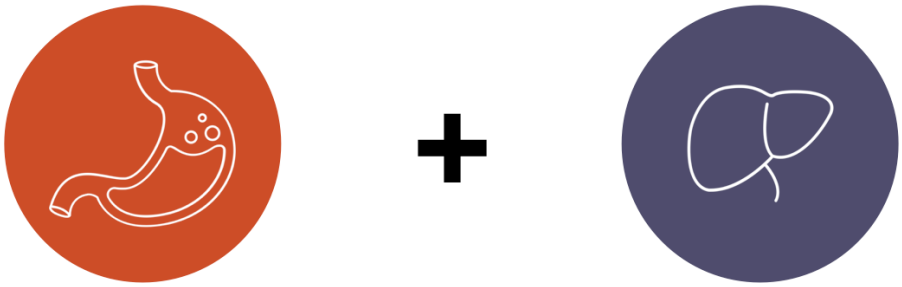
KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Gut: Treatment Protocols - SIBO, Part 4

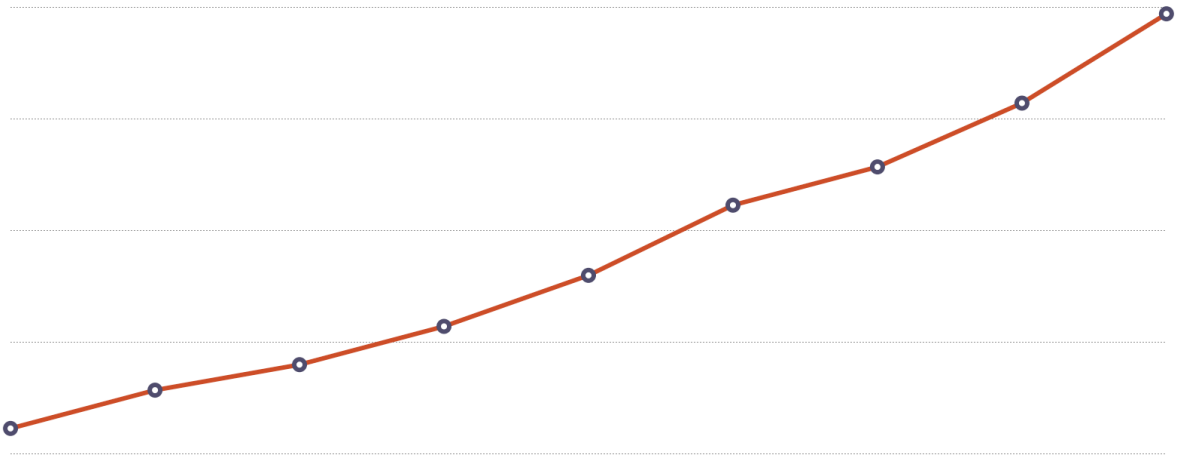
Hydrogen sulfide SIBO treatment



Core SIBO protocol + Liver detox support

So what about hydrogen sulfide with that flat-line lactulose breath test result? This is purely speculative at this point; we don't have any way of confirming hydrogen sulfide, and we know very little about how to alter treatment because of it, and I don't see it all that often, and the treatment of course will have to be empirical because we can't necessarily use breath tests to track treatment results in an accurate way. But what we will typically do is start with 30 to 60 days of the botanical protocol and see how symptoms improve, and hydrogen sulfide, as I mentioned before, should be eliminated by first-pass liver detox, so if you see a patient that you suspect hydrogen sulfide in, it's probably a good idea to support liver detoxification as well, and we will use things like liver nutrients from Seeking Health, or liver GI detox from Pure Encapsulations for that purpose.

Minimizing Herxheimer reaction on botanical treatment



Before we move on to pharmaceutical treatment, there are a couple things to be aware of. First is that botanical treatment is generally well tolerated, but it can cause a die-off or Herxheimer response. So, we'll start people on lower doses and ramp them up slowly over time, and this is explained in the patient handout that I'm going to give you. But if a patient still has a reaction, we have them go even slower and reduce the dose even further, or maybe move to every other day dosing, etc., and then ramp up over time. If they're still reacting, we might stop everything and then have them add the supplements back in one at a time, to see which is causing the biggest reaction, so that they can at least proceed with the other things. This can be a little bit laborious, but it's sometimes necessary if you have really sensitive patients.

