

Guidelines for oesophageal manometry and pH monitoring

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EXECUTIVE SUMMARY & RECOMMENDATIONS

In patients with suspected oesophageal symptoms, flexible endoscopy and/or contrast radiology (eg. barium swallow) should be performed before considering manometric assessment (**Evidence grade C**).

Oesophageal manometry is indicated for the evaluation of dysphagia not definitively diagnosed by means of endoscopy and/or radiology, as manometry is the most accurate method for diagnosing the well-characterised primary oesophageal motility disorders (achalasia and diffuse oesophageal spasm) (**Evidence grade C**).

Oesophageal manometry is the most accurate method for pH electrode placement (**Evidence grade B**).

Acid gastro-oesophageal reflux accounts for a significant proportion of non-specific manometric abnormalities and a therapeutic trial of a proton pump inhibitor is recommended in the initial management of patients with suspected oesophageal symptoms, who have non-specific motility abnormalities identified at manometry (**Evidence grade C**).

Pre-operative oesophageal manometry is of limited value but does prevent anti-reflux surgery in the rare patients who present with clinical features suggestive of acid gastro-oesophageal reflux and have a primary motility disorder, such as achalasia, and is therefore recommended (**Evidence grade C**).

In the absence of locally determined ranges for defining the limits of physiological acid reflux, the following data should be utilised: percentage total time oesophageal pH <4 <5%; percentage upright time oesophageal pH <4 <8%; percentage supine time oesophageal pH <4 <3%; number of episodes pH <4 for >5 minutes <3 (**Evidence grade B**).

Ambulatory oesophageal pH monitoring has clear limitations in defining pathological acid reflux due to false negative studies, but it is the only investigation that provides information on whether patients' symptoms are related to acid reflux. The optimal period for analysis is from two minutes before to the time the event marker on the data logger was pressed (**Evidence grade B**). A measure of the association of the patient's symptoms and acid reflux episodes, such as the symptom index, and the number of symptomatic events, should be included in the report of an ambulatory oesophageal pH study (**Evidence grade C**).

Ambulatory oesophageal pH monitoring has no role in the initial management of patients with symptoms suggestive of acid gastro-oesophageal reflux. A high dose therapeutic trial of a proton pump inhibitor is the diagnostic investigation of choice (**Evidence grade B**). In patients with symptoms suggestive of acid gastro-oesophageal reflux, who fail to respond during a therapeutic trial of a proton pump inhibitor, ambulatory oesophageal pH monitoring on a proton pump inhibitor may be of value to obviate the need for repeated, potentially futile, attempts at dose escalation (**Evidence grade C**).

Chest pain, throat and respiratory symptoms may be due to acid gastro-oesophageal reflux, particularly in patients with heartburn or acid regurgitation and no alternative explana-

tion for their symptoms. A high dose therapeutic trial of a proton pump inhibitor is indicated in such patients (**Evidence grade B**). In patients with throat or respiratory symptoms this trial should be for four months, as a symptomatic response may be delayed (**Evidence grade B**). Ambulatory oesophageal pH monitoring off therapy may be of value to exclude excess acid gastro-oesophageal reflux when this appears unlikely or pH monitoring on a proton pump inhibitor may be of value when there is an inadequate response to a therapeutic trial, to judge whether further dose escalation is appropriate (**Evidence grade C**).

Patients with endoscopic oesophagitis and a good response to a proton pump inhibitor do not require an ambulatory oesophageal pH study prior to anti-reflux surgery. Patients with symptoms suggestive of acid reflux without endoscopic oesophagitis and a good response to a proton pump inhibitor should undergo ambulatory oesophageal pH monitoring off therapy prior to anti-reflux surgery (**Evidence grade C**). Patients with symptoms potentially due to acid reflux who fail to respond to a high dose proton pump inhibitor should undergo ambulatory oesophageal pH monitoring on a proton pump inhibitor prior to anti-reflux surgery and a good correlation between the patient's symptoms and acid reflux episodes, as assessed by the symptom index, established (**Evidence grade C**). Ambulatory oesophageal pH monitoring should be undertaken in patients with persistent symptoms following anti-reflux surgery, particularly if further surgery is planned, to ensure there is evidence of persistent acid reflux and a good correlation between the patient's symptoms and acid reflux episodes (**Evidence grade C**).

Oesophageal manometry and ambulatory oesophageal pH monitoring are associated with minor morbidity, largely vasovagal episodes, discomfort from the catheter and a runny nose, and restrictions affecting diet and activity. Patients with a heart valve replacement or a previous episode of bacterial endocarditis should receive antibiotic prophylaxis (**Evidence grade C**). All patients undergoing oesophageal manometry or ambulatory oesophageal pH monitoring should give written informed consent (**Evidence grade C**).

To ensure high clinical standards in oesophageal function testing, all clinicians undertaking oesophageal manometry or pH monitoring in the United Kingdom should be registered with the Association of Gastrointestinal Physiologists (AGIP) (**Evidence grade C**).

1.0 INTRODUCTION

Oesophageal disorders are among the most common medical conditions. Symptoms of acid gastro-oesophageal reflux affect up to a third of the population in the UK. Oesophageal manometry and ambulatory oesophageal pH monitoring have become established clinical tools in the investigation of oesophageal symptoms. There have been significant developments in this field since the previous guidelines were formulated in 1996, particularly the advent of proton pump inhibitors and increasing awareness of the value of therapeu-

tic trials with these agents. These developments merit a reassessment of the clinical role of oesophageal manometry and ambulatory oesophageal pH monitoring and this is the purpose of these guidelines.

2.0 FORMULATION OF GUIDELINES

These guidelines have been produced in accordance with recommendations of the North of England evidence based guidelines development project.¹ They are based on a Medline literature search using the search terms "oesophageal manometry" and "oesophageal pH monitoring", and on expert opinion and review. The application of oesophageal studies in the paediatric population is considered beyond the scope of these guidelines.

2.1 CATEGORIES OF EVIDENCE

The strength of evidence used to formulate these guidelines was graded according to the following system:

- Ia—Evidence obtained from meta-analysis of randomised controlled trials.
- Ib—Evidence obtained from at least one randomised controlled trial.
- IIa—Evidence obtained from at least one well designed controlled study without randomisation.
- IIb—Evidence obtained from at least one other type of well designed quasi experimental study.
- III—Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case studies.
- IV—Evidence obtained from expert committee reports or opinions, or clinical experiences of respected authorities.

The evidence category is indicated after the citations in the reference section at the end of these guidelines.

2.2 GRADING OF RECOMMENDATIONS

The strength of each recommendation is dependent on the category of evidence supporting it, and is graded according to the following system:

- Grade A—requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency, addressing the specific recommendation (evidence categories Ia, Ib).
- Grade B—requires the availability of clinical studies without randomisation on the topic of recommendation (evidence categories IIa, IIb, III).
- Grade C—requires evidence from expert committee reports or opinions, or clinical experience of respected authorities, in the absence of directly applicable clinical studies of good quality (evidence category IV).

3.0 OESOPHAGEAL MANOMETRY

To perform oesophageal manometry in an accurate and reproducible way, a number of technical requirements must be satisfied. Furthermore, the operation and maintenance of manometric equipment requires technical expertise.

3.1 EQUIPMENT

Oesophageal manometry utilises a system of water-perfused catheters or solid-state transducers to determine pressure profiles for the oesophageal sphincters and oesophageal body muscle. In current UK practice, measurements of oesophageal physiology are confined generally to studies of the function of the oesophageal body and the lower oesophageal sphincter (LOS). Detailed examination of the upper oesophageal sphincter (UOS) or pharyngeal function is not considered part of the standard manometric assessment and requires special expertise.⁽²⁾ The basic hardware required for manometry

comprises a pressure sensing apparatus that detects changes in luminal pressure and converts this to an electrical signal, and a recording device that amplifies and stores this information for subsequent analysis. Manometric results are presented either as hard copy readouts (using ink or thermal writing polygraphs) or via computer-generated reporting using analog to digital conversion and software analysis.

There are two main forms of sensing/transducer device in current use:

Water-perfused catheters coupled to volume-displacement transducers

This type of catheter comprises a bundle of thin plastic tubes each with an outward facing side-hole. There are typically 3-8 pressure-sensing side holes spaced along the length of the catheter and radially orientated, thereby allowing simultaneous measurement of pressures at multiple locations. The tubes are continuously perfused with bubble-free water as a non-compressible medium and the pressure in each tube is monitored by a volume-displacement transducer. Water flow through the side holes is impeded by oesophageal contraction.

Solid-state strain gauges

This type of catheter is composed of a linear arrangement of miniature, solid-state strain gauges spatially and radially orientated along a flexible tube. The signal from each strain gauge provides a direct measure of intraluminal pressure. These catheters are technically easier to use and less cumbersome than traditional water-perfused systems, but are more expensive both to buy and repair. There have been no studies to compare the relative running costs of the two alternative systems. Absolute pressure values and normal ranges obtained with water-perfused versus solid state systems are not identical and the choice of laboratory reference range should reflect the type of catheter assembly.

High Resolution Manometry (HRM)

Miniaturisation of solid state pressure sensors has allowed the development of high resolution manometry (HRM), employing catheters with multiple sensors (up to 36) distributed longitudinally and radially.^(3,4) This allows topographical analyses with the generation of 2- and 3-dimensional contour plots based on simultaneous pressure readings taken at multiple sensors within the sphincters and oesophageal body. These catheters have the potential to reduce the need for re-positioning, thereby shortening the duration of the procedure. Simultaneous assessment of sphincters and body with a single series of swallows is possible with the catheter in a single, fixed position. The increased resolution and better radial information promised by HRM should reduce the problems of asymmetry and artefact inherent in existing systems.^(3,4) This type of equipment is not widely available in the UK and the present guidance relates to traditional water-perfused and solid state catheters.

