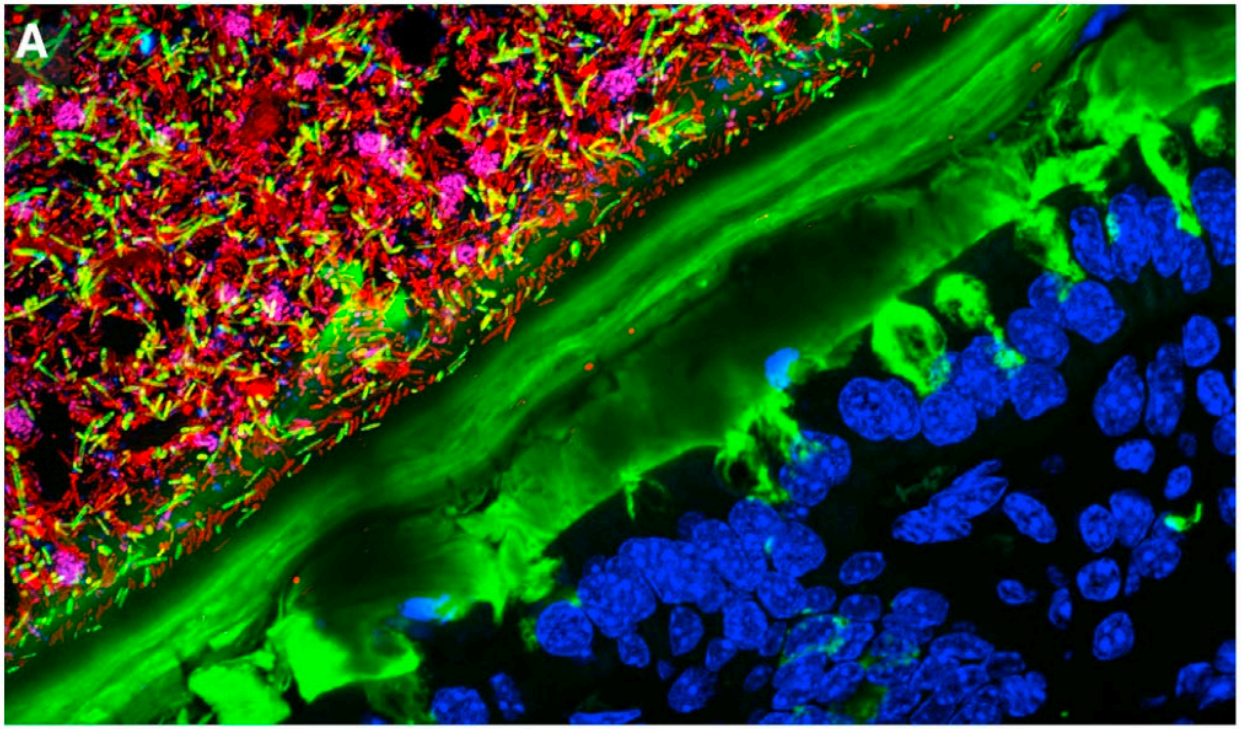
SIBO

Bible Class 02.10.2024
Giulia Santi

BIOGEOGRAPHY OF THE INTESTINE

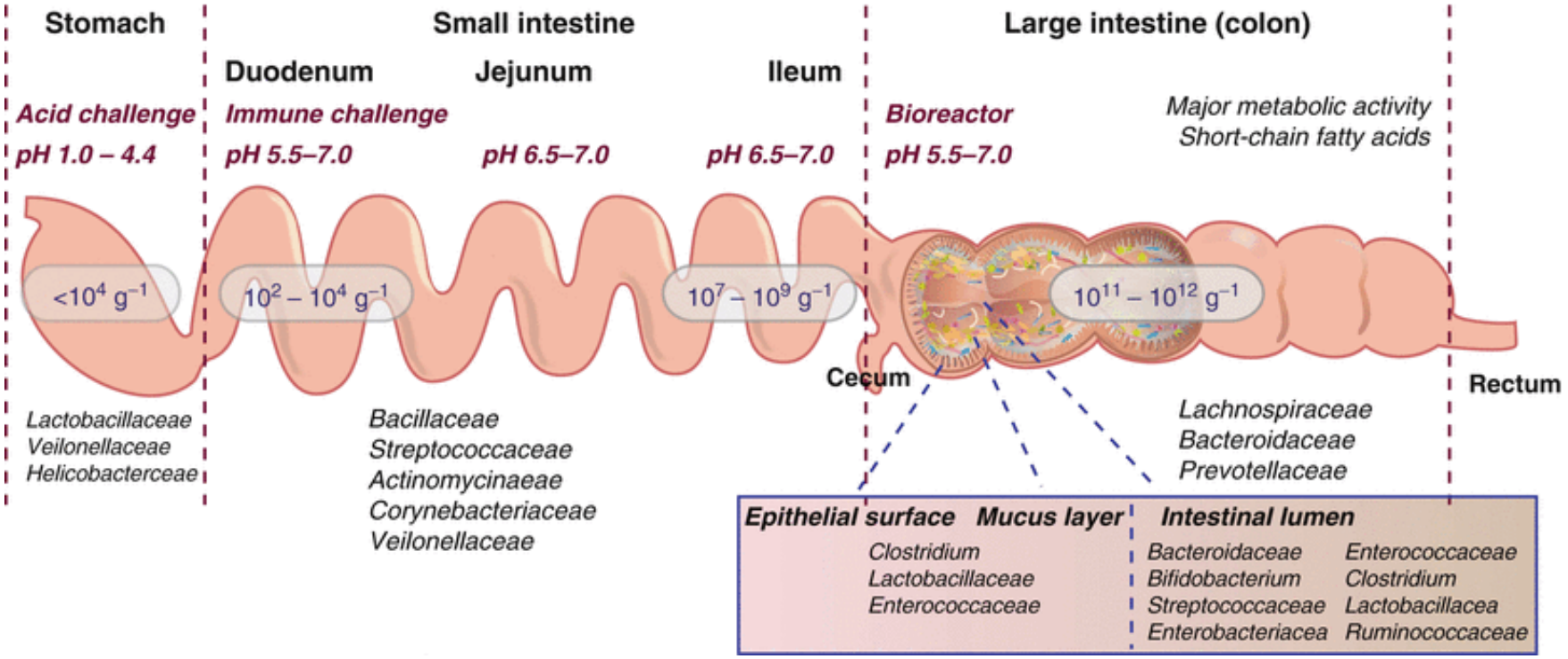


Mouse colon.
- Green: mucus (UEA-1)
- Blue: epithelial nuclei (DAPI)
- Red: bacterial DNA (DAPI)
- Yellow: Firmicutes (FISH)
- Maroon: Bacteroidales (FISH).

- The human body contains ~$4x10^{13}$ bacteria (40 trillion)
- 99% of these bacteria reside in the colon
- The number of human cells to bacterial cells is ~ 1:1
- Bacterial weight is 200g (ratio in biomass is 1:140)
- Bacteria and humans cells together form a „superorganism“

Tropini et al., Cell Host & Microbe 2017; 21: 433

BIOGEOGRAPHY OF THE INTESTINE



- Bacterial gradient: 10^4 bacteria → 10^{12} bacteria
- Oxygen gradient (cecum anaerob)

Kovatcheva-Datchary et al., 2013; The Gut Microiota in The Prokaryotes, pp 3-24
Tropini et al.,

DEFINITION OF SIBO

- Excessive numbers of bacteria in the small bowel causing gastrointestinal symptoms

