Barrett's Esophagus

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ABSTRACT

Gastroesophageal reflux disease (GERD) is a condition commonly managed in the primary care setting. Patients with GERD may develop reflux esophagitis as the esophagus repeatedly is exposed to acidic gastric contents. Over time, untreated reflux esophagitis may lead to chronic complications such as esophageal stricture or the development of Barrett's esophagus (BE). BE may progress to oesophageal adenocarcinoma. There is currently a rising incidence of BE. The pathogenesis of BE is not well-understood although genetic and environmental factors play significant roles. BE is characterized by the replacement of distal esophageal stratified squamous epithelium by columnar epithelium. It is rare in children and the risk factors may include mental retardation, cerebral palsy, esophageal atresia, etc. As patients with BE can be entirely asymptomatic, it is difficult to screen this population group. BE is present in 10–20% of patients with GERD and has also been detected in patients who deny classic GERD symptoms and are undergoing endoscopy for other indications.

Keywords: *Gastroesophageal reflux disease (GERD), Barrett's esophagus, oesophageal adenocarcinoma*

ABSTRAK

Penyakit refluks gastroesophageal (GERD) adalah kondisi umum yang dikelola dalam perawatan primer. Pasien dengan GERD dapat berkembang menjadi refluks esofagitis akibat asam lambung yang kembali ke esophagus berulang kali. Seiring waktu, reflux esophagitis yang tidak diobati dapat menyebabkan komplikasi kronis seperti striktur esofagus atau berkembang menjadi Barrett's esophagus (BE). BE dapat berkembang menjadi adenokarsinoma esofagus. Saat ini kejadian BE semakin meningkat. Patogenesis BE belum dipahami dengan baik meskipun faktor genetik dan lingkungan memainkan peran yang signifikan. BE ditandai dengan perubahan sel epitel skuamosa berlapis di distal esofagus oleh sel epitel kolumnar. BE jarang terjadi pada anak-anak dan faktor-faktor risiko yang mungkin pada anak-anak yaitu keterbelakangan mental, cerebral palsy, atresia esofagus, dll. Pasien dengan BE bisa sepenuhnya asimtomatik sehingga sangat sulit untuk diskrening pada populasi. 10 -20% pasien dengan GERD bisa menjadi BE dan juga bisa terjadi pada pasien dengan gejala GERD klasik yang disangkal dan sedang menjalani endoskopi untuk indikasi lain.

Kata kunci: *Gastroesophageal reflux disease (GERD), Barrett's esophagus, adenokasinoma esofagus*

INTRODUCTION

Barrett's esofagus (BE) is a metaplastic condition where columnar epithelium was replaced by squamous epithelium in distal part of esophagus. BE is the main risk factor of esophageal adenocarcinoma and gastroesophageal junction adenoma.[1]

Prevalence of BE in population was estimated around 1.6-1.7%. In 2000 at US, about 3.3 million of individual were reported to have this condition. In GERD patients, incidence of BE is 5-10%, while patients with esophageal peptic stricture have almost 30% incidence of BE. BE was found to be higher among male with ratio 3:1 to female.[2-4] Detection and treatment of BE is currently challenging. As the main risk factors of esophageal cancer, BE patients have 40 times risk compared to population.[5,6]

Esophageal cancer prevalence was increasing in recent years, especially among Western Countries. In Asia, most of the etiology of esophageal cancer is squamous cell carcinoma. Studies reported that progression of BE to esophageal cancer is progressively increasing in Asia as the prevalence of BE increasing.[7]

INCIDENCE BARRETT'S ESOPHAGUS

Incidence of BE among white race in developed countries were constant in recent two decades (studies published at 1990 and 2005). The first study report incidence in Minnesota with majority of Scandinavian, Germany, and other Europeans. In the second study conducted in Swedish, the sample population was quite larger. Therefore, both epidemiologic data were considered accurate to represent population.[8,9]

