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Hydrogen sulphide SIBO: pathological condition or physiological adaptation

A narrative review

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Abstract

Small Intestinal Bacterial Overgrowth (SIBO), particularly the Hydrogen Sulphide variant (H2S SIBO), remains a complex and challenging condition to manage due to its multifactorial nature and intricate pathophysiology. Traditional views on SIBO as merely a pathological overgrowth of bacteria are being reconsidered, with a novel hypothesis suggesting that the overgrowth of sulphate-reducing bacteria (SRB) may be a physiological adaptation in response to an impaired sulphur metabolism. This hypothesis implies a paradigm shift in treatment strategies, advocating for support of the body's sulphur metabolism in addition to managing the bacterial overgrowth. Antimicrobial therapy, including the use of pharmaceutical antibiotics such as Rifaximin and herbal antimicrobials, remains a key aspect of SIBO treatment. However, concerns about their effectiveness against SRB, the potential for antibiotic resistance, and their impact on beneficial gut flora necessitate exploration of alternative treatment strategies. These include dietary modifications, the use of pre- and probiotics, and supplementation with compounds which may support the body's sulphur metabolism. Despite the promise of these strategies, there is a clear need for further empirical evidence to substantiate their efficacy and safety. This review underscores the evolving understanding of H2S SIBO, the potential implications of the physiological adaptation theory, and the necessity for an integrated approach to management of the condition, thereby highlighting the need for continued research in this field.

Keywords: *hydrogen sulphide; SIBO; IBS; sulphur; sulphate*.

List with abbreviations

CH4	Methane
GAG	Glycosaminoglycan
H2	Hydrogen
H2S	Hydrogen sulphide
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
LAB	Lactic acid bacteria
SAA	Sulphurous amino acid
SCFA	Short-chain fatty acid
SIBO	Small intestinal bacterial overgrowth
SRB	Sulphate reducing bacteria
SUOX	Sulphite oxidase

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Introduction

Dysbiosis is a term that is widely used to indicate a state of imbalance in the composition of the intestinal microbiome. Repercussions of this are thought to be responsible for a large proportion of symptoms associated with functional bowel disorders such as irritable bowel syndrome (IBS). Especially an overgrowth of certain types of bacteria in the upper part of the small intestine, better known as small intestinal bacterial overgrowth (SIBO), has been implicated in causing symptoms such as flatulence, abdominal distention, discomfort, and altered bowel movements characterized by either constipation or diarrhoea. It is estimated that up to 78% of people suffering from IBS could have SIBO as an underlying cause. [1,2] Targeting SIBO can result in significant improvement in symptoms in many of such patients, implicating that further research could be of high value in improving many patients' lives.

SIBO can be subdivided into different types characterized by the main metabolite produced by the predominant bacteria. Originally, the two main types of SIBO found were either hydrogen-dominant or methane-dominant, the latter of which has recently been renamed as IMO – intestinal methanogen overgrowth – due to the methane being produced by methanogenic archaea instead of bacteria.[3] Relatively recently, however, a third variant characterized by an overproduction of hydrogen sulphide gas has been noted. This type differs from the other two types in several aspects. It is notoriously difficult to treat and very little research is available on the topic. Furthermore, symptomology differs from the other types. Unique symptoms such as an intolerance to dietary sulphur, H2S-induced lactic acidosis resulting in muscle weakness, and fatigue due to mitochondrial impairment, have been associated with this type of SIBO.[4–8] As these symptoms can be debilitating to the quality of life, there is a need for more information to form consensus and to develop new treatments.

This narrative review aims to provide a broad overview of the current available literature on H2S-dominant SIBO and relevant topics. Topics that will be discussed include sulphur metabolism to give a comprehensive background, and overall pathology of hydrogen sulphide SIBO. Several hypotheses for potential causes as well as proposed treatments will be discussed and evaluated on merit of evidence. The main goal of this review is to find gaps in current knowledge and determine the implications of this for further research.

Methods

In order to gather scientific literature for this review, databases that were utilised are PubMed and Scopus. These databases were selected for their comprehensive collection of articles in the field of life sciences and biomedical research.

Search terms that were used included: "*sulphur", "hydrogen sulphide", "SIBO", and "irritable bowel syndrome"*. The search was limited to articles published in English, without any date restrictions. Relevant articles were examined in detail and their reference lists were reviewed for additional applicable publications.

In addition to the database search, various resources such as interviews, podcasts, blog articles, and books were used to acquire a broad understanding of the subject matter.

Overview: Hydrogen sulphide SIBO

Diagnosis

Hydrogen sulphide (H2S) SIBO is characterised by an overgrowth of sulphate reducing bacteria (SRB) in the small intestine. These SRB produce large amounts of hydrogen sulphide gas, which has many toxic properties and can cause a variety of symptoms, including: [9–12]

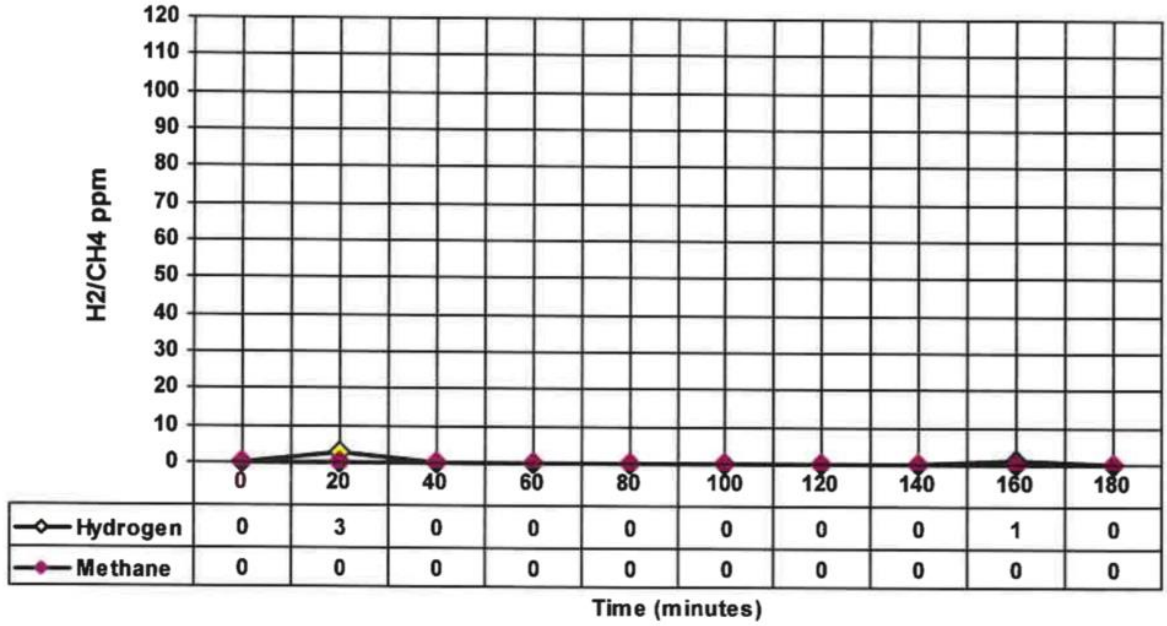
- Altered bowel movements: diarrhoea or constipation
- Odorous, sulphurous gas (H2S) production
- Abdominal distention and pain
- Visceral hypersensitivity
- Myalgia
- Halitosis
- Fatigue

