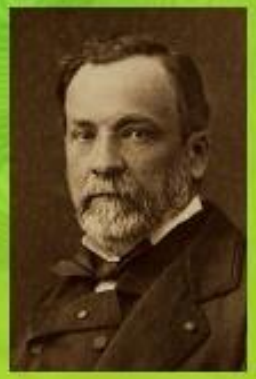
Postavenie probiotík v liečbe idiopatických črevných zápalov

Martin Huorka
Gastroenterologické a hepatologické oddelenie
V. interná klinika LFUK a UN Bratislava

The Probiotic History

•Ellie Metchnikoff, the first scientist who proposed the therapeutic use of lactic acid bacteria.



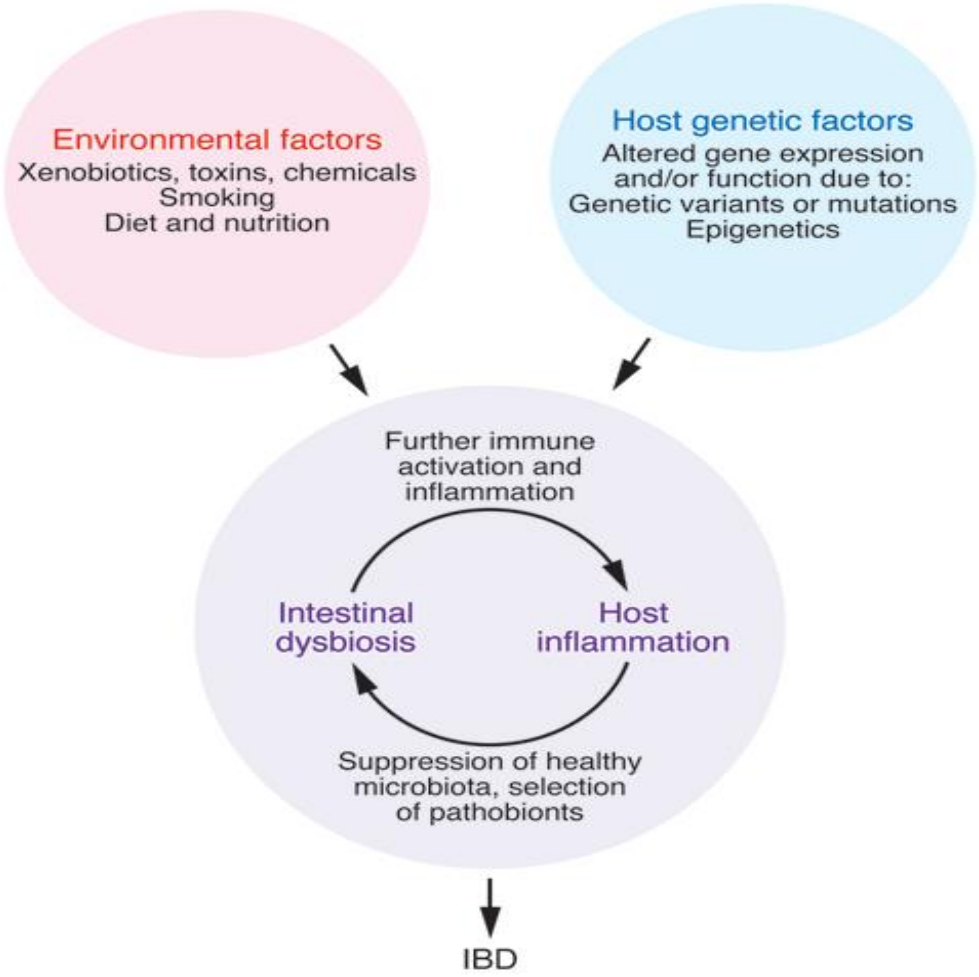
•Lactic acid bacteria were first discovered by Pasteur in 1857

•Their isolation from rancid milk was reported in 1878 by Lister.

In 1889 Tissier discovered Bifidobacterium spp.

•The first stable cultures of *Lactobacillus casei* strain Shirota were made in 1930 by Dr. Minoru Shirota

Patogenéza IBD

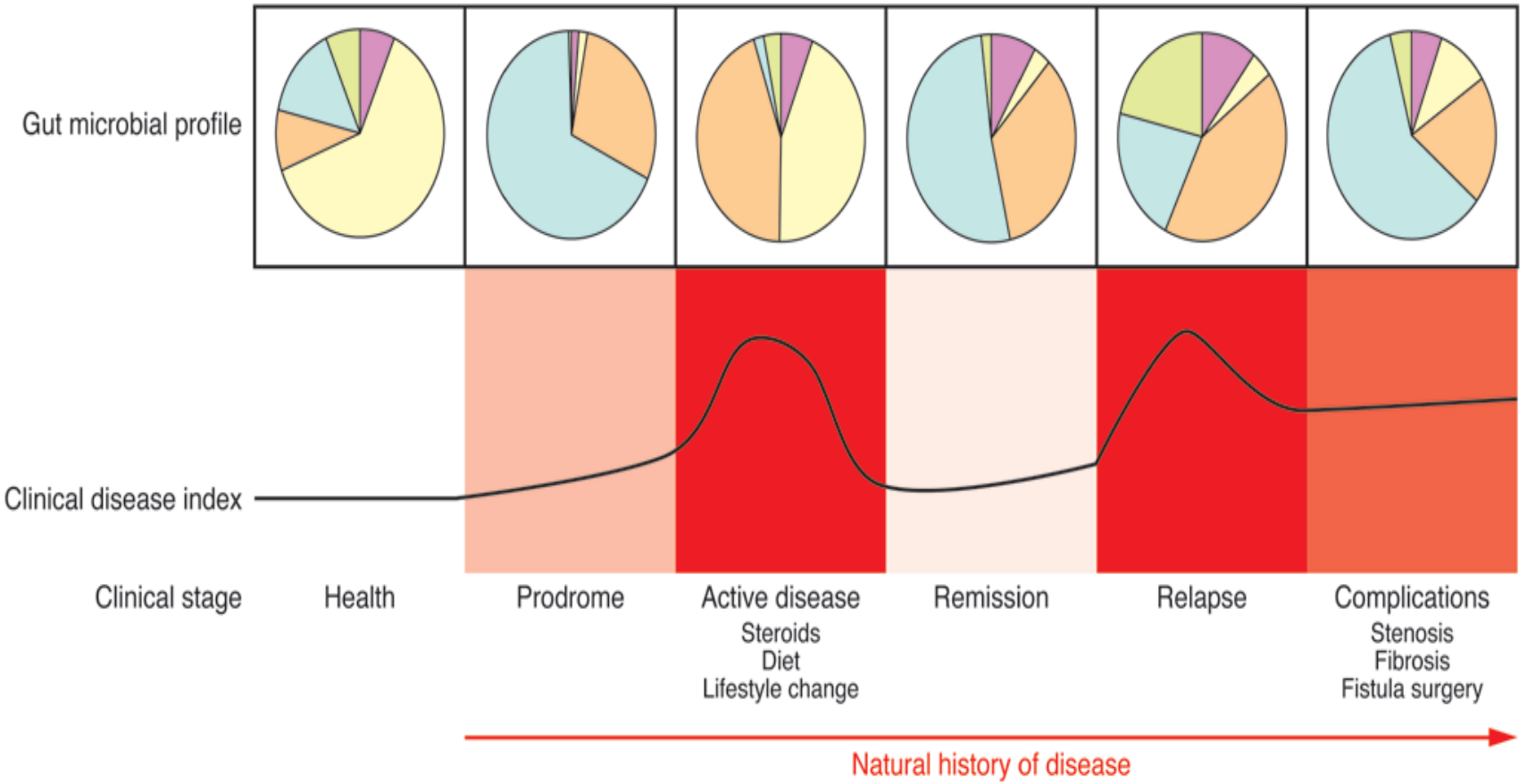


Pravdepodobne ide o interakciu medzi geneticky predisponujúcimi faktormi, exogénnymi a endogénnymi spušťačmi choroby a modifikujúcimi činiteľmi, výsledkom ktorej je spontánne sa opakujuci a remitujúci zápalovy proces, v ktorom je poškodenie tkaniva sprostredkované imunitným systémom

Katsuyoshi Matsuoka and Takanori Kanai The gut microbiota and inflammatory bowel disease Semin Immunopathol. 2015; 37: 47–55.

