Section Five Slides

Botanicals, Microbiome, Biofilms, and Chronic Infections

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http://naimh.com
Notes and readings http://naimh.com/csch-biofilms

Seminar Overview

SECTION One

- The New Microbiology
- The Human Microbiome

SECtION TWO

- Infection
- Biofilms
- Berberine and related alkaloids
- Microbial defenses

SECTION THREE

- Host defenses
- Constituent synergy herbal therapeutics

SECTION FOUR

- Antifungal therapeutics

SECTION FIVE

- Biofilms in the gut
- Internal Biofilms

Themes for the weekend

- Germs are not the enemy, and attempts to eradicate them have led to serious unintended consequences, collectively and individually
- Biofilms are the natural base state of bacteria, archaea, and some fungi. Biofilms are not the enemy, and attempts to eradicate them may also produce unexpected and unintended adverse consequences.
- The microbiomes in the various regions of the body perform essential functions, and, if damaged, can allow increased pathogenic infections
- A **single** course of antibiotics ***can*** cause lasting damage to the microbiome. **Repeated** courses ***will*** cause lasting and irreversible damage

Biofilms in the gut

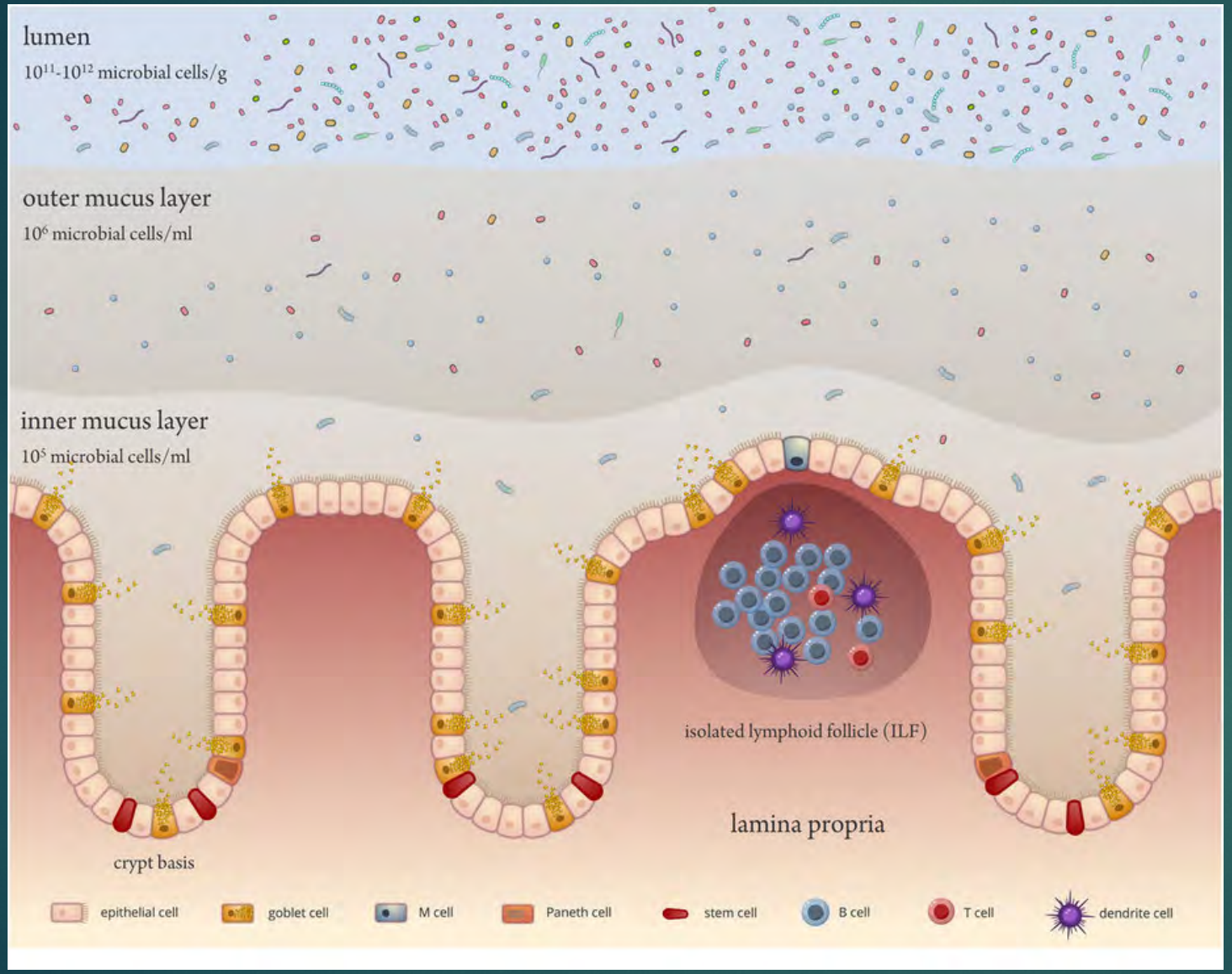
GASTROINTESTINAL BIOFILM STRUCTURES OF COMMENSAL MICROORGANISMS ARE ESSENTIAL TO NORMAL IMMUNOLOGICAL, METABOLIC, AND NEUROLOGICAL HEALTH

Biofilms in the gut

- Biofilms may form in the luminal food contents of the digestive tract.
- They also form within the mucin layer of the gut wall throughout the tract.
- The composition of the luminal and mucosal biofilms is different.
- The functions of the mucosal biofilms may be different from the identical organisms in the lumen due to quorum-sensing activation.
- Details of the composition of the mucin-layer biofilm in health and disease are scanty, and in some cases controversial.

Macfarlane S, Bahrami B, Macfarlane GT. Mucosal biofilm communities in the human intestinal tract. Adv Appl Microbiol. 2011;75:111-43.

de Bos WM. Microbial biofilms and the human intestinal microbiome. *npj Biofilms and Microbiomes* Article number: 15005 (2015)



