

## Gut Treatment Protocols: SIBO, Part 6

All right, let's move on to talk about rifaximin. Rifaximin is a really interesting drug with some unusual properties that make it different [from] other antibiotics.



- 1 Not systemically absorbed (*99.6% stays in gut*)
- 2 Very few adverse effects or interactions
- 3 Acts largely in the small intestine (*activated by bile acids*)
- 4 Does not adversely effect colonic flora (*may even have beneficial effect*)

Number one is that it's not systemically absorbed, so 99.6 percent of rifaximin stays in the gut. And if you recall from the basic physiology section, [the] inside of the gut is technically outside of the body. So rifaximin is best considered a topical antibiotic for the gut. Now, because of this localized activity, it has very few side effects or risks and a very low potential for drug interactions. That's number two. And number three is that rifaximin acts largely in the small intestine because it's activated by bile acids, and that's a really important thing to keep in mind. It doesn't have a significant impact on the colon, which then leads me to number four. Rifaximin does not seem to adversely affect the beneficial bacteria in the colon. Now, on the contrary, some studies have shown that rifaximin increases numbers of *Bifidobacterium*, which is another very beneficial species, [and a few others]. This is an antibiotic that may actually increase beneficial flora in the colon. Go figure. One other mention is that cholagogues are herbs that improve bile flow. Because we know that rifaximin is a bile-soluble antibiotic, this is one of the reasons it works so well in the small intestine.



**Xifaxan**



**Rifaximin**  
(generic)

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Image credits: <http://www.empr.com/xifaxan-550mg/drug/3607/>

There is a bit of a caveat to number one on the last slide. The brand name medication Xifaxan is not systemically absorbed. [For that one], 99.7 percent of it stays in the gut. But a couple of studies have shown that the generic form of rifaximin has increased systemic absorption compared to Xifaxan. Now, it's still relatively low compared to other systemically absorbed antibiotics, and it may not be an issue for most patients. But those with intestinal permeability, which you might expect to be somewhat common in people with SIBO or those with liver disease, can be more affected by this. And some practitioners have also found that the Xifaxan brand simply works better than the generic. And this may also explain why, because with Xifaxan, you have a lower systemic absorption, so you would expect a higher concentration of it in the mucosa of the intestine, which is where it exerts its action. If you look in the scientific literature, the vast majority of the studies [that] have been done looking at the efficacy and safety of the medication have been done using the Xifaxan brand name, so we really don't know for sure if the generic rifaximin has the safety pharmacokinetic profile that the Xifaxan brand does. And this is pretty unfortunate because the Xifaxan brand is extremely expensive. [It costs] thousands of dollars for a month-long course, depending on what dose you use, and it's not currently approved for SIBO. It is, however, approved for IBS-D, or diarrhea, and patients can sometimes get coverage for it if we use the IBS-D ICD-10 codes. But that's not always the case.

The other issue is that some patients will try to order it from India or Canada, and those are the generic form. They may not have the crystal alpha polymorph structure that leads to the low

systemic absorption, and they may have this other profile that we don't know as much about. So it's definitely a dilemma clinically. There is an option to order from the Center for Digestive Diseases in Australia. It's a cash pay-out-of-pocket expense, but this is the best option that we have at this time, and the patient can generally afford it. It's not cheap, but it's not astronomically expensive. It's also much more reasonable than that U.S. cost. At the time of this recording, the price from Australia can range from \$330 for 135 pills to \$440 for 180 pills, and that doesn't include shipping. The only caveat here is that they don't accept prescriptions for mid-level practitioners like nurse practitioners and [physician's assistants], so hopefully, you're able to work with another practitioner [who] may be able to comanage those prescriptions with you. The dose is generally 500 mg per capsule when ordering it from the [Center for Digestive Diseases] in Australia. So this can make Xifaxan a difficult option in some cases, especially if [the patients'] insurance won't cover it because many patients aren't able to afford it, especially for the longer courses that might be required for treatment. Looking back, I think that most of the time, we're able to work something out, but occasionally, [it] just isn't an option, and we find another plan. Hopefully, the FDA will approve it for SIBO at some point, and this will change. But in the meantime, we just have to do the best we can.

