REVIEW

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Small Bowel Bacterial Overgrowth – Pathogenesis, Symptoms, Diagnosis, and Treatment

Bakteryjny przerost flory jelita cienkiego – patogeneza, objawy, diagnostyka i leczenie

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Abstract

Overgrowth of intestinal bacterial flora is the excessive growth of bacteria in the small intestine which usually dwell in the large intestine, which leads to maldigestion, malabsorption, steatorrhea, and anemia. Hypochlorhydria, anatomic anomalies, motor disorders, disturbances in communication between various segments of the alimentary tract, and immunodeficiency predispose to the excessive proliferation of flora in the small intestine. There is no standard diagnostic procedure for an unequivocal diagnosis of bacterial overgrowth in the small intestine. Among the diagnostic methods are direct ones, i.e. quantitative and qualitative assessment of the intestinal content, and indirect ones based on bacterial metabolism, i.e. respiratory tests and a test with para-aminobenzoic acid. The treatment is mainly based on antibiotics active against Gram-negative bacteria and supplementation of nutritional deficiencies (**Adv Clin Exp Med 2009, 18, 2, 177–182**).

Key words: small bowel bacterial overgrowth, pathogenesis, diagnosis, treatment.

Streszczenie

Przerost flory jelitowej to nadmierne namnażanie w obrębie jelita cienkiego drobnoustrojów bytujących zwykle w jelicie grubym, prowadzący do zaburzeń trawienia i wchłaniania – zwłaszcza biegunki tłuszczowej i niedokrwistości. Rozwojowi zespołu przerostu bakteryjnego sprzyjają: hipochlorhydria, zaburzenia anatomiczne oraz motoryczne przewodu pokarmowego, zaburzenia komunikacji odcinków przewodu pokarmowego, upośledzona odporność. Nie istnieje standaryzowany test diagnostyczny pozwalający jednoznacznie rozpoznać zespół przerostu bakteryjnego flory jelita cienkiego. Do metod diagnostycznych należą metody bezpośrednie, czyli ilościowe i jakościowe badanie bakterii w treści bliższego odcinka jelita cienkiego oraz metody pośrednie opierające się na metabolizmie drobnoustrojów: testy oddechowe oraz test z kwasem paraaminobenzoesowym. Leczenie polega przede wszystkim na stosowaniu antybiotyków aktywnych wobec bakterii Gram-ujemnych oraz uzupełnianiu niedoborów pokarmowych (**Adv Clin Exp Med 2009, 18, 2, 177–182**).

Słowa kluczowe: jelitowy przerost bakteryjny, patogeneza, diagnostyka, leczenie.

The human intestine presents a complex and continuously developing bacterial ecosystem already in the first years of life. At the beginning the number of bacteria in the intestine is small, but increases with time. During and directly after delivery, the first bacterial colonization of the alimentary tract, which was sterile to that moment, occurs. The microflora of the intestine is characterized by an immense variety of bacterial species. It is estimated that in all segments of the intestine there are 400 to 500 various bacterial species, predominantly anaerobic, with a total of 10 to 100 billion organisms [1, 2]. Bacterial colonization takes place both in the intestinal lumen and mucous and on the surface. The upper part of the alimentary system is colonized by a small number of microbes, but their numbers increase in the direction of the lower part of the large intestine. Under physiological conditions there are less than 10^5 bacterial cells, mostly aerobic, in one milliliter of content of the stomach, duodenum, and ileum. In the distal segments of the small intestine, this number increases to 10^9 (there

is equilibrium of aerobic and anaerobic bacteria) and the large intestine is colonized by 10^{11}–10^{12} bacterial cells per ml [2]. They have important functions in, among others, protecting against infection, facilitating digestion, and indirectly supplying energetic substances to colonocytes.

This physiological distribution of bacteria in the alimentary tract is preserved by unspecific factors which regulate the number of bacteria either mechanically or chemically as well as by immunological factors. Among the mechanisms which maintain the homeostasis of bacterial flora in the intestines are [3–5]:

