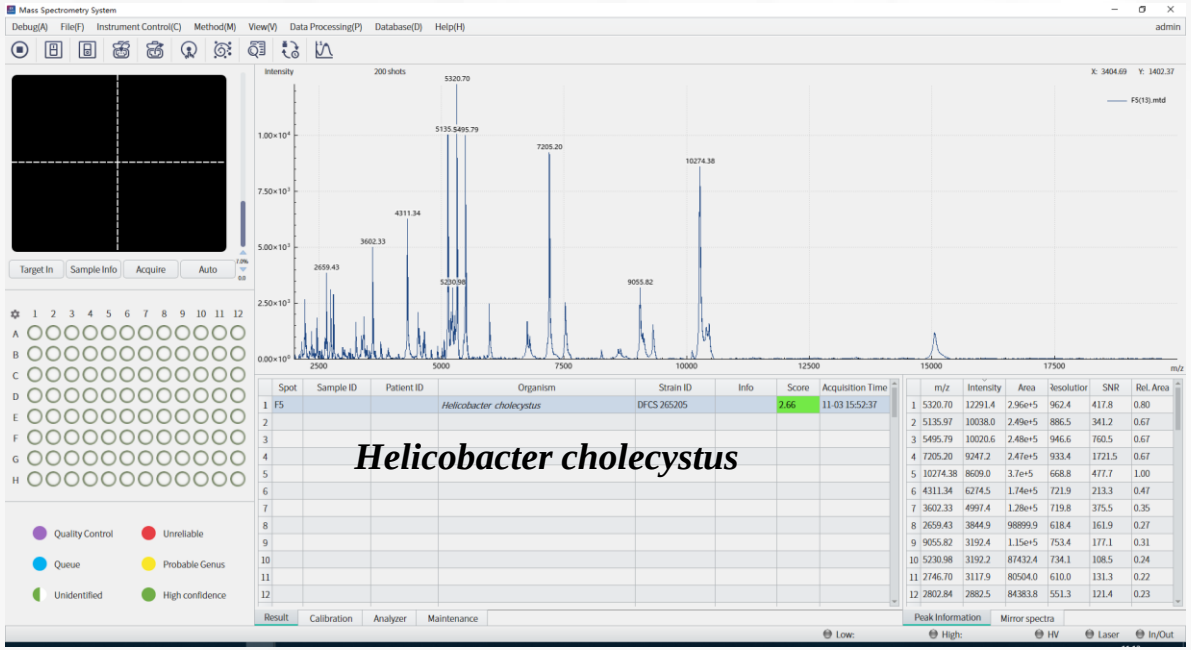


Figure 2. Distribution of cultivable gastric microbiota present in the gastric epithelium. Diversity of cultivable bacterial families isolated from gastric biopsies according to the *H. pylori* (HP+) and non-pylori species colonization (HP-). (BNF: Gram-negative non-fermenting bacilli). *: Significant statistical differences $p < 0.05$.

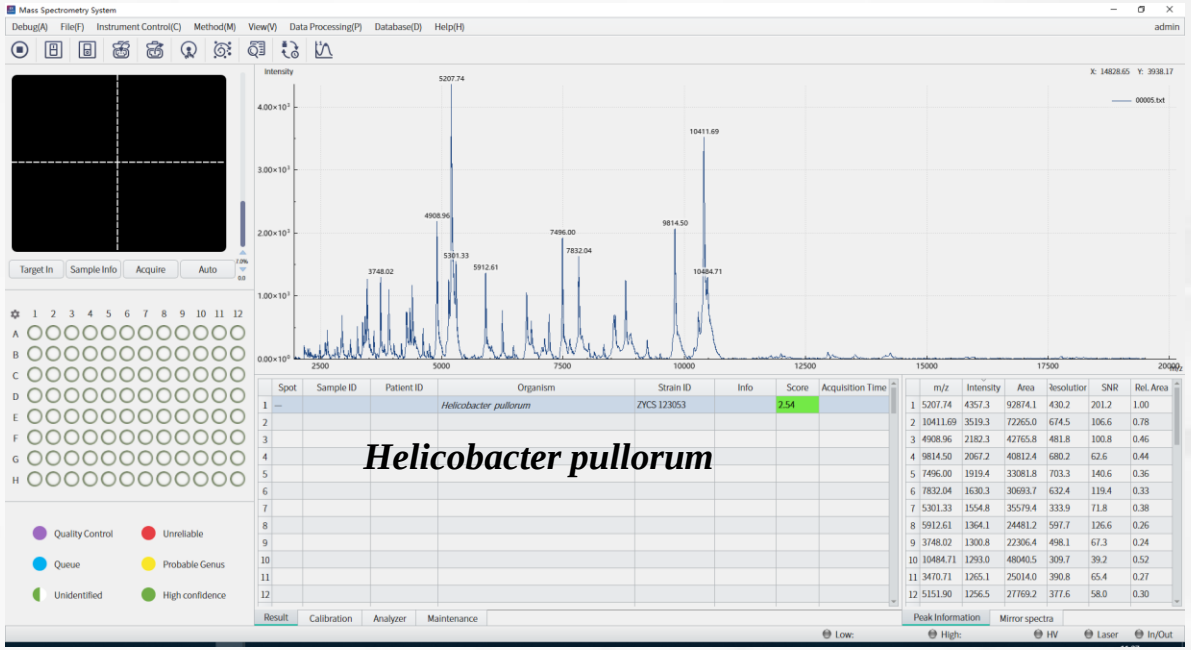
The *Helicobacter Group* Identification by MALDI-TOF MS



Spot	Sample ID	Patient ID	Organism	Strain ID	Info	Score	Acquisition Time
1 F5			*Helicobacter cholecystus*	DFCS 265205		2.66	11-03 15:52:37

	m/z	Intensity	Area	Resolution	SNR	Rel. Area
1	5320.70	12291.4	2.96e+5	962.4	417.8	0.80
2	5135.97	10038.0	2.49e+5	886.5	341.2	0.67
3	5495.79	10020.6	2.48e+5	946.6	760.5	0.67
4	7205.20	9247.2	2.47e+5	933.4	1721.5	0.67
5	10274.38	8609.0	3.7e+5	668.8	477.7	1.00
6	4311.34	6274.5	1.74e+5	721.9	213.3	0.47
7	3602.33	4997.4	1.28e+5	719.8	375.5	0.35
8	2659.43	3844.9	98899.9	618.4	161.9	0.27
9	9055.82	3192.4	1.15e+5	753.4	177.1	0.31
10	5230.98	3192.2	87432.4	734.1	108.5	0.24
11	2746.70	3117.9	80504.0	610.0	131.3	0.22
12	2802.84	2882.5	84383.8	551.3	121.4	0.23

Helicobacter cholecystus

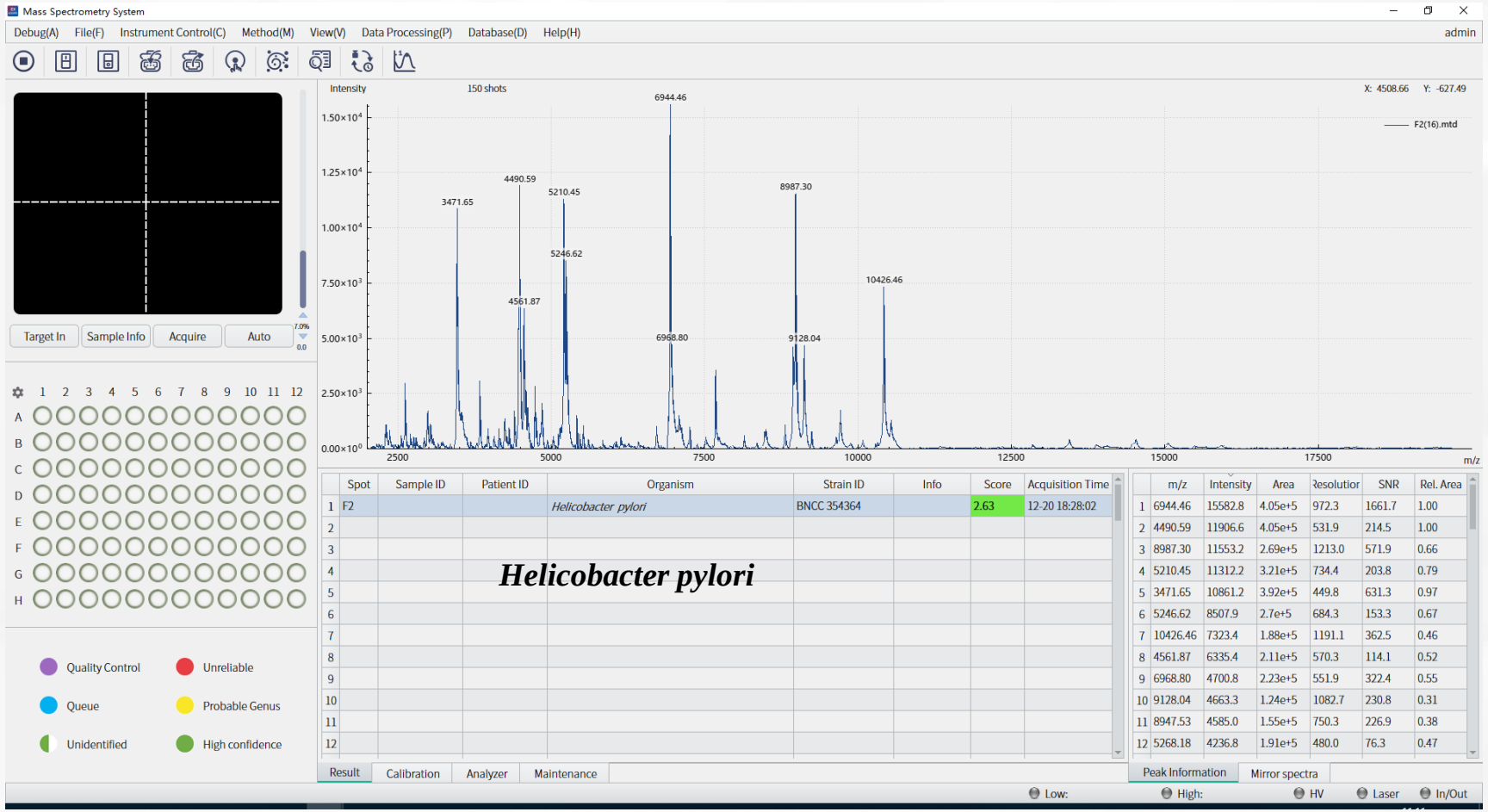


Spot	Sample ID	Patient ID	Organism	Strain ID	Info	Score	Acquisition Time
1 –			*Helicobacter pullorum*	ZYCS 123053		2.54	

	m/z	Intensity	Area	Resolution	SNR	Rel. Area
1	5207.74	4357.3	92874.1	430.2	201.2	1.00
2	10411.69	3519.3	72265.0	674.5	106.6	0.78
3	4908.96	2182.3	42765.8	481.8	100.8	0.46
4	9814.50	2067.2	40812.4	680.2	62.6	0.44
5	7496.00	1919.4	33081.8	703.3	140.6	0.36
6	7832.04	1630.3	30693.7	632.4	119.4	0.33
7	5301.33	1554.8	35579.4	333.9	71.8	0.38
8	5912.61	1364.1	24481.2	597.7	126.6	0.26
9	3748.02	1300.8	22306.4	498.1	67.3	0.24
10	10484.71	1293.0	48040.5	309.7	39.2	0.52
11	3470.71	1265.1	25014.0	390.8	65.4	0.27
12	5151.90	1256.5	27769.2	377.6	58.0	0.30

Helicobacter pullorum

The *Helicobacter Group* Identification by MALDI-TOF MS



	Spot	Sample ID	Patient ID	Organism	Strain ID	Info	Score	Acquisition Time
1	F2			*Helicobacter pylori*	BNCC 354364		2.63	12-20 18:28:02

	m/z	Intensity	Area	Resolution	SNR	Rel. Area
1	6944.46	15582.8	4.05e+5	972.3	1661.7	1.00
2	4490.59	11906.6	4.05e+5	531.9	214.5	1.00
3	8987.30	11553.2	2.69e+5	1213.0	571.9	0.66
4	5210.45	11312.2	3.21e+5	734.4	203.8	0.79
5	3471.65	10861.2	3.92e+5	449.8	631.3	0.97
6	5246.62	8507.9	2.7e+5	684.3	153.3	0.67
7	10426.46	7323.4	1.88e+5	1191.1	362.5	0.46
8	4561.87	6335.4	2.11e+5	570.3	114.1	0.52
9	6968.80	4700.8	2.23e+5	551.9	322.4	0.55
10	9128.04	4663.3	1.24e+5	1082.7	230.8	0.31
11	8947.53	4585.0	1.55e+5	750.3	226.9	0.38
12	5268.18	4236.8	1.91e+5	480.0	76.3	0.47

The Following Work of MALDI-TOF MS in *Helicobacter Group*

- ***H.pylori*** **typing - Toxicity typing, drug resistance typing, disease-related**
- ***H.pylori*** **database building - Process supplementation/optimization**
- ***Gastric flora*** **database building - Screening Related Diseases**
- **Other species of Helicobacter buildup**
- **Nucleic acid mass spectrometry to identify *H.pylori* based on Nucleic acid**

The Following Work of MALDI-TOF MS in *Helicobacter Group*

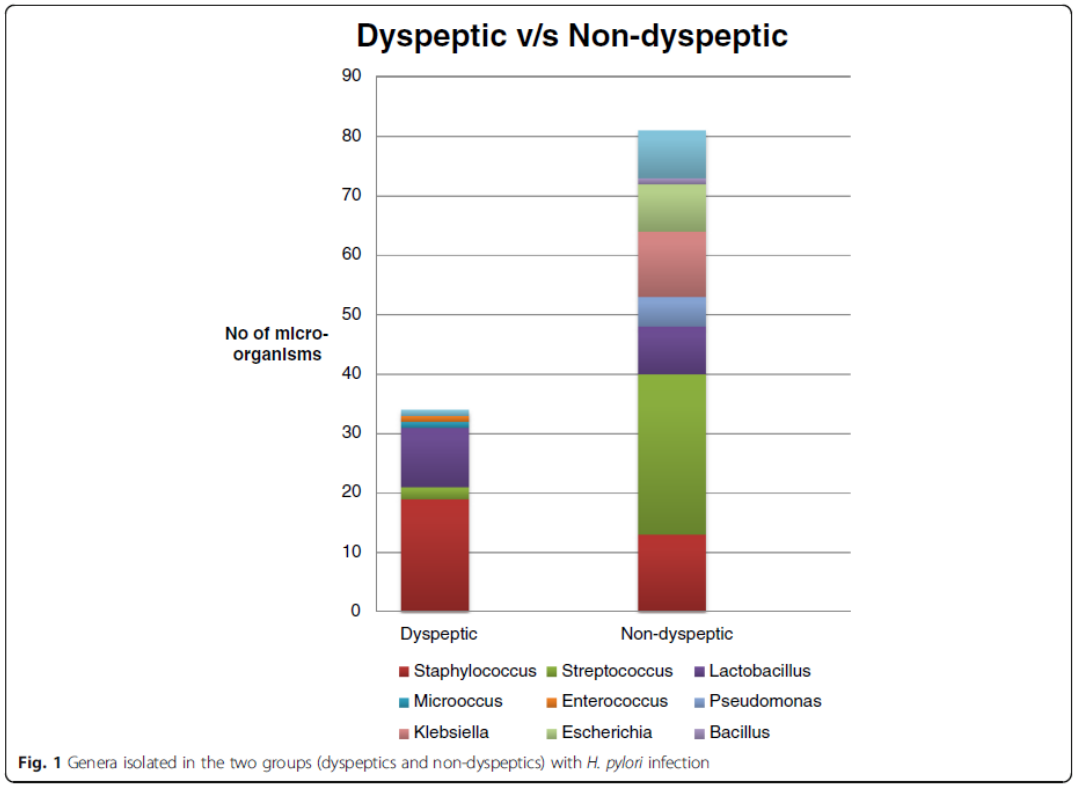


Fig. 1 Genera isolated in the two groups (dyspeptics and non-dyspeptics) with *H. pylori* infection

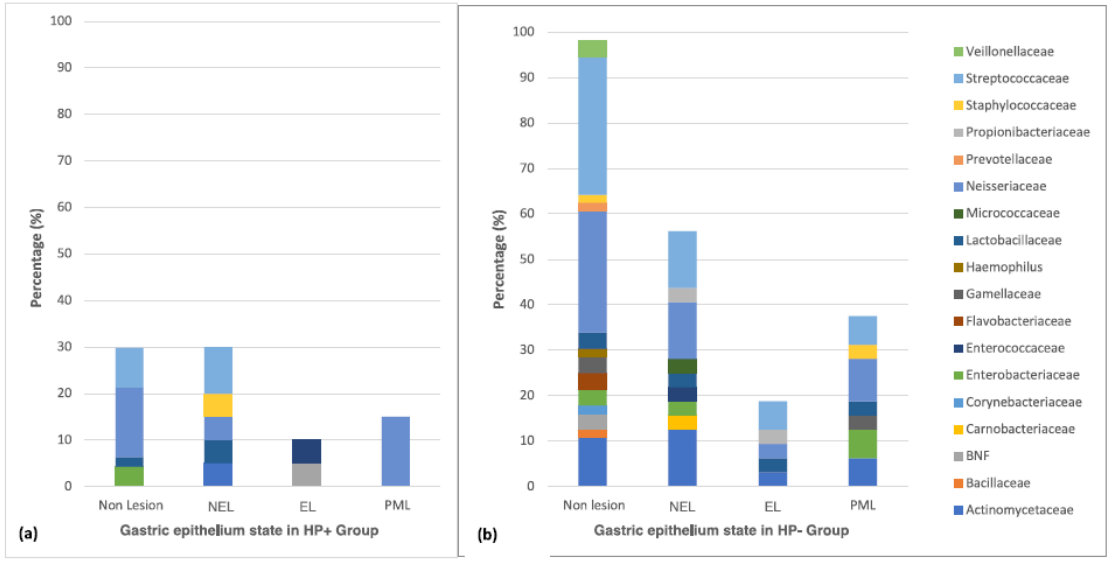


Figure 3. Cultivable gastric microbiota from the gastric epithelium. Distribution of cultivable bacteria present in the different states of the gastric epithelium, according to the HP+ group (**a**) and the HP- group (**b**). (NEL = Non-erosive lesion, EL = Erosive lesion, PML = Premalignant or Malignant lesion (atrophy or metaplasia). BNF: Gram-negative non-fermenting bacilli). BNF: Gram-negative non-fermenting bacilli.

Hp + indigestion vs. microecology

Hp producing toxins/not producing toxins vs. microecology

Hp+/- vs. microecology

Paper: *Pereira, V., et al. Gastric bacterial Flora in patients Harbouring Helicobacter pylori with or without chronic dyspepsia: analysis with matrix-assisted laser desorption ionization time-of-flight mass spectroscopy. BMC Gastroenterol 18, 20 (2018).*

Paper: *Troncoso C, et al. MALDI-TOF MS and 16S RNA Identification of Culturable Gastric Microbiota: Variability Associated with the Presence of Helicobacter pylori. Microorganisms. 2020 Nov 10;8(11):1763.*

The Following Work of MALDI-TOF MS in *Helicobacter pylori*

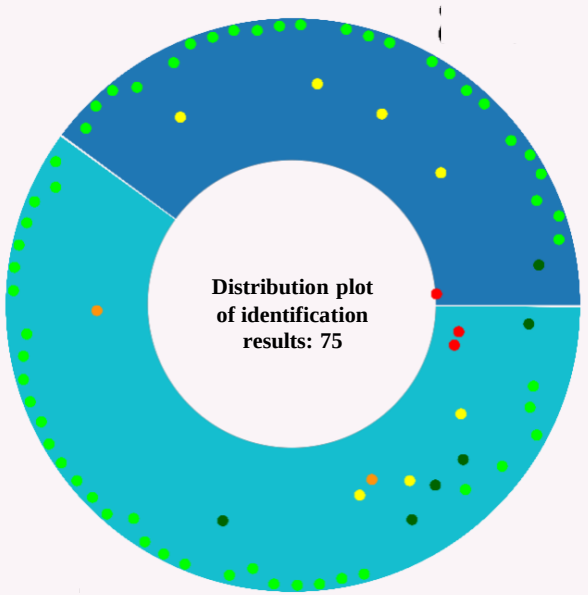
A	B	C	D	E
Menu Bar	Navigation	Function	Property	Output

- View
- File
- Help

- New Group
- Import
- Remove
- Rename

- Spectrum
- Mirror Plot
- Stack Plot
- Array Plot
- Gel Plot
- Peak Matrix
- Clustering
- Typing

Identification at the sub-species level



Resistance: 60.0% Sensitive: 40.0%

- Genotyping
- Virulence typing: CagA, VacA
- Resistance typing

MALDI-TOF Mass Spectrometry EXS 2600

- 96 samples in **7 mins**
- **60Hz** N_2 Laser with **400 million** shots
- Local database: ≥ **4,051 species, 15000 strains**

  Bacteria (3,147), Fungi (887), Archaea (17)
- Dual Mode: **Positive and Negative ion mode**
- Microbial **drug resistance detection module**
- Intelligent **clustering** and **subtyping analysis** software

  …

The Features of MALDI-TOFEXS2600

Methods	Kits	Suitable for bacteria
Directly smear method	Sample treatment matrix solution	Most of Microorganism
	Sample pretreatment solution	Some difficult-identify microorganism
	Microbe sample pretreatment kit	Bacteria, Yeast, Filamentous fungi and others
Extraction method	Microbe sample pretreatment kit	Bacteria, Yeast, Filamentous fungi and others
Decentralized method	Mold sample pretreatment kit	Especially for Filamentous fungi
Blood culture pretreatment	Blood culture positive sample pretreatment kit	Blood culture bacteria

Sample treatment matrix solution

Microbe sample pretreatment kit

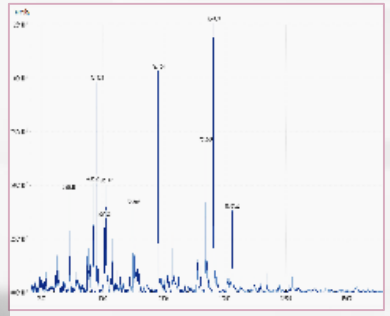
Mold sample pretreatment kit

Blood culture positive sample pretreatment kit

The Features of MALDI-TOFEXS2600

Workflow

Pretreatment



Step 1：Pick up fungi.

Step 2： Add matrix solution on the target.

Step 3： Dry for a few minutes and move target-in.

Step 4：Identification & Analysis

Klinički aspekti i novosti u liječenju virusnih hepatitisa

doc.dr.sc. Miloš Lalovac, dr.med.
Maja Mijić, dr.med.
Klinika za unutarnje bolesti, Zavod za gastroenterologiju, KB Merkur

Zagreb, 17.05.2024.

Virusni hepatitisi

- infekcije virusnim hepatitisima predstavljaju globalni javnozdravstveni problem
- danas razlikujemo 5 različitih tipova virusa
  - Hepatitis A
  - Hepatitis B
  - Hepatitis C
  - Hepatitis D
  - Hepatitis E

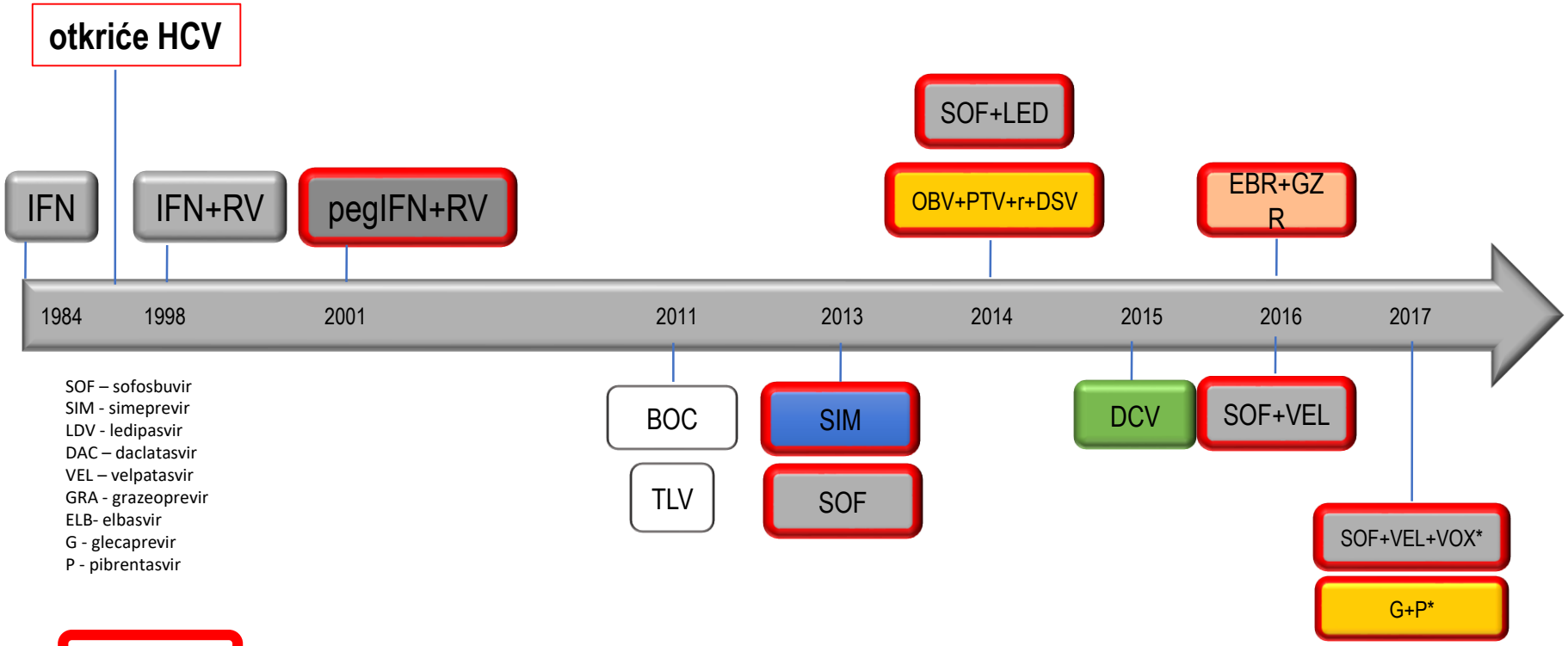
Virusni hepatitisi

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Genom	RNA	DNA	RNA	RNA	RNA
Genotip	6 (I-III infekcija kod ljudi)	10 (A do J)	8 (1 do 8)	8 (1 do 8)	8 (1 do 8)
Transmisija	feko-oralno	parenteralno, spolno, perinatalno	krvlju	krvlju i spolno	feko-oralno, transfuzijom krvi
Terapija	simptomatska	NA	DAA	pegilirani interferon alfa 2	ribavirin (kronična infekcija)
Profilaksa	DA (inaktivirano cjepivo)	DA (rekombinantno cjepivo)	NE	HBV cjepivo	NE
Klinički tijek	samolimitirajuća infekcija	samolimitirajuća infekcija ili kronična	samolimitirajuća infekcija ili kronična	samolimitirajuća infekcija ili kronična	samolimitirajuća infekcija
Kronična infekcija	NE	5-10% odraslih	80%	/	Kronična samo kod imunosuprimiranih bolesnika

*Pisano MB et al. Viral hepatitis update: Progress and perspectives. World J Gastroenterol. 2021

Hepatitis C (HCV)

Anti-HCV lijekovi



Hepatitis C (HCV)

- **Protokoli liječenja dostupni u RH**

Pangenotipski IFN-free protokoli

- **Sofosbuvir/velpatasvir**
- **Glecaprevir/pibrentasvir**

Genotip specifični IFN-free protokoli

- **Ledipasvir/sofosbuvir**
- **Grazoprevir/elbasvir**

Prethodno neuspješno liječeni DAA lijekovima

- **Sofosbuvir/velpatasvir/voksilaprevir**

HZZO lista lijekova: https://www.hzzo.hr/zdravstveni-sustav-rh/trazilica-za-lijekove-s-vazecih-lista/; Pristup: travanj 2023.

Preporuke za liječenje hepatitisa C 2023. godine; Klinika za infektivne bolesti „Dr. Fran Mihaljević“ Referentni centar za dijagnostiku i liječenje virusnih hepatitisa Ministarstva zdravstva; Autori: Prof. dr. sc. Adriana Vince, dr. med., dr. sc. Ivan Kurelac, dr. med., doc. dr. sc. Neven Papić, dr. med.

Hepatitis C (HCV)

1. LIJEČENJE BOLESNIKA S KRONIČNIM HEPATITISOM C BEZ CIROZE ILI S KOMPENZIRANOM CIROZOM

Genotip	Stadij fibroze	Prethodno liječenje	Sofosbuvir / velpatasvir	Glekaprevir / pibrentasvir	Grazoprevir / elbasvir	Sofosbuvir / ledipasvir
Genotip 1a, 1b, 2, 4, 5 i 6	F1- F3	Naivni	12 tjedana	8 tjedana	12 tjedana (samo genotip 1b)	12 tjedana (genotip 1 i 4)
		Prethodno liječeni				Ne
	Kompenzirana ciroza (CPA)	Naivni				12 tjedana (genotip 1 i 4)
		Prethodno liječeni		12 tjedana		Ne
Genotip 3	F1 – F3	Naivni	12 tjedana	8 tjedana	Ne	Ne
		Prethodno liječeni		16 tjedana		
	Kompenzirana ciroza (CPA)	Naivni	12 tjedana + ribavirin ili 24 tjedana bez ribavirina	12 tjedana		
		Prethodno liječeni		16 tjedana		

** SVR12 >95% za sve DAA

* Preporuke za liječenje hepatitisa C 2023. godine; Klinika za infektivne bolesti „Dr. Fran Mihaljević“ Referentni centar za dijagnostiku i liječenje virusnih hepatitisa Ministarstva zdravstva; Autori: Prof. dr. sc. Adriana Vince, dr. med., dr. sc. Ivan Kurelac, dr. med., doc. dr. sc. Neven Papić, dr. med.

** SVR – održani virološki odgovor (*eng. sustained viral response*); DAA – direktno djelujući lijekovi; EASL recommendations on treatment of hepatitis C: Final update of the series, J Hepatol. 2023

Hepatitis C (HCV)

Liječenje je indicirano:

- svi neliječeni i liječeni pacijenti s kompenziranom ili dekompenziranom bolesti jetre

Prednost u liječenju imaju:

- pacijenti sa značajnom fibrozom (F3 po Metaviru) ili cirozom (F4), uključujući dekompenziranu cirozu
- pacijenti s HBV ili HIV koinfekcijom
- pacijenti s indikacijom za transplantaciju jetre
- pacijenti s povratnom HCV infekcijom nakon transplantacije jetre
- pacijenti s HCV infekcijom prije i nakon transplantacije solidnih organa
- pacijenti s klinički značajnim ekstrahepatalnim manifestacijama infekcije

Liječenje je opravdano:

- pacijenti s umjerenom fibrozom (F1-F2 po Metaviru), a pri tome prednost imaju:
  - pacijenti s dugim trajanjem bolesti (>20 godina)
  - pacijenti s rizikom prijenosa HCV infekcije (žene generativne dobi koji žele trudnoću, pacijenti na hemodijalizi i druge visokorizične situacije)

Liječenje se može odgoditi:

- pacijenti bez ili s blagom bolesti (F0-F1 po Metaviru) i bez ekstrahepatalnih manifestacija

Liječenje se ne preporučuje:

- pacijenti s očekivanim ograničenim životnim vijekom zbog drugog komorbiditeta

* Preporuke za liječenje hepatitisa C 2023. godine; Klinika za infektivne bolesti „Dr. Fran Mihaljević“ Referentni centar za dijagnostiku i liječenje virusnih hepatitisa Ministarstva zdravstva; Autori: Prof. dr. sc. Adriana Vince, dr. med., dr. sc. Ivan Kurelac, dr. med., doc. dr. sc. Neven Papić, dr. med.

Hepatitis C (HCV)

- Pristup liječenju hepatitis C infekcije u bolesnika koji su kandidat za transplantaciju jetre (TJ)

1. **prvo transplantiranti, a potom liječiti DAA lijekovima:**
   a. bolesnike s dekompenziranom cirozom jetre (CTP B/C) i MELD skorom ≥18-20
   b. bolesnike s HCC i očekivanim vremenom čekanja na listi < 3-6 mjeseci

2. **prvo liječiti DAA lijekovima, a potom slijedi odluka o potrebi za TJ** u ovisnosti o aktualnoj težini osnovne bolesti:
   a. bolesnike s dekompenziranom cirozom jetre (CTP B/C) i MELD skorom <18-20
   b. bolesnike s dekompenziranom cirozom jetre (CTP B/C) i očekivanim vremenom čekanja na listi ≥ 6 mjeseci
   c. bolesnike s HCC-om i očekivanim vremenom čekanja na listi ≥ 6 mjeseci

CTP – Child-Turcotte-Pough; MELD - Model of End Stage Liver Disease

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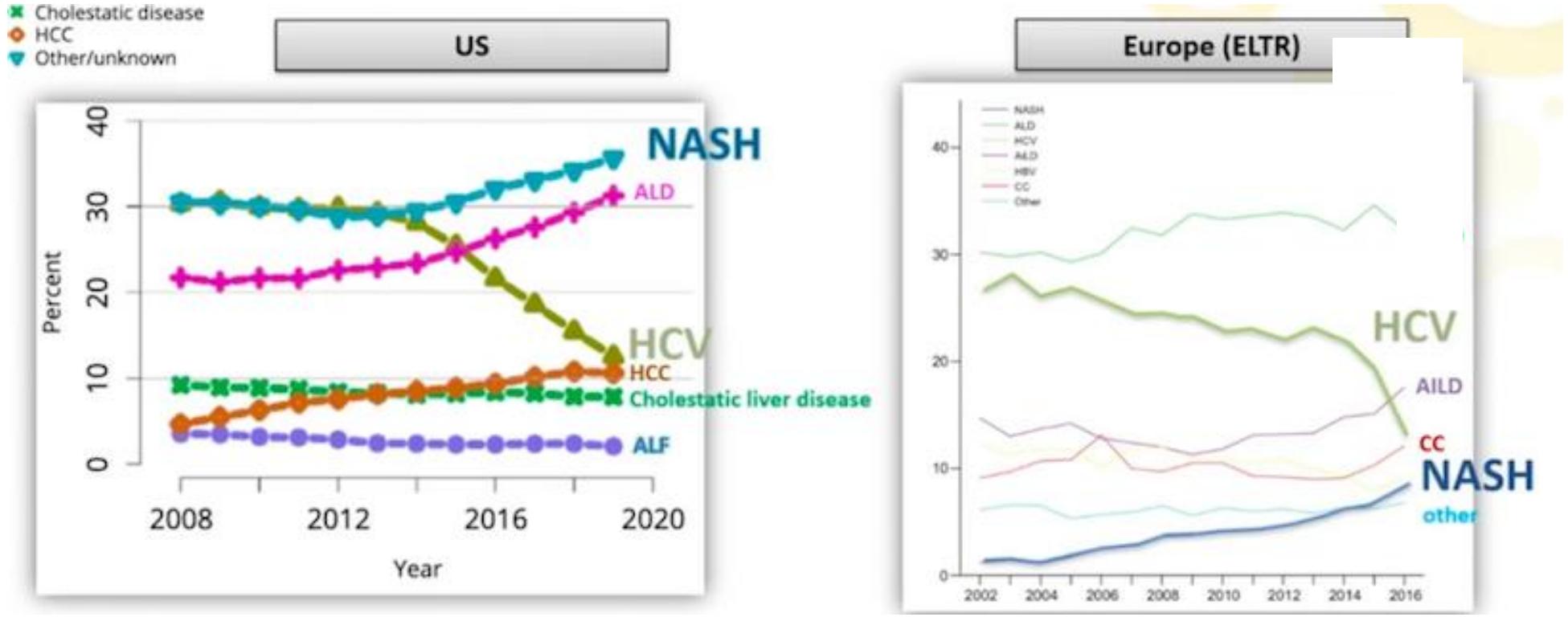
Hepatitis C (HCV)

- Trendovi u indikacijama za transplantaciju jetre



US – Sjedinjene Američke Države (eng. United States); ELTR - European Liver Transplant Registry; NASH – nealkoholna masna bolest jetre; ALD – alkoholna bolest jetre; ALF – akutno zatajenje jetre; HCC – hepatocelularni karcinom; CC – kolangiokarcinom;

* Kwong Am J Transpl 2021, Haladar J Hepatol 2019

Hepatitis B (HBV)

- Razlikujemo kronični B hepatitis i kroničnu hepatitis B infekciju

Tablica 1. Kronični B hepatitis

	HBeAg +	HBeAg -
HBV DNA	10 000 - 10 000 000 IU/ml ili >50 000 kopija/ ml	>2000 IU /ml ili >10 000 kopija /ml
ALT	iznad gornje granice normale	iznad gornje granice normale
PHD (indeks aktivnosti i stadij fibroze)	umjeren / izražen	umjeren / izražen
Nalaz elastografije	≥5,5 KPa	≥5,5 KPa
Stara terminologija	Imunoreaktivna faza	HBeAg neg. kronični hepatitis

Tablica 2. Kronična HBV infekcija

	HBeAg +	HBeAg -
HBV DNA	> 10 000 000 IU/ml	<2000 IU /ml ili <10 000 kopija/ ml
ALT	normalan	normalan
PHD (indeks aktivnosti i stadij fibroze)	0/ minimalan	0/ minimalan
Nalaz elastografije	<5,5 KPa	<5,5 KPa
Stara terminologija	Imunotolerantna faza	Inaktivni nosioc

* Smjernice za liječenje kroničnog hepatitisa B 2020.; Klinika za infektivne bolesti „Dr. Fran Mihaljević“ Referentni centar za dijagnostiku i liječenje virusnih hepatitisa Ministarstva zdravstva; Hrvatsko društvo za infektivne bolesti Hrvatskog liječničkog zbora

Hepatitis B (HBV)

Tablica 3. Indikacije za liječenje (ispunjena sva 3 uvjeta)

Povišen ALT
Prisustvo fibroze (F1-F4) ili sukladna vrijednosti elastografije
Viremija HBV DNA > 10000 kopija/ml tj. >2000 IU/ml
Ili prisustvo dodatnih indikacija za liječenje

Tablica 4. Nadopuna indikacija za liječene/profilaksu prema EASL preporukama iz 2017 god.

Svi bolesnici s cirozom (elastografija >12,5 KPa) bez obzira na razinu ALT i HBV DNA + ali visina nebitna
ALT 2x viši od normale, uz viremiju >100 000 kopija/ml (>20 000 IU/ml) bez obzira na fibrozu
HBeAg+, stariji od 30 godina, uz visoku viremiju, liječiti bez obzira na ALT i stadij fibroze
Ekstrahepatalne manifestacije HBV infekcije - bez obzira na ispunjenog drugih kriterija (vaskulitis, neuropatija, glomerulonefritis, poliarteritis nodosa i druge)
Hepatocelularni karcinom ili HBV ciroza u anamnezi kod roditelja i braće s HBV infekcijom
Profilaktička primjena kod trudnica koje imaju visoku viremiju radi sprečavanja vertikalne transmisije
Profilaktična primjena kod bolesnika na određenim oblicima imunosupresivne terapije
Snižavanje HBV viremije kod zdravstvenih djelatnika koji vrše invazivne postupke
Teški akutni hepatitis B

* Smjernice za liječenje kroničnog hepatitisa B 2020.; Klinika za infektivne bolesti „Dr. Fran Mihaljević“ Referentni centar za dijagnostiku i liječenje virusnih hepatitisa Ministarstva zdravstva; Hrvatsko društvo za infektivne bolesti Hrvatskog liječničkog zbora

Hepatitis B (HBV)

- Terapijske opcije u RH

Tablica 5. Nukleoz(t)idni analozi za liječenje HBV infekcije

TENOFOVIR DISOPROXIL FUMARAT (TDF)	1x1 tbl a 245 mg dnevno
ENTECAVIR (ETV)	1x1 tbl a 0,5 mg (ili 1 mg*) dnevno
TENOFOVIR ALAFENAMID (TAF)	1x1 tbl a 25 mg dnevno
LAMIVUDIN** (LAM)	1x1 tbl a 100 mg dnevno

*Bolesnici s dekompenziranom cirozom i oni prethodno izloženi lamivudinu dobivaju dnevnu dozu od 1 mg entecavira dnevno

**Primjenjuje se u iznimnim slučajevima

* Smjernice za liječenje kroničnog hepatitisa B 2020.; Klinika za infektivne bolesti „Dr. Fran Mihaljević“ Referentni centar za dijagnostiku i liječenje virusnih hepatitisa Ministarstva zdravstva; Hrvatsko društvo za infektivne bolesti Hrvatskog liječničkog zbora

Hepatitis B (HBV)

- Odabir lijeka ovisno o kliničkoj indikaciji

Tablica 6. Indikacije za primjenu TAF ili ETV umjesto tenofovira DF

TAF* ili entekavir su terapija izbora kod:
Dob >60 god
Osteoporoza ili sklonost frakturama u anamnezi
Kronična terapija kortikosteroidima
eGRF <60ml/min/1,73m2 ili pogoršanje postojeće eGRF za više od 25% u tijeku terapije TDF
Albuminurija >30 mg /dan, hiposfosfatemija<2,5 mg/dl
Hemodijaliza
Konkomitantna nefrotoksična terapija, hipertenzija, nekontrolirani diabetes

*TAF ako se zbog rezistencije ne može primijeniti entekavir

* Smjernice za liječenje kroničnog hepatitisa B 2020.; Klinika za infektivne bolesti „Dr. Fran Mihaljević“ Referentni centar za dijagnostiku i liječenje virusnih hepatitisa Ministarstva zdravstva; Hrvatsko društvo za infektivne bolesti Hrvatskog liječničkog zbora

Hepatitis B (HBV)

- Duljina trajanja terapije:

  - trajna u svih bolesnika s HBV cirozom
  - većinom trajna ili do negativizacije HBsAg
  - kod HBeAg pozitivnih, koji postanu u tijeku terapije anti HBe negativni, terapija se daje još 12 mjeseci od toga događaja, a pacijent se i dalje prate bolesti

* Smjernice za liječenje kroničnog hepatitisa B 2020.; Klinika za infektivne bolesti „Dr. Fran Mihaljević“ Referentni centar za dijagnostiku i liječenje virusnih hepatitisa Ministarstva zdravstva; Hrvatsko društvo za infektivne bolesti Hrvatskog liječničkog zbora

Hepatitis B (HBV)

- Reaktivacija HBV infekcije u uvjetima imunosupresije

Tablica 9. HBsAg neg, anti HBc pozitivni bolesnici - postupak kod bolesnika na imunosupresivnoj terapiji, kemoterapiji i terapiji kod transplantacije organa

HBsAg negativni, anti HBc pozitivni, (anti HBs pozitivan ili negativan)		
Stupanj rizika reaktivacije HBV	Vrste lijekova	Profilaksa reaktivacije hepatitisa
Umjeren rizik 1-10%	**Anti CD-20 protutijela** **Terapija kod tx matičnih stanica**	**Primaju profilaksu NA (TNF ili ETV ili TAF)** (po protokolu kao da su HBsAg pozitivni)
Mali rizik <1%	Anti CD- 52 protutijela Kortikosteroidi >20 mg/dan	Praćenje HBV DNA svakih 1 do 3 mjeseca a terapija u slučaju reaktivacije
Vrlo mali rizik	Citotoksična kemoterapija bez kortikosteroida Anti TNF Metotrexat Azathioprine	
Nepoznat rizik	Transplantacija solidnih organa Novi lijekovi, provjeriti SMPC	Individualne odluke

* Smjernice za liječenje kroničnog hepatitisa B 2020.; Klinika za infektivne bolesti „Dr. Fran Mihaljević“ Referentni centar za dijagnostiku i liječenje virusnih hepatitisa Ministarstva zdravstva; Hrvatsko društvo za infektivne bolesti Hrvatskog liječničkog zbora

Hepatitis D (HDV)

- „defektni„ RNA virus koji zahtjeva postojanje HBsAg za razvoj infekcije
- povećava morbiditet i mortalitet bolesnika s kroničnim HBV
- globalna prevalencija oko 5%

Clinical Practice Guidelines

JOURNAL
OF HEPATOLOGY

EASL Clinical Practice Guidelines on hepatitis delta virus☆

European Association for the Study of the Liver*

Received: 4 December 2023 | Accepted: 5 December 2023

DOI: 10.1097/HEP.0000000000000722

EDITORIAL

HDV screening in chronic HBV: An unmet need of growing importance

Shenoy A, Fontana RJ. Hepatology. 2024

Hepatitis D (HDV)

- Koga testirati za HDV?
  - barem jednom sve pacijente s kroničnom HBV infekcijom (**EASL**)*
  - re-testiranje za sve HBsAg+ pacijente s porastom transaminaza, pogoršanjem jetrene funkcije ili dekompenzacijom bolesti (**EASL**)*
  - 1x godišnje HBsAg+ pacijente s povišenim rizikom za HDV infekciju (**EASL**)*

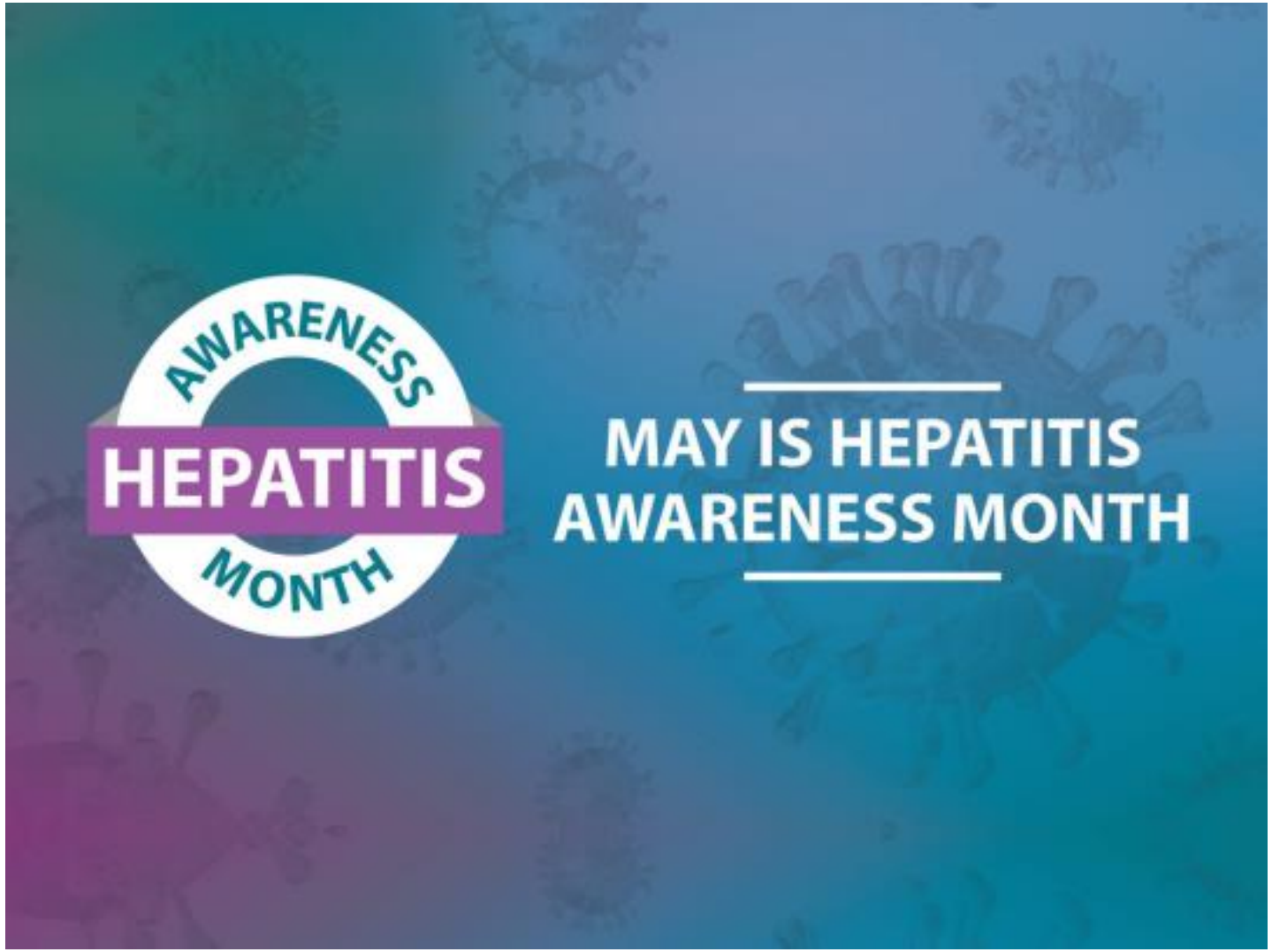
- Terapijske opcije:
  - pegiliranim interferonom alfa 2 kroz 48 tjedana uz primjenu NA ako je prisutna HBV replikacija**
  - Bulevirtide (BLV) – III. faza kliničkog ispitivanja u tijeku

* EASL CPG on hepatitis delta virus, J Hepatol. 2023

** Smjernice za liječenje kroničnog hepatitisa B 2020.; Klinika za infektivne bolesti „Dr. Fran Mihaljević“ Referentni centar za dijagnostiku i liječenje virusnih hepatitisa Ministarstva zdravstva; Hrvatsko društvo za infektivne bolesti Hrvatskog liječničkog zbora

Zaključak

- Virusni hepatitisi globalni javnozdravstveni problem
- Prevencija kroz edukaciju i imunizaciju
- Rano otkrivanje bolesti i početka adekvatne terapije u svrhu prevencije razvoja kronične bolesti jetre i komplikacija



* izvor: https://www.hiv.gov/blog/cdc-letter-may-hepatitis-awareness-month

Trendovi seroprevalencije i molekularna epidemiologije hepatitisa E u Hrvatskoj

Maja Bogdanić, Tatjana Vilibić Čavlek

pathogens

MDPI

Review

Hepatitis E Virus in Croatia in the "One-Health" Context

Anna Mrzljak [1,2,*], Lorena Jemersic [3], Vladimir Savic [4], Ivan Balen [5], Maja Ilic [6], Zeljka Jurekovic [7], Jadranka Pavicic-Saric [8], Danko Mikulic [9] and Tatjana Vilibic-Cavlek [2,10]

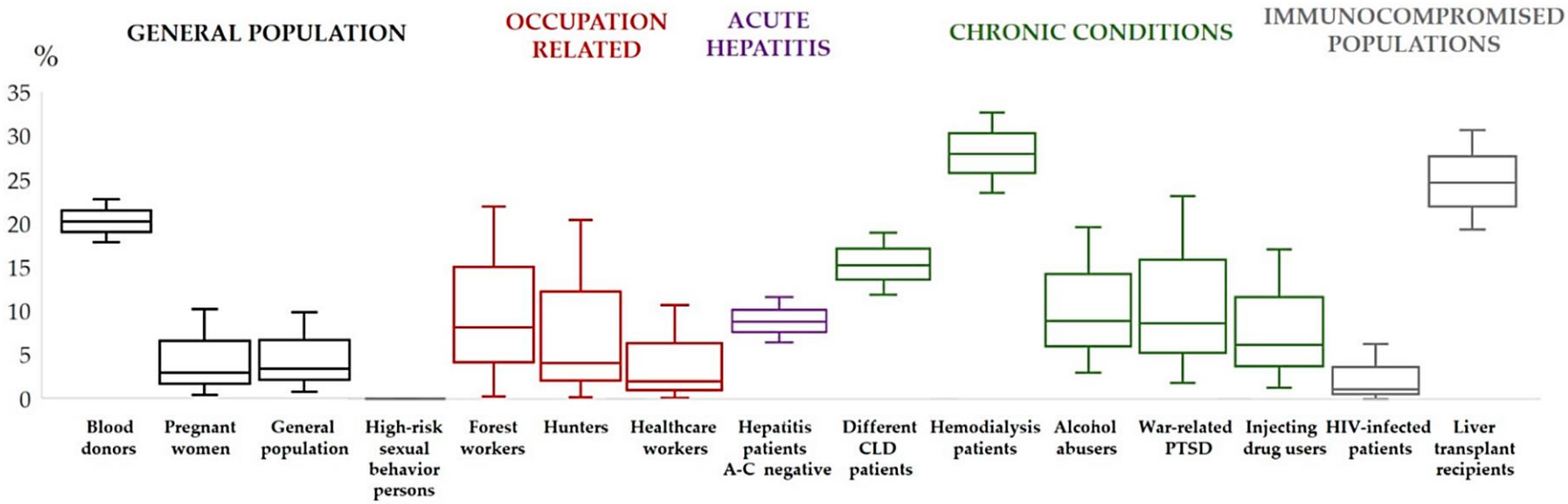


Figure 1. Hepatitis E virus IgG prevalence in different population groups in Croatia [51–59].

ORIGINAL ARTICLE

Seroepidemiology of Hepatitis E in Selected Population Groups in Croatia: A Prospective Pilot Study

T. Vilibic-Cavlek[1,2,*], M. Vilibic[3,*], B. Kolaric[4,5], L. Jemersic[6], J. Kucinar[7], L. Barbic[8], A. Bagaric[3], V. Stevanovic[8], I. Tabain[1], M. Sviben[2], V. Jukic[2,3] and G. Mlinaric-Galinovic[1,2]

Group	N tested (%)	HEV IgG N (%)	95%CI	AOR[a]	95%CI (AOR)
Overall	214 (100)	12 (5.6)	2.9–9.6	NA[b]	NA
Healthcare professionals (control group)	37 (17.3)	1 (2.7)	0.1–14.2	1	NA
Injecting drug users	49 (22.9)	3 (6.1)	1.3–16.9	4.69	0.35–62.26
Alcohol abusers	56 (26.2)	5 (8.9)	3.0–19.6	2.37	0.23–27.71
Individuals with high-risk sexual behaviour[c]	37 (17.3)	0 (0)	0–9.5	NA	NA
Patients with war-related PTSD[d]	35 (16.3)	3 (8.6)	1.8–23.1	2.47	0.17–35.05

Table 3. Seroprevalence of hepatitis E according to the sociodemographic characteristics and risk factors

Characteristic	Tested N (%)	HEV IgG N (%)	95% CI	*P*
Gender				
Male	170 (79.4)	9 (5.3)	2.4–9.8	0.715
Female	44 (20.6)	3 (6.8)	1.4–18.7	
Age group (years)				
≤30	44 (20.6)	1 (2.3)	0.1–12.0	0.023
31–40	57 (26.6)	1 (1.8)	0.1–9.4	
41–50	60 (28.0)	4 (6.7)	1.8–16.2	
50+	53 (24.8)	6 (11.3)	4.3–23.0	
Educational level				
≤Elementary school	38 (17.8)	1 (2.6)	0.1–13.8	0.657
High school	121 (56.5)	8 (6.6)	2.9–12.6	
University	55 (25.7)	3 (5.5)	1.2–15.1	
Marital status				
Married/stable relationship	120 (56.1)	10 (8.3)	4.1–14.8	0.071
Single/divorced/widowed	94 (43.9)	2 (2.1)	0.3–7.5	
Setting				
Urban	159 (74.3)	4 (2.5)	0.7–6.3	0.003
Suburban/rural	55 (25.7)	8 (14.5)	6.4–26.7	
Number of household members				
<2	57 (26.7)	1 (1.8)	0.1–9.4	0.046
2–4	124 (57.9)	7 (5.6)	2.3–11.3	
>4	33 (15.4)	4 (12.1)	3.4–28.2	
Water source				
Tap	194 (90.6)	9 (4.6)	2.1–8.6	0.089
Well	20 (9.4)	3 (15.0)	3.2–37.9	
Blood transfusion				
Yes	29 (13.5)	4 (13.8)	3.9–31.7	0.062
No	185 (86.5)	8 (4.3)	1.9–8.3	
Surgical intervention				
Yes	104 (48.6)	9 (8.7)	4–15.8	0.076
No	110 (51.4)	3 (2.7)	5.7–7.8	
Needle exposure (tattoo)				
Yes	67 (31.3)	6 (9.0)	3.4–18.5	0.199
No	147 (68.7)	6 (4.1)	1.5–8.7	
Travelling				
Yes	80 (37.4)	6 (7.5)	2.8–15.6	0.371
No	134 (62.6)	6 (4.5)	1.7–9.5	
Risk sexual behaviour[a]				
Yes	51 (23.8)	1 (2.0)	0.1–10.4	0.251
No	84 (39.3)	7 (8.3)	3.4–16.4	
Missing	79 (36.9)	–	–	
Sexual orientation				
Heterosexual	109 (50.9)	5 (4.6)	1.5–10.4	0.586
Homo-/bisexual	23 (10.8)	0 (0)	0–14.8	
Missing	82 (38.3)	–	–	

Vilibic-Cavlek T, Vilibic M, Kolaric B, Jemersic L, Kucinar J, Barbic Lj, Bagaric A, Stevanovic V, Tabain I, Sviben M, Jukic V, Mlinaric-Galinovic G. ***Seroepidemiology of hepatitis E in selected population groups in Croatia: a prospective pilot study.*** *Zoonoses Public Health 2016; 63(6):494-502.*

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ORIGINAL ARTICLE

Observational Study

Insights into hepatitis E virus epidemiology in Croatia

Pavle Jelicic, Thomas Ferenc, Anna Mrzljak, Lorena Jemersic, Natasa Janev-Holcer, Milan Milosevic, Maja Bogdanic, Ljubo Barbic, Branko Kolaric, Vladimir Stevanovic, Mateja Vujica, Zeljka Jurekovic, Jadranka Pavicic Saric, Maja Vilibic, Tatjana Vilibic-Cavlek

Table 2 Hepatitis E virus immunoglobulin G prevalence in exposed and nonexposed populations

Population group	Tested, *n* (%)	HEV IgG, *n* (%)	95%CI	*P* value
Hunters	74	11 (14.9)	8.2-14.2	0.003
Veterinarians	151	23 (15.2)	10.2-21.6	
Forestry workers	93	6 (6.5)	2.7-12.8	
General population	126	9 (7.1)	3.3-13.1	
Pregnant women	118	2 (1.7)	0.2-5.9	
Liver transplant recipients	83	16 (19.3)	11.4-29.4	
Kidney transplant recipients	43	3 (6.9)	1.5-19.1	
Hematopoietic stem cell recipients	39	2 (5.1)	0.6-7.3	

Table 3 Hepatitis E virus immunoglobulin G prevalence according to sociodemographic characteristics

Characteristic	Subjects[1], *n*	HEV IgG, *n* (%)	95%CI	*P* value
Sex				0.065
Male	238	29 (10.9)	7.6-15.0	
Female	282	22 (7.2)	4.7-10.6	
Age group in yr				< 0.001
< 30	99	3 (2.9)	0.8-7.6	
30-39	147	11 (7.0)	3.8-11.7	
40-49	94	5 (5.1)	2.0-10.7	
50-59	90	11 (10.9)	5.9-18.1	
60 +	62	19 (23.5)	15.3-33.5	
Area of residence				0.144
Rural	151	16 (9.6)	5.8-14.7	
Suburban	54	11 (16.9)	9.3-27.4	
Urban	255	24 (8.6)	5.7-12.3	
Number of household members				0.301
≤ 3	258	22 (7.9)	5.1-11.4	
> 3	177	21 (10.6)	6.9-15.5	
Educational level				0.467
Primary school	58	5 (7.9)	3.1-16.5	
High school	254	25 (9.0)	6.0-12.7	

VECTOR-BORNE AND ZOONOTIC DISEASES
Volume XX, Number XX, 2020

DOI: 10.1089/vbz.2020.2676

The Burden of Hepatitis E Infection in Chronic Liver Diseases in Croatia

Anna Mrzljak,[1,2] Petra Dinjar-Kujundzic,[1] Lorena Jemersic,[3] and Tatjana Vilibic-Cavlek[2,4]

Abstract

In patients with chronic liver disease (CLD), hepatitis E virus (HEV) may lead to decompensation and death. We tested 438 CLD patients (71.0% male; age 23–84 years) for HEV-IgG antibodies. Reactive samples were tested for HEV-IgM antibodies using ELISA. IgM positive samples were tested for HEV RNA using RT-PCR. HEV-IgG antibodies were found in 15.1% of patients, whereas 4.5% of IgG positive patients had detectable IgM antibodies. Not a single patient tested HEV RNA positive. Seroprevalence increased with age, from 9.7% (<45 years) to 17.4% (>60 years, $p=0.368$). There was no difference in HEV-IgG seropositivity related to gender, level of education, geographic region, area of residence, liver disease, or hepatocellular carcinoma presence. Previous exposure to HEV was detected in 15.1% of patients, corresponding with the data from other endemic European regions. Despite the high local exposure, we did not find any evidence of acute or chronic hepatitis E among CLD patients.

HEV IgG 15,1%

TABLE 1. HEPATITIS E IGG SEROPREVALENCE AMONG PATIENTS WITH CHRONIC LIVER DISEASES

Characteristics	*Tested,* N	*HEV IgG,* N *(%)*	p
Gender			0.968
Male	311	47 (15.1)	
Female	127	15 (15.0)	
Age group (years)			0.368
<45	62	6 (9.7)	
45–59	232	35 (15.1)	
>60	88	25 (17.4)	
Educational level			0.899
Elementary school	57	8 (14.0)	
High school	238	38 (16.0)	
College/university	78	12 (15.4)	
Unknown	65	8 (12.3)	
Geographic region			0.777
Continental	292	43 (14.7)	
Littoral	146	23 (15.8)	
Area of residence			0.244
Urban	210	36 (17.1)	
Suburban/rural	228	30 (13.2)	
Etiology of liver disease			0.207
Alcohol-related liver disease	257	41 (16.0)	
Viral hepatitis (HBV+HCV)	65	11 (16.9)	
Autoimmune liver disease	61	7 (11.5)	
NAFLD+cryptogenic cirrhosis	55	7 (12.7)	
Liver tumor			
No	300	44 (14.7)	0.729
Yes	138	22 (15.9)	

International Urology and Nephrology
https://doi.org/10.1007/s11255-019-02363-3

NEPHROLOGY - ORIGINAL PAPER

Seroepidemiology of hepatitis E in patients on haemodialysis in Croatia

Anna Mrzljak[1,2] · Petra Dinjar-Kujundzic[1] · Mladen Knotek[1,2] · Boris Kudumija[3] · Mario Ilic[4] · Marijana Gulin[5] · Lada Zibar[6,7] · Irena Hrstic[8] · Zeljka Jurekovic[1] · Branko Kolaric[9,10] · Lorena Jemersic[11] · Jelena Prpic[11] · Morana Tomljenovic[10,12] · Tatjana Vilibic-Cavlek[2,13]

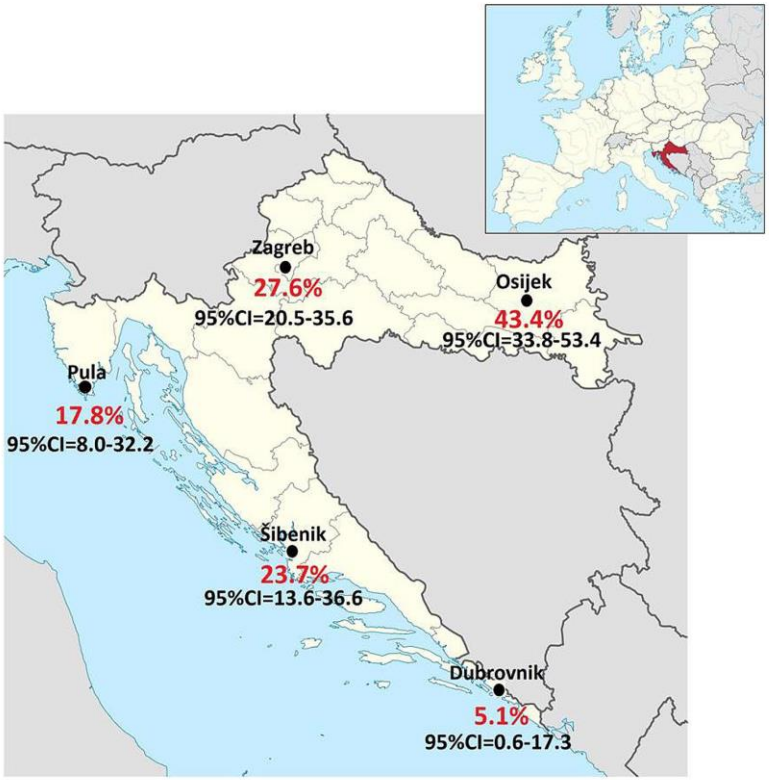

Fig. 1 Seroprevalence of hepatitis E in patients on haemodialysis according to geographic location in Croatia

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Vol.:52:e20190302: 2019
doi: 10.1590/0037-8682-0302-2019

Short Communication

Hepatitis E seroprevalence and associated risk factors in Croatian liver transplant recipients

Anna Mrzljak[1],[2], Petra Dinjar-Kujundzic[1], Tatjana Vilibic-Cavlek[2],[3], Lorena Jemersic[4], Jelena Prpic[4], Oktavija Dakovic-Rode[5],[6], Branko Kolaric[7],[8] and Adriana Vince[2],[9]

Abstract

Introduction: Solid-organ transplant recipients are at risk of hepatitis E virus (HEV) infection. We analyzed the seroprevalence/risk factors of HEV in Croatian liver transplant recipients. **Methods**: Two hundred forty-two serum samples were tested for HEV immunoglobuline IgG/IgM and HEV RNA. Sociodemographic data and risk factors were collected using a questionnaire. **Results**: HEV IgG seroprevalence rate was 24.4%. Positive/equivocal HEV IgM were found in two patients. HEV RNA was not detected. Logistic regression showed that older age, female gender, rural area/farm, water well, and septic tank were associated with HEV seropositivity. **Conclusions**: This study revealed a high exposure rate to HEV in Croatian liver recipients.

