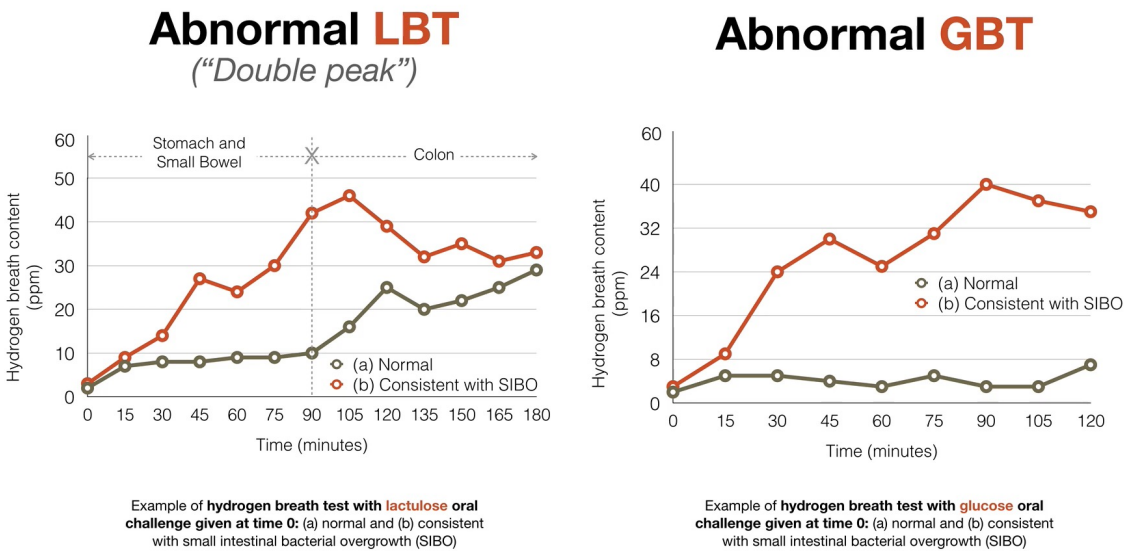
Gut: SIBO – Part 3

On this slide, I've put examples comparing a normal and abnormal lactulose breath test and glucose breath test.

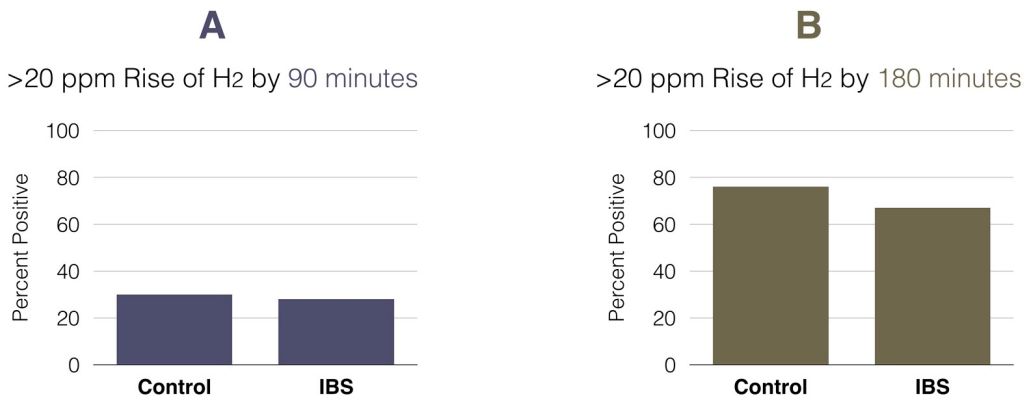


Adapted from: Bohm et al. Nutr Clin Pract. 2013 Jun;28(3):289-99

The bottom line, the olive-colored line, is normal, and the top orange-colored line is abnormal. Looking at the lactulose breath test, or LBT, we see what's called a classic double peak. This is an initial rise in hydrogen at least 15 minutes before it enters the colon. Here we are seeing it at 45 minutes. Then, it drops a little bit, and then it rises again as the lactulose goes into the colon, so this double peak is pretty much universally agreed to be a positive result for SIBO. It's one of the few interpretations of breath testing that almost everybody agrees on.

