Diagnosis and Management of Barrett's Esophagus

Adi Wijaya, Dharmika D**, Ari F Syam**, Toar JM Lalisang****

*Department of Internal Medicine, Faculty of Medicine, University of Indonesia/
Dr. Cipto Mangunkusumo General National Hospital
** Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine,
University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital
*** Department of Digestive Surgery, Faculty of Medicine, University of Indonesia/
Dr. Cipto Mangunkusumo General National Hospital

ABSTRACT

Incidence of esophageal adenocarcinoma is increasing in western countries and has poor prognosis due to late diagnosis. Barrett's esophagus is considered as premalignant lesion in which some of squamous epithelium in distal esophagus has been replaced by metaplastic columnar ephithelium. It occurs as complication of longstanding gastroesophageal reflux.

Endoscopic examination is very important for early detection especially in patients with chronic symptoms of gastroesophageal reflux disease (GERD) for more than 5 years. Aggressive antireflux treatment may reduce the risk of esophageal carcinoma. However, no single therapeutic modality had been proven superior compare to others, but until now surgery remains the most popular treatment of choice in the management of Barrett's esophagus.

***Keywords:** Barrett's esophagus,GERD, premalignant lesion, management*

INTRODUCTION

Barrett's esophagus is defined as the presence of squamous stratified epithelium replaced by columnar metaplasia epithelium at least 3 cm distances from distal part of esophagus.[1-13, 15,16] Barret (1950), an English surgeon first introduced it by writing a paper with the title chronic peptic ulcer of the esophagus and esophagitis. The paper discussed some death cases due to ulcer perforation and massive bleeding. It appeared that esophageal ulcer is surrounded by columnar epithelium. He described some cases which are now widely known as Barrett's esophagus.[1]

Data was collected from autopsy revealed approximately 1 million cases of Barrett's esophagus in US. Those patients had never been diagnosed Barrett's esophagus and most of them were treated with antacids. Mean age of the patients was 60 years old, although there were also some children recorded. This disease was twice fold more frequent in men (0.49%) compare to women (0.97%) and rarely found in black population.[2]

Incidence of esophageal adenocarcinoma is increasing in western countries and has poor prognosis due to late diagnosis. Management in early stage was not proven effective, although identification of lesion during observation has better prognosis. Patients with Barrett's esophagus have risk of esophageal carcinoma 30-125 times higher. Thus, better strategy is needed to prevent occurrence of Barrett's esophagus. After diagnosis has been confirmed, the median survival time is less than one year. Less than to 10% of patients had 5-year survival rate although they had been given combination therapy of surgery and chemotherapy.[1-4]

ETIOLOGY

Gastroesophageal reflux disease (GERD) had been recognized as the important etiologic factor of Barrett's esophagus since long time ago. GERD is caused by reflux of gastric acid and also small proportion of bile which passage into lower esophageal sphincter (LES). Reflux occurs due to transient relaxation or weaknesses of LES that cause backflow to esophagus.[1-3,13,14,17,18,28]

Secondary esophagitis due to esophageal reflux disorder is commonly found in western countries where 30% of adolescents suffer from heartburn at least once in a month. About 1/3 of them had been proven to have esophagitis by endoscopy. Forty percent of esophagitis will cure spontaneously, while 50% will be persistent esophagitis and 10% change into severe Barrett's metaplasia.

Esophageal clearance from acid reflux and its volume, the presence of hiatus hernia and intrinsic resistance of esophageal epithelium to reflux substance are the main factors in pathogenesis of GERD and Barrett's esophagus. Suggestion on the role of bile reflux in etiology of Barrett's esophagus was encouraged by conditions that occur in patients with perniciosa anemia, achlorhydrida, and total gastrectomy without biliary diversion. Bile reflux occurs through duodeno-gastroesophageal reflux. Increased concentration of bile acid which can be detected from esophageal aspiration and spectrophotometri analysis of bilirubin in patients with Barrett's esophagus compare to those with GERD and control group.

Congenital origin of Barrett's esophagus and the role of *Helicobacter pylori* as the etiologic factor have never been proven yet. Other etiologic factor is free radicals which produce oxygen resulting from mucosal reaction; for example superoxide anion, H_2O and hydroxyl radicals. Mechanism of columner re-epithelization was more presumed through differentiation of primordial intrinsic stem cell than gastric epithelial migration of the proximal part. The metaplasia process is accelerated by exposure to reflux substance.