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Review

Seroprevalence Trends and Molecular Epidemiology of Viral Hepatitis in Croatia

Tatjana Vilibic-Cavlek [1,2,*,†], Snjezana Zidovec-Lepej [3,*,†], Thomas Ferenc [4], Vladimir Savic [5], Tatjana Nemeth-Blazic [6], Mateja Vujica Ferenc [7], Maja Bogdanic [1], Maja Vilibic [8,9], Bojana Simunov [10], Natasa Janev-Holcer [11,12], Pavle Jelicic [11], Dominik Ljubas [13], Tian Kosar [1], Maja Ilic [6], Jasmina Kucinar [14], Ljubo Barbic [15], Vladimir Stevanovic [15] and Anna Mrzljak [2,16]

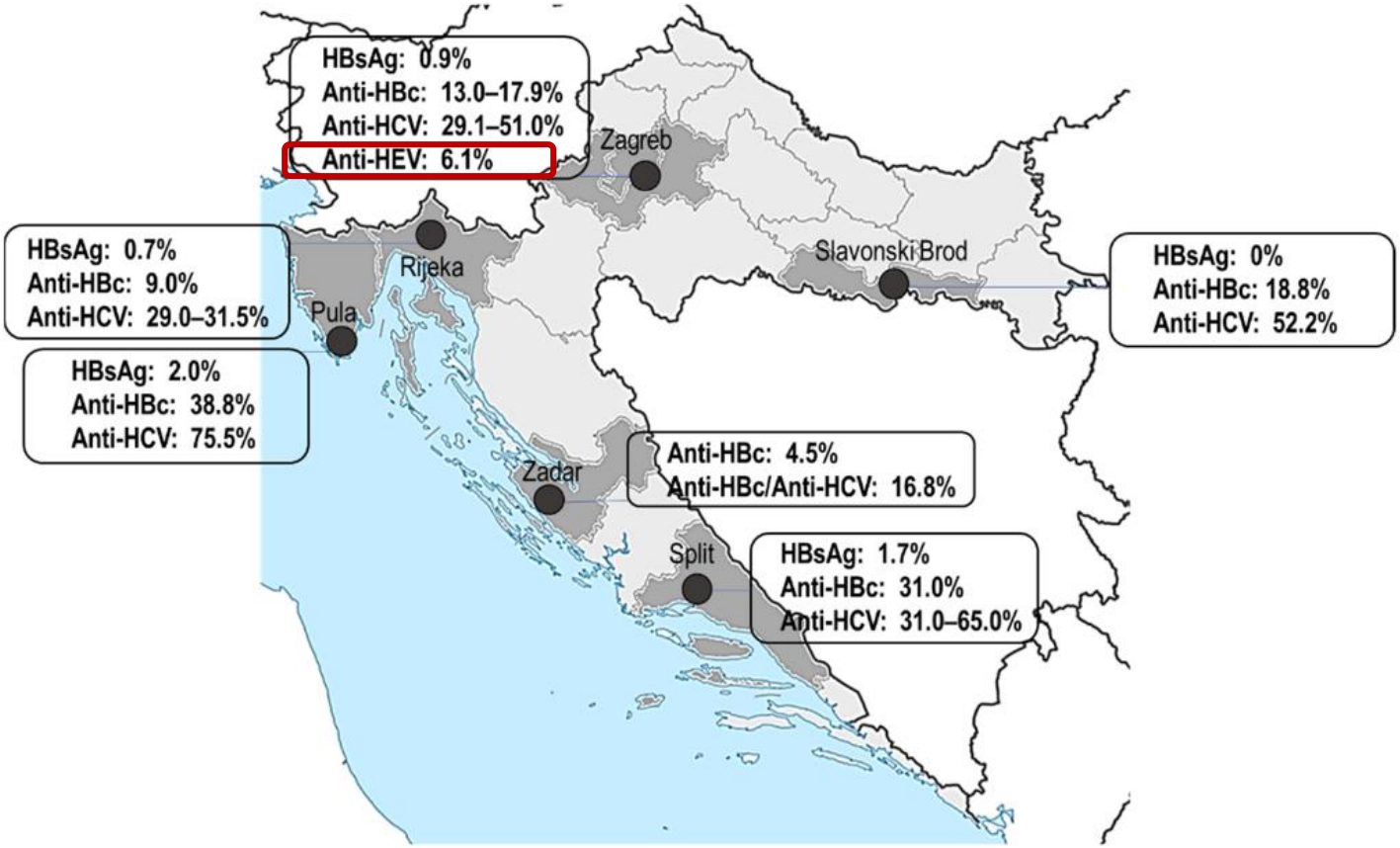

Figure 4. Prevalence of viral hepatitis markers in PWID in Croatia.

life

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Review

Seroprevalence Trends and Molecular Epidemiology of Viral Hepatitis in Croatia

Tatjana Vilibic-Cavlek [1,2,*,†], Snjezana Zidovec-Lepej [3,*,†], Thomas Ferenc [4], Vladimir Savic [5], Tatjana Nemeth-Blazic [6], Mateja Vujica Ferenc [7], Maja Bogdanic [1], Maja Vilibic [8,9], Bojana Simunov [10], Natasa Janev-Holcer [11,12], Pavle Jelicic [11], Dominik Ljubas [13], Tian Kosar [1], Maja Ilic [6], Jasmina Kucinar [14], Ljubo Barbic [15], Vladimir Stevanovic [15] and Anna Mrzljak [2,16]

Table 1. Prevalence of viral hepatitis markers in groups with high-risk sexual behavior in Croatia.

Population Group	Viral Hepatitis Marker	Year(s) Tested	N Tested	N (%) Positive	95%CI	Reference
Clients from voluntary counseling and testing centers [a]	HBsAg	2011–2013	443	11 (2.6)	1.3–4.5	[5]
	Anti-HBc	2011–2013	443	54 (12.1)	9.1–15.5	
MSM population	Anti-HAV	2006	360	(14.2)	9.1–19.8	[43]
	HBsAg	2006	360	2 (0.5)	0.1–1.9	
	Anti-HBc	2006	360	33 (9.2)	5.2–13.1	
	Anti-HCV	2006	360	11 (3.0)	1.1–5.3	
		2003–2006	205	6 (2.9)	0.5–5.2	[44]
	Anti-HEV	2014–2015 2018–2019	53	1 (1.9)	0.1–10.1	[33], CIPH, unpublished data
Persons with multiple sexual partners	Anti-HCV	2003–2006	378	24 (6.3)	3.9–8.8	[44]
Persons with a history of STDs		2003–2006	199	17 (8.5)	4.7–12.4	[44]

MSM = men who have sex with men; CSW = commercial sex workers; STDs = sexually transmitted diseases; CIPH = Croatian Institute of Public Health; [a] = includes MSM, bisexual persons, CSW or clients of CSW, and highly promiscuous persons.

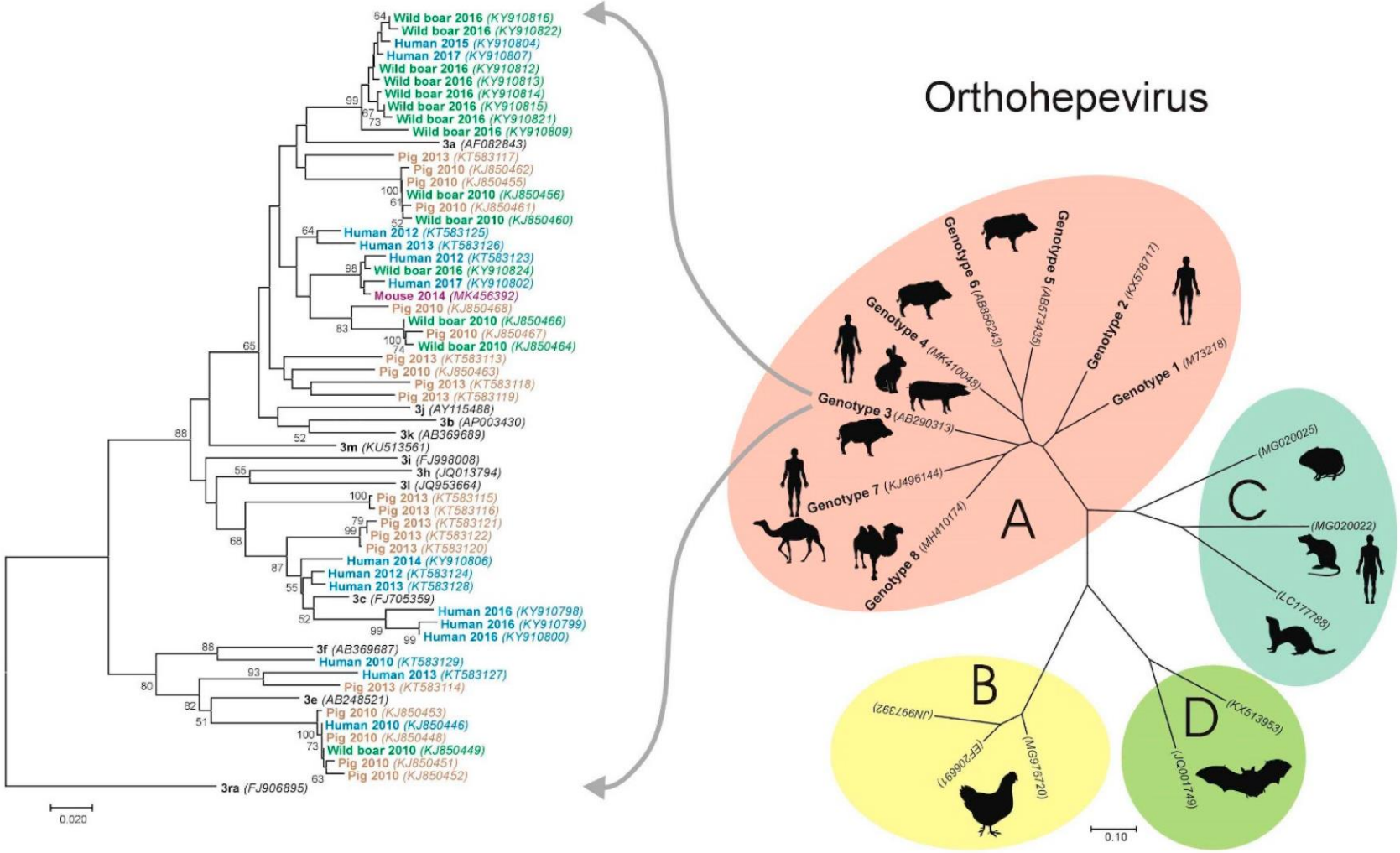

Figure 2. The radial phylogenetic tree displays genus *Orthohepevirus* comprising four species: *Orthohepevirus A*, *B*, *C* and *D*, respectively, with the main hosts indicated as figures. The rectangular phylogenetic tree displays the genetic and host diversity of the selected hepatitis E virus (HEV) isolates from Croatia, which belong to genotype 3 of *Orthohepevirus A*, as indicated in the radial phylogenetic tree. The evolutionary history was inferred using the Neighbor-Joining method. Supporting (≥50%) bootstrap values of 1000 replicates are displayed at the nodes in the rectangular tree. Scale bars indicate nucleotide substitutions per site. HEV isolates from Croatia are color-coded (blue—human origin, green—wild boar origin, brown—pig origin and purple—mouse origin). Designations also include detection years for Croatian strain and GenBank accession numbers. The taxa in black color in the rectangular tree are genotype 3 subtype reference strains, according to Smith et al. [62].

INFEKCIJE PROBAVNOG SUSTAVA: NOVOSTI U EPIDEMIOLOGIJI, KLINIČKOJ SLICI, DIJAGNOSTICI, TERAPIJI I PREVENCIJI

Zagreb, 17/05/2024

Hepatitis E infection in immunocompromised populations in Croatia

Anna Mrzljak, MD, PhD, FEBGH
University Hospital Centar Zagreb
School of Medicine, University of Zagreb

Increasing interest for HEV in immunocompromised setting

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hev and immunocompromised

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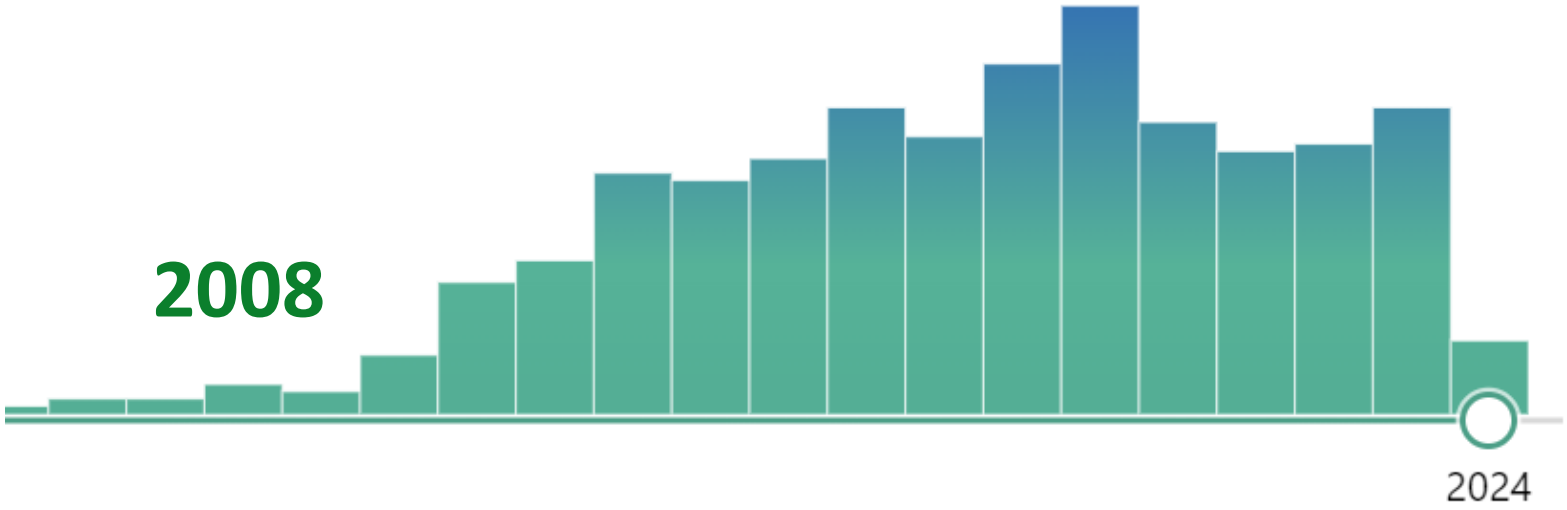


Chronic HEV infection after solid organ transplant

The NEW ENGLAND JOURNAL of MEDICINE

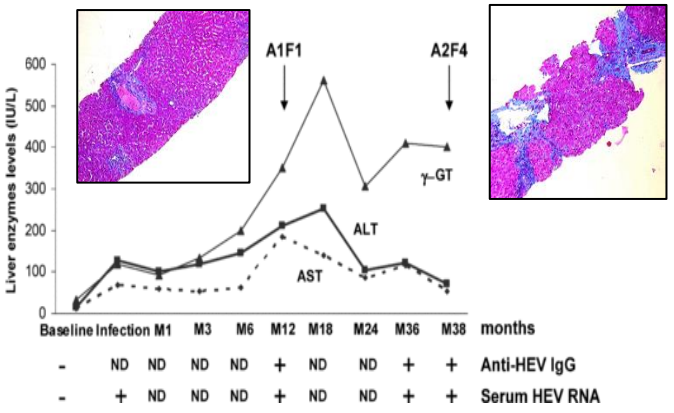
BRIEF REPORT

Hepatitis E Virus and Chronic Hepatitis in Organ-Transplant Recipients

Nassim Kamar, M.D., Ph.D., Janick Selves, M.D., Jean-Michel Mansuy, M.D., Leila Ouezzani, M.D., Jean-Marie Péron, M.D., Ph.D., Joëlle Guitard, M.D., Olivier Cointault, M.D., Laure Esposito, M.D., Florence Abravanel, Pharm.D., Marie Danjoux, M.D., Dominique Durand, M.D., Jean-Pierre Vinel, M.D., Jacques Izopet, Pharm.D., Ph.D., and Lionel Rostaing, M.D., Ph.D.

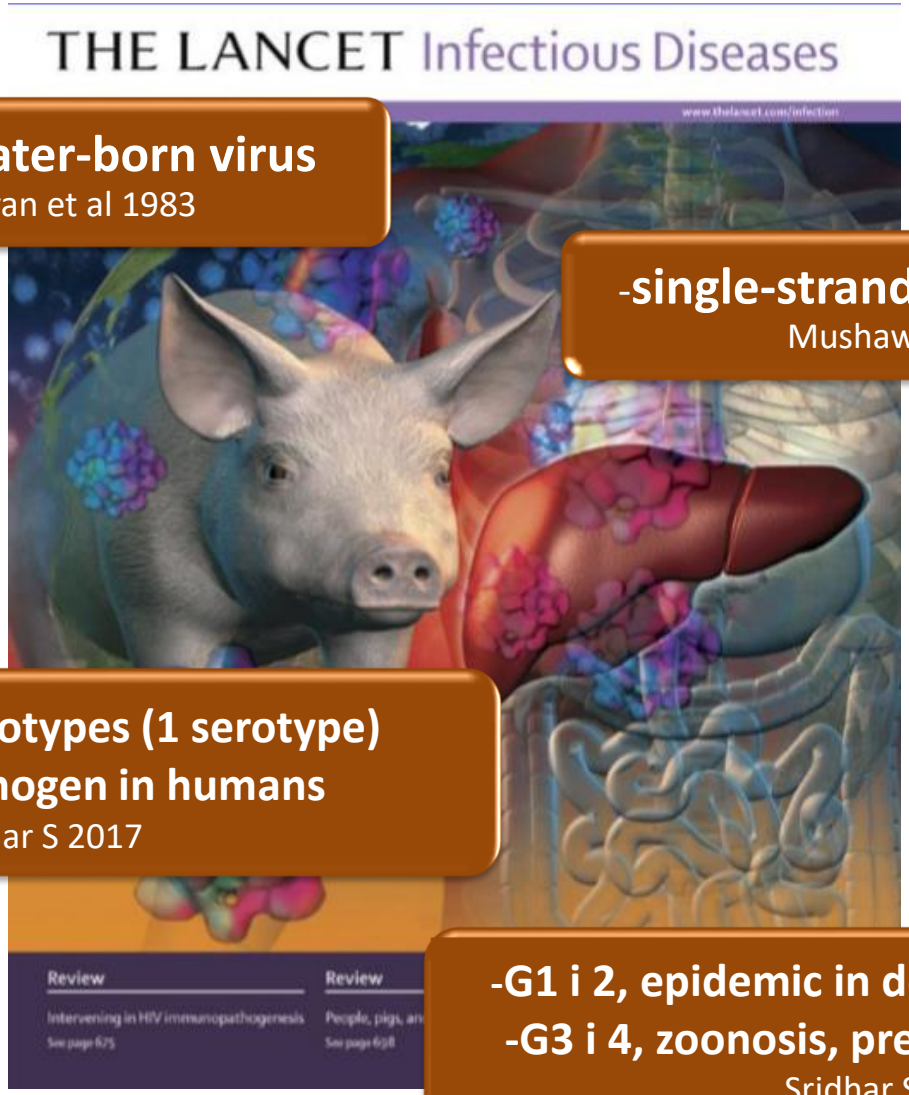
14 acute HEV cases after liver or kidney transplant
- 8 developed chronic hepatitis
- asymptomatic, anicetric
- ALT 200-300 IU/L

Chronic HEV
Rapid progression to cirrhosis after SOT



KAMAR et al, *Am J Transplant* 2008;8:1744-8

Hepatitis E virus



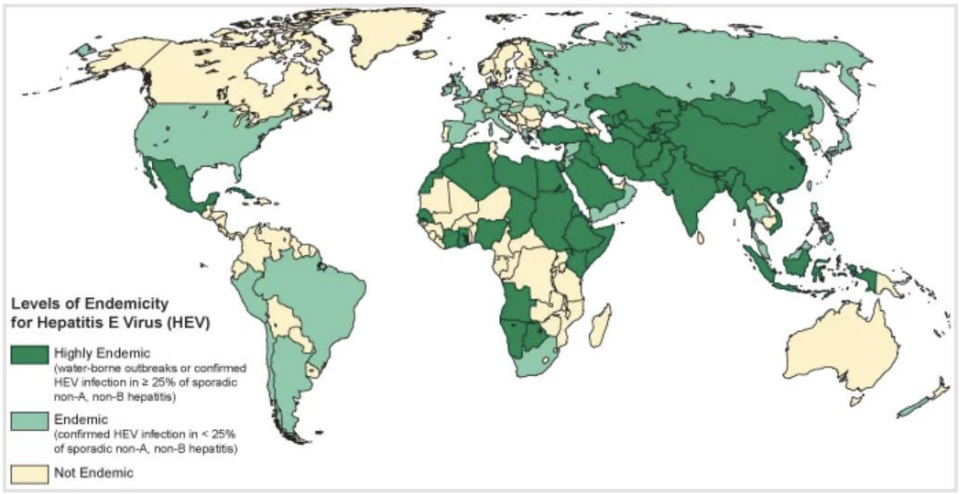
-1983, water-born virus
Balayan et al 1983

-single-stranded RNA virus
Mushawar 2008

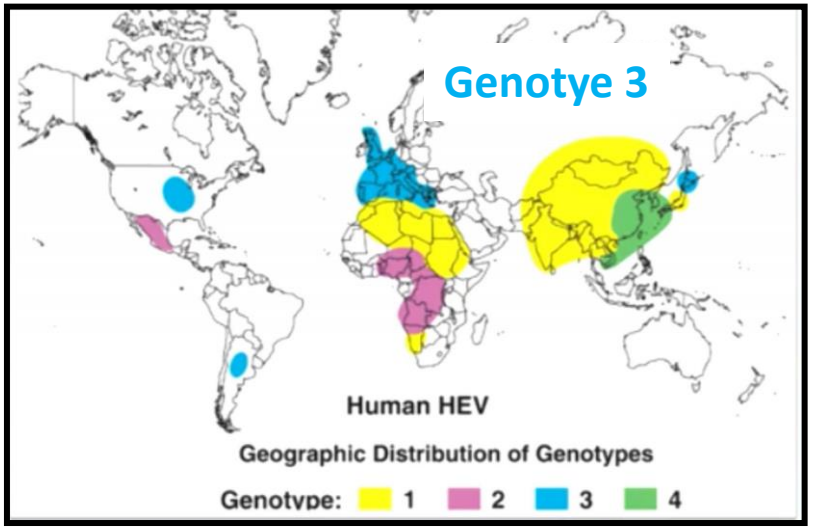
- 8 different genotypes (1 serotype)
-G 1-4,7 pathogen in humans
Sridhar S 2017

-G1 i 2, epidemic in developing countries
-G3 i 4, zoonosis, predominantly in pigs
Sridhar S 2017

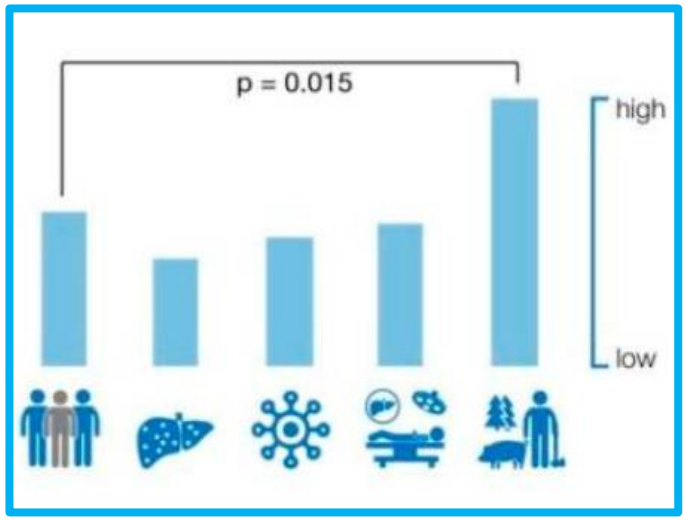
HEV: Geographic distribution



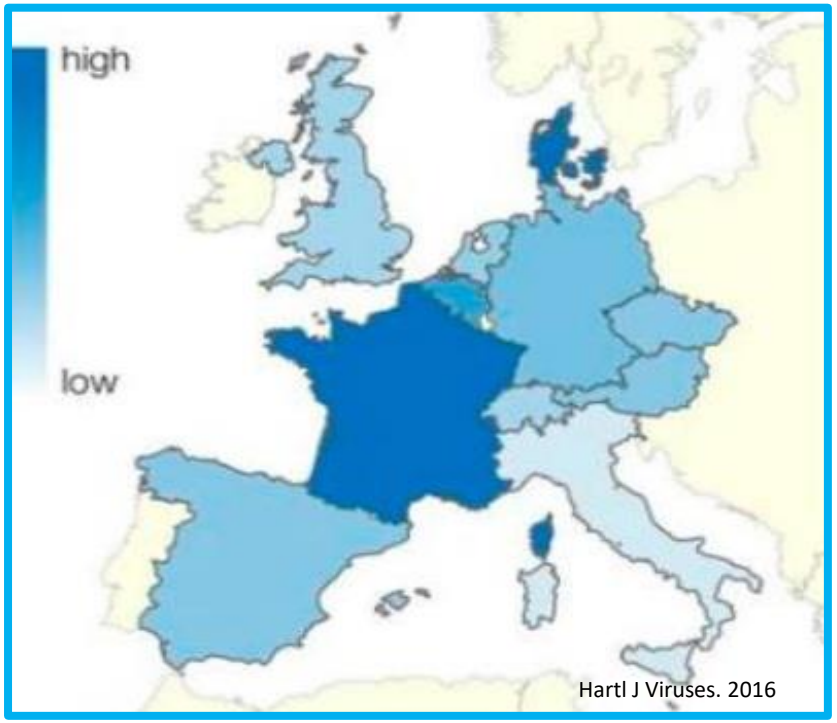
https://microbenotes.com/hepatitis-e-virus/



Europe seroprevalence rates
0.6% to 52.5%



general population, liver diseases**, HIV infections, transplant recipients**, swine/wild animal contact (farmers, veterinarians, slaughterhouse workers, forestry workers)



Hartl J Viruses. 2016

HEV infection: Symptoms

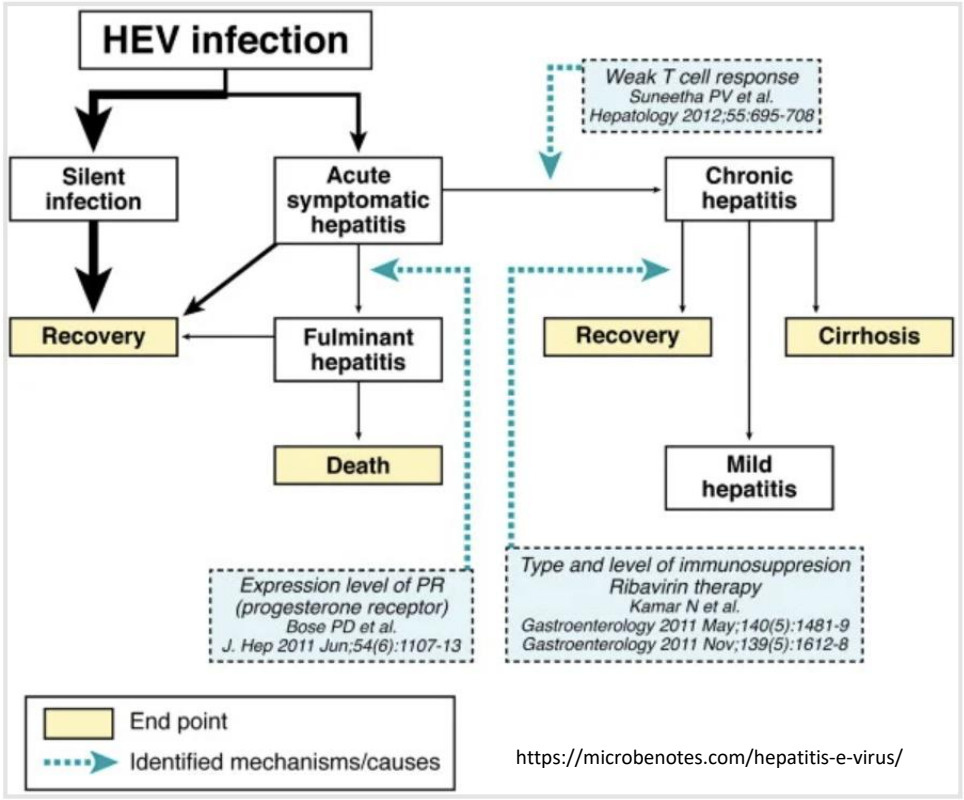
-acute self-limitating hepatitis

-anicteric ≈50% adults

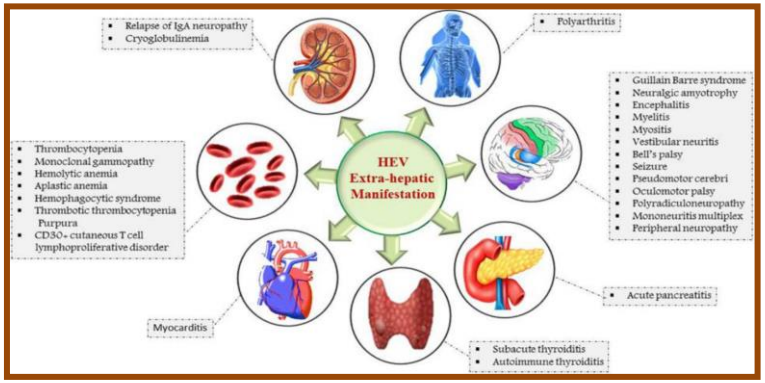
-acute liver failure (pregnant)

-acute-on-chronic (pre-existing liver disease)

-chronic hepatitis (immunocompromised)



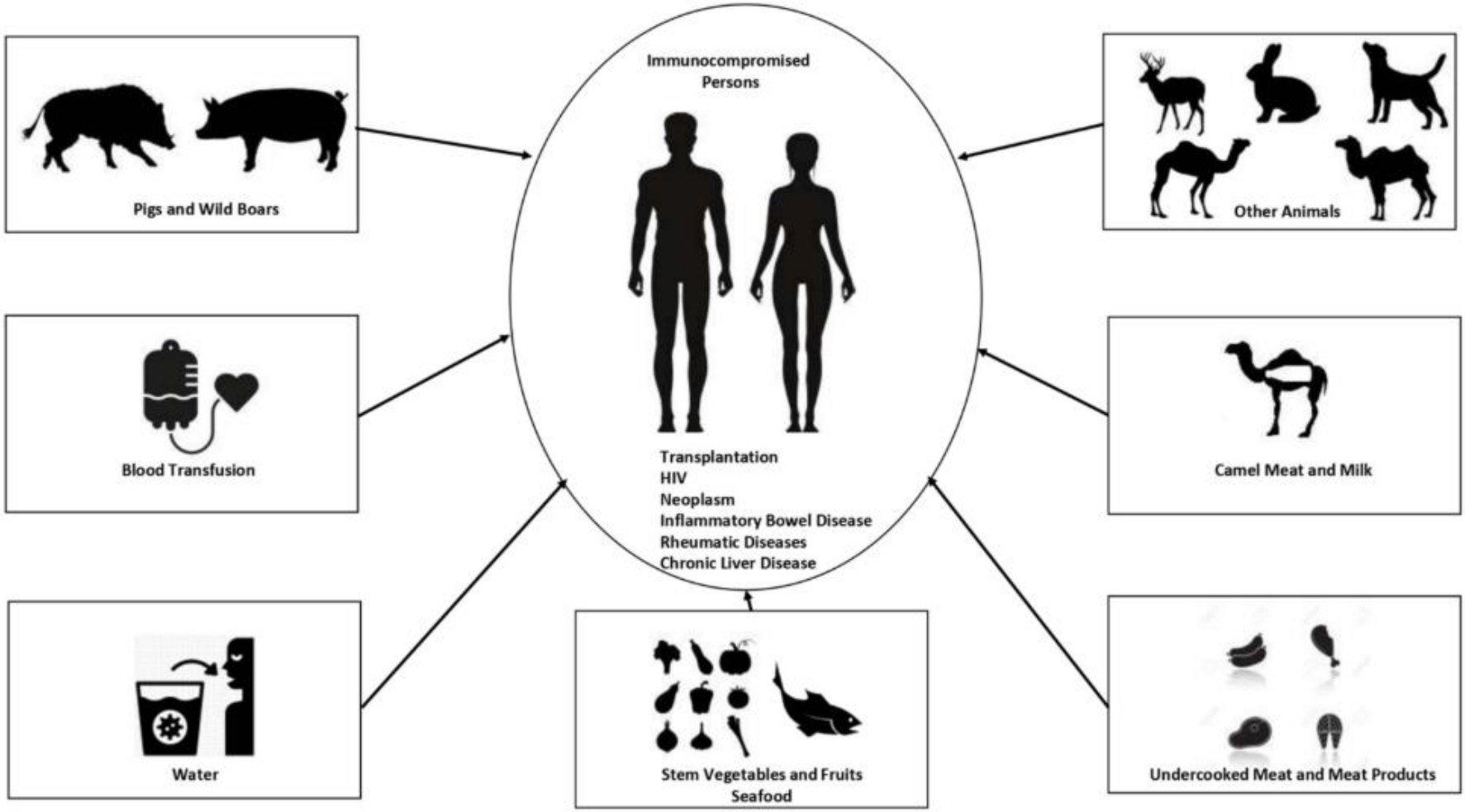
https://microbenotes.com/hepatitis-e-virus/



Extrahepatic manifestations

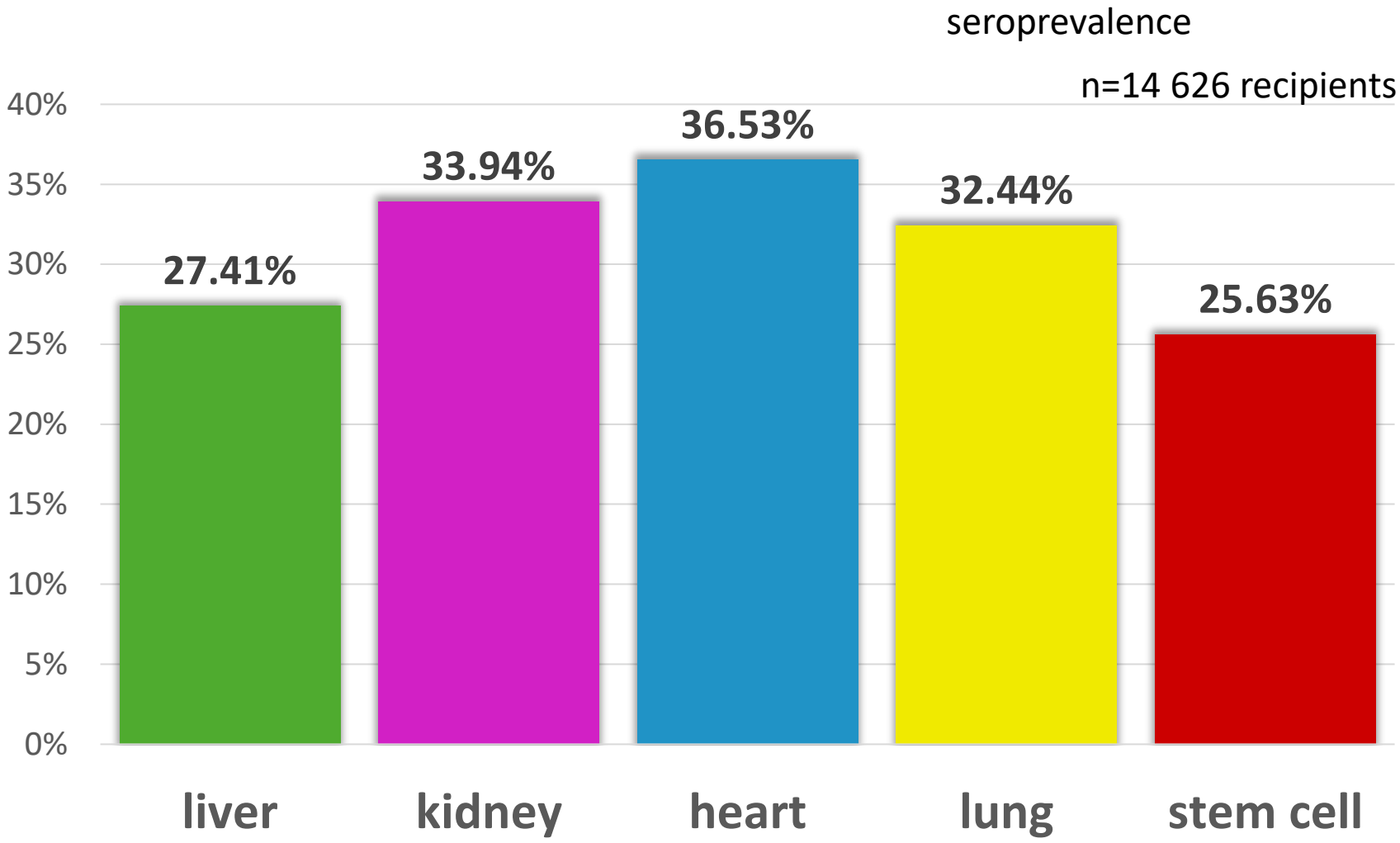
Thakur V. Front Microbiol. 2020

Transmission routes in immunocompromised



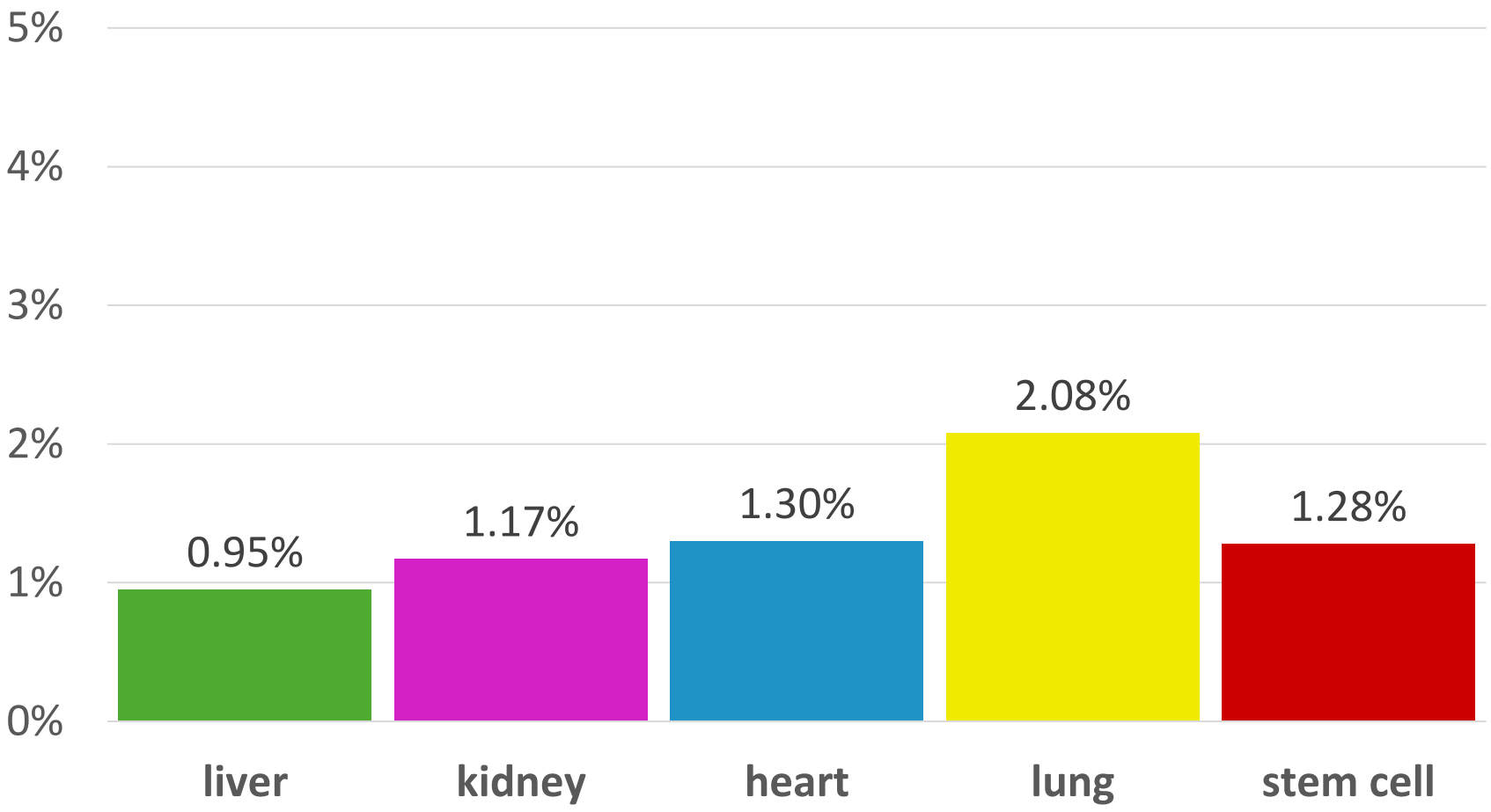
Alexandrova R, Infect Drug Resist. 2024.

The burden of HEV in transplant recipients



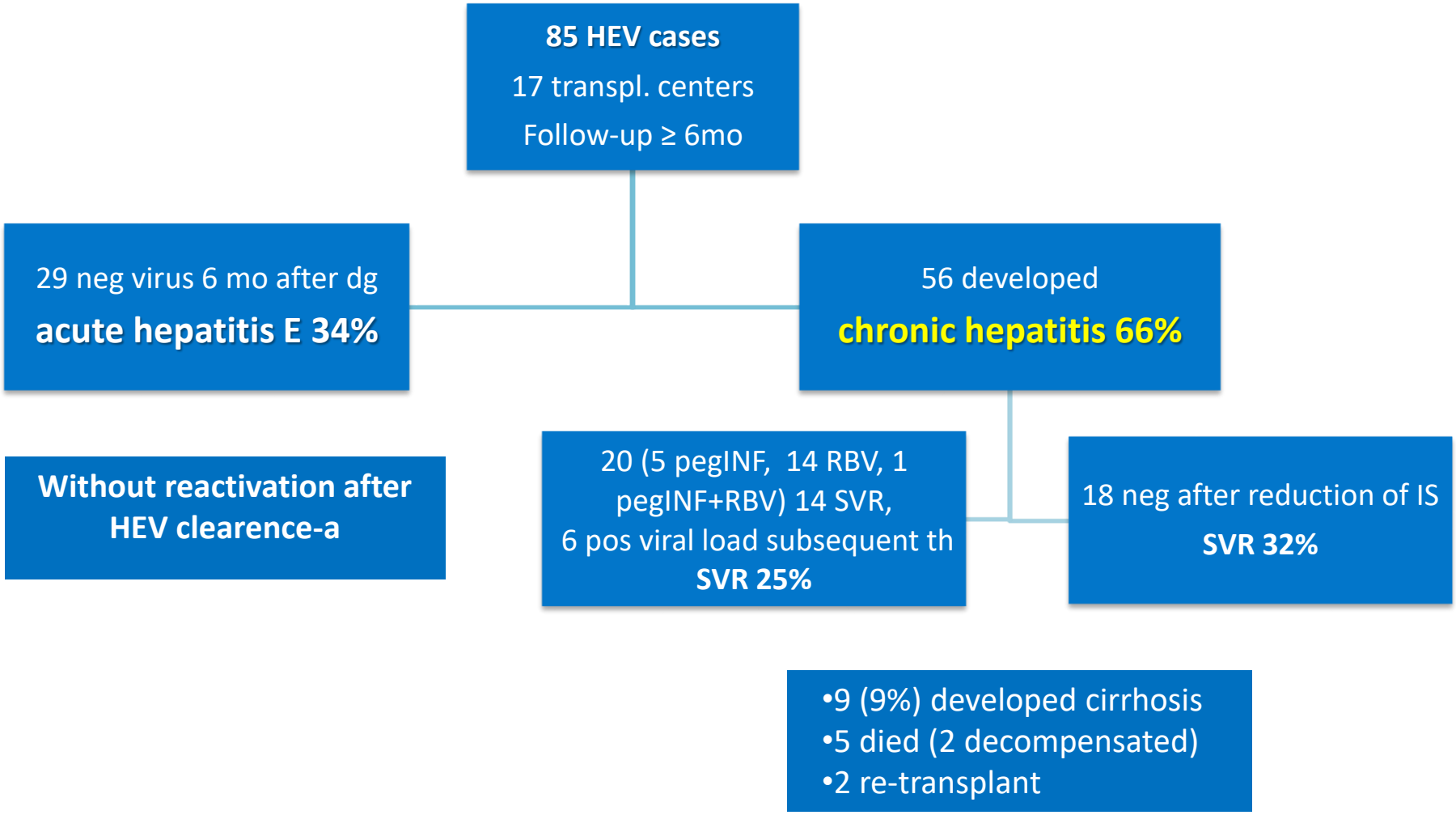
Buescher G. Liver Int. 2021.

HEV RNA prevalance in transplant recipients



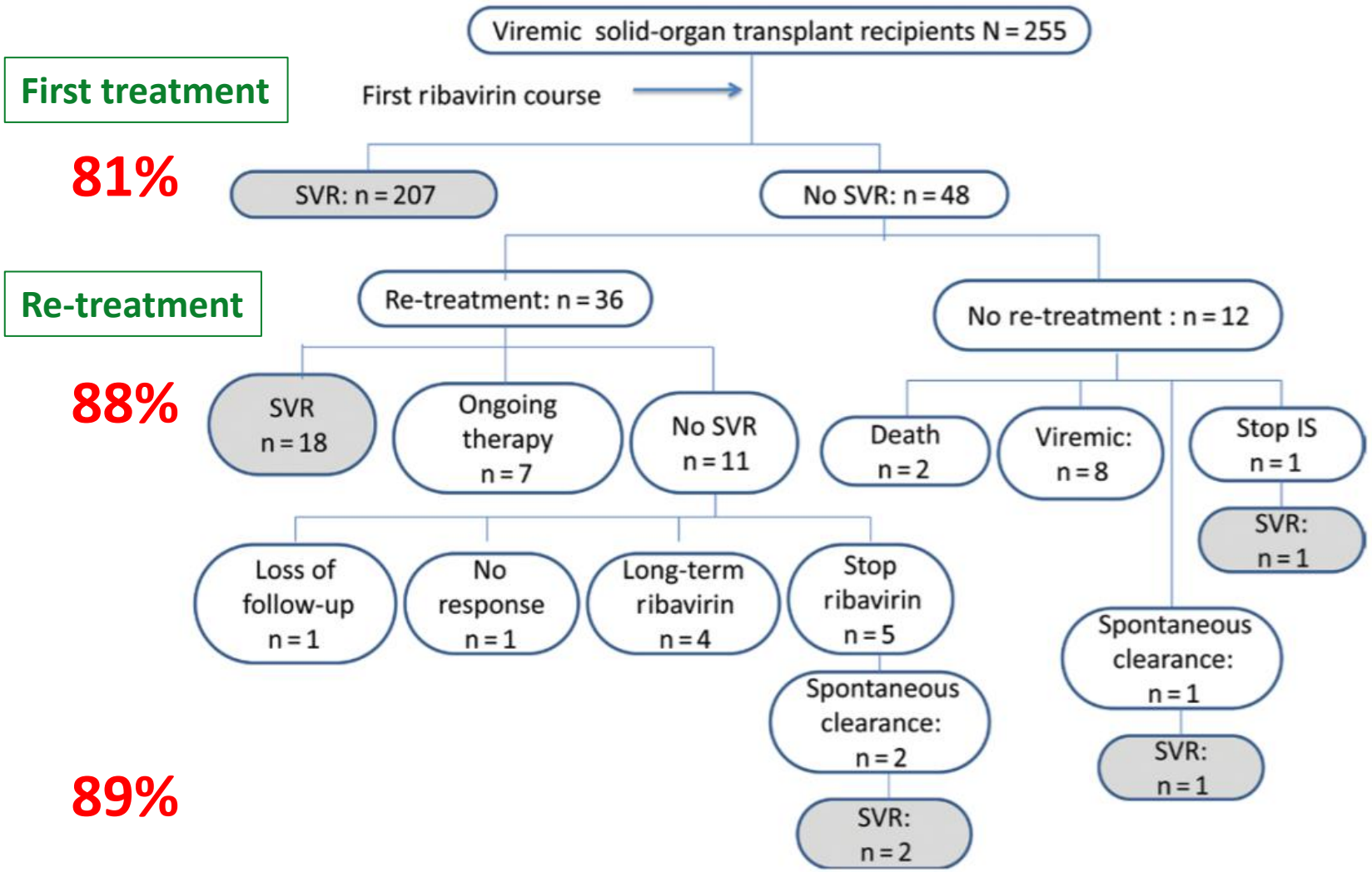
Buescher G. Liver Int. 2021.

Chronic HEV infection after SOT



Kamar A, Gastro 2011

Ribavirin for Hepatitis E Virus Infection After Organ Transplantation: A Large European Retrospective Multicenter Study



Karam et al Clinical Infectious Diseases 2020

Patient groups at risk of harm from persistent HEV infection

severe **primary immunodeficiency**

SOT, currently on IS

HSCT 12 months after IS or GVHD

malignant disease, IS chemotherapy or radiotherapy, or terminated treatment < 6 months

HIV, CD4 count of <200/mm3

systemic high dose steroids, until 3 months after

other IS drugs w/out steroids, until 6 months after

fetuses and neonates

transplant candidates, within 3 months of SOT

https://assets.publishing.service.gov.uk/media/5a7c41ea40f0b62dffde0e0f/Hepatitis_E_Guidelines.pdf

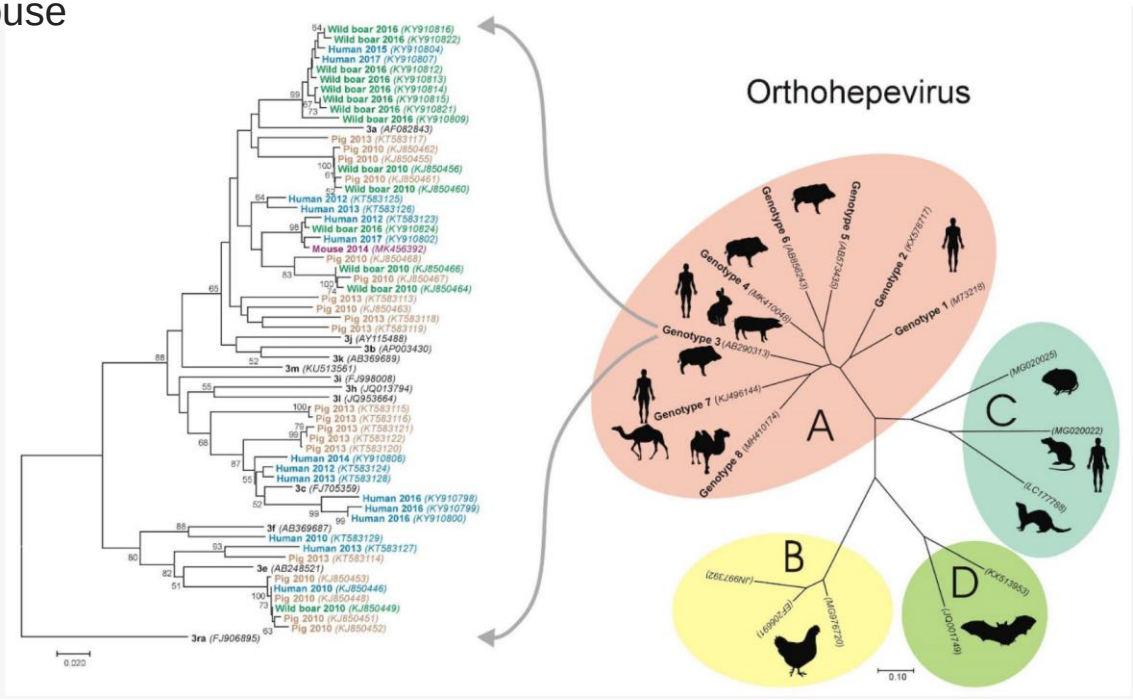
HEV genotypes in Croatia

endemic

- subtype 3a - 65.5%
  - humans, pigs, wild boars, mouse
- subtype 3c - 23.1%
  - humans and pigs

newly imported

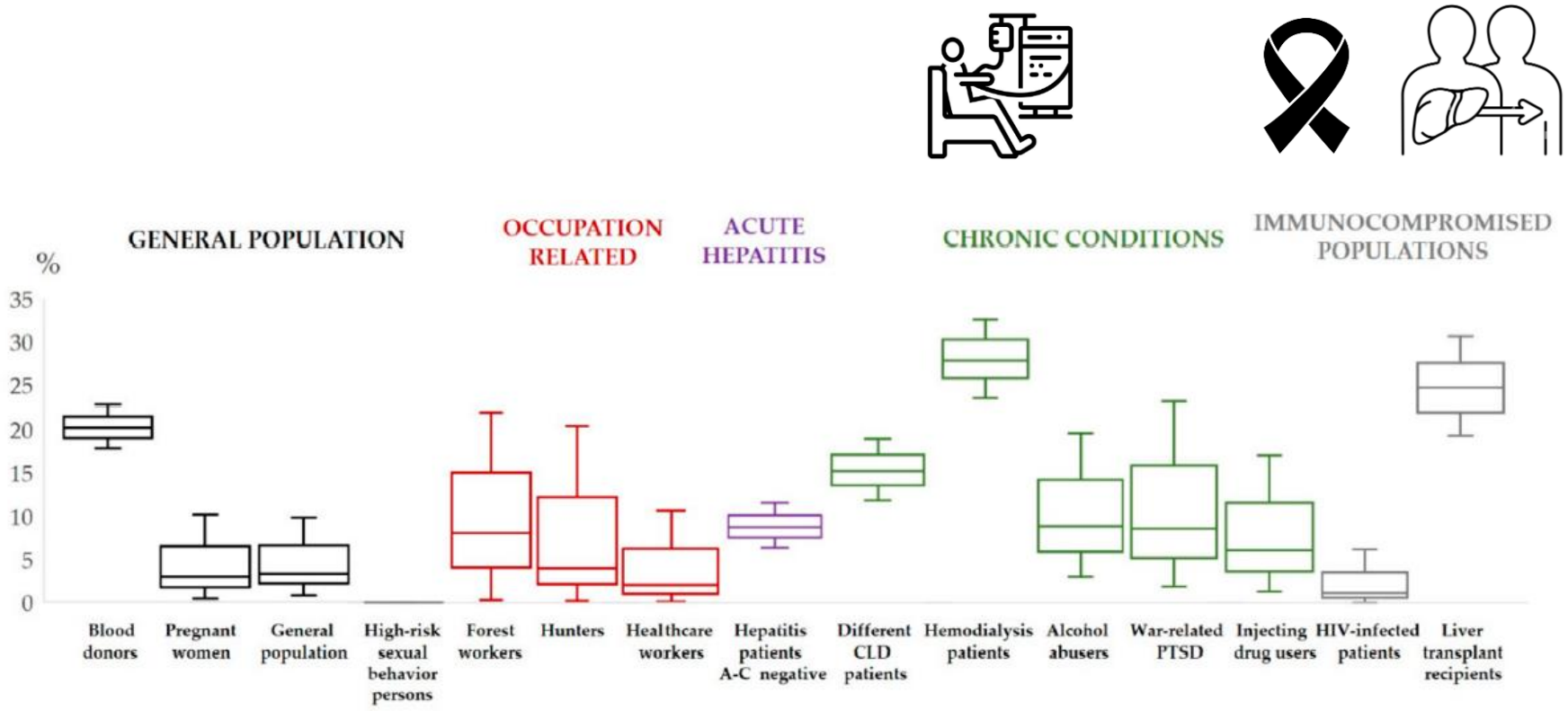
- subtype 3e – sporadically
  - humans and pigs
- subtype 3f – spordaically
  - humans



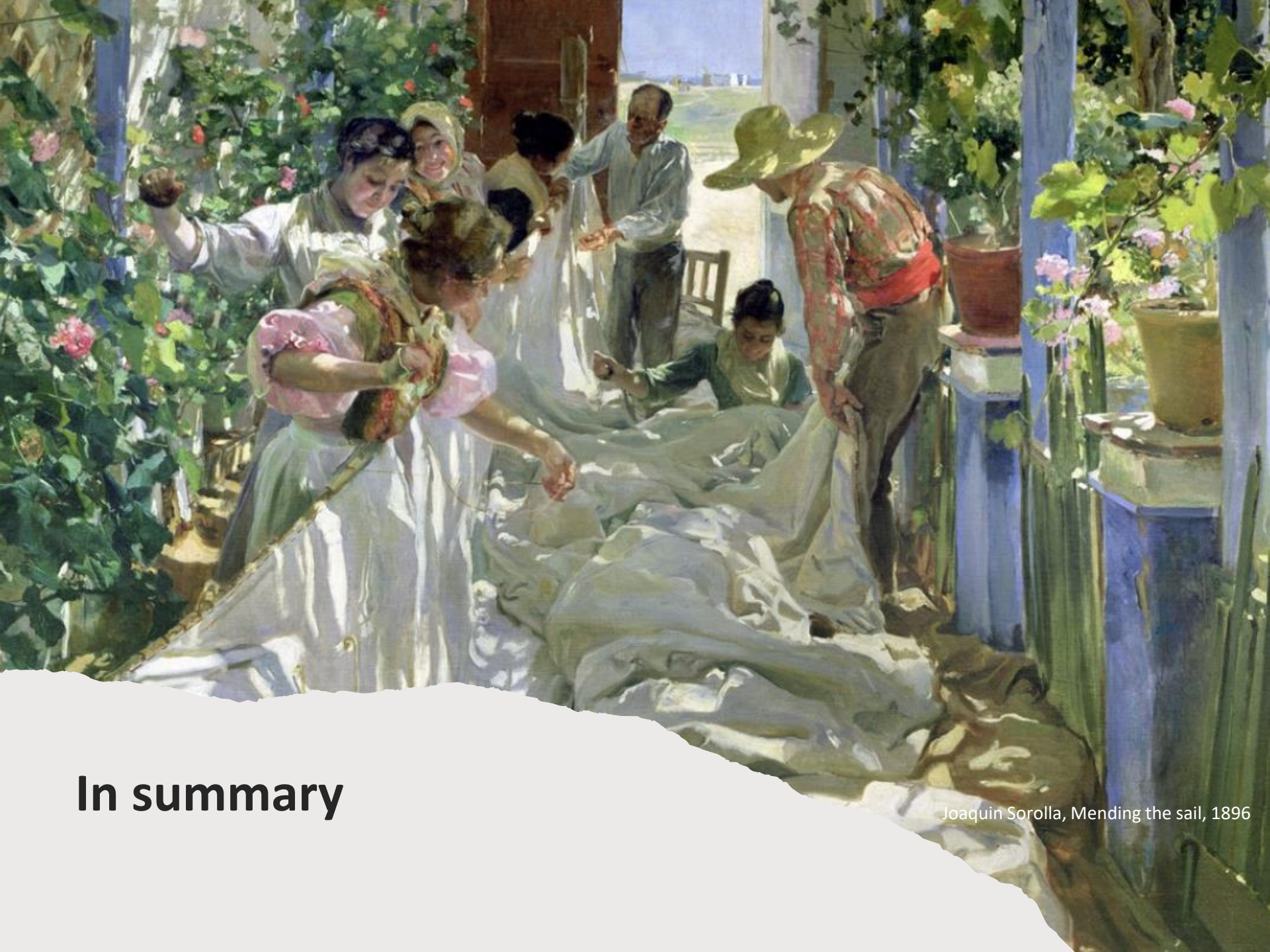
- homologous strains found in humans and animals
- the interspecies HEV transmission due to direct or indirect contact or as a foodborne infection cannot be excluded

Mrzljak A, et al. Pathognes 2021

Hepatitis E in Croatia



Mrzljak A, et al. Pathogens. 2021



In summary

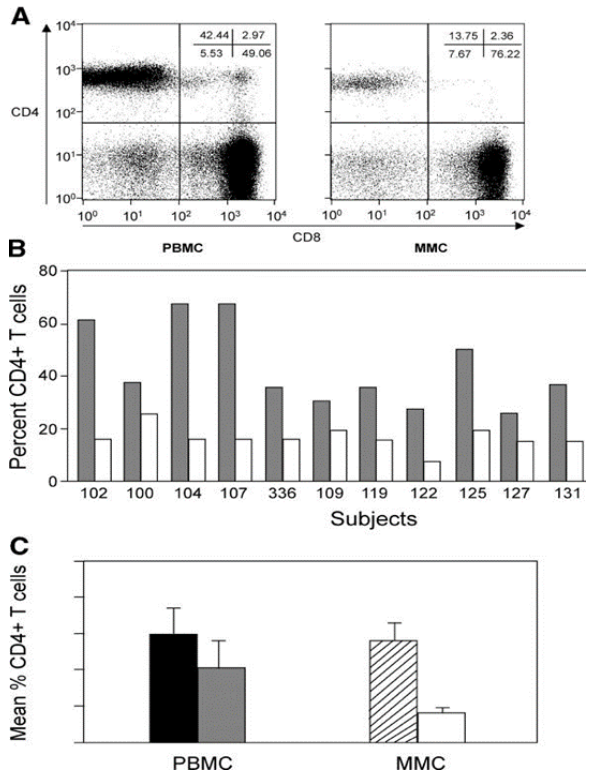
Joaquin Sorolla, Mending the sail, 1896

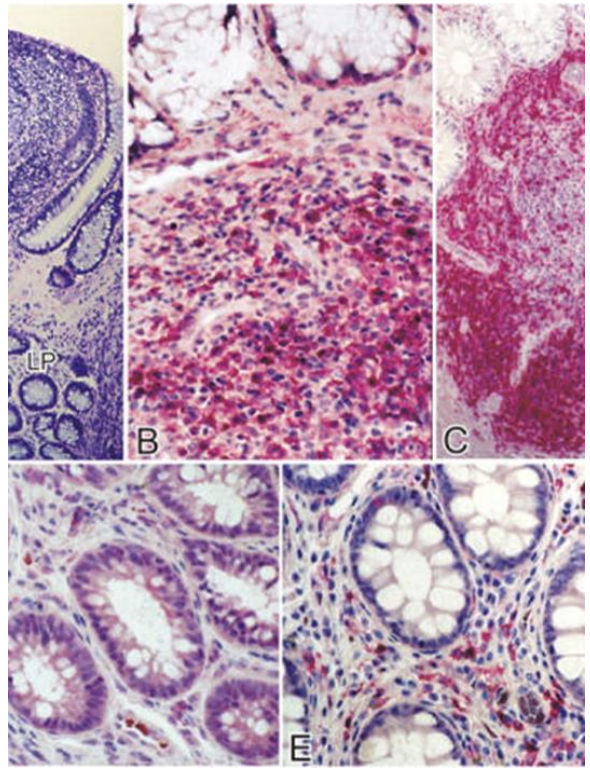
Gastrointestinal (GI) system infections in patients living with HIV (PLWH)

Marija Santini

GI system and HIV

- GI mucosal pathological changes occur early in the acute HIV infection
- Depletion of CD4+ lymphocytes in mucosa and in blood





Mehandru S, et al.J Exp Med. 2004; 200(6):761-70.

GI system and HIV

- Some infections occur at any phase of the HIV infection - HBV, HCV
- Opportunistic infections (OI) of the GI system are signs of advanced HIV infection
- Broad range of diseases with multiple etiologies
- ART is effective
- Effectively treated patients do not experience GI manifestations of the OI

Disorders of the esophagus and HIV

Signs and symptoms	ID causes	Non-ID causes	Diagnosis
Dysphagia Odinophagia Retrosternal pain Nausea Anorexia Weight loss	Candida CMV HSV VZV Primary HIV Mycobacteria Kaposi sarcoma	Reflux esophagitis Pill esophagitis (doxycycline) Malignancies (esophageal carcinoma, lymphoma) Idiopathic ulcers	Presumptive diagnosis with careful history and physical examination (oropharyngeal candidiasis → esophageal candidiasis) Upper endoscopy with lesion biopsy Culture PCR

Disorders of the stomach and HIV

Signs and symptoms	ID causes	Non-ID causes	Diagnosis
Nausea Vomiting Early satiety Anorexia Weight loss Abdominal pain Hematemesis	CMV Helicobacter pylori (↓ in PLWH) Cryptosporidium MAC Histoplasmosis Leishmeniasis Syphilis Kaposi sarcoma	Reflux esophagitis Pill esophagitis (doxycycline) Malignancies (esophageal carcinoma, lymphoma) Idiopathic ulcers	 Upper endoscopy with lesion biopsy Culture PCR

Disorders of the liver and HIV

Signs and symptoms	ID causes	Non-ID causes	Diagnosis
↑AST, ALT, AP	Chronic viral hepatitis (HBV, HCV) HIV-related OI CMV, EBV, HSV, adenovirus Mycobacteria Fungi Bartonella henselae Pneumocystis jirovecii	DILI Alcohol NAFLD Malignancy (Kaposi sarcoma, lymphoma)	Ultrasound Transient elastography CT MR Liver biopsy

Treatment and Monitoring of Persons with HBV/HIV Co-infection

Treatment indication

1. All persons with HBV/HIV co-infection should receive ART that includes TDF or TAF unless history of tenofovir intolerance
2. Stopping anti-HBV active ART should be avoided in persons with HIV/HBV co-infection because of the high risk of severe hepatitis flares and decompensation following HBV reactivation hepatitis

Treatment selection

3. If TDF or TAF is strictly contraindicated, entecavir may be prescribed in persons with no prior 3TC exposure and together with fully active ART
4. Persons with liver cirrhosis and low CD4 count require careful surveillance in the first months after starting ART in order not to overlook immune reconstitution syndrome and subsequent liver decompensation due to flares of liver enzymes (for management of cirrhotic persons, see pages 87-93). Please note that diagnosis of cirrhosis may be difficult in persons already on HBV treatment
5. Caution is warranted to switch from a TDF/TAF-based regimen to drugs with a lower genetic barrier, e.g. FTC or 3TC, in particular in 3TC-pretreated cirrhotic persons as viral breakthrough due to archived YMDD mutations is likely to happen. This has also been described in individuals with previous 3TC HBV-resistance who have been switched from TDF to entecavir. Therefore, HBV-DNA and transaminases should be checked regularly
6. Prior to ART simplification with a regimen without TDF/TAF, HBV status should be re-checked. In PLWH with isolated anti-HBc, relapse of HBV-DNA is possible, therefore transaminases and HBV-DNA should be checked regularly. PLWH with positive HBsAg should remain on TDF or TAF containing ART
7. For HBV/HIV co-infected persons with BMD changes or CKD, see recommendations for Dose Adjustment of ARVs for Impaired Renal Function and pages 78-83

Treatment goal

8. The optimal treatment duration for nucleos(t)ide analogues with anti-HBV activity has not yet been determined and experts recommend life-long therapy. In those on ART where the nucleoside backbone needs changing, anti-HBV therapy may be stopped cautiously after confirmed HBsAg-seroconversion. In persons with liver cirrhosis, stopping of effective anti-HBV treatment is not recommended, in order to avoid liver decompensation due to flares of liver enzymes

Treatment monitoring

9. Liver blood tests should be performed every 3 months during the first year and every 6-12 months thereafter
10. HBV-DNA should be determined every 3-6 months during the first year and every 12 months thereafter. HBsAg should be checked at 12 months intervals at least until loss of HBsAg(i)

HBV reactivation

11. In HBs-Ag negative, anti-HBc positive persons undergoing immunosuppression:
    - Those treated with severe immunosuppressive therapy (chemotherapy for lymphoma/leukaemia or stem-cell or solid-organ transplantation) should receive TDF/TAF therapy to prevent HBV reactivation. For persons with other markers of possible HBV exposure including isolated anti-HBs positivity (without a history of vaccination) careful monitoring for HBV reactivation is required
    - In persons treated with B-cell-depleting agents (rituximab, ofatumumab, natalizumab, alemtuzumab, ibritumomab) TDF/TAF should be part of the ART. If TDF/TAF is contraindicated, second line options include ETV, 3TC and FTC. However, cases of reactivation due to 3TC resistance have been described
    - In those not treated with HBV-active ART who receive other immunosuppressive therapy (e.g. TNF-alpha inhibitor), careful monitoring with HBV-DNA and HBsAg is required for HBV reactivation. If this is not possible, addition of TDF/TAF is recommended

i Quantitative HBsAg < 1000 IU/mL predicts HBsAg loss

EACS 2023

HCV Treatment Options in HCV/HIV Co-infected Persons

Preferred DAA HCV treatment options (except for persons pre-treated with Protease or NS5A inhibitors)				
HCV GT	**Treatment regimen**	**Treatment duration & RBV usage**		
		Non-cirrhotic	**Compensated cirrhotic**	**Decompensated cirrhotics CTP class B/C**
1 & 4	EBR/GZR	12 weeks[i]		Not recommended
	GLE/PIB	8 weeks	8-12 weeks[ii]	Not recommended
	SOF/VEL	12 weeks		12 weeks with RBV[ix]
	SOF/LDV +/- RBV	8-12 weeks without RBV[iii]	12 weeks with RBV[iv]	12 weeks with RBV[ix]
2	GLE/PIB	8 weeks	8-12 weeks[ii]	Not recommended
	SOF/VEL	12 weeks		12 weeks with RBV[ix]
3	GLE/PIB	8 weeks[v]	8-12 weeks[ii,v]	Not recommended
	SOF/VEL +/- RBV	12 weeks[vi]	12 weeks with RBV[vii]	12 weeks with RBV[ix]
	SOF/VEL/VOX	-	12 weeks	Not recommended
5 & 6	GLE/PIB	8 weeks	8-12 weeks[ii]	Not recommended
	SOF/LDV +/- RBV	12 weeks +/- RBV[viii]	12 weeks with RBV[iv]	12 weeks with RBV[ix]
	SOF/VEL	12 weeks		12 weeks with RBV[ix]

For HCV treatment options to be used if preferred options are not available, please see version 10.1 of the EACS Guidelines

EBR = elbasvir
GLE = glecaprevir
GZR = grazoprevir
LDV = ledipasvir
PIB = pibrentasvir
RBV = ribavirin
SOF = sofosbuvir
VEL = velpatasvir
VOX = voxilaprevir
RAS = resistance associated substitutions

EACS 2023

Disorders of the biliary tree, gallbladder and pancreas

Signs and symptoms	ID causes	Non-ID causes	Diagnosis
Postprandial pain, fever, right upper quadrant tenderness, elevated serum alkaline phosphatase	AIDS-associated acalculous cholecystitis and cholangiopathy- CD4+<50/µl: papilla Vateri stenosis, sclerosing cholangitis, a combination of papilla Vateri stenosis with sclerosing cholangitis, choledochal long stenosis or strictures CMV Cryptosporidium Microsporidia Multiple organisms	Non-AIDS associated cholelithiasis Atazanavir cholelithiasis	Ultrasound CT ERCP Endoscopic bile colection

Pancreatic disorders and HIV

Signs and symptoms	ID causes	Non-ID causes	Diagnosis
Pancreatitis	- AIDS cholangiopathy caused by CMV, Cryptosporidium, or microsporidia - Mycobacteria - abscess related to M. tuberculosis and disseminated M. avium-intracellulare complex - Fungi (C. neoformans and Candida spp.,P. jirovecii) - Toxoplasma gondii, - protozoa - CMV pancreatitis - Mumps	Alcohol, cholelithiasis, hyperlipidemia, drug-induced pancreatic inflammation (didanosine, pentamidine)	

Disorders of the small and large intestine and HIV

Signs and symptoms	ID causes	Non-ID causes	Diagnosis
- Small bowel - bloating, nausea, cramping, profuse diarrhea, malabsorption and weight loss - Colitis - abdominal discomfort and cramping, urgency, tenesmus, frequent small-volume diarrhea.	Bacteria (Salmonella spp., Shigella, Campylobacter jejuni, Escherichia coli, Listeria monocytogenes, Shigella, C. difficile Aeromonas, Plesiomonas, Yersinia, Vibrio spp., M. avium-intracellulare complex, M. tuberculosis). Cryptosporidium, microsporidia	Medication-related diarrhea GI ART AE colorectal malignant Inflammatory bowel diseases (e.g., ulcerative colitis, Crohn disease)	Stool examination Endoscopy Biopsy

HIV associated enteropathy

- Approximately 20% to 50% of patients with chronic diarrhea have a negative gastrointestinal tract evaluation.
- Patients without an identifiable cause of diarrhea may have HIV-associated enteropathy, the pathology of which is not fully understood but likely involves depletion of gut-associated CD4+ cells.
- Histologic evaluation of small bowel biopsy specimens may reveal a decrease in villous surface area and crypt cell proliferation in the absence of inflammation.
- ART may effectively control diarrhea in patients with HIV enteropathy and in patients with microsporidiosis and cryptosporidiosis.