- the acidic environment of the stomach, which is the first barrier protecting against excessive flow of bacteria into the intestine;
- intact motor activity of the intestine (especially the impact of the myoelectric migrating complex, MMC), which protects against overcolonization of the small intestine and removes excess microbes;
- an intact ileo-cecal valve (Bauhin), which creates a barrier against the retrograde flow of bacteria from the large to the small intestine;
- the bacteriostatic activity of biliary acids as well as proteolytic and lipolytic pancreatic enzymes;
- bacterial interaction, which provides defense by protective microflora (bacteria of *Lactobacillus* and *Bifidobacterium* species) against the colonization and proliferation of pathogenic bacteria in the alimentary tract due to:
  1) a change in intestinal pH, i.e. a reduction of pH by the liberation of metabolic products (lactic acid, acetic acid),
  2) competition for nutrient vitamins and growth factors,
  3) competition for receptors of the epithelium,
  4) the production of toxic metabolites and bactericidal substances for pathogenic bacteria (e.g. bacteriocines, hydrogen peroxide) [6, 7];
- mucous and secretory IgA, which prevent the adhesion of bacteria to the epithelial surface of the intestine.

Disturbance of even one of these protective mechanisms predisposes to excessive proliferation of bacterial flora in the upper part of the alimentary tract.

Definition of Bacterial Overgrowth in the Small Intestine

Bacterial overgrowth of the flora of the small intestine (synonyms: bacterial overgrowth syndrome, dysbacteriosis of the upper part of alimentary tract, small intestine bacterial overgrowth or SIBO, blind loop, stagnant loop) is defined as an increase in the number of bacteria in the upper part of the small intestine above 10^5/ml of intestinal content. Bacterial overgrowth is a quantitative disturbance and the bacterial species found in the patient are not pathogenic [3–5, 8].

The Causes of Bacterial Overgrowth in the Small Intestine

Among the disturbances predisposing to the excessive proliferation of small intestinal flora are: hypochlorhydria (in children mostly secondary to the use of proton pump inhibitors and H_2-blockers), anatomic disorders of the alimentary tract (primary: congenital anomalies of the alimentary tract, secondary: surgical procedures, tumors); motor disorders of the alimentary tract in: diabetic neuropathy, pseudo-obstruction, scleroderma; disturbances in the communication between various segments of the alimentary tract (lack of a Bauhin valve, fistulas, stomias); immune disorders: primary, secondary (immonosuppression); loss of microflora equilibrium (antibiotic therapy); advanced age, i.e. age-related progressive deficiency of hydrochloric acid and retention of intestine content [3–5, 9, 10].

The causes of bacterial overgrowth in the small intestine are presented in Table 1.

Clinical Symptoms of Bacterial Overgrowth in the Small Intestine

The clinical picture of small intestinal dysbacteriosis varies due to the high variability in proliferating bacterial flora. Among the symptoms of bacterial overgrowth are: chronic steatorrhea or watery diarrhea (secretory or osmotic); abdominalgia and abdominal flatulence; symptoms of deficiency of fat-soluble vitamins A and D (rickets, trophic disturbances of epidermis, nocturnal amblyopia); hypoalbuminemia; decrease in body mass; growth disturbances (in children); outside the alimentary tract: arthritis, tendinitis, tuberous erythema, papulo-macular rash, nephritis [3, 4, 9, 10].

The symptoms of bacterial overgrowth in the small intestine are presented in Table 2.

Table 1. Conditions predisposing to bacterial overgrowth in the intestines [based on 10]

Tabela 1. Sytuacje sprzyjające nadmiernemu rozrostowi bakterii w jelitach [wg 10]

Number (Lp.)	Causes of bacterial overgrowth in the small intestine (Przyczyny nadmiernego przerostu flory jelita cienkiego)
1.	Congestion of intestinal content (Zastój treści w jelitach) 1) anatomical: strictures, intestinal diverticulosis, surgery (ileo-ileal anastomosis, gastro-jejunal anastomosis – Billroth II, jejuno-ileal bypass, Kock's ileal pouches 2) motility disorders of the small intestine: sclerodermia, idiopathic ileal obstruction, autonomic neuropathy due to diabetes melitus
2.	Abnormal connection between proximal and distal part of the ileum (Nieprawidłowe połączenia między bliższym i dalszym odcinkiem jelita) 1) fistulas: gastro-colonic, gastro-jejuno-colonic 2) resection of the ileocecal valve
3.	Hypochlorhydria (Niedobór kwasu solnego) 1) chronic atrophic gastritis 2) antacids 3) surgery of ulcerative disease
4.	Immunodeficiency (Niedobory odporności) 1) primary immunodeficiency 2) acquired immunodeficiency syndromes 3) malnutrition

