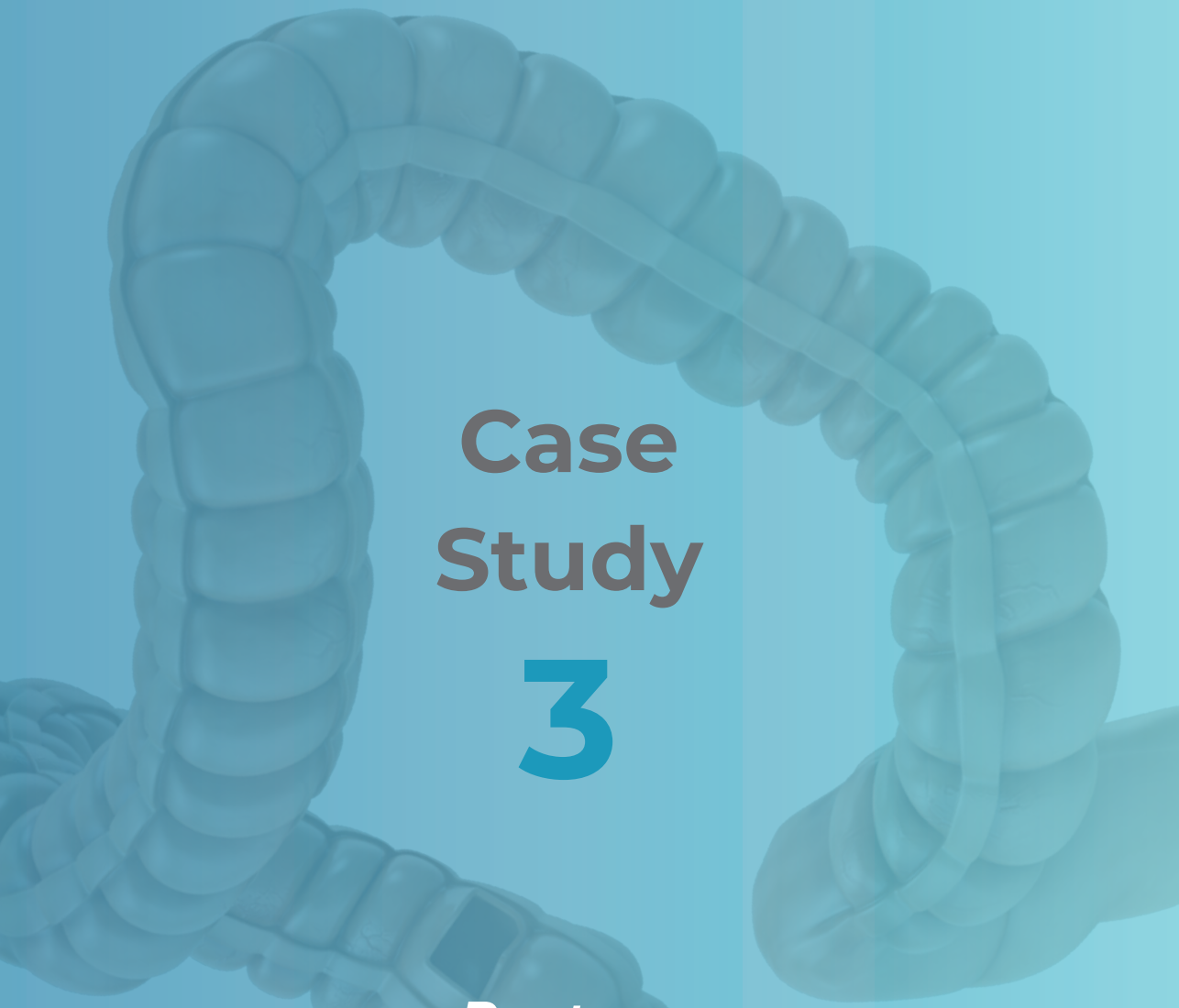


Case Study 3

Proteus and Proteus-like dysbiosis

IBS patients whose MS-microbiology/PCR tests reveal massive colonization by Proteus spc

