The Diagnosis and Management of Achlorhydria

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Keywords: Achlorhydria, kobalamin, vitamin, calcium

Abstract: Achlorhydria is defined as a decrease in secretion quantity or decrease in the acidity of gastric acid. Gastric acid has several functions including activating other digestive enzymes, deciphering the food particles in the digestive process, essential vitamins and minerals absorption, and eliminating most of the microorganisms that enter with the food. There is no specific management for achlorhydria. Patients with achlorhydria in addition to experiencing disorders of HCl formation generally also suffer from pepsin deficiency. Therefore, pepsin is usually given to support the provision of betaine HCl. Patients with achlorhydria should be periodically monitored for early diagnosis of anemia due to iron deficiency and/or cobalamin. Calcium and vitamin D deficiency can be monitored through serum 25 hydroxyvitamin D level as well as bone density examination.

1 INTRODUCTION

Achlorhydria is a condition of decrease in the quantity or the absence of gastric acid (Schubert et al., 2013). The most common risk factor of achlorhydria is Helicobacter pylori infection. H. pylori infection causes chronic atrophic gastritis with a manifestation of achlorhydria. The risk factors of the occurrence of achlorhydria include atrophic gastritis associated with Helicobacter pylori infection, autoimmune gastritis, elderly, and long-term use of proton-pump inhibitor (PPI) drugs (Calvet et al., 2013; Lombardo et al., 2010).

The clinical implications of achlorhydria are decreased digestive function and gastric barrier function, leading to important vitamin and mineral deficiencies, including cobalamin deficiency (vitamin B12), iron, and calcium, as well as an increased risk of gastrointestinal infection (Betesh et al., 2015).

Achlorhydria is also associated with an increased risk of intestinal and gastric metaplasia (De Vries et al., 2009). Patients with achlorhydria can encounter symptoms that are similar to general dyspeptic complaints, such as nausea, abdominal pain, weight loss, frequent burping or bloating after eating, diarrhea, and constipation.

The signs that often arise include being weak, weary, lethargic due to anemia, the occurrence of undigested food in the feces, neurological disorders, and bone fractures (Fujita, 2014).

The gold standard of achlorhydria diagnosis is established by Heidelberg's gastric analysis technique to measure the acidity of gastric acid. The diagnostic examination of achlorhydria often uses histamine/pentagastrin injection as a trigger for maximal gastric acid secretion during examination (Schubert and Kaunitz, 2013). The management of achlorhydria includes causative and symptomatic management.

Eradication of H. pylori with the combination of antibiotics and PPI, and the use of PPI in chronic gastritis patients is rationally causative management (Hsu et al., 2011). The provision of betaine HCl supplements aimed at increasing the amount and acidity of the stomach fluid is still debatable regarding its effectiveness. Vitamin and mineral deficiency as an implication of achlorhydria is overcome by supplemental drug administration. On the other hand, intestinal infection due to achlorhydria is treated with antibiotics (Salem and Ronald, 2014). This study aimed to analyze the diagnosis and management of Achlorhydria.

Febrianto, D., Nusi, I., Setiawan, P., Purbayu, H., Sugihartono, T., Maimunah, U., Kholili, U., Widodo, B., Vidyani, A., Miftahussurur, M. and Thamrin, H.
The Diagnosis and Management of Achlorhydria.
In *Proceedings of Surabaya International Physiology Seminar (SIPS 2017)*, pages 413-420
ISBN: 978-989-758-340-7

2 DEFINITION AND PREVALENCE OF ACHLORHYDRIA

Achlorhydria is a condition of decreasing the amount or absence of gastric acid. The absolute condition of gastric acid absence is very rare. Therefore, some writers or researchers often use the term hypochlorhydria or a decrease in the amount of gastric acid (Schubert and Kaunitz, 2013).

3 PATHOPHYSIOLOGY OF ACHLORHYDRIA

The Pyloric gland secretes mucus to preserve the pyloric mucosa against gastric acid. The cells that are responsible for the secretion function are located in the gastric mucosa. The variation of secretory cells lining the invagination consist of exocrine, endocrine, and paracrine glands (Hall, 2011).

