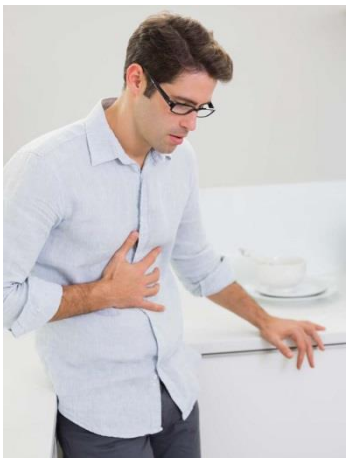
Cancer Association of South Africa (CANSA)

Fact Sheet
on
Atrophic Gastritis

Introduction

Atrophic gastritis (also known as Type A or Type B Gastritis) is a process of chronic inflammation of the stomach mucosa, leading to loss of gastric glandular cells and their eventual replacement by intestinal and fibrous tissues. As a result, the stomach's secretion of essential substances such as hydrochloric acid, pepsin, and intrinsic factor is impaired, leading to digestive problems, Vitamin B_{12} deficiency, leading to megaloblastic anaemia or malabsorption of iron, leading to iron deficiency anaemia. It can be caused by persistent infection with *Helicobacter pylori*, or can be autoimmune in origin.



[Picture Credit: Atrophic Gastritis]

Those with the autoimmune version of atrophic gastritis are statistically more likely to develop gastric carcinoma (stomach cancer), Hashimoto's thyroiditis (an autoimmune disease in which the thyroid gland is attacked by a variety of cells and antibody-mediated immune processes), and achlorhydria (a condition where the production of gastric acid in the stomach is absent or low).

Type A gastritis primarily affects the body/fundus of the stomach, and is more common with pernicious anaemia. Type B gastritis (most common overall) primarily affects the antrum, and is more common with *H. pylori* infection.
(Wikipedia).

Atrophic Gastritis (AG)

Atrophic gastritis (AG) is a histopathologic entity characterised by chronic inflammation of the gastric mucosa with loss of gastric glandular cells and replacement by intestinal-type epithelium, pyloric-type glands, and fibrous tissue. Atrophy (wasting away, especially as a result of the degeneration of cells) of the gastric mucosa is the endpoint of chronic processes, such as chronic gastritis associated with *Helicobacter pylori* infection, other unidentified environmental factors, and autoimmunity directed against gastric glandular cells.

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The two main causes of atrophic gastritis result in distinct topographic types of gastritis, which can be distinguished histologically. *H pylori*- associated atrophic gastritis is usually a multifocal process that involves both the antrum and oxyntic mucosa of the gastric corpus and fundus, whereas autoimmune gastritis essentially is restricted to the gastric corpus and fundus. Individuals with autoimmune gastritis may develop pernicious anaemia because of extensive loss of parietal cell mass and anti-intrinsic factor antibodies.

H pylori- associated atrophic gastritis is frequently asymptomatic (without symptoms), but individuals with this disease are at increased risk of developing gastric carcinoma (stomach cancer), which may decrease following *H pylori* eradication. Patients with chronic atrophic gastritis develop low gastric acid output and hypergastrinaemia, which may lead to enterochromaffin-like (ECL) cell hyperplasia and carcinoid tumours.
(Medscape).

Incidence of Atrophic Gastritis (AG) in South Africa
Because Atrophic Gastritis is not a cancerous condition, but rather a possible precursor to stomach cancer, the National Cancer Registry (2009) does not provide any information regarding the incidence of this condition.