Case Statistics

Number of cases:	75	Mean age:	30-50
Rate of success: >80%	Most common culprit:	Whey protein and glutamine supplement abuse	
Most common symptom:	Urgency for defecation	Treatment length:	3-6 months

Patient reported symptom score (Before-After)

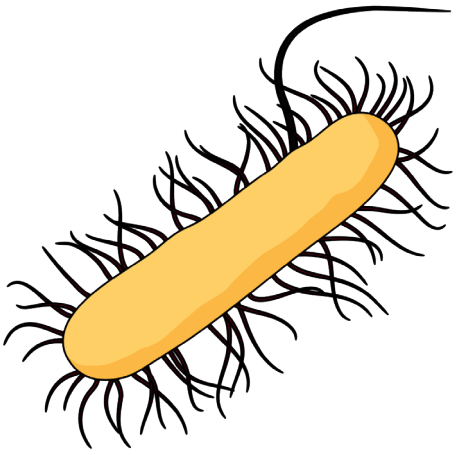
Case abstract

Explanation: *Proteus* and *Proteus*-like bacteria are strong non-commensal bacteria that possess many enzymatic activities and produce several symptoms within the spectrum of IBS. Most common recovered species are *P. mirabilis* and *P. vulgaris*. Other similar bacteria are *Morganella morganii* and *Providencia rettgeri*. Besides their overwhelming histamine–producing capacity, these microbes have the ability to translocate and perform an action that's called "swarming". Swarming takes place in response to several stimuli. One of the most studied stimuli is contact with excess glutamine. This is why glutamine should never be prescribed in IBS-D patients before Proteus colonization is excluded

Similar cases: Usually, this category of IBS patients presents with diarrhea and atopic phenomena (eczema, wheezing, asthma, migraines). During a detailed medical history, the trigger event that caused the initial inoculation of *Proteus*-like microorganisms in the patient's gut may be unveiled. Additionally, It is one of the IBS categories that men are equally affected by women. This is a pattern deviation that cannot be explained, besides the fact that men use glutamine supplements more often.

Treatment implementation: *Proteus* is a rather difficult bug to eradicate and this is why treatment is usually longer. This makes the patients less tolerant and that's why the doctor-patient communication is of big importance. It must be explained to the sufferer that what they are about to do is not a treatment, but a life plan that may last up to 6 months. *Proteus* cases are usually chronic, meaning that the damage that the gut ecosystem has suffered, because of its presence is larger in comparison with other cases.

Case Introduction



Our microbiome is a versatile organ and its composition is subject to very fast and extended modifications. Additionally, in response to several stimuli, like antibiotics, diet, stress etc, it can be extensively modified. Nevertheless, the healthy mucosal environment that our bacteria live and thrive on, possesses certain properties which define the correct genera and species that may inhabit it, while mucosal immunity prevents other, mostly pathogenic bacteria and fungi, to colonize. When these properties are modified (pH, mucus depth, sIgA content etc.) other species are favored which ultimately colonize the mucosal surface. Minor changes confer transient dysbiotic states which are usually resolved by themselves. On the other hand, extended modifications may make the mucosal environment friendly for bacteria like *Proteus mirabilis* to stay and thrive.

Once *Proteus* colonizes, it starts conditioning its environment making it more and more difficult to eradicate. *Pro-*

teus is capable of producing histamine, H_2S, urea and vast amounts of gas. All these can be very toxic to our gut and especially to other beneficial families of bacteria. This is why it is commonly found in stool microbiology tests of patients with Crohn's disease and ulcerative colitis.

Some of Proteus harmful products

Histamine	Biogenic amine that also causes extra-intestinal symptoms
H_2S	In large amounts becomes toxic to mucosal surfaces
Urea/NH_3	Alkalizes the acidic intestinal environment and permits pathogenic bacteria growth
Gas	Flatulence, bloating

Moreover, one of the main aspects of *Proteus* physiology that makes it notorious is the ability to swarm and translocate. Swarming is a property that may be enabled after specific molecular stimuli. Glutamine is well studied and it seems that it gives *Proteus* the ability to form swarms and resist antimicrobial substances. This is the reason why many patients experience worsening of their symptoms after consuming glutamine. This bacterium is also more common in people who use glutamine supplements for sports. The continuous exposure to glutamine favors *Proteus* colonization and expansion.