Table 2. Symptoms of bacterial overgrowth

Tabela 2. Objawy zespołu przerostu bakteryjnego

Symptoms of small bowel bacterial overgrowth (Objawy przerostu flory jelita cienkiego)		
Basic	rare	general
Chronic diarrhea steatorrhea anemia	loss of body mass abdominalgia abdominal distension flatus intestinal protein--loss syndrome hypoalbuminemia rickets trophic disorders of the epidermis, nocturnal amblyopia ataxia	arthritis tendinitis tuberous erythema papulo-macular rash nephritis hepatitis steatosis of the liver

Pathogenesis of Bacterial Overgrowth in the Small Intestine

The pathogenesis of bacterial overgrowth in the small intestine is the result of bacterial metabolism. The consequences of bacterial overgrowth in the upper part of the alimentary tract are [4, 10–12]:

– excessive deconjugation of bile acid salts:
  1) reduction of the conjugated fraction of bile acids: a decrease in the number of lipid micelles, leading to disturbances in fat and fat-soluble vitamin absorption (steatorrhea),
  2) the presence of free fatty acids: toxic effect on enterocytes (secondary impairment of protein and carbohydrate absorption), stimulation of the epithelium for water secretion in the large intestine;
– disaccharide fermentation:
  1) production of gases (hydrogen, carbon dioxide, methane, hydrogen sulfide): an excess of produced gases causes intestinal distention and also provokes intestinal peristalsis,
  2) production of short-chain fatty acids (mainly lactic acid, acetic acid, propionic acid, butyric acid): an excess of produced organic acids causes an osmotic gradient leading to an increased movement of water into the lumen of intestine, which in turn causes diarrhea;
– secretion of active proteases: damage to the brush border of the intestine leading to a decrease in disaccharidase activity (disturbance in disaccharide digestion) and increased absorption of bacterial antigens into the circulation and the production of immunological complexes (symptoms from outside the alimentary tract);
– decrease in enterokinase activity: impairment

of pancreatic protease activation with consequent enteropathy;
– conversion of vitamin B_{12} into inactive metabolites: the development of macrocytic anemia;
– disturbances of the myoelectric migrating complex (MMC): impairment of motor activity of the alimentary tract.

Diagnostics of Bacterial Overgrowth in the Small Intestine

There is no standardized and single diagnostic procedure permitting the unequivocal diagnosis of bacterial overgrowth in the small intestine [13].

A direct method used in the diagnosis of bacterial flora overgrowth in the intestine, regarded by some researchers as the gold standard, is microbiological examination of the small intestinal content. Samples of it are collected after fasting by a duodenal catheter inserted through the nose or during endoscopy or by a capsule inserted by mouth into the duodenum (Enterotest). A number of bacteria in one milliliter greater than 10^5 is regarded as a positive result of the microbiologic test. The possibility of sample contamination by external microorganisms and its use only in the proximal part of the jejunum are disadvantages of this method [4, 9, 14, 15].

Due to the above constraints, noninvasive indirect methods based on bacterial metabolism are applied. Among the indirect methods used in the diagnostics of intestinal bacterial overgrowth are respiratory tests with substances labeled with C^{14} and C^{13} and hydrogen respiratory tests with lactulose and lactose. A test with para-aminobenzoic acid is also used. The following respiratory tests are useful in the diagnostics of bacterial overgrowth in the small intestine.

Respiratory Tests with Substances Labeled with C^{14}

Two respiratory tests are used in the diagnostics: those with glycocholic acid and with D-xylose labeled with C^{14}. In both tests, radioactive carbon dioxide (i.e. the activity of radioactive carbon), which is created during the metabolic processes of decomposition, is measured in the breath. The advantage of these tests is their high sensitivity and specificity (almost 100% in the case of D-xylose test), while the disadvantages are the radioactivity of C^{14} and the high costs. The high costs of the test and, particularly, the cost of the equipment are also barriers to the use of the more stable (i.e. less radioactive) carbon isotope C^{13} [9, 16, 17].

Hydrogen Respiratory Tests with Lactulose and Lactose

These tests are based on the bacterial metabolism of sugars (glucose and lactulose), in which hydrogen and methane are produced and measured in the breath (calculated as the number of particles per million particles, i.e. ppm, of breath). They have many advantages: good tolerance and safety, the simplicity of the procedure, low cost, and high specificity. Among the disadvantages is low sensitivity (up to 75%). In 15–20% of the population there is a risk of the presence of bacterial flora which does not produce hydrogen [15, 17].