IBD are chronic, progressive diseases. The composition and function of the gut microbiota likely change through the course (natural history) of IBD, reflecting transitions in host-microbe relationships that arise from disease-intrinsic and confounding factors. Microbial factors that trigger the onset of disease may be quite different from those that sustain the inflammatory process or result from the consequences of long-term complications and interventions. The interpretation of gut microbial data in the absence of this contextual information can be limited and potentially misleading. The pie charts in this figure illustrate the concept of general shifts in microbial composition and/or function over time and are not meant to indicate any quantifiable information.

Sushila R. Dalal and Eugene B. Chang,The Journal of Clinical Investigation, September 2, 2015



And therefore...

- **the same treatment or intervention is unlikely to work for all cases and stages of IBD**. Our interventional goals should therefore be guided by a combination of microbial, genetic, and biological metrics that assess risk and states of health of patients on an individual basis. As **we approach the era of personalized medicine, this strategy is most likely to yield the best and most sustainable clinical outcomes.**

Sushila R. Dalal and Eugene B. Chang The microbial basis of inflammatory bowel diseases *Clin Invest.* 2014;124(10):4190–4196.

Sledované probiotiká pri IBD

- **Najviac skúmané probiotiká vhodné pre pacientov s IBD boli *Lactobacillus* sp, *Bifidobacterium* sp, *Sacchromyces bouladrii, E. coli Nissle* 1917 a probiotická zmes VSL#3**

- **VSL#3 je probioticky prípravok skladajúci sa zo štyroch kmeňov laktobacilov (*L. acidophilus, L. bulgaricus, L. casei, L. plantarum*), troch kmeňov bifidobakterii (*B. breve, B. infantis, B. longum*) a *Streptococcus thermophilus*, ktoré sú bežnou súčasťou črevnej mikroflory ľudi**

Damaskos D, Kolios G. Probiotics and prebiotics in inflammatory bowel disease: microflora 'on the scope'. *Br J Clin Pharmacol*. 2008;65:453–467.

Protizápalove vlastnosti rôznych kmeňov probiotík

- **Zníženie prozápalových cytokínov (TNF alfa, IL 8)**

- **Zvýšenie protizápalových cytokínov (IL 10)**

Borruel N, Carol M, et al. Increased mucosal tumour necrosis factor alpha production in Crohn's disease can be downregulated ex vivo by probiotic bacteria. *Gut.* 2002;51:659–664.

Imaoka A, Shima T, et al. Anti-inflammatory activity of probiotic Bifidobacterium: Enhancement of IL-10 production in peripheral blood mononuclear cells from ulcerative colitis patients and inhibition of IL-8 secretion in HT-29 cells. *World J Gastroenterol*. 2008;14:2511–2516

Drakes M, Blanchard T, Czinn S Bacterial probiotic modulation of dendritic cells. *Infect Immun.* 2004;72:3299–3309.

Tien MT, Girardin SE, et al. Anti-inflammatory effect of Lactobacillus casei on Shigellainfected human intestinal epithelial cells. *J Immunol.* 2006;176:1228–1237.

***Lactic Acid Bacteria – Microbiological and Functional Aspects*. 4th edn, edited by S. Lahtinen, A.C. Ouwehand, S. Salminen and A. Von Wright. CRC Press (Taylor & Francis Group), Boca Raton: FL, USA, 2012. ISBN 0 978-1-4398-3677-4.**

Cui HH, Chen CL, et al. Effects of probiotic on intestinal mucosa of patients with ulcerative colitis. *World J Gastroenterol.* 2004;10:1521–1525.

Možnosti použitia probiotík pri IBD

- **Probiotiká pri MC**
- **Udržiavacia fáza UC**
- **Pouchitis**
- **Pri superinfekcii Clostridium difficile**
- **IBS- like symptoms pri IBD**

Therapeutic Manipulation of Microbiota

- Probiotics
  (Gionchetti, *et al.* 2000; Bousvaros, *et al.* 2005, Rahimi, *et al.* 2008; Sood, *et al.* 2009)
  - Some efficacy in pouchitis, UC but not Crohn's
  - Potential of butyrate producing organsims
- Fecal bacteriotherapy
  (Bennet, *et al.* 1989, Borody, *et al.* 2003, 2011; Duplessis, *et al.* 2012)
  - Effective in *C. difficile* infection
  - Limited studies in IBD; potential in UC
  - Dosing intervals; method of administration; pre-treatment
- Dietary intervention
  (Wu, *et al.* 2011; Devkota, *et al.* 2012; Duboc, *et al.* 2012)
  - Dietary fiber and SCFA
  - Dietary fat and bile acid metabolism

Štúdie s probiotikami pri IBD

Table 2 Randomized controlled trials of probiotics for inflammatory bowel disease

Probiotics	Disease	Endpoint	Groups and subject no.	Duration	Conclusion	Ref.
VSL#3	UC	Induction	Conventional therapy+VSL#3, 77 Conventional therapy+placebo: 70	12 weeks	Effective	[63]
	UC	Induction	Conventional therapy+VSL#3, 71 Conventional therapy+placebo, 73	8 weeks	Effective	[62]
	UC	Induction Maintenance	Steroid/mesalazine+VSL#3, 14 Steroid/mesalazine+placebo, 15	1 year	Effective	[64]
	Pouchitis	Maintenance	VSL#3, 20 Placebo, 20	9 months	Effective	[60]
	Pouchitis	Maintenance	VSL#3, 20 Placebo, 16	12 months	Effective	[61]
Nissle 1917	UC	Induction	Steroid+mesalazine, 57 Steroid+*Nissle* 1917, 59	12 weeks	Equivalent to mesalazine	[66]
	UC	Maintenance	*Nissle* 1917, 162 Mesalazine, 165	12 months	Equivalent to mesalazine	[67]
	UC	Maintenance	Mesalazine, 50 *Nissle* 1917, 53	12 weeks	Equivalent to mesalazine	[68]
Lactobacillus GG	CD	Maintenance	Conventional therapy+*Lactobacillus* GG, 39 Conventional therapy+placebo, 36	~2 years	Not effective	[71]
	UC	Maintenance	*Lactobacillus* GG, 65 *Lactobacillus* GG+mesalazine, 62 Mesalazine, 60	12 months	Equivalent to mesalazine	[70]
Bifidobacteria-fermented milk (BFM)	UC	Induction	Conventional therapy+BFM, 10 Conventional therapy+placebo, 10	12 weeks	Effective	[74]
	UC	Maintenance	Conventional therapy+BFM, 11 Conventional therapy, 10	12 months	Effective	[75]
Bifidobacterium longum/Synergy 1	UC	Induction	*Bifidobacterium longum*/Synergy 1, 9 Placebo, 9	1 month	Effective	[73]

- Epidemiologický fakt

Z epidemiologického hľadiska je zaujímavé, že viac ako 43% pacientov s IBD v Nemecku užíva probiotikum (indikované lekárom alebo nasadené samým pacientom)

Probiotiká pri MC

Short Communication

Is *Lactobacillus* GG Helpful in Children With Crohn's Disease? Results of a Preliminary, Open-Label Study

Puneet Gupta, Haikaeli Andrew, Barbara S. Kirschner, and Stefano Guandalini

Section of Pediatric Gastroenterology, Hepatology and Nutrition, The University of Chicago Children's Hospital, Chicago, Illinois, U.S.A.

ABSTRACT

Background: *Lactobacillus* GG is a safe probiotic bacterium known to transiently colonize the human intestine. It has been found to be useful in treatment of several gastrointestinal conditions characterized by increased gut permeability. In the current study, the efficacy of *Lactobacillus* GG was investigated in children with Crohn's disease.

Methods: In this open-label pilot evaluation viewed as a necessary preliminary step for a possible subsequent randomized placebo-controlled trial, four children with mildly to moderately active Crohn's disease were given *Lactobacillus* GG (10^{10} colony-forming units [CFU]) in enterocoated tablets twice a day for 6 months. Changes in intestinal permeability were measured by a double sugar permeability test. Clinical activity was determined by measuring the pediatric Crohn's disease activity index.

Results: There was a significant improvement in clinical activity 1 week after starting *Lactobacillus* GG, which was sustained throughout the study period. Median pediatric Crohn's disease activity index scores at 4 weeks were 73% lower than baseline. Intestinal permeability improved in an almost parallel fashion.

Conclusions: Findings in this pilot study show that *Lactobacillus* GG may improve gut barrier function and clinical status in children with mildly to moderately active, stable Crohn's disease. Randomized, double-blind, placebo-controlled trials are warranted for a final assessment of the efficacy of *Lactobacillus* GG in Crohn's disease. ***JPGN 31:453–457, 2000.*** **Key Words:** Children—Crohn's disease—Intestinal permeability—*Lactobacillus* GG—Probiotics.