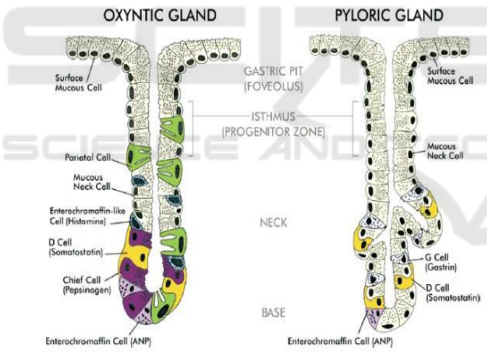

Figure 1: The schema of oxyntic and pyloric glands (Schubert and Kaunitz, 2013)

There are three types of exocrine cells found in the walls of the gastric sac and oxyntic gastric mucosal glands, namely (1) mucous cells lining the gastric sac, secreting a watery mucus; (2) chief cells that secrete pepsinogen enzyme precursors; and (3) parietal cells (oxyntic) to produce HCl and intrinsic factor. Oxyntic is defined as sharp. It refers to the ability of these cells to produce a very acidic state. All of this secretion exocrine is released to the lumen of the stomach and plays a role in forming gastric juice (Rizzo, 2010).

Normally, the stomach during fasting contains a small amount of gastric acid that gradually increases as the body ingests food. In general, HCl maintains its acidity between pH 1 and 2 in the stomach. Type of food eaten, integrity of the nervous system, levels of micronutrients in the blood, individual emotional atmosphere, and various factors that have not been identified affect the acidity of the stomach. Protein intake and unstable emotional states tend to increase the acidity of the stomach (Rizzo, 2010).

The function of HCl is as follows: (1) activates the pepsinogen enzyme precursor into pepsin active enzyme, and form an optimal acid environment for pepsin activity; (2) aids the breakdown of muscle fibers and connective tissue, so that large food particles can be broken up into more easily absorbed tiny particles; and (3) along with the saliva lysozyme, eliminates most of the microorganisms that enter with the food, although some can escape and continue to grow and multiply in the large intestine (Valle and Todisco, 2009).

The defense system can be divided into three levels of barrier consisting of pre-epithelial, epithelial, and sub-epithelial. First-line defense is the mucus bicarbonate layer, which acts as a psychochemical barrier to several molecules including hydrogen ions. Mucus is produced by epithelial cells of the stomach surface. The mucus consists of water (95%) and mixture of fat and glycoprotein (mucin). The function of the mucus gel is as a layer that cannot be passed by water and blocks ion diffusion and molecules such as pepsin (Hall, 2011).

The factors that can inhibit gastric secretions include the presence of food in the small intestine that triggers the occurrence of the reverse enterogastric reflex. In addition, the presence of food in the small intestine causes the release of secretion which results in retarding gastric secretions. If the pH of the gastric acid falls below 3 (increased acidity), the production of stomach acid will also be suppressed through a somatostatin release mechanism that decreases gastrin secretion, histamine, and ultimately decreases gastric acid secretion (Valle, 2012).

Gastritis or gastric mucosal inflammation can occur if there is an infection of the gastric mucosa. Gastritis is distinguished to be acute and chronic with atrophy and non-atrophy (Hansel, 2015). The consumption of ingredients that interfere with gastric, mucus and tight junctions can lead to gastritis. Chronic ongoing gastritis causes mucosal atrophy and impaired gastric secretions. This disturbance of gastric secretion often manifests as achlorhydria (Lahner and Annibale, 2009b).

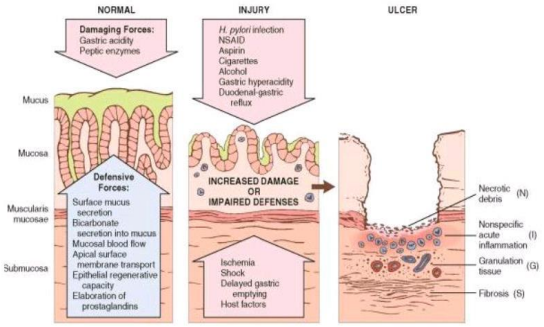

Figure 2: Gastric mucosal defense factor (Malfertheiner, 2014)

4 ETIOLOGY OF ACHLORHYDRIA

The most common risk factor for the occurrence of achlorhydria is Helicobacter pylori infection that causes atrophic gastritis. H. pylori infects almost half of the world's total population, and most chronically infected patients manifest as pan-gastritis and produce stomach acid less than normal (Calvet et al., 2013).