Conclusions

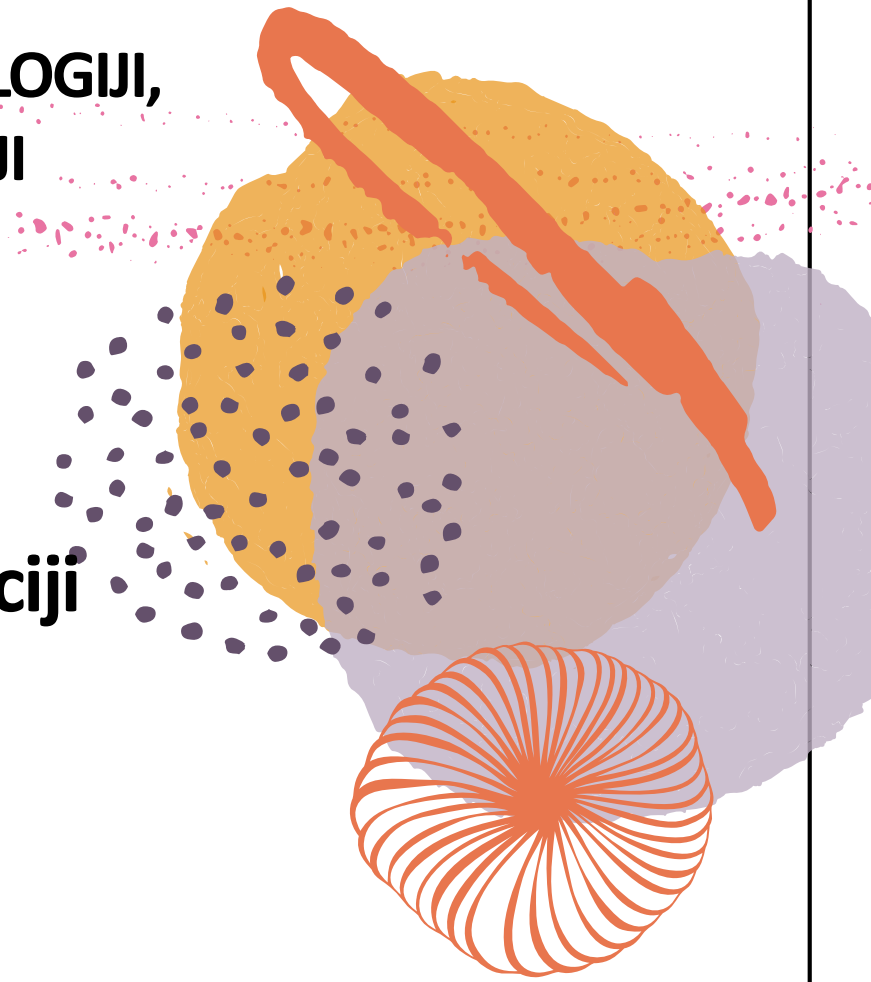
- HIV infection affects the GI system
- primary infection → advanced HIV infection
- It destroys the GI system as an immune organ
- It can affect any part of the GI system
- Beware of the extra-GI manifestations
- GI system signs, symptoms, and endoscopic findings are frequently missed opportunities to diagnose and timely treat HIV infection

INFEKCIJE PROBAVNOG SUSTAVA: NOVOSTI U EPIDEMIOLOGIJI, KLINIČKOJ SLICI, DIJAGNOSTICI, TERAPIJI I PREVENCIJI

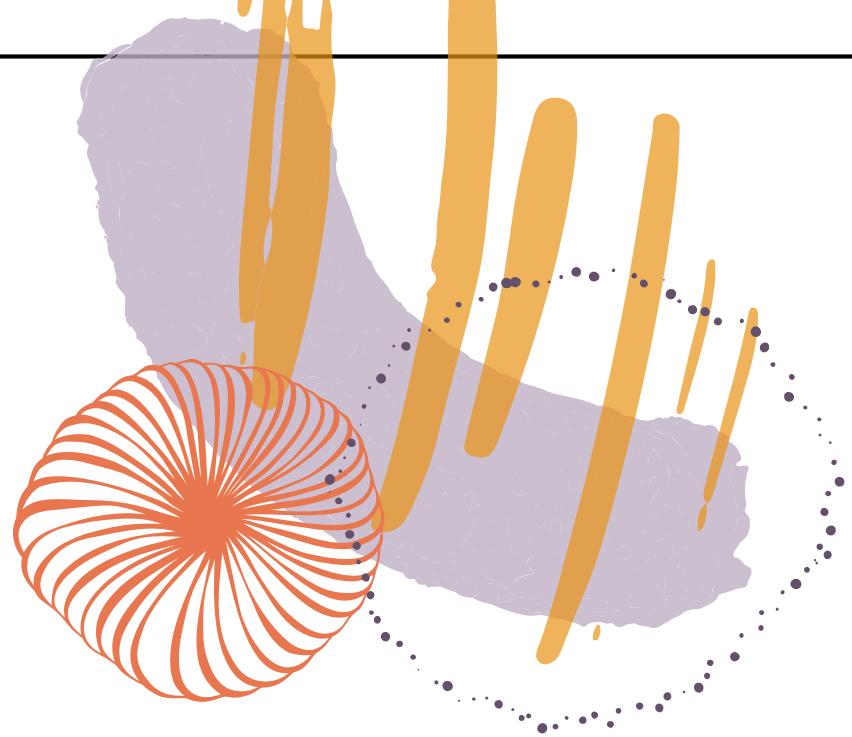
Zagreb, 17. svibanj 2024

Infekcije probavnog sustava u MSM populaciji

Vanja Romih Pintar



UVOD



- Sve su veće stope spolno prenosivih crijevnih infekcija (STEI), među muškarcima koji imaju spolne odnose s muškarcima (MSM).
- Gastrointestinalni simptomi u MSM populaciji predstavljaju za kliničara dijagnostički izazov zbog širokog spektra potencijanih uzročnika, većeg broja terapijskih mogućnosti (ovisno o patogenu) i potencijalnih problema u liječenju zbog multiplo-rezistentnih uzročnika.

Guidelines

INTERNATIONAL JOURNAL OF STD & AIDS

British Association of Sexual Health and HIV (BASHH) United Kingdom national guideline for the management of sexually transmitted enteric infections 2023

Daniel Richardson[1,2], Mark Pakianathan[3], Michael Ewens[4], Holly Mitchell[5], Hasan Mohammed[6], Elizabeth Wiseman[7], Marc Tweed[8], Kayleigh Nichols[1], Waseem Rawdah[1], Richard Cooper[1], Robert Macrowan[9], Matthew Irish[9], Amy Evans[4,10,*] and Gauri Godbole[5,*]

International Journal of STD & AIDS
2023, Vol. 0(0) 1–15

DOI: 10.1177/09564624231168217
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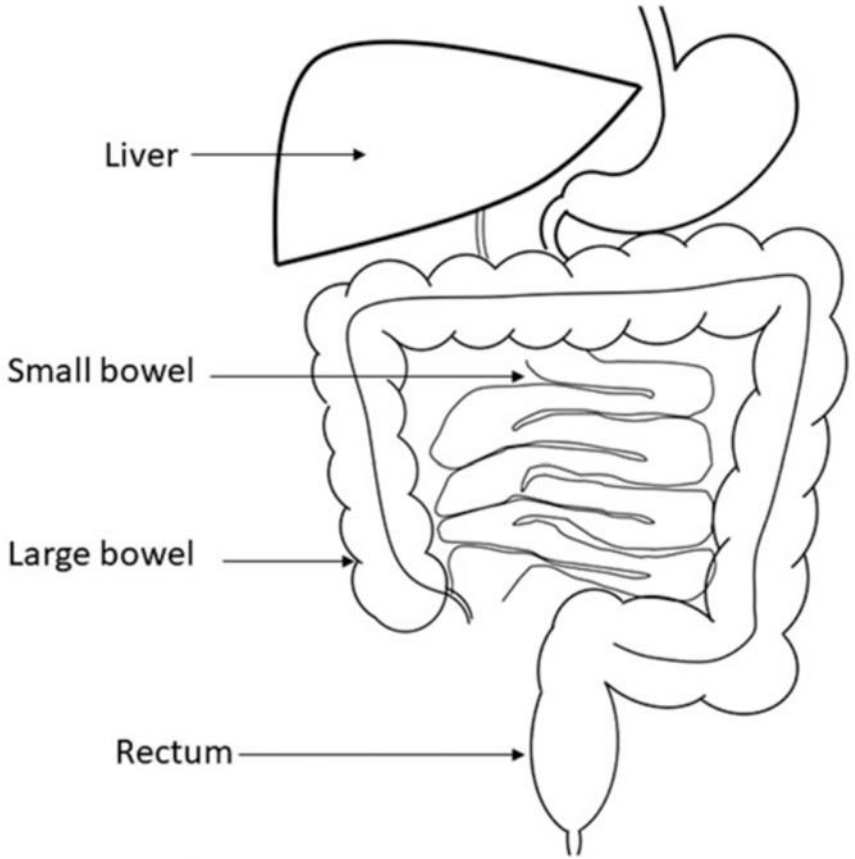
Syndromes and aetiology of sexually transmitted enteric infections



Hepatitis (liver)
Hepatitis A*

Enteritis (small bowel)
*Giardia duodenalis**

Procto-colitis (large bowel)
Bacterial:
*Shigella spp.**
*Campylobacter spp**
Shiga toxin producing *Escherichia coli* (STEC)*
*Salmonella spp.**
Protozoal: *Entamoeba histolytica**

Proctitis (rectum)
Neisseria gonorrhoeae
Chlamydia trachomatis (genotypes *D-K)*
Chlamydia trachomatis (genotypes L1-3: lymphogranuloma venereum [LGV])
Herpes simplex virus (HSV)
Treponema pallidum
Mpox*

*Notifiable organism

Robust evidence for sexual transmission of: hepatitis E, *Cryptosporidia* spp. *Strongyloides stercoralis,* microsporidiosis, intestinal spirochaetosis and *Enterobius vermicularis* is lacking and are outside of the scope of this guideline

Figure 1. Syndromes and aetiology of sexually trasmitted enteric infections.

Richardson D, Pakianathan M, Ewens M, *et al;* The new 2023 BASHH sexually transmitted enteric infections guideline, *Sexually Transmitted Infections* 2023;**99:**363-364.

DOI: 10.1111/jdv.17269 JEADV

GUIDELINES

2021 European Guideline on the management of proctitis, proctocolitis and enteritis caused by sexually transmissible pathogens

H.J.C. de Vries,[1,2,*] A.V. Nori,[3] H. Kiellberg Larsen,[4] A. Kreuter,[5] V. Padovese,[6] S. Pallawela,[7] M. Vall-Mayans,[8] J Ross[9]

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[5]Department of Dermatology, Venereology, and Allergology, HELIOS St. Elisabeth Hospital Oberhausen, University Witten-Herdecke, Oberhausen, Germany
[6]Genitourinary Clinic, Department of Dermatology and Venereology, Mater Dei Hospital, Msida, Malta
[7]The Florey Unit, Royal Berkshire Hospital, Reading, UK
[8]Infectious Diseases Department, Fight AIDS Foundation, Hospital Germans Trias Pujol, Badalona, Spain
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Abstract

This guideline intents to offer guidance on the diagnosis and management of patients with gastrointestinal symptoms and a suspected sexually transmitted cause. Proctitis is defined as an inflammatory syndrome of the anal canal and/or the rectum. Infectious proctitis can be sexually transmitted via genital–anal mucosal contact, but some also via digital contact and toys. *Neisseria gonorrhoeae, Chlamydia trachomatis* (including lymphogranuloma venereum), *Treponema pallidum* and herpes simplex virus are the most common sexually transmitted anorectal pathogens. Shigellosis can be transferred via oral–anal contact and may lead to proctocolitis or enteritis. Although most studies on these infections have concentrated on men who have sex with men (MSM), women having anal intercourse may also be at risk. A presumptive clinical diagnosis of proctitis can be made when there are symptoms

Table 1. Sexually associated causes of proctitis, proctocolitis and enteritis †

Causes of distal proctitis	Causes of proctocolitis	Causes of enteritis
Neisseria gonorrhoeae	*Shigella* spp.	*Giardia lamblia*, *Cryptosporidium* spp.
Chlamydia trachomatis:	*Campylobacter* spp.	Microsporidia §
Genotypes D-K	*Salmonella* spp.	Hepatitis A virus
Genotypes L_{1-3} (LGV)	*Escherichia coli*	
Treponema pallidum	*Entamoeba histolytica*	
Herpes simplex virus	*Cryptosporidium* spp.	
Mycoplasma genitalium ‡	Cytomegalovirus §	
Traumatic (sex toys, douching)	Intestinal spirochetosis ¶	

de Vries, H.J.C., Nori, A.V., Kiellberg Larsen, H., Kreuter, A., Padovese, V., Pallawela, S., Vall-Mayans, M. and Ross, J. (2021), 2021 European Guideline on the management of proctitis, proctocolitis and enteritis caused by sexually transmissible pathogens. J Eur Acad Dermatol Venereol, 35: 1434-1443. https://doi.org/10.1111/jdv.17269

Syndromes and aetiology of sexually transmitted enteric infections

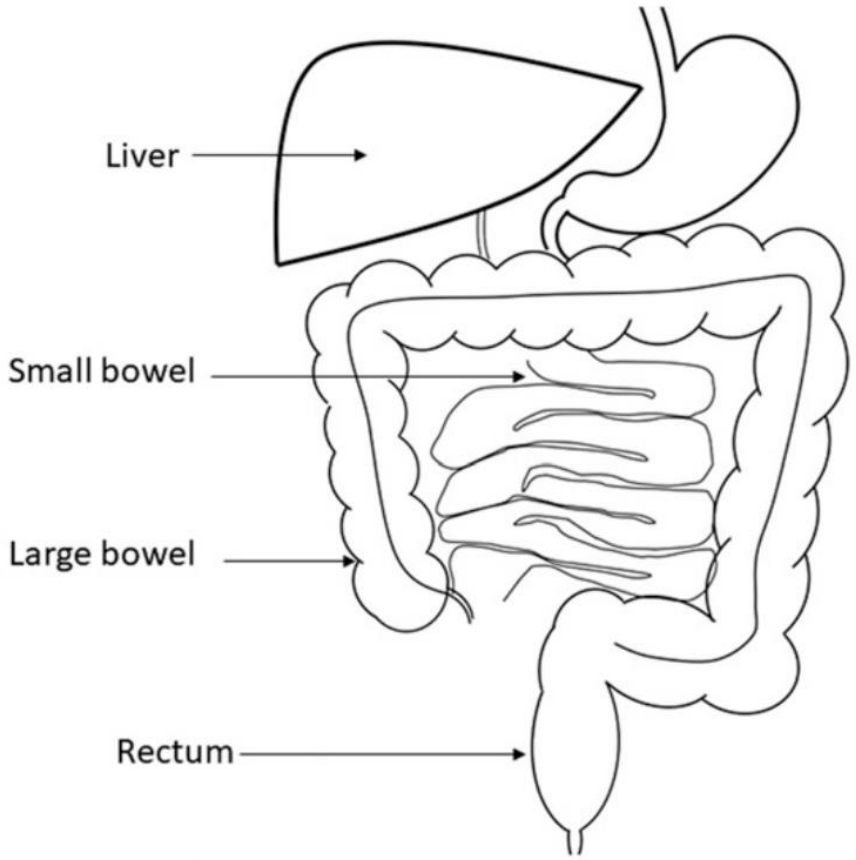

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Figure 1. Syndromes and aetiology of sexually trasmitted enteric infections.

Richardson D, Pakianathan M, Ewens M, *et al;* The new 2023 BASHH sexually transmitted enteric infections guideline, *Sexually Transmitted Infections* 2023;**99:**363-364.

Hepatitis A

ECDC 2022

- U Hrvatskoj je u 2022., došlo je do značajnog povećanja broja prijavljenih slučajeva hepatitisa A (stopa 5.3).

Većina slučajeva zabilježena je **među muškarcima**, u dobi od 25 do 44 godine i dogodila se u prva četiri mjeseca 2022.

- povezano s produljenom epidemijom hepatitisa A subgenotipa IA između siječnja i listopada 2022. u populaciji **MSM-a** koji žive s HIV-om i onih koji koriste preekspozicijsku profilaksu (PrEP).
- Izvješće o izbijanju epidemije naglašava da su MSM, uključujući osobe koje žive s HIV-om i MSM korisnike PrEP-a, ranjivi za infekciju virusom hepatitisa A i mogu biti potencijalni izvor šireg prijenosa virusa.

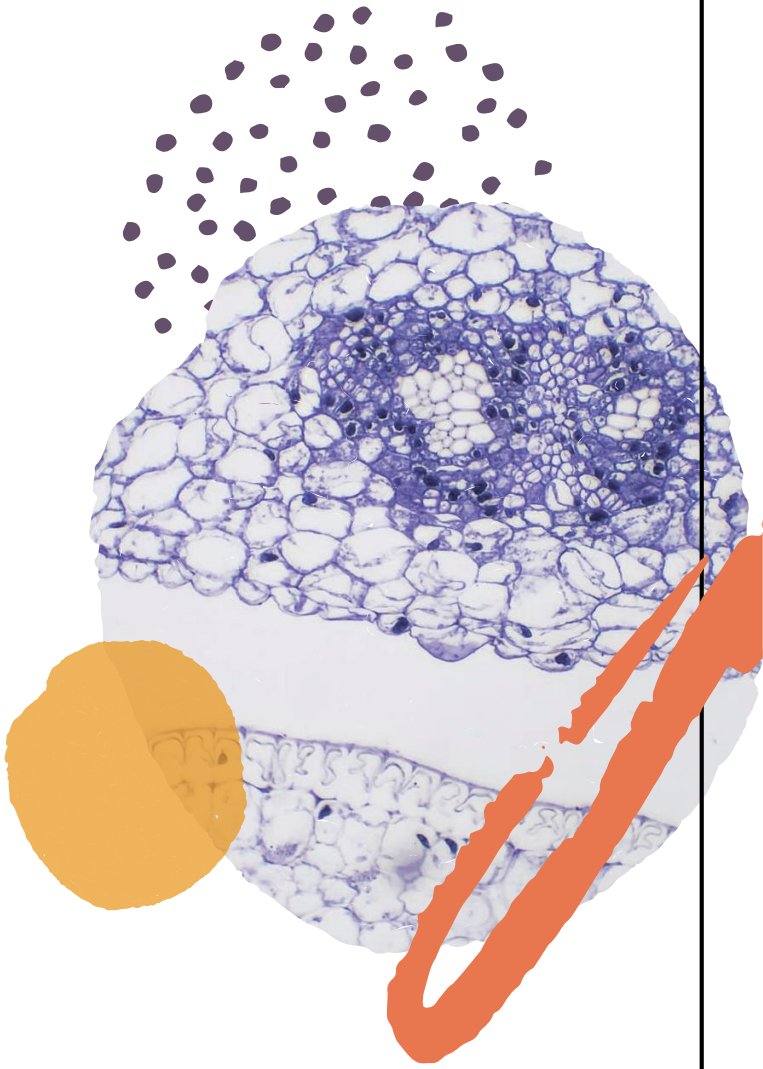
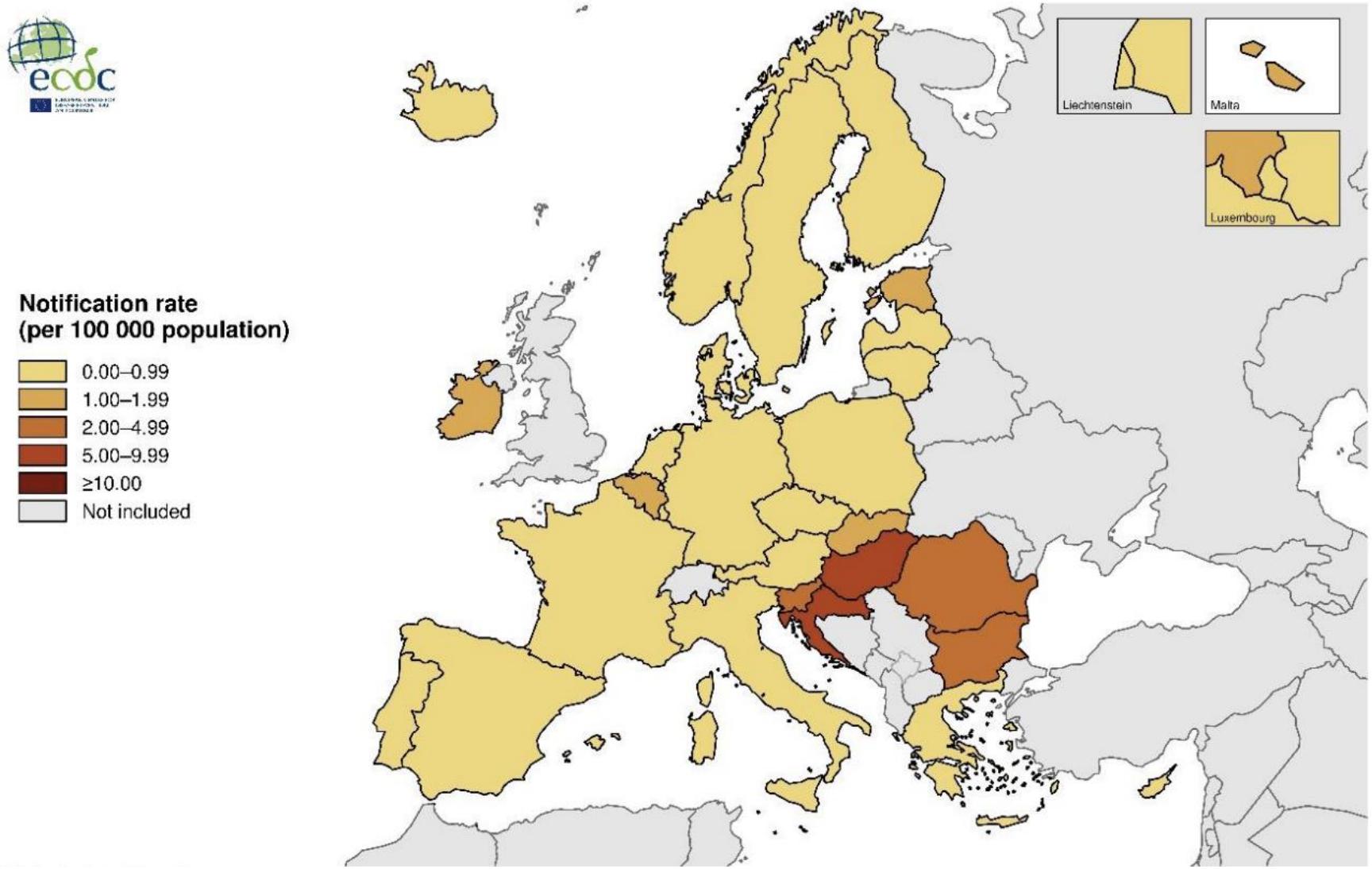


Figure 1. Confirmed hepatitis A cases per 100 000 population by country, EU/EEA, 2022

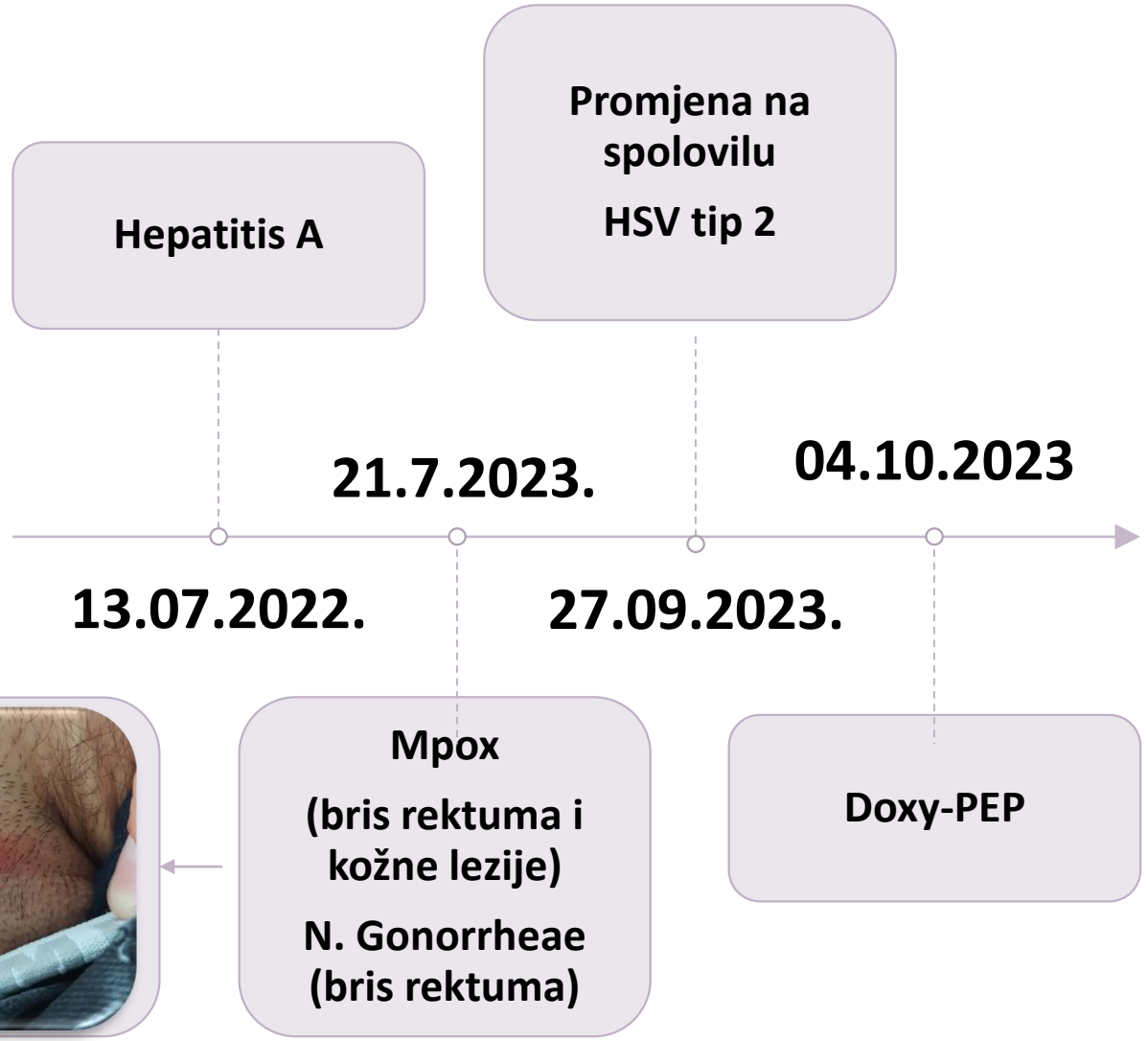


https://www.ecdc.europa.eu/sites/default/files/documents/HEPA_AER_2022_Report.pdf

Prikaz slučaja
Ivan, 35 godina

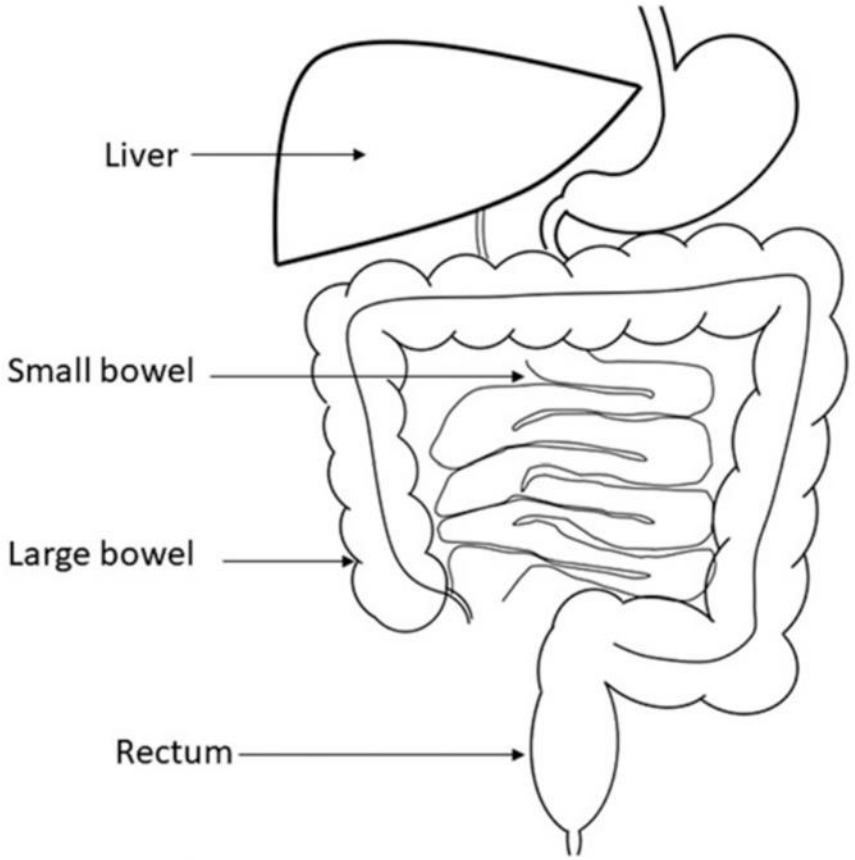
Prep ambulanta

- **20.10.2021.** prvi pregled radi započinjanja PrEP-a
- 13.07.2022. – Febrilitet 2 dana, mučnina, taman urin, učestalije normoklorirane stolice, jetrena lezija (**AST 1891, ALT 1556, ggt 365, ldh 118, bil 18**).
- 21.07.2022. – bolan l.č. u preponi i „prištić”



Data on file from University Hospital for Infectious Diseases „Dr Fran Mihaljević“, Croatian HIV Centre, Zagreb, Croatia, 2022-2023

Syndromes and aetiology of sexually transmitted enteric infections



Hepatitis (liver)
Hepatitis A*

Enteritis (small bowel)
*Giardia duodenalis**

Procto-colitis (large bowel)
Bacterial:
*Shigella spp.**
*Campylobacter spp**
Shiga toxin producing *Escherichia coli* (STEC)*
*Salmonella spp.**
Protozoal: *Entamoeba histolytica**

Proctitis (rectum)
Neisseria gonorrhoeae
Chlamydia trachomatis (genotypes *D-K)*
Chlamydia trachomatis (genotypes L1-3: lymphogranuloma venereum [LGV])
Herpes simplex virus (HSV)
Treponema pallidum
Mpox*

*Notifiable organism

Robust evidence for sexual transmission of: hepatitis E, *Cryptosporidia* spp. *Strongyloides stercoralis,* microsporidiosis, intestinal spirochaetosis and *Enterobius vermicularis* is lacking and are outside of the scope of this guideline

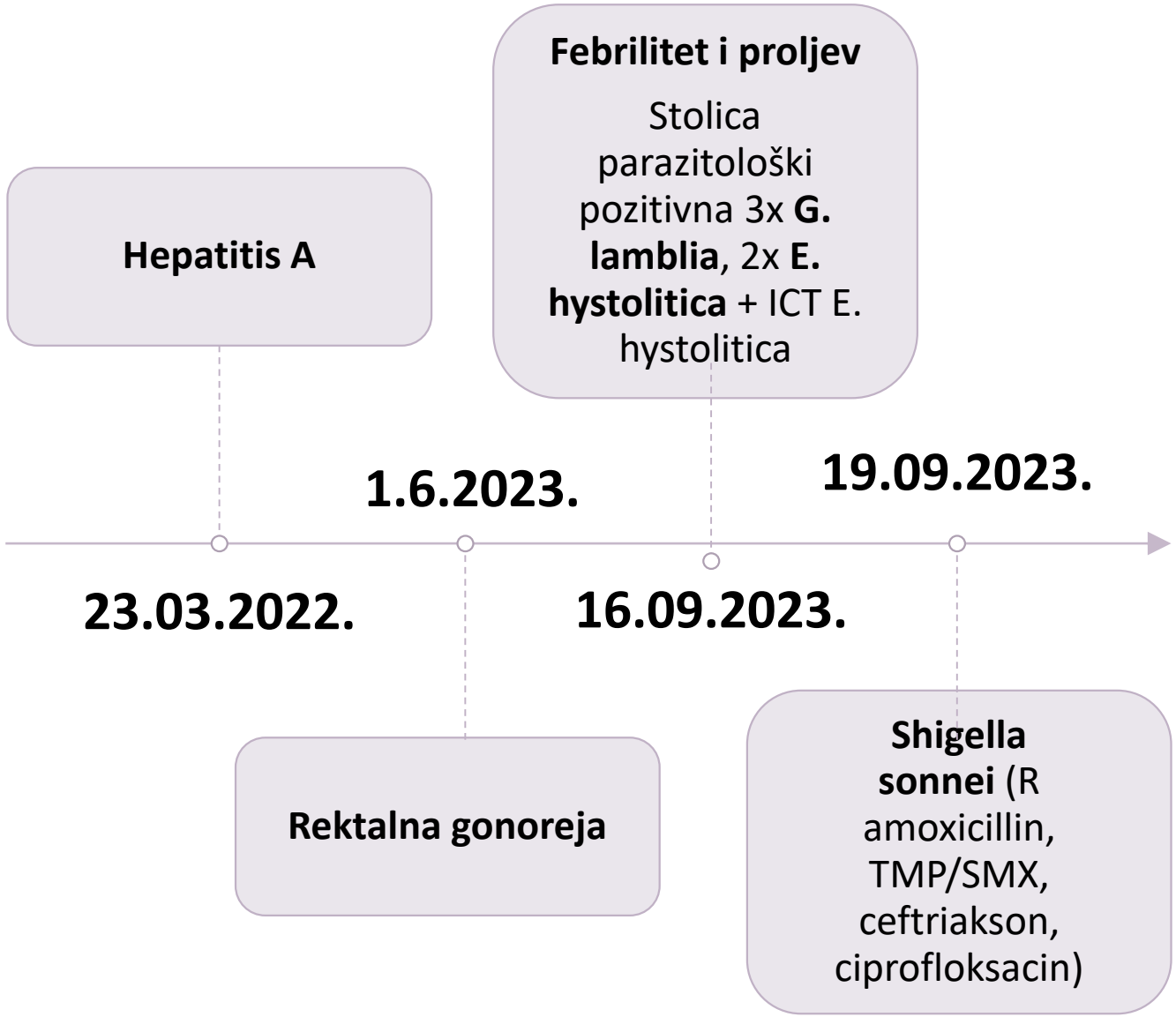
Figure 1. Syndromes and aetiology of sexually trasmitted enteric infections.

Richardson D, Pakianathan M, Ewens M, *et al;* The new 2023 BASHH sexually transmitted enteric infections guideline, *Sexually Transmitted Infections* 2023;**99:**363-364.

Prikaz slučaja
Marko, 36 godina

Prep ambulanta

- 23.03.2022. prvi pregled radi započinjanja PrEP-a
- HIV; markeri na hepatitis A, B; C, sifilis
- **ast 199, alt 304**, ggt 82, alp 76, ldh 331, ck 129
- AntiHAV pozitivna, IgM antiHAV pozitivan



Data on file from University Hospital for Infectious Diseases „Dr Fran Mihaljević“, Croatian HIV Centre, Zagreb, Croatia, 2022-2023

Shigella Infection Among Gay, Bisexual, and Other Men Who Have Sex with Men

Accessible Link **www.cdc.gov/shigella/msm.html**

Note: Content contains mature language

Gay and bisexual men are a group at high risk for *Shigella* infection.

Shigella Can Spread Easily and Rapidly During Sexual Activity

Shigella passes from the poop (stool) or unclean fingers of one person to the mouth of another person. This can happen during sexual activity through:

- **Direct sexual contact:** Oral or anal sex, or anal play (rimming, fingering)
- **Indirect sexual contact:** Handling contaminated objects, such as sex toys, used condoms or barriers, and douching materials

Symptoms usually start 1–2 days after swallowing the germs and include **bloody diarrhea**, **fever**, and **stomach pain**. Talk with your doctor about *Shigella* if you have any of these symptoms and feel very sick.

Multidrug-resistant *Shigella* infections have been on the rise in the U.S. since 2013.

These types of infections are difficult to treat because germs develop the ability to defeat the drugs designed to kill them. That means *Shigella* germs are not killed and continue to grow.

Protect Yourself and Your Partner

https://www.cdc.gov/shigella/msm.html

Outbreak of sexually transmitted, extensively drug-resistant *Shigella sonnei* in the UK, 2021–22: a descriptive epidemiological study

*Hannah Charles, Mateo Prochazka, Katie Thorley, Adam Crewdson, David R Greig, Claire Jenkins, Anais Painset, Helen Fifer, Lynda Browning, Paul Cabrey, Robert Smith, Daniel Richardson, Laura Waters, Katy Sinka, Gauri Godbole, on behalf of the Outbreak Control Team**

Summary

Background Shigellosis, traditionally a foodborne and waterborne infection, causes substantial morbidity globally. It is now a leading cause of sexually transmitted gastroenteritis among gay, bisexual, and other men who have sex with men (MSM). We describe an ongoing outbreak of extensively drug-resistant (XDR) *Shigella sonnei* in the UK.

Methods Routine laboratory surveillance (Second Generation Surveillance System, Gastrointestinal Data Warehouse) identified an exceedance of *S sonnei* clade 5 in England, first detected in September, 2021. Cases within this clade were subsequently reported from Scotland, Wales, and Northern Ireland. Confirmed cases in this outbreak were defined as individuals diagnosed with *S sonnei* clade 5 in the UK, with a specimen date between Sept 1, 2021, and Feb 9, 2022, who were genomically confirmed as part of a ten-single nucleotide polymorphism (SNP) linkage cluster. We used whole-genome sequencing with SNP typing to identify genomic clusters and antimicrobial-resistance determinants, analysing cases across the UK. We collected demographic, epidemiological, and clinical data from people infected with *S sonnei* clade 5 in England using questionnaires (standard and bespoke outbreak questionnaires). We used descriptive summary statistics to characterise cases.

Lancet Infect Dis 2022; 22: 1503–10

Published Online July 6, 2022 https://doi.org/10.1016/S1473-3099(22)00370-X

See **Comment** page 1409

*Members are listed at the end of the manuscript

UK Health Security Agency, London, UK (H Charles MSc, M Prochazka MD, K Thorley MSc, A Crewdson MSc, D R Greig MSc, C Jenkins PhD, A Painset MSc, H Fifer FRCPath, K Sinka PhD, G Godbole FRCPath); **NIRH**

Table 3. Antimicrobial resistance in isolates from confirmed shigellosis cases by pathogen, 2022

		Ampicillin (6 countries)		Azithromycin (0 countries)		Cefotaxime (5 countries)		Ceftazidime (6 countries)		Ciprofloxacin (6 countries)		SXT (3 countries)	
	Susceptibility	N	%	N	%	N	%	N	%	N	%	N	%
S. sonnei	R	541	80.6	NA	NA	134	49.5	18	2.7	208	31.9	41	97.6
	I/NWT	0	0.0	NDR	NA	1	0.4	388	57.9	187	28.7	0	0.0
	S/WT	130	19.4	NDR	NA	136	50.2	264	39.4	257	39.4	1	2.2
	Total	671	NA	NA	NA	271	NA	670	NA	652	NA	42	NA
S. flexneri	R	124	91.2	NA	NA	6	6.7	7	5.2	51	40.2	6	30
	I/NWT	0	0.0	NDR	NA	0	0.0	38	27.9	7	5.5	0	0.0
	S/WT	12	8.8	NDR	NA	84	93.3	91	66.9	69	54.3	14	70.0
	Total	136	NA	NA	NA	90	NA	136	NA	127	NA	20	NA

Source: country Reports from Austria, Belgium, Estonia, France, Italy, and Lithuania. TESSy data extracted 10 November 2023.

https://www.ecdc.europa.eu/sites/default/files/documents/SHIG_AER_2022_Report.pdf

Informative Note: Antimicrobial-resistant Campylobacter infection in men who have sex with men - April 5, 2024


PAHO

Informative Note: Antimicrobial-resistant Campylobacter infection in men who have sex with men

5 April 2024

Background

Given the identification of resistance in an outbreak of Campylobacter in men who have sex with men (MSM) in the United States that affected 13 people. And the history of previous outbreaks also involving individuals in both the United States and Canada. PAHO/WHO encourages Member States to be vigilant and maintain surveillance for outbreaks of diarrhea, particularly in these populations. Additionally, Member States are urged to be alert to an unusual increase in cases of Campylobacter infection, especially in at-risk groups, and to notify through the official channels of the International Health Regulations (IHR) according to the outcome of the decision algorithm, Annex 2 of the IHR.

Syndromes and aetiology of sexually transmitted enteric infections

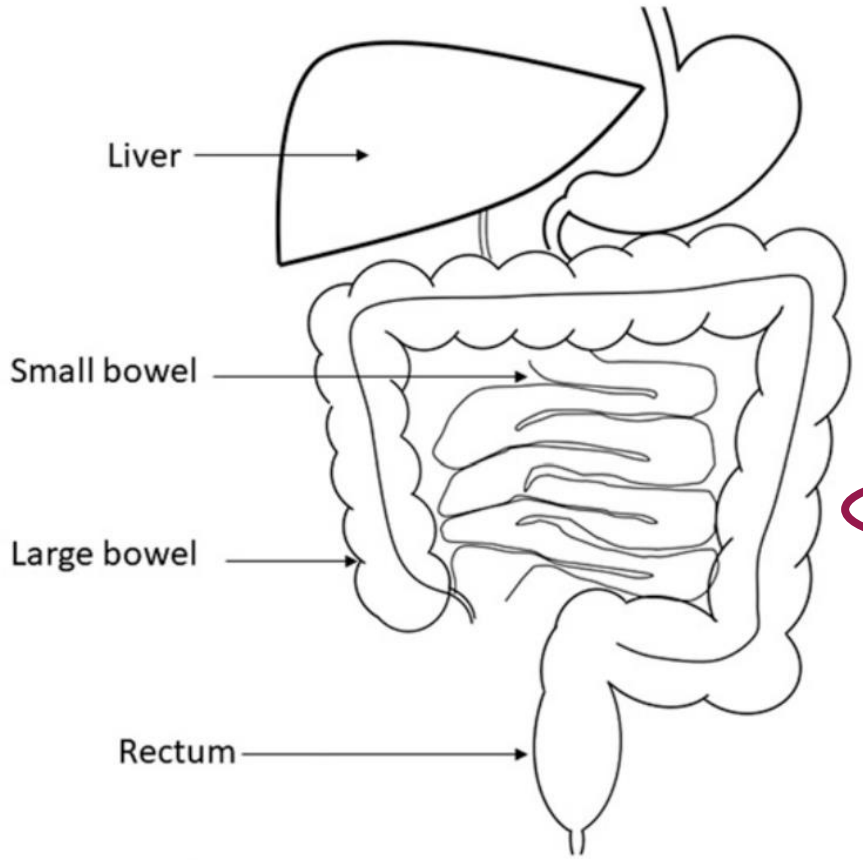


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Figure 1. Syndromes and aetiology of sexually trasmitted enteric infections.

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Delayed diagnosis of colorectal sexually transmitted diseases due to their resemblance to inflammatory bowel diseases

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[b] *Sackler Medical School, Tel Aviv University, Tel Aviv, Israel*
[c] *Microbiology Laboratory, Sheba Medical Center, Ramat Gan, Israel*
[d] *Ministry of Health, National Public Health Laboratory, Chlamydia National Reference Laboratory, Tel Aviv, Israel*
[e] *Ariel University, Ariel, Israel*
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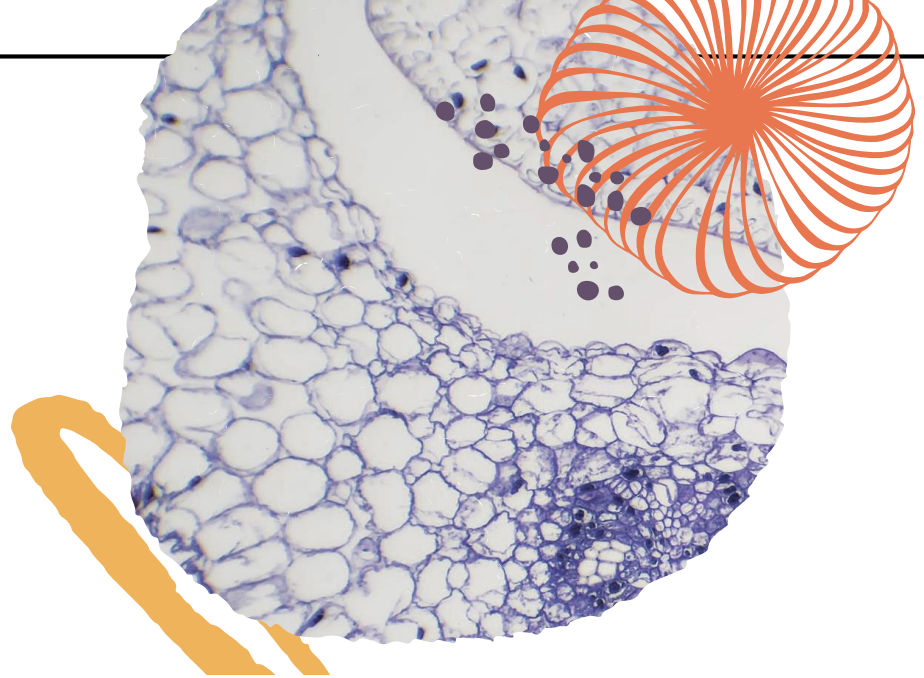
Lymphogranuloma venereum
Neisseria gonorrhoeae
Syphilis
Proctitis

ABSTRACT

Objective: Sexually transmitted diseases (STDs), mainly lymphogranuloma venereum (LGV), induce colorectal symptoms that may be misdiagnosed as inflammatory bowel disease (IBD). This study describes patients who presented with STDs masquerading as IBD in order to improve understanding of missed diagnosis of colorectal STDs and their association with LGV in Israel.
Methods: This retrospective, descriptive study characterized the clinical, endoscopic, and pathological findings of 16 patients who were diagnosed with a colorectal STD after erroneously being diagnosed with IBD. Molecular genotyping was used to characterize some of the *Chlamydia trachomatis* isolates.
Results: All patients were men who have sex with men (MSM), mostly HIV-1-positive, and had clinical and endoscopic findings compatible with IBD. The STD was diagnosed 1–36 months after the initial diagnosis: 14 were positive for *Chlamydia trachomatis*, of which three were of the LGV2b (ST58) serotype and one was ST 108 serotype. Five were positive for gonorrhea and four were positive for syphilis. Several pathogens were diagnosed in six episodes.



Pristup bolesniku sa simptomatskim proktitisom

Table 6. Investigations in patients with symptomatic proctitis.

Microscopy	Gram stain of rectal sample
	Dark field microscopy (DFM) from anal ulcer(s)
N. gonorrhoeae	Using NAAT and culture
C. trachomatis	Using NAAT including LGV genotype
Herpes simplex virus	Using PCR
T. pallidum	Using DFM, PCR and serology
Mpox	(See BASHH/UKHSA guidance)
Other sexually transmitted infections	HIV
	Hepatitis A (if non-immune)
	Hepatitis B (if non-immune)
	Hepatitis C

Richardson D, Pakianathan M, Ewens M, *et al;* The new 2023 BASHH sexually transmitted enteric infections guideline, *Sexually Transmitted Infections* 2023;**99:**363-364.

Klinički aspekti i liječenje *Helicobacter pylori* infekcije

prof.dr.sc. Tajana Filipec Kanižaj, dr. med.

Zavod za gastroenterologiju, Klinika za unutarnje bolesti, KB Merkur

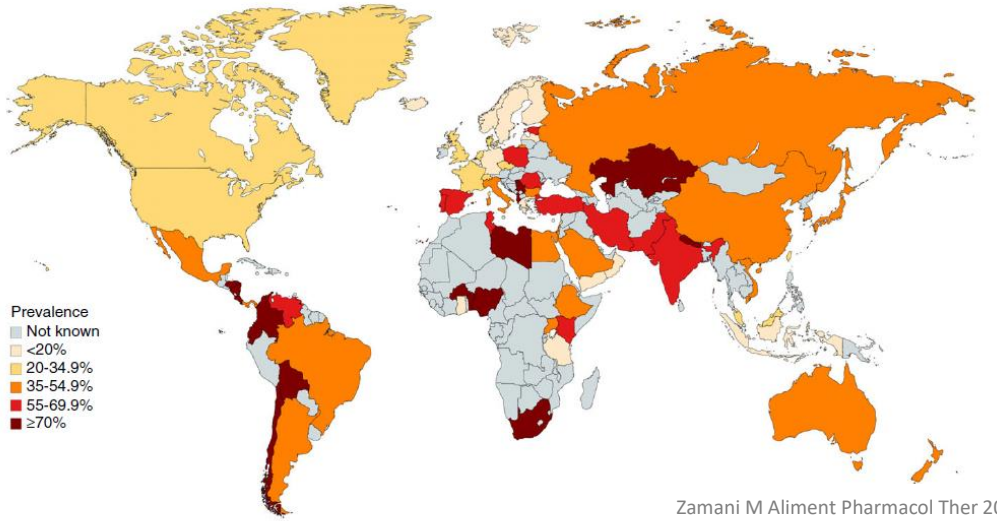
MEF, Zagreb

17.5.2024.

Prevalencija Helicobacter pylori (HP) infekcije

- najčešća bakterijska infekcija u ljudi (> 50% populacije)
- najčešće (99%) infekcija multiplim genotipovima

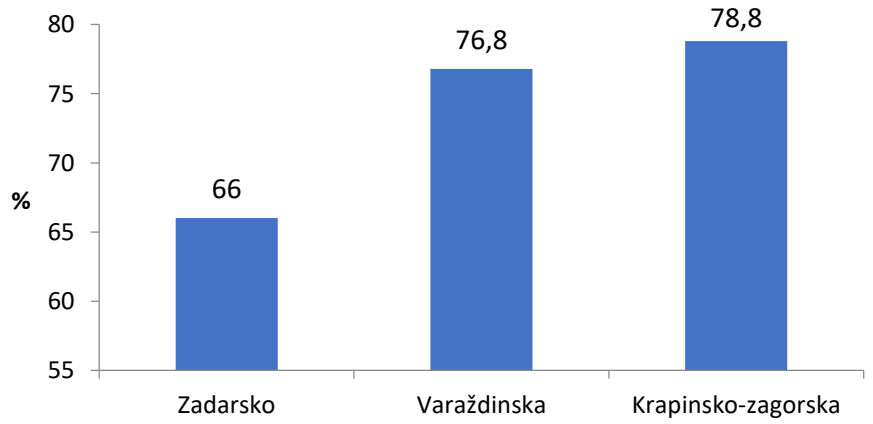
Ren L Int J Infect Dis 2012



Zamani M Aliment Pharmacol Ther 2018

FIGURE 2 Graphical presentation of prevalence of *Helicobacter pylori* infection across the world

- RH studija
  - ukupno 3082 ispitanika, oba spola dobi 20-70 godina
  - prosječno 60.4% odraslih inficirano



Babuš V Ljiječ Vjesn 1997

Presečki V Zbornik I hrvatskog epidemiološkog kongresa

Rizični faktori

- mlađa dob
- infekcija roditelja poglavito majki (OR 3.9-13)
- infekcija drugih članova obitelji
- niski socioekonomski status
- etnička pripadnost
- zemljopisna područja
- nerazvijenost
- nedostatak tekuće pitke vode
- institucionalni smještaj
- profesionalna ekspozicija
- genetika?

- rizik infekcije:
  - < 0,5% / godinu u razvijenim zemljama i u opadanju
  - 3-10%/ godinu u zemljama niskog socioekonomskog statusa

- nakon eradikacije:
  - razvijene zemlje: 1,45%/godišnje
  - nerazvijene zemlje: 12%/godišnje

Rothenbacher D Pediatr Infect Dis J 2002, Weyermann M Am J Gastroenetrol 2009, Webb PM BMJ 1994, Kivi M Epidemiol Infect 2005, Gao MF Aliment Pharmacol Ther 2002, Strebel K Sci Total Environ 2010, Parsonnet J Aliment Pharmacol Ther 1995, *Niv Y World J Gastroenetrol 2008*

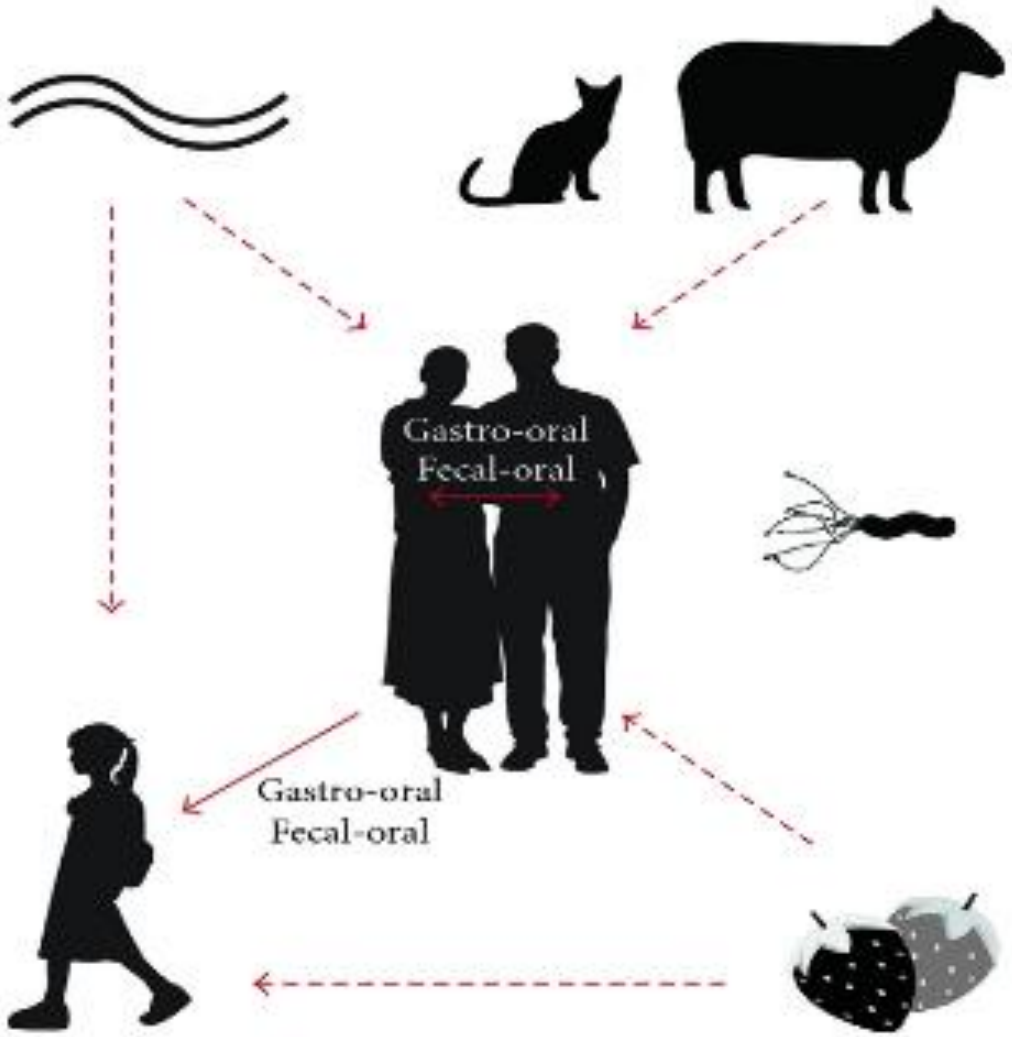
HP pronađen je u

- želučanom soku/sluznici
- slini
- tekućini sluznice rektuma i terminalnog ileuma
- usnoj šupljini
  - teže se eradicira (5,8% vrs 85,5%, OR 55.59)
  - pitanje rezervoara reinfekcije
- zubnom plaku
- u 40% inficirane djece i roditelja
- netretiranoj vodi (2-40%)
- krajnicima

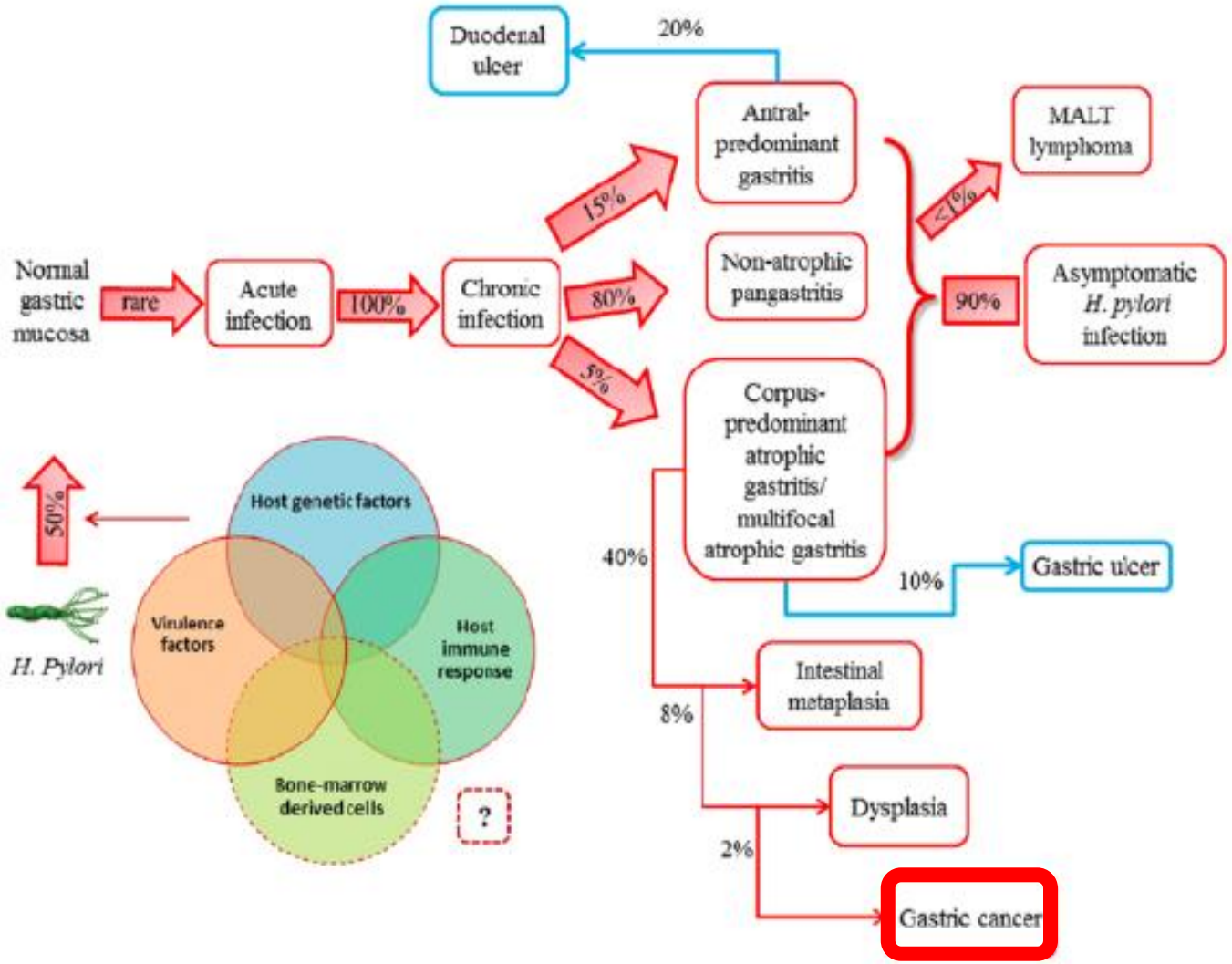
Kim do H Korean J Gastroenterol 2010, Zou QH J Clin Pthol Med 2011, Tsami A Eur J Pediatr Dent 2012, Al-Sulami AA East Mediterr Health J 2010, Samra ZQ J Water Health 2011, Linke S Int J Hyg Environ Health 2010, Lin HC Arch Otolaryngol Head Neck Surg 2010, Vilarinho S Int J Pediatr Otorhinolaryngol 2010

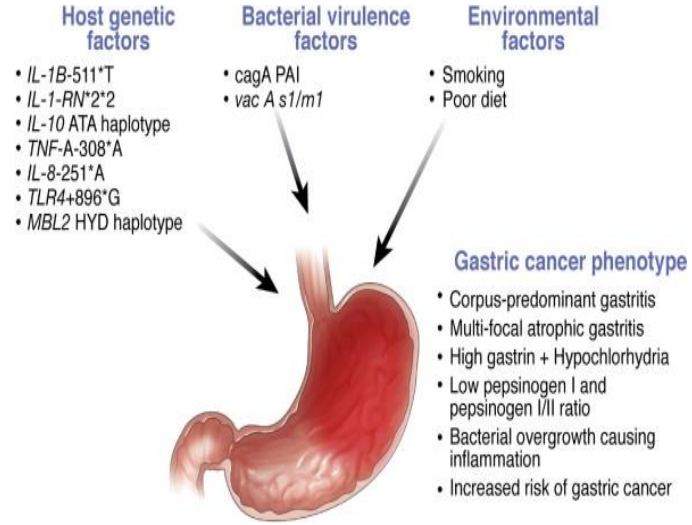
Putevi prijenosa

- način prijenosa
  - feko-oralni
  - oro-oralni
  - gastro-oralni?

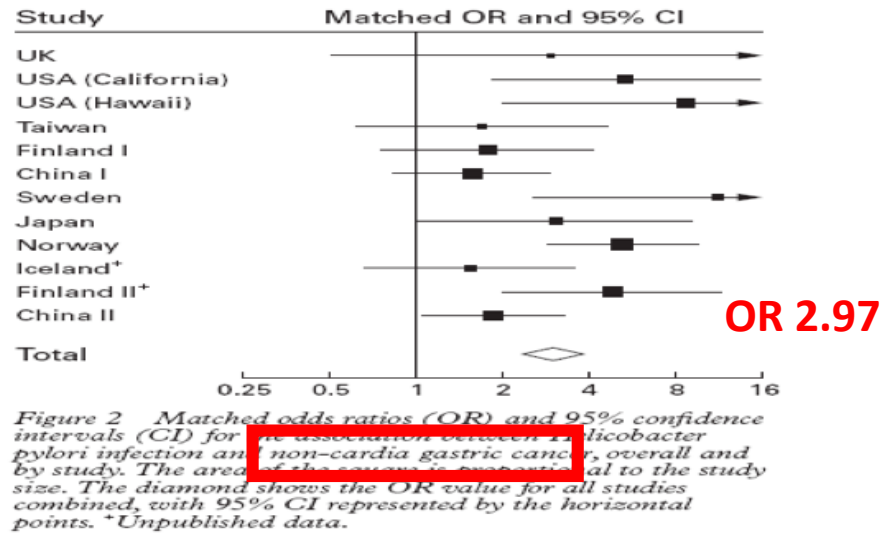


Uloga HP u bolestima





HP udio u patogenezi karcinoma > 90-95%



OR 2.97

Figure 2 Matched odds ratios (OR) and 95% confidence intervals (CI) for the association between Helicobacter pylori infection and non-cardia gastric cancer, overall and by study. The area of the square is proportional to the study size. The diamond shows the OR value for all studies combined, with 95% CI represented by the horizontal points. +Unpublished data.