DIAGNOSIS

Clinical appearances of Barrett's esophagus are symptoms of heartburn (81%), dysphagia (51%), and regurgitation (35%). However, most patients are asymptomatic (23-40%) and 10-19% have no symptoms of reflux. Approximately 50% patients with Barrett's esophagus have complications of erosive esophagitis (20%), carcinoma (15%), peptic stricture (10%), and ulcer (5%). The discrepancy between clinical symptoms and severity of endoscopic appearance is caused by exposure time of mucosa to acid that make esophageal sensitivity decrease.

Screening examination for Barrett's esophagus

In spite of being rarely used, radiologic appearance may become predictor of Barrett's esophagus such as stricture in proximal part of gastroesophageal border, esophageal ulcer, and the presence of radiological sign of reflux. Radiologic appearances of Barrett's esophagus are:[22]

- deep penetrating ulcer like those seen in gastric ulcer
- concomitant setting with stricture
- stricture without ulcer
- reticular pattern or barium filled space closed to stricture, widen to distal and short à suggestive for Barrett's esophagitis, candidiasis, viral esophagitis or carcinoma.
- sliding hiatus hernia with reflux
- Barrett's ulcer may be separated by hiatus hernia from normal mucosa. It is different from reflux esophagitis which there is no interval of normal mucosa

Manometry is used to measure peristaltic of esophageal and clearance in addition as one of parameter of LES. This evaluation is an important part of pre-operative evaluation to exclude dismotility disorder.

Endoluminal ultrasonography is used to observe epithelial depth of Barrett's esophagus, especially if macroscopic appearance shows normal epithelium. By this examination, it is still difficult to differentiate accurately between high grade dysplasia and carcinoma in situ. Brush cytology is used to observe normal epithelium macroscopically specially in high risk group patients. In a retrospective study on 72 patients revealed that biopsy and brush cytology had not much different significantly. There were 8 from 64 cases in which cytology could identify carcinoma or dysplasia although histologic result was negative.

Fluorescent endoscopy is used to differentiate between normal epithelium, dysplasia, and early malignant changes if epithelial was normal macro scopically. Abnormal epithelium has different fluorescent spectrum and intensity if were activated by light with specific wave length compare to normal epithelium. Screening and biopsy were conducted in abnormal area.[16-20,23,26-28]

When endoscopy is needed?

Barrett's esophagus may produce no symptoms. Symptoms that occur are associated with the presence of GERD such as heartburn or regurgitation. It is difficult to differentiate between patients with GERD who had Barrett's esophagus and those who did not based on severity of symptoms.

Study of serial endoscopy found the odd ratio of Barrett's esophagus in patients with symptoms of GERD more than 5 years was 5:1 compare to symptoms occurred less than 1 year. It is believed that chronic symptoms were more important than severity of

symptoms to predict the presence of Barrett's esophagus. That is why it is recommended to perform screening endoscopy in patients with symptoms of GERD for 5 years or more to exclude Barrett's esophagus. Other studies suggest higher risk of Barrett's esophagus and esophageal adenocarcinoma in patients with GERD were Caucasian, elderly and male gender.

Other reasons to perform endoscopy in patients with chronic GERD symptoms are dysphagia, weight loss with no clear causes, or anemia. These alarm symptoms increase the risk of esophageal adenocarcinoma. Patients with GERD are advised to undergo diagnostic endoscopy if there is no adequate responses to acid suppression therapy with PPI regardless the symptoms are already occur for 5 years or not.

The optimal frequency for surveillance endoscopy could not be explained yet. Analysis study using computer software program and cohort simulation revealed that endoscopy every 2-3 years would give better survival time, but the high cost should be considered furthermore. Endocopy conducted every 5 years could still improve survival time and had cost-effective ratio similar with other prevention measure at clinical practice.