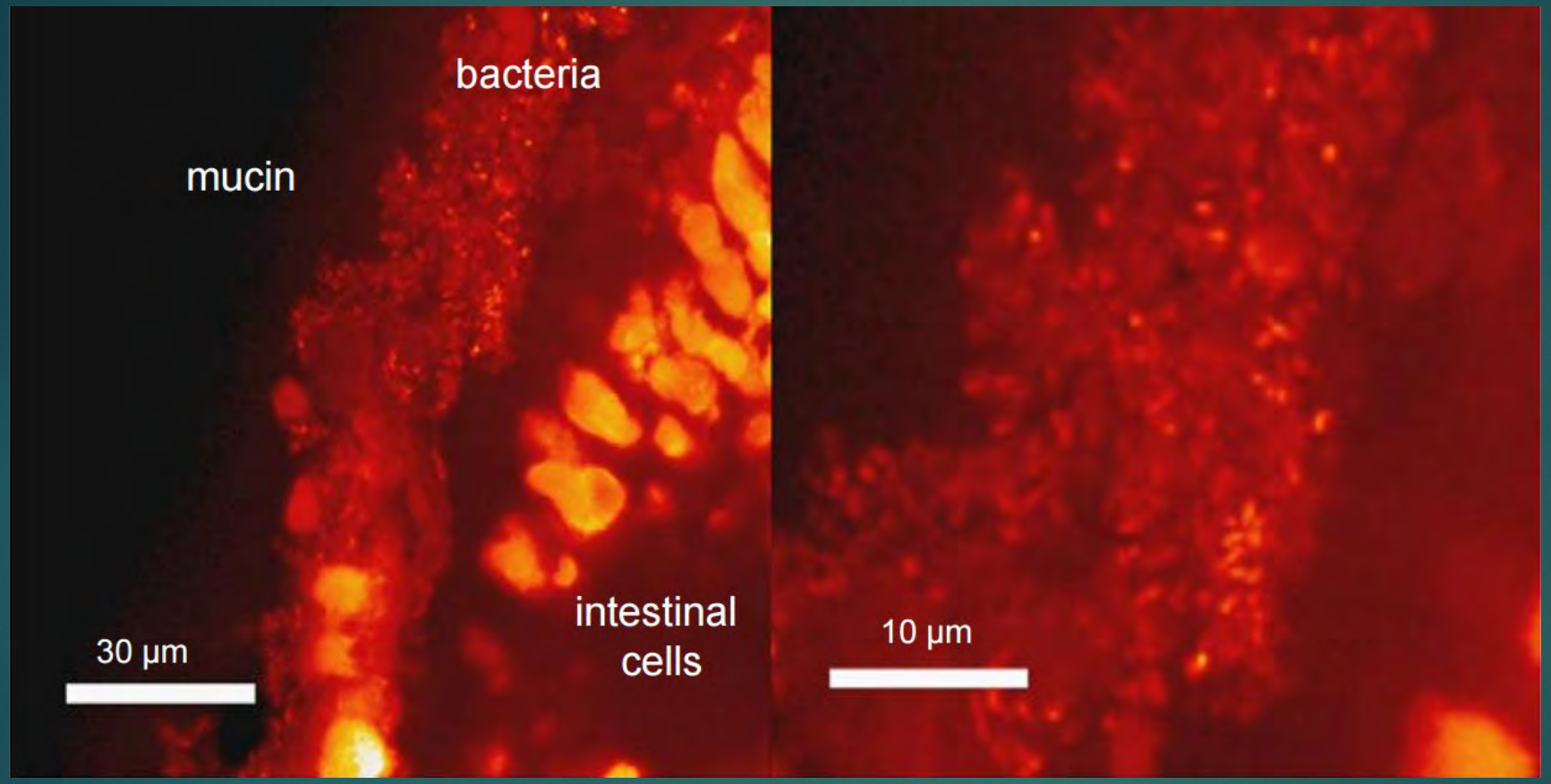
100,000,000,000/g

1,000,000 /mL

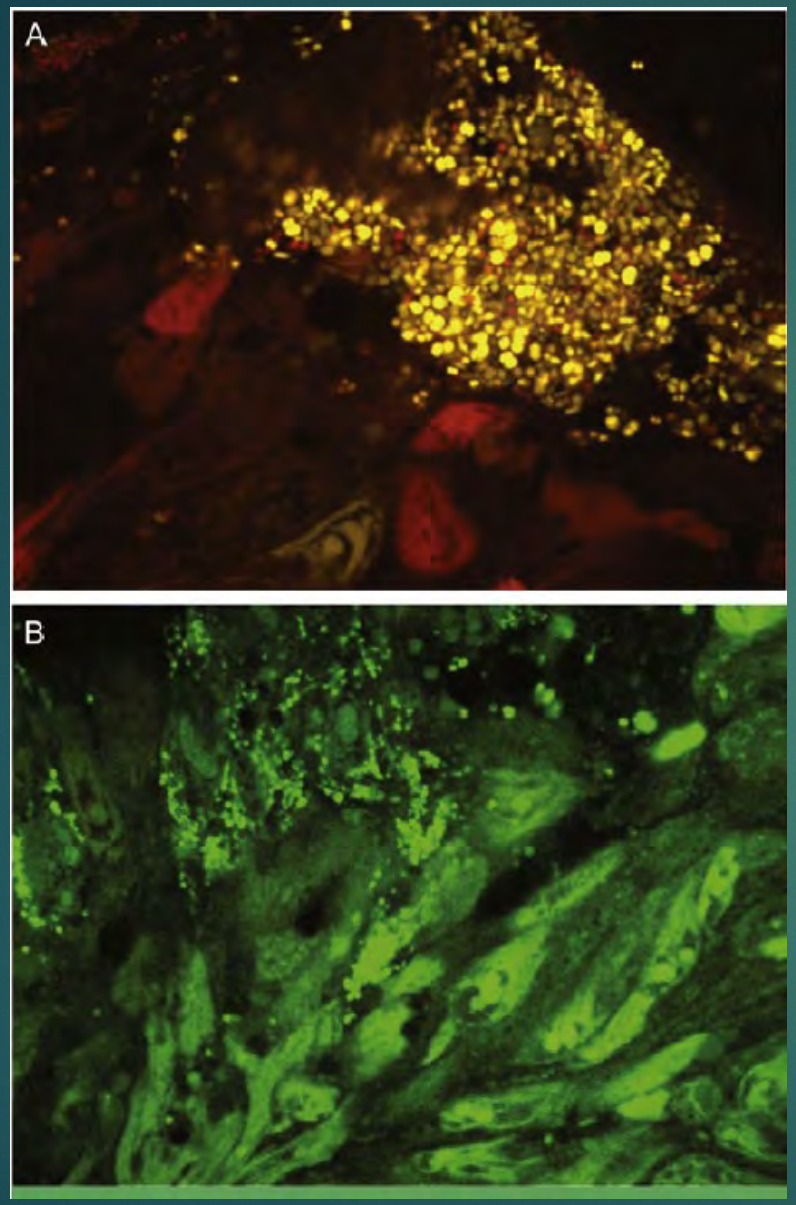
100,000/mL

About 5% of bacteria in feces is in biofilm form. Most bacteria in the mucus layer is in biofilms

De Weirdt R, Van de Wiele T. Micromanagement in the gut: microenvironmental factors govern colon mucosal biofilm structure and functionality. Biofilms and Microbiomes (2015) 1, 15026

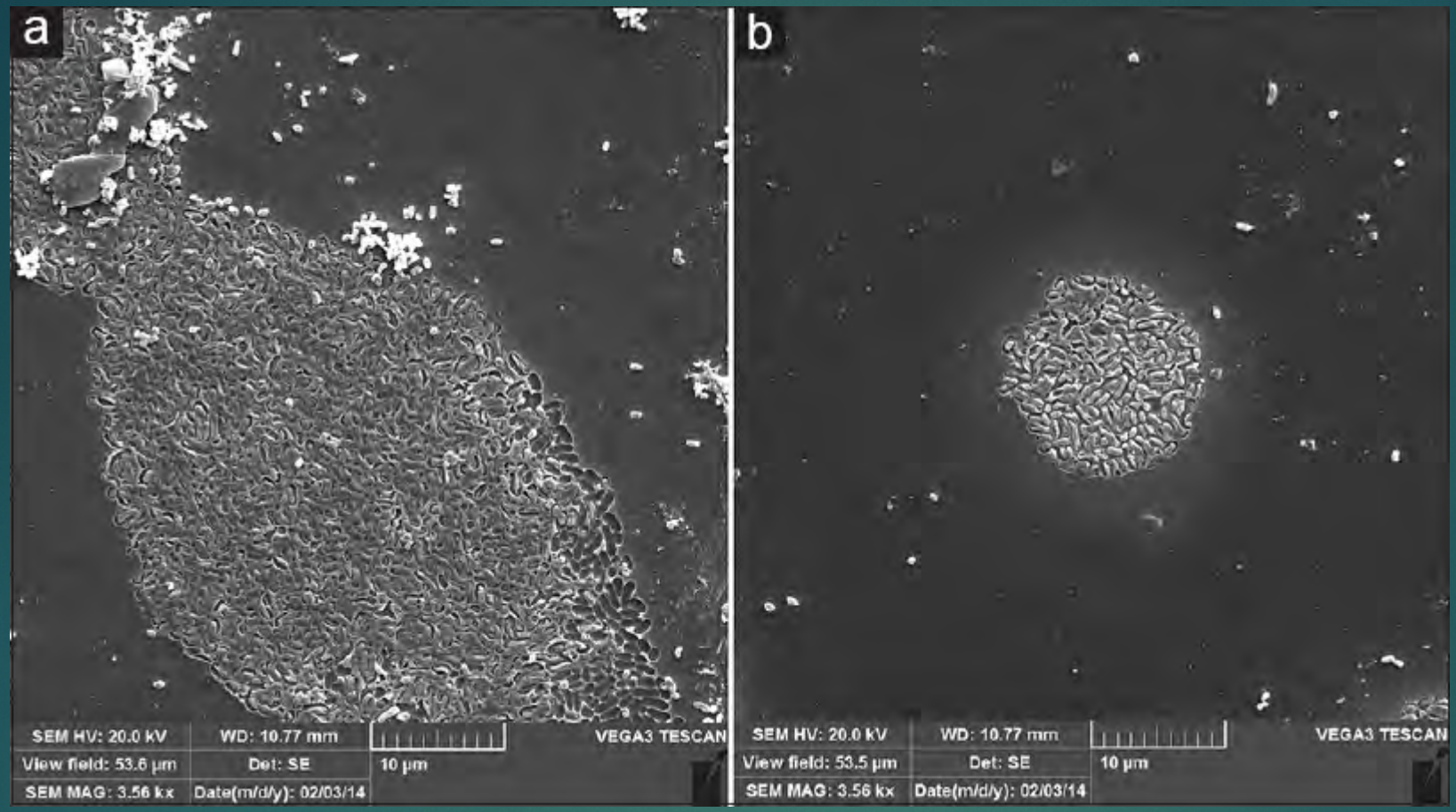


Bacterial biofilm in gut mucosal layer. Site not specified.

