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Keith C. Meyer
Ganesh Raghu *Editors*

Gastroesophageal Reflux and the Lung

Humana Press

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Keith Meyer and Ganesh Raghu dedicate this book to their families.
Keith Meyer to his wife, Emily, and his children, David, Beth, and Melanie; Ganesh Raghu to his parents; his wife and soul mate, Tina; and his children, Shanthi (Peace), Preethi (Love), Raghavendra Amit (Infinity), and Anand (Joy).

Preface

Considerable advances have been made over the past decade in understanding the physiology and pathophysiology of swallowing and foregut function, and a considerable amount of knowledge has accumulated that links swallowing disorders or gastroesophageal reflux (GER) to a variety of upper and lower respiratory tract syndromes and disease. While the processes of swallowing and breathing go unnoticed under normal physiological and anatomical conditions, aberrant foregut function can allow an excessive amount of gastric contents to reflux into the esophagus and induce a number of reflux-associated syndromes should refluxed secretions reach the larynx, pharynx, and airways. Under conditions of normal foregut function, the esophagus would not serve as an escape passage for gastric/foregut secretions and ingested food and/or fluids to reflux when the proximal gastrointestinal tract is functioning normally with intact upper and lower esophageal sphincter function. Significant retropulsion of gastric or gastroduodenal contents (which are usually acidic with low pH but can be weakly acidic or nonacidic and contain bile acids) into the esophagus places individuals at risk for esophageal disorders (e.g., ulceration, Barrett's esophagus) and is commonly recognized as gastroesophageal reflux disease (GERD), a term that is also used when GER is linked to a variety of respiratory syndromes and disorders. In addition to the consequences of excessive (abnormal) GER, the lungs are also at risk for aspiration from above due to disorders of deglutition or when food and fluids back up in the esophagus due to esophageal motility disorders that are often associated with connective tissue disorders.

This book is intended to provide a comprehensive review of current knowledge concerning normal deglutition and foregut digestive processes and examine how abnormalities of swallowing or excessive/abnormal GER can lead to respiratory tract dysfunction and lung disease. The first two chapters provide a review of current knowledge concerning deglutition, foregut function, and GER. Dr. Allen discusses the physiology of normal swallowing mechanisms and the causes and consequences of various abnormalities of deglutition in Chap. 1. As discussed by Dr. Johnston in Chap. 2, what separates benign reflux events from events that can cause esophageal damage and respiratory tract complications is the relative paucity

of such events in normal individuals and the rapid buffering and clearance of refluxed gastric/gastroduodenal secretions from the esophagus that occur in normal, healthy individuals.

Drs. Oelschlager and Auyang provide a review of current, state-of-the-art approaches to the diagnosis of GER and highlight problems and pitfalls in making a secure diagnosis of abnormal GER in Chap. 3. Drs. Spahr and Maguire review current knowledge of the link between GER and lung disorders in children in Chap. 4 and discuss the difficulty faced by pediatricians in determining whether GER, which is relatively common in normal infants and young children, is the cause of a respiratory disorder. Drs. Malo, Knox, and Fass examine foregut dysfunction and GER syndromes on the opposite end of the age spectrum in Chap. 5 and note that hiatal hernias are frequently present in the elderly and that GERD becomes more prevalent and problematic in older individuals.

Chapters 6–11 discuss the link between GER and a spectrum of lower respiratory tract disorders. Drs. Hayat, Yazaki, and Sifrim examine the role of GER in chronic cough and vocal cord dysfunction syndromes in Chap. 6, and Drs. Akkanti and Hanania review current knowledge that links GER to asthma and COPD in Chap. 7. Significant GER is not uncommon during sleep, and Dr. Harding comprehensively examines the link of sleep-related GER to GER symptoms, inefficient sleep, and sleep-disordered breathing in Chap. 8.

GER is increasingly recognized as a major problem in bronchiectasis and interstitial lung disease (ILD), has been linked to airway and parenchymal damage, and may play an important role in driving the destructive processes that occur in these disorders and precipitate disease exacerbations. Dr. Dupont examines the role of acid and nonacid GER in the pathogenesis and progression of bronchiectasis in patients with or without cystic fibrosis, and Drs. Meyer and Raghu discuss the role of esophageal motility disorders and GER in ILD and its increasingly recognized link to the pathogenesis of idiopathic pulmonary fibrosis (IPF). Finally, the importance of GER in lung transplantation and, especially, its role in triggering bronchiolitis obliterans syndrome are discussed by Drs. Meyer and Maloney in Chap. 11.

The last two chapters of the book focus on pharmacologic and surgical therapies for GERD. Dr. Gaumnitz discusses the status of current drug therapies in Chap. 12, and Drs. Hinojosa and Pellegrini examine the various endoscopic and surgical techniques that are now available to prevent reflux from stomach to esophagus in Chap. 13.

We sincerely hope that readers will find the contents of this book to be informative and useful to them in improving their knowledge of the role of GER in upper and lower respiratory tract disorders and assisting them in the management of patients who may have GERD-associated respiratory disease.

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Chapter 1
Deglutition, Swallowing, and Airway Protection: Physiology and Pathophysiology

Jacqui E. Allen

Keywords Deglutition • Dysphagia • Aspiration • Penetration • Upper esophageal sphincter • Lower esophageal sphincter • Gastroesophageal reflux disease • GERD • Laryngeal reflexes • Laryngopharyngeal reflux • Airway protection • Aerodigestive tracts reflexes

Introduction

Deglutition is a complex, patterned motor action that we seldom explicitly consider until dysfunction occurs. Yet problems with deglutition are common and increasing in prevalence in our aging society. Through evolutionary drive, as our larynx has descended, we have developed a unique pharyngolaryngeal anatomy that serves us well in its communication role. Unfortunately as a consequence of laryngeal descent, we now have an intrinsic design fault in that the pathways for respiration and deglutition have become both shared and crossed [1]. This affords the opportunity of misdirection of substances meant for the digestive tract into the airway and can give rise to the most profound and life-threatening problem in deglutition—that of aspiration. To address this, we have developed an intricate system of airway protection and cross talk between the larynx, pharynx, esophagus, and brain that is designed specifically to eliminate or minimize our pulmonary risk. This chapter reviews the physiology of airway protection in relation to deglutition and briefly reviews common problems that may arise when airway protection systems fail.

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Normal Deglutition

The sequence of a normal swallow is often described in phases—oral preparatory, oral propulsive, pharyngeal, and esophageal. Multiple interconnecting neural pathways coordinate these phases to ensure appropriate timing of events and sequential enactment of motor actions. Although intrinsically linked, these phases do demonstrate independence of each other. A central pattern generator in the brainstem integrates sensory information and synchronizes motor output. Swallowing must be coordinated with airway closure and protection, hyolaryngeal elevation, and respiratory reflexes to ensure safety:

1. *Oral preparatory phase*
   Ingested material is reduced by mastication to a lubricated cohesive bolus by alternating actions of the pterygoid, masseter, and temporal muscles. Mastication is important in physical breakdown of ingested substances, allowing early contact with saliva and thus initiation of enzymatic digestion. Mechanical degradation of foodstuffs releases nutrients within the material that may otherwise be inaccessible. A mobile, more homogeneous bolus is created that will be transportable through the pharynx and esophagus. Humans have a diet diverse in texture and composition. This benefits us from a nutrient perspective, but there is also a psycho-emotional aspect to eating. Many social activities revolve around deglutition, and inability to participate can lead to depression, isolation, and poor quality of life. Loss of dentition (and hence reduced efficiency of mastication) can markedly reduce the range of tolerable foods. Patients on altered consistency diets are at risk of dehydration, anorexia due to unpalatable textures or foods, protein malnutrition, and weight loss. A number of factors are considered before dietary changes are recommended including the masticatory ability of the patient (trismus and temporomandibular joint dysfunction), dentition and denture use, labial competence, oral control, tongue function, salivary function, and airway protection.

   Saliva is critical in the preparatory phase as it provides lubrication through mucins; initiates digestion through salivary amylase; acts as a solvent to solubilize tastants; retards microbial attack with immunoglobulin A, lysozyme, and lactoferrin proteins; protects dentition by mineralization of teeth (particularly calcium and phosphate); and provides a mechanical flushing action to remove particles from the gingivobuccal sulci to the mid-oral cavity in preparation for initiation of bolus transport (Table 1.1). Furthermore, it is a key buffering substance providing volume and salivary bicarbonate that is vital in neutralization of gastroesophageal acid. The severe consequences of xerostomia can be appreciated in patients suffering autoimmune diseases such as Sjögren's syndrome or after chemoradiotherapy for head and neck cancer where basal salivary production is markedly diminished (Table 1.1). These patients may exhibit gross dental caries; tooth loss and gingivitis; oral, oropharyngeal, and esophageal candidiasis (Fig. 1.1); halitosis; stomatopyrosis; odynophagia; food intolerance; uncontrolled reflux; esophageal dysmotility; esophageal strictures; weight loss; dysphonia; chronic cough; and pulmonary complications [2].

Table 1.1 Functions of saliva and consequences of xerostomia

Salivary function	Consequences of loss of saliva
Lubrication	Inability to manage food textures, form bolus Odynophagia Globus sensation
Immunologic	Dental caries and early tooth loss Oropharyngeal candidiasis Angular cheilitis Stomatopyrosis
Buffering	Esophageal dysmotility, stricture, globus sensation Enamel loss Dysphonia
Solvent	Loss of taste/dysgeusia Depapillation of tongue Anorexia
Mineralization	Loss of enamel and dentition Increased dental caries
Mechanical flushing	Increased oral debris Gingivitis Inability to form and control bolus

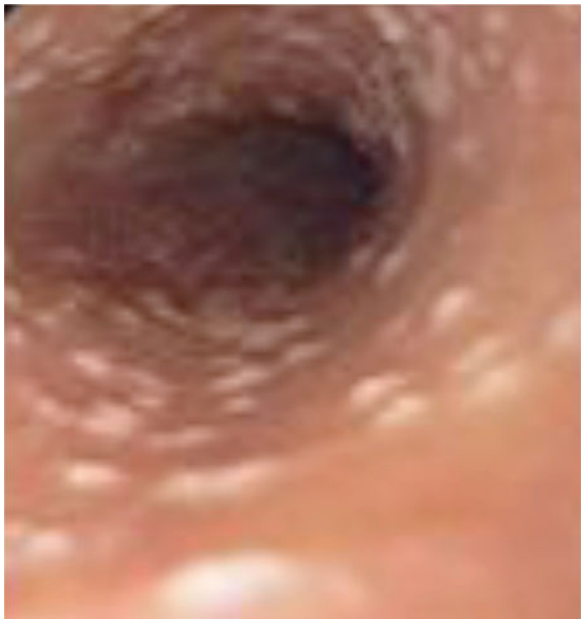

Fig. 1.1 Esophageal candidiasis in xerostomic patient

The oral preparatory phase is under cortical or voluntary control mediated through multiple cranial nerves (trigeminal, facial, glossopharyngeal, vagus, accessory, and hypoglossal) and integrated in the trigeminal (spinal) nucleus and reticular formation (central pattern generator) [3]. During this phase, the bolus may be

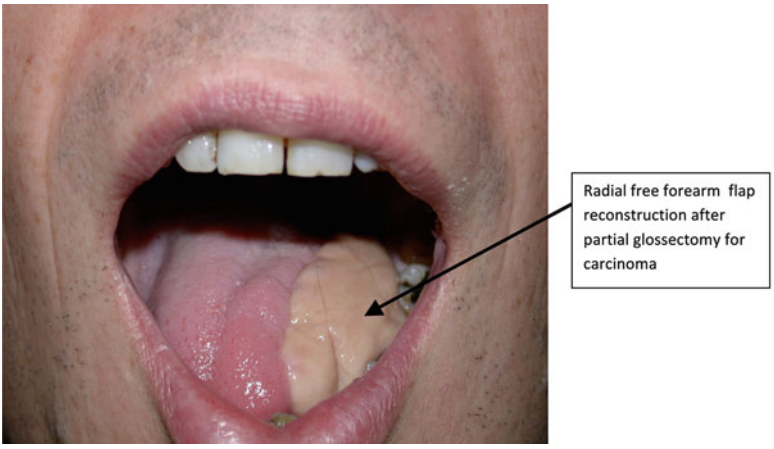

Fig. 1.2 Partial glossectomy defect reconstructed with a radial free forearm flap

voluntarily ejected from the oral cavity. Dysfunction in the oral preparatory phase may be wide ranging. Bolus loss due to labial and oral incompetence; poor bolus formation due to tongue weakness or deformity, xerostomia, lack of dentition, trismus, or temporomandibular joint dysfunction; and intolerance of foods due to hypersensitivity, infection, or mucositis will all affect this phase. Patients may be reluctant to eat due to the increased work or difficulty encountered in this phase. In some cases, simple strategies can be adopted to help such as use of dentures, chewing on one side, lubrication of food, or choice of food textures.

2. *Oral propulsive phase*
   Once the bolus has been formed and assembled on the dorsum of the tongue, there is a short oral propulsive phase that moves it into the oropharynx. Although there is voluntary control initially, the movements are stereotypic and directed by brainstem neuronal networks [3–5]. This marks the transition from voluntary control to involuntary preprogrammed deglutition. The soft palate elevates to close the nasopharynx and acts as a diaphragm against which the tongue can thrust bolus backward and distally into the pharynx. Palatal dysfunction such as seen in cleft palate or postsurgical defects may result in escape of material into the nasopharynx (velopharyngeal incompetence). Tongue wave motion propels the food bolus posteriorly, and the lateral curvature of the tongue margins retains the bolus along the dorsum of the tongue. Poor tongue function such as weakness, loss of bulk, tethering, or scarring (with inability to elevate or loss of sensation) will inhibit bolus control. The tongue may be affected by central neurological conditions such as stroke or Parkinson's disease; peripheral damage by surgery (Fig. 1.2), radiotherapy, trauma, infection, or neoplasia; myopathic disease such as polymyositis; or infiltrative conditions such as amyloidosis or sphingolipidoses.

   The bolus head will begin transfer to the oropharynx prior to initiation of the pharyngeal phase, and the stimulus that is evoked by this transfer is required to fully activate pharyngeal and then esophageal phases [3]. Early spill of the bolus

prior to airway closure can occur, and such an event may be common in the elderly. This may predispose to coughing or aspiration.

3. *Pharyngeal phase*

Once a threshold volume of bolus has been transferred to the pharynx, the pharyngeal phase of swallowing will begin. This always precedes the esophageal phase, and even if a swallow is initiated at the level of the pharynx (bypassing oral phases), the sequence will only continue in a distal (aborad) fashion, i.e., a pharyngeal reflexive swallow can continue to elicit the esophageal phase but cannot activate the oral phase of swallowing.

During this phase, the crucial events occurring are airway closure and elevation, pharyngeal peristalsis, and opening of the pharyngoesophageal segment (PES). Typical pharyngeal transit time is less than 1 s, and therefore timing of events is critical to protection of the airway, with little margin for error [6, 7].

Airway closure is a three-tiered process with vocal fold adduction beginning even as bolus is detected in the oral cavity. Initially the true vocal folds adduct and obliterate the rima glottidis, protecting the distal airway. This is followed by vestibular fold adduction, which partially closes the supraglottic larynx. Finally, epiglottic retroflexion occurs by a combination of hyolaryngeal elevation and tongue base pulsion. The aditus of the larynx is effectively closed, and the bolus is directed laterally via the piriform fossae. Hyolaryngeal elevation results in both an anterior and superior vector of movement which effectively removes the larynx from "harm's way" and assists in opening the PES such that pressure at the PES may even reach subatmospheric levels [6–9]. The larynx elevates approximately 2–3 cm during swallowing. Superior movement occurs first and appears responsible for protecting the airway, while anterior vector motion occurs slightly later and assists in opening (by distraction) the pharyngoesophageal segment [7]. Inspiration is inhibited during this time. With the airway closed, the bolus then traverses the pharynx to the PES and enters the esophagus, initiating the esophageal phase. Pharyngeal peristalsis occurs at a rate of about 15 cm/s and the peristaltic wave clears the bolus to the PES within approximately 1 s. Upper esophageal sphincter (UES) relaxation begins around 0.3 s after suprahyoid muscle contraction and well prior to the bolus arriving at the sphincter [6]. Vocal fold adduction occurs throughout the entire pharyngeal phase. The size of the bolus will affect the duration of hyolaryngeal elevation and UES opening, with larger boluses demanding longer opening duration and longer duration of elevation. A larger bolus also increases the bolus distending pressure at the UES assisting opening of the PES [6].

Impairment of the pharyngeal phase (premature spill, poor laryngeal adductor reflex, weak hyolaryngeal elevation, and pharyngeal residue) or incoordination in UES opening may result in opportunities for material to enter the larynx. If material enters the aditus of the larynx, across a plane running obliquely from the arytenoid peaks to the epiglottic tip, but does not pass through the vocal folds, then penetration has occurred. If material passes through the rima glottidis and is found below the vocal folds, then aspiration has occurred. Both penetration and aspiration may be accompanied by a response (i.e., a cough to clear inhaled

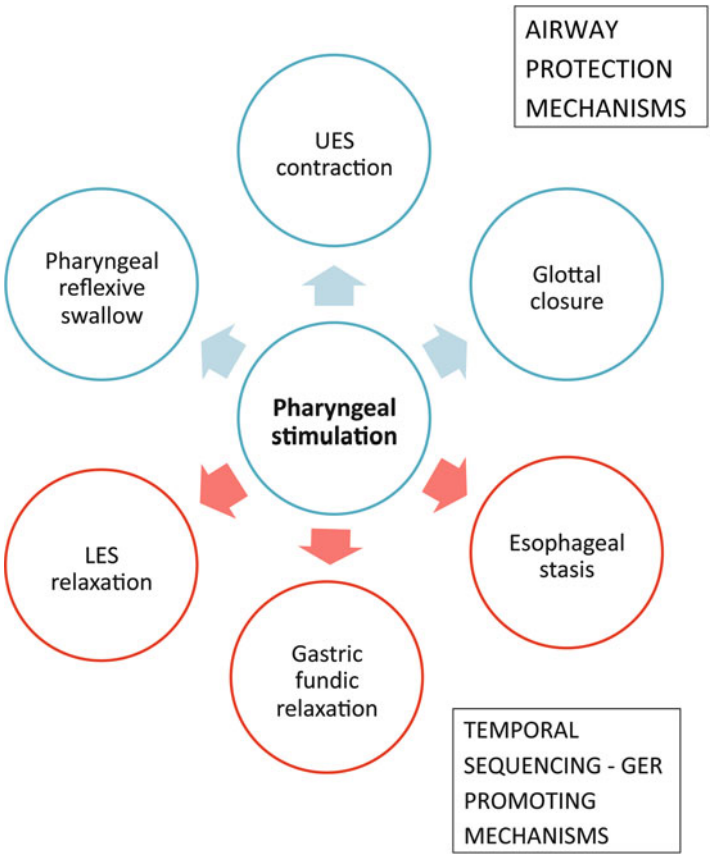

Fig. 1.3 Effects of pharyngeal stimulation on pharynx and esophagogastric region

material), but if a response is not evoked, silent aspiration has occurred. The latter situation presents the greatest pulmonary risk because silent aspiration may be difficult to detect clinically; the patient is unaware that an aspiration event has occurred and thus does not make an attempt to clear or protect the airway. Pneumonia, pneumonitis, bronchiectasis, lung abscess, pulmonary fibrosis, and poor gas exchange may result, particularly if aspiration is chronic. Investigators have shown that changes occur in the pharyngeal phase with aging and disease [6, 7]. Hyolaryngeal elevation duration is shorter and excursion is less in elderly subjects compared to young subjects [7]. Outlet obstruction at the PES due to noncompliance, stricture, or hypertrophy of the muscle (a cricopharyngeal bar) can cause proximal pharyngeal dilation and weakness with loss of bolus pressure [10]. Some patients may compensate by increasing hyolaryngeal elevation or pharyngeal pressures to enhance transphincteric flow. In others however, increased pharyngeal pressure may result in formation of a pulsion pseudodiverticulum (Zenker diverticulum), leading to bolus trapping in the pouch and late regurgitation (Fig. 1.3) [11].

Afferent neural information from the pharynx is primarily transmitted via the pharyngeal and superior laryngeal branches of the vagus nerve. Sensory function is critical, as it provokes reflex airway protection and a cascade of motor responses including propagation of the swallow. The vagal afferents synapse and converge at the nucleus tractus solitarius (NTS) (interstitial and intermediate subnuclei) in the medulla. Interneurons project to reticular formation neurons and then to the motor neurons (MN) in the nucleus ambiguus (NA) (semicompact and loose nuclei) with efferent output again via vagal branches (pharyngeal plexus, recurrent laryngeal nerve) [3–5]. Activation of neurons in the dorsal motor nucleus (DMN) of the vagus (DMNV) is also seen. As these are small neurons, it has been hypothesized that these may be inhibitory neurons that mediate deglutitive inhibition (see below) and esophageal inhibition when pharyngeal swallow is first initiated in order to maintain appropriate phase sequencing [3].

The pharyngeal phase of swallowing is usually initiated by primary peristalsis from a swallow originating in the oral cavity. However, it is possible to trigger a swallow starting within the pharynx alone. This is termed a reflexive pharyngeal swallow (RPS) and may be stimulated by a small amount of water instilled in the hypopharynx or by mechanical stimulation [3, 8]. It is thought to be a protective mechanism that serves to clear residue from the pharynx (whether it arrives in an antegrade or retrograde manner) to close the airway by stimulating the swallow sequence.

4. *Esophageal phase*

The esophageal phase is triggered by arrival of bolus at the esophagus and is thought to be a distention-mediated effect, although this may not be the only stimulus able to trigger esophageal contraction. Traditionally there has been a belief that two types of peristalsis occur in the esophagus. Primary esophageal peristalsis consists of a contraction that follows an ordinarily transmitted swallow, and secondary peristalsis is a contraction initiated within the esophagus itself due to distention from retained or refluxed content. More recent studies have suggested that this is not the case [3]. After a regular deglutitive sequence has been initiated orally, if the bolus is diverted from the pharynx before esophageal contact is made, then no esophageal peristalsis occurs [3]. Therefore, although the pharyngeal and esophageal phases are coupled, they are also independent in their onset and cannot be triggered solely by the swallow central pattern generator. The peristaltic wave travels sequentially in an orad direction with simultaneous activation of the circular and longitudinal muscle layers of the esophagus, with relaxation in front of the bolus and contraction behind it. Longitudinal muscle shortening elevates the gastroesophageal junction through the diaphragmatic hiatus, and circular muscle contraction thickens the esophageal wall behind the bolus, thereby increasing bolus propulsion. The peristaltic wave is propagated through *both* striated and smooth muscle components of the esophagus in an uninterrupted fashion, although amplitude of the wave is lowest at the transition zone. Specialized myogenic adaptations within the esophageal muscle have been noted that support a peripheral mechanism for peristalsis, but discussion of these are outside the scope of this chapter [6].

Afferent information from the esophagus travels in vagal fibers to the NTS (central subnucleus). The central subnucleus of the NTS (NTS_{cen}) houses

esophageal premotor neurons (PMN) that project directly to the NA (compacta). Additionally there are third-order projections to other subnuclei in the NTS (intermedius and interstitial nuclei have been demonstrated), which most likely coordinate swallow phases and interaction with the respiratory system. Efferent output relayed to the (striated) esophagus arises in the NA (compacta) and is augmented by DMNV outflow (for smooth muscle) [3–5]. The DMN projects both excitatory and inhibitory neurons to the esophageal smooth muscle and the lower esophageal sphincter. Appropriate timing of contraction of distal smooth muscle is required to ensure that peristalsis occurs in a cephalad to caudal direction. Lower esophageal sphincter (LES) opening is required during esophageal peristalsis to allow the food bolus into the stomach. Initial inhibition of smooth muscle and LES intrinsic fibers ensures the correct directional sequence of muscle contraction behind the bolus [3]. Muscle samples from different positions (rostral to caudal) in the esophagus have been demonstrated to have differing latencies, which also assists peristaltic coordination [6].

5. *Central pattern generator (CPG)*
   To achieve an efficient, directional, and safe swallow, critical timing events include (1) that airway protection should precede both pharyngeal and esophageal peristalsis, (2) that PES opening should occur prior to esophageal peristalsis, (3) that esophageal peristalsis should not start before pharyngeal peristalsis is near completion or complete, (4) that PES closure should occur directly following bolus transit, and (5) that esophageal smooth muscle activation should not precede striated muscle activation. Neuroanatomic studies now provide evidence of the central coordination of these events. Neural tracer studies have identified a population of PMNs connecting sites in the NTS, reticular formation, NA, DMNV, and hypoglossal nucleus that have both afferent and efferent contacts and that are believed to comprise the central pattern generator that coordinates phase timing and respiratory reflexes [4–6]. Two broad pools of neurons have been identified and described as the dorsal group (involved in processing peripheral incoming information and timing) and the ventral group (associated with distribution of swallow signals to individual motor neuron pools). These neurons interlink brainstem nuclei and comprise a cross-talk pathway that enables appropriate sequencing of swallowing and airway protective reflexes. In addition, the NTS also receives descending projections from cortical and supramedullary centers and ascending information from pharyngeal sympathetic afferents [6, 8, 9, 12].

Swallowing Neural Pathway Summary

Material in the oral cavity or pharynx stimulates afferent neurons projecting to the $NTS_{int/is}$ where oral, oropharyngeal, and laryngeal PMNs are situated. Interneurons project to laryngeal MNs to close the airway (NA_{sc}) and halt respiration, to pharyngeal MNs to initiate pharyngeal peristalsis and PES opening, and to esophageal PMNs

(NA_c and DMNV) to *inhibit* esophageal peristalsis. The bolus then arrives at the PES and cervical esophagus and triggers afferent activation of the NTS_{cen} with direct projection to NA_c MNs that initiate esophageal peristalsis. Feedback interneurons via the DMNV and the CPG briefly inhibit esophageal smooth muscle contraction and LES relaxation (ensuring cephalad to caudal peristaltic progression) and stimulate PES closure and contraction (prevents retrograde esophagopharyngeal reflux).

These pathways provide evidence in support of interphase reflexes, such as the phenomena of *deglutitive inhibition* and *failed swallows*. When several swallows occur in close proximity (within 6 s), the esophageal phase response occurs only after the final swallow. The pharyngeal phase inhibits the esophageal phase for a short time to prevent multiple peristaltic waves converging in the esophagus which might halt bolus flow. This is deglutitive inhibition. The CPG and feedback loop interneurons coordinate these events, and intrinsic muscle refractoriness also contributes. Another example is "failed swallows" where a small number of swallows, particularly dry swallows, may fail to elicit any esophageal phase response. This is estimated to occur in 3–4% of wet swallows and 29–38% of dry swallows [3]. During these "failed swallows," it is thought that the stimulus fails to reach the esophagus, and hence, no propagation of the deglutitive wave occurs [3].

Laryngeal Protection

As detailed above, the sequential coordination of deglutition is a complex sensorimotor phenomenon. However, swallowing cannot be considered in isolation—it must be understood in the context of its meticulous integration with laryngeal airway reflexes and responses that are crucial to harmonious and safe swallowing. Several additional mechanisms exist that enhance safety during swallowing and when the airway is threatened by retrograde transit of material. These will be discussed separately, although more than one mechanism may be involved at any time.

During Deglutition

Phylogenetically, the functions of our larynx are (1) airway protection, (2) respiration, and (3) phonation [1]. It is critical that mechanisms for airway protection function during swallowing to minimize transgression of the airway and protect us from pulmonary complications. As discussed above, airway protection begins when material is detected in the oral cavity. This elicits early adduction of the true vocal folds and inhibits respiration. As the oral phase of deglutition progresses, further closure occurs at the level of the supraglottis, and then as pharyngeal transport occurs, simultaneous anterosuperior elevation of the laryngeal complex draws the airway under the tongue base. Tongue movement assists epiglottic retroversion, deflecting ingested material away from the airway and through the piriform fossae

to the posterior cricoid region. With hyolaryngeal elevation, there is a simultaneous distraction at the pharyngoesophageal segment helping to open the upper esophageal sphincter and draw bolus into the esophagus. Pharyngeal peristalsis follows the bolus, clearing the hypopharynx. Airway protection is afforded by combination of the three-tier closure of the larynx, anterosuperior displacement, and appropriate timing of these actions in relation to transit of the bolus. If there is impairment in any of these fundamental components, the risk of violating the airway with possible penetration or aspiration arises.

During Retrograde Challenge: Vomiting, Regurgitation, Eructation, and Reflux Events

Retrograde transit of material into the pharynx may occur in many situations that are both physiological and pathological. Physiological retrograde movement of esophagogastric content may occur during belch/eructation, regurgitation, vomiting, or hiccoughs. These are stereotypic actions, again coordinated by brainstem centers [3, 6]. In contrast, esophagopharyngeal, gastroesophageal, and laryngopharyngeal reflux occur unpredictably and intermittently and can be pathological by putting the airway at risk. Dual sphincteric control (upper and lower esophageal sphincters) acts as the primary barrier to this type of retrograde transit, and a combination of sophisticated pharyngoesophageal-respiratory reflexes act as secondary protective mechanisms (Table 1.2):

1. *The upper esophageal sphincter*
   Function of the UES will be discussed in depth in later chapters. Its role in normal deglutition and airway protection is critical, and such protection is the primary function of the sphincter, which will be discussed briefly here. The UES is a zone of high pressure adjoining the pharynx to the esophagus. Primary anatomic components are fibers of the inferior pharyngeal constrictor, both the oblique thyropharyngeal fibers and the more horizontally oriented cricopharyngeal fibers. In addition, there may be some contribution from upper esophageal fibers. The anterior "wall" of the sphincter is composed of the cartilaginous cricoid laminae and overlying musculature and mucosa. This represents a firm and non-yielding surface in contrast to the musculomembranous posterolateral walls. Posteriorly, deep to the constrictor, is the cervical spine, another unyielding surface. Attachment of the muscular components to the laryngeal architecture means that this is a mobile region, elevating with deglutition. Cricopharyngeal muscle fibers are specialized and refined to perform the critical functions of the UES. The fibers are predominantly slow-twitch oxidative fibers interspersed to a lesser degree with fast twitch fibers and a moderate amount of connective tissue [6, 13]. This allows for prolonged contraction while also being able to accommodate a distending bolus as it traverses the sphincter. In fact, inhibition of contraction is not required to

Table 1.2 Aerodigestive tract protective reflexes

Reflex	Purpose	Afferent loop	Efferent loop
Pharyngoglottal	Close glottis, protect airway	CN IX, X	CN X
Reflexive pharyngeal swallow	Clear pharynx, remove residue, trigger airway closure	CN IX, X	CN X, XII, ansa cervicalis
Pharyngo-UES contractile	Limit reflux dispersion	CN IX, X	CN X
Esophagoglottal	Close glottis, protect airway	CN X, sympathetic	CN X
Esophago-UES contractile	Limit reflux	CN X, sympathetic	CN X, parasympathetic
Esophago-UES relaxation (belch)	Relieve gastric or esophageal pressure	CN X,	CN X
Secondary peristalsis	Clear residue, refluxate from esophageal lumen	CN X	CN X

Table 1.3 Factors affecting UES pressures

Increase UES pressure	Decrease UES pressure
Stress	Sleep
Esophageal acidification (gastroesophageal reflux)	Vomiting, regurgitation
Inspiration	Anesthesia
Slow esophageal (distal) distension (reflux)	Rapid esophageal (proximal) distension (belch)
Increasing age	Swallow (temporary)
Pharyngeal stimulation	Neurogenic disease (ALS, LMS, myopathy)
Singing/phonation	Head turn

open the UES if hyolaryngeal elevation and an adequate distending food bolus are present. Cricopharyngeal fibers are sling-like, without a posterior midline raphe, and fibers receive bilateral motor innervation from the NA_{sc} via the pharyngeal plexus. Complex interneural connections in the medulla and CPG modulate the motor outflow and contribute to reflex UES contractions as discussed below. The inferior constrictor is tonically contracted most of the time, thus keeping the UES closed and preventing aerophagia and reflux. Resting pressures vary with wakefulness, stress, and between individuals (Table 1.3), ranging from 30 to 110 mm Hg [6, 13, 14]. Pressure is also distributed asymmetrically with increased pressure in an anteroposterior plane compared to lateral plane. The UES opens for deglutition, regurgitation, eructation, and vomiting. This usually occurs with combined cessation of tonic contraction of IP fibers accompanied by suprahyoid muscle contraction that distracts the laryngeal cartilage forward. Because the posterior pharyngeal wall is adherent to prevertebral fascia, anterior

movement helps open the PES. The pharynx can move cephalad, however, and shortening of the pharynx does occur with hyoid elevation, thereby assisting pharyngeal bolus transit. Swallow-induced relaxation of the UES differs from that occurring during belch. Relaxation lasts 0.3–0.5 s during swallowing, and lack of tonic contraction combined with hyolaryngeal elevation opens the UES. During a belch, there is less hyolaryngeal movement, specifically less superior distraction and an opposite direction of rotation [6]. Bolus size does affect UES opening with larger boluses triggering longer UES opening duration.

2. *Upper aerodigestive tract protective reflexes*
   In addition to normal UES function, there are a number of reflexes designed to protect the airway during routine swallowing and when aberrant deglutition, or reflux, occurs (Table 1.2):

   (a) Pharyngo-UES contractile reflex
   Stimulation of pharyngeal mucosa (by pressure or liquid) results in dose-dependent increase in resting UES pressures—the pharyngo-UES contractile reflex. As increasing volumes of liquid are instilled, a pharyngeal reflexive swallow (PRS) is triggered (see b, below) [8, 15]. Selective nerve section experiments have suggested this reflex is mediated via glossopharyngeal afferents and vagal efferents, and topical anesthesia can abolish the response. Only small volumes (0.1 ml) are required to enhance UES pressures. Larger volumes are required to trigger PRS. This is presumed to protect the airway and pharynx from retrograde excursion of fluid from distal regions.
   (b) Pharyngeal reflexive swallow (PRS)/secondary pharyngeal swallow
   Stimulation of the oropharynx including supraglottic tissue (by pressure or injection of fluid) results in a prompt swallow initiated at the level of the stimulus and propagating to the esophagus if the bolus also travels to that point (see section "Normal Deglutition") [8, 15, 16] . This provides protection not only from inadvertently refluxed material but also from post-swallow residues or a prematurely spilled bolus that may reach the pharynx prior to initiation of deglutition. Residue in the vallecula or piriform fossae is common in neurological disease where pharyngeal peristalsis is weak or if cricopharyngeal dysfunction results in early closure of the PES. Residue may then be aspirated into the airway. Early spill can reach the airway before closure or hyolaryngeal elevation has occurred. Pharyngeal reflexive swallows clear threatening material from an area of risk preventing penetration or aspiration. The reflex arc is transmitted via cranial nerves IX and X with medullary integration.
   (c) Pharyngoglottal reflex
   Pharyngeal stimulation (without requiring preceding oral sensory input) also triggers glottal adduction mechanisms. Airway closure prevents misdirected transit into the airway. These combined pharyngeal reflexes (pharyngo-UES contractile reflex, PRS, pharyngoglottal reflex) provide reinforced protection for the airway [15]. If pharyngeal surveillance detects mechanical or chemical stimuli, the airway is closed, a clearing swallow is triggered, and the UES is augmented to limit spread of material and remove it from threatening the airway (Fig. 1.4).

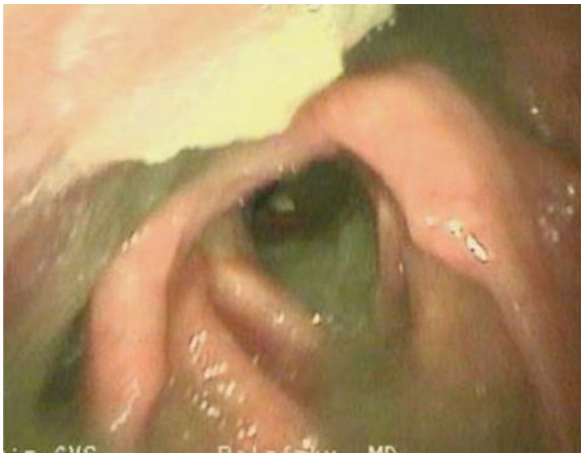

Fig. 1.4 Functional Endoscopic Swallowing Study in patient with gross penetration and aspiration of puree (tracheotomy tube can be seen in the distant trachea)

(d) Esophago-UES contractile reflex

The response of the UES to esophageal distension and acidification has been subject to much scrutiny, as this mimics the clinical situation of GER episodes. An abrupt increase in UES pressure has been demonstrated during acidic esophageal reflux episodes [17]. It was not possible to discern whether the resting pressure change was stimulated by distension via mechanoreceptors or by acidification via chemoreceptors, or a combination of both. Dua et al. [15] report that UES pressure increases in response to esophageal distention—the esophago-UES contractile reflex. The exact amount of pressure increase, the rapidity of distension, and the site of distension that triggers this reflex are somewhat less clear. In contrast, during eructation, where gas is vented proximally through the mouth, the UES relaxes in response to gastric and/or esophageal distension. There is also a carefully timed glottal closure reflex that shuts the airway *prior* to UES relaxation occurring (see e, below) [8, 16]. Increasing gastric distension promotes full supraglottic closure in addition to glottic and false vocal fold adduction. Thus, two different responses at the UES can occur with esophageal distension—a relaxation (coupled with glottal closure) or a contraction. It seems that the speed of distension is the primary determinant of UES response, with rapid distension resulting in relaxation (as in belch, vomit) and slower distension, as may occur with liquid reflux, augmenting the UES pressure [6]. Both responses may be important in reflux events as gaseous refluxate can be damaging to the laryngopharynx and may be more likely to result in UES relaxation (heightened belch-like response). Szczesniak et al. [18] found that patients with laryngitis demonstrated a UES relaxation in response to rapid esophageal distension significantly more often than subjects without laryngitis, and a lower volume was required to elicit relaxation compared to non-laryngitis subjects. The pharynx also lacks some of the intrinsic protective mechanisms found in the esophagus, making proximal reflux possibly more injurious.

(e) Esophagoglottal reflex
Cats and humans demonstrate reflexive glottal closure when the esophagus is distended rapidly. This appears to be a mechanoreceptor-mediated vagal reflex, as it can be abolished by vagotomy (at least in cats!). Several laryngeal adductors are involved, and this reflex demonstrates the close connection of the respiratory system with digestive tract physiology. It is provoked during eructation, vomiting, regurgitation, and GER [19]. The reflex may be attenuated with age or with esophagitis, raising the question as to loss of airway protection in patients with complications of GERD. Therefore, when refluxate is traveling retrograde up the esophagus, two reflexes are triggered—an airway closure response (esophagoglottal reflex) and a UES contractile response (esophago-UES contractile reflex). These reflexes are designed to work in concert to limit pharyngeal escape and airway violation. In preprogrammed patterned responses such as belch or vomit, the esophagoglottal reflex is activated (thyroarytenoid muscle is strongly active for the duration of the vomit), but there is a UES relaxation and aborad peristaltic wave that propels material from the stomach, through the esophagus and pharynx and into the oral cavity [19].
(f) Laryngo-UES contractile reflex
Air puff stimulation of the arytenoids, interarytenoid region, and epiglottis induces an increase in UES pressures. Again this is postulated to be a protective measure against either further refluxate traversing the UES or pharyngeal material violating the airway perimeter.

3. Laryngeal reflexes
The laryngo-UES contractile reflex is discussed above. Additionally the laryngeal adductor reflex (LAR) is well described [20, 21] and results in protective glottal adduction when supraglottic tissue is stimulated by mechanical air puffs. This reflex forms the basis of laryngeal sensitivity testing as described by Aviv and colleagues as Functional Endoscopic Evaluation of Swallowing with Sensory Testing (FEESST) [21]. The reflex arc involves the superior laryngeal nerve (afferent) and recurrent laryngeal nerve (efferent) and is therefore a vagal response. It is also a crossed response, with stimulation on the ipsilateral side resulting in bilateral closure. This can be attenuated by loss of central facilitation as occurs during anesthesia [20]. Otherwise it is an involuntary response and not suppressible if intact. Investigators have demonstrated reduced laryngopharyngeal sensitivity as measured by LAR in patients with chronic cough and GERD, and significant correlation with increased aspiration risk has been reported [22–27].
4. The lower esophageal sphincter
Composed of intrinsic esophageal muscle (dynamic) thickening (clasp and sling fibers) augmented by right crural diaphragmatic fibers, the lower esophageal sphincter (LES) is a mobile zone of increased pressure at the distal esophagus that is primarily responsible for limiting retrograde transit of gastric content into the esophagus [3, 6, 12]. It is augmented anatomically by the natural cardiac notch and angle of His at the gastroesophageal junction and is under complex neural control via both vagal (parasympathetic) fibers and splanchnic sympathetic fibers [12, 28]. It is also affected by neurohormonal signals to the smooth

muscle of the distal esophagus and LES, which are stimulated by preganglionic (cholinergic) motor neurons from the DMNV. Afferent supply of the distal esophagus and LES travels in vagal fibers to the NTS, and interneurons connect terminations directly to the DMNV. Depending on which site in the DMNV is stimulated, either contraction or relaxation of the LES ensues. Stimulation caudal to the opening of the fourth ventricle results in relaxation of the smooth muscle, while stimulation more rostral evokes a contractile response [12]. The nuclei of the NTS in which esophageal vagal afferents terminate (centralis) and the DMNV supplying preganglionic vagal efferents have been collectively termed the dorsal vagal complex.

Afferent sympathetic fibers run to the cervical and thoracic dorsal root ganglia (C1–T9) and typically convey painful stimuli [6, 12]. An overlapping distribution with cardiac sympathetic fibers accounts for the similarity in chest pain generated by esophageal and cardiac pathologies. The NTS_{cen} also connects to the NA_c which supplies PMNs for esophageal *striated* muscle. Splanchnic efferents to the esophagus terminate on myenteric neurons and modify their activity rather than directly on muscle fibers [6]. They also terminate on the interstitial cells of Cajal (ICC), which seem to act as intermediary between neurons and smooth muscle cells in the esophagus and LES [6].

Swallow-induced LES relaxation lasts about 6–8 s compared to a transient LES relaxation which lasts >10 s. Gastric distension and pharyngeal stimulation both result in LES relaxation. It is not clear what controls or triggers transient LES relaxations (TLESR) that are thought to relate closely to reflux disease [6]. There is a difference in muscle activation during TLESRs; esophageal longitudinal muscle contraction outlasts any circular contraction, and a reversal of polarity of the peristaltic wave occurs. Longitudinal muscle contraction progresses in an aborad direction during a TLESR [6]. When Smid and Blackshaw tested isolated strips of lower esophageal muscle from patients with known Barrett's metaplasia and adenocarcinoma vs patients with esophageal squamous cell carcinoma, a reduction in tension development was seen in those with Barrett's esophagus compared to subjects with squamous cell carcinoma, suggesting an intrinsic abnormality of the LES, although it could not be established whether this reduced pressure generation occurred as a result of carcinoma development or prior to development of the disease [29].

5. Changes during sleep

Deglutition and its associated protective airway reflexes mentioned above are affected by body state. During sleep, there are notable changes in supraesophageal and esophageal function. The most obvious is the reduced rate of spontaneous swallow, from around 25 per hour to 5 per hour when asleep. Saliva secretion is markedly reduced and may contribute to slower acid clearance from the esophagus. Pharyngeal musculature relaxes, which may promote airway obstruction and less vigorous swallows, and protective cough is diminished during sleep. Esophageal body contractions and LES pressures are largely unchanged by sleep, but the UES pressure diminishes significantly [30]. Loss of the crossed arm of the laryngeal adductor reflex has also been noted with increasing anesthesia, suggesting increased airway risk and weakened glottic closure ability when anesthetized [20].

Dysfunctional Deglutition

With the inherent complexity of deglutition, there are many opportunities for problems to arise. Disordered deglutition may arise from both central and peripheral pathology (from dysfunction in motor or sensory processing, central integration, or pattern generation) and may affect motility or timing with equally severe consequences. Poor bolus transfer causes dysphagia and may cause odynophagia or result in airway violation (either penetration or aspiration) (Fig. 1.5). Therefore, swallowing disorders present problems not only for the digestive tract but also for the respiratory system:

1. Sensory disorders
   Nearly all airway protective reflexes are initiated by sensory phenomena. Therefore, disorders of sensation create major risk to the airway. The pharynx as a whole is supplied by three primary cranial nerves—the trigeminal, glossopharyngeal, and vagus. Crucial integration occurs in the NTS in the medulla. Injury to cranial nerves may occur through trauma, surgery, neuropathic disease, autoimmune disease, neoplastic infiltration, chemoradiotherapy, or infective disorders. One of the most crucial nerves is the superior laryngeal (SLN) branch of the vagus.

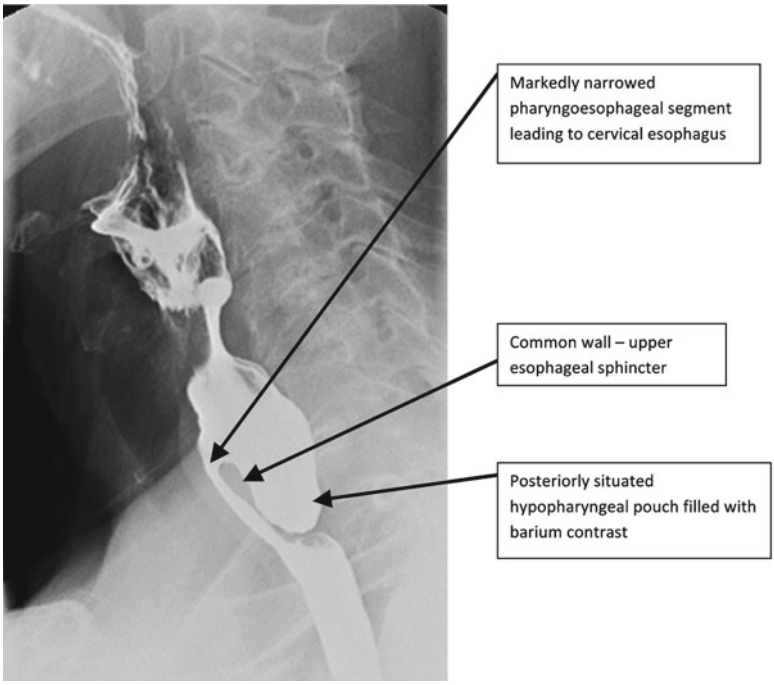

Fig. 1.5 Lateral fluoroscopic view of a Zenker diverticulum (hypopharyngeal pseudodiverticulum) filled with contrast agent

This nerve provides sensory information from the oropharynx, vallecula, and supraglottis. Loss of SLN function abolishes airway closure reflexes (laryngeal adductor reflex and pharyngoglottal reflex) and fails to trigger routine airway closure, hyolaryngeal elevation, and cessation of respiration, thus leaving the airway wide open as the bolus transits the pharynx. Even with viable motor function at the vocal folds, penetration and aspiration can occur, because the patient is not aware of the approaching material and fails to voluntarily protect the airway (Fig. 1.5). Dua and colleagues [15, 31] demonstrated that chronic and acute cigarette smoking results in reduction of pharyngeal protective mechanisms when compared to healthy nonsmokers. Reflexive pharyngeal swallows were lost in smoking subjects compared to healthy subjects with resulting laryngeal penetration seen in smokers but not in nonsmokers. When nonsmokers underwent pharyngeal anesthesia, they also demonstrated penetration, suggesting that loss of sensation was the crucial element in the breakdown of swallowing safety [15, 31]. Use of a nicotine patch did not cause the same reduction in RPS or the pharyngo-UES contractile reflex (PUCR), leading the authors to propose that smoking affects local pharyngeal sensation. They also tested systemic application of alcohol by IV infusion. When blood alcohol levels were within the legal driving range, a significant decrease in trigger thresholds was noted for both PRS and PUCR [31]. Phua et al. [22, 23] studied adults with pH- or endoscopy-confirmed GERD vs control subjects with normal pH-metry and found that laryngopharyngeal sensation as tested by FEESST (mechanostimulation) was significantly reduced (worse) in patients with GERD. They then compared chemostimulation of the pharynx by instillation of saline or hydrochloric acid in the same patients. This showed an *increased* sensitivity to acidic infusion in GERD patients compared with controls. The authors hypothesized that chemoreceptor thresholds may be reduced (i.e., more sensitive) to offset loss of mechanoreceptor function [22, 23]. Thompson demonstrated that laryngopharyngeal sensory thresholds as tested by FEESST in awake pediatric patients correlated with incidence of penetration and aspiration [27]. Worse (less sensitive) thresholds were associated with increasing degree of aspiration. Linking this to clinical outcomes, patients with GER were noted to have increased laryngopharyngeal sensory thresholds as well as an increased rate of pneumonia [27].

In the esophagus, distention or acidification results in several responses. There may be closure of the airway (esophagoglottal reflex), augmentation of UES pressure (esophago-UES contractile reflex), or relaxation of the UES (belch). Esophageal reflexes are triggered to clear refluxate or retained bolus (peristalsis) and to help transport saliva to neutralize refluxed acid [32]. An airway response may also be seen. Esophageal acidification in cats resulted in increased mucus production and decreased mucociliary transport in small airways indicating the close relationship of the esophagus and respiratory system [33].

2. Motor disorders

The critical motor actions during swallowing that result in airway protection are the closure of the airway (in stepwise fashion) by adduction of the true vocal

folds and supraglottic constriction, which is combined with anterosuperior movement of the larynx. Closure of the glottis appears to be a primary protective mechanism, and failure of closure results in an increased rate of airway intrusion. Medda and colleagues [6] studied decerebrate cats and induced airway-compromising injuries—unilateral cordectomy, suprahyoid muscle transaction, or epiglottectomy. Cordectomy resulted in intradeglutitive aspiration in all cats and post-deglutitive aspiration in 75%. Suprahyoid muscle transection resulted in markedly increased pharyngeal residue (in 88%) and intradeglutitive aspiration in 20% of animals. UES opening was reduced by suprahyoid muscle transection, likely increasing residue. Epiglottectomy did not result in aspiration in any phase of swallowing [9]. In humans with unilateral vocal fold paralysis, there is increased aspiration risk, and if the lesion responsible is central or a high vagal lesion, there may be associated dysfunction of the pharyngeal constrictors and UES on the same side resulting in increased pharyngeal residue. The presence of post-swallow residue predisposes to laryngeal penetration and aspiration because respiration can draw residue into the airway. Pharyngeal weakness is associated with increased risk of pneumonia and aspiration due to residue and poor swallow efficiency. Leonard and colleagues [34, 35] used a surrogate measure of pharyngeal strength (the pharyngeal constriction ratio, PCR) to demonstrate that pharyngeal weakness contributed to 75% of cases of aspiration in adults. There is a well-known association of dysphagia and pneumonia in patients suffering cerebrovascular accidents, neurodegenerative diseases such as Parkinson's disease, amyotrophic lateral sclerosis (ALS), and myopathic disorders (e.g., muscular dystrophies, inclusion body myositis, and polymyositis) [36, 37]. More than half a million people are treated for neurogenic dysphagia in the USA each year, and disorders of swallowing affect an estimated 40% of those over age 60 years [36, 37]. Age-related swallowing decrements (presbyphagia) occur even without a specific disease process. These include reduced tongue pressure generation, increased swallow duration, and increased incidence of penetration compared to younger adults [36]. With advanced age, there is an increasing incidence of comorbid conditions that may impact swallowing such as xerostomia, medication effects, diabetes, cardiovascular and respiratory disorders, and stroke. Head and neck and esophageal carcinomas occur more often in adults over 60 years and have significant impacts on swallowing both by disease invasion and through treatments such as ablative surgery (loss of muscle and neural tissue) or chemoradiotherapy (xerostomia, nerve dysfunction, mucositis and sensory changes, fibrosis, reduced muscle mass, and inflammation). Reflux is common in these patients and may exacerbate functional deficits. GERD has been implicated in esophageal dysmotility with increased acid contact times negatively influencing muscle contraction, particularly in diabetic autonomic neuropathy [38].

3. Timing disorders

   The importance of timing may be appreciated when one experiences food or fluid "going down the wrong way" as normal individuals can experience occasionally. An inadvertently open airway at the time of swallow allows material to reach the supraglottic and occasionally glottic tissue. In subjects with adequate

sensation, this usually results in a vigorous cough response and expulsion of offending material from the airway. In patients with timing issues due to peripheral insensitivity, central processing deficits, or slow motor function, coordination of airway closure with deglutition can go awry. Even if the airway is closed in a timely manner, if a swallow proceeds but the UES fails to open synchronously or for too short a duration, there may be incomplete bolus transfer. Residue may then be lost into the airway as respiration resumes and the airway opens again. Swallowing against a closed PES may result in redirection of material into the airway, pharyngeal dilation, or formation of a "pressure release" pouch (e.g., a hypopharyngeal pseudodiverticulum or Zenker diverticulum), depending on patient anatomy, chronicity, and physiological reserve (Fig. 1.3). In some cases voluntary control over airway closure may be utilized as a behavioral compensatory strategy, with an active breath hold prior to swallowing and a forceful expiration to clear unwanted laryngeal material post-deglutition.

Future Research

Although our understanding of physiology of normal deglutition has substantially improved in the past 10 years, several gaps in knowledge remain. Future research should be aimed at identifying pathways linking the digestive and respiratory systems and identifying how various abnormalities are responsible for disease processes such as adult-onset asthma, GERD-related airway hypersensitivity, chronic cough, globus pharyngeus, and noncardiac chest pain. Understanding of the molecular vehicles and receptors involved will suggest targets for novel therapies. Neural plasticity in the swallowing system and the effect of rehabilitative therapies also warrants further research, in particular, in neurological diseases, which will continue to increase in prevalence with our aging population. In-depth knowledge of normal age-related changes in deglutition and airway protective mechanisms will also provide additional insight for prevention of problems.

Clinical Summary

The close functional relationship between deglutition and airway protection is key to a safe and efficient swallow. Without significant coordination between respiratory and digestive systems, humans would be exposed to recurrent pulmonary insults with severe consequences. Dysphagia is increasing in prevalence in our society as it ages, and this will have a greater impact on health resources in the future. Understanding the dynamics of normal and disordered swallowing allows preventative strategies and therapeutic manipulations to be planned and implemented. Gastroesophageal reflux disease is prevalent in the West and contributes to disordered swallowing and significant symptoms. Its impact on the airway is only now being

more fully appreciated and will require increasing research and novel intervention. This chapter outlines our current understanding of normal deglutition, the key physiological elements, and how dysfunction produces symptoms. These processes can be borne in mind and considered, as one reads further chapters that will delve into specific pathologies associated with GERD and the lung.

