February 2014 Issue | Antonio Gasbarrini, MD The Catholic University of Rome

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Welcome to February 2014 *Functional Medicine Update*. Well, I promised you in the January issue that we were going to start off this year with a bang, with one of those epic "a-ha's," those clinical news-to-use, those paradigm-shifting concepts that may translate in health care to alleviating suffering for millions of people. That's a pretty big claim, I might say, but I think we can deliver on it. This month we're so fortunate to have as our clinician and researcher of the month probably the only person that I could think of that I know in the world that could follow on from the extraordinary presentation that we had from Dr. Fasano in January, and that's Dr. Antonio Gasbarrini, who you will learn, from his own background, is arguably one of the world's great functional gastroenterological researchers at Rome University. He is highly published (in excess of 600 publications), and I believe he is creating the work that relates to how gastrointestinal function is related to health and systemic long-term health span.

Dr. Gasbarrini, as you will hear from him himself, has a wide-ranging series of interests in gastroenterology—ranging from the effect of PPIs (proton pump inhibitors) on nutrient absorption, to pre- and probiotics, to the microbiome, to translocation of Gram-negative bacteria and activation of the immune system, to partial protein breakdown products and how they influence the MALT and the GALT, and interestingly enough, he and Dr. Fasano were colleagues in Italy before Dr. Fasano came to America, and were contemporaries in their research. So there is a consanguinity here with regard to intellectual background between the two of them, and I think between the two, you will hear in the months of January and February, they are carving out a new extraordinary paradigm-shifting concept that is not just esoteric , but it's really that which can be applied, starting now, for the alleviation of so many chronic conditions that were previously of unknown origin.

With that, let's move to our discussion with Professor/Doctor Antonio Gasbarrini.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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Well as I promised, we are so privileged. In fact, I would say we've never been as privileged as we are in

this back-to-back discussion with two—what I consider the pace-leading, paradigm-shifting—science clinicians that are contributing to our understanding of the complex milieu of the gut and its relationship to systemic immunity and how the gut/diet/microbiome/liver interconnects with systemic function across many different organ systems and disease states. As you probably heard from my preliminary introduction, we are privileged to have as the second heavy-hitter in this series of discussions, Dr. Antonio Gasbarrini, who I had the privilege of meeting and listening to this past summer in Milan, Italy at a seminar that we both presented at. I was just thoroughly overwhelmed, to say the least, by the scope, the magnitude, and the depth of Dr. Gasbarrini's work over the many years in the area of gastrohepatology and its interrelationship to systemic function and systemic disease.

Let me just give you a quick kind of thumbnail of just the tip of the iceberg of Dr. Gasbarrini's background. From 1990 to 1993 he was a Clinical Research Fellow at the gastroenterology and liver transplantation department at the University of Pittsburgh and became an assistant professor of internal medicine at the Catholic University of Rome in 1995 and associate professor in 2000, of internal medicine. He teaches postgraduate courses in internal medicine, gastroenterology, and digestive endoscopy, allergy and immunology at the University Medical School and Catholic University in Rome. From 2006 to 2008 he was the Secretary General of the Italian Association for the Study of Liver-Related Diseases and the President of the Italian Foundation for Research in Hepatology. He is a member of—as you can imagine—many national Italian societies in the area of medicine and is an international luminary, publishing in excess of 800 papers, 460 of which as full papers or indexed in international scientific journals, and co-authored more than 1200 abstracts presented at national and international meetings in this area. His work has an overall impact; his publications number over 1200 with a high index of over 55, so his work has always been considered very, very significant.

When I heard him speak in Milan, I was almost mesmerized because not only did he present such a wide volume—expansive volume—of material about the gut immune system and its interrelationship to the microbiome and to function, but he also gave a paradigm-shifting view of a topic that we have been speaking to indirectly, without the benefit of all the work that Dr. Gasbarrini has done, that we called leaky gut some 25 years ago—metabolic endotoxemia, transcellular transport of molecules across an injured GI epithelium. His work has done the heavy lifting to really understand that.

Dr. Gasbarrini, thank you so much for being available all the way between Seattle, Washington and Rome, Italy. We really appreciate your availability to talk with us.

AG: Yes, thanks to you. I think it is a great honor for me to be here now.