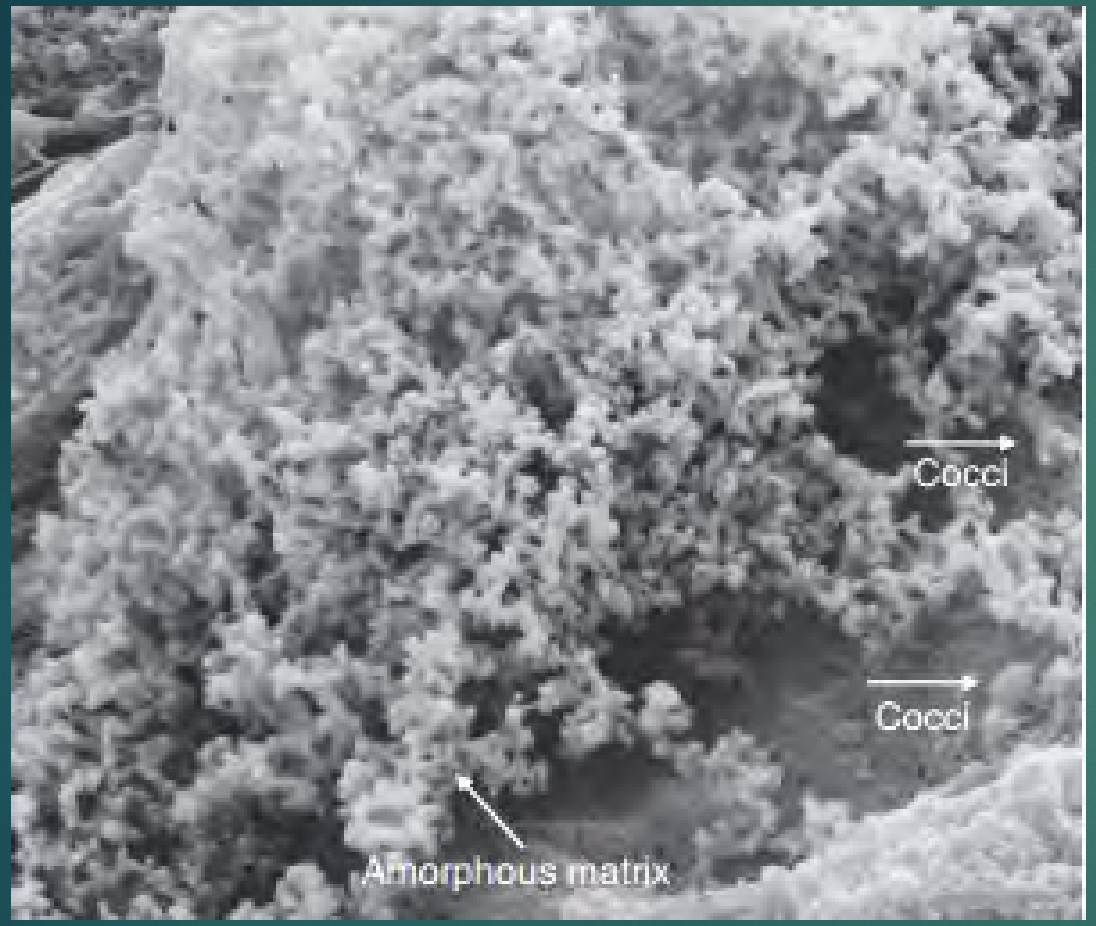


Stained multispecies biofilms in the esophageal mucus of patient with Barrett's esophagus (A) and normal (B)

Macfarlane S, Bahrami B, Macfarlane GT. Mucosal biofilm communities in the human intestinal tract. Adv Appl Microbiol. 2011;75:111-43



Scanning electron micrographs of *Helicobacter pylori* biofilms in the lab dish. *H pylori* settles into the mucous layer of the stomach wall where the pH remains neutral.

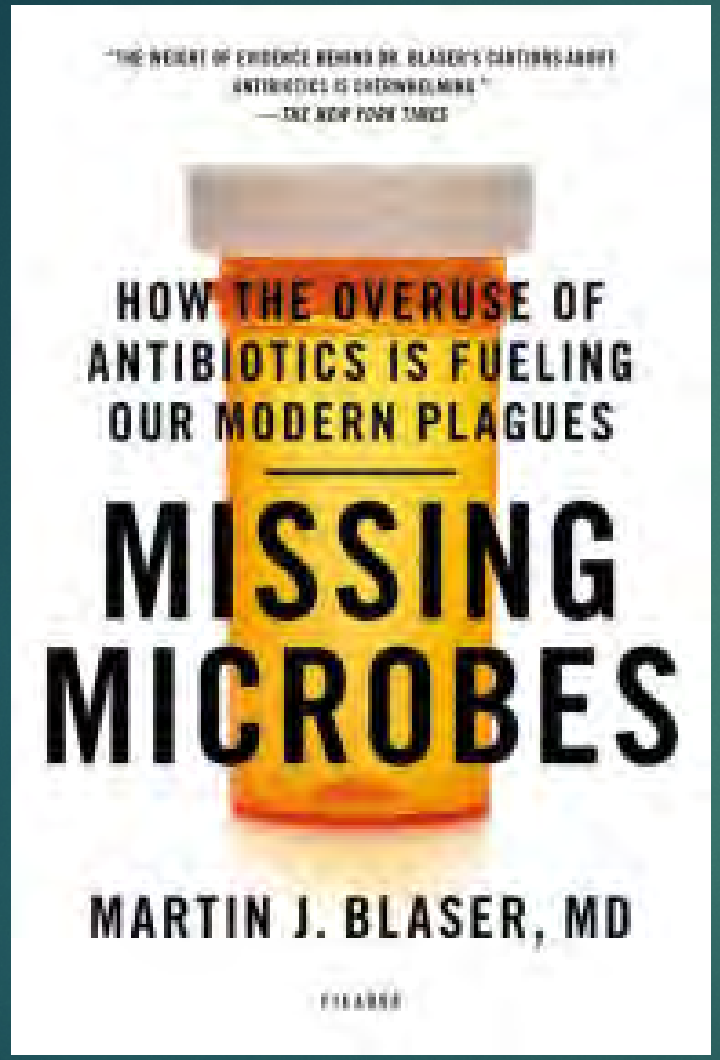


Dense extracellular matrix in gastric mucosal biopsy patient positive for *H. pylori* infection on breath analysis.

Cammarota G, Sanguinetti M, Gallo A, Posteraro B. Review article: biofilm formation by Helicobacter pylori as a target for eradication of resistant infection. Aliment Pharmacol Ther. 2012 Aug;36(3):222-30.

Helicobacter pylori

- *H. pylori* is a normal component of the gastric microbiome, present in the majority of the world's population, and in up to 90% of the population of third world countries.
- Sometimes the dominant species, and commensal, and produces no symptoms in 20% or fewer individuals in first-world studies.
- In one sample, 10/23 healthy individuals with no gastric symptoms tested positive for *H pylori.*
- Normally grows in a mucosal biofilm at neutral pH, in multispecies biofilm
- Pathology may be due to disruption or loss of the mucous layer.



- Blaser is one of the original researchers that discovered *H. pylori.*
- Eradication of *H. pylori* can assist in the healing of ulcers and chronic gastritis, but at a cost to the microbiome and the immune system.
- Patients without *H pylori*, either naturally or after eradication have a 2-8x incidence of GERD.
- Likewise patients without H pylori have a 30-40% increased incidence of asthma. Allergies, as measured on skin prick tests, are also increased.

Roberts formula for ulcers

- Roberts formula for ulcers was developed mid 20th century, long before the possible infectious basis of gastric ulcers was known, and before the discovery of H pylori.
- Most of the herbs are those that would traditionally be used on topical ulcers or poorly healing wounds.
- Most of the herbs have antiseptic and/or anti-biofilm properties.
- Later in the 20th century, J. Bastyr added *Baptisia* and pancreatic enzymes to the formula.

Roberts Formula for Ulcers

		Antiseptic	Anti biofilm	EPI	Local Immunity	Anti-inflammatory	Vulnerary
Althaea	cool	x			x	x	x
Geranium maculatum	cool	X*	x	x			
Hydrastis (leaf)	cold	X*	(x)	(x)			
Echinacea	cool	x		x	x	x	x
Phytolacca	cold	x			x		
(Baptisia)	cold	x	x	x	x		

*Specific strong activity against *H. pylori* in vitro

Duodenal ulcer

Exemplar drawn from of many similar cases at NCNM clinic during the 1980s before the discovery of *H. pylori,* using capsules of Bastyr's modified Roberts Formula

- **Patient:** 26 year-old high school teacher.
- **History:** Duodenal ulcer diagnosed by MD.
- **Botanical treatment**:
  - 8 parts Marshmallow *(Althea off.)*
  - 4 parts Wild Indigo *(Baptisia tinctoria)*
  - 8 parts *Echinacea angustifolia*
  - 8 parts Spotted Cranebill *(Geranium mac.)*
  - 8 parts Golden Seal *(Hydrastis canadensis)*
  - 8 parts Poke *(Phytolacca americana)*
  - 8 parts Slippery Elm *(Ulmus fulva)*
  - 2 parts pancreatin
  - 1 part niacinamide
  - 2 parts duodenal substance
  - One quart of cabbage juice per day.
- **Other treatments:**
  - Eliminate alcohol and coffee. Stress reduction techniques.
- **Follow up:** two weeks
- Patient is cutting back on the herbal formula and cabbage juice, and all symptoms are relieved.