For the glucose breath test on the right, you'll typically see an earlier rise in hydrogen since glucose is absorbed much further up in the digestive tract than lactulose. For example, in this test result, you're seeing the glucose is already rising compared to the normal control value at 15 minutes. At 30 minutes, there's a really substantial difference. The control value is something like four parts per million, and the elevated value is 24 parts per million, so six times the control. In healthy controls, it's important to note that with a lactulose breath test, you'll still see a rise in hydrogen when lactulose reaches the colon because there should be bacteria in the colon to ferment lactulose, but you wouldn't expect to see that with glucose because glucose is never supposed to reach the colon anyway. It's supposed to be absorbed much further up in the digestive tract. If you look at the control values here, for lactulose you see that gas production

stays low until around 90 minutes, and then it starts to increase as lactulose enters the colon, and so that's still a normal result, whereas with the positive result, you can see that the increase in breath gases, hydrogen in this case, happens much sooner, before the lactulose enters the colon, and that's indicative of SIBO, whereas with the glucose, a normal result for glucose is just to stay low the entire time throughout the test, and a positive result would typically be an increase very early on, starting at 15 minutes or 30 minutes.



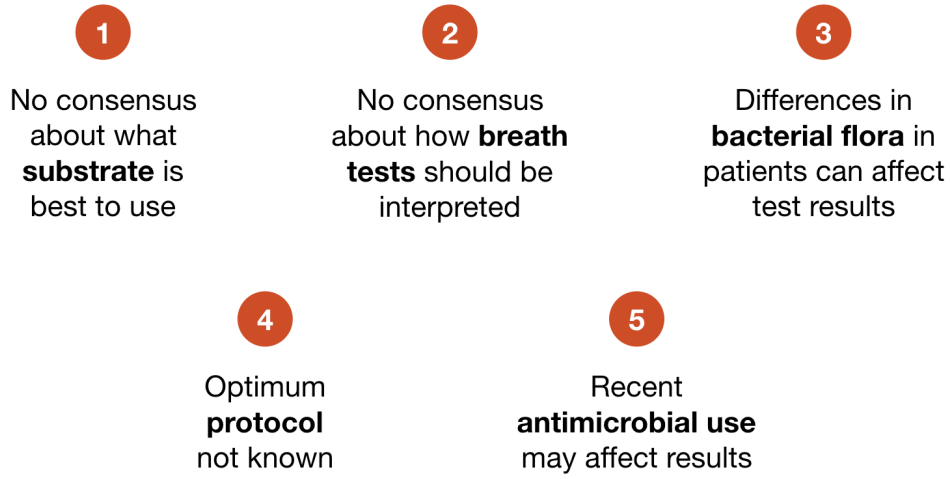
Comparison of the **lactulose** hydrogen breath test *(LHBT)* in IBS patients (open bars; n=39) and controls (closed bars; n=20) applying either a **Rise in H_2 of >20 ppm by 90 min (A) or 180 min (B).** No significant differences are seen between the two groups.

Adapted from: Walters & Vanner. Am J Gastroenterol. 2005 Jul;100(7):1566-70

In 2003, Dr. Mark Pimentel and colleagues proposed revised criteria. Dr. Pimentel—you may have heard me interview him on my podcast, we're going to link to that—he's considered to be one of the global experts in SIBO. His revised criteria suggested that any rise of hydrogen or methane before 90 minutes with a rise never above 20 parts per million during 180 minutes of measurement was a positive result for SIBO. It wasn't specified in those criteria what magnitude of rise of hydrogen before 90 minutes constituted an abnormal test, but later on, Dr. Pimentel in various venues, conferences, and conversations has stated that most patients had a rise of 20 parts per million or more within that first 90-minute period.