Second thing is that although botanicals have less impact on beneficial bacteria than antibiotics, they likely still have some, and we've seen this in retesting, the Doctor's Data stool panel that measures beneficial bacteria after botanical protocols. So after you have eradicated the SIBO or pathogens that you're treating, you'll need to move on to phase two of the treatment, which is rebuilding a healthy gut ecosystem, and we'll talk more about that later.

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)*

All right, let's move on to talk about rifaximin. Rifaximin is an interesting drug with some unusual properties that make it different than most other antibiotics. 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, 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 interaction, so that's number two. 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 leads 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 and F. prausnitzii, which is another very beneficial species, so this is an antibiotic that actually increases beneficial flora in the colon, go figure.

Xifaxan

Rifaximin
(generic)

So there is a caveat to number one on the last slide. The brand name medication Xifaxan is not systemically absorbed, that has 99.7 percent of it stays in the gut, but one study, or a couple studies actually, 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 explain why, because with Xifaxan you have a lower systemic absorption, 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 which have been done looking at the efficacy and safety of the medication have been done using the Xifaxan brand name, so we don't really know for sure if generic rifaximin has the safety, pharmacokinetic profile that the Xifaxan brand does. And this is unfortunate, because the Xifaxan brand is extremely expensive, it's about $1,000 or $1,500 for a month-long course, depending on what dose you use, and it's not currently approved for SIBO. It is approved for IBS-D, 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 here is that some patients will try to order it from India or Canada, and those are the generic form, and 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. It makes Xifaxan just not really an option in a lot of cases, if their 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, so hopefully the FDA will

approve it for SIBO at some point, and this will change. In the meantime, we just have to do the best that 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 for an antibiotic; it's been studied for periods up to two years at a dose of 1,100 milligrams 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 randomized clinical trials.

When to consider rifaximin

If patient has **failed** botanical protocol

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

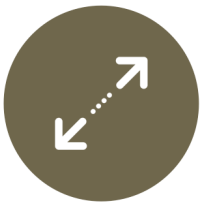
When should you consider using rifaximin versus the botanical protocol? There are basically two considerations that lead us to consider in our practice. Number one is if a patient has tried a

botanical protocol 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, H2/CH4, underlying cause