N-acetyl cysteine and UGI biofilms

- N-acetyl cysteine has been used in clinical trials for *Helicobacter pylori* eradication.
- Pretreatment with N-acetyl-cysteine at 10 mg.
- All patients receive standard antibiotic therapy.
- Antibiotics more effective after pretreatment

Cammarota G, Sanguinetti M, Gallo A, Posteraro B. Review article: biofilm formation by Helicobacter pylori as a target for eradication of resistant infection. Aliment Pharmacol Ther. 2012 Aug;36(3):222-30.

Lactobacillus in stomach and duodenum

- Patients with bacterial overgrowth in stomach and duodenum (SIBO) after long-term PPI use.
- 10 billion mixed *Lactobacillus* organisms
- 30 mg of N-acetyl-cysteine (anti-biofilm)
- 2.34 g potato maltodextrin (prebiotic)
- QD with main meal for 10 days.

Del Piano M, Anderloni A, Balzarini M, Ballarè M, Carmagnola S, Montino F, Orsello M, Pagliarulo M, Tari R, Soattini L, Sforza F, Mogna L, Mogna G. The innovative potential of Lactobacillus rhamnosus LR06, Lactobacillus pentosus LPS01, Lactobacillus plantarum LP01, and Lactobacillus delbrueckii Subsp. delbrueckii LDD01 to restore the "gastric barrier effect" in patients chronically treated with PPI: a pilot study. J Clin Gastroenterol. 2012 Oct;46 Suppl:S18-26.

- Strong bacterial overgrowth in the stomach and duodenum of people treated with PPIs compared with subjects with a normal intragastric acidity.
- Overgrowth was stronger after long-term treatment with a PPI
- “Marked antagonistic activity” of *Lactobacillus* towards 5 strains of *E. coli*
- Significantly reduced bacterial overgrowth.
- *Lactobacilli* dominated bacterial counts (gastric/duodenal) post-treatment.
- Demonstrated ability to colonize/recolonize the stomach and duodenum.
- A significant decrease in fecal enterococci, total coliforms, E. coli, molds, and yeasts in subjects treated was recorded at the end probiotic supplementation compared with baseline.

TABLE 3. Quantification of Total Bacterial Cells and Total Lactobacillus (Mean ± SEM, log10 CFU/mL of Gastric Juice or Gram of Duodenal Brushing) at d_0 (all Groups) and d_{10} (Group B): Comparison Between Time 0 (d_0) and d_{10} in Group B

	Group B		
Time	log CFU/mL or log CFU/g	% of Total *Lactobacillus*	*P*†
d_0			
Gastric juice			
Total bacteria	8.60 ± 0.17		*
Total Lactobacillus	7.15 ± 0.25	3.51	*
Duodenal brushing			
Total bacteria	8.32 ± 0.33		*
Total Lactobacillus	6.76 ± 0.33	2.74	*
d_{10}			
Gastric juice			
Total bacteria	7.71 ± 0.27		0.0023
Total Lactobacillus	7.70 ± 0.27	98.03	0.0742
Duodenal brushing			
Total bacteria	7.47 ± 0.32		0.0256
Total Lactobacillus	7.44 ± 0.32	93.50	0.0355

*Comparison reference time (d_0).
†Comparison between baseline (d_0) and d_{10}.

	Day 0	Day 10
Gastric juice		
Total bacteria	600,000,000	71,000,000
Lactobacillus	11,500,000	70,000,000

Duodenal brushing		
Total bacteria	320,000,000	47,000,000
Lactobacillus	7,600,000	44,000,000

TABLE 8. Quantification of Specific Microbial Groups in Fecal Samples at d_0 (all Groups) and d_{10} (Group B): Comparison Between Baseline (d_0) and d_{10} in Group B

Time	Group B $\log_{10}$ CFU/g	*P*†
d_0		
Enterococcus spp.	7.80 ± 0.25	*
Total coliforms	9.55 ± 0.16	*
Escherichia coli	9.44 ± 0.18	*
Yeasts	5.95 ± 0.14	*
Molds	5.64 ± 0.14	*
d_{10}		
Enterococcus spp.	6.99 ± 0.23	0.0155
Total coliforms	8.01 ± 0.24	0.0064
Escherichia coli	7.97 ± 0.23	0.0105
Yeasts	3.56 ± 0.18	0.0066
Molds	4.30 ± 0.15	0.0053

Results are expressed as $\log_{10}$ CFU/g of feces (mean ± SEM).
*Comparison reference time (d_0).
†Comparison between baseline (d_0) and d_{10} in group B.

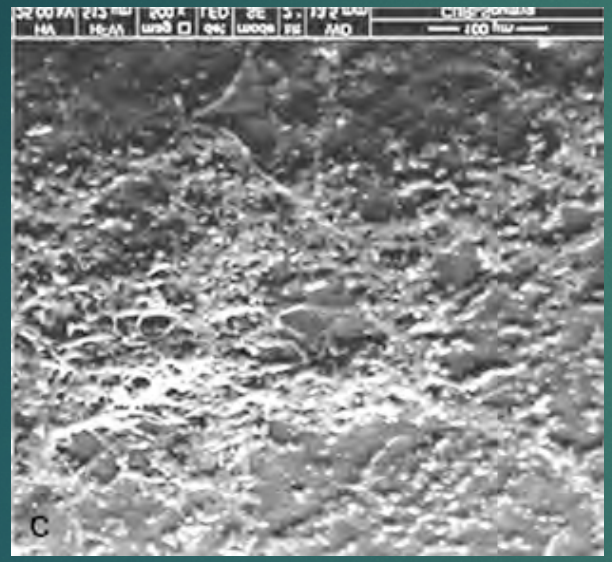
Stool bacterial counts of the measured species declined on the order of 10-100 times.

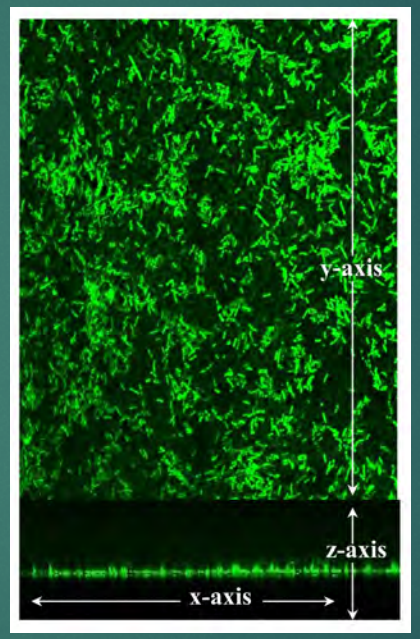
N-acetylcysteine and biofilms clinical trials review

Promising results when NAC can directly contact the biofilm

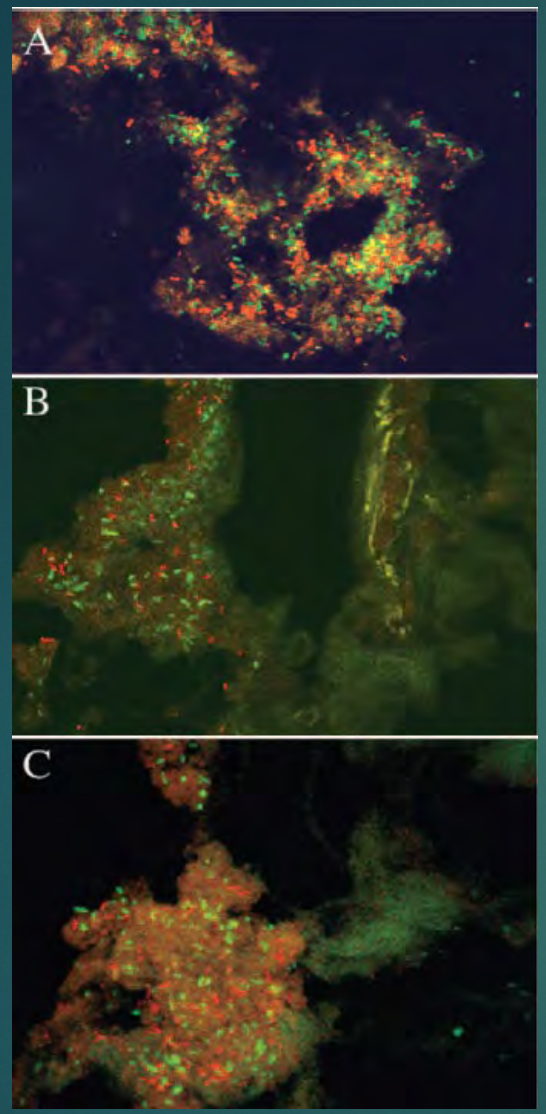
Dinicola S, De Grazia S, Carlomagno G, Pintucci JP. N-acetylcysteine as powerful molecule to destroy bacterial biofilms. A systematic review. Eur Rev Med Pharmacol Sci. 2014 Oct;18(19):2942-8. Review.