Surveillance examination is performed depends of dysplasia grade. How long is the interval for patients without dysplasia? To answer this question, serial prospective study is conducted involving 5 different centers (table 1). This study indicated that every year, approximately 4-11% patient with Barrett's esophagus were developed to dysplasia. The risk of adenocarcinoma was only 5 (3%) of 150 patients in the follow-up studies in 3rd, 6th - 10th year. This data suggested that it needs surveillance interval for at least 3 years in patients with Barrett's esophagus who had not been detected to have dysplasia (figure 1).

Low grade dysplasia needs follow-up endoscopy and biopsy to exclude cancer. High grade dysplasia needs diagnostic confirmation from pathologist.

Prospective data of low grade dysplasia development to esophageal adenocarcinoma is still very limited. Only 45% of patients with low grade dysplasia had been evaluated with the interval of 1.4-4.3 years. Eight (18%) patients developed cancer during follow-up.

Table1. Esophageal Adenocarcinoma Prospective Development Based on Dysplasia Grade

Dysplasia Grade	Number of Patient	Number of Patient with Cancer	Duration of Follow up (Year)
None	150	5 (3%)	3.6 - 10
Low grade	45	8 (18%)	1.5 - 4.3
High grade	115	32 (28%)	0.2 - 9.5

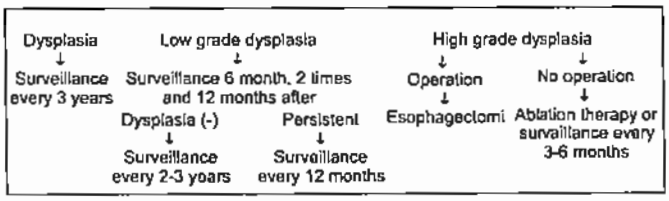
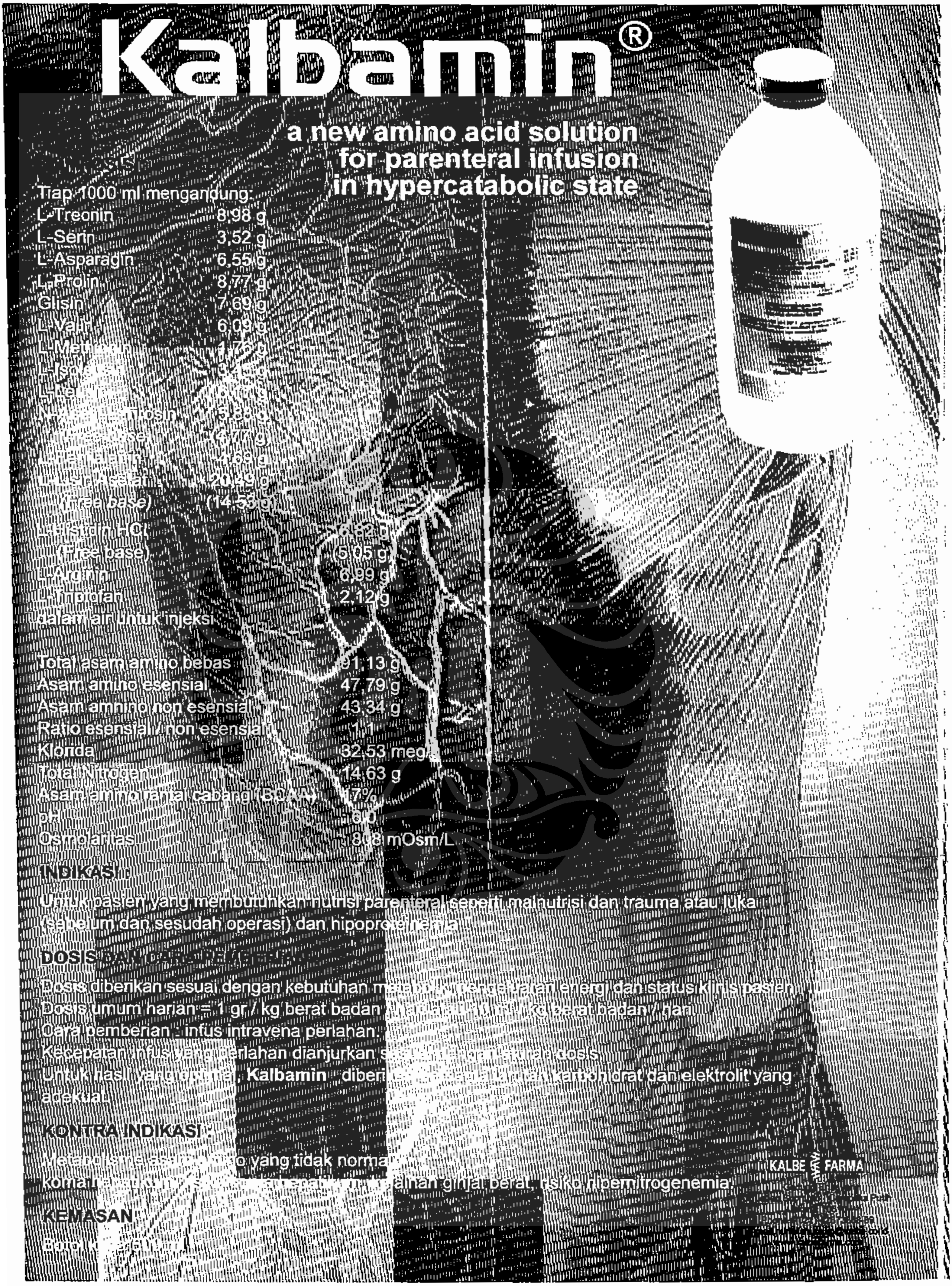