3.2 PATIENT PREPARATION AND TECHNIQUE

There a number of published guides and reviews dealing with technical aspects of performing oesophageal manometry.^(2,5-12) Equipment should be checked and calibrated before commencing each study. Patients should fast for a minimum of four hours for solids and two hours for liquids prior to the procedure. A longer period of fasting may be appropriate for patients with evidence of fluid or food residues at endoscopy/radiology (eg. in achalasia). Medications known to affect oesophageal motor function should be avoided for 24 hours prior to the test where clinically appropriate (eg. β -blockers, nitrates, calcium channel blockers, anticholinergic drugs, prokinetics, nicotine, caffeine, opiates).⁽²⁾ Any concurrent medication should be recorded.

Local anaesthetic may be used and if so, its use should be documented. A brief history and review of the patient's case records should alert the technician to any contra-indications to performing oesophageal studies (See **Section 5.0**) or to the existence of conditions that may hinder the performance or interpretation of the test (eg. large hiatal hernias, previous oesophageal surgery).

The catheter may be placed via either the trans-nasal or trans-oral route. Once the catheter has been inserted, the patient should be placed in the recumbent position if a water-perfused catheter is used and allowed a period of 5-10 minutes to accommodate to the catheter. Water-perfused systems exhibit an upward shift of pressure baseline when the subject moves into an upright position, such that studies are best performed supine.(8) Although this shift in pressure doesn't occur with solid state systems, many published values for either type of system are based on studies performed in the traditional supine position.(8)

At the beginning of the manometric assessment, one or more (preferably three) of the most distal recording sites should be in the stomach. This can be verified by asking the patient to take a deep breath. Intra-abdominal pressure readings go up with inspiration and down on expiration. Conversely, pressure readings taken within the thoracic cavity go down on inspiration and up on expiration.(8)

The station pull-through technique allows identification of the location and length of the sphincter high pressure zone (HPZ).(2,13-16) The lower oesophageal sphincter (LOS) resting pressure (pressure of HPZ minus intra-gastric pressure) is estimated from the mean of at least three radially orientated ports/transducers. A series of wet swallows (5mL of water) are used to examine LOS relaxation. Alternative methods for determining LOS relaxation and pressure include, respectively, the use of a sleeve sensor (2,10,11,13-26) or a rapid pull-through technique. (2,10,13,15-17,22,27-29) Normal values vary according to the precise technique employed and clinicians should familiarise themselves with their local laboratory protocol and reference values.(**Evidence Grade: B**)

Oesophageal body motility is assessed using several sensors (at least three) positioned 3-5cm apart above the LOS. Both the distal (lower) and proximal (upper) oesophageal body are assessed, using a further series of wet swallows (at least 10 for both upper and lower oesophagus). (30) At least 20-30 seconds should be allowed between swallows as rapid repetitive swallowing inhibits peristalsis.(2,10,31) If peristalsis appears absent, the function of the sensors should be checked by asking the patient to cough. Available data suggest that water swallows provide a more consistent and vigorous peristaltic response than simple saliva swallows, so the latter are not recommended (**Evidence Grade: B**).(32)

3.3 INDICATIONS FOR OESOPHAGEAL MANOMETRY

Oesophageal manometry is the only investigation that enables a precise diagnosis of oesophageal motility disorders, whether primary or secondary to local or systemic disease. However, it should not be used as a first-line investigation for patients with dysphagia or chest pain. Oesophageal manometry is generally undertaken after more routine investigations for oesophageal structural disease (ie. endoscopy and/or contrast radiology). The procedure is reserved for situations where there is diagnostic doubt or where the identification of an oesophageal dysmotility disorder will alter clinical management.

In patients with suspected oesophageal symptoms, we recommend that flexible endoscopy and/or contrast radiology (eg. barium swallow) is performed before considering manometric assessment (**Evidence grade C**). This approach will ensure that significant oesophageal pathology (eg. oesophagitis, oesophageal ulcers or stricturing oesophageal disease) is excluded prior to seeking less common dysmotility disorders.

SUMMARY OF INDICATIONS FOR OESOPHAGEAL MANOMETRY

- 1) To diagnose suspected primary oesophageal motility disorders (eg. achalasia and diffuse oesophageal spasm)
- 2) To diagnose suspected secondary oesophageal motility disorders occurring in association with systemic diseases (eg. systemic sclerosis)
- 3) To guide the accurate placement of pH electrodes for ambulatory pH monitoring studies
- 4) As part of the pre-operative assessment of some patients undergoing anti-reflux procedures
- 5) To reassess oesophageal function in patients who have been treated for a primary oesophageal disorder (eg. sub-optimal clinical response to pneumatic balloon dilatation) or undergone anti-reflux surgery (eg. dysphagia following fundoplication)

The main indications for oesophageal manometry are summarised in **Panel 1 (Evidence Grade C)**. A primary indication for manometry is the evaluation of **dysphagia** not definitively diagnosed by means of endoscopy and/or radiology.(2,6,7,9-12,33-40) Manometry provides the gold standard method for formal diagnosis of the well-characterised primary oesophageal motility disorders (achalasia and diffuse oesophageal spasm).

Hence, manometry may allow formal diagnosis of a primary oesophageal motility disorder in a patient with non-cardiac chest pain and/or dysphagia.(2,6,7,9-12,33-40) However, achalasia and diffuse oesophageal spasm are relatively uncommon conditions and require well-defined manometric criteria for their diagnosis. The significance of other manometric findings, such as hypertensive contractions (including so-called "nutcracker oesophagus") are more controversial. One classification system for oesophageal dysmotility disorders is provided in **Section 3.4**.

There have been many descriptive studies reporting manometric findings in large series of patients referred for manometry.(17,26,41-52) These reports describe findings in subjects with suspected oesophageal symptoms (eg. non-cardiac chest pain, suspected oesophageal pain or dysphagia) and some include data for symptom-free controls.(42-44,46,53,54) Achalasia and diffuse oesophageal spasm appear to be specific disorders that are absent in healthy volunteer groups. Other non-specific motility disorders are reported to be found in a proportion of apparently symptom-free volunteers. The clinical significance of non-specific motility disorders is therefore uncertain. Available data suggest that neither symptom severity nor clinical course correlate closely with non-specific manometric findings(51;55) and these manometric abnormalities may be inconsistent over time.(56)

Blinded therapeutic trials in non-specific motility disorders have shown active treatments may improve manometric parameters but not symptom response,(57) or improve symptoms without detectable changes in manometric parameters.(58) A single controlled trial has reported improvements in both manometry and symptom scores in nutcracker oesophagus using the calcium antagonist, diltiazem.(59) Hence, repeat manometry is not recommended as a routine part of the assessment of patient response to pharmacological treatment of non-specific dysmotility (**Evidence grade: C**)

Manometric assessment of oesophageal function is not recommended in the routine diagnosis of gastro-oesophageal reflux disease (GORD). A wide array of manometric abnormalities has been described in GORD, including dysfunction of the LOS (eg. hypotension,(60) increased transient relaxations(61) or a shorter length(26)) and defective

peristalsis.(62) Such findings are not required for the diagnosis of GORD and do not contribute to management decisions for most patients. Manometry is, however, recommended to guide the placement of pH electrodes in subjects requiring ambulatory monitoring studies (**Evidence grade B**). (5,7,9,10,37,38,63,64)

It is recognised that GORD may account for a significant proportion of non-specific manometric abnormalities. A therapeutic trial of anti-reflux therapy (eg. a proton pump inhibitor) is recommended prior to using less conventional, unlicensed drug treatments in patients with suspected oesophageal symptoms who have non-specific motility abnormalities identified at manometry (**Evidence grade C**). In patients being considered for anti-reflux surgery, the role for pre-operative manometry prior to fundoplication is controversial.(35,36,65-69) There has been concern about a risk of obstructive complications following total fundoplication in patients with impaired oesophageal motor function. Some authorities have considered impaired peristaltic function to be a relative contra-indication to anti-reflux surgery. However, there are conflicting reports on the ability of pre-operative manometry to predict outcomes. Furthermore, improvements in pre-operative peristaltic abnormalities (failed or hypotensive peristalsis) have been demonstrated following fundoplication surgery. Pre-operative manometry does prevent anti-reflux surgery in the rare patients who present with clinical features suggestive of GORD but have a primary motility disorder such as achalasia. Data are insufficient to support a firm recommendation, though our consensus view is that pre-operative manometry is a desirable investigation (**Evidence grade: C**)

3.4 A CLASSIFICATION OF MOTILITY DISORDERS

There is no internationally agreed classification system for the primary oesophageal motility disorders, though one proposed scheme is given in **Panel 2**.(70) A detailed review of the manometric features of these disorders is beyond scope of these guidelines but a brief summary follows:

A CLASSIFICATION OF PRIMARY OESOPHAGEAL MOTILITY DISORDERS

- Inadequate LOS relaxation
 - Achalasia
 - Atypical disorders of LOS relaxation
- Uncoordinated contraction
 - Diffuse oesophageal spasm
- Hypertensive contraction
 - Nutcracker oesophagus
 - Hypertensive LOS
- Hypotensive contraction
 - Ineffective oesophageal motility
 - Hypotensive LOS

Achalasia is the only primary motility disorder for which an underlying pathological process has been well characterised.(34,40,71) Manometric features of achalasia include: (1) Aperistalsis in the oesophageal body – whereby all wet swallows are followed by simultaneous identical contractions (isobaric or “mirror images”). Generally, these contractions are of low amplitude (10-40 mmHg) and may be repetitive. Aperistalsis may occur with normal or increased amplitude contractions in some patients, so-called “vigorous achalasia”; and (2) Abnormal lower oesophageal sphincter relaxation – sphincter relaxation is absent or incomplete with wet swallows in 70-80% of patients with achalasia. In the remainder, relaxations of the LOS are complete to gastric baseline but are of short duration and functionally inadequate. The resting LOS pressure is often high in achalasia (not low) although it can be within the normal range (eg. 10-45 mmHg).