Another reason why *Proteus* may be difficult to eradicate is that it possesses an inherent resistance against a vast array of antibiotics. It seems that several antibiotics work in favor of *Proteus* as they sterilize parts of our gut making room for *Proteus* to expand. Any antimicrobial therapy against *Prote-*

us-like bacteria should be performed with caution and after analytical sensitivity testing.

Meeting with Jason

Jason's symptoms began about a year before coming to my office. He was on vacation with his family in rural Greece and he first noticed bloating and itching after eating seafood in a taverna. He thought it was just something transient but as the symptoms worsened he visited a gastroenterologist as soon as he got home. The first diagnosis was IBS and the doctor started him on spasmolytics and probiotics. He did not notice any improvement so he went to a second gastroenterologist who made the same diagnosis and prescribed him the same treatment, but with different brands. In the meantime, things were getting worse and he noticed that his stools were looser and the itching had spread throughout his body.

Three terrible months later, he visited yet another gastroenterologist who gave him rifaximin and domperidone in the belief that the problem was the slow passage of food from the stomach to the gut. His symptoms lessened for a while, but within a month of the new treatment he had a regression after eating a salad.

Jason was an open-minded and educated man but he was very anxious about having something serious and I tried to assure him that these symptoms are usual of a functional etiological nature.

The first thing I noticed was that Jason scratched himself throughout our consultation. I also discovered that he had a past history of heavy antibiotic use because as a child he had recurrent episodes of otitis media - we calculated that he had taken up to 30 courses of several antibiotics until the age of 18! He had a car accident a decade ago and had undergone major surgery.