Conteduca V Int J Oncol 2013

Helicobacter and Cancer Collaborative Group Gut 2001, Huang JQ. Gastroenterology 2003, Amieva MR Gastroenterology 2008, de Martel C Lancet Oncol 2012, González CA Ann Oncol 2012

Testiranje na HP

- testiranje za HP potrebno je provesti u slučajevima u kojima se planira i provesti eradikacijsko liječenje (*test and treat* strategija)
    - simptomatski bolesnici
    - asimptomatski s rizikom komplikacija HP povezanih bolesti
- odluku o dijagnostičkim metodama koju(e) se planira primijeniti potrebno je temeljiti na:
    - procjeni nužnosti pregleda gornje probavne cijevi
    - razumijevanju prednosti/nedostataka, vremena potrebnog do rezultata i cijene pojedinog testa
    - postojanja čimbenika koji utječu na pouzdanost testiranja

Katicic M i sur. Hrvatski postupnik za dijagnostikui liječenje Helicobacter pylori infekciju. 2013, Malfertheiner P et al. Management of Helicobacter pylori infection —The Maastricht VI, Gut, 2022

Pristup dispeptičnom bolesniku

Dispeptični bolesnik

"Testiranje i liječenje" strategija
dob < **50** god *
i bez
alarmantnih simptoma**
i
prevalencija HP > 20%

Klinički pregled bolesnika

Testiranje na *H. pylori*
neinvazivnim metodama

Ako je bolesnik HP pozititivan
treba liječiti infekciju

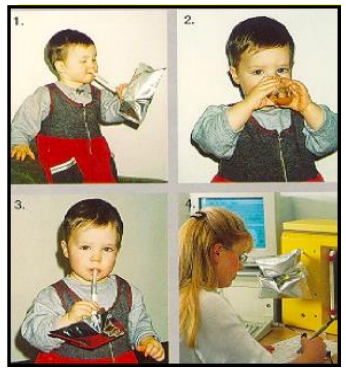
"Pregled i liječenje" strategija
dob > **50** god
ili
s alarmantnim simptomima
ili
prevalencija HP < 10%

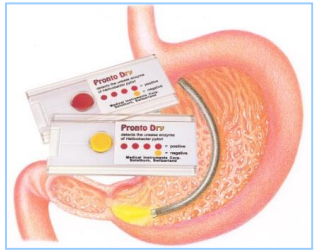
FEGD / GE-log

*dobna granica može biti i ispod 45 god., a što ovisi o lokalnim razlikama u incidenciji želučanih malignoma

** nenamjerni gubitak na TT, disfagija, odinofagija, neobjašnjiva sideropenična anemija, dugotrajno povraćanje, tumorska masa u gornjem abdomenu, obiteljska anamneza carcinoma želuca

Pregled dijagnostike HP



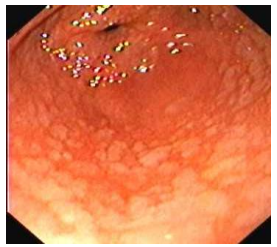


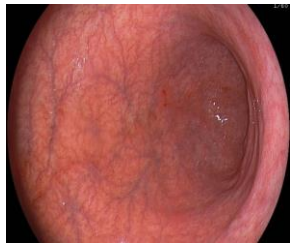
Neinvazivni testovi

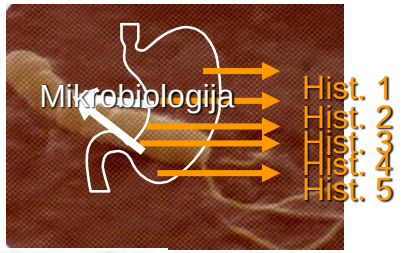
1. 13/14C - urejni izdisajni testovi
2. antigen H. pylori u stolici (monoklonski ELISA !)
3. serologija (IgG)

Prije testiranja potreban je prethodni prekid

antisekretorne terapije tijekom barem 2
antibiotske terapije i bizmuta barem 4 tjedna



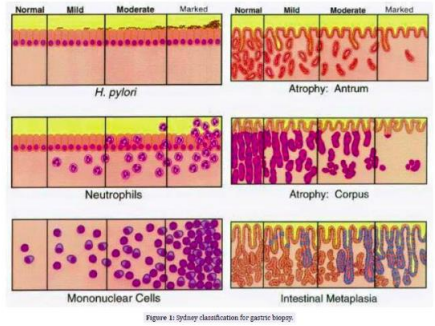




Invazivni testovi

1. brzi test ureaze
2. histologija: senzitivnost: 42-99%, specifičnost 100%
3. kultura (izolacija/rezistencija)
4. molekularni (istraživanja/PCR/rezistencija)

atrofija
intestinalna metaplazija
displazija
karcinom



Gensko testiranje rezistencije HP na antibiotike

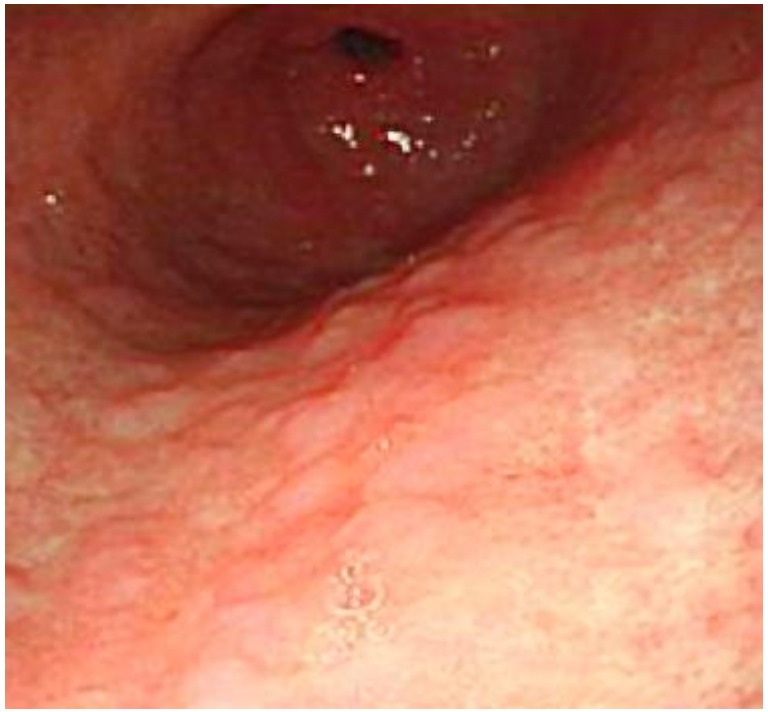
Table 3. Genes Associated With Antibiotic Resistance in *Helicobacter pylori* Infection

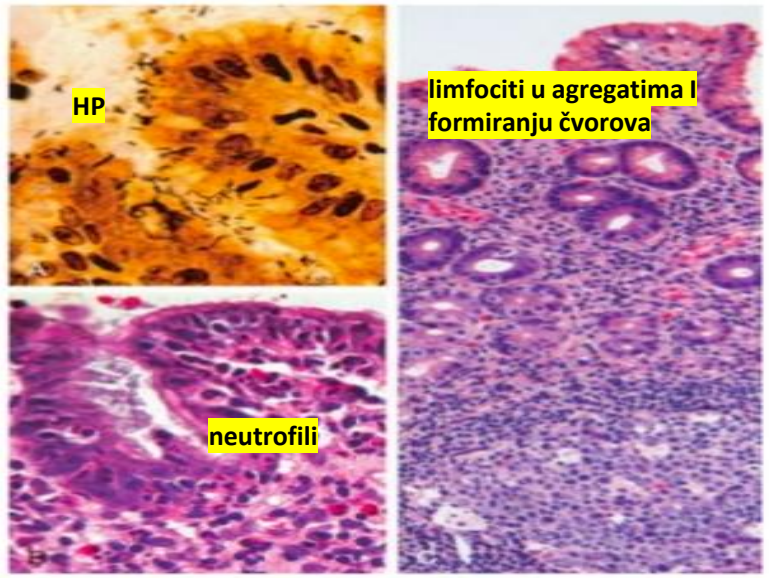
Antibiotic medication/group	Genes concerned
Macrolides	*rrn*23S
Metronidazole	*rdx*A, *frx*A*
Quinolones	*gyr*A
Rifamycins	*rpo*B
Amoxicillin	*pbp*-1 *
Tetracyclines	*rrn*16S

- iznimno kompleksne i za neke mutacije genska testiranja niske senzitivnosti imajući u vidu učinak na fenotip rezistencije

Graham DY Gastroenetrol Hepatol 2024

Nalaz endoskopije i PHD





Što dalje ?

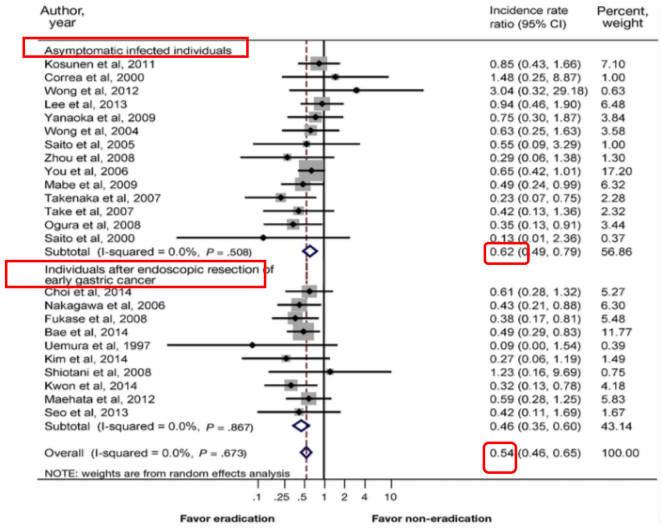
HP i gastritis / gastritisom uvjetovanu dispepsiju, rizik karcinoma

Eradikacijom HP može se postići **dobar** terapijski učinak u slučajevima **ne-atrofičnog kroničnog gastritisa**, te **djelomično** dobar terapijski učinak u slučajevima **atrofičnog gastritisa**.

Eradikacija HP **nema** učinka na regresiju **intestinalne metaplazije**, ali može **usporiti** razvoj displazije/karcinoma, te se prema tome preporučuje kao izbor liječenja.

Katicic M i sur. Hrvatski postupnik za dijagnostikui liječenje Helicobacter pylori infekciju. 2013Malfertheiner P et al. Management of Helicobacter pylori infection —The Maastricht V, Gut, 2016

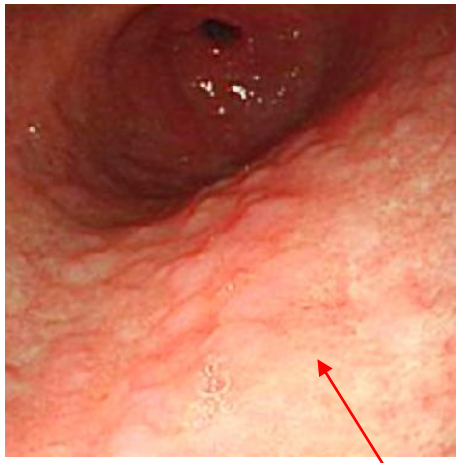
- uspijeh izraženiji u bolesnika **<u>bez</u>** atrofičnog gastritisa ili intestinalne metaplazije i s urednom razinom pepsinogena (RR nastanka želučanog karcinoma 0.24 *vs* 0.78)

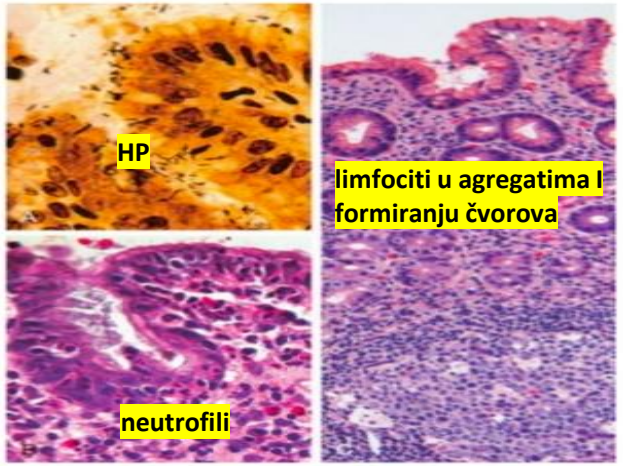


Wong BC-Y JAMA 2004

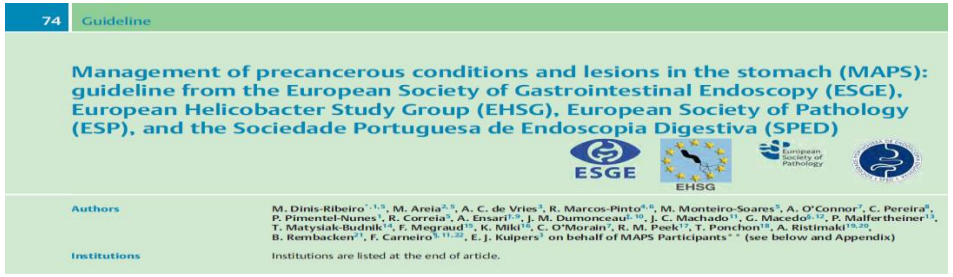
Lee YC Gastroenterology 2016

Nalaz endoskopije i PHD





difuzna metaplazija (OLGA/IM III/IV
↓
EGD svake 3 godine


74 Guideline

Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED)

ESGE EHSG

Authors M. Dinis-Ribeiro, M. Areia, A. C. de Vries, R. Marcos-Pinto, M. Monteiro-Soares, A. O'Connor, C. Pereira, P. Pimentel-Nunes, R. Correia, A. Ensari, J. M. Dumonceau, J. C. Machado, G. Macedo, P. Malfertheiner, T. Matysiak-Budnik, F. Megraud, K. Miki, C. O'Morain, R. M. Peek, T. Ponchon, A. Ristimaki, B. Rembacken, F. Carneiro, E. J. Kuipers on behalf of MAPS Participants* * (see below and Appendix)

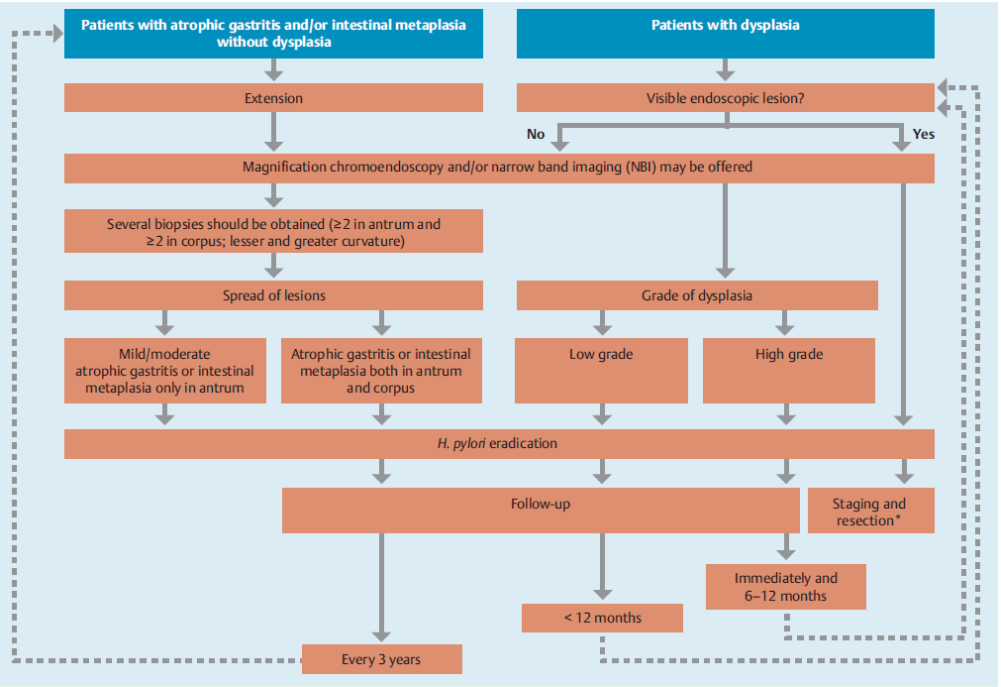
Institutions Institutions are listed at the end of article.

Što dalje:

Eradikacija HP

+

endoskopsko praćenje ?



HP i gastritis / gastritisom uvjetovanu dispepsiju

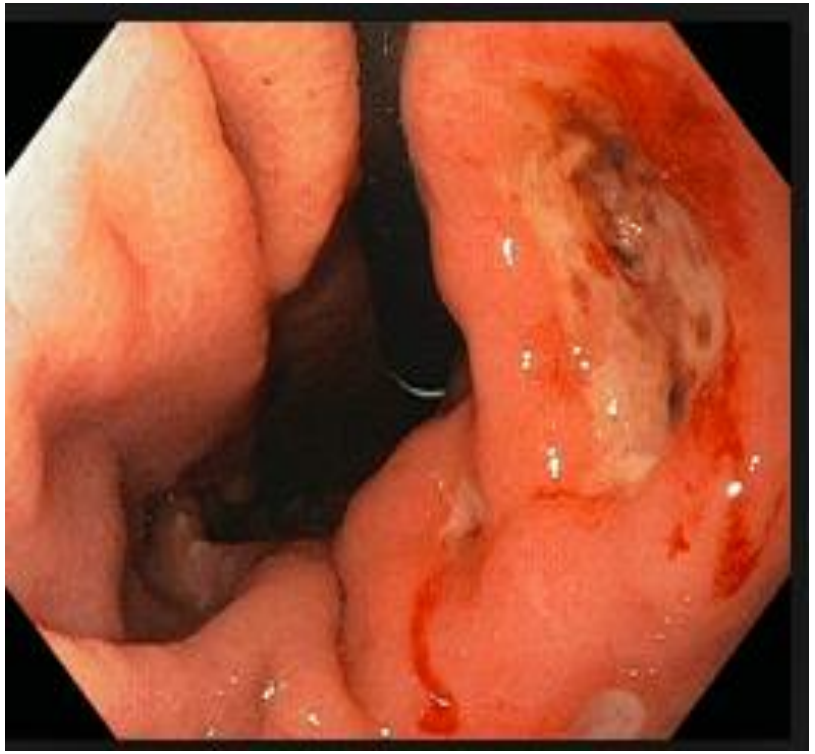
Dugotrajno liječenje s PPI u HP pozitivnih pacijenata **povezano** je s razvojem **gastritisa korpusa želuca** i **atrofičnog gastritisa.**
Stoga **prije uvođenja PPI** potrebno je provesti terapiju eradikacije HP.

Učinak eradikacije na **dispeptične simptome**: **6-13%** (značajno ovisi o prevalenciji infekcije/drugim etiološkim faktorima), **NNT 14,** učinak za cca **6 mjeseci** – oporavak upale.

Odgovor pojedinog bolesnika nemoguće predvidjeti i vjerojatno ovisi o statusu lučenja kiseline prije eradikacije.

Katicic M i sur. Hrvatski postupnik za dijagnostikui liječenje Helicobacter pylori infekciju. 2013, Malfertheiner P et al. Management of Helicobacter pylori infection —The Maastricht VI, Gut, 2022

Ulkusna bolest



rizik ponovne pojave s HP povezanih ulkusa/kompliciranih ulkusa nakon eradikacije minimalna (<6%)

Hopkins RJ Gastroenterology 1996, Laine L Am J Gastroenterol 1998, Niv Y World J Gastroenetrol 2008

HP i NSAIL, ASK

HP infekcija povezana je sa **povećanim rizikom** nastanka **nekompliciranih** i **kompliciranih gastroduodenalnih ulkusa** kod uporabe NSAIL i ASK:

1. eradikacija smanjuje taj rizik u **novih** korisnika NSAIL (ne kroničnih)
2. učinak na ASK kontroverzan
3. nema učinak na korisnike koksiba

Eradikaciju HP potrebno je učiniti **prije uvođenja** NSAIL i ASK.
To je osobito važno u bolesnika sa pozitivnom anamnezom ulkusne bolesti.

Izolirano eradikacija HP **ne smanjuje pojavljivanje gastro-duodenalnih ulkusa** u bolesnika koji već duže vrijeme uzimaju NSAIL i ASK.
Takvi bolesnici zahtijevaju **kontinuirano uzimanje inhibitora protonske pumpe (IPP).**

Katicic M i sur. Hrvatski postupnik za dijagnostikui liječenje Helicobacter pylori infekciju. 2013, Malfertheiner P et al. Management of Helicobacter pylori infection —The Maastricht VI, Gut, 2022

Terapijske opcije liječenja HP?

Malfertheiner P et al. Management of Helicobacter pylori infection —The Maastricht VI, Gut, 2022

Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report

Peter Malfertheiner [1,2] Francis Megraud [3] Theodore Rokkas [4,5] Javier P Gisbert [6,7] Jyh-Ming Liou [8] Christian Schulz [1,9] Antonio Gasbarrini,[10] Richard H Hunt,[11,12] Marcis Leja [13,14] Colm O'Morain,[15] Massimo Rugge [16,17] Sebastian Suerbaum,[9,18] Herbert Tilg [19] Kentaro Sugano [20] Emad M El-Omar [21] On behalf of the European Helicobacter and Microbiota Study group

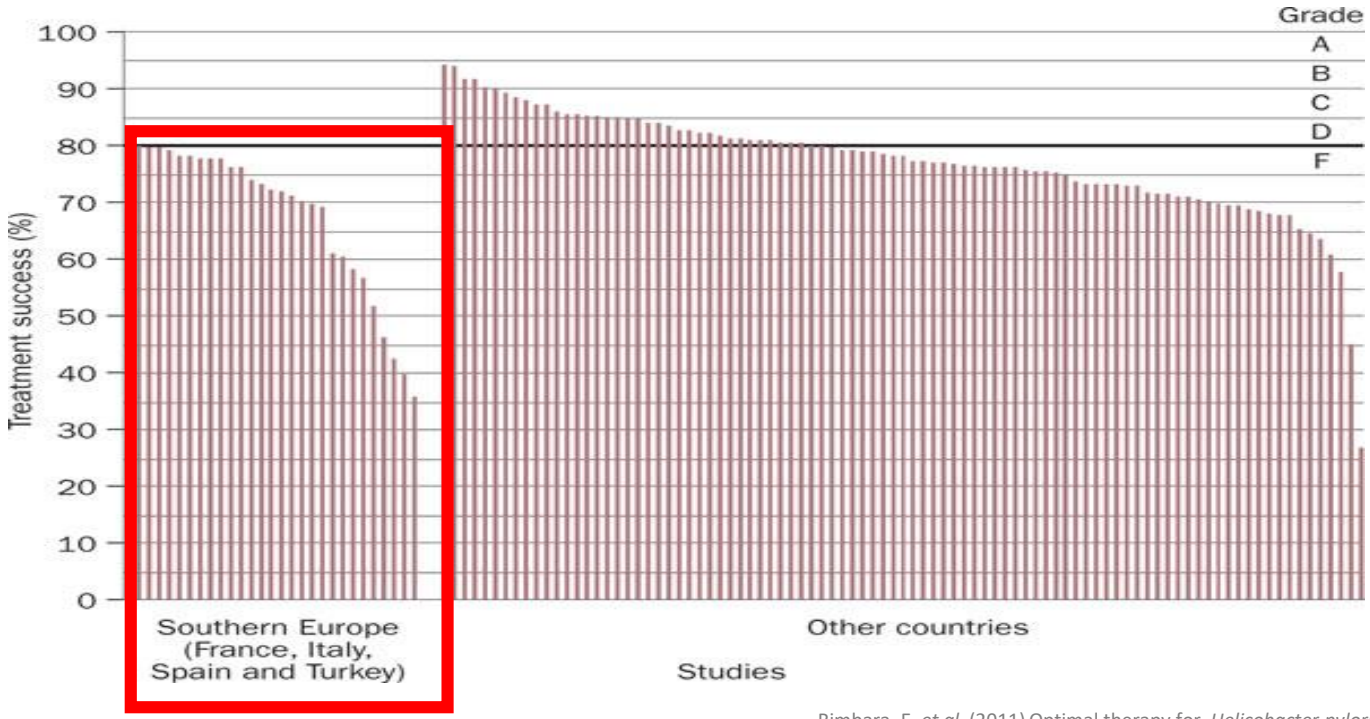
Uspješnost trojne terapije u kliničkim studijama

ITT analiza

Da bi se neka kombinacija lijekova za liječenje HP infekcije smatrala uspješnom mora postići najmanje:

- 90% izlječenja prema PP (“per-protocol”) analizi
- 80% izlječenja prema ITT (“intention-to-treat”) analizi

Malfertheiner P et al. Management of Helicobacter pylori infection —The Maastricht V, Gut, 2022



Rimbara, E. *et al.* (2011) Optimal therapy for *Helicobacter pylori* infections *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2010

Faktori povezani s nepovoljnim ishodom eradikacijske terapije

Ključni faktori:

1. **dužina liječenja**
2. **porast antimikrobne rezistencije**
3. nedovoljna kontrola želučanog pH s posljedičnom neefikasnošću antibiotika
4. brzina metabolizma IPP-a zbog CYP polimorfizma

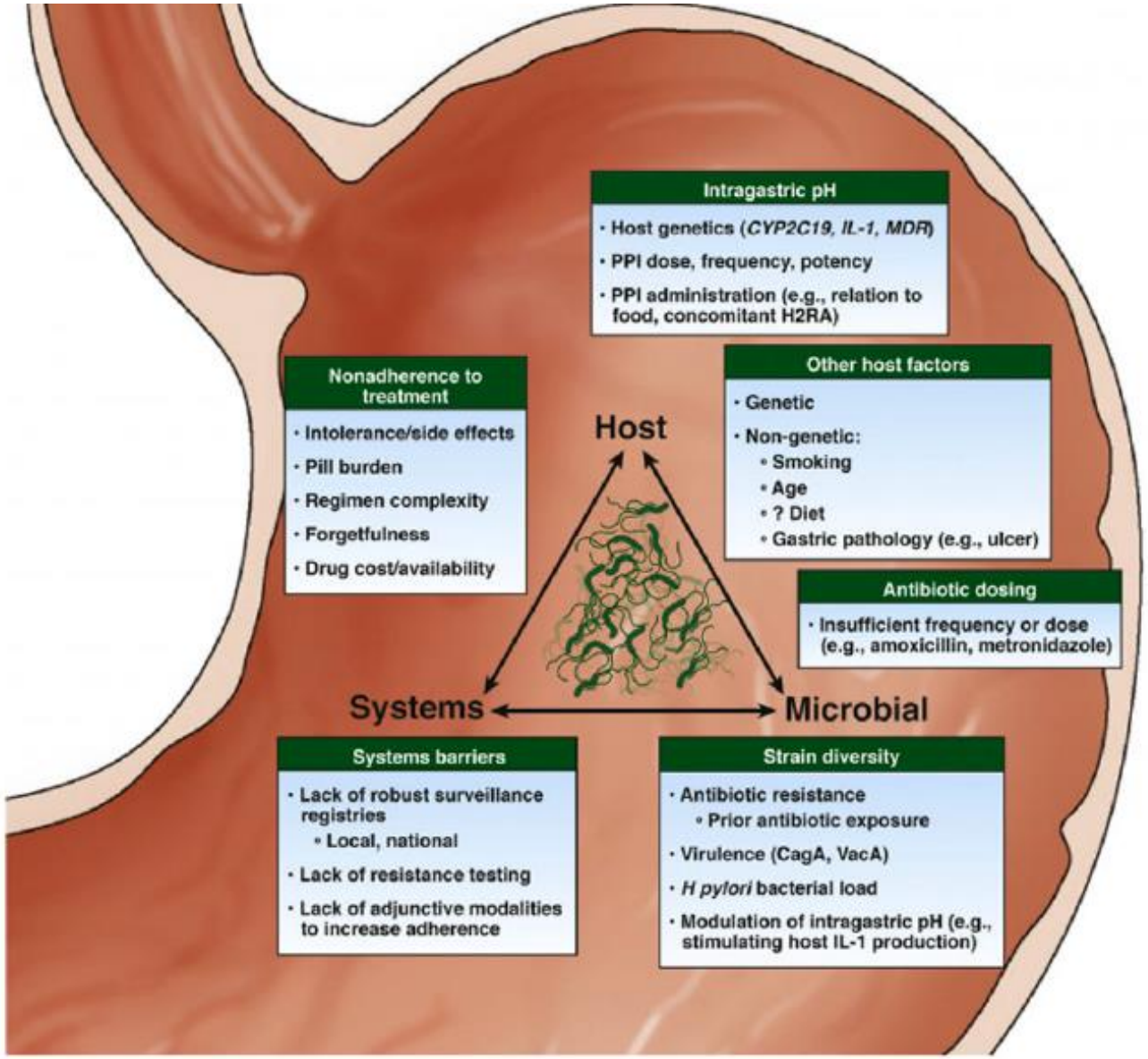
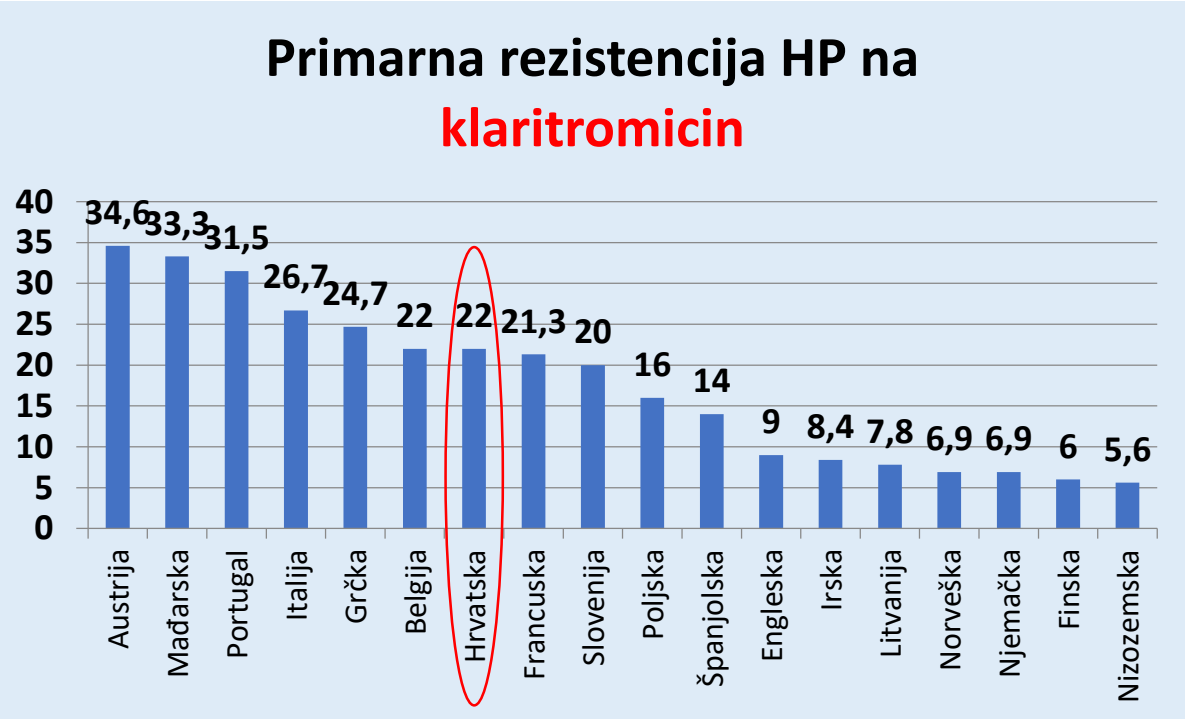
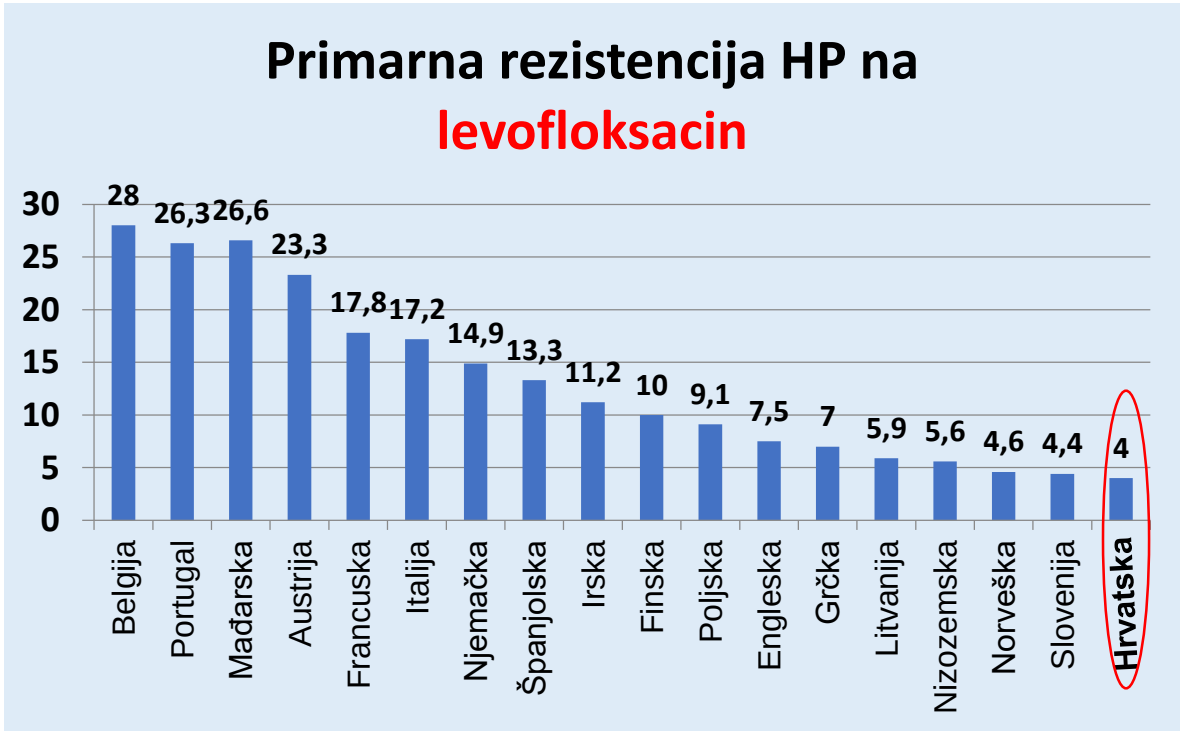


Figure 1.
Factors impacting failure to eradicate *H. pylori* infection. CagA cytotoxin-associated antigen A; IL, interleukin; VacA, vacuolating cytotoxin A.

Glavni razlog neuspijeha th: porast primarne rezistencije



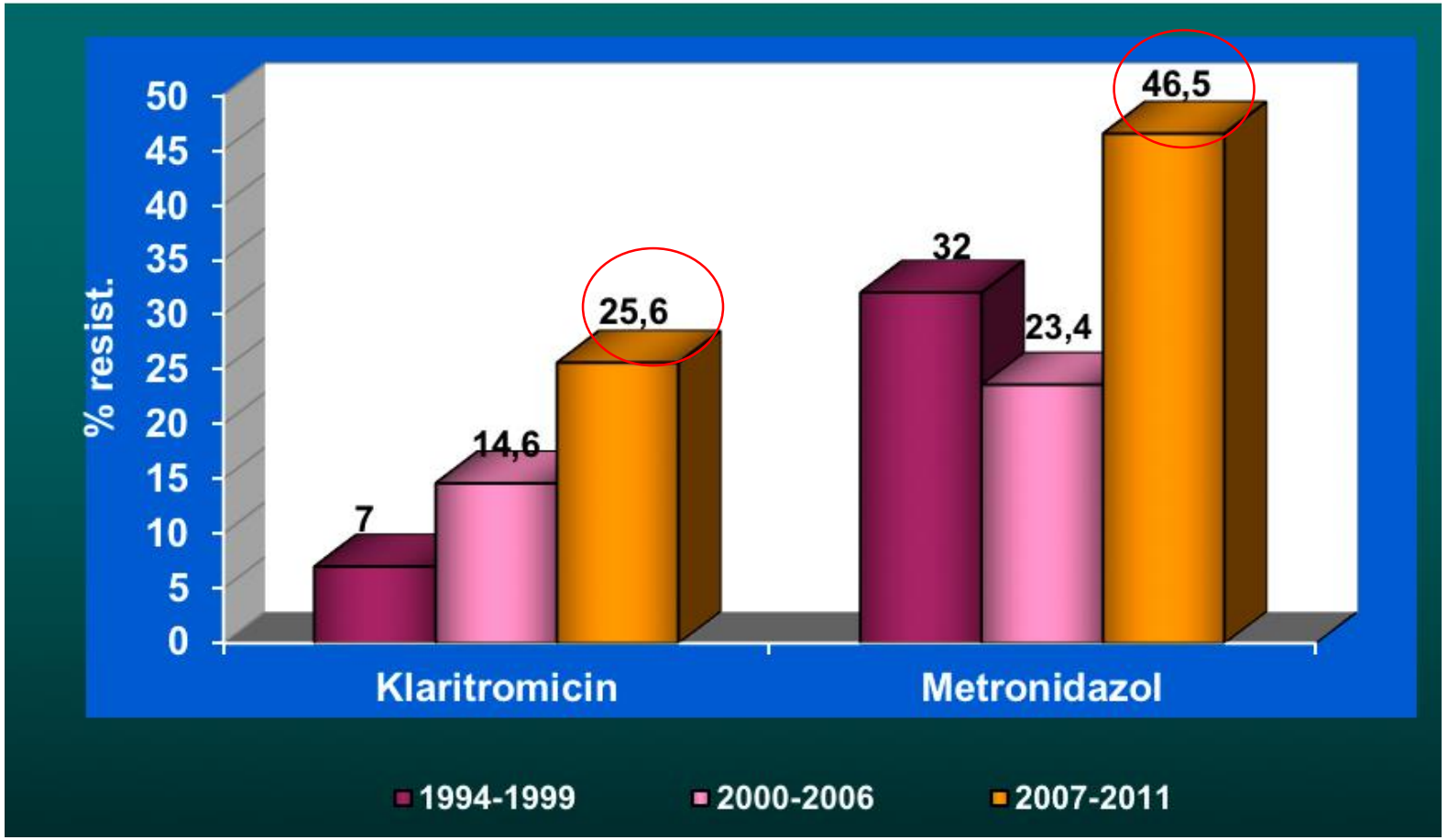


- klinički značajna individualna i populacijska rezistencija na klaritromicin, metronidazol i levofloksacin (ne amoksicilin i tetraciklin)

- visoka rezistencija:
  klaritromicin >15%
  metronidazol > 40%
  dualna klaritromicin+metronidazol >15%

Megraud F, Coenen S, Versporten A, et al. Gut (2012). doi:10.1136/gutjnl-2012-302254

Glavni razlog neuspijeha th: porast primarne rezistencije sojeva HP na najčešće korištene antibiotike (KB Merkur)



Rezistencija na metronidazol problematična u kombinaciji s drugim rezistencijama na antibiotike

Rezistencija na klaritromicin

Poželjno je, ako se radi endoskopski pregled i odrediti osjetljivost HP na antibiotike:

1. **u prvoj liniji u zemljama gdje je rezistencija na klaritromicin >20%**
2. **prije uvođenja druge linije terapije** (očekivana rezistencija na klaritromicin 60-70%)
3. **obavezno je prije uvođenja treće linije terapije.**

Katicic M i sur. Hrvatski postupnik za dijagnostikui liječenje Helicobacter pylori infekciju. 2013

Meta analiza: eradikacija HP trojnom terapijom s klaritromicinom

senzitivni sojevi 90%
rezistentni sojevi 20% !!!

Luther J Am J Gastroenterol 2010

Uloga rezistencije na klaritromicin na ishod liječenja

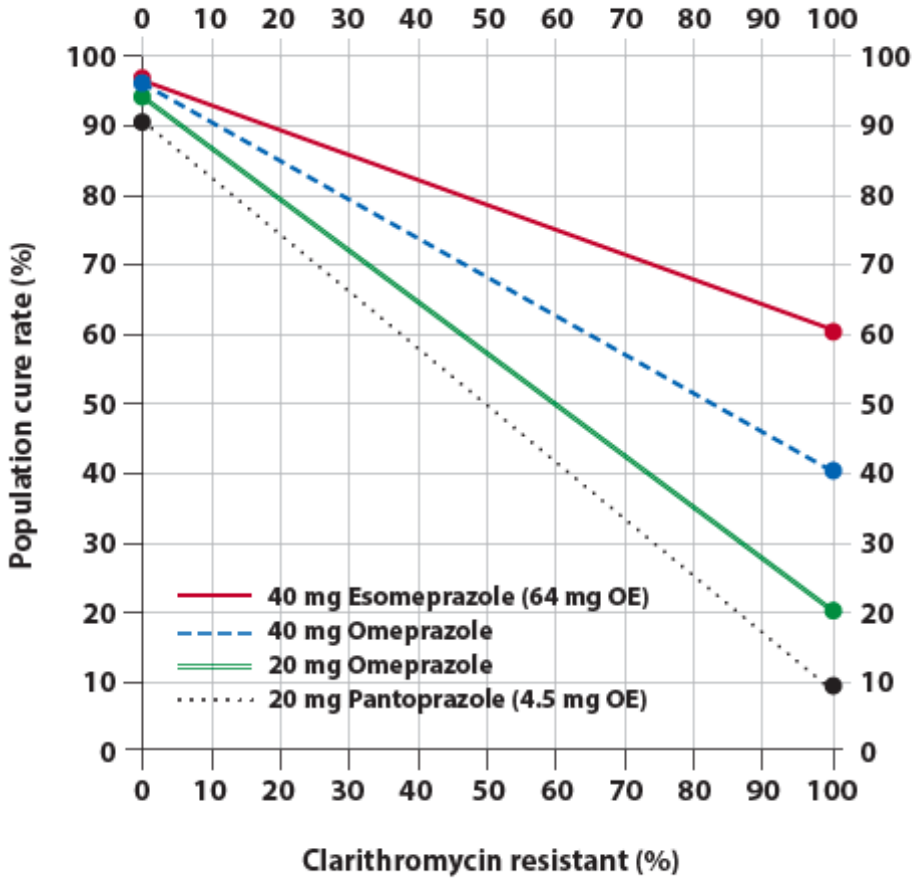


Figure 4. *Helicobacter pylori* nomogram illustrating the effect of clarithromycin resistance on the effectiveness of a clarithromycin and amoxicillin plus PPI triple therapy 14-day regimen. The population cure rates are high with clarithromycin triple therapy (ie, with only slight differences related to relative PPI potency). In contrast, the ability to suppress acid (PPI potency) is the major determinant of the effectiveness of the amoxicillin plus PPI dual therapy component.

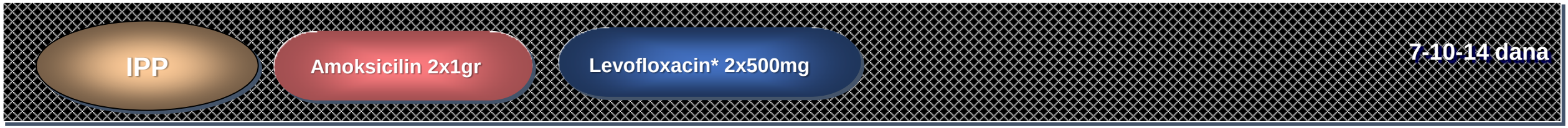
OE, omeprazole equivalent; PPI, proton pump inhibitor.

Graham DY Gastroenetrol Hepatol 2024

Četverostruka th s bizmutom (BQT)

*14 dana uz visoku (>40%) metronidazolsku rezistenciju

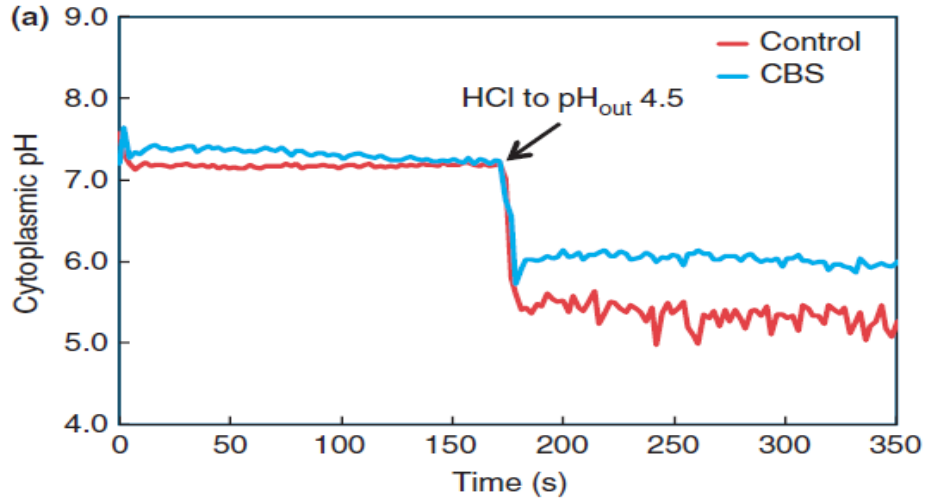
Kinolonska terapija

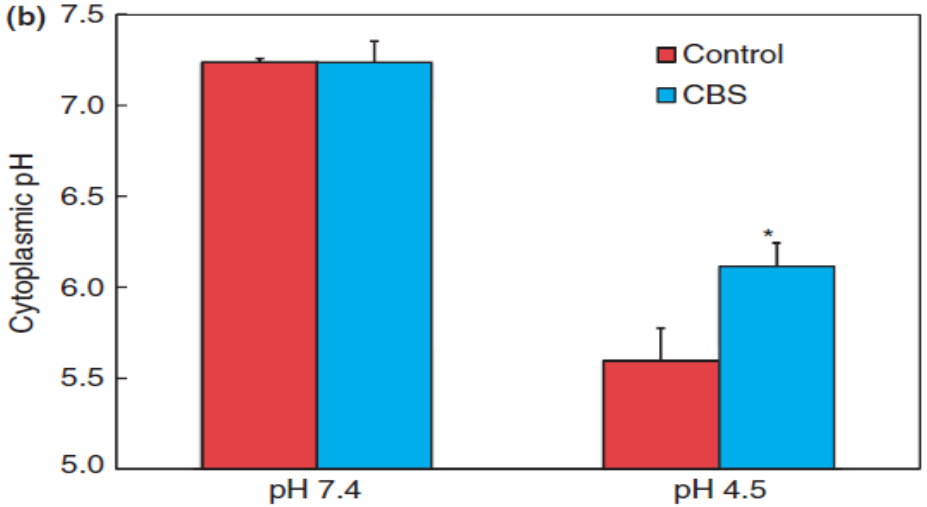


*rezistencija smanjuje učinkovitost za 20-40%

Rifabutinska terapija

Bizmut povisuje citoplazmatski pH HP čime bakterija postaje osjetljivija na djelovanje antibiotika





- CBS održava citoplazmatski pH i time transkripciju gena uključenih u metabolizam I replikaciju HP stanica čime osigurava
- bolju osjetljivost na djelovanje antibiotika čija učinkovitost ovisi o procesu dijeljenja stanica (amoxicilin, klaritromicin, levofloksacin,…)

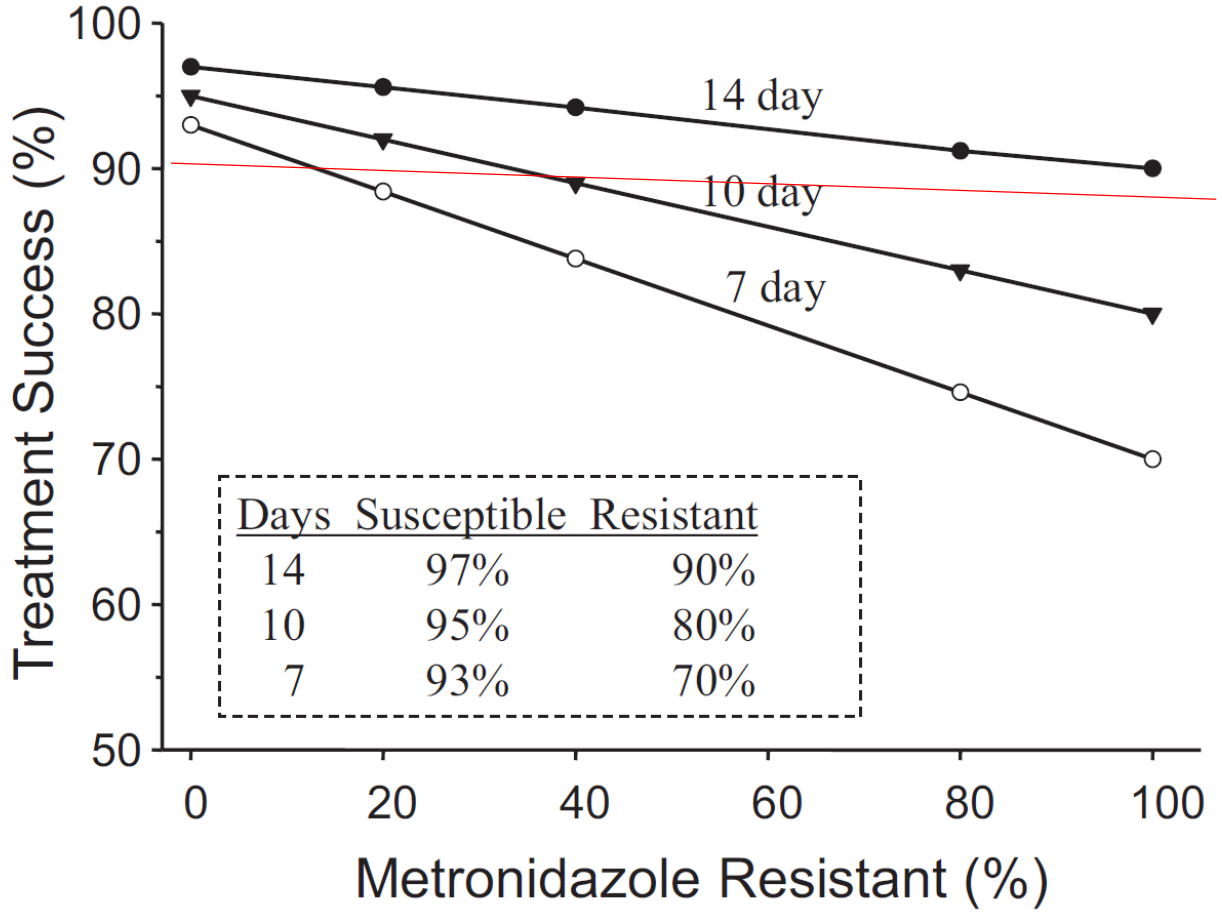
- aditivni učinak IPP (HP se najbolje djeli uz pH 6-8)

- veže toksine koje stvara HP, smanjuje viskoznost sluzi, smanjuje adherenciju HP na sluznicu želuca

CBS: Colloidal bismuth subcitrate

Lee SP. Scand J Gastroenterol Suppl. 1991, .Lambert JR Aliment Pharmacol Ther 199, Marcus EA Aliment Pharmacol Ther 2015

Četverostruka terapija s bizmutom osigurava >90% stope eradikacije kod 14-dnevnog liječenja

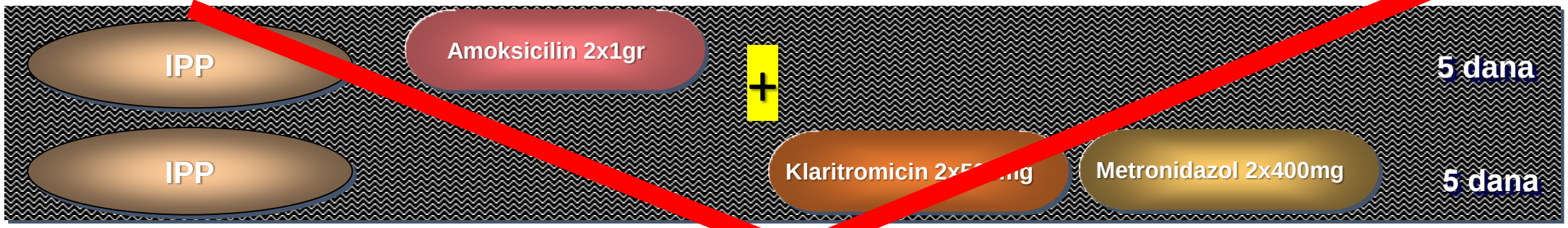


Graham DY Gastroenterol Clin N Am 2015

non-BQT- nepotrebna izloženost jednom od antibiotika na koji je HP rezistentan

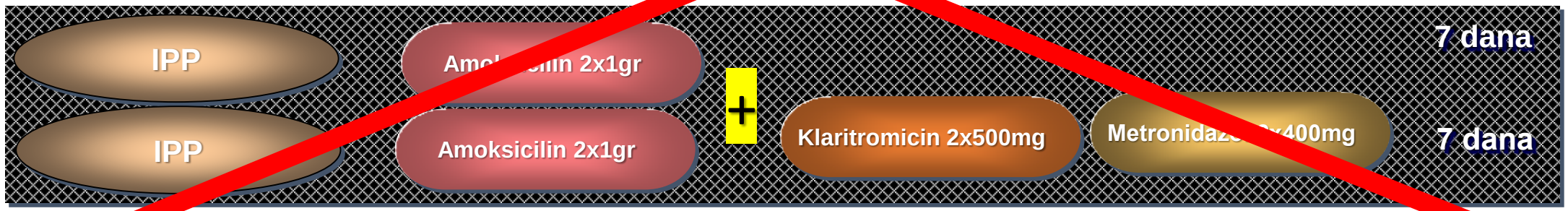
Rezistencija

Sekvencijska terapija



Klaritromicin i/ili Metronidazol

Hibridna terapija



Klaritromicin + Metronidazol

Konkomitantna terapija

Klaritromicin + Metronidazol

Dualna rezistencija na klaritromicin i metronidazol (>15%) negativno utječe na učinkovitost svih non-bizmut baziranih protokola

(neovisno o populacijskom riziku osobni rizik za dualnu rezistenciju je visok ako je pojedinac bio izložen klaritromicinu i/ili metronidazolu)

Graham DY Clin Gastroenterol Hepatol 2014

Učinak vrste IPP

- metabolizam prve generacije IPP ovisan o prevalenciji raznih polimorfizama CYP2C19 i MDR
- izraženi metabolizatori IPP češći u bjelačkoj populaciji (56-81%)
- učinak ovisan i o dozi
  - 2 x 40mg povećava uspjeh trojne terapije za 6-10%

Statement 10: The use of high dose PPI twice daily increases the efficacy of triple therapy. Esomeprazole and rabeprazole may be preferred in Europe and North America where the prevalence of PPI extensive metabolisers is high.

Level of evidence: low **Grade of recommendation: weak**

Malfertheiner P et al. Management of Helicobacter pylori infection —The Maastricht VI, Gut, 2016

Seven-day vonoprazan and low-dose amoxicillin dual therapy as first-line *Helicobacter pylori* treatment: a multicentre randomised trial in Japan

Sho Suzuki [1,2] Takuji Gotoda [1] Chika Kusano,[1] Hisatomo Ikehara,[1] Ryoji Ichijima,[1] Motoki Ohyauchi,[3] Hirotaka Ito,[3] Masashi Kawamura,[4] Yohei Ogata,[4] Masahiko Ohtaka,[5] Moriyasu Nakahara,[6] Koichi Kawabe[7]

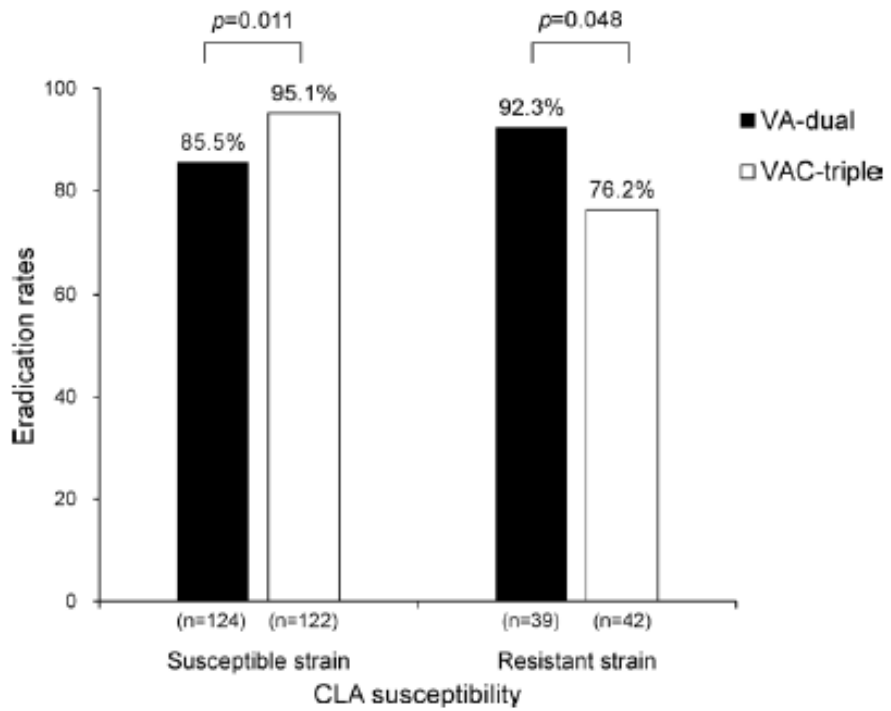


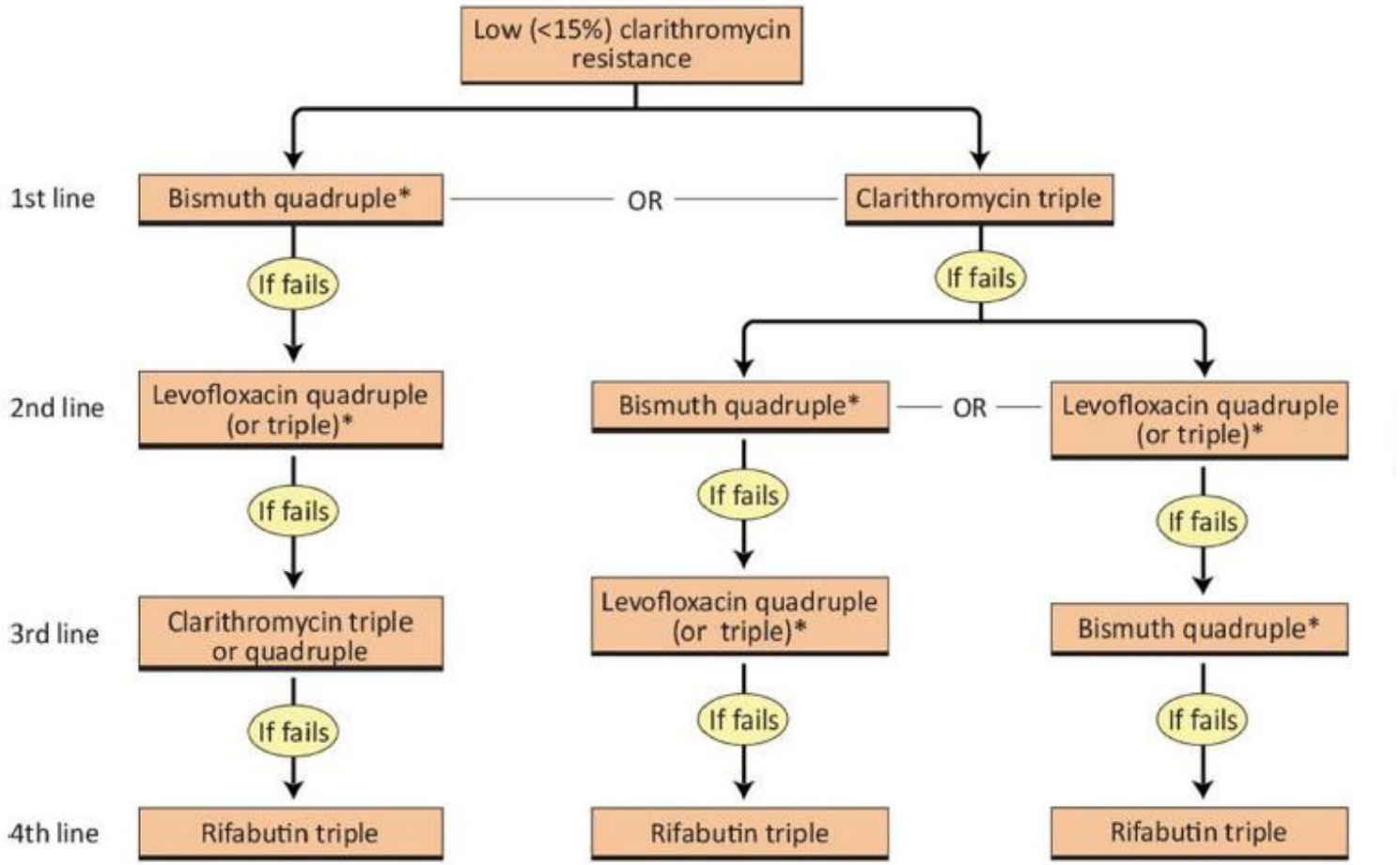
Figure 2 Eradication rates of each therapy groups in the presence of clarithromycin resistance in PP population. CLA, clarithromycin; PP, per protocol; VA-dual, vonoprazan and amoxicillin dual therapy; VAC-triple, vonoprazan, amoxicillin and clarithromycin triple therapy.

P-CABs potassium-competitive acid blockers

Suzuki Sho Gut 2020

Prva linija emipirijskog liječenja

klaritromicin rezistencija < 15%



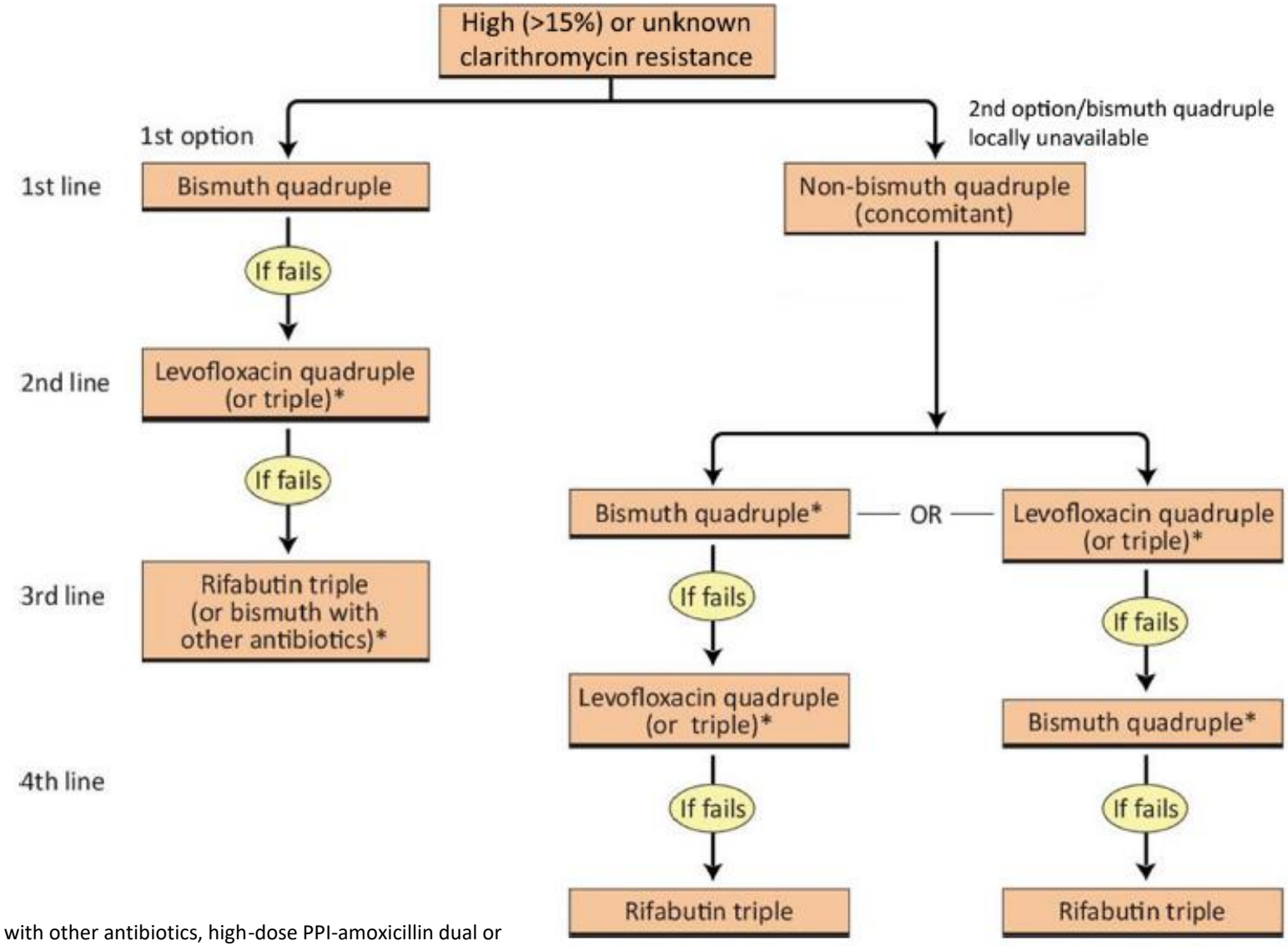
In cases of high fluoroquinolone resistance (>15%), the combination of bismuth with other antibiotics, high-dose PPI-amoxicillin dual or rifabutin, may be an option.

*High-dose PPI or P-CAB (vonoprazan where available) plus amoxicillin may be another option. P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

Malfertheiner P et al. Management of Helicobacter pylori infection —The Maastricht VI, Gut, 2022

Prva linija empirijskog liječenja

klaritromicin rezistencija > 15%



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*High-dose PPI or P-CAB (vonoprazan where available) plus amoxicillin may be another option. P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

Malfertheiner P et al. Management of Helicobacter pylori infection —The Maastricht VI, Gut, 2022

Da li trebamo sve bolesnike u prvoj liniji liječenja tretirati prema testiranju rezistencije ili empirijski?

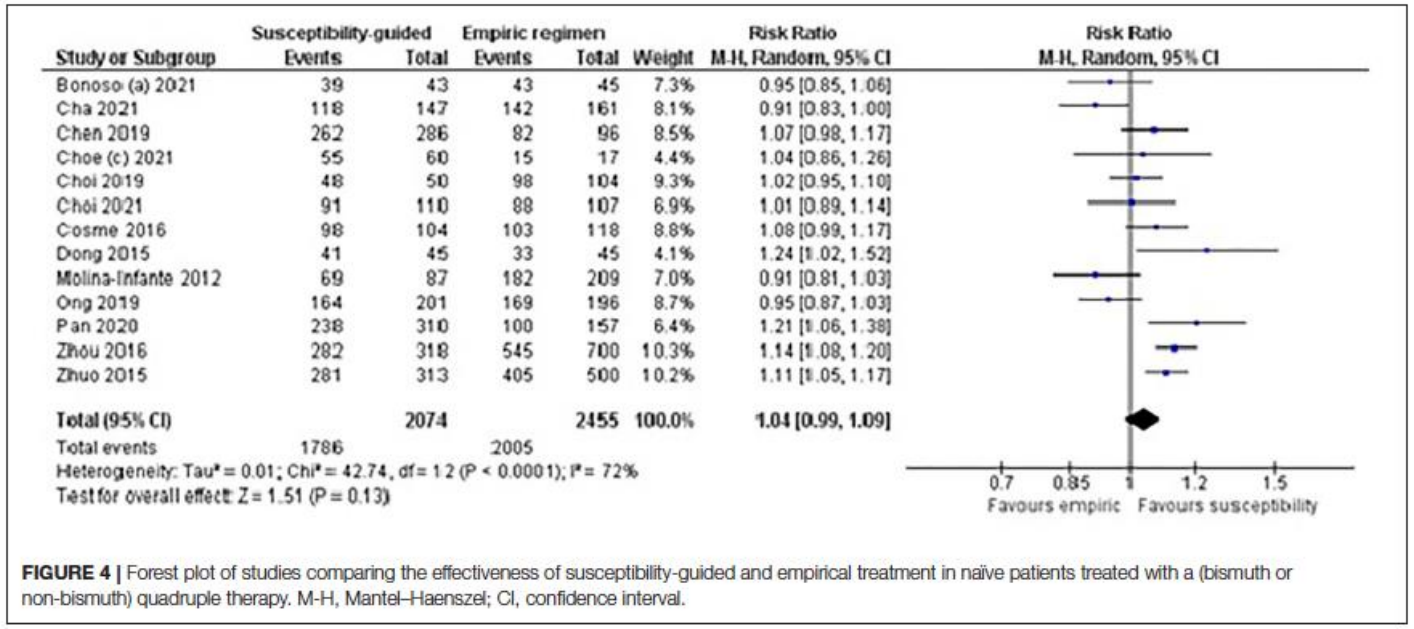


FIGURE 4 | Forest plot of studies comparing the effectiveness of susceptibility-guided and empirical treatment in naïve patients treated with a (bismuth or non-bismuth) quadruple therapy. M-H, Mantel–Haenszel; CI, confidence interval.