Lactobacillus and *Bifidobacterium* form complex biofilms within the mucosal layer of the intestinal tract





Lactobacillus biofilms on surface of an olive (left) and in lab dish (right).

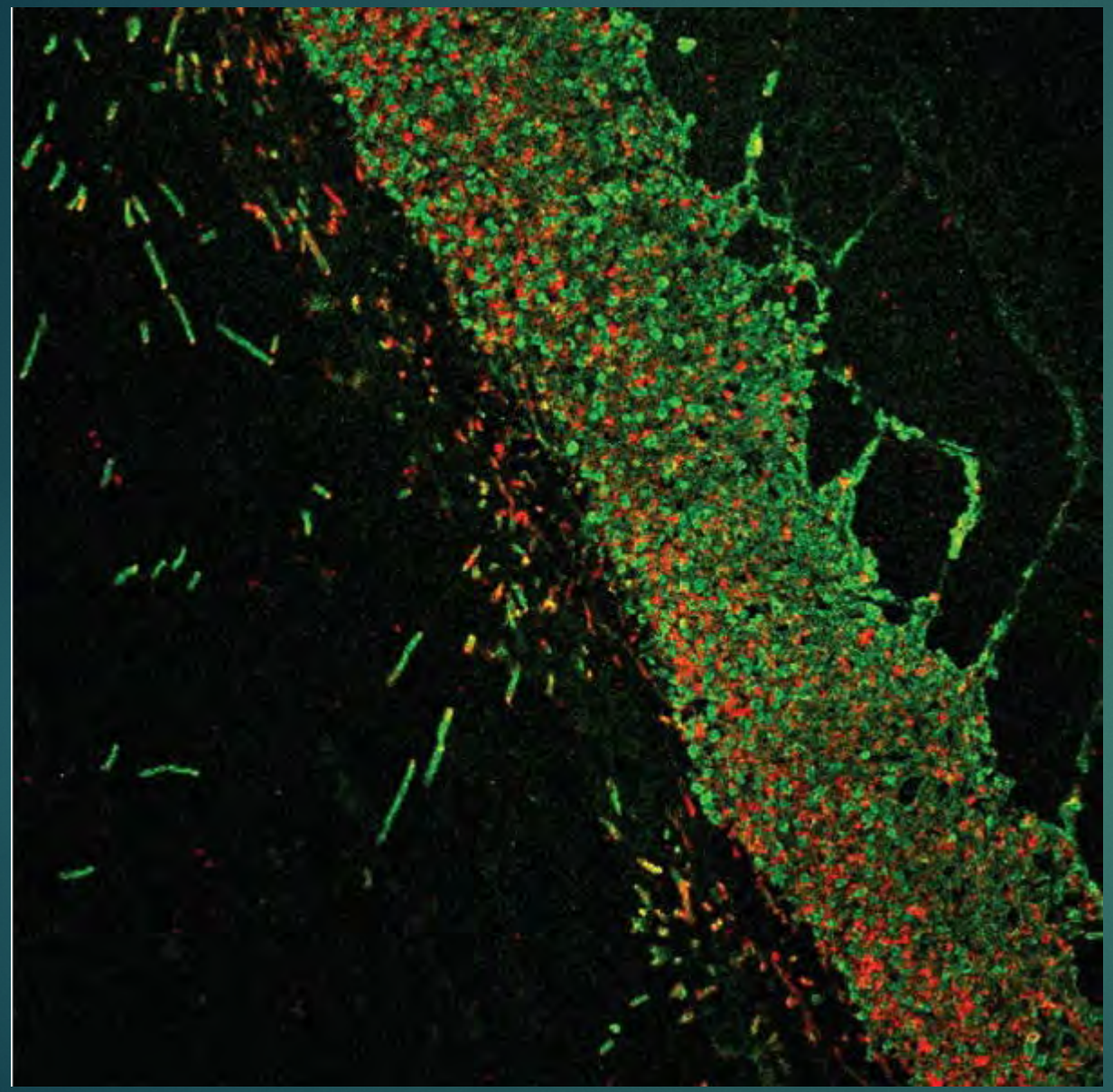


Cells growing in microcolonies in the mucosal layer of the

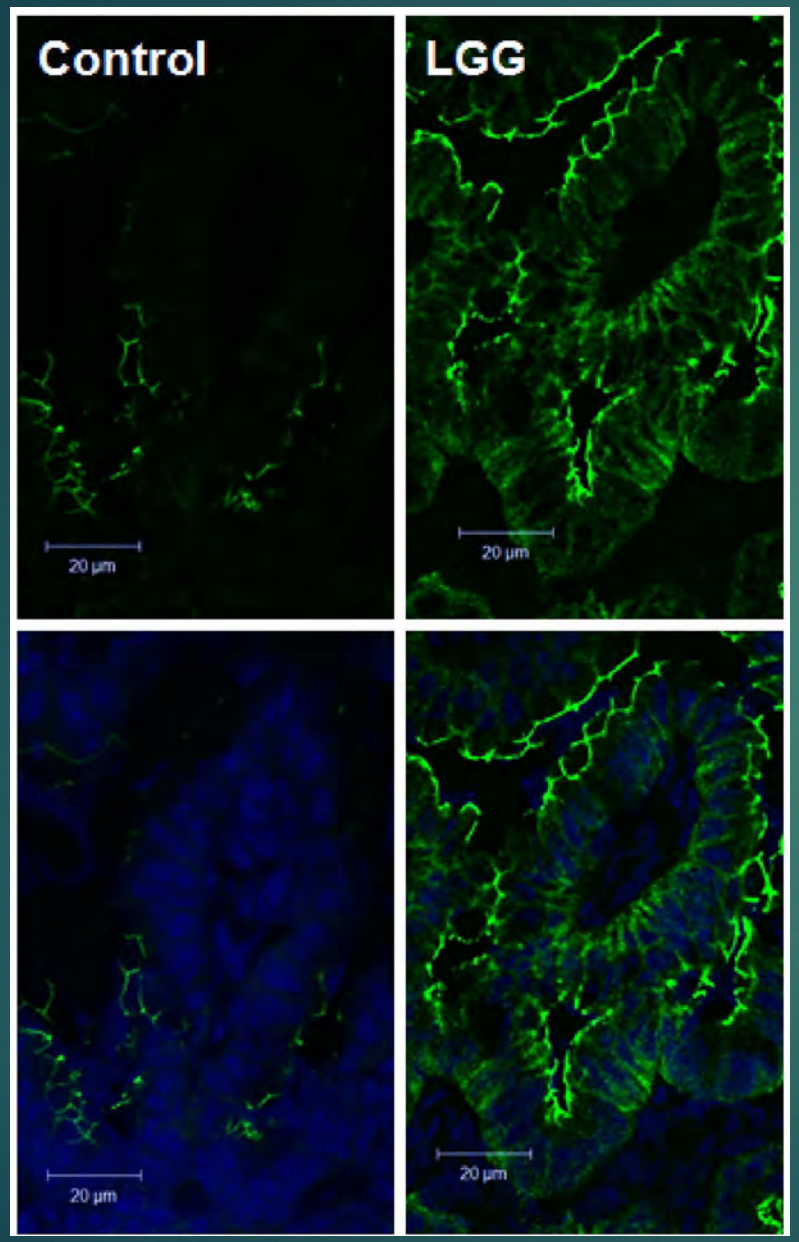
- ascending colon (A)
- transverse colon (B)
- descending colon (C).

Not shown are samples from the terminal ileum, which had the most bacterial density.

Ahmed S, Macfarlane GT, Fite A, McBain AJ, Gilbert P, Macfarlane S. Mucosa-associated bacterial diversity in relation to human terminal ileum and colonic biopsy samples. Appl Environ Microbiol. 2007 Nov;73(22):7435-42.



Candida albicans biofilm on in-vitro oral mucosa model. Candida is stained green, the biofilm matrix is stained red. The red matrix predominates on the mucosal side of the biofilm (left).



Images of intestinal *Lactobacillus* biofilms in humans are difficult to find. More common are images in mice and birds.

In this scan of a mouse intestine, before and after treatment with a Lactobacillus species (LGG), the effects of the LGG mucosal colonization on the expression of junction protein claudin-3 is shown with the luminescent dye.

Patel RM, Myers LS, Kurundkar AR, Maheshwari A, Nusrat A, Lin PW. Probiotic bacteria induce maturation of intestinal claudin 3 expression and barrier function. Am J Pathol. 2012 Feb;180(2):626-35.