Atypical variants of achalasia are recognised and interpretation of manometry depends on clinical features and the results of other tests (eg. barium radiology). Patients with LOS abnormalities that fail to fully meet manometric criteria for achalasia may be categorised as having an atypical disorder of the LOS. Such patients may have some degree of preserved peristalsis, oesophageal body contractions exceeding 40mmHg and/or seemingly complete relaxation of the LOS but of inadequate duration.

Diffuse oesophageal spasm is characterised manometrically by uncoordinated oesophageal contractions. Published criteria have varied, but a key feature is the finding of simultaneous contractions induced by wet swallows. (34,43,45,70,71) One proposed set of manometric criteria are: (1) Simultaneous contractions associated with >10% of wet swallows and (2) Mean simultaneous contraction amplitude >30mmHg.(70) Other features may occur, including spontaneous contractions, repetitive contractions and multiple-peaked contractions. Normal peristalsis should be present intermittently. Incomplete relaxation of the LOS is not a typical feature.(70)

Other **non-specific disorders of motility** are described in which there is manometric evidence of either ‘hypertensive’ or ‘hypotensive’ oesophageal contraction. The definition and clinical significance of these entities remains controversial.(72) **Nutcracker oesophagus** is a term used to describe hypertensive peristalsis, typically defined as an average distal peristaltic amplitude of >180mmHg.(34,59,70,71,73) **Hypertensive LOS** refers to the finding of elevated resting LOS pressure (eg. >45mmHg).

The finding of weak and/or non-transmitted distal oesophageal contractions has led some authors to suggest a hypotensive category of **ineffective oesophageal motility**.(72) Proposed criteria for this manometric phenomenon are the finding of >30% of swallows associated with low amplitude contractions (eg. Less than 30 mm Hg) at one or more of the distal recording channels in the lower oesophagus. This entity includes low amplitude waves that may be either propagated (peristaltic) or non-propagated (failed peristalsis) or mixtures of the two. Studies involving simultaneous monitoring of bolus transit at the time of manometry, either radiologically or with the emerging technique of intraluminal impedance, are beginning to clarify the functional significance of non-specific disorders.(74)

The term **hypotensive LOS** is used to describe a weak resting LOS. Other non-specific manometric observations include triple-peaked contractions or peristaltic waves of prolonged duration. The functional significance of these findings and their relationship to symptoms are poorly defined at present.

Secondary disturbances of oesophageal motor function occur in association with systemic diseases such as collagen vascular disease (eg. Systemic Sclerosis), diabetes, amyloidosis, Chaga’s disease, multiple sclerosis, alcoholism, hypothyroidism and during ageing.(40)

3.5 RECOMMENDATIONS FOR MANOMETRY REPORTING

This section proposes a minimum dataset for oesophageal manometry reporting, based on elements that are common to many published technical reports.(2,6-8,11,12,34,40,71,75) Many units will produce more detailed reports but the proposed scheme represents a minimum standard.(**Evidence Grade C**)

General information: The report should include patient identification details, the date and timing of the test, the indications for the procedure and a list of current medications. The report should stipulate whether the catheter was placed via the mouth or nares. Details of the type of apparatus should be recorded (ie. type of catheter and recording device). Any medications used during the procedure should be noted. If any technical difficulties were encountered during the proce-

dures, such as patient intolerance or problems with catheter placement or equipment function, these should be recorded.

Lower oesophageal sphincter: The *location* of the upper and lower border of the *high pressure zone* (HPZ) should be noted, as measured from the nares or incisors. This allows calculation of *LOS length*. Data for the baseline *lower oesophageal sphincter (resting) pressure* should be recorded. A maximal resting pressure and/or the mean (+/- range) should be provided. Pressures are measured relative to gastric pressure in millimetres of mercury. It is useful to state if LOS pressures have been measured in relation to respiration (ie. end-expiratory values) or as an average of all pressures.

Information relating to swallow-induced *LOS relaxation* is essential, as assessed by the residual pressure during maximal LOS relaxation. The number and/or percentage of wet swallows accompanied by complete relaxation should be given.

Oesophageal body: Measurements (eg. mean values +/- range) should be provided for the *amplitude* of pressure waves at a number of standard locations within the distal oesophagus. An oesophageal pressure wave is defined as transient elevations of intra-oesophageal pressure of >20 mmHg above the baseline. Values for the percentage of wet swallows that produce (i) normally propagated peristalsis, (ii) failed peristalsis, (iii) simultaneous pressure waves, (iv) low pressure / feeble peristaltic waves (<30 mmHg) and (v) repetitive waves (>3 peaks at a recording site) are noted.

Interpretation: A meaningful *summary* should be provided. There should be a manual review of any automated reports with the aim of providing a clinically interpretable result. A manometric diagnosis should be given where possible, though it is important to emphasise that the final diagnostic formulation for an individual patient should be based on a careful consideration of clinical features, radiological and/or endoscopic findings in addition to the manometric information. Quality radiological studies (standard barium swallow or 'marshmallow' swallow) can provide important information about bolus transit. *Treatment decisions should not be based solely on manometric findings* (**Evidence grade: C**).

4.0 OESOPHAGEAL PH MONITORING

4.1 TECHNICAL ASPECTS OF AMBULATORY OESOPHAGEAL PH MONITORING

pH electrodes

There are two forms of commercial pH electrode – antimony and glass. Antimony electrodes are less expensive, of smaller diameter and are better tolerated but have a shorter operational life. Antimony electrodes have been reported to drift more during recordings and have a less linear response than glass electrodes but appear adequate for clinical purposes. (76,77)

Prior to and following ambulatory oesophageal pH monitoring, a calibration using neutral and acidic buffers should be undertaken with appropriate temperature compensation to ensure the electrode is responsive and has not drifted during the study by more than 0.5 pH units (**Evidence grade C**). (77)

A wireless pH telemetry capsule has recently been developed for ambulatory oesophageal pH monitoring. (78) Two comparative studies with conventional pH electrodes have been published. (79,80) Both studies revealed lower levels of acid exposure with the wireless system compared with catheter-based monitoring. However, detailed analysis has suggested that the discrepancies found largely relate to a fault in the thermal calibration system for the catheter electrode and very similar acid exposure was found when appropriate compensation was made. (79) The National Institute for Health and Clinical Excellence have recently approved wire-

less pH monitoring for clinical use within the United Kingdom. The wireless system has the potential advantage of extended recording up to 48 hours but is also considerably more expensive than catheter-based monitoring, as endoscopy is required to place the pH telemetry capsule. Wireless pH monitoring is of obvious value in patients intolerant of catheter-based monitoring but its wider clinical role remains to be established.

Data loggers

Data loggers should sample pH at least eight times a minute for clinical purposes. (81) Data loggers should include an event marker for patients to record the occurrence of symptoms during the monitoring period.

Electrode positioning

By established convention, the pH electrode is placed 5cm above the manometrically determined upper border of the lower oesophageal sphincter, to prevent the electrode temporarily entering the stomach during the oesophageal shortening associated with swallowing. (82) Simultaneous monitoring of pH at 5 and 10cm above the lower oesophageal sphincter has revealed reduced acid exposure at 10 cm and reduced sensitivity in discriminating between patients with normal and abnormal acid reflux on ambulatory oesophageal pH monitoring. (83)

Alternative methods of pH electrode placement have been described. However, pH step-up, fluoroscopy, endoscopic measurements and body height formulas have all been found to be inferior to manometry (**Evidence grade B**). (84, 85)

Restrictions prior to and during ambulatory oesophageal pH monitoring

If the pH recording is to be carried out in the absence of acid suppressing drugs, proton pump inhibitors should be withdrawn seven days and Histamine H2 antagonists three days before the study. (77) Antacids should not be consumed on the day of the study.

Historically, restrictions on diet, smoking, alcohol and exercise have been imposed during ambulatory oesophageal pH monitoring. Increasing awareness of the importance of correlating symptoms and oesophageal acid exposure has led to such restrictions being abandoned to increase the chance of symptoms occurring during the recording period. However, exclusion of the meal period from the analysis of the pH recording does improve the separation of normal and abnormal oesophageal acid exposure. (86) Patients should therefore complete a diary during oesophageal pH monitoring documenting the timing of meals, symptoms and supine periods.

Duration of ambulatory oesophageal pH monitoring

Poor tolerance of 24-hour ambulatory oesophageal pH monitoring in a minority of patients has led to assessments of shorter recording periods. Unfortunately, published studies have compared a 24-hour recording with a shorter period of the same recording. (87-89) The studies therefore imply that patients should still undergo 24-hour monitoring but that potentially only a shorter period of the recording requires analysis, which is of little clinical value. The reproducibility of ambulatory oesophageal pH monitoring depends on the length of the study (90) and therefore in the absence of true comparative studies, ambulatory oesophageal pH monitoring should be for 24 hours (**Evidence grade C**).

Reproducibility

Intra-subject reproducibility of ambulatory oesophageal pH monitoring has been studied on consecutive (90) or two separate (91) days. 85% of subjects had either a normal or abnormal total time oesophageal pH<4 on both occasions but an individual's total time oesophageal pH<4 could vary by up

to three-fold between studies. (91) Furthermore, a study of simultaneous recordings from two pH electrodes positioned at the same point in the oesophagus revealed surprising discrepancies, even to the point that two out of ten patients changed from having a normal to an abnormal total time oesophageal pH<4. (92)

4.2 INTERPRETATION OF OESOPHAGEAL PH DATA

Criteria for acid reflux event

A fall below pH 4 in oesophageal pH has been conventionally taken to indicate acid reflux. Other pH thresholds have been studied for their ability to discriminate patients with gastro-oesophageal reflux disease (GORD) from asymptomatic controls. (93) Although pH 4 tends to underestimate acid reflux, it is still considered the most appropriate threshold for clinical use. (93) The most accurate method for detecting gastro-oesophageal reflux events, whether they contain acid or not, is oesophageal impedance monitoring. (94) Preliminary experience with impedance monitoring suggests reflux events with a nadir pH between 4 and 7, which are termed weakly acidic reflux events, may be associated with symptoms in patients with persistent reflux symptoms despite a proton pump inhibitor (94) or chronic cough. (95) However, the clinical role of combined pH and impedance monitoring remains to be defined.