Gupta P et al. J Pediatr Gastroenterol Nutr 2000;31:453Y7.

Maintenance of Medical-Induced Remission of Crohn's Disease

Reference	Study	n	Duration	Probiotic	Control	Relapse rate (Probiotic)	Relapse rate (Placebo)	*p* value
Malchow et al. 1997	RCT	28	12 months	E.Coli Nissle	Placebo	Response: 70%	Response: 30%	ns
Guslandi et al. 2000	Open-label	32	6 months	Saccharomyces boulardii + mesalamine 2g/d	Mesalamine 3g/d	Response: 94% Relapse 6%	Response: 38% Relapse 38%	0.04
Schultz et al. 2004	RCT, DB	11	6 months	LGG	Placebo	60%	67%	ns
Bousvarous et al. 2005	RCT, DB	75	24 months	LGG	Placebo (inulin)	31%	17%	0.18

Probiotic - S. Boulardii in CD – Adults

First Author Date	Design duration	Probiotic	Concomitant Therapy	Results
Vilela et al ; Scand J Gastroenterol. 2008	DB, R, C 3mo	S. Boulardii (4108 CFU) n=15	Mesalamine, Azathioprine Prednisone, metronidazol/ thalidomide	Improved permeability (P=0.0005) and maintenance of remission
Bourreille A, et al Clin Gastroenterol Hepatol. 2013	RCT, 1 yr	S. Boulardii		Frequency of relapses - Saccharomyces boulardii group - (47.5 %) Placebo - (53.2 %) Time to relapse was also not statistically different

Odporúčania pre použitie probiotík pri MC

ÚROVEŇ ODPORÚČANIA	MIKROORGANIZMUS	DÁVKA	REFERENCIE
Indukcia remisie, C	Synbiotická zmes B. breve B. longum L. casei	3 x 1010 1,5 x 1010 3 x 1010	Fujimori, 2007 (57)
C	L. salivarius	1 x 1010	McCarthy, 2001 (58)
C	LGG	4 x 1010	Gupta, 2000 (59)
Udržanie po medikamentózne navodenej remisii, neodporúča sa, B	LGG		Bousvaros, 2005 (60)
B	S. boulardii + mesalazín 2g	1g	Guslandi, 2000 (61)
Neodporúča sa, B	EcN	5 x 1010	Madsen, 2008 (62)
Udržanie po chirurgickom zákroku, A	VSL#3	1 vrecko, 3 x 1011	Madsen, 2008 (62)
Neodporúča sa	L. johnsonii		Van Gossum, 2007 (63)
Neodporúča sa	Synbiotic 2000		Chermesh, 2007 (64)

- **úroveň A: konzistentné kontrolované klinické štúdie, kohorty, klinické rozhodnutia sú platné v rôznej populácii**
- **úroveň B: konzistentné, retrospektívene kohorty, ekologické štúdie, kauzistické štúdie, extrapolácia z úrovne A**
- **úroveň C: extrapolácia z úrovne B, kazuistiky**

Summary
Probiotics in CD

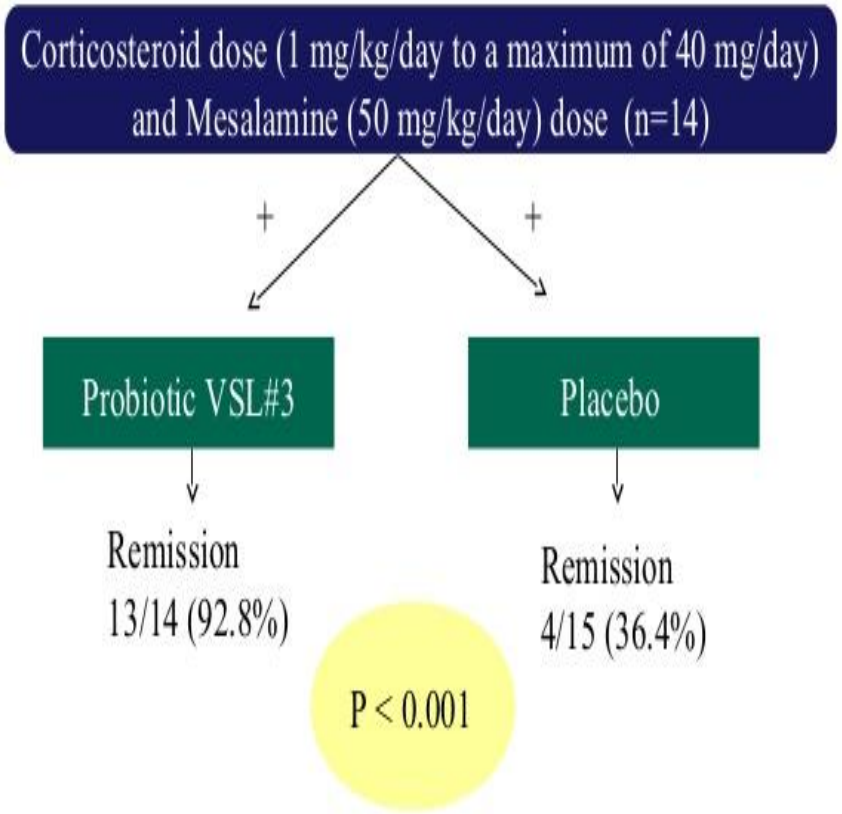
- There is no evidence of efficacy for any used strain in pediatric / adult CD unlike UC.

- The pathogenesis of UC and CD, especially the role of microbes-host interaction, is different between these 2 disease entities .

- Given the array of genotype & phenotype of CD, we need to identify the specific Probiotic that may be beneficial.

Probiotiká pri UC

Probiotics in Ulcerative Colitis (Mod. to Sev.) in Children



Miele E et al. Am J Gastroenterol. 2009;104:437–443.

Probiotics in Ulcerative Colitis (UC) in Children – Recent Trial

- 31 children with mild to moderate ulcerative proctitis / proctosigmoiditis with mild to moderate disease activity
- Study duration 8 weeks

Mesalazine + Enema solution with L. reuteri ATCC 55730.

Mesalazine + Placebo

- Clinical and endoscopic improvements better in the probiotic group.
- Histological score significantly decreased in the L. reuteri group (P<0.01).
- A significant increase in the mucosal expression levels of IL-10 and a significant decrease in the levels of IL-1b, TNFa, and IL-8 mucosal expression levels (P\0.01) were documented only in the L. reuteri group.

Oliva S. et al . Aliment Pharmacol Ther. 2012; 35(3):p. 327–34.

Probiotics in adults

Sood et al. *Clin. Gastroenterol. Hepatol.* ***2009, 7, 1202–1209***

- Multicenter, randomized, double blind, placebo-controlled trial from India.
- VSL#3 in adults with mild-to- moderate UC.
- Dose - 3.6 × 1012 CFU VSL#3 (N = 77) or placebo (n = 70) twice daily for 12 weeks.

	Probiotic	Placebo	p Value
Primary end point (50% decrease in *UCDAI) at 6 weeks	32.5%	10%	0.001
Secondary end points - 12 weeks	42.9%	15.7%	0.001

*UC disease activity index

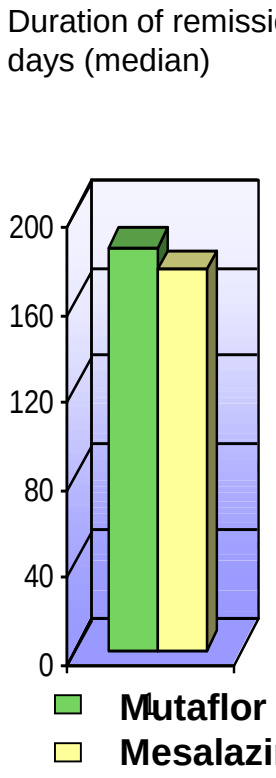
Štúdie s probiotikami použitými na udržanie remisie UC