A prospective study in Minnesota for 18 months from 1986-1987 conducted an esophageal specimen autopsies, choosen if having more than 3 cm of mucosal layer with salmon-like colour. From 733 subjects, 7 were having severe long-segment Barrett Esophagus with prevalence of 376 per 100.000 cases or 0.34.[8-10] Incidence of long-segment BE in Asia is low (<1 % from all BE patients), while short-segment BE is high, approximately 96%.[7]

RISK FACTORS OF BARRETT'S ESOPHAGUS

Age

Since BE is an acquired disease, its incidence is increasing by age. Mean age of clinical diagnosis are 63 years old. Long-segment BE is rarely found in children. In a recent cohort study, 8 from 166 child receiving long term proton pump inhibitor treatment developed BE, mostly in patients with chronic gastroesophageal reflux with impaired mental status and having predisposing risk factors such as down syndrome or cerebral palsy.[8-10]

There were shifting trends of BE incidence relatet to age which mostly found in age above 70 years old. Pathophysiology of BE migh be different in Asia (mostly short-segment) and in Western (mostly long-term).[7]

In a review article by Suzanne et al in 2011, there were four cohort studies that showed 37 pediatric patients developed BE at mean 12.4 years old, mostly caused by GERD. Other 14 studies reported mean age of 9.5 years old. BE was diagnosed approximately 5 years after GERD symptoms detected.[11]

Gender

A study in Mayo Clinic on patients underwent endoscopy at 1976-1989 reported that long-segment BE were found higher in male compared to female. A multicenter study in Italy at 1987-1989, BE ratio in male to female is 2.6.[7]

Ethnicity and geography

Long-segment BE were found higher in Western countries. In a retrospective cohort study of 2100 individuals (37.7% white race, 11.8% black race, and 22.2% hispanic), BE prevalence were 6.1%, 1.6%, and 1.7%, respectively.[7]

Reflux

Around 15-20% adult in US were reported a history of heartburn once a week and 7% among them felt it every day. In GERD patients, 3-7% were found to have BE on endoscopic examination, while it only 1-2% in non-GERD patients. [12] In individuals complaining heartburn twice or more a week, BE were foun in 7 of 378 patients (1.8%) after endoscopic examination. Patients with short-segment BE will have more reflux symptoms.[12]

PATHOPHYSIOLOGY OF BARRETT'S ESOPHAGUS

The main etiology of BE is unknown, but GERD is the main risk factors of the disease. Although not all patients with GERD will developed BE, 3 from 5 BE patients have history of GERD. BE is the major predisposition condition for esophageal adenocarcinoma.[13]

GERD is a serious condition of gastroesophageal reflux (GER). GER occurred when lower esophageal sphingter spontaneously open in several occasion and do not completely closing, so that gastric content would reach to esophagus. GER also known as acid reflux or acid regurgitation because of digestion enzyme follow gastric content during reflux.[13]

In BE, there were metaplasial changes from columnar epithelium to squamous epithelium in distal esophagus. Hiatal hernia, weakness of lower esophageal sphincter, and acid exposure in esophageal is common in BE patients compared to normal population. Researchers hypothize that hiatal hernia and impaired lower esophageal sphincter as the beginning process to develop metaplasia as seen in Figure 1.[7,12,14,15]

There was a direct causal between duration of acid exposure in esophagus and severity of mucosal damage. Increase exposure of acid was among the etiology of mechanical defect in lower esophageal sphincter and also reduce its contraction rhythm. This dysmotility imparted reflux material clearing so that contact time will be increasing.[6,12]