The hydrogen respiratory test with lactulose is based on the fermentation of lactulose (lack of a specific disaccharidase in the brush border: it is not decomposed under physiological conditions in the alimentary tract). In this process, particles of hydrogen are produced, absorbed, and breathed out. The hydrogen is measured by an electrochemical detector or spectrophotometer every 15 minutes for 1.5 hour after oral administration of 0.5 g/kg lactulose (not more than 10 g). An initial hydrogen concentration greater than 20 ppm or an increase in this concentration by more than 20 ppm in the first hour is regarded as a positive result. Measurement of methane in the breath by a spectrophotometer is also possible (methane is produced by methanegenic bacteria from hydrogen coming from the fermentation of unabsorbed lactulose). In such a test an increase in methane expiration by 20 ppm in the first hour is also regarded as a positive result [4, 9, 15, 16, 18–20].

The hydrogen respiratory test with lactose is based on the concentration of hydrogen, produced from undigested lactose in the intestine, in the breath. The measurement of breath hydrogen is performed in fasted condition every 30 minutes for two hours after ingestion of 2 g/kg lactose (up to 50 g). Breath samples are collected using a plastic mouthpiece. Modern equipment analyzes the respiration samples in a fully automatic and computerized manner [13, 17, 18, 21]. The interpretation of the hydrogen respiratory test is presented in Table 3.

The test with para-aminobenzoic acid is based on the capability of bacteria to deconjugate bile acids. The para-aminobenzoic acid (PABA)-cholic acid complex is deconjugated by bacteria and the para-aminobenzoic acid is absorbed and secreted in urine. An increase in the concentration of para-aminobenzoic acid in the urine is regarded as

Table 3. Interpretation of the hydrogen breath test

Tabela 3. Interpretacja wyników wodorowego testu oddechowego

Result of the hydrogen breath test (Wynik testu wodorowego)	Interpretation of the hydrogen breath test (Interpretacja wyniku testu wodorowego)
< 20 ppm	norm
> 20 ppm up to 60 min (do 60 min)	dysbacteriosis of the upper part of the alimentary tract
> 20 ppm after 60 min (po 60 min)	disturbances in carbohydrate digestion and absorption

ppm – pats per million.

ppm – cząsteczek na milion.

a positive result. Use of this test is rare due to its low specificity and sensitivity [5].

Other diagnostic methods, such as the measurement of free bile acids in serum, measurement of folic acid in the stool, the Indican test, and the phenole test, are applied exclusively in scientific research.

The diagnosis of bacterial overgrowth in the small intestine is an indication for further diagnostics of risk factors, such as an X-ray of the alimentary tract in search of anatomical anomalies, fistulas, or obstacles to intestinal passage.

Treatment of Bacterial Overgrowth in the Small Intestine

Of fundamental importance in the prevention of recurrence of bacterial overgrowth is treatment of the underlying condition predisposing to bacterial overgrowth, and this is not always possible. There are several disorders, for example jejunal diverticulosis, in which surgical correction of the cause of bacterial overgrowth is the ideal approach that will remove the cause and should cure the patient. In most patients, surgical correction of intestinal anatomical abnormalities is not feasible and the therapy of the bacterial overgrowth will depend on antibiotic treatment. This treatment is based on antibiotics active against Gram-negative aerobic and anaerobic bacteria. Metronidazole is usually the drug of first choice. The treatment should be applied for 7 to 10 days, and in cases of recurrence 4 to 8 weeks. Alternatively, tetracycline, amoxicillin with clavulanic acid, trimethoprim with sulfamethoxazole, ciprofloxacin, norfloxacin, and vancomycin can be used. Adjuvant roles in therapy are played by cholestyramine (binds free bile acids, alleviates diarrhea), prokinetic drugs (small doses of octreopeptide, a synthetic analog of somatostatin), and probiotics (although their efficacy is poorly documented) [22–24].

Important in alimentary treatment are nutrients containing medium-chain triglycerides (MCTs), as they provide a concentrated source of calories while decreasing the degree of steatorrhea which occurs with a normal (long-chain-fat-containing) diet, supplementation of vitamin deficiency (A, D, E, B_{12}), and sometimes a decrease in lactose content in the diet. Considering that bacteria produce a significant amount of vitamin K, there is no deficiency of this vitamin; however, in patients taking oral anticoagulants there is a problem of establishing their dosage.

References

[1] Berg RD: The indigenous gastrointestinal microflora. Trends Microbiol 1996, 4, 430–435.

[2] Sobieszczańska BM: The influence of intestinal dysbiosis on human's health. Gastroenterol Pol 2008, 15, 287–290.

