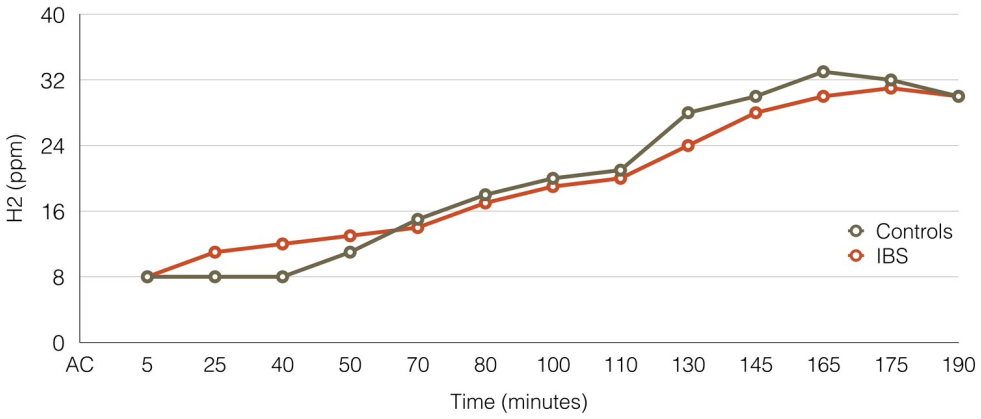
Gut: SIBO – Part 4

Applying the single-peak criteria that was proposed by Dr. Pimentel, which is a rise in hydrogen above 20 parts per million within 90 minutes, has never been validated. That's another problem we're facing with the SIBO testing. Lactulose breath testing was originally used as a measure of orocecal transit time, and really, the rise in hydrogen on these tests often reflects the entry of lactulose in the colon. Also, studies comparing a rise in hydrogen in IBS patients and controls show very similar results. A few slides back, I showed you a couple of bar charts showing that both controls and IBS patients had similar rises in hydrogen at 90 minutes. In one study, 28 percent of IBS patients had a rise of over 20 parts per million of hydrogen before 90 minutes, 69 percent had a rise of over 20 parts per million by 180 minutes, but very similar results were found in the control group without IBS, and that's the chart that I'm showing here on this slide.



Comparison of the **rise in H2 over time** in the IBS cases (solid line; n=39) and controls (dotted line; n=20) No significant differences are seen between the two groups over time.

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

You can see that the lines are virtually identical, so the increase in hydrogen throughout the test for controls and patients with IBS was the same. Other studies have found prevalence of SIBO using lactulose breath testing in controls as high as 75 to 85 percent, which certainly should raise our eyebrows. If 75 to 85 percent of healthy controls have SIBO according to lactulose breath tests, that should make us wonder about its accuracy. On the other hand, some of Dr. Pimentel's studies have shown rates of SIBO in healthy controls as low as 20 percent using the lactulose breath test, so there is definitely some discordance in the scientific literature. The key point here that I hope is coming across is that changes in hydrogen levels as measures on a lactulose breath test can just be a reflection of differences in transit time rather than pathology

like SIBO. If someone has an orocecal transit time that's on the shorter end of the scale, maybe 65 or 70 minutes, you will see a rise in the hydrogen at 65 or 70 minutes as the lactulose enters their colon, and that will be falsely labeled as a positive result on all of the various breath testing labs.

SIBO using lactulose and GBT in IBS patients and controls

		SIBO	Non-SIBO
Lactulose	Controls (n=150)	45 (30%)	105 (70%)
	Patients (n=175)	60 (34.3%)	115 (65.7%)
Glucose	Controls (n=150)	1 (0.66%)	149 (99.3%)
	Patients (n=175)	11 (6.2%)*	164 (93.8%)
* $p < 0.01$ for glucose between controls and patients			

Adapted from: Rana et al. Digestion. 2012;85(3):243-7

There are a few studies that have compared lactulose breath testing with glucose breath testing directly in both IBS patients and controls, and what they found was that SIBO was present in 34 percent of IBS patients if you use the lactulose breath test but only 6 percent of patients using the glucose breath test. The numbers in controls were even more dramatic. Using the lactulose breath test, 30 percent of healthy controls had SIBO versus just 0.7 percent with glucose breath testing. SIBO was not statistically different in patients with lactulose breath testing, but it was statistically different in IBS patients and controls with glucose breath testing. Put another way, only glucose breath testing was able to distinguish between IBS patients and controls, whereas lactulose breath testing was not able to distinguish between them.