Several experimental data showed that not only gastric acid that damage esophageal mucose but also pepsin. Acid reflux contribute to metaplasia process but not act as the main etiology. Other duodenal materials such as pancreatic enzymes, bile secretion, and lysolechitin were also played an important role in intestinal metaplasia and malignancy process. Pepsin and tripsin damage mucosa by its proteolytic effect. In acidic condition, pepsin and tripsin altered intracellular junction thus lead to epithelial breaks. Bile secretion impaired both cell and intraceullar organ functions. Otherwise, gastric acid is needed to activate several enzymes such as pepsinogen and also enhance bile secretion impact on mucosa. In neutral pH condition, deconjucated bile secretion have more destruction effect compared to conjugated. Deconjugated bil secretion were formerly precipitating in neutral pH condition.[7,12,14]

Inflammation that results from chronic reflux might be a key to the development of BE. Damaged mucosal layer was infiltrated by inflammatory cell, mainly T lymphocyte in metaplasial area.[7,14]

Inflammatory cells infiltration also induce production of reactive oxygen species (ROS). ROS implicated in cell cycle, signal transduction, protein degreadation, and also DNA repair process.[7,14] ROS induce cytokine production that stimulate epithelial proliferation, survival, and also migration. This inflammatory response involving growth factor-β, interleukin-1β, IL-10, IL-4, interferon-γ and TNF-α. This showed that there are specific cytokines reaction to mucosal damaged by reflux.[7,14]

Individual with esophagitis would have acute inflammatory response via Th-1 cell with increasing IL-1β, IL-8 and IFN-γ level. This response was related to common cellular immune response to infection or malignancy. Cytokine Th-2 increase IL-10 and IL-4 and laso related to BE which induce goblet cell metaplasia and mutation in mucin gen in respiratory epithelial cells.[7,14]

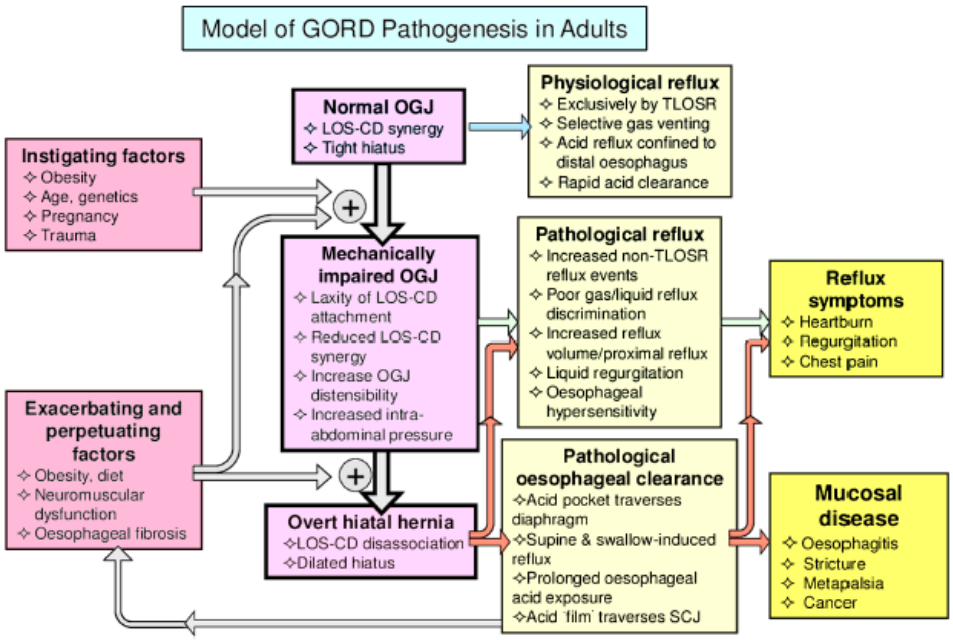

Figure 1. Pathogenesis of GERD to the development of metaplasia (Barrett's esophagus)[15]