Key Points

- Deglutition is a complex, sensorimotor function involving multiple cranial nerves and central integration in the medulla. Both voluntary and involuntary control may be exerted during deglutition. The key neural pathways involve CN V, VII, IX, X, XII, nucleus tractus solitarius, nucleus ambiguous, reticular formation, and dorsal motor nucleus of the vagus.
- The central pattern generator for swallowing is likely to be a pool of premotor neurons in the nucleus tractus solitarius and ventral medulla that interconnect with other brainstem nuclei and are modulated by cortical and peripheral activity. The dorsal pool receives and integrates afferent information and coordinates sequencing. The ventral pool distributes outputs to appropriate motor neuron nuclei.
- Airway protective mechanisms are coordinated through the same brainstem nuclei and are crucial for safe and timely deglutition. Respiratory activity is closely coupled to and influenced by aerodigestive tract activity.
- Dysfunctional deglutition increases the risk of airway violation by ingested material, saliva, or refluxed material. Most protective mechanisms are designed to prevent penetration or aspiration of material into the airway.
- Gastroesophageal reflux may impact both swallowing and airway protection. GERD may induce structural or functional changes in the pharynx, larynx, and esophagus and trigger airway protective mechanisms.
- Transient lower esophageal sphincter relaxations (TLESRs) differ from swallow-induced LES relaxation because they are longer (6 vs >10 s), differentially involve esophageal longitudinal muscle, and demonstrate antiperistaltic polarity of the transmitted wave.
- TLESRs contribute to proximal excursion of refluxate and can trigger airway protective mechanisms and cause laryngopharyngeal symptoms.

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Chapter 2
The Pathophysiology of Gastroesophageal Reflux

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Keywords Esophagus • Gastroesophageal reflux (GERD) • Larynx • Laryngopharyngeal reflux (LPR) • Defense mechanisms • Nonacid reflux • Acid • Pepsin • Bile • Trypsin

Gastroesophageal Reflux

The backflow of gastric contents into the esophagus, gastroesophageal reflux (GER), is a normal physiological phenomenon that occurs in most people, particularly after meals. Brief and infrequent exposure of the esophagus to gastric contents does not result in injury and disease, implying that there are intrinsic defense mechanisms that act to maintain mucosal integrity. In fact, based upon pH monitoring studies, up to 50 reflux episodes a day (below pH 4) are considered normal. However, esophageal symptoms and complications arise when reflux is prolonged and/or there is a breakdown in the defense mechanisms. When reflux is in excess, heartburn is experienced, described as a burning sensation behind the sternum. Most people experience heartburn from time to time. Patients with long-term GER may develop esophagitis (inflammation of the esophagus) thought to occur when the normal defense mechanisms break down. This is termed gastroesophageal reflux disease (GERD). GERD is accepted as possibly the most common chronic disease of adults in the USA, affecting more than 30% of Western society [1, 2].

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GER is a major factor in the development of Barrett's esophagus in which the esophageal epithelia are changed from stratified squamous to pseudostratified columnar intestinal-type epithelium. Approximately 10% of patients with esophagitis develop Barrett's esophagus. Barrett's esophagus is a premalignant condition with an associated risk of developing esophageal adenocarcinoma, with reflux playing a major role [3].

Laryngopharyngeal Reflux

When gastric reflux travels more proximally into the laryngopharynx, it is termed laryngopharyngeal reflux (LPR) [4]. Other terms, such as gastropharyngeal reflux (GPR) and esophagopharyngeal reflux (EPR), have been used synonymously. These are all considered as part of extra-esophageal reflux (EER), reflux involving structures other than, or in addition to, the esophagus. LPR contributes to several otolaryngologic symptoms, inflammatory disorders, and perhaps also neoplastic diseases of the laryngopharynx [4–9] and appears to be as common in children and infants as in adults [10]. It is estimated that 10% of patients visiting otolaryngology clinics have reflux-attributed disease, and up to 55% of patients with hoarseness have reflux into their laryngopharynx [4, 8]. LPR is actually one of the most common factors associated with inflammation in the upper airways. Compared to the esophagus, where up to 50 reflux episodes (below pH 4) a day are considered normal or physiologic, the laryngopharynx and other extra-esophageal structures appear to be more sensitive to injury by gastric refluxate. It has been shown experimentally that three or less reflux episodes per week into the laryngopharynx result in severe laryngeal damage [4, 11].

Symptoms of LPR include dysphonia, throat clearing, postnasal drip, chronic cough, dysphagia, globus pharyngeus, excessive phlegm, heartburn, dyspnea, laryngospasm, and wheezing [12]. Signs of LPR are commonly associated with posterior laryngitis and include erythema and edema of the larynx, especially in the post-cricoid and hypopharyngeal areas. Additionally, signs of chronic laryngitis including vocal fold edema, diffuse laryngeal erythema and edema, pseudosulcus vocalis, obliteration of the laryngeal ventricles, thickened laryngopharyngeal mucus, and mucosal granulomata are commonly associated with LPR [12].

Review of Gastric Reflux Contents and Their Role in Reflux Disease

Gastric Acid

Gastric acid is produced by parietal cells in fundic glands of the gastric mucosa. Parietal cells contain an extensive secretory network, called canaliculi, from which

gastric acid is secreted into the lumen of the stomach. Chloride and hydrogen ions are secreted separately from the cytoplasm of parietal cells and mixed in the canaliculi. Gastric acid is then secreted into the lumen of the oxyntic gland and gradually reaches the stomach lumen. Gastric acid is approximately pH 2 in the human stomach lumen, the acidity being maintained by the proton pump H^+/K^+ ATPase. The resulting highly acidic environment in the stomach lumen causes proteins from food to denature, exposing the protein's peptide bonds. The chief cells of the stomach secrete inactive enzymes, pepsinogen and renin, for protein breakdown. Gastric acid then activates pepsinogen into pepsin, which enzymatically aids digestion by breaking the bonds linking amino acids, a process known as proteolysis. In addition, the acidic environment of the stomach inhibits the growth of many microorganisms, thereby controlling the gut's bacterial load to help prevent infection.

In hypochlorhydria and achlorhydria, there is low or no gastric acid in the stomach, potentially leading to problems as the disinfectant properties of the gastric lumen are decreased. In such conditions, there is greater risk of infections of the digestive tract (such as infection with *Helicobacter* bacteria). In Zollinger–Ellison syndrome and hypercalcemia, there are increased gastrin levels, leading to excess gastric acid production, which can cause gastric ulcers. Reflux of gastric acid into the esophagus and airway also causes injury and disease. Erosive esophagitis and heartburn are consequences of abnormal gastric acid exposure [13]. Intraesophageal perfusion experiments with acidic solutions demonstrated symptoms of heartburn at pH 6 and below [14]. Combined multichannel intraluminal impedance—pH monitoring studies have shown a significant correlation between both acid and nonacid reflux episodes and heartburn [15–17].

Dilated intracellular spaces are associated with impaired mucosal integrity and are detected in patients with GER as well as in animal models and healthy volunteers exposed to acidic contents [18–20]. The mucosal immune response and presence of specific inflammatory mediators, such as interleukins IL-8 and IL-6, are well characterized in GERD [1].

The H^+/K^+ pump in the stomach is the target of proton pump inhibitors, used to increase gastric pH to treat reflux disease. Histamine H_2 antagonists indirectly decrease gastric acid production, and antacids neutralize existing acid.

Pepsin

Pepsin is expressed as a pro-form zymogen, pepsinogen, whose primary structure has an additional 44 amino acids. Chief cells in the stomach release the zymogen, pepsinogen. This zymogen is activated by hydrochloric acid (HCl), which is released from parietal cells in the stomach lining. The hormone, gastrin, and the vagus nerve trigger the release of both pepsinogen and HCl from the stomach lining when food is ingested. Hydrochloric acid creates an acidic environment, which allows pepsinogen to unfold and cleave itself in an autocatalytic fashion, thereby generating pepsin, the active form of the enzyme. Pepsin then cleaves the 44 amino acids from pepsinogen

creating more pepsin. Pepsin will digest up to 20% of ingested amide bonds by cleaving preferentially after the N-terminus of aromatic amino acids such as phenylalanine, tryptophan, and tyrosine. Pepsin exhibits preferential cleavage for hydrophobic, preferably aromatic, residues in P1 and P1′ positions. Increased susceptibility to hydrolysis occurs if there is a sulfur-containing amino acid close to the peptide bond, which has an aromatic amino acid. Pepsin cleaves Phe–Val, Gln–His, Glu–Ala, Ala–Leu, Leu–Tyr, Tyr–Leu, Gly–Phe, Phe–Phe, and Phe–Tyr bonds in the B chain of insulin. Peptides may be further digested by other proteases in the duodenum and eventually absorbed by the body. Pepsin is stored as pepsinogen so it will only be released when needed and not digest the body's own proteins in the stomach's lining.

Pepsin is maximally active at pH 2 but has activity up to pH 6.5. While inactive at pH 6.5 and above, it remains stable to pH 8. The enzyme is not irreversibly inactivated (denatured) until the ambient pH reaches 8 [21, 22]. While the stomach is designed to resist damage by pepsin, reflux of pepsin into the esophagus and laryngopharynx causes damage even above pH 4. Pepsin is considered an important etiological factor in reflux disease of the aerodigestive tract and a biomarker for reflux, whose levels and acidity can be related to the severity of damage. Pepsin compromises cell membrane integrity by disrupting the intracellular junction complexes and increasing intracellular space [23]. Pepsin also increases esophageal tissue permeability by increasing cell influx of H^+ ions, K^+ ions, and glucose and by decreasing the recovery of titrated water, causing cellular disruption [24].

Bile

Bile is produced by hepatocytes in the liver, draining through the many bile ducts that penetrate the liver. During this process, the epithelial cells add a watery solution that is rich in bicarbonates that dilutes and increases alkalinity of the solution. Bile then flows into the common hepatic duct, which joins with the cystic duct from the gallbladder to form the common bile duct. The common bile duct in turn joins with the pancreatic duct to empty into the duodenum. If the sphincter of Oddi is closed, bile is prevented from draining into the intestine and instead flows into the gallbladder, where it is stored and concentrated to up to five times its original potency between meals. This concentration occurs through the absorption of water and small electrolytes, while retaining all the original organic molecules. Cholesterol is also released with the bile, dissolved in the acids and fats found in the concentrated solution. When food is released by the stomach into the duodenum in the form of chyme, the duodenum releases cholecystokinin, which causes the gallbladder to release the concentrated bile into the duodenum to complete digestion.

Bile acts to some extent as a surfactant, helping to emulsify the fats in food. Bile salt anions have both a hydrophilic and hydrophobic site and therefore tend to aggregate around droplets of fat (triglycerides and phospholipids) to form micelles, with the hydrophobic sides toward the fat and hydrophilic to the outside. The hydrophilic

sides are positively charged due to the lecithin and other phospholipids that comprise bile, and this charge prevents fat droplets coated with bile from reaggregating into larger fat particles.

The dispersion of food fat into micelles thus provides an increased surface area for the action of the enzyme, pancreatic lipase, which digests the triglycerides and is able to reach the fatty core through gaps between the bile salts. A triglyceride is broken down into two fatty acids and a monoglyceride, which are absorbed by the villi on the intestine walls. After being transferred across the intestinal membrane, fatty acids are reformed into triglycerides, then absorbed into the lymphatic system through lacteals. Without bile salts, most of the lipids in food would be passed out in feces, undigested.

The alkaline bile also has the function of neutralizing any excess stomach acid before it enters the ileum, the final section of the small intestine. Bile salts also act as bactericides, destroying many of the microbes that may be present in ingested food.

Reflux of bile is known to cause esophagitis and is likely to play a role in extra-esophageal reflux disease [25]. The mechanism of bile-induced mucosal injury is thought to be related to "intramucosal trapping" of bile acids that results in mucosal damage primarily by disorganizing membrane structure or interfering with cellular metabolism. Taurocholic acid does this at pH 2, and chenodeoxycholic acid at pH 7. Some bile acids cause damage at high pH due to their lipophilic properties at the pH at or near the pK_a value, for example, taurocholic acid (which is a conjugated bile acid with a $pK_a \sim 2$) and chenodeoxycholic acid (which is an unconjugated acid with $pK_a \sim 7$) are unionized and therefore can enter the cell at an acidic and neutral pH, respectively. Once inside the cell, bile acids are trapped by ionization and subsequently cause mucosal damage.

Trypsin

Trypsin is secreted into the duodenum, where it acts to hydrolyze peptides into their smaller building blocks—amino acids (these peptides are the result of the enzyme pepsin breaking down the proteins in the stomach). This enables the uptake of protein in the food because peptides (though smaller than proteins) are too big to be absorbed through the lining of the ileum. Trypsin catalyzes the hydrolysis of peptide bonds. They have an optimal operating pH of about 8 and optimal operating temperature of about 37°C.

Trypsin is produced in the pancreas in the form of an inactive zymogen, trypsinogen. When the pancreas is stimulated by cholecystokinin, trypsinogen is then secreted into the small intestine. Once in the small intestine, the enzyme, enteropeptidase, activates it into trypsin by proteolytic cleavage. The resulting trypsins themselves activate more trypsinogens (autocatalysis), so only a small amount of enteropeptidase is necessary to start the reaction. This activation mechanism is common for most serine proteases and serves to prevent autodigestion of the pancreas.

Studies have shown that trypsin can stimulate the production of inflammatory mediators. Chemokines and prostaglandins are increased in human esophageal epithelial cells when exposed to trypsin in vitro [26]. Trypsin has also been shown to induce chronic esophageal inflammation in rats [27].

Esophageal Defense Mechanisms to Protect Against Reflux

The integrity of the human esophageal mucosa depends on several defense mechanisms that protect it against luminal aggressive factors such as gastric reflux. These protective mechanisms can be classified as pre-epithelial, epithelial, and post-epithelial defenses [28].

Pre-epithelial Defense Mechanisms

Lower Esophageal Sphincter

The lower esophageal sphincter (LES), detected by the presence of elevated pressure in the most distal esophageal segment relative to intragastric pressure, is an important factor preventing reflux of gastric contents into the esophageal lumen. It has been shown that physiological acid reflux episodes occur during periods of transient LES relaxations in healthy individuals [29]. Patients with reflux disease often have an increased frequency of transient LES relaxations [30, 31]. Hypotension of the LES has also been demonstrated to play a fundamental role in LPR [32].

Peristalsis

Peristalsis is the mechanism by which food boli are transported through the esophagus to the stomach. This process also plays an important role in clearing acid from the esophageal lumen. It has been shown that decreased peristalsis is responsible for impaired acid clearance in one third of patients with GERD [33].

Saliva

Saliva is secreted by the major (parotid, submandibular sublingual) and minor salivary glands. Saliva contains bicarbonate ions, which are thought to be produced by carbonic anhydrase (CA) (isoform II) present in these glands [34]. Although both CAII and CAVI isoenzymes are localized in the secretory granules of the serous acinar cells in the parotid and submandibular glands, only CAVI is secreted into the saliva. It is thought that CAII supplies the saliva with bicarbonate, while CAVI

present in the saliva is responsible for removing acid via the hydration of carbon dioxide [34], thus forming a mutually complementary system regulating salivary pH. Studies have shown that the secretory glycoprotein CAVI is significantly reduced in patients with esophagitis and esophageal ulcers [35].

Saliva is normally secreted at 0.5 ml/min, but this rate doubles during mechanical or chemical stimulation of the esophagus [36]. Aspiration of saliva has been shown to significantly increase esophageal acid clearance time and to lower luminal pH below 4 [37]. Besides bicarbonate, saliva contains epidermal growth factor (EGF) produced in the submaxillary ductal cells. EGF has been shown to enhance wound healing and decrease the permeability of the esophageal mucosa to hydrogen ions [38, 39].

Epithelial Defense Mechanisms

Unlike the stomach and duodenum, the esophagus does not appear to have a well-defined surface mucous layer. Thus, if pre-epithelial defenses fail to inactivate the injurious components of the gastric refluxate, the surface epithelium will be exposed to these components. The esophageal epithelium maintains its integrity by both structural and functional defenses. Structural defenses include the physical barrier of cell membranes and intercellular junctions. Functional defenses include intracellular buffers, Na^+/H^+ and Na^+-dependent Cl^-/HCO_3^- exchange systems.

Structural Defenses

Surface epithelial cells are surrounded by a glycocalyx that contains both neutral and acidic mucosubstances derived from membrane-coating granules. Acidic mucosubstances are more abundant in the superficial cell layers, where they are thought to provide a barrier against the gastric refluxate.

Cell adhesion molecules and intermediate filaments play an important role in maintaining epithelial integrity. Both desmosomes and hemidesmosomes have been identified in the human esophageal epithelium. These cell-to-cell and cell-to-matrix adhesion complexes have been shown to play an important role in epithelial defense. Hemidesmosomes mediate adhesion of epithelial cells to the basement membrane and connect the cytoskeleton to the extracellular matrix (ECM). These structures are present in the basal cell layer of the esophageal stratified squamous epithelium. A family of transmembrane receptors called integrins mediates the interaction between cells and the ECM. The α6β4 integrin, a major component on hemidesmosomes, can transduce signals from the ECM to the interior of the cell to organize the cytoskeleton and induce proliferation, apoptosis, or differentiation [40]. Desmosomes can also be found in the esophageal epithelium, particularly in the prickle cell layer where they often form “desmosome fields” [41]. Desmosomes bind cells together and link intermediate filament networks thus conferring structural continuity and tensile strength. The demosomal glycoproteins are members of the cadherin family.

Cell-to-cell interactions in the esophageal epithelium are mediated by E-cadherin in a Ca^{2+}-dependent manner [42].

As basal epithelial cells mature they migrate to form the prickle and functional cell layers, before being sloughed off into the lumen. This process results in the constant renewal of esophageal epithelial cells maintaining tissue integrity, which would not be possible without modulating cell-to-basement membrane and cell-to-cell adhesion. This is supported by the finding that integrins are present in a gradient of decreasing intensity as cells move toward the lumen, perhaps allowing shedding to occur [43].

Epidermal Growth Factor

EGF is a 6 kDa, 53 amino acid polypeptide that interacts with target cells by binding to a 170-kDa transmembrane receptor. The EGF receptor (EGF-R) has three distinct regions: an extracellular ligand-binding domain, a single hydrophobic transmembrane domain, and a cytoplasmic domain that possesses tyrosine kinase activity (reviewed by Jankowski et al.) [44]. Binding of EGF to its receptor results in clustering of the ligand–receptor complexes in clathrin-coated pits, receptor dimerization, autophosphorylation, and subsequent activation of signal transduction pathways [45]. These downstream signaling pathways include activation of tyrosine kinase activity with subsequent activation of phospholipase-C-γ1, which induces cell motility following phosphorylation of the E-cadherin–catenin complex [46–48]. Activation of tyrosine kinase can also result in the activation of protein kinase C, which induces mitogenesis [46].

EGF is thought to play an important role in maintaining esophageal mucosal integrity and rapid epithelial regeneration. Studies have shown that patients with low salivary EGF levels are predisposed to severe esophageal damage if they develop GERD [49, 50]. Salivary EGF has also been found to be significantly decreased in patients with LPR compared to a control group [51].

The esophagus secretes salivary EGF from submucosal glands present in the lamina propria. It has been demonstrated that exposure of the esophageal mucosa to acid and pepsin increases salivary EGF and bicarbonate output from the salivary glands [52–55], which are involved in restoration of mucosal integrity and wound healing [56].

Transforming Growth Factor

The human esophagus also synthesizes transforming growth factor alpha (TGF-α) [57], which shares sequence homology with EGF [58]. TGF-α can interact with target cells by binding to the EGF-R. In vitro and in vivo studies have shown that both EGF and TGF-α can promote proliferation and differentiation of epithelial cells [59]. TGF-α mRNA is differentially expressed compared to EGF. TGF-α is predominantly expressed in the superficial cell layers [57]. The expression of both

EGF and TGF-α in the esophageal epithelium is intriguing, as both exert similar biological effects. The physiological significance of TGF-α is unknown; however, it is hypothesized that both of these growth factors are involved in defense and restitution following mucosal injury.

Carbonic Anhydrase

Carbonic anhydrase (CA) catalyzes the reversible hydration of carbon dioxide [60–62] in the reaction:

$$CO_2 + H_2O \overset{CA}{\leftrightarrow} HCO_3^- + H^+$$

The bicarbonate ions produced are actively pumped out of the cell, via anion exchange, into the extracellular space where they can neutralize refluxed gastric acid and therefore indirectly reduce peptic activity. Eleven catalytically active isoenzymes have been isolated to date, each showing differences in activity, susceptibility to inhibitors, and tissue-specific distribution. The esophagus has been shown to express CAI–IV in the epithelium [63]. The high-activity isoenzymes CAII and IV are localized in the suprabasal cell layers, while low-activity CAI and III are in the basal cell layers. The presence of CA in the esophagus is important because endogenous bicarbonate production is capable of increasing the low pH environment, as a result of a reflux episode, from 2.5 to almost neutrality [63–65]. Patients with GERD have increased expression of CAIII in inflamed esophageal mucosa with a relocalization of expression in the basal and lower prickle cell layers in normal esophageal tissue to the suprabasal layer (which would be in contact with gastric refluxate) in inflamed tissue [28]. These findings suggest that the expression of CAIII is modified in patients with GERD as a potential protective mechanism to increase the buffering capacity of the epithelium. In contrast, patients with LPR neither show an upregulation or a redistribution [66], implying that low levels of CA isoenzymes could contribute to the pathogenesis of LPR. As already mentioned, studies have shown that the amount of CAVI, a secretory glycoprotein found in saliva, is significantly reduced in patients with esophageal and other gastric disorders [35].

Na^+/H^+ Exchanger

In addition to the buffering capacity from the production of HCO_3^- by carbonic anhydrase, a Na^+/H^+ exchanger has been demonstrated that maintains intracellular pH by removing H^+ ions from the cells [67–69]. Intracellular H^+ ions are exchanged for extracellular Na^+ via an ATPase [70–72]. Osmotic balance is maintained by active extrusion of Na^+ ions via a Na^+/K^+ ATPase [73, 74].

Na^+-dependent Cl^-/HCO_3^- Exchanger

A Na^+-dependent Cl^-/HCO_3^- exchanger has been demonstrated in rabbit esophageal cells [20, 69]. Intracellular Cl^- is exchanged for extracellular HCO_3^- to neutralize H^+ ions. In return, a Na^+-independent Cl^-/HCO_3^- exchanger, also identified by Tobey et al. [69], prevents the pH rising to alkaline levels. Future work identifying the presence of such exchangers in human esophageal and laryngeal epithelial cells is required.

Heat Shock Proteins

The esophageal epithelium regularly experiences thermal stress, and as a result heat shock proteins are produced [28]. This stress response pathway provides increased cellular protection by inducing thermotolerance to subsequent heat shock. If cells are subjected to a sublethal heat shock and allowed to recover, they can survive a second heat shock that would otherwise be lethal [75]. The majority of these stress-induced proteins are constitutively expressed and are thought to function as molecular chaperones, enabling cellular proteins to remain correctly folded and be transported to the correct destination [76]. Heat shock proteins are also thought to protect cytoskeletal structures [77, 78]. Furthermore, they have been shown to act as proteases to destroy damaged proteins that would otherwise cause the cell to undergo apoptosis [77]. Interestingly, induction of heat shock proteins has also been shown by a variety of agents other than heat, such as ethanol and acid [75, 79]. Thus many investigators now refer to these proteins more generally as the stress proteins. Yagui-Beltran et al. [79] revealed an induction of the squamous epithelium stress protein (SEP70) in cultured cells exposed to low pH, suggesting a role for this protein in acid-mediated stress response. Furthermore, the authors noted a reduction in SEP70 in samples of Barrett's esophagus. Absence of this stress-induced protein may contribute to the increased damage caused by acid reflux in patients with Barrett's esophagus. It has been shown that patients with LPR have depleted stress protein levels [80]. Furthermore, the authors demonstrated depletion of these stress proteins by pepsin in vitro. An altered stress response in LPR patients may lead to cellular injury and thus play a role in the development of disease.

Post-epithelial Defense Mechanisms

This line of defense is largely dependent on the blood supply, which delivers bicarbonate produced by erythrocyte carbonic anhydrase [81] that may neutralize refluxed acid. An increase in blood flow has been reported following exposure to low pH and bile acids [82–84].

Pathophysiology of GERD

Intermittent exposure of the esophagus to gastric refluxate does not result in the development of disease in the majority of the population because the defense mechanisms described above act to maintain mucosal integrity. In fact, based upon pH monitoring studies, up to 50 reflux episodes per day (below pH 4) are considered normal. It is proposed that inflammation and Barrett's esophagus arise when there is a breakdown in these defense mechanisms.

Pathophysiology of LPR

Gastric refluxate, containing acid, pepsin, bile, and trypsin, obviously passes through the esophagus (GER) to enter the laryngopharynx (LPR), yet patients with laryngeal symptoms and injury do not often have esophageal symptoms or injury. It is thought that LPR patients have intact esophageal defense mechanisms that prevent esophageal injury by the refluxate. For example, in the esophagus, peristaltic motility helps clear the refluxate, salivary bicarbonate neutralizes the refluxate, and mucous secretions prevent the refluxate from penetrating the epithelium. In addition, the upper esophageal sphincter (UES) closes to prevent refluxate from entering the laryngopharynx. It is thought that UES function is defective in many patients with reflux-attributed laryngeal symptoms and endoscopic findings. The larynx lacks many of the intrinsic defense mechanisms present in their esophageal counterparts such as peristalsis and salivary bicarbonate, perhaps explaining its increased sensitivity to gastric refluxate compared to the esophagus.

Reflux is thought to cause laryngeal symptoms and pathology by several different mechanisms. First, by direct contact of acid and pepsin with the epithelium—the microaspiration theory [5]. Second, the trauma theory suggests that exposure of the laryngeal epithelium to gastric refluxate alone is not sufficient to cause injury and that an additional factor, such as vocal abuse or concomitant viral infection, is necessary to cause mucosal lesions [4, 85]. Finally, the esophageal–bronchial reflex theory suggests that acid in the distal esophagus stimulates vagally mediated reflexes that cause chronic cough, which in turn causes laryngeal symptoms and lesions [86].

Differences Between LPR and GERD

Ossakow et al. compared symptoms of patients with reflux esophagitis with those of patients with laryngitis [87]. They found that hoarseness was the most prevalent symptom of patients with LPR (100%), although none of the patients with GERD reported experiencing hoarseness. Heartburn was present in the majority of patients

with GERD (89%), but only a small percentage of LPR patients (6%). Wiener et al. demonstrated abnormal pH studies in 78% of patients with hoarseness. Despite abnormal pH studies, all had normal esophageal manometry and 72% had normal endoscopy with biopsy [88]. This supports the theory that the majority of LPR patients have normal acid clearance mechanisms [32, 89]. Although both esophagitis and laryngitis are likely to be caused by the damaging effects of the corrosive refluxate, significantly more damage occurs in the larynx compared to the esophagus following exposure to acid and pepsin. This may be because the esophagus has better defense mechanisms to counteract such damage, for example, peristalsis, saliva, and bicarbonate production [4, 23]. Therefore, although there may not be sufficient reflux to cause esophagitis, it may be enough to develop symptomatic LPR.

The pattern and mechanism of LPR and GERD are different. LPR patients typically have upright (daytime) reflux with good esophageal motor function and no esophagitis, whereas GERD patients have supine (nocturnal) reflux and esophageal dysmotility [4, 90, 91]. GERD patients often have a dysfunction of the lower esophageal sphincter, while the upper esophageal sphincter has been reported to be a primary defect in LPR patients [92]. The different pattern and mechanism of reflux may explain the different manifestations observed in LPR and GERD.

Role of Nonacid Reflux in Laryngeal Inflammation Disease

Studies using combined multichannel intraluminal impedance with pH monitoring (MII–pH) reveal a positive symptom association with nonacidic reflux and a significant association between non- and weakly acidic reflux and persistent symptoms on PPI therapy [17, 93, 94]. Using multichannel intraluminal impedance (MII)–pH monitoring, Tamhankar et al. [93] showed that PPI therapy decreases the H^+ ion concentration in the refluxed fluid, but does not significantly affect the frequency or duration of reflux events. Kawamura et al. [95] reported on a comparison of GER patterns in 10 healthy volunteers and 10 patients suspected of having reflux-attributed laryngitis. Using a bifurcated MII–pH reflux catheter, the investigators found that gastric reflux with weak acidity (above pH 4) is more common in patients with reflux-attributed laryngitis compared to healthy controls. Oelschlager et al. [96] demonstrated that the majority of reflux episodes into the pharynx are in fact nonacidic. Sharma et al. [17] reported that 70/200 (35%) patients on at least twice daily PPI had a positive symptom index for nonacidic reflux. Finally, Tutuian et al. [94] also recently reported that reflux episodes extending proximally are significantly associated with symptoms irrespective of the pH of the refluxate.

Patients with signs and symptoms associated with nonacidic and weakly acidic reflux would likely have a negative pH test and would not benefit from PPI therapy. Diagnosis and treatment has focused on the acidity of the refluxate because it was thought that the other components of the refluxate would not be injurious at higher pH. However, it is now known that certain bile acids are injurious at higher pH [97, 98], and recent data supports a role for pepsin in reflux-attributed laryngeal injury

and disease, independent of the pH of the refluxate [99, 100]. Given (1) the multiple reports of refractory reflux-attributed laryngeal symptoms and endoscopic findings on maximal PPI therapy, (2) that studies using MII–pH reveal a positive symptom association with non- and weakly acidic reflux events, and (3) we now know that pepsin and bile acids are injurious at higher pH, the role of acid alone in reflux-attributed signs and symptoms has to be questioned and, subsequently, the efficacy of acid suppression therapy alone for treating reflux.

Anti-reflux fundoplication surgery is one of the few options for patients with persistent reflux-attributed symptoms and endoscopic findings. Unlike medical therapy, which does not stop reflux from occurring but only increases the pH of the refluxate, surgical therapy restores the physiologic separation between the abdomen and thorax and strengthens the LES, thereby preventing refluxate from coming up the esophagus. Iqbal et al. [101] recently reported a study in which 85% of patients who had a fundoplication for extra-esophageal symptoms of reflux had a positive outcome. The majority of these patients had refractory symptoms on maximal acid suppression therapy. Once again, these findings question the role of acid alone in the development of reflux-related pathology and highlight a potential role for the other components of the refluxate.

A role for pepsin in nonacid reflux has been postulated in the recent literature. As already stated, this enzyme is maximally active at pH 2 but can cause tissue damage above this pH, with complete inactivation not occurring until pH 6.5 is reached [21, 22, 102]. While pepsin is inactive at pH 6.5, it remains stable up to pH 8 and thus can be reactivated when the pH is reduced. Pepsin is not irreversibly inactivated until pH 8.0 is reached [1, 22]. Thus, even if pepsin that has been detected in, for example, laryngeal epithelia, is inactive [66, 80] (mean pH of the laryngopharynx is 6.8), it would be stable and thus could reside in an inactive/dormant form in the laryngopharynx but have the potential to become reactivated by a decrease in pH, either triggered by a subsequent acid reflux event that lowers ambient pH or, perhaps, once it is taken up by laryngeal epithelial cells and transported through an intracellular compartment of lower pH [99, 100, 103, 104].

We have proposed mechanisms by which pepsin may cause laryngeal epithelial cell damage at pH 7, and this may occur when refluxate is nonacidic. This may help explain why some patients have refractory symptoms on maximal PPI therapy as well as help explain the reported symptom association with nonacidic reflux events. We have reported mitochondrial and Golgi damage in laryngeal epithelial cells exposed to pepsin at pH 7 [103], and cell toxicity was demonstrated using the MTT cytotoxicity assay. Pepsin at pH 7 was also found to significantly alter the expression levels of multiple genes implicated in stress and toxicity. Of greatest clinical significance, pepsin (0.1 mg/ml, pH 7) was found to induce a pro-inflammatory cytokine gene expression profile in hypopharyngeal FaDu epithelial cells in vitro under conditions that were similar to those that contribute to disease in gastroesophageal reflux patients [104]. Collectively, these data suggest a mechanistic link between exposure to pepsin (even in nonacidic refluxate) and cellular changes that lead to laryngopharyngeal inflammatory disease. In this context, the unexpected finding that pepsin is taken up by human laryngeal epithelial cells by receptor-mediated

endocytosis is highly relevant. Pepsin has been previously assumed to cause damage by its proteolytic activity alone, but the discovery that pepsin is taken up by laryngeal epithelial cells by receptor-mediated endocytosis opens the door to a new mechanism for cell damage. It is possible that inactive, but stable, pepsin at pH 7 taken up by laryngeal epithelial cells becomes reactivated once inside the cell in compartments of lower pH, such as late endosomes and the trans-reticular Golgi (TRG) where pepsin's presence has been confirmed [100]. The role of pepsin in nonacid extra-esophageal reflux that can reach other sites of the aerodigestive tract including the lung needs to be investigated, since the refluxate is not likely to be acidic by the time it reaches these proximal structures. The therapeutic potential of receptor antagonists and irreversible inhibitors of peptic activity to prevent pepsin uptake and/or reactivation are currently being studied.

Other Clinical Manifestations of EER

EER has been implicated as a source or cofactor of inflammatory disease of the mucosa of the entire head and neck. Subsites affected by reflux include mucosa of the nose, paranasal sinuses, eustachian tube and middle ear, nasopharynx, oropharynx, hypopharynx, larynx, subglottis, trachea, and lower airway. Connection of EER to specific disease states has been demonstrated in an ever expanding list of conditions of the aerodigestive tract including otitis media, sinusitis, cough, sleep-disordered breathing, laryngitis, laryngospasm, airway stenosis, and lower airway problems such as asthma, chronic obstructive pulmonary disease, interstitial pulmonary fibrosis, and chronic lung transplant rejection. Evidence for these has been based largely on clinical findings that correlate with pH probe studies confirming extra-esophageal reflux or detection of elements of refluxate in the subsite in question. Animal and basic science studies have been used to propose or confirm a mechanism, but in most cases, direct cause and effect in the human condition has yet to be confirmed. Mechanism for disease is typically explained as occurring either by direct contact of refluxate and resulting inflammation of the mucosa or via a vagally mediated neurogenic process as previously discussed.

Key Points

- Reflux is a common source of chronic inflammation in the esophagus and laryngopharynx.
- LPR is different from GERD. Common symptoms of LPR include hoarseness, cough, throat clearing, globus sensation, and dysphagia. GER is more commonly associated with heartburn.
- Intermittent reflux is a physiological process and does not result in injury/disease in the majority of the population, as there are several defense mechanisms present

to protect against its damaging factors. When reflux is in excess and/or there is a breakdown in the defense mechanisms, injury and disease result.

- Extra-esophageal reflux has been implicated in the development of multiple conditions of the aerodigestive tract including Barrett's esophagus, laryngitis, pharyngitis, otitis media, sinusitis, chronic cough, airway stenosis, asthma, and other respiratory diseases. It is also thought to play a significant role in carcinogenesis of the esophagus and laryngopharynx.
- Recent evidence highlights a role for nonacid reflux in injury and disease. Pepsin and bile acids can cause cell damage at high pH and thus in nonacidic reflux. The potential therapeutic role of pepsin inhibitors and receptor antagonists is currently being studied.

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Chapter 3
Making an Accurate Diagnosis of GERD

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Keywords Reflux • pH • Manometry • Endoscopy • Gastroesophageal reflux disease (GERD)

Introduction

Gastroesophageal reflux disease (GERD) is a common problem, affecting 20% of the population in some manner on a monthly basis [1]. For most individuals with GERD, the gastric refluxate in the esophagus causes heartburn, the most common symptom associated with GERD. Most patients are both diagnosed and treated by a trial of acid antagonist, most commonly, proton pump inhibitors (PPIs). Although less common, a substantial number of patients experience symptoms outside the esophagus, usually in the throat or lungs. It is accepted that gastroduodenal contents refluxed into the esophagus and aspirated through the vocal cords may result in what is often referred to as extraesophageal or airway-type symptoms and pathology. These can range from cough and hoarseness to asthma and pulmonary fibrosis. It is important to realize that almost all of these presentations may have other etiologies and contributing factors. Therefore, although it is important to recognize the possible role that GERD may be playing, it is also imperative that GERD is worked up and diagnosed appropriately in order to select the proper patients to treat and to select the proper therapy.

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Etiology of Reflux and Associated Symptoms

The primary anatomic cause for GERD is a dysfunction of the anti-reflux barrier complex located around the lower esophageal sphincter (LES). Within this complex are several components that all contribute to the prevention of reflux. The LES acts as a one-way valve that is designed to allow passage of food from the esophagus to the stomach while preventing the reflux of gastric contents into the esophagus. The LES maintains a resting pressure that is designed to relax during a swallow. A phenomenon of transient lower esophageal sphincter relaxation, in which the LES relaxes independent of swallow induction, has been associated with reflux events. When the pressure drops and is overcome by increased intra-abdominal pressure, the reflux episode is generated. In addition, there is a small group of patients who have a chronically hypotensive LES such that the resting pressure is insufficient, allowing free reflux to occur. Another component of the anti-reflux barrier complex is the angle of His, an angulation formed by the esophagus, hiatus of the diaphragm, and cardia of the stomach at the level of the gastroesophageal junction (GEJ). Most commonly, the angle of His is disrupted secondary to a hiatal hernia, a weakness of the diaphragmatic crura that results in a gap between the crus and the GEJ. The natural evolution of hiatal hernias is to gradually widen over time due to increased pressure and stress on the diaphragm. Common causes for this are chronic cough, obesity, pregnancy, and repetitive straining. The hernia defect allows the GEJ to slide in and out of the mediastinum. The loss of external compression in combination with the loss of the angle of His causes the anti-reflux complex and LES to become functionally incompetent allowing reflux to occur.

In addition to defects of the LES, reflux can be augmented by anatomic dysfunction proximal and distal to the LES. Dysmotility disorders of the esophagus can contribute to incomplete clearance of the esophagus. While this does not directly cause reflux, it can result in prolonged exposure of refluxate to the distal esophagus and regurgitation, thus accentuating reflux-related symptoms and manifestations. Similarly, delayed gastric emptying and gastric atony can cause pooling of material in the stomach, providing a larger pool of material that can be refluxed in a patient who already has LES dysfunction.

Understanding how dysfunction of the anti-reflux complex causes GERD helps explain why patients can develop a multitude of typical and atypical symptoms. Typical reflux symptoms are heartburn, regurgitation, acid/water brash, chest pain, and dysphagia. Heartburn and regurgitation have a high probability (and thus some diagnostic value) for being associated with GERD. As one proceeds further down the list of symptoms, there is a lower likelihood of association with GERD. Atypical symptoms of GERD include cough, hoarseness, aspiration, globus sensation, and nausea. These symptoms are called atypical because there are multiple disease processes other than reflux that can produce these symptoms. Patients with primary pulmonary disease can often present with atypical symptoms such as cough. Therefore, additional confirmatory testing is needed to help make an accurate diagnosis if GERD is suspected to play a role in a patient's symptoms or disease.

Endoscopy

Flexible endoscopy of the esophagus and stomach can help identify anatomic etiologies for GERD and resultant pathologic changes. Examination of the esophageal mucosa allows for visual identification of erosions and changes in epithelium such as metaplasia that may be secondary to reflux and acid exposure. If any of these changes are visualized, biopsies should be taken to make a histologic diagnosis. Visualization of the esophagus at the level of the *Z*-line can also identify the presence of a hiatal hernia. Progressing further into the stomach, gastric dilation and retained food may suggest gastric dysmotility that could contribute to reflux. Visualization of bile may also suggest a component of bilio-duodenal reflux. Retroflexion of the endoscope in the stomach allows for visualization of the gastroesophageal junction and cardia of the stomach (Fig. 3.1). It is at this point that hiatal hernias can often be more clearly identified. With large hiatal hernias or paraesophageal hernias, patients can develop Cameron's ulcerations, which can contribute to the atypical presentation of anemia.

Upon endoscopic retroflexion, the flap valve of the GE junction can be graded, based on the Hill classification to assess the competency of the valve. The Hill classification grades the gastroesophageal valve from I to IV. The grading system is as follows: Grade I—prominent fold of tissue close to the endoscope extending 3–4 cm along the lesser curve, Grade II—less prominent fold with occasional opening and closing of the valve around the endoscope during respiration, Grade III—no prominent fold and loose gripping of the endoscope by the tissue, and Grade IV—hiatal hernia with no fold or gripping of the endoscope by the tissue resulting in visible esophageal squamous epithelium. The altered geometry of the gastroesophageal flap valve is associated with deterioration of LES pressure and a mechanically compromised sphincter. Grade I valves are seldom associated with reflux, while Grade IV valves have a high

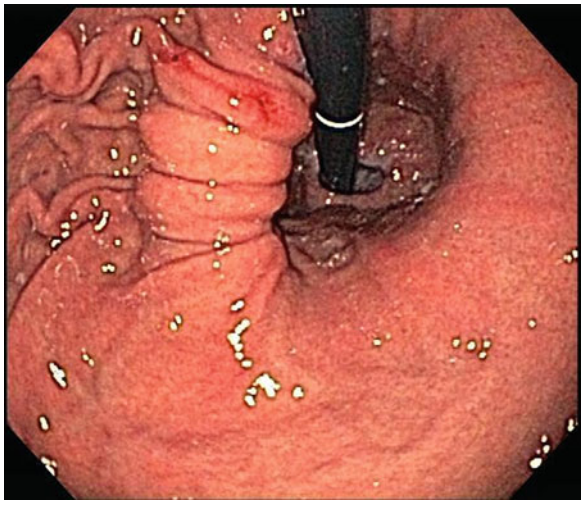

Fig. 3.1 Endoscopic gastroduodenoscopy (EGD) showing a hiatal hernia

association with reflux. There is more of a gray area with Grade II and Grade III valves, and prediction of GERD strictly based on these endoscopic findings is not strong. Therefore, additional testing should be performed to confirm GERD [2].

Upper Gastrointestinal Esophagram

A real-time esophagram performed under fluoroscopy can help identify anatomic abnormalities that can cause GERD. For example, being able to identify the location of the GEJ relative to the diaphragm can determine the presence of a sliding hiatal hernia. Stomach that is visualized above the diaphragm can help with the diagnosis of a more severe hiatal hernia or a paraesophageal hernia. As discussed earlier, these changes in the LES and angle of His are major contributors to the development of reflux. Watching a contrast bolus being swallowed can provide the unique view of active reflux of contrast material from the stomach into the esophagus. An esophagram can also identify other etiologies for reflux-like symptoms that are due to other disorders. For example, patients with dysphagia could have esophageal dysmotility disorders such as achalasia or esophageal spasm as opposed to a reflux etiology such as a peptic stricture. The esophagram for these motility disorders shows characteristic findings of a dilated esophagus with bird's beak tapering or a corkscrew esophagus that are pathognomonic for nonreflux etiologies of dysphagia. Esophageal neoplasms and diverticula can also cause dysphagia, yet can be visualized as specific anatomic entities on an upper gastrointestinal (UGI) series in which reflux is not related to the abnormality. While these are just some of the findings that can be seen on esophagram, these examples emphasize the importance of differentiating anatomic etiologies for reflux from other anatomic pathologies that share overlapping symptomatic presentations, since the treatment plans for each disease process is very different. Because obtaining an UGI esophagram is a relatively noninvasive way to characterize the anatomy of the esophagus, GEJ, and stomach, it should be considered when evaluating a patient for reflux. Given its particular benefit of displaying the relational anatomy of the esophagus and stomach, it is particularly useful to surgeons involved in the evaluation of GERD (Fig. 3.2).

Manometry

Just as characterizing the anatomy of the GEJ and LES is important for understanding reflux, characterizing the physiology of the LES also contributes to making the diagnosis of GERD and helping to develop a treatment plan. Esophageal manometry is a diagnostic tool that characterizes esophageal pressure, propulsion, and coordination. This procedure involves insertion of a multichannel catheter transnasally, across the esophagus, and beyond the LES into the stomach. Typically, ten liquid swallows are performed. With each swallow, the catheter's transducers capture the pressure generated by the segments of the esophagus in a temporal fashion.

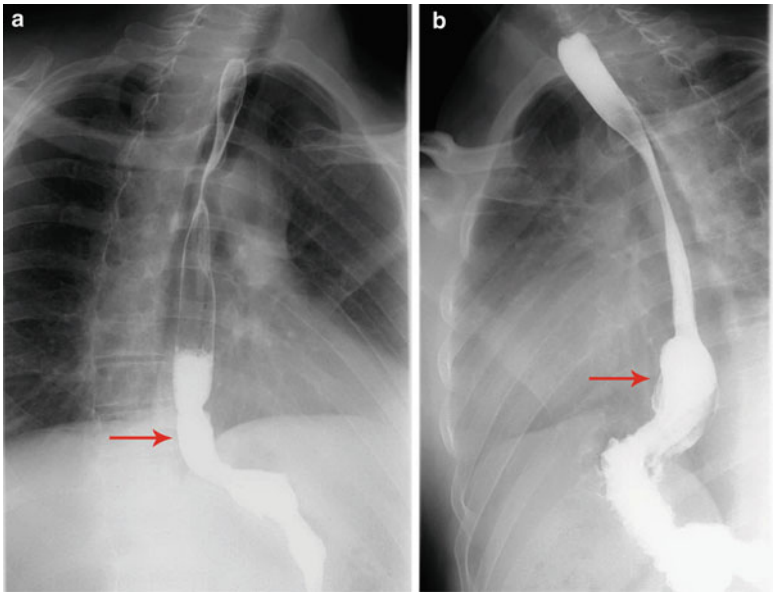

Fig. 3.2 (**a**, **b**) UGI esophagram demonstrating a hiatal hernia

In doing so, the upper esophageal sphincter, esophageal body, and lower esophageal sphincter are evaluated. The exact location of the lower esophageal sphincter can be identified, which is important for accurate placement of a pH probe. pH monitoring, discussed later in this chapter, is the gold standard for the detection of reflux and requires exact placement of the distal probe 5 cm above the LES in order to provide accurate measurements.

A temporal view of the peristaltic waveform helps to characterize the coordination of the esophageal contraction and give insight into the efficiency of propulsion. Weakness of the lower esophageal sphincter (defined by low resting pressure) in the absence of motility disorders can help identify an anatomic cause of reflux [3]. The length of the LES can also be measured with manometry. Short LES length has been shown to be associated with reflux. In addition, a dual high-pressure zone on esophageal manometry testing can help identify the presence of a hiatal hernia that can also result in reflux (Fig. 3.3).

As discussed earlier, abnormalities with esophageal motility and LES function can result in pathologies that are not related to reflux, but have reflux-like symptoms. Esophageal dysmotility can result in uncoordinated propulsion of food into the stomach. Coupled with an incompetent LES this can result in stasis of gastric contents in the esophagus and regurgitation, particularly in the supine position. While a patient may be regurgitating and having dysphagia symptoms, treatment for dysmotility is very different from treatment for reflux, and in the case of surgical treatment, the operations are completely different. Because of the ability of manometry to differentiate between primary esophageal motility disorders from reflux, it is an

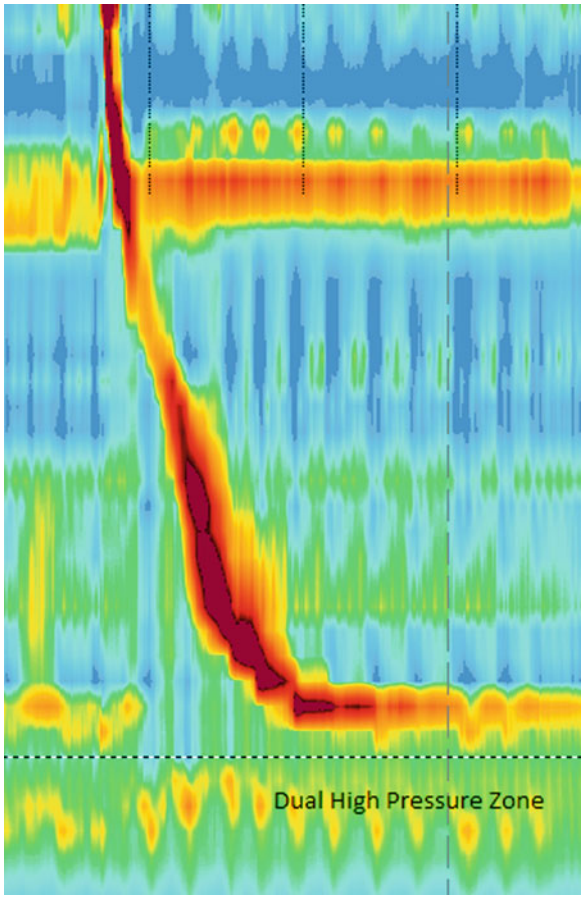

Fig. 3.3 High-resolution manometry tracing showing decreased LES pressure and a hiatal hernia

important and necessary preoperative test to help operative decision-making should an anti-reflux operation be indicated. Specifically, for a patient who has been identified to have reflux and is a candidate for a surgical anti-reflux operation, if the patient is also shown to have severe esophageal dysmotility, a complete fundoplication may cause a functional esophageal obstruction, resulting in worsening symptoms and inappropriate treatment of disease.

Ambulatory pH Monitoring

Ambulatory pH monitoring has long been established as the gold standard for measuring GERD [4–6]. pH monitoring is performed most commonly with a transnasally placed catheter that has a pH electrode at the distal tip (Fig. 3.4). The electrode

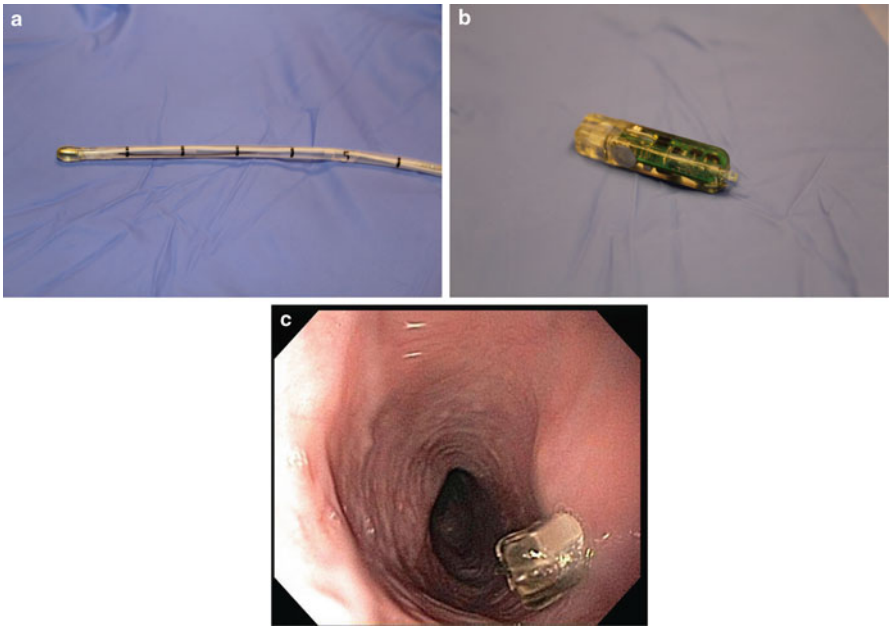

Fig. 3.4 (**a**) pH catheter. (**b**, **c**) A Bravo probe

is positioned 5 cm above the GEJ as determined by an in-line pressure transducer and pull-through technique, esophageal manometry, or upper endoscopy (though by far the most accurate method is manometry). The electrode is connected to a portable recording device that streams continuous pH readings from the electrode. The recorder also allows the patient to simultaneously mark when symptoms are present to allow for symptomatic correlation analysis. Alternatively, a wireless capsule with a pH electrode can be placed in a similar fashion to record continuous distal esophageal pH (Bravo system, Medtronic, Minneapolis, MN). The probe communicates to a portable recording device via a radio signal and is often tolerated better by patients because of the lack of transnasal catheter (Fig. 3.4).

All acid-suppression and promotility medications are stopped prior to testing. Proton pump inhibitors are withheld for 7 days, and H2 blockers are withheld for 48 h prior to the testing to determine maximum esophageal acid exposure. The probe is worn for a 24-h period during which the patient is instructed not to alter their daily routine or diet in order to most accurately represent a typical day. After the 24-h period is complete, the pH catheter is removed, and the data are downloaded and analyzed. Alternatively, the wireless capsule pH probe disengages over time and is expelled from the body.

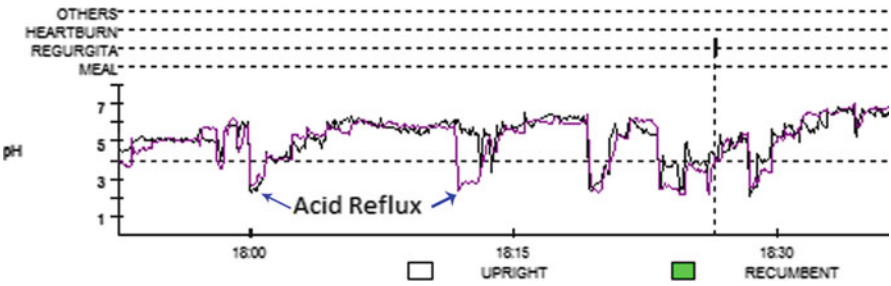

Fig. 3.5 24-h Ambulatory pH tracing

Several parameters are measured to analyze for GERD: (1) Percentage of time pH < 4.0, (2) number of reflux episodes, (3) number of reflux episodes >5 min, (4) mean duration of reflux episodes, and (5) longest reflux episode. These are analyzed for both upright and supine periods and for the total duration of the test (Fig. 3.5). A calculation is performed based on these parameters, and a score is generated based on the work by Johnson and DeMeester [7]. The DeMeester score is positive for acid reflux when the value is greater than 14.72. The score has been shown to have good correlation with a diagnosis of acid reflux. When a score is borderline, correlation of a patient's symptoms with quantitative measurements of pH can be further examined to assist in making a diagnosis of GERD.

Despite the excellent predictive value of pH testing for diagnosing GERD, the sensitivity for detecting reflux that travels more proximally and is at risk for aspiration is not ideal. Therefore, discerning the role of GERD in patients with respiratory symptoms with traditional pH monitoring is less clear. Studies have been performed to measure pharyngeal pH as a surrogate for pharyngeal reflux by positioning the probes relative to the upper esophageal sphincter as opposed to the LES [3, 8]. The value of doing so is that there can be objective measurement of pharyngeal acid exposure. Studies have shown good correlation between positive pharyngeal pH testing with response to medical and surgical therapies for reflux, thus adding value to pharyngeal pH monitoring [9, 10]. Interestingly, however, based on the current data, the correlation between positive pharyngeal pH and esophageal pH is not strong, which emphasizes that patients can still have reflux and associated respiratory symptoms or microaspiration without a quantitatively positive study [3]. Ultimately, the current opinion is that in a patient who has a positive esophageal pH test with related respiratory symptoms without other identifiable causes for those respiratory symptoms, there is a reasonable probability that reflux is the etiology. Similarly, in a patient with a positive pharyngeal pH test, there is a strong correlation with microaspiration and respiratory symptoms. Nonetheless, the pH monitoring still should be evaluated in the context of the patient's symptoms, anatomy, and other functional information obtained from studies described above.

pH Impedance Testing

A limitation of pH testing is the inability to determine reflux while patients are on acid-suppression medication. In addition, pH testing also does not detect the presence of nonacidic gastroduodenal reflux. Impedance testing has been used in combination with pH monitoring to attempt to evaluate these patients [11, 12]. Impedance probes have multiple sensors placed in a circumferential orientation along the length of the catheter (Fig. 3.6). As refluxate progresses proximally up the esophagus, the resistance measured by the electrode decreases (liquid conducts electrical current more easily than air). As the refluxate continues to move proximally, the resistance measurements decrease in sequence along the more proximal electrodes. The progressive decrease in resistance results in a characteristic tracing. The accuracy of impedance testing is controversial, though some studies have suggested that the combination of traditional pH testing with impedance monitoring provides a more sensitive test for acid and nonacid reflux. However, there are still few definitive studies available showing the ability of impedance monitoring to predict the response to medical or surgical GERD therapies.