Oesophageal pH monitoring variables

A number of variables have been described that have value in discriminating patients with acid reflux symptoms from asymptomatic controls: percentage total time oesophageal pH<4; percentage time upright oesophageal pH<4; percentage time supine oesophageal pH<4; number of episodes oesophageal pH<4; number of episodes oesophageal pH<4 for more than 5 minutes; and the longest single episode oesophageal pH<4. (96) A composite score was developed to express them. It has subsequently been recognised that unlike the other variables the number of episodes oesophageal pH<4 has poor reproducibility. (91) Furthermore, the composite score has no advantage over the simpler percentage total time oesophageal pH<4 in discriminating patients with GORD from asymptomatic controls. (97,98)

It has been suggested that oesophageal pH values of >7 may represent alkaline or duodeno-gastro-oesophageal reflux. (99) However, studies utilising a fiberoptic probe to detect bilirubin found no association between bilirubin reflux and "alkaline" reflux (100) and this variable is of no clinical value.

Oesophageal pH monitoring variables in asymptomatic subjects

Oesophageal pH recordings in asymptomatic subjects have revealed that acid reflux is a normal, physiological occurrence. (96) Attempts have therefore been made to define physiological acid reflux in order to differentiate it from pathological acid reflux associated with acid reflux symptoms with or without endoscopic oesophagitis. Initially, physiological acid reflux was defined as the mean plus two standard deviations of oesophageal pH variables derived from studying asymptomatic subjects. (96) However, it became apparent that pH variables are not normally distributed (98,101) and non-parametric 95% percentiles have subsequently been used to define physiological acid reflux. (102)

In the absence of locally determined ranges for physiological acid reflux, it has been recommended that data from the largest published series are utilised: percentage total time oesophageal pH<4 <5%; percentage upright time oesophageal pH<4 <8%; percentage supine time oesophageal pH<4 <3%; number of episodes pH<4 for >5 minutes <3. (77,102) (**Evidence grade B**).

Oesophageal pH monitoring variables in patients with oesophagitis

Ambulatory oesophageal pH monitoring is both sensitive (>85%) and specific (>90%) in differentiating patients with endoscopic oesophagitis from asymptomatic subjects, using the percentage total time oesophageal pH<4. (97,98,103-105) However, up to a quarter of patients with oesophagitis still had a percentage total time oesophageal pH<4 within the physiological range, emphasising that oesophageal pH monitoring is associated with a significant false negative rate. (103,104) Furthermore, endoscopic evidence of oesophagitis establishes a diagnosis of GORD and ambulatory oesophageal pH monitoring is of no value in this context.

Oesophageal pH monitoring variables in patients with acid reflux symptoms without oesophagitis

Discriminating between patients with acid reflux symptoms without endoscopic oesophagitis and asymptomatic subjects is potentially more clinically relevant. However, although ambulatory oesophageal pH monitoring in this context remains a specific test (>90%), sensitivities of only 0, 61% and 64% due to false negative tests have been reported, limiting its value as a diagnostic test. (103-105).

Analysis of symptoms

Although ambulatory oesophageal pH monitoring has clear limitations in defining pathological acid reflux, it is the only investigation that is able to provide information on whether patients' symptoms are related to episodes of acid reflux. A detailed analysis of different time windows has suggested that the optimal period for analysis is from two minutes before to the time the event marker on the data logger was pressed (**Evidence grade B**). (106)

Symptom index

The symptom index is the number of symptom episodes associated with acid reflux as a percentage of the total number of symptom episodes. (107) Further experience suggested that a symptom index of at least 50% was the optimal threshold. (108) However, the value of the symptom index depends on the number of symptoms during the monitoring period. Few symptoms and frequent acid reflux episodes may lead to a positive symptom index due to a chance association.

Symptom sensitivity index

The symptom sensitivity index was developed in an attempt to account for the limitations of the symptom index. It is defined as the number of acid reflux episodes associated with symptoms as a percentage of the total number of acid reflux episodes. (109) A positive symptom sensitivity index was arbitrarily defined as at least 10%. (109)

Symptom association probability

Neither the symptom index nor the symptom sensitivity index utilise all of the available data to determine the association of symptoms with acid reflux. The symptom association probability is a potentially useful statistical attempt to rectify this. It is calculated by dividing the data into two-minute sections and determining whether acid reflux or symptoms occurred in each section. (110) Fisher's exact test is used to determine whether the distribution of the four possible permutations – symptom and reflux, symptom no reflux, reflux no symptom, no symptom or reflux – occurred by chance. A symptom association probability of >95% is considered positive.

Only the symptom index has been prospectively shown to be of clinical value. A positive symptom index predicted a response to dose escalation in patients poorly responsive to standard dose proton pump inhibitors. (111) It has also been

shown to predict a successful response to a proton pump inhibitor (112) or used as a criterion for successful anti-reflux surgery (113) in patients with acid reflux symptoms without oesophagitis and a percentage total time oesophageal pH < 4 within the physiological range.

4.3 CLINICAL ROLE OF AMBULATORY OESOPHAGEAL PH MONITORING

The indications for ambulatory oesophageal pH monitoring are summarised in panel 3. Patients should be studied after withdrawal of proton pump inhibitors if the purpose of pH monitoring is to exclude excess acid exposure. However, when analysis of the correlation between symptoms and acid exposure is required, the patient should be studied while taking a proton pump inhibitor

INDICATIONS FOR AMBULATORY OESOPHAGEAL PH MONITORING

- 1) Patients with symptoms clinically suggestive of acid gastro-oesophageal reflux, who fail to respond during a high dose therapeutic trial of a proton pump inhibitor (Evidence grade C).
- 2) Patients with symptoms clinically suggestive of acid gastro-oesophageal reflux without oesophagitis or with an unsatisfactory response to a high dose proton pump inhibitor in whom anti-reflux surgery is contemplated (Evidence grade C).
- 3) Patients with persistent acid gastro-oesophageal reflux symptoms despite anti-reflux surgery (Evidence grade C).

Patients with heartburn or acid regurgitation

Ambulatory oesophageal pH monitoring has no role in the initial management of patients with heartburn or acid regurgitation who have evidence of endoscopic oesophagitis, as the diagnosis of GORD has already been established.

A therapeutic trial of a proton pump inhibitor rather than ambulatory oesophageal pH monitoring has become the diagnostic investigation of choice in patients with heartburn or acid regurgitation and no evidence of oesophagitis at endoscopy. (114) (**Evidence grade B**). A therapeutic trial with a proton pump inhibitor is cheaper, less invasive and more readily available than ambulatory oesophageal pH monitoring. (115) Although placebo-controlled therapeutic trials of a proton pump inhibitor in patients with heartburn or acid regurgitation and no oesophagitis are difficult to compare due to differences in trial design, drug dose, length of treatment and patient population, some conclusions can be drawn. High dose proton pump inhibitor trials (e.g. omeprazole 40mg BD) increased sensitivity to more than 80% compared with abnormal ambulatory oesophageal pH monitoring. (116) A seven-day trial appeared sufficient (117) and a symptomatic improvement of at least 75% provided the highest sensitivity compared with ambulatory oesophageal pH monitoring. (115) A one-week high dose proton pump inhibitor trial in routine clinical practice without a placebo, in patients with heartburn or acid regurgitation and no oesophagitis, revealed 97% sensitivity compared with ambulatory oesophageal pH monitoring confirming the value of this approach. (118)

Patients with heartburn or acid regurgitation refractory to medical therapy

Patients who continue to have heartburn or acid regurgitation despite a high dose proton pump inhibitor may benefit from ambulatory oesophageal pH monitoring (**Evidence grade C**). Combined oesophageal and gastric pH monitoring in such patients may reveal persistent gastric acid secretion despite the proton pump inhibitor. (119)

Patients with persistent acid reflux on ambulatory oesophageal pH monitoring and a positive symptom index despite continuing to take omeprazole 20mg BD during pH monitoring, responded to doubling the omeprazole dose but patients with a negative symptom index did not. (111) It could be argued that such patients should simply have their proton pump inhibitor dose increased but assessment of the correlation of symptoms and acid reflux during oesophageal pH monitoring does obviate the need for repeated, potentially futile, attempts at dose escalation.

PATIENTS WITH CHEST PAIN, THROAT OR RESPIRATORY SYMPTOMS

Chest pain

A number of studies have reported that up to 50% of patients with chest pain and unremarkable cardiac investigations have abnormal ambulatory oesophageal pH monitoring and/or a positive symptom association between episodes of chest pain and acid reflux. (120-123) However, many of the patients investigated in these studies had chest pain and typical acid reflux symptoms (120,122) and it is therefore not surprising that many were found to have an abnormal pH study or a positive symptom association.

It has been suggested that patients with chest pain and acid reflux symptoms be treated without further investigation but that patients with chest pain alone should be investigated with ambulatory oesophageal pH monitoring. (124) Although a therapeutic trial of a high dose proton pump inhibitor in patients with chest pain has been reported to have a sensitivity of 78% and a specificity of 86% compared with a diagnosis of GORD by endoscopy or ambulatory oesophageal pH monitoring (125), the vast majority of these patients had acid reflux symptoms. A study of a therapeutic trial of a proton pump inhibitor in patients with chest pain but no acid reflux symptoms has not been undertaken. However, given the cost advantages (125), availability and less invasive nature of a therapeutic trial, it seems logical to recommend this approach in all patients with chest pain and unremarkable cardiac investigations (**Evidence grade C**).