Figure 1. Management algorithm and surveillance of patients with Barrett's esophagus based on dysplasia grade (detected by repeated endoscopic biopsy)

As the consequences of cancer development and sample error, endoscopy was performed after early detection of low grade dysplasia to exclude cancer more accurately. Endoscopy and biopsy are recommended within interval of 6 months during 1 year and repeated after 12 months if dysplasia is not detected. Low grade dysplasia may improve and this is probably caused by cellular atypic reflexion due to changes like inflammation, sample error and resolution. Thus, if dysplasia is not found in 2 years of observation, then next surveillance can be done in 2-3 years. If after 2 years, low grade dysplasia is still detected but not worsening then surveillance should be done every year.

Treatment for patients with high grade dysplasia is still controversial. Some experts believed that patients should undergo esophagectomy due to high risk of developing cancer. On the other hand, some experts had other opinion that endoscopic surveillance would be sufficient. One study reported that aggressive biopsy could differentiate accurately patients with high grade dysplasia and early carcinoma. However, intensive biopsy procedure is not practical for routine examination. Recent study found that biopsy protocol used could not always exclude cancer; for example 4 of 12 patients (mean age was 58 years) with high grade dysplasia found to have cancer on esophagectomy.

Although invasive cancer is excluded when high grade dysplasia is diagnosed, the risk of developing cancer is still high. A prospective serial study indicated that 32 (28%) of 115 patients with high grade dysplasia had developed to adenocarcinoma during 9.5 years of follow-up. This data supported to perform esophagectomy in patients with