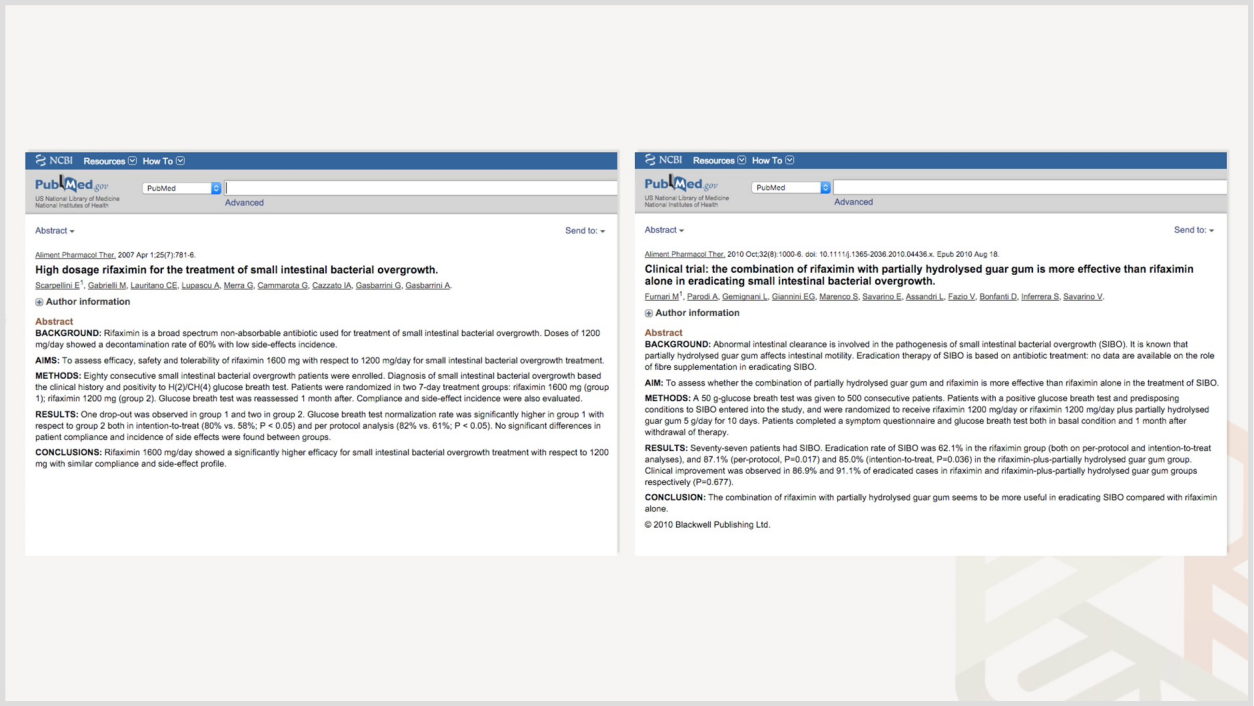
Ranges from
<30% to 87%

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 is significant heterogeneity in studies. They use different doses, different durations, the severity of SIBO differed considerably, they had different presentations, so some might have been hydrogen only and some might have been hydrogen plus methane, and then a typical course in a lot of these studies was seven to 10 days, which as we saw is unlikely to be enough in perhaps a majority of cases of SIBO. And then there was that study that showed that rifaximin plus partially hydrolyzed guar gum 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, 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 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 milligram and 550 milligram quantities. The three-times-a-day study doses are typically given at 8 a.m., 2 p.m., and 8 p.m. So it can be dosed at 400 milligrams three times a day, which is a total of 1,200 milligrams a day for 10 to 14 days, or 550 milligrams three times a day, which is 1,650 milligrams 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 at this point. For children, different protocols have been used. One is 600 milligrams per day for seven days, that led to a 64 percent lactulose breath test normalization in kids ranging from three to 15 years of age, that are an average of 10 years old. Other studies in kids with IBD who were treated with rifaximin, rifaximin can be used for IBD as we'll discuss later, they used dosages ranging from 10 to30 milligrams per kilogram of body weight and achieved a 61 percent symptom relief.



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Abstract

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Aliment Pharmacol Ther. 2007 Apr 1;25(7):781-6.

High dosage rifaximin for the treatment of small intestinal bacterial overgrowth.

Scarpellini E[1], Gabrielli M, Lauritano CE, Lupascu A, Merra G, Cammarota G, Cazzato IA, Gasbarrini G, Gasbarrini A.

Author information

Abstract

BACKGROUND: Rifaximin is a broad spectrum non-absorbable antibiotic used for treatment of small intestinal bacterial overgrowth. Doses of 1200 mg/day showed a decontamination rate of 60% with low side-effects incidence.

AIMS: To assess efficacy, safety and tolerability of rifaximin 1600 mg with respect to 1200 mg/day for small intestinal bacterial overgrowth treatment.

METHODS: Eighty consecutive small intestinal bacterial overgrowth patients were enrolled. Diagnosis of small intestinal bacterial overgrowth based the clinical history and positivity to H(2)/CH(4) glucose breath test. Patients were randomized in two 7-day treatment groups: rifaximin 1600 mg (group 1); rifaximin 1200 mg (group 2). Glucose breath test was reassessed 1 month after. Compliance and side-effect incidence were also evaluated.

RESULTS: One drop-out was observed in group 1 and two in group 2. Glucose breath test normalization rate was significantly higher in group 1 with respect to group 2 both in intention-to-treat (80% vs. 58%; P < 0.05) and per protocol analysis (82% vs. 61%; P < 0.05). No significant differences in patient compliance and incidence of side effects were found between groups.

CONCLUSIONS: Rifaximin 1600 mg/day showed a significantly higher efficacy for small intestinal bacterial overgrowth treatment with respect to 1200 mg with similar compliance and side-effect profile.