- Bacteria typically found in the colon, predominantly Gram-negative aerobic and anaerobic species that ferment carbohydrates producing gas

- The most common species: *Bacteroides*, *Enterococcus* and *Lactobacillus*

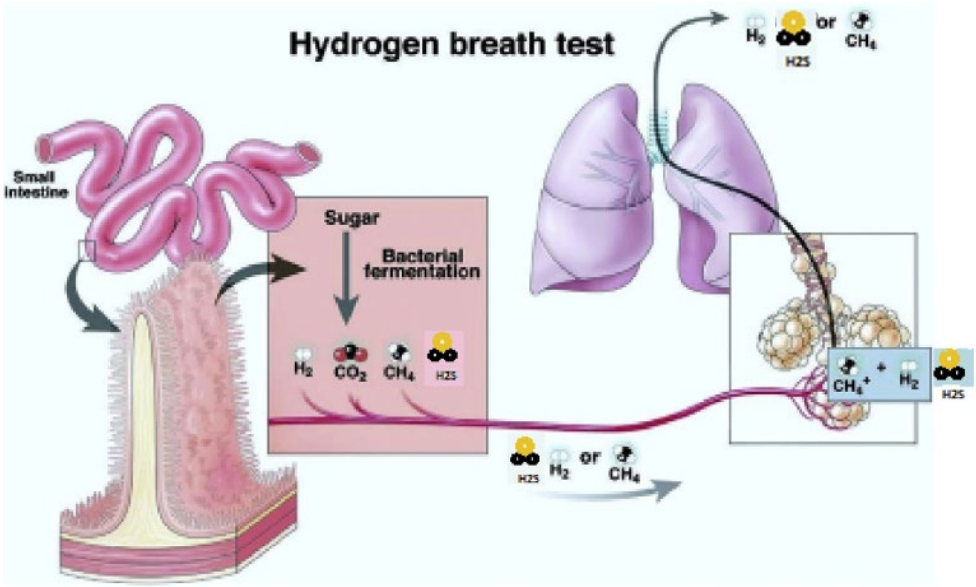
Bohm M, Siwiec RM, Wo JM, . Diagnosis and management of small intestinal bacterial overgrowth. *Nutr Clin Pract* 2013;28:289–99.

HOW CAN WE MEASURED IT?

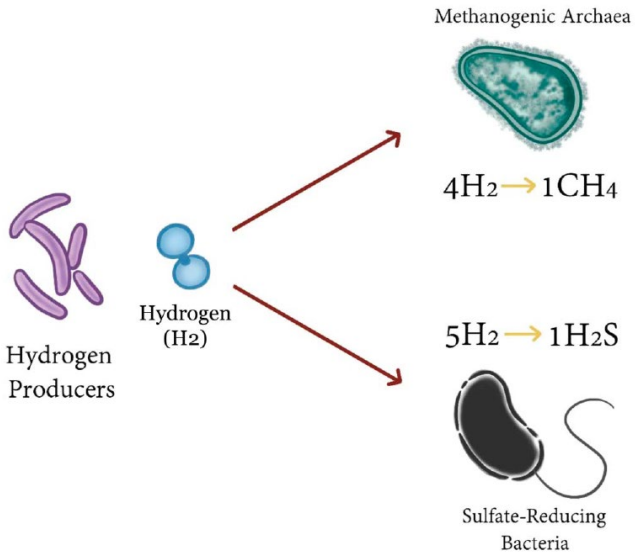
- **Duodenal/ jejunal aspirate**: North American Consensus, bacterial colony count of ≥ 10^3 (10^5) colony-forming units per milliliter (CFU/mL)

HOW CAN WE MEASURED IT?

- **Breath Test**: exhaled hydrogen gas on the breath, after the ingestion of a carbohydrate (10g glucose or 75g lactulose)
  - exhaled hydrogen (H_2) ≥ 20 parts per million (ppm) within 90 minutes of oral ingestion
  - exhaled methane (CH_4) ≥ 10 ppm at any point during the test (methanogenic overgrowth)



WICH BACTERIA?