H. pylori colonization is generally contracted during childhood, mostly in densely populated areas with poor sanitation hygiene. The incidence of H. pylori in children in developed countries is quite low in line with improved living standards and widespread use of antibiotics (Atherton and Blaser, 2013).

In H. pylori infection, atrophy occurs in the oxyntic gland resulting in loss of parietal cells and irreversible achlorhydria. It has been proved that H. pylori can play an important role in the development of autoimmune gastritis in sensitive individuals (Argent et al., 2008).

Helicobacter pylori examination is important to conduct, given the fact that infection by these germs causes many achlorhydria complications. Although achlorhydria may be considered a pre-neoplastic process that carries a risk of 0.1-0.2% per year and 5% throughout life for the occurrence of adenocarcinoma, endoscopic examination for surveillance is not recommended.

H. pylori infection is considered carcinogenic by the WHO and plays a role in the pathogenesis of most atrophic gastritis; thus, it is reasonable to examine the presence of these organisms and to eradicate them (Busuttil and Boussioutas, 2009). The invasive method of H. pylori examination is performed with endoscopic gastric tissue biopsy.

A non-invasive method is conducted by examination of antibody (immunoglobulin G) to H. pylori, urea breath test, and feces antigen test using enzyme immunoassay (HpSA). H. pylori culture is the most specific test but it is difficult to be implemented (Yamada and Inadomi, 2013).

Autoimmune gastritis is also a risk factor for achlorhydria. As with most autoimmune diseases, autoimmune gastritis is more common in females (Calvet et al., 2013). Antrectomy surgery in case of peptic ulcer disease is also a risk factor for the occurrence of achlorhydria because the antrum is a part of the stomach that primarily secretes acids during the digestion of food, as well as the main hormone responsible for the growth of the oxyntic mucosa (Zhang et al., 2013).

The treatment of chronic gastritis with a long-term (more than 8 weeks) proton-pump inhibitor (PPI) may increase the risk of achlorhydria.

5 SYMPTOMS AND SIGNS OF ACHLORHYDRIA

Patients with achlorhydria often do not have any complaints, but some experience several unspecific symptoms and signs. The most common symptoms include weakness, fatigue, belching or bloating after eating, diarrhea or constipation, frequent exhaustion, burning in the chest, pruritus ani, malaise, food allergies, nausea, vomiting, prolonged fullness after eating, and a dry mouth.

The signs in patients with achlorhydria are as a consequence of decreased function of stomach acid, such as iron deficiency anemia, chronic candidiasis, chronic intestinal parasite, glositis (inflammation of the tongue), increased excretion of urine indications, acne in adulthood, the discovery of undigested food in the feces, weak and fragile nails, and susceptibility to osteoporosis and bone fractures (Yamada and Inadomi, 2013).

6 DIAGNOSIS ESTABLISHMENT OF ACHLORHYDRIA

Exposure to histamine triggers gastrin to produce stomach acid which can be measured by quantitative endoscopy techniques, i.e. the amount of stomach acid secreted per unit of time. This test quantitatively classifies patients as achlorhydria,

severe hypochlorhydria, normal gastric acid secretion, and high gastric acid secretion (Betesh et al., 2015). To perform the measurement of production of stomach acid, the patient is positioned left lateral decubitus. Previously, the patient has fasted for at least 8 hours.

A nasogastric tube is inserted into the antrum with fluoroscopy guidance. Initial aspiration fluid is removed, and then a gastric specimen is taken every 15 minutes for the first hour. The production of gastric acid is further stimulated by administration of intravenous histamine/pentagastrin with a dose of 2 units/kgBW. An hour after that, the stomach fluid specimen is again taken four times every 15 minutes.

The acidity of the specimen fluid is examined using a methyl red indicator or using a pH electrode. Patients with achlorhydria do not respond to an increase in gastric acid production after stimulation of histamine/pentagastrin (Betesh et al., 2015).