Fig. 3.6 (**a**) Impedance catheter. (**b**) Tracing showing reflux

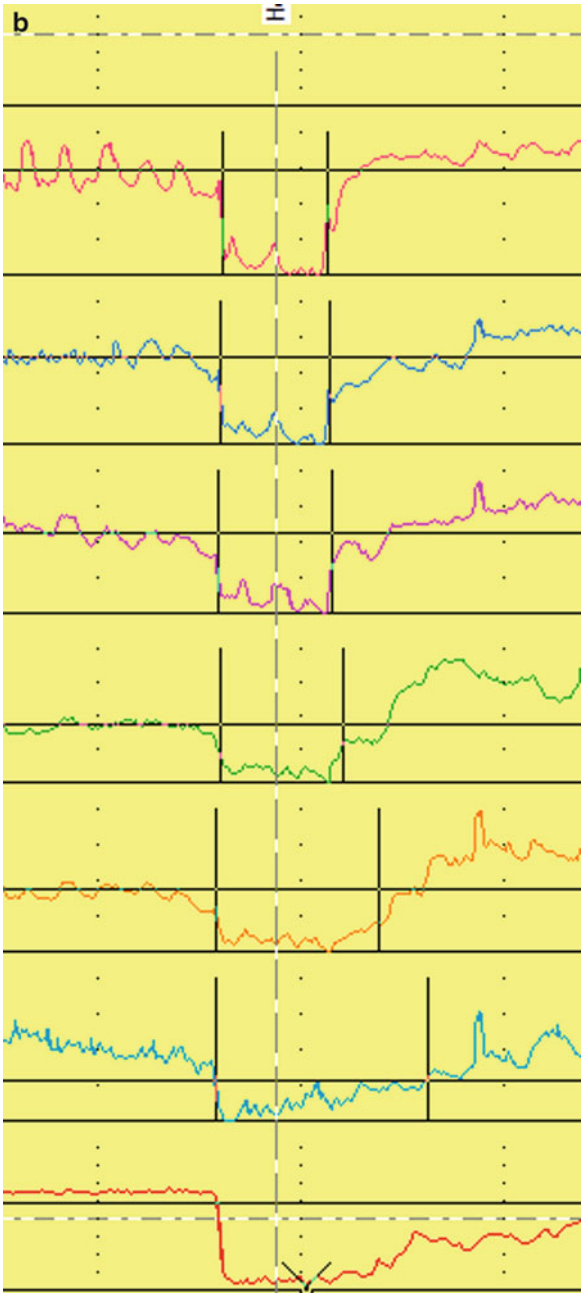

Fig.3.6 (continued)

Alternative Testing Modalities for Reflux

Several other tests are being investigated that may help with the diagnosis of reflux. These tests are based on the reflux and subsequent microaspiration of unique gastric markers. In addition to being more specific for microaspiration, they may also be less invasive tests compared to traditional 24-h pH monitoring and BRAVO probe placement. Sputum pepsin analysis is one such test. Pepsin is made only in the stomach and when refluxed out of the esophagus is phagocytosed by laryngeal epithelium. Therefore, induced sputum can be analyzed with immunoassay testing to identify the presence and quantify the density of pepsin protein [13, 14]. This test appears to have a high specificity for reflux based on initial studies. A similar test involves analyzing macrophages of induced sputum specimens for the presence of lipid [15, 16]. The lipid-laden macrophage index (LLMI) is a calculation of intracellular lipid that comes from food particles that are refluxed and aspirated. Alveolar macrophages are isolated and stained. The amount of lipid is then graded by a pathologist or, more recently, with high-resolution automated 3-D imaging. The LLMI is then calculated, and if it exceeds a defined threshold, suggests a diagnosis of reflux. While these are both new methods that still require more validation, they may offer less invasive alternatives to assist in the diagnosis of reflux.

Conclusion

Gastroesophageal reflux disease is a common problem that affects the general population. GERD can manifest itself in multiple ways and can present with atypical respiratory symptoms. Because multiple disease processes can share these same symptoms, accurate diagnosis of GERD is critical in order to select the correct patients for treatment. Understanding the gastroesophageal anti-reflux complex and how changes in gastroesophageal and hiatal anatomy contribute to reflux will allow the practitioner to understand and interpret the tests that are available in order to differentiate GERD from other diagnoses. Each diagnostic test and a further understanding of the unique information each provides adds components for making an accurate diagnosis of GERD. pH testing is the gold standard test for diagnosing reflux. Endoscopy and upper gastrointestinal esophagram can help characterize the esophageal, LES, and gastric anatomy. Esophageal manometry contributes valuable information about the physiology of the esophagus and LES, findings of which may contribute to augmentation of reflux symptoms. By synthesizing all of the data, the practitioner can then differentiate GERD from other disease processes that have similar symptoms and select the appropriate patients for treatment.

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Chapter 4
GER and Aspiration in Children

Jonathan E. Spahr and Raymond C. Maguire

Keywords Gastroesophageal reflux (GER) • Aspiration • Children • Lung disease • Mechanism for reflux

Mechanisms for Reflux and Aspiration Causing Lung Disease in Children

The developmental and anatomic differences in infants and children, in comparison to adults, present a situation that allows for reflux and aspiration to occur quite readily, even in healthy individuals. The degree and secondary effects of reflux are what determine whether reflux should be termed GERD [3]. Infants, especially, spend a good portion of their day supine and consume a mostly liquid diet, which allows for a greater chance of gastric contents to be refluxed toward the upper airway and potentially gain access to the lower respiratory tract. This coupled with other factors that could occur (such as improper feeding and burping) or swallowed air (aerophagia) can turn normal reflux into GERD.

Aspiration of oral contents or refluxed stomach contents can occur more readily in an infant with poor suck–swallow–breathe coordination or less developed airway protective mechanisms. Additionally, the presence of disorders such as laryngomalacia, laryngeal clefts, and other less common defects can further compromise normal mechanisms

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that protect the airway and lead to lung disease. Neurocognitive and neuromuscular disease can compromise swallowing and airway protection. Acute respiratory disease that causes tachypnea and/or upper airway congestion can also disrupt normal swallowing in infants and children. Finally, obstructive lung disease and its treatments can exacerbate GERD. Increased work of breathing and increased end-expiratory pressure from the thorax can put pressure on the stomach and consequently overcome lower esophageal sphincter (LES) tone, leading to reflux of gastric contents. Beta-agonists used to treat acute obstructive lung disease can also decrease LES tone.

Aspiration from Above Versus Below

Aspiration of anything into the lungs can have significant consequences. Certainly gastric contents that contain acid and pepsin can have injurious effects on the lungs. However, whether the aspirate starts in the oral cavity or from the stomach may have little significance on the end result because aspiration from either direction can cause lung disease. This can be especially true in infants and children, who are likely to have nonacid reflux [4]. Determining the origin of the aspirate, however, can have implications for diagnostic testing and treatment strategies.

Antegrade aspiration often occurs due to disorders of swallowing, anatomic defects of the glottis and tracheoesophageal structures, and neurocognitive defects, which can lead to aspiration of oral contents. Swallowing coordination develops at around 34 weeks gestation. Infants born prematurely and with medical complications are at risk for disorders of swallowing and, consequently, aspiration. Infants and children with certain disorders are predisposed to having aspiration from above. Such disorders include neurocognitive and neuromuscular syndromes, craniofacial abnormalities, and anomalies of the glottis and esophagus. Finally, infants and children without underlying medical conditions may also develop a disorder of swallowing. Fatigue and intercurrent illness can acutely impact swallowing coordination, as can prolonged intubation for severe illness. In the above conditions, when a child presents with respiratory tract disease, aspiration is usually suspected. In fact, in children who have recurrent pneumonia, underlying defects in aerodigestive tract or aspiration syndromes account for the root cause of pneumonia greater than half of the time [5]. When a predisposing factor is not readily evident, antegrade aspiration or GERD may not be immediately suspected.

Gastroesophageal reflux can lead to aspiration and symptoms of airway disease. If refluxed gastric contents travel retrograde and reach the glottis, they can be aspirated into the lungs. The aspirated gastric contents, whether acidic or nonacidic, can be irritating to the airways and lead to inflammation and mucus secretion. Furthermore, silent aspiration of acidic or nonacidic gastric contents can provoke upper airway receptors and precipitate asthma symptoms. This is often manifested in a cough, but even as the aspirated material is cleared by the cough, the stimulus remains and bronchospasm occurs, which can exacerbate obstructive lung diseases like asthma, cystic fibrosis (CF), and bronchopulmonary dysplasia (BPD). Finally, reflux can stimulate airway obstruction by a reflex initiated in the lower esophagus, and receptors in the lower esophagus, when stimulated by acid or pressure, can cause bronchospasm.

There are subsets of patients that can have both antegrade aspiration and GERD. Children with tracheoesophageal fistulas (TEF) are at particular risk for having clinically significant aspiration and reflux. Reflux often persists even after TEF repair, but functional impairment from GERD after TEF repair appears to be minimal [6]. Finally, reflux and aspiration can be seen more frequently in children with certain respiratory diseases associated with congenital diaphragmatic hernias, prematurity, cystic fibrosis, asthma, hiatal hernias, and other diseases of the aerodigestive tract. Treatment of such diseases with agents such as beta-agonists and anticholinergics can exacerbate GER.

When to Suspect GERD and Aspiration

Whether aspiration is from above or below, the most common signs of aspiration are wheeze and cough, which are often more pronounced at night or after eating. Chronic cough is a common manifestation of GER. Other signs of reflux and aspiration include gagging, stridor, and hoarseness. However, an infant with GER may simply have colic. Older children with GER may be able to describe symptoms as "baby barfs," "wet burps," or "hot burps," but reflux may occasionally be silent. In extreme cases, infants and children may present with failure to thrive, apnea, and recurrent pneumonias. In most cases, however, a clinical syndrome affecting the child's lungs is identified, and deciding whether GERD has a role in causing or exacerbating that clinical syndrome can be challenging. Some of those clinical syndromes are discussed below (Table 4.1).

Asthma and Reflux

The pediatric data supporting a relationship between reflux and asthma is not as robust as the adult data. Nevertheless, there does appear to be a relationship between asthma and GERD. Controversy occurs, however, in whether reflux exacerbates asthma or is exacerbated by asthma, or if the two pathologies are unrelated. Epidemiologic data from children with asthma would suggest that GERD has a

Table 4.1 Clinical syndromes associated with reflux in infants and children

Asthma
Vocal cord dysfunction
Recurrent pneumonia
Bronchiectasis
Cystic fibrosis
Non-cystic fibrosis bronchiectasis
Bronchiolitis obliterans
Chronic lung disease of infancy (bronchopulmonary dysplasia)
Apnea
Recurrent croup

significant prevalence in this patient population (19.3–80%) [7, 8], and multiple mechanisms for reflux-related asthma symptoms have been proposed [8].

Given that there are many phenotypes of asthma, GERD should be considered in children with nonatopic features and difficult-to-control asthma. Kwiecien et al. [9] found that in children fulfilling diagnostic criteria for asthma, nonatopic children had more intense acid GERD, nocturnal asthma symptoms that were more difficult to control, and asthma symptoms that developed earlier in life. Stratifying wheezing infants into atopic (those with eczema or allergy) and nonatopic phenotypes may allow for better recognition of GERD-induced asthma and explain why conventional asthma therapy may not be effective for certain children with asthma symptoms.

Most pediatric pulmonologists would consider treatment of GERD, whether silent or symptomatic, in a child who has difficult to control asthma. Clearly, there is a relationship between asthma and GERD. What is not clear is whether there is a significant relationship between treatment of GERD and asthma control. That is, there are few data to suggest that treating GERD has any impact on asthma control. While GERD symptoms can be improved with medical treatment, results appear to be mixed when it comes to the effects of GERD treatment on improving asthma control [10, 11]. Some studies would even suggest potential harm of using reflux medications in poorly controlled asthmatics without symptoms of GER [12]. Antegrade aspiration would be unusual in asthma unless the child was experiencing a severe asthma exacerbation.

Vocal cord dysfunction (VCD) should be considered in difficult to control asthma, either as an explanation for symptoms or as a comorbid condition associated with asthma. It is especially necessary to consider VCD in the adolescent and young adult population with asthma symptoms when patients do not respond to standard asthma therapy. The exact cause of VCD (or paradoxical vocal fold motion—PVFM) is unknown. However, GERD has been identified as a common comorbidity in patients diagnosed with VCD [13]. It may be that acidic or nonacidic reflux to the level of the glottis induces an airway protective reflex leading to PVFM, or chronic reflux irritates the glottis allowing for other stimuli to provoke PVFM.

Recurrent Pneumonia and Reflux/Aspiration

Children who have underlying conditions predisposing them to aspiration are at risk for pneumonia. Neurocognitive disability is the most common cause of recurrent pneumonia in children with chronic health conditions [5]. Either poor motor control of oral secretions or diminished sensory response to aspirated materials allows oral contents to enter the lower airways. The oral contents serve as a vehicle for oral flora, usually bacteria, to invade the lung and cause pneumonia. Poor dentition is a common comorbidity in children with neurocognitive disability, and the enhanced colony count of aspirated bacteria can more readily overwhelm the anatomic and immune defenses that protect the lower respiratory tract and lead to aspiration pneumonia.

It would be unusual for otherwise healthy infants and children to have aspiration of oral contents. However, aspiration of oral contents may be "silent." That is, the aspirated contents may not cause immediate symptoms of choking or gagging yet result in recurrent lower airway infection. In this situation, anatomic defects should be considered. Defects may exist at the glottic level (laryngeal clefts) or between the trachea and esophagus (TEF). Modified barium swallow studies can be helpful in distinguishing whether aspiration of oral contents occurs. If TEF is suspected, barium must occasionally be instilled into the esophagus under pressure to demonstrate connections between the esophagus and trachea, and these relatively noninvasive barium studies can serve as screening studies to determine if further evaluation is needed with airway endoscopy.

Aspiration of refluxed gastric secretions can also predispose children to recurrent pneumonia. This is another situation that occurs predominantly in children with neurocognitive disorders that have poor airway protective mechanisms. While reflux and aspiration can occur in otherwise healthy children, this is infrequent, and refluxed material is often cleared by pulmonary host defense mechanisms. In children with chronic lung disease, aspirated gastric contents can exacerbate their lung disease.

The geographic location of pneumonic infiltrates is partially dictated by the age and developmental status of the patient and can be an important consideration when evaluating children with recurrent pneumonia. In infants or children who spend most of their time lying supine, aspirated contents may preferentially localize to upper and posterior lung zones. In older individuals who are mostly upright, aspirated contents tend to reach lower lung zones.

Bronchiectasis and Reflux

Chronic aspiration can lead to bronchiectasis, and reflux and aspiration can also exacerbate bronchiectasis. In children, bronchiectasis is usually due to cystic fibrosis (CF), but non-CF bronchiectasis may be present. In patients with CF with or without bronchiectasis, GERD is quite common and linked to the fact that this obstructive lung disease and its treatments increase the likelihood that GERD will occur. In CF, manual chest physiotherapy (CPT) can predispose infants and children to have worsened GERD. When performed in the "head down" position over many years, CPT may lead to worsened pulmonary outcomes in patients with CF [14]. In a progressive lung disease such as CF, the mitigation of any exacerbating factors is of utmost importance and constitutes the reason why most patients with CF will be aggressively treated for GERD.

In non-CF bronchiectasis, aspiration can be a significant contributor to lung disease. Li et al. [15] found in 101 children with non-CF bronchiectasis that nearly 25% of the cases could be attributed to aspiration, and 11% had symptoms of GERD. Additionally, chronic aspiration of oral or gastric contents can lead to repeated infection or injury of the lower airways; with associated repetitive episodes of chronic infection and inflammation, bronchiectasis can occur and evolve.

Bronchiolitis Obliterans and Reflux

Bronchiolitis obliterans (BO) rarely occurs in healthy children. When it is diagnosed, it is usually the result of an acute insult such as viral infection or toxic inhalation. In children with lung transplantation, however, BO is quite common and represents a devastating manifestation of chronic rejection that is often relentlessly progressive and leads to allograft loss and recipient death. Bronchiolitis obliterans is an irreversible scarring of small airways that can be rapidly and relentlessly progressive and is largely responsible for mortality rates following lung transplantation that are substantially higher than that for recipients of other solid organ transplants. Recipients of hematopoietic stem cell transplantation (HSCT) are also predisposed to developing BO, but this occurs less often than in the lung transplant recipient.

Because of its poor prognosis, prevention of BO and treatment of its causes are of paramount importance. GERD has been identified as a prevalent factor following lung transplantation that appears to have a role in promoting the development of BO. Factors that may predispose individuals with lung transplantation to the development of GERD-associated BO include delayed gastric emptying (with or without vagal nerve damage), immunosuppression, and preexisting GERD from end-stage lung disease. GERD is highly prevalent in adult lung transplant recipients, and GERD is nearly universal in children who have received lung transplants [16].

Medical therapy can be helpful in controlling the symptoms of GERD, but there is concern that acid suppression alone may not be sufficient to control the effects of GERD on the induction and/or progression of BO, as pepsin and bile acids in refluxed gastric material can also provoke an inflammatory response in the lungs and have been linked to BO [17]. Due to concern that any inflammatory reaction in the transplanted lung can have significant long-term consequences that lead to BO and the high prevalence of GERD in lung transplant recipients, many transplant centers choose to be aggressive with treating GERD and recommend antireflux surgery.

Chronic Lung Disease of Infancy and Reflux/Aspiration

Children with chronic lung disease of infancy (bronchopulmonary dysplasia, BPD) have a high prevalence of GERD, but whether there is a clinical correlation between severity or symptoms of BPD and GERD is unknown. This may represent a situation in which these two clinical entities exist in parallel and have no significant effect on each other. Akinola et al. looked at a large, single-center population of children (born <32 weeks gestation) and found no link between clinical symptoms of BPD and acidic GERD, even though the incidence of GERD was 63% in this patient population [18].

It is easy to see why GERD may be implicated as a mechanism for lung disease in this patient population. Reflux events occur very frequently in all infants, and it

is magnified in premature infants who are mostly supine, are fed relatively large volumes of milk, have nasogastric tubes placed for enteral nutrition, are given medications such as beta-agonists and caffeine that promote reflux, and can act irritable some or most of the time. Therefore, GERD is often implicated and treated in neonates, but with little supporting data.

Diagnosing GERD in the neonate can be difficult and often requires pH monitoring and/or esophageal manometry. Esophageal pH monitoring on its own can underestimate the frequency of reflux events due to the buffering of gastric contents by milk. Furthermore, emerging evidence suggests that bile acids and pepsin can have proinflammatory effects on the injured lung, and these components of refluxed gastric secretions are not detected by pH monitoring. In a study that measured pepsin in tracheal aspirates of premature infants, Farhath et al. showed that the incidence of BPD and severe BPD correlated with the presence and level of pepsin found in the airways of premature infants [19]. This has several implications. First, it may be that gastric acid may not be the factor that accounts for an adverse effect of GERD on neonatal lungs (or it may not be the only factor). Second, current methods of diagnosing significant GERD may be limited if pH monitoring is the only modality used. Finally, treating GERD with acid suppression may help some symptoms of GERD but may not be the ideal method of treatment, especially in severely compromised neonates.

Apnea and Reflux

Reflux has long been implicated as a causative factor of infantile apnea. There are conflicting reports in the literature that support or refute this association [20–22]. Apnea of the neonate is a common clinical problem encountered by pediatricians, pediatric pulmonologists, and pediatric otolaryngologists. Most evaluations for neonatal apnea do not reveal any life-threatening condition. Therefore, because GER is so prevalent in the neonate (as discussed above), GER is often implicated as the cause. However, physiologic mechanisms exist that might explain why apnea and reflux could be linked. Apneas of the neonate can be obstructive, central, or mixed. Additionally, distinguishing obstructive from central apneas in neonates can be challenging. GERD may cause obstructive apneas to occur via stimulation of reflexes in the glottic region that activate closure of the glottis at several points including the epiglottis and aryetenoids, and GERD could trigger central apneas via afferent input from the glottic reflexes. Therefore, mixed apneas, both obstructive and central, could be induced by GERD.

Recurrent Croup and Reflux

Croup is a common respiratory complaint among infants and toddlers, and acute croup is frequently caused by viral infection in the glottic region (viral supraglottitis). Recurrent croup or croup that occurs outside of the toddler age range should arouse

suspicion that something more than a recurrent viral illness is present. Diseases such as subglottic stenosis and tracheobronchomalacia can cause symptoms of croup, but GERD can also cause symptoms of croup. Furthermore, GERD can exacerbate subglottic stenosis and tracheobronchomalacia leading to protracted or frequent episodes of croup. Hoa et al. have found that a significant proportion of children evaluated for recurrent croup to have GERD. Furthermore, treatment of GERD significantly improved symptoms in those children with recurrent croup [23].

Diagnosis

There are many different diagnostic approaches available to evaluate pediatric GERD. A thorough history and physical exam will often reveal the diagnosis in infants when symptoms of vomiting associated with secondary sequelae are identified and in older children when symptoms of regurgitation and heartburn can be elicited. Carr et al. [24] found that multiple symptoms were present in a cohort of 235 children with at least one positive test for GERD (Table 4.2). However, many infants and children will not display the more obvious signs of reflux and will require further studies to document the presence of GERD.

When the history and physical examination are suggestive of GER, one method of confirming the diagnosis is to try an empiric trial of antireflux therapy. The first-line medications for GERD are antisecretory agents, including histamine-2 receptor antagonists (H2 blockers) and proton pump inhibitors (PPIs). These agents are favored over antacids and prokinetics because of their superior efficacy and convenience. A positive response to the medication strongly correlates with the presence of GERD and avoids delays in treatment.

A fluoroscopic upper GI series represents a useful, noninvasive test that may reveal the presence of anatomic abnormalities such as tracheoesophageal fistula, esophageal stricture, hiatal hernia, pyloric stenosis, annular pancreas, or malrotation in children presenting with vomiting. This study is neither sensitive nor specific for diagnosing GERD. However, if a reflux event occurs during the fluoroscopy, the diagnosis is confirmed.

Table 4.2 Symptoms associated with reflux in infants and children (from Carr et al. [24])

Symptom	Percent present
Chronic cough	51
Nasal congestion	45
Frequent emesis	39
Hoarseness	34
Wet burps	30
Throat clearing	25
Dysphagia	24
Stertor	23
Stridor	22

Esophageal pH monitoring is the gold standard for the diagnosis of GERD in children and in adults, although some individuals may have normal pH values when GERD is present. An episode of reflux is defined as an esophageal pH of <4 for a duration of 15–30 s as measured by a sensor proximal to the LES. Many factors may affect the measurement of esophageal pH including diet, position of the sensor, and activity. With the advent of dual channel pH probes, both proximal and distal pH measurements may be collected. More events occur distally in these studies, although there is evidence that suggests that proximal reflux may be present without distal reflux, which has implications for the treatment of airway symptoms [24, 25]. Testing with pH probes will not detect nonacid reflux episodes, which may occur after a feeding in infants.

Multichannel intraluminal impedance (MII) with pH probe provides additional information that includes the direction of reflux flow and bolus height, which can identify episodes of nonacid reflux. This information is especially important in the postprandial period where the reliability of a pH probe to detect reflux is decreased for 2 h secondary to neutralization of the acidic pH of the stomach contents. Utility of MII has also been shown in patients with persistent symptoms despite treatment with acid suppression therapy and for the evaluation of treatment efficacy. There is much debate as to whether diagnosing nonacid reflux episodes affects patient treatment enough to justify the increased cost and time needed for interpretation of the data [26, 27].

A nuclear scintiscan or milk scan test can be performed after the ingestion of technetium-labeled formula or food into the stomach to examine specific areas of interest (the stomach, esophagus, and lungs) by scanning for the presence of the radiolabeled material and evidence of GERD and aspiration. Unlike a pH probe, a milk scan will record episodes of nonacid reflux and is highly specific for GERD and aspiration. Milk scans can also reveal delayed gastric emptying in children; however, the lack of age-specific normative data and standardized technique limit the utility of this study in clinical practice.

Esophagoscopy allows for both the visualization and biopsy of the epithelium, which may impact patient care. The appearance of pallor and erythema may be present in the absence of histopathologic esophagitis, and mucosal inflammation may be present in an esophagus that appears to be normal. Vertical and horizontal ("trachealization") furrowing may indicate an inflammatory process within the esophageal lumen; however, the severity of the disease may not correlate with biopsies since the lesions may be patchy in their distribution and sampling may be limited by the relatively small sample size of the biopsies. Basal zone hyperplasia and increased papillary length in biopsy specimens have been shown occur with increased acid exposure. Eosinophilic esophagitis may also be present and is defined as greater than 24 eosinophils per high-power field in the esophageal epithelium.

Functional endoscopic evaluation of swallowing (FEES) provides a useful tool for the evaluation of children with dysphagia and GERD. Endoscopy of the upper airway may reveal other causes for symptoms of dysphagia including nasal obstruction with choanal atresia/stenosis or adenoid tissue hypertrophy. Structurally, the presence of a laryngeal cleft may be identified in the correct clinical situation or abnormal movement of the vocal folds may be present, and both of these entities

may lead to aspiration and chronic lung disease. Findings such as edema, erythema, vocal fold nodules, or polyps may indicate the presence of laryngopharyngeal reflux on exam. FEES has a high specificity and low sensitivity for the evaluation of aspiration because of the "white out" phase during swallowing when the larynx cannot be visualized secondary to pharyngeal muscle contraction. Because aspiration may occur during this phase, a modified barium swallow may be useful in ruling out any silent aspiration. It has been shown that reflux may decrease the sensation of the endolarynx on sensory testing, leaving it more prone to silent aspiration.

A salivagram is a nuclear medicine study where aspiration of saliva can be detected by gamma cameras after administration of technetium-99m sulfur colloid on the tongue. This test is useful in neurologically impaired children and in children who cannot feed orally and are thought to have aspiration of their oral contents. The results of this study can guide practitioners to the cause of recurrent pneumonias and chronic lung disease.

The lipid-laden macrophage index (LLMI) has been used to evaluate for the presence of chronic aspiration. Lipid-laden macrophages discovered in bronchoalveolar lavage (BAL) fluid are considered to be an indicator of aspiration of fat-containing material. The LLMI appears to be a sensitive index for aspiration, but because other chronic lung conditions may yield high LLMIs, it has poor specificity. The LLMI may have a role as an indicator supportive of the diagnosis of chronic aspiration syndromes and GERD with aspiration.

Pepsin found in respiratory secretions is another possible irritant to the tracheobronchial mucosa. There currently are relatively few studies that show any relationship between pulmonary disease and the potential effects of pepsin, and more research is needed to correlate pepsin effects on lung tissues.

Treatment of Reflux and Aspiration in Children

Treatment of reflux and aspiration is largely dependent upon whether these entities are causing significant disease in the child. Three parameters are often cited as triggers for deciding whether GERD and aspiration are significant enough to warrant treatment: failure to thrive, esophagitis, and respiratory compromise. However, significant respiratory compromise is frequently not present, and chronic or recurrent cough, wheeze, or respiratory illness are then used as indications for treating GERD and aspiration. Also, children at risk for failure to thrive and respiratory compromise may be given an empiric or prophylactic treatment for GERD. This is evident in neonates born prematurely, as it is common practice to prescribe reflux therapies to babies with BPD. Because nonsurgical therapies for GERD are relatively inexpensive, safe, and effective in reducing reflux events, the threshold for treatment is influenced by the balance between the risk of treatment (which is often low) and potential benefit (which may also be low, but still outweighs risk). Again, the question is often not whether GERD and aspiration can be controlled, but whether controlling GERD and aspiration have any beneficial effects on respiratory disease.

Medical Treatment of GERD

The simplest form of GERD treatment is non-pharmacologic and involves lifestyle and diet changes. Caregivers should be instructed to feed children while in the upright position with small, frequent feedings along with frequent burping during the feed to prevent significant aerophagia. Part of what makes reflux so prevalent in infants is that their diet is exclusively or nearly exclusively liquid. The average fluid intake of an infant is about 180 ml/kg/day, which can correspond to nearly 14 l/day in an adult [28]. This is a significant volume of fluid in the gut, and reflux can readily occur. Therefore, thickening of formula with up to one tablespoon of rice-cereal per ounce of formula can help to keep the fluid in the stomach. Finally, positioning of infants during sleep can affect reflux. Ideally, the prone position would be best for an infant with GERD. However, significant progress has been made in preventing sudden infant death syndrome (SIDS) by having infants sleep in the supine position; therefore, prone position sleeping cannot be recommended for babies with reflux. Perhaps the best solution for sleep position is to elevate the head of the bed/crib. However, this can also have its drawbacks once infants become more mobile in the crib and start rolling down to the end of the crib. Certainly, bottle feeding in the crib, "propping" bottles for infants to feed, and feeding immediately before sleep should be discouraged.

For older children who take a regular diet, modification of their diet can be helpful in preventing reflux. Dieting to lose excess weight can be helpful. Likewise, avoiding caffeine, nicotine, alcohol, and foods that exacerbate reflux can also be helpful. As mentioned earlier, certain medications can exacerbate reflux, and certain medications can increase the risk of aspiration. This can be especially true in children with seizure disorders who are already prone to aspiration even without the use of such medications. Therefore, a close look at a patient's medication list is often warranted when evaluating and treating GERD and aspiration.

When non-pharmacologic therapies do not adequately control reflux, the two categories of medication that can be employed to control GERD are acid suppressors (H2 blockers and PPIs) and prokinetics. The H2 blocker, ranitidine, is commonly used for GERD treatment in infants and children. It is usually given twice daily, but TID dosing significantly decreases gastric pH over a longer time period. The PPIs are often reserved for children in whom the H2 blockers do not seem to have had a significant effect. Both the H2 blockers and PPIs have favorable safety profiles and are well tolerated by infants and children. Caregivers should be cautioned that treatment with H2 blockers and PPIs may take time until the full effect is seen, and a bimodal distribution of improvement is often seen with these medications. One should see some improvement in symptoms (e.g., colic or heartburn) immediately due to the acid suppression. A second (and more important) effect occurs over a longer time period as the lower esophagus and lower esophageal sphincter have time to heal, thus producing a more effective means of keeping food and acid secretions in the stomach. For this reason, caregivers and patients should be instructed to give at least 4–6 weeks time with treatment before deciding whether or not the acid suppressor has been effective.

The prokinetic agents are often reserved for situations when acid suppression does not seem to be completely effective or in situations where GERD can have significant consequences (as in the case of preventing bronchiolitis obliterans following lung transplantation). Currently, metoclopramide and erythromycin are the two prokinetic agents available for use in children. Both cisapride and domperidone are not available in the USA (and not recommended for children). Metoclopramide can have significant cardiac and neurologic side effects that make it less attractive than erythromycin. Erythromycin is a macrolide antibiotic that, when used in low doses, can have beneficial prokinetic effects. Usually, prokinetic agents are added to H2 blockers and PPIs to enhance the medical treatment of GERD.

Surgical Treatment of GERD

When medical treatment of GERD is not successful and GERD is significantly compromising the child's health, surgery should be considered. Such situations would include children with persistent failure to thrive, recurrent pneumonia leading to bronchiectasis, posttransplant recipients at risk for bronchiolitis obliterans, and patients with chronic lung disease such as cystic fibrosis with significant GERD. Nissen fundoplication is the most common surgical procedure for GERD and can be performed laparoscopically. In the case of failure to thrive, a fundoplication procedure can be coordinated with gastric feeding tube insertion. In some situations, it may be advantageous to place a nasojejunal (or gastrostomy–jejunostomy tube) prior to fundoplication to assess efficacy. If a patient is fed via a tube inserted into the jejunum, the likelihood of GERD is remote, given that refluxate would have to travel through two sphincter points (the pylori and the gastroesophageal junction). Feeding into the jejunum for a period of time may also give the clinician an indication of whether fundoplication would have a significant benefit for the patient.

Medical Management of Aspiration

Whether treating aspiration medically or surgically, the optimal approach is to treat the underlying problem that predisposes the child to aspiration. If a child aspirates as a consequence of having seizures, the primary focus should be on controlling seizures. If oral-motor discoordination is present, treatment would best consist of measures to train or retrain the individual to swallow correctly. If there is an anatomic abnormality such as a laryngeal cleft, correction of that anatomic abnormality would provide an optimal result.

However, treatment of the underlying condition is frequently not feasible. Such is the case for individuals with swallowing disorders from static or progressive neurologic conditions such as cerebral palsy or neuromuscular weakness. In these cases, treatment is aimed at mitigating exacerbating factors that could lead to

aspiration. Such initiatives involve eliminating the "vehicle" that serves to promote aspiration. In the case of discoordinated swallowing, food is the vehicle, and successful treatment may require limiting or eliminating nutrition by mouth. However, nutrition must still be provided, and naso- or orogastric tubes can help determine whether eliminating oral feedings would lead to benefit. If so, surgical treatments (discussed later) could be considered.

Sometimes oral secretions, saliva, comprise the vehicle of aspiration, and medical management of oral secretions can help prevent aspiration. Additionally, surgical techniques can also be employed if necessary. Certain antisialogogues are available to decrease the amount of saliva in the oral cavity. Anticholinergics such as glycopyrrolate or scopolamine act as antisialogogues and can be used as on a trial basis to determine if long-term use can control oral secretions. Another medical treatment that can be used long-term (or as a test to determine whether surgical treatment would be effective) is botulinum toxin injection of the salivary glands. Injection of the four main salivary glands that supply saliva to the oral cavity with botulinum toxin (usually performed under ultrasound guidance) can temporarily diminish or halt saliva production in the mouth. The effect of botulinum toxin on diminishing saliva production persists from 2 to 5 months, and most patients will require injections every 3 months. By eliminating excessive saliva production as a vehicle of aspiration, children can show significant improvement in pulmonary health with fewer events of aspiration and associated pneumonia [29]. If botulinum toxin injection appears to be helpful, consideration can then be made for salivary gland excision or salivary duct ligation.

Surgical Treatment of Aspiration

If medical treatments are not successful, surgical therapies can mitigate aspiration, and surgical techniques may also be considered if medical therapy gives undesired effects. One potential undesired effect from anticholinergic antisialogogues is desiccation of lower airway secretions leading to mucus plugging and respiratory distress. Finally, surgical techniques can be employed after medical "temporizing" measures have tested whether secretion control can potentially improve a patient's outcome if a surgical procedure is performed.

There are some conditions for which surgery is the only viable option for controlling aspiration. In the case of TEF or laryngeal cleft, surgery is indicated to close the connection between esophagus and trachea. In low grades of laryngeal cleft, injection of the intra-arytenoid space with gelfoam or carboxymethylcellulose (Radiesse Voice Gel™) can augment the tissue in the glottis and thereby eliminate any potential communication between esophagus and trachea. However, this is a temporary measure due to resorption of these materials with time, but such an approach may provide an adequate time period during which an infant can learn to swallow appropriately and compensate for a relatively minor laryngeal cleft. If the swallowing function temporarily improves after laryngeal injection therapy, a formal repair of the cleft may be subsequently performed.

In cases where an anatomic abnormality is not identified and the aspiration comes more from a functional deficit, surgery can be employed to either bypass the swallowing mechanism or to eliminate the risk of aspiration of oral secretions. Ligation of salivary ducts or removal of salivary glands can irreversibly eliminate saliva entry into the oral cavity. This procedure can be approached in a stepwise manner; the main salivary gland ducts can be ligated in stepwise fashion until the desired effect is met.

If it is determined that oral feedings are contributing to aspiration, gastrostomy or jejunostomy tubes can be placed to maintain enteral nutrition while bypassing the upper aerodigestive tract. In rare cases, laryngotracheal separation may be necessary to ensure that no oral or gastric contents enter the respiratory tract. This approach requires performing a tracheostomy, and phonation cannot occur after this procedure. Therefore, this approach represents a last resort when all other options have failed.

Summary

Reflux is very common in children, especially in infants. Therefore, GERD is often implicated as causing respiratory symptoms in infants and children. Aspiration can also be common in certain clinical situations. Deciding whether reflux and aspiration are causative factors for respiratory symptoms or respiratory disease can be challenging, and both testing and the decision to treat require careful consideration, and management approaches are usually based upon the patient's clinical situation. In most children without significant respiratory disease, diet and feeding modifications or empiric trials of antireflux medications can be employed and clinical response assessed. When significant lung disease is present, the risk of further decline is great and treatment for GERD is often warranted.

Key Points

- Gastroesophageal reflux is a common occurrence in children and is universally present in newborns and infants.
- In infants and children, developmental and anatomic factors can increase the likelihood that reflux and aspiration can be detrimental the lung.
- Determining the clinical significance of reflux and its relationship to lung disease can be of great importance in the evaluation of children with respiratory symptoms. However, determining whether respiratory disease and reflux are related or just coexistent processes is inherently difficult.
- Reflux and aspiration is often manifested as cough, and GER can exacerbate obstructive lung diseases including asthma, CF, and BPD.
- Other disease states in children in which GERD and aspiration can play a role are neonatal apnea, recurrent croup, recurrent pneumonia, bronchiectasis, and bronchiolitis obliterans.

- Modalities used to aid in the diagnosis of GERD and aspiration in the infant and child include response to GERD medications, radiographic and nuclear medicine scans, pH probes, esophageal manometry, endoscopy (both esophageal and airway), pathology studies that evaluate esophageal mucosal integrity, and BAL.
- Treatment of reflux and aspiration is largely dependent upon whether these entities are causing significant disease in the child. Three parameters are often cited as triggers for deciding whether GERD and aspiration are significant enough to warrant treatment: failure to thrive, esophagitis, and respiratory compromise.
- Treatment often involves medical therapy with acid suppressants and, rarely, prokinetic agents. Surgical treatment is reserved for cases in which GERD and aspiration have serious consequences on lung health.

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Chapter 5
Dysphagia, GER, and Aspiration in the Elderly

Joshua Malo, Kenneth S. Knox, and Ronnie Fass

Keywords Dysphagia • GER • Aspiration • Elderly • Swallowing disorders • Parkinson's Disease • Stroke • Zenker's diverticulum • Rheumatoid arthritis • Diabetes mellitus • Thyrotoxicosis • Dermatomyositis

Introduction

Within the United States, where it is estimated that >20% of the population will be over the age of 65 by 2050 [1], a greater understanding of the impact of disorders affecting older adults is paramount. Due to physiologic changes of aging, an increased prevalence of comorbid conditions, and abundance of medication usage, the elderly comprise a distinct segment of the population at increased risk for upper gastrointestinal (GI) disorders. Furthermore, the risk for lung disease, either directly or indirectly related to impaired swallowing or GI function, is high among older adults. The elderly manifest distinct presentations of certain GI disorders when compared to younger adults. Additionally, as people age, alterations in normal lung physiology place them at risk for pulmonary complications of GI disorders.

Older adults typically exhibit altered pulmonary immune responses to aspirated pathogens, placing them at risk for pneumonia. As such, lung disease due to swal-

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lowing difficulties, gastroesophageal reflux disease (GERD), or aspiration may be under recognized in the older adult. This chapter will highlight the prevalence and importance of upper GI disorders in elderly patients.

Swallowing Disorders in the Elderly

Presbyphagia and swallowing disorders cause significant morbidity in the elderly. Older adults are at increased risk for impaired swallowing due to age-related physiologic changes in the upper GI tract. In addition, GI disorders, systemic comorbidities, and medication side effects contribute to impaired swallowing in almost 40% of older patients [2].

All three phases of swallowing may be affected by these changes, including the oral phase, pharyngeal phase, and esophageal phase (Table 5.1). The oral phase involves formation of a food bolus, which incorporates mastication and salivation, and the movement of the food bolus into the pharynx. Although salivary gland function is well preserved in otherwise healthy older adults, they are more susceptible to experiencing decreased saliva production secondary to medications and comorbid conditions than younger patients. The resultant xerostomia can impair bolus formation and transit during all phases of swallowing [2, 3]. Decreased muscle mass, weakness, and poor dentition may contribute to impaired mastication [4]. Decrements in oral sensory innervations may lead to impaired transfer of the food bolus to the pharynx. The pharyngeal phase appears to be slowed by increased upper esophageal sphincter (UES) resistance or delayed relaxation. Lastly, although primary peristalsis in the esophagus appears to be preserved, reduced secondary peristalsis increases the food bolus clearance time from the esophagus [5]. Due to impaired salivation and poor lubrication of the food bolus, secondary peristaltic activity may often be necessary for clearance.

Many comorbidities that commonly afflict elderly patients can lead to impaired swallowing [6]. Stroke and other neurologic disorders, such as dementia and Parkinsonism, are the most common conditions associated with a high risk of altered swallowing. Up to 75% of patients with acute stroke may develop abnormal

Table 5.1 Changes in swallowing in the elderly that are associated with risk for dysphagia

Oral phase
Sarcopenia
Decreased lingual pressure
Xerostomia
Altered sensation
Pharyngeal phase
Delayed/repeated swallowing
Increased upper esophageal sphincter connective tissue
Decreased UES area
Esophageal phase
Impaired secondary peristalsis

Adapted from [2, 3]

Table 5.2 Medications associated with risk of dysphagia and GERD in the elderly

GERD	Dysphagia
Antibiotics	Amiodarone
Aspirin	Antiepileptics
Bisphosphonates	Antihypertensives
Calcium channel blockers	Antiparkinsonian drugs
Nitrates	Antipsychotics
NSAIDs	Digoxin
Potassium tablets	Diuretics
Theophylline	Phenothiazines
Anticholinergics	
Antidepressants	
Benzodiazepines	
Opiates	

Adapted from [2, 32, 74]

swallowing, leading to an increased risk of further complications, such as aspiration and pneumonia. The incidence of dysphagia in nursing home populations, which typically include many patients with neurological disorders, has been reported to range from 50% to 75% [7]. Conditions involving the head and neck, such as malignancies, and surgeries aimed at treating them can also be associated with difficulty swallowing, either as a result of nerve injury or anatomical deformities.

Malnutrition is a common systemic problem that can result from dysphagia that is not recognized or addressed. In acute stroke patients, dysphagia is associated with an increased risk of malnutrition. Furthermore, malnutrition can result in increased morbidity in elderly patients, which may precipitate further deterioration of swallowing [8, 9].

Polypharmacy is a well-recognized cause of morbidity and mortality in elderly individuals. Several medications may contribute to impaired swallowing by altering any of the phases described above (Table 5.2). Additionally, some medications may impair swallowing by worsening xerostomia. Anticholinergics and antipsychotics, in particular, are commonly prescribed in the elderly population and cause dry mouth. Sedating medications, such as opiates and benzodiazepines, may also contribute to dysphagia.

In summary, the combination of presbyphagia, comorbidities, and medication side effects in older adults results in a high prevalence of clinically evident and subclinical oropharyngeal and esophageal dysphagia in this population.

Causes of Oropharyngeal Dysphagia in the Elderly

Stroke

Cerebrovascular accident is a common source of neurogenic dysphagia and often affects the swallowing center in the brain or the cranial nerves that modulate the swallowing process. It is estimated that up to one half of stroke survivors experience oropharyngeal dysphagia. However, it is important to recognize that most patients with stroke-related swallowing dysfunction improve spontaneously within the first

2 weeks after the event. Stroke-related swallowing difficulties may lead to an increased rate of complications such as aspiration pneumonia, dehydration, malnutrition, and depression.

Parkinson's Disease

Parkinson's disease is primarily a disorder of the central nervous system resulting from the gradual degeneration of dopaminergic neurons, which are replaced by cholinergic neurons. Dysphagia develops in approximately 50% of patients and may be due to injury to both the central and enteric nervous systems. In patients with Parkinsonism, oropharyngeal dysphagia may also result from tremor of the tongue or hesitancy in swallowing. The most common abnormalities observed during the pharyngeal phase include impaired motility, vallecular and piriform sinus stasis, supraglottic and glottic aspiration, deficient epiglottis positioning, and range of motion. Esophageal abnormalities include delayed transport, stasis, bolus redirection, and tertiary contractions [10].

Zenker's Diverticulum

Oropharyngeal dysphagia with regurgitation of undigested foods is the classic presenting complaint of Zenker's diverticulum and can occur regardless of the size of the diverticulum. When the diverticulum becomes large enough to retain food, patients develop persistent cough, fullness in the neck, gurgling in the throat, postprandial regurgitation, malnutrition, and voice changes. As many as 30–40% of patients describe experiencing chronic cough, hoarseness, and halitosis. The most common important complication for Zenker's diverticulum is aspiration pneumonia. However, other complications such as bleeding and perforation can also develop in these patients.

Oropharyngeal Structural Lesions

Dysphagia may be caused by a variety of oropharyngeal lesions, including inflammatory processes, benign or malignant tumors, an enlarged thyroid gland, and cervical hypertrophic osteoarthropathy. A systematic review of the literature shows that dysphagia resulting from lesions of the cervical spine is primarily caused by anterior osteophytic bridges due to diffuse idiopathic skeletal hyperostosis or ankylosing spondylosis [11, 12]. Compression by osteophytes is most common at the C5–C7 levels. Cervical abnormalities are most prevalent in men older than 50 years of age. Another lesion involves abnormal bony protuberance of the anterior atlas.

The typical clinical presentation includes difficulty swallowing solid foods, odynophagia (occasionally), a foreign body sensation or globus, cough, and

hoarseness. Barium swallow with lateral views confirms this diagnosis. For patients with persistent symptoms, surgical excision of the osteophytes may be considered. Biswas and Mal [11] reported a very rare case of a skeletal benign neoplastic lesion where dysphagia was the primary presentation of the tumor.

Causes of Esophageal Dysphagia in the Elderly

Gastroesophageal Reflux Disease (GERD)

Dysphagia is observed in 45–50% of patients with severe reflux esophagitis in the absence of stricture. The pathogenetic mechanism of esophagitis-associated dysphagia remains speculative, though esophageal dysmotility and mucosal inflammation, per se, have been proposed as potential culprits [13, 14].

Esophageal Stricture

Esophageal strictures are divided into those with a malignant origin and those with a benign origin. The most common benign esophageal strictures are peptic (due to acid exposure). Other common etiologies for benign strictures include previous caustic ingestion, history of radiation therapy, prior use of sclerotherapy, prior photodynamic therapy, reaction to a foreign body, infectious esophagitis, or surgical alterations of normal esophageal anatomy [15]. Strictures can also be aggravated by NSAIDs and aspirin.

Peptic strictures occur in 7–23% of patients with untreated reflux disease. The strictures are typically smooth, tapered, and of varying lengths [16]. It is thought that benign strictures of the esophagus result from collagen deposition and fibrous tissue formation that is stimulated by esophageal injury [17]. Some authors suggest that esophagitis in patients with strictures tends to aggravate the symptom of dysphagia independently from the degree of stenosis [18]. The diagnostic evaluation for these patients often begins with a barium esophagram, but in most patients, an upper endoscopy is performed as the initial test. Findings on barium esophagram can help direct further endoscopic evaluation and intervention depending upon the location, size, and complexity of the stricture. Barium esophagram can also raise suspicion for malignant strictures.

Malignant esophageal strictures are mainly caused by primary esophageal cancer but can also be caused by extraesophageal malignancies that compress the esophagus. In esophageal cancer, dysphagia is usually progressive, initially for solids and subsequently for liquids, and is often associated with weight loss. In patients with squamous-cell carcinoma of the esophagus, there is often a history of tobacco and alcohol use. The principal risk factor for adenocarcinoma of the esophagus is Barrett's esophagus caused by gastroesophageal reflux (GER). The diagnosis of esophageal cancer may be suggested by a barium esophagram, but confirmation requires an upper endoscopy with biopsy.

Medications

Pill-induced esophageal injury is relatively frequent but often under recognized and overlooked. The most common medications that can result in esophageal injury include alendronate, NSAIDs, ascorbic acid (vitamin C), potassium chloride, guanidine, ferrous sulfate, and antibiotics such as tetracycline and clarithromycin. Large pills with a sticky surface are more commonly retained in the esophagus than smaller and less adherent pills. The precise mechanism of injury for many of the pills remains speculative. Generally, the content of these pills is sufficiently caustic to cause injury of the mucosa when it is retained and released in the esophagus. Common symptoms are odynophagia 75%, chest pain 60%, vomiting 58%, dysphagia 33%, and hematemesis 15% [19, 20].

Upper gastrointestinal endoscopy is commonly warranted due to the presence of alarm symptoms such as odynophagia, dysphagia, anemia, anorexia, or hematemesis. Endoscopy usually shows focal areas of erythema, mucosal denudation, erosions and ulcerations, or even esophageal stricture. The common site of pill-induced esophageal injury is the middle third of the esophagus. Medications can exacerbate swallowing difficulties by causing local complications, such as oral or pharyngeal inflammation, or by affecting peristalsis.

Neuromuscular (Motility) Disorders

Achalasia

Achalasia, a chronic condition, is characterized by slowly progressive dysphagia for solids and liquids, regurgitation, chest pain, gradual weight loss, heartburn, and aspiration pneumonia. The neuroanatomic change responsible for achalasia is the loss of ganglionic cells within the myenteric plexus leading to esophageal body aperistalsis and failure of the LES to fully relax.

Diffuse Esophageal Spasm

Diffuse esophageal spasm (DES) is a relatively uncommon esophageal motor disorder that is thought to be caused by defective inhibitory innervations of the esophageal smooth muscle [21]. Manometry shows normal peristalsis interrupted by nonperistaltic contractions. DES is characterized by intermittent dysphagia for both solids and liquids, often associated with chest pain.

Rheumatoid Arthritis

Patients with rheumatoid arthritis may develop oral and pharyngeal motility disorders. Dysphagia related to cricoarytenoid joint dysfunction has been reported, and xerostomia

may also contribute to dysphagia in these patients. Dysphagia in rheumatoid arthritis can also be due to pill-induced esophagitis from nonsteroidal anti-inflammatory drugs (NSAIDs) or bisphosphonates (usually used to retard bone loss secondary to corticosteroid use) [22].

Amyloidosis

Amyloidosis is a condition caused by deposition of insoluble fibril protein in various tissues throughout the body. Amyloidosis can cause various oral, pharyngeal, and esophageal motility disorders. Amyloidosis leads to severe esophageal dysmotility and dysphagia in 35% of the patients due to amyloid protein deposits in all layers of the esophageal wall [13].

Diabetes Mellitus

A variety of esophageal motility disorders have been described in patients with diabetes mellitus. Esophageal transit has been found to be delayed in up to 63% of diabetic patients. Assessment of glucose control should be carried out in all patients, as poor control might predict altered esophageal motility.

Dermatomyositis

Dermatomyositis can affect swallowing by involving the striated muscle of the esophagus. According to some reports, the esophagus can be affected in 50–70% of the patients with dermatomyositis. Patients with dermatomyositis tend to have low (UES) pressure and low-amplitude contractions in the pharynx and cervical esophagus due to inflammatory reaction [23].

Thyrotoxicosis

Dysphagia is considered an extremely rare manifestation of thyrotoxicosis. It may occur in association with chronic thyrotoxic myopathy or acutely. The possible causes of dysphagia in thyrotoxicosis include neuromuscular dysfunction and mechanical compression by an enlarged goiter [24].

Miscellaneous Causes of Dysphagia

In older patients, dysphagia may also result from cognitive or psychiatric problems, physical disability of the upper limbs, weakness of the mastication muscles, dental deterioration, and osteoporosis that affects the mandible [16].

Prevention and Treatment

Typically, the physiologic changes that occur with aging are not sufficient enough, in isolation, to cause significant dysphagia. Attempting to reduce other conditions or exposures that might worsen dysphagia is an important aspect of prevention. Polypharmacy remains a common problem in this population, and, thus, minimizing medications, in particular those that contribute to impaired swallowing, should be a priority in any elderly patient with dysphagia.

Decisions regarding management of dysphagia in elderly patients are complex and require the involvement of the patient, caregivers, and often a multidisciplinary team that includes a speech therapist a gastroenterologist and a nutritionist. Many of the interventions that focus on improving dysphagia in this population are behavioral. Pharmacotherapy is, at this time, extremely limited and not supported by any rigorously controlled trials.

Interventions to improve swallowing in the elderly can be divided into two categories: compensatory and rehabilitative. Compensatory techniques are generally directed toward the circumventing of underlying anatomical or physiologic abnormalities that cause dysphagia. Rehabilitative strategies, on the other hand, aim to address and alter these underlying abnormalities directly [2].

Compensatory strategies are, generally, implemented more easily and have been more commonly employed in older adults. Older patients can often use the same techniques as younger patients. Positioning strategies, such as upright posturing and chin tuck, are commonly used due to the ease of instruction and performance of these maneuvers. In stroke patients with hemiparesis, rotation of the head toward the hemiparetic side will reduce food bolus entry into that portion of the pharynx. Use of sauces or condiments to aid bolus formation may be of particular benefit in older patients with xerostomia. Other useful strategies are similar to those for younger groups such as diet modification and use of adaptive equipment. Modification of liquid consistency with thickeners is one commonly employed technique. In a recent study of 711 patients with dementia or Parkinson's disease, the majority of whom were elderly, the occurrence of aspiration detected by video fluoroscopy was significantly lower with the administration of thickened liquids than with chin tuck, with honey-consistency liquids more effective than nectar consistency [25]. Despite the relative success of these interventions, the rate of aspiration remained high in all three treatment groups. However, patients generally prefer chin tuck to thickened liquids, which may lead to greater compliance with chin tuck compared to the risk of inadequate nutritional intake in patients who do not want to consume thickened liquids. Whichever intervention is employed, patients should be closely followed to ensure that oral intake is adequate for their nutritional needs. Strategies incorporating variation in food temperature and daily oral care also appear to stimulate improvement in swallowing function and can be incorporated into any other intervention with little or no risk [26, 27].

As discussed above, neuromuscular weakness and decreased muscle mass are prominent components contributing to increased risk of dysphagia in elderly patients. Rehabilitative strategies seek to address these problems directly by means

of exercise targeted at improving lingual pressure and pharyngeal function. In the past, these methods have been generally avoided due to a concern for the ability of older, debilitated patients to tolerate the exercise. However, safe and effective regimens have been developed to improve strength in muscles involved in swallowing and subsequently reduce the risk for laryngeal exposure [28, 29].

As in the general population, anatomical defects contributing to dysphagia often require surgical intervention for correction. However, due to advanced age and comorbidities, elderly patients are often at higher risk for complications. Therefore, the risks and benefits of invasive procedures should be carefully considered.

Pharmacotherapy currently offers little for the management of dysphagia. Several studies have demonstrated a reduction in aspiration and pneumonia with angiotensin-converting enzyme (ACE) inhibitor therapy for hypertension among stroke patients [30–32]. This effect may be due to prevention of breakdown of the neurotransmitter substance P, which appears to participate in the modulation of cough and swallowing function. However, no placebo-controlled trials have confirmed this benefit, and this therapeutic modality is not widely used. Topical capsaicin, olfactory stimulation with black pepper, and levodopa therapy have also been demonstrated to improve the swallowing reflex in older patients with dysphagia. Despite potential benefit of these therapies, confirmation of their clinical utility in larger trials is needed [33–35].