- H_2 : sulfate Reducing Bacteria

- CH_4 : methanogenic Archaea
  - Methanobrevibacter smithii: → responsible for breath methane production
  - Intestinal methanogen overgrowth (IMO)
  - Constipation is associated with > levels of breath methane and stool M. smithii

SIGN/SYMPTOMS

- No single symptom can be specifically attributed to SIBO

- Most common symptoms 2/3 of patients:
  - **Abdominal pain**
  - **Bloating**
  - **Distension**
  - **Flatulence**
  - **Diarrhea**

- …fatigue, poor concentration, constipation, steatorrhea, weight loss, anemia, nutritional deficiencies (Vitamines - fat soluble, iron, folate may be elevated in SIBO as bacteria produce folate)

CONDITIONS ASSOCIATED WITH SIBO

Category	Specific condition
Mechanical causes	Small bowel tumor Volvulus Intussusception Postsurgical causes
Systemic disease	Diabetes Scleroderma Amyloidosis
Motility	IBS Pseudo-obstruction Visceral myopathies Mitochondrial diseases
Medications	Opiates Potent antisecretory agents
Malabsorptive conditions	Pancreatic insufficiency Cirrhosis (altered bile acid composition Other malabsorptive conditions
Immune-related	Human immunodeficiency virus Combined variable immunodeficiency IgA deficiency
Other	Aging (the elderly) Small bowel diverticulosis

MECHANISMS RESPONSIBLE FOR MAINTAINING THE SIBO

Mechanism	Rationale
Gastric acid	Most ingested bacteria in food cannot survive the acidic stomach.
Pancreatic enzymes	Digestive enzymes in the proximal small bowel may also digest bacterial products. Efficient digestion of nutrients leaves less substrates for bacteria.
Bile acids	As detergents, bile acids can have an effect on bacterial membranes.
Small bowel motility	Migrating motor complexes and other events cleanse the small intestine of debris during fasting.
IC valve	The IC valve protects the small bowel from retrograde movement of colonic flora into the small bowel.
Immune system	Mucosal immunity may be important in the maintenance of a stable microbiota of the intestinal lumen.

IC, ileocecal.

DIAGNOSIS 1 – **Small bowel aspiration/culture**

- Gold Standard
- Gastroscopy, 3–5 mL of duodenal fluid is aspirated → sent to a microbiology laboratory for aerobic/anaerobic culture
- Concentration of bacterial colony count of ≥ 10^3 (10^5) colony-forming units per milliliter (CFU/mL): SIBO
- (-) Time-consuming, expensive, invasive procedure, sedation, risks of endoscopy, include difficulty in aspirating a sufficient, risks of gastric or oropharyngeal cross-contamination

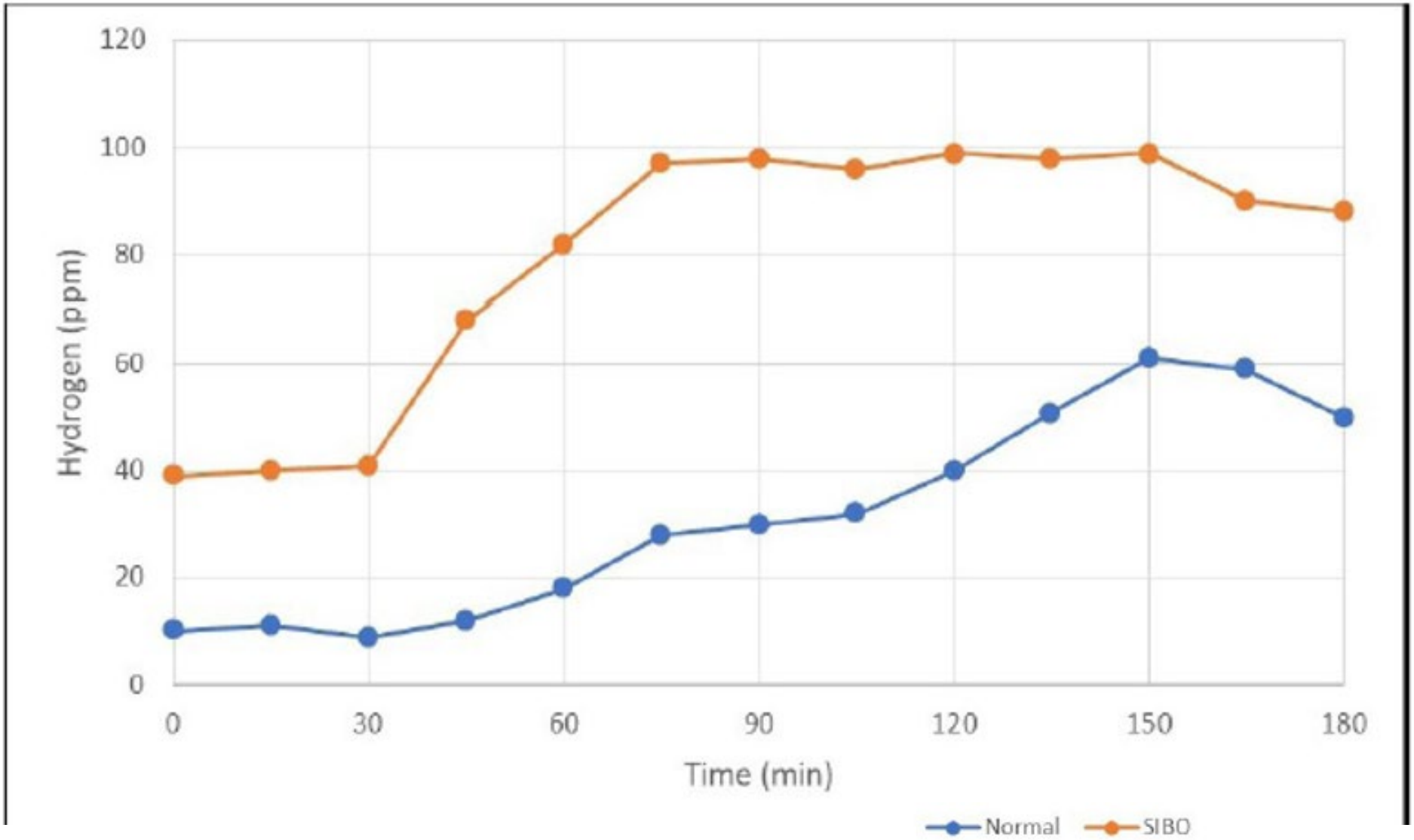
DIAGNOSIS 2 - **Breath Test**

- Carbohydrates used: glucose (75g) and lactulose (10G) followed by 1 cup of water (250 mL), breathing into the machine every 30 minutes