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Abstract

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Aliment Pharmacol Ther. 2010 Oct;32(8):1000-6. doi: 10.1111/j.1365-2036.2010.04436.x. Epub 2010 Aug 18.

Clinical trial: the combination of rifaximin with partially hydrolysed guar gum is more effective than rifaximin alone in eradicating small intestinal bacterial overgrowth.

Furnari M[1], Parodi A, Gemignani L, Giannini EG, Marenco S, Savarino E, Assandri L, Fazio V, Bonfanti D, Inferrera S, Savarino V.

Author information

Abstract

BACKGROUND: Abnormal intestinal clearance is involved in the pathogenesis of small intestinal bacterial overgrowth (SIBO). It is known that partially hydrolysed guar gum affects intestinal motility. Eradication therapy of SIBO is based on antibiotic treatment: no data are available on the role of fibre supplementation in eradicating SIBO.

AIM: To assess whether the combination of partially hydrolysed guar gum and rifaximin is more effective than rifaximin alone in the treatment of SIBO.

METHODS: A 50 g-glucose breath test was given to 500 consecutive patients. Patients with a positive glucose breath test and predisposing conditions to SIBO entered into the study, and were randomized to receive rifaximin 1200 mg/day or rifaximin 1200 mg/day plus partially hydrolysed guar gum 5 g/day for 10 days. Patients completed a symptom questionnaire and glucose breath test both in basal condition and 1 month after withdrawal of therapy.

RESULTS: Seventy-seven patients had SIBO. Eradication rate of SIBO was 62.1% in the rifaximin group (both on per-protocol and intention-to-treat analyses), and 87.1% (per-protocol, P=0.017) and 85.0% (intention-to-treat, P=0.036) in the rifaximin-plus-partially hydrolysed guar gum group. Clinical improvement was observed in 86.9% and 91.1% of eradicated cases in rifaximin and rifaximin-plus-partially hydrolysed guar gum groups respectively (P=0.677).

CONCLUSION: The combination of rifaximin with partially hydrolysed guar gum seems to be more useful in eradicating SIBO compared with rifaximin alone.

However, more recent studies suggest that a higher dose and longer duration may be required, as we talked about before. So, the study on the left showed that 1,600 milligrams per day led to a better result than 1,200 milligrams 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 90 minutes, or the sum is, but we also discussed studies suggesting that adding agents like partially hydrolyzed guar gum may increase treatment efficacy without needing to take it for much longer. So we still have a lot to learn here, 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	**Sum of H2** @80/90 min	**Duration**
<45 ppm	<160 ppm	**4 weeks**
45-70 ppm	160–250 ppm	**8 weeks**
>70 ppm	>250 ppm	**12 weeks**

So here's some guidelines if rifaximin is used alone, and again, this is the same as the slide before, it's based on the Korean study I mentioned, and you could use 1,200 milligrams per day or 1,650 milligrams per day.

Rifaximin + nutraceutical treatment duration based on LBT results

H2 @80/90 min	**Sum of H2** @80/90 min	**Duration**
<45 ppm	<160 ppm	**2 weeks**
45-70 ppm	160–250 ppm	**3 weeks**
>70 ppm	>250 ppm	**4 weeks**

If you add partially hydrolyzed guar gum, Interfase Plus, Lauricidin, or Prescript-Assist and MegaSporeBiotic 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 these other agents. You could also consider a lower dose of rifaximin of 1,200 milligrams per day instead of 1,650 because you're adding these other agents that would improve the efficacy, so this is more what we're moving to in our clinic, and I think it's more practical given the high cost of rifaximin, so as you can see here, even with patients with very high hydrogen levels, we're suggesting a maximum dosage of four weeks with these other agents added, and that would be covered by most people's insurance if they have an IBS-D diagnosis.

Improving rifaximin efficacy for patients with impaired bile metabolism

3,000–6,000 mg per day

20 drops before each meal

Some other considerations for improving rifaximin efficacy for patients with impaired bile metabolism: I mentioned that rifaximin is activated by the bile acids in the small intestine, so if you have a patient that has an issue with bile, low bile output like fat malabsorption or burping after 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, and you can use Iberogast, which is our preferred form of bitters, and you can continue those during the protocol.