## Rifaximin safety



Studied for periods  
up to 2 years at  
**1,100 mg/d**



**No increase** in rate of  
infections or development  
of resistance



Side effects  
generally similar  
to **placebo**

Rifaximin is remarkably safe [as] an antibiotic. It's actually been studied for periods of up to two years at a dose of 1,100 mg per day. And in these studies, there was no increase in the rate of infections, including with *Clostridium difficile* or development of bacterial antibiotic resistance. It's generally very well-tolerated by patients, with side effects similar to placebo in the randomized clinical trials.

## When to consider **ifaximin**



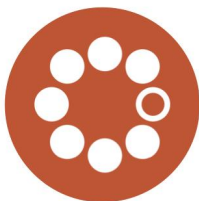
If patient has **failed** botanical protocol



If patient **can't tolerate** botanical protocol

When should you consider using rifaximin vs. the botanical protocol? There are basically two considerations that lead us to consider this in our practice. Number one is if a patient has tried at least one, sometimes two, botanical protocols and failed. And number two is if the patient is hypersensitive to supplements and knows or suspects that they won't tolerate the botanical protocol.

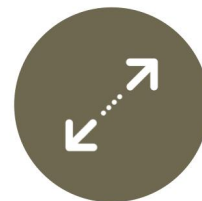
## Rifaximin efficacy



Highly **heterogenous**



**Depends** on dose, duration, severity of SIBO, H<sub>2</sub>/CH<sub>4</sub>, underlying cause



Ranges from **<30% to 87%**

As mentioned on the previous slide, meta-analyses have found that the efficacy of rifaximin for SIBO is about 50 percent, but that is somewhat misleading because there's a significant [heterogeneity] in the studies. They are using different doses, different durations, the severity of SIBO differed considerably, and they all had different presentations. So some might have been hydrogen only, some might have been hydrogen plus methane. And then a typical course in a lot of these studies was seven to 10 days only, which, as we saw, is unlikely to be enough in perhaps a majority of cases of SIBO. And then there was a study that showed that rifaximin plus [PHGG] for 10 days showed 87 percent efficacy, which is quite good. Other studies, especially in kids, have shown much lower normalization rates of even below 30 percent. So in those cases, it's possible that the kids didn't have SIBO in the first place, and that they just had more rapid transit time. That points to one of the issues with the lactulose breath test that we talked about earlier. And kids tend to have faster transit time than adults anyway, so that's one possibility to consider with [the] efficacy of rifaximin in kids.