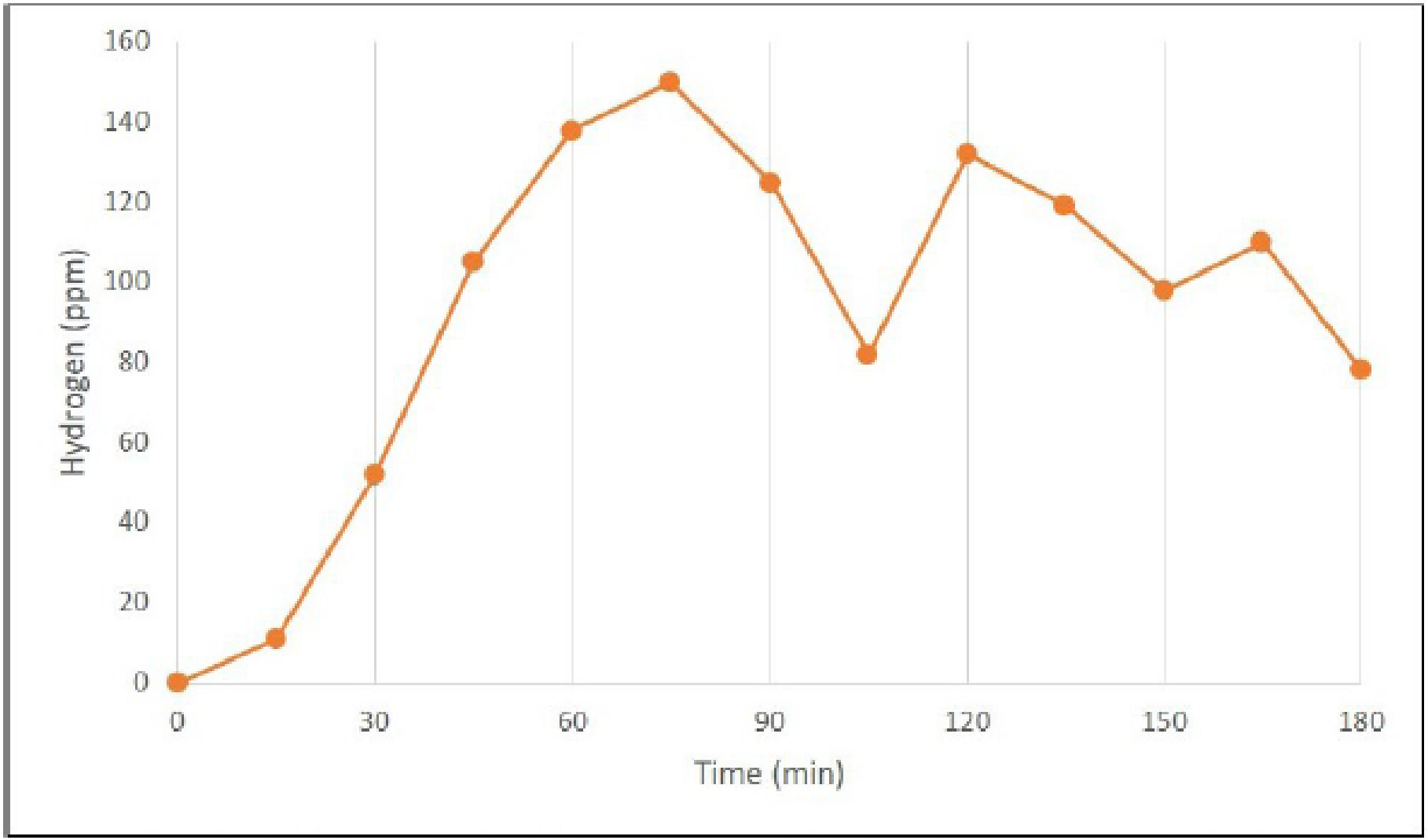
- (+) it is non-invasive, safe and easy (home testing kits)

- Before the test:
  - No antibiotics for 4 weeks
  - No promotility agents and laxatives for at least 1 week
  - No fermentable foods the day before (e.g., complex carbohydrates)
  - Fast for 8–12 hours
  - During the breath test: no smoking and minimize physical activity