Ambulatory oesophageal pH monitoring should be reserved for patients with chest pain, who fail to respond to a high dose proton pump inhibitor, to judge whether further dose escalation is appropriate. Patients should be studied while taking a proton pump inhibitor. (**Evidence grade C**).

Throat symptoms

Symptoms of throat clearing, soreness, globus and dysphonia may relate to gastro-oesophageal reflux and may be associated with evidence of chronic laryngitis, with erythema, oedema and nodularity on laryngeal examination. (126) Such symptoms and laryngeal signs may improve with treatment with a proton pump inhibitor. (127) Simultaneous ambulatory pH monitoring of the lower oesophagus and pharynx in such patients has been reported to reveal increased pharyngeal but not lower oesophageal acid reflux, compared with patients with GORD without throat symptoms. (128)

However, ascribing throat symptoms and laryngeal abnormalities to gastro-oesophageal reflux has become an area of considerable controversy. A study of asymptomatic volunteers found a high prevalence of laryngeal signs previously attributed to gastro-oesophageal reflux, questioning their clinical value. (129) Two placebo-controlled trials of a high dose proton pump inhibitor in patients with symptoms and signs suggestive of chronic laryngitis failed to show any advantage of active treatment over placebo, as both groups tended to slowly improve with time. (130,131) Unfortunately, pharyngeal pH recordings have been shown to lack sensitivity and to be poorly reproducible, limiting their value. (132) Furthermore, pharyngeal and oesophageal pH monitoring

failed to predict which patients would respond to a proton pump inhibitor in the controlled trials. (130,131)

In patients with throat symptoms and laryngeal signs, particularly with heartburn or acid regurgitation and no obvious alternative explanation for the throat symptoms, it would seem appropriate to undertake a therapeutic trial of a proton pump inhibitor (**Evidence grade C**). Studies suggest this should be high dose and for four months as a symptomatic response may be delayed. (133) Ambulatory oesophageal pH monitoring off therapy may be of value to exclude excess acid gastro-oesophageal reflux when this appears unlikely or pH monitoring on a proton pump inhibitor may be of value when there is an inadequate response to a therapeutic trial to judge whether further dose escalation is appropriate (**Evidence grade C**).

Respiratory symptoms

Diagnostic protocols evaluating patients with chronic cough report abnormal ambulatory oesophageal pH monitoring in a substantial minority despite the absence of heartburn or acid regurgitation in many cases. (134) Ambulatory oesophageal pH monitoring with distal and proximal pH probes in patients with chronic cough reveals a better correlation between distal acid exposure and episodes of coughing, suggesting an oesophagotracheobronchial reflex. (135) Placebo-controlled therapeutic trials of high dose proton pump inhibitors in patients with chronic cough have reported significant improvements in symptom frequency. (136,137). However, the results of ambulatory oesophageal pH monitoring did not predict patients who would respond, as all patients had abnormal pH monitoring results but only a minority responded to a proton pump inhibitor. (136)

Patients with a chronic cough, particularly with heartburn or acid regurgitation and no alternative explanation for their cough, should undergo a therapeutic trial of a proton pump inhibitor (**Evidence grade B**). As with throat symptoms, this should be high dose and for at least two months. (137) Ambulatory oesophageal pH monitoring off therapy may be of value to exclude excess acid gastro-oesophageal reflux when this appears unlikely or pH monitoring on a proton pump inhibitor in patients with cough may be of value when there is an inadequate response to therapy to judge whether further dose escalation is appropriate (**Evidence grade C**).

A temporal relationship between episodes of acid reflux and 50% of episodes of coughing or wheeze has been reported in asthmatics (138). Unfortunately placebo-controlled studies of proton pump inhibitors in patients with asthma and abnormal oesophageal pH monitoring have been too small (139) or too short (140) to show a significant benefit. Uncontrolled data suggests that at least three months high dose therapy is required for an improvement in asthma symptoms and FEV1. (141) Patients with asthma should be managed, as patients with chronic cough, if there is a clinical suspicion of GORD, with a therapeutic trial of a proton pump inhibitor and ambulatory oesophageal pH monitoring on a proton pump inhibitor should be reserved for patients with an inadequate response to therapy, to judge whether further dose escalation is appropriate (**Evidence grade C**).

Patients contemplating anti-reflux surgery

Patients with endoscopic oesophagitis and a good response to a proton pump inhibitor do not require a pre-operative ambulatory oesophageal pH study. (142) Successful surgical series of patients undergoing anti-reflux surgery have used an abnormal total time oesophageal pH<4 or, if this is within the physiological range, a positive symptom index as a selection criterion. (143) An abnormal total time oesophageal pH<4 is also an independent predictor of a good outcome following anti-reflux surgery. (144) Patients with symptoms suggestive of acid reflux but no endoscopic oesophagitis and a good

response to a proton pump inhibitor should therefore undergo pre-operative ambulatory oesophageal pH monitoring off therapy (**Evidence grade C**).

Patients with symptoms potentially due to acid reflux who fail to respond to a high dose proton pump inhibitor should undergo ambulatory oesophageal pH monitoring prior to anti-reflux surgery, since a poor response is an independent predictor of a poor outcome following surgery. (144) (**Evidence grade C**) The pH study should be undertaken while continuing to take a high dose proton pump inhibitor and evidence of persistent acid reflux and a good correlation between the patient's symptoms and acid reflux episodes, as assessed by the symptom index, established.

Ambulatory oesophageal pH monitoring should also be undertaken in patients with persistent heartburn or acid regurgitation following anti-reflux surgery, particularly if further surgery is planned, to ensure there is evidence of persistent acid reflux and a good correlation between the patient's symptoms and acid reflux episodes, as assessed by the symptom index (**Evidence grade C**).

4.4 RECOMMENDATIONS FOR PH MONITORING REPORTING

General information: The report should include patient identification details, the date and timing of the test, and a list of current medications, in particular whether acid suppressing drugs were withdrawn or continued during the study.

Oesophageal acid exposure: percentage total time pH<4; percentage upright time pH<4; percentage supine time pH<4; number of episodes pH<4 for >5 minutes.

Symptom analysis: symptom index and the number of symptomatic events during the study. (**Evidence grade C**).

5.0 CONTRAINDICATIONS TO OESOPHAGEAL MANOMETRY AND PH MONITORING

Oesophageal manometry and pH monitoring should not be performed in cases of suspected or confirmed pharyngeal or upper oesophageal obstruction, in patients with severe coagulopathy (but not anticoagulation within the therapeutic range), bullous disorders of the oesophageal mucosa, cardiac conditions in which vagal stimulation is poorly tolerated, or in individuals who are not able to comply with simple instructions. Patients with peptic strictures, oesophageal ulcers, oesophageal or junctional tumours, varices or large diverticulae are at increased risk of complications from blind oesophageal intubation and such conditions are a relative contra-indication to performing manometry and pH monitoring. There may be special circumstances in which manometry or pH monitoring is indicated in certain of the above categories of patient, in which case special precautions should be considered (eg. endoscopic or radiological guidance). (**Evidence Grade C**).

6.0 MORBIDITY, MORTALITY AND CONSENT

Oesophageal manometry and ambulatory oesophageal pH monitoring are associated with minor morbidity, largely vaso-vagal episodes, discomfort from the catheter and a runny nose, and restrictions affecting diet and activity. (145,146) Theoretically, intubation with a manometric catheter or pH electrode may result in trauma to the nose, pharynx, larynx or oesophagus resulting in bleeding, perforation, vocal cord injury or bronchospasm. However, the occurrence and the frequency of these events have not been documented in the published literature.

Patients with a heart valve replacement or a previous episode of bacterial endocarditis are potentially at risk of bacteraemia during intubation. Although there are no documented cases of bacterial endocarditis following oesophageal manometry or pH monitoring, antibiotic prophylaxis

laxis, as recommended in the British Society of Gastroenterology guidelines for antibiotic prophylaxis in gastrointestinal endoscopy (147), should be given to such patients (**Evidence grade C**).

All patients undergoing oesophageal manometry or ambulatory oesophageal pH monitoring should give written informed consent (**Evidence grade C**). This process should include discussion of the morbidity associated with the procedure and available alternative investigations.

6.0 GOVERNANCE ISSUES

To ensure high clinical standards in oesophageal function testing, all clinicians undertaking oesophageal manometry or pH monitoring in the United Kingdom should be registered with the Association of Gastrointestinal Physiologists (AGIP) (**Evidence grade C**). Units undertaking oesophageal manometry or pH monitoring should be regularly assessed by AGIP to ensure good clinical practice.

7.0 AUDIT

The following topics are suggestions for audit:

Minimum number of procedures per year within a unit performing oesophageal manometry and ambulatory oesophageal pH monitoring should be 100 of each.

Oesophageal manometry and pH monitoring reports should contain the recommended minimum dataset.

Clinicians undertaking oesophageal manometry and ambulatory oesophageal pH monitoring should be registered with the Association of Gastrointestinal Physiologists and their units assessed on a regular basis.

8.0 CONFLICTS OF INTEREST

Both of the authors have received honoraria from manufacturers of proton pump inhibitors for speaker's fees.