Specific Therapeutic Modalities for Dysphagia

Therapeutic options for achalasia are pneumatic dilatation of the esophagogastric junction, laparoscopic cardiomyotomy combined with fundoplication, and botulinum toxin injection into the lower esophageal sphincter [21]. The treatment options in patients with severe DES are limited. Injection of botulinum toxin has been shown to improve symptoms for the short run, but the value of this therapeutic modality for the long run is unclear. Smooth muscle relaxants, such as calcium channel blockers or nitrates, provide only temporary relief of symptoms and are also associated with side effects. The treatment for Zenker's diverticulum is indicated for all symptomatic patients with or without complications. Treatment options include surgical or endoscopic therapy. The most common treatments are diverticulectomy with or without cricopharyngeal myotomy [10].

Benign esophageal peptic strictures are best managed by esophageal dilation with aggressive long-term acid-suppression treatment. In most patients, through-the-scope balloon and Savary-Gilliard® dilation are equally effective [36]. However, 30–40% of patients with benign strictures will have recurrence of symptoms after dilation within the first year, even with the use of acid-suppressing medications. If dysphagia recurs, repeat dilation should be performed [37]. Patients should also be evaluated for compliance.

Intervention for refractory strictures, especially in patients with history of caustic exposure or radiation therapy, may require injection of intralesional corticosteroids prior to dilation. It is thought that steroids may impede collagen deposition and enhance collagen breakdown, thereby reducing scar formation [21, 38]. Novel treatment modalities

for refractory strictures include stent placement and incisional therapy [39, 40]. Patients with complex and multiple benign strictures may require surgical intervention.

The treatment of choice for patients with esophageal cancer (squamous cell or adenocarcinoma) is surgical resection. In patients with unresectable tumor, palliation with radiotherapy, chemotherapy, photodynamic therapy, photocoagulation, or stent insertion should be considered. The latter is commonly a self-expanding metal stent. In case of tissue overgrowth through the stent or stent migration, a second stent placement or, in some cases of migration, stent repositioning is pursued. Brachytherapy with or without external beam radiation therapy is another option, which has so far been mainly used in some European studies. Patients who are in poor medical condition can receive nutritional support using a nasoduodenal feeding tube or a percutaneous endoscopic gastrostomy (PEG).

Until the past few years, it was generally believed that dysphagia due to extrinsic compression should be treated with an uncovered stent to prevent stent migration. However, studies have documented that covered stents also can be used [39].

GERD in the Elderly

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents causes troublesome symptoms or complications and is a highly prevalent problem [41]. In the United States, GERD has been estimated to afflict 40% of the adult population monthly [42]. Elderly individuals also demonstrate a high prevalence of GERD, although the outcomes of studies are varied as to the prevalence relative to the general population. However, older adults often present with atypical symptoms and more severe erosive esophagitis than those in younger cohorts [43]. In a recent study of 12,000 patients with erosive esophagitis by endoscopy, only 30% of the cohort of patients >70 years old reported severe heartburn, while each cohort in a younger decade reported a higher prevalence [44]. Despite lack of symptoms, the older cohort demonstrated a 35% prevalence of severe erosive esophagitis, which was significantly higher than in the younger decades. Due to the increased severity and atypical presentation, elderly patients with GERD are more likely to develop complications such as esophageal stricture and Barrett's esophagus [45]. Since GERD is primarily a clinical diagnosis, increased awareness of the discrepancy between severity of disease and symptoms is critical in elderly patients to allow for earlier treatment and prevention of complications.

Several changes in the physiology of the aging esophagus and stomach may impact the presentation of GERD in the elderly. As was previously discussed, elderly patients have alterations in esophageal motility, which may lead to decreased clearance of esophageal contents [46]. Delay in gastric emptying can further contribute to GER. Alterations in oropharyngeal and esophageal sensory perception [47], which are often the combined result of normal aging along with comorbidities and medications, affect the perception of reflux among older adults. These alterations can make the diagnosis challenging. Elderly patients with GERD may present with vomiting, anorexia, and

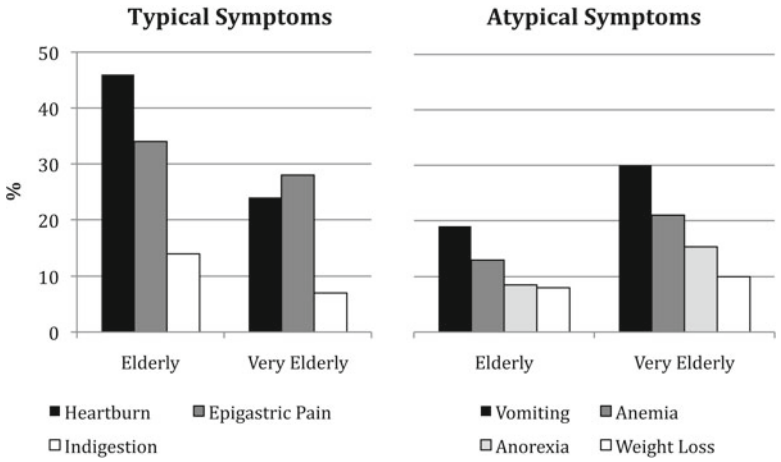

Fig. 5.1 Symptoms of GERD in the elderly (70–84) and very elderly (85 or older) (Adapted from [31])

dysphagia (Fig. 5.1). Respiratory symptoms may be present in approximately 60% of such patients [48]. Due to this challenge, a screening tool focused on upper GI symptoms in elderly patients (UGISQUE) has been developed [49].

Chronic conditions and medication use are also associated with increased risk of GERD. Commonly used medications (Table 5.2) can both reduce the tone of the LES (nitrates, calcium channel blockers) and cause a direct injury to the esophageal mucosa (NSAIDs, bisphosphonates) [50]. Reductions in saliva production due to medications can also impair the delivery of salivary bicarbonate to the esophagus, leading to lower esophageal pH.

Hiatal hernias have been found in higher prevalence in older adults seeking medical care. In a study of 840 consecutive patients with GERD, elderly and very elderly patients were found to have a higher prevalence of hiatal hernias and larger hernias than younger patients. In the very elderly, defined as 85–101 years of age in this study, the prevalence was almost 64%. However, this was not associated with a greater risk of severe erosive esophagitis [51].

Clinical Presentation and Diagnosis

In clinical practice, the diagnosis of GERD is based on patient reports of symptoms. In the elderly, however, heartburn is not frequent and acid regurgitation is present in <25% of patients [52]. In a study by Mold et al. [53], heartburn was reported by only 54% of elderly patients with GERD. In contrast, atypical symptoms such as vomiting, anorexia, dysphagia, respiratory symptoms, belching, dyspepsia, hoarseness, and postprandial fullness are common presentations in elderly patients with GERD [48]. Raiha et al. [48] demonstrated that approximately 60% of elderly patients with GERD symptoms also

had at least one respiratory symptom (hoarseness, chronic cough, and wheezing). The main clinical concern of an atypical presentation of GERD in the elderly is delay in diagnosis and consequent delay in proper treatment.

Elderly patients have more severe GERD, as manifested by the extent of mucosal injury and the frequency of complications, including Barrett's esophagus and adenocarcinoma of the esophagus. Zhu et al. [54] noted that 21% of elderly patients with GERD had grade III–IV erosive disease using the Savary-Miller criteria, as compared with only 3.4% of younger patients ($P < .002$). This was further supported by Collen et al. [55], who demonstrated a higher prevalence of erosive esophagitis and Barrett's esophagus in patients older than 60 years as compared with those younger than 60 years of age (81% vs. 47%, respectively; $P < .000002$).

Several studies have demonstrated a clear discrepancy between the reported symptom severity of elderly GERD patients and the degree of esophageal mucosal inflammation. Pilotto et al. [51] have shown that elderly (mean age 77.3 years) and very elderly (mean age 88.4 years) patients with erosive esophagitis had a significantly lower prevalence of typical GERD symptoms (heartburn, regurgitation, and epigastric pain) as compared with young (mean age 36.7 years) and older adult (mean age 59.1 years) patients with erosive esophagitis. Elderly patients with erosive esophagitis also were more likely to have other symptoms like anorexia, weight loss, vomiting, and dysphagia. In contrast, the severity of erosive esophagitis increases with the age of the patient. Johnson and Fennerty [44] showed, in a post hoc analysis, that progressive increase in the prevalence of severe erosive esophagitis was observed with each decade of age, ranging from 12% in patients aged <21 years to 37% in patients aged >70 years. Among patients with severe esophagitis, severe heartburn was less frequent in the older age groups, ranging from 82% of patients <21 years to 34% of those aged >70 years. Each of these associations was statistically significant ($P < .001$).

Altered esophageal pain perception to chemical and mechanical stimuli, which has been documented in older subjects, is one explanation for the pronounced decrease in severity and frequency of GERD-related symptoms despite increase in the degree of esophageal inflammation. Fass et al. [47] found that older patients with GERD demonstrated a longer lag time to initial heartburn symptoms and lower symptom intensity score during acid perfusion into the esophagus. Consequently, their acid perfusion sensitivity score was significantly lower than that of younger patients ($P < .05$). In addition, there was a significant correlation between increase in age and increase in lag time to initial symptom perception and decrease in sensory intensity rating and acid perfusion sensitivity score [47].

Diagnostic modalities for GERD that are available for elderly patients parallel those for younger patients. These include barium swallow studies, upper endoscopy, 24-h esophageal pH monitoring, impedance with pH sensor, and the proton pump inhibitor (PPI) test. Referral to a gastroenterologist is recommended for elderly patients with GERD and alarm symptoms (e.g., dysphagia, odynophagia, hematemesis, anorexia) or possibly those who have failed antireflux treatment. Barium swallow could be ordered for those with dysphagia but should not substitute for referral to a gastroenterologist for upper endoscopy. Impedance + pH should be considered in elderly patients who failed treatment on PPI given twice daily. The technique is invasive,

however, and requires placement of a probe through the nasal passages and into the esophagus for 24-h duration. Thus, empiric treatment would be more appropriate for elderly subjects with severe comorbidity. The PPI test has not been shown to be age specific and, thus, could also be used in the elderly to diagnose GERD. The test requires high-dose PPI (two or three times daily) for a period of 7–14 days.

Prevention and Treatment

Treatment of GERD in older patients is similar to that in younger patients; however, increased severity of erosive esophagitis and GERD complications are more prevalent in elderly patients and thus may demand more aggressive therapy. Antacids and sucralfate appear to be of very limited benefit in the elderly, and they have limited efficacy in addressing severe erosive esophagitis. Furthermore, the frequency of dosing required could lead to nonadherence to therapy [56].

As in younger patients, the mainstay of therapy is pharmacologic suppression of acid production. H_2 receptor antagonists may have a greater role in symptom control than antacids due to acid-suppression effect and less frequent dosing. However, in the setting of severe erosive esophagitis, they demonstrate inadequate sustained acid suppression to allow mucosal healing at standard doses. Although higher doses may be more efficacious in this setting, proton pump inhibitors (PPIs) have proven to be superior in clinical outcomes and cost effectiveness [57]. Additionally, safety concerns regarding the use of H_2 receptor antagonists in the elderly are significant. For example, they have been shown to cause cognitive impairment [58], and cimetidine has profound effects on cytochrome P450, causing altered metabolism of other medications in this vulnerable population.

Proton pump inhibitors are currently the recommended therapy for management of GERD in the elderly. PPIs have demonstrated efficacy for the treatment of esophagitis and have been shown to be superior to H_2 receptor antagonists in relieving symptoms and promoting esophageal healing in multiple trials [59]. In a retrospective analysis of patients greater than 65 years of age from two clinical trials comparing omeprazole 20 mg daily to H_2 receptor antagonists, 68% of patients in the omeprazole group were found to be symptom-free and have healed esophagitis after 4–8 weeks of therapy compared to only 23% in the H_2 receptor antagonist group [60]. Esophageal healing rates as high as 94% percent have been reported with PPI therapy in the elderly [61]. Long-term PPI therapy is often required due to very high relapse rates of esophagitis once therapy is stopped. When compared with placebo, PPI therapy has been shown to achieve an approximate 50% absolute risk reduction of GERD relapse.

PPIs generally have an excellent safety profile. Although some impairment in clearance has been demonstrated in elderly patients [62], there does not appear to be any clinically relevant need for dose reduction. There are no clear data demonstrating adverse outcomes in the elderly with renal or hepatic disease, but caution and use of lower doses should be considered in these populations [63]. PPIs are metabolized

via the hepatic cytochrome P450 system [64]. Elderly patients are commonly on medications, such as warfarin, which may have altered metabolism due to PPI use. In recent years, a great deal of attention has been focused on clopidogrel, which is metabolized by CYP2C19 to its active antiplatelet form [65]. Omeprazole and esomeprazole has been demonstrated to decrease the platelet inhibition effect of clopidogrel. Other PPIs, on the other hand, appear to have less effect on the anti-platelate activity of clopidogrel [66]. However, results of clinical studies examining the risk of adverse cardiovascular outcomes with concomitant clopidogrel and PPI use have varied [43], and no studies have examined this issue specifically in older adult patients. Nevertheless, the possibility of such drug interactions in older patients with cardiac disease should be addressed as in the general patient population, and patients should be informed of the potential risks of concurrent PPI and clopidogrel use.

Several studies have investigated a potentially increased risk of hip fracture, a common and highly morbid condition in elderly patients, in association with PPI use. A case-control study of greater than 13,000 patients with hip fracture matched against greater than 130,000 controls demonstrated an odds ratio for suffering a hip fracture of 1.44, and the strength of this association increased with increasing duration of PPI use [67]. Results of subsequent attempts to substantiate these findings have been conflicting [68, 69]. At this time, it is prudent to make patients aware of the potential risks and benefits of PPI therapy with regard to hip fracture and to consider either withholding chronic PPI therapy in patients with increased risk of hip fracture or performing aggressive surveillance for, and treatment of, osteoporosis should they require PPI therapy.

Increased risks of community-acquired pneumonia and *Clostridium difficile* colitis have also been reported with PPI use. This increase is presumably mediated by alterations in intestinal flora due to the marked suppression of gastric acid production caused by PPIs [70, 71]. These risks may be of special interest in the elderly due to higher rates of hospitalization, potential exposure to resistant organisms, and increased risk for aspiration.

Prokinetic agents, such as metoclopramide and cisapride, have some efficacy in relieving symptoms in patients with mild esophagitis [45]. However, due to an unacceptable side effect profile in the elderly and the availability of better tolerated, more effective treatments, they are not generally used in this population for GERD treatment [72]. Also, given the high prevalence of severe esophagitis in the elderly, therapies with proven efficacy in healing esophagitis are preferable.

Lifestyle modifications should always be attempted in the elderly GERD patient. However, only weight loss and elevation of the head of the bed have been demonstrated to be effective interventions, with both improving esophageal pH profiles. Additionally, weight loss has been shown to improve symptoms [73]. Other interventions, such as smoking cessation and dietary modification, are prudent recommendations for health but have not shown specific benefit in GERD outcomes.

Invasive techniques to manage GERD, include surgical and endoscopic therapies. Surgical therapies have demonstrated an efficacy and safety profile in the elderly population that is similar to that in younger patients [74, 75]. In addition, it also demonstrated similar rates of recurrence, in the range of 10% [76]. The presence

of significant comorbidities in some older patients may preclude anti-reflux surgery; however, the indications in the elderly are the same as those in younger patients. Although endoscopic therapies offer a potentially less invasive alternative, adequate studies have not assessed their safety and efficacy in elderly patients. To date, the overall efficacy of these therapies in the general population remains in question, and further development is needed [77].

Treatment of GERD in the elderly carries special considerations due to the severity of esophagitis and increased prevalence of GERD complications in this population. The presence of comorbid conditions and polypharmacy further complicate the decision of which modality to choose. Careful consideration of risks versus benefits should be undertaken, and patients should be made aware of potential side effects prior to the initiation of therapy.

Aspiration in the Elderly

Aspiration has increasingly become recognized as a major cause of morbidity and mortality in elderly populations. The impairments in swallowing discussed above along with diminished cough, medical comorbidities, and an altered immune response all contribute to a high incidence of pneumonia in the elderly in community, long-term care, and acute care settings. Elderly patients with pneumonia demonstrate greater morbidity and mortality compared to younger patients. Studies have demonstrated higher rates of hospitalization for elderly patients with community-acquired pneumonia (CAP) [78] and markedly increased mortality rates among nursing home patients with pneumonia.

The distinction between aspiration pneumonitis and aspiration pneumonia can be complex in clinical practice. Aspiration pneumonitis results from aspiration of gastric contents, and its severity is inversely correlated with pH of gastric contents. Aspiration pneumonitis is also usually seen in the setting of higher-volume aspirations [3]. Conversely, aspiration pneumonia is the result of aspiration of oropharyngeal material into the larynx and, subsequently, into the lower respiratory tract. This is the more common entity observed in elderly patients and is the focus of this section.

Although the term *aspiration pneumonia* typically refers to pneumonia in the setting of risks for aspiration or a known aspiration, CAP develops after aspiration of pathogens that have colonized the oropharynx [79]. As such, an understanding of the various mechanisms by which aspiration contributes to pneumonia in the elderly is necessary for prevention strategies in this population. The pathogenesis of pneumonia involves failure of protective mechanisms to prevent aspiration, increases and alterations in microbial burden delivered during an episode of aspiration due to changes in oral flora, and impaired immune responses upon exposure.

Due to the impaired swallowing mechanisms as previously discussed, older patients are at increased risk to have laryngeal exposure to food as well as to esophageal and gastric contents. Despite the presence of impaired swallowing in otherwise

healthy elderly patients, there does not appear to be an increased rate of aspiration compared to younger cohorts. Impaired swallowing alone is insufficient to explain higher rates of aspiration in elderly patients [3]. An impaired cough reflex, however, is one potential mechanism by which aspiration might occur. Although the cough reflex is preserved in healthy older patients, patients with a history of aspiration have been demonstrated to have a higher threshold for stimulation of cough. Furthermore, medical conditions, such as stroke and neurodegenerative diseases, are likely to further contribute to suppression of cough. An increased risk for pneumonia is observed in patients with concurrent impaired swallowing and suppression of cough [80].

Alterations in oropharyngeal flora are also common in elderly patients. Patients with gingivitis and periodontal disease have oral flora and bacterial burdens that differ from those of healthy, matched controls. Many common risk factors for periodontal disease, such as diabetes, hormonal changes, inadequate nutrition, osteoporosis, and medication usage, are common in the elderly [81]. Xerostomia, dependence for oral care and feeding, and burden of tooth decay have all been demonstrated to contribute to alterations in oral bacterial flora. Multiple studies have demonstrated that risk of pneumonia increases with the number of decaying teeth [82]. In a study examining nursing home residents, suctioning, presence of a feeding tube, a mechanically altered diet, and dependence for oral care were all found to be predictors of risk for aspiration pneumonia that relate to oral hygiene [83].

Elderly patients have been demonstrated to have alterations in lung physiology and immune response that may further contribute to the development of pneumonia upon aspiration. Reductions in mucociliary clearance and respiratory muscle strength may lead to impaired mobilization of secretions and provide an appropriate milieu for bacteria to propagate [7, 84]. These physiologic changes of aging are also accompanied by an age-related decline in immune function in the elderly as well as an increased prevalence of chronic diseases, such as congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease, and malnutrition, all of which may further impair immune function. In the absence of comorbid conditions, the most prominent age-related change appears to be alteration in T lymphocyte profiles and function. However, many aspects of the immune system are affected by aging and can contribute to the development of chronic pulmonary diseases and pneumonia (Table 5.3) [85].

Diagnosis of aspiration pneumonia in the elderly is complicated, and the clinical presentation is often atypical. Traditional markers of pulmonary infection, such as fever and cough, are less common. Tachypnea may be the most common early physical finding [86]. Clinical suspicion for aspiration pneumonia should be high in patients with any of the risk factors discussed above, particularly in debilitated patients with chronic illnesses and those treated with multiple medications.

Prevention and Treatment

Many of the strategies to prevent aspiration in the elderly are targeted at improving swallowing. Alternate strategies are generally meant to prevent the major complication

Table 5.3 Age-related changes affecting pulmonary immunity

Lymphocytes	Macrophages
Decreased antigen-specific responses	Altered bacterial killing
Decreased T cell diversity	Decreased proinflammatory cytokine production
Increases in total number, memory and "immunosenescent" T cells	Decreased influx of macrophage numbers into organs
Increased immunoglobulin concentration with qualitative defects in antibody production	Altered anti-inflammatory macrophage responses

of aspiration pneumonia. As interventions to improve swallowing and reduce the risk of laryngeal exposure of oral and gastric contents were addressed earlier, this section will focus on reducing the risk for pneumonia and the treatment of aspiration pneumonia in the elderly.

Poor oral care has been demonstrated to be a risk factor for development of aspiration pneumonia [87] and has been examined as a potential point of intervention for prevention. In a randomized, controlled trial of 417 patients assigned to an intensive oral care regimen versus no oral care, a reduced risk of pneumonia and mortality was noted in the intervention group [88]. The implementation of such interventions requires the involvement of healthcare practitioners, identification of at-risk patients, and development of an adequate oral care regimen. Comprehensive approaches to this issue have been published [81, 89], although further studies are needed to demonstrate efficacy and advocate a specific approach. Regardless, the current data strongly favor oral care regimens for all elderly patients deemed to be at risk for aspiration. Expanding the awareness of the importance and effectiveness of these interventions among healthcare providers remains an important challenge.

In situations in which the underlying dysphagia cannot be adequately addressed, enteric feeding tubes are often employed as a means to reduce the risk of aspiration and pneumonia. In patients with acute stroke, for example, gastrostomy tubes were found to significantly reduce mortality at 6 weeks compared to nasogastric tubes, a finding that appeared to be mediated by improved nutritional status in the intervention group [90]. However, there is inadequate evidence at this time to support the routine use of gastrostomy tubes to reduce the risk of aspiration pneumonia, perhaps because aspiration pneumonia has been linked by microbiology to the aspiration of oropharyngeal microorganisms, which is not affected by gastrostomy tube placement [91]. The results of studies examining the impact of distal placement of feeding tubes into the jejunum have been conflicting and do not definitively demonstrate a reduced risk of aspiration pneumonia [92]. In the subset of patients with dementia, feeding tubes are often placed due to malnutrition and a high risk of aspiration. In fact, 30% of percutaneous endoscopic gastrostomy (PEG) tubes are placed in patients with dementia [93]. There are no data, however, supporting a reduction in aspiration pneumonia or an improvement in mortality with PEG placement in patients with dementia [94]. Furthermore, the mortality for patients with dementia at 30 days and 1 year after PEG placement is reportedly 54% and 90%, respectively [95]. Thus, the decision to place an enteric feeding tube remains complex. Older

patients with specific diagnoses, such as stroke or oropharyngeal malignancy, may benefit from PEG placement. Careful consideration of the underlying disease and prognosis are important in patient selection [2].

Treatment of aspiration pneumonia in the elderly should be guided, whenever possible, by culture results. Unfortunately, the bacterial etiology of pneumonia is infrequently identified, particularly in the elderly [96]. Therapy for suspected pneumonia should not be delayed, as culture information is not available at the time of initial diagnosis, can take days before it becomes available, and may not provide accurate information. Empiric therapy should be chosen based on likely causative organisms and local antibiotic susceptibility profiles. In a study of 95 institutionalized elders with severe aspiration pneumonia, gram-negative enteric bacilli were the most commonly isolated organisms, encompassing 49% of isolates [97]. Anaerobes and *Staphylococcus aureus* were also commonly recovered, representing 16% and 12% of all isolates, respectively. Although it was common for initial coverage for anaerobic organisms to be inadequate in this study, it was also found that patients who grew anaerobic isolates had an adequate clinical response despite seemingly inadequate antimicrobial therapy according to culture results. This study calls into question the necessity for anaerobic coverage in these patients. However, given the small sample size, it would be prudent at this point to continue to empirically treat for gram-negative enteric bacteria and anaerobes in addition to standard CAP coverage until these results are confirmed by larger trials.

Future Directions

In summary, there is limited information regarding the effect of aging on dysphagia, GERD, and aspiration in isolation from the many medication side effects and comorbidities that concomitantly affect the older population. Studies that include elderly and very elderly subjects are needed to better delineate the effects of aging. Ongoing longitudinal cohort studies should be leveraged to study GI and lung disorders in older adults. Studies designed to examine whether invasive procedures are clinically beneficial or cost-effective compared to medical therapy in the treatment of GERD are needed. Finally, an overall awareness of the complexities of caring for the aging patient with GI and pulmonary disorders deserves emphasis in future society guidelines.

Key Points

- Age related changes in normal swallowing, comorbidities and medication consumption increase the risk of elderly patients to develop dysphagia.
- GERD is very common in the elderly but less likely to present with classic symptoms, like heartburn or regurgitation, more likely to be minimally symptomatic, and is commonly associated with a more severe mucosal disease.

- Treatment of GERD in the elderly should always balance risk versus benefit.
- Clinical presentation of aspiration pneumonia in the elderly is frequently atypical, requiring high suspicion in patiants with risk factors.

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Chapter 6
Chronic Cough and Vocal Cord Dysfunction: The Role of GER

Jamal Hayat, Etsuro Yazaki, and Daniel Sifrim

Keywords Gastro-esophageal reflux • Reflux induced cough • Esophago-bronchial reflex • Vocal cord dysfunction • Impedance-pH monitoring • Proton pump inhibitors • Anti-reflux surgery • Paradoxical vocal fold motion

Introduction

Gastroesophageal reflux (GER), the retrograde flow of gastric contents into the esophagus, can occur in the normal physiological state, often in the post-prandial period. Each episode is usually short-lived and asymptomatic. Symptomatic individuals usually complain of heartburn or regurgitation. However, there has been increasing recognition of the contribution of GER to atypical symptoms such as hoarseness, globus sensation, throat clearing, and cough. The Montreal Definition and Classification of Gastroesophageal Reflux Disease (GERD) in 2006 recognized GER-related cough as one of three established extra-esophageal syndromes along with laryngitis and asthma [1].

Vocal cord dysfunction (VCD), also commonly known as paradoxical vocal fold motion, refers to the abnormal movement of the vocal folds during inspiration.

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For many years it was thought to be due to an underlying psychological disturbance and was initially given the name, Munchausen's stridor, in 1974. Other names that have been given which reflect the presumed non-organic etiology include functional upper airways obstruction, emotional laryngeal wheezing, and factitious asthma.

Terminology has recently been modified to help avoid confusion with other glottal disorders, such as periodic occurrence of laryngeal obstruction (POLO) and irritable larynx syndrome. This diversity in nomenclature highlights a lack of consensus with regards to the underlying pathophysiology. An increasing body of evidence has emphasized the importance of underlying organic disease. For the purpose of this chapter, we will use the term vocal cord dysfunction (VCD).

Causative Factors and Epidemiology

Chronic Cough

In the most part, coughing is an involuntary response designed to clear the upper airways in response to certain stimuli. Chronic cough has been defined by the American College of Chest Physicians as cough lasting for more than 8 weeks in a non-smoking, immunocompetent patient [2] who is not on any cough-inducing drugs such as angiotensin converting enzyme inhibitors and has a normal chest radiograph. A subacute cough is defined as one lasting between 3 and 8 weeks.

There is a diverse spectrum of causative factors. The most commonly diagnosed are asthma, upper airways cough syndrome (formerly known as postnasal drip) and GER [2–4]. Along with chronic bronchitis secondary to cigarette smoking and bronchiectasis, these disorders are thought to account for approximately 94% of all cases of chronic cough [5]. Other causes associated with chronic cough include bronchogenic carcinoma, sarcoidosis, interstitial lung disease, left ventricular failure, post-infectious cough, and eosinophilic bronchitis.

A number of new causes for chronic cough have been identified over the past 10 years. Obstructive sleep apnea can present with cough as its sole manifestation [6]. These patients are usually obese, female, and have coexistent GERD. Tonsillectomy for patients with chronic tonsillar enlargement and a hypersensitive cough reflex has been shown to improve cough scores [7]. There is also a significantly increased prevalence of chronic cough in patients with organ-specific autoimmune disease, bronchoalveolar lymphocytosis, and inflammatory bowel disease [8].

Richard Irwin's group was one of the first to recognize an epidemiological association between GER and chronic cough in 1981 [9]. This has been confirmed from various studies around the world [9–15]. In a study of over 4,000 healthy subjects in the UK [10], both irritable bowel syndrome and regurgitation were found to be strong predictors of cough. In Sweden, Ruhls et al. [11] performed a population-based study of almost 7,000 participants and found an increased risk of hospitalization with respiratory diseases for patients identified as having reflux esophagitis or a hiatal hernia. Both the ProGERD study and the Trondelarg health

Survey [12, 13] identified a high prevalence of acid reflux symptoms associated with asthma and extra-esophageal symptoms including cough.

Despite this recognition of a strong association between cough and GER, there has been a wide range in the reported prevalence of GER-associated cough around the world, ranging from 0% in Japan [14] to as high as 73% in Australia [15]. This large variation in prevalence may, in part, be due to different population groups, but the methodology used to establish the reflux–cough association (i.e., questionnaires, abnormal findings on upper GI endoscopy, cough during pHmetry, and symptom response to acid reflux therapy) is also likely to account for the considerable variation. Clinical awareness of GER-related chronic cough, both from the pulmonary medicine, otolaryngology and gastroenterology perspectives, has also influenced prevalence estimates. For example, studies published by Irwin's group have shown that the prevalence of GER as the cause of chronic cough increased from 10% in 1981 ([9]), 21% in 1990 ([16]) to 36% in 1998 ([17]).

Vocal Cord Dysfunction

Patients commonly present with symptoms that mimic asthma, such as coughing, wheeze, and dyspnea that responds poorly to beta-agonists and inhaled corticosteroids. They may also present with symptoms such as globus pharyngeus, throat clearing, hoarseness, and chest tightness. These symptoms are non-specific and often lead to a delay in diagnosis. In acute episodes this can even lead to unnecessary tracheal intubation or tracheostomy. The gold standard investigation for diagnosis is laryngoscopy. The hallmark of the diagnosis of VCD is vocal fold adduction during the inspiratory phase of the respiratory cycle, which leaves a diamond-shaped posterior 'chink'. Spirometry is important to confirm the diagnosis and to exclude asthma. During symptomatic periods, there will be inspiratory loop flattening of the flow-volume loop that is indicative of extra-thoracic airways obstruction with a normal expiratory phase [18].

The first series of patients with VCD was published by Christopher et al. in 1983 [19]. They described five patients under investigation for severe asthma refractory to treatment. These patients were mostly female health care workers with a history of physical or sexual abuse, and they responded to speech therapy and psychotherapy.

The difficulty in diagnosis is likely, in part, to be responsible for the discrepancy in the reported prevalence of VCD. This diagnosis is mainly limited to select patient groups such as those presenting with acute dyspnea rather than in the general population.

Jain et al. [20] reported that 22% of patients with multiple admissions to an inner city hospital for acute shortness of breath (SOB) had VCD, whereas Kenn et al. [21] found a lower prevalence of 2.8% out of 1,025 patients presenting with dyspnea. Ciccolella et al. [22] had also reported a similar prevalence of 2.5% in patients with acute dyspnea.

VCD is most frequently diagnosed in females aged 20–40 with a female/male ratio of between 2:1 and 3:1 [23, 24]. However, it has also been reported in neonates,

infants, and adolescents. Different population groups appear to be at particular risk. De la Hoz et al. [25] found that VCD was frequently diagnosed in workers following the World Trade Center disaster who were exposed to a large amount of inhaled irritants as well as considerable psychological stress.

VCD has also been described in high performance athletes with exertional dyspnea. Rundell et al. [26] evaluated 370 athletes at an Olympic training camp and found that 5% had inspiratory stridor that was suggestive of VCD; however, this was not confirmed on laryngoscopy. A high prevalence of VCD has also been reported in the military population. Morris et al. [27] found that 15% of patients presenting with exertional dyspnea at a tertiary army care center had evidence of VCD on laryngoscopy. In a separate study they found that this was the second most common cause of exertional dyspnea after obstructive lung disease in active duty military personnel [28]. Patients with a high level of occupational irritant exposure [29] also have an increased incidence of VCD. Exposure to irritants such as ammonia vapor, smoke, tile dust, soldering gas, and cleaning chemicals has been shown to be temporarily associated with the onset of symptoms.

Retrospective studies have shown that GERD and asthma are the most frequent comorbid conditions [25–27, 30, 31]. It should be born in mind that these conditions are also very common in the general population; however, their prevalence in patients with VCD is reportedly higher. Gurevich-Uvena et al. [30] reported that GERD was a comorbid condition in 61% of military personnel with objective evidence of VCD, and asthma was the second most common comorbidity at 36%. However, a serious limitation to these data was the reliance on patient notes for documentation of GERD.

Boger at al. [32] identified 32 patients with VCD on laryngoscopy and found that 31% had abnormal DeMeester scores on 24-h pH studies, and two of these patients had endoscopic evidence of esophagitis. Half of these patients did not have typical reflux symptoms.

Pargeter et al. [33] investigated the prevalence of GERD in patients diagnosed with VCD on laryngoscopy and found that 79% of VCD-confirmed patients had evidence of GER based on either barium swallow or 24-h pH monitoring. Denoyelle et al. [34] reported that four of nine infants with documented inspiratory vocal cord adduction had evidence of GER on pH monitoring, and an additional four had symptoms of GER.

Pathophysiology

GER-Related Cough

Cough can be precipitated by GER directly through microaspiration, or it can be triggered indirectly through activation of an esophago-bronchial reflex or by increasing the sensitivity of the cough reflex.

Microaspiration

Human studies have shown that the cough reflex pathway is mediated by vagal afferent neurons [35]. These are found in abundance along the respiratory tract mucosa and in the lung parenchyma. Slowly adapting pulmonary stretch receptors are involved with bronchodilation, whereas rapidly acting stretch receptors (RARs) mediate bronchoconstriction. Acid has been shown to activate the ion channel/receptor, TRPV1, which is found on C-fibers and cough receptors innervating the larynx, trachea, and bronchi [36].

Microaspiration of refluxate can be demonstrated by the presence of gastric contents in bronchoalveolar lavage fluid (BALF) or sputum and is suggested by their presence in saliva. Detection of lipid-laden macrophages in BALF or sputum has been used as a marker for microaspiration in children. Studies showed that lipid-laden alveolar macrophages were present in 85% of children with chronic respiratory tract disorders and GER [37, 38]. However, recent reports showed that this method had low specificity, and its prevalence in adult patients with chronic, unexplained cough was unknown [39, 40]. Pepsin and bile acids (BA) are currently assessed in saliva, sputum and BALF in patients with respiratory disorders. While pepsin and BA are clearly increased in patients with cystic fibrosis and lung transplant [41], there is no difference in pepsin concentrations of BALF between chronic cough patients and healthy controls [40].

Studies using flexible endoscopic evaluation of swallowing with sensory testing (FEESST) have shown that patients with GERD and chronic cough have reduced laryngopharyngeal mechanosensitivity when compared with healthy subjects [42], which could potentially result in an increased risk of aspiration. On the other hand, recent studies using pH/impedance monitoring failed to demonstrate an increased number of reflux episodes with high proximal extent in patients with chronic cough [43, 44], indicating that other pathophysiological mechanisms are involved.

Esophago-bronchial Reflex

The esophagus is innervated by sensory-type nociceptors that express the acid-sensitive channel, TRPV-1 [45]. These afferents of the vagus nerve converge centrally with capsaicin-sensitive C-fibers and capsaicin-insensitive, acid-sensitive mechanoreceptors from the respiratory tract in the nucleus of the solitary tract in the brainstem [46]. This convergence of vagal afferent neurons in the brainstem may allow sensation of vagally mediated reflexes from the distal esophagus to be triggered by chemical or mechanical stimuli [47].

Ing et al. [48] reported that acid perfusion with 0.1 N HCL into the distal esophagus of patients with cough and GERD significantly increased cough frequency, duration, and intensity when compared with 0.9% saline infusion. Cough was inhibited in these patients by topical esophageal anesthesia with 4% lidocaine 15 min before repeat acid perfusion In contrast, when the anticholinergic agent ipratropium was instilled into the esophagus of these patients, there was no

effect on cough frequency, while inhaled ipratropium inhibited cough. The authors concluded that this was indirect evidence of a vagally mediated esophago-bronchial reflex, with the lidocaine inhibiting the afferent and the ipratropium the efferent limb of the pathway.

Cough Reflex Hypersensitivity

Such an esophago-bronchial reflex can be sensitized in patients with GER and chronic cough. Javorkova et al. [49] studied nine patients with GER and chronic cough (>8 weeks), 16 patients with GER without chronic cough, and 18 healthy subjects. They studied cough sensitivity to inhaled capsaicin after infusion of either saline or HCl into the distal esophagus. They found that the cough reflex sensitivity was increased in patients with GER and chronic cough after distal esophageal acidification but not in the other groups. Unlike Ing et al. [48], they did not find that distal esophageal acidification directly increased the frequency of cough in these patients.

The dynamic nature of the cough reflex threshold has also been studied by Benini et al. [50] who found that treatment with oral PPI could increase the cough reflex threshold to inhaled capsaicin after 5 days in patients with esophagitis, and further improvement was observed after 60 days of treatment in patients who also had evidence of laryngitis.

A lowered upper airway cough threshold can become stimulus non-specific, and any other stimulus (not necessarily reflux) could trigger cough (i.e., cold air, stress, etc.). This has recently been labeled as “chronic cough hypersensitivity syndrome” [51].

Non-acidic Stimulation of Cough

Acid sensitive nerve endings are the most widely accepted mediators of chemical agents in the esophagus. Substances such as prostaglandins and ethanol as well as temperature have also been shown to have a sensitizing effect [52], and pepsin, bile, and trypsin have also been implicated in causing reflux-related symptoms [53]. By stimulating afferent vagal nerves in the esophagus, these agents may act in similar ways to stimulate an esophago-bronchial reflex or by increasing the cough reflex sensitivity. Their activity has been shown at pH levels between 4 and 7, which may explain the findings of studies using pH monitoring and objective cough recordings. These have shown that both acid and non-acid reflux events can be temporarily associated with cough [43, 54]. Furthermore, an equal number of patients may have a positive reflux-cough association (SAP) with acid and non-acid reflux events [55]. This suggests that the acidity of the refluxate may be unimportant if the esophago-bronchial reflex is already sensitized.

The finding that a third of patients had an equal number of cough events preceding as well as following reflux episodes suggests that a self-perpetuating cycle of reflux–cough–reflux occurs in some patients. These events rarely occurred within a 10-s window, suggesting that straining from coughing itself is unlikely to be the cause. This raises the possibility that cough precipitates transient lower esophageal sphincter relaxations, which runs a similar neural pathway to the medulla. Taken together, the current information suggests that reflux should not be considered as a single independent cause but rather as a contributing factor as well as a consequence of chronic cough [55]. Finally, it should be noted that cough and GERD are very prevalent in the general population, and these two phenomena can coexist without any clinical pathophysiological relationship.

VCD

Precipitating factors can be classified into organic and non-organic. The non-organic precipitants relate to the psychological disturbances that have been well described in VCD, such as conversion disorder, depression, obsessive-compulsive disorder, and a history of physical and sexual abuse. How this results in VCD is unknown. Organic precipitants include GER, asthma, exercise, sinusitis/rhinitis and extrinsic exposure-associated stimuli (e.g., foods, perfumes, air pollutants and chemical agents).

Microaspiration and Laryngopharyngeal Reflux

Recent evidence (as highlighted above) suggests that microaspiration plays a less prominent role in GER-induced cough but may play a more important role with VCD. Patel et al. [56] performed a retrospective review of patients with VCD to investigate the presence of concurrent laryngeal abnormalities. They found that 53% of 30 patients reviewed had findings classical for laryngopharyngeal reflux (LPR), such as arytenoid erythema and pseudosulcus. This was particularly common in patients whose symptoms were induced by exercise. Powell et al. [57] found that 21 out of 22 pediatric patients with VCD had laryngoscopoic signs suggestive of chronic reflux laryngitis (e.g., arytenoid and interarytenoid edema and pachyderma). There was, however, no objective evidence to confirm GER.

Altered Autonomic Balance and Laryngeal Hyperresponsiveness

The vocal cords are located in the larynx, which is responsible for phonation and airway protection. Sensory afferents from the larynx run a similar pathway to the

cough pathway via the vagus nerve to the medulla in the brainstem. During the inspiratory phase of respiration, the posterior cricoarytenoid muscle is stimulated by the respiratory center in the medulla to contract and thus abduct the vocal cords. Morrison et al. [58] hypothesized that repeated stimulation of the laryngeal sensory afferents by noxious stimuli resulted in a hyperexcitable state of the laryngeal muscle that was activated by repeated stimuli (such as GER) at pathologically low thresholds. This lowered sensory threshold may explain why up to 80% of patients with VCD also have cough.

Cukier-Blaj et al. [59] measured laryngeal sensitivity via the laryngeal adductor reflex and LPR symptom scores in patients with VCD. They analyzed data from 75 patients and found a high prevalence of LPR symptom scores along with markedly reduced laryngeal sensitivity. They hypothesized that VCD was a result of a compensatory motor response via the recurrent laryngeal nerve in response to altered sensitivity of the laryngeal afferent fibers of the superior laryngeal nerve.

This altered autonomic balance has also been demonstrated in asthmatic patients (who are more likely to have both reflux disease and VCD). Asthmatics have been shown to have a decreased parasympathetic tone in response to noxious stimuli, whilst in normal subjects this is higher [60]. This decrease in vagal tone may become persistent with constant repeated stimuli such as with GER, which may explain why symptoms of VCD can be exacerbated by differing emotional states, hyperventilation and exercise, which can also affect parasympathetic activity.

Clinical History of GER-Related Cough and Exclusion of Other Causes

After consulting their primary care physician, patients are usually referred to pulmonologists, or, if associated with other symptoms such as globus, throat clearing, or hoarseness, to an otolaryngologist. Gastroenterologists are becoming increasingly involved to provide objective evidence for the presence of GER. They are also involved when there is inadequate resolution of symptoms despite oral PPI therapy or if patients are considering surgical treatment.

Up to 75% of patients with GER-related cough do not have typical reflux symptoms (“silent reflux”) [61], but patients may find that their cough is worse after foods that lower the LES pressure, such as chocolate, carminatives, peppermint, and foods with a high fat content. Certain medications that can induce GER may also worsen cough, such as B2-adrenergic agonists, theophyllines, and corticosteroids.

Prior to investigating patients for GER, it is important to exclude other causes as outlined by Irwin and Madison [62] (Table 6.1). This includes either (1) ruling out asthma with a methacholine/histamine challenge, or (2) ensuring that the patient has appropriately treated asthma. A computed tomogram (CT) of the sinuses can help to exclude upper airway cough syndrome, or, alternatively, a 1-month trial of topical nasal corticosteroids can be tried. Sputum cytology should be performed to exclude eosinophilic bronchitis.

Table 6.1 Criteria for selection of patients with chronic cough in whom GERD should be investigated

Chronic cough (>8 weeks)
Not on angiotensin-converting enzyme inhibitor
Not a present smoker or exposed to other environmental irritants
Chest radiograph is normal (or near normal)
Symptomatic asthma has been ruled out[a]
Post nasal drip syndrome has been ruled out[a]
Eosinophilic bronchitis has been ruled out[a]

[a]By appropriate tests (e.g., normal sinus CT scan, negative histamine provocation, normal sputum eosinophilia, no improvement on steroids)

Adapted from [62]

In addition to the above approach, there are various scoring systems that have been proposed to help identify those patients with reflux-induced extra-esophageal symptoms. The Reflux Symptom Index (RSI) developed by Belafsky et al. [63] is a self-administered, nine item outcome scale including symptoms such as cough, globus, and throat clearing. It has a scoring range of 0–45, and a value of greater than 13 is considered to be indicative of laryngopharyngeal reflux (LPR). Morice et al. [64] recently proposed the Hull Airway Reflux Questionnaire (HARQ), which is self-administered and comprises 14 items with a maximum score of 70. The questionnaire is responsive to treatment; the minimum clinically significant change was estimated to be 16 points, and the authors propose that it can be used as a diagnostic instrument in reflux-related cough [64].

Such clinical questionnaires may help the initial selection of patients. However, the establishment of an association between GER and cough depends upon the accurate detection of both GER and cough as well as an appropriate statistical analysis that is used to understand the temporal relationship between these two phenomena. Finally, to establish a causal relationship between GER and cough in an individual patient, treatment of reflux should improve the cough.

Detection of Reflux

Traditionally, acid reflux has been assessed in these patients using single or double probe pH monitoring. However, as refluxate ascends up the esophagus, it becomes progressively more neutralized by saliva before reaching the alkaline environment of the pharynx. This leads to poor sensitivity of proximal and pharyngeal pH monitoring. In addition to this, the pharyngeal pH probe has a tendency to dry out, leading to spurious drops in the pH. More recently pH/impedance monitoring has been used, because it detects both acid and non-acid reflux [43, 54]. It can also detect the presence of gas reflux and assess the proximal extent of the refluxate. Because non-acid or weakly acid reflux can be associated with extra-esophageal symptoms, pH/impedance measurements are preferable to pHmetry in patients with suspected GERD-related cough.

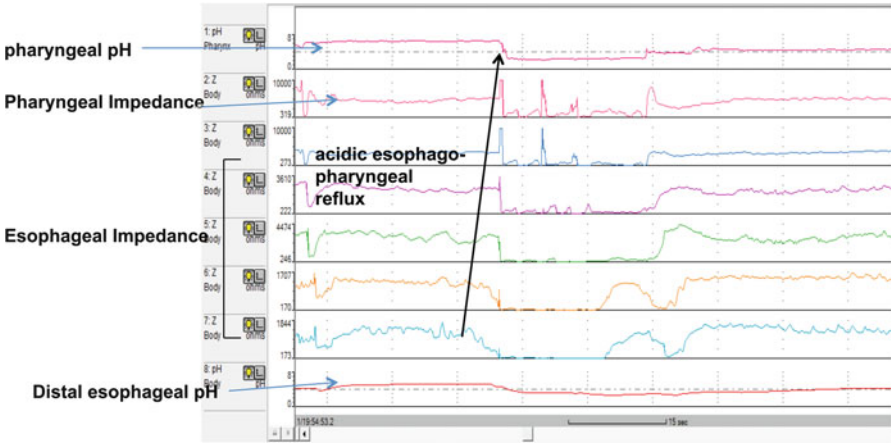

Fig. 6.1 Esophago-pharyngeal reflux

For the detection of pharyngeal reflux, a specialized, bifurcated impedance pH catheter has been designed to detect impedance changes across the upper esophageal sphincter along with pH changes (Fig. 6.1). By temporarily correlating impedance and pH changes or the lack thereof, the physical and pH properties of pharyngeal reflux can be accurately delineated. Normative data suggests that as little as one LPR event can be considered abnormal [65]. Kawamura et al. [66] demonstrated that patients with chronic cough were the only group to have weakly acidic gas esophago-pharyngeal reflux (EPR) as well as swallow-induced acidic or weakly acidic EPR when compared to GERD patients and healthy controls.

Finally, a pharyngeal pHmetry technique, using a newly designed pH sensor, is proposed as capable of detecting aerosolized oropharyngeal pH (Dx-pH System, Restech, USA). However, changes in oropharyngeal pH have not been shown to be temporally associated with GER as measured by impedance [67].

Detection of Cough

Cough events can be marked by the patient on a reflux monitoring data logger and/or a study diary during a 24-h ambulatory pH recording to give a temporal relationship between reflux events and cough episodes. This relies on the compliance of the patient to press the symptom marker in a timely manner and does not take into account subconscious cough episodes such as those that occur during the night.

Manometric cough detection uses a secondary catheter placed simultaneously alongside a pH/impedance catheter [54] that consists of two pressure sensors separated by 15 cm. The sensors are located on either side of the diaphragm in the stomach and 5 cm above the LES in the esophagus. Coughing provokes a typical

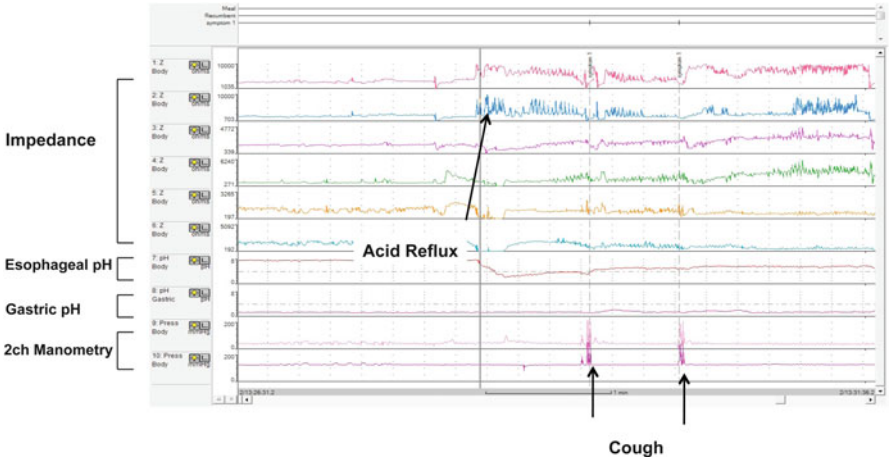

Fig. 6.2 Esophageal impedance-pH combined with manometric cough detector

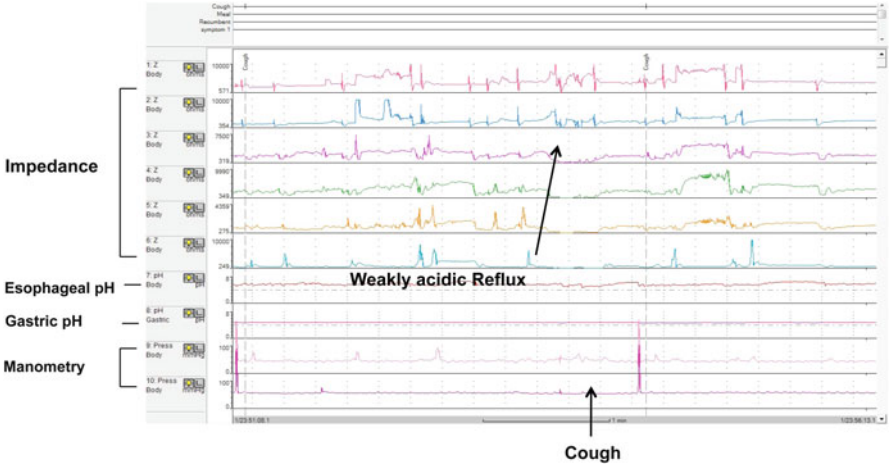

Fig. 6.3 Esophageal impedance-pH combined with manometric cough detector showing cough preceded by weakly acidic reflux

pressure pattern with simultaneous peaks in both pressure sensors, and cough bursts can be identified objectively by this system, and the presence of acid and non-acid reflux before the cough can be recognized in a predetermined preceding time window. Figures 6.2 and 6.3 show examples of bursts of cough preceded by a reflux event using simultaneous monitoring of pH/impedance and intra-abdominal & thoracic pressure.

Smith et al. [55] used an ambulatory sound recording device to detect cough along with simultaneous impedance pHmetry in a group of unselected patients with chronic

cough. This method is very sensitive for detecting single cough events that may be considered as an artifact with manometric recordings, and the sound detection component enables it to identify 2–3 times more cough events versus the manometric method and 9–12 times more than cough events recorded by the patient.

Association Between Reflux and Cough

Several statistical algorithms have been designed to analyze the time association between reflux and symptoms [68]. The symptom index (SI) has been defined as the percentage of reflux-associated symptom episodes within the total symptoms and is considered positive if >50%. The disadvantage of the SI is that it does not take into account the total number of reflux episodes and symptoms. The symptom association probability (SAP) calculates the statistical relationship between symptoms and reflux episodes using the Fischer's exact test, taking into account the number of associated reflux-symptom episodes as well as the total number of reflux and symptom events [69]. The SAP is considered positive when greater than 95% [68]. A time window of 2 min is used to assess the association of reflux with cough, and we could identify SAP positive patients in which the time association might not be by chance alone. It is important to stress, however, that the SI and SAP were designed to study the relationship between reflux and heartburn or chest pain and not for the reflux-cough association. The optimal time window for GERD-related cough needs further investigation. Finally, Hersh et al. [70] recently reported hierarchical use of parameters from ambulatory pH testing to predict response to anti-reflux medical therapy on patients with suspected GERD-related cough. The study showed that the highest likelihood of a sustained, durable response (high degree response) to anti-reflux therapy was achieved when acid exposure time, SAP and SI were all positive.

Treatment of GER-Related Cough

As has been highlighted, chronic cough can be a multifactorial process. Therefore, treating reflux may result in only partial symptomatic improvement. Treatment of GER can either be directed at blocking acid production or preventing reflux from occurring. Dietary and lifestyle measures to reduce GER include reducing daily fat content to <45 g as well as avoiding tea, coffee, mints, citrus products, alcohol and smoking.

Acid Suppression

The American College of Chest Physicians recommends an empiric course of acid suppression in all patients with possible reflux-induced cough [2], whereas the British Thoracic Society specifies that this should be performed in patients who

also have typical reflux symptoms [71]. The high likelihood that GER is linked to chronic cough versus the reported slight increase in risk of pneumonia with PPI treatment [72] should be balanced before undertaking an empiric trial of PPI therapy.

Kiljander et al. [73] reported significant improvement of cough after 8 weeks of PPI treatment (omeprazole 40 mg daily) in a prospective, double-blind, placebo-controlled trial. However, the limitations of this study included a small sample size, lack of improvement with nocturnal cough, and lack of an independently validated symptom score. Ours et al. [74] reported improvement or resolution of cough in only 35% of patients with GERD-related cough after 12 weeks of PPI treatment (omeprazole 40 mg twice daily). A recent Cochrane review [75] concluded that PPI administration was not efficacious for cough associated with GERD symptoms in infants and very young children and should not be used to suppress cough in these patients. They also highlighted that there was insufficient evidence to conclude that treating GER in adults for cough associated with GER was beneficial, but they did observe a slight improvement in cough scores in response to treatment with omeprazole. Whilst there may be some benefit at 4 weeks, a trial of 8–9 weeks should be long enough to see a significant benefit. There was no evidence to support more protracted courses of up to 6 months.

Nocturnal acid breakthrough has been shown to occur despite twice daily dosing of oral PPIs [76], and this is often accompanied by esophageal reflux, particularly in patients with complicated GERD or esophageal dysmotility [77, 78]. The addition of a night-time dose of oral ranitidine has been shown to improve nocturnal gastric acid control [79]; however, the effects may be temporary [80], and the clinical significance is unknown.

A possible reason for ineffective PPI therapy in a subgroup of patients could be the association of cough with non-acid reflux, and this can be assessed using pH/impedance monitoring [43, 54]. In general, patients presenting with a positive SAP between weakly acidic reflux and cough do not have an increased number of weakly acidic reflux episodes, suggesting the possibility of hypersensitivity to such refluxate.

A key mechanism of GER is known to be transient LES relaxation. Baclofen is a gamma-aminobutyric acid agonist (GABAB-agonist) that reduces the number of reflux episodes by reducing the number of transient LES relaxations. Baclofen was reported to reduce frequency of acid and weakly acidic reflux, and it also has an anti-tussive effect by altering the cough reflex [81, 82]. However, baclofen is known to have significant side effects, and the ability of patients to tolerate baclofen therapy is relatively low [82].