REFERENCIA	DIZAJN A TRVANIE	PROBIOTIKUM	POROVNANIE	KONKOMITANTNÁ LIEČBA	VÝSLEDOK
Kruis et al, 1997 (41)	randomiz., 12 týž	EcN	mesalazín	0	NSR v CAI skóre a pomere relapsov
Rembacken, 1999 (34)	randmiz., DBPC, 12 mesiacov	EcN	Asacol	indukcia CS GEN	NSR medzi skupinami
Ishikawa, 2003 (42)	randomiz., 12 mesiacov	Yakult	0	CS, mesalazín	menej exacerbácií v Yakult skupine
Kruis et al, 2004 (43)	randomiz., DBPC, 12 mesiacov	EcN	mesalazín	0	rovnosť vo výskyte relapsov
Zocco, 2006 (44)	randomiz., open, 12 mesiacov	LGG	mesalazín	mesalazín/0	NSR v relapsoch v 6., 12. mesiaci
Miele et al, 2009 (45)	randomiz., DBPC	VSL#3	mesalazín	CS	relaps počas 12 mesiacov 21% PB, 73% placebo

- **EcN- *E.coli* kmeň Nissle 1917**
- **NSR- nesignifikantný rozdiel**
- **CAI- klinický index aktivity**
- **GEN- gentamycin**
- **CSD- kortikosteroidy**

MUTAFLOR® *vs.* mesalazine for the treatment of ulcerative colitis

Duration of remission

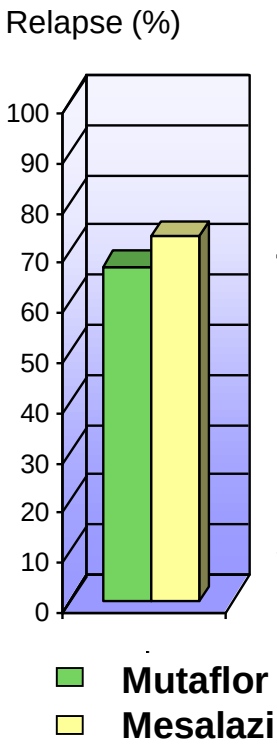


185 days with Mutaflor

175 days with mesalazine

Equivalence is statistically significant ($p < 0.05$)

Patients who suffered a relapse over the period of 12 months



67% of patients treated with Mutaflor

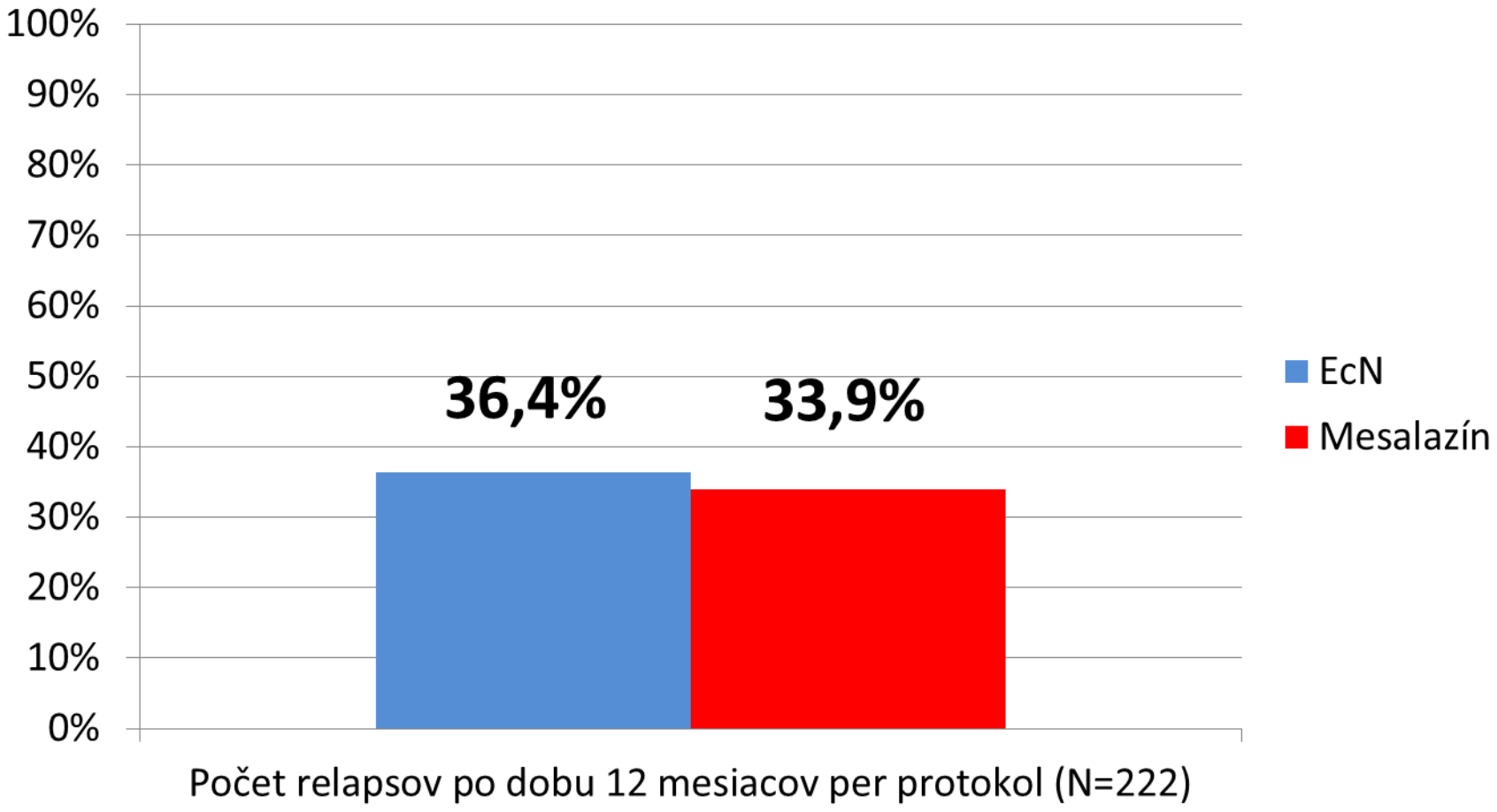
73% of patients receiving mesalazine

Equivalence is statistically significant ($p < 0.01$)

B J Rembacken et al. Lancet 1999; 354: 635-9.

Počet recidív pri liečbe UC pomocou EcN alebo mesalazínom po dobu 12 mesiacov.

Kruis, W., et al. (2004). *Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle1917 is as effective as with standard mesalazine.* Gut. **53**



W Kruis al. Gut 2004; 53: 1617-23

Nežiadúce a vedľajšie účinky mesalazinu

Mesalazin sa nesmie užívať pri:

- známej precitlivenosti na kyselinu salicylovú, jej deriváty alebo na inú zložku lieku;
- ťažkých poruchách funkcie pečene a obličiek;
- výskyte žalúdkových alebo dvanástnikových vredov (ulcus ventriculi, ulcus duodeni);
- chorobne zvýšenej krvácavosti (hemoragická diatéza).

Špeciálna pozornosť pri užívaní

- Podľa zváženia ošetrujúceho lekára sa majú urobiť pred liečbou a počas liečby vyšetrenia krvi (diferenciálny krvný obraz; pečeňové funkcie ako ALT alebo AST; sérový kreatinín) a moču (testovacie prúžky / sediment).
- Kontrolné vyšetrenia sa odporúčajú urobiť 14 dní po začatí liečby, potom ešte 2 x až 3 x v intervaloch 4 týždne. Pri normálnych nálezoch sú potrebné ďalšie kontrolné vyšetrenia raz za štvrť roka, pri výskyte ďalších chorobných príznakov okamžite.
- Opatrnosť je nutná u pacientov s poruchami funkcie pečene a obličiek.
-Pri poruchách funkcie pľúc, najmä pri bronchiálnej astme, je v priebehu užívania mesalazinu potrebné dôsledné sledovanie
- dojčenie- u detí hnačky

UC a probiotiká

- **Metaanalýza 13 štúdii (sledovala skóre remisii a rekurenčných epizód) ukázala, že probiotická terapia bola efektívnejšia ako placebo v udržaní remisie pri UC**
  (Li-Xuan San get al. WJG, 2010)

- **Zlepšenie imunologického statusu a redukcia zápalových markerov**
  (Lorea B, et al. Clin Exp Immunol, 2007)
  (Furrie,E. Gut,2005)

- **Menší počet relapsov**

- **Porovnateľnosť s mesalazinom**
  (Zocco, A.M., Aliment Pharmacol Ther ,2006)

- **Zlepšenie extraintestinálnych príznakov (najmä kĺbnych a očných)**
  (Cain AM et al. Alternative Ther in Health and Med, 2011)

Summary of Probiotics in UC

- Over the past 3 years we have seen a more robust efficacy of probiotics, such as VSL#3, to induce remission in mild-to-moderately active UC
- The efficacy of probiotics as an "ADJUNCT" therapy for patients who fail standard therapy and who otherwise have to step up to steroids and/or immunosuppressives is an important contribution to the clinical field.
- This beneficial effect was also reported in children with UC, a group in which we would like to avoid the use of steroids that could lead to further growth retardation. 25