JB: Could you tell us a little bit—with this volume of work that you've done over the many years—how your path led you into this whole association and understanding of gut mucosal barrier function and its interrelationship ultimately to diseases?

Gut Mucosal Barrier Function and Disease

AG: Yes, I think that this is a really great area, because as you know, I am a gastroenterologist and an expert in liver disease, so basically when I try to put together all of the diseases that I work with—and I mean inflammatory bowel disease, irritable bowel disease, celiac disease and gluten sensitivity, but also liver disease—what I found is there were kind of key words that put in common all these diseases and the function of the gut barrier. First of all, we have to know that the gut barrier is not only the small bowel,

because with the gut barrier we can say the barrier of the esophagus, the barrier of the stomach, the barrier of the small bowel, and the barrier of the colon, so I mean every different anatomical tract of the GI has its own peculiarity.

Probably the most intriguing part of the gut, however, is the small bowel, because, you know, it is a six-meter-long organ with a lot of different functions, and basically most of the functions are dedicated to digestion and to immune control, because as we know, most of the GALT or the lymphoid tissue of the human body are located in the small bowel—more than 70 percent of all the lymphocytes are resident in the small bowel to keep in control everything that we eat, because you can understand that to be controlled very, very well by the gut. The point is that this bilayer—this six-meter-long bilayer—is made by different components. We have enterocytes, we have the mucus layer, we have for sure the good gut microbiota, but we also have—below the enterocytes—the immune system and the enteric system. You know, all of these systems have to work together in a very, very balanced equilibrium.

There are a lot of conditions that can determine an increasing permeability. Permeability can be physiological. In particular, for example, there are conditions of physiological hyper-permeability. When we are stressed we can have physiological hyper-permeability. After a very important sport we can have increased hyper-permeability. And some peculiar foods can increase or decrease gut permeability. This means that in the physiological condition, we can have an increasing permeability and a decreasing permeability. There are some pathological conditions where the permeability is increased for a long, long time in a very severe way. The typical example is the people with celiac disease, but with celiac disease you have a disruption of the gut barrier with an increased permeability. Or another condition—when you are cirrhotic patient (a patient with chronic liver disease), for example determined by hepatitis C, or by steatohepatitis, or by alcohol where there is portal hypertension, in this case where the small bowel is suffering because the pressure of the vein is too high. Now, in all these conditions, we have pathological gut permeability, also called leaky gut. And another condition that seems to be not related to liver disease, but to some form of irritable bowel syndrome, you have—again—a leaky gut. All of these conditions are characterized by translocation of fragments of the bacteria that are resident in the gut. I mean the fragments of the good bacteria that are found in the gut that go into contact with the immune system, and some of them can enter into the bloodstream, determining the so-called endotoxemia.

Leaky Gut and Microinflammatory Disease

Another thing that is very important in this situation is that you don’t translocate only fragments from gut bacteria, but you can also translocate the peculiar part of what we eat. So we can have a translocation, for example, of macro components of the food. As you can understand, if this barrier is interrupted, you can have a kind of inflammation below the enterocytes, and this can be a kind of pathological microinflammation. This concept is so important. Now we know that at least 30 to 40 percent of people with irritable bowel syndrome, they already have a microinflammatory disease characterized by a leaky gut. So really the leaky gut condition is a kind of peculiar condition that puts together many areas of medicine that probably, in the old times, were not considered linked one to the other one. So the leaky gut is some people with irritable bowel syndrome, people with Crohn’s disease, people with liver disease, and for sure people with extra digestive diseases, such as, for example, people with metabolic syndrome of diabetes. In all of these conditions, the leaky gut is characterized by endotoxemia and a systemic kind of inflammation.