A high prevalence of esophageal dysmotility has been demonstrated in patients with chronic cough, which could potentially lead to more prolonged stimulation of esophageal afferent neurons and microaspiration [83]. Prokinetic drugs are frequently used in GERD treatment to accelerate gastric emptying and improve esophageal motility. However, their efficacy in GERD-related cough has not been formally tested, and gastric emptying has not been shown to be delayed in patients with GER-related cough [84]. Azithromycin (AZI) belongs to the group of macrolide antibiotics, which

that is known to have prokinetic effects, and these agents are often used in lung transplant recipients to prevent or treat bronchiolitis obliterans syndrome [85]. Standard esophageal pH monitoring revealed increased esophageal acid exposure in 70% of lung transplant recipients [86, 87]. When Mertens et al. [88] studied the effect of AZI on GER in lung transplant recipients, they found that AZI reduced esophageal acid and volume exposure as well as the number of proximal reflux events, and AZI is currently under investigation in patients with reflux-associated cough.

Surgical Treatment

Fundoplication provides an alternative method to medical treatment for GERD. The procedure is known to be highly effective in reducing esophageal acid exposure time and reflux symptoms [89]. Various mechanisms are responsible for a decrease in reflux frequencies after fundoplication (i.e., correction of the anatomy with reduction of a hiatus hernia, reduction in number of TLESRs, increased residual pressure during TLESRs, increased basal LES pressure and possible reduction in volume of the refluxate) [90, 91]. More recently, Broeders et al. [92] showed that fundoplication similarly controlled acid and weakly acidic reflux, but gas reflux was reduced to lesser extent. For patients with a clearly demonstrated association between reflux and cough, ARS would be a treatment option. To date, outcomes of uncontrolled studies in surgical treatments are encouraging [93–98]. These studies showed that 56–100% of surgically-treated patients with cough had a positive response.

Allen et al. [98] reported factors that predict good symptom outcome after ARS. Their results suggested that a positive Bernstein test, a higher pre-operative cough symptom score and a good cough response to PPI therapy were factors that predict good surgical outcome in patients with suspected reflux-induced cough. Mainie et al. [93] showed that a positive SI between non-acid reflux and cough was a good predictor of successful surgical outcome, and Hersh et al. [70] showed that 67% of the patients who had ARS achieved a long-term, high magnitude response. Allen and Anvari [97] reported long-term outcomes in 528 surgically treated patients using a validated cough scale, and they found a decrease in the cough response from 83% (6 month post surgery) down to 71% over a period of 5 years (assessed at the 5-year post-ARS timepoint).

VCD Treatment

Several case reports have highlighted the link between GER and VCD in both the pediatric and adult populations and have shown improvement with anti-reflux treatment. Heatley et al. [99] presented the case of a 4-month-old baby

with VCD in whom pH monitoring revealed multiple episodes of reflux into the upper third of the esophagus, and the two symptomatic periods were temporally associated with reflux events, Following the initiation of treatment with ranitidine and metaclopramide, the baby's symptoms resolved over the subsequent few weeks.

Suttiwathil et al. [100] presented the case of a 36-year-old female with mild depression presenting with a 10-year history of dyspnea, hoarseness and chest pain with confirmed VCD on laryngoscopy. Spirometry revealed attenuation of the inspiratory flow-volume loop, and esophageal manometry demonstrated a nutcracker esophagus. A 24-h pH study was carried out that showed normal acid exposure time but a positive symptom index, indicating a hypersensitive esophagus. A Bernstein test was performed with infusion of 0.1 N HCL into the distal esophagus, which reproduced the patient's symptoms, and the acid infusion also reproduced the characteristic flow-volume loop changes previously seen on spirometric testing. She was started concurrently on a low-dose calcium channel blocker, an anti-depressant, and a PPI with rapid resolution of her symptoms. Silvers et al. [101] presented the case of a 50-year-old man with a chronic cough, hoarseness, dyspnea, and globus. Spirometry revealed inspiratory loop flattening, and laryngoscopy confirmed changes consistent with VCD. There was no history of psychosocial disturbance, and the patient had a normal CT of the sinuses and chest. Two endoscopies performed initially were normal. However, he had slightly increased distal esophageal acid exposure. The patient was treated for allergic rhinitis, postnasal drip and GERD. However, his symptoms persisted, which led to a third endoscopy that revealed an inlet patch of gastric mucosa. The patient was started on a twice daily regime of ranitidine along with lansoprazole, which resolved his symptoms.

There have not been any recent interventional trials designed to look at GER treatment in VCD. Of those patients, Pargeter et al. [33] reported that only 22% of patients with VCD and evidence of GER responded to anti-reflux therapy. However, there was no indication of timing, dosage or length of treatment. They subsequently found that there was a non-statistically significant improvement in VCD scores in patients with GER who presented with predominant respiratory symptoms and underwent Nissen fundoplication [102].

Diagnostic Algorithm for Patients with Suspected GERD-Related Cough

We follow the management strategy proposed by Galmiche et al. [103] when evaluating and treating our patients (Fig. 6.4). The first step involves a careful exclusion of other causes of cough plus consideration of clinical criteria that suggest a possible reflux-cough association (Table 6.1).

We can follow two possible pathways: (1) An empiric trial with PPI, or (2) obtaining diagnostic investigations including high-resolution manometry and

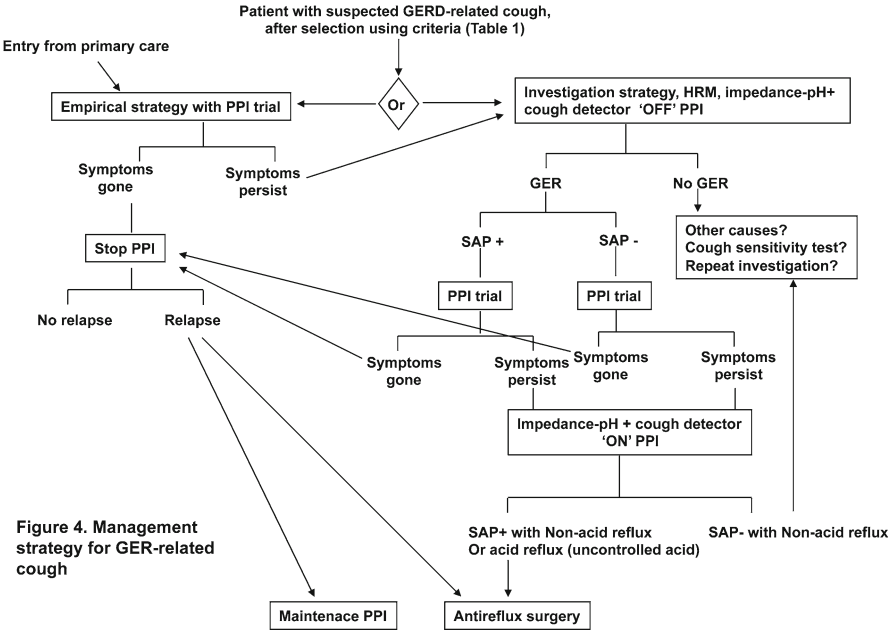

Figure 4. Management strategy for GER-related cough

Fig. 6.4 Management strategy for GER-related cough

simultaneous reflux-cough monitoring. We use a pressure-based objective system that is designed to detect cough to assess the temporal reflux-cough association, and the SAP plays an important role in our strategies [43, 54]. The empirical trial with PPI (double dose) for 3 months is simple and widely used, but it should be noted that this strategy has not been supported by strong scientific evidence. If the empiric trial of PPI is successful, the patient should stop taking PPI for further symptom evaluation. If symptoms relapse, maintenance PPI therapy or ARS can be considered, but reflux and cough monitoring prior to surgery is strongly recommended.

When the empiric trial of PPI fails, patients should be subjected to the investigation strategy that includes monitoring for the detection of both reflux and cough. We perform high-resolution manometry to assess esophageal motility, and prokinetic agents can be added if esophageal hypo-motility is associated with liquid retention and proximal retrograde flow (as detected with impedance). Reflux-cough monitoring is performed while PPI therapy is withheld with special emphasis given to analyzing total esophageal acid exposure, detecting a severe supine acid reflux pattern, and identifying a temporal relationship between cough and acid reflux episodes at this stage. In patients without evidence of GERD, further investigations to identify underlying problems other than reflux should be performed. Patients with increased esophageal acid exposure and/or positive SAP for acid reflux are given a double dose of PPI. If the PPI trial fails to improve cough, repeat reflux-cough

monitoring is performed while patients remain on PPI therapy. This can identify patients with residual acid reflux that occurs despite the use of a PPI as well as patients with non-acid reflux-related cough.

Future Directions

Much progress has been made in mapping out the cough reflex pathway in both humans and animals, and hopefully this will lead to targeted therapy of particular components of the pathway, such as modulation of the afferent pathway or ion channel expression.

The rapid advancement in the objective assessment of cough epochs using acoustic cough detection together with simultaneous pH/impedance recordings with a fast capture rate to detect events has led to more accurate, objective characterization of the cough–reflux relationship in patients. Along with pharyngeal reflux and non-acid reflux detected with impedance monitoring, therapeutic trials need to be performed to prove and support the clinical usefulness of these tests. Non-invasive biomarkers for detecting extra-esophageal reflux are currently under investigation, such as saliva pepsin measurement. These could be utilized to rapidly detect evidence of supra-esophageal reflux, particularly in the pediatric population. However the sensitivity and specificity of such testing needs to be adequately validated.

New GABAB-agonists and other medications to reduce TLESRs and reflux yet trigger less neurological side effects are currently under development and might provide benefit for GERD-related extra-esophageal symptoms in the future.

Although outcomes of uncontrolled surgical studies are encouraging, controlled studies are absolutely necessary to define the real role of ARS in GER-related cough. This is even more important when considering ARS in patients not responding to PPI who have a positive association between non-acid reflux and cough.

The link between VCD and GER is at a much more primitive stage; future studies incorporating the detection of pharyngeal reflux using pH/impedance technology along with extra-esophageal biomarkers of reflux are required to establish more than just an epidemiological association and support using interventions such as ARS.

Key Points

- GERD is one of the three commonest causes of chronic cough, currently thought to occur predominantly via an esophago-bronchial reflex.
- Detection of reflux events with simultaneous cough detection allows for an objective assessment of the relationship between the two.
- GERD is increasingly recognized in patients with VCD, possibly as a result of microaspiration or laryngeal hyper-responsiveness.

- Chronic cough may be multifactorial, and adequate treatment of GERD may result in only partial symptomatic improvement.
- Cough and VCD may be precipitated by both acid and non-acid reflux.
- Future studies using impedance pH technology are needed to help provide a causal association for GERD in VCD.

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Chapter 7
GER in Asthma and COPD

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Keywords Asthma • Gastroesophageal reflux • Chronic obstructive pulmonary diseases • Cough • Microaspiration • Asthma • Lower esophageal sphincter

Introduction

Multiple studies have suggested an association between airway diseases and GER. The mechanisms behind this association have been investigated in great depth, and such investigations have provided an elegant understanding of the complex interplay of GER and airway disease pathophysiology. While we have come to understand some of these mechanisms, we have yet to elucidate others that may lead to the discovery of new treatment modalities that can improve the outcome of patients affected with these disorders.

While asthma and COPD are different disease states with distinct risk factors, pathophysiology, and prognosis, their clinical presentation may significantly overlap, and in certain situations, the distinction between them may not be clear. GER is one of the major comorbidities that patients suffering from either of these disorders often experience. In this chapter, we review the current and relevant literature related to the prevalence, pathophysiology, and treatment options for GER in these two different yet somewhat similar diseases.

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Prevalence of GER in Asthma

It is estimated that about 24 million Americans carry a diagnosis of asthma. About 20% of Americans experience classic GERD symptoms at least once a week, and the prevalence of GERD in asthmatics has ranged from 34% to 89% in various studies. Havemann et al. [1] performed a systematic review to examine the association between GERD and asthma and reported that 59.2% of asthmatics had GERD, whereas the prevalence in controls was 38.1%. Furthermore, the prevalence of abnormal esophageal pH, esophagitis, and hiatal hernia in patients with asthma was 50.9%, 37.3%, and 51.2%, respectively. They reported an odds ratio of 5.5 (95% CI 1.9–15.8) for studies reporting the prevalence of GERD symptoms in individuals with asthma and 2.3 (95% CI 1.8–2.8) for those studies measuring the prevalence of asthma in patients with GERD [1].

In another study, patients with asthma were at significantly increased risk of developing GERD, which occurred mainly during the first year following diagnosis [2]. This study utilized the UK General Practice Research Database to identify a cohort of patients with a first diagnosis of GERD ($n=5,653$) and another cohort of patients with a first diagnosis of asthma ($n=9,712$). The authors demonstrated that the incidence rates of GERD and asthma among the control cohorts were 4.4 and 3.8 per 1,000 person–years, respectively. During the follow-up period, the RR of an incident asthma diagnosis in patients with a new diagnosis of GERD was 1.2 (95% CI 0.9–1.6), while the RR of an incident GERD diagnosis among patients with a new diagnosis of asthma was 1.5 (95% CI 1.2–1.8) after adjustment for age, sex, smoking, prior comorbidity, and number of health-care contacts [2]. In another study, Field et al. [3] determined the prevalence of symptomatic GER, reflux-associated respiratory symptoms (RARS), and reflux-associated beta-agonist inhaler use in asthmatics in a questionnaire-based, cross-sectional analytic survey. The asthma group consisted of 109 patients referred to an outpatient asthma clinic, and the control groups consisted of one cohort of 68 patients visiting their family physicians and a second group of 67 patients with thyroid disease, hypercholesterolemia, or diabetes participating in drug trials. Among the asthmatics, 77%, 55%, and 24% experienced heartburn, regurgitation, and swallowing difficulties, respectively. Furthermore, at least one antireflux medication was required by 37% of asthmatics ($p<0.001$ vs. controls). Interestingly, none of the asthma medications were associated with an increased likelihood of symptomatic GER, but inhaler use correlated with the severity of heartburn ($r=0.28$, $p<0.05$) and regurgitation ($r=0.40$, $p<0.05$) [3].

GER has also been reported to be a risk factor for asthma-related hospitalizations in the elderly [4]. Factors that affected asthma-associated hospitalizations were examined in a prospective cohort of 6,590 adults with asthma in 15 managed care organizations in the USA. At baseline, older patients reported a greater frequency of asthma-related symptoms such as daily cough (36% vs. 22%, $p<0.001$) and wheezing (27% vs. 22%, $p<0.002$). They were also more likely to report comorbid conditions such as sinusitis (50% vs. 38%), heartburn (35% vs. 23%),

chronic bronchitis (43% vs. 16%), emphysema (19% vs. 1%), congestive heart failure (8% vs. 1%), and a history of smoking (54% vs. 34%) (for all $p<0.001$). Factors independently associated with hospitalization included being female, non-white, less educated, less physically healthy, and having more frequent asthma symptoms. However, multivariate analyses revealed that age itself was not an independent risk factor for hospitalization [4].

Prevalence of GER in COPD

In contrast to the prevalence studies of GER in patients with asthma, there are very few studies that examined the prevalence of GER in patients with COPD. There is also a paucity of literature related to the effect of GER on COPD. It is suspected that better management of GER may improve COPD symptoms [5]. However, there have been very few longitudinal studies that have examined the effects of GER on the course of COPD. The latest study that partially fulfilled this missing link was the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study where data of 2,138 patients with stage II–IV COPD were prospectively analyzed for exacerbation frequency and determinants of COPD exacerbation were examined [6]. The authors demonstrated that GER was independently associated with increased risk of COPD exacerbation; other factors were severity of disease (FEV1), history of prior exacerbations along with poorer quality of life and an elevated white blood cell count [6].

El-Serag et al. [7] retrospectively examined data from United States Veterans Affairs database that included patients who carried a diagnosis of erosive esophagitis or esophageal stricture and who were discharged from hospital between 1981 and 1994. In a multivariate logistic regression analysis, the presence of sinus, pharyngeal, laryngeal, or pulmonary disease was compared between cases with esophagitis or stricture and an equal number of controls without esophagitis or stricture. Out of the 101,366 subjects who were analyzed, erosive esophagitis and esophageal stricture were associated with chronic bronchitis (OR 1.28; 1.22–1.34), asthma (1.51; 1.43–1.59), chronic obstructive pulmonary disease (1.22; 1.16–1.27), and pulmonary fibrosis (1.36; 1.25–1.48) [7]. Increased prevalence of GER symptoms was seen in patients with COPD in another prospectively designed, questionnaire-based, cross-sectional study from a single medical center [8]. One hundred veterans with mild-to-moderate COPD based on ATS criteria were compared to 51 control patients from the general medicine clinic. Compared to control subjects in this study, a greater number of COPD patients had significant GER symptoms (defined as heartburn and/or regurgitation) once or more per week (19% vs. 0% for COPD vs. control patients, $p<0.001$), chronic cough (32% vs. 16%; $p=0.03$), and dysphagia (17% vs. 4%, $p=0.02$). [8].

Another study examined the UK General Practice Research Database to investigate the relationship between the diagnosis of COPD and GER in primary care [9]. Two patient cohorts that consisted of patients with an initial diagnosis of GERD ($n=4,391$)

or patients with an initial diagnosis of COPD ($n=1,628$) were compared to a control population that was age- and gender-matched. Their analysis demonstrated that during the 5-year follow-up period, the RR of an incident COPD diagnosis in patients with GERD was 1.17, while the RR of an incident GERD diagnosis among patients with a diagnosis of COPD was 1.46, and a GERD diagnosis in the COPD cohort was also associated with a prior diagnosis of ischemic heart disease [9].

A more recent study from Iceland examined the relationship of nocturnal GER (nGER) with lung diseases [10]. A random sample of 1,325 adults aged 40 years or greater was selected, and pre- and post-bronchodilator testing was performed on all patients. Study participants who had symptoms of nGER were found to have a significantly higher prevalence of respiratory and OSA symptoms than subjects without nGER. Of interest was an additional finding that the nGER group also had a higher prevalence of COPD (GOLD stage 1+) (25.0% vs. 15.6%) ($p=0.02$) and lower FEV(1)/FVC ratio (95.9% vs. 98.9% of the predicted values, $p=0.01$), and these associations remained significant after adjusting for smoking, weight, and other possible confounders [10].

Another investigation examined patients with severe COPD who were matched with age-appropriate controls, and pathological GER was documented in 62% of the patients (26 of 42). Fifteen of the 26 (58%) patients with documented GERD did not report any reflux symptoms. Furthermore, the finding that oxygen desaturation coincided with episodes of esophageal acid exposure events in 40% of patients with GERD was notable [11]. An additional, recently performed study in patients with advanced COPD showed similar results; pH monitoring demonstrated that GER was highly prevalent, and some patients showed evidence of proximal GER on pH monitoring without corresponding distal GER [12].

Pathophysiology of GER in Asthma: What Is the Link?

Multiple mechanisms have been described to explain the potential interactions between the esophagus and the lung that lead to the complex interplay between GER and asthma. These have been broadly categorized below as related to embryonic origins, vagal and axonal reflexes, increased bronchial reactivity, and aspiration of gastric contents (Fig. 7.1).

Embryonic Origins

The interplay between asthma and GER can be traced back to the embryological roots of the two different organ systems. They both arise from the embryonic foregut, which is innervated by the vagus nerve. This shared origin may be one of the root causes of the association between GER and asthma. A recent paper identifies the Nogg and BMP4 genes as playing a key role in mice that have combined defects

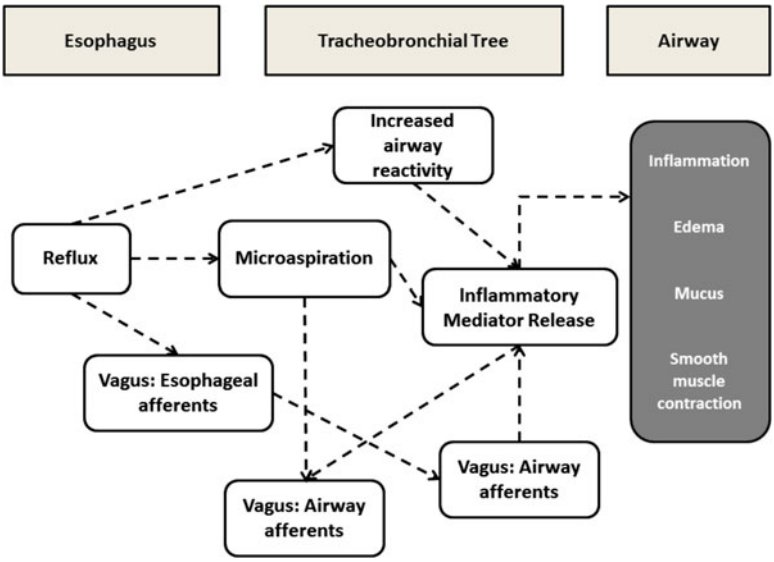

Fig. 7.1 Mechanisms by which bronchoconstriction can be induced by esophageal acid exposure (Adapted from Harding, Up-to-date, GER in Asthma, 2012)

in the esophagus and the trachea [13]. Future attempts to explore the molecular interplay between these two organs at the embryologic level may improve our understanding of disease states that evolve with aging.

Role of the Nervous System

Multiple sensory nerve reflexes play a role in the complex interplay of GER and asthma. Airway chemoreceptors and mechanoreceptors act together as they converge in the CNS at key sites that integrate visceral sensory nerve input. The integration of information relayed by impulses from these receptors is necessary for the initiation of pulmonary symptoms upon stimulation of esophageal receptors by stimuli such as acid exposure [14]. Several physiology studies have demonstrated that there are nonadrenergic, noncholinergic neurons that exist in the esophageal myenteric plexus that communicate with the trachea, and these neurons play an important role in direct interaction between the two structures. Hamamato et al. [15] studied a guinea pig model in which HCl was instilled into the esophagus, and the release of tachykinin-like substances (like substance P) in the airways was measured. They demonstrated that tracheal plasma extravasation was significantly inhibited in animals with bilateral vagotomy, suggesting the role of the vagus nerve. Additionally, they described vascular pathways that communicate between the esophagus and the airways via local circulation [15].

It also appears that the CNS plays a direct role in reflex mechanisms mediated by vagal sensory pathways. When normal volunteers were given capsaicin to evoke cough, activation in multiple brain regions including multiple areas of the primary sensory cortex, insula, and cerebellum was observed. This study provided the first evidence that cortical neuronal networks are involved in sensing airway irritation and modulating cough in humans [16].

Several additional studies have been performed on humans in which intraesophageal acid infusions were used to evaluate airway responsiveness. One study monitored peak expiratory flow (PEF) to assess airway responsiveness, and intraesophageal acid infusion was found to cause a decrease in PEF in the absence of evidence of microaspiration, validating a vagally mediated reflex mechanism [17]. When compared to asthmatics without reflux, asthmatics with reflux also had a further decline in PEF despite successful acid clearance.

Increased Bronchial Reactivity

Increased bronchial reactivity has been correlated with acid reflux. The classic study by Herve et al. [18] measured airway responses in 12 asthmatics and 7 controls following the instillation of saline or acid infusions into the esophagus. The resultant bronchoconstriction was worse in patients who received acid infusions and potentiated methacholine-driven hyperresponsiveness, and these results allow one to conclude that the stimulation of esophageal vagal receptors intensifies bronchoconstriction [18].

Aspiration of Gastric Contents

Microaspiration has been linked to significant worsening of asthma, and this has been demonstrated by several studies. The instillation of acid into the trachea showed a five-fold increase in total lung resistance when compared to a 1.5-fold increase in lung resistance with acid instillation into the esophagus in a cat model [19]. Additional studies have shown that the effect of tracheal acid is abolished with vagotomy, demonstrating that the vagal nerve plays a crucial role in this type of model. A recent study in rats that examined the effects of reflux of gastroduodenal contents into the lungs demonstrated evidence of aspiration pneumonia that was characterized by severe peribronchiolar neutrophilic and lymphocytic infiltrates, goblet cell hyperplasia, prominence of blood vessels, and increased thickness of the smooth muscle layer [20]. Bronchiolitis obliterans (BO)-like lesions consisting of granulation tissue with macrophages, spindle cells, and multinucleated giant cells in the lumen of respiratory bronchioles were also noted.

Chronic aspiration has also been linked to the induction of chronic airway inflammation and altered immune responses. Barbas et al. [21] used a murine model

of asthma to demonstrate that chronic aspiration of 10 μL of murine gastric fluid once weekly for 8 weeks produced an injury pattern that was characterized by hyperplasia and neutrophil infiltration of the bronchioles with relative parenchymal sparing, and these changes were distinguishable from that found with a single episode of acute aspiration. Additionally, they showed that there was a significant shift toward a predominantly Th2 inflammatory response [21].

Observations from various murine models mentioned above have led to human studies that examined the effect of acid reflux events on pulmonary function in asthma. Jack et al. [22] inserted catheters in the trachea and esophagus of four patients with asthma and reported that reflux events associated with a fall in tracheal pH from 7.1 to 4.1 were also associated with a reduction in peak expiratory flow rate (PEFR from 84 to 8 L/min).

Pathophysiology of GER in COPD

The pathophysiology of GER in patients with COPD has been primarily evaluated in studies that included patients with asthma and examined possible mechanisms such as the shared embryonic origins, vagal innervation, bronchial hyperresponsiveness, microaspiration, and immune-mediated inflammation that may play a role in GER-induced alterations in pulmonary function.

Tuchman et al. [21] demonstrated that the instillation of acid into the trachea or distal esophagus evoked bronchoconstriction in cats. However, a study performed on 12 patients with COPD to assess esophageal function and GER during sleep and wakeful states did not show any major difference in airway resistance and esophageal manometry, but acid clearance was delayed in the COPD patients during daytime [23]. Major limitations of this study, however, were its small size and the lack of a control group.

Another factor that may affect patients with COPD is a reduced lower esophageal sphincter (LES) tone that can be induced by oral theophylline, which was commonly used to treat COPD prior to the advent of newer, safer medications. Although performed in asthmatics with GER and normal volunteers, a study that measured LES pressure via manometry before and after intravenous infusion of a dose of aminophylline demonstrated a significant decrease in LES pressure both in normal and asthmatic volunteers [24]. Additionally, diaphragm flattening in COPD patients is thought to lower esophageal sphincter tone [25].

To determine the influence of smoking habits on patients with GERD, Sontag et al. [26] studied 184 healthy, ambulatory outpatients who received endoscopy as the initial diagnostic procedure to evaluate GER. They found that the LES pressure, acid contact time, and frequency of reflux episodes were highly associated with the presence of a hiatal hernia ($p < 0.003$ for all parameters) and that the presence of esophagitis was associated with a 16.5-fold increase in the incidence of hiatal hernia versus healthy subjects without evidence of esophagitis. They also found that cigarette smoking was not correlated with esophagitis, but it was significantly associated

with increased LES pressure ($r=0.18$; $p<0.03$). They concluded that the presence of a hiatal hernia but not altered LES pressure was the most important predictor of reflux frequency, acid contact time, and esophagitis. Additionally, they also suggested that if smoking and LES pressure are causally related to esophagitis, it must be through mechanisms other than increased frequency of reflux episodes or increased acid contact time [26].

Diagnosis of GER in Asthma and COPD

It is crucial to establish if reflux is contributing to a patient's symptoms by obtaining a detailed history (Table 7.1). Esophageal and extraesophageal manifestations of GER should be carefully considered along with nocturnal asthma or COPD exacerbations. Esophageal symptoms to consider include dysphagia, water brash, regurgitation, and heartburn. Extraesophageal symptoms include sore throat, choking, hoarseness, dental erosions, chest pain, or cervical pain. As noted, many patients with asthma and COPD have silent GER. However, there is no current rationale or recommendation to aggressively pursue (e.g., using pH probes) such a diagnosis in asymptomatic individuals with poor disease control.

The American Gastroenterological Association recommends antisecretory drugs for the treatment of patients with GERD syndromes (to heal esophagitis and provide symptom relief) (Grade A evidence) [27]. The use of proton pump inhibitor (PPI) therapy is more effective than histamine2 receptor antagonists (H2RAs), which are more effective than placebo. Additionally, endoscopy is recommended to evaluate patients with a suspected GERD syndrome who have not responded to an empiric trial of twice-daily PPI therapy. Endoscopic biopsies should target any area of suspected metaplasia, dysplasia, or malignancy. Esophageal manometry is also recommended to evaluate patients with a suspected GERD syndrome who have not responded to an empiric trial of twice-daily PPI therapy and have normal endoscopic findings. Ambulatory pH/impedance, catheter pH, or wireless pH monitoring (after PPI therapy is withheld for 7 days) are recommended to evaluate patients with a suspected GERD syndrome who have not responded to an empiric trial of PPI therapy, have normal findings on endoscopy, and have no major abnormality

Table 7.1 Potential clues to GERD-related asthma

Asthma that begins in adulthood
No family history of asthma
Absence of an allergic component
Diagnosis of GERD that precedes onset of asthma
Asthma is worsened by eating, exercise, or supine posture
Nocturnal respiratory symptoms
Asthma that is worsened by theophylline
Asthma that is difficult to control or that requires systemic steroids

(Adapted from Richter, Semin Gastrointest Dis. 1997;8(4):210)

on manometry. Wireless pH monitoring has superior sensitivity to catheter studies for detecting pathological esophageal acid exposure because of the extended period of recording (48 h) and has also shown superior recording accuracy compared with some catheter designs [27].

Treatment of GER in Asthma and COPD

Medical Therapy of GER in Asthma

Multiple trials have examined the treatment of GERD in asthma. However, a major limitation of the majority of these trials is linked to their imprecise definition of asthma, as objective measures to substantiate an asthma diagnosis were infrequently used, and many studies failed to document airway reactivity. Imprecise definitions of GERD as well as a lack of documentation of GERD by pH testing and assessments of GERD severity in the individual patient also pose problems for study interpretation. Furthermore, those investigations that utilized pH monitoring focused mainly on assessment of acid reflux and did not assess weakly acid or nonacid reflux, and some studies have significant flaws in study design, such as a very small sample size or inadequate dosing of PPI therapy. However, all of these studies have contributed to the design of subsequent large, randomized controlled trials that have had a significant impact on our understanding of the link between GER and asthma and the clinical care of these patients [28].

Littner et al. [29] reported the effect of 24 weeks of lansoprazole therapy (30 mg of lansoprazole vs. placebo for 24 weeks) on asthma symptoms, exacerbations, quality of life, and pulmonary function in adult patients with moderate to severe persistent asthma and acid reflux symptoms. The primary outcome of asthma symptoms (as recorded in patient diaries) did not improve. However, asthma exacerbations were significantly reduced, and quality of life was significantly improved compared to placebo [29].

Another study by Kiljander et al. [30] evaluated the effects of esomeprazole 40 mg twice daily for 16 weeks in patients with persistent moderate to severe asthma. Patients ($n=770$) were stratified by a diagnosis of GERD and nocturnal respiratory symptoms in a multicenter, multinational, randomized, placebo-controlled trial, and the primary outcome measure was the change in mean morning PEFR from baseline versus placebo. The only group that demonstrated statistically significant benefit was the group of patients who had nocturnal asthma symptoms plus symptomatic GERD in contrast to those with nocturnal respiratory symptoms only or GERD only [30].

A Cochrane systematic review evaluated the results of 12 trials of medical interventions for GER in asthma [31]. Four trials investigated histamine antagonists, six investigated PPIs, and one assessed conservative treatment of GER. Additionally, one trial had three arms that included an antireflux surgical approach, a histamine antagonist, and a placebo control. All 12 trials were randomized controlled trials of

which nine were crossover trials and three were of a parallel design. The review concluded that the treatment of GER did not reveal a consistent benefit for patients with asthma. Similarly, there was no effect on lung function, airway responsiveness, or asthma symptoms. Furthermore, even though 9 of the 12 trials reported at least one significant outcome, there was no consistency in these effects [31].

Based on the above studies, the pursuit of further testing in patients that have moderate to severe asthma who suffer from *symptomatic* GERD is not recommended. Lifestyle modifications generally prescribed for GERD should be stressed with patients along with prescription of a twice-daily PPI. Lifestyle modifications for GERD suggested by evidence-based medicine include head-of-bed elevation and weight loss. Other interventions such as dietary modification, smoking cessation, and early meal prior to sleep can be recommended to patients. Patients should be monitored after initiation of the PPI to ensure that their symptoms of GER abate. An improvement of ≥20% in PEFR, an improvement in asthma symptoms, or a 20% decrease in steroid dose is generally accepted as a successful outcome [32].

In patients with asymptomatic GER and uncontrolled asthma, there is no current evidence that suppressing acid reflux improves asthma outcomes. The Study of Acid Reflux in Asthma (SARA) (a multicenter, randomized controlled trial that evaluated the effects of 40 mg esomeprazole twice a day compared to placebo in 412 poorly controlled asthmatics despite ICS therapy) showed that PPI therapy with esomeprazole does not improve asthma control or lung function in patients with minimal or no GER symptoms [33]. These patients had minimal or no symptoms of GER, and all patients underwent 24-h pH probe monitoring. Additionally, 40% of these patients were found to have abnormal GER upon esophageal pH monitoring. Of note, this study identified an important gap in our knowledge regarding the prevalence of GER in asthmatics without GER symptoms. Interestingly, ambulatory pH probe measures did not identify a subgroup that benefits from the PPI therapy used in this study. Nonetheless, patients with proximal GER reported significantly worse asthma and health-related quality of life despite a lack of physiologic impairment [33], and a similar study that was just completed by the American Lung Association Asthma Clinical Research Centers in children with asthma yielded very similar results [34]. However, one must recognize that these studies did not evaluate the effect of treating nonacid reflux on asthma control.

Medical Therapy of GER in COPD

No large-scale studies have evaluated therapeutic options for GER in patients with COPD, and this issue deserves future investigation. A preliminary single-blind, controlled trial performed in Japan studied the effect of lansoprazole therapy on 100 patients with COPD who lacked a previously documented history of GER. Most of the patients were evenly distributed between GOLD stages I–III and were predominantly men in their eighth decade of life. Lansoprazole was given for 1 year, and the primary outcome was the number of COPD exacerbations, which were significantly reduced

(0.34 ± 0.72 vs. 1.18 ± 1.40; $p < 0.001$) for patients receiving lansoprazole. An adjusted odds ratio of 0.23 for having exacerbation in the PPI group compared with the control group ($p = 0.004$) was reported [35]. Future randomized controlled trials are needed to further evaluate these findings.

Surgical Therapy

Surgical intervention for abnormal GER is an option for patients who have failed to respond to medications, have experienced complications of GER (GERD), or have elected to have surgery despite apparently successful medical therapy. However, few controlled studies have examined anti-reflux surgery (ARS) in patients with asthma and COPD. One case series reported clinical improvement in the majority of 13 patients that had undergone ARS [36]. A review of 24 trials evaluating ARS in a total of 417 asthmatic patients with GERD reported that ARS improved reflux symptoms in 90% of patients, reduced asthma symptoms and asthma medication use in 88%, and improved pulmonary function in 27% [37]. However, only two of these studies were controlled trials; the remainder were case series, retrospective reviews, or uncontrolled studies.

Conclusions

The reported prevalence of GER in asthma patients is high, but many patients are asymptomatic. The exact prevalence of GER in COPD is unknown and needs further study. Several mechanisms are involved in the complex interplay between the esophageal and tracheobronchial neural networks. Common embryonic origins, vagus nerve-mediated mechanisms, and chronic microaspiration are among the most common mechanisms or predisposing conditions cited in the literature. The relationship between GER and the clinical course of asthma and COPD needs to be better understood. Nonetheless, it is clear that abnormal GER may worsen asthma symptoms and has been associated with increased risk of COPD exacerbations. Diagnosis of GERD should be established in patients with asthma by obtaining a detailed history of esophageal and extraesophageal symptoms and manifestations of GERD, and special care should be taken to elicit symptoms that can occur during both the wakeful and sleep states. Patients with uncontrolled asthma or COPD who have symptomatic GERD should undergo empiric therapy with a PPI administered twice daily. Patients with refractory GERD should be referred to a gastroenterologist to establish a precise diagnosis and rule out other etiologies, and esophageal manometry and pH monitoring may be considered in these patients. Additionally, pH/impedance testing may detect weakly acid or nonacid reflux. Surgical interventions may be offered to carefully selected patients, but more studies to establish appropriate indications and ARS outcomes are indicated. No evidence

currently exists to suggest that patients with uncontrolled asthma with minimal or no GERD symptoms may benefit from empiric acid suppression therapy.

Key Points

- The prevalence of GER in patients with asthma ranges from 30% to 79%, although many patients are asymptomatic.
- The shared embryonic origins of the esophageal and tracheobronchial structures, shared vagus nerve innervation, and chronic microaspiration play major role in the linkage of GER to asthma.
- Medications used to treat COPD and asthma may decrease LES tone and consequently increase episodes of abnormal GER.
- For patients with asthma who have GER symptoms, recommendations for lifestyle modifications and empiric prescription of acid suppression therapy are appropriate.
- Evidence-based recommendations for lifestyle modifications to reduce GER include head-of-bed elevation and strategies to promote weight loss.
- Current evidence does not support the initiation of antireflux therapy in asthma patients who lack symptoms that suggest the presence of GER.
- Current guidelines recommend endoscopy to evaluate patients with a suspected esophageal GERD syndrome who have not responded to an empiric trial of twice-daily PPI therapy.
- Esophageal manometry is recommended to evaluate patients with a suspected GERD syndrome who have not responded to an empiric trial of twice-daily PPI therapy and have normal findings on upper GI tract endoscopy.
- Ambulatory pH/impedance, catheter pH monitoring, or wireless pH monitoring (after PPI therapy has been withheld for 7 days) are also recommended to evaluate patients with a suspected GERD syndrome who have not responded to an empiric trial of PPI therapy, have normal findings on endoscopy, and have no major abnormality on manometry.
- The presence of GER in patients with COPD, especially elderly patients, may increase the risk of an exacerbation of COPD.

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Chapter 8
Sleep and GER

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Keywords Sleep-related GER • Transient LES relaxations • Upper esophageal sphincter • Insomnia • Sleep quality • Arousals • Wake time sleepiness • Obstructive sleep apnea • Nasal CPAP • Proton pump inhibitors

Introduction

Esophageal and gastric function change during sleep, and gastroesophageal reflux (GER) also occurs [1]. When GER occurs, it is often associated with arousals, awakenings, insomnia, unrefreshing sleep, altered daytime functioning, and excessive wake time sleepiness [2]. Patients with sleep-related GER have a higher risk of developing esophageal adenocarcinoma [3]. Patients with obstructive sleep apnea (OSA) commonly have sleep-related GER, and nasal continuous positive airway pressure (CPAP) used to treat OSA also improves sleep-related GER [4]. Treatment of sleep-related GER improves many outcomes; however, since medical GER therapy targets acid secretion and not esophageal motility, nonacid GER still occurs during sleep and may explain why some patients continue to have symptoms despite medical therapy [1, 5].

This chapter will review esophageal and gastric physiology during sleep as well as potential mechanisms of sleep-related GER. It will also examine the prevalence and clinical manifestations of sleep-related GER and discuss the co-occurrence of sleep-related GER and OSA. Prevention and treatment of sleep-related GER and

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future directions for managing this condition will be discussed. Although the literature utilizes the terms “nighttime GER,” “nocturnal GER,” and “supine GER,” people sleep throughout the 24-h period, so “sleep-related GER” is a more correct term [1].

Esophageal and Gastric Physiology During Sleep

Sleep impacts esophageal function, with physiologic changes noted during the transition from wakefulness to sleep, during arousals, during non-rapid eye movement (NREM; sleep stages N1, N2, and N3) sleep, and during rapid eye movement (REM) sleep. Upper esophageal sphincter (UES) pressure decreases significantly with sleep onset, dropping from a mean of 44 to 10 mm Hg in normal volunteers [6]. Recent work notes that UES pressure progressively declines during stage N3 sleep (also referred to as slow-wave NREM sleep) [7]. This lower UES pressure predisposes to aspiration if proximal migration of esophageal refluxate occurs. Using small-volume liquid infusions into the proximal esophagus to examine the UES contractile reflex and secondary esophageal peristalsis during sleep, Bajaj et al. [7] noted that for the UES contractile reflex and secondary peristalsis to occur during stage N3 sleep, an arousal is required. However, the UES contractile reflex and secondary peristalsis are still present during REM sleep, even in the setting of generalized skeletal muscle atonia characteristic of REM sleep [7]. Despite sleep-related changes in UES pressure, lower esophageal sphincter (LES) pressure does not change significantly from wakefulness to sleep during the different sleep stages, or during arousals from sleep [2].

Mechanisms of individual GER events include a low basal LES pressure and impaired gastric emptying; however, the main mechanism for individual GER events is transient LES relaxations. Transient LES relaxations are responsible for 63–74% of GER episodes and are vagally mediated [8]. Sleep increases the vagal threshold for triggering transient LES relaxations [2]. Thus, these relaxations occur during arousals and not during stable sleep.

Other physiologic events also occur during sleep that can impact GER and/or refluxate clearance. Sleep impairs gastric motility as it decreases gastromyoelectric function, resulting in delayed gastric emptying [9]. Basal gastric acid secretion is under circadian rhythm control and peaks between 8 pm and 1 am [10]. The bicarbonate-rich content of saliva neutralizes esophageal acid, but salivary secretion is not measurable during stable sleep [1]. Swallowing stimulates esophageal primary peristalsis, assisting in refluxate clearance. Swallowing does not occur during stable sleep and requires brief arousals or awakenings [11]. Taken together, these physiologic events prolong esophageal refluxate clearance if GER occurs during sleep.

Mechanisms of Sleep-Related GER

A GER event occurs when gastric contents traverse the LES high-pressure zone into the esophagus. The contents can migrate proximally, even past the UES and into the upper airway. If a GER event occurs, the esophagus clears the refluxate by initiating swallows and primary and secondary esophageal peristalsis [2]. Gastric acid neutralization is facilitated by swallowed bicarbonate-rich saliva. Transient LES relaxations are responsible for most GER events; however, other predisposing factors for GER include LES hypotension, hiatal hernia, esophageal dysmotility, delayed gastric emptying, increased gastric acid secretion, obesity, large pleural-abdominal pressure gradients, and increased gastric pressure [8]. Sleep-related GER occurs most often during arousals and awakenings in the sleep period, but not necessarily during stable sleep [2].

Unlike wake time GER that occurs primarily postprandially and consists of short episodes that are rapidly cleared from the esophagus, sleep-related GER events are less frequent but are associated with prolonged esophageal refluxate clearance [12]. Sleep-related GER episodes are also caused by transient LES relaxations that occur during brief arousals or awakenings [13]. Reflux events most commonly occur during awakenings out of stage N2 of NREM sleep. For instance, Dickman et al. [14] examined 15 GER subjects with GER symptoms ≥3 times weekly and noted that 62% of the GER events occurred out of arousals from stage N2 of NREM sleep and 14% occurred out of arousals from REM sleep. Only 5% of GER events were not associated with an arousal (i.e., during stable sleep) [14]. Figure 8.1 shows these data. Another study looked at conscious awakenings. Poh et al. [15] examined 39 GER patients with heartburn and/or regurgitation at least three times weekly and nine control subjects with esophageal pH and actigraphy monitoring. The number of conscious awakenings was higher in the sleep-related GER group compared to a control group (3.0 ± 0.3 vs 1.8 ± 0.4, $p < .05$). Of the conscious awakenings, 52% of these were associated with a GER event in the GER group compared to zero events in the control group [15]. Only 16% of the recorded conscious awakenings were symptomatic such that subjects were not aware that GER occurred. This work verifies that GER events occur without awareness of awakenings [15].

Power spectral analysis of a sleep electroencephalogram (EEG) is another way to evaluate sleep architecture and arousals [16]. Alpha bandwidths are associated with arousals and wakefulness, while delta bandwidths are associated with stable sleep. Eleven GER patients with esophagitis and six patients with functional heartburn (normal endoscopy and pH and no response to proton pump inhibitors) were evaluated. The GER patients had lower delta power and higher alpha power noted during sleep. In the GER patients, the alpha power was more prominent in the later part of the night (3 h after sleep onset). Esophageal pH testing was not performed simultaneously, so it is not known if GER events occurred during these alpha-band shifts [16].

Sleep prolongs the latency to the first swallow if acid is instilled into the esophagus. Sleep also facilitates proximal acid migration toward the UES [17]. Swallowing

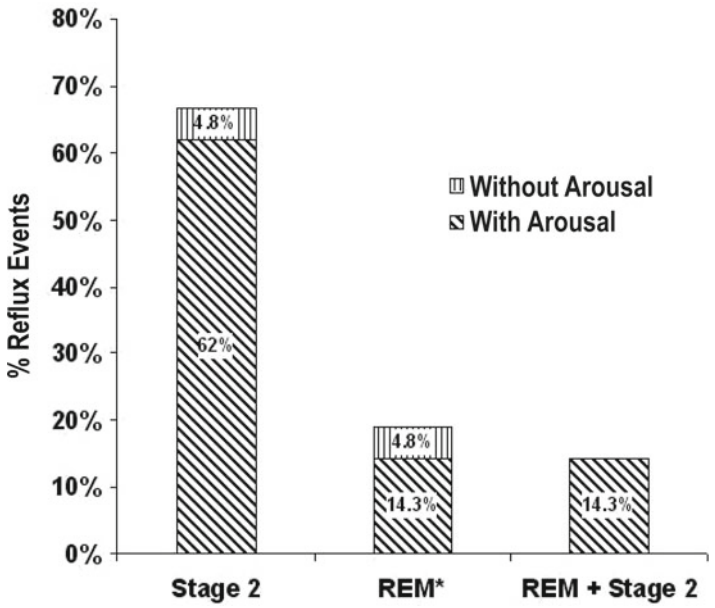

Fig. 8.1 Distribution of acid-reflux events according to stage of sleep. Reprinted with permission from the American Academy of Sleep Medicine. Figure 3 from Dickman R, et al. Relationship between sleep quality and pH monitoring findings in persons with gastroesophageal reflux disease (J Clin Sleep Med. 2007;3:505)

initiation requires an arousal. Furthermore, medications that depress the arousal response, including benzodiazepines, prolong esophageal refluxate clearance [18].

Research shows that sleep-related GER events occur more frequently during the first half of the sleep period [11, 19]. Most events occur during the recumbent-awake period, not during the recumbent-sleep period in experiments utilizing esophageal pH with actigraphy [20].

Sleep-related GER is more likely to occur if food is consumed shortly before sleep time. Subjects eating a meal within 2 h of going to bed were 2.45 times more likely to develop sleep-related GER compared to those who did not eat within 2 h of going to bed [19]. In 261 asthmatics and 218 controls, 50% of the asthmatics had awakenings from sleep-related GER, of which 33% noted reflux-associated asthma symptoms [21]. Notably, 60% of these asthmatics ate before bedtime, and this was associated with sleep-related GER [21].

Sleep positions can also influence the likelihood of GER events. In a small study of 10 subjects with sleep-related GER documented by esophageal pH monitoring, the right lateral decubitus position was associated with greater percentage of time with pH < 4 ($p < .003$) and more prolonged esophageal acid clearance times ($p < .05$) compared to the left, prone, and supine positions [22]. However, GER episodes were more frequent in the supine position ($p < .04$) and occurred within 1 min after a change in the sleeping position 28% of the time. Therefore, it appears that sleeping in the left lateral decubitus position may be protective against sleep-related GER [22].

Sleep-related GER does occur; however, it is less frequent than wake time GER. Sleep alters esophageal physiology in that UES pressure decreases with sleep onset and is lowest during stage N3 NREM sleep, which may predispose to aspiration if GER occurs, especially since sleep facilitates proximal refluxate migration. Esophageal refluxate clearance is prolonged during sleep and requires an arousal. Furthermore, swallowing does not occur during stable sleep, and salivary secretion does not occur, further impairing esophageal refluxate clearance. Transient LES relaxations are the primary mechanism of sleep-related GER and occur during arousals. Most events occur during arousals from stage N2 NREM sleep and are more likely to occur during the first 2 h of sleep time.

Prevalence of Sleep-Related GER

Population-based studies show that sleep-related GER is quite prevalent, especially in GER patients. The American Gastroenterological Association sponsored a national, population-based telephone survey of 1,000 people with heartburn at least three times weekly (conducted by the Gallup Organization) that noted that 79% of people had sleep time heartburn [23]. Of those with sleep time heartburn, 75% reported that heartburn disrupted their sleep, 63% believed that this heartburn negatively affected their ability to sleep, and 40% believed that it impaired their wake time functioning [23]. Of those subjects taking prescribed GER medications, only 49% of subjects had adequate control of sleep-related GER symptoms, and in those subjects taking over-the-counter GER medications, only 29% had control of sleep-related GER symptoms [23]. It should be noted, however, that this study was performed before PPIs were available for use over the counter.

Gerson et al. [24] reviewed all literature published between 1984 and 2007 and identified 59 studies that evaluated sleep-related GER. In five population studies, the mean prevalence of sleep-related heartburn was 54 ± 22%. A high prevalence rate was also noted in a French population survey of 562 general practitioners evaluating 36,663 patients [25]. They noted a GER prevalence of 8%, and of these, 65% reported sleep-related GER symptoms or 5% of the entire patient population [25].

In a study utilizing existing cardiovascular cohorts evaluating outcomes of sleep-disordered breathing, the Sleep Heart Health Study, Fass et al. [18] examined sleep-related heartburn prevalence in 15,315 participants. Twenty-five percent reported sleep-related heartburn more than once weekly [18]. Using multivariate logistic regression models, they found predictors of sleep-related heartburn, including the presence of snoring and daytime sleepiness, insomnia, and the use of benzodiazepines as outlined in Table 8.1.

Dean et al. [26] asked if sleep-related GER correlates with GER severity. This cross-sectional study utilizing an internet-based survey of 2,603 adults matching the US general population noted a GER symptom prevalence of 27%. Forty-five percent of symptomatic GER participants had sleep-related GER symptoms. Participants

Table 8.1 Predictors of heartburn during sleep

Variable	Odds ratio	95% CI	*p* value
Body mass index	1.29	1.22–1.37	<0.0001
Consumption of carbonated soft drinks	1.31	1.16–1.48	<0.0001
Snoring and daytime sleepiness	2.31	2.05–2.59	<0.0001
Insomnia	2.29	2.08–2.52	<0.0001
Hypertension	1.37	1.26–1.49	<0.0001
Asthma	1.57	1.30–1.89	<0.0001
Use of benzodiazepines	1.65	1.30–2.10	<0.0001
College education	0.72	0.66–0.79	<0.0001

Reprinted with permission from the American College of Chest Physicians (Abstracted from Table 2 in Fass R, et al. Predictors of heartburn during sleep in a large prospective cohort study. Chest. 2005;127:1654)

with sleep-related GER symptoms had more severe GER severity ($p < .0001$) than those GER participants who did not have sleep-related GER [26].

Gastroesophageal reflux can disrupt sleep, and it can be asymptomatic. Orr et al. [27] evaluated the occurrence of sleep-related GER in normal controls and in disturbed sleepers who did not have heartburn and who did not have another cause to explain their disturbed sleep. Eighty-one disturbed sleepers and 39 normal controls underwent two nights of esophageal pH monitoring with polysomnography. The disturbed sleep group had higher esophageal acid contact times (9.5% vs. 1.6%; $p < .05$), longer sleep onset latency ($p < .05$), and lower total sleep time ($p < .05$) compared to the control group. In the disturbed sleep group, 27% had at least one acid GER event. Thus, sleep-related GER can be clinically silent and can disrupt sleep [27].

These data taken together show that sleep-related GER symptoms are present in as many as 25% of the adult population and may be as high as 79% in GER patients. Furthermore, in disturbed sleepers without GER symptoms, sleep-related GER is disturbing sleep in 27% of disturbed sleepers who did not have another cause to explain their poor sleep. In general, sleep-related GER is more common than clinically recognized.

Clinical Manifestations of Sleep-Related GER

Clinical manifestations of sleep-related GER include esophageal and extraesophageal findings. Patients with sleep-related GER are more likely to have erosive esophagitis, Barrett's esophagus, and adenocarcinoma of the esophagus compared to those GER patients without sleep-related GER [28, 29]. Orr et al. noted that esophageal acid contact times during sleep time as opposed to diurnal time were associated with erosive esophagitis and mucosal damage [28]. This was confirmed by Frazzoni et al. [29] who examined 220 GER patients with 24-h esophageal pH testing. Patients with complicated GER (ulcerative esophagitis, esophageal strictures, and

Barrett's esophagus) had marked increases in esophageal acid contact times during sleep ($p = .024$) [29]. There were no differences in diurnal esophageal acid contact times [29]. Another study noted that patients with Barrett's esophagus had markedly prolonged esophageal acid contact times during sleep [30]. Sleep-related GER symptoms are also associated with esophageal adenocarcinoma. Lagergren et al. [3], in a case-controlled population-based study in Sweden, noted that subjects with heartburn, regurgitation, or both, occurring at least once weekly during sleep time were associated with an increased risk for esophageal adenocarcinoma (odds ratio 10.8, 95% confidence intervals 7.0–16.7).

Common presenting sleep-related GER symptoms include heartburn, regurgitation, and chest pain occurring during sleep time [31]. Extraesophageal manifestations of sleep-related GER include sleep and daytime symptoms. Sleep symptoms include insomnia, awakenings, unrefreshing sleep, laryngospasm, and wheezing [31]. Daytime symptoms include fatigue and excessive daytime sleepiness [31].

Fass et al., in the Sleep Heart Health Study, noted that sleep-related GER symptoms were associated with insomnia [18]. Dickman et al. [14] evaluated 15 subjects with sleep-related GER noting that disorders of initiating and maintaining sleep were associated with higher GER symptom index and frequent awakenings. Furthermore, overall poor sleep quality was associated with longer esophageal acid contact times during sleep [20]. A recent placebo-controlled trial utilizing esomeprazole 20 mg, 40 mg, or placebo for 4 weeks in 750 subjects with sleep-related GER noted that at baseline, 83% of subjects reported poor sleep quality (defined as a global Pittsburgh Sleep Quality Index score of greater than 5) [32]. After 4 weeks of proton pump inhibitor (PPI) therapy, 73% of the treated subjects had resolution of their sleep disturbance. Work productivity also improved in the PPI-treated group, as did the number of work hours [32]. DiMarino et al. [33] examined the effect of omeprazole on arousals, awakenings, and sleep efficiency in subjects with sleep-related GER. Omeprazole decreased the number of arousals from 11.6 ± 3.8 to 1.5 ± 0.8 ($p < .05$), decreased the number of awakenings from 3.7 ± 0.9 to 1.3 ± 0.5 ($p < .05$), and increased sleep efficiency from 70.2% to 81.6% ($p < .05$) [33]. In a larger study, Fass et al. [34] examined 305 patients with sleep-related heartburn and sleep disturbance in a placebo-controlled trial using dexlansoprazole MR 30 mg for 4 weeks. Prior to treatment, patients noted difficulty falling asleep, multiple nights with awakenings and difficulty getting back to sleep, early morning awakenings, and waking up feeling tired [34]. The PPI-treated group had significant improvement in of all of these outcomes. Furthermore, the PPI-treated group had improvement in work productivity, overall sleep quality, sleep-related GER symptoms, and health-related quality of life [34].