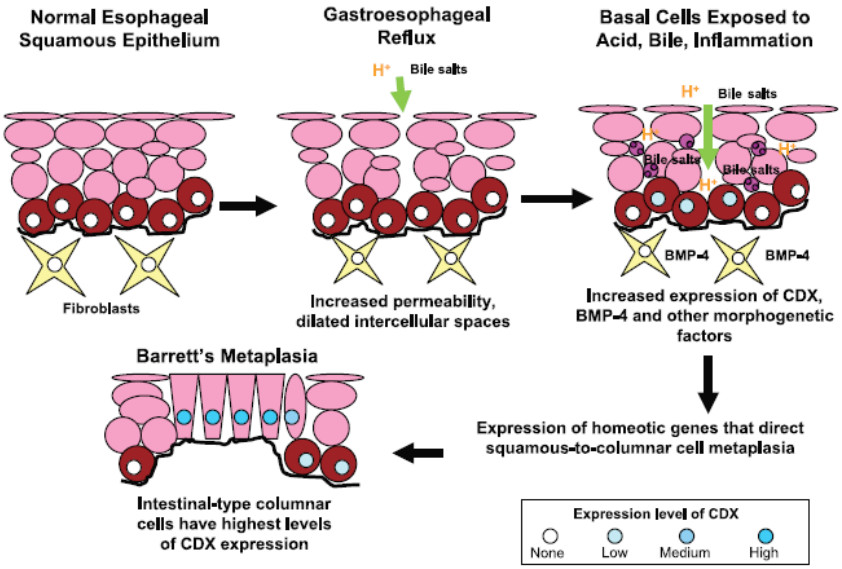

Figure 2. Scheme representing how GERD results in Barrett's esophagus development[16]

In biomolecular area, transformation of squamous epithelium to Barret metaplasia were not fully known, but recent studies showed several key areas involving morphogenic factors and homeobox (HOX) gene which encode transcription factors of intestinal epithelium. BE was a consequence of chronic GERD, so that caudal Homeobox (CDX) gene expression were hypothize as the basic molecular mechanism of the disease pathogenesis, as shown in Figure 2.[16]

Expression of CDX, bone morphogenetic protein (BMP)-4, and other morphogenetic factors in basal cell or stromal cell would mediate metaplastic process from squamous cell into columnar cell, thus BE cell express CDX1 and CDX2 higher than normal cells. Hypothetically, there are two ways how GERD might induce CDX expression: (1) Stimulation from gastric content (acid, bile salt); (2) Inflammation of esophagus (esophagitis).[16]

ENDOSCOPIC CLASSIFICATION OF BARRETT'S ESOPHAGUS

Classification of Barrett's esophagus based on endoscopic and biopsy were divided into three main categories: long-segment, short segment, and cardiac intestinal metaplasia. Previously, Barrett's esophagus only classified based on its segment size (≥ 3 cm or ≤ 3 cm), while cardiac intestinal metaplasia was defined as intestinal metaplasia in gastroesophageal junction. Cut off value of 3 cm were used since 1970 to prevent overdiagnosis if physician fail to recognize gastric herniation during endoscopy procedure. The size of barrett's esophagus do not correlate significantly to risk of adenocarcinoma and do not have clinical importance.[17]

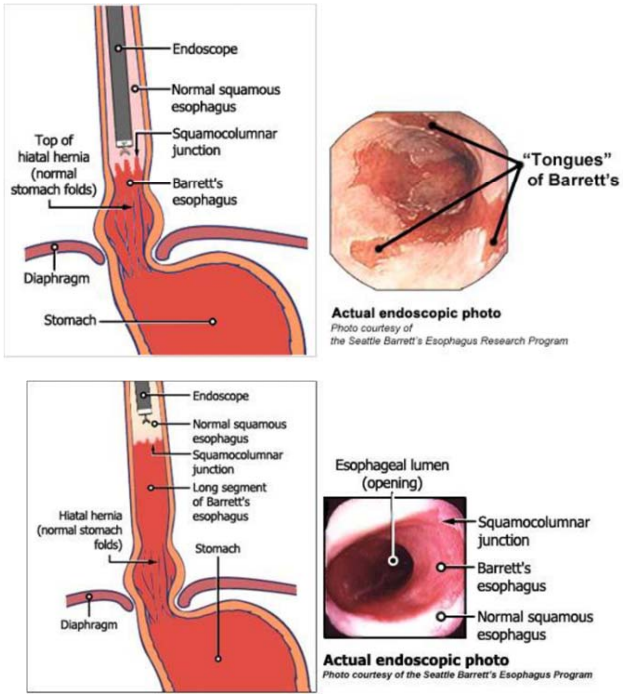

Figure 3. Barret's esophagus[17]