According to the National Cancer Registry (2011) the following number of stomach cancer cases were histologically diagnosed in South Africa during 2011:

Group - Males 2011	No of Cases	Lifetime Risk	Percentage of All Cancers
All males	668	1:193	2,08%
Asian males	28	1:183	4,39%
Black males	235	1:348	2,37%
Coloured males	134	1:84	6,35%
White males	271	1:112	1,54%

Group - Females 2011	No of Cases	Lifetime Risk	Percentage of All Cancers
All females	337	1:553	1,06%
Asian females	21	1:333	2,87%
Black females	148	1:873	1,08%
Coloured females	65	1:269	1,75%
White females	101	1:321	0,76%

The frequency of histologically diagnosed cases of stomach cancer in South Africa for 2011 were as follows (National Cancer Registry, 2011):

Group - Males 2011	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	1	9	24	75	166	196	139	53
Asian males	0	0	1	2	12	4	6	3
Black males	1	5	13	27	77	58	42	10
Coloured males	0	2	3	19	28	41	32	7
White males	0	2	7	27	49	93	59	33

Group - Females 2011	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	0	4	18	60	66	66	86	31
Asian females	0	0	0	4	3	6	6	2
Black females	0	2	13	31	29	23	34	13
Coloured females	0	1	4	10	11	13	21	4
White females	0	1	1	15	23	24	25	12

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Causes of Atrophic Gastritis (AG)
The main causes of Atrophic Gastritis are:

Helicobacter pylori usually infects the stomach in childhood and the infection progresses if not treated. This type of bacteria can be passed from person to person through direct contact with faeces, vomit, or saliva, and can also be spread through contact with contaminated food or water.

Autoimmune AG occurs when the body produces antibodies that attack the stomach cells responsible for acid production. Antibodies also attack a substance released by these cells known as intrinsic factor. Intrinsic factor helps one to absorb vitamin B_{12}. Its destruction can cause an illness known as pernicious anaemia, in which a lack of vitamin B_{12} leaves one unable to make enough red blood cells.

For both causes, the condition is usually found later in life. Most of those diagnosed with AG are 50 years of age or older.
(Healthline).

Signs and Symptoms of Atrophic Gastritis (AG)
Often there are no symptoms, and as a result, many cases of AG go unrecognised.

An *H. pylori* infection may cause:
- stomach pain
- nausea and vomiting
- loss of appetite
- weight loss
- stomach ulcers
- stomach cancer
- iron deficiency anaemia that does not respond to treatment

Autoimmune AG can lead to vitamin B_{12} deficiency, with symptoms of anaemia, including:
- feeling weak
- lightheadedness
- dizziness
- chest pain
- palpitations
- tinnitus (ringing in the ears)

Vitamin B_{12} deficiency can also cause nerve damage, leading to:

- limb numbness and tingling
- unsteadiness when walking
- mental changes

(Healthline).

Diagnosis of Atrophic Gastritis (AG)

The diagnosis of atrophic gastritis can only be ascertained histologically.

- The endoscopic findings are not helpful for diagnosis, but endoscopy is essential to perform multiple gastric biopsy sampling. At least 2 biopsy samples from the gastric antrum, 2 from the corpus and 1 from the incisure should be obtained and submitted to the pathology laboratory in separate vials.
- Decreased serum pepsinogen I levels and the ratio of pepsinogen I to pepsinogen II in the serum can be used to assess gastric atrophy. The finding of low pepsinogen I levels (< 20 ng/mL) has a sensitivity of approximately 96.2% and a specificity of 97% for detection of fundus atrophy.
- Identifying the underlying cause of atrophic gastritis and assessing specific complications can require several laboratory tests.

Diagnosis of *H pylori*-associated atrophic gastritis is as follows:

- Histologic examination of gastric biopsy with *H pylori* special stains: Histologic identification of *H pylori* is the standard method to assess if the organism is the underlying cause of atrophic gastritis. Histologic examination also helps evaluate the degree and distribution of atrophy, which helps identify the type of atrophic gastritis. Although histologic identification of *H pylori* is the standard approach to identify the infection, at late stages of extensive atrophic gastritis, the number of *H pylori* organisms is decreased markedly because intestinal metaplasia creates an unfavourable environment for *H pylori*. In these cases, other tests, such as the urea breath test (i.e., with nonradioactive isotope 13C or with radioactive isotope 14C), and serologic evidence of infection may provide evidence for *H pylori* infection.
- Rapid urease test from gastric biopsy tissue
- Bacterial culture of gastric biopsy specimens: This usually is performed in the research setting or to assess antibiotic susceptibility in patients in whom first-line eradication therapy fails.
- Serologic detection of anti-*H pylori* antibodies

Diagnosis of autoimmune gastritis is as follows:

- Antiparietal achlorhydria (the absence or lowered production of gastric acid in the stomach) and anti-IF (anti-instrinsic factor) antibodies in the serum
- Achlorhydria, both basal and stimulated, and hypergastrinemia
- Low serum cobalamin (B-12) levels (< 100 pg/mL)
- Shilling test: Results may be abnormal and can be corrected by IF.