Diagnostic utility of different criteria for the diagnosis of SIBO compared with upper gut aspirate culture

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
GHBT	27	100	100	85.5	86.2
LHBT *(double peak)*	0	98.5	0	81	80
LHBT *(early peak)*	33.3	64.6	17.8	80.7	58.7
Methane	13.3	58.7	7.1	74	50

GHBT, glucose hydrogen breath test; LHBT, lactulose hydrogen breath test; NPV, negative predictive value; PPV, positive predictive value; SIBO, small intestinal bacterial overgrowth.

Adapted from: Ghoshal et al. Eur J Gastroenterol Hepatol. 2014 Jul;26(7):753-60

Another study compared bacterial culture, diagnosing SIBO via endoscopy with both lactulose breath testing and glucose breath testing. In terms of the bacterial culture, a total bacterial count of over 10 to the fifth is considered diagnostic for SIBO. For breath testing, a rise in hydrogen above 12 parts per million over the baseline value is considered to be diagnostic for glucose, and then a rise in hydrogen above 20 parts per million within 90 minutes was considered to be a positive result for lactulose, and a rise in methane of at least 10 parts per million from the baseline value was also considered to be diagnostic for SIBO.

The data are summarized here on the slide, and the key takeaway is this: when compared to culture, glucose breath testing is most accurate, followed closely by a double-peak positive result on a lactulose breath test. Single-peak result, like just a single-peak increase in hydrogen on a lactulose breath test, and the methane-positive criteria on the breath test were less well-correlated with bacterial culture. You notice that glucose breath testing and lactulose breath testing when you use the double-peak criteria were highly specific. That meant there was little chance of a false positive, but they were both not very sensitive. They had low sensitivity, which means that there's a pretty good chance of a false negative. On the other hand, a single-peak criteria using lactulose breath testing is the most sensitive. It will catch the greatest number of patients, but it's only 65 percent specific, which means there will be a lot of false positives, and that explains the positive predictive value of only 18 percent.

2017 North American Breath Testing **Consensus**

1. H2 increase ≥ **20 ppm** before **90 min**

2. CH4 ≥ **10** ppm at **any point** during test

In the spring of 2017, 17 clinicians and researchers who are experts in SIBO were recruited to develop a consensus on breath testing. They sent out questionnaires, and they also had a live meeting. After extensive discussion, they came to an agreement in five domains: indications for breath testing, preparation, performance, interpretation, and knowledge gaps. Then, they wrote a paper where they issued 26 consensus statements in all five of these domains. We're not going to review all of them because in this module we are already current with most of their recommendations. I'm just going to point out the most important highlights and differences from how things were done before so that you are aware of them.

First, they changed the interpretation guidelines so that an increase in hydrogen greater than or equal to 20 parts per million before 90 minutes is considered positive. They also argued that a double peak should not be used to diagnose SIBO and has not validity. In other words, the only relevant factor is whether there is an increase of hydrogen above or equal to 20 parts per million before 90 minutes. This also means then that a rise in hydrogen of equal to or greater than 20 parts per million that occurs after 90 minutes, such as a late single peak that shows up at 110 or 120 minutes, which is currently marked positive on many SIBO breath tests, is not actually a positive result or should not be considered to be a positive result.

This changes the criteria in a couple major ways. First is the double peak is not emphasized as much as it used to be and, in fact, is not used in this consensus. Second, the cut period for the

increase in hydrogen that marks a positive result was reduced from 120 minutes to 90 minutes, so that single peak has to occur before 90 minutes in order to be considered a positive result.

The second big change was that they now consider a methane level of greater than or equal to 10 parts per million at any point during the test to be positive for methane. That means even once the lactulose has reached the colon if you see a value of above 10 parts per million at 140 minutes or 160 minutes that would still be considered a positive result, whereas before the Quintron criteria looked at an increase in methane over the baseline value as the criteria. Now, we're just looking at an absolute value at any point during the test. This is because we are looking for people who are methane producers not just whether methane is produced in the small intestine, but whether they are methane producers at all, which has been correlated with decreased transit time and a number of other issues. That is a really important development.