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REFERENCES

- Eccles M, Clapp Z, Grimshaw J, *et al*. North of England evidence-based guidelines development project: methods of guidelines development. *Br Med J* 1996;312:760-2. **IV**
- Murray JA, Clouse RE, Conklin JL. Components of the standard oesophageal manometry. *Neurogastroenterol.Motil.* 2003;15:591-606. **IV**
- Pandolfino JE, Ghosh SK, Zhang Q, Jarosz A, Shah N, Kahrilas PJ. Quantifying EGJ morphology and relaxation with high-resolution manometry: a study of 75 asymptomatic volunteers. *Am J Physiol Gastrointest Liver Physiol.* 2006;290(5):G1033-40. **III**
- Ghosh SK, Pandolfino JE, Zhang Q, Jarosz A, Shah N, Kahrilas PJ. Quantifying esophageal peristalsis with high-resolution manometry: a study of 75 asymptomatic volunteers. *Am J Physiol Gastrointest Liver Physiol.* 2006 May;290(5):G988-97. **III**
- SGNA Position Statement: Performance of gastrointestinal manometry studies and provocative testing. *Gastroenterol.Nurs.* 2003;26:264-5. **IV**
- Castell DO, Dieterich L, Castell JA. Esophageal Motility Testing. Denver Colorado: Sandhill Scientific, 2002. **IV**
- Evans DF, Buckton GK, British Society of Gastroenterology CMA. Clinical Measurement in Gastroenterology: The Oesophagus. Oxford: Blackwell Science Ltd, 1999. **IV**
- Gideon RM. Manometry: technical issues. *Gastrointest.Endosc.Clin.N.Am.* 2005;15:243-55. **IV**
- Henderson RD. Esophageal manometry in clinical investigation. New York: Praeger, 1983. **IV**
- Kahrilas PJ, Clouse RE, Hogan WJ. American Gastroenterological Association technical review on the clinical use of esophageal manometry. *Gastroenterology* 1994;107:1865-84. **IV**
- Passarelli S, Zaninotto G, Di Martino N, Leo P, Costantini M, Baldi F. Standards for oesophageal manometry. A position statement from the Gruppo Italiano di Studio Motilità Apparato Digerente (GISMAD). *Dig.Liver Dis.* 2000;32:46-55. **IV**
- Wehrauch TR. Esophageal manometry : methods and clinical practice. Baltimore: Urban & Schwarzenberg, 1981. **IV**
- Greaney MG, Irvin TT, Chattopadhyay DK. The measurement of resting and stimulated lower esophageal sphincter pressure using the rapid pull-through technique of esophageal manometry. *Scand.J.Gastroenterol.* 1978;13:799-806. **III**
- Hay DJ, Goodall RJ, Temple JG. The reproducibility of the station pullthrough technique for measuring lower oesophageal sphincter pressure. *Br.J.Surg.* 1979;66:93-7. **III**
- Staiano A, Clouse RE. Reproducibility of the rapid pull-through technique for categorizing lower esophageal sphincter pressure. *Am.J.Gastroenterol.* 1991;86:1134-7. **III**
- Welch RW, Drake ST. Normal lower esophageal sphincter pressure: a comparison of rapid vs. slow pull-through techniques. *Gastroenterology* 1980;78:1446-51. **IIb**
- Clouse RE, Staiano A. Manometric patterns using esophageal body and lower sphincter characteristics. Findings in 1013 patients. *Dig.Dis.Sci.* 1992;37:289-96. **III**
- Dent J. A new technique for continuous sphincter pressure measurement. *Gastroenterology* 1976;71:263-7. **III**
- Goodall RJ, Hay DJ, Temple JG. Assessment of the rapid pullthrough technique in oesophageal manometry. *Gut* 1980;21:169-73. **III**
- Hananoki M, Haruma K, Tsuga K, Hata J, Sumii K, Kajiyama G. Evaluation of lower oesophageal sphincter pressure using endoscopic manometric sleeve assembly. *J.Gastroenterol.Hepatol.* 2000;15:121-6. **III**
- Lydon SB, Dodds WJ, Hogan WJ, Arndorfer RC. The effect of manometric assembly diameter on intraluminal esophageal pressure recording. *Am.J.Dig.Dis.* 1975;20:968-70. **IIb**
- Radmark T, Pettersson GB. Lower esophageal sphincter pressure in normal individuals and patients with gastroesophageal reflux. A comparison between end-hole and side-hole recording techniques. *Scand.J.Gastroenterol.* 1989;24:842-50. **IIa**
- Richter JE, Wu WC, Johns DN *et al*. Esophageal manometry in 95 healthy adult volunteers. Variability of pressures with age and frequency of "abnormal" contractions. *Dig.Dis.Sci.* 1987;32:583-92. **III**
- Schneider JH, Crookes PF, Becker HD. Four-channel sleeve catheter for prolonged measurement of lower esophageal sphincter pressure. *Dig.Dis.Sci.* 1999;44:2456-61. **III**
- Wilson JA, Pryde A, Cecilia A, Macintyre CC, Heading RC. Normal pharyngo-oesophageal motility. A study of 50 healthy subjects. *Dig.Dis.Sci.* 1989;34:1590-9. **III**
- Zaninotto G, DeMeester TR, Schwizer W, Johansson KE, Cheng SC. The lower esophageal sphincter in health and disease. *Am.J.Surg.* 1988;155:104-11. **III**
- Campos GM, Oberg S, Gastal O *et al*. Manometry of the lower esophageal sphincter: i. *Dig.Dis.Sci.* 2003;48:1057-61. **IV**
- Pettersson GB, Radmark T. The problem of lower esophageal sphincter manometry. An experimental study in vitro. *Scand.J.Gastroenterol.Suppl* 1988;152:17-27. **IIb**
- Radmark T, Pettersson GB. Improved lower esophageal sphincter manometry: application of the end-hole recording technique in vivo. *Scand.J.Gastroenterol.* 1989;24:833-41. **III**
- Dantas RO. Effect of successive swallows on oesophageal motility of normal volunteers, patients with Chagas' disease and patients with idiopathic achalasia. *Neurogastroenterol.Motil.* 2003;15:57-62. **IIa**
- Sifrim D, Janssens J, Vantrappen G. A wave of inhibition precedes primary peristaltic contractions in the human esophagus. *Gastroenterology* 1992;103:876-82. **III**
- Dodds WJ, Hogan WJ, Reid DP, Stewart ET, Arndorfer RC. A comparison between primary oesophageal peristalsis following wet and dry swallows. *J Appl Physiol* 1973;35:851-7. **IIb**
- Adhami T, Shay SS. Esophageal motility in the assessment of esophageal function. *Semin.Thorac.Cardiovasc.Surg.* 2001;13:234-40. **IV**
- Adler DG, Romero Y. Primary esophageal motility disorders. *Mayo Clin.Proc.* 2001;76:195-200. **IV**
- Beckingham IJ, Cariem AK, Bornman PC, Callanan MD, Louw JA. Oesophageal dysmotility is not associated with poor outcome after laparoscopic Nissen fundoplication. *Br.J.Surg.* 1998;85:1290-3. **IIb**
- Booth M, Stratford J, Dehn TC. Preoperative esophageal body motility does not influence the outcome of laparoscopic Nissen fundoplication for gastroesophageal reflux disease. *Dis.Esophagus.* 2002;15:57-60. **IIb**
- Dent J, Holloway RH. Esophageal motility and reflux testing. State-of-the-art and clinical role in the twenty-first century. *Gastroenterol.Clin.North Am.* 1996;25:51-73. **IV**
- Ergun GA, Kahrilas PJ. Clinical applications of esophageal manometry and pH monitoring. *Am.J.Gastroenterol.* 1996;91:1077-89. **IV**
- Feussner H, Kauer W, Siewert JR. The place of esophageal manometry in the diagnosis of dysphagia. *Dysphagia* 1993;8:98-104. **IV**
- Richter JE. Oesophageal motility disorders. *Lancet* 2001;358:823-8. **IV**
- Bak YT, Lorang M, Evans PR, Kellow JE, Jones MP, Smith RC. Predictive value of symptom profiles in patients with suspected oesophageal dysmotility. *Scand.J.Gastroenterol.* 1994;29:392-7. **III**
- Bancewicz J, Osugi H, Marples M. Clinical implications of abnormal oesophageal motility. *Br.J.Surg.* 1987;74:416-9. **III**
- Bassotti G, Pelli MA, Morelli A. Clinical and manometric aspects of diffuse esophageal spasm in a cohort of subjects evaluated for dysphagia and/or chest pain. *Am.J.Med.Sci.* 1990;300:148-51. **III**
- Bassotti G, Pelli MA, Morelli A. Esophageal motor disorders in patients evaluated for dysphagia and/or noncardiac chest pain. *Dysphagia* 1992;7:3-7. **III**
- Dalton CB, Castell DO, Hewson EG, Wu WC, Richter JE. Diffuse esophageal spasm. A rare motility disorder not characterized by high-amplitude contractions. *Dig.Dis.Sci.* 1991;36:1025-8. **III**