Standard diagnosis of SIBO is done by performing a breath test measuring production of hydrogen (H2) and methane (CH4) gas after consumption of a fermentable oligosaccharide, typically lactulose. During the test, gas samples are taken at time intervals of 20 minutes up to 180 minutes from baseline. Gasses produced prior to 120 minutes are considered to be result of fermentation more proximally in the intestinal tract. Thus, high levels measured in this time period would indicate excessive fermentation and an overabundance of bacteria in the small intestine.[13] These tests do not usually measure H2S, making them mostly unfit for diagnosing H2S SIBO, although they are thought to give indications which will be discussed in the following section. Only recently, a new test has been developed that does measure H2S, making it the current gold standard for diagnosing H2S SIBO. However, only few laboratories worldwide perform this test, making it inaccessible to most clinicians.[14]

Beforehand, H2S-dominant SIBO was mostly diagnosed empirically and according to flatlining of the lactulose breath test results. An example of such a result is shown in Figure 1. Flatlining of the H2 and CH4 is thought to be due to funnelling of the H2 towards H2S production, rendering it unavailable for CH4 production and thus detection. SRB can utilise this H2 by coupling it to a sulfide molecule through a cross-feeding mechanism.[14] If other symptoms typical of SIBO do occur early-on during the test, such as bloating and gas formation carrying a sulphurous odour, this could be indicative of H2S production. This result would be confirmed by conjunction with other symptoms associated with H2S SIBO.

Stool tests are not a valid way of diagnosing small intestinal bacterial overgrowth. This is because the origin of the bacteria present in stool samples cannot be determined to be from either the small or large intestine.[15] The most accurate way of diagnosing SIBO is by taking samples of fluid using small bowel aspiration and analysing the bacterial composition.[16] However, due to the invasiveness and higher cost of this method, breath tests are generally preferred for diagnosing SIBO.

Figure 1. *Flatlining result of lactulose breath test.*[17] *Flatlining of the H2 and CH4 is thought to be due to funnelling of the H2 towards H2S production, rendering it unavailable for CH4 production and detection. If other symptoms typical of H2S production present during the test, this could be indicative of H2S SIBO.*



	0	20	40	60	80	100	120	140	160	180
Hydrogen	0	3	0	0	0	0	0	0	1	0
Methane	0	0	0	0	0	0	0	0	0	0

It is not entirely clear which specific bacterial strains are implicated in H2S SIBO. Potential candidates are SRB such as Desulfovibrio piger and Bilophila wadsworthia, as these are the main producers of H2S in the gut via a dissimilatory sulphate reduction pathway and through taurine degradation with subsequent sulphite respiration, respectively.[18] However, there are other genera in the SRB category which are able to produce H2S and therefore might play part in the condition as well, namely Desulfobacter, Desulfomonas, Desulfobulbus, and Desulfotomaculum.

It is difficult to establish the exact bacteria implicated in causing the symptoms, as the only reliable method for measuring is taking small bowel aspirates from patients in which the condition has already been diagnosed. Due to rarity of the condition and the invasiveness of such studies, clinicians will have to rely on limited data. Additionally, it is not unlikely that there will be variation in between patients, meaning that different cases can be attributed to different strains.

Symptomology and hydrogen sulphide toxicity

As previously mentioned, H2S SIBO may be accompanied by a variety of symptoms. While symptoms such as abdominal distention, excessive flatulence, and altered bowel movements can be seen in the other two types of SIBO as well, H2S SIBO may carry some unique symptoms. These unique symptoms are result of the properties that H2S gas carries.

Endogenously produced H2S can have multiple toxic effects when in excess, including:[19–23]

- Gastrointestinal effects: large amounts of H2S in the gut have been associated with altered bowel movements characterised by either diarrhoea or constipation, abdominal pain and bloating.
- Inflammation: excessive H2S production in the gut can trigger an inflammatory response, which can be damaging to tissues.
- Neurotoxicity: H2S produced in the gut can migrate to the bloodstream and enter circulation. As H2S can easily pass the blood-brain barrier, it can reach brain tissues causing neurotoxicity and impairing cognitive functioning.
- Mitochondrial impairment: at high concentrations, H2S is highly cytotoxic by inhibiting mitochondrial energy production.
- Carcinogenic effects: higher concentrations of H2S in the gut have been linked to an increased risk of colorectal cancer.

Apart from the acute gastrointestinal effects, chronically elevated levels of H2S can have multiple detrimental effects on the gut through various mechanisms. One of the key mechanisms is its effect on the gut microbiota. For instance, a key concern is the inhibitory effect H2S has on lactic acid bacteria (LAB). LAB are a group of beneficial bacteria known for their role in maintaining gut health and functioning. These bacteria improve the integrity of the gut barrier, compete with pathogenic bacteria, and have immunomodulatory properties. These bacteria are, however, highly sensitive to H2S. Excessive levels of H2S can inhibit their growth and thus disrupt the balance of the gut microbiota.[8]

Furthermore, production of short-chain fatty acids (SCFAs) can be diminished when H2S levels are elevated. SCFAs, such as acetate, propionate, and butyrate, play a crucial role in gut health. For instance, butyrate, a type of SCFA, provides up to 70% of the energy requirements of colonocytes. It has anti-inflammatory properties and supports the integrity of the gut barrier. Overproduction of H2S could therefore possibly lead to a chronic energy deficiency in the colon, increase inflammation, and impair barrier function.[8]

Manifestations of these symptoms may make patients adverse to eating particular foods that trigger H2S production. In later chapters will be discussed which foods are the main culprit and whether avoidance of these foods is beneficial or not.