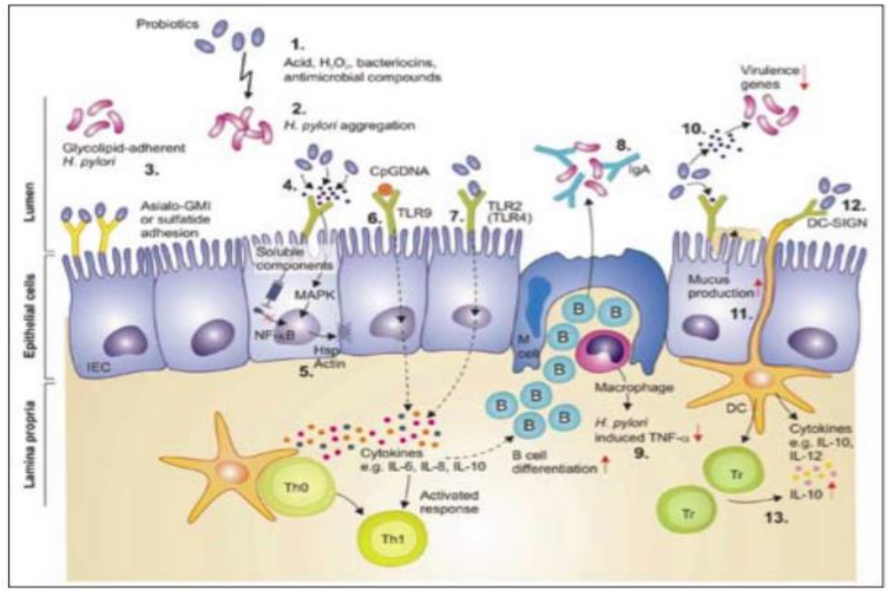
Nyssen OP Front Mycrobiol 2022

Učinak probiotika na eradikaciju HP

- uspijeh eradikacijske terapije s probioticima **14%** (95% CI 4-25%)
  - **OR u odnosu na placebo 7.91** (95% CI 2.97-21.05)
    - *Lactobacillus spp* 16% (95% CI 1-31%), 7 studija
    - *Saccharomyces boulardii* 12% (95% CI 0-29%), 2 studije
    - više sojeva 14% (95% CI 0-43%), 2 studije

- adjuvantna terapija antibioticima (META analiza)[1]
  - poboljšano izlječenje OR 2.1
  - smanjenje nuspojava OR 0.3

- inhibitorni učinak na HP[2]



Losurdo G World J Gastroenterol 2018
[1]Wang ZH J Clin Gastroenterol 2013
[2]Gotteland M Aliment Pharmacol Ther 2006
Papastergiou WJG 2014

Zaključci

- potrebno je pratiti
  - prevalenciju HP infekcije u zdravih ljudi i bolesnika
  - osjetljivost HP na najčešće upotrebljavane antibiotike (klaritromicin, metronidazol, levofloksacin)

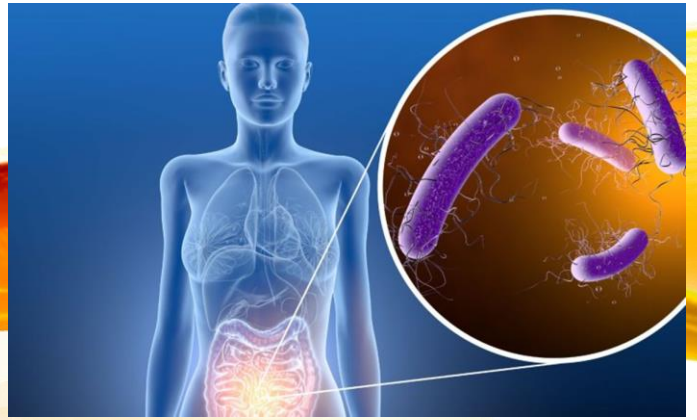
- u regijama Hrvatske u kojima je primarna rezistencija na klaritromicin >15% potrebno je prije uporabe klaritromicina u trojnoj terapiji uvijek dokazati osjetljivost ili započeti eradikaciju bizmut baziranim preparatima ev. konkomitantnom terapijom (rezistencija na metronidazol <40%)

- u 3. liniji terapije uvijek učiniti testiranje rezistencije na antibiotike

CLOSTRIDIOIDES DIFFICILE

KLINIČKI ASPEKTI I NOVOSTI U LIJEČENJU

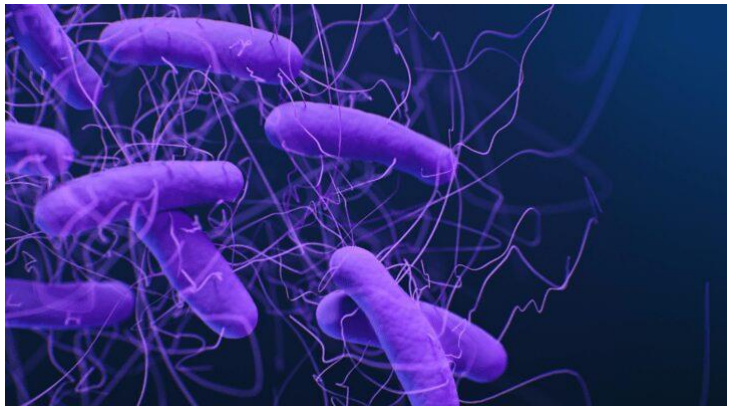
doc. dr. sc. Vladimir Krajinović, dr. med.
Infektolog, subspecijalist intenzivne medicine
Klinika za infektivne bolesti „Dr. Fran Mihaljević”
Zagreb



CDI

UVOD

- ***Clostridioides difficile***
  - anaerobna G+ bakterija koja ima spore i producira toksin
  - uzrokuje postantimikrobni kolitis



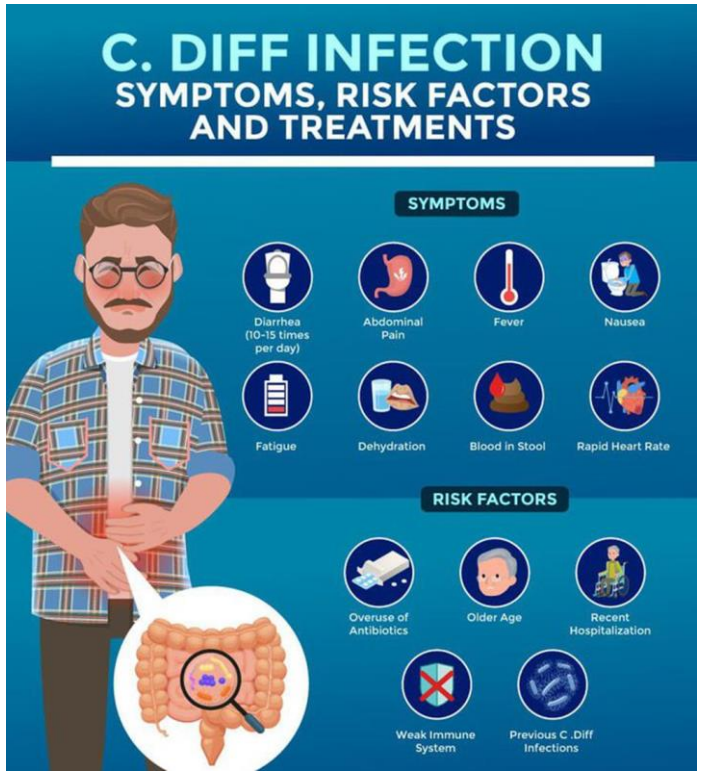
- kolonizira gastointestinalni trakt čovjeka obično nakon disregulacije normalne crijevne flore (najčešće primjena ATB)

- jedna od najčešćih infekcija povezanih sa zdravstvenom skrbi

- značajan uzrok morbiditeta i mortaliteta
  - osobito starijih i hospitaliziranih bolesnika

KLINIČKA SLIKA

- **Proljev s kolitisom**
  - Blaga do srednje teška bolest
  - Teški i fulminantni kolitis
- **Rekurentna bolest**
- **Asimptomatsko kliconoštvo**
- **Neuobičajene prezentacije**



KLINIČKA SLIKA

PROLJEV S KOLITISOM

Blagi do srednje teški oblik bolesti

Vodenaste stolice (3 ili više u 24h), ponekad sluz i krv

Grčevi u trbuhu

Vrućica (15% slučajeva), obično nižih vrijednosti (ponekad preko 38,5 C), mučnina, gubitak apetita

Anamneza prethodne primjene antibiotika (fluorokinoloni, klindamicin, cefalosporini, penicilini, ali i bilo koji drugi), ali nije nužan podatak o prethodnoj primjeni ATB

Dodatni faktori rizika:

dob >65, nedavna hospitalizacija, primjena IPP

Često leukocitoza

- L ≤15,000 cells/microL i serumski kreatinin <1.5 mg/dL (133 mcmol/L) – blaži oblik bolesti

KLINIČKA SLIKA

PROLJEV S KOLITISOM

Teški i fulminantni kolitis

Proljev, jaki grčevi, nadutost trbuha, vrućica, hipovolemija laktacidoza, hipoalbuminemija, visoke vrijednosti kreatinina, izražena leukocitoza (40,000 L/mikroL ili više)

Fulminantni kolitis

hipotenzija, šok, ileus, megakolon; moguća perforacija crijeva i peritonitis

ponekad samo ileus s malo proljevastih stolica uz teško opće stanje

megakolon – teško opće stanje, radiografski (CT abdomena i zdjelice) dokaz proširenog kolona (>7 cm promjen kolona i/ili >12 cm promjer u cekumu), moguća perforacija i zrak u peritoneumu

- obvezno kirurško liječenje

KLINIČKA SLIKA

RECIDIVIRAJUĆA BOLEST

- **2-8 tjedana nakon završetka liječenja prethodne epizode CDI**
- Moguće u 25% slučajeva unutar 30 dana nakon završenog liječenja
- Jedan recidiv znači rizik za nove recidive
- Može biti blaga, teška, fulminantna
- Faktori rizika: >65 godina, kronične bolesti, potreba za nastavkom ATB liječenja
- Recidiv može biti uzrokovn istim ili drugim sojem CD, češće se radi o relapsu

KLINIČKA SLIKA

ASIMPTOMATSKO KLICONOŠTVO

Oko 20% hospitaliziranih bolesnika – šire bakteriju, ali nemaju proljev

Do čak u 50% osoba u ustanovama s produljenim boravkom

Ne treba liječiti!

RIJETKE MANIFESTACIJE

Enteropatija s gubitkom proteina

hipoproteinemija (ispod 20g/L) s akutnom CDI, bez fulminantnog kolitisa

ascites i edemi

Liječi se uobičajenom shemom ATB za CDI.

Zahvaćanje izvan kolona

enteritis tankog crijeva (kolektomija s ileostomom) i ekstraintestinalna infekcija npr. apendicitis, celulitis, bektrijemija, reaktivni artritis

LIJEČENJE

OPĆI PRINCIPI

- **Kontrola širenja infekcije**
  - Mjere kontaktne izolacije
  - Pranje ruku vodom i sapunom
- **Prekid primjena ATB koji je doveo do CDI**
  - odmah
  - ako je potrebno nastaviti liječenje onda neki iz skupina koji rjeđe izazivaju CDI
- **Nadoknada tekućine, elektrolita, dijeta, lijekovi za proljev**
  - Nadoknaditi izgubljeno, dati tekućinu za održavanje
  - Normalna prehrana, eventualno dijata bez puno vlakana (da se smanji broj i volumen stolica)
  - Dijeta bez laktoze nema koristi
  - Antidijareici (npr. loperamid) tradicionalna preporuka je da se trebaju izbjegavati no nema jakih dokaza da su štetni
    - Mogu se dati ponekad ako postoji jaki gubitak tekućine u odsustvu ileusa i distenzije kolona

LIJEČENJE

NEFULMINANTNA BOLEST

- INICIJALNA EPIZODA
  - Blagi i umjereni oblik bolesti (L<15,000 st/ml i kreatinin <133 mcmol/L)
    - Fidaksomicin 2x200 mg 10 dana
    - Vankomicin 4x125 mg 10 dana
    - Alternativa: metronidazol 3x500 mg 10-14 dana
  - Teški bolest (L>15,000 st/ml i kreatinin >133 mcmol/L)
    - Kao i blaga i umjereni oblik bolesti

LIJEČENJE

NEFULMINANTNA BOLEST

- REKURENTNA EPIZODA
  - 1. rekurentna epizoda
    - Fidaksomicin 2x200 mg 10 dana ILI 2x200 mg 5 dana pa još 1x200 mg još 20 dana
    - Vamkomicin kao „tapered” ili kao pulsni režim:
      - 4x125 mg 10-14 dana zatim
      - 2x125 mg 7 dana zatim
      - 1x125 mg 7 dana i na kraju
      - 125 mg 2-3x tjedno tijekom 2-8 tjedana ILI
      - 4x125 mg 10 dana (pulsni)
  - 2. rekurentna epizoda i sljedeće
    - Fidaksomicin 2x200 mg 10 dana ILI 2x200 mg 5 dana pa još 1x200 mg još 20 dana
    - Vankomicin kao „tapered” ili pulsni režim
    - Vankomicin kojeg slijedi rifaximin
      - Vankomicin 4x125 mg 10 dana, zatim rifaximin 3x400 mg tijekom 20 dana

Za bolesnike koji su primili ispravnu ATB terapiju za 3 rekurentne epizode, a dobiju 4. epizodu, preporučuje se fekalna transplantacija (ako je moguće provesti, ako ne onda opet ATB)

Dodatna terapija: bezlotoxumab 1x10 mg/kg iv tijekom primjene antibiotika

ZINPLAVA™ (bezlotoxumab) Injection 25 mg/mL

LIJEČENJE

FULMINANTNA BOLEST (hipotenzija ili šok, ileus, megakolon)

- Odsustvo ileusa (peroralni vankomicin plus parenteralni metronidazol)
  - Vankomicin 4x500 mg per os **+** metronidazol 3x500 mg IV

- Ako je prisutan ileus:
  - Transplantacija fekalne mikrobiote ILI
  - Rektalni vankomicin (4x 500 mg u 100 ml FO rektalna klizma, da ostane u rektumu što duže)

Probiotici u liječenju Helicobacter pylori infekcije i postantibiotske diareje

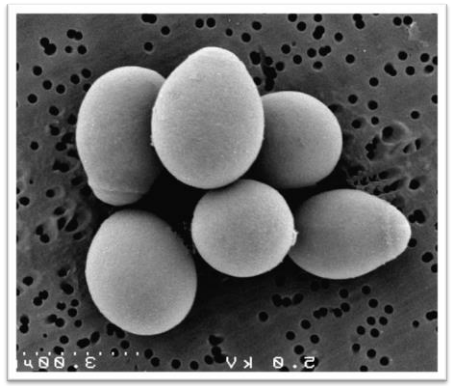
prof.dr.sc. Tajana Filipec Kanižaj, dr. med.

Zavod za gastroenterologiju, Klinika za unutarnje bolesti, KB Merkur

MEF, Zagreb

17.5.2024.

Saccharomyces boulardii

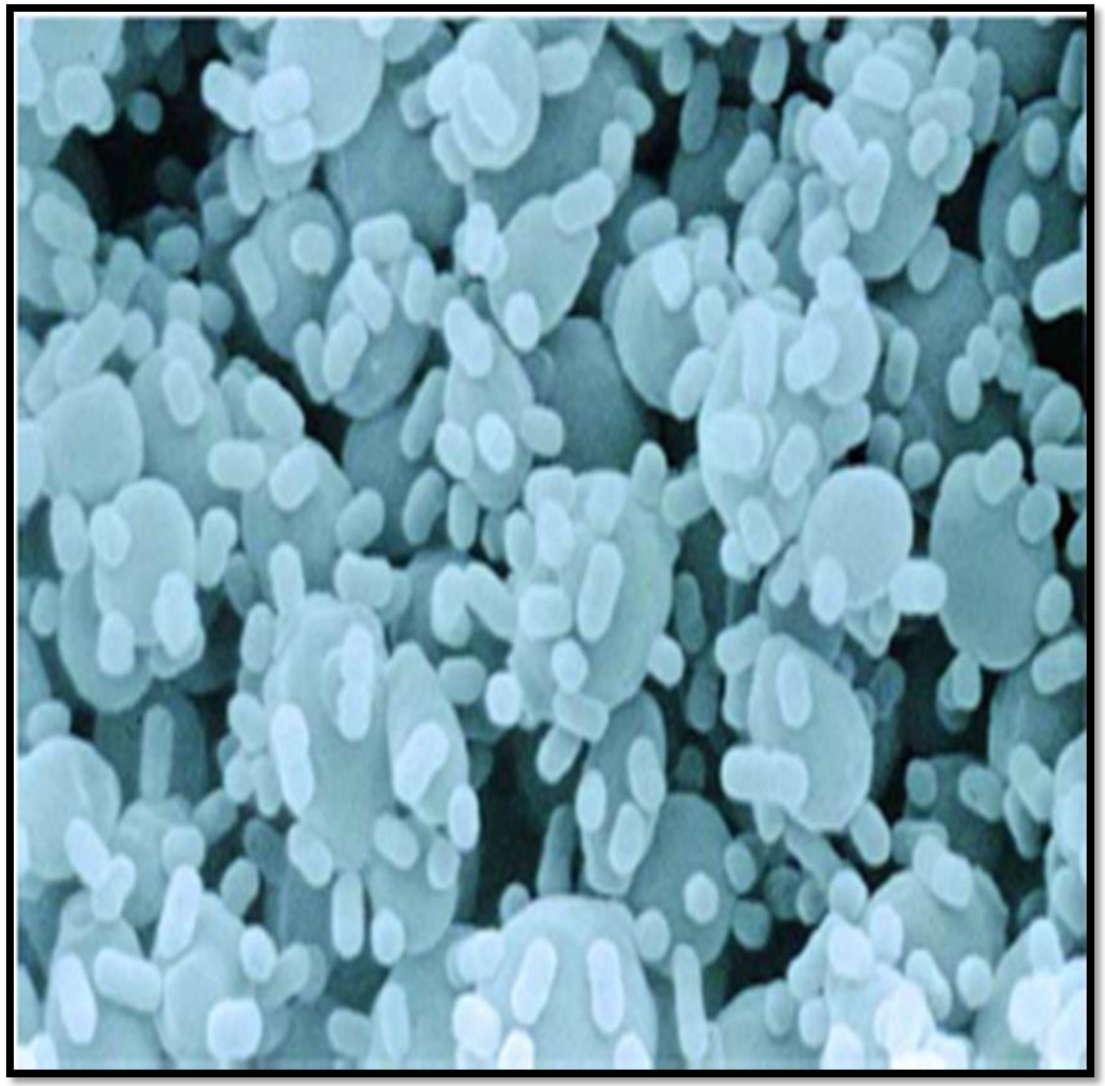


- 1923. Henri Boulard, francuski znanstvenik, iz kore voća Lychee
- **Živi kvasac** (koristi se kao **probiotik**)
- **Ne kolonizira crijevni trakt,** brzo se uklanja stolicom
- **Potpuna eliminacija 3-5 dana** nakon prestanka uzimanja

1. T. Kelesidis et al. Efficacy and safety of the probiotic Saccharomyces boulardii for the prevention and therapy of gastrointestinal disorders. Therapeutic Advances in Gastroenterology 2012; 5(2): 111–125. 2.F. Guarner et al. WGO Global Guideline Probiotics and prebiotics. 2017.

Saccharomyces boulardii

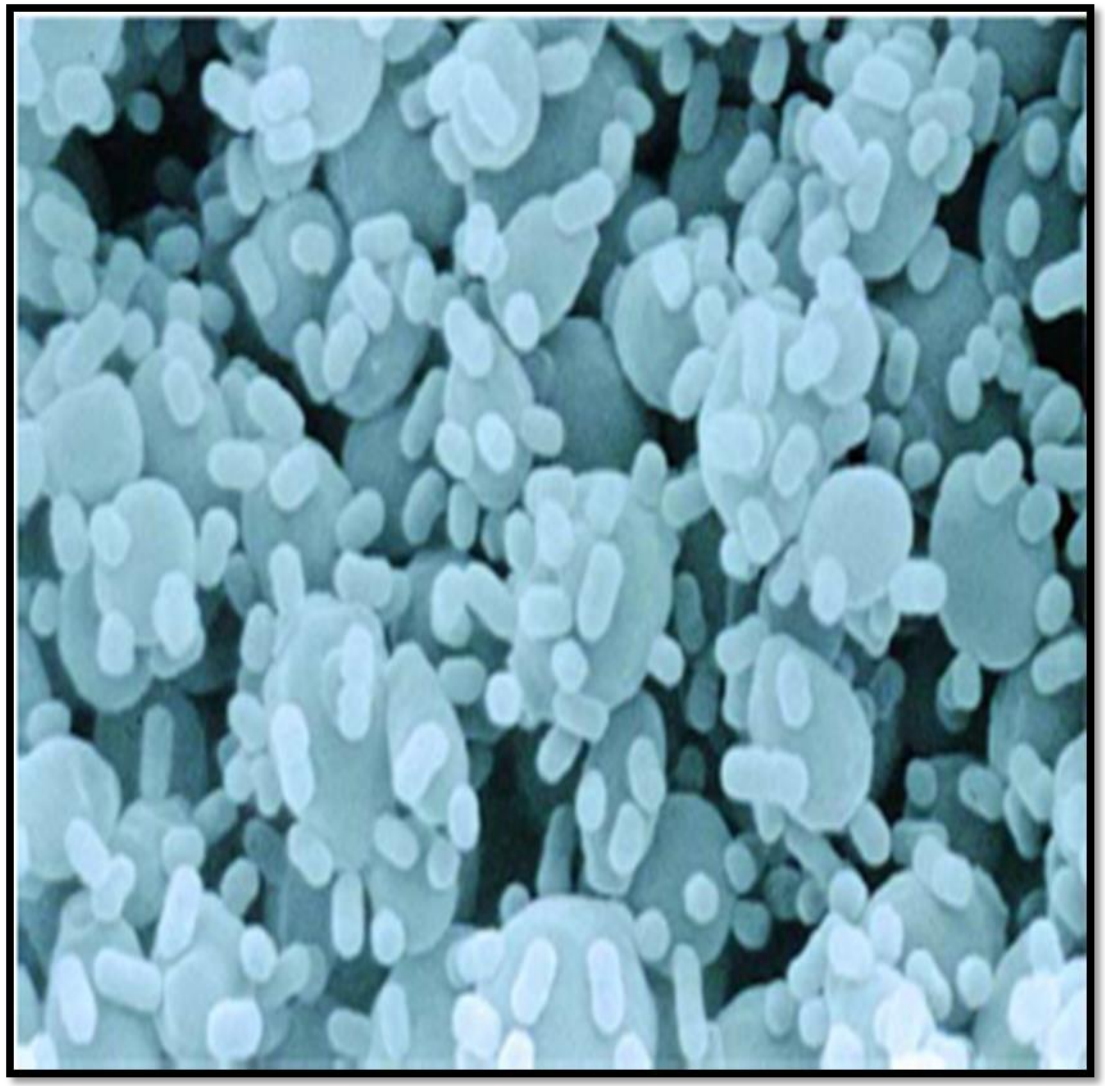
- 10x veći u odnosu na bakterije
- Veže na sebe veći broj patogena
- Ubrzava njihovu eliminaciju iz crijeva



*Adherence of enterohemorrhagic *E. coli* serogroup 0157:H to the surface of ***S. boulardii***. Electron microscopic photograph, magnitude ×5,000

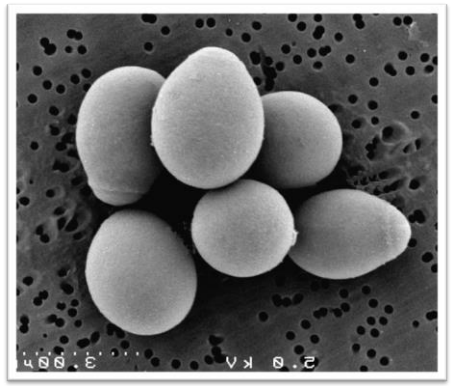
Saccharomyces boulardii

- **Luči** proteaze i fosfataze
- **Inaktivira** enterotoksine
- **Inhibira** vezanje enterotoksina za epitel crijeva



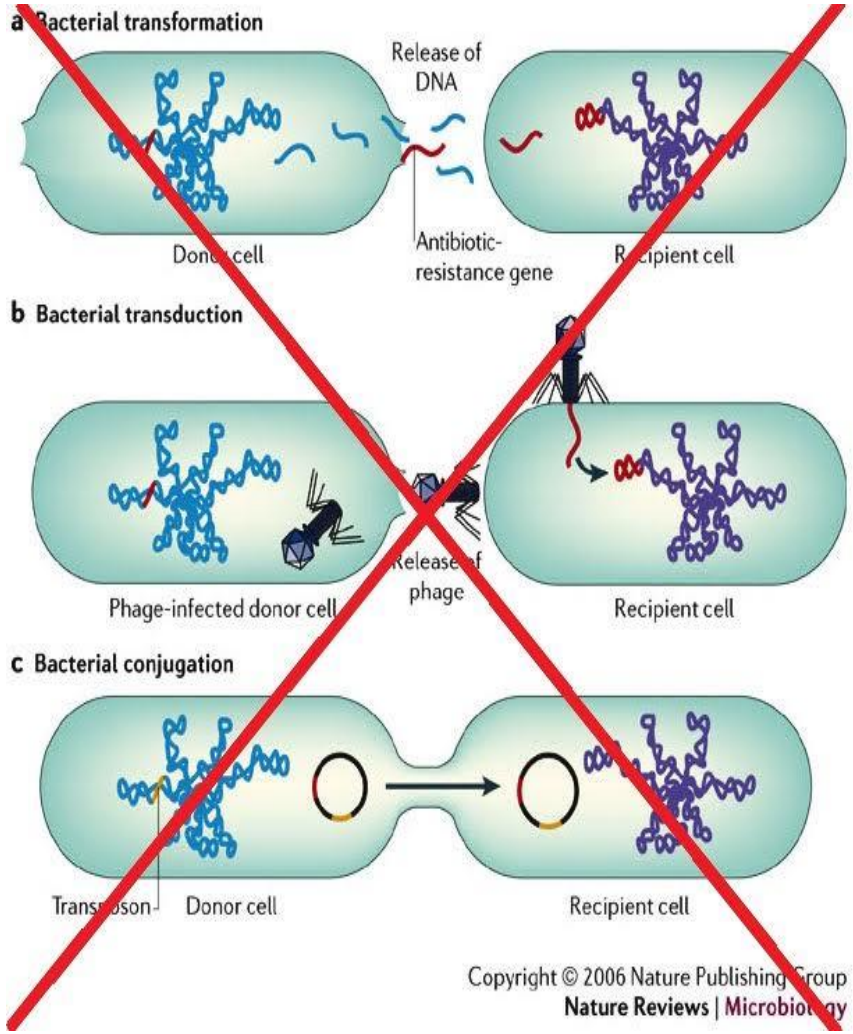
*Adherence of enterohemorrhagic *E. coli* serogroup 0157:H to the surface of ***S. boulardii***. Electron microscopic photograph, magnitude ×5,000

Saccharomyces boulardii



- ✓ **Otporan na sve vrste antibiotika**
- ✓ **Ne postoji mogućnost transfera genetičkog materijala**
  - Nema prenosa rezistencije
  - Bakterija vs kvasac
  - (prokariot) vs (eukariot)

- ✓ **100% SIGURAN za istovremenu primjenu s antibioticima!**



Mehanizam djelovanja

U lumenu

Razgrađuje **toksine**
Ometa veziavanje **patogena**
Modulira normalnu **mikrobiotu**
Čuva prirodnu intestitnalnu **fiziologiju**

Trofički učinak

Pomaže uspostavljanju ravnoteže **masnih kiselina kratkog lanca**

Mukozno-protuupalni signalni učinci

Povećava **IgA** (sIgA)
Djelovati kao **imunomodulator** putem utjecaja na razine **citokina**

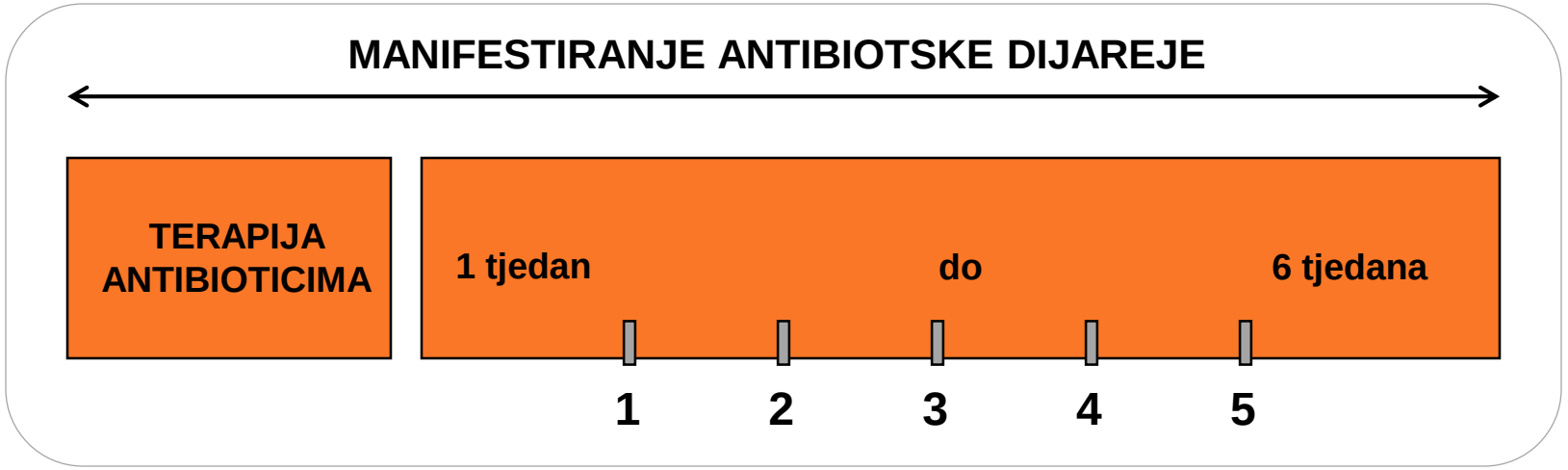
McFarland et al Systematic review and meta-analysis of Saccharomyces boulardii in adult patients. World J Gastroenterol 2010 May 14; 16(18): 2202-2222.

INDIKACIJE

- ✓ infektivne diareje
- ✓ postantibiotske diareje (AAD i CDI)
- ✓ sprečavanje recidiva *C. DIFFICILE* infekcije
- ✓ prevencija putničke diareje
- ✓ dodatak eradikacijskoj terapiji kod *H. PYLORI* infekcije
- ✓ Jačanje imuniteta i regulacija flore

EPIDEMIOLOGIJA (AAD)

- ANTIBIOTICI - često korišteni lijekovi
- 15-25% pts dobije dijareju
- 10-20% pseudomembranozni kolitis (CDAD)*

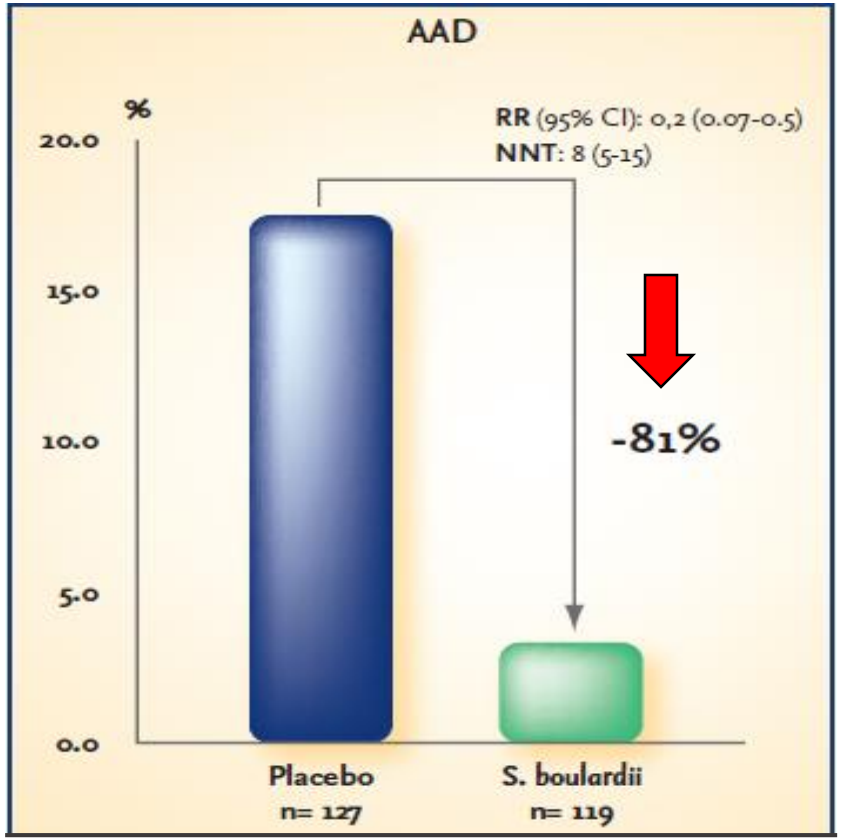


*Bartlett J.G. (2002) Clinical practice: Antibiotic associated diarrhoea. *N Engl J Med* 346: 334–339


FAKTORI RIZIKA
HOSPITALIZACIJA
IMUNOKOMPROM-ITIRANE OSOBE
ŠIRINA SPEKTRA ANTIBIOTIKA
DUŽINA PRIMJENE
INFLAMATORNE BOLESTI CRIJEVA
1 Ampicilin
2 Amoksicilin+ klavulanska kis.
40%
3 Cefalosporini
35%
4 Klindamicin
5 Fluorokinoloni
↑ 3 dana = ↑ rizik
Ponavljane terapije
UZRAST
↓ 6 godina ↑ 60 godina

ANTIBIOTSKA DIJAREJA (AAD) - djece

S. boulardii efikasno sprječava pojavu antibiotske dijareje*



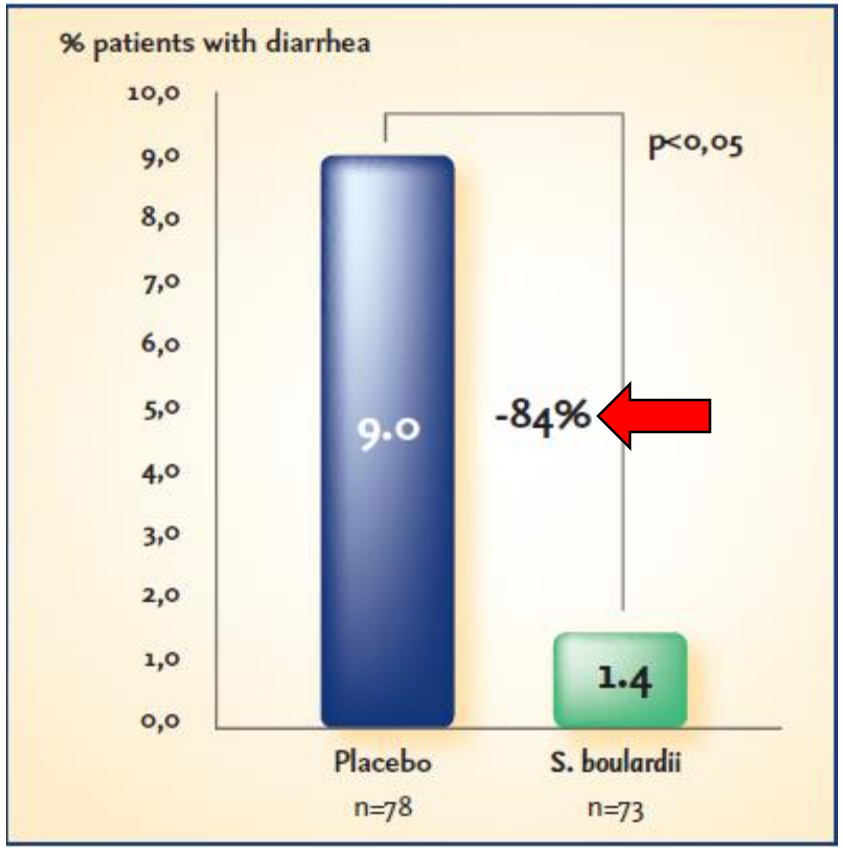
Metodologija:

- Randomizirana, dvostruko slijepa, placebo kontrolirana studija
- **269 djece uzrasta od 6. mjeseca do 14 godina** (137 - AB + placebo, 132 - AB + *S. boulardii*)
- *S. boulardii:* doza 1x250 mg dnevno uz AB Th

*Saccharomyces boulardii in the prevention of antibiotic-associated diarrhea in children:a randomized double-blind placebo-controlled trial. Kotowska et al. *Aliment Pharmacol Ther.* 2005; 21(5): 583-590

ANTIBIOTSKA DIJAREJA (AAD) - odraslih

S. boulardii efikasno sprječava pojavu antibiotske dijareje*



Metodologija:

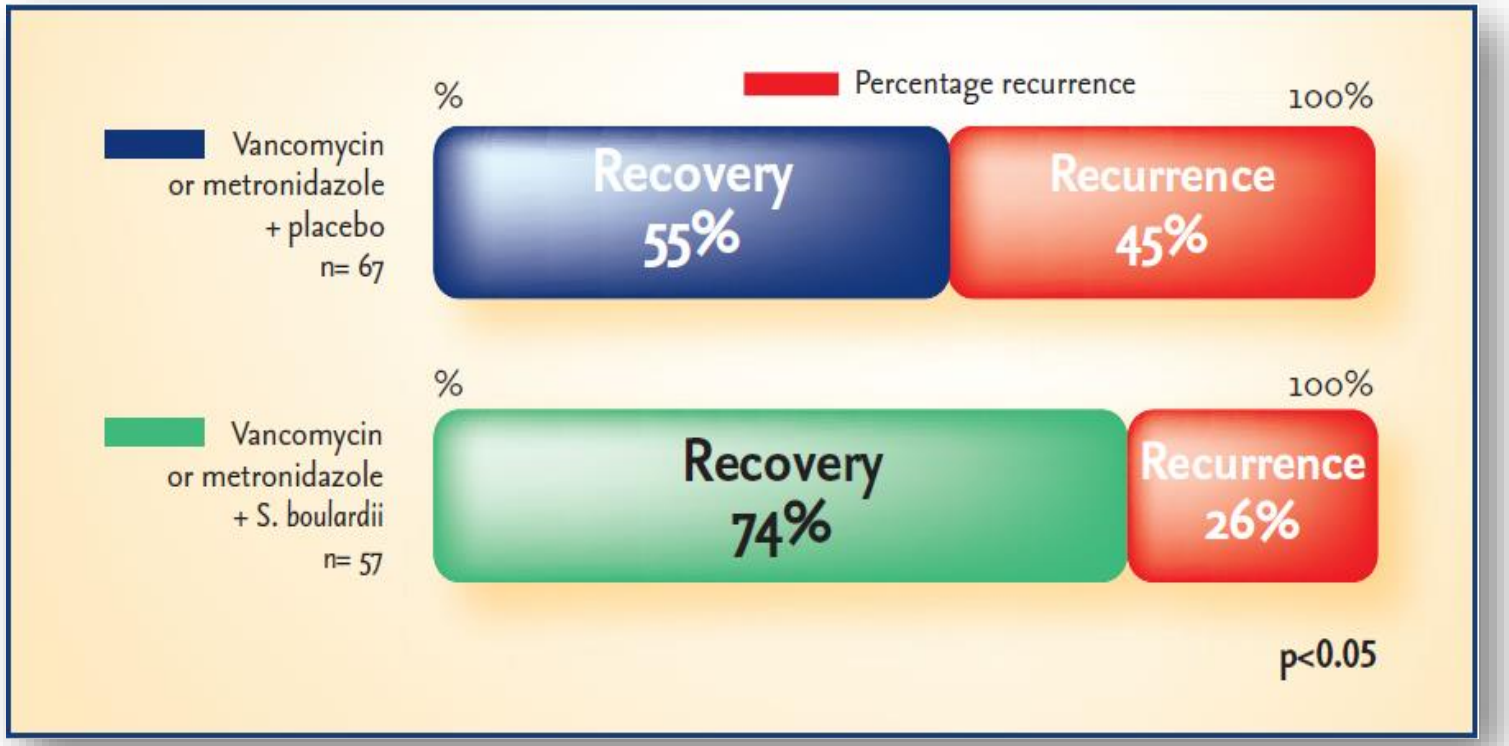
- Randomizirana, dvostruko slijepa, placebo kontrolirana studija
- 151 pacijent uzrasta 25-50 godina (78 - AB + placebo, 73 - AB + *S. boulardii*)
- *S. boulardii:* doza 2x250 mg dnevno uz AB Th

*Prophylactic *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhea: a prospective study. Can et al. *Med Sci Monit.* 2006; 12(4): PI19-22

SEKUNDARNA PREVENCIJA CDAD

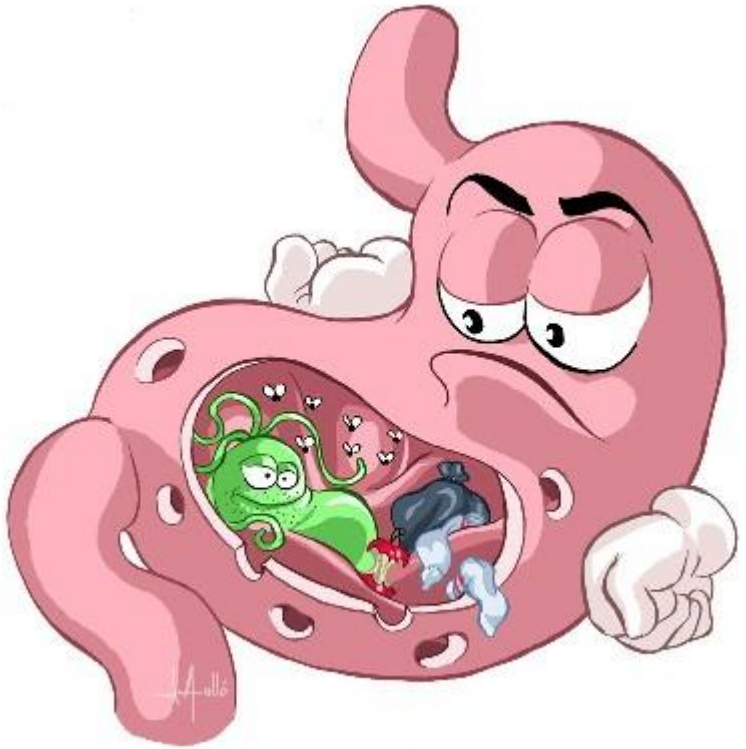
''**Only *S. boulardii*** was effective for CDAD"*

*McFarland LV. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of *Clostridium difficile* disease. *Am J Gastroenterol*. 2006;101(4):812-822



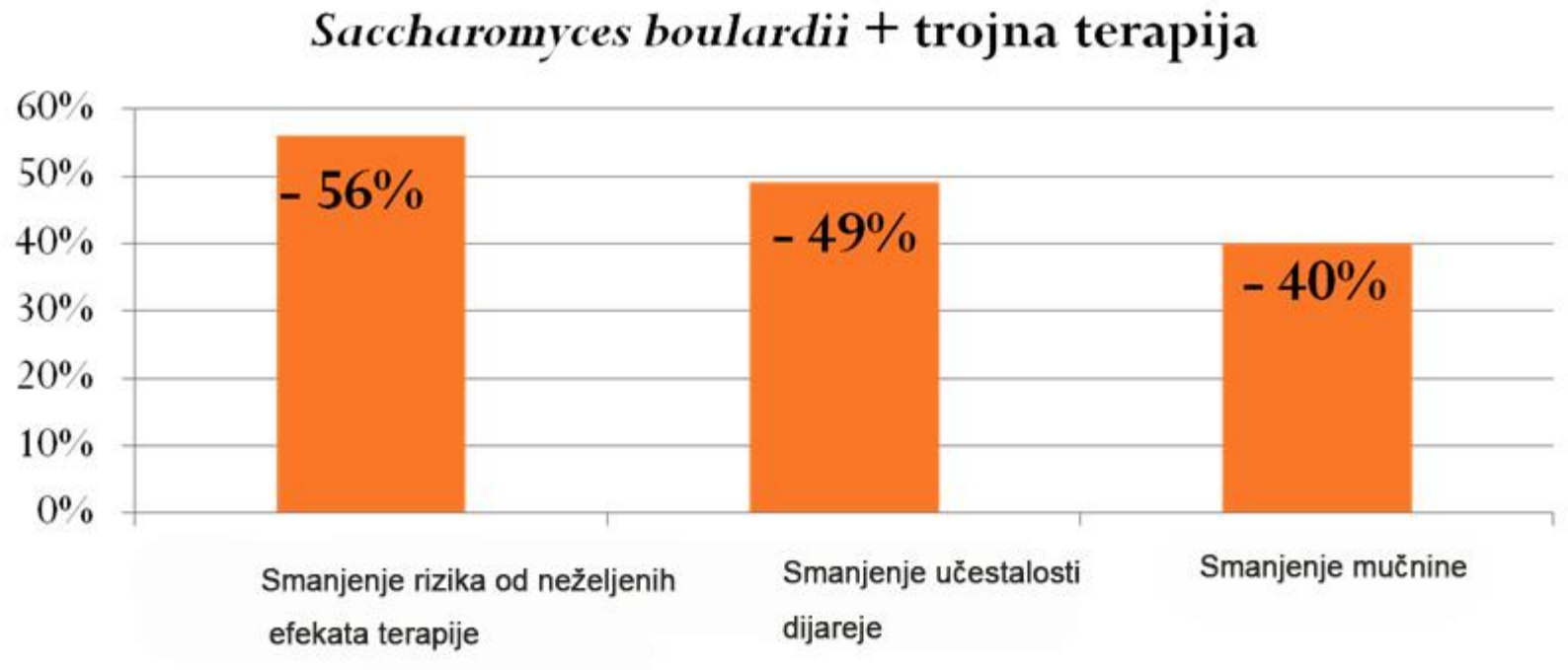
ERADIKACIJA *H. pylori*

- ✓ Smanjuje neželjene efekte eradikacijske terapije 56%
- ✓ Povećava stopu eradikacije
- ✓ Smanjuje broj recidiva



ERADIKACIJA *H. Pylori*

- Meta-analiza, 11 studija, 2.200 pacijenata, među kojima 330 djece



Szajewska H. et al. Systematic review with meta-analysis: *Saccharomyces boulardii* supplementation and eradication of *Helicobacter pylori* infection. *Aliment Pharmacol Therap* 2015; 41(12):1237-45.

Gut. 2022 Aug 8;gutjnl-2022-327745. doi: 10.1136/gutjnl-2022-327745. Online ahead of print.

Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report

Peter Malfertheiner [1 2], Francis Megraud [3], Theodore Rokkas [4 5], Javier P Gisbert [6 7],

Benefit only applies to specific strains !!!

Lactobacilli and **Saccharomyces boulardii**:

- **decrease side effects** associated with H. pylori antibiotic th **if given >2 weeks**
- **reduce risk** of **overall adverse events** ranging from 0.44 to 0.47

*Probiotics **increase eradication rate** by **reducing side effects** related to eradication therapy,
not through **direct** effects on *H. pylori*

ESPGHAN 2022
Probiotics and synbiotics

Table 1. Summary of preliminary recommendations from the ESPGHAN Working Group's position paper on the efficacy of probiobics in the management of pediatric GI disorders

GI disorders	Positive recommendations	Negative recommendations
Acute gastroenteritis	*L. rhamnosus* GG ATCC 53103 *S. boulardii* CNCM I-745 *L. reuteri* DSM 17938 *L. rhamnosus* 19070-2 with *L. reuteri* DSM 12246	*L. helveticus* R0052 with *L. rhamnosus* R0011 *B. clausii* strains O/C, SIN, N/R, and T
Antibiotic-associated diarrhea	*S. boulardii* CNCM I-745 *L. rhamnosus* GG ATCC 53103 ➔ start simultaneously with antibiotic treatment	
Nosocomial diarrhea	*L. rhamnosus* GG ATCC 53103	*L. reuteri* DSM 17938
Necrotizing enterocolitis	Refer to ESPGHAN's 2020 position paper[3]	
***Helicobacter pylori* infection**	*S. boulardii* CNCM I-745	
Inflammantory bowel disease	No recommendation	
Infant colic	In breast-fed infants: *L. reuteri* DSM 17938 *B. lactis* BB-12 No positive or negative recommendation in formula-fed infants[4]	
Functional constipation		Any probiotic strains evaluated so far

World Gastroenterology Organisation Global Guidelines

Probiotics and prebiotics

February 2023

Review Team
Francisco Guarner (Chair, Spain), Mary Ellen Sanders (Co-Chair, USA),
Hania Szajewska (Co-Chair, Poland), Henry Cohen (Uruguay),
Rami Eliakim (Israel), Claudia Herrera (Guatemala),
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Balakrishnan Ramakrishna (India), Seppo Salminen (Finland)

World Gastroenterology Organisation, 2023

Saccharomyces boulardii CNCM I-745

Probiotics and prebiotics

February 2023

Adults:

• **Acute diarrhea** in adults	5 x 10e9 cfu or 250 mg, twice daily	(3)
• Antibiotic associated diarrhea (**AAD**)	5 × 10e9 cfu or 250 mg, twice daily	(1)
• Prevention of **C. difficile–AD** (or prevention of recurrence)	10e9 cfu or 250 mg, twice daily	(2)
• Coadjuvant therapy for **H. pylori eradication**	10e9 cfu or 250 mg, twice daily	(2)
• **IBS**	2 × 10e11 cfu, twice daily	(3)

Pediatric:

• **GEC**	250–750 mg/day, for 5–7 days	(1)
• Prevention of **AAD**	≥ 5 billion cfu per day, during tx	(1)
• Prevention of **C. Difficile**	250–500 mg	(1)
• **H. pylori**	500 mg	(1)

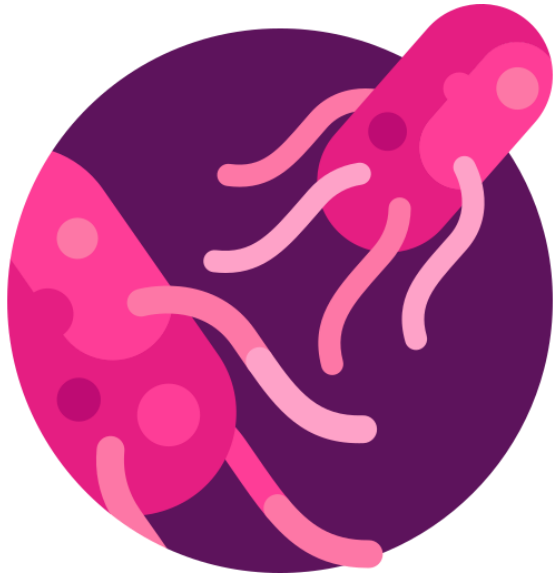
Zaključak

- S. Boulardii je živi kvasac koji se koristi probiotik
- Jedini je probiotik koji se može uzimati u isto vrijeme s antibiotikom
- Efikasan u prevenciji i liječenju dijareja uzrokovanih upotrebom antibiotika
- Dokazima potkrepljeni učinici kod odraslih i kod djece
- Uz rijetke kontraindikacije, siguran za upotrebu


Bio-Kult®
S.Boulardii
Advanced Multi-Action Formulatio
Digestive and Immune System
30
capsules

TRBUŠNI TIFUS

ETIOPATOGENEZA, DIJAGNOSTIKA, TERAPIJA, PREVENCIJA



ANA GVERIĆ GRGINIĆ

Služba za mikrobiologiju, NRL za salmonele za ECDC, HZJZ

Tifusna *Salmonella* sp.

Salmonella enterica subsp. enterica

Serovar Typhi

Serovar Paratyphi A

Serovar Paratyphi B (d-tartarat negativna) ⚠ d-tartarat pozitivan_netifusni serovar Java

Serovar Paratyphi C

Ne-tifusna *Salmonella* sp.

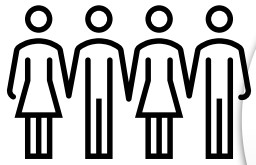
ostali serovari 2597

/Antigenic formulae of the Salmonella serovars 2007., 9th edition

https://www.pasteur.fr/sites/default/files/veng_0.pdf/

Gabriel Frantcevich Vogralik
izvor: https://en.tsu.ru/

- **Izvor zaraze je isključivo čovjek**



Izvor zaraze

Bolesnik

- zaraznost za okolinu od posljednjih dana inkubacije do kraja bolesti
- izlučuju uzočnika stolicom, mokraćom, može se naći u slini, usnoj šupljini, povraćenom sadržaju, gnoju u slučaju komplikacija, prljavim rukama/

Kliconoša

- trajno ili povremeno, 3-5% bolesnika ostanu trajni doživotni kliconoše bez obzira na liječenje
- Kronično kliconoštvo >12 mjeseci
- stolica ili mokraća
- češći kliconoše stolicom /češća kolelitijaza/
- mokraćom

- Izravnim dodirom nečistim rukama bolesnika ili kliconoše

- Posredno dodirom predmetima onečišćenim njihovim izlučevinama /”kontaktne” epidemije kod osoba u bliskom kontaktu zbog loših higijenskih uvjeta/

- Onečišćenom hranom i/ili vodom /epidemije „eksplozivnog” karaktera_ onečišćenje vode za piće npr. gnojivom, onečišćenje hrane tijekom pripreme_”Typhoid Mary”/

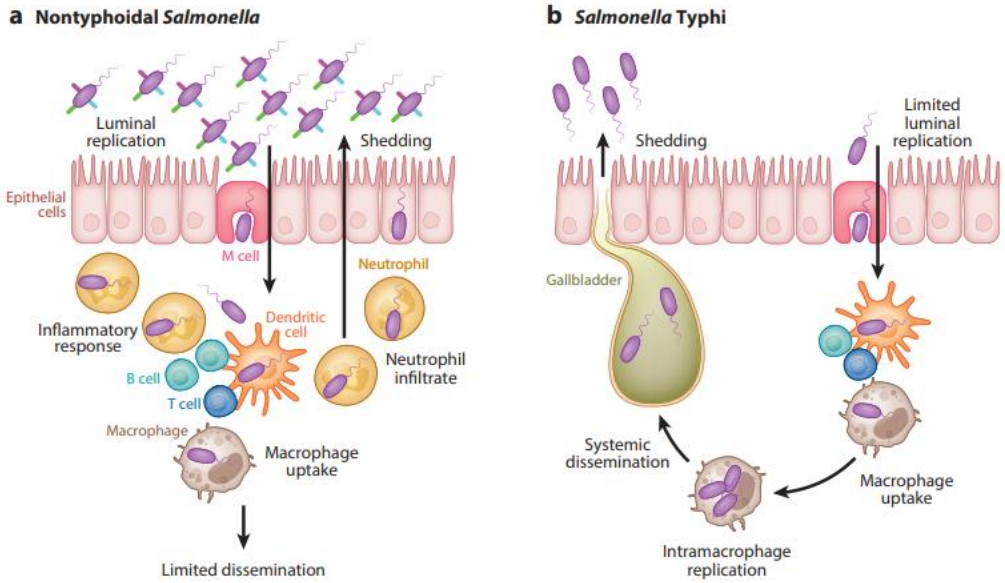
- MSM oralno-analni spolni prijenos

Crump JA. Progress in Typhoid Fever Epidemiology. Clin Infect Dis. 2019 Feb 15;68(Suppl 1):S4-S9. doi: 10.1093/cid/ciy846.

- Ulazno mjesto su usta ingestijom infektivne doze_10 000 uzročnika

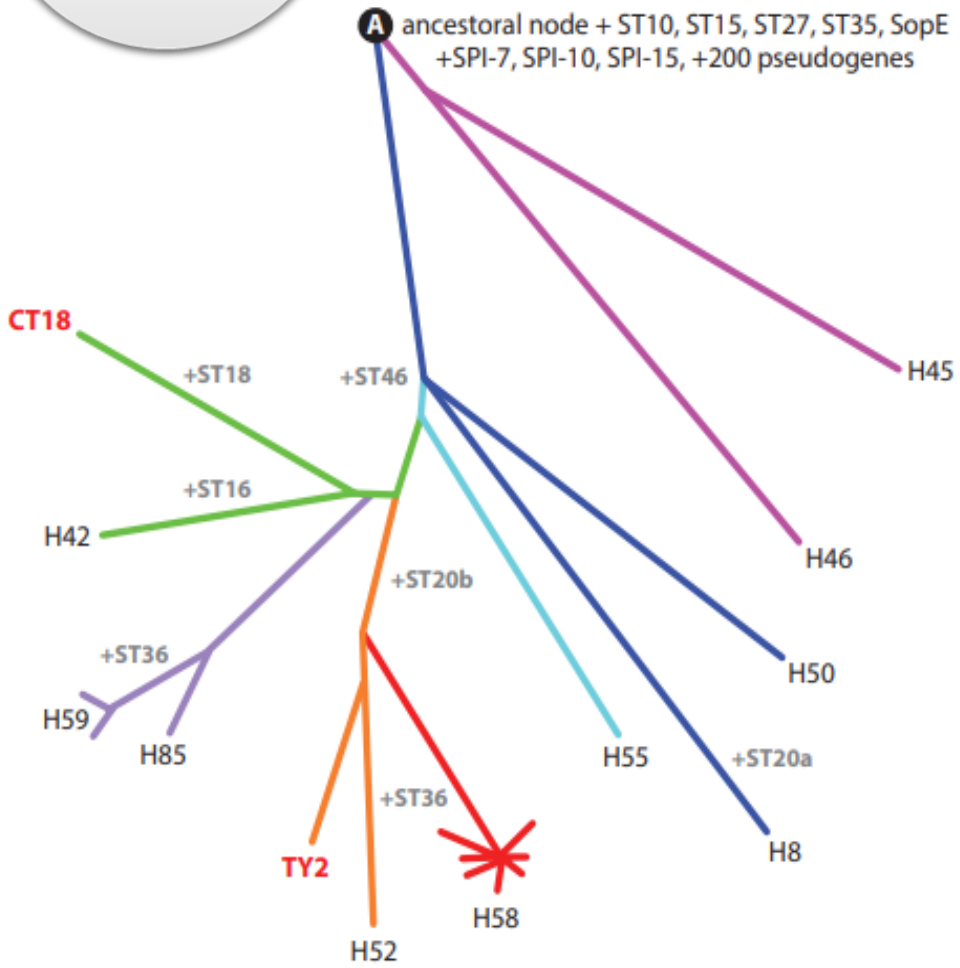
Ulazno mjesto

- Infektivna doza može biti i manja
  /ovisi o kiselost želučanog sadržaja, različita ovisno o individualnim osobitostima oboljelog/



Dougan G, Baker S. Salmonella enterica serovar Typhi and the pathogenesis of typhoid fever. Annu Rev Microbiol. 2014;68:317-36. doi: 10.1146/annurev-micro-091313-103739

Uzročnik



- S. Typhi_grupa D, O9-12, faza 1 H:d (monofazna) , Vi kapsularni antigen pozitivan, rijetki Vi negativni sojevi
- Izolati iz Indonezije imaju alternativnu ekspresiju 1 faze kao H: j /mutacija gena delecijom 261 parova baza/

- alternativna ekspresija faze 2 u indonezijskim izolatima zbog linearnog plazmida pBSSB1 omogućuje ekspresiju z66
- *flg* lokus koji kodira fazu 2 u flagelama ostalih serovara nije prisutan

- izrazito konzervirani genom koji dijeli 90% sekvenci s ostalim serovarima

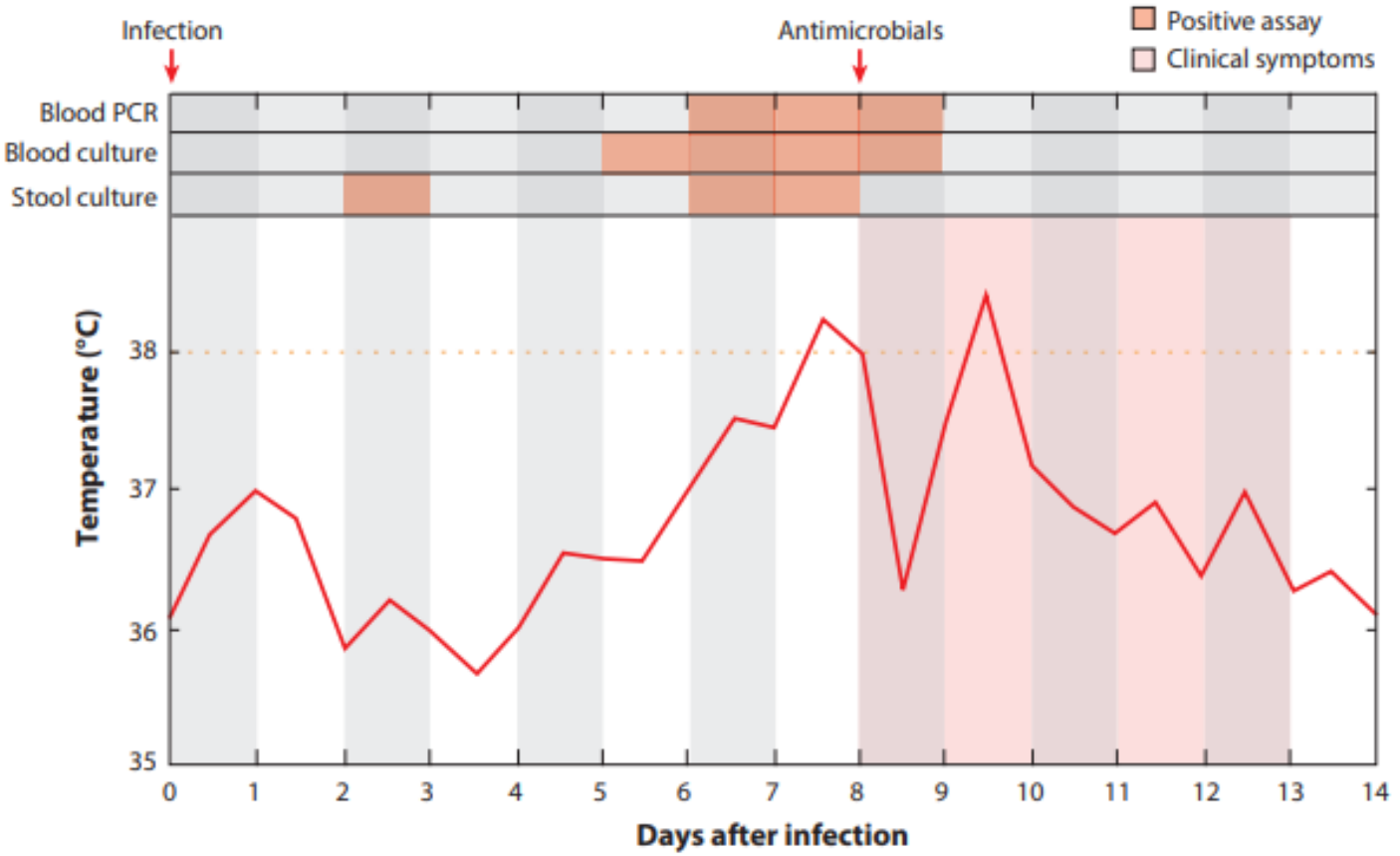
- 300-400 gena specifičnih za S. Typhi na profagima i SPI /-7, -15, -17, i -18/
- Kodiraju čimbenike patogenosti koji omogućuju invaziju, izbjegavanje imunološkog odgovora u stijenci crijeva i diseminaciju bez proljeva

- sustavni simptomi

Uzročnik

- Krv za hemokulturu
- 2-3 seta
- Urinokultura/2. tjedan/
- Kultura punktata koštane srži
- Stolica

- Serum_Widalova reakcija
- Nakon 2. i 3. tjedna bolesti
- parni serum u razmaku od 7-10 dana
- Reakcija na poznate antigene salmonela
- niska specifičnost
- Najčešća upotreba u područjima u kojima nisu dostupne hemokulture

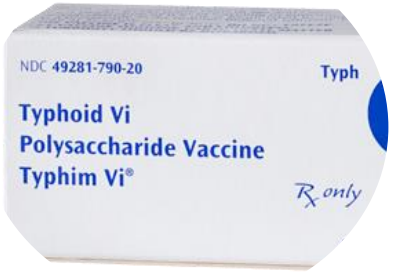


Osjetljivost domaćina

Cijepljenje

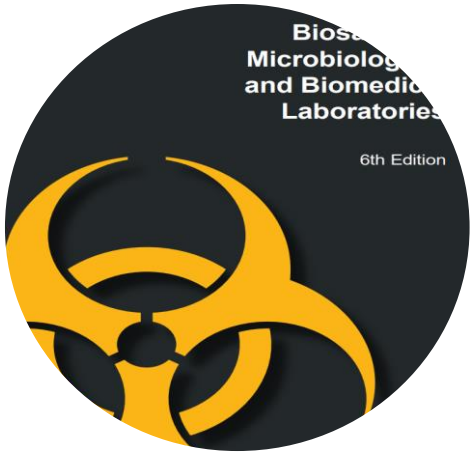
- obavezno podliježu sve osobe koje žive u zajedničkom kućanstvu s kliconošom i osobe s epidemiološkim indikacijama

- živo oslabljeno peroralno cjepivo protiv tifusa (soj Ty21a); koristi se u putnika u endemska područja /oralno svaki drugi dan, ukupno 4 doze, što treba završiti tjedan dana prije putovanja/
- booster doza je potrebna nakon 5 godina za ljude koji su i dalje pod rizikom bolesti
- kontraindicirano je u imunosuprimiranih bolesnika
- U SAD–u se Ty21a cjepivo ne primjenjuje u djece <6 god.



- jednokratno, IM Vi kapsularno polisaharidno cjepivo, dano ≥ 2 tjedna
- putnici u endemska područja, migranti, zdravstveno i vojno osoblje
- ne koristi se u djece < 2 godine
- booster doza je potrebna nakon 2 godine

Osjetljivost domaćina



Mjere zaštite prilikom laboratorijske obrade

- BSL 2: nasađivanje izolata, lab. obrada u kojoj se ne producira aerosol
- BSL 3: obrada prilikom koje postoji mogućnost stvaranja aerosola

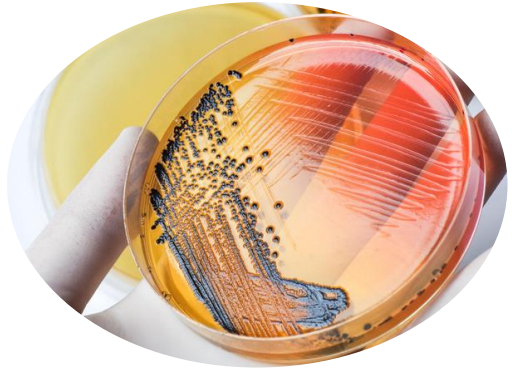
Pravilnik o zaštiti radnika od rizika zbog izloženosti biološkim štetnostima na radu NN 129/2020

Pravilnik o načinu prijavljivanja zaraznih bolesti

Članak 4.
doktor medicine ili drugi zdravstveni radnik obavješćuje odmah telefonom organizacijsku jedinicu za HE zaštitu i HZJZ,
samu prijavu dostavlja naknadno na način propisan ovim Pravilnikom

Prijava epidemiologu

Slanje izolata u NRL za salmonele HZJZ-a



Zakon o zaštiti pučanstva od zaraznih bolesti

Advancing Gastrointestinal Health

Molecular Biology & POC

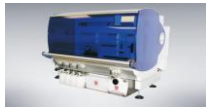
Dr. Adem Nasraddin • 17 May 2024 • Zagreb

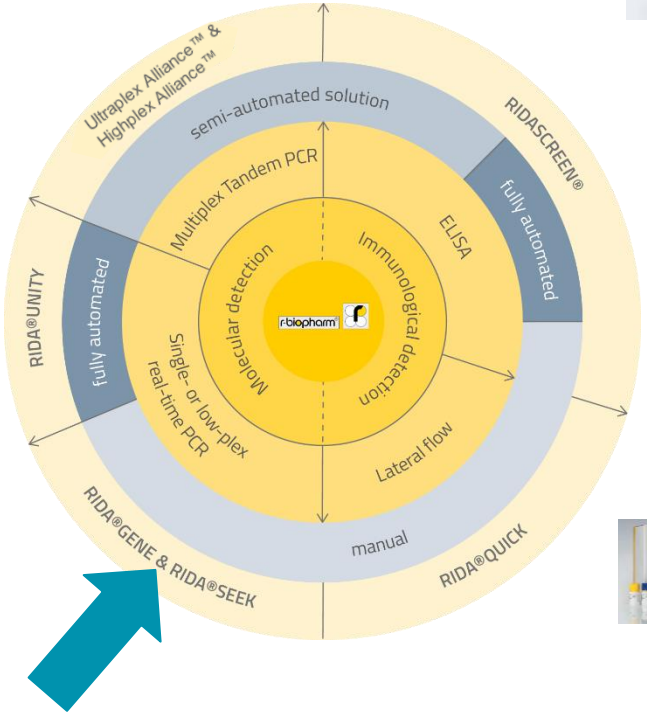
Innovative Solutions for Infection Identification and Management

Diarrhea causing pathogens – Who are they?

Bacteria	Toxin-producer	Viruses	Protozoans
E. coli (EPEC, EAEC, EIEC) Yersinia enterocolitica Campylobacter spp. Salmonella spp. Shigella spp. Vibrio cholerae ...	Clostridium difficile Clostridium perfringens E. coli (EHEC, STEC, ETEC)	Norovirus Rotavirus Adenovirus Astrovirus Sapovirus	Giardia lamblia Cryptosporidium parvum/hominis Entamoeba histolytica Dientamoeba fragilis ....