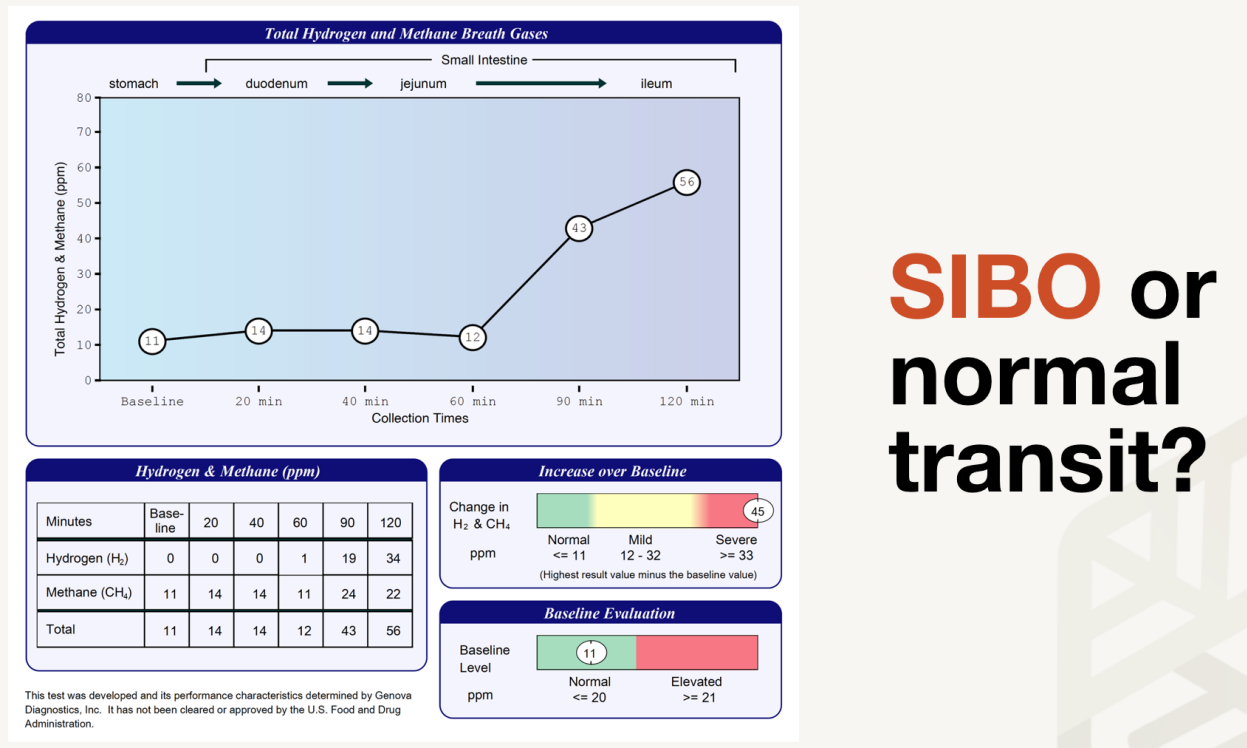
These criteria were a lot more liberal than the traditional double peak that I showed you on the last slide, and the problem with them is that studies correlating lactulose breath tests with bacterial culture results for SIBO use that traditional double-peak criteria, so the single-peak criteria that Dr. Pimentel is proposing has never been validated against another method of testing for SIBO like bacterial culture. In fact, some studies, like the ones I've put here on this slide comparing increases in hydrogen in IBS patients in controls after lactulose challenge have found no difference at all between them at 90 minutes or 180 minutes.

Let me just clarify that: they took a group of control patients who didn't have IBS, and they took a group of patients with IBS, and they gave them the lactulose breath test. Then they measured their hydrogen levels at 90 minutes or 180 minutes, and they used Dr. Pimentel's proposed revised criteria as a way of indicating whether someone had a positive result. In these charts on the slide, there was no significant difference seen between the two groups. What some researchers are concerned about is that the revised criteria that Dr. Pimentel proposed haven't really been validated against the bacterial culture tests for SIBO, and they may be over-diagnosing SIBO.