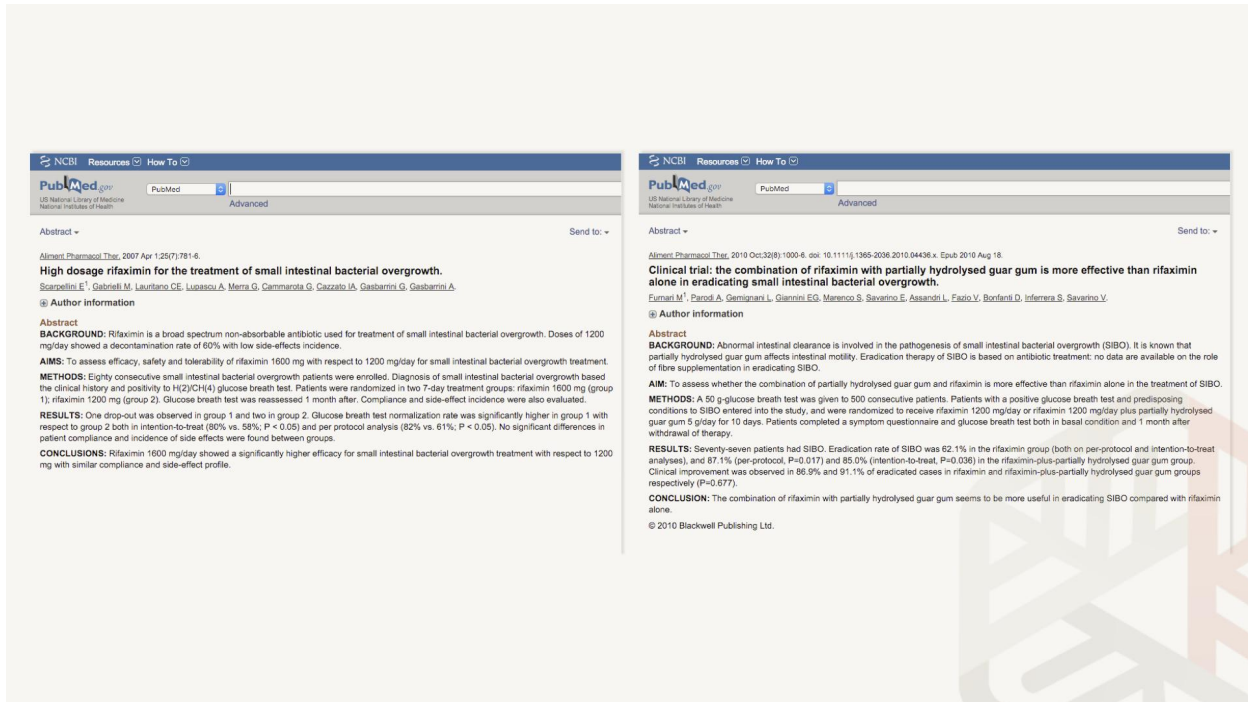
## Common rifaximin dosing regimens

Population	Dosage
Adults	400 mg TID for 10-14 days
Adults	550 mg TID for 10-14 days
Children	200 mg TID for 10 days
Children	10-30 mg/kg/d for 10 days

Let's talk a little bit more about how to use it. There are dose regimens commonly used with adults. Rifaximin comes in 200 mg and 550 mg quantities. The three-times-a-day study doses are typically given at 8:00 a.m., 2:00 p.m., and 8:00 p.m.. So it can be dosed at 400 mg three times a day, which is a total of 1,200 mg a day for 10 to 14 days, or 550 mg three times a day, which is 1,650 mg a day for 10 to 14 days. And that second dose, the higher dose, is what's more commonly used by specialists who treat SIBO, including myself. For children, different protocols have been used. One is 600 mg per day for seven days, and that led to a 64 percent lactulose breath test normalization in kids ranging from 3 to 15 years of age. That's an average of 10 years

old. Other studies in kids with IBD who were treated with rifaximin—so rifaximin can be used for IBD, as we'll discuss a little bit later. But they use[d] dosages ranging from 10 to 30 mg per kilogram of body weight and achieved 61 percent symptom relief.

However, more recent studies suggest that a higher dose and longer duration may be required, as we've talked about before.



The study on the left showed that 1,600 mg per day led to a better result than 1,200 mg per day without increasing adverse effects or resistance. We talked about that Korean study suggesting that up to 12 weeks may be required in cases where hydrogen is significantly elevated at that 90-minute mark. But we also discussed studies suggesting that added agents like [PHGG] may increase treatment efficacy without needing to take it much longer. So we still have a lot to learn. And given that, I'm going to provide some guidelines on the next slide, but just understand that some of this is still empirical and exploratory.

## Rifaximin treatment duration based on LBT results

H2 @80/90 min	Duration
<45 ppm	<b>4 weeks</b>
45-70 ppm	<b>8 weeks</b>
>70 ppm	<b>12 weeks</b>

Here are some guidelines for if rifaximin is used alone. And again, this is the same as the Hydrogen SIBO Botanical Protocol slide because it's based on the Korean study I mentioned previously. So you could use 1,200 mg per day or 1,650 mg per day. And just a quick reminder that this is one study that showed the benefit of basing your treatment duration on the lactulose breath test results. In practice, I have found it difficult to either get a 12-week supply authorized by insurance or for the patient to afford the cost of that much rifaximin. So we have to get creative sometimes.

## Rifaximin + botanical/nutraceutical treatment duration based on LBT results

H2 @80/90 min	Duration
<45 ppm	<b>2 weeks</b>
45-70 ppm	<b>3 weeks</b>
>70 ppm	<b>4 weeks</b>

One of the more creative options is combining botanical or nutraceutical treatments with prescription treatments. This can be done in a variety of ways, and I will give you some examples of how I do this in practice. If you add your botanical treatments to rifaximin and take them at the same time, here are the durations that you could consider. For instance, if you added [PHGG], Interfase Plus, Lauricidin, and Terraflora or Seed to the rifaximin treatment, the expectation would be that it would become more effective and that you could therefore reduce the treatment duration because of those other agents. I don't want this to get too confusing, and I'll provide more examples soon on how this can be arranged. But I very rarely do two weeks, only if I'm combining the two. I will often do at least 14 days of rifaximin plus [the] botanical treatment, then continue on with the botanical treatment only for another two to six weeks, of course, depending on the lactulose breath test results and the severity of symptoms. Other considerations could be doing a lower dose of rifaximin of 1,200 mg per day instead of 1,650 mg, because you're adding these other agents that would improve the efficacy, and you could get the prescription to last a little longer and fit the treatment duration plan.