INTERPRETATION OF BREATH TEST



INTERPRETATION OF BREATH TEST



INTERPRETATION OF BREATH TEST

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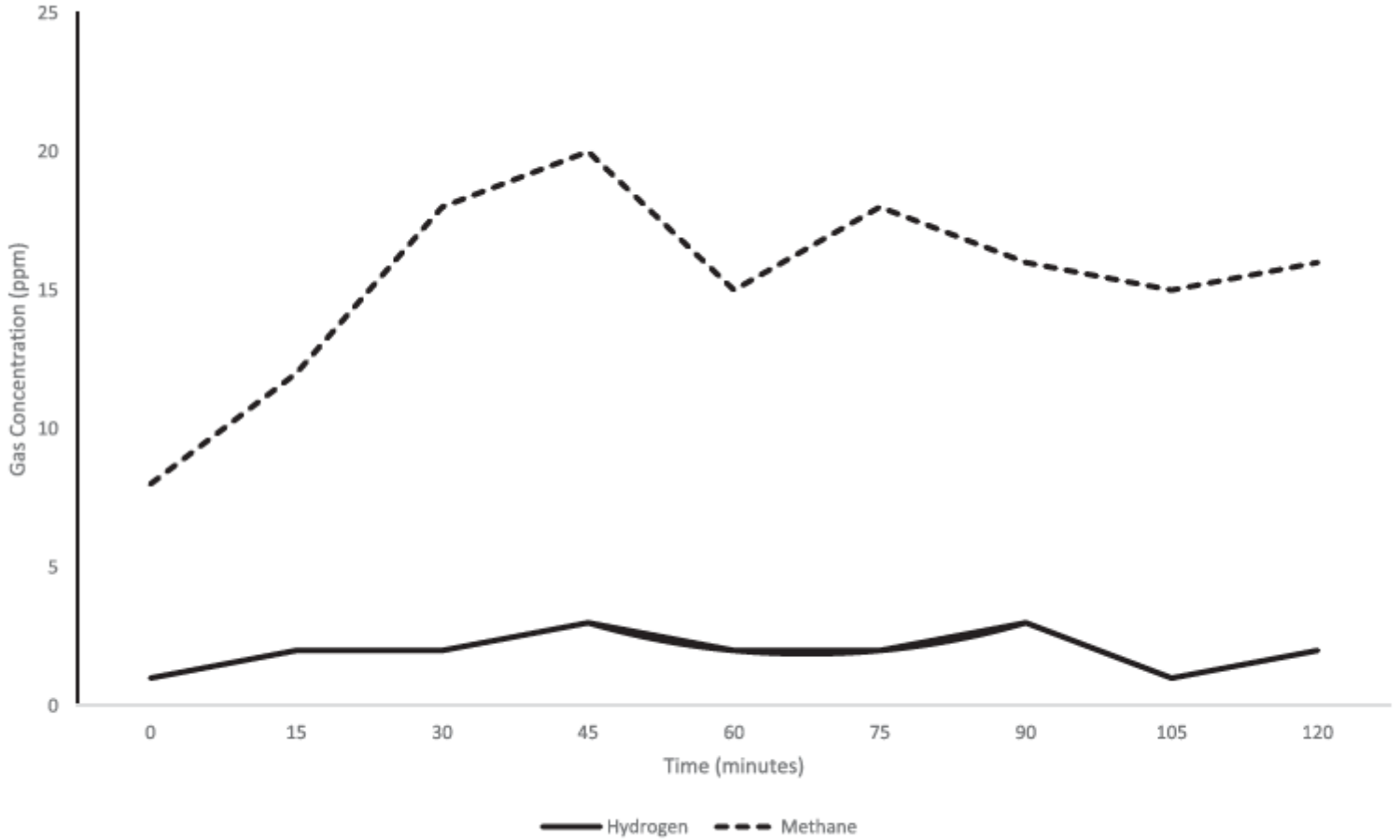

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Methane-positive breath: intestinal methanogen overgrowth (IMO)

GLUCOSE vs LACTULOSE…

- Lactulose breath test: high false-positive values (because of the accelerated transit and colonic fermentation in some individuals)
  - Specificity 85%
  - Sensitivity 52%

- Glucose breath test: low sensitivity, absorbed in proximal duodenum
  - Specificity 80%
  - Sensitivity 62%

European Association for Gastroenterology, Endoscopy and Nutrition, European Society of Neurogastroenterology and Motility, and European Society for Paediatric Gastroenterology Hepatology and Nutrition consensus. United European Gastroenterol J. 2022 Feb;10(1):15-40. doi: 10.1002/ueg2.12133. Epub 2021 Aug 25. PMID: 34431620; PMCID: PMC8830282.

NAGGING CONCERNS REMAIN…

→ Diagnosis of SIBO depending of the wide variation in transit time (stomach, small intestine, cecum)

REVIEW ARTICLE

Neurogastroenterology & Motility NGM WILEY

Critical appraisal of the SIBO hypothesis and breath testing: A clinical practice update endorsed by the European society of neurogastroenterology and motility (ESNM) and the American neurogastroenterology and motility society (ANMS)

Purna Kashyap[1] | Paul Moayyedi[2] | Eamonn M. M. Quigley[3] | Magnus Simren[4] | Stephen Vanner[5]

→ Lack of standardization (dosage, symptom assessment)

→ Can we really reduce the complexity of the microbiota to «just» the H_2/ CH_4 signal?

DIAGNOSIS 3 - **Capsule**

Measurement in vivo hydrogen

SIBO and…**IBS/PPI**

- **IBS**: up to 78% of IBS subjects suffer from SIBO

Shah ED, Basseri RJ, Chong K, et al. Abnormal breath testing in IBS: A meta-analysis. Dig Dis Sci 2010;55:2441–9.

- **PPI**:
  - All patients neg. glucose hydrogen breath tests before PPI use. On follow-up, 26% of the patients positive for, more bloating, flatulence, abdominal pain, diarrhea
  - Not clear relationship between the duration of PPI therapy and SIBO, double-dose PPI +++ associated with SIBO than single dose

Compare D, Pica L, Rocco A, et al. Effects of long-term PPI treatment on producing bowel symptoms and SIBO. Eur J Clin Invest 2011;41:380–6.

SIBO and… **IBD**

1. **Prospective study**: CD patients, 16.8% of those in endoscopic remission had SIBO therapy

Sanchez-Montes C, Ortiz V, Bastida G, et al. Small intestinal bacterial overgrowth in inactive Crohn's disease: Influence of thiopurine and biological treatment. World J Gastroenterol 2014;20:13999–4003.