46. Ferguson SC, Hodges K, Hersh T, Jinich H. Esophageal Manometry in Patients with Chest Pain and Normal Coronary Arteriogram. *Am.J.Gastroenterol.* 1981;75:124-7. **III**
47. Hewson EG, Dalton CB, Hackshaw BT, Wu WC, Richter JE. The prevalence of abnormal esophageal test results in patients with cardiovascular disease and unexplained chest pain. *Arch.Intern.Med.* 1990;150:965-9. **III**
48. Johnston PW, Johnston BT, Collins BJ, Collins JS, Love AH. Audit of the role of oesophageal manometry in clinical practice. *Gut* 1993;34:1158-61. **III**
49. Katz PO, Dalton CB, Richter JE, Wu WC, Castell DO. Esophageal testing of patients with noncardiac chest pain or dysphagia. Results of three years' experience with 1161 patients. *Ann.Intern.Med.* 1987;106:593-7. **III**
50. Ragnath K, Williams JG. A review of oesophageal manometry testing in a district general hospital. *Postgrad.Med.J.* 2002;78:34-6. **III**
51. Reidel WL, Clouse RE. Variations in clinical presentation of patients with esophageal contraction abnormalities. *Dig.Dis.Sci.* 1985;30:1065-71. **III**
52. Suthahar DR, Malathi S, Vidyathan V et al. Oesophageal manometry in noncardiac chest pain. *Trop.Gastroenterol.* 1994;15:87-97. **III**
53. Traube M, Albibi R, McCallum RW. High-amplitude peristaltic esophageal contractions associated with chest pain. *JAMA* 1983;250:2655-9. **III**
54. Benjamin SB, Richter JE, Cordova CM, Knuff TE, Castell DO. Prospective manometric evaluation with pharmacologic provocation of patients with suspected esophageal motility dysfunction. *Gastroenterology* 1983;84:893-901. **IIb**
55. Achem SR, Crittenden J, Kolts B, Burton L. Long-term clinical and manometric follow-up of patients with nonspecific esophageal motor disorders. *Am.J.Gastroenterol.* 1992;87:825-30. **III**
56. Swift GL, Alban-Davies H, McKirdy H, Lowndes R, Lewis D, Rhodes J. A long-term clinical review of patients with oesophageal pain. *Q.J.Med.* 1991;81:937-44. **III**
57. Richter JE, Dalton CB, Bradley LA, Castell DO. Oral nifedipine in the treatment of noncardiac chest pain in patients with the nutcracker esophagus. *Gastroenterology* 1987;93:21-8. **IIa**
58. Clouse RE, Lustman PJ, Eckert TC, Ferney DM, Griffith LS. Low-dose trazodone for symptomatic patients with esophageal contraction abnormalities. A double-blind, placebo-controlled trial. *Gastroenterology* 1987;92:1027-36. **IIb**
59. Cattau EL, Jr., Castell DO, Johnson DA et al. Diltiazem therapy for symptoms associated with nutcracker esophagus. *Am.J.Gastroenterol.* 1991;86:272-6. **IIb**
60. Cohen S, Harris LD. Does hiatus hernia affect competence of the gastroesophageal sphincter? *N.Engl.J.Med.* 1971;284:1053-6. **III**
61. Dodds WJ, Dent J, Hogan WJ et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. *N.Engl.J.Med.* 1982;307:1547-52. **III**
62. Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A. Esophageal peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 1986;91:897-904. **IIb**
63. An American Gastroenterological Association medical position statement on the clinical use of esophageal manometry. *American Gastroenterological Association. Gastroenterology* 1994;107:1865. **IV**
64. Mones J, Clave P, Mearin F. Esophageal pH monitoring: are you sure that the electrode is properly placed? *Am.J.Gastroenterol.* 2001;96:975-8. **III**
65. Fibbe C, Luyer P, Keller J, Strate U, Emmermann A, Zornig C. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. *Gastroenterology* 2001;121:5-14. **IIb**
66. Heider TR, Behrns KE, Koruda MJ et al. Fundoplication improves disordered esophageal motility. *J.Gastrointest.Surg.* 2003;7:159-63. **III**
67. Mughal MM, Banciewicz J, Marples M. Oesophageal manometry and pH recording does not predict the bad results of Nissen fundoplication. *Br.J.Surg.* 1990;77:43-5. **III**
68. Ortiz EA, Martinez de Haro LF, Parrilla PP, Aguayo Albasini JL, Garcia Marcilla JA, Morales CG. Surgery improves defective oesophageal peristalsis in patients with gastro-oesophageal reflux. *Br.J.Surg.* 1991;78:1095-7. **III**
69. Rydberg L, Ruth M, Lundell L. Does oesophageal motor function improve with time after successful antireflux surgery? Results of a prospective, randomised clinical study. *Gut* 1997;41:82-6. **IIb**
70. Spechler SJ, Castell DO. Classification of oesophageal motility abnormalities. *Gut* 2001;49:145-51. **IV**
71. Kahrilas PJ. Esophageal motility disorders: current concepts of pathogenesis and treatment. *Can.J.Gastroenterol.* 2000;14:221-31. **IV**
72. Leite LP, Johnston BT, Castell DO. Perspectives on Esophageal Manometry: 'Lumpers Versus Splitters'. *Gastroenterology* 1995;109:2053-4. **IV**
73. Achem SR, Kolts BE, Wears R, Burton L, Richter JE. Chest pain associated with nutcracker esophagus: a preliminary study of the role of gastroesophageal reflux. *Am.J.Gastroenterol.* 1993;88:187-92. **III**
74. Tutuian R, Castell DO. Clarification of the esophageal function defect in patients with manometric ineffective esophageal motility: studies using combined impedance-manometry. *Clin Gastroenterol Hepatol.* 2004 Mar;2(3):230-6. **III**
75. Di Lorenzo C, Hillemeier C, Hyman P et al. Manometry studies in children: minimum standards for procedures. *Neurogastroenterol.Motil.* 2002;14:411-20. **IV**
76. McLauchlan G, Rawlings JM, Lucas ML, et al. Electrodes for 24-hour pH monitoring: a comparative study. *Gut* 1987;28:935-939. **III**
77. Galmiche JP, Scarpignato C. Esophageal pH monitoring. Functional evaluation in esophageal disease. *Front. Gastrointest. Res. Basel, Karger,* 1994;22:71-108. **IV**
78. Pandolfino JE, Richter JE, Ours T, et al. Ambulatory esophageal pH monitoring using a wireless system. *Am J Gastroenterol* 2003;98:740-749. **III**
79. Pandolfino JE, Schreiner MA, Lee TJ, et al. Comparison of the Bravo wireless and Digitrapper catheter-based pH monitoring systems for measuring esophageal acid exposure. *Am J Gastroenterol* 2005 ;100 :1466-1476. **IIa**
80. Bruley des Varannes S, Mion F, Ducrotte P, et al. Simultaneous recordings of oesophageal acid exposure with conventional pH monitoring and a wireless system (Bravo®). *Gut* 2005;54:1682-1686. **IIa**
81. Emde C, Garner A, Blum AL. Technical aspects of intraluminal pH-metry in man: current status and recommendations. *Gut* 1987;28:1177-1188. **III**
82. Akglaede K, Funch-Jensen P, Thommesen P. Intra-oesophageal pH probe movement during eating and talking. *Acta Radiologica* 2003;44:131-135. **III**
83. Anggiansah A, Sumboonnanonda K, Wang J, et al. Significantly reduced acid detection at 10 centimeters compared to 5 centimeters above lower esophageal sphincter in patients with acid reflux. *Am J Gastroenterol* 1993;88:842-846. **III**
84. Klausner AG, Schindlbeck NE, Muller-Lissner SA. Esophageal 24-h pH monitoring: is prior manometry necessary for correct positioning of the electrode? *Am J Gastroenterol* 1990;85:1463-1467. **III**
85. Mattox HE, Richter JE, Sinclair JW, et al. Gastro-esophageal pH step-up inaccurately locates proximal border of lower esophageal sphincter. *Dig Dis Sci* 1992;37:1185-1191. **III**
86. Wo JM, Castell DO. Exclusion of meal periods from ambulatory pH monitoring may improve the diagnosis of esophageal acid reflux. *Dig Dis Sci* 1994; 39:1601-1607. **III**
87. Rokkas T, Anggiansah A, Uzoehina E, et al. The role of shorter than 24-H pH monitoring periods in the diagnosis of gastro-oesophageal reflux. *Scand J Gastroenterol* 1986;21:614-620. **III**
88. Ghillebert G, Demeyere AM, Janssens J, et al. How well can quantitative 24-hour intraesophageal pH monitoring distinguish various degrees of reflux disease? *Dig Dis Sci* 1995;40:1317-1324. **III**
89. Arora AS, Murray JA. Streamlining 24-hour pH study for GERD. Use of a 3-hour postprandial test. *Dig Dis Sci* 2003;48:10-15. **III**
90. Johnsson F, Joelsson B. Reproducibility of ambulatory oesophageal pH monitoring. *Gut* 1988;29:886-889. **IIa**
91. Wiener GJ, Morgan TM, Copper JB, et al. Ambulatory 24-hour esophageal pH monitoring - reproducibility and variability of pH parameters. *Dig Dis Sci* 1988;33:1127-1133. **IIa**
92. Murphy DW, Yuan Y, Castell DO. Does the intraesophageal pH probe accurately detect acid reflux? Simultaneous recording with two pH probes in humans. *Dig Dis Sci* 1989;34:649-656. **III**
93. Weusten BLAM, Roelofs JMM, Akkermans LMA, et al. Objective determination of pH thresholds in the analysis of 24h oesophageal pH monitoring. *Eur J Clin Invest* 1996;26:151-158. **IIa**
94. Sifrim D, Blondeau K. Technology insight: the role of impedance testing for esophageal disorders. *Nat Clin pract Gastroenterol Hepatol* 2006;3:210-219. **IV**
95. Sifrim D, Dupont L, Blondeau K, et al. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH and impedance monitoring. *Gut* 2005;54:449-454. **III**
96. Johnson LF, DeMeester TR. Twenty-four hour pH monitoring of the distal esophagus: a quantitative measure of gastroesophageal reflux. *Am J Gastroenterol* 1974;62:325-332. **III**
97. Johnsson F, Joelsson B, Isberg PE. Ambulatory 24 hour intraesophageal pH-monitoring in the diagnosis of gastroesophageal reflux disease. *Gut* 1987;28:1145-1150. **III**
98. Schindlbeck NE, Heinrich C, Konig A. Optimal thresholds, sensitivity and specificity of long-term pH-metry for the detection of gastroesophageal reflux disease. *Gastroenterology* 1987;93:85-90. **III**
99. Pellegrini CA, DeMeester TR, Wernly JA, et al. Alkaline gastroesophageal reflux. *Am J Surg* 1978;135:177-184. **III**
100. Champion G, Richter JE, Vaezi MF, et al. Duodenogastroesophageal reflux: relationship to pH and importance in Barrett's esophagus. *Gastroenterology* 1994;107:747-754. **III**
101. Jamieson JR, Stein HJ, DeMeester TR, et al. Ambulatory 24-H esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity and reproducibility. *Am J Gastroenterol* 1992;87:1102-1111. **III**
102. Richter JE, Bradley LA, DeMeester TR, et al. Normal 24-hr ambulatory esophageal pH values. Influence of study center, pH electrode, age, and gender. *Dig Dis Sci* 1992;37:849-856. **III**
103. Vitale GC, Cheadle WG, Sadek S, et al. Computerized 24-hour ambulatory esophageal pH monitoring and esophagogastroduodenoscopy in the reflux patient. *Ann Surg* 1984;20:724-728. **III**
104. Mattioli S, Pilotti V, Spangaro M, et al. Reliability of 24-hour home esophageal pH monitoring in diagnosis of gastroesophageal reflux. *Dig Dis Sci* 1989;34:71-78. **III**
105. Masclee AAM, De Best ACAM, De Graaf R, et al. Ambulatory 24-hour pH-metry in the diagnosis of gastroesophageal reflux disease. *Scand J Gastroenterol* 1990;25:225-230. **III**