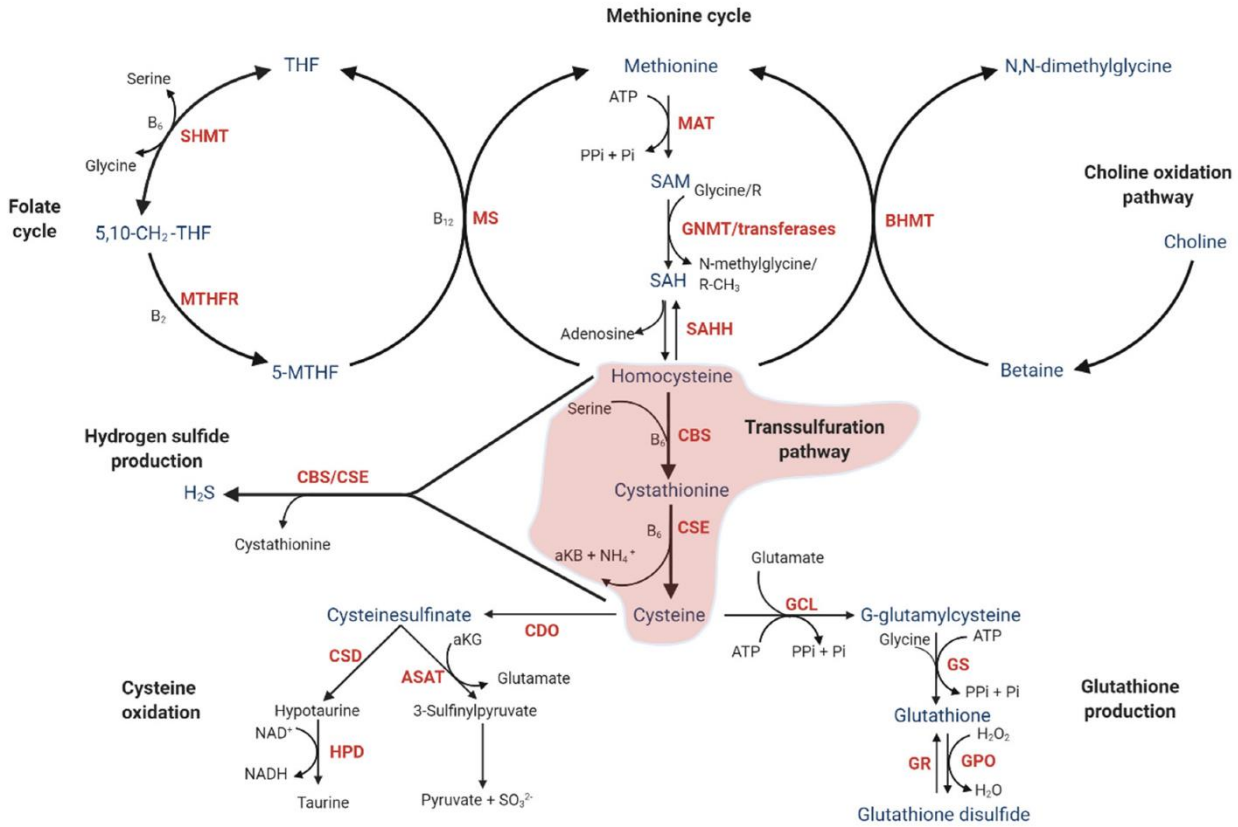
Background

Sulphur in the human body

Sulphur is the third most abundant mineral element in the human body, following calcium and phosphorus.[24] Dietary intake of sulphur mainly comes from sulphurous amino acids (SAAs), primarily cysteine and methionine, and a smaller contribution from inorganic sulphate and organosulphur compounds found in certain vegetables, such as cruciferous vegetables (broccoli, cabbage) and allium type vegetables (onions, garlic). [25]

Cysteine can be formed from methionine and is therefore considered non-essential. This conversion happens in the liver through multiple metabolic pathways. In this process, methionine is first converted into homocysteine through the methionine cycle. This homocysteine can subsequently be used in either the methylation pathway, generating the active form of folate, 5-methyltetrahydrofolate (5-MTHF), or in the transsulphuration pathway, resulting in cysteine formation.
An overview of these pathways is depicted in Figure 2.

Figure 2. *Important metabolic pathways in dietary sulphur metabolism. Cysteine can be formed from methionine through the methionine cycle and subsequent transsulphuration.*[26]



These SAAs can be used to form protein structures, but can also be metabolised to produce a variety of sulphur-containing compounds. These compounds play important roles in human physiology. Some of the most important sulphur-containing compounds include:[24,27]

Glutathione

Glutathione, a tripeptide composed of glutamate, cysteine and glycine, is one of the most important endogenous antioxidants. It protects cells from oxidative damage and helps detoxification of harmful compounds.

Taurine

Taurine, a sulphur-containing amino acid that is synthesized in the body from cysteine, plays an important role in maintaining the function of the heart, muscles and nervous system. Additionally, taurine is involved in the production of bile acids in the liver, therefore aiding fat digestion.

Sulphate and glycosaminoglycans (GAGs)

Sulphate is a key component of important glycosaminoglycans (GAGs). GAGs are long, unbranched polysaccharides that are composed of repeating disaccharide units. Some important examples include chondroitin sulphate, dermatan sulphate, heparan sulphate, heparin, and keratan sulphate. These are a major component of the extracellular matrix providing structural support to various tissues, including cartilage and other connective tissues such as the skin. Other functions include regulating cell signalling and adhesion, and regulating inflammation and blood coagulation.

Sulphur in the gut

Sulphur serves multiple important physiological functions in the gut. These functions range from structural support to facilitating the digestive process. It occurs in various forms, depending on the specific function. To discuss the various roles of sulphur in the gut, a distinction should be made between the different forms that sulphur occurs in. First, you have the SAAs, cysteine and methionine. These SAAs contribute to the synthesis of proteins that form the structural components of the gut, including mucins and tight junction proteins. These proteins are crucial in maintaining the gut barrier function and prevent the integrity of the gut wall from degrading.[28,29]

Sulphate, another pivotal form of sulphur, can enter the gut directly through the diet, but can also be formed in the liver through the metabolism of SAAs. In the gut, sulphate's main role is in the synthesis of GAGs. It constitutes a critical component of heparan sulphate and chondroitin sulphate, two GAGs integral to the gut lining.[30] Aside from the formation of GAGs, sulphate can be used for the endogenous production of H2S by colonocytes. H2S is not only formed by microbiota, but can also arise from enzymatic processes in the epithelial cells of the gut lining and other tissues spread throughout the body (Figure 2).[31]

At physiological concentrations, H2S exerts multiple regulatory effects on cell functioning. H2S is recognised as a crucial gasotransmitter, akin to nitric oxide and carbon monoxide, carrying out several important functions. It can regulate inflammatory processes, modulate oxidative stress, and act as a neuromodulator. Additionally, it facilitates maintenance of the mucosal barrier and gut motility, and exhibits cytoprotective effects.[32] It is only when a certain threshold is reached, that H2S elicits toxic effects. These concentrations will, however, not be reached through endogenous production alone.