2. **Metaanalysis:** 11 studies (1175 adult patients with IBD and 407 controls). All studies utilized breath test for diagnosis of SIBO:
   - SIBO prevalence in IBD patients: 22.3% (95% CI 19.9-24.7)

   → CD: 25.4%; UC: 14.3%
   - IBD prevalence in SIBO patients: 9.5% (95% CI 3.4-26.7)
   - Risk factors in CD:
     - Fibrostenosing disease (OR 7.5)
     - Prior bowel surgery (OR 2.4), especially resection of the ileocecal valve
     - Immunsuppression was no risk factor

Shah et al., Aliment Pharmacol Ther. 2019; 49:624

TREATMENT OF SIBO

Identify and treat any predisposing factors using a combination of dietary, lifestyle, medical and surgical therapies

TREATMENT OF SIBO 1 - Antibiotics

Antibiotic	Recommended dose	Efficacy
Nonabsorbable antibiotic		
Rifaximin	550 mg t.i.d.	61%–78%
Systemic antibiotic		
Amoxicillin-clavulanic acid	875 mg b.i.d.	˜50%
Ciprofloxacin	500 mg b.i.d.	43%–100%
Doxycycline	100 mg q.d. to b.i.d.	[a]
Metronidazole	250 mg t.i.d.	43%–87%
Neomycin	500 mg b.i.d.	33%–55%
Norfloxacin	400 mg q.d.	30%–100%
Tetracycline	250 mg q.i.d.	˜87.5%
Trimethoprim-sulfamethoxazole	160 mg/800 mg b.i.d.	˜95%

TREATMENT OF SIBO 1 – Recurrence after Antibiotics

- Antibiotics success:
  - 60% (!); 40% have persistent symptoms
  - Recurrence: 3 month: 13%, 6 months: 28%; 9 months: 44% Lauritano EC, Gabrielli M, Scarpellini E, et al. Small intestinal bacterial overgrowth recurrence after antibiotic therapy. Am J Gastroenterol 008;103:2031–5.

- SIBO recurrence frequent → retreat with another course of antibiotics

- FR for recurrence: older patients, a surgical history of appendectomy and those with a history of long-term PPI use

TREATMENT OF SIBO 1 – Prophylactic therapy

- Prophylactic antibiotics should be considered patients who have had repeated courses of antibiotic treatment ≥4 episodes in 1 year
- Prophylactic regimen, 2 or 3 different low-dose long-term antibiotics: rotation 5–10 days every month
- No controlled trials to guide the duration/management of recurrent SIBO
- Study from 2021: rotating antibiotics vs a single course → more effective in maintaining remission (70.8% vs 50.8%), improving quality of life and reducing bloating

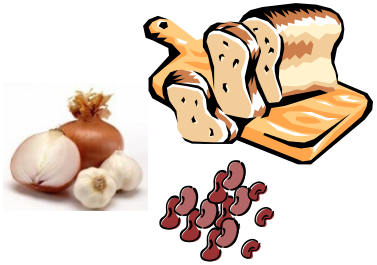
Richard N, Desprez C, Wuestenberghs F, *et al.* The effectiveness of rotating versus single course antibiotics for small intestinal bacterial overgrowth. *United European Gastroenterol J* 2021;9:645–54

TREATMENT OF SIBO 2 – Diet

- Reduction of fermentable products
  - low fiber approach
  - avoidance of alcohol sugars, other fermentable sweeteners, prebiotics (inulin)

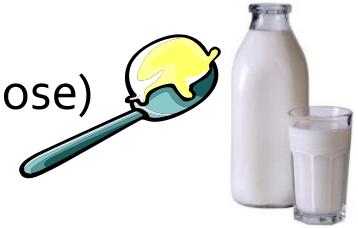
- FODMAP (Fermentable Oligo-, Di-, Mono-saccharides And Polyols)
  - associated with fewer fermentation products, as assessed by the breath test

F*ermentable*



Oligosaccharides → **Fructo-oligosaccharide** (Fructane)
Galacto-oligosaccharide (GOS)

Disaccharides → **Lactose** (Lactulose)



Monosaccharides

→ **Fructose**

***A**nd*

Polyol**s** → **Sorbitol, Mannitol**

TREATMENT OF SIBO 3 – Probiotics

- Counterintuitive (?)
- Probiotics may include prokinetic actions, shiftings in bacteria
- Meta-analysis of 18 studies: no significant difference in the improvement of symptoms SIBO vs the control group

Zhong C, Qu C, Wang B, *et al*. Probiotics for preventing and treating small intestinal bacterial overgrowth: a meta-analysis and systematic review of current evidence. *J Clin Gastroenterol* 2017;51:300–11.

TREATMENT OF SIBO 3 – Fecal microbiota transplant (FMT)

- No concrete data on the effects of (FMT)

- Screened donor patients for SIBO, + breath test did not preclude donation of fecal material
  - Subjects with C. difficile receiving stool from donors with a + breath test > GI symptoms after FMT (without statistical significance)

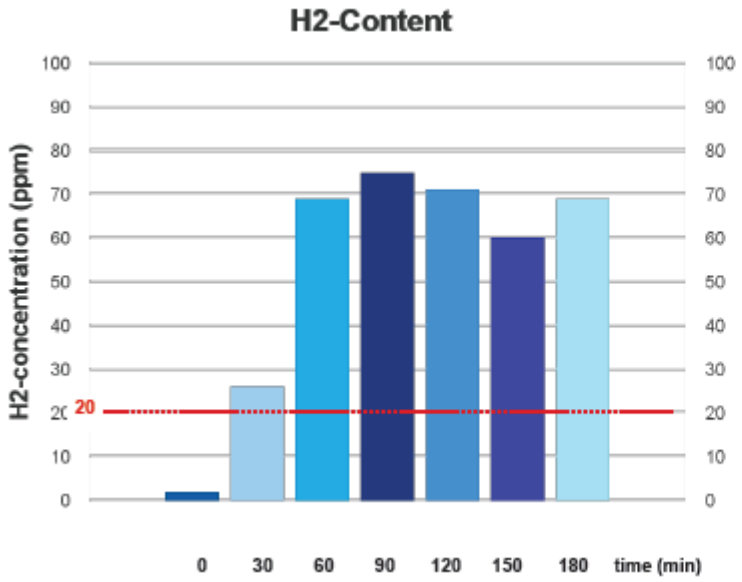
Allegretti JR, Kassam Z, Chan WW. Small intestinal bacterial overgrowth: Should screening be included in the pre-fecal microbiota transplantation evaluation? Dig Dis Sci 2018;63:193–7.