R-Biopharm - GI Protfolio Overview





RIDA®GENE – Basic facts

1. Easy handling

- Just 3 Pipetting steps per reaction:
  - Reaction Mix
  - Taq-Polymerase
  - Internal Control

2. Transport and storage

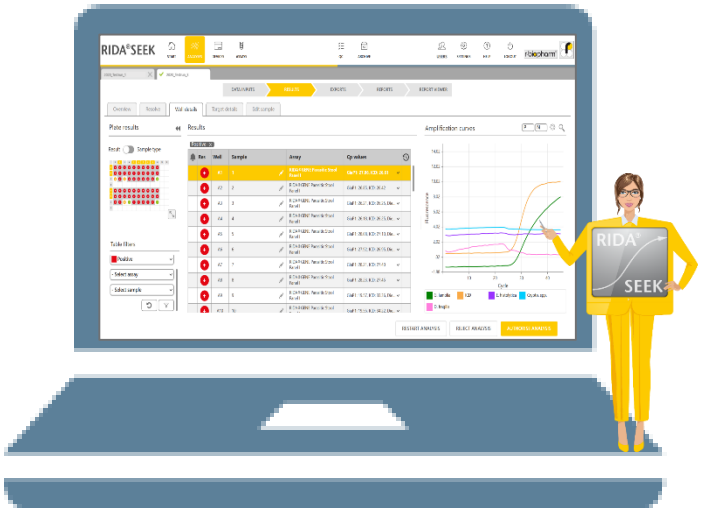
- Shipment on cool packs (~ 4 °C)
- Storage at -16 to -28 °C immediately after arrival

3. Stability

- Shelf-life: 24 months after production
- Stable for up to 20 freeze/thaw cycles

Components of the Master Mix	Quantity per reaction
Reaction Mix	19.3 µl
Taq-Polymerase	0.7 µl
Internal Control DNA	1.0 µl
Total	**21.0 µl**

Your one-program evaluation and documentation assistant



Functions and benefits

- **Optimization of laboratory workflow through automated result interpretation and documentation of analysis** with RIDA®GENE real-time PCR assays.
- **Quality management is made easy** e.g. by monitoring the positive control results in runs; by searching the archive.
- **Easy to train new employees** - only 5 clicks are necessary to get to the results; the software's interface is intuitive.
- **Simplifies data management and avoids errors** - direct communication with the laboratory information system (LIS).
- **Data security** - local system, no risk to store sensitive data in a cloud.

RIDA®GENE – Features and benefits

Efficient

- Harmonized workflow for all RIDA®GENE Assays → Parallel processing is possible
- Fast → results in less than 1,5 h → multiple runs per day
- Flexible sample numbers

Intuitive

- Fully automated evaluation and result analysis with the RIDA®SEEK Software
- Easy handling
- Ready to use reagents
- Reliabel → including IC, PC, NTC

Universal

- Universal real-time PCR profile
- Combination of DNA & RNA Assays
- All Kit components can be stored at the same temperature

Fast

- Minimum set up time
- Ready-to-use reagents
- Time-to-result: 3 h 30 min
- Start second run after 2 h 30 min

Save

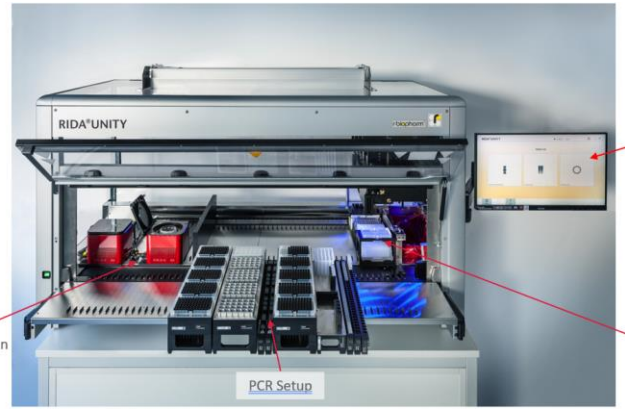
- Consistent barcoding
- Check loading
- Complete traceability
- Full process controls
- Secure supply chains

RIDA®UNITY

- Fully automatic
- Reuse reagents
- Eluates reusable
- Matrix-independent extraction

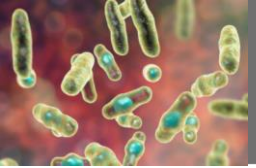
RIDA®UNITY

- Combinability of the assays
- Modular processing
- Integration of external cyclers



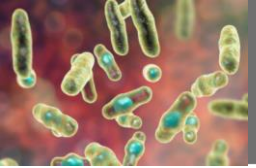
Product portfolio – Enteric Pathogens

	Target	REF	Features and benefits	Device
RIDA®GENE Norovirus	Norovirus RNA	PG1405	Qualitative detection of Norovirus (genogroup I and II)	Manually
RIDA®GENE & RIDA®UNITY Norovirus I & II	Norovirus RNA	PG1415 & UN1415	Differentiation of Norovirus GGI and GGII	Manually & RIDA®UNITY
RIDA®GENE Sapovirus	Sapovirus RNA	PG1605	Real-time PCR test for direct qualitative detection of sapovirus	Manually
RIDA®GENE Enterovirus	Enterovirus RNA	PG4705	Stool and cerebrospinal fluid (CSF)	Manually
RIDA®GENE Viral Stool Panel I	Norovirus RNA Rotavirus RNA Adenovirus DNA Astrovirus RNA	PG1315	One kit for all relevant viral pathogens causing diarrhea	Manually
RIDA®GENE & RIDA®UNITY Viral Stool Panel II	Rotavirus RNA Adenovirus DNA Astrovirus RNA	PG1325 & UN1325	One 4plex kit for nearly all relevant viral pathogens causing diarrhea; compatible with most PCR instruments	Manually & RIDA®UNITY
RIDA®GENE Viral Stool Panel III	Norovirus RNA Rotavirus RNA Adenovirus DNA	PG1335	4plex assay, compatible with most PCR instruments	Manually
RIDA®UNITY Viral Stool Panel IV	Norovirus RNA Sapovirus RNA Enterovirus RNA	UNXXXX	Fullfill relevant viral pathogens causing diarrhea (Noro, Sapo, Entero)	RIDA®UNITY



Product portfolio – Enteric Pathogens

	Target	REF	Features and benefits	Device
RIDA®GENE & RIDA®UNITY Bacterial Stool Panel	*Salmonella* spp. DNA *Campylobacter* spp. DNA *Yersinia enterocolitica* DNA	PG2405 & UN2405	Analysis of the three most relevant pathogens causing notifiable bacterial gastroenteritis in GER & EU	Manually & RIDA®UNITY
RIDA®GENE Bacterial Stool Panel I	*Salmonella* spp. DNA *Campylobacter* spp. DNA EIEC/*Shigella* spp. DNA STEC DNA	PG2415	Most important pathogens causing bacterial gastroenteritis in industrial countries	Manually
RIDA®GENE Helicobacter pylori	*Helicobacter pylori* DNA, Clarithromycin resistance	PG2305	Qualitative detection of pathogen and potential Clarithromycin resistance	Manually
RIDA®GENE E. coli Stool Panel I	STEC EHEC EPEC	PG2285	Differentiation of Shiga toxin genes stx1 and stx2	Manually
RIDA®GENE & RIDA®UNITY EHEC/EPEC	EHEC STEC EPEC EIEC/*Shigella* spp.	PG2205 & UN2205	• Stool and culture samples • Differentiation for EHEC, STEC, EPEC and EIEC/Shigella possible	Manually & RIDA®UNITY
RIDA®GENE ETEC/EIEC	ETEC EIEC/*Shigella* spp.	PG2225	• Stool and culture samples • Differentiation of ETEC virulence-factor genes	Manually
RIDA®GENE EAEC	EAEC	PG2215	Stool and culture samples	Manually



Product portfolio – Enteric Pathogens

	Target	REF	Features and benefits	Device
RIDA®GENE Parasitic Stool Panel I	*Giardia lamblia* DNA *Entamoeba histolytica* DNA *Cryptosporidium* spp. DNA *Dientamoeba fragilis* DNA	PG1715	Panel to analyze the most relevant diarrhea-causing protozoa	Manually
RIDA®GENE & RIDA®UNITY Parasitic Stool Panel II	*Giardia lamblia* DNA *Entamoeba histolytica* DNA *Cryptosporidium* spp. DNA	PG1725 & UN1725	4plex kit to analyse the most relevant diarrhea-causing protozoa; compatible with most PCR instruments	Manually & RIDA®UNITY

MT-PCR: Multiplex Tandem PCR

The reaction consists of:

Nucleic acid amplification (2-step nested-PCR) → subsequent amplicon analysis

STEP 1

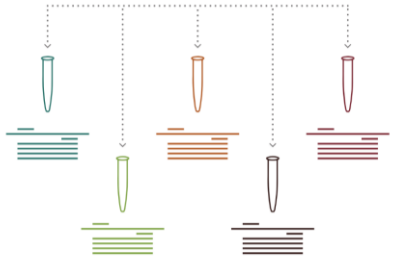
One tube per patient (takes place in step 1 tubes)

- Tube contains primers for all target sequences detected in the panel
- Highly multiplexed amplification of up to 40 targets
- Low cycle number (no competition)

STEP 2

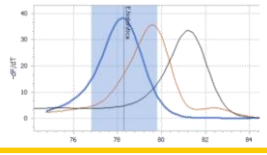
One well per parameter (384-well plate, low volume)

- Highly specific amplification via nested primers
- Real-time PCR (intercalating dye, no competition due to different wells)



AMPLICON ANALYSIS

Analysis via amplification curves and melt curves



MT-PCR: Devices

Highplex Alliance™ HP

Medium sample throughput
(≤ 66 samples/ 8h shift)

MT-Prep™ 24
Sample Purification

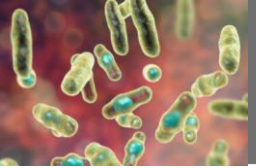
Highplex
Processor
+ Analyser

Ultraplex Alliance™ UP

Medium to high sample throughput
(≤ 282 samples/ 8h shift)

MT-Prep™ XL
Sample Purification

Ultraplex 3 Processor + Analyser



Product portfolio – Enteric Pathogens

Product	REF	Targets				Devices
Fecal Pathogen M 16-well	25039	*Salmonella* spp *Shigella* spp *Campylobacter* (*jejuni*, *doyeli*) Shigatoxin 1 Shigatoxin 2	*Aeromonas spp* *Clostridium difficile* toxin A *Clostridium difficile* toxin B *Yersinia enterocolitica* *Yersinia pseudotuberculosis*	Rotavirus A Norovirus genogroup I Norovirus genogroup II Adenovirus (F, G) Sapovirus Astrovirus	Giardia *Cryptosporidium* (*parvum* and *hominis*) *Entamoeba histolyticaa*	UP + HP
Fecal Pathogen A 16-well	25031	*Salmonella* spp. *Shigella* spp. *Campylobacter (jejuni, coli, doyeli)*	*Aeromonas hydrophila (RUO)* *Clostridium difficile* toxin B *Yersinia* spp.	Rotavirus Norovirus genogroup I Norovirus genogroup II Adenovirus (F, G)	Giardia *Cryptosporidium* *Dientamoeba fragilis* *Entamoeba histolytica* *Blastocystis hominis*	UP* + HP
Fecal Pathogen B 16-well	25033	*Salmonella* spp. *Shigella* spp. *Campylobacter (jejuni, coli, doyeli)* Shigatoxin 2 ***E. coli* O157**	*Clostridium difficile* toxin B	Rotavirus A Norovirus genogroup I Norovirus genogroup II Adenovirus (F, G) Sapovirus Astrovirus	Giardia *Cryptosporidium* *Entamoeba histolytica*	UP* + HP

Fecal Pathogen M → focused on better bacterial and viral coverage

Fecal Pathogen A → Focus on complete coverage of parasites (including conditional pathogenic parasites)

Fecal Pathogen B → Includes the detection of E. coli O157 in a separate target.

*** Available soon**

Product portfolio – Enteric Pathogens

Product	REF	Targets				Devices
Fecal Bacteria and Parasites 12-well	25041	*Salmonella* spp *Shigella* spp *Campylobacter* Shigatoxin 1 Shigatoxin 2	*E. coli* O157 *Clostridium difficile* toxin A *Clostridium difficile* toxin B *Yersinia enterocolitica* *Yersinia pseudotuberculosis*		Giardia *Cryptosporidium spp.* *Entamoeba histolytica*	HP
Parasites 8-Well	25021				Giardia *Giardia lamblia* *Cryptosporidium (parvum and hominis)* *Dientamoeba fragilis* *Entamoeba histolytica* *Blastocystis hominis* type 1 *Blastocystis hominis* type 3 *Cyclospora cayetanensis*	UP* + HP
Enteric Viruses 8-well	25037			Rotavirus A Norovirus genogroup I Norovirus genogroup II Enterovirus Adenovirus (F, G) Sapovirus Astrovirus		HP

Fecal Bacteria and Parasites + Enteric Viruses = Fecal M Parasites

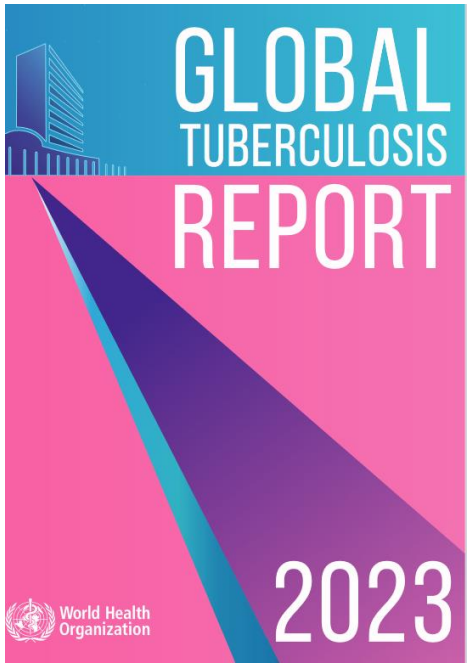
→ Enables separate testing of viruses and bacteria plus parasites

→Additionally *Cyclospora* included

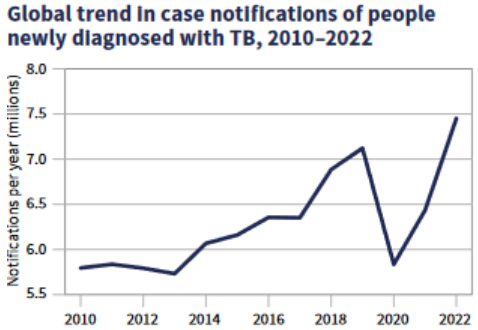
*** Available soon**

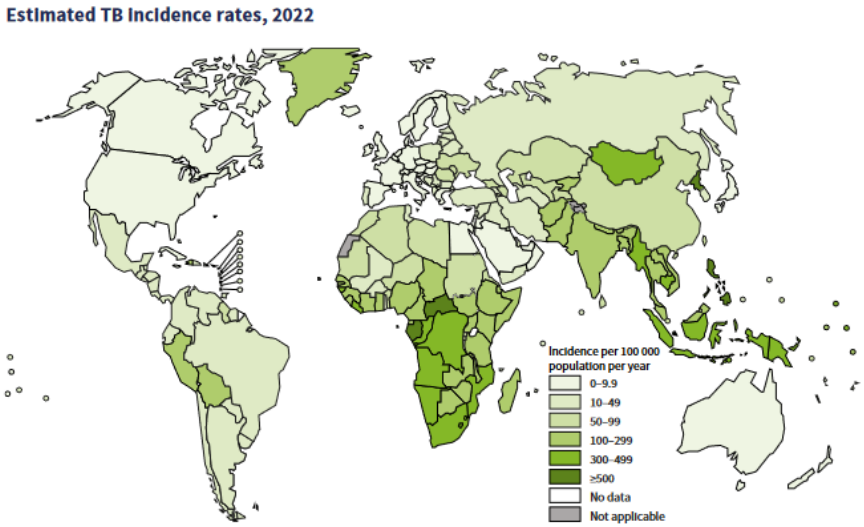
Klinički aspekti i dijagnostika tuberkuloze probavnog sustava

Doc.dr.sc. Ljiljana Žmak, prim.dr. med.
Hrvatski zavod za javno zdravstvo,
Medicinski fakultet Sveučilišta u Zagrebu

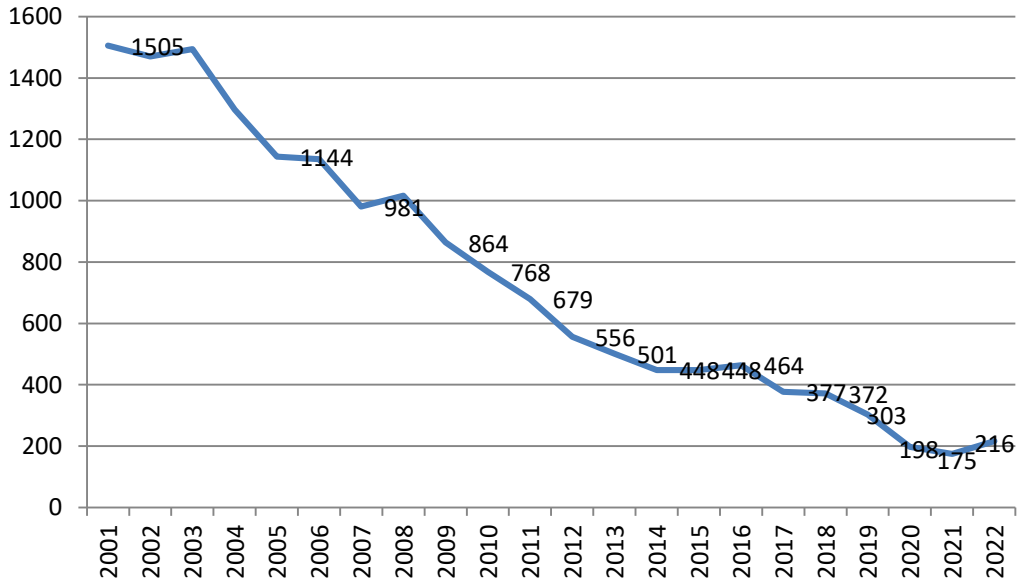


10,6 m pacijenata
1,5 m smrti
incidencija globalno 133/100 000

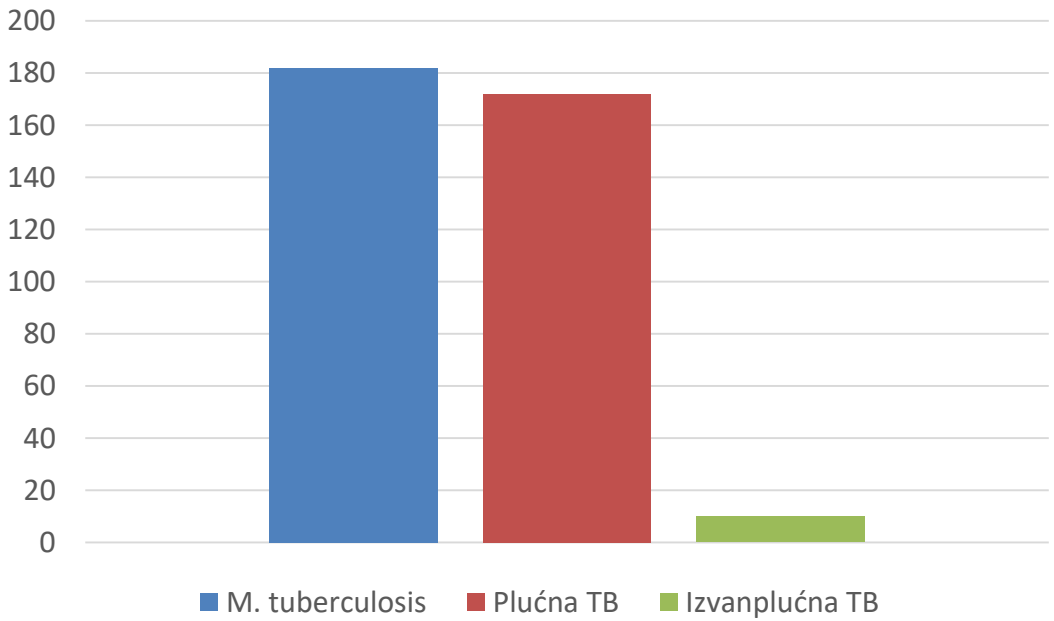




Broj oboljelih od TB u RH, 2001.-2022.



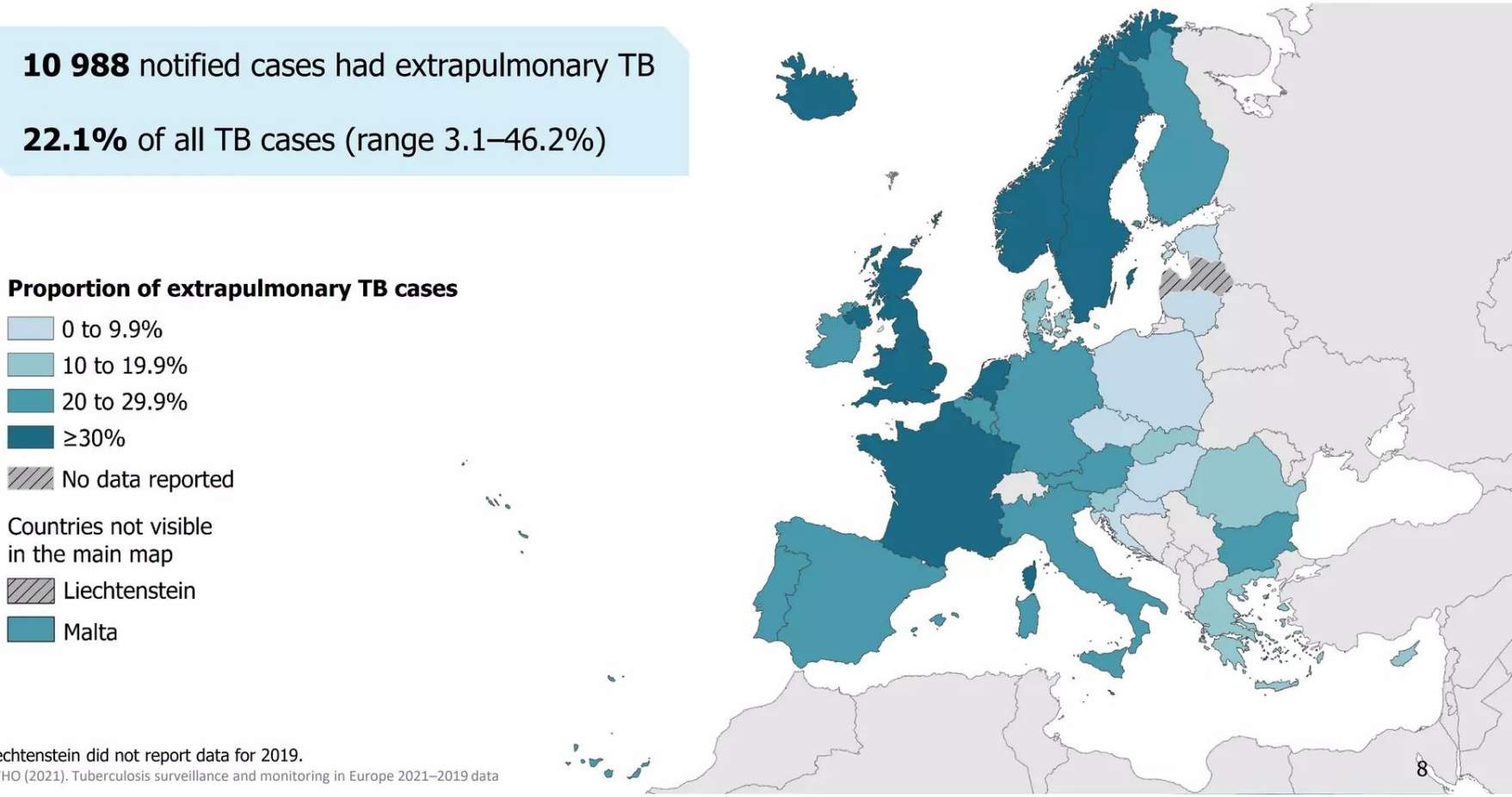
-Tijekom 2022. godine genotipizirano je 182 izolata *M. tuberculosis* iz cijele Hrvatske.
-*M. tuberculosis* je najčešće izoliran iz plućnih uzoraka
-10 (5,5%) izvanplućnih bakteriološki dokazanih slučajeva



Extrapulmonary TB, EU/EEA*, 2019

10 988 notified cases had extrapulmonary TB

22.1% of all TB cases (range 3.1–46.2%)



* Latvia and Liechtenstein did not report data for 2019.

Source: ECDC/WHO (2021). Tuberculosis surveillance and monitoring in Europe 2021–2019 data

Abdominalna tuberkuloza

-6. najčešće sijelo tuberkuloze

-klinička prezentacija nije specifična-kasna dijagnoza i razvoj komplikacija

-15-25% abdominalnih TB ima i plućnu zahvaćenost

- TB abdomena obično se prezentira u 4 oblika:
    - 1. TB limfadenopatija
    - 2. Peritonealna TB
    - 3. **G-I TB**
    - 4. Visceralna TB (zahvaćenost solidnih organa; jetra, slezena)

ROD *MYCOBACTERIUM*

MTBC kompleks - *M. tuberculosis*
- *M. bovis…*
NTM – više od 200 vrsta

- infekcija preko dišnog sustava
- govor, kašalj i kihanja (aerosol veličine 0.5 to 5μm)
- prilikom kihanja oslobađa se 40000 kapljica
- aktivni bolesnici zaraze 10-15 kontakata godišnje

Epidemiologija/patogeneza G-I tuberkuloze

1. Zaraza putem ingestije zaraženog sputuma (vlastitog) ili mlijeka

    -zahvaćanje mukoze GI trakta te stvaranje epiteloidnih tuberkula u limfnom tkivu submukoze

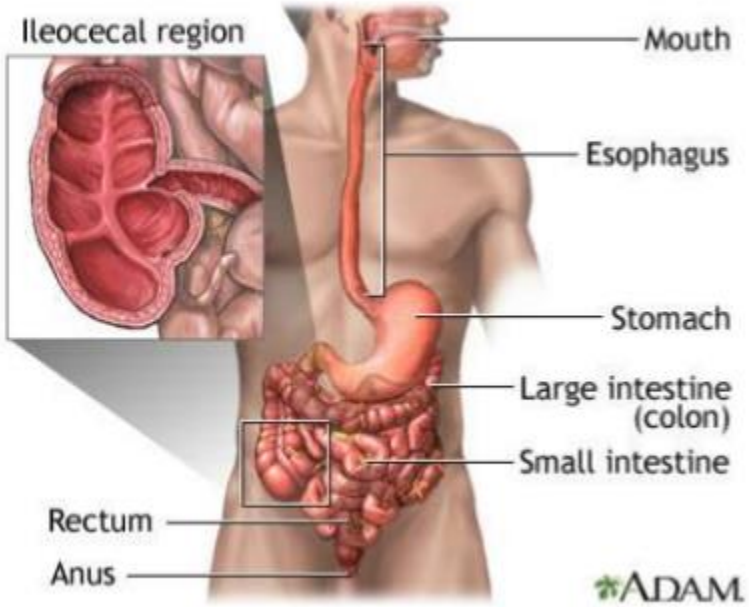
    -nakon 2-4 tjedna stvara se kazeozna nekroza i ulceracije s mogućim širenjem u limfne čvorove i peritoneum

2. Hematogeni rasap primarne tuberkuloze (najčešće pluća)

3. Direktno širenje iz drugih sijela (genitourinarni sustav)

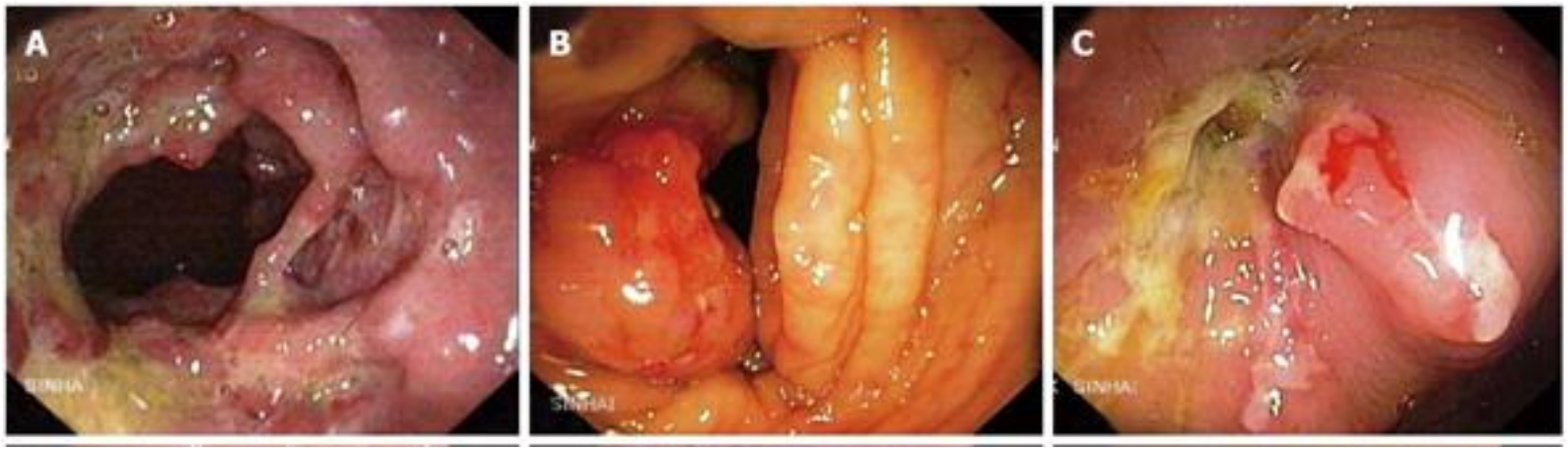
Gastro-intestinalna tuberkuloza

- Najčešće sijelo je ileocekalna regija
- Slijede jejunum i kolon
- Jednjak, želudac i duodenum rijetko zahvaćeni



- Typical site of TB
- Pain
- Anorexia
- Diarrhea
- Palpable mass

Izgled zahvaćenog područja

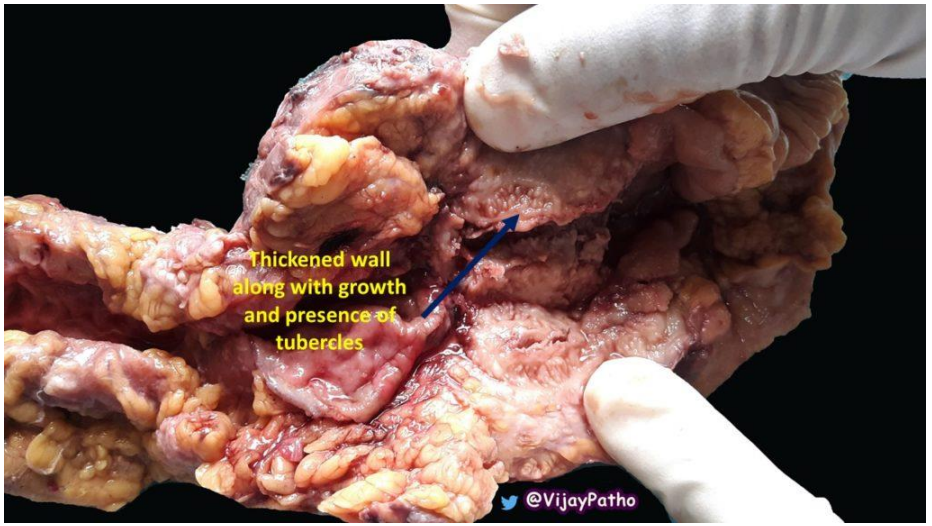


A-ulceracije
B-hipertrofična masa u lumenu
C-striktura ileocekalne valvule

Klinička prezentacija

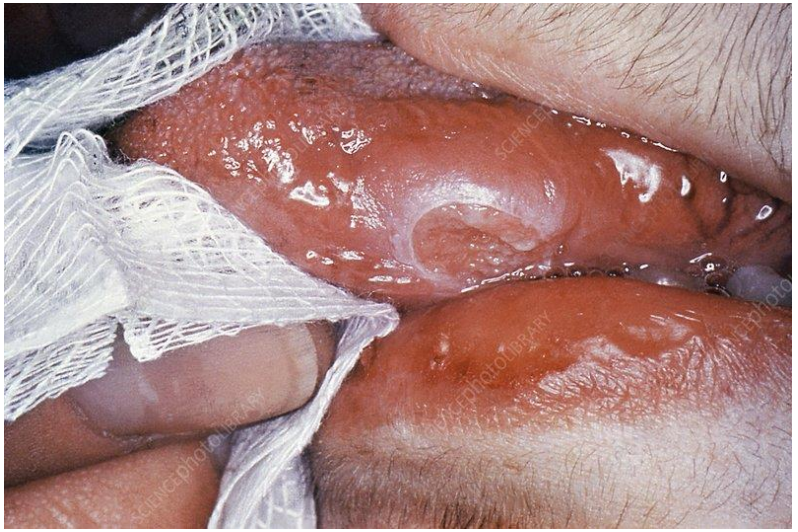
D.D
-upalna bolest crijeva, malignitet, apendicitis, ileus, druga infektivna etiologija

- znatno ovisi o sijelu
- vrućica
- bol u trbuhu
- povraćanje
- konstipacija/proljev
- gubitak na težini
- ascites
- palpabilna abdominalna masa kod 10-40% pacijenata
- do 30% bolesnika javlja se kao kao akutni abdomen



Naša iskustva

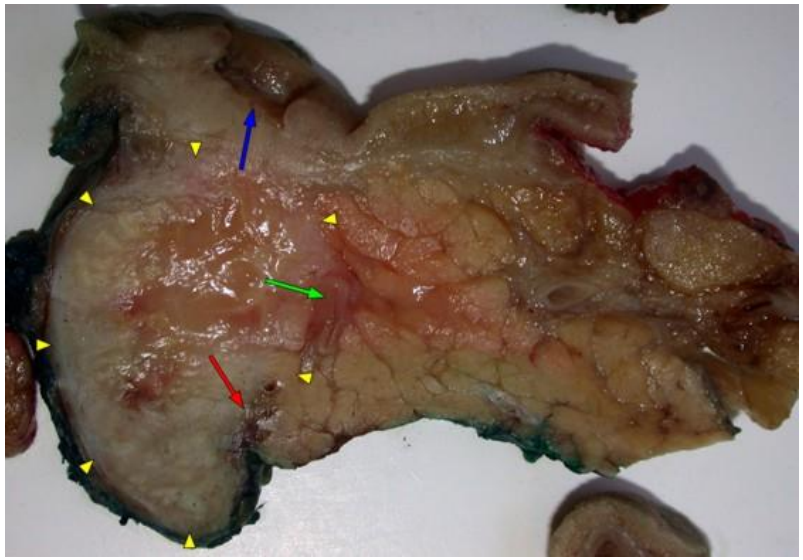
1. **TB jezika**
-muškarac 1960. godište
- uzorak bioptata jezika uzet na Stomatološkom fakultetu

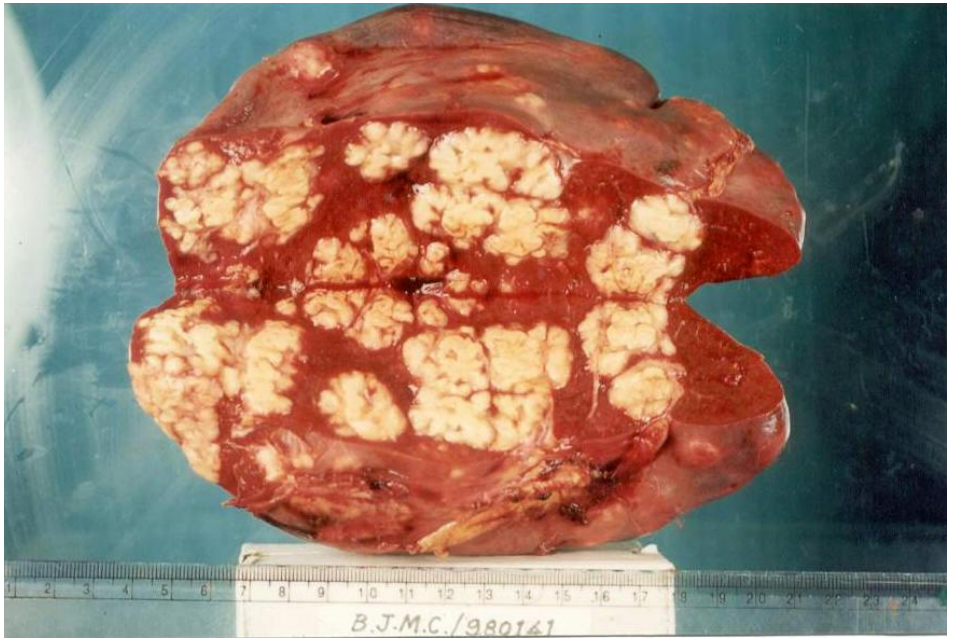


2. **Ileocekalna TB**
- muškarac 1997. godište
- uzorak - intraoperativni bioptata uzet tijekom op. mogućeg apendicitisa
- kultura pozitivna na *M. tuberculosis*

3. Visceralna TB

- muškarac 1935. god. –bioptat slezene
- žena 1950. god. –bioptat tvorbe uz rep guštarače
- žena 1938. god. – uzorak ascitesa
- žena 1964. god. – bioptat tvorbe uz glavu gušterače





Laboratorijska dijagnostika:

-uzorci za lab. analizu

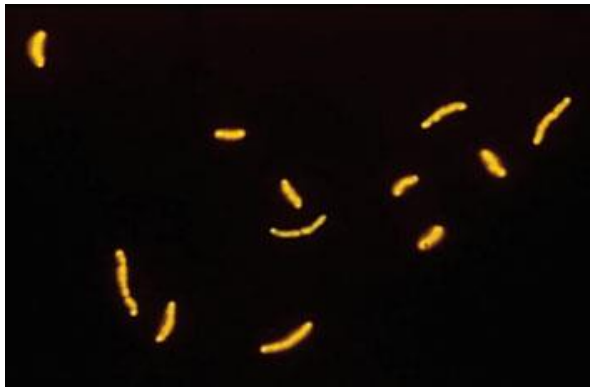
- bioptati lezija (granulomatozna upala)

- ascitesna tekućina rijetko pozitivna (od 130 uzoraka u posljednjih 5 godina, 1 kultura pozitivna

- stolica nije preporučljiv uzorak (iznimke HIV+ bolesnici, ali za dijagnostiku plućne TB)

- u zadnjih 5 godina niti jedan uzorak stolice nije bio pozitivan na M. tbc

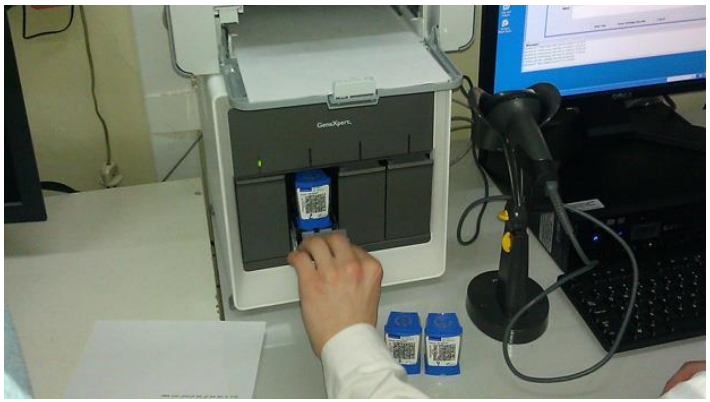
Laboratorijska dijagnostika



1. Mikroskopija: unutar 24 sata, pozitivna kad imamo >10^4 bacila/mL uzorka (3%)

OPREZ: pozitivan nalaz mikroskopije odnosi se na cijeli rod *Mycobacterium*

2. Brzi dokaz infekcije: GeneXpert Ultra test



3. Kultivacija i testiranje osjetljivosti: tekuće podloge (20%)

QUANTIFERON NEPOUZDAN !!

-negativan u velikom broju slučajeva

Advancing Gastrointestinal Health

Immunology and rapid solutions

Dr. Adem Nasraddin • 17 May 2024 • Zagreb

Innovative Solutions for Infection Identification and Management

Infectious diarrhea

- One of the leading cause of death in children worldwide
- Diarrhea is defined as **the passage of three or more loose or liquid stools per day** (or more frequent passage than is normal for the individual).
- There are three clinical types of diarrhea:
  - **acute watery diarrhea** – lasts several hours or days, and includes cholera;
  - **acute bloody diarrhea** – also called dysentery; and
  - **persistent diarrhea** – lasts 14 days or longer
- In the past, **severe dehydration and fluid loss** were the main causes of diarrhea deaths. Now, **other causes and risk factors such as septic bacterial infections, impaired immunity, HIV, malnutrition,** are likely to account for an increasing proportion of all diarrhea-associated deaths.
- mostly self-limited and can be treated either by symptomatic and/or specific treatment

https://de.freepik.com/vektoren-kostenlos/toilettenpapier-haengt-an-einem-halterelement_16352164.htm#page=2&query=toilet&position=27&from_view=search&track=sph

Diarrhea causing pathogens
Who are they?

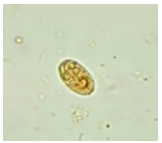
Bacteria	Toxin-producer	Viruses	Protozoans
E. coli (EPEC, EAEC, EIEC) Yersinia enterocolitica Campylobacter spp. Salmonella spp. Shigella spp. Vibrio cholerae ...	Clostridium difficile Clostridium perfringens E. coli (EHEC, STEC, ETEC)	Norovirus Rotavirus Adenovirus Astrovirus Sapovirus	Giardia lamblia Cryptosporidium parvum/hominis Entamoeba histolytica Dientamoeba fragilis ....

Clinical diagnosis of Gastrointestinal Infections

- Symptoms and appearance
- Duration of complaints
- Community or hospital acquired
- Use of antibiotics
- Relation to food or travel

Pathogens	Clinical features					
	Abdominal pain	Fever	Fecal evidence of inflammation	Vomiting, nausea	Heme-positive stool	Bloody stool
Shigella	++	++	++	++	+/–	+
Salmonella	++	++	++	+	+/–	+
Campylobacter	++	++	++	+	+/–	+
Yersinia	++	++	+	+	+	+
Norovirus	++	+/–	–	++	–	–
Vibrio	+/–	+/–	+/–	+/–	+/–	+/–
Cyclospora	+/–	+/–	–	+	–	–
Cryptosporidium	+/–	+/–	+	+	–	–
Giardia	++	–	–	+	–	–
Entamoeba histolytica	+	+	+/–	+/–	++	+/–
Clostridium difficile	+	+	++	–	+	+
Shiga toxin-producing *Escherichia coli* (including O157:H7)	++	0	0	+	++	++

Key: ++, common; +, occurs; +/–, variable; –, not common; 0, atypical/often not present.


- The clinical features of GI are ***nearly identical***
- Difficult, nearly impossible to determine the pathogenic cause
- on the basis of clinical features alone
- ***Laboratory diagnosis is essential***

Treatment

Symptomatic treatment

→ Antidiarrheal agents: Loperamide, bismuth subsalicylate

→ Oral re-hydration, Oral re-hydration solutions

https://de.freepik.com/vektoren-kostenlos/pillen-und-rezept-in-der-flachen-vektorillustration-der-menschlichen-haende-patienten-die-medikamente-oder-vitamine-einnehmen-medizin-gesundheitswesen-behandlungskonzept-fuer-banner-website-design-oder-landing-webseite_29119349.htm#query=treatment%20medication&position=1&from_view=search&track=sph"

Specific treatment

→ Medication that is specific acting against the pathogen

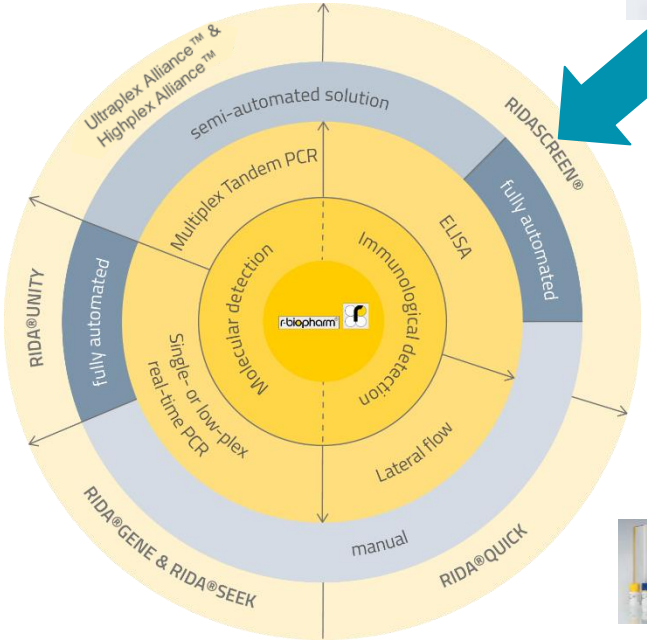
Note:

Antibiotic agents do not act against viruses.

Some infections can’t be treated with specific medication as none is available.

Identification of the cause of a medical condition improves patient care and saves costs.

R-Biopharm - GI Protfolio Overview



RIDASCREEN® ELISA
GI parameter overview

Viruses
Rotavirus
Norovirus
Adenovirus
Astrovirus

Bacteria
Campylobacter
Clostridium difficile GDH
Clostridium difficile Toxin A/B
C. perfringens Enterotoxin
H. pylori
Verotoxin
Legionella

Parasites
Cryptosporidium
Entamoeba histolytica
Giardia lamblia

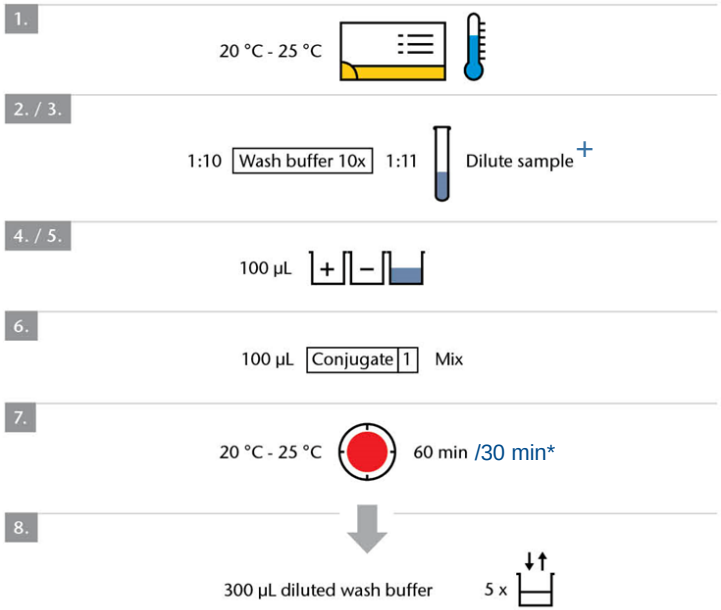
Storage RIDASCREEN® 2 - 8 °C

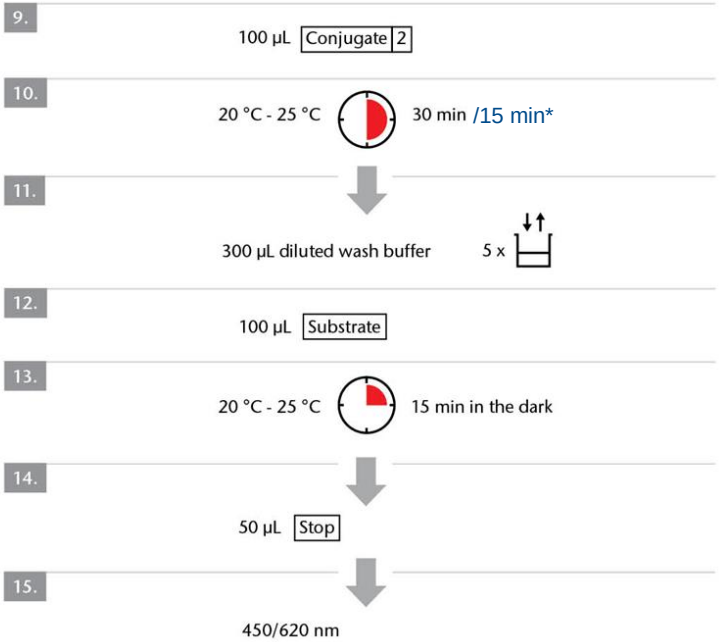
Quality Controls for internal laboratory quality assurance and result control

ELISA Reference Controls (positive and negative)
Clostridium perfringens Enterotoxin
C. difficile GDH
C. difficile Toxin A/B
Rotavirus
Adenovirus
Astrovirus
Norovirus
Entamoeba
Giardia
Verotoxin
Campylobacter
H. pylori
Legionella

Note: test run controls are used to validate the test run; quality controls are mostly used to assure diagnostic accuracy in the lab

Uniform application protocol for RIDASCREEN® - infectious disease





- shortened protocol. Incubation times of parasite ELISA
+ Verotoxin/ Legionella supernatant and undiluted samples areused

Automatic processing with RIDASCREEN® infectious disease parameters

Agility®

up to 12 plates
up to 16 assays

DSX®

up to 4 plates at once
costumized racks

DS2®

up to 2 plates

Verified application protocols available for all RIDASCREEN® infectious disease parameters*

* Legionella application on Agility is not verified; DS2 application is possible but not supported by R-Biopharm AG

RIDASCREEN® Features and benefits

User-friendly
- uniform test protocols allow combining tests
- breakable microtiter-strips

Time savings
- universal pre-analytics

Simple procedure
- cross-lot and -parameter reagents
- ready-to-use reagents
- color coded reagents and bottles

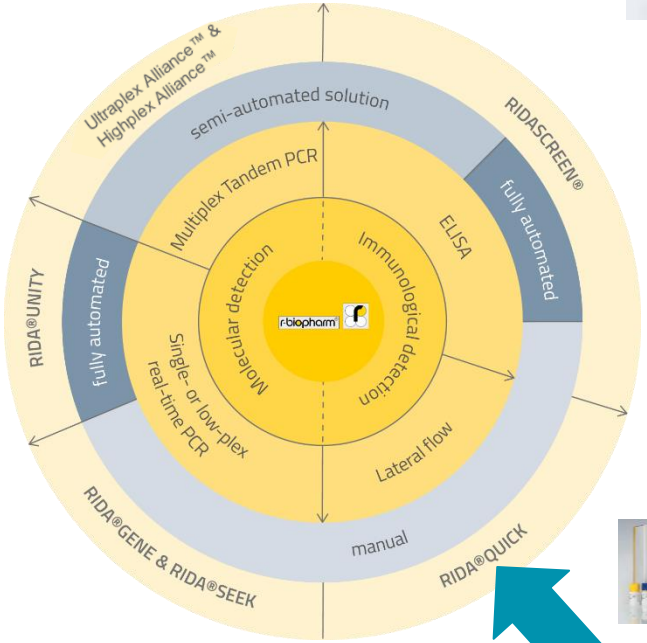
Scientific literature
- More than 50 publications

Sensitive detection
- Biotin-streptavidin signal amplification technology for increased sensitivity

Reliable
- Ready-to-use control material for each parameter

Efficient
- easy to automate
- verified application protocols
- combinable broad product spectrum to detect infectious pathogens

R-Biopharm - GI Protfolio Overview

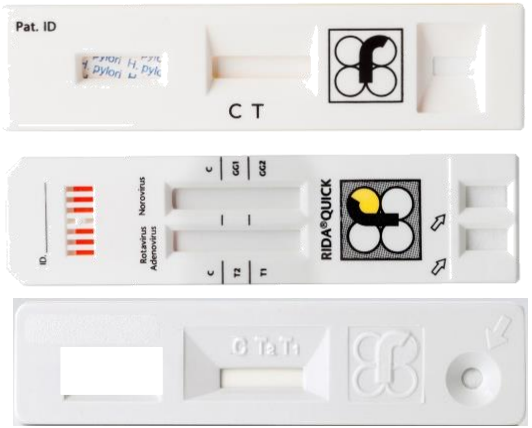


RIDA®QUICK rapid tests (lateral flow) overview

Viruses
Rotavirus
Adenovirus
Norovirus

Bacteria
Campylobacter
Clostridium difficile GDH
Clostridium difficile Toxin A/B
H. pylori

Parasites
Giardia Lambilia
Cryptosporidium
Entamoeba histolytica



RIDA®QUICK cassettes

Storage: 2 – 25/30 °C

RIDA®QUICK rapid tests (lateral flow) – test format overview

Mono

Campylobacter
Clostridium difficile GDH
Clostridium difficile Toxin A/B
H. pylori
Rotavirus
Norovirus (GI/GII)
Giardia
Cryptosporidium
Entamoeba

Duplex

Rotavirus/Adenovirus
Cryptosporidium/Giardia

Triple

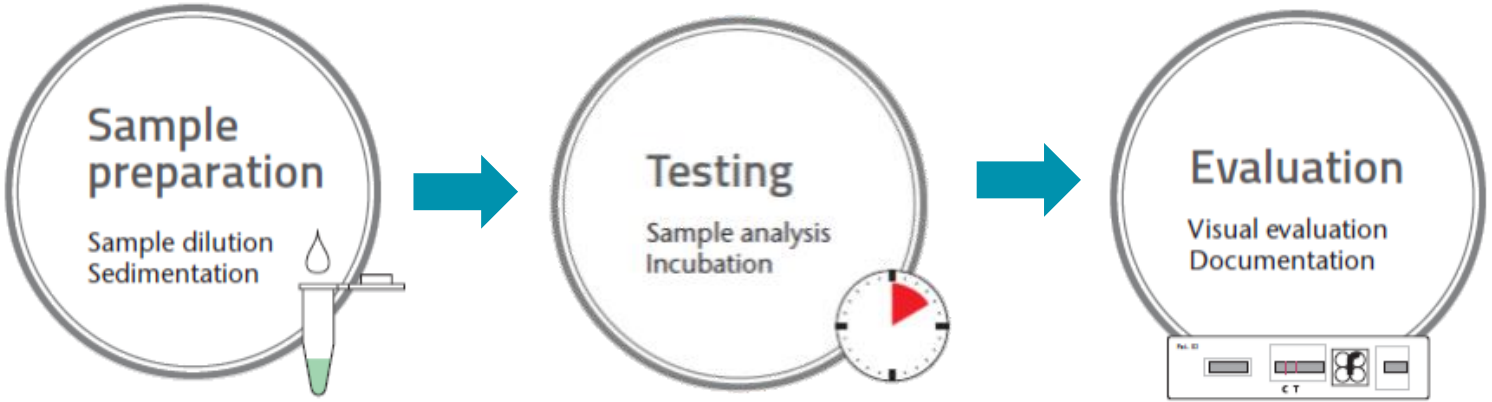
Rotavirus/Adenovirus/Norovirus (GI/GII)
Cryptosporidium/Giardia/Entamoeba

Quality Controls for internal laboratory quality assurance and result control

Rapid Reference Controls (positive)
C. difficile GDH
C. difficile Toxin A/B
Rotavirus/Adenovirus
Norovirus
Parasites (Cryptosporidium, Entamoeba, Giardia)
H. pylori
Campylobacter

Note: test run controls are used to validate the test run; quality controls are mostly used to assure diagnostic accuracy in the lab

General workflow of lateral flow assays



Time to result:
Less than 30 min

RIDA®QUICK Features and benefits

Rapid results
- in less than 30 min

Simple procedure
- ready-to-use reagents
- color coded reagents and bottles

Safe and accurate
- integrated control line
- parameter specific color/labeling of strips visible in viewing window of the cassette
- space for Patient ID-labeling on the test device

Practical
- individual packaged determinations

Robust
- storage within a broad temperature range

Sensitive
- Non-invasive detection of the most common enteropathogenic organisms

Reliable
- Ready-to-use control material for each parameter

Thank you

for your attention!

Helminti kao uzročnici probavnih infekcija

Izv.prof. dr. sc. Mario Sviben,dr.med.

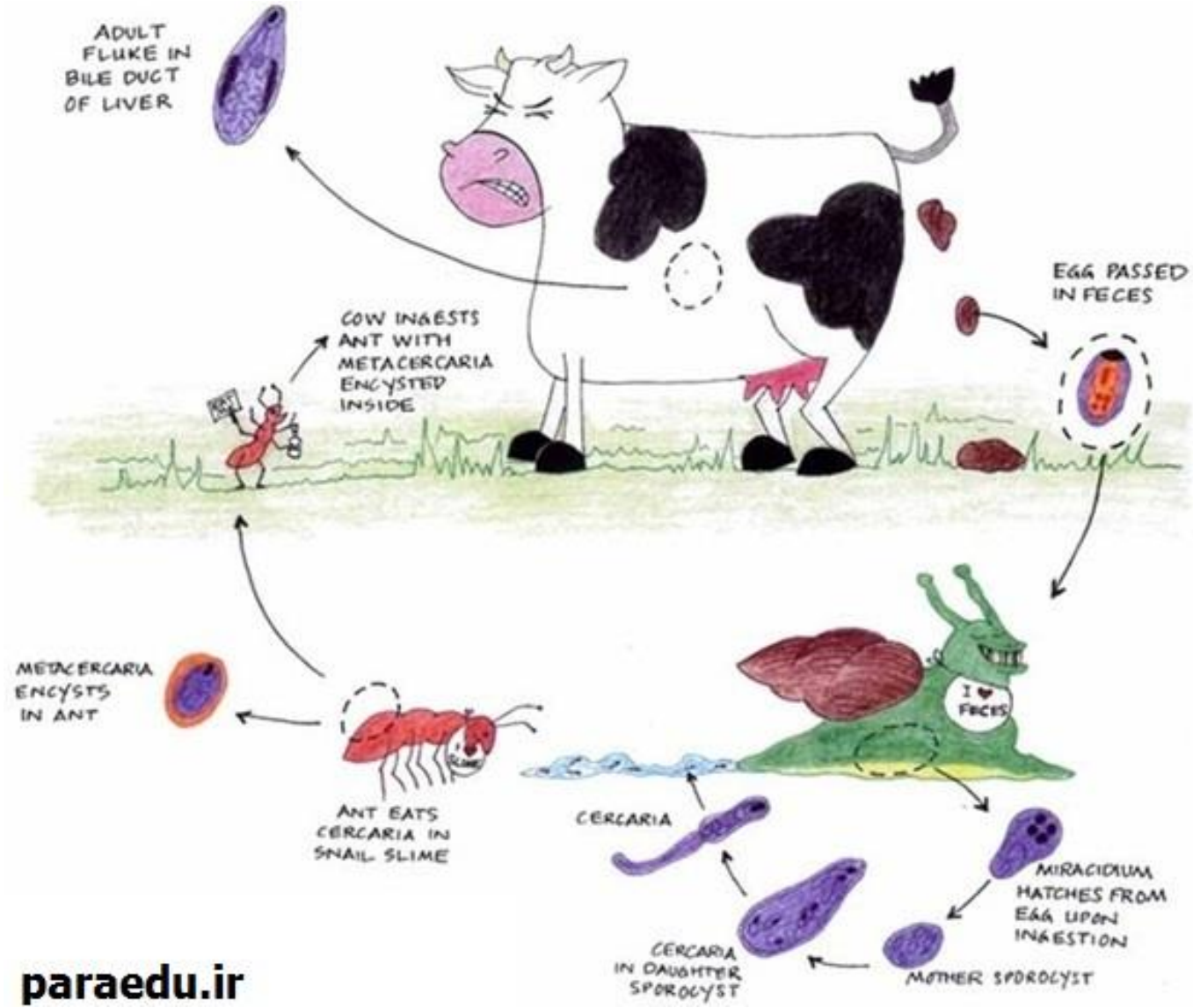
Medicinski fakultet Sveučilišta u Zagrebu

i

Hrvatski zavod za javno zdravstvo

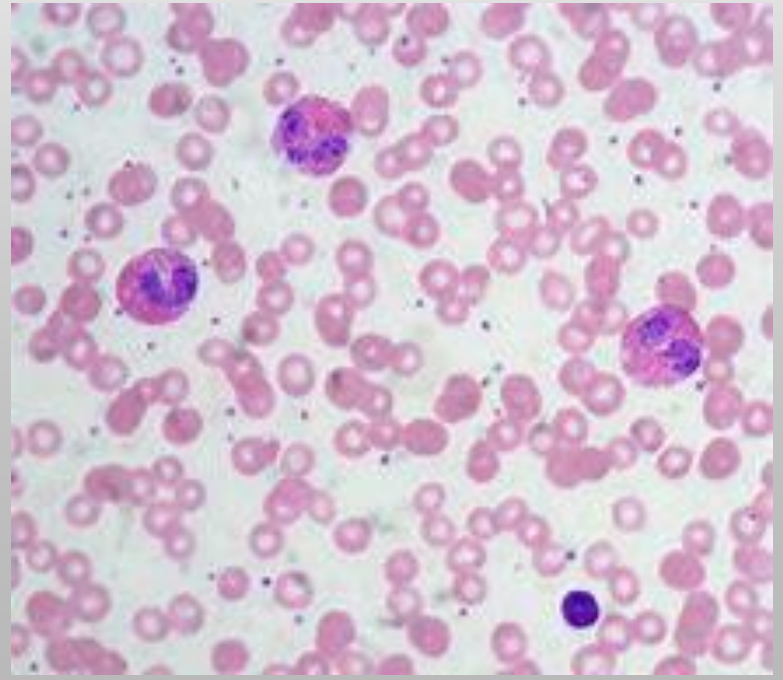
HELMINTNE INFEKCIJE

- Među najučestalijim infekcijama u svijetu posebice u nerazvijenim dijelovima svijeta
- Putovanja, prehrambene navike pod utjecajem globalizacije, klimatske promjene, migracije
- Nematode, trematode, cestode
- Neki organizmi isključivo kod ljudi, neki kod ljudi i životinja, neki inficiraju ljude incidentalno
- Višestanični organizmi – manje od 1 cm do više od 10 m
- Trajanje ograničeno životnim vijekom adulta – uglavnom nema multiplicirajuće infekcije
- Nisu uniformno raspoređene u populaciji – većina pacijenata asimptomatska sa malim opterećenjem, manjina teške infekcije


ADULT FLUKE IN BILE DUCT OF LIVER
COW INGESTS ANT WITH METACERCARIA ENCYSTED INSIDE
EGG PASSED IN FECES
I ♥ FECES
METACERCARIA ENCYSTS IN ANT
ANT EATS CERCARIA IN SNAIL SLIME
CERCARIA
MIRACIDIUM HATCHES FROM EGG UPON INGESTION
CERCARIA IN DAUGHTER SPOROCYST
MOTHER SPOROCYST

HELMINTNE INFEKCIJE

- Patogeneza – mehanička opstrukcija, invazija stanica ili tkiva sa oštćenjem njihove funkcije, natjecanje za hranjive sastojke
- Nema sterilizirajućeg imuniteta
- Eozinofilija – migrirajući, ne stacionarni organizmi
- Smanjivanje ekspresije alergijskih bolesti?!
- Izbjegavanje imunološkog odgovora – enkapsulacija, intraluminalna lokacija, inibicija i/ili modlacija imunološkog odgovora domaćina



HELMINTNE INFEKCIJE

- Dijagnostika – klinička slika, epidemiološka anamneza, radiološke metode vizualizacije
- Mikrobiološka – mikroskopska, makroskopija, serologija, kultivacija, detekcija antigena, PCR
- Th: albendazol, mebendazol, praziquantel, ivermektin + kortikosteroidi
- Kontrolni programi
- Higijena, podizanje standarda, edukacija

HELMINTNE INFEKCIJE PROBAVNOG SUSTAVA

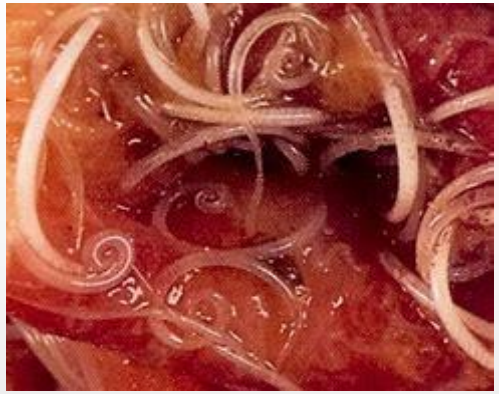
- Feko oralno stjecanje

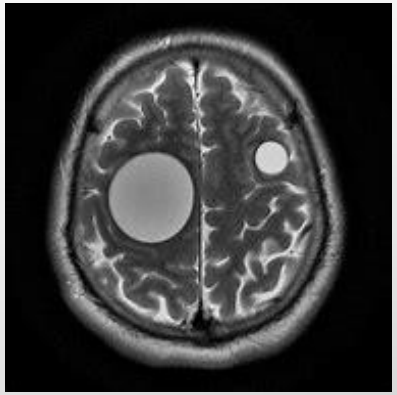
- Simptomi od strane infekcije probavnog sustava

- Simptomi infekcije radi invazije u organe izvan probavnog sustava

VALJKASTI CRVI – NEMATODE





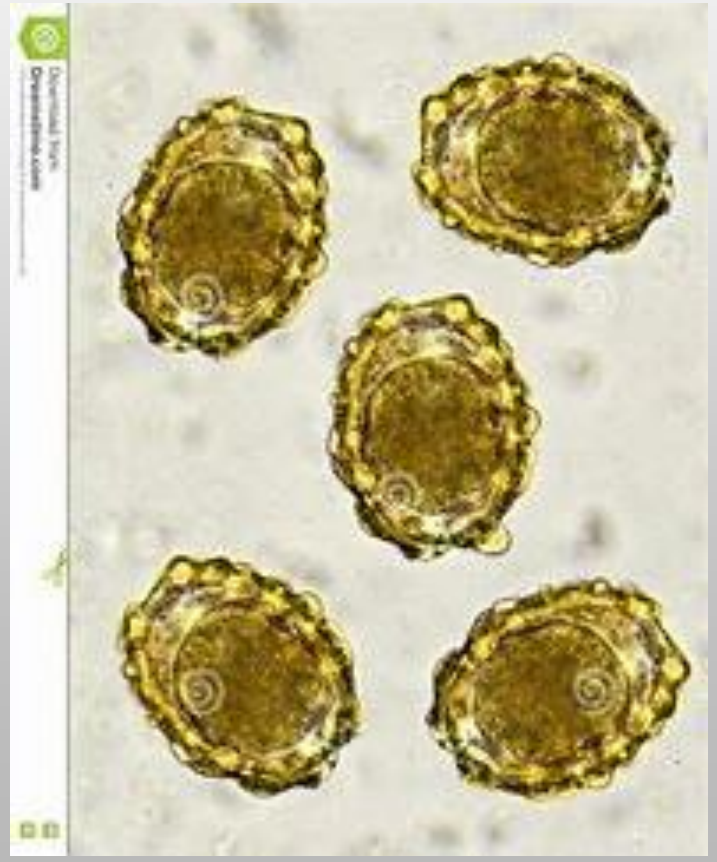


ASCARIS LUMBRICOIDES

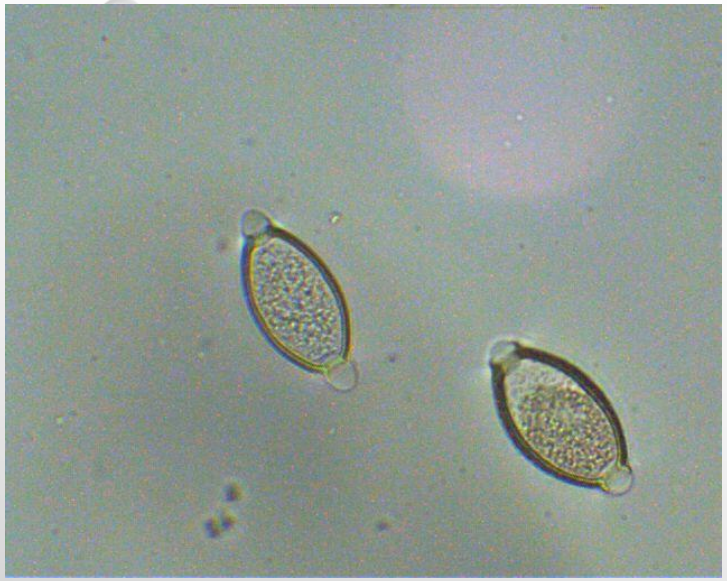
- Najčešća helmintna infekcija - ¼ populacije
- Najčešće asimptomatska, mortalitiet 60 000 ljudi godišnje
- Adulti – tanko crijevo
- 200 000 jaja dnevno, nakon 2-6 tjedana infektivna, nakon 2 mjeseca od infekcije adulti u crijevima, životni vijek 10-24 mjeseca
- Simptomi: kašalj, temperatura, eozinofilija, dispneja, eozinofilna pneumonija;
- Malnutricija, abdominalna nelagoda, mučnina, gubitak apetita, intestinalna opstrukcija, opstrukcija žučnih i pankretičnih vodova, apendicitis, perforacija crijeva