Summary of Probiotics in UC

	Probiotics Strains	Evidence
Inductions of Remission	VSL#3	Level A
Maintenance of Remission	VSL#3	Level A
	E coli Nissle 1917	Level B
Pouchitis	VSL#3	Level A

26

ECCO statement

Pouchitis a probiotiká

Liečba pouchitídy

- **ATB terapia je základným kameňom terapie pouchitídy, najviac využívaný metronidazol a to aj v dlhodobom podávaní, tiež ciprofloxacin a rifaximín**

- **Viac ako 50% pacientov pri tejto liečbe udáva rôzne dyspeptické ťažkosti rôznej intenzity, ktoré mu zhoršujú kvalitu života**

(Cima RR, Pemberton JH. In Gastrointestinal and Hepatology, 2010)

Nezanedbateľnou komplikáciou pri dlhodobom používaní najmä metronidazolu je riziko periférnej neuropatie

Pouchitis and probiotics

Pouchitis

- Maintenance of antibiotic-induced remission
- Treatment of acute active pouchitis
- Postoperative prevention of pouchitis

Clinical Trials in Pouchitis: Acute Active Pouchitis

Reference	Study	n	Duration	Probiotic	Control	Response to Probiotic (Remission)	Response to Placebo (Remission)	p value
Kuisma et al. 2003	RCT, DB	20	3 months	Lactobacillus rhamnosus GG	Placebo	0%	0%	ns
Gosselink et al. 2004	Open -label	117	36 months	Lactobacillus rhamnosus GG	Historical controls	Relapse rate: 8%	Relapse rate: 35%	0.01
Laake et al. 2003	Open-label	10	1 month	Cultura	None	50% endoscopic improvement; no histologic improvement	n/a	-
Laake et al. 2005	Open-label	51	1 month	Cultura	None	Significant decrease in GI symptoms p<0.0005; decrease in eye symptoms p=0.02 59% remission	n/a	-

Clinical Trials in Pouchitis: Acute Active Pouchitis

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Clinical Trials in Pouchitis: Post-Operative Prevention

Reference	Study	n	Duration	Probiotic	Control	Response to Probiotic (Remission)	Response to Placebo (Remission)	p value
Gionchetti et al. 2003	RCT, DB	40	12 months	VSL#3 (3g)	Placebo	90% Relapse: 10%	60% Relapse: 40%	<0.05

Probiotiká pri IPAA v klinických štúdiách

- **Efektivitu zmesi VSL#3 pri udržaní remisie pri pouchitíde sledovali tri štúdie s uspokojivým výsledkom. Z hľadiska prevencie pouchitídy sa sledoval v otvorenej štúdii kmeň *L.rhamnosus* GG po dobu 3 rokov, incidencia pouchitídy v tejto skupine bola len 7% oproti kontrolnej s výskytom 29%**

(Gosselink MP et al. Dis Colon Rectum,2004)

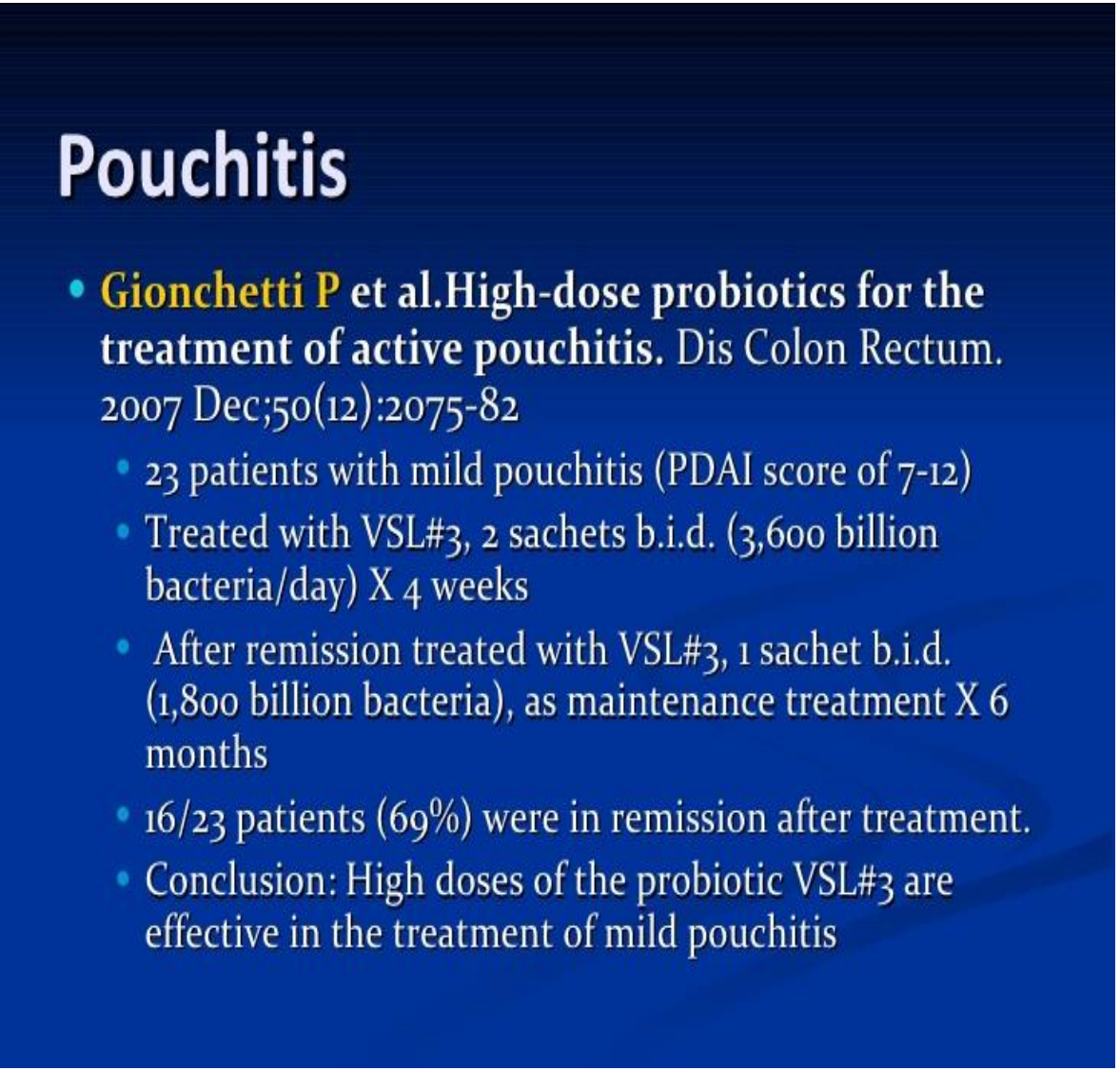
- **Sľubné výsledky v prevencii pouchitídy tiež priniesla štúdia s VSL#3, ktorý sa podával počas 1 roku. Pouchitída sa objavila len u 10% pacientov s probiotikom a až u 40% v placébovej skupine.**

(Gionchetti P et al, Gastroenterology,2003)

Štúdia (Gionchetti a spol,2007) s použitím probiotického koktailu VSL#3 pri indukovaní remisie pri pouchitíde počas 4 týždňov dokázala redukciu skóre indexu aktivity pri pouchitíde (podľa Sandborna) a navodila remisiu v 69%. Pri pokračujúcom podávaní VSL#3 počas 6 mesiacov sa remisia udržala

(Gionchetti P et al. Dis Colon Rectum, 2007)

Pouchitis



Benefit terapie pri indukcii remisie pomocou EcN: Kužela a spol, Induction and maintenance of remission with nonpathogenic E. coli in patients with pouchitis.