Breath testing has become the de facto test for SIBO, particularly in the clinical setting, and it does certainly have advantages over culture, but it's far from perfect and quite problematic, in fact, much more so than is commonly acknowledged, I think, even by experts like Dr. Pimentel. The first issue is that there's no consensus about what the best substrate is to use in the testing. Some argue that glucose is best. Others argue that lactulose is best. I think both have pros and cons, which we're going to cover in detail. Second, there's no consensus about how breath tests should be interpreted, and we'll talk more about this later. Third is that differences in bacterial flora in patients can affect test results. For example, 10 percent of adults and 15 percent of kids don't produce hydrogen at all. They only produce methane, so if you're not testing for methane, you're going to miss those people. Some people don't produce much hydrogen or methane at all, and they actually produce more hydrogen sulfide, and that's not measured on any of the current breath tests, so that's a problem. Fourth is the optimal protocol for timing, collection, and method of administering breath tests is not really known or agreed upon. Fifth is recent antimicrobial use may affect results, but the proper antimicrobial-free interval prior to doing the test is not known. We're using two weeks in our clinic. That seems to be an interval that's commonly used, but we're not really sure because there haven't really been a lot of studies done to establish what the proper interval is.

In short, the breath test is an easy test to perform, but it's difficult to interpret the results. I mentioned on the last slide that each of the substrates that are used clinically, lactulose and glucose primarily at this point, has its own pros and cons, so let's start with glucose. The main problem with glucose is that it's absorbed in the proximal small intestine in the duodenum, so if overgrowth of bacteria is occurring in the jejunum or ilium, you may get a false negative with a glucose breath test. That said, the Rome Consensus Conference recommends glucose breath testing over lactulose breath testing. It has a positive predictive value of 80 percent and a negative predictive value of 66 percent versus a positive predictive value of 62 percent for lactulose and a negative predictive of 54 percent for lactulose. In terms of diagnostic accuracy, glucose breath testing is 72 percent versus 55 percent for lactulose breath testing.



Lactulose is not absorbed at all in the small intestine. It goes all the way to the colon where it is fermented by bacteria. The advantage of this is it means you can detect SIBO in the jejunum and ileum when you are using lactulose as a substrate. The biggest problem is that the lactulose breath test is based on the idea that orocecal transit time in healthy people is always longer than 90 minutes. Most labs interpret a rise in hydrogen over a certain cutoff before 90 minutes as a positive result. However, some studies have shown that orocecal transit in healthy people averages between 72 and 85 minutes. A study in India found a median transit time of 65 minutes, and a study in Taiwan found a median transit time of 85 minutes. This suggests that transit time may vary according to race, ethnicity, and geography. One recent study in Western population used radio-labeled lactulose and tracked the progress of lactulose through the gut while the patients were performing a SIBO test. That study showed that a high percentage of people with IBS had an early single peak of hydrogen before 90 minutes on the lactulose breath

test, but in 88 percent of cases, lactulose had already reached the colon according to this radio label assay. That meant that 88 percent of these patients would have had a false-positive on the lactulose breath test for SIBO.

A 2016 study found that a hydrogen peak within the first 60 to 80 minutes significantly increases the specificity of lactulose breath testing. That suggested late single peaks that occur after this time and like the one pictured on this slide may often be false-positive results. Shortly, we are going to be talking about new consensus on SIBO breath testing that recognizes this fact that the 120-minute cutoff that is used by many labs is too long and that lactulose is probably already in the colon in many cases at that time period.

The fact that lactulose has a laxative effect complicates this issue further because lactulose itself accelerates transit. If a patient is fasting and they consume lactulose, that would be expected to move more quickly through the small intestine to the colon, which again could raise the risk of a false positive.

The final note here. Patients with lactose allergies should probably not do lactulose breath test. However, most patients with lactose intolerance rather than a true allergy are able to do the lactulose breath test, but they may experience discomfort while they are doing it. For that matter, a lot of people with SIBO experience discomfort with the lactulose breath test because lactulose is not absorbed, and it causes fermentation if there is bacteria in the small intestine, and that can cause gas, bloating, and a lot of other symptoms for people who have SIBO. You might want to warn your patients about that before they do this test.