Causes of Leaky Gut

So the main point, I think, for a gastroenterologist, now, is to try to identify the people with a leaky gut, in order to try to determine the causes of leaky gut. For sure it is open to all of us, a new theoretical possibility, because we know, for example, that leaky gut can be determined by an infectious disease, can be determined by an autoimmune disease, can be determined by a stressful condition, can be determined by the diet, so it is not so easy for a doctor to identify what is the reason for the leaky gut. Number two, it is also important to say that it is now so easy to assess the leaky gut. In my unit, for example, we utilize a nuclear medicine test (the EDTA banded with chromium 51—it is a nuclear magnetics test) that isn't quite easy, but not all of the units perform this kind of test, so the main problem is, number one, to recognize the leaky gut condition; number two, to try to assess what is the reason of the leaky gut; and number three is to try to correct the leaky get. And for sure, you know, there are different possibilities. If you have an autoimmune disease, you have to use a monosuppressor, but if you have a disease of the mucus layer, you have to try to reestablish the mucus layer. If you have an increase in gut microbiota or an imbalanced gut microbiota, you have to work with the gut microbiota. If you have a bad diet, you have to control the diet, for example to eliminate all the food that can somehow be responsible for the leaky gut. Really, I think that with the leaky gut concept we are opening a broad area of research, and I think that all the new physicians of the future have to absolutely recognize leaky gut and try to treat it.

JB: That was absolutely brilliant. Thank you so much. I tell you, that was a whole lecture in five minutes. Incredible! I'd like to go back and maybe just trace through a couple of things you said in a little more detail. Let's first talk about the transport of these macro components, like protein components of the diet that are partially digested, and then get exposure as protein breakdown products to the immune system. Are these things that are genetically preprogrammed? Are they related to such things as secretion of hydrochloric acid from the parietal cells and digestive enzymes from the exocrine pancreas? What are the determinants for these transports of these small bioactive/immune active protein fragments?

Genetic and Epigenetic Determinants of Gastrointestinal Conditions
AG: I think this is a very, very, very difficult question. For sure there are some conditions that are genetically determined, but in a lot of other conditions there is a kind of epigenetics. I mean, you can have a genetic predisposition, but is the factor seen in your life when you are a child or when you are an adult, because that is so important to determine the expression of peculiar genes. So, if I can do another example, very often we used to take a proton pump inhibitor for a kind of small gastritis, and there are so many people that take a proton pump inhibitors to handle acid for a long, long time. In this case, you are blocking the gastric pH, and the gastric pH is so important to control the bacteria that come from the colon and can overgrow in the small bowel. You know, if you have an overgrowth of colonic bacteria in the small bowel, you can also have damage of the gut barrier. So it is very difficult at this moment to say if this is a genetic predisposition, or if it is an epigenetic manifestation, or if it is just determined by something that we do wrong. One example is to do an excessive anti-acid. Another example: Helicobacter gastritis. Helicobacter can determine atrophic gastritis. You don't produce acid anymore. You cannot control the microbiota in the small bowel that can determine leaky gut. I think it is a very complex combination of factors, and we have to be somehow very human in order to understand what is happening in this peculiar person.

JB: Thank you. Very, very good explanation! Let's move on to the next area, which is this translocation of bacteria, and/or bacterial cell wall debris—lipopolysaccharides (LPS) from the Gram-negative bacterial cell walls. I would presume, from what you've said, that your work must indicate that there are a variety of different severities of expression of this, because one could imagine a very leaky gut, meaning one that

is highly permeable to fairly large molecules, or one that was not so permeable, maybe only to selected smaller molecules. Is it true that you would have different severities and different responses to things like LPS?

Translocation: Lipopolysaccharides and Other Fragments

AG: Yes, yes, I think—again—this is a great problem. Because, for sure we have a physiological translocation of LPS (lipopolysaccharide), but not only LPS, because we know that there are a lot of other fragments that translocate. For example, LPS is just one of the many pathogen-associated molecular peptides (the so-called PAMPs) that can translocate in the bloodstream. Physiological translocation happens every day, and probably the physiological translocation is absolutely important to keep, somehow, our acquired immune system activated. So probably a low level of translocation is absolutely physiological. The big problem is when we have a pathological level of translocation. In this case, we need other cofactors. The typical example is people with chronic hepatitis due to C virus or B virus. In this case, you have damage of the liver determined by hepatitis C or hepatitis B, and then determined by chronic hepatitis. When you have the constant chronic hepatitis and you have a portal hypertension, you start to have a translocation of LPS from the small bowel to the liver. When LPS enters into the liver in these people with chronic hepatitis, you have the activation of toll-like receptor 4, and this determines the position of collagen, and this is the main cause of cirrhosis. So I mean, in this case, you have two different conditions—hepatitis C or hepatitis B—that determine the chronic inflammation in the liver and portal hypertension, and number two, when you have portal hypertension you have a translocation of LPS that arrives in the liver, and this is the main determinant of cirrhosis. So the point is that very often we don't have only one factor involved. It can be a combination of different conditions.