Apart from the intrinsic functions of sulphur for overall gut physiology, its impact on the gut microbiome cannot be understated. The various forms of sulphur can be metabolised by SRB in the gut, mainly resulting in production of H2S. Through cysteine degradation and subsequent sulphate reduction, substantial amounts of H2S can be formed. However, the effect of H2S follows an inverted U-shaped curve, where high concentrations can have deleterious effects. At these high concentrations, H2S promotes mucosal inflammation, degrades the integrity of the mucus layer, and deregulates gut motility.[31,32]

In certain gut conditions, such as inflammatory bowel diseases (IBD) and colorectal cancer, an increased presence of SRB and concurrent rise in H2S production has been observed.[32,33] It is hypothesised that this increase in H2S production could be a contributing factor to the progression of these diseases and onset of symptoms, underlining the significance of understanding the precise mechanisms of sulphur metabolism in gut health and disease.

The gut-liver axis and its connection with sulphur

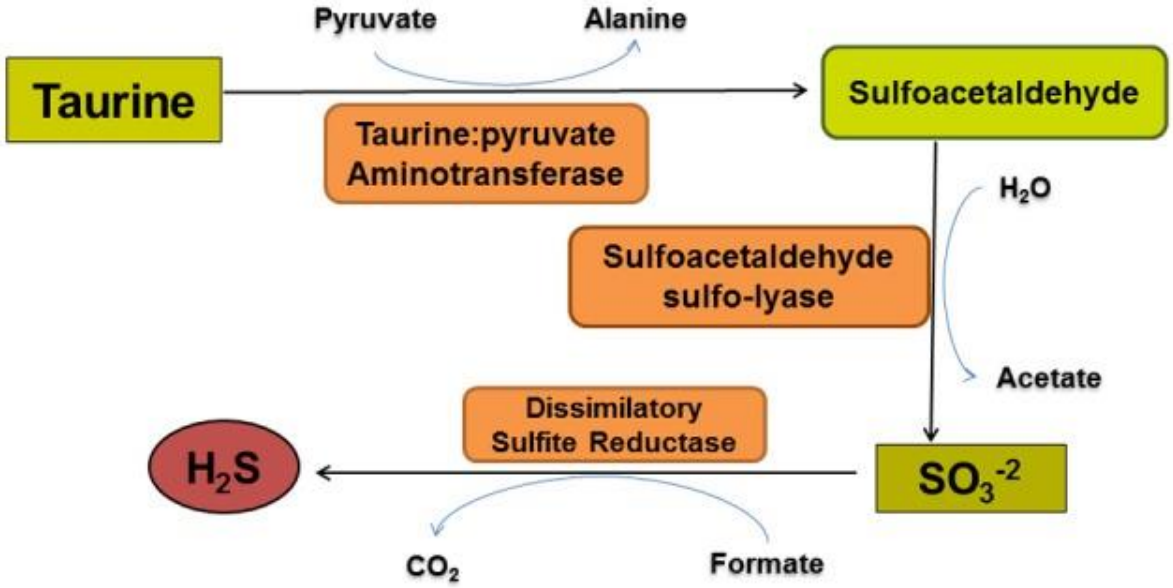
In discussing a condition of the small intestine, it might seem odd to discuss the role of the liver. Gut health, however, is intimately linked to liver health and vice versa. This symbiotic relationship, often referred to as the gut-liver axis, is a critical component of overall health and wellness. The gut and liver work together to regulate metabolism, immune function, and detoxification, among other important physiological processes.[34]

One essential aspect of this axis is the role of sulphur metabolism, which is primarily carried out in the liver. SAAs, such as cysteine and methionine, are metabolised in the liver, leading to the production of several sulphur-containing compounds including taurine and sulphate. As previously discussed, sulphate serves multiple roles in the gut environment. In the liver, sulphate plays a vital role in detoxification processes. It is a key component of Phase II liver detoxification, aiding in the transformation of xenobiotics to make them more water-soluble, and therefore easier to excrete from the body.[35]

Taurine, a derivative of cysteine, is essential in the production of bile acids. Bile acids are significant not only for their role in lipid absorption, but also for their interaction with the gut microbiota. They can influence the composition of the gut microbiota and, conversely, are subject to modification by certain gut bacteria, thereby creating a complex interplay between the host and the microbiota. One of the main strains of SRB responsible for H2S production and suspected for its involvement in H2S SIBO, Bilophila wadsworthia, can utilise the taurine moiety from taurine-conjugated bile acids as substrate (Figure 3).[18] This emphasises that SRB are not only fed by dietary sources. Endogenous sources of sulphur, including taurine and sulphate coming from the liver, are important sources of substrate and should not be neglected.

The regulatory effect of bile acids on the gut microbiome is primarily observed in the small intestine as over 90% of bile acids is reabsorbed via active transport in the ileum.[36] This dynamic interaction suggests that variations in either bile composition or production may significantly impact the microbiome of the small intestine. Indeed, a disrupted gut-liver axis is evident in many chronic liver disease patients, wherein 20-75% show significant alterations in gut flora, often marked by a pronounced prevalence of SIBO.[37] This connection underscores the intricate interplay between liver function, bile production, and the microbial health of the small intestine.

Figure 3. *H2S production of Bilophila wadsworthia using taurine as substrate. Taurine is first degraded through two enzymatic reactions resulting in sulphite production. Via the action of a dissimilatory sulphite reductase, sulphite can be converted into H2S.*[18]



Aetiology

In order to prevent H2S SIBO from occurring or to develop treatments, it is necessitated to first understand the aetiology of the condition. Due to rarity of the condition, no studies have been performed on this topic specifically as of yet. There are, however, multiple hypotheses which have been proposed by clinicians on what could potentially be the cause of H2S SIBO. This chapter will evaluate these hypotheses on their validity and evidence.

To understand the different theories on the origin of H2S SIBO, it is first important to distinguish the two contradicting views on a macroscopic level. The traditional view of H2S SIBO is it being a pathological condition that serves no function in the human body and both clinicians and patients ought to take priority in tackling the bacterial overgrowth. There are, however, other theories that propose that an overgrowth of SRB in the gut and subsequent H2S production are result of a physiological adaptation to an impaired sulphur metabolism. These theories will both be discussed in the following sections.

H2S SIBO as a pathological condition

Most clinicians view H2S SIBO solely as a pathological condition. It is thought that multiple factors can come into play for this condition to occur. While risk factors for H2S SIBO specifically have never been established, this research has been done on the other types of SIBO. Important factors that can be considered are:[38,39]

- Reduced gut motility: Slow gut motility, as oftentimes seen in conditions such as IBS, can lead to stagnation, which forms a risk factor for developing an overgrowth of bacteria in the small intestine.
- Structural abnormalities: Abnormal structures in the gut, such as strictures, adhesions, or surgical alternations, can affect its functioning and might encourage the growth of bacteria contributing to SIBO.
- Medication use: Proton pump inhibitors (PPIs), histamine type 2 receptor blockers (H2RAs), and antibiotics are examples of drugs that have the potential to disrupt the gut microbiome and increase the risk for developing SIBO.
- Comorbidities: Patients with conditions such as celiac disease, IBD, diabetes, or liver disease may be at a higher risk for developing SIBO.
- Lifestyle factors: Certain lifestyle factors such as an unhealthy diet rich in processed sugars or chronic stress may also contribute to the development of SIBO.