Sleep-related GER is also associated with laryngospasm occurring during sleep. Patients with sleep-related laryngospasm have an abrupt interruption of their sleep accompanied by a feeling of acute suffocation and stridor. Although there is minimal data evaluating GER, Thurnheer et al. [35] reported a case series of 10 patients with sleep-related laryngospasm. Of these patients, nine had sleep-related GER documented by esophageal pH testing, and six responded to GER medical therapy [35].

Sleep-related GER may also impact asthma, COPD, aspiration-associated lung diseases, and interstitial lung diseases; however, these findings are discussed in other chapters.

One final comment is that some patients with sleep-related GER may present with excessive daytime sleepiness without a known cause. As previously noted, these patients may have significant sleep disruption related to GER events without esophageal symptoms or an awareness of what is causing their sleep problem [27].

Sleep-Related GER and Obstructive Sleep Apnea

Because the most common mechanism of sleep-related GER events are transient LES relaxations occurring during arousals, primary sleep disorders causing arousals may also predispose to sleep-related GER. Obstructive sleep apnea is one such disorder. Multiple studies note an association between OSA and sleep-related GER; however, causality cannot be determined at this time.

Population-based and cohort studies note the association. The Sleep Heart Health Study noted that snoring and daytime sleepiness predicted the presence of heartburn during sleep with an odds ratio of 2.31 (95% confidence interval 2.05–2.59, $p < .0001$) [18]. In the European Community Respiratory Health Survey, respondents with sleep-related GER, compared to those without sleep-related GER, were more likely to report snoring ($p < .001$) and apnea ($p < .01$) [36]. In a cohort of 331 OSA patients, sleep-related GER symptoms were present in 62% [4]. In another cohort of 135 OSA patients, heartburn and/or regurgitation was present in 58% of patients [37].

Thus, GER symptoms are common in OSA patients, but there are conflicting data as to whether sleep-related GER severity is associated with higher OSA severity based on the apnea-hypopnea index (AHI). Morse et al. [38] noted no relationship between AHI and heartburn severity index; however, disturbed sleep was associated with higher GER severity. Kim et al. [39], in a cohort of more than 1,000 consecutive patients referred for OSA, noted that GER symptom scores did not correlate with OSA variables including AHI. However, Guda et al. [40] noted in 94 consecutive patients being evaluated for OSA that those with GER symptoms had higher AHI (59.1 events/h) versus those without GER symptoms (34.1 events/h; $p = .04$).

Abnormal esophageal acid contact times are also prevalent in OSA patients. Friedman et al. [41] noted abnormal esophageal acid contact times in 68% of 77 patients with OSA. This was verified by Wang et al. [42] who observed abnormal esophageal acid contact times in 63% of consecutive OSA patients. Furthermore, patients with OSA are more likely to have proximal reflux, including reflux above the UES [43]. Wise et al. [43] noted abnormal esophageal acid contact times in 64% of OSA patients including esophageal acid events occurring 1 cm above the UES. Not all OSA patients with GER have esophageal symptoms. Hawrylkiewicz et al. [44] noted in 21 OSA patients who did not have reflux symptoms that 66% had abnormal esophageal acid contact times. Thus, GER may be clinically silent.

Esophagitis is also seen in OSA patients. In 57 consecutive OSA patients with GER symptoms undergoing endoscopy, erosive esophagitis prevalence was higher in OSA patients having an AHI greater than 30 events/h compared to those with an AHI of less than 30 events/h ($p = .004$) [45]. Logistic regression analysis found a positive correlation between erosive esophagitis and higher AHI ($p = .016$). Thus, heartburn, abnormal esophageal acid contact times, and esophagitis are prevalent in patients with OSA, although these findings alone do not prove causality.

Studies evaluating the temporal association between OSA events and esophageal GER events note that 81% of esophageal acid events were associated with OSA events [46]. However, correlation analysis did not show a relationship between esophageal acid events and magnitude of esophageal pressure swings. Other studies note that esophageal acid events may occur at the end of apnea events; however, many events occur in the absence of apnea events [47].

There are many potential mechanisms whereby GER and OSA can interact. For instance, both have common predisposing factors including obesity and alcohol use [48, 49]. They have a common site of end-organ tissue injury including the pharynx and upper airway. OSA events can cause arousals and thus transient LES relaxations. Furthermore, there is evidence of common skeletal muscle control of the upper airway and the upper esophagus [50]. Because multiple coexisting mechanisms are present, evaluating one mechanism solely may not have a significant impact on the entire process, such that causality is more difficult to ascertain.

Obesity increases GER risk with increasing body mass index (BMI), and higher BMI is associated with OSA up to age 60 [48, 49, 51]. Alcohol decreases LES pressure and thus predisposes to GER, and it also decreases upper airway muscle tone and alters the arousal threshold to apnea events [52, 53].

Although some investigators hypothesize that increased respiratory effort resulting in more negative intrathoracic pressure during obstructive apneic events could result in insufficiency of the LES, research does not support this hypothesis. Carefully performed studies note no relationship between esophageal acid events, pleural/esophageal pressure swings, and obstructive apneic events in OSA patients [46]. Recently, Kuribayashi et al. [50] performed a study using state-of-the art sleep and esophageal techniques (including high-resolution esophageal manometry, pH, and impedance with polysomnography) in 15 controls, nine GER patients without OSA, six OSA patients without GER, and 11 patients with OSA and GER. Although there were only a few GER events during monitoring of these subjects, they noted that during individual OSA events, end-inspiratory esophageal pressure progressively decreased and end-inspiratory gastroesophageal junction pressure progressively increased. Interestingly, end-inspiratory UES pressure progressively increased during apneic events [50]. The increases in gastroesophageal junction and UES pressures counterbalanced the decrease in esophageal pressure. The authors concluded that during an individual OSA event, there were marked changes in respiratory effort associated with esophageal pressure changes that may actually be protective against GER events [50]. Of note, it appears that the UES and crural diaphragm (which participate in LES pressure generation) appear to be under the same neural control as the upper airway muscles in OSA patients. Of note, none of these patients had

hiatal hernias, and they had high basal LES pressures [50]. This study suggests that physiological events occur to augment the antireflux barrier during OSA events. Hopefully, more research will further elaborate the interaction between individual GER events and obstructive apneic events.

Despite our inability to definitively look at the causal relationship between OSA and sleep-related GER, treatment of OSA, especially with CPAP, improves sleep-related GER. Green et al. [4] noted in 331 OSA patients that compliant CPAP patients have a 48% reduction in sleep-related GER symptoms ($p<.001$). A strong association was noted between higher CPAP pressures and improvement in sleep-related GER symptoms ($r=0.7$, $p<.001$), and noncompliant CPAP patients did not have sleep-related GER symptom improvement [4]. Another study by Tawk et al. [54] noted that esophageal acid contact times improved significantly with 1 week's use of CPAP. Esophageal acid contact times in 16 OSA patients with an AHI of >20 events/h and sleep-related GER documented by pH monitoring showed that esophageal acid contact times decreased from $16.3 \pm 18.8\%$ to $3.8 \pm 7.6\%$ with CPAP [54]. Shepherd et al. [55] examined whether CPAP altered LES function in 10 healthy, awake subjects without utilizing CPAP and while utilizing 15 cm H_2O of nasal CPAP. CPAP increased intrathoracic pressure (compressing the esophagus) and decreased the pressure gradient across the diaphragm. Nasal CPAP also increased basal LES pressure, esophageal pressure, and gastric pressure. Additionally, CPAP decreased the duration of LES relaxations triggered by swallowing. Thus, CPAP alters LES function, even during wakefulness [55]. The same group then went on to evaluate eight OSA patients with sleep-related GER using polysomnography during sleep with and without CPAP at 10 cm H_2O [56]. They verified that OSA events and sleep-related GER events were not directly related in a temporal sense. Nasal CPAP increased the nadir pressure during LES relaxations and decreased the duration of LES relaxations. Thus, these studies note the efficacy of CPAP in controlling sleep-related GER [56].

Surgical treatment of OSA may also improve sleep-related GER. Wang et al. noted a correlation between improved AHI and arousal index and reduction of esophageal acid contact times ($r=0.607$, 0.730, both $p<.001$) [42]. Medical treatment of GER with PPIs does not improve OSA variables. Stewart et al. [57] prospectively examined 27 OSA patients both before and after receiving pantoprazole 40 mg daily for 3 months as well as GER lifestyle modifications. There was no significant change in AHI or snore index with high dose PPI. It is noteworthy that PPI therapy did improve Epworth Sleepiness Scale, total GER score, bed partner's score, and GER-associated awakenings [57]. To further address the effect of acid suppression on OSA, Orr and colleagues performed a single-site study evaluating 25 patients with mild OSA and sleep-related GER [58]. Patients received 8 weeks of rabeprazole 20 mg twice a day. Improvements in subjective measures of sleep quality including the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale were noted; however, the AHI did not significantly change with PPI therapy [58].

In conclusion, sleep-related GER is prevalent in OSA patients; however, the temporal relationship between individual GER and OSA events is complex and does not show causality. Treatment of OSA with CPAP improves sleep-related GER.

Because sleep-related GER mechanisms are multifactorial, it is likely that there is a two-way, mutually reinforcing relationship between these two common conditions that have similar predisposing risk factors for disease development.

Diagnosis, Prevention, and Treatment of Sleep-Related GER

Sleep-related GER can be diagnosed in many ways, primarily through symptoms. Symptoms include multiple awakenings due to substernal burning or chest discomfort, indigestion, heartburn, a sour or bitter taste in the mouth upon awakening, regurgitation, water brash, and coughing or choking during sleep [2]. Some patients do not have any symptoms and yet have significant sleep-related GER as previously noted [27]. Esophageal pH testing can be utilized to document sleep-related GER, especially in those who do not have GER symptoms; however, it is not required for the diagnosis of sleep-related GER. Esophageal pH testing is performed over a 24-h period to increase the test's specificity and sensitivity, which approximates 90% [59]. Esophageal pH combined with impedance monitors both acidic and nonacidic GER events and can be useful in patients with persistent symptoms despite being on acid-suppressive therapy [60]. Esophageal pH testing can be integrated with polysomnographic techniques to assess the temporal relationship of GER events with other sleep events; however, this is usually used in a research setting [10]. Again, diagnostic testing is not required to make a diagnosis of sleep-related GER [24].

Prevention of sleep-related GER focuses on mechanisms predisposing to GER development. Table 8.2 displays interventions that can prevent sleep-related GER. Since the major mechanism of sleep-related GER is transient LES relaxations that occur with arousals, any primary sleep disorder that causes arousals should be evaluated and treated, including OSA. As previously noted, nasal CPAP improves sleep-related GER in OSA patients [4]. Other causes of arousals, including environmental elements such as a snoring bed partner, animals in the bedroom, or bedroom noises or lights, should also be controlled. Other preventative measures include behavioral approaches [61]. These include weight loss (if the person is obese) and avoidance of

Table 8.2 Prevention of sleep-related GER

Treat primary sleep disorders that can cause arousals
Remove from the sleep environment arousal-causing things (animals, light, noise, snoring bed partners)
Nasal CPAP in OSA patients
Lose weight if obese
Smoking cessation
Avoid foods that worsen GER and acidic food and drinks (sodas)
Avoid eating at least 2–3 h before bedtime, including alcohol
Sleep with the head of the bed elevated
Sleep in the left lateral decubitus position
If risk-benefit analysis allows, avoid medications known to worsen GER

substances and medications that predispose to GER development. Tight fitting bedclothes can impair LES function and should be avoided [61]. Meal timing is important since gastric emptying is reduced during sleep. Patients should avoid eating for at least 2–3 h before bedtime [21]. This is especially important, since most GER events occur within the first few hours of the sleep period. Avoidance of foods that promote GER is also important. Foods with high fat content decrease gastric motility and emptying [62]. Furthermore, caffeine decreases LES pressure and impairs adenosine-mediated sleep mechanisms [63]. Chocolate and peppermint also decrease LES pressure, as does alcohol. Alcohol also disrupts sleep architecture and is associated with arousals that can also trigger transient LES relaxations and, thus, GER events [52]. Avoidance of acid-containing foods may be helpful. The pH of carbonated sodas ranges from 1 to 3, and the release of carbon dioxide gas can cause gastric distension and trigger LES relaxations [64]. Recently, Dr. Jamie Koufman along with a New York-based chef, Marc Bauer, measured the pH of common foods and developed a cookbook with recipes that focus on the use of non-acidic ingredients [65]. Smoking also worsens GER, since nicotine decreases LES pressure and disrupts sleep architecture [66]. If the patient is not open to smoking cessation, then smoking abstinence for an hour or more before bedtime should be strongly recommended. In one study, positional therapy (elevating the head of the bed 6–8 in.) decreased esophageal acid contact times [67]. As previously mentioned, a small study showed that GER episodes occurred less frequently in the left lateral decubitus sleeping position [22]. Data are minimal in evaluating these behavioral preventative approaches in a systematic way; however, a recent evidence-based review noted significant effectiveness of weight loss and head of bed elevation in patients with GER [68].

Another way to prevent sleep-related GER is to avoid medications that can potentiate GER. These medications predispose to GER development, lower skeletal muscle tone, or impair the arousal response during sleep. Before discontinuing these medications, the risk-benefit ratio for the individual patient in doing so should be evaluated. Medications that have the potential to potentiate GER include intravenous and oral theophylline and aminophylline, beta-2 receptor agonists (inhaled, oral or intravenous), and oral prednisone [2]. Other medications include nitrates, calcium antagonists, tricyclic antidepressants, prostaglandins, bisphosphonates, and progesterone [2]. As previously noted, benzodiazepine use was predictive of heartburn during sleep and should be avoided if possible [18]. Zolpidem, the most commonly prescribed sleep medication, decreases the arousal threshold. Gagliardi et al. [69] noted that zolpidem significantly increased esophageal acid contact times ($p < .05$) and decreased the arousal response associated with GER events compared to placebo. These effects waned after the first 3 h, especially since the elimination half-life of zolpidem is 2.5 h [69]. However, because most sleep-related GER events occur during the first 2 h of sleep, this finding may be important. Although more data are needed, this effect has the potential to extend to the other non-benzodiazepine hypnotic medications in this class. Because sleep-related GER is a cause of insomnia and this class of medications is commonly used to treat this disorder, these medications have the potential to worsen sleep-related GER and, thus, insomnia.

Treatment of sleep-related GER should also include preventive measures as previously discussed. Medical GER therapy includes antacids and acid-suppressive medications. Although antacids provide acute symptom relief, they really play no role in sleep-related GER. Alginates may offer some protection against the damaging effects of refluxate [70]. The alginates settle on the surface of gastric contents and form a raft-like suspension that may offer a protective effect to the esophageal mucosa. Unfortunately, therapeutic alginate preparations are not available in the USA [61, 70]. Acid-suppressive medications include H_2 receptor antagonists and PPIs. They suppress gastric acid secretion and reduce the acidity of the refluxate, but they do not prevent GER events [60, 61]. The H_2 receptor antagonists are readily available over the counter, and all have equal efficacy if dosed correctly, but cimetidine has a higher potential for drug interactions, including clopidogrel. Dosing before bedtime may be helpful. Proton pump inhibitors provide superior gastric acid suppression [61]. Dosing of PPIs for sleep-related GER should be 30 min before the dinner meal versus bedtime. Many studies have compared PPIs to one another, and there are only minimal differences noted that are generally not clinically important [71]. Some PPIs are available for over-the-counter use in the USA. Careful attention to drug interactions should be noted with PPIs. Research also shows that nocturnal gastric acid breakthrough occurs in up to 90% of control subjects using omeprazole 20 mg twice daily [72]. Initial studies showed that taking an H_2 receptor antagonist before bedtime improved this finding; however, the effect was lost after 7 days. So, taking an H_2 receptor antagonist is generally not recommended for nocturnal gastric acid breakthrough [73, 74].

More recently, a new formulation of the PPI dexlansoprazole has become available that does not require dosing before meals [75]. As previously mentioned, a placebo-controlled trial using this formulation markedly improved sleep-related GER outcomes [34]. Gastroesophageal reflux is a motility disorder, and acid inhibition may alter the refluxate pH, but not the primary GER event itself. Orr et al. [5] studied acidic and nonacidic reflux during sleep using combined esophageal pH and impedance monitoring under conditions of powerful PPI treatment. Proton pump inhibitor treatment reduced the overall number of reflux events during sleep; however, nonacidic reflux events still occurred. This may explain why some individuals continue to have GER symptoms despite PPI treatment [5].

Unfortunately, no prokinetic agents are available for use in the USA that are without significant side effects. Use of metoclopramide is not recommended [61]. However, in resistant cases, baclofen can be used. Baclofen reduces the frequency of transient LES relaxations by approximately 50% and GER events by 43% [76]. Unfortunately, it causes significant central nervous system side effects that include dizziness and lightheadedness. Hopefully, future medications will be developed that target transient LES relaxations and other esophageal motility phenomena predisposing to GER.

Other treatments for GER include endoscopic therapies and surgical fundoplication. At this time, there is insufficient evidence to recommend endoscopic therapies for sleep-related GER [77]. Surgical fundoplication includes both open and laparoscopic techniques. There are minimal outcome data in patients with sleep-related

GER, so careful selection of potential surgical candidates is essential. Potential surgical indications include refractory GER despite medical therapy, esophagitis, and GER-associated recurrent aspiration [78, 79].

In conclusion, treatment of sleep-related GER includes preventive measures and behavioral therapy as well as aggressive acid suppression utilizing PPIs. Response to medical therapy should be monitored with diaries. Potentially, if symptoms improve, then step-down therapy can be implemented. If symptoms return, then stepping back to higher doses of PPI is indicated. If sleep-related GER symptoms persist, consideration should be given to investigating GER with combined esophageal pH and impedance monitoring to see if sleep-related GER is controlled with medical therapy. At this point in time, it is recommended that a referral to a gastroenterologist should be made. Additionally, one should remember that nasal CPAP is effective, especially in OSA patients. No studies to date have evaluated long-term outcomes for treatment of sleep-related GER.

Future Directions

There are many unanswered questions concerning sleep-related GER. Despite its high prevalence, more work is needed that examines mechanisms and how sleep impacts esophageal function. Sleep-related GER disrupts sleep and daytime functioning, yet practitioners do not diagnose it or treat it aggressively. Many studies have examined outcomes with short-term sleep-related GER therapy, mostly with PPIs; however, there are no data available to guide long-term therapy. Sleep-related GER is common in OSA patients, and nasal CPAP improves sleep-related GER, but more research is needed to evaluate how these two common conditions interact with each other. Because current medical therapy primarily targets gastric acid secretion, research is needed to see if nonacid GER events impact sleep outcomes. Medications are needed that target transient LES relaxations. Currently, only baclofen has an effect on transient LES relaxations; however, side effects limit its usefulness. There are minimal to no data evaluating the effects of endoscopic and surgical fundoplication on sleep-related GER outcomes. Hopefully, future research will examine these questions and lead to improved sleep and wakeful outcomes as well as quality of life in our patients.

Key Points

- Esophageal changes during sleep include decreases in UES pressure, which is lowest during stage N3 NREM sleep. If GER occurs, there is proximal refluxate migration toward the UES. Transient LES relaxations occur primarily during arousals from sleep, as does swallowing and esophageal peristalsis.
- Sleep-related GER occurs primarily during arousals in the first few hours of the sleep period and is primarily caused by transient LES relaxations.

- The prevalence of sleep-related GER is approximately 79% in GER patients and 25% in the adult population.
- Esophageal manifestations of sleep-related GER include heartburn, regurgitation, chest pain, complicated GER (ulcerative esophagitis, esophageal strictures, and Barrett's esophagus), and esophageal adenocarcinoma.
- Extraesophageal manifestations of sleep-related GER include insomnia, awakenings, unrefreshing sleep, excessive daytime sleepiness, laryngospasm, and wheezing during sleep. Note that some patients may not have any symptoms.
- Up to 62% of OSA patients have sleep-related GER symptoms, and CPAP improves GER symptoms and reduces esophageal acid contact times.
- Diagnosis of sleep-related GER is made clinically. Esophageal pH and impedance testing can be used in patients who do not improve with GER therapy. Testing may be helpful in patients without esophageal symptoms who have disrupted sleep without an identifiable cause found despite having undergone polysomnographic sleep testing.
- Prevention of sleep-related GER in patients includes treating sleep disorders that cause arousals, weight loss if the patient is obese, not eating prior to bedtime, and avoiding foods and medications known to worsen GER or depress the arousal threshold.
- Treatment of sleep-related GER includes behavioral treatment noted above and proton pump inhibitor therapy given an hour before the last meal. Fundoplication can be helpful in selected patients; however, outcome data is limited. Nasal CPAP is useful in patients with GER and OSA.

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Chapter 9
Gastroesophageal Reflux in Cystic Fibrosis and Non-CF Bronchiectasis

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Keywords Gastroesophageal reflux (GER) • Cystic fibrosis • Non-CF bronchiectasis • Aspiration of gastric content • Hiatal hernia • Postprandial acid pocket • Gastroesophageal pressure gradient (GEPG)

Gastroesophageal reflux (GER) or the retrograde flow of gastric contents into the esophagus is a physiologic phenomenon that occurs most often after meals and is restricted to the distal esophagus [1, 2]. These occasional GER episodes are of brief duration, cleared rapidly, and generally well tolerated [3]. GER can be accompanied by typical symptoms, like heartburn and regurgitation, but also by atypical symptoms such as noncardiac chest pain, cough, wheezing, and ear, nose, and throat symptoms [1, 2]. Pathological GER or GERD (GER disease) has been described as the increased frequency or duration of exposure of the esophagus to regurgitated gastric contents [4]. Reflux has been clearly associated with the presence of esophagitis and Barrett's esophagus, and it has also been implied in the pathophysiology of different respiratory disorders [5, 6]. This chapter deals with the literature data on the prevalence, mechanisms, and role of GER in cystic fibrosis as well as in non-CF bronchiectasis.

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Cystic fibrosis (CF) is an autosomal recessive disease occurring in approximately 1/2,000–1/4,000 live births in the Western world caused by mutations of the CF transmembrane conductance regulator (CFTR) gene (CFTR-gene) mapped on chromosome 7 [7]. This gene encodes a chloride channel expressed in epithelial cells of multiple organs. Mutations in the CFTR-gene lead to the production of an abnormal CFTR-protein, which results in a low rate of Cl^- secretion, and a high rate of Na^+ reabsorption along with water and leads to mucus desiccation [7, 8]. The first symptoms of CF, i.e., malnutrition and chronic airway infections, arise mostly during infancy or early childhood. Although chronic airway infections resulting in mucopurulent plugging and bronchiectasis are the hallmark of CF, it is defined as a multiorgan disease with additional characteristic abnormalities in the upper airways, gastrointestinal tract, pancreas, and reproductive tract [7–10]. Although CF remains a life-threatening disease, thanks to better management, survival of CF patients has substantially improved in the last 20 years, resulting in a median survival of 37 years [7, 9]. Patients with CF can have a variety of symptoms regarding the gastrointestinal tract, but the two most prevalent entities are obstruction of the small bowel (distal intestinal obstruction syndrome or DIOS) and gastroesophageal reflux [7, 10].

Non-CF bronchiectasis (NCFB) is a chronic respiratory condition characterized by an abnormal, irreversible dilatation of one or more bronchi and chronic sputum production that results from recognized causes other than CF [11, 12]. Different underlying etiologies causing NCFB have been identified ranging from idiopathic to congenital conditions, immunological disorders, and post-infective causes [11–13]. There is also a link between gastrointestinal pathology and bronchiectasis. NCFB can occur as a respiratory manifestation of inflammatory bowel disease (IBD), especially ulcerative colitis, even in patients whose IBD is under control by medical therapy or after surgery [11, 14, 15]. There is indirect evidence that aspiration and *Helicobacter pylori* (HP) may have a role in the development of bronchiectasis through the production toxins, urease, catalase, and mucolytic factor by HP [15–17]. The clinical presentation of bronchiectasis may also be complicated by the coexistence of GER, although the association of GER and NCFB has not been studied as extensively as GER and CF.

Prevalence and GER Characteristics in Cystic Fibrosis and Non-CF Bronchiectasis

The occurrence of GER in CF bronchiectasis was first described by Feigelson in 1975 [18]. Since then, several cross-sectional studies have reported a high prevalence of GER in both patients with CF and NCFB, ranging from 19% to 90% [17, 19–36]. Study data are listed in Tables 9.1 and 9.2 for CF and NCFB, respectively, and these data are plotted according to CF/NCFB and age in Fig. 9.1. Prevalence appears to be higher in CF patients as compared to NCFB patients, although the data in NCFB are limited.

Table 9.1 Studies reporting prevalence data of GER in patients with CF

Study	Study population	GER diagnostics	GER prevalence
Scott et al. [19]	68 Children (>5 years)	Typical GER symptoms	27% Pyrosis 21% Regurgitation
Gustafsson et al. [21]	12 Adults	24 h pH	67%
Malfroot et al. [20]	26 Children (<60 months)	24 h pH	77%
Vic et al. [22]	25 Children (<36 months)	24 h pH	76%
Ledson et al. [25]	50 Adults	GER symptom questionnaire	80% Pyrosis 52% Regurgitation 56% Dyspepsia
	10 Adults with typical GER symptoms	24 h pH	80%
Heine et al. [24]	26 Children (<6 months)	24 h pH	19%
Bosheva et al. [26]	12 Children	24 h pH	58%
Brodzicki et al. [27]	40 Children (1–20 years)	24 h pH	55%
Button et al. [28]	11 Adults with end-stage CF	24 h pH	90% (40% symptomatic)
Blondeau et al. [32, 37]	23 Adults	24-h pH-impedance	74% (41% symptomatic)
Blondeau et al. [34]	24 Children(<15 years)	24-h pH-impedance	67%
Sabati et al. [35]	204 Adults	GER symptom questionnaire	63% >1 Symptom 24% Frequent symptoms 61% on acid suppression
Doumit et al. [36]	20 Children (8–34 months)	24-h pH-impedance	50%

The prevalence of increased acid exposure varies from 15% to 76% in infants with CF, from 20% to 55% in CF children and appears to increase up to 90% in adults with CF (Table 9.1) [19–22, 24–28, 32, 34–36]. The large variation between the different studies is probably due to the different CF age groups studied and the different techniques used to study reflux. The "gold standard" method to detect reflux until the last 5–10 years was 24-h esophageal pH monitoring [39]. This technique only allows detection of acid GER. The acidity of gastroesophageal reflux depends on the acidity, volume, and distribution of gastric contents. It has been suggested that in the early postprandial period and during the night, gastroesophageal reflux might have a less acid pH (between 4 and 7). In the last decennium, a newer technique, impedance-pH monitoring, has become available and is able to measure not only acid reflux but also nonacid reflux episodes as well as additional GER characteristics (bolus exposure, proximal extent of GER) [39, 40]. Using this technique, Blondeau

Table 9.2 Studies reporting prevalence data of GER in patients with non-CF bronchiectasis

Study	Study population	GER diagnostics	GER prevalence
Ahmed et al. [23]	19 Adults	Tracheal and esophageal pH monitoring	42%
Tsang et al. [17]	100 Adults	Typical GER symptoms	32%
Banjar [29, 38]	151 Children	24-h pH	32%
Koh et al. [30]	58 Adults with NTM lung disease	24-h pH	26%
Fortunato et al. [31]	10 Adults	24-h pH	50%
Babayigit et al. [33]	66 Children	RX, scintigraphy	9%

NTM nontuberculous mycobacterial

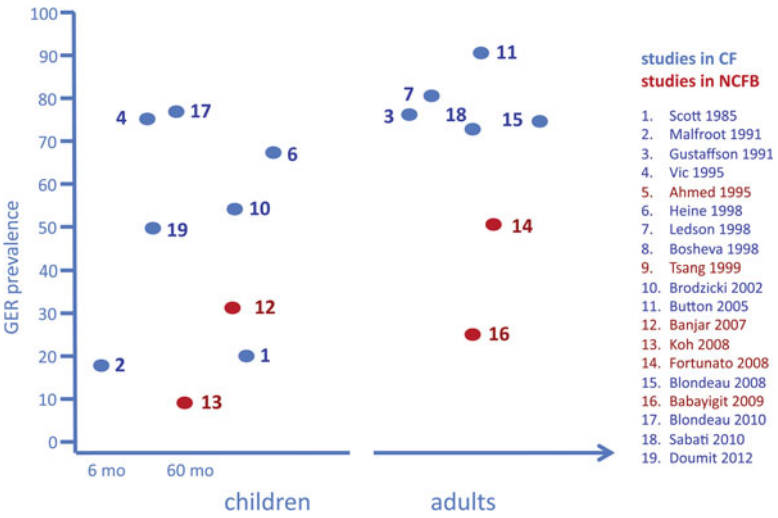

Fig. 9.1 Plotted GER prevalence study data according to age in both patients with CF (*blue*) and NCFB (*red*). Prevalence increases with age and appears to be higher in CF patients as compared to NCFB patients, although the data in NCFB are limited

et al. [32] studied 23 adult CF patients and found increased reflux in 20. Acid reflux was most common. However, there appeared to be a subgroup of CF patients (21%) having increased weakly acidic reflux [41]. Similarly, Pauwels assessed GER in 42 adult CF patients by means of pH-impedance and found a prevalence of 71%, of whom the majority (77%) had acid GER; 13% had nonacid GER, and 10% had combined acid/nonacid GER [42]. In a group of 24 CF children, increased reflux was found in 67% with the majority of reflux events being acid [34]. One-third (32%) of reflux events contained gas. Palm et al. [43] evaluated GER by means of pH-impedance in 35 children with CF on PPI once daily and noted a higher proportion (49%) of nonacid GER and suggested that treatment with PPI appears to shift the total

reflux burden from predominantly acid to combined acid/nonacid. The predominance of acid reflux in CF might be due either to increased gastric acid secretion, increased length or duration of a subcardial acid pocket, or decreased gastric neutralization due to reduced bicarbonate pancreatic secretion [44–48]. In addition to the refluxate, impaired esophageal clearance could also contribute to the high esophageal acid exposure in patients with CF. Saliva is important for esophageal acid clearance, and saliva volume and its composition or buffering capacity can be altered in CF [49]. Gender, BMI, diabetic status, and pancreatic function were similar in CF patients with and without increased GER. There was no difference in reflux parameters between patients with genotype DF508 homozygote, DF508 heterozygote, and patients with other genotypes [32, 34, 42].

Six studies (Table 9.2) have evaluated the prevalence of GER and its clinical significance in patients with NCFB, using a combination of symptomatic and objective tools [17, 23, 29–31, 33]. Symptomatic evaluation found that 32% of 100 patients with NCFB experienced typical GER symptoms [17]. Four studies have examined GER in NCFB using 24-h esophageal pH monitoring [23, 29–31]. A pilot study of 19 patients with bronchiectasis utilized simultaneous tracheal and esophageal pH monitoring [23]. A total of eight patients demonstrated reflux based on the DeMeester score [23]. In a study of seven patients with advanced NCFB awaiting lung transplantation, 33% experienced an increased number of distal reflux episodes, specifically in the supine position [31]. In two larger studies of both children and adults with NCFB, GER was diagnosed using pH monitoring in 32% and 26%, respectively [29, 30]. Impedance-pH monitoring has not yet been reported in the NCFB population.

Symptom anamnesis is insufficient for the diagnosis of increased GER in CF because of limited sensitivity. Although most CF patients presenting with typical GER symptoms had increased reflux parameters, 50–60% of CF patients with abnormal GER did not report reflux symptoms and have silent reflux [32, 34]. This is similar to what was described in a study by Button et al. [28], and data published by our group in CF patients allow us to calculate a specificity of 100% and 80% as well as a sensitivity of 56% and 41%, in children and adults, respectively, for typical GER symptoms [32, 34]. CF patients may be hyposensitive to (acid) reflux, and this might explain the underestimation of typical GER symptoms. Because reflux could lead to aspiration of gastric contents into the lungs, silent reflux is important in CF patients, and additional means of assessing whether GER is present should be considered despite the absence of typical GER symptoms. Similar data on the occurrence of “clinically silent” GER were reported in NCFB. Asymptomatic nocturnal GER was diagnosed in a group of 25 patients with a range of respiratory conditions including bronchiectasis using a barium esophagogram, with only 40% of patients reporting heartburn and 16% reporting dysphagia [50]. Koh et al. [30] investigated the prevalence of GER disease in patients with NCFB due to nontuberculous mycobacterial disease. In patients with nodular bronchiectasis, the prevalence of GERD was 26%, and only 27% of these patients had typical GER symptoms.

The availability of pH-impedance data allows a comparison of GER characteristics in adults and children with CF [32, 34] to data in healthy subjects (from a study by

Zerbib et al.) and data on GER characteristics in nonerosive reflux disease (NERD) patients and erosive reflux disease (ERD) patients (from a large cohort studied by Savarino et al.) [51, 52]. Data from these studies are listed in Table 9.3. The extent of GER was significantly more severe in adults with CF as compared to children. The CF adult population had more reflux compared to a healthy group, and the number of acid reflux episodes was higher compared to the healthy group but comparable to that observed for the NERD patients. The number of nonacid reflux episodes is slightly higher compared to healthy subjects but similar to the NERD and ERD patients, and acid exposure is clearly higher compared to the healthy group but lower than in the ERD patients. The proximal extent of reflux defined as the number of reflux episodes reaching 15 cm or more above the LES was significantly higher in adults with CF as compared to children with CF, comparable to patients with NERD, and lower than in patients with ERD (Table 9.3). Doumit et al. [36] recently reported a higher proportion (72%) of GER episodes reaching the proximal esophagus in a group of younger CF children, suggesting that proximal reflux may occur more frequently in infancy, improves with age during childhood, and increases again during adulthood as the CF disease severity worsens. Overall as a group, it appears that CF patients behave similarly to NERD patients concerning reflux parameters. No data are available on GER characteristics in patients with NFCB.

GER may not only be acid or nonacid, but it may also contain bile and other duodenopancreatic secretions. Duodenogastroesophageal reflux (DGER) is common in severe gastroesophageal reflux disease, and increased DGER is associated with Barrett's esophagus and adenocarcinoma [53]. Hallberg et al. [54] demonstrated increased concentrations of bilirubin in the stomach of CF patients compared to healthy volunteers, suggestive of increased duodenogastric reflux in the CF population. We recently assessed the occurrence of DGER in a small group of adults with CF by means of combined 24-h impedance-pH-Bilitec monitoring. The Bilitec fiber-optic catheter placed transnasally, together with the impedance-pH catheter, measured DGER episodes, defined as an increase in esophageal bilirubin absorbance [55–57]. Increased DGER was present in 35% of the adult CF patients, and the increased DGER was clearly associated with increased acid reflux [42]. Increased DGER was related to high volume acid refluxate, similar to what already was shown by Freedman et al. in patients with GERD [58]: CF patients with increased DGER had more reflux episodes with high proximal extent [42]. There was no difference in DGER parameters between patients taking oral bile salts supplements compared to those not taking these supplements [42]. The occurrence of DGER has not yet been assessed in NCFB.

Aspiration of Gastric Content in Cystic Fibrosis and Non-CF Bronchiectasis

The highest concern about increased reflux in CF is the alleged occurrence of aspiration of (duodeno)-gastric contents into the lungs, which may result in an exaggerated bronchial inflammatory reaction. Ledson et al. [25] described tracheal

Table 9.3 Comparison between reflux characteristics in children and adults with CF, healthy subjects, and different patient populations with reflux disease, as reported in the literature

GER characteristic	Children with CF Blondeau et al. [34] ($n=24$)	Adults with CF Blondeau et al. [32] ($n=28$)	Healthy adults Zerbib et al. [52] ($n=72$)	NERD patients Savarino et al. [51] ($n=168$)	ERD patients Savarino et al. [51] ($n=58$)
Total # reflux events	41 (26–61)	66 (51–85)*	44 (25–58)	NA	NA
Total # acid reflux events	25 (14–39)	40 (29–57)*	22 (10–35)	34 (22–51)	52 (39–75)
Total # NA reflux events	14 (8–21)	23 (16–32)*	14 (5–18)	23 (15–38)	22 (15–39)
Bolus exposure (%)	1.3 (0.8–1.7)	1.7 (1.2–2.4)	0.8 (0.4–1.2)	NA	NA
Acid exposure (%)	3.5 (2.3–12.3)	5.5 (2.9–13.2)	1.6 (0.5–2.6)	4.2 (1.2–6.4)	7.4 (4.2–9.9)
# Proximal extent	13 (6–23)	22 (16–37)*	9 (4–17)	24 (14–41)	44 (29–60)

Data are shown as median (25th–75th percentile). For each patient population, the number of reflux events (total, acid, and nonacidic), the acid exposure (the time the esophageal body was exposed to acid), the bolus exposure (the time the esophageal body was exposed to impedance detected refluxate), and the proximal extent of reflux (the number of reflux episodes reaching 15 cm or more above the LES) was listed

Abbreviations: NA nonacid, *NERD* nonerosive reflux disease, *ERD* erosive reflux disease

*$p<0.05$ as compared to children with CF

acidification in 4/11 CF patients and suggested that aspiration occurs in CF. Measuring specific markers of aspiration may help to establish the potential role of GER and aspiration in CF. The gold standard in detecting aspiration would be measuring (duodeno)-gastric contents in bronchoalveolar lavage (BAL) fluid. A recent study showed that pepsin concentration in BAL fluid was higher in patients with CF as compared to controls [59]. However, performing BAL is invasive and not routinely performed in adults with CF. Detection of gastric markers in saliva or sputum has been proposed as a surrogate for high proximal extent of GER [60] and might provide a noninvasive alternative to identify those CF patients with increased risk for lung aspiration. Bile acids were found in saliva of almost half of the CF adults and in 35% of CF children [32, 34]. The prevalence of increased bile in saliva was significantly increased in CF as compared to healthy controls, patients with GERD, and patients with chronic unexplained cough [32], and the median concentration of bile acids in saliva was significantly higher in patients with CF [34]. Pauwels et al. [61] measured increased bile acid levels in sputum in CF as compared to healthy controls. Sputum bile acid levels were similar in patients with genotype F508del homozygote, F508del heterozygote, and other CF mutations and were not related to BMI or age. Similarly, Blondeau et al. [37] showed that transplanted CF patients had higher pepsin and bile acids levels in BAL than non-CF transplanted patients. Importantly, half of the CF patients with bile acids in BAL or saliva did not have typical GER symptoms [32, 37, 61].

Ahmed et al. [23] assessed patients with NCFB using simultaneous tracheal and esophageal pH monitoring. Of those with abnormal GER, 88% experienced symptoms of heartburn, nocturnal cough, or disturbed sleep suggestive of an association of reflux with associated nocturnal symptoms. However, no microaspiration of gastric contents was demonstrated with tracheal pH monitoring [23]. There are currently no additional data on the occurrence of aspiration of (duodeno)-gastric contents into the lungs of patients with NCFB.

Mechanisms of Increased Reflux in Cystic Fibrosis and Non-CF Bronchiectasis

In GERD, different pathophysiological mechanisms have been proposed to explain the increased number of reflux episodes, including delayed gastric emptying, a reduced basal pressure of the lower esophageal sphincter (LES), an increased number of transient LES relaxations (TLESRs), the presence of a hiatal hernia, and, more recently, the presence and position of a postprandial acid pocket that is close to the gastroesophageal junction [1, 2].

Some data are available about the mechanisms of increased reflux in patients with CF and involve gastric factors, sphincteric factors, and esophageal factors. Secondary factors will also be dealt with separately. There is a significant lack of data on the pathophysiology of GER in NCFB.

Gastric Factors

It has been proposed that a delay in gastric emptying could increase reflux in GERD patients by prolonging gastric distention and gastric secretion in the stomach [62]. A delay in gastric emptying was shown in approximately 30% of GERD patients [63]. Although studies showed a correlation between the level of gastric retention and the proximal extent of reflux [64], a clear causal relationship between rate of gastric emptying and reflux parameters remains controversial [65].

Although gastric emptying has been widely studied in CF patients, data are not conclusive. Cavell et al. and Collins et al. described accelerated gastric emptying as compared to healthy subjects [66, 67], and Kuo et al. [68] showed that rapid gastric emptying in CF normalized with pancreatic enzyme replacement therapy. In contrast, Bodet-Milin et al., Cucchiara et al., and Hauser et al. found evidence of delayed gastric emptying in CF [69–71], but Symonds et al. [72] found no difference in rate of gastric emptying between healthy and CF children. A recent study by Pauwels et al. [42] confirmed that gastric emptying was delayed in approximately 1/3 of CF adults and found a positive correlation between rate of gastric emptying and severity of DGER (bile reflux). The relationship between gastric emptying and acid GER was less evident in this study (no correlation between rate of gastric emptying and extent of acid reflux), although it was postulated that in a subgroup of CF patients with delayed gastric emptying, this delay could result in an increased number of high volume acid and bile reflux episodes [42]. This association between delayed gastric emptying and severity of DGER appears to be specific for CF. Previous studies by Freedman et al. and Hoffman et al. [58, 73] showed no correlation between rate of gastric emptying and bile reflux in non-CF GERD patients.

Sphincteric Factors

The esophagogastric junction (EGJ) is the first line in the defense against reflux. It comprises two important components, the lower esophageal sphincter (LES) and the crural diaphragm, and regulates the exchange of contents between the esophagus and the stomach [74].

A chronically weak LES would be unable to prevent reflux from occurring, but this mechanism is mostly confined to patients with severe esophagitis, large hiatal hernias, and Barrett's esophagus [75, 76]. Low LES pressure, particularly in the postprandial period, can facilitate reflux, but many GERD patients have normal LES pressures [77].

Transient LES relaxations (TLESRs), defined as relaxations of the LES not triggered by swallowing, account for the majority of reflux episodes, both in healthy subjects and in GERD patients [75, 78]. In healthy subjects, almost half of the TLESRs are followed by a reflux episode, which is significantly higher in GERD patients, where approximately 70% of the TLESRs lead to reflux [77–81].

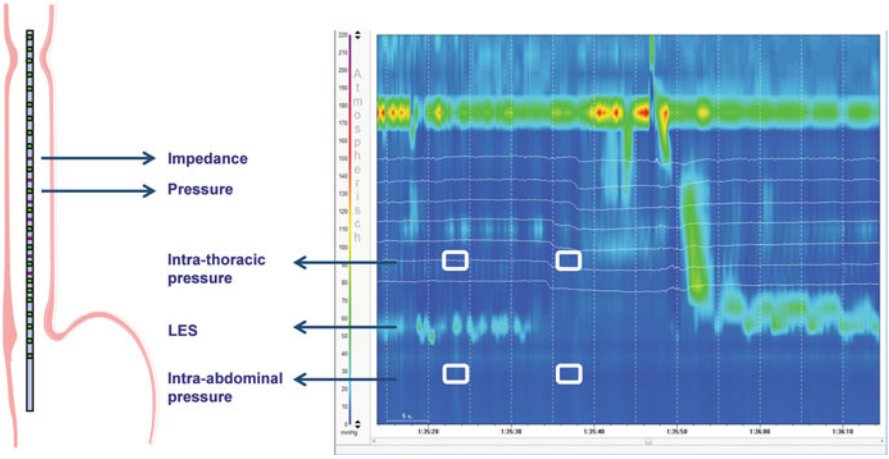

Fig. 9.2 Schematic representation of the high-resolution manometry-impedance assembly and corresponding tracing with an example of a TLESR accompanied by reflux in a patient with CF. The *white* lines on the color plot indicate impedance. Intrathoracic pressures were measured in the distal esophagus, 3 cm above the proximal border of the LES, and intra-abdominal pressures were measured in the proximal stomach, 2 cm below the distal border of the LES (*white* squares)

Compared to non-CF GERD, much less is known about the sphincteric mechanisms underlying increased reflux in CF and NCFB. LES function and esophageal motility were studied many years ago in CF using standard perfused manometry. Ledson et al. [25] described low basal LES pressure in 6/10 CF adults with proven reflux. The patients with a LES pressure lower than 5 mm Hg demonstrated more reflux episodes, suggesting that low LES pressure may have a role in the pathogenesis of reflux in CF [25]. Manometry studies in NCFB patients by Fortunato et al. [31] showed LES hypotonia in 57% of those patients with upper esophageal sphincter hypotonia in 14% of patients. Cucchiara et al. [82] found that half of reflux events in 12 CF patients occurred during a TLESR and argued that the predominant mechanism of reflux in CF was the occurrence of TLESRs rather than a low basal LES pressure. The same study also showed that the frequency of TLESRs in CF children was higher compared to GER patients [82]. Pauwels et al. [41] recently evaluated sphincteric mechanisms for GER in CF using high-resolution manometry-impedance (Fig. 9.2). Basal LES pressure was lower in CF patients compared to healthy subjects, both in the pre- and postprandial period, and TLESRs were the main mechanism for reflux both in CF and in healthy individuals. Although the total number of TLESRs was not increased in CF compared to healthy subjects, reflux occurred more frequently during TLESRs in CF compared to healthy volunteers, and CF patients also showed a higher proportion of reflux episodes with a high proximal extent [41].

A *hiatal hernia*, which is the separation of the LES from the crural diaphragm, diminishes the capacity of the EGJ to prevent reflux and is associated with more severe esophagitis, a lower LES pressure, and more overall reflux [83–85]. The

presence of a hiatal hernia is not often described in CF patients. In an early study by Stringer et al. [86], the prevalence of a hiatal hernia was 17% in a group of CF children with proven reflux.

Recently the presence of a *postprandial acid pocket* in the proximal stomach was shown, and it appeared to act as an unbuffered reservoir of acid [46]. It has been proposed that a larger postprandial acid pocket located across or above the crural diaphragm is responsible for the increased number of acid reflux episodes during TLESRs [87, 88].

Regardless of the EGJ condition (low LES pressure, TLESR, and/or hiatal hernia), reflux occurs following a positive *gastroesophageal pressure gradient (GEPG)*. According to Scheffer et al. [89], TLESRs with acid reflux are associated with a higher GEPG compared to TLESRs without acid reflux. GERD patients have a higher GEPG during a TLESR compared to healthy subjects [90, 91], and Pandolfino et al. [92] showed that patients with typical GERD symptoms have a higher GEPG compared to patients with atypical symptoms. The elevated GEPG found in all of these studies was due to a higher intra-abdominal pressure, which explains the association between obesity and GER [91–93]. It has also been shown that respiratory oscillations can modify thoracoabdominal pressure gradients and favor reflux [94].

The role of altered thoracoabdominal pressure gradients for reflux facilitation in CF was evaluated by Pauwels et al. [41]. GEPG during TLESRs was significantly higher in CF than in controls during inspiration and reflux occurred mostly during the inspiratory phase of the respiratory cycle. Unlike non-CF GERD patients (with increased intra-abdominal pressure), reflux during TLESRs in CF appeared to be due to an increased GEPG mainly generated by an increased negative intrathoracic pressure during inspiration [41].

Esophageal Factors

The esophageal body is highly important in the defense against reflux. Clearance of acid in the esophagus occurs in two steps: first, volume is mechanically cleared by peristalsis of the esophageal body, and, secondly, acid is neutralized by bicarbonate in the swallowed saliva. Several studies found increasing peristaltic dysfunction with increasing grades of esophageal mucosal inflammation in GERD patients. However, it is still unclear whether peristaltic dysfunction in patients with reflux disease is a primary phenomenon or whether it is secondary to chronic esophageal inflammation [76, 88, 95].

In a study by Cucchiara et al. [82], the amplitude of primary peristalsis and the ability of primary peristalsis to clear acid from the esophagus were both lower in CF compared to patients with symptomatic GER, suggesting that mechanical clearance of reflux is altered in the CF population. Little is known concerning chemical clearance in CF patients. In a study by Aps et al. [96], no differences were found in levels of bicarbonate in saliva of CF patients compared to healthy volunteers.

Secondary Factors

There has been some debate on whether cough precedes reflux or whether reflux is a cause of cough. Blondeau et al. [32] showed that cough in CF patients only provoked a small percentage of the reflux episodes. The number of reflux-cough sequences was significantly higher than the number of cough-reflux sequences, and only a small fraction of the esophageal acid exposure and volume exposure appeared to be due to cough.

There is conflicting evidence regarding the effect of chest physiotherapy (CPT) on GER. Doumit et al. [36] assessed GER by means of pH-impedance in young infants with CF during CPT and did not demonstrate a difference in the number of reflux episodes in the modified and gravity-assisted positions or when CPT was compared to a background period. Similarly, Phillips et al. [97] found that acid GER was not exacerbated during CPT in 11 children with CF. These findings contrast with Button et al. who found a greater number of acid reflux episodes with gravity-assisted postural drainage in a group of 27 infants with CF [98], although there were no significant differences in median GER episode duration or fractional reflux time. A potential reason for the observed differences may be the age of the study population. The mean age of infants studied by Button et al. was 2 months, as compared to 8 months and 12 months in the studies by Phillips et al. and Doumit et al., respectively [36, 97, 98]. Another methodological difference between the studies involved the degree of head-down tilt used. While Button et al. used 30° of head-down tilt, both of the other studies used 20° head-down tilt. In the study by Button et al., left lateral positioning during CPT was associated with fewer reflux episodes, and more reflux episodes occurred during CPT in supine and prone positioning [36, 97, 98]. These data are insufficient to recommend that physiotherapists refrain from using head-down postural drainage positions in children with CF because of fear of worsening GER.

The Effect of Reflux and Aspiration on Lung Disease in Cystic Fibrosis and Non-CF Bronchiectasis

Approximately 32% of the patients with reflux disease have extraesophageal symptoms, and respiratory symptoms like cough and asthma are reported in 15–18% of the patients with GERD [99]. In addition, GER has been implicated as a causative factor in the pathogenesis of sinusitis, pulmonary fibrosis, rejection after lung transplantation, and recurrent otitis media [2]. GER with or without aspiration may also reduce health-related quality of life and accelerate the rate of pulmonary decline and progression of bronchiectasis, both in CF and NCFB. Understanding the impact of GER/aspiration on bronchiectatic lung disease could thus be important in the overall management of both these conditions.

Increasing data have become available on the potential impact of increased GER or aspiration on lung function impairment in CF. An early study by Stringer et al.

[86] reported lower lung function values in CF children with proven reflux compared to those without reflux. These results were confirmed in 2001 with data from the European Epidemiologic Registry of CF showing that CF patients with GER have lower pulmonary function than those without GER [100]. However, Blondeau et al. and Pauwels et al. [32, 42] did not show that CF patients with abnormal GER had reduced lung function. Because pulmonary function in CF patients is determined by a variety of parameters, it is challenging to demonstrate a clear relationship between reflux and lung function by studying small cohorts of CF patients. However, Blondeau et al. [32] did find that those CF patients with a significant positive association between reflux and cough had a significantly lower pulmonary function (% predicted FEV_1) compared to patients without this association. They also demonstrated a significant correlation between the number of coughs and esophageal acid exposure. An enhancement of the physiological cough reflex and an esophageal acidification-induced increase in mucus secretion might explain the increased coughing in CF patients with GER. An experimental study in cats showed that esophageal acidification increases tracheobronchial mucus secretion [101]. A recent study by Palm et al. [43] evaluated 35 CF patients on PPI by means of pH-impedance and found that children with chronic *Pseudomonas aeruginosa* (Pa) infection had a significantly higher total acid and proximal nonacid reflux burden. There was a negative correlation between nonacid reflux burden and total number of reflux events and FEV_1 [43]. Palm et al. [43] argued that increased reflux burden is associated with Pa infection and worse lung function. Similarly van der Doef et al. [102] found that there was an earlier onset of first acquisition of both *P. aeruginosa* and *Staphylococcus aureus* in 12 children with pathologic GER diagnosed by pH probe.

It might be that increased reflux is not harmful per se, but that aspiration of (duodeno)-gastric contents into the lungs as a consequence of reflux is essential in the pathogenesis of reflux-related disease in CF. Aspiration of (duodeno)-gastric contents into the lungs can lead to chemical injury, which can be followed by an inflammatory response. The observation that CF patients with bile acids in saliva or sputum [32, 61] or with pepsin in BAL [59] did not have a significantly lower FEV_1 argues against this hypothesis. Similarly, Pauwels et al. [42] did not find a difference in lung function values between patients with normal and patients with increased bile exposure using combined 24-h impedance-pH-Bilitec monitoring. However, there was a significant negative correlation between lung function values and bile acid concentrations as well as between bile acid concentrations and the number of days of IV antibiotic therapy in those CF patients with detectable bile acids in sputum [61]. Kazachkov et al. [102] found a raised lipid-laden macrophage index (LLMI) in children with CF and with other chronic pulmonary conditions, but no normal controls were assessed. The LLMI was higher in the CF group, but this did not correlate with inflammatory markers in BAL fluid or symptoms suggestive of GER in either group [102]. Levels of sputum neutrophil elastase, an inflammatory marker in CF airways, were significantly higher in patients with bile acids in sputum compared to those without detectable bile acids [61]. In children with CF who had raised pepsin concentrations in BAL, higher levels of IL-8 in the BAL fluid

were measured than in those with a pepsin concentration comparable to controls [59]. Aspiration of pepsin or bile acids in CF appears to be associated with more airway inflammation, and the degree of aspiration appears to be related to the extent of airway inflammation.

Although the above findings suggest that GER and aspiration may play an important role in CF, further prospective intervention studies using objective detection of increased GER or aspiration are required to confirm the impact of GER on the progression of lung disease in CF.

Antireflux treatment has been associated with an improvement of the evolution of the FEV_1 [27, 103, 104]. A retrospective cohort study in 218 children with CF by van der Doef et al. [105] showed that CF patients on acid suppression therapy had a smaller yearly decline of the maximum mid-expiratory flow between 25% and 75%. However, a Cochrane analysis failed to show any relationship between reflux treatment and improvement of pulmonary damage in CF [106]. Despite the lack of controlled trials, proton pump inhibitors (PPI) or PPI combined with prokinetics have become common therapies for patients with GER and declining lung function or for persistent symptoms. In CF children treated with PPI, 62% showed incomplete acid suppression [36]. Efficacy of PPI may be reduced if medications are not given 15 min before a meal, which has been shown to be the most effective dosing window [107, 108], or because pancreatic insufficiency affects the absorption of the medication.

Recent studies have also suggested that acid suppression may increase the risk of community-acquired pneumonias [109, 110]. In patients with CF, acid suppression may result in gastric bacterial overgrowth [111–113]. Indeed, when the nonacid, bacterial laden contents are refluxed, lung flora can be significantly altered and could potentially lead to pulmonary exacerbations with resultant worsening of lung function. Pseudomonas has been shown to grow particularly well in pH neutral gastric fluid [114], and this may be responsible for the observed association of reflux burden with Pa infection and worse lung function in CF. This may also explain the increase in airway inflammation in CF patients with GER [43]. Mertens et al. [115] showed that gastric juice with a high pH (obtained in patients taking acid-suppressive therapy) induces higher levels of IL-8 production in bronchial epithelial cells in vitro compared to gastric juice of patients not taking PPI. This proinflammatory effect of gastric juice from PPI-treated patients was even more exaggerated in primary bronchial epithelial cells obtained from CF patients [116].

Antireflux surgery has been proposed as an alternative treatment in CF patients with demonstrated increased GER. In a group of 25 CF children who underwent Nissen fundoplication, those who had a FEV_1 of less than 60% predicted at the time of the fundoplication showed an improvement in FEV_1 slope as compared to those with a FEV_1 of 60% and more [117]. A recent uncontrolled study by Fathi et al. [118] showed that Nissen fundoplication was associated with significant benefit and reduced both cough and exacerbation rate in a group of CF patients. Randomized controlled outcome studies are needed to further identify the role of GER and aspiration in CF patients.