ASCARIS LUMBRICOIDES

- Nalaz jaja u mikroskopskom preparatu
- Ličinke u sputumu ili aspiratu želuca
- Adulti
- Serologija
- Th: albendazol (400 mg –jdnokratno); mebendazol (500 mg jednokratno ili 100 mg 2x dnevno kroz 3 dana); pyrantel pamoat (11 mg/kg jednokratno do maksimalno 1 gr); ivermektin (150 microgr/kg jednokratno)



TRICHURIS TRICHIURA



- Crv vlašnjak
- 800 mil. ljudi
- Veličina 4 cm, stražnji kraj deblji od prednjeg, debelo crijevo
- Jaja, razvoj embrija 2-4 tjedna
- Ovipozicija nakon 3 mjeseca; parazit živi 1-3 godine
- Simptomi: bolovi u trbuhu, proljev, mikrocitna anemija, zaostajanje u rastu, dizenterija
- Dg: mikroskopski pregled stolica –jaja, nema dostupne rutinske serologije u dijagnostici
- Th: albendazol, mebendazol, pyrantel pamoat

GASTROENTEROLOGY 2005;128:825–832

Trichuris suis Therapy for Active Ulcerative Colitis: A Randomized Controlled Trial

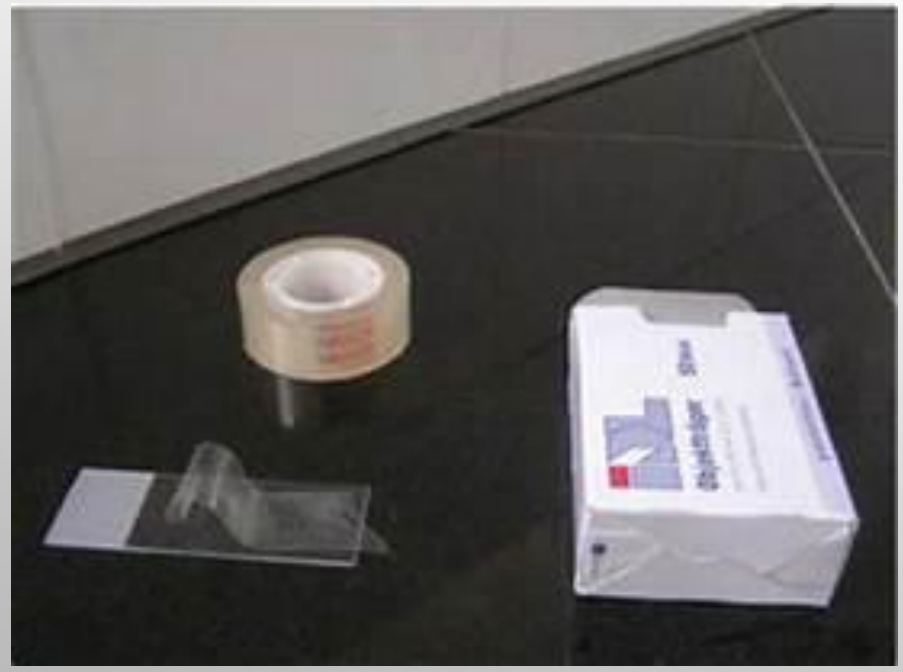
ROBERT W. SUMMERS,* DAVID E. ELLIOTT,* JOSEPH F. URBAN, Jr,[†,§] ROBIN A. THOMPSON,* and JOEL V. WEINSTOCK*

*James A. Clifton Center for Digestive Diseases, Department of Internal Medicine, Iowa City, Iowa; [†]University of Iowa Carver College of Medicine, University of Iowa, Iowa City, Iowa; and [§]Nutrient Requirements & Functions Laboratory, Beltsville Human Nutrition Research Center, Agricultural Research Service, United States Department of Agriculture, Beltsville, Maryland

ENTEROBIUS VERMICULARIS

- Mala dječja glista
- Najčešća helmintna infekcija u razvijenim dijelovima svijeta
- Djeca, osobe u institucijama i zajedničkom domaćinstvu; nije povezana sa socioekonomskim statusom
- Veličina 1cm, ženka polaže jaja tijekom noći u perianalnoj regiji
- Embrionalizacija – 6 sati, jaja vijabilna 20 ak dana, STI, autoinfekcija
- Razvoj adulta 5-6 tjedana, žive oko 1 mjesec
- Simptomi: analni pruritus, ektopične lokacije -upala

ENTEROBIUS VERMICULARIS



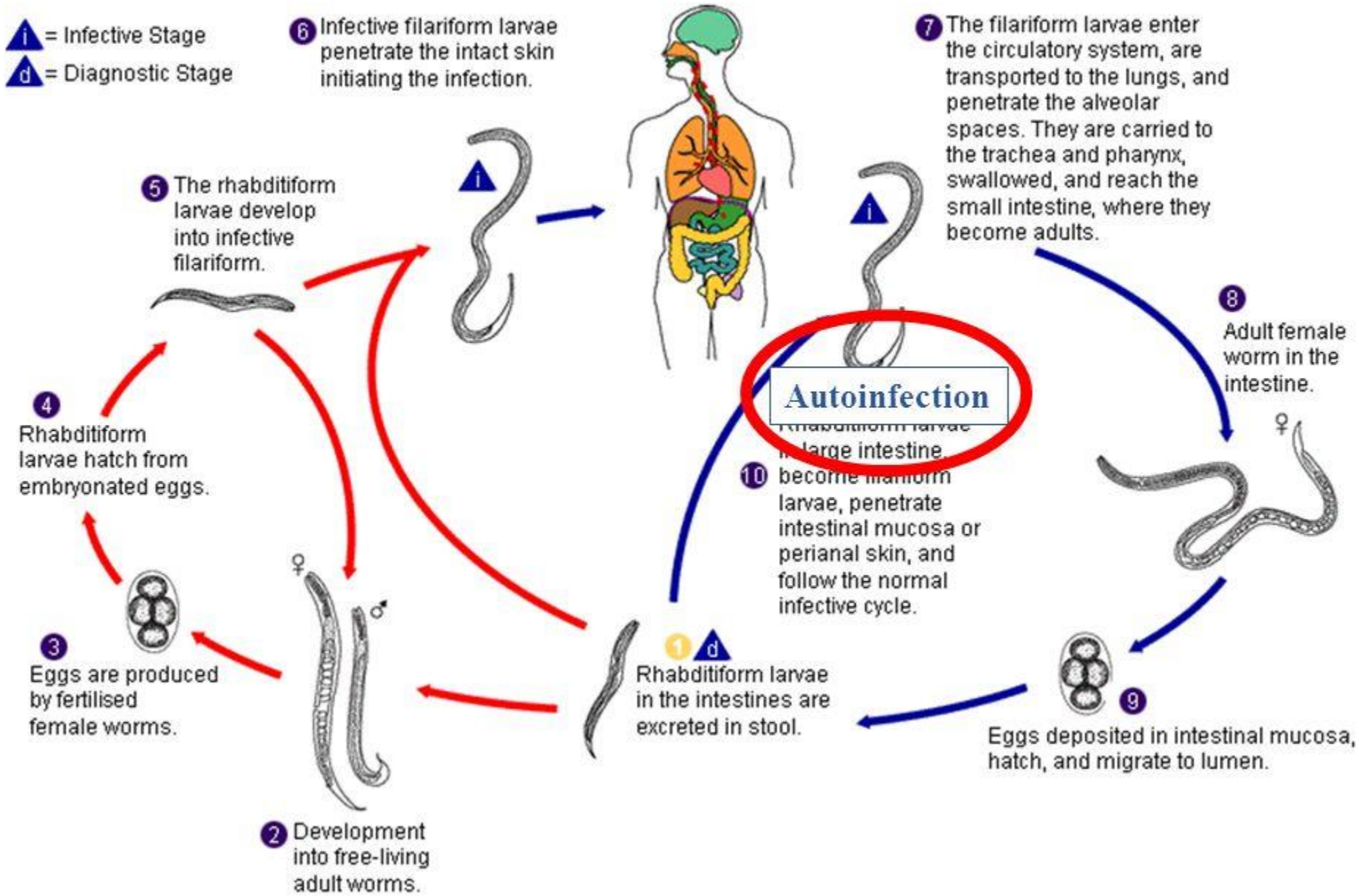
- Analni otisak ljepljivom trakom (1x-50% infekcija,

  3x-90% infekcija)
- Th: jednokratna doza albendazola 400 mg, mebendazola 100 mg, ivermektina ili pyrantel pamoata
- Druga doza nakon dva tjedna radi česte reinfekcije, liječenje bliskih osoba

STRONGYLOIDES STERCORALIS

- Prevalencija – 100 mil.
- Medicinski značaj – mogućnost preplavljujuće infekcije u imunodeficijentnih pacijenata – mogućnost umnožavanja i autoinfekcije unutar domaćina

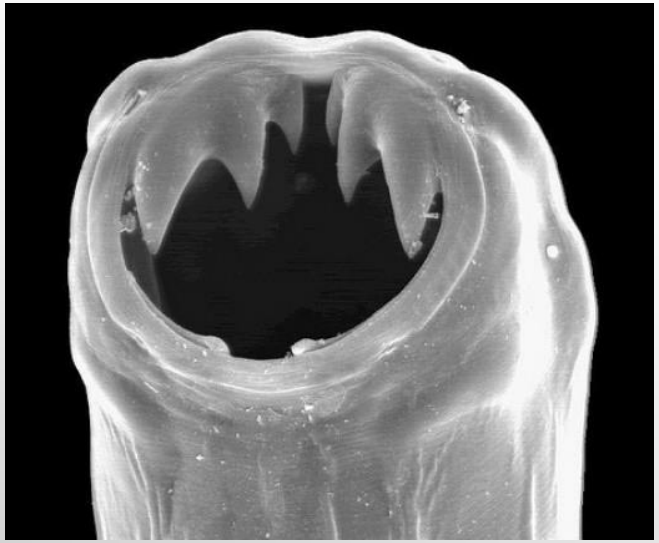
Strongyloides stercoralis life cycle

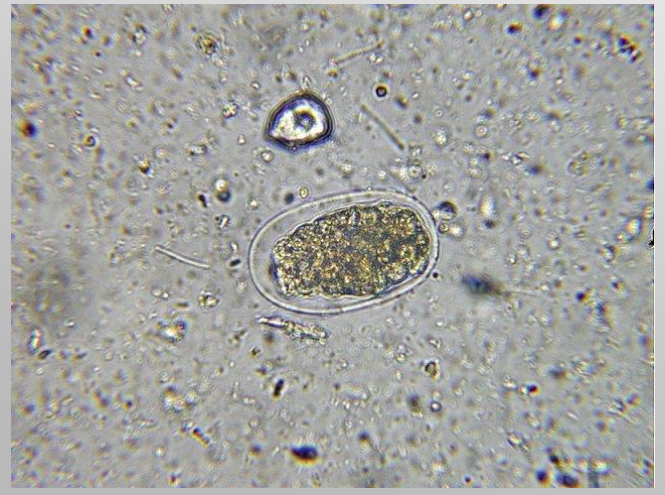


STRONGYLOIDES STERCORALIS

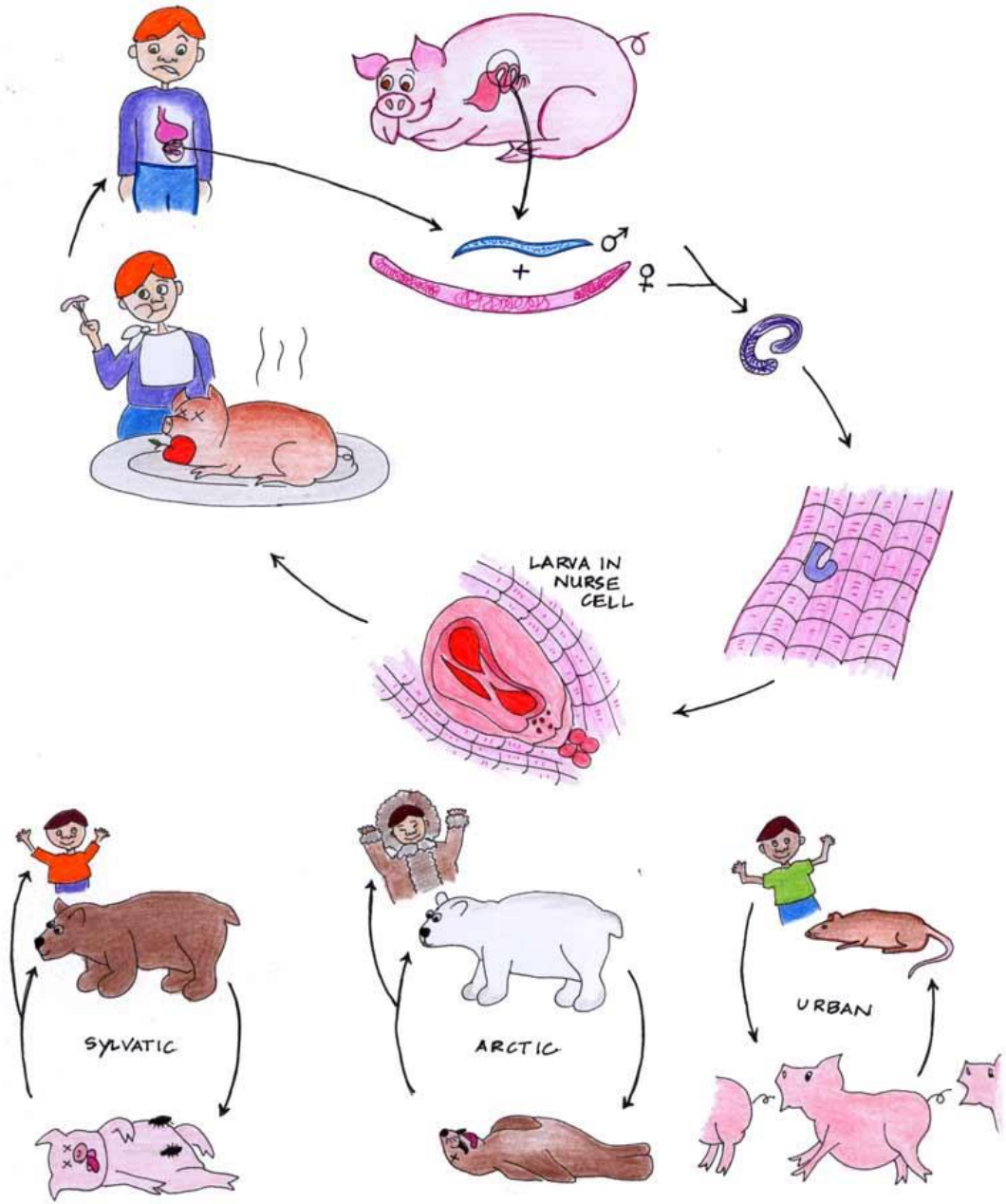
- Klinička slika: pruritički osip kod penetracije ličinki, pulmonalni simptomi, proljev i bolovi u abdomenu nekoliko tjedana nakon infekcije
- Kronična infekcija kod imunološki zdravih ljudi– asimptomatska
  (75 % ima povremenu eozinofiliju)
- Imunodeficijentni pacijenti-upotreba kortikosteroida, TNF alfa inhibitora, kemoterapije, dijabetes, HIV bolest – teška preplavljujuća autoinfekcija – mortalitet 100% bez liječenja, 25% sa liječenjem
- Dijagnostika: nalaz ličinki u stolici, serologija
- Th: ivermektin, tiabendazol, albendazol

ANCYLOSTOMA DUODENALE

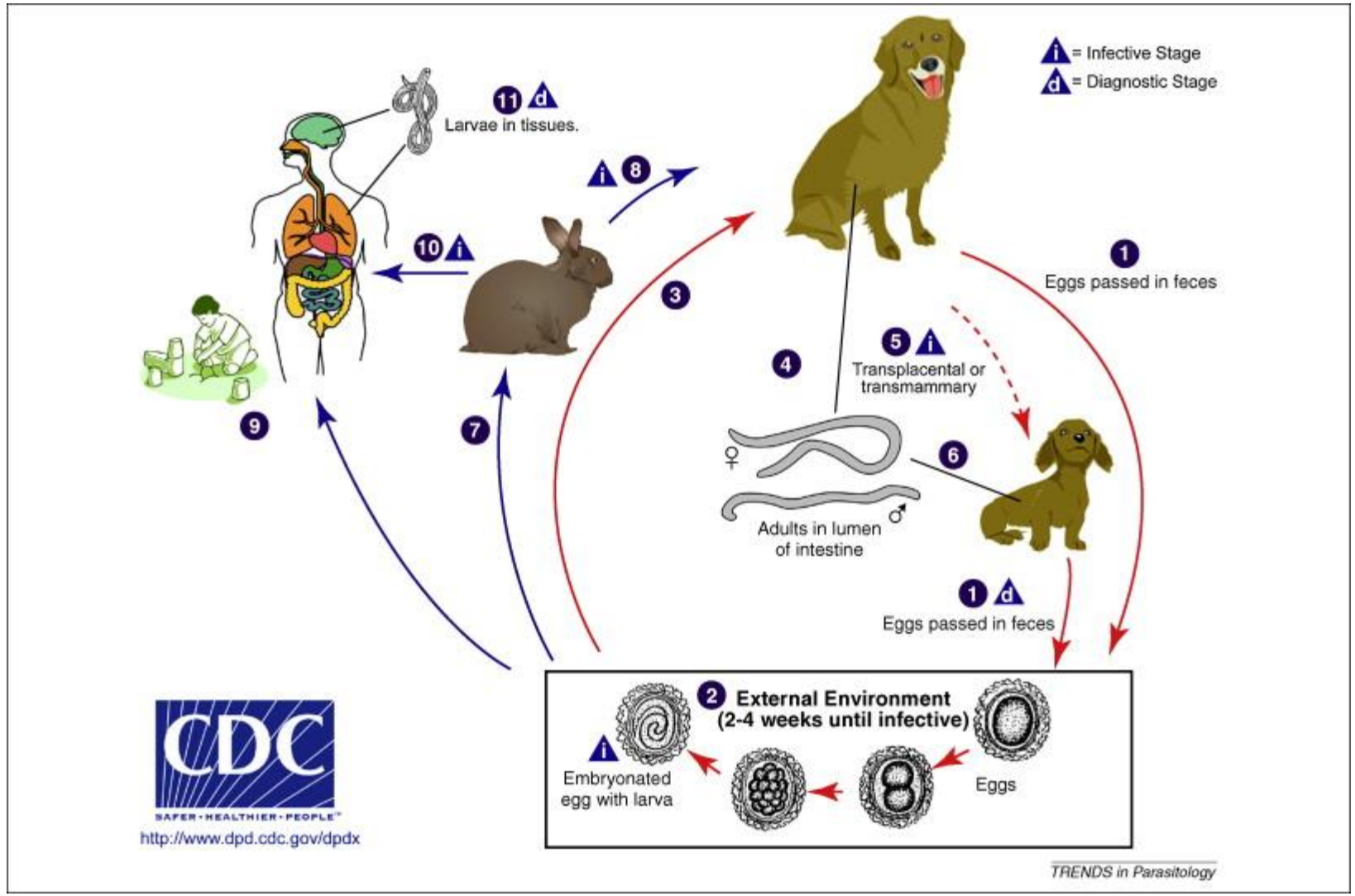


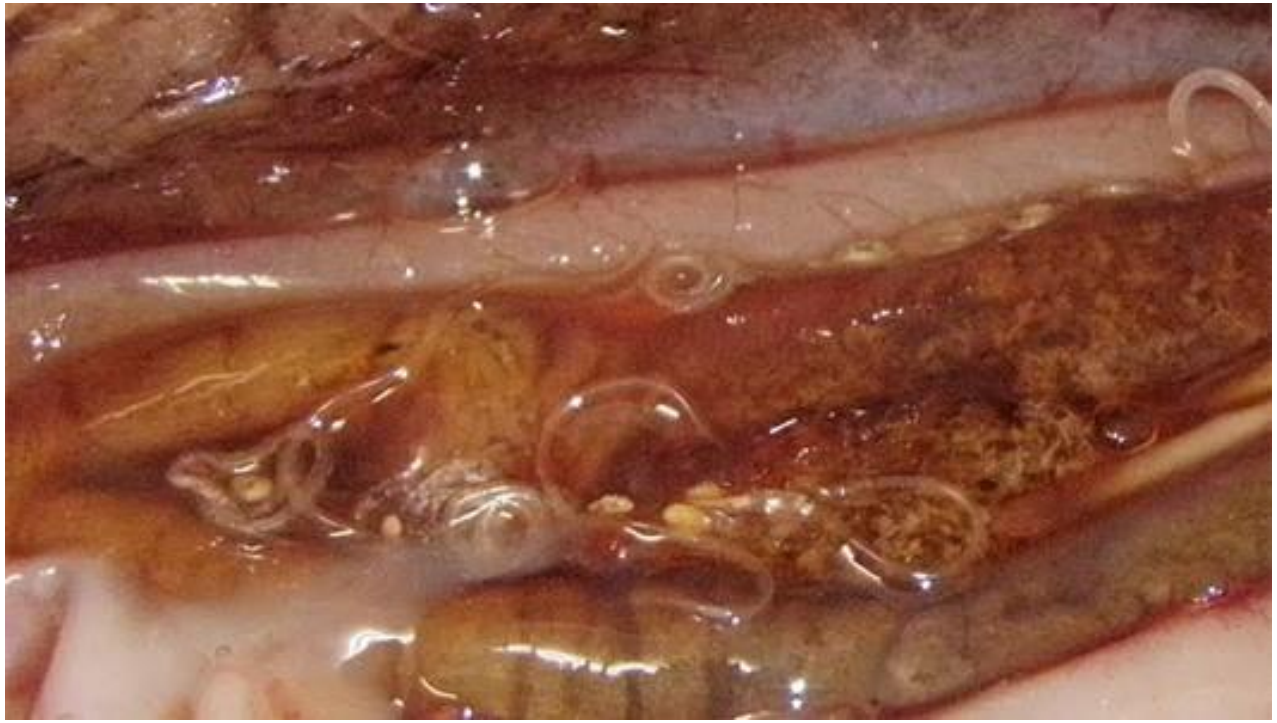


- Rudarska glista – 10 % svjetske populacije inficirano
- 7-13 mm velika nematoda
- Adult nakon migracije živi u tankom crijevu, živi oko 2 godine
- Hrani se krvlju – kožni simptomi; pneumonitis; anemija – 60 000 smrti godišnje – kongestivno zatajenje srca
- Eozinofilija, kronični bolovi u trbuhu
- Dg: nalaz jaja u stolici, koprokultura
- Th: jednokratno 400 mg albendazola; mebendazol 100 mg 2x dnevno/ 3 dana; pyrantel pamoat
- Vakcina – u ispitivanju



VARIOUS LIFE CYCLES OF *Trichinella* spp.

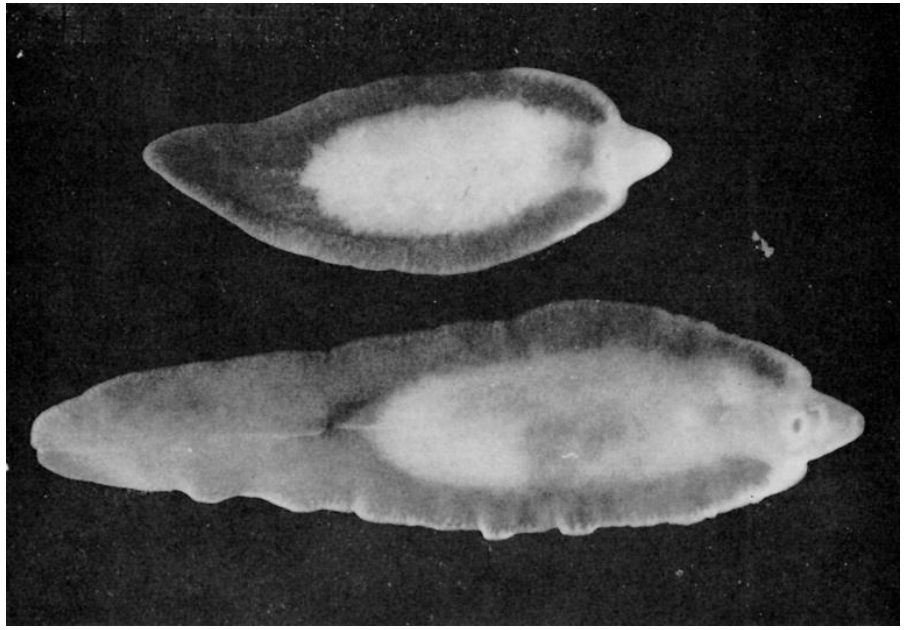

i = Infective Stage
d = Diagnostic Stage
1 Eggs passed in feces
2 External Environment
(2-4 weeks until infective)
Embryonated egg with larva
Eggs
3
4
5 i
Transplacental or transmammary
6
Adults in lumen of intestine
1 d
Eggs passed in feces
7
8 i
9
10 i
11 d
Larvae in tissues.
CDC
SAFER · HEALTHIER · PEOPLE™
http://www.dpd.cdc.gov/dpdx
TRENDS in Parasitology

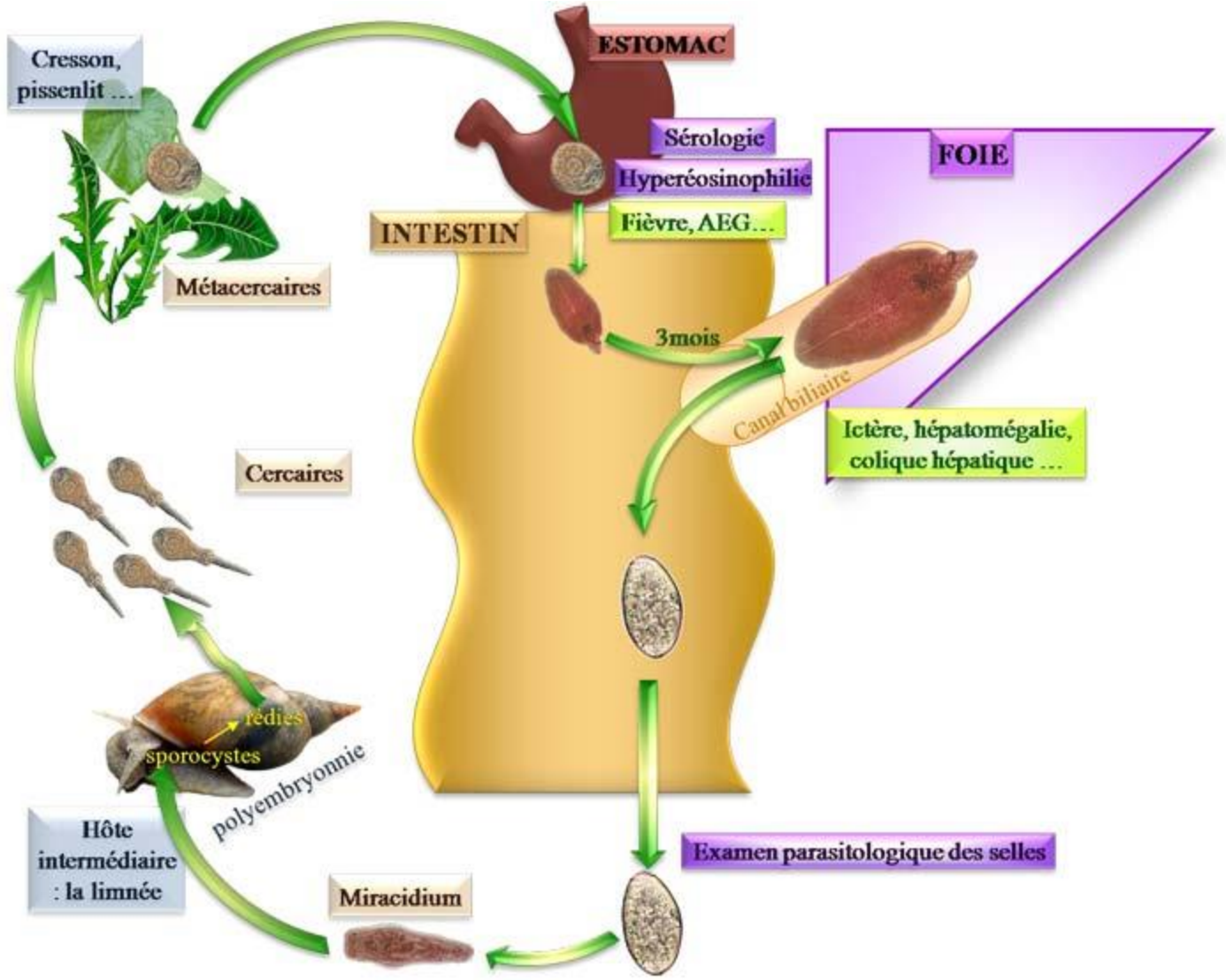


METILJI - TREMATODE

- Jetreni (Fasciola hepatica, Fasciola gigantica, Clonorchis sinensis, Opistorchis viverini, Opistorchis felineus, Opistorchis guayaquilensis, Metorchis conjunctus, Dicrocoelium dendriticum)
- Intestinalni (Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai)
- Plućni (Paragonimus westermani)

FASCIOLA HEPATICA





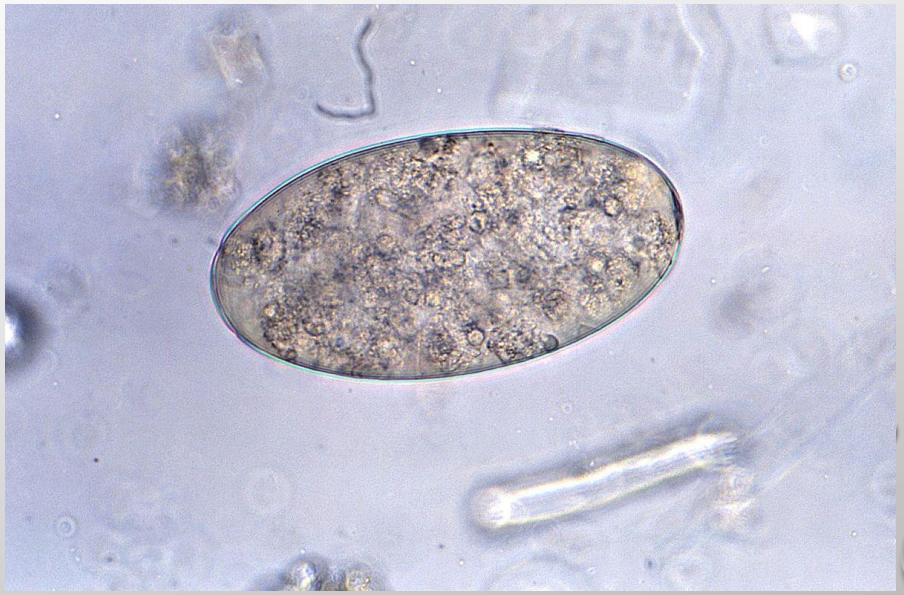
FASCIOLA HEPATICA

- Prevalenca 3 mil. ljudi
- Adult 3x1.5 cm, živi 10 ak godina
- Živi u žučnim vodovima
- Simptomi:

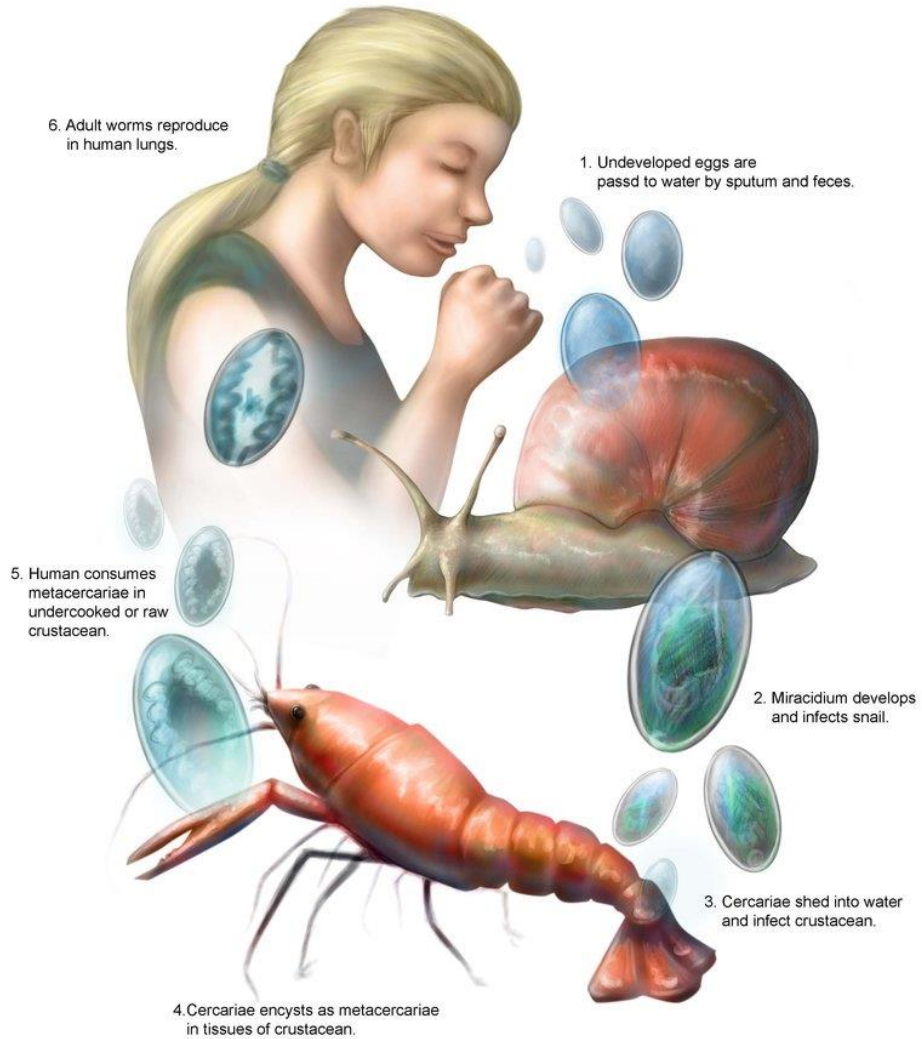
- Početni: eozinofilija, abdominalna bol, urtikarija, gubitak na težini, žutica, elevacija jetrenih enzima
- Kasna faza: simptomi kolecistitisa i kolangitisa, žutica, hepatomegalija
- Dijagnostika: nalaz jaja u stolici, serologija – EIA i WB
- Th: triklabendazol

FASCIOLOPSIS BUSKI

- Infekcija endemska na dalekom istoku, jugoistočnoj Aziji, južnoj Aziji
- Adult 2-7.5 cm
- Žive u duodenumu i jejunumu
- Metacerkarije vijabilne do 1. godinu na biljkama
- Bolest često asimptomatska, ponekad epigastrična bol i proljev, ileus i opstrukcija kod masivnih infekcija
- Dg: nalaz jaja ili adulta u stolici
- Th: prazikvantel



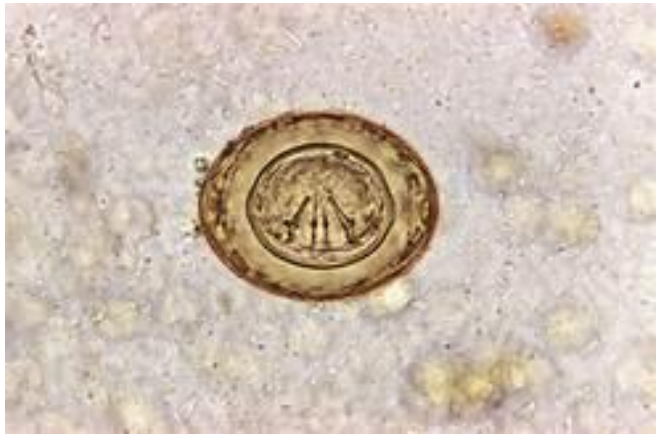
Life Cycle of *Paragonimus westermani*

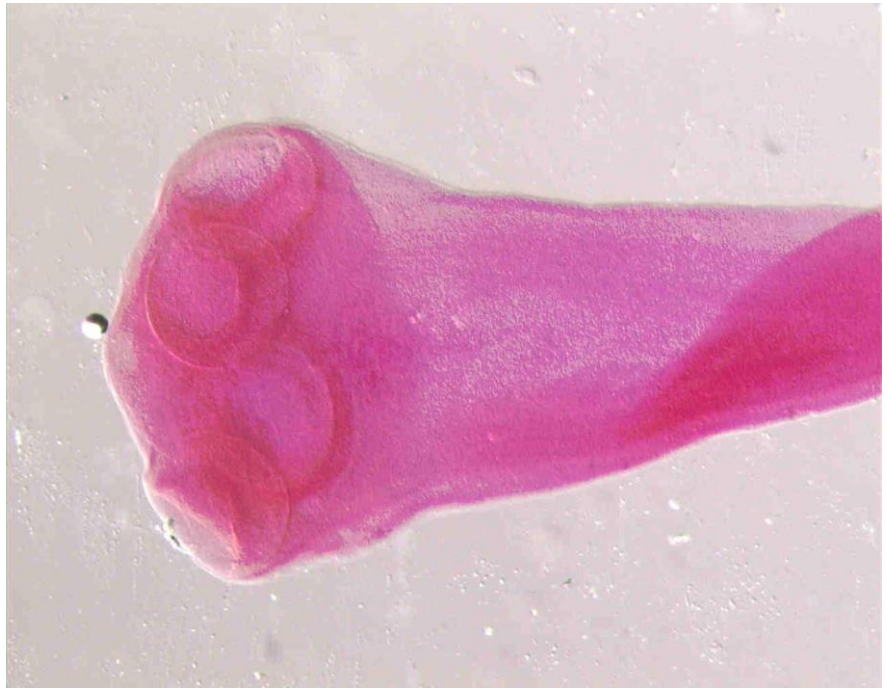


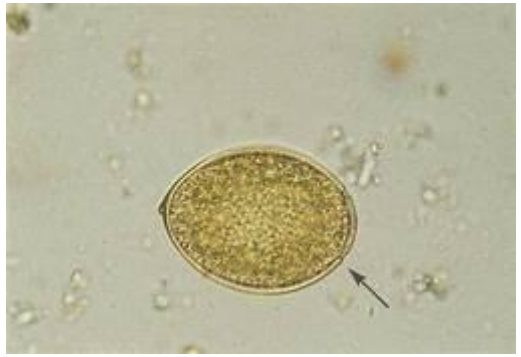
PARAGONIMUS

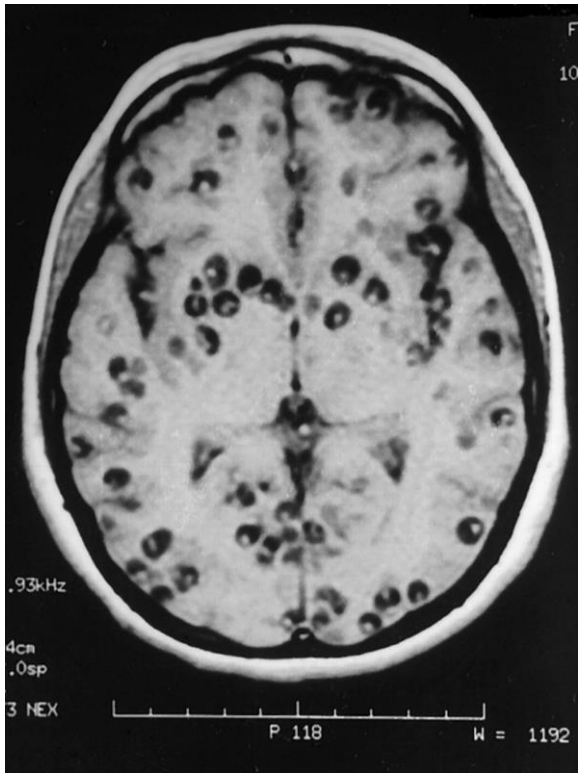
- Osam vrsta uzrokuje infekciju kod ljudi
- P. westermani - daleki istok – Koreja, Japan, Taiwan, Kina, Filipini
- Adulti 7 -16 mm žive inkapsulirani u cističnim šupljinama u plućima blizu bronhiola
- Adulti mogu živjeti 20-25 godina
- Ks: stadij invazije- bolovi u abdomenu, febrilitet, kašalj, urtikarija, eozinofilija
- Kronični stadij- kašalj s intermitentnom hemoptizom, bolovi u prsima, dispneja,
- Ekstrapulmonalni oblici – mozak, jetra, slezena, peritoneum, intraabdominalni limfni čvorovi
- Dijagnostika: nalaz jaja u sputumu, stolici, serologija
- Th: prazikvantel

TRAKAVICE - CESTODE



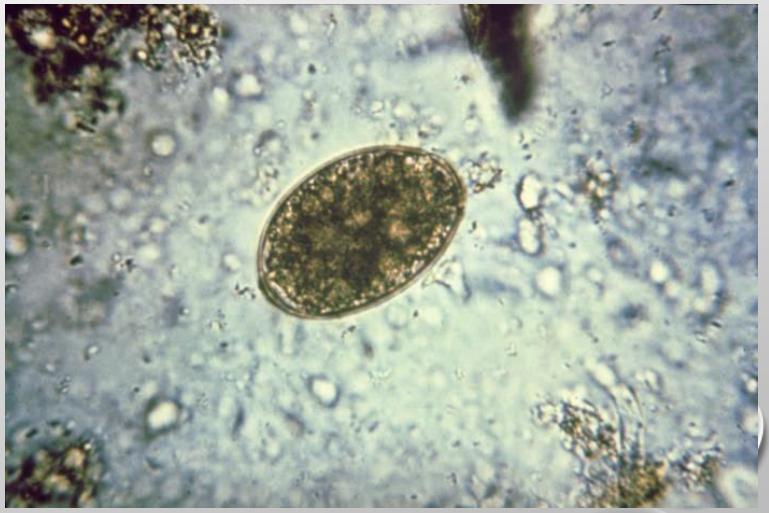






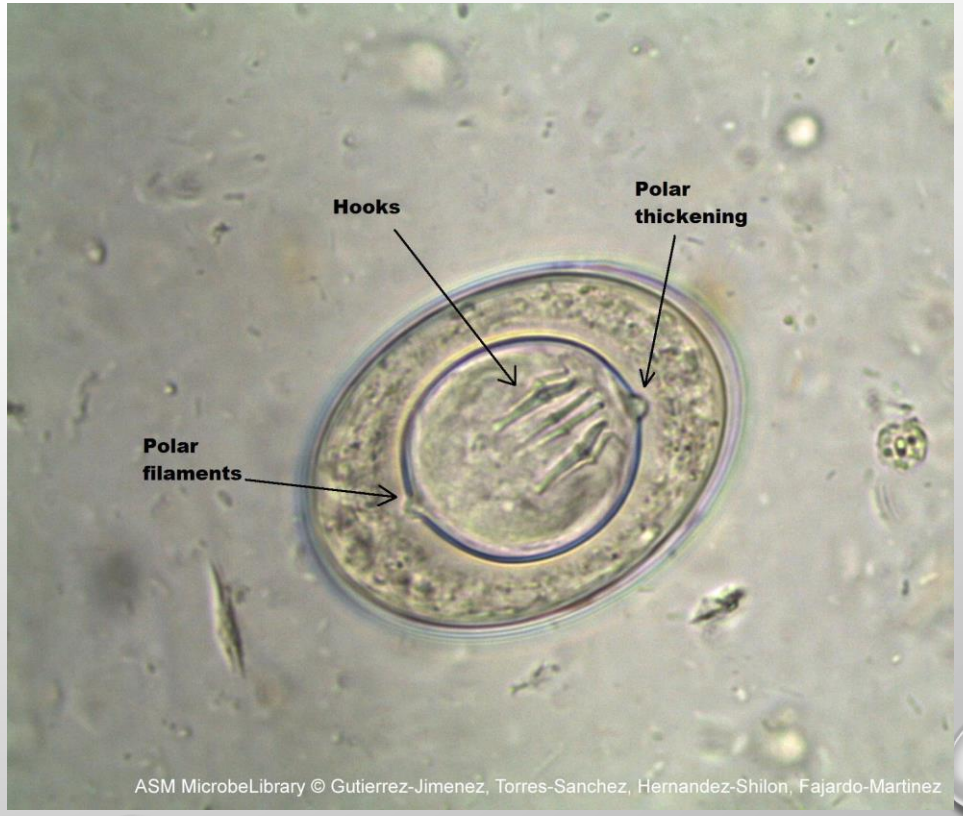
DIPHYLLOBOTHRIUM LATUM

- Riblja trakavica - jedenje ribe koja sadrži plerocerkoid trakavice
- Sushi, sashimi – losos (Sibir, Skandinavija, Baltičke zemlje), Sjeverna Amerika, Japan, Čile
- Zoonoza – konačni domaćini mogu biti tuljani, mačke, medvjedi, lisice, vukovi – održavanje ciklusa u prirodi
- Adult do 25 metara, dugovječna 30 godina i više
- Često asimptomatska, slabost, proljev, bolovi u trbuhu
- Megaloblastična anemija
- Dg: nalaz jaja u stolici
- Th: niklozamid, prazikvantel



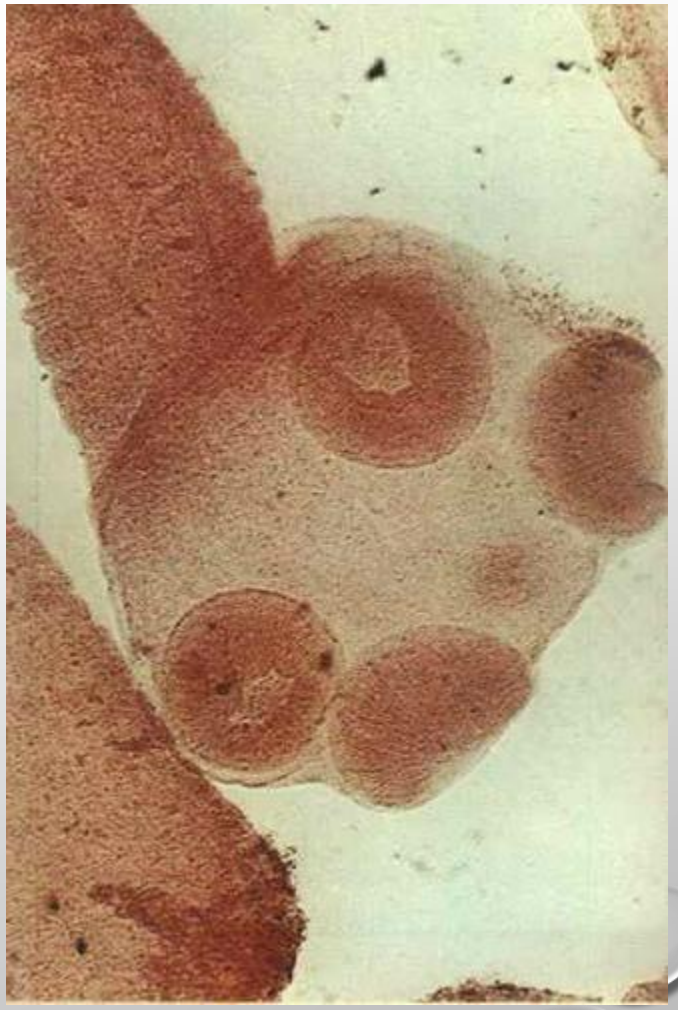
HYMENOLEPIS NANA

- Patuljasta trakavica
- Jedina trakavica koja se može širiti direktno sa čovjeka na čovjeka
- Globalna proširenost
- Autoinfekcija
- KS: abdominalni grčevi, anoreksija, proljev
- Dg: nalaz karakterističnih jaja u stolici
- Th: niklozamid, prazikvantel



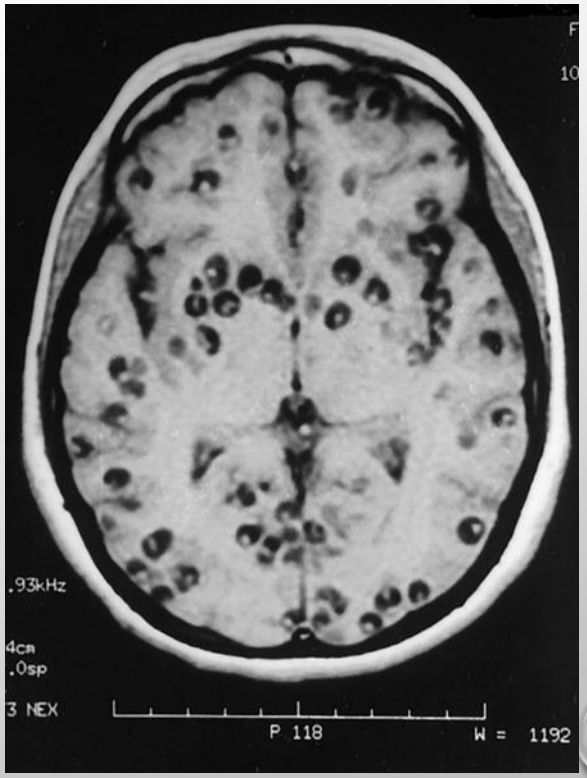
TAENIA SAGINATA

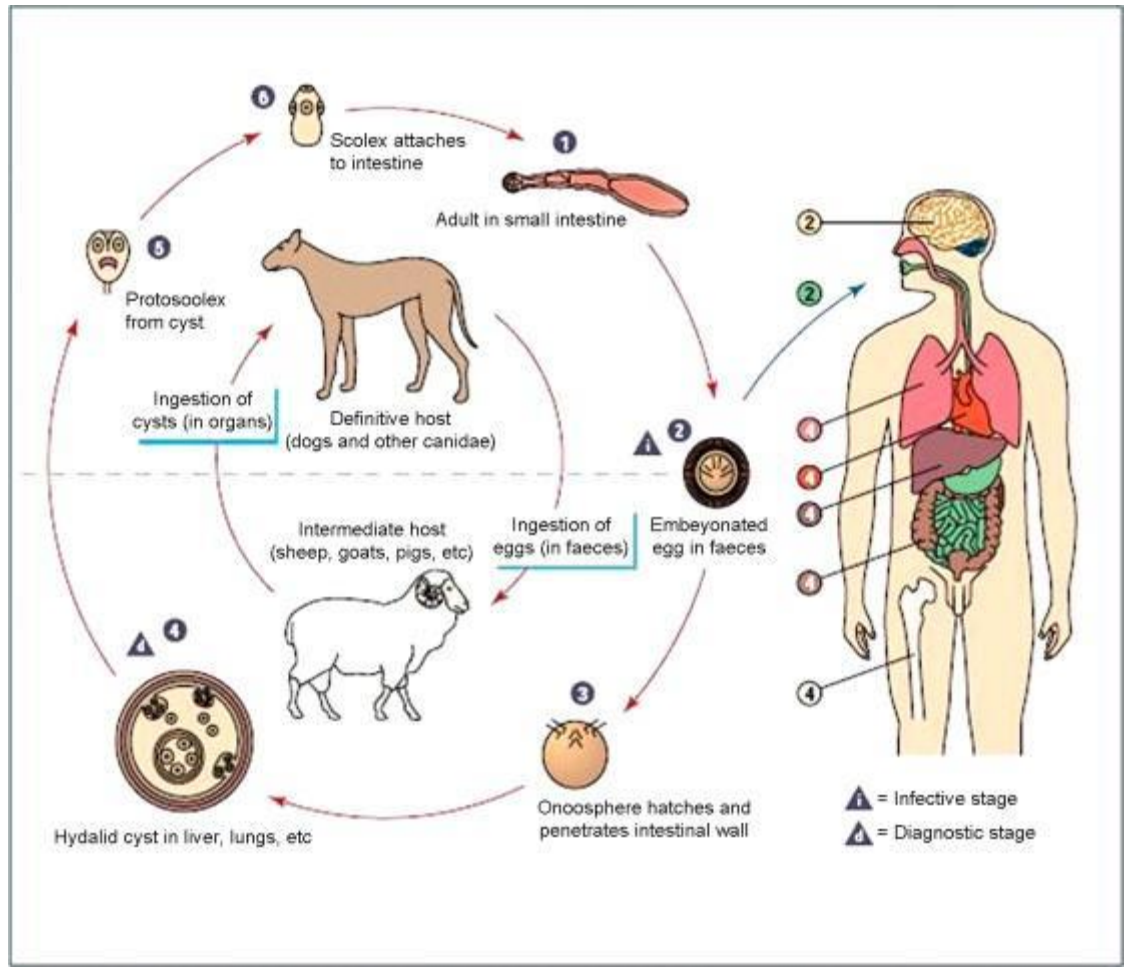
- Goveđa trakavica
- Infekcija putem goveđeg mesa koje sadrži ličinku
- Učestalost najveća u Centralnoj Aziji, Centralnoj i Istočnoj Africi
- Polusirov odrezak, kebab ili tatarski odrezak najčešći put za infekciju
- Veličina do 10 metara
- Većinom asimptomatska infekcija, ponekad bolovi u trbuhu i slabost
- Mobilne proglotide ponekad migriraju iz anusa ili vidljive u uzorku stolice
- DG: nalaz jaja ili proglotida u stolici
- Th: prazikvantel, niklozamid

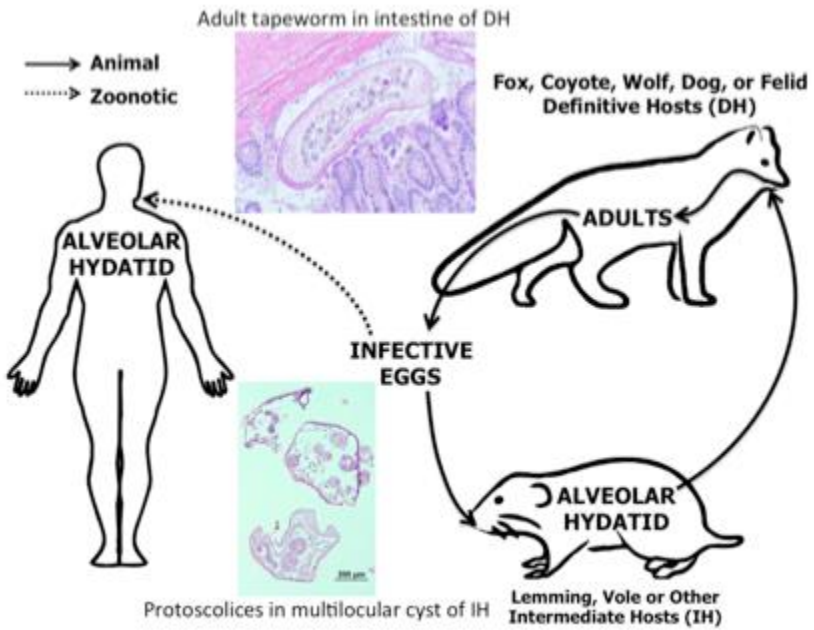


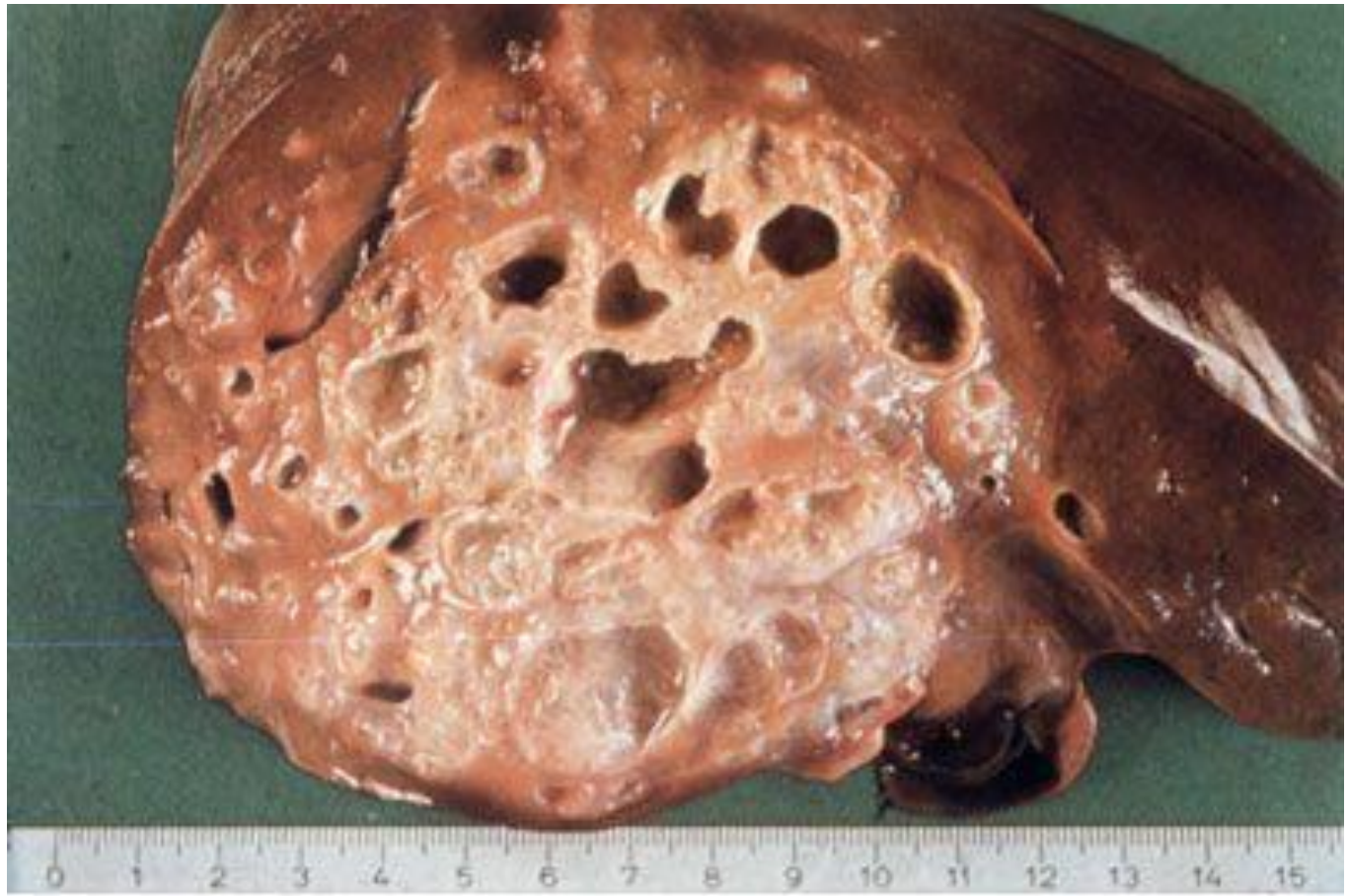
TENIA SOLIUM

- 2-8 metara, život do 20 godina
- Autoinfekcija
- Cisticerkoza
- Dg: nalaz jaja u stolici, serologija (ELISA, western blot)
- Detekcija antigena u serumu (cisticerkoza mozga)
- Th: prazikvantel, niklozamid




Scolex attaches to intestine
Adult in small intestine
Protoscolex from cyst
Definitive host (dogs and other canidae)
Ingestion of cysts (in organs)
Intermediate host (sheep, goats, pigs, etc)
Ingestion of eggs (in faeces)
Embeyonated egg in faeces
Hydalid cyst in liver, lungs, etc
Onoosphere hatches and penetrates intestinal wall
= Infective stage
= Diagnostic stage



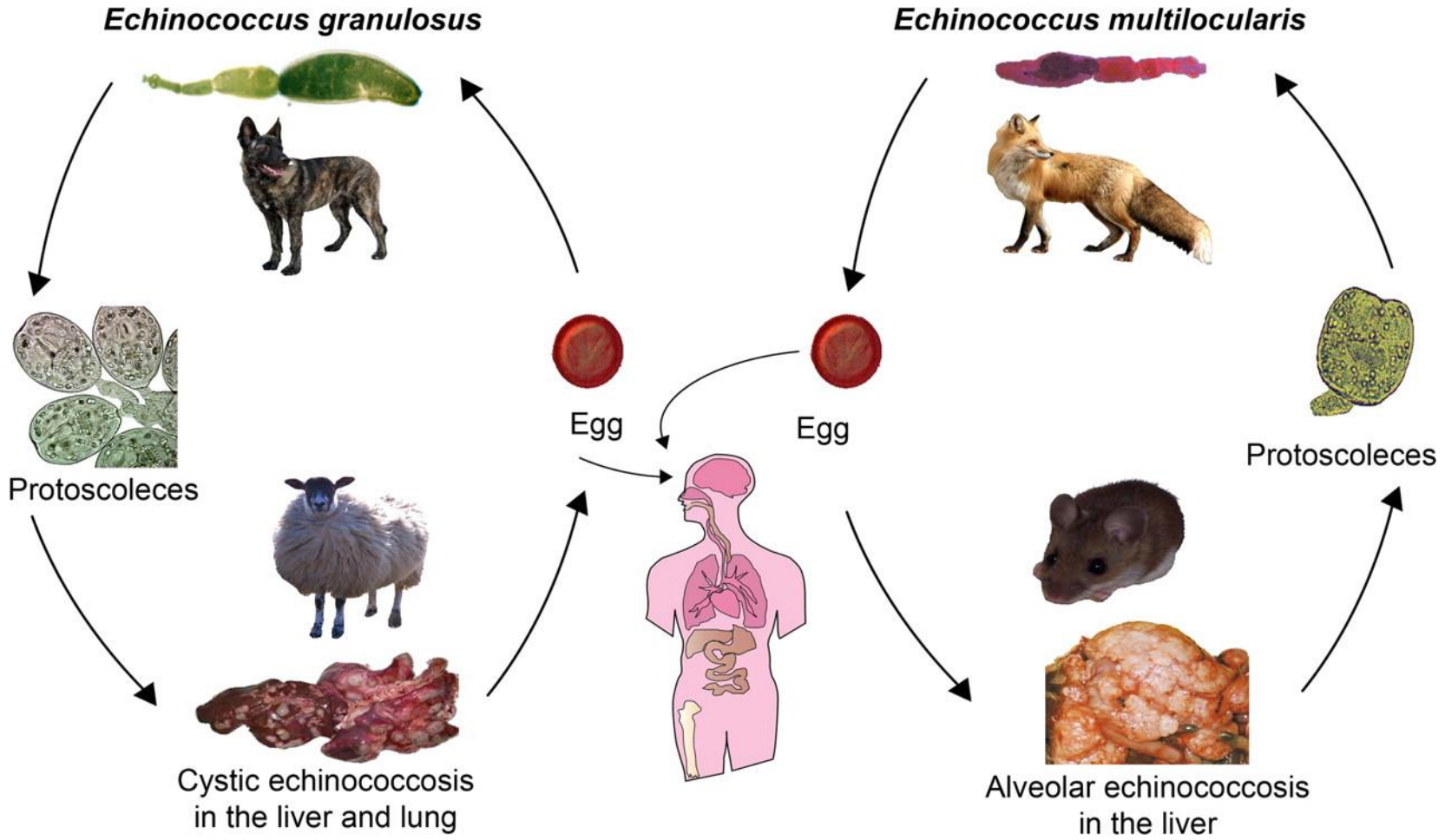


Human liver with *Echinococcus multilocularis* cyst

Pojava „lisičje trakavice“ – *Echinococcus multilocularis* infekcije u pacijenata u Hrvatskoj

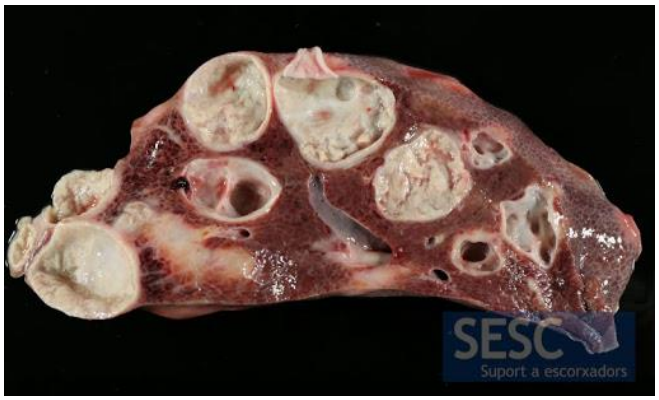
Izv. prof. dr. sc. Mirjana Balen Topić, dr. med.
Odjel za gastrointestinalne infekcije
Klinika za infektivne bolesti “Dr.Fran Mihaljević”

Životni ciklusi

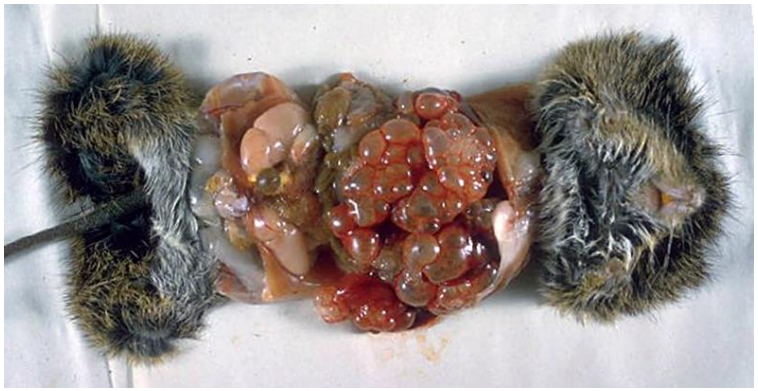


Karakteristike cisti u prijelaznom domaćinu

E. granulosus



E. multilocularis



Klasifikacija alveolarne ehinokokoze

Table 2. Staging of alveolar echinococcosis on the basis of PNM classification

Stage of AE	P	N	M
Stage I	P1	N0	M0
Stage II	P2	N0	M0
Stage IIIa	P3	N0	M0
Stage IIIb	P1–3	N1	M0
	P4	N0	M0
Stage IV	P4	N1	M0
	Any P	Any N	M1

P, dissemination of the parasite in the liver; N, involvement of the adjacent organs; M, distant metastasis.

PNM classification of alveolar echinococcosis

P	Hepatic localization of the parasite
PX	Primary tumor cannot be assessed
P0	No detectable tumor in the liver
P1	Peripheral lesions without proximal vascular and/or biliar involvement
P2	Central lesions with proximal vascular and or biliar involvement of 1 lobe*
P3	Central lesions with hilar vascular of biliar involvement of both lobes and/or with involvement of 2 hepatic veins
P4	Any liver lesion with extension along the vessels and the biliary tree¶
N	Extrahepatic involvement of neighboring organs (diaphragm, lung, pleura, pericardium, heart, gastric and duodenal wall, adrenal glands, peritoneum retroperitoneum, parietal wall [muscles, skin, bone], pancreas, regional lymph nodes, liver ligaments, kidney)
NX	Not evaluable
N0	No regional involvement
N1	Regional involvement of contiguous organs or tissues
M	The absence or presence of distant metastasis (lung, distant lymph nodes spleen, central nervous system, orbital, bone, skin, muscle, kidney, distant peritoneum, and retroperitoneum)
MX	Not completely evaluated
M0	No metastasis$^{\Delta}$
M1	Metastasis

PNM classification denotes the extension of the parasitic mass in the liver (P), involvement of neighboring organs (N), and metastases (M).

* For classification, the plane projecting between the bed of the gall bladder and the inferior vena cava divides the liver in two lobes.
¶ Vessels mean inferior vena cava, portal vein and arteries.
Δ Chest X-ray and cerebral computed tomography negative.