While these risk factors could potentially play part in developing SIBO in general, it is not exactly clear why SRB specifically overgrow leading to H2S SIBO. This, however, is still a mystery for the other types of SIBO, hydrogen and methane, as well.

To favour the growth of SRB, dietary factors might be of particular importance. A diet providing ample substrate for SRB may increase the chances of those species overgrowing, especially after disruption of the gut microbiome by medications such as antibiotics. To determine which foods promote the growth of SRB leading to H2S SIBO, it is first important to specify the strains of SRB implicated in the condition. As this has not been done, the only available clues can be derived from studies looking at the impact of various foods on the growth of SRB strains in the human gut in general.

Certain dietary components can serve as a substrate for SRB, potentially promoting their growth and subsequent H2S production. Sulphur-containing compounds present in various foods are the preferred substrate for SRB. As explained in the previous chapter, the main sources of dietary sulphur include SAAs from high-protein animal products such as meats, dairy and eggs, and plant sources providing inorganic sulphate and organosulphur compounds. From these food sources, SAAs from animal products have been identified as a particularly efficient source for SRB to produce H2S, and higher intake of these foods could lead to excessive levels of H2S in the gut.[18,40] This suggests that a diet rich in animal products might influence the gut microbiome to promote the growth of SRB, potentially contributing to the development of H2S SIBO. This mechanism could also provide an explanation for the emergence of H2S-dominant SIBO specifically, rather than hydrogen- or methane-dominant SIBO.

This notion is consistent with the observation that hydrogen is redirected towards H2S production, favouring H2S production over methane (CH4). A study conducted by Christl et al. found that a high-sulphate diet decreased CH4 production and increased H2S production in the human colon, highlighting the potential role of dietary factors in modulating the balance between CH4 and H2S production in the gut.[41]

The following chapter on proposed treatments will discuss whether avoidance of sulphur-containing foods is beneficial or not in treating H2S SIBO.

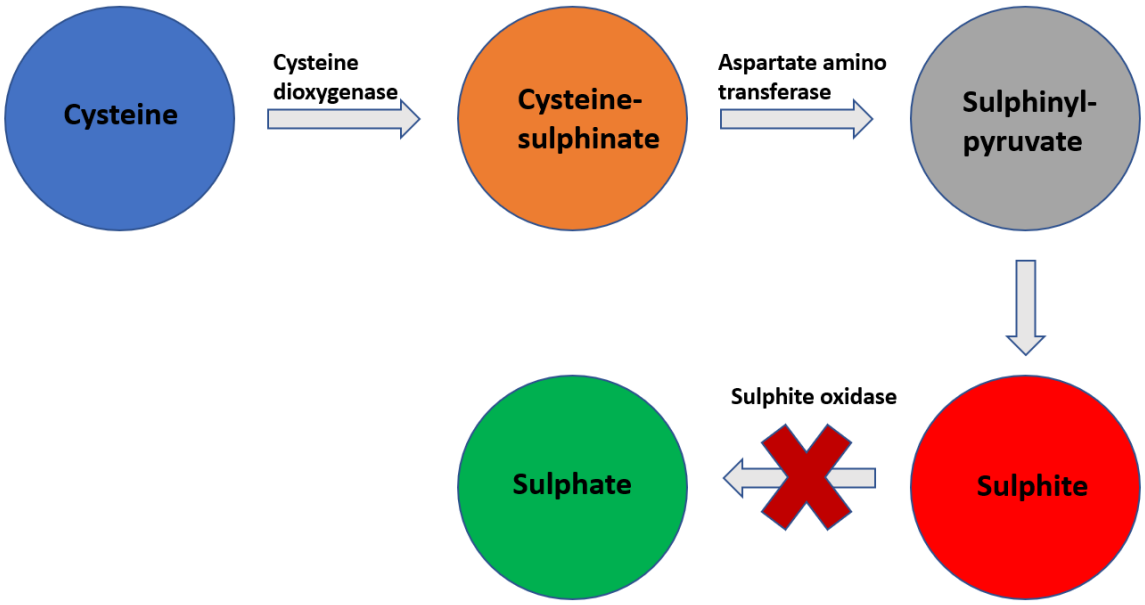
H2S SIBO as a physiological adaptation

An intriguing hypothesis suggests that H2S SIBO might not entirely be pathological, but rather serves as a physiological adaptation in certain individuals. In this context, the overgrowth of SRB in the small intestine is considered a protective mechanism aimed at neutralising sulphite and increasing sulphate supply, an essential nutrient required for various physiological processes as explained in the previous chapter.

This theory proposes that due to the crucial role of sulphate for various bodily functions, such as the synthesis of GAGs, the body prioritises its supply. It states that individuals with H2S SIBO may experience an increased demand for sulphate due to impaired liver sulphate generation, which could be induced by factors such as genetic predisposition, nutrient deficiencies, or exposure to environmental toxins.

The metabolism of cysteine in the liver involves several enzymatic reactions that could ultimately yield sulphate. One crucial step in this process is the conversion of sulphite to sulphate, which is facilitated by the enzyme sulphite oxidase (SUOX).[42] In cases where SUOX functionality is compromised, sulphite would accumulate, with no sulphate being produced. This process is illustrated in Figure 4.
Given the potential deleterious effects of excessive sulphite, it must either be excreted or neutralised. Bacterial processing by SRB presents one potential method of sulphite elimination, thereby benefiting the host.[18]

Figure 4. *Liver metabolism of cysteine for the production of sulphate. Through multiple enzymatic processes, cysteine is converted into sulphite. Sulphite is subsequently converted into sulphate through the enzymatic action of sulphite oxidase (SUOX). Impaired SUOX functionality can result in sulphite accumulation and reduced sulphate supply.*
Adapted from Stipanuk et al. (2002)[42]



Several factors that could inhibit SUOX functionality are proposed in this theory, including:

- Molybdenum deficiency: As a crucial dietary mineral, molybdenum serves as a necessary cofactor for proper SUOX functioning.[43]
- SUOX genetic polymorphism: A single nucleotide polymorphism in the SUOX gene, which codes for the SUOX enzyme, may impede the speed and efficiency of this enzyme's function.[43]
- Environmental toxins: Certain environmental toxins, including metals such as tungsten, copper, cadmium and arsenic, have been shown to be inserted into the molybdenum cofactor within SUOX, thereby impairing its function.[44]

When considering these factors, it becomes evident that the body may need to find alternative pathways to convert sulphite into sulphate, and this is where SRB come into play. Certain SRB can metabolise sulphite, producing H2S as a by-product (Figure 3).[18] This could potentially explain the overgrowth of SRB observed in cases of H2S SIBO. In this context, H2S is not an unwanted waste product, but rather serves as a valuable intermediate in sulfur metabolism. It has been shown that all human cells can oxidise H2S back to sulphate locally.[45] This conversion therefore provides an alternative route for the body to generate sulphate, especially when the traditional pathway via SUOX in the liver is compromised.