## Improving rifaximin efficacy for patients with impaired bile metabolism



3,000–6,000 mg per day



20 drops before each meal

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Image credits: <http://www.iherb.com/Allergy-Research-Group-Ox-Bile-125-mg-180-Veggie-Caps/35162>,  
<http://www.lekarnaavicina.cz/www-lekarnaavicina.cz/eshop/26-1-TRAVICI-SOUSTAVA/199-2-STREVA/5/2627-Iberogast-tct-1x50ml>

Some other considerations for improving rifaximin efficacy for patients with impaired bile metabolism, I mentioned that rifaximin is activated by bile acids in the small intestine. So if you have a patient who has an issue with bile, low bile output like fat malabsorption or burping fish oil, itchy skin, some of those classic symptoms, you could do a two-week lead-in with phosphatidylcholine and bitters to stimulate that bile production. You can use Iberogast, which is our preferred form of bitters, and you can continue those during the protocol.



Standard is **Neomycin** 500 mg BID for 10 days

**Pimentel/Cedars Sinai** trial with metronidazole (Flagyl) with some success > 250 mg TID for 10 days

**Metronidazole** doesn't appear to adversely affect gut microbiota > but not as well tolerated as rifaximin/neomycin

If you use **neomycin** or **metronidazole** with longer course of rifaximin then limit their use to 10 days

If methane is elevated in addition to hydrogen, the typical protocol is to add neomycin at a dose of 1,000 mg per day for 10 days. It's available in 500 mg quantities, so you do 500 mg twice a day, once at 8:00 a.m. and once at 8:00 p.m. If you do a little research with neomycin, you might get scared away from it because you'll see that it's associated with some serious adverse effects. It does have a black box warning for neurotoxicity, including ototoxicity and nephrotoxicity. However, if you dig a little deeper, you will find that this happens almost exclusively to topical neomycin applied directly to the ear, and parenteral neomycin, not oral neomycin.

In 25 years of oral neomycin use, there have only been a few cases of ototoxicity, and this is in patients [who] were taking it long-term for more than six months and had pre-existing kidney problems or serious [GI] inflammation. It doesn't have quite the stellar safety profile that rifaximin has, but overall, I believe it's quite safe. It's only 3 percent absorbed in the GI tract. That said, it does have some contraindications that [you] should be made aware of. Neomycin and aminoglycoside can cross the placenta and cause fetal harm. So it should not be used during pregnancy, and it should be contraindicated in patients with serious inflammatory or ulcerative [GI] disease, like ulcerative colitis or IBD, because of the potential for enhanced [GI] absorption in those cases. It's worth pointing out that metronidazole, which is Flagyl, is also being used for methane with some success, but neomycin, I think, is still the preferred choice at the time of this recording. Metronidazole is used at 250 mg three times a day for 10 days. If you use neomycin or metronidazole with a longer course of rifaximin, you want to be sure to limit their use to 10 days.

So if you do 30 days of rifaximin, you'd still only be doing 10 days of metronidazole or neomycin in the first 10 days of treatment.

## **Addition of Neomycin to Rifaximin treatment for elevated methane**

<b>Treatment</b>	<b>Clinical Response</b>	<b>Breath Test Normal</b>
<b>Rifaximin alone</b>	<b>56%</b>	<b>28%</b>
<b>Neomycin alone</b>	<b>63%</b>	<b>33%</b>
<b>Rifaximin + Neomycin</b>	<b>85%</b>	<b>87%</b>

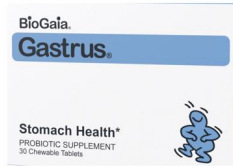
Adapted from: Low et al. J Clin Gastroenterol. 2010 Sep;44(8):547-50

You can see here on this slide, adding neomycin to rifaximin is 85 percent effective in terms of clinical response vs. just 56 percent effective for rifaximin alone, or 63 percent for neomycin alone. And it's 87 percent effective for normalizing the breath test vs. much lower 28 percent for rifaximin alone or 33 percent for neomycin alone. So, as you can see, it's very important to customize the treatment if methane is elevated.