Another thing that now is very, very important, because from an immunological point of view it is so increasing, is the metabolic syndrome and the steatohepatitis. This means that when you have a bad diet you can have liver steatosis, and after a while, when you have bad steatosis, again you have portal hypertension, and when you have portal hypertension, LPS can translocate—it can arrive in the liver—and if you have other cofactor events of inflammation, at this point you can start to have steatohepatitis. We absolutely know how important the leaky gut condition is in the progression from steatohepatitis to liver cirrhosis. So again, very complex mechanisms, many cofactors that go together at the same time, and are important in determining the progression of the liver disease.

JB: That is so clinically helpful for us. In the United States, we are seeing a virtual epidemic of what has been termed nonalcoholic fatty liver disease that is associated with marginally elevated liver function tests (LFTs). People have said, "Well, this is a consequence of fat infiltration into the liver due to insulin resistance, hyperinsulinemia, and metabolic syndrome." But it sounds to me—the way you're describing it—that it's more complex. It's the interplay between insulin resistance, hepatic function, and gastrointestinal barrier function, and the potential role that endotoxemia plays in this complex etiology. Am I interpreting correctly what you just said?

AG: Absolutely right. Absolutely right! I am a gastroenterologist, so I see everything from the gut. But I can say that really the gut is a big organ—a huge organ. You know, six meters long. Everything has to be absorbed by the gut, and we know, at the moment, that the community of bacteria is very important for us in order to extract all the good things from the diet. But, as you know, these bacteria can become very dangerous. When a person dies, the putrefaction of the body is determined by these bacteria—if they are not fed in the right way, they can be dangerous. They can destroy the body. So we have to have a lot of

respect for these gut microbiota. We have to feed the gut microbiota the right way, with good, healthy food, and for sure we have to avoid all the kinds of food that can determine an imbalance of the gut microbiota.

Leaky gut is a very important concept because it means that the gut barrier is a very complex system, and the real interface between the internal and external body. For example, if a person has a heart insufficiency, what can be the relationship between a heart insufficiency and the gut? If you have a heart insufficiency, you have an increase in the venous pressure, and this again is a determinant of portal hypertension and bacterial translocation, and we know very well how important inflammation is in the progression of heart insufficiency. So I mean that the gut barrier concept is not a concept for gastroenterology but is a concept for all the people that deal with the human body.

Explaining PAMPs and DAMPs

JB: That's very, very powerful. You used a little acronym earlier on. I'd like to come back and just define it for some of our listeners. You talked about PAMPs, and then there are DAMPs. Could you tell us a little bit about what these are and how they are players in this whole scheme?

AG: Yes, absolutely. As we say, the gut microbiota is a very complex ecosystem that is made by different microbes. I mean, we have bacteria, we have histamine, we have bacteriophage (kinds of viruses). All of these components of these microbes can translocate in the bloodstream, especially dealing now with bacteria, we know that most of the bacteria are anaerobic type of bacteria. We know that usually they don't survive in the bloodstream because there is too much oxygen for this kind of bacteria. Very often, these bacteria, when they die, bacterial fragments can translocate and enter into the bloodstream. We have a lot of different kinds of bacteria: Gram-positive, Gram-negative—many, many, many different species and many different strains. Every species is characterized by different fragments, so when we say a pathogen-associated molecular peptide (or PAMP), this means the peculiar peptide of these bacteria can translocate in the bloodstream and they can activate specific receptors in the human body that are called pathogen-recognition receptor. A typical case of pathogen-recognition receptor are the toll-like receptors that are present in all the body. So, you know, for example, LPS can activate and can bind the toll-like receptor 4 that is in the liver, that is in the joints, that is in a lot of different parts of the human body. So this means that physiological translocation can be very important to activate pathogen recognition receptors , but pathological translocation can activate too much pathogen recognition receptors, and this can be a very important driving force of inflammation and the concept of inflammation.