To illustrate, let's consider a situation where an individual has a SUOX genetic polymorphism, leading to impaired sulphate production in the liver. In such a case, sulphite starts to accumulate. This sulphite will subsequently be dumped in the gut, where SRB can utilise it to produce H2S. This H2S is then absorbed into the bloodstream and spread through circulation. In cells all throughout the body, the H2S can be locally oxidised back to sulphate, essentially bypassing the impaired SUOX enzyme in the liver. Therefore, in this scenario, H2S SIBO may indeed be seen as a physiological adaptation to meet the body's sulphate requirements.

However, while this proposed mechanism can be seen as beneficial in certain circumstances, it could potentially lead to an overproduction of H2S, which, as previously discussed, can have detrimental effects on gut health and overall wellbeing. Therefore, while SRB overgrowth might serve a purpose under certain circumstances, it becomes a problem when the production of H2S exceeds the body's ability to handle it, leading to the symptoms associated with H2S SIBO.

Furthermore, while this theory is certainly intriguing, it cannot be denied that it is mostly speculative at this point and needs further research for solid confirmation. Despite the current lack of extensive studies, clinicians are already exploring alternative treatment strategies aimed at improving sulphur metabolism in the liver and finding other ways to provide sulphate. These strategies will be discussed in the following chapter on proposed treatments.

Proposed treatments

Current treatment of H2S SIBO usually involves dietary changes to manage symptoms. This is often accompanied by the use of specific compounds which either target the bacterial overgrowth or support (liver) metabolism of sulphur-containing compounds. In the following section, proposed treatments will be evaluated according to the available literature on their rationale.

Low-FODMAP diet

As a primary dietary treatment strategy for SIBO, the low-FODMAP diet is oftentimes used. This diet or, more accurately, regimen is a strategy where certain food groups containing fermentable carbohydrates are eliminated for a certain period of time, whereafter the different groups will be reintroduced in a structured manner. FODMAP is an acronym for '**F**ermentable **O**ligosaccharides, **D**isaccharides, **M**onosaccharides **A**nd **P**olyols'. These are specific carbohydrates that have been associated with symptoms, such as gas formation, bloating, and flatulence, in patients with IBS and SIBO.[46]

The low-FODMAP diet regimen consists of three phases. The first phase entails eliminating all foods containing high levels of FODMAPs. This phase will last for a period of 2-6 weeks. After this period, patients will move on to the second phase, the reintroduction phase. The different FODMAP groups will now be reintroduced one by one to determine the patient's tolerance. Finally, the third phase consists of personalising the diet according to the individual's tolerance levels.[47]

The low-FODMAP diet is not a permanent diet and is ought to be followed under the guidance of a trained professional. While this diet regimen has great potential for reducing symptoms in patients, it is not a cure for underlying conditions such as SIBO. The low-FODMAP diet is therefore oftentimes used as an addition to standard treatment with either antibiotics or antimicrobials, mainly to reduce symptoms and improve the patient's quality of life. It is, however, not an effective SIBO treatment on its own, as it will only reduce the bacteria's activity, but will not eliminate the overgrowth.

Clinically, the low-FODMAP diet has been used for the treatment of H2S SIBO as well. However, its effectiveness for the condition has never been established. SRB do not specifically feed on FODMAP-containing foods. However, since SRB can utilise the hydrogen produced through fermentation of FODMAPs by other bacteria via a cross-feeding mechanism, this might help in reducing H2S production.

However, in the past few years, certain clinicians have warned against the use of the low-FODMAP diet for all types of SIBO, including H2S SIBO, as it has the potential to reduce microbiome diversity, therefore possibly worsening the patient's gut health.[48] This notion emphasises the importance of a holistic approach so that patients will not only be helped in the short-term, but will sustain long-term improvements.

Low-sulphur diet

For H2S SIBO specifically, a low-sulphur diet has been proposed as an alternative dietary strategy to reduce symptoms associated with H2S production. This diet strategy typically involves the avoidance of foods containing higher levels of sulphur, including:

- Animal products high in SAAs, such as:
    - Eggs
    - Dairy
    - Meat
- Vegetables high in inorganic sulphate and organosulphur compounds:
    - Brassica family vegetables, such as broccoli, cauliflower and kale;
    - Allium family vegetables, such as onions and garlic.

The theory behind this treatment strategy is that by reducing the amount of sulphur in the diet, less substrate will be available for SRB. This in turn would reduce H2S production, therefore alleviating the major symptoms associated with the condition. It is, however, not clear whether all sulphur-containing foods actually lead to H2S production. To evaluate this, it would first be necessary to establish the specific SRB producing the H2S, thereby causing the issue. Subsequently, it is required to conduct tests on various sulphur-containing foods to determine their suitability as a substrate for these SRB. Following this, results can be confirmed by human studies measuring real time H2S production in patients with confirmed H2S SIBO after consumption of those foods.

While these studies have not been performed on this level of detail, there are studies looking at effects of high-sulphur foods on gut health and on certain SRB. One of these is a study by Jowett et al. from 2004 that found that intake of high-sulphur foods – both protein-rich animal products containing SAAs and Brassica vegetables containing inorganic sulphate – was associated with relapses in inflammatory bowel disease.[49] This is in line with the finding that SRB are oftentimes elevated in these conditions and potentially contribute to some of the symptoms.[33]

In contrast, a study from 2017 by Kellingray et al. found that consumption of a diet rich in Brassica vegetables was associated with a reduced abundance of SRB.[50] This study, however, was performed on healthy adults, which might be the explanation for these contradicting results, although this is speculative.

A low-sulphur diet is, similar to the low-fodmap diet, not a permanent solution. Avoidance of multiple food groups could provoke nutrient deficiencies and has the potential to be socially isolating, thereby reducing the patient's quality of life. Additionally, long-term effects have not been studied sufficiently to confirm its safety nor effectiveness. It is therefore advised that patients suffering from this condition only follow such dietary measures under supervision of an experienced clinician.

Firm conclusions can thus not be made on whether a low-sulphur diet will be helpful in treating H2S SIBO. Considering that foods high in sulfur may exacerbate symptoms in H2S SIBO patients, it remains beneficial to take this factor into consideration. However, diet should be tailored to the individual patient according to their tolerance so that it does not become too restrictive that it reduces microbiome diversity.