Am J Gastroenterol,2001,96:3218-9

Odporúčania pre probiotiká pri pouchitíde

POUCHITIS	HLADINA ODPORÚČANIA	MIKROORGANIZMUS	DÁVKA
Indukcia remisie	B	VSL#3	12g/deň
	B	Cultura milk	500ml/deň
	C	EcN	2,5 x 1010 bid
Udržanie remisie	A	VSL#3	6g/deň
Prevencia	A	VSL#3	3g/deň
	A	L.rhamnosus GG	1,4 x 1010/deň

Summary IBD and probiotics

- Evidence for use strongest in pouchitis esp. with VSL#3. Reasonable option along with medical therapy. Long-term efficacy uncertain.
- E.coli Nissle equivalent to 5 ASA in UC and may be used as enemas for distal disease. Could be considered in patients intolerant or resistant to 5-ASA preparations
- Studies of probiotics in CD have been disappointing and a recent systematic review has concluded that their use could not be recommended on the available evidence (Rolfe et al. 2006)

Infekcia Cl. difficile

Fecal microbiota transplantation (FMT)

Fecal microbiota transplantation (FMT) is a promising therapy for *Clostridium difficile* infection (CDI). However, questions remain regarding efficacy and safety in inflammatory bowel disease (IBD) patients, as well as longitudinal stability of donor stool composition. This report describes an IBD patient with two CDIs 18 months apart, each successfully treated with FMT with no IBD flares or complications. Microbiome composition analysis of patient samples during each infection revealed low-diversity microbiota patterns similar to those previously described in non-IBD patients with CDI and active IBD alone. Samples taken after each transplant demonstrated quick remodeling towards the donor's sample composition coinciding with symptom resolution. Of note, samples taken from the same donor 18 months apart reflected marked differences in microbiota abundances, suggesting that the use of single donors in FMT programs offers little benefit in ensuring predictability of donor stool composition over time. This report describes similar microbial composition patterns during CDI in IBD patients to those described previously in non-IBD patients, and supports FMT as safe and effective treatment for recurring CDI in this patient population.

Chantalle Brace, Gregory B. Gloor, Mark Ropeleski, Emma Allen-Vercoe, Elaine O. Petrof
Microbial composition analysis of Clostridium difficile infections in an ulcerative colitis patient treated with multiple fecal microbiota transplantations, JCC,2014

Fecal microbiota transplantation (FMT)

- **Meta- analýza (Anderson JL et al, 2012), 17 štúdii, 9 z nich case reports (case series or case reports), v 8 použitá FMT s infekciou Cl. difficile, z 25 pts v 19 prípadoch s úspechom**

Anderson JL et al Aliment Pharmacol Ther,2012

- **Kunde et al,2013 open label study- 10 detí so stredne ťažkou UC liečených FMT (5 dní) s odpoveďou 6 detí z 9, ktoré dokončili štúdiu**

Kunde S, et al J Pedr gastroenterol Nutr, 2013

Fecal microbiota transplantation for severe enterocolonic fistulizing Crohn's disease.

- Authors Zhang FM, et al. Show all Journal
- World J Gastroenterol. 2013 Nov 7;19(41):7213-6. doi: 10.3748/wjg.v19.i41.7213.

Affiliation

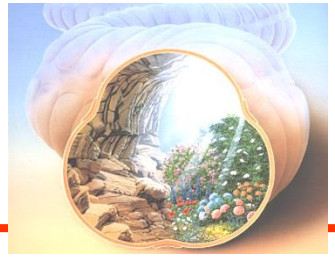
Fa-Ming Zhang, Hong-Gang Wang, Min Wang, Bo-Ta Cui, Zhi-Ning Fan, Guo-Zhong Ji, Digestive Endoscopy and Medical Center for Digestive Diseases, the Second Affiliated Hospital of Nanjing Medical University, Nanjing 210011, Jiangsu Province, China.

Abstract

The concept of fecal microbiota transplantation (FMT) has been used in traditional Chinese medicine at least since the 4(th) century. Evidence from recent human studies strongly supports the link between intestinal bacteria and inflammatory bowel disease. We proposed that standardized FMT might be a promising rescue therapy for refractory inflammatory bowel disease. However, there were no reports of FMT used in patients with severe Crohn's disease (CD). Here, we report the successful treatment of standardized FMT as a rescue therapy for a case of refractory CD complicated with fistula, residual Barium sulfate and formation of intraperitoneal large inflammatory mass. As far as we know, this is the first case of severe CD treated using FMT through mid-gut.

Source

http://www.ncbi.nlm.nih.gov/m/pubmed/24222969/



A new approach in pseudomembranous colitis: probiotic *Escherichia coli* Nissle 1917 after intestinal lavage

K J Goerg et al. Eur J Gastroenterol Hepatol 2008; 20(2): 155-6.

- 8/10 PMC patients (57 – 83 years of age), *Clostridium difficile* and the toxin were detected in stools.

Treatment

Initial gut lavage (3 – 4 l Klean-Prep®)

Subsequent Mutaflor®: once by endoscope (20 ml = 12.5 x 10^{10} CFU) and further orally (3 x 1 capsule/day) for 3 weeks

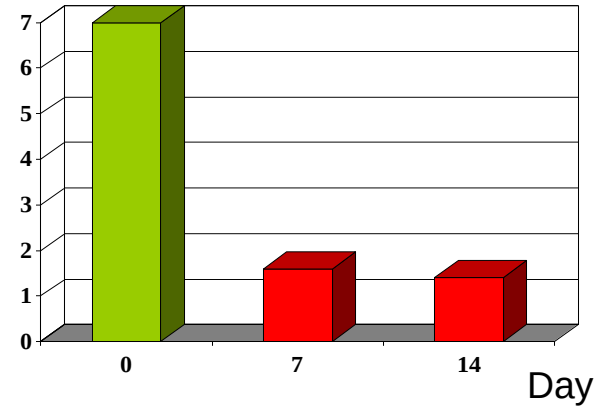
Results

Normalisation of

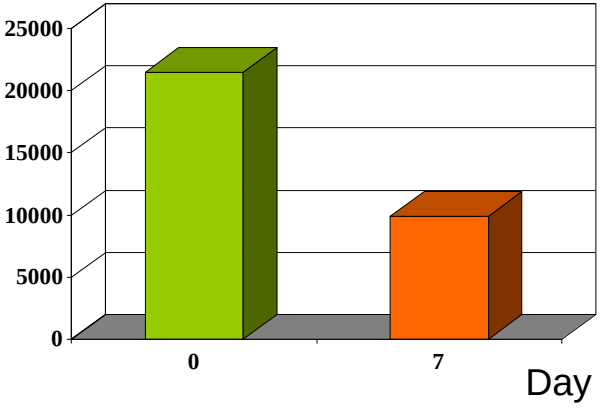
a) stool frequency
b) blood leukocytes
c) body temperature

100% recovery and no relapse within 6 weeks.

Stool frequency



Blood leukocytes



IBD a IBS like sy

IBD a IBS

Inflammatory bowel disease and irritable bowel syndrome: similarities and differences
Giovanni Barbara, Cesare Cremon, and Vincenzo Stanghellini, Current Opinion in gastroenterol,2014

Summary

IBD and IBS remain separate conditions although there are some overlapping mechanisms. Both research and clinical management would benefit from considering a functional approach for certain manifestations of IBD and accepting an organic view in subsets of IBS patients

- Meta-analýza 1703 pts ukazuje, že prevalencia IBS symptómov u pts s IBD v remisii je 35%
- MC je s vyšším rizikom IBS sy ako UC (OR: 1,74, 95% CI: 1,24-2,43)

Halpin SJ, Am J Gastroentrol,2012

- IBS sy sa u pts s UC vyskytuje v 19% pri ročnej kontrole

IBS sy je asociovaný so ženským pohlavím, u pts s udaním únavy,úzkosti a strachu pri dotazníku kvality života

Jonefiall B et al, Neurogastroentrol Motil, 2013

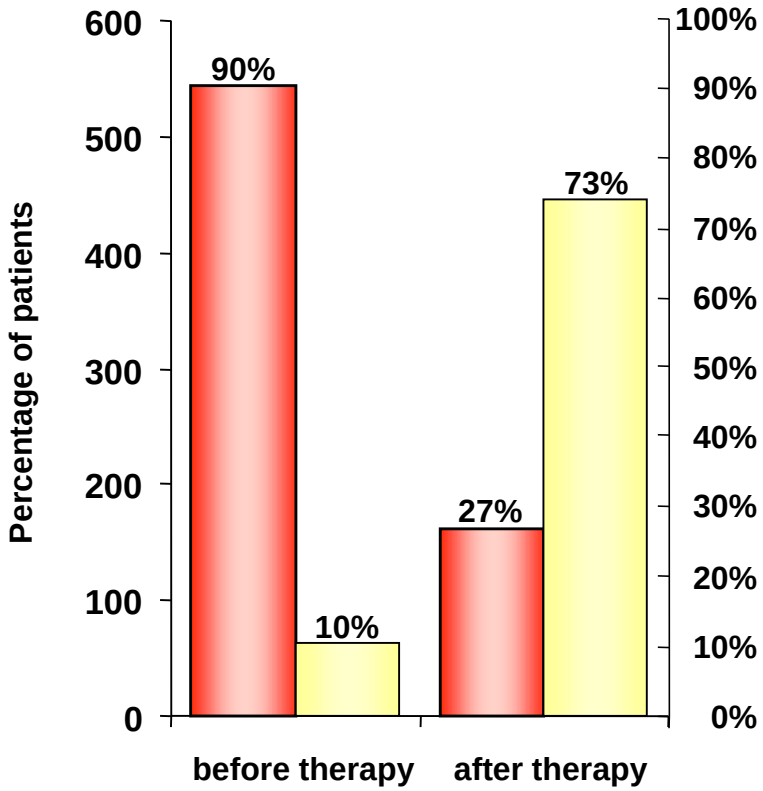
- Fekálny kalprotektín je signifikantne vyšší u pts s IBD a zároveň s IBS sy ako bez sy IBS