Another non-invasive qualitative examination using dye-resin was published by Barton et al. in Salisbury, England, in 1959. The dye-resin of granula-shaped, mixed in water in a certain amount, was drunk and observed in urine excretion. The basic principle of this examination is to utilize the properties of compounds in resins that can only be released in the stomach if there is stomach acid. The compound is then absorbed into the blood and excreted through the urine, producing a green or blue color in the urine within two hours. If the green or blue color does not appear or has appeared after four hours, the person is suffering from achlorhydria (Barton and AH., 1959).

A non-invasive sophisticated examination of achlorhydria was discovered at the University of Heidelberg, West Germany, in 1961. The Heidelberg gastric analytical technique uses the principle of radiotelemetry to measure the ability of gastric acid secretion of parietal cells. The required equipment is a radiotelemetry capsule of a 2x0.8 cm hard plastic capsule containing miniature radio transmitters, pH gauges, and batteries. In addition, an antenna is required to receive the signal from the capsule and forward it to the receiver. There are two methods of conducting the Heidelberg test: tethered capsule repeat challenge test and flow-through method. For both procedures, the test is performed after the patient fasts for at least 8 hours (Noeller, 1962).

The tethered capsule repeat challenge test uses a Heidelberg capsule tied to cotton yarn measuring approximately 1 meter. Capsules are swallowed using a minimum of water. The initial pH starts from 7. About five minutes after swallowing, the capsule reaches the base of the stomach, and the pH normally drops to between 1 and 2. The rest of the yarn on the outside is attached to the cheek to fix the capsule inside the stomach in order to not descend into the intestine. If fasting abdominal pH is normal, it is tested by drinking 5 ml of alkaline solution (baking soda).

Within 30 minutes, the pH will normally rise to 7 and will return again to between 1 and 2 in 20 minutes. The test is repeated four times (Schubert and Kaunitz, 2013). In the flow-through method, the Heidelberg capsule is not tied and left freely following the flow from the stomach to the duodenum, intestines, to the exit with the feces. This method allows assessment of the time of gastric emptying and intraluminal pH (Schubert and Kaunitz, 2013).

7 CLINICAL IMPLICATIONS OF ACHLORHYDRIA

7.1 Absorption of Iron

In patients with achlorhydria, ferric chloride and ferric ascorbate are absorbed better if administered together with acidic solutions. Iron deficiency anemia can be traced by monitoring routine blood tests and serum iron levels. Iron deficiency anemia is characterized by hypochromic and microcytic red blood cells by peripheral blood smears (Iida et al., 2012).

7.2 Absorption of Zinc

Zinc solubility depends on the pH, in which the solubility increases as the pH becomes more acidic. Sandstrom et al. found a decrease in the absorption of zinc in individuals with achlorhydria compared to normal subjects, but it was not significant (Iida et al., 2012).

7.3 Vitamin Deficiency

Various studies show patients with pernicious anemia due to gastritis generally have achlorhydria. Cobalamin deficiency (B12) can cause symptoms such as fatigue and lethargy, pale skin, bitter tongue, stomach pain, weight loss, diarrhea or constipation, and neurological disorders (Lahner and Annibale, 2009b). The process of cobalamin deficiency takes years because the deposits of cobalamin in the body are quite large. Cobalamin deposits can be monitored by blood tests as serum cobalamin levels

Table 1: Helicobacter pylori eradication therapy regimen (Hsu et al., 2011; Malfertheiner, 2014; Graham et al., 2014).

First-line therapy		
Triple therapy regimen	Omeprazole Amoxicillin Clarithromycin	For patients with penicillin allergy, amoxicillin can be replaced with metronidazole
Quadruple therapy regimen	(1) PPI + amoxycillin + clarithromycin + metronidazole (2) PPI + bismuth + amoxycillin/metronidazole + tetracycline (3) PPI + bismuth + tetracycline + furazolidone	Resistance to furazolidone is still low, but not yet available in Indonesia.
	(1) PPI + PPI + amoxycillin (5 days), followed by PPI + clarithromycin/levofloxacin + metronidazole (5 days) (2) PPI + amoxycillin (7 days), followed by PPI + amoxycillin + clarithromycin + metronidazole (7 days)	
Second-line therapy		
(1) Re-treatment with a quadruple or sequential therapy regimen (2) PPI + amoxicillin or metronidazole + levofloxacin (10-14 days) (3) PPI + rifabutin + amoxicillin (14 days)		