106. Lam HGT, Breumelhof R, Roelofs JMM, et al. What is the optimal time window in symptom analysis of 24-hour esophageal pressure and pH data? *Dig Dis Sci* 1994;39:402-409. **III**
107. Wiener GJ, Richter JE, Copper JB, et al. The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. *Am J Gastroenterol* 1988;83:358-361. **III**
108. Singh S, Richter JE, Bradley LA, et al. The symptom index – differential usefulness in suspected acid-related complaints of heartburn and chest pain. *Dig Dis Sci* 1993;38:1402-1408. **III**
109. Breumelhof R, Smout AJPM. The symptom sensitivity index: a valuable additional parameter in 24-hour esophageal pH recording. *Am J Gastroenterol* 1991;86:160-164. **III**
110. Weusten BLAM, Roelofs JMM, Akkermans LMA, et al. The symptom association probability: an improved method for symptom analysis of 24-hour esophageal pH data. *Gastroenterology* 1994;107:1741-1745. **III**
111. Katzka DA, Paoletti V, Leite I, et al. Prolonged ambulatory pH monitoring in patients with persistent gastroesophageal reflux disease symptoms: testing while on therapy identifies the need for more aggressive anti-reflux therapy. *Am J Gastroenterol* 1996;91:2110-2113. **IIb**
112. Watson RGP, Tham TCK, Johnston BT, et al. Double blind cross-over placebo controlled study of omeprazole in the treatment of patients with reflux symptoms and physiological levels of acid reflux – « the sensitive oesophagus ». *Gut* 1997 ;40 :587-590. **IIb**
113. Booth MI, Strafford J, Thompson E, et al. Laparoscopic antireflux surgery in the treatment of the acid-sensitive oesophagus. *Br J Surg* 2001 ;88 :577-582. **III**
114. Dent J, Brun J, Fendrick AM, et al. An evidence-based appraisal of reflux disease management – the genval workshop report. *Gut* 1999;44(suppl2):S1-S16. **IV**
115. Fass R, Ofman JJ, Gralnek IM, et al. Clinical and economic assessment of the omeprazole test in patients with symptoms suggestive of gastroesophageal reflux disease. *Arch Intern Med* 1999;159:2161-2168. **IIb**
116. Schindlbeck NE, Klausner AG, Voderholzer WA. Empiric therapy for gastroesophageal reflux disease. *Arch Intern Med* 1995;155:1808-1812. **III**
117. Johnsson F, Hatlebakk JG, Klintonberg AC, et al. One-week esomeprazole treatment : an effective confirmatory test in patients with suspected gastroesophageal reflux disease. *Scand J Gastroenterol* 2003;38:354-359. **IIb**
118. Juul-Hansen P, Rydning A. Endoscopy-negative reflux disease: what is the value of a proton pump inhibitor test in everyday practice? *Scand J Gastroenterol* 2003;38:1200-1203. **III**
119. Leite LP, Johnston BT, Just RJ, et al. Persistent acid secretion during omeprazole therapy : a study of gastric acid profiles in patients demonstrating failure of omeprazole therapy. *Am J Gastroenterol* 1996;91:1527-1531. **III**
120. Peters L, Mass L, Petty D, et al. Spontaneous noncardiac chest pain evaluation by 24-hour ambulatory esophageal motility and pH monitoring. *Gastroenterology* 1988;94:878-886. **III**
121. Breumelhof R, Nadorp JHSM, Akkermans LMA, et al. Analysis of 24-hour esophageal pressure and pH data in unselected patients with noncardiac chest pain. *Gastroenterology* 1990;99:1257-1264. **III**
122. Hewson EG, Dalton CB, Richter JE. Comparison of esophageal manometry, provocative testing and ambulatory monitoring in patients with unexplained chest pain. *Dig Dis Sci* 1990;35:302-309. **III**
123. Hewson EG, Sinclair JW, Dalton CB, et al. Twenty-four-hour esophageal pH monitoring: the most useful test for evaluating noncardiac chest pain. *Am J Med* 1991;90:576-583. **III**
124. Klausner AG, Heinrich C, Schindlbeck NE, et al. Is long term esophageal pH monitoring of clinical value? *Am J Gastroenterol* 1989;84:362-366. **III**
125. Fass R, Fennerty MB, Ofman JJ, et al. The clinical and economic value of a short course of omeprazole in patients with noncardiac chest pain. *Gastroenterology* 1998;115:42-49. **IIb**
126. Hanson DG, Conley D, Jiang J, et al. Role of esophageal pH recording in management of chronic laryngitis: an overview. *Ann Otol Rhinol Laryngol* 2000;109:4-9. **IV**
127. Kamel PL, Hanson D, Kahrilas PJ. A prospective trial of omeprazole in the treatment of posterior laryngitis. *Am J Med* 1994;96:321-326. **III**
128. Jacob P, Kahrilas PJ, Herzon G. Proximal esophageal pH-metry in patients with « reflux laryngitis ». *Gastroenterology* 1991;100:305-310. **III**
129. Hicks DM, Ours TM, Abelson TI, et al. The prevalence of hypopharynx findings associated with gastroesophageal reflux in normal volunteers. *J Voice* 2002;16:564-579. **III**
130. Eherer AJ, Haberman W, Hammer HF, et al. Effect of pantoprazole on the course of reflux-associated laryngitis: a placebo-controlled double-blind crossover study. *Scand J Gastroenterol* 2003;38:462-467. **IIb**
131. Vaezi MF, Richter JE, Stasney CR, et al. Treatment of chronic posterior laryngitis with esomeprazole. *Laryngoscope* 2006;116:254-260. **IIb**
132. Vaezi MF, Schroeder PL, Richter JE. Reproducibility of proximal probe pH parameters in 24-hour ambulatory esophageal pH monitoring. *Am J Gastroenterol* 1997;92:825-829. **III**
133. Wo JM, Grist WJ, Gussack G, et al. Empiric trial of high – dose omeprazole in patients with posterior laryngitis: a prospective study. *Am J Gastroenterol* 1997;92:2160-2165. **III**
134. McGarvey LPA, Heaney LG, Lawson JT, et al. Evaluation and outcome of patients with chronic non-productive cough using a comprehensive diagnostic protocol. *Thorax* 1998 ;53 :738-743. **III**
135. Irwin RS, Zawacki JK, Curley FJ, et al. Chronic cough as the sole presenting manifestation of gastroesophageal reflux. *Am Rev Respir Dis* 1989;140:1294-1300. **III**
136. Ours TM, Kavuru MS, Schilz RJ, et al. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. *Am J Gastroenterol* 1999;94:3131-3138. **IIb**
137. Kiljander TO, Salomaa ERM, Hietanen EK, et al. Chronic cough and gastro-oesophageal reflux: a double-blind placebo-controlled study with omeprazole. *Eur Respir J* 2000;16:633-638. **IIb**
138. Avidan B, Sonnenberg A, Schnell TG, et al. Temporal associations between coughing or wheezing and acid reflux. *Gut* 2001;49:767-762. **III**
139. Ford GA, Oliver PS, Prior JS, et al. Omeprazole in the treatment of asthmatics with nocturnal symptoms and gastroesophageal reflux : a placebo-controlled cross-over study. *Postgrad Med J* 1994 ;70 :350-354. **IIb**
140. Kiljander TO, Salomaa ER, Hietanen EK, et al. Gastroesophageal reflux in asthmatics : a double-blind, placebo-controlled crossover study with omeprazole. *Chest* 1999;116:1257-1264. **IIb**
141. Harding SM, Richter JE, Guzzo MR, et al. Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. *Am J Med* 1996;100:395-405. **III**
142. Waring JP, Hunter JG, Oddsottir M, et al. The preoperative evaluation of patients considered for laparoscopic antireflux surgery. *Am J Gastroenterol* 1995;90:35-38. **III**
143. Gotley DC, Smithers BM, Rhodes M, et al. Laparoscopic nissen fundoplication – 200 consecutive cases. *Gut* 1996;38:487-491. **III**
144. Campos GMR, Peters JH, DeMeester T, et al. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. *J Gastrointest Surg* 1999;3:292-300. **III**
145. Fass R, Hell R, Sampliner RE, et al. Effect of ambulatory 24-hour esophageal pH monitoring on reflux-provoking activities. *Dig Dis Sci* 1999;44:2263-2269. **III**
146. Lim PL, Gibbons MJ, Crawford EJ, et al. The effect of lifestyle changes on results of 24-h ambulatory oesophageal pH monitoring. *Eur J Gastroenterol Hepatol* 2000;12:655-656. **III**
147. Antibiotic prophylaxis in gastrointestinal endoscopy. London : British Society of Gastroenterology. 2001. **IV**

These guidelines have been prepared by the British Society of Gastroenterology. They represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability.