(Medscape).

Treatment of Atrophic Gastritis (AG)
Once atrophic gastritis is diagnosed, treatment can be directed:

(1) to eliminate the causal agent, which is a possibility in cases of *H pylori*–associated atrophic gastritis
(2) to correct complications of the disease, especially in patients with autoimmune atrophic gastritis who develop pernicious anaemia (in whom vitamin B_{12} replacement therapy is indicated)
(3) to attempt to revert the atrophic process.

No consensus from different studies exists regarding the reversibility of atrophic gastritis; however, removal of *H pylori* from the already atrophic stomach may block further progression of the disease. Until recently, specific recommendations for *H pylori* eradication were limited to peptic ulcer disease.

If *H pylori* is identified as the underlying cause of gastritis, subsequent eradication now is almost generally accepted practice. Protocols for *H pylori* eradication require a combination of antimicrobial agents and antisecretory agents, such as a proton pump inhibitors (PPIs), ranitidine bismuth citrate (RBC), or bismuth subsalicylate. Despite the combinatorial effect of drugs in regimens used to treat *H pylori* infection, cure rates remain, at best, 80-95%.

Lack of patient compliance and antimicrobial resistance are the most important factors influencing poor outcome. Currently, the most widely used and efficient therapies to eradicate *H pylori* are triple therapies (recommend as first-line treatments) and quadruple therapies (recommended as second-line treatment when triple therapies fail to eradicate *H pylori).* In both cases, best results are achieved by administering therapy for 10-14 days, although some studies have limited the duration of treatment to 7 days. The accepted definition of cure is no evidence of *H pylori* four or more weeks after ending the antimicrobial therapy.

- Triple therapy, with indicated adult dose
    - Twice-a-day (bid) PPI or RBC triple therapies include lansoprazole (Prevacid), 30 mg PO bid; omeprazole (Prilosec), 20 mg PO bid; or RBC (Tritec), 400 mg bid. Antibiotic therapy includes clarithromycin (Biaxin), 500 mg PO bid; amoxicillin, 1000 mg PO bid; or metronidazole, 500 mg PO bid.
    - Pack kits containing combination triple therapies are available as combinations of lansoprazole, amoxicillin, and clarithromycin (PrevPac) and bismuth subsalicylate, tetracycline, and metronidazole (Helidac). PrevPac contains drug combinations in the dosage recommended as first-line treatment by the Maastricht 2-2000 Consensus report from Europe.
    - PrevPac components include lansoprazole (Prevacid), 30 mg PO bid; clarithromycin (Biaxin), 500 mg PO bid; and amoxicillin, 1000 mg PO bid.
    - Helidac triple-therapy components include bismuth subsalicylate, 525 mg (two 262.4-mg chewable tabs) 4 times per day (qid); metronidazole, 250 mg qid; and tetracycline HCL, 500 mg qid.

- Quadruple therapy, with indicated adult dose is a PPI bid, including lansoprazole (Prevacid), 30mg per mouth twice a day or omeprazole (Prilosec), 20mg per mouth twice a day, and antibiotics, including tetracycline HCl, 500mg per mouth four times per day; bismuth subsalicylate, 120mg per mouth four times a day; and metronidazole, 500mg per mouth 3 times per day).

- Handle subsequent *H pylori* eradication failures on a case-by-case basis.

(eMedicine).

About Clinical Trials

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer.

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or "trial arms": (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.

- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has

proven safe and effective in a clinical trial, it may become a new standard of care (National Cancer Institute).

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