Several studies have explored the causal relationship between GER and NCFB. Using a mix of diagnostic tools that included distal channel esophageal pH monitoring, barium esophagogram, and radiological findings, GER was suggested as a causative factor in 3–32% of children with NCFB [38, 119]. Upper gastrointestinal symptoms, including epigastric pain, abdominal distention, vomiting, heartburn, and acid regurgitation, were identified in 32% of a cohort of 100 adults with NCFB, 82% of whom had idiopathic bronchiectasis [17]. The significance of these symptoms is highlighted by the reduced lung function associated with acid regurgitation and the link between epigastric pain and a higher number of lobes affected by bronchiectasis [17]. In an equally large study of 100 adults with NCFB, GER was identified as a causative factor in 3% of patients, based on gastrointestinal symptoms and symptomatic improvement following antireflux medication [120]. Shoemark et al. [121] found aspiration to be a cause of bronchiectasis in 1% of NCFB patients. While these reports suggest a degree of causality, the lack of objective diagnostic confirmation of GER implies that further clarification is necessary in patients with NCFB using an objective measurement of GER.

In four patients with end-stage bronchiectasis, who completed dual-channel esophageal pH monitoring, the prevalence of distal reflux of 75% and proximal reflux of 50% suggests that patients with more severe bronchiectasis may be more likely to have GER [122]. In a prospective study in a group of 58 adults with nontuberculous mycobacterial lung disease with associated bronchiectasis, GER was diagnosed in 26%, and those with GER demonstrated more extensive bronchiectasis and bronchiolitis on high-resolution computed tomography with more lobes affected compared to those without GER [30]. However, the relationship of reflux to clinical presentation or its association with lung disease severity in NCFB was not evaluated to a larger extent.

Conclusion

GER is an important comorbidity in patients with bronchiectasis (both CF and NCFB), and the reported prevalence is currently higher as compared to the general population. While our understanding of GER and its relationship to bronchiectasis have been significantly enhanced by studies using esophageal pH monitoring, it is evident that the clinical presentation may not include typical symptoms of GER, emphasizing the ongoing value of objective evaluation. Acid reflux is most predominant in CF, but a subgroup of patients may only have increased, weakly acidic reflux. CF patients also have increased GER with high proximal extent of reflux into the esophagus. Many CF patients have esophageal body hypomotility and low basal LES pressure. The number of TLESRs is similar to controls, but TLESRs are more often associated with reflux in CF. During TLESRs, CF patients have a higher GEPG than normal subjects, mainly generated by reduction in thoracic pressure during inspiration. The features of GER have not been well studied in NCFB.

Patients with CF and NCFB have a high risk for gastric aspiration, even in the absence of typical reflux symptoms. Circumstantial evidence suggests a possible relationship between GER and aspiration and the severity of CF lung disease, symptom generation (cough), and, possibly, progression of lung disease. The degree of compromise to health-related quality of life in patients with CF and NCFB has not been examined. Further work is required to identify specific gastroesophageal features or respiratory mechanics that may heighten the risk of GER in patients with bronchiectasis. Likewise, the optimal treatment approaches for managing GER in this population are yet to be established.

Key points

- GER is an important and prevalent comorbidity in patients with bronchiectasis (both CF and NCFB). GER in patients with bronchiectasis may often not be associated with typical symptoms of GER.
- Acid reflux is most predominant in CF, but a subgroup of patients may only have increased, nonacid reflux. CF patients also have increased GER with high proximal extent of reflux into the esophagus.
- In CF patients, the number of TLESRs is similar to controls, but TLESRs are more often associated with reflux in CF, which seems to be due to an exaggerated reduction in thoracic pressure during inspiration.
- The available evidence suggests a possible relationship between GER and aspiration and the severity of CF lung disease, symptom generation (cough), and, possibly, progression of the lung disease.
- The optimal treatment approaches for managing GER in this population are yet to be established.

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Chapter 10
GER and Aspiration in Interstitial Lung Disease

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Keywords Gastroesophageal reflux (GER) • Aspiration • Interstitial lung disease • Pulmonary fibrosis (IPF) • Scleroderma • Connective tissue diseases (CTD) • Microaspiration

Introduction

The interstitial lung diseases (ILD) are a heterogeneous group of acute and chronic lung diseases that are characterized by abnormal parenchymal infiltrates on thoracic imaging that are usually diffuse, and many of these disorders are complicated by progressive pulmonary fibrosis that can lead to impaired lung function, respiratory insufficiency, and death. Many forms of advanced lung disease have been associated with gastroesophageal reflux (GER). Notably, idiopathic pulmonary fibrosis (IPF) has been linked to a high prevalence of abnormal GER that is often asymptomatic [1], and anti-reflux therapies have been recently correlated with improved survival of patients with IPF [2]. Additionally, abnormal GER has been linked to pulmonary fibrosis in scleroderma [3, 4] and has also been associated with other forms of connective tissue disease (CTD) [5, 6] as well as other non-IPF ILD [6, 7].

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Gastroesophageal reflux disease (GERD) is quite prevalent in the general population, and GERD has been estimated to affect up to 40% of the adults in the USA at least once per month [8]. It has been postulated that GER and microaspiration of proximal GI tract secretions may play a key role in the induction of the patchy but diffuse lesions of usual interstitial pneumonia (UIP), which are typically of different age and gradually lead to distorted areas of lung where fibrosis has altered lung architecture and led to tissue contraction as excessive new lung matrix is deposited, suggesting an abnormal wound-healing response to injurious stimuli. The histopathologic pattern of UIP, which is the hallmark lesion of IPF, can also be seen with various forms of CTD (e.g., scleroderma, rheumatoid arthritis, undifferentiated CTD) [9, 10]. This chapter will examine the role of abnormal GER and microaspiration in the pathogenesis and progression of various forms of ILD and the fibrotic changes that can damage lung tissue, lead to impaired lung function, and ultimately cause respiratory failure.

Gastroesophageal Reflux and Microaspiration

Brief episodes of GER are a normal physiologic phenomenon [11]. However, an intact and well-functioning lower esophageal sphincter (LES) at the junction of the esophagus and stomach combined with the ability to rapidly clear refluxate from the esophagus should prevent proximal gastrointestinal (GI) tract secretions from refluxing and gaining sustained access to the proximal esophagus and larynx. Nonetheless, proximal GER has been documented in healthy subjects during sleep [12], and resting upper esophageal sphincter (UES) pressure falls considerably during sleep as well [13]. Indeed, Gleeson et al. [12] found that nearly half of the healthy adult subjects that they evaluated aspirated small amounts of their oropharyngeal secretions during sleep, and the term "silent" microaspiration has been coined to describe the asymptomatic aspiration of small volumes of oropharyngeal or gastric secretions into the lungs.

Aspiration pneumonitis can occur with inhalation of a sizable bolus of oropharyngeal/gastric secretions via the larynx into the lower respiratory tract [14], and the clinical consequences of such aspiration depend upon the nature (acidity, presence of bile acids, and other gastric juice constituents), volume, frequency of aspiration, and the host's ability to neutralize and clear the aspirated material from the lungs and thereby prevent/limit mucosal damage, inflammation, and subsequent infectious pneumonia. Although normal host defense mechanisms such as glottis closure and cough/gag reflexes can protect the airway from aspiration, patients with disorders such as degenerative neurologic conditions and cerebrovascular disease are at increased risk of aspiration. Silent microaspiration that occurs with significant frequency and intensity may lead to pulmonary symptoms and signs such as cough, wheezing, or mild abnormalities in gas exchange. Additionally, GER and silent microaspiration have been associated with a number of lung disorders such as lipoid pneumonia and chronic bronchiolar diseases [15].

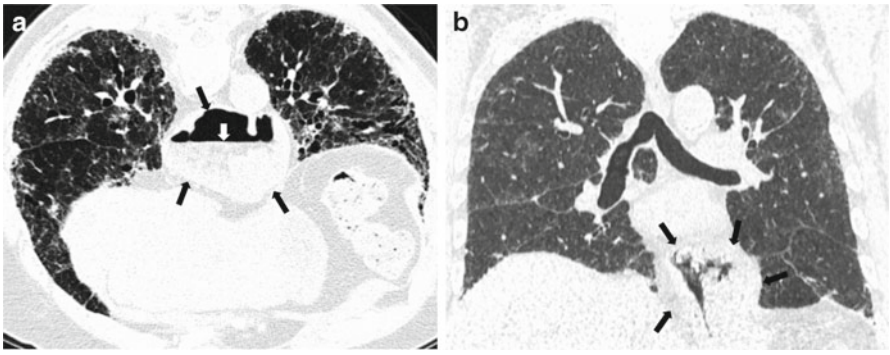

Fig. 10.1 (**a**) Transverse HRCT image with prone positioning in a patient with advanced parenchymal fibrosis due to IPF showing a large hiatal hernia (*black arrows*) with an internal air-fluid level (*white arrow*). (**b**) Coronal view showing hiatal hernia (*black arrows*) in a patient with usual interstitial pneumonia on surgical lung biopsy but relatively well-preserved lung function

Physiologic function of the GI tract changes with advancing age, and these changes include a decline in motility (decreased esophageal peristalsis amplitude, delayed gastric emptying), changes in UES function (decreased UES pressure, increased UES resistance, and delayed post-deglutition UES relaxation), and diminished esophageal sensation [16]. However, age-associated changes in esophageal motility tend to be mild and are often subclinical [17]. Additionally, hiatal hernias (HH) appear with advancing age and have been detected in up to 60% of patients older than 60 years (Fig. 10.1), and the formation of a HH, which tends to increase in size with aging, is associated with LES dysfunction (diminished LES basal pressure, greater esophageal acid exposure, and increased likelihood of erosive esophagitis) [18–20]. However, although the severity of esophageal inflammation tends to increase with advancing age, the severity and frequency of symptoms associated with GERD (heartburn, epigastric discomfort, regurgitation) tend to decrease [20].

Animal and In Vitro Studies

Many groups have evaluated the effects of the instillation of acidic solutions or gastric secretions on lung tissue in various animal models. Gastric secretions instilled into a main bronchus in dogs have been shown to rapidly distribute throughout the lung and reach subpleural areas within 20 s of instillation [21]. A wide range of histopathologic changes (neutrophil sequestration, epithelial damage, increased

epithelial permeability, pulmonary edema, pulmonary hemorrhage) can be seen in dog or rabbit lungs following delivery of a single bolus of an acidic solution to the lungs [22–26], and gastric juice (GJ) instillation in pig lungs has been shown to cause alveolar damage and subsequent intra-alveolar and interstitial fibrosis that were causatively linked to gastric acid and pepsin [27].

Histopathologic specimens from rodents taken after repetitive, sequential episodes of gastric fluid aspiration show prominent giant cells, lymphocytic bronchiolitis, obliterative bronchiolitis, and parenchymal fibrosis associated with increased TGF-beta production [28]. Loss of normal parenchymal lung architecture accompanied by diffuse collagen deposition has been described at 2 weeks following acid challenge in a low-mortality lung injury model of acid aspiration [29], and Mitsuhashi et al. [30] observed extensive degeneration and necrosis of type I alveolar epithelial cells followed by collapse of alveoli and alveolar ducts, the adherence of septae and ductal walls to each other, and interstitial fibroblast proliferation in a rabbit model of intratracheal instillation of trisodium citrate and acid–citrate–dextrose. Increased TGF-beta 1 expression in lung lavage accompanied by increased collagen III and IV expression and fibronectin has been demonstrated in acid-treated rodent lungs [31], and the finding of increased collagen and TGF-beta suggests that pro-fibrotic mechanisms are likely involved in pulmonary fibrosis induced by aspiration of acidic secretions. Interestingly, another chronic aspiration model using whole gastric fluid revealed granulomatous interstitial pneumonitis that was independent of the pH of the gastric fluid [32]. Most recently, Meers et al. [33] reported a pig model of GJ instillation in which hemorrhage, edema, and neutrophilic inflammation on histopathology, elevated neutrophils, pepsin, bile acids, and interleukin-8 in bronchoalveolar lavage, and impaired gas exchange and lung compliance occur within 2 h of GJ challenge.

Gastric juice can contain food particles, trypsin, pepsin, bile acids, or bacterial products, particularly if increased intragastric pH allows bacterial overgrowth [34]. Bile salts have been shown to be particularly injurious to lung epithelial cells and can alter surfactant and surfactant apoprotein production and function [35]. Chenodeoxycholic acid has been shown to induce TGF-beta expression by human airway epithelial cells via a p38 MAP-kinase-dependent pathway [36], and chenodeoxycholic acid can induce fibroblast proliferation [32]. Additionally, gastric juice obtained at gastroscopy from patients on acid-suppressive therapy has been reported to induce an even greater IL-8 secretory response from primary bronchial epithelial cells in vitro than gastric juice from patients not receiving acid suppression therapy [37].

GER in Idiopathic Pulmonary Fibrosis

IPF has been associated with various exposures (cigarette smoking, metal and wood dusts, certain drugs), viral infection, and inherited genetic factors [38, 39]. IPF does not show any biased expression linked to race or ethnic background, but the incidence

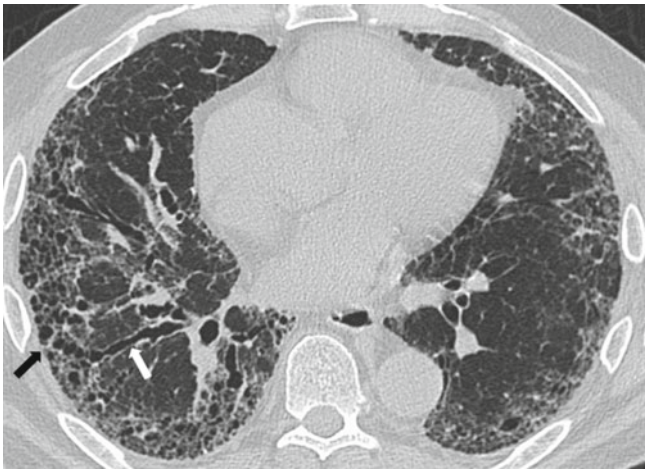

Fig. 10.2 Transverse HRCT image that is diagnostic of idiopathic UIP (IPF) in the appropriate clinical setting with reticular lines, subpleural honeycomb change (*black arrow*), and traction bronchiectasis (*white arrow*)

and prevalence of IPF is highly linked to advanced age with an estimated incidence and prevalence of 71 and 271 per 100,000/year for men and 67 and 266 per 100,000/year for women age 75 years or greater versus an overall incidence and prevalence of 16.3 and 42.7 per 100,000/year using broad diagnostic criteria [40]. Interestingly, many observations suggest that the aged lung is more susceptible to injury and fibrosis induced by a variety of stimuli, and this susceptibility may be linked to age-associated changes in gene expression or genetic polymorphisms [39, 41, 42]. Of particular interest is the recently identified, age-associated reduction in telomerase activity in human somatic cells [43], and a reduction in telomerase activity has been reported to cause a decline in its inhibitory effect on the differentiation of fibroblasts into myofibroblasts [44]. Mutations in the reverse transcriptase protein component (hTERT) of the telomerase ribonucleoprotein complex have been linked to dyskeratosis congenita as well as sporadic bone marrow failure, and hTERT mutations have recently been linked to familial PF [45, 46]. However, the observation that hTERT mutations and telomere shortening occur in family members without pulmonary fibrosis indicates that other factors (e.g., environmental effects, other genes) likely modulate clinical expression of disease. Additionally, senescent fibroblasts display altered expression of plasminogen activator inhibitor-1, which has been associated with fibrosis [44]. Impaired stem cell responses as a consequence of advanced age may also play a significant role in susceptibility to lung injury and fibrosis due to altered responses to injurious events or stimuli as well as diminished ability to maintain the integrity of well-functioning lung tissues [47, 48].

IPF is characterized by a histopathological pattern of usual interstitial pneumonia (UIP) on surgical lung biopsy, although a confident clinical diagnosis may be made on the basis of a constellation of a thoracic high-resolution computed tomography (HRCT) that shows typical changes of UIP (Fig. 10.2) combined with clinical criteria

that predict a confident diagnosis of IPF in the absence of a surgical lung biopsy [38]. When the diagnosis of IPF is made, it infers that patients lack other explanations for the presence of a UIP lesion, such as an associated CTD or an iatrogenic/environmental exposure that can cause a UIP histopathological pattern. Lung histopathology in UIP demonstrates areas of essentially normal lung interspersed with fibrotic lesions that are characterized by temporal heterogeneity, and architectural distortion of the lung parenchyma is a hallmark characteristic of UIP. Other histopathologic findings that are characteristic of UIP include the presence of fibroblast foci (discrete collections of fibroblasts, myofibroblasts, and newly formed collagen), smooth muscle hyperplasia, and honeycomb cysts (dilated airspaces lined with bronchiolar epithelium and usually filled with inspissated mucus and inflammatory cells).

Median survival in IPF has been estimated to range between 2 and 5 years [49], and survival of patients with IPF is clearly worse than that of patients with other forms of idiopathic interstitial pneumonia (IIP) such as cellular nonspecific interstitial pneumonia (NSIP). However, survival varies according to various factors such as age, extent of fibrosis, the presence of secondary pulmonary hypertension, or other specific features of the clinical presentation. Some patients can have sustained and relatively rapid decline in lung function that leads to respiratory failure versus others with fairly stable and relatively gradual decline in lung function over more prolonged periods of time [50]. The trigger(s) and determinants for acute and/or rapid decline in respiratory status are largely unknown, and acute exacerbations can occur in patients who are otherwise stable and result in a precipitous decline and death [51, 52].

A considerable body of literature has emerged that links abnormal GER to IPF (Table 10.1). Pearson and Wilson [53] had described the association of HH and GER with the diagnosis of diffuse pulmonary fibrosis in 1971. Subsequently, Mays et al. [54] reported a significantly increased incidence of GER (54%) in a group of 38 patients with radiographic evidence of pulmonary fibrosis versus 270 age-matched controls (8.5% with GER) and speculated that repetitive aspiration of small amounts of gastric secretions over a sustained period of time could lead to pulmonary fibrosis. Subsequently, El-Serag and Sonnenberg [56] reported findings from a Veterans Administration case–control study of 101,366 subjects from 1981 to 1994 that examined the incidence of paranasal sinus, laryngeal, or pulmonary disorders in subjects with GERD versus control subject without evidence of GER. Interestingly, erosive esophagitis and esophageal stricture significantly increased the risk of a number of conditions that included pulmonary fibrosis with an odds ratio of 1.36 (95% confidence interval of 1.25–1.48). Raiha et al. [55] reported an OR for the presence of pulmonary fibrosis of 8.7 (95% confidence interval 2.4–22.4) for patients with a total reflux time >10% versus those with <10%, and more evidence of pleural and parenchymal scarring was observed in the patients with high total reflux time.

Tobin et al. [1] found a very high prevalence of significantly increased proximal and distal esophageal acid exposure (16 of 17 subjects) in a well-character-

Table 10.1 Gastroesophageal reflux and pulmonary fibrosis

Ref	Year	Study cohort	Findings
[53]	1971	• 143 Consecutive patients with HH and GER	• Six cases with radiographic PF (4%)
[54]	1976	• GER Detected via radiographic UGI imaging (48 subjects with PF of unknown etiology by CXR, 270 age-matched controls)	• PF Group: 41 of 48 (85%) with HH; 26 of 48 (54%) with reflux • Age-matched control group: 76 of 270 (28%) with HH; 23 of 270 (8.5%) with reflux
[55]	1992	• 137 Patients >60 years of age referred for endoscopy (abdominal symptoms) • 24-h esophageal pH monitoring	• Odds ratio for bilateral pleural thickening or pulmonary scars were 3.1 (95% CI 0.8–11.5) and 5.8 (95% CI 1.1–29.6), respectively, for total reflux time >10% versus patients with normal reflux time
[56]	1997	• Retrospective cohort study (101,366 patients from 172 VA hospitals with erosive esophagitis or esophageal stricture, 1981–1994)	• OR for PF was 1.36 (95% CI 1.25–1.48) versus 101,366 random control subjects without GERD
[1]	1998	• 17 Consecutive patients with biopsy-proven IPF, eight controls with other ILD • Dual-channel, ambulatory esophageal pH monitoring	• Abnormal distal and/or proximal esophageal acid exposure in 16 of 17 IPF patient (4 of 8 with other ILD) • 4 of 16 IPF patients with typical GER symptoms
[57]	2005	• 18 IPF patients (waitlisted for LTX) • EM and ambulatory pH monitoring	• 12 of 18 (66% with GERD, clinically silent in four)
[58]	2006	• 66 Consecutive patients with IPF • 24-h pH monitoring and EM	• Abnormal GER in 87% (76% distal, 63% proximal) • Classic GER symptoms in 47% • No correlation of IPF severity and GER severity
[59]	2006	• Prospective study of 28 patients with PF • HRCT, PFT, EM, 24-h pH monitoring	• Typical reflux symptoms in 57% of total cohort • Abnormal esophageal acid exposure in 19 (68%); 13 of these 19 (68%) with typical reflux symptoms
[60]	2006	• Retrospective case series (four patients with IPF and acid GER) treated with PPI (plus fundoplication in one)	• Serial follow-up over 2–6 years to ascertain adequate suppression of acid GER • Stabilization/improvement in all patients (no decline in FVC or DLCO)
[61]	2006	• 14 Patients with IPF listed for lung transplantation (2001–2005)	• Pre-transplant Nissen fundoplication performed • No perioperative complications • Stable lung function, 6MWT, and oxygen requirements during 15-month follow-up

(continued)

Table 10.1 (continued)

Ref	Year	Study cohort	Findings
[62]	2007	• 30 Patients with IPF • EM and dual sensor 24-h pH monitoring performed	• Abnormal GER present in 20 (67%) • Symptoms unreliable for screening (sensitivity 65%, specificity 71%) • Hypotensive LES in 65% with abnormal GER • Abnormal peristalsis in 50% with abnormal GER
[2]	2011	• Retrospective analysis of two longitudinal IPF cohorts ($N=204$) • GER-associated variables examined (anti-reflux medications used by 47%; Nissen fundoplication in 5%)	• Use of GER medications associated with: – Less severe fibrosis on thoracic imaging – Longer survival time
[63]	2012	• Prospective of 100 IPF patients with multi-detector CT (MDCT) • Comparison to severe asthma ($N=24$) and COPD ($N=60$)	• HH found in 39% of IPF cohort versus 13% for COPD and 17% for severe asthma • For IPF cohort subsets: – Presence of HH did not correlate with lung function ($N=74$) – Better DLCO and CPI for subset with HH on anti-reflux therapy (19 of 33 IPF patients) • Presence of HH correlated with higher DeMeester score (23 for nine patients with HH; 10 for five patients without HH)
[64]	2012	• 30 Patients with stable IPF (controls) versus 24 patients with AEIPF • BAL fluid pepsin levels obtained	• BAL pepsin increased in some stable patients • Increased BAL pepsin in patients with AEIPF versus controls • Increased pepsin mostly due to subset (8 of 24 patients)

AEIPF acute exacerbation of IPF, *BAL* bronchoalveolar lavage, *CPI* clinical pulmonary index, *CXR* routine chest radiograph, *DLCO* diffusion capacity of the lung for carbon monoxide, *EM* esophageal manometry, *GER* gastroesophageal reflux, *HH* hiatal hernia, *HRCT* high-resolution computed tomography of the thorax, *LES* lower esophageal sphincter, *LTX* lung transplant, *OR* odds ratio, *PF* pulmonary fibrosis, *PFT* pulmonary function testing, *UGI* upper gastrointestinal series, *VA* Veterans Administration

ized cohort of patients with IPF (even in an upright position), and, interestingly, only 25% had reflux symptoms (heartburn, regurgitation) associated with GER. Subsequent investigations have also established a strong association of GER with IPF [57–59, 62]. The prevalence of GER as determined via 24-h esophageal pH monitoring has been estimated at 67–88% for the distal esophagus and 30–71% for proximal GER. Additionally, these studies have shown that typical GER symptoms (heartburn, regurgitation) are poor predictors of GER in patients with IPF.

Nonetheless, a causal relationship between GER and IPF has yet to be firmly established, although two case series have suggested a link between GER suppression and clinical stabilization. Raghu et al. [60] described four patients with IPF that were solely given acid suppression via administration of proton pump inhibitors and, if necessary, fundoplication to adequately suppress acid GER as ascertained via 24-h esophageal pH monitoring; all four patients stabilized or improved over a 4-year period of time. Similarly, Linden et al. [61] reported a series of 14 patients and found that oxygen requirements stabilized in those patients who underwent Nissen fundoplication. More recently, Lee et al. [2] reported that use of agents to suppress GER in a cohort of 204 patients with IPF was associated with a lower radiologic fibrosis score on HRCT and was an independent predictor of longer survival time. Finally, Noth et al. [63] reported a high prevalence of HH in patients with IPF via multi-detector computed tomography (and the presence of HH correlated with higher DeMeester scores), and Lee et al. [64] detected pepsin in BAL fluid from a substantial number of patients with acute exacerbations of IPF.

GER in Connective Tissue Disorders

The lungs and GI tract are the most frequently involved visceral organs in patients with scleroderma [65, 66], and ILD is estimated to affect up to 86% of patients with scleroderma [67]. Abnormal GER is strongly associated with pulmonary fibrosis in scleroderma [3, 4, 68], and abnormal GER has also been linked to other forms of CTD–ILD [5, 6, 69] (Table 10.2). Fagundes et al. [69] found that impaired esophageal motility, esophageal dilatation (Fig. 10.3), and GER were highly prevalent in a large cohort of patients with mixed connective tissue disease (MCTD), and esophageal motility is commonly impaired in patients with scleroderma and has been observed in up to 90% of patients [3, 70, 72]. Esophageal dysmotility has also been reported in non-scleroderma CTD other than MCTD [5, 6], although Patti et al. [5] reported that esophageal peristalsis was preserved in patients with CTD if advanced pulmonary fibrosis was not present. However, for those subjects in whom advanced pulmonary fibrosis was present, half were found to have esophageal aperistalsis.

Savarino et al. [3] examined a cohort of 40 consecutive patients with scleroderma for acid and nonacid GER and correlated their findings with pulmonary fibrosis scoring via HRCT. Patients with ILD displayed a significantly higher degree of esophageal acid exposure, higher acid and nonacid episodes of reflux, and a higher number of reflux episodes that reached to proximal esophagus as compared to patients with normal HRCT scoring. Additionally, the HRCT fibrosis scores correlated highly with the number of reflux episodes that reached the distal as well as proximal esophagus. Interestingly, ineffective esophageal motility patterns were found in 55% of the patients with pulmonary involvement and 45% of those without

Table 10.2 Gastroesophageal reflux and CTD–ILD

Ref	Year	Study cohort	Findings
[68]	1989	• 13 Patients with SS • Upper endoscopy, esophageal biopsy, ENT evaluation, Tc 99m sulfur colloid aspiration scan, PFT, 24-h pH monitoring performed in all	• Macro- and microscopic evidence of proximal esophagitis in 11 • Laryngeal changes suggestive of aspiration in 12 • DLCO impairment correlated with proximal and distal reflux episodes • Reflux severity and pulmonary disease severity (DLCO) showed significant inverse correlation via MRA ($r=0.84$; $P<0.04$)
[70]	2001	• 43 Consecutive patients with SS • EM, PFT, HRCT performed in all	• Esophageal dysmotility; severe ($N=21$) versus moderate ($N=11$) versus no dysmotility ($N=11$) correlated with: – DLCO (68% vs. 94% vs. 104% predicted) – HRCT prevalence of ILD changes (57% vs. 27% vs. 18%) • Severe group had faster decline in DLCO and higher frequency of ILD on HRCT versus group with no dysmotility over 2-year follow-up
[5]	2008	• 48 Patients with CTD • EM, 24-h pH monitoring • 20 Patients with CTD evaluated for foregut symptoms (4 with SS) • 28 with CTD and ESLD undergoing LTX evaluation (18 with SS) • 286 Consecutive patients with GERD without CTD as controls	• Esophageal peristalsis preserved in all patients with GERD and CTD without presence of ESLD • Peristalsis absent in 11 of 28 (46%) patients with CTD and ESLD (versus none in the other groups) • Median DeMeester scores: – 83 for patients with CTD and ESLD – 42 for CTD group without ESLD – 49 for GERD controls
[69]	2009	• 50 Consecutive patients with MCTD • HRCT, PFT, EM, 24-h pH monitoring, detection of esophageal dilatation on HRCT	• ILD by HRCT in 39 of 50; esophageal dilatation in 28 of 50; abnormal GER in 18 of 36, esophageal dysmotility in 30 of 36 • Presence of ILD correlated with esophageal dilatation ($P<0.01$) and severe motor dysfunction ($P<0.001$)
[3]	2009	• 40 Consecutive patients with SS (15 diffuse, 25 limited) • HRCT, 24-h impedance-pH monitoring of PPI therapy	• Patient group with ILD by HRCT had higher esophageal acid exposure, higher number of acid and nonacid reflux episodes, and higher number of reflux episodes reaching proximal esophagus • HRCT PF scores correlated highly with distal ($P<0.001$) and proximal ($P<0.001$) reflux episodes

(continued)

Table 10.2 (continued)

Ref	Year	Study cohort	Findings
[71]	2009	• 28 SS patients with open lung biopsy • HRCT, PFT, esophageal analysis	• Isolated CLF present in six (21%) patients: – Intraluminal foreign bodies present in two of six – Central distribution of lung involvement by HRCT in four of six – All six had esophageal abnormalities • NSIP HRCT pattern present in 19 (68%): – CLF present in 84% of patients with NSIP pattern
[6]	2011	• 44 Patients with ILD; IPF ($N=16$), CTD (total $N=18$; SS = 11, non-SS = 7), or sarcoidosis ($N=10$) • EM, 24-h pH monitoring	• Esophageal dysmotility in 15 of 18 (82%) of patients with CTD (aperistalsis in 10) • Abnormal GER in 78% with CTD (91% of patients with SS)

CLF centrilobular fibrosis, *CTD* connective tissue disease, *DLCO* diffusion capacity of the lung for carbon monoxide, *EM* esophageal manometry, *ESLD* end-stage lung disease, *HH* hiatal hernia, *GER* gastroesophageal reflux, *GERD* gastroesophageal reflux disease, *HRCT* high-resolution computed tomography of the thorax, *ILD* interstitial lung disease, *LTX* lung transplant, *MCTD* mixed connective tissue disease, *MRA* multiple regression analysis, *NSIP* nonspecific interstitial pneumonia, *PF* pulmonary fibrosis, *PFT* pulmonary function testing, *PPI* proton pump inhibitor, *SS* systemic sclerosis (scleroderma)

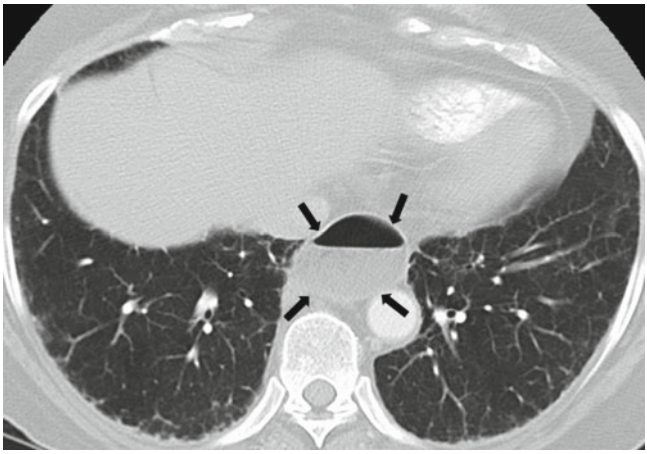

Fig. 10.3 Dilated esophagus with air-fluid level in a patient with systemic sclerosis and esophageal aperistalsis

ILD, and although reflux was found in 70% of the entire cohort, typical GERD symptoms were reported by only 50%.

De Souza et al. [71] examined a series of 28 patients with scleroderma who had surgical lung biopsies performed and evaluated these biopsy specimens for the distribution of lesions and the presence of intraluminal matter. A substantial subset of patients (21%) were found to have a bronchocentric pattern with centrilobular fibrosis associated with intraluminal basophilic material, and two subjects had foreign bodies. These findings suggest that aspiration of food particles in addition to gastric juice contributes to the induction of ILD in patients with scleroderma, and patients with esophageal dilatation on HRCT imaging and significantly impaired esophageal peristalsis are highly prone to aspiration [4].

Fagundes et al. [69] evaluated a cohort of 50 patients with MCTD and found a high prevalence of lung parenchymal abnormalities (78%), esophageal dilatation (56%), esophageal motor impairment (83%), and GER (50%). The presence of CTD–ILD was highly associated with the presence of esophageal dilatation and severe motor dysfunction. Similarly, Patti et al. [5] found that esophageal motor function was preserved in patients with CTD with GERD unless advanced pulmonary fibrosis was present.

In summary, CTD–ILD has been linked to the presence of GERD for scleroderma as well as other forms of CTD, and some studies suggest that advanced pulmonary fibrosis is more likely to be found when esophageal motor function is severely impaired.

GER in Other ILD

The prevalence of GER in forms of ILD other than IPF and CTD–ILD has not been widely examined. A number of reports have described a nodular granulomatous inflammatory process that is consistent with a foreign body reaction in patients with neurological disease and/or esophageal motility impairment who appeared to have aspirated partially digested vegetable matter [73–77]. Although infiltrates can be seen on thoracic imaging, this entity has been labeled diffuse aspiration bronchiolitis or aspiration-related lung disease [76, 77]. Organizing pneumonia has been sporadically linked to GERD [78–81], and one case series described five patients who entered a sustained remission when treated solely for GERD [82]. In contrast to patients with diffuse aspiration bronchiolitis, aspirated foreign matter has not been described in patients with GERD-associated organizing pneumonia. Although a recent study found that 7 of 10 patients with sarcoidosis had significant GER based upon a DeMeester score above 14.7 [6],whether GER may play a role in other ILD such as sarcoidosis, in which some patients develop progressive pulmonary fibrosis and severe respiratory impairment, remains unclear.

GER and Aspiration: A Possible Cause of Acute Exacerbations of ILD?

Acute exacerbations of ILD can lead to rapid deterioration in lung function, respiratory insufficiency, and death [52, 83, 84]. An episode of AEIPF is characterized by the development of diffuse alveolar damage (DAD) that is superimposed on chronic, underlying UIP, and causative agents such as viruses are usually not identified in patients with AEIPF [85]. Daniels et al. [86] reported an autopsy study of 42 consecutive patients who succumbed to IPF and identified AEIPF (DAD histopathology) as the most common cause of death (12 of 42) and also found evidence of aspiration, pneumonia, and drug-induced lung injury in some subjects. Aspiration of gastric contents is known to cause a DAD response in the lungs, and we speculate that GER and aspiration of refluxate can be a cause of AEIPF.

Lee et al. [64] recently reported that pepsin was present in BAL fluid from a substantial number of patients who met criteria for AEIPF. BAL pepsin levels and neutrophil percentages on differential BAL cell counts were significantly increased for the group with AEIPF versus stable patients, and an increase in BAL pepsin concentration by one standard deviation from that of the stable group was associated with an odds ratio of 1.46 (95% CI 1.03–2.09, $P = 0.04$) for AEIPF. However, BAL pepsin levels were not predictive of survival, and the increased pepsin levels were driven by a subgroup (33% of cases) with markedly elevated pepsin levels in BAL. These findings support the hypothesis that microaspiration plays a role in IPF pathogenesis, and aspiration and translocation of refluxed gastric juice to distal areas of the pulmonary parenchyma may initiate an episode of AEIPF. Additionally, we speculate that acute exacerbations that have been reported for other forms of ILD [87, 88] may also be linked to reflux and aspiration of gastric secretions.

Diagnosis of Abnormal GER

Over the past two decades, the diagnosis and monitoring of GERD has focused especially on the detection of gastric acid refluxing into the esophagus, and most of the studies of GER in patients with ILD have used only pH monitoring. It is now recognized that gastric secretions can still gain access to the esophagus and that such refluxate may not be acidic enough to be detected by pH monitoring, especially when patients are receiving acid-suppressive pharmacologic therapies that can increase gastric juice pH and blunt symptoms of GER but not necessarily prevent it. Combined impedance and pH monitoring allows the detection of both acid and nonacid reflux and can determine the proximal extent to which refluxate penetrates into the esophagus [89].

Symptoms associated with GER (heartburn, dyspepsia, dysphagia, regurgitation) are limited in sensitivity and specificity [1, 57, 58, 62, 90]. A relatively

recent study by Sweet et al. [62] found that symptom screening had relatively low sensitivity (≈65%) and specificity (≈71%). Various radiologic techniques can be used to detect and/or estimate the extent of GER and aspiration. These include modified barium swallow [91] or nuclear medicine techniques [92, 93], and thoracic CT scanning can be used to identify the presence of a hiatal hernia or abnormal esophagus (air-fluid level, dilatation) as well as pulmonary parenchymal changes that are suggestive of microaspiration [94, 95]. Additionally, an upper GI swallow with a radiopaque agent can identify impaired gastric emptying, which may be a contributing factor to GER.

Many studies of GER in patients with ILD used only esophageal pH monitoring, but more recently developed instruments can detect a fluid bolus regardless of pH that places patients at risk for aspiration of refluxate. Dual sensor 24-h pH monitoring with esophageal manometry provides continuous monitoring of acid pH (pH < 4) in both the distal and proximal esophagus along with measurement of esophageal peristalsis [90, 96, 97]. However, although this has been endorsed as the gold standard for the diagnosis of GERD, it does not detect nonacid reflux or quantify the volume of refluxate [97, 98]. Multichannel intraluminal pH-impedance monitoring, in contrast, can discriminate between fluid and gas reflux regardless of pH, estimate the size of a refluxate bolus, and measure the proximal extent of GER while also detecting nonacid reflux [89, 96–98].

An evolving approach to detecting reflux is the detection of biomarkers of aspiration in respiratory secretions, and pepsin and bile salts have been quantitated in sputum and bronchoalveolar lavage (BAL) fluid as markers of aspiration [35, 64, 99–104]. However, patients found to have GER via pH monitoring do not necessarily have elevated pepsin levels in BAL fluid [104], which suggests that detecting GER does not mean that microaspiration is also occurring. Starosta et al. [103], however, found that the number of proximal reflux events detected by 24-h pH monitoring correlated with pepsin levels in BAL fluid. The sampling of exhaled breath condensate (EBC) represents a less invasive and rapid method of detecting biomarkers of aspiration [105–108]; however, EBC results have not necessarily correlated well with BAL content of aspiration biomarkers and can be affected by components of the upper airway [108].

Although the detection of BAL pepsin or bile salts may represent a direct marker of refluxed GJ aspiration and mounting evidence that suggests that GER and microaspiration may play an important role in IPF pathogenesis [90], measurements of pepsin and bile salts in BAL fluid accompanied by correlation with disease severity, risk of progression, or the development of acute exacerbation have yet to be reported for patients with ILD. The publication by Lee et al. [64] represents an advance in this area, but future studies with measurement of components of gastroduodenal secretions (e.g., pepsin, bile salts) are needed to correlate with ILD severity, risk of progression, and onset of acute exacerbations. Such studies have been widely performed in lung transplant recipients, and the presence of bile acids has been correlated with increased risk for the development of bronchiolitis obliterans syndrome [35].

Treatment of GER

Although many investigations have implicated GER and microaspiration as a potential risk for developing pneumonitis and pulmonary fibrosis, and a role in acute exacerbations of ILD has been suggested, there are no convincing data that directly demonstrate that microaspiration of GJ causes IPF or other forms of ILD such as scleroderma (despite the correlation of severity of reflux and HRCT fibrosis scores for patients with scleroderma). Therefore, a validated approach to screening for GER/microaspiration and the implementation of strategies to prevent/manage it have yet to be established.

GER may be reduced by conservative measures that include lifestyle modifications (limited meal size, avoiding certain foods, avoiding alcohol or caffeine), improving sleeping habits, or pharmacologic interventions (proton pump inhibitors, H2 blockers, pro-kinetic agents), and proton pump inhibitors (PPIs) are widely prescribed for patients with symptoms of GER or established GERD. However, although PPIs may lessen the acidity of refluxate (thereby reducing or eliminating symptoms, if present), PPI therapy should not be assumed to prevent reflux (e.g., nonacid reflux) and microaspiration of gastric juice. Indeed, standard acid suppression therapy was shown to be inadequate in 63% of patients with IPF when repeat testing was performed with a pH probe while on therapy [1]. Additionally, PPIs have been linked to an increased risk for community-acquired pneumonia [109] and associated with an increased risk of hip fracture [110]. An alternative to lifestyle modification and pharmacologic therapies is the creation of a surgical barrier to prevent GER/microaspiration (e.g., Nissen fundoplication), and studies of fundoplication in lung transplant recipients suggest that the risk of delayed allograft dysfunction due to BOS is reduced for recipients who have undergone surgical fundoplication for documented GER [111, 112].

Despite a lack of resolution of the controversy whether GER/microaspiration causes an ILD such as IPF versus GER/microaspiration occurring as a consequence of the presence of UIP/IPF or simply as a manifestation of advanced age, some investigations have suggested benefit for patients with IPF when strategies to reduce/eliminate GER have been implemented. As previously mentioned, Raghu et al. [60] reported a well-characterized series of four patients with IPF whose lung function stabilized or improved when adequate, GER-suppressing treatment (ascertained via 24-h pH probe monitoring) was maintained via PPI therapy (PPI only for three, PPI with subsequent fundoplication for one) for a period of 2–6 years. Additionally, the recent analysis of a large cohort ($N = 204$) of patients with IPF [2] found that GER-related findings are common (34%) in IPF and that the reported use of GER medications was associated with less radiologic fibrosis. Additionally, the use of medications (PPI for 86 patients, H2 blocker for 12) to suppress/prevent GER was an independent predictor of longer survival time (HR = 0.47; 95% CI 0.24–0.93; $P = 0.03$ via regression analysis; adjusted predictor). Eleven patients underwent Nissen fundoplication, which conferred significant protection via independent analysis (unadjusted predictor) with HR 0.29 (CI 0.09–0.92; $P = 0.04$), but the

adjusted predictive value via regression analysis was not significant. Finally, fundoplication was well tolerated and appeared to be associated with lung disease stabilization in a case series of 14 patients with IPF [61].

If GER symptoms are present and/or objective testing has identified the presence of GER, measures to reduce/prevent GER and the risk of microaspiration may be offered to patients with ILD. Additionally, screening with pH-impedance testing could be offered to asymptomatic patients with IPF. Interventions that have been advocated to reduce total reflux time include elevating the head of the bed during sleep, avoiding the right lateral decubitus position when recumbent, avoiding recumbency within 3 h after meals, and avoiding alcohol and smoking [113]. Additionally, certain drugs that have been shown to be associated with diminished LES pressure (e.g., calcium-channel blockers, benzodiazepines, anticholinergics, corticosteroids) may worsen GER (Morehead [7]) and should be avoided if possible. Acid suppression with PPIs can be offered and may be effective, particularly if monitoring for efficacy is performed [60]. Patients with symptoms of dysphagia should be referred for evaluation, and weight reduction may benefit obese patients, although benefit may not occur if a HH is present [114]. Finally, sleep-disordered breathing is highly prevalent in patients with IPF [115], and screening for sleep apnea with application of CPAP for those found to have obstructive sleep apnea may decrease nocturnal reflux [116].

For patients who are being considered for lung transplantation, evolving literature suggests that an assessment of esophageal function and impedance-pH testing should be performed. If significant GER is present, consideration should be given to preoperative measures to prevent GER, including the possibility of preoperative or early postoperative fundoplication for persistent and significant GER [112, 117–119]. If lung transplant candidates have significant esophageal dysfunction due to depressed motility (e.g., patients with scleroderma), a comprehensive evaluation should be performed to determine what approach should be taken to prevent postoperative aspiration. Patients with esophageal aperistalsis may be candidates for partial fundoplication to prevent reflux yet avoid dysphagia [5], and carefully selected patients with CTD–ILD and esophageal dysmotility can tolerate anti-reflux surgery [120].

Summary and Conclusions

Over the last decade, mounting evidence has associated abnormal GER with the presence of various types of ILD, and abnormal GER is highly associated with the diagnoses of IPF and scleroderma. Interestingly, an increasing incidence and prevalence of both IPF and GER are associated with advancing age, and we speculate that advanced age increases susceptibility to the development of a pulmonary inflammatory/fibrotic response when aging individuals develop GER and have events in which microaspiration of refluxed GJ occurs [121]. However, asymptomatic GER can be present in a substantial number of patients with IPF or other ILD,

and semi-invasive screening with impedance-pH monitoring is necessary to detect presence of acid and nonacid GER in asymptomatic individuals. GER plus microaspiration has been implicated in the pathogenesis of IPF, and the recent study by Lee et al. [2] suggests that treatment of GER with pharmacologic agents or fundoplication may improve survival for patients with IPF. Additionally, the detection of pepsin in BAL fluid in patients with AEIPF [64] suggests that reflux and microaspiration may trigger an episode of AEIPF, and prevention of gastric microaspiration and consequent lung disease exacerbation may account, in part, for the findings of Lee et al. [2]. However, no reports have appeared in the literature that have identified biomarkers of gastric juice microaspiration in patients with stable ILD or acute exacerbations of non-IPF ILD. Additional studies of GER in ILD are needed, especially studies that examine biomarkers of microaspiration in respiratory secretions and correlate such biomarkers with measures of respiratory impairment, degree of fibrosis on HRCT, and the occurrence of acute exacerbations of ILD (e.g., AEIPF). Finally, it must be recognized that nonacid GER and microaspiration of nonacid components of gastroduodenal secretions may play a role in the pathogenesis of pulmonary fibrosis and acute exacerbations, and the pharmacologic interventions to suppress acidity of such secretions may not prevent GER [122]. Thus, conservative measures to decrease the risks of GER and laparoscopic anti-reflux surgery (LARS) represent likely key therapeutic interventions to decrease/prevent abnormal GER and microaspiration.

Future Research

Future research should focus on biomarkers of microaspiration in respiratory secretions or exhaled breath. Detection of pepsin and/or bile salts should be correlated with severity of reflux as measured by impedance-pH monitoring, risk for developing IPF, severity of pulmonary fibrosis, risk of disease progression, and risk of developing acute exacerbations of ILD (e.g., AEIPF). Future investigations should also seek to determine how exposure to GJ triggers respiratory mucosal injury and promotes fibrotic responses and whether genetic abnormalities (e.g., age-related telomerase dysfunction) must be present for fibrotic responses to be initiated or driven when microaspiration of refluxed GJ occurs.

Clinical Summary

Abnormal GER is a common finding in patients with ILD, especially those with IPF or CTD–ILD. Studies in patients with scleroderma have shown a correlation of HRCT fibrosis score with the severity/extent of GER. Additionally, abnormal GER appears to occur in a majority of patients with IPF but is often clinically occult.

Recent investigations suggest that measures that may diminish abnormal GER (which can decrease the risk of microaspiration) are associated with lung disease stabilization [60] and improved survival [2] of patients with IPF. Interventions to diminish or prevent GER may represent an important therapeutic intervention for patients with ILD, especially when pulmonary fibrosis is present.

Key Points

- GER is commonly found in patients with ILD and affects a majority of patients with pulmonary fibrosis due to IPF or scleroderma.
- Advanced age is associated with an increased incidence and severity of GER, susceptibility to microaspiration, and an increased likelihood of developing IPF.
- Significant GER is frequently asymptomatic in patients with IPF.
- Treatment/prevention of GER may delay progression of IPF and improve survival.
- Biomarkers of GJ aspiration have not been evaluated and validated in patients with IPF, scleroderma, and other ILD.
- The diagnostic gold standard for microaspiration remains unknown, but biomarkers that indicate that gastroduodenal secretion contents have reached the pulmonary parenchyma may prove to be clinically useful.

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Chapter 11
GER in Lung Transplantation

Keith C. Meyer and James D. Maloney

Keywords Abnormal gastroesophageal reflux (GER) • Pulmonary fibrosis • Bronchiectasis • Bronchiolitis obliterans syndrome (BOS) • Obliterative bronchiolitis (OB) • Microaspiration

Introduction

Lung transplantation (LTX) can be offered to patients with progressive, advanced lung disease, and it is often the only intervention that can prolong survival and improve quality of life for those individuals who are acceptable candidates for the procedure [1]. However, LTX recipients are at risk for numerous posttransplant complications such as acute allograft rejection, opportunistic infection, and chronic lung allograft dysfunction (CLAD). CLAD is usually caused by obliterative bronchiolitis (OB), which is recognized as the cause of bronchiolitis obliterans syndrome (BOS) and generally considered to be due to chronic allograft rejection [1–3].

Gastroesophageal reflux (GER) and microaspiration of proximal gastrointestinal tract secretions have been implicated as a potential cause of airway mucosal injury in LTX recipients, which may lead to the consequent development of bronchiolar inflammation and fibrosis. Although GER and microaspiration are not generally perceived as being directly linked to alloimmune processes [4, 5], bronchiolar injury

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and inflammation induced by microaspiration of gastric juice may induce alloimmune responses that lead to acute and/or chronic rejection [6, 7]. Additionally, alloimmune responses have been linked to the induction of autoimmune responses [8, 9], and autoimmune responses have recently been linked to both BOS and GER [10].

GER in Advanced Lung Disease

Patients with advanced lung disease who are referred for LTX often have evidence of ongoing abnormal GER that is frequently asymptomatic, and these patients are at risk for microaspiration of refluxed gastroduodenal secretions. Multiple studies (Table 11.1) have reported a high prevalence of abnormal GER among patients with advanced lung disease and among patients referred for transplantation [11–21], and esophageal abnormalities are frequently present on thoracic imaging studies (Fig. 11.1).

Symptoms of GER have been reported by a majority of adult patients with CF [22], and approximately 70% of patients who undergo transplant evaluation have some evidence of abnormal GER, although symptoms of GER are frequently absent. Button et al. [12] evaluated 11 patients with cystic fibrosis (CF) prior to lung transplantation as well as a cohort of 13 transplant recipients. Both groups had high DeMeester scores (36.6 ± 22.3 for pre-TLX, 40.0 ± 37.3 for post-LTX; normal <14.7), and both groups had significantly increased proximal esophageal acid exposure with significant GER found to be present in 91% of pre-LTX patients. Additionally, a number of pre-LTX (60%) as well as post-LTX patients (18%) had silent GER. A number of other studies have indicated that GER is highly prevalent in CF. Blondeau et al. [18] documented GER in 28 of 33 patients with CF via impedance-pH monitoring, and some had weakly acid or nonacid reflux. Additionally, a substantial number of reflux episodes were not associated with cough, but there was a positive correlation of esophageal exposure to reflux with cough. Interestingly, bile acids have been identified in sputum in up to 56% of patients [20, 23], and fundoplication for adult patients with CF has been associated with a dramatic fall in cough and with the frequency of respiratory exacerbations [24].

Patients with IPF have also been found to have a high prevalence of abnormal GER, and GER with microaspiration has been suggested as an important event in disease pathogenesis. Mays et al. [25] reported a significantly increased incidence of abnormal GER (54%) in a group of 38 patients with radiographic evidence of pulmonary fibrosis versus 270 age-matched controls (8.5% with GER). Tobin et al. [26] found a high prevalence of significantly increased esophageal acid exposure (16 of 17 subjects) in a well-characterized cohort of patients with IPF, and only 25% had reflux symptoms (heartburn, regurgitation) associated with GER.

Other investigations have also established a strong association of GER with IPF [15, 27–29]. Some investigators have reported stabilization of IPF with acid suppression and/or Nissen fundoplication [13, 30], and the use of agents to suppress GER was recently reported to be an independent predictor of longer survival time for patients with IPF [31]. A high prevalence of abnormal GER has been documented in other forms of ILD, including connective tissue disorders (CTD) such as scleroderma [32–34] and other CTD including mixed connective tissue disease [35–37].

Table 11.1 Abnormal GER in patients evaluated for lung transplantation

Author	Ref	Year	Type of study	Lung disease type	*N*	Type of screening	Number with abnormal GER	Comments
D'Ovidio	[11]	2005	P,C	IPF (26); COPD (21); SS (10); CF (5); Other (7)	78	• 24-h pH monitoring • EM • Gastric emptying	• 38% total • 20% with proximal GER	• Hypotensive LES in 72% • ED in 33% • Delayed gastric emptying in 44%
Sweet	[14]	2006	R	LTX referral (indications not specified)	109	• 24-h pH monitoring • EM	• Distal GER in 68% • Proximal GER in 37%	• GER symptoms had low sensitivity (67%) and specificity (26%) for reflux events • ED in 47% • Hypotensive LES in 55%
Sweet	[15]	2007	R	IPF only	30	• 24-h pH monitoring • EM	67%	• Abnormal esophageal peristalsis in 50% of patients with abnormal GER • Hypotensive LES in 65% of those with abnormal GER

(continued)

Table 11.1 (continued)

Author	Ref	Year	Type of study	Lung disease type	*N*	Type of screening	Number with abnormal GER	Comments
Fortunato	[17]	2008	P	COPD (17); PF (17); CF (3); Other (18)	55	• 24-h pH monitoring • EM	23%	• Abnormal manometry in 80% • LES hypotonia in 54% • UES hypotonia in 14%
Basseri	[70]	2010	C	COPD (16); IPF (10); other (5)	30	pH monitoring	• Distal esophageal acid exposure—36% • Proximal esophageal acid exposure—25%	• 23 (77%) had esophageal peristaltic dysfunction
Murthy	[69]	2011	R	COPD (45); IPF (44); CF/BE (16); other (8)	114	24-h pH monitoring	32 (28%)	• Only 3 of 32 had GERD symptoms at time of LTX • Pre-LTX GERD reduced early post-LTX survival

Hoppo	[21]	2011	R	IPF (11); COPD (3); CF (2); SS (1); other (2)	19	• 24-h pH/ impedance • 48-h pH monitoring • EM • Upper endoscopy • Barium esophagram	• 12 of 13 in upright position • LPR in 4 of 13 (31%)	• Esophageal motility: – Normal in 10 – Aperistalsis in four • HH in 11 of 18 (61%) • Esophagitis in 7 of 11 (64%)

BE non-CF bronchiectasis, *C* consecutive, *CF* cystic fibrosis, *COPD* chronic obstructive pulmonary disease, *ED* esophageal dysmotility, *EM* esophageal manometry, *GER* gastroesophageal reflux, *HH* hiatal hernia, *IPF* idiopathic pulmonary fibrosis, *P* prospective, *PF* pulmonary fibrosis, *R* retrospective, *SS* systemic sclerosis

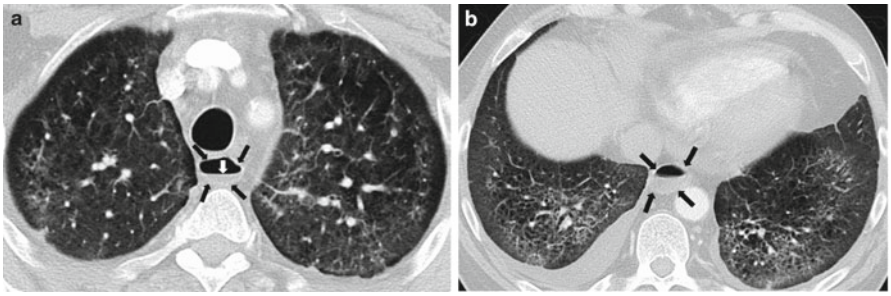

Fig. 11.1 Esophageal Abnormalities on HRCT. (**a**) shows a dilated esophagus (*black arrows*) with air-fluid level (*white arrow*) adjacent to the trachea in a patient with pulmonary fibrosis due to scleroderma and esophageal aperistalsis; (**b**) shows the dilated esophagus (*black arrows*) with air-fluid level in the lower thorax (same patient)

Proximal GER, abnormal LES pressure, esophageal dysmotility, and prolonged gastric emptying are all highly prevalent in patients with end-stage lung disease (ESLD) at the time of referral for LTX. D'Ovidio et al. [11] evaluated 78 consecutive patients with ESLD referred for LTX and reported that 63% had typical GER symptoms. The lower esophageal sphincter (LES) pressure was hypotensive in 72%, 33% had esophageal body dysmotility, 44% had delayed gastric emptying, and pH testing detected abnormal GER in 38% with 20% having proximal GER by pH probe monitoring (32% had increased DeMeester scores). Sweet et al. [14] evaluated GER in a cohort of 109 patients awaiting LTX and found a hypotensive LES in 55%, esophageal dysmotility in 47%, distal GER in 68%, and proximal GER in 37%. The presence of GER symptoms had low sensitivity (67%) and specificity (26%) in this cohort. Additionally, 20 of 30 patients with IPF referred for LTX had significant GER, and abnormal esophageal peristalsis was commonly observed in patients with reflux (50%); proximal GER for greater than 1% of total study time was found in nine (30%) of the patients [15]. Similarly, Fortunato et al. [17] reported that abnormal GER was highly prevalent in LTX candidates with abnormal esophageal manometry in 80%; LES hypotonia (80%) and abnormal esophageal manometry (94%) were highly prevalent in patients with COPD, and GER was documented in 50% of patients with bronchiectasis. Lastly, Hoppo et al. [21] reported that laryngopharyngeal reflux (LPR) was present in 31% of pre-LTX candidates with ESLD.