high grade dysplasia which had proved to have significant regression from time to time. One study reported 27% patients had lower grade of dysplasia or no dysplasia during follow-up observation. In addition, experts reported mean mortality rate of esophagectomy was 3-6% and morbidity 40%. Thus, experts recommended conducting endoscopic surveillance in patients with high grade dysplasia and esophagectomy is performed only in patients who develop cancer. The surveillance is 3-6 months interval. If cancer was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Glisin 7,69 g
L-Valin 6,09 g
(Free base) (4,77 g)
L-Lisin Asetat 20,49 g
(Free base) (14,53 g)
L-Histidin HCl 6,82 g
(Free base) (5,05 g)
L-Arginin 6,99 g
L-Triptofan 2,12 g
dalam air untuk injeksi
Total asam amino bebas 91,13 g
Asam amino esensial 47,79 g
Asam amino non esensial 43,34 g
Ratio esensial / non esensial 1,1
Klorida 32,53 meq
Total Nitrogen 14,63 g
Asam amino rantai cabang (BCAA) 17%
pH 6,0
Osmolaritas 808 mOsm/L
INDIKASI :
Untuk pasien yang membutuhkan nutrisi parenteral seperti malnutrisi dan trauma atau luka (sebelum dan sesudah operasi) dan hipoproteinemia.
DOSIS
Dosis diberikan sesuai dengan kebutuhan
Dosis umum harian = 1 gr / kg berat badan
Cara pemberian : infus intravena perlahan.
Kecepatan infus yang perlahan dianjurkan
Untuk hasil yang optimal, Kalbamin diberi karbohidrat dan elektrolit yang adekuat.
KONTRA INDIKASI :
yang tidak normal
ginjal berat, risiko hipernitrogenemia.
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L-Serin	4,4 g
L-Aspar	5,7 g
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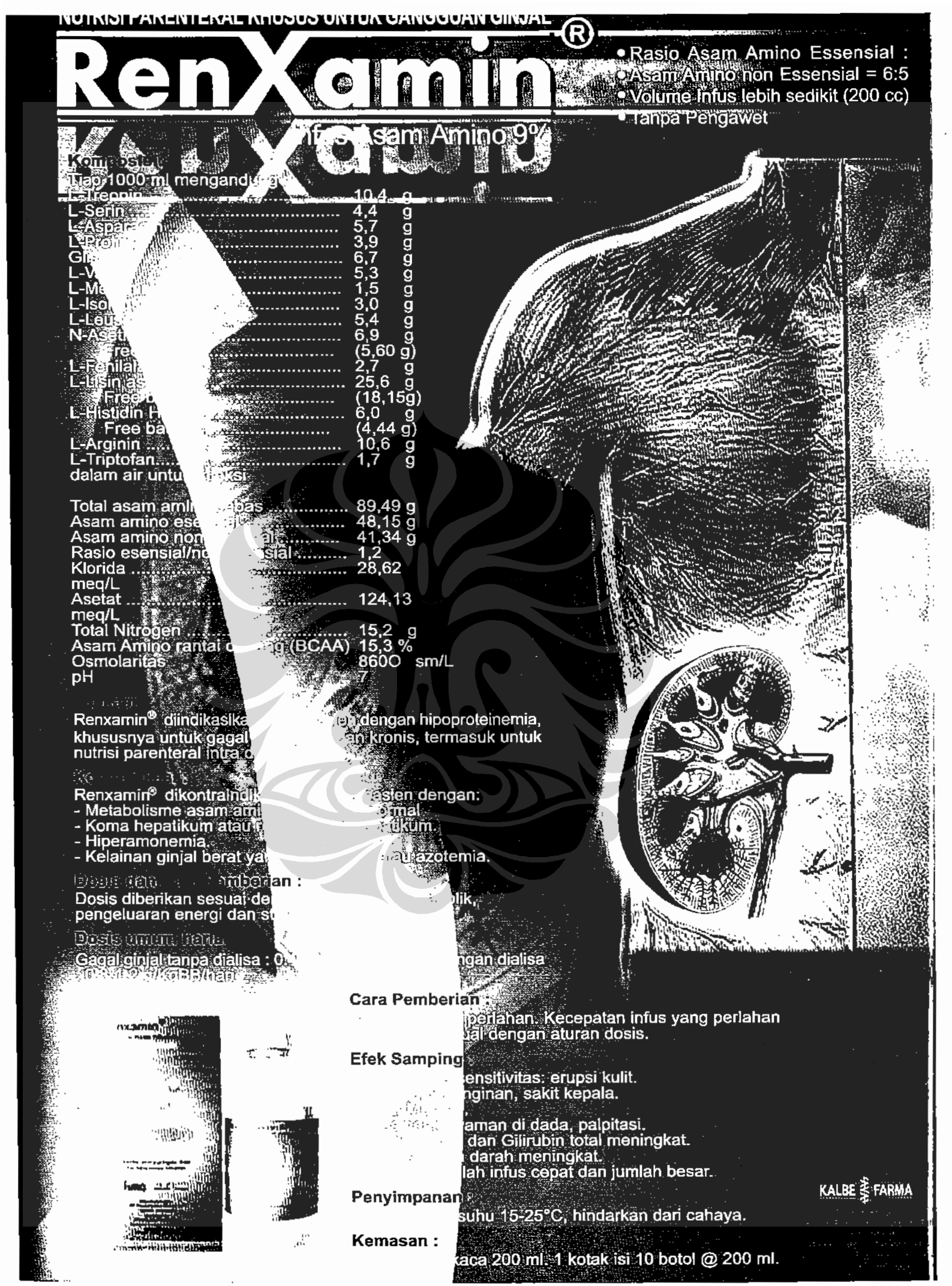
Gl	6,7 g
L-V	5,3 g
L-Me	1,5 g
L-Iso	3,0 g
L-Leu	5,4 g
N-Asetil	6,9 g
fre	(5,60 g)
L-Fenilal	2,7 g
L-Lisin as	25,6 g
Free b	(18,15g)
L-Histidin H	6,0 g
Free ba	(4,44 g)
L-Arginin	10,6 g
L-Triptofan	1,7 g