Note:
Dose of omeprazole 2 x 20 mg/day
Dose of amoxycillin 2 x 1000 mg/day
Dose of metronidazole 2 x 500 mg/day
Dose of bismuth 4 x 120 mg/day

(Den Elzen et al., 2008). Plasma vitamin C concentrations in patients with achlorhydria are significantly lower than individuals with a pH of less than or equal to 4 (Lewerin et al., 2008).

7.4 Intestinal infections

Stomach acids kill the dangerous microorganisms that come with food. As a result of the decline in the role of gastric acid, patients with achlorhydria are reported to be more susceptible to Clostridium difficile, Salmonella, Campylobacter, and spontaneous bacterial peritonitis, and SIBO (small intestinal bacterial overgrowth)(Fujita, 2014; Rohof et al., 2014).

SIBO is defined as an increase in the amount of bacteria and/or bacterial type changes, typically causing nutrient malabsorption in the proximal portion of the small intestine. The most common used definition is the quantitative definition, i.e. the presence of 105 or more colony units per milliliter (CFU/mL) of bacteria was obtained from intestinal aspirate samples. SIBO usually presents with various clinical manifestations, including full stomach, nausea, abdominal pain, chronic diarrhea, frequent flatus, nutritional deficiency, and weight loss (Salem and Ronald, 2014).

7.5 Osteoporosis or Bone Fracture

In some population-based retrospective studies, long-term proton pump inhibitors (PPI) have been associated with an increased risk of calf fractures in older adults, although the absolute risk is very low. Gastric acid secretion is necessary for calcium absorption. In addition, patients with achlorhydria have a high prevalence of bacterial infection in the small intestine causing impaired absorption of calcium. This calcium absorption disorder triggers osteoporosis and the occurrence of bone fracture.

7.6 Adenocarcinoma and Gastric Carcinoid Tumors

Achlorhydria is associated with intestinal metaplasia and has a risk factor three times greater for the occurrence of adenocarcinoma (De Vries et al., 2009). Gastric metaplasia from chronic atrophic gastritis is three times more common in females (Calvet et al., 2013).

8 MANAGEMENT OF ACHLORHYDRIA

Management of achlorhydria includes causative management and symptomatic management.

8.1 Causative Management

There is no specific management for achlorhydria. Considering the most common risk factor for the occurrence of achlorhydria is H. pylori infection, the prevention and eradication of H. pylori through improved sanitation and effective antibiotic regimens can be expected to prevent achlorhydria (Atherton and Blaser, 2013). However, H. pylori eradication cannot reduce the risk of chronic atrophic adenocarcinoma of gastritis or intestinal metaplasia (De Vries et al., 2009).

Although the standard initial therapy for H. pylori infection is triple therapy for 10-14 days, the success of therapy with this regimen is less than 80%, primarily due to increased resistance to clarithromycin. A more effective initial regimen consists of a quadruple therapy regimen (four different drugs) and sequential therapy. These regimens are administered for 10-14 days. Second-line therapy is administered if both eradications are not successful (Graham et al., 2014).

Achlorhydria caused by long-term use of PPI can be resolved by gradually reducing the PPI dose until final stoppage. The use of PPI in patients with dyspepsia should be conducted rationally to prevent achlorhydria (Schubert et al., 2008). Reduced surgery for peptic ulcer disease decreases the incidence of achlorhydria, since antrum, as the main source of gastrin, can be maintained.

Achlorhydria due to autoimmune gastritis is more difficult to treat because once the gastric secretory mucosa is damaged by the immune process, its function to produce stomach acid is difficult to return to normal. Achlorhydria due to the aging process is also difficult to prevent and only symptomatically treated (Calvet et al., 2013).

8.2 Symptomatic Management

Historically, some substances are believed to stimulate gastric acid secretion or improve digestion. These substances include lemon or vinegar that is mixed in food, ginger, black pepper, caffeine, and alcohol (Bruno, 2014).