Multispecies commensal biofilms in distal ileum

- Terminal ileum and proximal colon characterized by multi-species heterogenous mucosal biofilms Of SCFA producing bacteria.
- Acetate production is highest in these adjacent areas.
- SFCA production and its benefits may be dependent on mucosal bound commensal biofilms.
- SCFA provide essential calories (10% of total mitochondrial fuel)
- SCFA promote tight junction in the gut, and surface immunity.
- SCFA have systemic metabolic effects, promote insulin sensitivity.

Macfarlane, S., Macfarlane, G. T., Composition and metabolic activities of bacterial biofilms colonizing food residues in the human gut. *Appl. Environ. Microbiol.* 2006, *72*, 6204–6211.

Macfarlane S, Bahrami B, Macfarlane GT. Mucosal biofilm communities in the human intestinal tract. Adv Appl Microbiol. 2011;75:111-43.

Lactobacillus in distal small intestine

Table 1
Rod-shaped bacteria tightly associated with ileal epithelial cells.

Biopsy n°	Strain name	Species[a]	Gene bank accession number
1	SF1031	*Lactobacillus mucosae*	FN400925
1	SF1036	*Bifidobacterium breve*	FN400926
2	SF1087	*Lactobacillus mucosae*	FN400927
2	SF1091	*Lactobacillus mucosae*	FN400928
2	SF1108	*Lactobacillus mucosae*	FN400929
2	SF1109	*Lactobacillus gasseri*	FN400930
3	SF1111	*Lactobacillus mucosae*	FN400931
4	SF1146	*Lactobacillus mucosae*	FN400932
5	SF1183	*Lactobacillus gasseri*	FN400933
6	SF1232	*Lactobacillus mucosae*	FN400934
7	SF1233	*Lactobacillus mucosae*	FN400935

[a] Assessed on the basis of the nucleotide sequence of the gene coding for 16S RNA and of biochemical (API) tests.

On recovery, most species

- Produced antimicrobial substances
- Formed biofilms
- Degraded mucin
- Survived simulated gastric environment

Fakhry S, Manzo N, D'Apuzzo E, Pietrini L, Sorrentini I, Ricca E, De Felice M, Baccigalupi L. Characterization of intestinal bacteria tightly bound to the human ileal epithelium. Res Microbiol. 2009 Dec;160(10):817-23.

Clinical questions

- If biofilms are part of the normal and even essential functioning of the microbiome, should we use caution before we attempt to eradicate them in the gut?
- Is it clinically possible to deliver biofilm disrupting agents to the middle or lower digestive tract?
- If we attempt to treat internal biofilms with agents which disrupt biofilms in the lab dish, but with unknown pharmacokinetics, can we damage healthy structures in the gut?

Small Intestine Bacterial Overgrowth (SIBO)

IS SIBO THE NEW “CANDIDA”?

Small Intestine Bacterial Overgrowth

- Small intestine bacterial overgrowth.
- Bloating and general GI dysfunction
- SIBO biofilms documented secondary to PPI, achlorhydria, and various disorders of the liver and pancreas.
- A form of SIBO specific to the distal ileum, and characterized by diarrhea and weight loss, has been recognized since the 1950s.
- The contemporary diagnosis of “Functional SIBO” as a primary cause of digestive and systemic symptoms is controversial and lacks scientific validation or consensus.
- The condition is treated with antibiotics to reduce the bacterial load in the intestine.

Chandra S, Dutta U, Noor MT, Taneja N, Kochhar R, Sharma M, Singh K. Endoscopic jejunal biopsy culture: a simple and effective method to study jejunal microflora. Indian J Gastroenterol. 2010 Nov;29(6):226-30.

- Traditionally diagnosed by collection of the intestinal fluids.
- New breath test measures the release of hydrogen and methane from bacteria in the 2-3 hours after metabolic gasses from the gut bacteria in the few hours after ingesting a sample of lactulose.
- Humans cannot digest lactulose but gut bacteria can. The gasses they produce go into the bloodstream and are exhaled through the lungs.
- The test looks for an early spike of gasses, which is presumed to be produced by bacteria in the small intestine, and a high number theoretically indicates an overgrowth there.

2019 SIBO Review Article

- Researchers have no commonly accepted definition of SIBO, other that that which accompanies malabsorption, achlorhydria, amotility, and some diseases of the liver and pancreas.
- No agreement that such an entity as “functional” SIBO exists.
- No commonly accepted level of diagnostic criteria.
- No commonly accepted explanation for peaks that appear on the SIBO breath test.
- “It should come as no surprise that there are no reliable data on the true prevalence of SIBO in the general population or even in at risk groups.”

Quigley, E. M. M. (2019). *The Spectrum of Small Intestinal Bacterial Overgrowth (SIBO). Current Gastroenterology Reports, 21(1).*

The CHO breath-test/antibiotic paradigm

- Is **convenient** for the practitioner who
  - a) orders a test (hydrogen/methane breath test)
  - b) gets a number
  - c) give a quick treatment by the book until
  - d) the number changes (or not).
- **Usually does not work**. The breath test typically reduces to normal in less than half of patients after treatment. Frequently more antibiotics are then prescribed to the treatment failures. Net success for changes on breath test is less than 20%.
- Of those for whom the lab value changes, the majority have the same lab results and symptoms within 1-3 months.
- **Never addresses the root, and ignores the inevitable damage to the microbiome of antibiotics**

Quigley EM. Small intestinal bacterial overgrowth: what it is and what it is not. Curr Opin Gastroenterol. 2014 Mar;30(2):141-6.

Multiple factors contribute to the normally low bacterial content of the human small intestine

- Gastric acidity that kills ingested organisms
- Immune components (IgA) secreted in bile and by the intestinal epithelium.
- Antimicrobial peptides secreted by epithelial cells
- Propulsive intestinal motility producing a fast transit time of the small intestine, typically about 2 hours.
- Long-chain fatty acids in conjugated bile

“Biofilm busters”

- Many products now purporting to break up biofilms within the gut or within the body are now available.
- These play into the paradigm of “biofilm as enemy.”
- The last thing you want to do for gut health is to disrupt the normal protective commensal biofilms.
- The basis for their use is lab dish studies against biofilm or matrix material.
- The positive assertions for their clinical worth have greatly exceeded any evidence of their value, which in SIBO is zero.
- Multiple cases of adverse reactions to antibiotics and “biofilm busters” in medical students at the National University of Natural Medicine in Portland, which has a SIBO specialty center.

Advocates practice ***selective citation*** of the mixed scientific literature, ignoring trials which:

- Criticise the breath testing method
- Show lack of efficacy of antibiotics on the breath test results in a majority of patients.
- Demonstrate lack of symptom improvement even in those with breath test improvement
- Show a preponderance of negative or equivocal results in recent trials.

Long SK, Di Palma JA. Does Carbohydrate Challenge Testing Predict Clinical Response in Small Intestinal Bacterial Overgrowth? South Med J. 2016 May;109(5):296-9.

Boltin D, Perets TT, Shporn E, Aizic S, Levy S, Niv Y, Dickman R. Rifaximin for small intestinal bacterial overgrowth in patients without irritable bowel syndrome. Ann Clin Microbiol Antimicrob. 2014 Oct 17;13:49.

Chang MS, Minaya MT, Cheng J, Connor BA, Lewis SK, Green PH. Double-blind randomized controlled trial of rifaximin for persistent symptoms in patients with celiac disease. Dig Dis Sci. 2011 Oct;56(10):2939-46.

Collins BS, Lin HC. Double-blind, placebo-controlled antibiotic treatment study of small intestinal bacterial overgrowth in children with chronic abdominal pain. J Pediatr Gastroenterol Nutr. 2011 Apr;52(4):382-6.

Biancone L, Vernia P, Agostini D, Ferrieri A, Pallone F. Effect of rifaximin on intestinal bacterial overgrowth in Crohn's disease as assessed by the H2-Glucose Breath Test. Curr Med Res Opin. 2000;16(1):14-20.

The typical patient diagnosed with SIBO and prescribed antibiotics, by the end of a second course of antibiotics, will have their original symptoms, and now including a permanent loss of diversity in their microbiome, with the many unintended consequences of dysbiosis.

Despite advocating for “natural” medicine, this course of treatment is frequently followed by functional medicine practitioners and by naturopathic physicians, without regard to the negative effects on the microbiome and the unintended consequences that can follow.