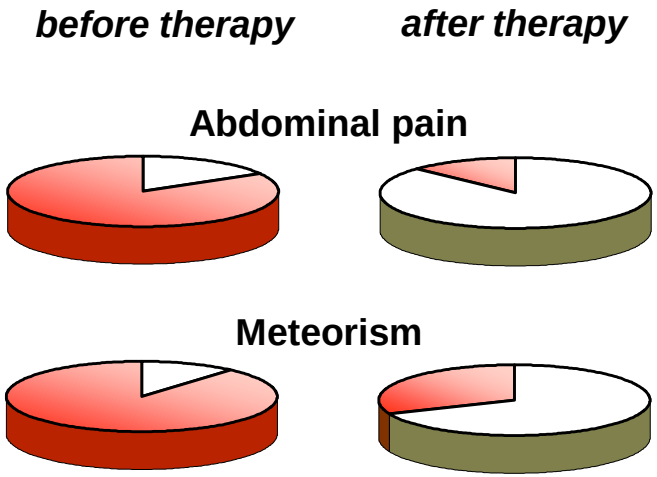
Keohane J et al, Am J Gastroentrol, 2010

- Narušená diverzita črevnej mikroflóry u IBD a IBS

Major G et al, Curr Opin Endocrinol Diabetes Obes, 2014
Cader MZ, Gut,2013
Rajilic-Stojanovic M et al, Inflamm Bowel Dis, 2013

Irritable bowel syndrome
(Adults N=607)





Stool consistency:

- Normal
- Altered

- ∅ Treatment duration: 60 days
- ∅ Dose: 2 cps. Mutaflor / day

E. Coli kmeň Nissle 1917- skúsenosti

- **18 pts s UC**
- **Stupeň aktivity- mierna až stredne ťažká forma**
- **Pôvodná terapia: kortikoidy, mesalazin, imuran (aj kombinácia)**

- **Súčasnosť- pts v remisii, z toho:**

- **11 pts len na terapii mutaflorom**
- **5 kombinácia mutaflor a mesalazin (1-1,5 g)**
- **2 kombinácia s imuranom (1 na dávke 50 mg a 1 na dávke 100 mg)**
- **Nie je nutná eskalácia terapie**

Záver

Aj napriek veľkému množstvu nezodpovedaných otázok v oblasti probiotík by bolo v praxi vhodné pri výbere probiotického prípravku pre pacientov s IBD prejsť od všeobecného pojmu „probiotikum“ ku konkrétnym bakteriálnym kmeňom, či prípravkom s potvrdenými pozitívnymi účinkami u týchto pacientov. Preto je potrebné realizovať kontrolované štúdie s dobrým dizajnom, ktoré by priniesli v budúcnosti odpovede na otázky ohľadom účinnosti, dávkovania, trvania podávania, alebo používania jednotlivych kultúr alebo mixtúr

Ďakujem za pozornosť

Probiotics: *Bifidobacterium* and *Lactobacillus*

Pinky Sheetal V

M.tech Bioinformatics

Life without gut bacteria would be extremely unpleasant, if not impossible

GR Gibson & CM Williams. Brit J Nutr 1999; 81: 83-4.

Role of the bacteria in the pathogenesis of IBD

several scenarios can be considered

- **Pro-inflammatory bacteria, such as enteroinvasive *Escherichia coli* strains, are more frequently seen in the ileal mucosa of patients with Crohn's disease than in healthy controls, which suggests that these bacteria can initiate disease**

Darfeuille-Michaud, A. *et al.* High prevalence of adherent-invasive *Escherichia coli* associated with ileal mucosa in Crohn's disease. *Gastroenterology* 127,412–421 (2004).

- **An alternative hypothesis suggests that the reduced frequency of a Firmicutes species, *Faecalibacterium prausnitzii*, in the intestinal microbiota is a causative factor of Crohn's disease16. This strain releases an unidentified soluble factor, which inhibits pro-inflammatory epithelial cell responses *in vitro* and attenuates inflammation in a mouse model of colitis**

Sokol, H. *et al. Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc. Natl Acad. Sci. USA* 105, 16731–16736 (2008).

- **other studies, however, suggest that more global changes in the composition of the microbiota are associated with IBD,such as abnormal adherence of bacteria to the gut mucosa, reduced bacterial diversity, decreased levels of resident Firmicutes spp.and/or *Bacteroides* spp. and an overgrowth of proteobacteria**

Frank, D. N. *et al.* Molecular-phylogeneticcharacterization of microbial community imbalances in human inflammatory bowel diseases. *Proc. Natl Acad.Sci. USA* 104, 13780–13785 (2007).

Sokol, H. *et al.* Specificities of the fecal microbiota in inflammatory bowel disease. *Inflamm. Bowel Dis.* 12,106–111 (2006).

Swidsinski, A., Weber, J., Loening-Baucke, V., Hale, L. P.& Lochs, H. Spatial organization and composition of the mucosal flora in patients with inflammatory bowel disease. *J. Clin. Microbiol.* 43, 3380–3389 (2005).

Clostridium difficile - probiotiká

Table 1
Randomized, controlled clinical trials of probiotics for the treatment of *Clostridium difficile* infections.

Probiotic	Population	Daily dose	Duration (days)	Frequency of CDI relapses in probiotic	Frequency of CDI relapses in controls	References
S. boulardii	124 adult patients on varied doses of vancomycin or metronidazole; recurrent and initial CDAD cases	3×10^{10}	28, followed for another 4 weeks	15/57 (26.3%*)	30/67 (44.8%)	McFarland 1994 [35]
S. boulardii	National, 1993–1996, 170 adult patients recurrent CDAD; on vancomycin (500 mg/d, $n=83$) or (2 g/d, n=32) or metro (1 g/d, $n=53$)	2×10^{10}	28, followed for another 4 weeks	Vanco (2g/d) 3 (17%*) Vanco (500 mg/d) 23 (51%) ns Metro (1g/d) 13 (48.1%) ns	7 (50%) 17 (44.7%) 13 (50%)	Surawicz 2000 [36]
Lactobacillus rhamnosus GG	25 Adults on vancomycin or metronidazole, recurrent and initial CDAD	Not reported	21	4/11 36.4% ns	5/14 35.7%	Pochapin 2000 [37]
L. plantarum 299v	29 Enrolled, 20 adults finished, 9 sites, 1–5 prior episodes, Over 2 yrs	5×10^{10}	38 days, followed until Day 70	4/11 (36%) ns	Metro only, 6/9 (67%)	Wullt 2003 [38]
L. rhamnosus GG and 64 mg inulin	15 Adults on vanco or metro with CDAD, Enrolled over 9 months	8×10^{10}	Duration of abx + 21 days	3/8 (37.5%) ns	1/7 (14.3%)	Lawrence 2005 [39]