[3] King CE, Toskes PP: Small intestine bacterial overgrowth. Gastroenterology 1979, 76, 1035–1055.

[4] Kirsch M: Bacterial overgrowth. Am J Gastroenterol 1990, 85, 231–237.

[5] Toskes PP: Bacterial overgrowth of the gastrointestinal tract. Adv Int Med 1993, 38, 387–406.

[6] van der Waaij D: Colonization resistance of the digestive tract-mechanism and clinical consequences. Nahrung 1987, 31, 507–517.

[7] van der Waaij D: The microflora of the gut: recent findings and implications. Dig Dis 1991, 9, 36–48.

[8] Bouhnik Y, Alain S, Attar A, Flourié B, Raskine L, Sanson-Le Pors MJ, Rambaud JC: Bacterial population contaminating the upper gut in patient with small intestinal bacterial overgrowth syndrome. Am J Gastroenterol 1999, 94, 1327–1331.

[9] Gracey M: The contaminated small bowel syndrome: pathogenesis, diagnosis, and treatment. Am J Clin Nutr 1979, 32, 234–243.

[10] Li E: Bacterial overgrowth. In: Textbook of Gastroenterology. Ed.: Yamada T, Lippincott Company, Philadelphia 1995, 1673–1680.

[11] Salyers AA: Energy sources of major intestinal fermentative anaerobes. Am J Clin Nutr 1979, 32, 158–163.
[12] Su J, Smith MB, Rerknimitr R, Morrow D: Small intestine bacterial overgrowth presenting as protein-losing enteropathy. Did Dis Sci 1998, 43, 679–681.
[13] Khoshini R, Dai SC, Lezcano S, Pimentel M: A systematic review of diagnostic tests for small intestinal bacterial overgrowth. Dig Dis Sci 2008, 53, 1443–1454.
[14] Orenstein SR, Whitington PF: Intestinal bacterial overgrowth in the pediatric patient. J Tenn Med Assoc 1984, 77, 198–201.
[15] Corazza GR, Menozzi MG, Strocchi A, Rasciti L, Vaira D, Lecchini R, Avanzini P, Chezzi C, Gasbarrini G: The diagnosis of small bowel bacterial overgrowth. Reliability of jejuna culture and inadequacy of breath hydrogen testing. Gastroenterology 1990, 98, 302–309.
[16] Walters B, Vanner SJ: Detection of bacterial overgrowth in IBS using the lactulose H_2 breath test: comparison with ^{14}C-D-Xylose and healthy controls. Am J Gastroenterol 2005, 100, 1566–1570.
[17] King CE, Toskes PP: Breath tests in the diagnosis of small intestinal bacterial overgrowth. Crit Rev Clin Lab Sci 1984, 21, 269–281.
[18] Kerlin P, Wong L: Breath hydrogen testing in bacterial overgrowth of the small intestine. Gastroenterology 1988, 95, 982–988.
[19] Riodan SM, McIver CJ, Walker BM, Duncombe VM, Bolin TD, Thomas MC: The lactulose breath hydrogen test and small intestinal bacterial overgrowth. Am J Gastroenterol 1996, 91, 1795–1803.
[20] Pimentel M, Mayer AG, Park S, Chow EJ, Hasan A, Kong Y: Methane production during lactulose breath test is associated with gastrointestinal disease presentation. Dig Dis Sci 2003, 48, 86–92.
[21] Lupascu A, Gabrielli M, Lauritano EC, Scarpellini E, Santoliquido A, Cammarota G, Flore R, Tondi P, Pola P, Gasbarrini G, Gasbarrini A: Hydrogen glucose breath test to detect small intestinal bacterial overgrowth: a prevalence case-control study in irritable bowel syndrome. Aliment Pharmacol Ther 2005, 22, 1157–1160.
[22] Hill ID, Mann MD, Househam KC, Bowie MD: Use of oral gentamicin, metronidazole, and cholestyramine in the treatment of severe persistent diarrhea in infants. Pediatrics 1986, 77, 477–481.
[23] Soudah HC, Halser WL, Owyang C: Effect of octreotide intestinal motility and bacterial overgrowth in scleroderma. N Engl J Med 1991, 325, 1461–1467.
[24] Attar A, Flourie B, Rambaud JC: Antibiotic efficacy in small intestinal bacterial overgrowth-related chronic diarrhea: a crossover, randomized trial. Gastroenterology 1999, 117, 794–797.

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