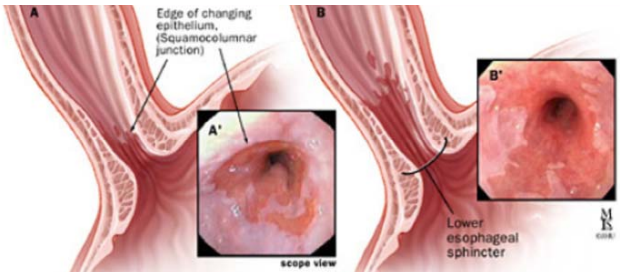

Figure 4. A. Short segment. B Long segment Barret's esophagus. A' B' endoscopic view[17]

Z-line classification were used to know extension of short segment BE during endoscopy. This system also used 3 cm as the cut off to differ between Grade

II and Grade III, but proven to be inaccurate to predict progression or regression of BE. The recent classification, known as Prague criteria C and M, is now being used by clinician. This system use circular diameter (C) and maximum distance (M), as shown in Figure 5 below. [18]

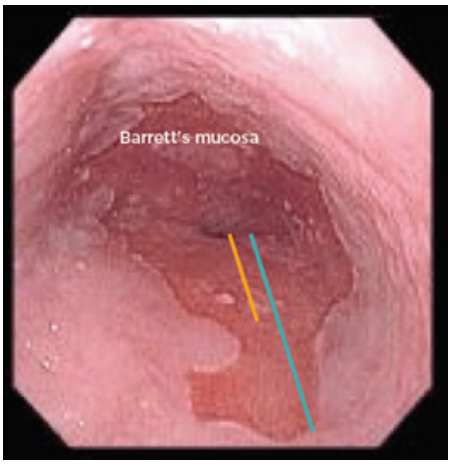

Figure 5. Endoscopic findings showed a salmon-like mucosa with distal extension (suspected of Barrett's esophagus). Prage C (yellow) and M (blue) were estimated to be 2 cm and 4 cm, respectively[18]

Prague C and M were firtly introduced by Sharma et al. This classification was used during endoscopic examination. It has good prediction value when the lesion size is above 1 cm.[18]

CLINICAL MANIFESTATION OF BARRETT'S ESOPHAGUS

Principally, BE is asymptomatic. The most common complaint of BE patients is the symptom of GERD, such as heartburn or regurgitation. It is difficult to differ between BE and GERD only by its symptom. Individuals who had GERD symptoms for more than 5 years were at higher possiblility to develop BE. Therefore, GERD patients with unimproved symptoms for 5 years were recommended to undergo endoscopic examination.[19]

Rex et al (2003) found that almost 8% of BE have a history of heartburn (compared to normal population, 6%), while Ward et al (2006) found 20% and 15%, respectively. In a meta analysis by Cook et al, reflux symptoms were foung in 8-20% of BE patients.[3,19]

DIAGNOSIS OF BARRETT'S ESOPHAGUS

Diagnosis of BE was based on history taking, physical examination, and supporting examination. History taking should be specific to clinical features of BE: heartburn (81%), dysphagia (51%), regurgitation (35%), chest pain, hematemesis, and melena, while 23-40% among them is asymptomatic and 10-19% do not have reflux symptoms.[19] Other risk factors of BE are white race, male, and adult age.[19]