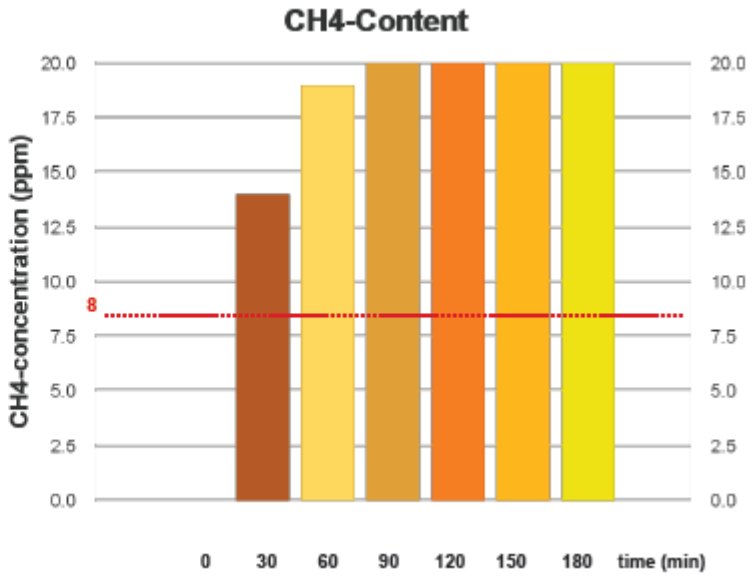
  - Severe constipation, recipient acquired the phenotypes of constipation and a methane-positive breath test from the FMT donor

Chang BW, Rezaie A. Irritable bowel syndrome-like symptoms following fecal microbiota transplantation: A possible donor-dependent complication. Am J Gastroenterol 2017;112:186–7.

CASE STUDIES

Laktulose 30g





Diagnose Bakterielle Überwucherung des Dünndarmes mit H2- und CH4-bildender Darmflora

3. **A 57-year-old man presented to hospital with persistent, non-bloody, watery diarrhoea. His GP had trialled management for irritable bowel syndrome, and there had been some improvement with a wheat- and dairy-free diet. He had had severe peptic ulcer disease for which he underwent a Billroth II procedure 10 years previously, after presenting in hypovolaemic shock.**

Investigations:

anti-tissue transglutaminase antibodies	12 U/mL (< 15)
faecal calprotectin	36 µg/g (< 50)
faecal elastase	356 µg/g (> 200)
stool microscopy and culture	negative
hydrogen breath test (see Figure 2.1)	

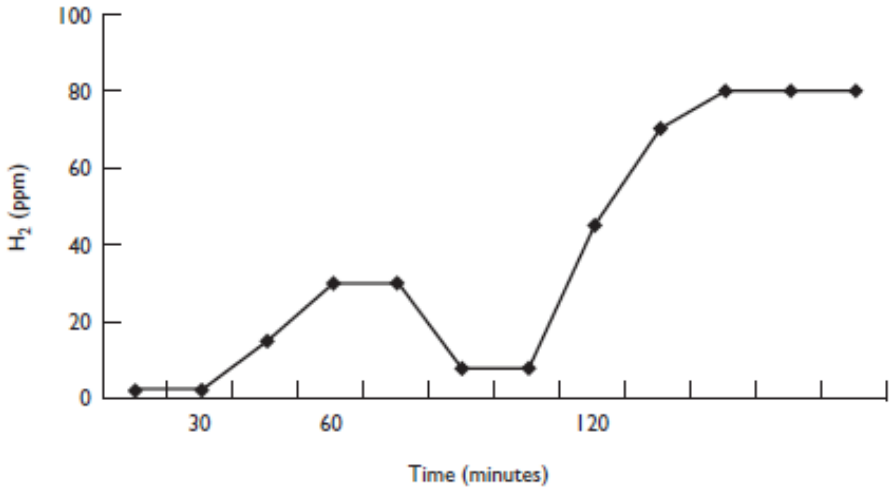
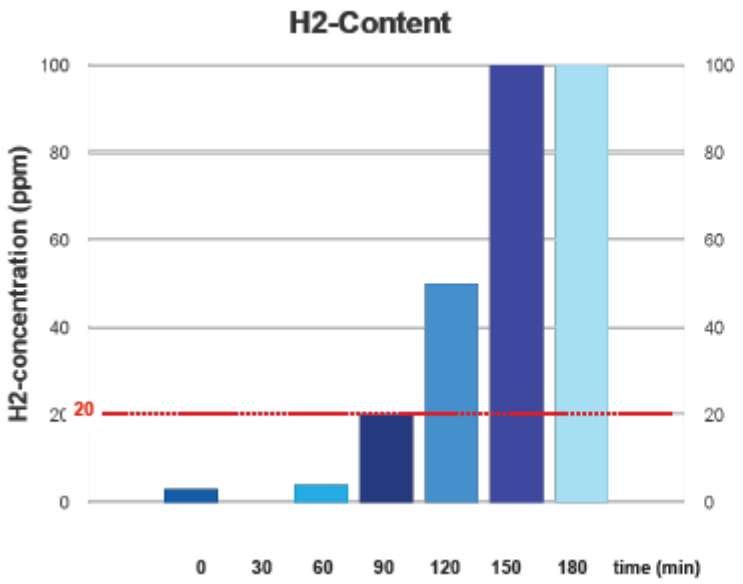