Low-fat diet

The rationale behind lowering fat in the diet of patients suffering from H2S SIBO mainly comes from reducing bile release. Certain SRB, specifically B. wadsworthia, can utilise the taurine moiety from taurine-conjugated bile acids as an energy source to produce H2S (Figure 3).[18] A study by Devkota et al. from 2012 found that mice fed a diet high in saturated fat from milk demonstrated an overrepresentation of B. wadsworthia when compared to mice fed a low fat or high polyunsaturated fat diet. The study further revealed that milk fat was essential for the colonisation of B. wadsworthia in the colon of germ-free mice, and that these effects were mediated by taurine-conjugated bile acids.[51]

Swann et al. (2011) provided additional insight, suggesting that the absence of an established microbiota tends to favour a dominance of taurine-conjugated bile acids over their unconjugated or glycine-conjugated counterparts.[52] Similar effects were observed when antibiotic treatment was given, illustrating how reducing diversity of the gut microbiome can affect the composition of bile acids, resulting in an increase in taurine available for B. wadsworthia.

In view of these findings, a reduction in fat intake could potentially limit the availability of bile – and in turn, taurine – for B. wadsworthia to metabolise into H2S, thereby alleviating symptoms. However, it is important to discern the type of fat being consumed, as only diets rich in saturated fat have been implicated in promoting the growth of B. wadsworthia. As such, the assertion that all types of fats, including polyunsaturated fats, would induce similar effects remains unsupported by current evidence. Thus, a strategy focused on reducing saturated fat intake, particularly from milk, might prove beneficial, although this needs to be confirmed in humans.

Diversification through diet and supplements

In recent years, a shift in perspective has been proposed by some clinicians when it comes to the treatment of H2S SIBO. Rather than focusing on the elimination of food groups, they suggest expanding the diversity of fibre in the diet with the aim of increasing the microbial diversity in the gut. By promoting a broader microbial diversity, the competitive advantage of SRB could potentially be diminished, thus restoring a more balanced gut environment. Given the resilience of SRB and the potential downsides of eliminating various food groups, this diversification strategy may present a more sustainable approach. Although this strategy has not been specifically studied in the context of confirmed H2S SIBO patients, numerous studies highlight the benefits of increasing the diversity of fibre intake for the overall health of the digestive tract.[53,54]

In addition to dietary diversification, certain supplements could further support in diversifying the microbial composition. Two types of supplements which have the most research to them in this regard are prebiotics and probiotics. Prebiotics are types of non-digestible carbohydrates that form substrate for multiple beneficial gut bacteria. In the treatment of SIBO, particular prebiotics have been found effective in improving treatment outcomes. For instance, combination of antibiotic treatment (Rifaximin) with the prebiotic fibre partially hydrolysed guar gum (PHGG) was observed to be more effective than antibiotic treatment alone.[55] However, the type of SIBO was not specified in the study.

Interestingly, another type of prebiotic fibre, namely agave inulin, has been found to significantly deplete species of Desulfovibrio, a prominent SRB, by 40%. At the same time, it increased Bifidobacterium species.[56] This prebiotic might therefore prove useful in the treatment of H2S SIBO specifically.

Probiotics, comprising live microorganisms, are capable of modifying the gut microbiome either through direct interactions with existing gut bacteria or by mediating immune responses.[57] Similarly to prebiotics, specific probiotics have been investigated for their role in SIBO treatment. Strains belonging to the Lactobacillus and Bifidobacterium genera are of particular interest considering their widely-recognised beneficial effects on overall gut health. These strains can contribute to a healthier gut by enhancing gut barrier function, modulating the immune system, and competing with pathogenic bacteria.[58,59]

Studies investigating whether these probiotics prove useful for SIBO treatment show positive outcomes, where supplementation was more effective in treating SIBO, showing better response to hydrogen breath testing and reduced clinical symptoms.[60,61] However, while results of these studies appear promising, sample sizes were limited. Additionally, no studies have been performed on H2S SIBO patients specifically. Thus, pre- and probiotics could potentially prove useful as adjunct treatments, however, this needs to be confirmed by further research.

H2S reduction

Next to dietary strategies, reduction of H2S can be achieved through certain compounds that either hinder production of H2S by SRB, or directly bind H2S in the gut or bloodstream and facilitate its excretion. This can give quick relief for the patient, as it is supportive in reducing oxidative stress and other negative effects resulting from the H2S. In the following section, a selection of these compounds will be discussed.

Bismuth

Bismuth in the form of Pepto-Bismol™ is arguably the most frequently used means of reducing malodorous gasses resulting from excessive flatulence. The active compound responsible for this effect is the chemical element bismuth. Bismuth directly binds with the sulphide part of H2S to form insoluble bismuth sulphide.[62] This bond cannot be broken in the digestive tract and is therefore excreted in the faeces. Because of this effect, bismuth in various forms has been used to reduce symptoms related to H2S production in patients with H2S SIBO. Not only can this be helpful in reducing already formed H2S, but it can also hinder H2S production directly. It does this by inhibiting SRB metabolism which not only reduces H2S production, but also hinders their growth.[63] In combination with antibiotics, bismuth could therefore be particularly useful in targeting SRB.

An additional benefit of bismuth is that the bond that is formed with sulphide, bismuth sulphide, is darkly coloured, which can be visible in the faeces. Because of this attribute, it could be useful as a supplementary diagnostic tool to indicate excessive H2S production.

While these effects all sound promising, it is important to note that long-term use of bismuth has the potential to produce neurotoxic side effects.[64] It should therefore only be used for a limited amount of time and only under the guidance of a trained professional.

Zinc acetate and iron citrate

In a similar fashion to bismuth, poorly absorbed forms of zinc and iron, such as zinc acetate and iron citrate, respectively, have been found to be effective in reducing H2S in the gut. These metals achieve this through binding to sulphide.[65] While bismuth appears to be most effective in doing this, zinc and iron have the advantage of being less toxic, therefore being more suitable to be used long-term.

Hydroxocobalamin

Hydroxocobalamin is a supplemental analogue of vitamin B12. This form has been used in the treatment of acute H2S toxicity. It is thought that hydroxocobalamin can form a complex with H2S in the bloodstream, which aids in detoxification pathways.[66] Theoretically, this could support bodily symptoms in patients with H2S SIBO, although this has not been confirmed by any studies.