Comparison of glucose vs. lactulose as substrate for breath test

Substrate	Advantage	Disadvantage	Risk
Glucose	More specific	Greater risk of *false negative*	Under-treatment
Lactulose	More sensitive	Greater risk of *false positive*	Over-treatment

So I know that this might be a little overwhelming or confusing, so let me bring all of it together for you. Glucose breath testing favors specificity over sensitivity, so if you choose glucose breath testing, you're accepting a greater possibility of false negative in the case of SIBO that's happening in the middle or lower parts of the small intestine, and you're erring toward undertreatment rather than overtreatment. But overall, glucose breath testing does have more diagnostic accuracy than lactulose breath testing. On the other hand, lactulose breath testing favors sensitivity over specificity—if you choose lactulose breath testing, there's a greater possibility of a false positive, especially if the patient has normal or faster-than-normal transit

time. So here you are erring toward overtreatment, and overall, there's less diagnostic accuracy than glucose breath testing.

So with all of this in mind, what test do I use? The answer is lactulose breath testing, and that might be somewhat surprising given what we've covered in the previous slides and the overall lower level of diagnostic accuracy compared to glucose breath testing. But here's the thing: I think the risk of undertreating SIBO is higher than overtreating, and this is true especially because the treatments for SIBO, whether you're doing a botanical antimicrobial protocol, or whether you're using pharmaceutical treatments for SIBO, are both remarkably safe and aren't likely to cause a lot of side effects and don't have a lot of complications or risks. So, we're always making calculations as clinicians, we're weighing benefits versus consequences, and in the case of SIBO, I think the potential benefits of treatment far outweigh the potential consequences because of the safety of the treatment interventions. I will sometimes order glucose breath testing, all of that said, if I think it will clarify the clinical picture, but to be honest I haven't done this very much because I've found that if glucose breath testing is negative, it still doesn't rule out SIBO because it's so insensitive, and it will not stop me from doing a therapeutic trial if I really suspect the patient has SIBO. So I haven't found it to be all that useful even as a clarifying test.

1

Should use
Quintron machine

2

Should test both
H_2 and CH_4

Many labs offer both lactulose and glucose breath testing, so there are several considerations in terms of which you should use. The first is you should always choose a lab that uses the Quintron machine. That is the machine that has been used in most studies, and it is the one that has been validated. Second, the lab should test for both hydrogen and methane. Some labs just do hydrogen, but as we now know, methane is very important, so we need to look at that as well. Keeping this in mind, there are three labs that can be a good option for SIBO breath testing.

The first is BioHealth. And they have a panel called the 900-C, where C stands for consensus. This is the only lab that has updated their interpretation criteria to meet the North American Consensus, and has changed the test timing to every 15 minutes for a total of 135 minutes of collection time. BioHealth feels the peer-reviewed studies support a collection time of 120 minutes, rather than 180 minutes, which was what was previously recommended before the North American Consensus criteria came out. They have provided one extra collection time at 135 minutes to accommodate patients that may have slower orocecal transit time. Their glucose test has been updated to 901-C with an increase in 20 parts per million more for hydrogen values as per the Consensus. And it is important to note that BioHealth does still have the original 900 panel, without the C, that collects samples every 20 minutes and does not apply the new Consensus interpretation. That test is scheduled to fade out eventually, so depending on when you are listening to this, it may or may not be available. One of the advantages to the BioHealth panel, in addition to the fact that it is following the North American Consensus, is that it has a relatively quick turn around time, averaging five to six days, in our experience.

Another option is the Genova SIBO Breath Test. They are also using the North American Consensus Criteria for interpretation, at least in part. They are collecting at 20 minute intervals. The North American criteria suggests looking at a 90 minute value in determining the rise in hydrogen, but with 20 minute intervals, there is no 90 minute value. So what you can do is look at the 80 minute value and the 100 minute value and half the increase between the two values to estimate a 90 minute value. That isn't as accurate as measuring at 90 minutes, but it is probably close enough in most cases. Genova offers both a two and a three hour test. And they report a seven day turn around time that has been pretty consistent in our experience using them.

Finally there is NUNM, or NCNM as it is sometimes called, and we were regularly using that lab because of the calibration of their machines and clear billing procedures. Unfortunately, the have not updated their interpretation criteria to the North American Consensus recommendations, and they also have the slowest turn around times of the three labs discussed. We have stopped using NUNM, at this point, as of the fall of 2018.

Note that Commonwealth lab also offered SIBO breath testing. They went out of business for a while; I think they have recently come back. We are not using them. We had some issues with their billing practices. And we are happy with the BioHealth and Genova options for patients. However, on some of the following slides, you will see some Commonwealth lab results because we did use that lab at one point.