The allopath sees an increase in bacteria, and thinks only to try to kill the bacteria. A natural healer wants to find out why the system is not working, and then support:

- normal gastric acid secretion
- normal secretions of the pancreas and intestinal epithelium
- normal bile flow
- normal peristalsis
- ***all of which can be routinely accomplished by medicinal herbs***

Restoring the intestinal terrain

- Remove inflammatory foods. Food intolerance induced inflammation reduces acid and other secretions, and can also affect peristalsis and intestinal permeability.
- Remove injurious drugs, especially proton pump inhibitors which suppress gastric acidity, and also NSAID.
- Use herbal medicines with bitter, carminative, anti-inflammatory, and barrier-supporting activities, as well as mild cholagogues.
- Probiotic therapy and diet to restore/improve the microbiome

Probiotic therapy

- Probiotics are superior to antibiotics in the treatment of SIBO
  - Lykova EA, Bondarenko VM, Parfenov AI, Matsulevich TV; Bondarenko; Parfenov; Matsulevich (2005). "[Bacterial overgrowth syndrome in the small intestine: pathogenesis, clinical significance and therapy tactics]". *Eksp Klin Gastroenterol* (in Russian) (6): 51–7, 113.
- Probiotics superior to metronidazole in treatment of SIBO
  - Soifer LO, Peralta D, Dima G, Besasso H. [Comparative clinical efficacy of a probiotic vs. an antibiotic in the treatment of patients with intestinal bacterial overgrowth and chronic abdominal functional distension: a pilot study]. Acta Gastroenterol Latinoam. 2010 Dec;40(4):323-7. Spanish.
- Following AB for SIBO with 7 days of probiotics improves outcomes
  - Rosania R, Giorgio F, Principi M, Amoruso A, Monno R, Di Leo A, Ierardi E. Effect of probiotic or prebiotic supplementation on antibiotic therapy in the small intestinal bacterial overgrowth: a comparative evaluation. Curr Clin Pharmacol. 2013 May;8(2):169-72.
  - Khalighi AR, Khalighi MR, Behdani R, Jamali J, Khosravi A, Kouhestani Sh, Radmanesh H, Esmaeelzadeh S, Khalighi N. Evaluating the efficacy of probiotic on treatment in patients with small intestinal bacterial overgrowth (SIBO)--a pilot study. Indian J Med Res. 2014 Nov;140(5):604-8.

Cholagogues are anti-microbial

- Bile and unconjugated bile acids inhibit bacterial growth *in vitro*
- Feeding of bile or conjugated bile acids abolishes bacterial overgrowth and reduces bacterial translocation to intestinal lymph nodes
- Reduced bile acid levels in the gut are associated with bacterial overgrowth and inflammation.
- Bile reduces bacterial numbers, but stimulates the formation of commensal biofilms.
- ***Bile acids appear to be a major regulator of the small intestine microbiota***

Hofmann AF, Eckmann L. How bile acids confer gut mucosal protection against bacteria. Proc Natl Acad Sci U S A. 2006 Mar 21;103(12):4333-4.

Ridlon JM, Kang DJ, Hylemon PB, Bajaj JS. Bile acids and the gut microbiome. Curr Opin Gastroenterol. 2014 May;30(3):332-8.

Antimicrobial herbs and SIBO

- Berberine-containing and other herbs with in vitro antimicrobial properties are frequently recommended for SIBO on the theory that they may reduce bacterial counts, an effect which has never been demonstrated in humans.
- High dose purified berberine in rats significantly alters the composition of the microbiome, causing significant increases in some genera and decreases in others, and extinction of some, but does not reduce the overall bacterial count. In the high amounts given to test animals (200 mg/kg) it also causes dysbiosis and diarrhea.
- The authors note an increase in bacteria which produce short chain fatty acids (SFCA) and propose this as a beneficial despite loss of diversity.
- Berberine on the other hand produces reduction or eradication of some species, causing a ***net loss of diversity.*** The authors do not comment on the possible unforeseen consequences of such loss.

Zhang X, Zhao Y, Xu J, Xue Z, Zhang M, Pang X, Zhang X, Zhao L. Modulation of gut microbiota by berberine and metformin during the treatment of high-fat diet-induced obesity in rats. Sci Rep. 2015 Sep 23;5:14405

Typical dose in trials for blood sugar control in diabetics is 500 mg 2 or 3 times a day. This would be the equivalent of the berberine in 10 ounces of Hydrastis tincture per day.

Liang Y, Xu X, Yin M, Zhang Y, Huang L, Chen R, Ni J. Effects of berberine on blood glucose in patients with type 2 diabetes mellitus: a systematic literature review and a meta-analysis. Endocr J. 2019 Jan 28;66(1):51-63.

In human clinical trials, only a small percentage of patients reported nausea, vomiting, diarrhea, or constipation with BBR treatment, and no severe side effects were observed with standard doses (Sabir and Bhide 1971; Zhang et al. 2010).

Chang, W., Chen, L., & Hatch, G. M. (2015). Berberine as a therapy for type 2 diabetes and its complications: From mechanism of action to clinical studies. Biochemistry and Cell Biology, 93(5), 479–486.

Digestive side effects in some trials lead to a drop out rate between 10-20%

Zhang, H., Wei, J., Xue, R., Wu, J.-D., Zhao, W., Wang, Z.-Z., … Jiang, J.-D. (2010). *Berberine lowers blood glucose in type 2 diabetes mellitus patients through increasing insulin receptor expression. Metabolism, 59(2), 285–292.*

Berberine is antimicrobial, but in the living system, it is also cholagogue, promotes normal gastric and intestinal secretions, is protective to tight junctions, stabilizes irritable peristalsis.

Meng S, Wang LS, Huang ZQ, Zhou Q, Sun YG, Cao JT, Li YG, Wang CQ. Berberine ameliorates inflammation in patients with acute coronary syndrome following percutaneous coronary intervention. Clin Exp Pharmacol Physiol. 2012 May;39(5):406-11.

Cao M, Wang P, Sun C, He W, Wang F. Amelioration of IFN-γ and TNF-α-induced intestinal epithelial barrier dysfunction by berberine via suppression of MLCK-MLC phosphorylation signaling pathway. PLoS One. 2013 May 3;8(5):e61944. doi: 10.1371/journal.pone.0061944. Print 2013. PubMed PMID: 23671580; PubMed Central PMCID: PMC3643960.

Takase H, Yamamoto K, Ito K, Yumioka E. [Pharmacological studies on antidiarrheal effects of berberine and geranii herba]. Nihon Yakurigaku Zasshi. 1993 Aug;102(2):101-12. Japanese.

Clinical questions

- If herbs such as Coptis, Achillea, Artemisia, Allium, Tabebuia, etc improve symptoms of SIBO, is this due to antimicrobial/antifungal activity.?
- Or is it due to the effects of strong bitter and carminative herbs on gastric secretions, bile secretions, and intestinal motility?

Clinical experience

- Over a period of 20 years, at our teaching clinics in Boulder, CO, we have treated and closely observed at least 1000 patients and students who symptomatically would be diagnosed with SIBO.
- We have routinely accomplished a normalization of GI health, in those who can comply, without resorting to an antimicrobial strategy, whether conventional or herbal.
- Some occasional treatment failures in compliant patients has improved with anti-parasitic drugs after conventional diagnosis of giardia.

- Remove injurious drugs/substitutions with herbs
- Remove food intolerance with generic anti-inflammatory diet.
- Popular diets for SIBO have in common the removal of common allergens.
- Use probiotics and prebiotics.
- Application of flexible and generic GI formula.

	Anti-inflammatory	Chola-gogue	Carminative	Vulnerary	Antimicro-bial	Anti-biofilm	EPI	Local Immunity
Matricaria	x	x	x		x	-	-	
Mentha pip	x		x		x	x	x	
Calendula	x	x	x	x	x		x	x
Plantago	x	x		x	x	x	x	x
Althaea	x			x	x	x	x	x
Glycyrrhiza	x				x	x		
Foeniculum	x		x		x		x	
Hypericum	x			x	x	x	x	x

BOLD = base formula from Jillian Stansbury Useful additions or substitutes: *Filipendula, Agrimonia*

Internal biofilms

Internal biofilms

- These usually require surgical/mechanical assistance to remove.
- High doses of single antibiotics are usually ineffective
- High doses antibiotic combinations *may* be effective.
- Medical devices and implants
- Tissue fillers
- Osteomyelitis
- Endocarditis
- Infectious kidney stone
- Tooth abscess
- Chronic tissue infection (Borrelia, other?)