Reproduced from: Brunetti E, Kern K, Vuitton DA, Writing Panel for the WHO-IWGE. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Tropica 2009; 114:1. Table used with the permission of Elsevier Inc. All rights reserved.

Najčešće komplikacije

Experience of liver transplantation for incurable alveolar echinococcosis: a 45-case European collaborative report.

Koch S [1], Bresson-Hadni S , Miguet JP , Crumbach JP , Gillet M , Mantion GA , Heyd B , Vuitton DA , Minello A , Kurtz S , European Collaborating Clinicians

Life-threatening hepatobiliary complications of AE include biliary stricture and recurrent cholangitis from hilar invasion, secondary biliary cirrhosis, gastrointestinal bleeding from portal hypertension, liver abscess, acute inferior vena cava thrombosis, and Budd-Chiari syndrome.

Transplantation, 01 Mar 2003, 75(6):856-863
https://doi.org/10.1097/01.tp.0000054230.63568.79

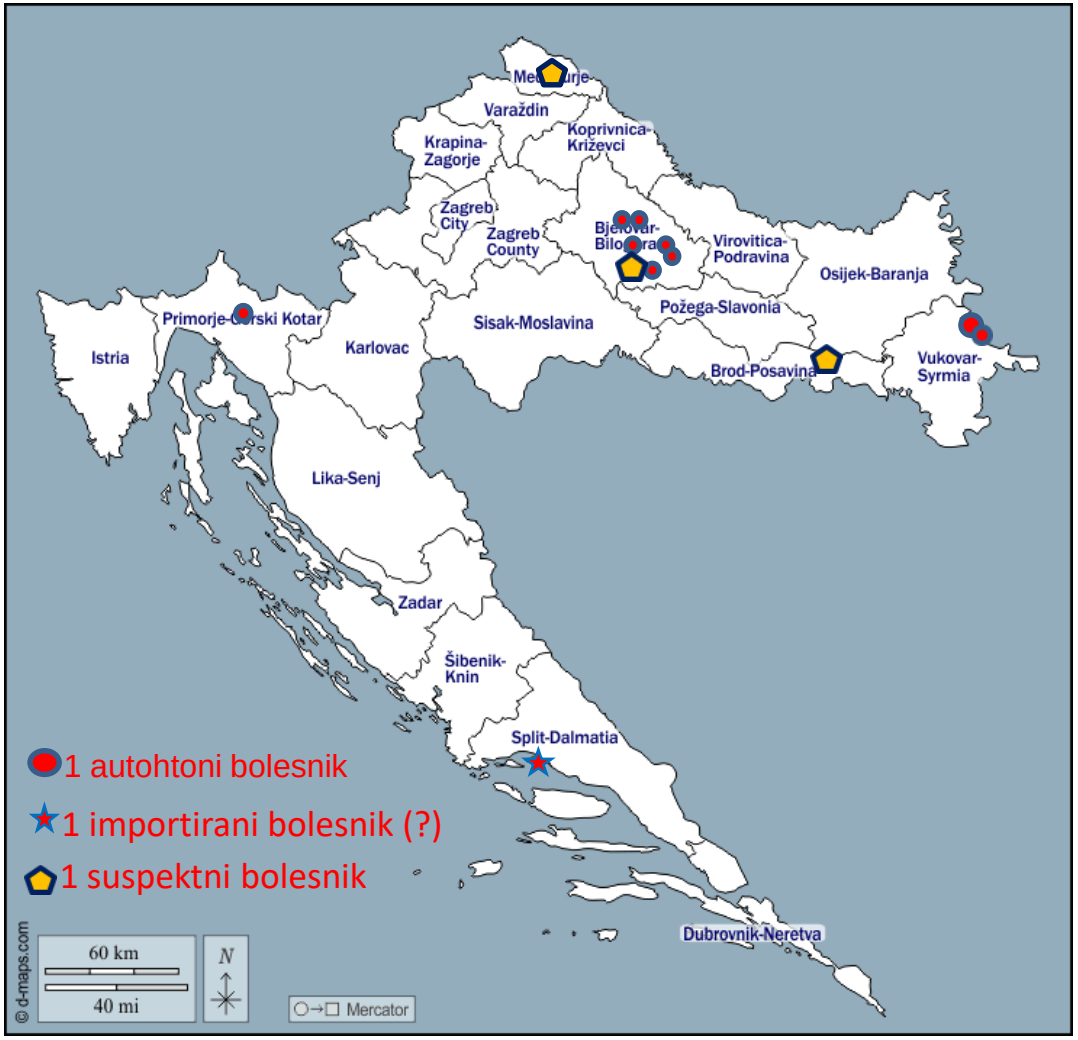
Liječenje alveolarne ehinokokoze

Stage-specific treatment approach to alveolar echinococcosis

WHO Classification	Surgery	Interventional treatment	Drug therapy	Suggested	Resources setting
P1N0M0	X		X	Radical resection (R0) BMZ for 2 years PET/CT controls	Optimal
				Radical resection (R0) BMZ for 3 months	Minimal
P2N0M0	X		X	Radical resection (R0) BMZ for 2 years	Optimal
				Radical resection (R0) BMZ for 3 months	Minimal
P3N0M0			X	BMZ continuously PET/CT/MRI scan initially and in 2 years intervals	Optimal
				BMZ continuously	Minimal
P3N1M0		X	X	BMZ continuously plus PET/CT/MRI scan initially and in 2 years intervals	Optimal
				Surgery, if indicated	Minimal
P4N0M0		X	X	BMZ continuously plus PET/CT/MRI scan initially and in 2 years intervals	Optimal
				Surgery, if indicated	Minimal
P4N1M1		X	X	BMZ continuously plus PET/CT/MRI scan initially and in 2 years intervals	Optimal
				Surgery, if indicated	Minimal

R0: no residue following resection; BMZ: benzimidazoles; PET: positron emission tomography; CT: computed tomography; MRI: magnetic resonance imaging.

Distribucija AE u ljudi u Hrvatskoj



10 bolesnika s dokazanom AE:

Spol:
5 Ž + 5 M

Dob:
34 – 73 g.
(medijan 64 g.)

Rizik:
- Vrt blizu šume: 8
(+ 1 lovac
+ 1 drvosječa)
- branje šumskog voća
- šetnje u šumi u Bavarskoj

Pacijent 1 (2017): M, 63 g.

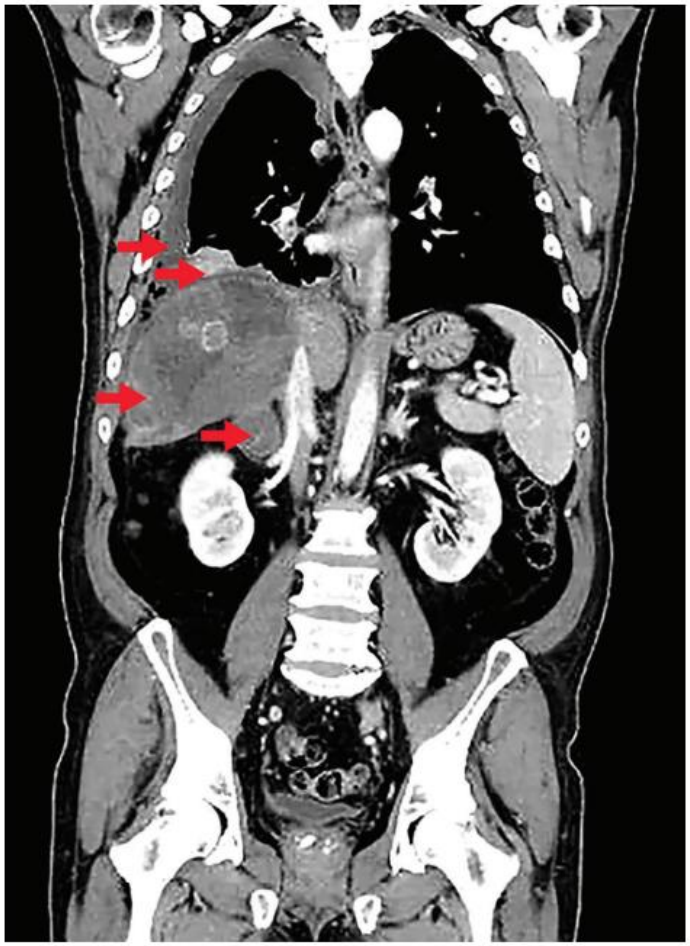
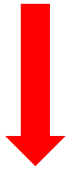


Figure. Computed tomography scan of a patient diagnosed with alveolar echinococcosis, Croatia. Arrows indicate right pleural effusion, lung lesions, an enlarged right adrenal gland, and a 13 × 12 × 12 cm lesion in the liver caused by *Echinococcus multilocaris*.

Zaključno....

- Od 2017 broj bolesnika s autohtonom AE u RH raste



- Provesti dijagnostiku za AE (serologija...) u osoba iz endemskih područja s fokalnim lezijama jetre
- Edukacija liječnika / interdisciplinarni pristup (infektolog, radiolog, gastroenterolog, kirurg...)
- Prijavljivanje bolesti!!!

NASTAVNI ZAVOD ZA JAVNO ZDRAVSTVO DR. ANDRIJA ŠTAMPAR

Stvaramo zdraviju budućnost

Mikrobiološki nadzor hrane i alimentarne toksikoinfekcije

DR.SC.IVANČICA KOVAČEK, DR.MED. SPEC. MED. MIKROB. S PARASIT.

Sadržaj predavanja

- EU Direktiva 2073/05, HACCP sustav
- Vodič za mikrobiološke kriterije za hranu
- Kako mikrobiološka struka može pomoći proizvođaču hrane
- Novi izazovi

Hrana

- Neophodna potreba svih živih bića
- Nije sterilna
- Moramo vjerovati da je sigurna

Kako smo to radili prije?

- Pravilnik o mikrobiološkim kriterijima za hranu
- Zakon o hrani

Zašto nam treba Vodič za mikrobiološke kriterije za hranu?

Subjekti u poslovanju s hranom provode, prema potrebi, sljedeće posebne mjere:

- poštivanje mikrobioloških kriterija za hranu
- postupke potrebne za postizanje ciljeva određenih ovim zakonskom regulativom
- udovoljavanje zahtjevima o praćenju temperature za hranu
- održavanje hladnog lanca
- uzorkovanje i analize.

Obaveze subjekata u poslovanju s hranom

- U svakoj fazi proizvodnje, prerade i distribucije treba poduzimati mjere – kao dio svojih postupaka temeljenih na načelima sustava analize opasnosti i kritičnih kontrolnih točaka (HACCP) zajedno s provedbom dobre higijenske prakse
- Subjekti u poslovanju s hranom provode, prema potrebi, sljedeće posebne higijenske mjere:

➢ poštivanje mikrobioloških kriterija za hranu

➢ postupke potrebne za postizanje ciljeva određenih zakonskom regulativom

➢ udovoljavanje zahtjevima o praćenju temperature za hranu

➢ održavanje hladnog lanca

➢ uzorkovanje i analize.

- Svaki subjekt u poslovanju s hranom mora moći pokazati da su njegovi proizvodi usklađeni s mikrobiološkim kriterijima
    - Uspostaviti vlastiti kontrolni program obzirom na mikrobiološke kriterije – ako dođe do odstupanja u kriterijima procesa moguće je poduzeti korektivne mjere

PROCES ANALIZE OPASNOSTI I KRITIČNIH KONTROLNIH TOČAKA U PROIZVODNJI KOJE OBUHVAĆAJU CIJELI NIZ PREVENTIVNIH POSTUPAKA ZA KOJI IMAJU KRAJNJI CILJ OSIGURATI ZDRAVSTVENO ISPRAVNU HRANU

SUSTAV SAMOKONTROLE, ALI I SUSTAV KVALITETE KOJIM OSIGURAVAMO NEŠKODLJIVOST HRANE

HACCP

PREDUVJETNI PROGRAMI ZA USPJEŠNO FUNKCIONIRANJE HACCP SUSTAVA

- Preduvjetni programi predstavljaju opće aktivnosti koje utječu na zdravstvenu ispravnost hrane, a sastoje se od:
  - dobre higijenske prakse (GHP)
  - dobre proizvođačke prakse (GMP)
  - standardnih operativnih postupaka (SOP)
  - sanitacijskih standardnih operativnih postupaka (SSOP)
  - **PRP + HACCP – sustav zdravstveno ispravna hrana**

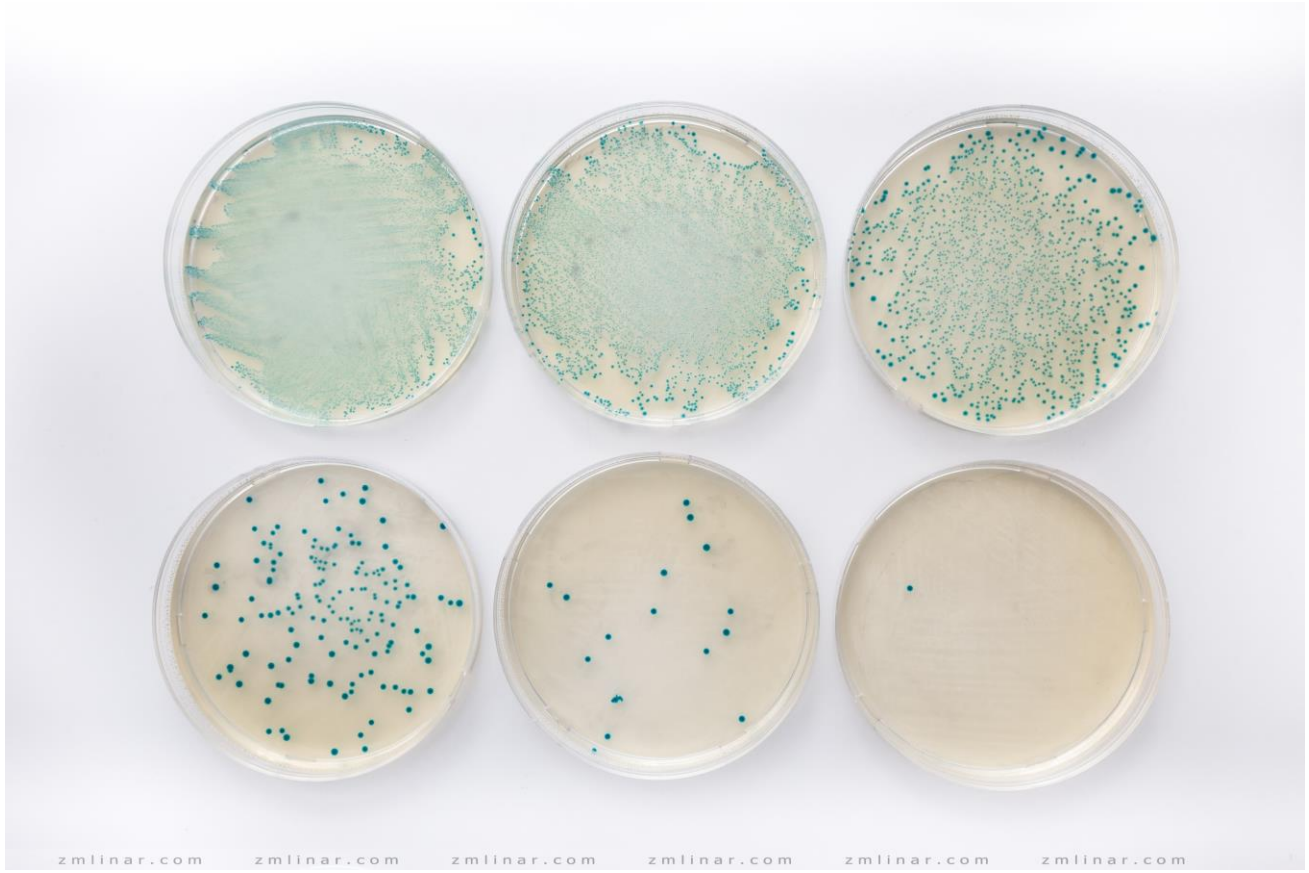
Dobra higijenska praksa (GHP)

- pravila ponašanja radnika
- nošenje zaštitne opreme
- nošenje posebne odjeće
- zaštita kose
- zabrana upotrebe kozmetičkih sredstava
- prikladnost prostorija za pušenje i jelo
- postupci pranja i dezinfekcije
  - Sredstva za čišćenje i dezinfekciju
    - ne smiju se skladištiti u prostorijama u kojima se rukuje hranom
    - moraju se skladištiti pod nadzorom

Dobra proizvođačka praksa (GMP)

- minimalni zahtjevi za kontrolu procesa i sanitaciju u proizvodnji hrane
  - prikladna oprema i materijal opreme
  - lokacija zgrade
  - kontrola štetnika
  - okoliš proizvodnje
  - logistika procesa

Kakvu hranu želimo?



Novi izazovi: *Listeria*

- Danas je dovoljno u neku tražilicu upisati pojam bakterija listeria i odmah na prvoj stranici možemo pročitati naslove kao „ infekcija koja vreba iz hrane”, „opasna bakterija odnosi živote u ...”, ili „zbog opasne bakterije povlači se proizvod s hrvatskog tržišta”

- Prvo službeno trovanje– krajem 20 stoljeća (1980.) potvrđeno da se ova bakterija prenosi hranom
  - trovanje kupusom – gnojenim organiskim gnojem (ovca)
    - umrlo je 18 Kanađana, potvrđeno je da *Listeria* ulazi u naš organizam putem hrane

Novi izazovi: EHEC

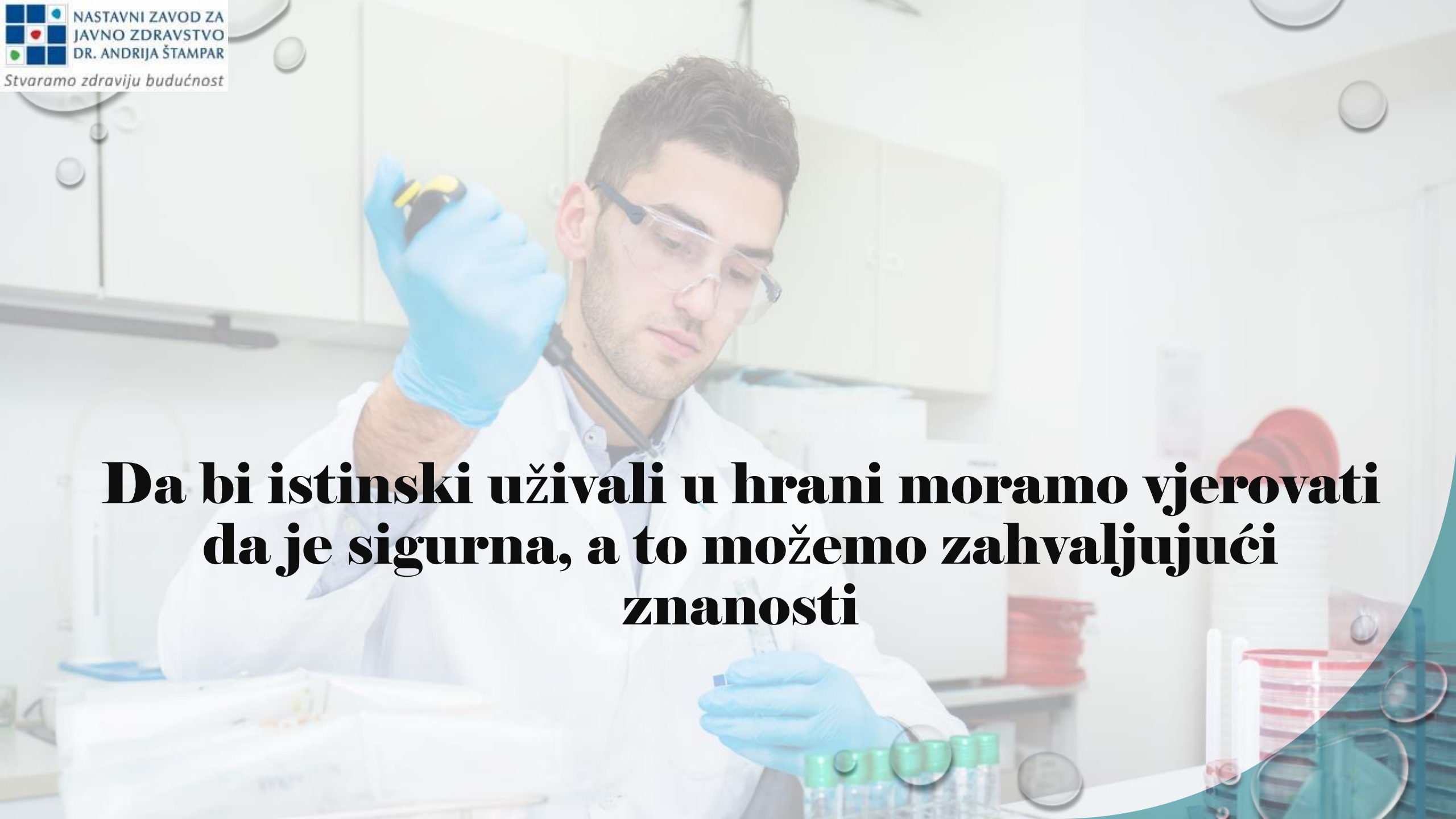
- u razvijenim zemljama
- veoma niska infektivna doza (manje od 100 bakterija), tako da se preko kontaminirane namirnice može prenositi i putem zaraženih osoba dodirom
- može preživjeti temperature od 7 do 50 ° C, uz optimalnu temperaturu od 37 ° C
- raste u kiseloj hrani kod pH 4,4 i hrani s minimalnim udjelom vode (aw) preko 0,95
- ovaj patogen može biti uništen kroz termičku obradu hrane na temperaturama preko 70 ° C
- EHEC zaraze prenose se fekalno-oralnim putem
- uzrokuje krvavi proljev (hemoragični kolitis), ne-krvavi proljev i hemolitičko uremički sindrom: očituje se trombocitopenijom, hemolitičkom anemijom i zatajenjem bubrega
- glavni rezervoar EHEC je goveđi probavni trakt, a prve epidemije su bile povezane s konzumacijom nedovoljno termički obrađenih hamburgera
- širok izbor namirnica povezuje s bolestima kojima je uzročnik ovaj patogen, uključujući i kobasice, nepasterizirano mlijeko, salatu, dinju, sok od jabuke i rotkvice
- rotkvice su bile odgovorne za izbijanje 8.000 slučajeva zaraze u Japanu

ZAKLJUČAK

- Mikrobiološki nadzor hrane je neophodan
- Potreba kontrole procesa proizvodnje hrane
- Potreba edukacije proizvođača hrane
- Potrošači također trebaju biti svjesni svoje odgovornosti
- Upoznavanje liječnika s novim izazovima

NASTAVNI ZAVOD ZA JAVNO ZDRAVSTVO DR. ANDRIJA ŠTAMPAR

Stvaramo zdraviju budućnost



Da bi istinski uživali u hrani moramo vjerovati da je sigurna, a to možemo zahvaljujući znanosti

Antimikrobna rezistencija crijevnih patogena

Silvija Šoprek Strugar, spec.mikrobiolog
Klinika za infektivne bolesti „Dr. Fran Mihaljević”

Infekcije probavnog sustava: novosti u epidemiologiji, kliničkoj slici, dijagnosici, terapiji i prevenciji, 17.svibnja 2024, Zagreb

HRVATSKA AKADEMIJA MEDICINSKIH ZNANOSTI
KOLEGIJ JAVNOG ZDRAVSTVA
ODBOR ZA PRAĆENJE REZISTENCIJE BAKTERIJA NA ANTIBIOTIKE U REPUBLICI HRVATSKOJ
CROATIAN ACADEMY OF MEDICAL SCIENCES
PUBLIC HEALTH COLLEGIUM
COMMITTEE FOR ANTIBIOTIC RESISTANCE SURVEILLANCE IN CROATIA

KLINIKA ZA INFEKTIVNE BOLESTI "DR. FRAN MIHALJEVIĆ"
REFERENTNI CENTAR ZA PRAĆENJE REZISTENCIJE BAKTERIJA NA ANTIBIOTIKE MINISTARSTVA ZDRAVSTVA
UNIVERSITY HOSPITAL FOR INFECTIOUS DISEASES "DR. FRAN MIHALJEVIĆ"
REFERENCE CENTER FOR ANTIBIOTIC RESISTANCE SURVEILLANCE
CROATIAN MINISTRY OF HEALTH

HRVATSKO DRUŠTVO ZA KLINIČKU MIKROBIOLOGIJU
HRVATSKOG LIJEČNIČKOG ZBORA
SEKCIJA ZA REZISTENCIJU NA ANTIBIOTIKE
CROATIAN SOCIETY FOR CLINICAL MICROBIOLOGY
OF THE CROATIAN MEDICAL ASSOCIATION
SECTION FOR ANTIBIOTIC RESISTANCE

Osjetljivost i rezistencija bakterija na antibiotike u Republici Hrvatskoj u 2022.g.

Izdavač
HRVATSKA AKADEMIJA MEDICINSKIH ZNANOSTI

Antibiotic resistance in Croatia, 2022

Published by
The Croatian Academy of Medical Sciences

SCIENTIFIC REPORT

APPROVED: 31 January 2023

doi: 10.2903/j.efsa.2023.7867

The European Union Summary Report on Antimicrobial Resistance in zoonotic and indicator bacteria from humans, animals and food in 2020/2021

European Food Safety Authority (EFSA) and
European Centre for Disease Prevention and Control (ECDC)

Campylobacter spp.

ecdc efsa JOURNAL

Section B.1. Antimicrobial resistance in *Campylobacter* spp. from humans

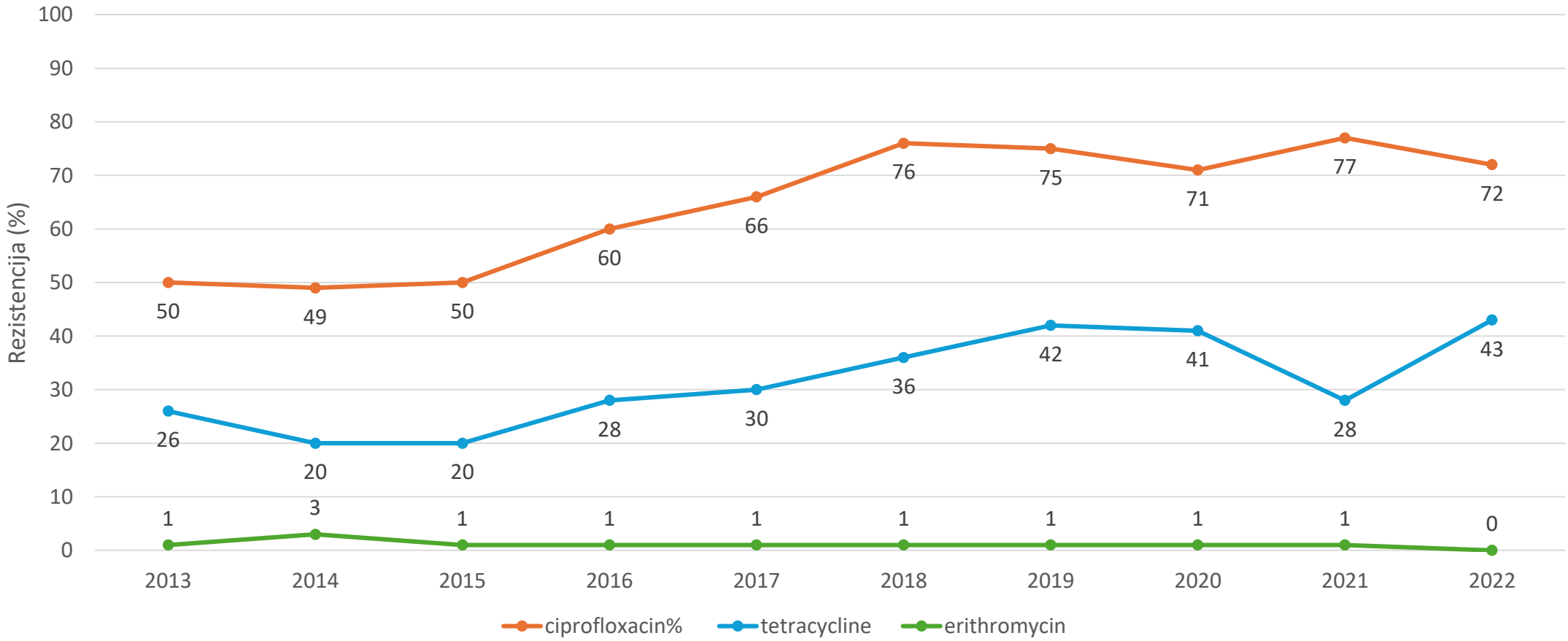
Table 1: Antimicrobial resistance in *Campylobacter jejuni* from humans per country in 2021

Country	Gentamicin		Coamoxiclav		Ciprofloxacin		Erythromycin		Tetracycline	
	N	% Res	N	% Res	N	% Res	N	% Res	N	% Res
Austria	419	0	-	-	419	85.2	419	0	419	59.2
Bulgaria	4	NA	-	-	20	75.0	19	0	20	40.0
Cyprus	-	-	-	-	25	84	25	0	25	76.0
Denmark	285	0	-	-	285	49.1	285	0	285	27.0
Estonia	184	0	-	-	184	85.9	184	0.5	184	54.9
Finland	-	-	-	-	991	37.1	997	0.6	412	11.2
France	5,842	0.3	6,802	0.2	6,807	61	6,797	0.4	6,792	46.5
Germany	1,295	0.2	1311	41.9	1312	66.6	1302	2.2	1312	46.5
Hungary	-	-	-	-	415	88.9	414	0.2	414	51.5
Ireland	-	-	-	-	174	27.6	184	0.5	184	17.4
Italy	105	0	-	-	105	75.2	105	0	105	57.1
Lithuania	-	-	-	-	206	92.2	206	1.9	97	48.5
Luxembourg	187	0	187	0	187	64.7	187	0.5	187	43.3
Malta	3	NA	3	NA	200	79	200	0	4	NA
Netherlands	-	-	-	-	1,311	55.2	1,297	1.9	1,162	40.7
Poland	14	0	1	0	30	100	72	0	30	60
Portugal	278	0.4	-	-	278	92.5	278	5.4	278	77.3
Romania	2	NA	2	NA	2	NA	2	NA	2	NA
Slovakia	3	NA	193	1	1115	74.7	1104	0.1	922	38
Slovenia	-	-	-	-	797	81.1	797	0.4	797	46.4
Spain	436	9.6	27	3.7	450	86.9	458	14.2	459	72.6
Sweden	244	0	-	-	244	44.3	244	0	244	13.5
Total (22	9.301	0.7	8526	6.6	15.557	64.5	15.576	1.1	14.334	45.3

Table 2: Antimicrobial resistance in *Campylobacter coli* from humans per country in 2021

Country	Gentamicin		Co-amoxiclav		Ciprofloxacin		Erythromycin		Tetracycline	
	N	% Res	N	% Res	N	% Res	N	% Res	N	% Res
Austria	49	0	-	-	49	75.5	49	2	49	44.9
Cyprus	-	-	-	-	7	NA	7	NA	7	NA
Denmark	14	0	-	-	14	50.0	14	14.3	14	50
Estonia	27	0	-	-	27	100	27	25.9	27	77.8
Finland	-	-	-	-	35	82.9	33	24.2	19	42.1
France	897	0.6	996	0.8	998	60.3	997	7.5	995	76.7
Germany	234	6	234	44	234	70.9	233	6.	234	72.2
Hungary	-	-	-	-	137	83.9	137	0.7	137	48.9
Ireland	-	-	-	-	18	22.2	18	0	18	16.7
Italy	34	2.9	-	-	34	79.4	34	23.5	34	64.7
Lithuania	-	-	-	-	11	72.7	11	9.1	5	NA
Luxembourg	21	0	21	28.6	21	61.9	21	14.3	21	57.1
Malta	1	NA	1	NA	44	77.3	44	2.3	1	NA
Netherlands	-	-	-	-	92	71.7	91	5.5	83	66.3
Poland	1	NA	-	-	1	NA	4	NA	1	NA
Portugal	47	2.13	-	-	47	100	47	55.3	47	100
Slovakia	-	-	27	3.7	125	72.8	123	2.4	105	41.9
Slovenia	-	-	-	-	57	86.0	57	0	57	52.6
Spain	109	11.9	4	NA	109	93.6	112	17.0	112	91.1
Sweden	6	NA	-	-	6	NA	6	NA	6	NA
Total (20 MSs)	1440	2.4	1283	9.2	2066	69.6	2065	12.6	1972	60.6

C. jejuni rezistencija u HR (%)



C. coli rezistencija u HR (%)

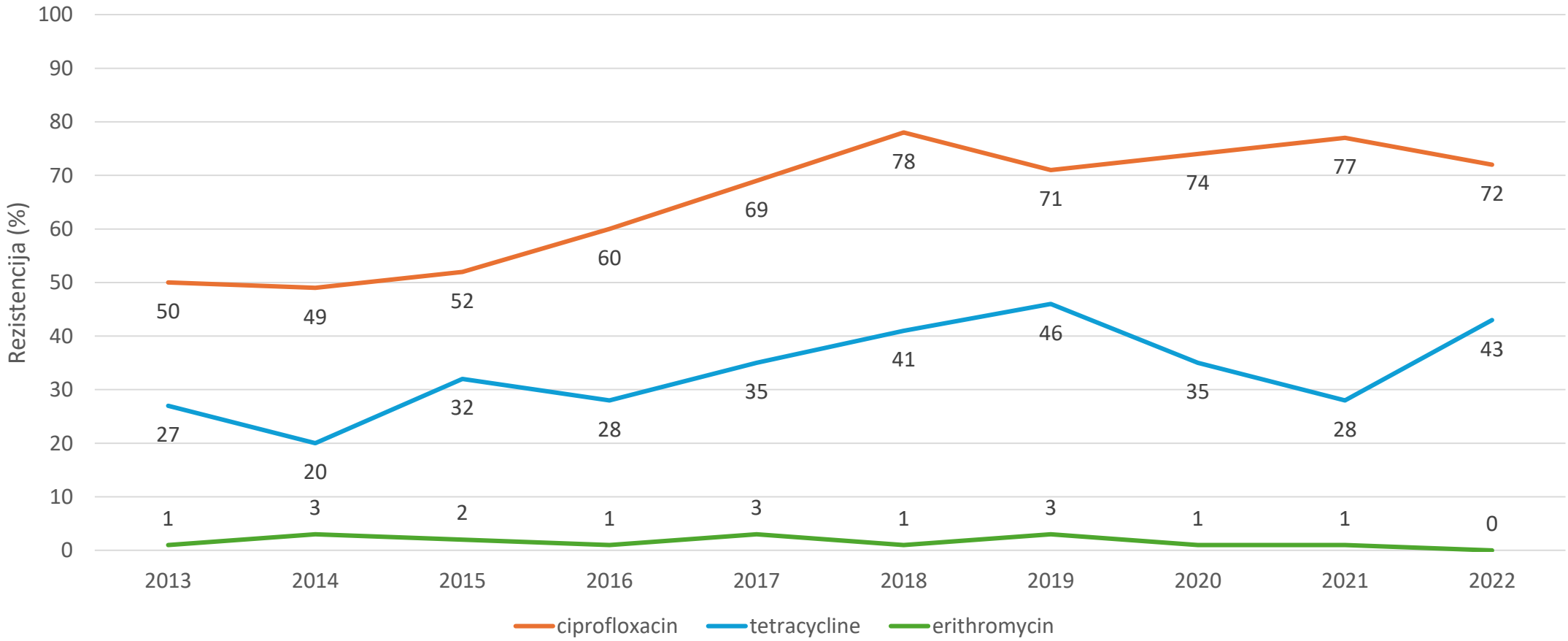


Table 2: Antimicrobial resistance in *Campylobacter coli* from humans per country in 2021

Country	Gentamicin		Co-amoxiclav		Ciprofloxacin		Erythromycin		Tetracycline	
	N	% Res	N	% Res	N	% Res	N	% Res	N	% Res
Austria	49	0	-	-	49	75.5	49	2	49	44.9
Cyprus	-	-	-	-	7	NA	7	NA	7	NA
Denmark	14	0	-	-	14	50.0	14	14.3	14	50
Estonia	27	0	-	-	27	100	27	25.9	27	77.8
Finland	-	-	-	-	35	82.9	33	24.2	19	42.1
France	897	0.6	996	0.8	998	60.3	997	7.5	995	76.7
Germany	234	6	234	44	234	70.9	233	6.	234	72.2
Hungary	-	-	-	-	137	83.9	137	0.7	137	48.9
Ireland	-	-	-	-	18	22.2	18	0	18	16.7
Italy	34	2.9	-	-	34	79.4	34	23.5	34	64.7
Lithuania	-	-	-	-	11	72.7	11	9.1	5	NA
Luxembourg	21	0	21	28.6	21	61.9	21	14.3	21	57.1
Malta	1	NA	1	NA	44	77.3	44	2.3	1	NA
Netherlands	-	-	-	-	92	71.7	91	5.5	83	66.3
Poland	1	NA	-	-	1	NA	4	NA	1	NA
Portugal	47	2.13	-	-	47	100	47	55.3	47	100
Slovakia	-	-	27	3.7	125	72.8	123	2.4	105	41.9
Slovenia	-	-	-	-	57	86.0	57	0	57	52.6
Spain	109	11.9	4	NA	109	93.6	112	17.0	112	91.1
Sweden	6	NA	-	-	6	NA	6	NA	6	NA
Total (20 MSs)	1440	2.4	1283	9.2	2066	69.6	2065	12.6	1972	60.6
Iceland	-	-	-	-	1	NA	1	NA	-	-
Norway	3	NA	-	-	3	NA	3	NA	3	NA

N: number of isolates tested; % Res: percentage of resistant isolates; –: no data reported; NA: not applicable – if fewer than 10 isolates were tested in an individual member state; MSs: Member States.

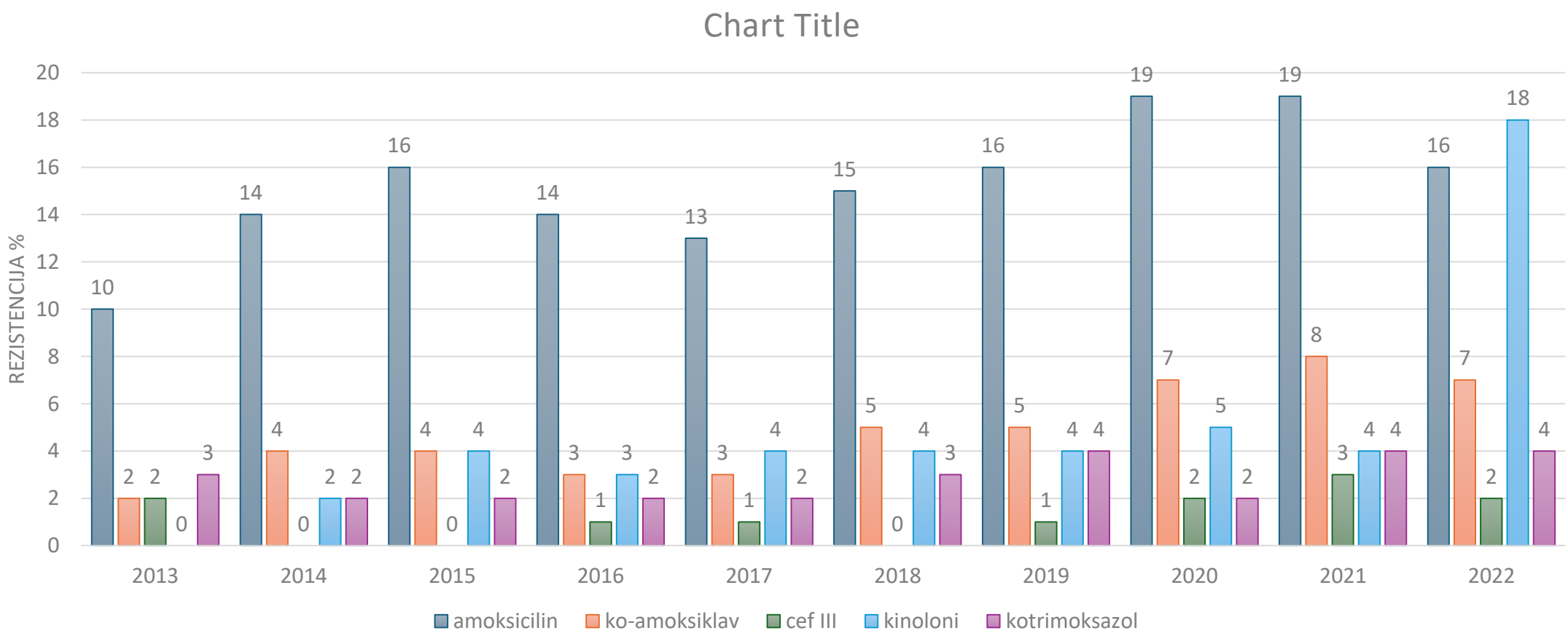
Salmonella spp.

A.1. Antimicrobial resistance in *Salmonella* spp. from humans

Table 1: Antimicrobial resistance in *Salmonella* spp. (all non-typhoidal serovars) from humans per country in 2021

Country	Gentamicin		Chloramphenicol		Ampicillin		Cefotaxime		Ceftazidime		Meropenem		Tigecycline	
	N	% Res	N	% Res	N	% Res	N	% Res	N	% Res	N	% Res	N	%
Austria	1,052	0.5	1,052	1.7	1,052	12.3	1,052	0.4	1,052	0.3	1,052	0	1,052	0
Belgium	747	1.1	747	6.3	747	42.6	747	0.3	-	-	747	0	-	-
Bulgaria	2	NA	-	-	1	NA	-	-	2	NA	1	NA	-	-
Cyprus	75	6.7	-	-	75	20.0	31	0	75	0	75	0	-	-
Denmark	343	0.6	343	3.8	343	20.4	343	0.3	343	0.3	343	0	343	2.6
Estonia	130	0	130	2.3	130	35.4	130	0	130	0	130	0	130	0
Finland	167	1.2	167	18.6	167	26.9	167	1.8	-	-	167	0	-	-
France	832	1.4	833	5.3	833	20.2	833	0.8	833	0.5	833	0	833	3.4
Germany	2,986	1.1	2,986	5.0	2,985	26.2	2,981	1.1	2,981	0.9	2,979	0	-	-
Greece	249	0.4	249	1.6	249	4.0	249	0.4	249	0.4	248	0	-	-
Hungary[a]	533	1.5	534	15.4	534	47.9	534	3.4	534	5.1	531	0	-	-
Italy	693	3.6	692	7.2	692	44.7	693	4.8	693	4.5	693	0	532	0.2
Latvia[a]	-	-	-	-	8	NA	-	-	-	-	-	-	-	-
Lithuania[a]	98	2.0	65	4.6	212	19.8	142	0	60	0	65	0	-	-
Luxembourg	116	1.7	116	4.3	116	25.0	116	0	116	0	116	0	-	-
Malta	205	2.0	-	-	205	33.2	205	0	205	0.5	205	0	-	-
Netherlands	612	3.9	612	6.7	612	28.1	612	1.0	612	0.5	612	0	612	3.4
Poland	75	2.7	75	2.7	75	9.3	75	1.3	75	1.3	75	0	75	1.3
Portugal	278	14.7	278	4.0	278	32.0	278	0.4	278	0	278	0	278	0.4
Romania	25	0	25	4.0	25	20.0	25	0	25	0	25	0	-	-
Slovakia[a]	-	-	2	NA	696	8.3	562	0.7	325	2.2	326	0	-	-
Slovenia	176	1.7	176	5.7	176	17.6	176	3.4	176	2.3	176	0	-	-
Spain	1,002	1.4	1,002	5.2	1,002	25.0	1,002	0.8	1,002	0.5	1,002	0	-	-
Sweden[d]	619	0.3	619	0.8	619	14.4	619	0.3	619	0.3	619	0	619	0
Total (24 MSs)	**11,015**	**1.8**	**10,703**	**5.3**	**11,832**	**25.3**	**11,572**	**1.1**	**10,385**	**1.1**	**11,298**	**0**	**4,474**	**1.4**
Iceland	-	-	-	-	48	14.6	-	-	-	-	-	-	-	-
Norway	-	-	200	6.5	200	16	200	0.5	200	0.5	200	0	-	-

Salmonella spp. rezistencija u HR (%)



Shigella spp.

Shigella spp. rezistencija u HR (%)

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
amoksicilin	4	100*	69	43	100	58	86		100	1
ko-amoksiklav	0	100*	33	0	57	42	48		31	0
cef III	0	0	7	0	0	0	3		69	0
kinoloni	13	0	6	0	43	47	52		75	0
kotrimoksazol	89	100*	75	67	43	72	90		86	1
azitromicin										2
ukupan broj izolata	27	1	16	7	7	36	29		16	4

Prevencija probavnih infekcija cijepljenjem

Vesna Višekruna Vučina, dr.med.
Ivan Mlinarić, dr.med.

Služba za epidemiologiju zaraznih bolesti
Hrvatski zavod za javno zdravstvo

Infekcije probavnog sustava: novosti u epidemiologiji, kliničkoj slici, dijagnostici, terapiji i prevenciji
Hotel Dubrovnik, Zagreb, 17. svibnja 2024.

Probavne infekcije koje se mogu spriječiti cijepljenjem

- Rota (dojenačka dob)
- Hepatitis A (junior od 1 do 15 godina; adult ≥16 godina)
- Trbušni tifus (≥ 2 godine)
- Kolera (≥ 2 godine)

Rota

Dva registrirana cjepiva u RH (per os):

- **Rotateq** – serotipovi G1 G2 G3 G4 i P1A(8), shema u 3 doze, u dobi od 6. do 32. tjedna
- **Rotarix** – humani rotavirus soj RIX4414, shema u 2 doze, u dobi od 6. do 24. tjedna

Vaccine effectiveness

A recent meta-analysis of real-world effectiveness of Rotarix and RotaTeq[41] found that vaccine effectiveness against laboratory-confirmed severe RVGE among children aged <12 months was 86% in low-mortality countries, 77% in medium-mortality countries, and 63%–66% in high-mortality countries. Among children aged 12–23 months, vaccine effectiveness against laboratory-confirmed rotavirus was 84%–86% in low-mortality countries, 54% in medium-mortality countries (Rotarix only), and 58% in high-mortality countries (Rotarix only). Similar trends were reported from case-control studies of RVGE-related health-care encounters summarized in the recent Cochrane review[38] which found that Rotarix and RotaTeq reduced RVGE-related health-care encounters by 79%–83% in low-mortality countries, 58% in medium-mortality countries (Rotarix only), and 48%–69% in high-mortality countries. There were no observational studies assessing the effectiveness of ROTASIIL or Rotavac on laboratory-confirmed rotavirus or RVGE-related health-care encounters.

Data from case-control studies show that Rotarix and RotaTeq are more effective when the full course is given, but some protection may also be achieved following an incomplete vaccination series.[37, 42] Additionally, a meta-analysis of data from middle- and high-income countries showed that Rotarix and RotaTeq have similar effectiveness against homotypic and heterotypic rotavirus strains.[43] There are no studies examining the effectiveness of an incomplete series of ROTASIIL or Rotavac or their effectiveness against homotypic and heterotypic rotavirus strains.

WHO Position paper rota vaccines https://iris.who.int/bitstream/handle/10665/342905/WER9628-301-319-eng-fre.pdf?sequence=1

Hepatitis A

- Registrirana monovalentna cjepiva ili kombinirana s hepatitisom B, formulacije za odrasle i djecu (kod nas dostupna inaktivirana cjepiva)
- Dvije doze s razmakom od 6-12 mjeseci (druga doza – „booster” za postizanje dugotrajnije zaštite) – monovalenta cjepiva
- Tri doze po shemi 0, 1, 6 mjeseci kod kombiniranih cjepiva (zbog hep B komponente)

The effectiveness of inactivated hepatitis A vaccines in preventing HAV infections and in providing strong, durable immune responses has been demonstrated in a wide range of single- and 2-dose studies in a variety of contexts.[46] The impact at the population-level of hepatitis A inactivated vaccines has been widely demonstrated. The first studies were in Native American and Alaska Native communities.[47,48] The impact on hepatitis incidence in 2-dose studies of inactivated HAV vaccine in a variety of contexts (Australia, China, Israel, Panama and the United States) demonstrated a reduction in incidence in all age groups ranging from 76% to 98%.[46]

WHO Position Paper Hepatitis A vaccines https://iris.who.int/bitstream/handle/10665/363396/WER9740-eng-fre.pdf?sequence=1

Trbušni tifus

- Kod nas dostupno polisaharidno nekonjugirano inaktivirano cjepivo protiv trbušnog tifusa (u svijetu registrirano i živo atenuirano cjepivo, te konjugirano)
- Zaštita se osigurava cijepljenjem s jednom dozom cjepiva (0,5 ml). Ako je osoba izložena stalnom riziku, docjepljivanje se provodi svake tri godine.

In pre-licensure trials in Nepal, South Africa and China, vaccine efficacy was 72% [95% CI: 42–86],[42] 64% [95% CI: 36–79],[43] and 69% [95% CI: 28–87][50] over 17 months, 21 months and 19 months of follow-up, respectively. In a post-licensure cluster randomized trial in Kolkata, India, vaccine effectiveness was 56% [95% CI: 18–77] among children aged 5–14 years, and 80% [95% CI: 53–91] in children aged 2–4 years. This finding of a higher level of protection in younger children was unusual among field trials of typhoid vaccines. The Kolkata trial involved mass vaccination of individuals 2 years of age and older living within the same community. This may have resulted in herd immunity, particularly among children aged less than 5 years.[51] Another

WHO position paper Typhoid fever
https://iris.who.int/bitstream/handle/10665/272272/WER9313.pdf?sequence=1

Trbušni tifus

Table 1 **Characteristics of different typhoid vaccines**[15, 36]
Tableau 1 **Caractéristiques des différents vaccins antityphoïdiques**[15, 36]

	Typhoid conjugate vaccine (Typbar-TCV®) – Vaccin antityphoïdique conjugué (Typbar-TCV®)	**Unconjugated Vi polysaccharide vaccine – Vaccin polyosidique Vi non conjugué**	**Live attenuated Ty21a vaccine – Vaccin vivant atténué Ty21a**
Composition	25 µg of purified Vi capsular polysaccharide conjugated to TT – 25 µg de polyoside capsulaire Vi purifié, conjugué à l'anatoxine tétanique	25 µg of purified Vi capsular polysaccharide – 25 µg de polyoside capsulaire Vi purifié	2 to 6 × 109 CFU of Ty21a (attenuated Ty2 strain of *S.* Typhi) – 2 à 6 × 109 UFC de Ty21a (souche Ty2 atténuée de *S.* Typhi)
Route, dose – Voie d'administration, posologie	IM, 1 dose – Intramusculaire, 1 dose	IM/SC, 1 dose – Intramusculaire/sous-cutanée, 1 dose	Oral, 3 (4 in USA and Canada) doses every second (alternate) day – Orale, 3 doses (4 aux États-Unis d'Amérique et au Canada) administrées 1 jour sur 2
Presentation – Présentation	Liquid – Liquide	Liquid – Liquide	Enteric- coated capsules – Gélules gastrorésistantes
Recommended target age for vaccination – Âge cible recommandé pour la vaccination	Adults and children ≥6 months to ≤45 years of age – Adultes et enfants âgés de ≥6 mois à ≤45 ans	Adults and children ≥2 years of age – Adultes et enfants âgés de ≥2 ans	Adults and children older than 6 years – Adultes et enfants de plus de 6 ans

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Kolera

- U RH registrirano jedno cjepivo, no trenutno nije dostupno zbog globalnog problema s opskrbom tržišta
- Serogrupe O1, per os
  - 2 doze – odrasli i djeca u dobi od navršenih 6 godina
  - 3 doze – djeca u dobi od 2 do ispod 6 godina
- Razmak između doza – najmanje tjedan dana
- Booster unutar 2 godine

WHO Position paper Cholera vaccines
https://iris.who.int/bitstream/handle/10665/258763/WER9234.pdf?sequence=1

The Bangladesh trial (Matlab, 1985–1990) involved a total of 63 498 Bangladeshi children aged 2–15 years and women aged over 15 years. Participants received 3 doses of WC-BS, WC, or placebo.[49] At the time of the trial, El Tor and classical cholera strains co-circulated in the study population. At 4–6 months following WC-BS vaccination the protective efficacy against El Tor and classical cholera combined, for vaccinees aged >2 years, was 85% (95% CI: 56–95%), dropping to 62% (95% CI: 46–74%) after one year of follow-up. During the second and third year of follow-up, the corresponding protective efficacies were 58% (95% CI: 40–71%) and 18% (95% CI: -21–44%), respectively. The cumulative efficacy of the 2 vaccine doses over 3 years was 51% (95% CI: 40–60%) against El Tor and classical cholera combined, and slightly lower against El Tor than against classical cholera.

Kolera

Generic name – Dénomination commune	WC-rBS – WC-rBS	Modified bivalent WC – WC bivalent modifié
Trade name – Nom commercial	Dukoral® (first licensed in Sweden) – Dukoral® (première homologation en Suède)	mORCVAX™ (licensed in Viet Nam), Shanchol™ (licensed in India), Euvichol® (licensed in the Republic of Korea) – mORCVAX™ (homologué au Viet Nam), Shanchol™ (homologué en Inde), Euvichol® (homologué en République de Corée)
Target – Cible	O1 (Classical, El Tor – Ogawa and Inaba) Cholera toxin B subunit – O1 (classique, El Tor – Ogawa et Inaba) Sous-unité B de la toxine cholérique	O1 (Classical, El Tor – Ogawa and Inaba), and O139 No cholera toxin subunit – O1 (classique, El Tor – Ogawa et Inaba) et O139 Pas de sous-unité de la toxine cholérique
Regimen – Schéma vaccinal	2 doses given 1–6 weeks apart – 2 doses espacées de 1 à 6 semaines 3 doses for children aged 2–5 years – 3 doses pour les enfants âgés de 2 à 5 ans	2 doses given 14 days apart – 2 doses espacées de 14 jours
Age recommended for vaccination – Âge recommandé pour la vaccination	≥2 years – ≥2 ans	mORCVAX™: ≥1 year – mORCVAX™: ≥1 an Others: ≥1 year – Autres: ≥1 an

WHO Position paper Cholera vaccines
https://iris.who.int/bitstream/handle/10665/258763/WER9234.pdf?sequence=1

Potencijalna cjepiva za sprečavanje probavnih infekcija

- Shigella – nekoliko kandidata u različitim fazama pretkliničkog i kliničkog razvoja
- ETEC, Cryptosporidium, Norovirus...

Još nema cjepiva za navedene bolesti iz više razloga - neki su vezani specifično za patogene (npr. velika antigenska raznolikost različitih sojeva), a drugi su više generički (ograničeno znanje o mukoznom imunološkom sustavu crijeva)...

Table 1.

Licensed vaccines and vaccine candidates designed to prevent gastroenteritis caused by rotavirus, norovirus and *Vibrio cholerae*.

Pathogen	Vaccine (s)	Status*	Comment	Selected references
Rotavirus	*RotaTeq* ®/*Rotarix* ®	Worldwide License	Eight years post-licensure; worldwide distribution; demonstrated effectiveness. Both prequalified by WHO.	Giaquinto et al., 2011[10]; O'Ryan et al., 2011[13]
	Rotashield®	First licensed rotavirus vaccine in 1998 (USA); was withdrawn due to association with intestinal intussusception.	Currently in clinical trials using a 2-dose regimen beginning within the first 30 d of life demonstrating 64% efficacy for the first 12 months of life.	Armah et al., 2013[42]
	LLR®/*Rotavin-M1*®/*Rotavac*®	Restricted license	Used only in China/Vietnam/India respectively; lack of robust effectiveness data.	Fu et al., 2012;[61] Dang et al., 2012;[62] Bhandari et al., 2014[65]
	RV3BB/UK reassortant	Early clinical development	Phase I or early phase II studies.	Danchin et al., 2013;[63] Luna et al., 2013[66]
	Subunit vaccines/Inactivated rotavirus vaccine	Early clinical development	Immunogenic in the BALB/c mice model.	Lappalainen et al., 2013;[67] Jiang et al., 2008[70]
Norovirus	Intramuscular vaccine candidate containing GI.1 and GII.4 VLPs	Advanced clinical development	Phase I adult challenge study completed, moving into phase IIb/III studies.	Treanor et al., 2014[118]
	P particle-based vaccines	Preclinical development	Considered as a norovirus vaccine as well as a delivery system for other antigens, such as rotavirus, influenza and hepatitis E; immunogenic in the mouse model.	Tan and Jiang, 2014[17]
	Trivalent vaccine including norovirus GII.4 and GI.3 VLPs and rotavirus rVP6	Preclinical development	Immunogenic in the BALB/c mouse model.	Tamminen et al., 2013[115]
	Multivalent alphavirus replicon particles (VRPs)	Preclinical development	Considered as a delivery system or adjuvant; immunogenic in a BALB/c mouse model.	LoBue et al., 2009[113]
V. cholerae	*Dukoral*®	Worldwide License	Licensed in 65 countries. Short-term protection and potential herd effect. Prequalified by WHO.	Taylor et al., 2000;[132] Ali et al., 2005[139]
	Shanchol®	Worldwide License	Prequalified by WHO. Demonstrated effectiveness.	Sur et al., 2011[134]
	mORCVAX®	Restricted License	Identical to *Shanchol*®. Distributed in Vietnam only.	Anh et al., 2007;[136] 2011[137]
	CVD-103HgR	Restricted License	Production as *Orochol*®/*Mutacol*® stopped in 2004. New clinical studies are ongoing.	Chen et al., 2014[128]
	Peru-15 (CholeraGarde®)	Early clinical development	Safe and immunogenic. Efficacy evidenced in volunteers in the USA. A phase II trial in an endemic region is ongoing.	Cohen et al., 2002[141]; Qadri et al., 2007[143]
	V.cholerae 638	Early clinical development	Safe and immunogenic. Efficacy evidenced in volunteers in Cuba. Phase I/II trials in endemic regions are required.	García et al., 2005;[146] Diaz Jidy et al., 2010[147]
	CVD 112	Early clinical development	Safety, immunogenicity and efficacy evidenced in phase II trials. No information about further trials.	Tacket et al., 1995[148]
	VA1.3 / 1.4	Early clinical development	Safe and immunogenic after phase I trial. Phase II trials suggested.	Mahalanabis et al., 2009;[149] Kanungo et al., 2014[150]
	IEM 108	Preclinical development	Prevent fluid accumulation in rabbit ligated loops	Liang et al., 2003[151]
	VCUSM2	Preclinical development	Prevent fluid accumulation in rabbit ligated loops and RITARD model	Ravichandran et al. 2006[152]
	TLP01	Preclinical development	Safe and immunogenic in rabbits and rats	Ledon et al., 2012[153]

*Status: Worldwide Licensed in an important number of countries in several continents; restricted license in one or few countries; Advanced clinical development (phase IIb/III); Early clinical development (phase I/II); Preclinical development in animal models

O'Ryan M, Vidal R, del Canto F, Salazar JC, Montero D. Vaccines for viral and bacterial pathogens causing acute gastroenteritis: Part I: Overview, vaccines for enteric viruses and Vibrio cholerae. Hum Vaccin Immunother. 2015;11(3):584-600. doi: 10.1080/21645515.2015.1011019. PMID: 25715048; PMCID: PMC4514277.

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8 TJEDANA:

NAJKRAĆI PUT DO IZLJEČENJA[1]

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Maviret je indiciran za liječenje kronične infekcije virusom hepatitisa C (HCV) u odraslih i djece u dobi od 3 godine i starije[2]

JEDNOKRATNO LIJEČENJE 8 TJEDANA

za prethodno neliječene bolesnike[2]

98%

VISOKI POSTOTAK IZLJEČENJA (98%)

za sve genotipe i prethodno neliječene bolesnike (N=1218/1248)[3]

DOZIRANJE 1 X DNEVNO

3 tablete s hranom[2]

Maviret 100 mg/40 mg filmom obložene tablete (glekaprevir/pibrentasvir). Lijek se izdaje na recept. Prije propisivanja lijeka Maviret, molimo pročitati cjelokupni odobreni Sažetak opisa svojstava lijeka/Uputu o lijeku, uključujući detaljne informacije o indikacijama, kontraindikacijama, nuspojavama, upozorenjima i mjerama opreza te doziranju i načinu primjene dostupno na sljedećoj poveznici:
https://www.ema.europa.eu/en/documents/product-information/maviret-epar-product-information_hr.pdf
Nositelj odobrenja za stavljanje lijeka u promet: AbbVie Deutschland GmbH & Co. KG, Knollstrasse, 67061 Ludwigshafen, Njemačka. Lokalni predstavnik nositelja odobrenja: AbbVie d.o.o., Strojarska 20, 10 000 Zagreb. tel. 01 562 55 01, fax. 01 562 55 60. Broj odobrenja za stavljanje lijeka u promet: EU/1/17/1213/001.

Literatura:

1. European Medicines Agency. European public assessment reports. Dostupno na: www.ema.europa.eu, datum pristupanja 22.5.2022.
2. Sažetak opisa svojstava lijeka Maviret
3. Zuckerman E, Gutierrez JA, Dylla DE, et al. Eight weeks treatment with glecaprevir/pibrentasvir is safe and efficacious in an integrated analysis of treatment-naïve patients with hepatitis C virus infection. Clin Gastroenterol. Published online July 1, 2020. doi:10.1016/j.cgh.2020.06.044

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*Combined with the detection of HEV RNA by PCR

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12 tjedana

JEDNA

Jedna tableta, jednom dnevno 12 tjedana[1]

IZLJEČENJE

95-100% izliječeno u HCV GT 1–6[1,b]

STR

JEDNOSTAVNO

Jedina STR-opcija bez RBV i bez PI-a za skoro svakog HCV-bolesnika[1,a]

Referanca: 1. EPCLUSA - Sažetak opisa svojstava lijeka. Datum revizije teksta: 08/2023. **Kratice:** GT = genotip; HCV = virus hepatitisa C; RBV = ribavirin; STR - Jednotabletni režim (*Single-Tablet Regimen*); SmPC = Sažetak opisa svojstava lijeka (*Summary of Product Characteristics*). **Bilješke: a** EPCLUSA pruža opciju jednotabletnog režima bez RBV-a za većinu HCV-bolesnika, isključujući one s dekompenziranom cirozom. Za daljnje informacije o ograničenjima, pogledajte SmPC. RBV se preporučuje za liječenje bolesnika s dekompenziranom cirozom, a može biti uzet u obzir za liječenje HCV GT3 bolesnika s kompenziranom cirozom i preporučuje se za liječenje bolesnika s dekompenziranom cirozom - pogledajte RBV SmPC za potpunu informaciju.[1] **b** U ASTRAL-1,-2 i -3 studijama kod bolesnika s monoinfekcijom HCV i kompenziranom bolešću primarni ishod SVR-omjera bio je 99%, 99% i 95%. Kroz sve genotipove, omjer izlječenja bio je 95-100% u bolesnika koji su liječeni lijekom Epclusa tijekom 12 tjedana.[1]

NAZIV LIJEKA: Epclusa 400 mg/100 mg filmom obložene tablete. Epclusa 200 mg/50 mg filmom obložene tablete. **BROJ ODOBRENJA ZA STAVLJANJE LIJEKA U PROMET:** EU/1/16/1116/001; EU/1/16/1116/002 **NAČIN IZDAVANJA:** Lijek se izdaje na ograničeni recept. **NOSITELJ ODOBRENJA ZA STAVLJANJE LIJEKA U PROMET:** Gilead Sciences Ireland UC; Carrigtohill, County Cork, T45 DP77; Irska. **DJELATNA TVAR:** Epclusa 400 mg/100 mg filmom obložene tablete Jedna filmom obložena tableta sadrži 400 mg sofosbuvira i 100 mg velpatasvira. Epclusa 200 mg/50 mg filmom obložene tablete. Jedna filmom obložena tableta sadrži 200 mg sofosbuvira i 50 mg velpatasvira. **TERAPIJSKE INDIKACIJE:** Epclusa je indicirana za liječenje kronične infekcije virusom hepatitisa C (HCV) u bolesnika u dobi od 3 i više godina. **KONTRAINDIKACIJE:** Preosjetljivost na djelatne tvari ili neku od pomoćnih tvari navedenih u dijelu 6.1. Lijekovi koji su jaki induktori Pglikoproteina (Pgp) i/ili jaki induktori citokroma P450 (CYP) (karbamazepin, fenobarbital, fenitoin, rifampicin, rifabutin i gospina trava) (vidjeti dio 4.5). **POSEBNA UPOZORENJA I MJERE OPREZA PRI UPORABI:** Epclusa se ne smije primjenjivati istodobno s drugim lijekovima koji sadrže sofosbuvir. Teška bradikardija i srčani blok Slučajevi teške bradikardije i srčanog bloka koji mogu biti opasni po život uočeni su kada su se režimi koji sadrže sofosbuvir koristili u kombinaciji s amiodaronom. Koinfekcija HCV-om/HBV-om (virusom hepatitisa B) Tijekom ili nakon liječenja antiviroticima koji djeluju izravno, zabilježeni su slučajevi reaktivacije virusa hepatitisa B (HBV), neki od njih sa smrtnim ishodom. Bolesnici u kojih je prethodna terapija režimom koji sadrži inhibtor NS5A bila neuspješna Nema kliničkih podataka koji bi poduprli djelotvornost sofosbuvira/velpatasvira za liječenje bolesnika u kojih je liječenje režimom koji sadrži drugi inhibitor NS5A bilo neuspješno. Oštećenje bubrega Podaci o sigurnosti primjene ograničeni su u bolesnika s teškim oštećenjem bubrega (eGFR < 30 ml/min/1,73 m²) i ESRDom koji zahtijeva hemodijalizu. Primjena s umjerenim induktorima Pgpa i/ili umjerenim induktorima CYPa Lijekovi koji su umjereni induktori Pgpa i/ili umjereni induktori CYPa (npr. efavirenz, modafinil, okskarbazepin ili rifapentin) mogu smanjiti koncentracije sofosbuvira ili velpatasvira u plazmi što dovodi do smanjenog terapijskog učinka lijeka Epclusa. Istodobna primjena takvih lijekova s lijekom Epclusa se ne preporučuje. Upotreba s određenim antiretrovirusnim režimima za HIV Pokazalo se da Epclusa povećava izloženost tenofoviru, naročito kada se koristi zajedno s režimom za HIV koji sadrži tenofovirdizoproksilfumarat i farmakokinetički pojačivač (ritonavir ili kobicistat). Primjena u bolesnika s dijabetesom Nakon uvođenja liječenja HCV infekcije direktno djelujućim antivirotikom, bolesnici s dijabetesom mogu imati bolju kontrolu glukoze u krvi, što može dovesti do simptomatske hipoglikemije. Ciroza jetre CPT stadija C Sigurnost i djelotvornost lijeka Epclusa nije procijenjena u bolesnika s cirozom jetre CPT stadija C. Bolesnici s transplantiranom jetrom Sigurnost i djelotvornost lijeka Epclusa u liječenju infekcije HCV-om u bolesnika u kojih je transplantirana jetra nisu procijenjene. Pomoćne tvari Ovaj lijek sadrži manje od 1 mmol (23 mg) natrija po tableti, tj. zanemarive količine natrija. **NUSPOJAVE:** . Gastrointestinalni poremećaji: povraćanje– vrlo često; Poremećaji kože i potkožnog tkiva: Osip – često **DOZIRANJE I NAČIN PRIMJENE:** U odraslih, preporučena doza lijeka Epclusa je jedna tableta od 400 mg/100 mg, peroralno, jedanput na dan s hranom ili bez nje. U pedijatrijskih bolesnika u dobi od 3 i više godina preporučena doza lijeka Epclusa temelji se na tjelesnoj težini kako je navedeno u tablici 3. **UPUTA ZDRAVSTVENIMA RADNICIMA: ZA DODATNE INFORMACIJE POGLEDATI CJELOVITI ODOBRENI SAŽETAK OPISA SVOJSTAVA LIJEKA I UPUTU O LIJEKU. DATUM REVIZIJE TEKSTA:** 08/2023 Detaljnije informacije o ovom lijeku dostupne su na internetskoj stranici Europske agencije za lijekove http://www.ema.europa.eu.

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