JB: That was a great primer course in immunology. Thank you, that was very, very specific. Let me talk just briefly with you about a study that I recall that was published a number of years ago in the Lancet in which they looked at patients that had had hospitalization from Crohn's disease, and they measured their gut permeability. They showed that those patients on discharge from the hospital that still had a permeable gut, had very high relapse rate versus those that were discharged from the hospital after a crisis event with Crohn's disease who had a low permeability who had very low relapse rate, suggesting that if you were to discharge patients at a hospital and not be attending to their gut mucosal integrity, you were just asking for a readmission later.[1] Is that something that has been proven correct from your experience?

Leaky Gut Can Manifest for Different Reasons

AG: I think this is a good point, but I have to tell you that I think we are really in the first step of

understanding what is the role of a leaky gut as a determinant of diseases. Because I have also to tell you that in my studies we also have a group of control people, who have kind of a leaky gut and they don't have diseases. For sure a leaky gut is highly important in order to maintain a lot of inflammation, but the problem is that at the moment we cannot say what are the real consequences of a leaky gut. It is something that for sure is involved in all the pathology of the human body, for sure is involved in higher bacterial translocation, but I have to tell you I really cannot say at the moment that for sure we have to correct leaky gut in every condition. Because remember that after a very stressful condition, you can have a leaky gut that is just a consequence of the brain-gut activation. I mean, a leaky gut in a very stressful condition can be a good condition of how the brain decides to activate the immune system. So the point is that we have to absolutely discriminate leaky gut as a momentum of pathology and leaky gut as a momentum of a transient condition, because probably in some conditions a short time of leaky gut can be good for the human body.

JB: That's a really interesting observation. I recall a study on trainees. These are men and women that go into very severe training for combat readiness. And they actually measured, as part of the study, the pre- and post-gut permeability. I think they used the lactulose mannitol test in this particular study, and they demonstrated a very significant increase in gut permeability after the training, which was sleep deprivation, and marching, and all sorts of…you know, probably gunfire over their heads and things. But they showed that stress had a very significant increase in their gut permeability, which seems to be consistent with what you just said.[2] Then I guess the question is, was that a desirable adaptation to the stress for the moment that gave them higher immune function or their brain was enlightened in a different way? I guess that's a very interesting question.

AG: Yes, yes. I think, you know, there is another study that was performed after a triathlon competition.[3]So the point is this one. Probably a transient leaky gut is just a physiological consequence of a stressful or tiring condition. The problem is this one. If in this moment, when I have a leaky gut as a consequence of a stressful condition—if in this moment I have a bad diet, and if in the same moment, I also have, for example, a rotavirus gastroenteritis, this could be damaging because I already have a leaky gut (I can have an extremely bad leaky gut in this condition), and if I have a genetic predisposition, for example—I don't know—DQ2/DQ8 that can predispose you to develop celiac disease, you know, in this time you can become celiac, or in this time you can activate a pattern recognition of microbial PAMPs and I can develop Crohn's disease. The point is when you have two or three bad conditions at the same time.

JB: Yes, thank you. I know you've been doing quite a bit of work on this microbiome, which seems to be at the center stage of people's interest now, recognizing how much DNA there is in the genomes of our enteric microbiota and how that may influence our function. What are your thoughts about how this research is progressing, looking at the microbiome and its interrelationship to diet in health and disease.

We Are In the Era of the Gut Microbiome

AG: I think now we are in the era of the gut microbiota, or microbiome, or gut metabolome. Probably it is not so much important what kind of bacteria do we have, but it is what do they do? The main problem is that these incredible communities that are distributed both in the colon and the small bowel, there are so many, many functions. In the small bowel, basically, they control the immune system and they can help us in order to degrade and digest what we eat. In the colon they have a very, very important metabolic function. The point is that there is a kind of common concept in all the inflammatory disease of the bowel

(irritable bowel syndrome and inflammatory bowel diseases). The common thinking is that we decrease the heterogeneity of these bacteria. I mean in a good condition we have a lot of different bacteria, and every bacteria is somehow specialized into something. In a lot of inflammatory conditions, we have a decrease of the species, and this is very important because this can determine inflammation. The gut microbiota concept is really the concept of the future, and if you see the studies that were published last year in the top journals—Nature, Science, and PLoS—all of the studies are being performed not only be gastroenterology, but are being performed by diabetology, people that deal with rheumatoid arthritis, people that deal with obesity.[4],[5],[6] You know, the gut microbiota concept is not only a diving force for inflammation, but it is a driving force of nutrition, obesity, and so-called metainflammation.