dalam air untu ksi

Total asam aml bas	89,49 g
Asam amino ese	48,15 g
Asam amino non al	41,34 g
Rasio esensial/no sial	1,2
Klorida meq/L	28,62
Asetat meq/L	124,13
Total Nitrogen	15,2 g
Asam Amino rantai g (BCAA)	15,3 %
Osmolaritas	860O sm/L
pH	7



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Dosis umum dewasa
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kgBB/hari

Cara Pemberian :
perlahan. Kecepatan infus yang perlahan
al dengan aturan dosis.

Efek Samping :
ensitivitas: erupsi kulit.
nginan, sakit kepala.

aman di dada, palpitasi.
dan Gilirubin total meningkat.
darah meningkat.
lah infus cepat dan jumlah besar.

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detected, esophagectomy would be the curative treatment procedure. So far, morbidity and mortality of esophagectomy would be lower in patients with high grade dysplasia who had regression or no changes.

However, clinical data from serial surgery revealed that if esophagectomy was only conducted in patients with high grade dysplasia, then there would be good chance that adenocarcinoma to be identified. Serial examination on patients with high grade dysplasia showed that 50 (41%) of 122 patients with high grade dysplasia and underwent esophagectomy were found of having cancer histopathologically according to biopsy result. A more recent study reported that patients with Barrett's esophagus and found to have adenocarcinoma on resection procedure of high grade dysplasia had better 5-year survival rate compare to those whose cancer was detected outside the surveillance program. The data indicated that if esophagectomy was in high grade dysplasia, cancer would be removed at curative stage. After confirmation of high grade dysplasia by pathology expert, resection surgery by well experienced surgeon and well equipped health facility.

From endoscopy to microscopic examination

Barrett's esophagus is diagnosed histologically. When endoscopy is performed, intestinal metaplasia on the basal segment of red mucosa is highly suggestive of columnar epithelium. However, diagnosis has not been confirmed until histologic examination identifies intestinal metaplasia. The presence of this epithelium suggest high risk of developing carcinoma and should be differentiate from other type of columnar epithelium including the normal junctional type in gastric-cardiac mucosa and normal epithelial type on mucosa of gastric fundus.

Many experts believed that endoscopic surveillance is aimed merely to identify intestinal metaplasia containing goblet cell. Combination of hematoxillin-Eosin-Alcian blue staining at pH gradient of 2.5 is sufficient to identify the presence of goblet cell and intestinal metaplasia.

Predictor of increased risk of cancer[14,16]

Prognosis of esophageal cancer after symptoms is poor with survival time less than and 5-years survival rate less than 10%. That is why it needs early detection of neoplasia in Barrett's esophagus. Recent study focuses on the use of DNA abnormality and P53 mutation as the marker of increased risk of cancer in Barrett's esophagus. Meanwhile, this marker has never been used for clinical practice, but it is a promising marker for cancer surveillance in patients with dysplasia.

Dysplasia that found in Barrett's esophagus indicates the potency to develop invasive adenocarcinoma and on the other hand, the chance to improve survival time. Dysplasia is defined as neoplastic epithelium on basal membrane where it grows. It is classified into low grade or indefinite dysplasia and high grade dysplasia. In low grade dysplasia, the nucleus is big, crowded, hyperchromatic, and might be also stratified, but limited on the lower half of the cell. In high grade dysplasia, there is back-to-back distortion of crypta with cybriform or glands. Abnormality from nucleus until luminal surface of the cell is more clearly seen in low grade dysplasia compare to high grade dysplasia.