Around the 1930s, betaine hydrochloride was once used to treat the symptoms of gastric acid deficiency. Although the US association of clinicians in 1993 stated that the use of betaine HCl is not clinically proven to be effective for patients, currently betaine HCl is still available as a dietary supplement for achlorhydria patients. Hydrochloric acid (HCl) is available primarily as betaine HCl, although glutamic HCl is also found in several formulas. The potential of capsules or tablets varies between 5-10 grains with 1 grain equivalent to 64.75 mg.

Clinically, clinicians have reported giving betaine HCl of 5 grains three times daily to 60-80 grams a day. Betaine HCl is especially indicated in elderly with dyspepsia, and in individuals with bacterial or fungal growth due to decreased basal HCl production. It is recommended that one betaine HCl capsule is administered between meals three times daily (Bruno, 2014).

Patients with achlorhydria in addition to experiencing disorders of HCl formation generally also suffer from pepsin deficiency. Therefore, pepsin is usually given to support the provision of betaine HCl. The usual dose is about 500 mg with 1: 3000 pepsin potential. The dose of HCl to produce optimum effect in each individual is different. It is usually recommended to start from the smallest dose and be raised in titration. If the side-effects such as burning in the pit of the liver, diarrhea, or nausea appear, the last dose should be returned to before the adverse effects appeared (Bruno, 2014).

Cobalamin deficiency (vitamin B12) can be treated by administration of parenteral cyanocobalamin (intramuscular). The dose of cyanocobalamin is 1000 micrograms intramuscularly once daily for 1 week, followed by 1000 micrograms once a week for 4 weeks, followed by 1000 micrograms once a month for life if it is needed (Lahner and Annibale, 2009b).

Iron administration orally along with ascorbic acid (vitamin C) is conducted to overcome iron deficiency. Parenteral iron may be given intramuscularly, but intravenously is recommended. The recommended doses of iron supplements are: (1) 325 mg of oral ferrous sulfate three times daily, (2) 325 mg of fumarate ferrous orally 3 times daily, or (3) 325 mg of gluconate ferrous orally 3 times daily.

There are no specific recommendations for the prevention or treatment of calcium deficiency in patients with achlorhydria. However, given the high risk of fracture in the elderly, it is reasonable to provide additional calcium therapy.

The choice of treatment is 1000-1500 mg of calcium carbonate orally once daily and 800 units of

ergocalciferol orally once daily. Reduced gastric acid may interfere with the absorption of some drugs, such as levothyroxine, atazanavir, ketoconazole, itraconazole, enoxacin and dipyridamole. Increased doses may be needed to achieve efficacy.

9 MONITORING

As there is no screening, no specific checks are required to be monitored (Loor and Dumitrascu, 2016). However, patients with achlorhydria should be periodically monitored for early diagnosis of anemia due to iron deficiency and/or cobalamin. Calcium and vitamin D deficiency can be monitored through serum 25 hydroxyvitamin D level as well as bone density examination

10 SUMMARY

Achlorhydria is defined as a decrease in the quantity of secretion or decrease in the acidity of the stomach acid. Gastric acid has many functions, including activating other digestive enzymes, helping to break down particles of food in the digestive process, helping to absorb important vitamins and minerals, and killing most of the microorganisms that enter with food. Risk factors for the occurrence of achlorhydria include atrophic gastritis associated with Helicobacter pylori infection, autoimmune gastritis, advanced age, and long-term use of proton-pump inhibitor (PPI) drugs.

Although initially it often does not give symptoms, after a long time the achlorhydria can cause various implications. Decreased function of vitamins and minerals leads to essential vitamin and mineral deficiencies, including cobalamin deficiency (vitamin B12), iron deficiency, and calcium deficiency. The function of stomach acid killing the microorganisms in food can also be disrupted. This results in an increased risk of intestinal infection in patients with achlorhydria. Achlorhydria is also associated with an increased risk of intestinal metaplasia and gastric carcinoid tumors. There is no special screening for early diagnosis of achlorhydria. Management of achlorhydria may vary because it is based more on the need to address the implications that occur in each patient.

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