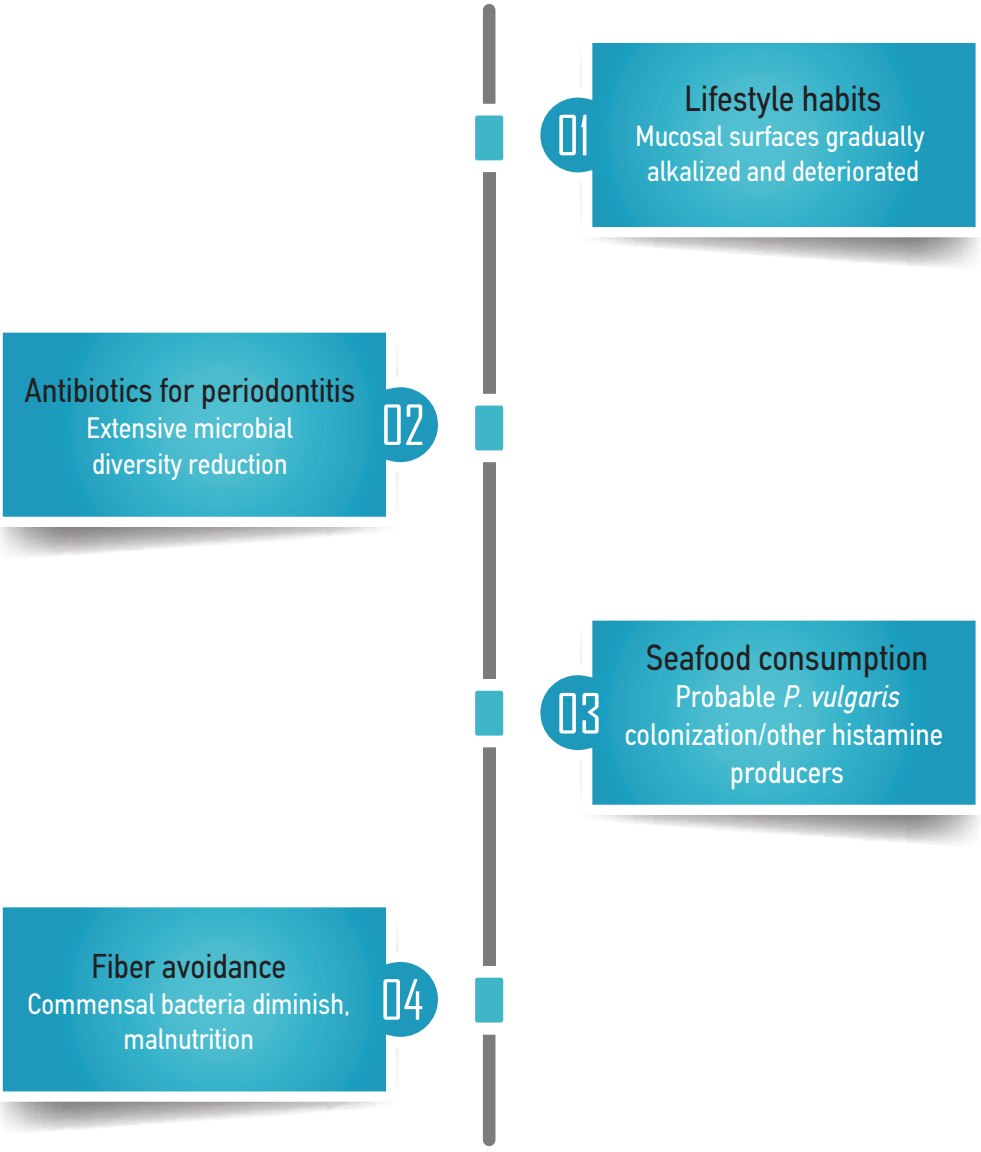
Several months before his seafood incident, he had been diagnosed with periodontitis. He was prescribed 3 different strong antibiotics and he took them for 35 straight days. During this treatment he had felt a bit bloated and he had 2 incidences of diarrhea but he did not consider it to be of great importance. His stools were softer than usual and a strange feeling around his belly button appeared, which disappeared for several hours after defecation. Finally, I discovered that he had included a lot of whey protein and glutamine in his diet as a member of an amateur weight-lifting team as a youth.

Three weeks before Jason came to my office, he went through a full endoscopic check-up which revealed nothing but an unspecific slightly inflamed ileum. His blood test showed low values of vitamin D3, low B12 and very elevated IgE.

IgE is an antibody that reflects the allergic status of a person. Normal values are considered below 100 but Jason's count was 655! This value could explain the allergic reactions he had, mainly the itching and the migraines he was suffering once or twice a week.

Trigger- effect timeline

Proteus dysbiosis



Case Diagnostics

Having already seen a lot of IBS-D patients with similar symptoms, I suspected that a gram-negative, histamine producer with potent fermentative capacity could be the culprit. I told him to stop eating high sulfur-containing vegetables (garlic, onion, broccoli, cabbage, turnips) and everything that comes from the sea. Also, I gave him a potent supplement containing quercetin which is an anti-histamine substance. He did not want to take any more drugs, otherwise levocetirizine would have been an excellent temporary solution.

A complete stool test was ordered to have a thorough look at Jason's microbiota. It also included a measure of eosinophil derived proteins, a check on the status of mucosal immunity, the amount of secretory IgA and the excretion of fats, proteins and starch. In addition, I wanted to measure the activity of the histamine-degrading enzyme DAO, along with the general histamine burden on Jason.