Endoscopy

With only standard endoscopy procedure, it is difficult to distinguish between cancer and precancer lesion. Only 10% of GERD patients who had BE and those individuals need to have routine endoscopic examination to monitor the progression into malignancy lesion. Gold standard of BE diagnosis is upper GI tract endoscopy and recommended only in patients with chronic reflux (above 5 years) or unimproved GERD.[20]

Normally, junctional area between gastric columnar epithelium and esophageal squamous epithelium is found in distal part of esophagus. In BE, this junction is found more proximal so that it is easier to recognize. Other endoscopic examination should to investigate the correlation between its lesion and esophagitis reflux, esophageal ulcer, stricture, hiatal hernia, or nodul/ mass suggestive of malignancy.[21]

Biopsy

In general, BE were consist of three main epithel: 1) columnar (intestinal metaplasia); (2) gastric (gastric epithel); (3) junctional. Although debatable, intestinal metaplasia were considered as gold standard of BE. In these intestinal metaplasia, Goblet cell could be found.[22]

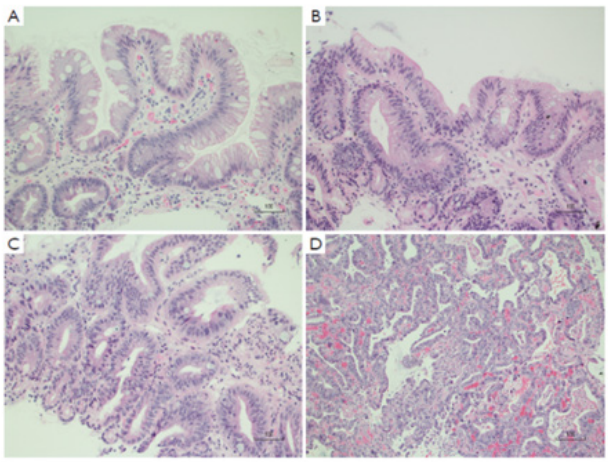

Figure 6. Barrett's esophagus dysplasia/neoplasia[23]

(A) Barrett esophagus, negative for dysplasia. Hematoxylin and Eosin stain ×200;
(B) Barrett esophagus with low grade dysplasia. Hematoxylin and Eosin stain ×200;
(C) Barrett esophagus with high grde dysplasia. Hematoxylin and Eosin stain ×200;
(D) Barrett esophagus with intramucosal adenocarcinoma. Hematoxylin and Eosin stain ×100.

Pathologist played an important role in BE evaluation by examining its dysplasia from biopsy result. Dysplasia was defined as atypical neoplastic epithel. Biopsy result was evaluated according to surface of the glands, atypical cytology, and the presence of inflammation/erosion. There were four main categories of BE: negative for dysplasia (NDS); indefinite for dysplasia (IND); low-grade dysplasia (LGD) and high-grade dysplasia (HGD) as seen in Figure 6.[23]

Negative for dysplasia (NDS): the BE mucosa shows maturation characterized by dark-staining nuclei with stratification at the base of glands as compared to the surface where nuclei are paler, maintain polarity and lack stratification. The cytologic atypia is limited to the basal portion of glands.[23] Indefinite for dysplasia (IND): the BE mucosa shows changes in deeper glands suggestive with dysplasia, however, the surface maturation is preserved. Cytologic atypia includes nuclear hyperchromasia, nuclear membrane irregularities and increased mitosis.[23] Low-grade dysplasia (LGD): the Barrett's mucosa shows loss of surface maturation and distortion with glandular crowding, without active inflammation. There is a difference between neoplastic and non-neoplastic mucosa. Nuclei show hyperchromasia, enlargement, stratification and mucin loss.[23]

High-grade dysplasia: the Barrett's mucosa shows loss of surface maturation (as in LGD) and glandular crowding. The nuclei show loss of polarity and are rounded, enlarged, hyperchromatic with inconspicuous nucleoli. Mitoses are frequent. Inflammation is less in comparison to the architectural and cytologic atypia.[23] Intramucosal adenocarcinoma defined as invasive carcinoma to lamina propria but do not infiltrate to muscularis mucosa layer, presented as single cell and a small group in lamina propria.[23]