Antimicrobial therapy

Antimicrobial therapy forms the cornerstone of SIBO treatment. For this, both pharmaceutical antibiotics and herbal antimicrobials have been used to target the bacterial overgrowth. The main antibiotic prescribed for SIBO is Rifaximin, as this antibiotic was specifically designed for this use. Rifaximin is particularly advantageous due to its minimal systemic absorption and its targeted action within the gastrointestinal tract, thereby reducing the risk of systemic side effects. It demonstrates high efficacy in reducing bacterial overgrowth and alleviating associated symptoms and is therefore considered gold standard for antimicrobial SIBO treatment.[67–69]

However, the effectiveness of antibiotics can be impacted by several factors, including the type of bacteria being targeted, potential resistance mechanisms, and the overall diversity of gut microbiota.[60] Consequently, antibiotic therapy may not always be effective or lead to complete resolution of SIBO symptoms. Rifaximin has been used for the treatment of H2S SIBO as well, although its effectiveness for this condition has never been established. It is not clear whether Rifaximin targets SRB specifically, or that it works by eradicating hydrogen-producing bacteria, thereby reducing the substrate hydrogen needed for H2S production.[9] If the latter is the case, this could result in relapses after hydrogen-producing bacteria return. Because of this uncertainty, concerns have been raised about potential antibiotic resistance and disruption of the beneficial gut flora, especially when multiple rounds are done. This has led to the exploration of alternative and complementary treatment strategies to address the overgrowth.

Herbal antimicrobials have been suggested as an alternative to conventional antibiotic therapy. Herbal antimicrobials, such as oregano oil, berberine, and allicin, have demonstrated antimicrobial properties against a wide spectrum of bacteria. Preliminary research suggests that these herbal agents may be equally effective as Rifaximin in reducing SIBO-associated symptoms.[70] However, similarly to Rifaximin, these herbal antimicrobials have not been studied for their effectiveness against SRB.

Furthermore, the use of herbal antimicrobials is not without challenges. Since the application of these agents has not been studied extensively, optimal dosing, duration of therapy, and potential interactions with other therapies remain to be established. Additionally, while preliminary findings are promising, well-designed clinical trials of larger scale are necessary to further evaluate their efficacy and safety profile in the management of SIBO. Thus, while antimicrobial therapy remains a fundamental aspect of SIBO management, an integrated approach combining this with dietary modifications and pre- and probiotics may be necessary to achieve optimal patient outcomes.

Supporting sulphur metabolism

The proposed physiological adaptation theory of H2S SIBO suggests a shift in treatment strategies, focusing not only on eradicating the overgrowth of SRB but also on supporting sulphur metabolism in the body. A key aspect of this approach is enhancing the body's ability to produce sulphate, primarily through the liver.

Molybdenum supplementation could be a potential strategy in this regard. As a crucial cofactor for SUOX, sufficient molybdenum may support the enzyme's function in converting sulphite to sulphate in the liver, thus potentially reducing the accumulation of sulphite and the consequent need for bacterial processing.[71] However, it's noteworthy to consider that molybdenum might exert a direct effect on SRB as well, possibly by inhibiting their growth or reducing their sulphate-reducing capabilities.[72]

Another facet of this approach revolves around supporting overall sulphur metabolism. Certain B vitamins, such as B6, B9 (folate), and B12, are known to play critical roles in SAA metabolism. Deficiency in these vitamins could potentially impair the body's ability to metabolise SAA, thereby increasing the demand for sulphate.[73] Supplementation with these vitamins might therefore support efficient sulphur metabolism, although more research is needed to confirm their specific role in the context of H2S SIBO.

To complement the aforementioned strategies, providing an alternative source of sulphate could be beneficial. Epsom salt, which contains magnesium sulphate, has been suggested as a possible source. Research indicates that bathing in Epsom salts can raise sulphate levels in the body, potentially satisfying the body's demand for sulphate and reducing reliance on bacterial H2S production.[74]

Another potential source of sulphate is the sulphur-containing compound methylsulfonylmethane (MSM). MSM has been shown to increase plasma sulphate levels in humans, suggesting its potential usefulness in cases of increased sulphate demand. As an oral supplement, MSM has greatest potential, as it is absorbed quickly, thereby reducing risk of SRB using it as a source of sulphur, especially SRB in the distal small intestine and colon.[75] However, caution is still advised.

While providing alternative sources of sulphate might seem logical, certain sulphate sources could potentially exacerbate H2S SIBO. Glucosamine and chondroitin sulphate are dietary supplements commonly used for their benefits to joint health. However, it was shown that these compounds promote the growth SRB, thereby potentially worsening the condition.[76,77] Therefore, these supplements should generally be avoided in individuals with H2S SIBO until further research is available.

Concluding, the treatment strategies proposed by the physiological adaptation theory represent a shift from the traditional approach of eradicating bacterial overgrowth. It emphasises the need to support the body's sulphur metabolism, providing alternative sources of sulphate, and reducing the body’s reliance on bacterial H2S production. While this approach is promising, it is still largely speculative and requires more empirical evidence for validation.

Discussion

The evolving understanding of H2S SIBO presents intriguing implications for the diagnosis and management of the condition. As we delve deeper into the pathophysiology of H2S SIBO, it is becoming increasingly clear that our understanding of the condition is still in its formative stages. The physiological adaptation theory, in particular, has shed light on the potential significance of sulphur metabolism in the pathogenesis and treatment of H2S SIBO.

The theory proposes that the overgrowth of SRB may not merely be a pathological process, but rather a physiological adaptation to an impaired sulphur metabolism. This paradigm shift in understanding H2S SIBO could substantially impact the approach to managing this condition. Instead of solely focusing on eradicating the bacterial overgrowth, supporting the body's sulphur metabolism becomes a pivotal strategy. However, as promising as this theory is, it remains largely speculative, necessitating more rigorous, empirical evidence to validate it.

In terms of treatment, the findings suggest a move away from the sole reliance on antimicrobial therapy, although it remains the cornerstone of SIBO management. While Rifaximin has been the gold standard for antimicrobial therapy, its effectiveness against SRB is yet to be established. The potential for antibiotic resistance and disruption of beneficial gut flora further exacerbates the complexity of its application. These concerns have led to the emergence of alternative treatment strategies, such as herbal antimicrobials, dietary interventions, and supplementation with pre- and probiotics, which appear promising but require further validation.

Supporting sulphur metabolism introduces a novel dimension to H2S SIBO treatment strategies. This approach entails enhancing the body's ability to produce sulphate, primarily through the liver, and supplying alternative sources of sulphate. Theoretically, supplementation with molybdenum, certain B vitamins, and sulphate sources like Epsom salts and MSM could prove useful in this regard. This potential shift in treatment paradigm underscores the need for a more integrated approach, one that balances antimicrobial strategies with support for the body's physiological processes. However, these strategies warrant further empirical evidence to substantiate their efficacy and safety.

Conclusions

In conclusion, our understanding of H2S SIBO is continually evolving. From its diagnosis to its aetiology and treatment, each aspect presents unique challenges and opportunities for further exploration. The emergence of the physiological adaptation theory offers a renewed perspective and potentially expands our treatment strategies. However, it also underlines the need for further, more rigorous research to elucidate the mechanisms underlying H2S SIBO and to validate potential therapeutic interventions. The complexity of this condition necessitates a multidisciplinary, integrated approach to improve patient outcomes and advance our understanding of this intriguing condition.

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