Biochemistry Data Mining

Main	Useful
• Urgency • Residual feeling after defecation • Stomach discomfort • Loose stool >3 times/ daily	• Triggered by seafood consumption • Exaggeration of symptoms after consuming high sulfur foods • Rectal itching and heartbeating (vagotonia) • Chronic use of glutamine supplements • Low grade ileal inflammation • Social life limited due to sudden defecation feeling

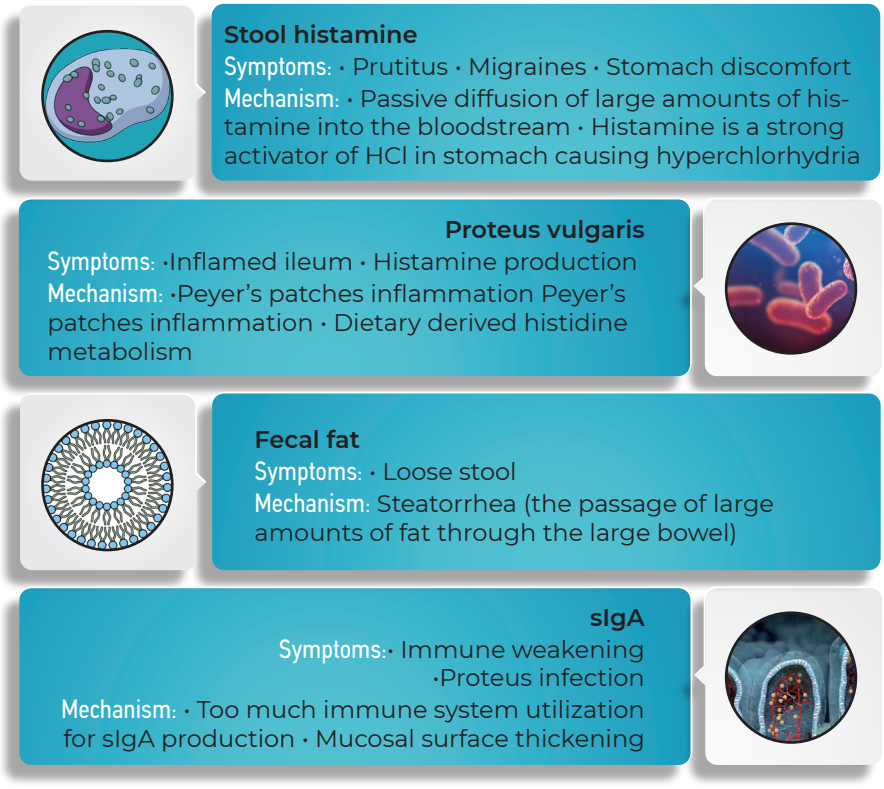
	Possible causes	*Tests Indicated*
Itching/ migraines	· Histamine producing bacteria · DAO insufficiency · Excess histamine	· Stool microbiology/mycology · Blood enzyme activity · Stool histamine/Blood tryptase
Loose stool/ diarrhea	· Bile loss · Rapid transit time · Inflamed ileum	· Fecal bile acids / elastase · Fecal fat/starch · Stool microbiology/sIgA
Bloating	· Disordered microflora · Intestinal immune activation · Undigested particles rotting	· Stool microbiology/mycology · EPX/sIgA · Fecal elastase

Case Results

The results were consistent with what really happened to his gut ecosystem during the past year. The tests revealed a histamine excess in his gut and an elevated sIgA titer, with a bacterium capable of releasing vast amounts of histamine as the culprit. Indeed, his microbiology profile showed markedly elevated levels of *Proteus vulgaris*, and, in fact, the levels were off the upper limit of the test's sensitivity.

In addition, elevated fecal fat was detected on his stool, something that may be explained by the fact that *Proteus* species prefer to inhabit the terminal ileum. This could also be a reason why his ileum looked inflamed during his colonoscopy; as the ileum is inflamed, more fat gets into the large bowel and the looser the stools appear.

What was obvious was that his prior nutritional and lifestyle habits had already weakened his microbiota potential. Once he started the strong antibiotic course for his prostatitis diagnosis, the gut microbial diversity declined substantially and the mucosal properties changed, favoring non-commensal bacteria to colonize and thrive. The first encounter with *P. vulgaris* happened when he ate seafood, and in general, seafood is the major source of histamine-producers. *Proteus* found a very comfortable and alkaline environment and started multiplying by taking advantage of Jason's already glutamine rich diet.



Find the treatment and the follow up in

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