## Other options for methane



Lactobacillus  
plantarum



Lactobacillus  
Reuteri



Atrantil



Rifaximin  
30 days

Image credits: [http://www.jarrold.com/product/539/Ideal\\_Bowel\\_Support](http://www.jarrold.com/product/539/Ideal_Bowel_Support), <http://www.empr.com/xifaxan-550mg/drug/3607/>

A reminder that if you don't want to use neomycin or metronidazole, just remember the alternatives and the additions that we discussed earlier. *L. plantarum* at a dose of 10 billion CFU per day, Atrantil at a dose of two capsules three times a day, and/or a longer course like 30 days or more for rifaximin.

## Pharmaceutical/combo protocol for SIBO

Therapeutic Agent	Dosage
<b>Rifaximin</b>	Depends on breath test results
<b>Lauricidin</b>	1 scoop TID with each meal
<b>InterFase Plus</b>	3–4 capsules BID on an empty stomach
<b>Terraflora</b>	1 capsule BID upon rising and before bed
<b>Atrantil (optional)</b>	(Only if methane elevated) 2 capsules TID
<b><i>L.plantarum</i> and/or <i>L.reuteri</i> (optional)</b>	(Only if methane elevated) 10 billion CFU/d
<b>Iberogast (optional)</b>	(Only with bile issues) 20 drops TID with meals
<b>Ox bile (optional)</b>	(Only with bile issues) 100–500 mg with meals

Here’s an example of a combination drug and botanical protocol that I was talking about previously. The rifaximin dose and duration may depend on breath test results and, of course, insurance coverage or cost. Lauricidin, Interfase Plus, and Terraflora would be the basic additions to the core protocol. Then you may consider adding Atrantil if methane is present. You may consider *L. plantarum* or *L. reuteri* if methane is elevated since they are methane degrader[s]. And you might consider Iberogast or ox bile if bile issues are present. I think you get the pattern here with these additions and substitutions based [on] what’s happening with the patients and the results of the SIBO test. These could be taken together for two, three, or four weeks in duration, as we previously discussed. And I always think it’s important to mention to be cognizant of the pure load for the patients, just how many pills they’re going to be taking and how many supplements they’re going to be taking. So just keep that in mind as you’re picking and choosing and prioritizing what protocol combination to put them for.

## Pharmaceutical/combo protocol for SIBO

Rifaximin for 2–4 weeks	Dosage
Rifaximin	1200 mg to 1650 mg daily for the first 2–4 weeks
Botanical protocol for 4–8 weeks	See previous slides for dosage
GI-Synergy or Biocidin	Core protocol
Terraflora or Seed	Core protocol
InterFase Plus	Core protocol
Allimax Pro and/or Atrantil (optional)	IMO add-on
<i>L. plantarum</i> and/or <i>L. reuteri</i> (optional)	IMO add-on
Iberogast or Ox bile (optional)	Bile issues add-on
Bismuth (optional)	H2S add-on

Here are a variety of other options for combination protocols. Some versions of this start with rifaximin, 1,200 to 1,650 mg daily by itself for two to four weeks, depending on the severity of symptoms, lactulose breath test results, and/or the ability to get it covered or paid for. I then follow up the rifaximin treatment with the botanical protocol. The botanical protocol should be customized to the person’s SIBO results and symptoms. I’ve listed a few possible add-ons and configurations for this protocol and how it could go. The takeaway here is that I generally start with rifaximin for two to four weeks and then add on a botanical protocol for an additional four to eight [weeks], depending on the factors that we’ve discussed. Occasionally, I will do a sandwich

protocol with rifaximin for two weeks, [a] botanical protocol for four [weeks], and then another round of rifaximin for two [weeks]. I've not come across any studies that have looked at the efficacy of this combination protocol, but I have found it fairly effective in practice, and [it's] something I've been doing with my patients [who] have recalcitrant and difficult-to-treat SIBO. I never start with this treatment option but will often work my way through a botanical protocol on its own first, followed by possibly rifaximin on its own. And then if they're still struggling with SIBO, but they are clearly making progress or did respond to either of those treatments, then I'll move on to some version of the rifaximin plus botanical combo protocol as described here. I should also note that I monitor these patients closely; [I] check a [comprehensive metabolic panel] for liver function and kidney function halfway through, just to make sure their bodies are handling the protocol well.