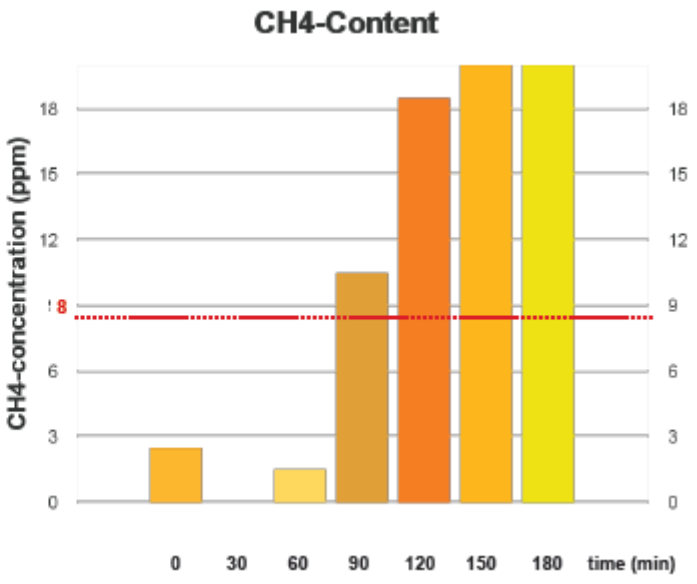
Figure 2.1 Hydrogen breath test

Which is the most likely diagnosis?

A. Bile salt malabsorption
B. Coeliac disease
C. Lactose intolerance
D. Pancreatic insufficiency
E. Small bowel bacterial overgrowth

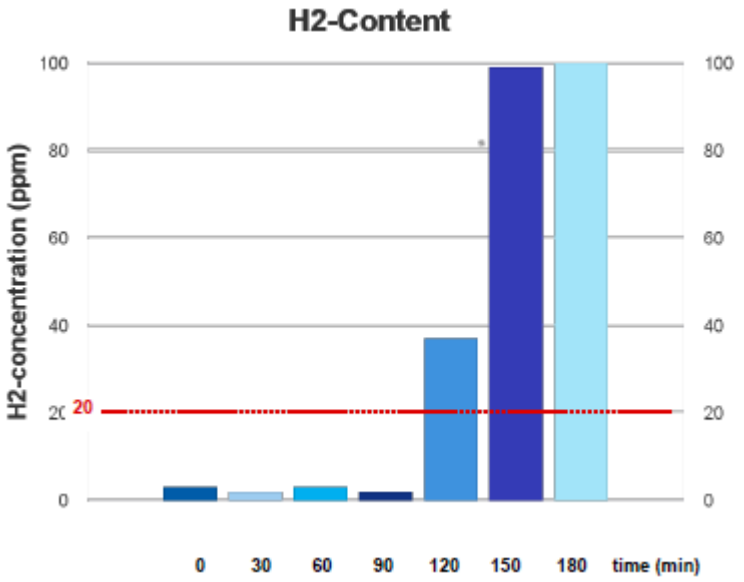
Laktulose 30g

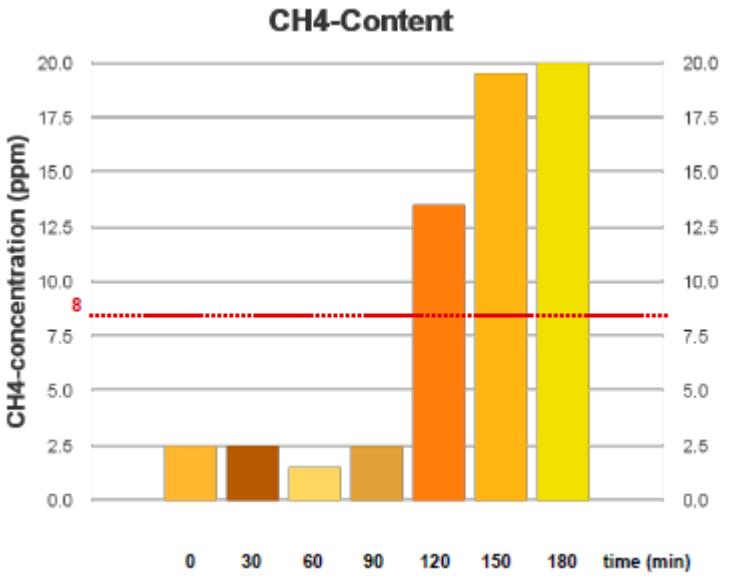




Diagnose **Bakterielle Überwucherung des Dünndarmes möglich (DD rasche orozökale Transitzeit). H2-und CH4-produzierende Darmflora.**

Laktulose 30g





Diagnose Kein Hinweis auf eine bakterielle Überwucherung des Dünndarms.

11. A 44-year-old woman was referred to the gastroenterology clinic with a 6-month history of diarrhoea, weight loss, and fatigue. She was diagnosed with scleroderma 10 years ago, but took no medications for this. She ate a varied diet, and no particular foods exacerbated her symptoms. On examination you noted skin bruising and a peripheral neuropathy in a glove-and-stocking distribution.

Investigations:

haemoglobin	108 g/L (115–165)
mean cell volume	103 fL (80–96)
serum vitamin B_{12}	145 ng/L (160–760)
serum folate	10.5 µg/L (2.0–11.0)
anti-TTG antibodies	negative

Which would be the most appropriate investigation to make a diagnosis?

A. Faecal calprotectin
B. Flexible sigmoidoscopy
C. Gastroscopy with duodenal aspirate and D2 biopsies
D. Hydrogen breath test
E. SeHCAT scan

Thank you for your attention!