JB: I remember during your presentation you talked a little bit about this ratio between the Firmicutes and the Bacteroidetes and how those might be markers as we're looking at stasis of health versus disease relative to the microbiome. Does that seem to be proving true?

AG: I don't know because really the papers are coming out every month. You see so many new concepts. Number one, we have to be somehow careful, because most of the disease data, and also the Firmicutes-to-Bacteroidetes ratio that we know is different in obese people, is determined by the concentration of Firmicutes-to-Bacteroidetes in the feces, so the point is this: is the bacteria found in the feces really the expression of what's happening in the gut microbiota? Because there are also studies out that say that fecal microbiota is very different from the mucosal gut microbiota. You know, in the real world probably we have to assess the fecal microbiota and the microbiota taken by the biopsy directly. And number two, is the microbiota of the colon is the same as the gut microbiota in the small bowel? Probably not. So, I mean, we have to work much more on this concept. But what is true is that the gut microbiota is actively involved in obesity, and metainflammation, and metabolic syndrome. There are plenty of papers out that say that if you transplant the gut microbiota from obese mice, for example the ob/ob obese mice, to wild type mice, the wild type can become obese. And if you transplant the microbiota from lean mice to ob/ob mice, the ob/ob, which are fat mice, become lean.[7] This has been also demonstrated in a human being. There is a paper out published by De Vos in Gastroenterology that showed that if you transplant the microbiota from a lean subject to a person with insulin resistance, you can determine a significant amelioration of insulin resistance, both parathyroid hormone insulin resistance and hepatic insulin resistance.[8] This means the gut microbiota can really help us in controlling metainflammation and controlling the way we take the energy from what we eat.

JB: That really relates to one last question, and thank you so much for your time. This one last question is a follow on. What about pro- and prebiotic supplementation? Do you feel that there is a role or a place for this in restoring GI function?

Pre- and Probiotics: What Role Does Supplementation Play in GI Health?

AG: This is a very difficult question. I hear some good things and some bad things. Good things are that for sure there very nice papers out that show that some probiotics—and in particular, the most important are Lactobacillus and Bifidobacteria (a combination of Bifidobacteria and Lactobacillus) and for sure Saccharomyces boulardii—they can have a good action in some peculiar clinical conditions. In particular, it has been demonstrated they can help us in infectious viral diarrhea, they can help us in antibiotic-associated diarrhea, and in some peculiar cases of inflammatory bowel disease and irritable bowel syndrome. However, the main problem is that the more important bacteria that are in the gut—the more important species of the bacteria where we have most of the evidence of their function—at the moment are

not produced as probiotics. So really the main problem is that the probiotics that we have in the market are not the most important species we have in the gut. I think that to have a good answer to your question, we have to wait for when a big company can produce the real species that are in the gut in order to give this kind of species. So my idea is that probiotics is a great option for the future, but we have to work a lot. And the same for prebiotics. It would be very nice to have the possibility to feed specific bacteria with specific prebiotics, but the real fact is at the moment a prebiotic is utilized by ALL the bacteria (probably also by the bad bacterial). So the real answer is we have to wait in order to have great probiotics and prebiotics with specific functions for specific bacteria.

JB: I think that's a very good place for us to leave because we're moving into—again, as you said—a personalized differentiated therapeutic, looking at each individual's genotype and microbiome in unique ways and personalizing therapy for their individual condition. What I would like to say in just close, is having had the privilege now of meeting you personally and listening to you speak and reading now a number of your papers, you're really creating the new medicine. You're really taking the concept of gastroenterology well beyond that which it has often been narrowly defined, and on behalf of all of our functional medicine docs and researchers and clinicians over the years, I want to thank you. I think this is very, very challenging work. Very difficult, complex work, but you have really started to, I think, establish a path of clarity through this confusion that's going to open up this field in ways that we never even believed were possible. Thank you so much, Dr. Gasbarrini. You're a guide and a vision for all of us.

AG: Okay, thank you, Jeffrey. Thank you to everybody.

JB: You be very well. Thank you.

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