The evidence of dysplasia that precede cancer is based on frequent found of high grade dysplasia developing to esophageal adenocarcinoma according to a prospective study. There was hypothesis that adenocarcinoma in Barrett's esophagus occurred through chronic GERD, change of intestinal metaplasia to dysplasia and finally cancer.

MANAGEMENT

Conservative

Management of Barrett's esophagus consists of controlling of symptoms and ideally regression of epithelial metaplasia. Diagnosis only cannot determine surgical therapy but it need long and intensive observation on particular part that potential for malignant transformation.

GERD is the important etiologic factor (bile reflux). Treatment of GERD consists of 3 points:

- supportive therapy is aimed to life style like eat ing habit, especially food which can influence LES tonus
- pharmacologic therapy. This therapy can be classified into symptomatic and definitive therapy. Use of antacids to neutralize gastric acid and sucralfate to increase gastric mucosa defense are the symptomatic one. It is only given for short time. Definitive therapy is given for 4 weeks while maintenance therapy given for 4 weeks. The new method treatment is step down single agent therapy using PPI. For the first 4 weeks, the dose of PPI is twice per day and continued half dose after on the second 4 weeks. Treatment failure may be caused by the failure to prevent duodeno-gastroesophageal reflux. Relapse or patients who refuse conservative treatment with no evidence of high grade dysplasia should be considered for anti-reflux surgery.

Surgery

Principal of the surgery is to improve esophageal hiatus by suturing non-absorbable part and mobilization from gastric fundus using big esophageal bouginage (50 fr). Thus, LES pressure will be improved because of the pressure effect of gastric smooth muscle and extra intrinsic action from LES due to gastric surrounding cover. The length of LES including the intra abdominal parts is reconstructed.

After laparoscopic method was widely known and relapse rate was still high on conservative therapy had made surgical therapy was more popular.

Anti-reflux surgery may cause partial regression of epithelial metaplasia although there was hot debate on determining location and border of squamo-columnar. In addition, columnar epithelium was reported as basal regeneration of squamous epithelium, thus it needs further observation.

Reports on post operative complete regression indicate there was no supporting evidence that anti-reflux surgery can be used as prophylaxis of adenocarcinoma. Bile reflux may be inhibited by duodenal diversion procedure because it can decrease inflammation but does not make regression of metaplasia epithelium.

Laser therapy

Diagnosis of high grade dysplasia is a dilemma whether it indicates high risk esophagectomy, ablation by local endoscopy or observation only. High incidence carcinoma in situ after esophagectomy (50%) had suggested the presence of high grade dysplasia and the need of interventions.

Laser ablation by endoscopy using Nd YAG with concomitant use of high dose proton pump inhibitor (PPI), as matter of fact, it could not make regression of epithelial metaplasia compare to control. However, this finding would not discourage ongoing study regarding combination of reflux surgery and Nd YAG laser ablation.

Other therapy

Plasma coagulation by argon endoscopy had been encourage some studies on regenerating squamous epithelium of Barrett's esophagus and treatment in early stage of upper GI malignancy. This had given alternative therapy of surgery although it would need long time of observation.

Mucosa resection by local endoscopy resulted relapsing rate of 3 - 7% with 5 years survival rate of 95 - 100% and low morbidity. This thing indicated development in the management of Barrett's esophagus.

Photodynamic therapy by endoscopy on high grade dysplasia had encouraged conducting short term studies. Treatment using oral 5-levulanic acid; a photosensitive substance which synthesized endogenously such as sodium porfimer, protoporphirin IX were selected by epithelial dysplasia. This could be detected by fluorescent microscope showed necrosis appearance in dysplasia epithelium induced by laser.

Barr et al, reported squamous epithelial regeneration that occurred after PPI treatment in 5 patients. The presence of non-dysplasia columnar epithelium before epithelial regeneration was found in 2 patients and required further observation.

CONCLUSION

Screening examination, especially endoscopy must be considered in patients who have already symptoms of GERD for more than 5 years, have alarm symptoms of malignancy, and included in higher risk group. However, aggressive anti reflux therapy may reduce risk of cancer in patients with GERD. There had not been adequate evidence that each therapeutic modality had high successful/cure rate, but up to now, surgery remains the most popular treatment of choice.

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