Based on American College of Gastroenterology, diagnosis of BE should follow: (1) BE should be diagnosed when there is extension of salmon-colored mucosa into the tubular esophagus extending ≥ 1 cm proximal to the gastroesophageal junction (GEJ) with biopsy confi rmation of IM (strong recommendation, low level of evidence); (2) Endoscopic biopsy should not be performed in the presence of a normal Z line or a Z line with < 1 cm of variability (strong recommendation, low level of evidence); (3) In the presence of BE, the endoscopist should describe the extent of metaplastic change including circumferential and maximal segment length using the Prague classifi cation (conditional recommendation, low level of evidence); (4) The location of the diaphragmatic hiatus, GEJ, and squamocolumnar junction should be reported in the endoscopy report (conditional recommendation, low level of evidence); (5) In patients with suspected BE, at least 8 random biopsies should be obtained to maximize the yield of IM on histology. In patients with short (1–2 cm) segments of suspected BE in whom 8 biopsies may be unobtainable, at least 4 biopsies per cm of circumferential BE, and one biopsy per cm in tongues of BE, should be obtained (conditional recommendation, low level of evidence); (6) In patients with suspected BE and lack of IM on histology, a repeat endoscopy should be considered in 1–2 years of time to rule out BE (conditional recommendation, very low level of evidence).

MANAGEMENT OF BARRETT'S ESOPHAGUS

Three main targets for BE managements are: (1) stop reflux; (2) induce repair or regression of epithel metaplasia in order to prevent risk of metaplasia; (3) inhibit the development of dysplasia and cancer. Most of BE patients were treated using pharmacological treatment, but sometimes it is inadequate due to lower esophageal sphincter dysfunction and impaired esophageal motility function. Medical therapy was based on diet, lifestyle changes, promotility agents, and acid repressing therapy.[20]

Role of PPI in BE Management

PPI do not improve symptoms if BE had present, although it could decrease disease extension. PPI regiment twice a day was allowed with target pH of < 4 in most patients until symptoms were controlled.[3]

Gerson et al reported that reflux severity in BE is worse compared to GERD patients. Yeh et al reported that reflux symptom control using PPI is not effective and 62% among patients had severe gastric acidity during night although it symptoms had been controlled. Gerson et al that investigate using three different PPI found gastric pH < 4 in patients receiving omeprazole, lansoprazole, and rabeprazole are 46%, 71%, and 51%, respectively.[3]

Endoscopic-based Management

Ablation therapy using endoscopy in BE patients were indicated in uncontrolled reflux after medical or surgical treatment. It has been previously reported that ablation therapy is effective in randomized controlled trial.[24] BE management using endoscopy could be classified as using histological examination

(endoscopic mucosal resection [EMR] and endoscopic submucosal dissection) and ablation therapy. Ablation therapy was further classified as heat-generating thermal (Radiofrequency ablation [RFA], multipolar electrocoagulation, and argon plasma coagulation) and photochemical technique (photodynamic therapy [PDT]) and cryotherapy. Multimodality therapy using resection followed by ablation therapy to eradicate Barret's epithel was the most used comprehensive management in BE.[24]

Esophagectomy

Surgical management is among the choice of therapy in BE. During esophagectomy, surgeons resect almost all part of esophagus and only left a small part of gaster. Several risk factors of surgery are bleeding, infection, and dysfunction in esophagus-gaster junction. Because of its high risk, this treatment options is less considered than other treatment. The main benefit of surgical approach is a less further routine endoscopic examination.[24]

EVALUATION AND EDUCATION

How frequent endoscopy should be done were based on patient clinical features. If biopsy results showed "no dysplasia", it could be done annually. If the next biopsy result is "no dysplasia" again, endoscopy could be done once in every three years. A finding of "low grade dysplasia" suggest a medical treatment of GERD and endoscopic reexamination after 6 months. Periodic endoscopic examination was aimed to prevent any undetected lesion due to its small area of presentation.[20] The following table are the time recommendation for endoscopy examination:

Guidelines	NDBE	IND	LGD	HDG
BOB CAT[90]	Not recommended[1]	⩽ 12 mo	6-12 mo	Not recommended
ACPG[57]	< 3 cm 3-5 yr ⩾ 3 cm 2-3 yr	⩽ 6 mo	6 mo	Not recommended
BSG[58]	< 3 cm 3-5 yr ⩾ 3 cm 2-3 yr	⩽ 6 mo	6 mo	Not recommended
ASGE[100]	3-5 yr	No specific time frame	12 mo[2]	3 mo[3]
ACP[101]	3-5 yr	Not recommended	No specific time frame	No specific time frame
AGA[59]	3-5 yr	Not recommended	6-12 mo	3 mo[3]

[1]If undertaken, surveillance should be directed at high-risk groups (*i.e.*, composite risk factors including but not limited to 50 years of age or older, white race, male sex, central obesity, the length of the segment, and the symptom duration, frequency and severity), unless the life expectancy ⩽ 5 yr; [2]Six months to confirm LGD; [3]In the absence of eradication therapy. BOB CAT: Benign Barrett's and Cancer Taskforce; ACPG: Australian Clinical Practice Guidelines; BSG: British Society for Gastroenterology; ASGE: American Society for Gastrointestinal Endoscopy; ACP: American College of Physicians; AGA: American Gastroenterological Association; NDBE: Non-dysplastic Barrett's esophagus; IND: Indefinite for dysplasia; LGD: Low-grade dysplasia; HGD: High-grade dysplasia.

Figure 7. Surveillance table of endoscopic examination in BE[20]

The principle of education in patients with BE are similar to GERD patients. They should avoid fatty foods, alcohol, carbonated drinks, lemon, tomato sauce, mustard, aspirin, and non-steroid anti-inflammatory drugs (NSAID). Patients should also divide its mela portion, avoid eating meals 3 hours before sleep, elevate head for 6 inches when sleeping, lower body weight, and stop smoking. Another lifestyle changes that related to improve lower esophageal sphincter functions are avoidance of chocolate, caffeine, and any type of candies.[24]

COMPLICATION

High-grade dysplasia mostly preceed esophageal cancer. If it is found during endoscopy examination, endoscopic ultrasonography (EUs) is recommended to evaluate its surgical resectability. Although BE is clearly a precancer lesion, only a small proportion of patients develop cancer. Researches are now focus on risk stratification of which BE patients that need routine endoscopic treatment for disease monitoring.[20]

PROGNOSIS

Long standing GERD had been induce cellular changes that lining esophagus in most patients. Risk of adenocarcinoma in BE patients approximately 0.5% every year. Otherwise, the etiology of cancer progression is unknown. Periodic endoscopic examination is recommended in order to find any sign of dysplasia or cancer lesion. Prognosis is mainly based on patient functional condition, risk factors, and early diagnosis and prompt treatment.[25]

CONCLUSION

Barrett's esophagus (BE) is a condition in which columnar epithel replace squamous epithel in distal part of esophagus. Most of the cases were a sequalae of reflux esophagitis that known as the main risk factors of adenocarcinoma. Studies showed that BE patients had long standing GERD symptoms that conversely related to disease progression.

Basically, BE is asymptomatic. Symtpoms found in BE patients were related to GERD, such as heartburn and regurgitation, so that it is difficult to distinguish them. Barium enema are insensitive to detect BE, so

that diagnosis is mainly guided by biopsy via endoscopy.

Three main targets for BE managements are: (1) Stop reflux; (2) Induce repair or regression of epithel metaplasia in order to prevent risk of metaplasia; (3) Inhibit the development of dysplasia and cancer.

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