“Biofilm busters” for internal biofilms

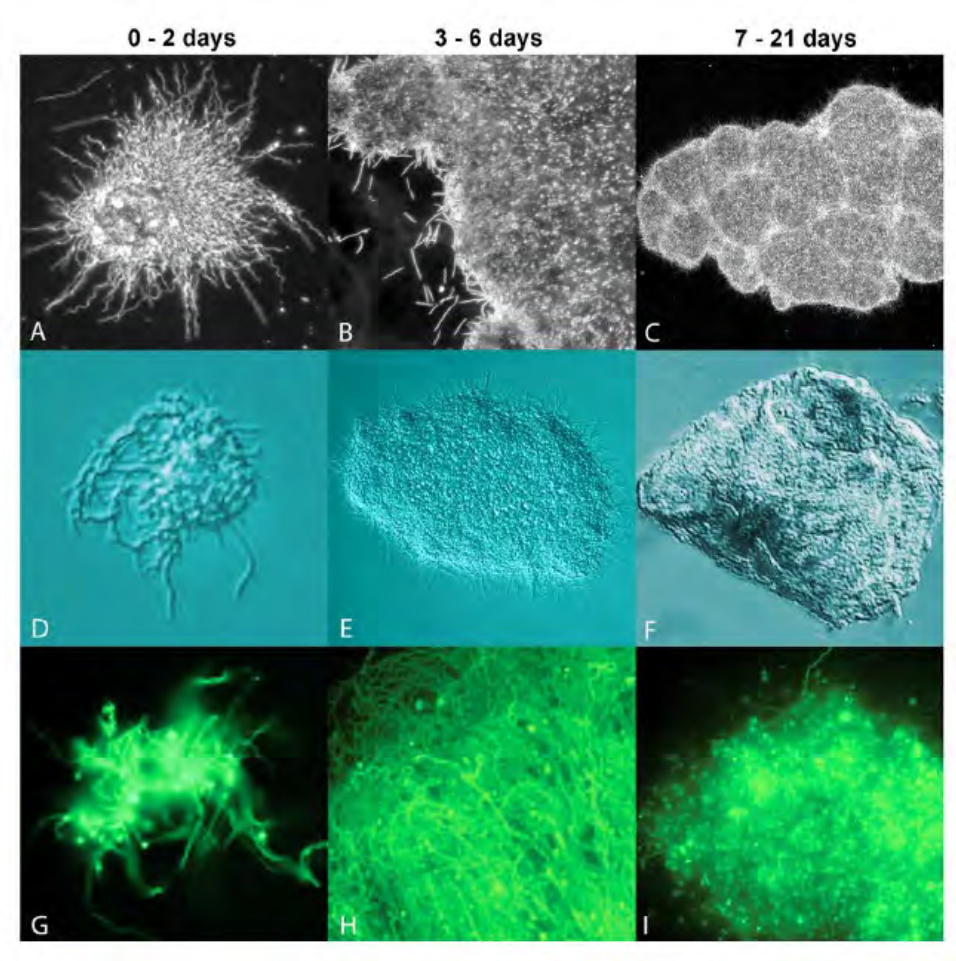
- Many products now purporting to break up biofilms within the gut or within the body are now available.
- These play into the paradigm of “biofilm as enemy.”
- The last thing you want to do for gut health is to disrupt the normal protective commensal biofilms.
- The basis for their use is lab dish studies against biofilm or matrix material.
- The positive assertions for their clinical worth have greatly exceeded any evidence of their value which in chronic infection is zero.
- Almost nothing known about the pharmacokinetics of anti-biofilm constituents, whether they enter the system and circulate.
- Because biofilms can’t be studied within the tissues, effects of constituents or drugs on the biofilms can’t be directly determined.

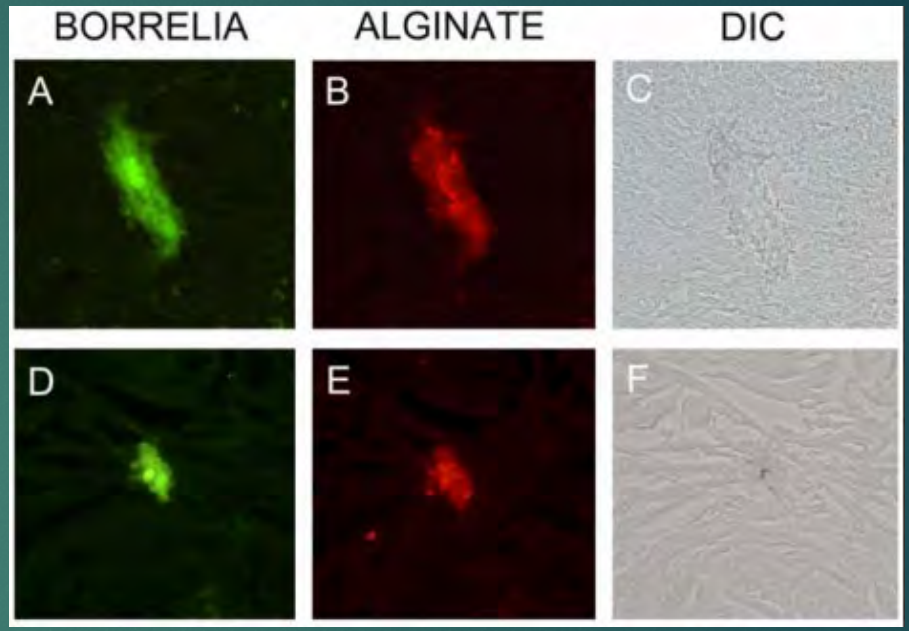
Many enzymes can disrupt existing biofilms in the lab dish.
Can these survive the gut and liver when taken orally to produce
An effective serum dose for internal biofilms?

Some substances with lab-dish anti-biofilm effects promoted for use in Lyme disease

- Lactoferrin/apolactoferrin
- N-acetyl-cysteine
- Lumbrokinase and nattokinase
- Various formulas of enzymes
  - InterFase Plus
  - Biofilm Defense
- Of these, evidence for effectiveness is based on in-vitro effects, or effects in the upper GI.

Borrelia biofilms *in vitro* and *in vivo*





Borrelia biofilms *in vitro* are large enough to be seen with the naked eye. In human tissue, the samples above were visible only at 400x magnification.

Sapi E, Balasubramanian K, Poruri A, Maghsoudlou JS, Socarras KM, Timmaraju AV, Filush KR, Gupta K, Shaikh S, Theophilus PA, Luecke DF, MacDonald A, Zelger B. Evidence of In Vivo Existence of Borrelia Biofilm in Borrelial Lymphocytomas. *Eur J Microbiol Immunol (Bp).* 2016 Feb 9;6(1):9-24.

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Treponema palladium biofilm *in vitro*

Subspecies are responsible for syphilis and yaws

Smilax glabra

- History of use in China against chronic spirochetal disease.
- *Treponema pallidum* subspecies -- syphilis, yaws
- Reportedly will, in formula, effect complete cure of chronic syphilis in some cases, even third stage.
- These likely include internal biofilms, though these have not been imaged.
- Contemporary reports effective to reduce symptoms of Lyme
- Contemporary report of rapid relief of recurrent symptoms of neurological Lyme. Specifically *S glabra* and not other Smilax species tested according to one practitioner

Classical Chinese formula for spirochete disease

- *Smilax glabra*
- *Scutellaria* radix
- *Coptis chinensis*
- *Taraxacum* herba
- *Lonicera* flos
- *Polygonum cuspidatum* rhizome
- *Glycyrrhiza uralensis*

Most of these have not been tested in lab trials for anti-biofilm activity. Such activity can be implied in the formula because of clinical effects.

Garlic vs Flagyl for Bacterial Vaginosis

- 500 mg powder of *Allium sativum*
- 250 mg Metronidazole
- Two tablets with meals orally each 12 hrs.
- Successful oral application with reduction of the biofilm implies that the anti-microbial and possibly the anti-biofilm constituents are delivered systemically to the vaginal mucosa

Mohammadzadeh F, Dolatian M, Jorjani M, Alavi Majd H, Borumandnia N. Comparing the therapeutic effects of garlic tablet and oral metronidazole on bacterial vaginosis: a randomized controlled clinical trial. Iran Red Crescent Med J. 2014 Jul;16(7):e19118.

Table 4. Comparison of Laboratory Improvement in Women With Bacterial Vaginosis [a,b]

Group	Garlic	Metronidazole	Total
Lab Improvement	41 (68.3)	33 (55)	74 (61.7)
Lack of Lab Improvement	19 (31.7)	27 (45)	46 (38.3)
Total	60 (100)	60 (100)	120 (100)

[a] Data are presented as No. (%).
[b] Chi square = 2.256 and P > 0.05.

Table 5. Comparison of Treatment Success in Women With Bacterial Vaginosis [a,b]

Group	Garlic	Metronidazole	Total
Successful Treatment	38 (63.3)	29 (48.3)	67 (55.8)
Failure in Treatment	22 (35.7)	31 (51.7)	53 (44.2)
Total	60 (100)	60 (100)	120 (100)

[a] Data are presented as No. (%).
[b] Chi square = 2.737 and P > 0.05.

Table 6. Comparison of Medication Side Effects in Women With Bacterial Vaginosis [a,b]

Group	Garlic	Metronidazole	Total
With Side Effect	9 (15)	20 (33.3)	29 (24.2)
Without Side Effect	51 (85)	40 (66.7)	91 (75.8)
Total	60 (100)	60 (100)	120 (100)

[a] Data are presented as No. (%).
[b] Chi square = 5.502 and P > 0.032.

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