* $P<0.05$ compared to controls, ns=not significant, abx=antibiotics

Clostridium difficile - probiotiká

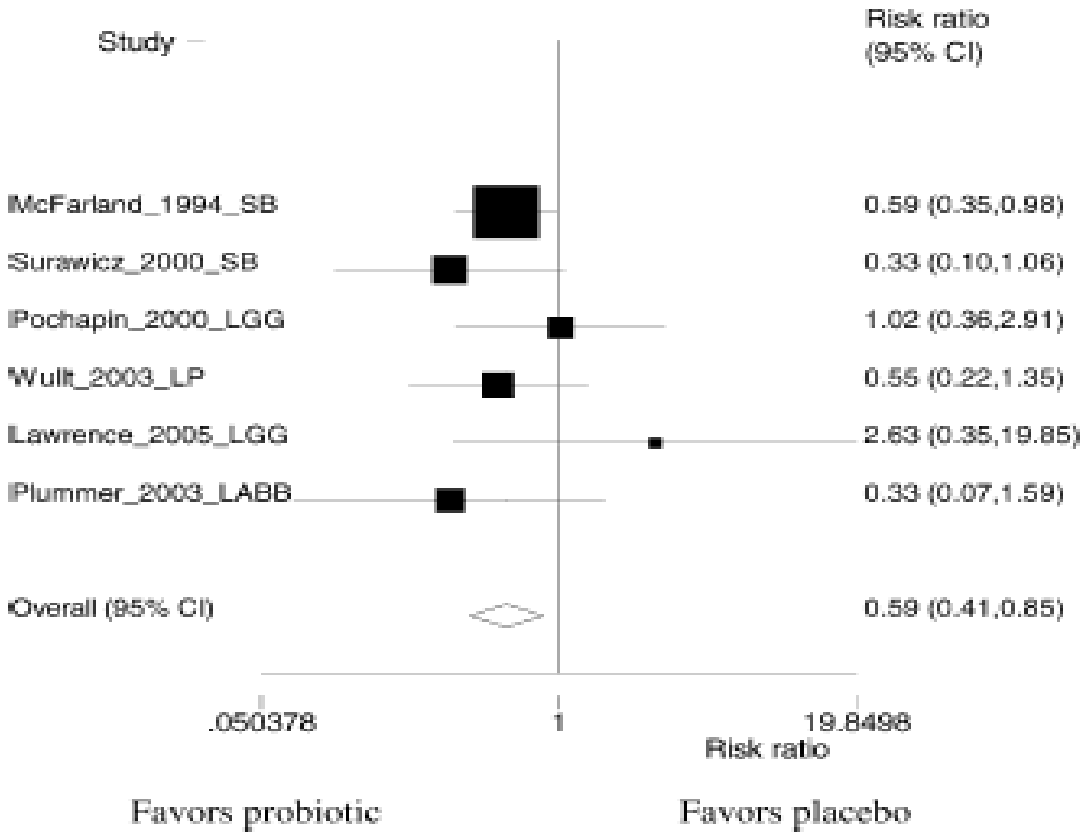


Figure 4. Forest Plot of six randomized controlled trials of probiotics for the treatment of *Clostridium difficile* disease showing crude and pooled risk ratios. SB = *Saccharomyces boulardii*; LGG = *Lactobacillus rhamnosus* GG; LP = *Lactobacillus plantarum* 299v; LA = *Lactobacillus acidophilus*; BB = *Bifidobacterium bifidum*.

microbiome

We are only NOW learning microbes are involved in a lot of processes.

2008 began microbiome, but only in 2011 and 2012 did microbiome broke out in the scientific literature

Protizápalove vlastnosti rôznych kmeňov probiotík

- *Lactobacillus casei* DN-114-001 **znižuje pro-zápalovy cytokin TNFα u pacientov s Crohnovou chorobou**

Borruel N, Carol M, et al. Increased mucosal tumour necrosis factor alpha production in Crohn's disease can be downregulated ex vivo by probiotic bacteria. *Gut.* 2002;51:659–664.

- *Bifidobacterium breve* Yakult a *B. bifidum* Yakult **indukovali produkciu IL-10 v ľudských periférnych krvných mononukleárnych bunkách u pacientov s ulceróznou kolitidou a inhibovali produkciu zápalovych cytokínov IL-8 v HT-29 bunkových líniach**

Imaoka A, Shima T, et al. Anti-inflammatory activity of probiotic Bifidobacterium: Enhancement of IL-10 production in peripheral blood mononuclear cells from ulcerative colitis patients and inhibition of IL-8 secretion in HT-29 cells. *World J Gastroenterol*. 2008;14:2511–2516

Protizápalove vlastnosti rôznych kmeňov probiotík

- **VSL#3 zvyšuje produkciu protizápalového cytokinu IL-10 pomocou dendritických buniek**

Drakes M, Blanchard T, Czinn S Bacterial probiotic modulation of dendritic cells. *Infect Immun.* 2004;72:3299–3309.

- ***L. casei* (23) vykazoval protizápalovy účinok na *Shigella* -infikovaných ľudských črevnych epiteliálnych bunkách prostredníctvom inhibície aktivácie NFκB (nuklearny faktor kappa B)**

Tien MT, Girardin SE, et al. Anti-inflammatory effect of Lactobacillus casei on Shigellainfected human intestinal epithelial cells. *J Immunol.* 2006;176:1228–1237.

***Lactic Acid Bacteria – Microbiological and Functional Aspects*. 4th edn, edited by S. Lahtinen, A.C. Ouwehand, S. Salminen and A. Von Wright. CRC Press (Taylor & Francis Group), Boca Raton: FL, USA, 2012. ISBN 0 978-1-4398-3677-4.**

- **je opisaná súvislosť medzi expresiou IL-10 a prevenciou recidívy chronickej UC po uživani probiotík**

Cui HH, Chen CL, et al. Effects of probiotic on intestinal mucosa of patients with ulcerative colitis. *World J Gastroenterol.* 2004;10:1521–1525.

Treatment of Acute Active Crohn's Disease

Reference	Study	n	Duration	Probiotic	Control	Remission rate (Probiotic)	Remission rate (Placebo)	*p* value
Malchow et al.1997	RCT	28	12 weeks	Steroid taper +E.Coli Nissle	Placebo	No difference		-
Gupta et al.2000	Open-label	4 children	24 weeks	LGG	n/a	100%	n/a	-
McCarthy et al.2001	Open-label	25	12 weeks	Lactobacillus salivarius	n/a	76%	n/a	-
Fujimori et al. 2007	Open-label	10	13 months	Synbiotic mixture: Bifidobacterium Breve, lactobacillus casei, Bifidobacterium longum and psyllium	n/a	Significant improvement	n/a	-

UC a probiotiká

- **Metaanalýza 13 randomizovaných kontrolovaných štúdií sledovala skóre remisii a rekurenčných epizód. Skupiny s administráciou probiotík sa porovnávali s placebom. Metaanalýza ukázala, že probiotická terapia bola efektívnejšia ako placebo v udržaní remisie pri UC**

(Li-Xuan San get al. WJG, 2010)

- **Probiotická liečba pri UC okrem zlepšenia klinického stavu mala priaznivý efekt aj na imunologický stav v zmysle antiinflamačného pôsobenia, čo sa dokázalo aj krvnými vyšetreniami**

(Lorea B, et al. Clin Exp Immunol, 2007)

- **Synergy 1 (*Bifidobacterium longum* v kombinácii s inulin-oligofruktózou)- redukcia zápalových markerov**

(Furrie,E. Gut,2005)

UC a probiotiká

- *S.boulardii* v kombinácii s 5 ASA vedie k nižšiemu počtu relapsov ako podávanie samotné
- LGG je rovnako efektívny v udržaní remisie ako mesalazin

(Zocco, A.M., Aliment Pharmacol Ther ,2006)

- Pacienti s UC pri užívaní probiotík s produkciou kyseliny mliečnej majú menej relapsov a dlhšiu dobu pokoja medzi relapsami v spojení s konvenčnou liečbou a aj samostatne
- Niektoré štúdie dokazujú zlepšenie extraintestinálnych (najmä kĺbnych a očných) príznakov pri užívaní probiotík s produkciou kyseliny mliečnej

(Cain AM et al. Alternative Ther in Health and Med, 2011)

IBD a IBS

Inflammatory bowel disease and irritable bowel syndrome: similarities and differences

Giovanni Barbara, Cesare Cremon, and Vincenzo Stanghellini, Current Opinion in gastroenterol,2014

- **Purpose of review**

  Inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) are classically viewed as dichotomous conditions. The former is perceived as a typical organic disease, and the latter is regarded as a disorder of gut function driven by mood. Recent research identified some shared contributing factors, which will be discussed here.

. **Recent findings**

Mounting evidence shows the importance in both IBD and IBS of genetic, microbiological, epithelial, and immunological factors. In some instances, these factors overlap in the two conditions as shown by: involvement of brain–gut axis dysfunction in IBD, implication of TNFSF gene in Crohn's disease and IBS, evidence of abnormal microbiota and its impact on host functions, identification of low-grade inflammation in subsets of IBS patients, and development of IBS symptoms in patients with IBD in remission.

- **Summary**

IBD and IBS remain separate conditions although there are some overlapping mechanisms. Both research and clinical management would benefit from considering a functional approach for certain manifestations of IBD and accepting an organic view in subsets of IBS patients