Although esophageal dysmotility and gastroparesis may also exist among patients undergoing lung transplant evaluation, the prevalence of these disorders is less clear. Gastroparesis may be present in patients with CF [38] and increases the likelihood of abnormal GER and bezoar formation following LTX [39]. Esophageal motility is commonly impaired in patients with scleroderma and has been observed in up to 90% of patients [33, 40, 41]. Fagundes et al. [35] found that impaired esophageal motility, esophageal dilatation, and GER were highly prevalent in a large cohort of patients with mixed connective tissue disease (MCTD), and esophageal dysmotility has also been reported in non-scleroderma CTD other than MCTD [36, 37], although Patti et al. [36]

reported that esophageal peristalsis was preserved in patients with CTD if advanced pulmonary fibrosis was not present. Interestingly, the degree of esophageal acid exposure correlates very well with high-resolution computerized tomography (HRCT) pulmonary fibrosis scores in patients with scleroderma [33]. Additionally, patients with scleroderma are at high risk for aspiration of food particles. De Souza et al. [42] examined a series of 28 patients with scleroderma and surgical lung biopsies and found that a substantial subset of patients (21%) had a bronchocentric pattern with centrilobular fibrosis associated with intraluminal basophilic material, and two subjects had foreign bodies. These findings suggest that aspiration of food particles in addition to gastric juice microaspiration contributes to the induction of ILD in patients with scleroderma, and patients with esophageal dilatation on HRCT imaging and significantly impaired esophageal peristalsis are highly prone to aspiration [34], which places the lung allograft at significant risk for injury, rejection, and infection if such patients undergo LTX.

Animal Models and In Vitro Investigations

The effects of the instillation of acidic solutions or gastric secretions on lung tissue have been examined by a number of investigators using various animal models. Gastric secretions have been shown to rapidly distribute throughout the lung and reach subpleural areas within 20 s following instillation into a main bronchus in dogs [43], and delivery of a single bolus of an acidic solution to the lungs of dogs or rabbits elicits a wide range of histopathologic changes that include neutrophil sequestration, epithelial damage, increased epithelial permeability, pulmonary edema, and pulmonary hemorrhage [44–48]. Additionally, the instillation of gastric juice into pig lungs has been shown to cause alveolar damage followed by subsequent intra-alveolar and interstitial fibrosis that were causatively linked to gastric acid and pepsin [49]. Repetitive, sequential episodes of gastric fluid aspiration in rodents have been reported to show prominent giant cells, lymphocytic bronchiolitis, obliterative bronchiolitis, and parenchymal fibrosis on histopathologic specimens that were associated with increased TGF-beta production [50], and loss of normal parenchymal lung architecture and diffuse deposition of collagen have been described at 2 weeks following acid challenge in a low-mortality lung injury model of acid aspiration [51].

In addition to having caustic properties due to low pH, gastric juice may contain food particles, trypsin, pepsin, and bile acids, and it may also contain bacterial products, particularly if increased intragastric pH allows bacterial overgrowth [52]. Bile acids are especially capable of injuring lung epithelial cells and can alter surfactant and surfactant apoprotein production and function [53]. Additionally, chenodeoxycholic acid has been shown to induce transforming growth factor-beta expression by human airway epithelial cells via a p38 MAP-kinase-dependent pathway [54], and chenodeoxycholic acid has been shown to induce fibroblast proliferation [55]. A recent, interesting observation by Mertens et al. [56] is that gastric juice obtained at gastroscopy from patients on acid suppressive therapy can induce an even greater IL-8 secretory response from primary bronchial epithelial cells in vitro than gastric juice obtained from patients not receiving acid suppression therapy.

Meers et al. [57] recently reported a pig model of gastric juice instillation in which hemorrhage, edema, and neutrophilic inflammation on histopathology were associated with the presence of elevated neutrophils, pepsin, bile acids, and interleukin-8 in bronchoalveolar lavage. Additionally, impaired gas exchange and lung compliance occurred within 2 h of gastric juice challenge in this model. Hartwig et al. [58] examined allografted lungs in a rat model of isograft or allograft implantation followed by chronic injection of filtered GJ (once weekly for 4–8 weeks). Allografts subjected to gastric juice instillation showed changes compatible with severe acute rejection, monocyte infiltration, and fibrosis. These lungs were noted to become firm and lost their distensibility, while allograft lungs that were not subjected to gastric juice instillation retained essentially normal architecture. When rats were given cyclosporine, bronchiolar inflammation, fibrosis, and luminal obliteration still occurred in the gastric juice-challenged animals [59]. This group of investigators subsequently examined the effects of chronic gastric juice instillation into normal, non-transplanted rats to evaluate the nature of the induced inflammatory response and found histopathologic changes of lymphocytic bronchiolitis and obliterative bronchiolitis associated with high levels of TNF-alpha, TGF-beta, and interleukins 1 and 2 [50]. Another group of investigators used a model of repetitive gastric juice aspiration (daily instillation of gastric juice was performed via a transtracheal catheter for 50 days) in miniature swine treated with cyclosporine following allogeneic LTX and observed changes consistent with induction of an indirect alloresponse to donor class I antigen [60]. Lastly, Garantziotis [61] used a murine model of MHC-mismatched bone marrow transplantation and found that mice challenged with aerosolized lipopolysaccharide (LPS) developed bronchiolar changes consistent with histologic lymphocytic bronchiolitis and obliterative bronchiolitis that were dependent on intact TLR4 signaling by donor-derived hematopoietic cells.

Abnormal GER and Dysmotility in Lung Transplant Recipients

Numerous investigators have shown a high prevalence of abnormal GER in lung transplant recipients (Table 11.2), and many of these investigations also showed a high prevalence of esophageal dysmotility and delayed gastric emptying. Hadjiliadis et al. [62] retrospectively evaluated 43 transplant recipients who had survived to 6 months post-LTX and had 24-h pH monitoring; 30 (69.3%) were found to have abnormal total acid contact times, and a negative correlation was found between total or upright GER and FEV1 ratio. An expanded, retrospectively identified cohort of 128 LTX recipients was also reported by Davis et al. [63], and 93 (73%) were found to have abnormal GER by pH monitoring. Benden et al. [64] evaluated GERD in 10 pediatric lung allograft recipients, and only one patient, who had received a fundoplication, did not have abnormal GER. D'Ovidio et al. [65] examined 50 consecutive LTX recipients and detected abnormal GER via pH monitoring in 32% at 3 months and 53% at 12 months post-LTX. Additionally, they examined gastric

Table 11.2 Prevalence of abnormal GER in lung transplant recipients

Author	Ref	Year	Study type	*N*	Type of screening	Number with significant reflux	Comments
Hadjiliadis	[62]	2003	R	43	pH monitoring	30 (70%)	• Performed at 558 days post-LTX (mean) • Negative correlation of total or upright acid contact time with FEV1
Davis	[63]	2003	R	128	pH monitoring	93 (73%)	• pH assessment performed on average at 207 days post-LTX (range 29–2,502 days)
Benden	[64]	2005	O	10	pH monitoring	9 (90%)	• 3–6 months post-LTX (children only) • One patient without GERD had previously undergone Nissen fundoplication
Button	[12]	2005	P	13	pH monitoring	11	• Patients with CF only
D'Ovidio	[65]	2006	P	50	pH monitoring	• 16 of 50 (32%) at 3 months • 16 of 30 (53%) at 12 months	• 3 and 12 months post-LTX • Gastric emptying also evaluated • Bile acids measured in BAL fluid
Blondeau	[84]	2008	O	45	pH/impedance	22 (49%)	• Acid reflux in 16 • Nonacid reflux in 6
Robertson	[66]	2009	L	9	pH/impedance (acid exposure)	• 5 (at 3 months) • 6 (at 6 months)	• Studied at 3 and 6 months post-LTX • Two improved at 6 months • Five worsened at 6 months
King	[67]	2009	O	59	pH/impedance	• 37 (65%) with acid GER • 16 (27%) with nonacid GER	• HR for BOS was 2.8 if nonacid GER detected
Blondeau	[71]	2009	O	24	pH/impedance	13 (54%)	• Selected LTX recipients at 1 year post-LTX • Increased acid exposure—nine subjects • Weakly acid reflux—four subjects
Davis	[68]	2010	C	35	pH/impedance	15 (48%)	• Esophageal acid clearance significantly prolonged in recipients with GERD

(continued)

Table 11.2 (continued)

Author	Ref	Year	Study type	*N*	Type of screening	Number with significant reflux	Comments
Hoppo	[21]	2011	R	24	• 24-h pH/impedance • 48-h pH monitoring • EM • Upper endoscopy • Barium esophagram	• 13 of 16 in upright position • LPR in 9 of 16 (56%)	• Esophageal motility: - Normal in 11 - Abnormal in 10 (aperistalsis in seven) • HH in 7 of 21 (33%) • Esophagitis in 8 of 13 (62%)

C consecutive cohort, *EM* esophageal manometry, *FEV1* forced expiratory volume in 1 s, *GERD* gastroesophageal reflux disease, *L* longitudinal, *LTX* lung transplant, *O* observational, *P* prospective, *R* retrospective cohort

emptying and assayed bile acids in BAL fluid. Gastric emptying was prolonged in 8 of 22 (36%) at 3 months and 4 of 7 (57%) at 12 months for liquids, while emptying of solids was prolonged in 39 of 43 (91%) at 3 months and 17 of 21 (81%) at 12 months. Lastly, bile acids were detected in BAL fluid of 21 of 39 (54%) patients at 3 months and 18 of 35 (50%) at 12 months post-LTX. Button et al. [12] found that 10 of 11 (91%) of recipients transplanted for CF had significant GER, and two patients had silent abnormal GER. Robertson et al. [66] followed a small cohort of patients who had pH/impedance monitoring at 3 and 6 months post-LTX and reported that the majority of recipients had abnormal GER that worsened in some patients between 3 and 6 months. King et al. [67] evaluated 59 LTX recipients and detected abnormal GER in 37 (65%) and abnormal nonacid reflux in 16 (27%); although abnormal GER itself was not associated with an increased risk for BOS, the presence of nonacid reflux was associated with a hazard ratio (HR) of 2.8. Davis et al. [68] evaluated 35 lung recipients and found abnormal GER via pH/impedance monitoring in 15 (48%) and GERD via endoscopy in three additional subjects, and esophageal acid clearance was significantly prolonged in the recipient group with GERD. Murthy et al. [69] found a prevalence of abnormal GER in 32 of 114 (28%) of LTX candidates; only 3 of 32 had symptoms associated with GERD at the time of LTX, and the presence of pre-LTX GERD was associated with reduced early post-LTX survival. Basseri et al. [70] found a similar prevalence of abnormal GER in a cohort of 30 LTX candidates (distal esophageal acid exposure in 36% and proximal exposure in 25%), and 23 (77%) had esophageal peristaltic dysfunction. Additionally, Blondeau et al. [71] detected abnormal GER in 13 of 24 recipients at 1-year post-LTX, of whom four had weakly acid reflux and nine had acidic reflux, and concentrations of bile acid in BAL fluid were higher in association with increased esophageal nocturnal volume exposure and a greater number of nocturnal weakly acidic reflux events.

In addition to a high incidence of abnormal GER in patients referred for LTX, acid reflux may worsen following transplantation. Young et al. [72] evaluated GER pre- and post-LTX in 23 patients with 24-h pH monitoring, esophageal manometry, and gastric-emptying assessments, and acid suppression as well as gastric motility stimulants were held prior to testing. Abnormal acid contact times increased from 35% of patients pre-LTX to 65% post-LTX, and this change did not correlate with changes in esophageal or gastric motility. Additionally, only 20% of post-LTX recipients with abnormal pH studies had symptoms of GER. The data reported by D'Ovidio et al. [65] also suggested that the incidence of abnormal GER was increased at 12 months versus 3 months post-LTX.

Dysfunctional swallowing mechanisms may also increase the risk of aspiration for LTX recipients. Atkins et al. [73] retrospectively reviewed clinical records of 263 LTX recipients and identified patients who underwent swallowing assessments. They found that 105 of 149 (70.5%) who had swallowing assessments had evidence of postoperative oropharyngeal dysphagia (laryngeal penetration or tracheal aspiration of thin liquids). A substantial number of recipients who aspirated (52 of 67, 78%) displayed no protective mechanisms and were classified as having silent aspiration. Only 29.5% (44 of 149) LTX recipients had a completely normal study. The presence

of abnormal GER prior to LTX was a predictor of postoperative oropharyngeal dysphagia; however, the presence of oropharyngeal dysphagia was not predictive of developing BOS [74].

GER as a Risk Factor for Lung Allograft Dysfunction

Many advances in management of lung transplant recipients have led to improved outcomes over the past decade. These include the creation of sound guidelines for candidate selection, improved surgical techniques, advances in donor lung preservation, an improved ability to suppress and treat allograft rejection, the development of prophylaxis protocols to decrease the incidence of opportunistic infection, more effective therapies for treating infectious complications, and the development of novel therapies to treat chronic allograft rejection [1].

A major obstacle to prolonged survival beyond the early postoperative time period is the development of bronchiolitis obliterans syndrome (BOS) [3, 7]. The histopathologic correlate of BOS is considered to be detection of obliterative bronchiolitis (OB) on lung biopsy specimens (Fig. 11.2). However, the surrogate marker of persistent FEV1 decline to less than 80% of the best posttransplant FEV1 value (without alternative explanation) is used to diagnose OB/BOS due to the low sensitivity of diagnostic testing short of performing surgical lung biopsy. The diagnosis can be supported by changes such as air trapping on HRCT (Fig. 11.3), and diagnostic changes can occasionally be detected by expert transplant pathologists upon analysis of transbronchial tissue biopsy specimens. The diagnosis of BOS has been associated with many risk factors that include primary graft dysfunction (PGD), acute cellular rejection, lymphocytic bronchiolitis, antibody-mediated rejection (AMR), cytomegalovirus (CMV) pneumonitis, other infections (symptomatic community-acquired respiratory virus infections, colonization and infection of the lung by *Pseudomonas aeruginosa*, and *Aspergillus* colonization or fungal pneumonitis), and autoimmune sensitization to collagen V [3, 7, 75]. In addition to these proposed risk factors, GER with microaspiration has been linked to both subacute and chronic lung allograft dysfunction [62, 63, 76–80].

Despite some variation in definitions of abnormal GER with some studies measuring only pH and not measuring nonacid reflux via pH/impedance monitoring, a consistent association has been observed between the presence and/or severity of GER and an increased risk for allograft dysfunction and BOS. The increased incidence of abnormal GER and microaspiration following LTX is undoubtedly multifactorial and linked to altered LES and UES function, esophageal dysmotility and depressed ability to clear refluxate, and impaired gastric emptying that occurs in a substantial number of LTX recipients. Esophageal motility and gastric emptying may be impaired prior to LTX, and vagal nerve injury or altered sphincter function and/or esophageal motility due to displacement of structures and/or surgical scar formation may impede transit of ingested fluids and solids and increase the likelihood of gastric juice reflux into the esophagus that may lead to microaspiration events.

The cough reflex may be significantly impaired due to denervation of the implanted allografts, and mucociliary clearance tends to be severely depressed [81, 82].

GER with microaspiration may cause allograft dysfunction due to airway injury, increase susceptibility to infection, or trigger acute allograft rejection. Halsey et al. [79] detected nonacid reflux via pH/impedance testing that was associated with diffuse alveolar damage (DAD) on sequential lung biopsies and progressive loss of allograft function in a patient on twice daily PPI therapy. The patient's lung function recovered, and the DAD changes disappeared following successful Nissen fundoplication and prevention of subsequent nonacid reflux. Shah et al. [6] followed 60 LTX recipients and found that GERD was associated with a significantly increased incidence of acute rejection episodes as well as earlier onset of acute rejection and a tendency to have multiple episodes. These findings are consistent with recent studies in animal models of LTX that suggest that gastric aspiration might enhance allorecognition and promote lung allograft rejection [59, 60].

Hadjiliadis et al. [62] were the first to report a negative correlation between increasing severity of acid reflux (as measured by 24-h pH study) and posttransplant FEV1, and a number of groups have subsequently reported various observations that link abnormal GER to an increased risk of developing BOS. Molina et al. [83] reported a correlation between GERD and BOS in a cohort of 162 LTX recipients, but GERD did not appear to have an impact on survival. However, this was a retrospective study that evaluated only symptomatic patients and only used esophagogastroduodenoscopy and/or esophagography to detect GERD. Interestingly, King et al. [67] reported that the presence of nonacid reflux as measured by impedance testing increased the risk for BOS nearly threefold, but risk was not significantly associated with acid reflux. Although a randomized, prospective study of the ability of fundoplication to prevent BOS in LTX recipients has not been reported to date, a number of studies indirectly suggest that preventing reflux via fundoplication may prevent the development of BOS [21, 80].

Although abnormal acid GER can be detected via esophageal pH probe monitoring and nonacid reflux can be detected via pH/impedance monitoring, the detection of abnormal GER does not identify microaspiration of refluxed gastroduodenal secretions. However, recent studies have used biomarkers of microaspiration—pepsin and bile acids—to identify patients with microaspiration. D'Ovidio et al. [53] were the first group to report a link between GER and aspiration of bile acids in patients with BOS. Bile acids were detected in BAL fluid from 71 of 107 recipients who underwent surveillance bronchoscopies at 6 months post-LTX, and the level of total bile acids were significantly increased in patients with BOS (stages 0p and 1–3), but this increase was essentially limited to patients who developed early BOS (≤12 months post-LTX) versus those with late BOS. Additionally, high levels of bile acids in BAL fluid correlated positively with IL-8 and neutrophil levels in BAL, and high bile acid levels in BAL fluid posed a significantly increased risk for developing BOS. D'Ovidio et al. [65] subsequently found that high bile acid levels in BAL fluid were associated with significantly depressed levels of SP-A, SP-D, and dipalmitoylphosphatidylcholine, and one effect of aspirated bile acids may be depression of lung allograft innate immune function. Blondeau et al. [84] also evaluated

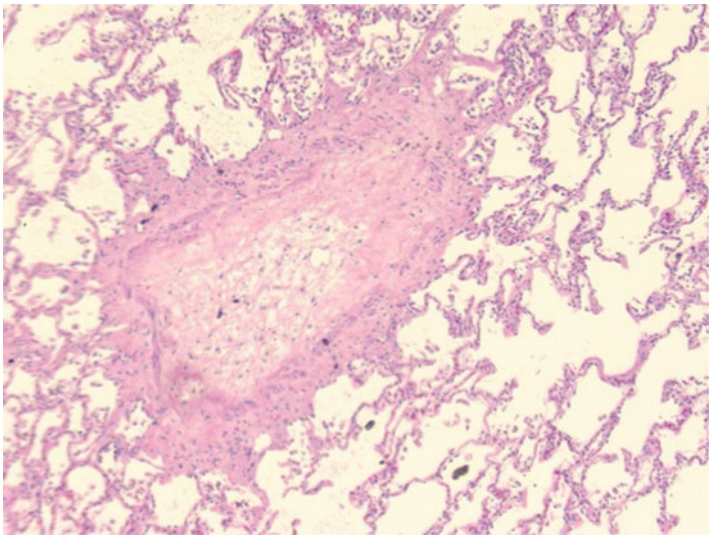

Fig. 11.2 Histopathology of obliterative bronchiolitis. Hematoxylin & eosin stain (high power) of a bronchiole with a fibrosed and obliterated lumen and surrounding normal alveolar walls

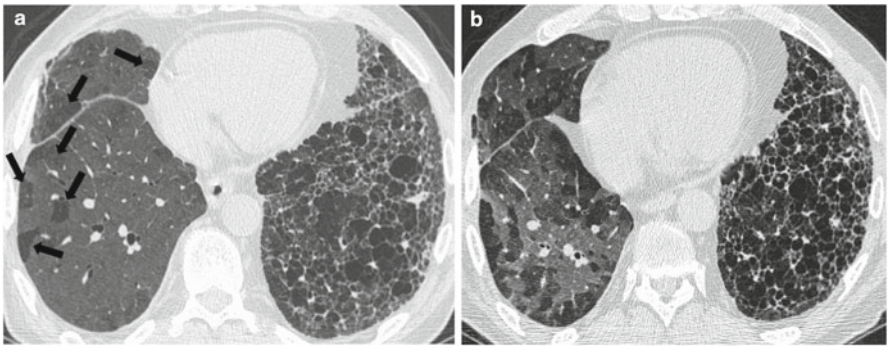

Fig. 11.3 HRCT imaging of BOS. (**a**) shows multiple areas of air-trapping (arrows) in the lung allograft of the recipient of a right single-lung transplant for pulmonary fibrosis; (**b**) shows progression of air-trapping due to progressive obliterative bronchiolitis on repeat HRCT obtained 1 year later

a cohort of 45 LTX recipients and detected abnormal acid and nonacid GER in 22 of 45 patients and measured bile acids and pepsin in BAL fluid. All LTX recipients had detectable levels of pepsin in BAL fluid, but levels of pepsin were 23-fold increased over that of control subjects. Twenty-two LTX recipients had bile acids detected in BAL fluid, and, although pepsin levels showed no correlation with FEV1 values, bile acids were significantly increased in patients with BOS stages 1–3. An additional, interesting aspect of this study was the persistence of abnormal GER, especially weakly acidic GER, in patients on PPI therapy (7 of 18 patients, five with weakly acid reflux), although esophageal acid exposure and acid reflux events were

significantly reduced for patients on PPI when compared to a cohort of patients studied off PPI therapy. Vos et al. [85] found a significant association of allograft colonization by *P. aeruginosa* with the presence of bile acid aspiration in a matched LTX recipient cohort of 24 subjects. Indeed, taken together, these investigations suggest that bile acids aspirated into the lower respiratory tract may be particularly injurious to respiratory mucosae and induce airway injury and dysfunction that can lead to chronic infection and/or BOS.

GER and Autoimmunity

Autoimmune sensitization to self-antigens has been recently recognized as a risk factor for early allograft dysfunction [86] and for the development of BOS [75]. T cell sensitization to collagen V (ColV), which is expressed in small airways of the normal lung, has been associated with a substantially increased risk of developing BOS and with increased severity of BOS, and this T cell response appears to require CD4+ T cells and monocytes along with IL-17, TNF-alpha, and IL-1beta [75]. Additionally, patients with advanced lung disease who have been sensitized to ColV pre-LTX may be at increased risk for primary graft dysfunction [86].

We recently identified an association of abnormal GER with collagen V sensitization and BOS [10]. Twenty-six of 54 prospectively evaluated LTX recipients were found to have GERD, and T cell responses to ColV were significantly increased in recipients with GERD. Additionally, BOS-free survival was significantly reduced for the recipient group with GERD. Interestingly, when ColV-specific T cell responses were assessed in a second cohort of 53 patients awaiting transplant, significantly increased ColV reactivity was found in the subset of patients who had GERD.

Diagnosis of GER and Aspiration

Dual sensor 24-h pH monitoring with esophageal manometry provides continuous monitoring of acid pH (pH < 4) in both the distal and proximal esophagus along with measurement of esophageal peristalsis [85–87]. However, although this had been endorsed as the gold standard for the diagnosis of GERD, it does not detect nonacid reflux or quantify the volume of refluxate [88, 90]. As technology has evolved, diagnosis and monitoring of GERD have switched from focusing on the detection of an abnormal degree of gastric acid refluxing into the esophagus to simultaneous monitoring of pH and reflux volume to detect both acid and weakly acid/nonacid reflux. Multichannel intraluminal pH-impedance monitoring, in contrast to pH monitoring alone, can discriminate between fluid and gas reflux regardless of pH and estimate the size of a refluxate bolus and measure the proximal extent of GER while differentiating acid from nonacid reflux [87–90].

A substantial number of LTX recipients have been found to be asymptomatic when abnormal GER is objectively documented. A relatively recent study by Sweet

et al. [15] found that symptom screening had a sensitivity of ≈65% and specificity of ≈71%, and other investigators have found that symptoms associated with GER (heartburn, dyspepsia, dysphagia, regurgitation) are quite limited in sensitivity and specificity [21, 84]. It is now well recognized that gastric secretions can still gain access to the esophagus and that such refluxate may not be acidic enough to be detected by pH monitoring and may not evoke any symptoms classically associated with reflux. This may especially be the case when patients are receiving acid-suppression pharmacologic therapies that can blunt symptoms of GER but not necessarily prevent it. Combined impedance and pH monitoring allows the detection of both acid and nonacid reflux and can determine the proximal extent to which refluxate penetrates into the esophagus [87], and methods that utilize these instruments can detect a fluid bolus regardless of pH and have shown that LPR is not uncommon in LTX candidates or LTX recipients [21].

Various radiologic techniques can be used to detect and/or estimate the extent of GER and aspiration. These include modified barium swallow [91] or nuclear medicine techniques [92, 93], and thoracic CT scanning can be used to identify the presence of a hiatal hernia or abnormal esophagus (air-fluid level, dilatation) as well as pulmonary parenchymal changes that are suggestive of microaspiration [94, 95]. Additionally, an upper GI swallow with a radiopaque agent can identify impaired gastric emptying, which may be a contributing factor to abnormal GER.

The detection of biomarkers of aspiration (e.g., BAL fluid pepsin and bile acids) in BAL fluid is increasingly recognized as a tool for detecting microaspiration of refluxed gastroduodenal secretions into the lung [53, 84, 96]. Ward et al. [97] reported that BAL pepsin levels were increased in LTX recipients and that pepsin levels did not correlate with PPI therapy. A larger, prospective study by this group again found significantly increased pepsin levels in LTX recipients, and higher pepsin levels were associated with acute allograft rejection [98]. However, Blondeau et al. [84] found that pepsin levels in BAL did not correlate with FEV1, but the presence of bile acids correlated with risk for BOS, which agrees with the correlation of high levels of bile acids with the development of BOS that was reported by D'Ovidio et al. [53]. Although additional studies correlating BAL markers of microaspiration with the presence of abnormal GER and BOS risk are needed to validate the predictive capability of such measurements, the combination of BAL aspiration biomarkers with pH/impedance and proximal foregut motility studies may facilitate the accurate selection of recipients at risk for allograft dysfunction due to GERD as well as recipients who begin to display manifestations of the onset of BOS for more aggressive interventions to prevent reflux, particularly fundoplication.

Unfortunately, current methodology used to detect abnormal GER and microaspiration requires invasive procedures, and new technology that can noninvasively detect reflux and microaspiration of gastroduodenal secretions would represent an important diagnostic advance [99, 100]. The detection of depressed pH and 8-isoprostane in exhaled breath condensate (EBC) has been associated with GERD-induced lung inflammation [101], and the detection of bile acids or pepsin may indicate that microaspiration is present. However, Jackson et al. [102] did not find good correlation of biomarker levels in BAL with levels measured in EBC, although

various biomarkers were detectable in EBC. Furthermore, although Dupont et al. [103] reported that a low pH in EBC correlated with acute and chronic allograft in LTX recipients, Soter et al. [104] found that EBC pH did not differentiate stable LTX recipients from patients with BOS. Although the noninvasive nature of using EBC to detect microaspiration of gastroduodenal secretions is attractive, it does not appear to be useful as a diagnostic technique using currently available technology.

Our institutional approach is to perform manometry and pH/impedance studies on LTX candidates prior to LTX. The inclusion of impedance plethysmography allows assessment of the proximal nature of the refluxate and can detect mildly acid and nonacid reflux. Additionally, impedance can be useful to assess therapeutic efficacy for patients taking acid-suppression medications. We may also perform esophagrams and gastric-emptying studies in selected patients, such as those with connective tissue disorders. If significant abnormal GER is detected, a decision is made as to whether to treat medically or perform pre-LTX fundoplication. If significant abnormal GER is present pre-LTX and fundoplication is not performed prior to LTX, fundoplication is performed post-LTX once the patient has stabilized. Preferably, fundoplication is performed 3–6 months after transplantation in patients unable to tolerate general anesthesia and surgery prior to transplantation. Significant esophageal dysmotility presents an additional challenge, particularly if aperistalsis is present. If there is considerable stasis of contents within the esophagus, intraesophageal reflux can occur with potential macro or microaspiration without true reflux of gastroduodenal secretions. In patients with poor peristalsis, partial fundoplication (Dor, Toupet) may be performed with less risk of dysphagia (if these patients are not disqualified from undergoing LTX). Gastroparesis also increases the risk of abnormal GER and is seen in a significant portion of patients with end-stage lung disease, and current immunosuppression regimens that include calcineurin inhibitors may increase gastroparesis. Procedures that improve gastric emptying, such as pyloroplasty, can be performed if gastric stasis and distention are contributing to GER. Though less commonly performed than fundoplication, this procedure can be achieved safely and effectively in a minimally invasive fashion. Pyloroplasty can be used to augment the effects of fundoplication in patients with preserved esophageal function but documented abnormal GER. It can also be performed in lieu of fundoplication in patients with compromised esophageal clearance if impaired gastric emptying and distention are documented.

Treatment and Prevention of GER

Because pharmacologic suppression of gastric acid secretion does not appear to significantly suppress abnormal GER (especially weakly acid or nonacid reflux) and gastric secretion aspiration, other interventions such as gastric fundoplication have been investigated as means of preventing of LTX complications and as a treatment for BOS when reflux appears to be present. Azithromycin has been shown to stabilize and possibly reverse BOS [105–107], especially when BAL neutrophilia [105] or

evidence of GER [107] is present. A recent prospective, randomized trial of azithromycin versus placebo starting prior to hospital discharge post-LTX showed a significant decrease in the development of BOS over a 2-year time period [108]. Interestingly, azithromycin therapy has been shown to decrease GER and microaspiration in lung transplant recipients [109], but it appears to have reduced efficacy when patients with BOS have evidence of bile acid aspiration [110].

Fundoplication at the gastroesophageal junction can greatly reduce or prevent abnormal GER. Laparoscopic Nissen fundoplication can be performed with reasonable safety on lung transplant candidates with advanced lung disease prior to LTX [13, 16, 21] and may prevent the reflux and aspiration of gastroduodenal secretions that increase the risk of allograft dysfunction post-LTX. There are several options for fundoplication, the most common being Nissen 360-degree fundoplication in which the greater curvature of the stomach is freed from the short gastric vessels and wrapped posteriorly around the GE junction. Endoscopic approaches for fundoplication have been described, but results can be adversely affected by poor esophageal motility and the presence of a hiatal hernia [111], which are frequently present in the advanced lung disease population. Partial fundoplication has been shown to result in less obstructive symptoms and gas bloat syndrome, particularly in patients with esophageal dysmotility, and partial fundoplication has been reported to be as effective in reducing proximal, mid, and lower GER episodes as 360-degree fundoplication [112–114].

Davis et al. [63] reported that 16 of 26 patients diagnosed with BOS in whom GER was detected via esophageal pH probe underwent laparoscopic Nissen fundoplication, and these patients subsequently improved with 13 of 16 subjects no longer meeting criteria for BOS. A follow-up study [115] demonstrated safety and efficacy that was not significantly different from a matched cohort of non-transplant recipients who received fundoplication for GERD. Additionally, Cantu et al. [80] published a retrospective analysis of 457 LTX recipients in which the incidence of GER was 76%. A small subgroup of 14 patients who underwent fundoplication within 90 days posttransplant had significantly improved freedom from BOS at 1 and 3 years posttransplant.

Other investigators have shown that anti-reflux surgery is both safe and effective. Burton et al. [116] performed fundoplication on 21 recipients with clinically confirmed abnormal GER at a mean of 768 days posttransplant; GER symptoms significantly improved. However, one perioperative death occurred, and progression to BOS stage 1 was not altered, although a decreased likelihood to progress to BOS stage 2 or 3 was suggested by their data. Fisichella et al. [117] compared safety and efficacy of laparoscopic fundoplication for 29 consecutive LTX recipients and found no difference in outcomes as compared to 23 non-LTX patients, and no mortality was reported. This group also showed that anti-reflux surgery was associated with reduced BAL pepsin levels [118]. Hoppo et al. [21] reported significant improvement in FEV1 in 20 of 22 LTX recipients following anti-reflux surgery. Surgery was well tolerated in the entire cohort of 24 patients, and no operative mortality or significant morbidity occurred. Finally, Hartwig et al. [119] prospectively collected data on 297 LTX recipients and reported that LTX recipients with abnormal GER

via pH testing attained lower peak allograft lung function at 1-year post-LTX, but early fundoplication appeared to preserve allograft function.

To date, no prospective, randomized controlled clinical trials of fundoplication for BOS have been reported to validate the efficacy of pre-LTX or early post-LTX fundoplication versus more conservative therapy (e.g., PPI therapy, azithromycin) in patients with abnormal GER. Similarly, a randomized trial of the effects of fundoplication on allograft function for patients with abnormal GER who are newly diagnosed with BOS has not been performed. Nonetheless, successful anti-reflux surgery can successfully recreate an anatomical barrier that prevents reflux. Although treatment with PPIs may neutralize gastric acid and relieve reflux symptoms (if present), the administration of pharmacologic agents alone to suppress gastric secretion may not prevent lung allograft dysfunction if suppression of reflux is suboptimal and microaspiration of bile acids and other injurious components of gastroduodenal secretions persists. Indeed, currently available data suggest that minimally invasive fundoplication performed by expert surgeons may prevent or stabilize a decline in lung function associated with the presence of abnormal GER.

Summary and Conclusions

GER and microaspiration have been strongly linked to allograft dysfunction, and these are present in a substantial number of patients with advanced lung disease and may worsen following successful lung transplantation. Proximal gastrointestinal tract motility studies and pH/impedance testing can be used to diagnose motility abnormalities and acid and/or nonacid GER, but a true gold standard for detecting abnormal GER combined with high risk of penetrance of refluxed secretions into the lung is lacking. Nonetheless, the identification of patients with abnormal GER appears to be important in management decisions and assessing risk for posttransplant allograft complications such as BOS. However, a definitive marker of GER combined with microaspiration that identifies patients at significant risk for associated allograft injury and dysfunction and in whom clinical intervention such as fundoplication should be recommended needs to be determined. To date, only retrospective studies have linked prophylactic fundoplication for recipients with GER to improved outcome and decreased incidence and/or severity of BOS.

Future Research

Future research endeavors should seek to identify the most effective protocols that can detect susceptibility to abnormal GER and microaspiration in lung transplant candidates and recipients, and the optimal timing of diagnostic testing should be determined. Prospective, multicenter, adequately powered clinical trials should be performed to determine the timing and efficacy of fundoplication and whether

fundoplication is definitely superior to more conservative approaches to effectively suppress abnormal GER and prevent lung allograft injury.

Clinical Summary

Abnormal GER and foregut dysmotility have been detected in a substantial number of patients with ESLD referred for lung transplantation, especially in patients with IPF, CTD-ILD, CF, or non-CF bronchiectasis. Additionally, a large proportion of LTX recipients have also been found to have significant GER, and evidence of microaspiration of refluxed gastroduodenal secretions has been identified via the identification of biomarkers of aspiration (pepsin and bile acids) in BAL fluid. Because microaspiration of refluxed secretions has been strongly linked to lung allograft dysfunction and especially to the development of BOS, therapeutic interventions to prevent abnormal GER and microaspiration should be considered to prevent allograft dysfunction and the threat of graft loss and recipient death. Administration of agents to suppress production of acidic gastric secretions and/or azithromycin may have limited efficacy, especially if silent aspiration continues to occur and aspirated secretions contain injurious agents such as bile acids. Minimally invasive, laparoscopic fundoplication can be safely performed in carefully selected patients with advanced lung disease or LTX recipients and can successfully prevent or significantly limit abnormal GER in a majority of patients.

Key Points

1. Abnormal GER is a common finding in patients with advanced lung disease and in lung transplant recipients, and GER has been linked to allograft dysfunction syndromes, especially BOS.
2. Symptoms commonly associated with GER have limited sensitivity and specificity for the detection of patients who have abnormal GER and/or microaspiration.
3. pH/impedance monitoring provides a means of detecting both abnormal acidic reflux as well as weakly acid or nonacid reflux, and esophageal motility and gastric-emptying studies may provide additional information that complements pH/impedance findings.
4. Aspirated bile acids appear to be particularly injurious to respiratory mucosae and surfactant function and have been found to correlate with risk for developing BOS.
5. Biomarkers of gastroduodenal secretion aspiration in BAL fluid may prove particularly useful in identifying patients who require aggressive therapies to prevent and/or treat lung allograft dysfunction.
6. Pharmacologic therapies (e.g., PPI, H-2 blockers) may diminish reflux symptoms but may not prevent abnormal GER and microaspiration, and this may especially

be the case for mildly acid or nonacid reflux and patients with laryngopharyngeal reflux (LPR).

7. Minimally invasive laparoscopic Nissen fundoplication appears to be safe and effective in LTX candidates as well as LTX recipients and may provide the best intervention to prevent post-LTX acute and chronic allograft dysfunction due to abnormal GER and microaspiration.

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Chapter 12
Pharmacologic Treatment of GERD

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Keywords Pharmacologic treatment • Gastroesophageal reflux disease (GERD) • Treatment strategies • Reflux-moderating agents • Acid-suppressing agents • Prokinetic medications

Introduction

Gastroesophageal reflux disease (GERD) is extremely common, affecting 7–10% of the adult population in the United States on a daily basis [1]. GERD has been found to have a greater negative impact on quality of life for a patient than more severe chronic diseases, including hypertension, heart failure, and angina [2]. The clinical range of GERD has expanded from classic esophageal symptoms of heartburn and regurgitation to now include symptoms and disease outside the esophagus, namely, the entire aerodigestive tract. Treatment of the spectrum of reflux diseases, be it isolated to the esophagus or proximal disease of the oropharynx or lungs, shares a common pathophysiology, and therefore, similar treatment strategies can be implemented with only slight variations. There is a range of effective pharmacologic treatment options for patients with reflux disease: acute symptoms of classic reflux may simply require over-the-counter (OTC) acid-neutralizing medications, while other individuals with more persistent, recurring symptoms need a more directed, long-term strategy requiring systemic medications. The nature of the disease is one of chronicity. Thus, a majority

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of patients started on acid-suppressant medications will have symptoms that require long-term pharmacologic treatment. With the high prevalence of reflux disease, the spectrum of reflux manifestations, and the array of products available to treat reflux, the clinical and financial burden of treating reflux patients is high. This chapter focuses on the pharmacologic treatment for reflux disease.

Treatment Strategies

The goals of treatment of reflux disease, irrespective of type or location, are to relieve symptoms, heal tissue damage, and prevent complications. The pathophysiology of reflux disease is multifactorial, involving not only the caustic nature of the gastric refluxate but also factors of motility, (transiently relaxing lower esophageal sphincter, inefficient esophageal motility, delayed gastric emptying), decreased mucosal neutralization, and anatomic factors; attempts to address these pathophysiologic factors have been targeted in treatment strategies. The motility dysfunctions in reflux are difficult to normalize, and pharmacologic options remain limited. The anatomic factors can be improved with antireflux positioning, such as raising the head of the bed; however, hiatal hernias, when large, may require surgery to adequately address. Pharmacologic treatments of reflux have therefore been directed at minimizing the volume and caustic nature of the gastric refluxate. Of all the components of gastric refluxate, including acid, bile, pancreatic enzymes, pepsin, and ingested contents, acid remains the most directly caustic. In addition, acid has indirect effects on the activity of bile and pepsin, the two other components that show some capacity to trigger mucosal damage and symptoms. There have been no attempts to alter secretion of bile, pancreatic enzymes, or pepsin, nor should there be. Strategies to control reflux have therefore focused on treating the acid component of gastric refluxate.

Reducing stomach acid has been proven to be safe and not to affect normal digestion and is attainable pharmacologically. The two main categories of pharmacologic agents to address the acid component of reflux are (1) acid-neutralizing or acid-moderating medications, such as antacids and alginic acid and (2) gastric acid-suppressing medications, including two classes of agents, namely, histamine type 2 receptor antagonists or "blockers" (H2-RAs) and proton pump inhibitors (PPIs).

Reflux Treatment Strategies

The most accepted strategy in addressing acid reflux symptoms for the majority of patients with intermittent symptoms or mild to moderate esophagitis is "step-up" therapy. "Step-up" medication strategies are commonly adopted by patients,

recommended by pharmacists, as well as prescribed by physicians. By employing a "step-up" strategy of GERD pharmacologic therapy, patients start with the cheapest, easiest, and safest medication and advance to the more expensive, scheduled systemic therapy. With this strategy, patients might start treatment with OTC acid-neutralizing or acid-modulating agents. Patients then progress to H2-RA therapy and proceed to single-dose and then double-dose PPI therapy if symptoms are not controlled with the less potent medications. H2-RA-based therapy was the mainstay of GERD treatment for decades until the more potent acid-suppressing PPIs replaced them in efficacy. Nonetheless, it remains that many patients can adequately be treated with the simpler and cheaper H2-RAs and would ultimately not require PPI, which is the argument for starting with the H2-RA. Since PPIs have been available to physicians in the late 1980s and more recently as OTC medications, PPIs have become the most common therapy for acid reflux treatment for both classic GERD and extraesophageal reflux. With the wide availability and good safety profile, the ready use of PPI therapy has expanded exponentially and has now become standard to use as a first-line agent for new GERD symptoms. Many experts now argue for more of an inverse pyramid approach to treating reflux disease and advocate for a "step-down" therapy, where patients are placed on PPI acid suppressants directly [3] and then are tapered down to less potent acid suppressants as tolerated. Mathematical modeling has shown this to be a cost-effective approach to managing chronic reflux disease. A recent primary-care-based study compared step-up and step-down therapy and has shown that both strategies have similar success in symptom relief; however, step-up strategy is ultimately more cost-effective at 6 months following initiation of treatment [4].

As opposed to a set pyramidal protocol for pharmacologic treatment for all types of reflux, treatment strategy may be prescribed depending on the local reflux manifestation, be it the esophagus, the oropharynx as in laryngopharyngeal reflux disease (LPR), or airways in the lungs, as in asthma. GERD is commonly self-diagnosed and often initially managed with a range of OTC medications readily available as described above as part of a step-up treatment strategy. Alternatively, individuals with LPR or airway diseases of reflux are generally not self-diagnosed, but rather are diagnosed by subspecialists such as allergists, pulmonologists, otolaryngologists, or gastroenterologists, often after extensive testing has been performed. These patients are empirically placed on aggressive acid suppression therapy directly, as acid-neutralizing strategies are less useful in this population and thus are much more in line with step-down strategy. As outlined by the American Academy of Otolaryngology policy statement adopted in 2006, patients suspected of having LPR should be placed directly onto double-dose PPI treatment for a prolonged period, rather than a step-up strategy adopted by most physicians for esophageal symptoms. Whereas standard GERD treatment may get low-dose acid suppression for a 2-month period, comparatively, LPR is treated for at least 3 months and may be doubled to a 6-month trial. The acid-neutralizing agent Gaviscon may be added to treatment for LPR to decrease proximal esophageal or oropharyngeal reflux as it decreases proximal regurgitation, which is a factor in LPR. Patients with LPR and reflux-related

asthma, where proximal reflux of liquid or even gaseous reflux is critical to the pathophysiology, should also receive intensified anatomic antireflux recommendations to prevent proximal reflux (antireflux positioning) and may have a lower threshold for surgical fundoplication. Patients with aerodigestive symptoms would concurrently require organ-specific treatments for symptom control, such as inhalers and decongestants, which are not a part of classic GERD therapy.

Reflux-Moderating Agents

Antacids and alginic acid are products that neutralize or moderate stomach contents, are nonabsorbable, and work locally in the stomach and esophagus. These formulas represent the first-line therapy most commonly used by patients experiencing acute heartburn. These are OTC medications that are widely available and sold in several different formulations and offered in multiple forms (liquid, chewable tablets, gum, and dissolvable tablets). They provide fast, short-term relief of symptoms of heartburn.

Antacids

Acid-neutralizing strategies were the first treatments of peptic disorders developed and marketed. In the 1900s, early attempts at acid neutralization included the "Sippy regimen" of hourly ingestion of milk and cream, the gradual addition of eggs and cooked cereal, and alkaline powders, which provided symptomatic relief for peptic diseases by attempting to neutralize gastric acid. Since the early attempts at acid neutralization, many different formulations have become available as antacids: calcium carbonate (Rolaids, Tums), aluminum hydroxide and magnesium hydroxide (Maalox, Mylanta), and aluminum hydroxide and magnesium carbonate (Gaviscon). Any of these antacids are reasonable initial treatments for mild to moderate reflux symptoms. These medications are suggested to be used "on demand" for symptoms up to four times per day. Antacids are shown to be more effective than placebo in the relief of symptoms of postprandial heartburn [5, 6]. These medications can be used alone, in combination, or in addition to scheduled acid suppressants for breakthrough symptoms.

Adverse Effects

Acid-neutralizing formulations are effective in the immediate relief of esophageal symptoms of heartburn and regurgitation. However, effects are usually not durable,

which may then lead to overuse and precipitate adverse effects. Occurrence of side effects from antacids varies depending on the individual, as well as other medications that may be concurrently prescribed. The most common side effects reported are changes in bowel functions, such as diarrhea, constipation, or flatulence. Constipation has been an issue with calcium-containing antacids. Calcium-containing compounds may increase calcium output in the urine and precipitate renal stones. Carbonate at regular high doses may cause alkalosis, affecting the subsequent excretion of other drugs and playing a role in precipitating renal stones. Aluminum-containing drugs may cause problematic constipation, hypophosphatemia, and osteomalacia if used chronically. Magnesium has a laxative effect and can lead to hypermagnesemia with cardiovascular and neurological complications. In attempts to alleviate the common side effect of bowel disruption, combinations of magnesium plus aluminum antacids have been developed, which helps counteract the bowel disruption.

Alginic Acid

Gaviscon contains both antacid components (calcium carbonate, sodium bicarbonate, and magnesium carbonate) and the gelling agent alginic acid, which is an anionic polysaccharide extracted from algae. This combination not only provides neutralization from the antacid component, but it also creates a foam barrier that floats on the surface of the gastric refluxate, thereby reducing the number of spontaneous reflux episodes. Gaviscon should be taken 30–60 min after meals and up to four times per day. A meta-analysis of randomized controlled trials suggests that alginic acid may be the most effective OTC acid-neutralizing treatment for GERD [7]. The combination of antacids with alginic acid has been found to have increased symptom control compared to antacids alone [8].

Acid-Suppressing Agents

As acid-neutralizing products are not lasting in effect nor do they adequately heal mucosal disease, the treatment target remains that of acid suppression. Esophageal mucosal healing and relief of symptoms occur quite effectively when acid suppression improves pH to >4 for a prolonged amount of time [9]. Patients with moderate to severe symptoms of reflux will generally be placed on acid-suppressing medications to acutely heal injury and relieve symptoms. Acid suppressants are also used for maintenance of mucosa and to minimize future damage. Two classes of acid-suppressant medications are widely available: histamine type 2 receptor antagonists (H2-RAs) and the newer and more potent PPIs. Both of these medications effectively decrease the amount of acid secreted by the parietal cell into the gastric lumen. These acid-suppressant medications both raise the effective pH of the gastric fluid and decrease the volume of gastric secretions. Studies have found that both mucosal healing

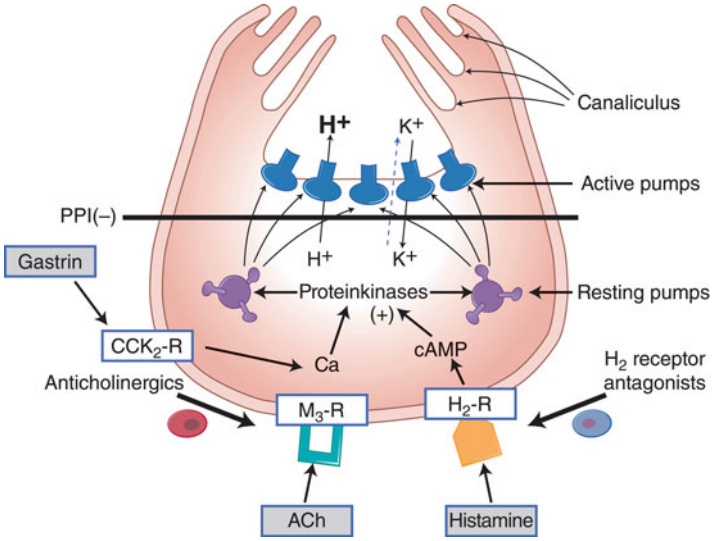

Fig. 12.1 Parietal cell has three receptor systems active at the basolateral membrane and the terminal H+/K+ adenosine triphosphatase (ATPase) pump active on the apical surface that are targeted by pharmacologic therapy to reduce the secretion of acid [10]

and relief of symptoms correlate to the number of hours that the intragastric pH is >4. In addition to the clinical proof of reflux control with maintaining the pH>4, biochemical studies have revealed that pepsin and bile acids are less active when the pH is >4. Thus, acid suppression diminishes the caustic nature of pepsin and bile [9].

The Parietal Cell

The parietal cell is the acid-secreting cell of the stomach and therefore the pharmacologic target of acid-suppressant medications. Several components of the parietal cell are targeted by acid-suppressant medications as shown in Fig. 12.1 [10]. Parietal cells are located within the gastric mucosa (predominantly in the main body and antrum) and will produce up to 2 l of acidic gastric secretions per day. Acid is secreted by the parietal cell continuously and as a stimulated response to eating. The basolateral side of the parietal cell has receptors that are responsive to three physiologic stimulants for acid secretion: gastrin, acetylcholine, and histamine. The release of the hormone gastrin is stimulated by the presence of food in the stomach or duodenum and reaches the parietal cell through the bloodstream. Acetylcholine is released from the vagus nerve in response to sight, smell, and taste of food as well as distention of the stomach. Histamine is released through the stimulation of

neuroendocrine cells known as enterochromaffin-like cells (ECLs) located in the gastric mucosa in the vicinity of the parietal cells. Second messengers within the parietal cells triggered by these three receptors subsequently stimulate the H+/K+ adenosine triphosphatase (ATPase) pumps on the luminal membrane, functioning as the final pathway to secretion of acid into the stomach. The H2-RA therapy specifically blocks the histamine-stimulated receptor pathway only, whereas the other sources of receptor stimulation using second messenger pathways are not blocked. Conversely, PPI medications block the final common pathway, the H+/K+ ATPase, and thus more completely antagonize parietal cell acid secretion than the H2-RAs.

H2-Receptor Antagonists

Histamine type 2 receptor antagonists (H2-RAs) are competitive antagonists of histamine and bind irreversibly to the histamine type 2 receptor on the basolateral side of the parietal cell, thus blocking the histamine-induced signal to the H+/K+ ATPase pump to secrete acid. These antagonists additionally are thought to work in an indirect mechanism, whereby gastrin and acetylcholine have subsequent reduced effect on parietal cells with H2-RA therapy.

H2-RAs were the first acid-suppressant medications available and the standard treatment for GERD for several decades. H2-RAs were first developed in the mid-1960s and then marketed in 1976. Trials in the 1970s and 1980s confirm significant relief of symptoms of GERD, as well as mucosal healing on endoscopic evaluation. In the United States, this class of drugs includes four formulations: cimetidine, famotidine, nizatidine, and ranitidine. All of these medications are available over the counter as well as in a prescription strength.

There are negligible differences in efficacy regarding acid suppression, symptom relief, or healing capacity amongst the H2 RA formulations. The H2-RAs appear to be more effective for blocking basal secretion of acid rather than meal-induced acid release. Oral absorption of H2-RAs is rapid, generally within 1–3 h. Acid suppression is directly correlated to plasma concentration, therefore most effective within 4 h after taking the drug. The formulations have similar potency and efficacy of acid suppression: reduced basal acid secretion by 60–70% and >80% reduction for nocturnal acid secretion for up to 6–10 h after taking [11]. The H2-RA formulations are dosed at differing milligram amounts but all recommended as a twice-daily dose: cimetidine at 400 mg at twice per day, ranitidine at 150 mg at twice per day, famotidine at 20 mg p.o. twice per day, and nizatidine at 150 mg twice per day. Dosages of H2-RAs need to be reduced for patients with renal failure, but not liver failure. Several trials have looked at high-dose H2-RAs with regard to improved symptom control and esophageal mucosal healing capacity and have found some benefit at higher doses. Ranitidine at 150 mg q.i.d. or 300 mg b.i.d. or nizatidine at 300 mg b.i.d. reveals increased healing: up to 83% healed at 12 weeks in addition to better symptom control [12].

Studies have promoted the use of H2-RAs for nocturnal use, either as primary treatment or as part of combination therapy for patients already on a PPI with breakthrough nighttime symptoms. It has been suggested that the breakthrough nocturnal acid secretion in patients on PPI therapy is likely explained by a histamine-related response. Clinical studies have found that H2-RAs are more efficacious for nocturnal acid suppression compared to adding another dose of PPI [13]. Mainie et al. used impedance-pH testing to compare nocturnal acid breakthrough between patients on PPI alone versus those on PPI + nocturnal H2-RA and found a significant increase in the time that the intragastric pH remains >4 for patients taking evening H2-RAs in combination with PPI [14]. Other recent studies have disputed the benefit of adding H2-RAs to PPIs, finding that there was no significant lasting increase in acid suppression for nocturnal acid [15, 16]. The issue of addition of a scheduled H2-RA to PPI therapy for breakthrough symptoms remains unproven and questionable for a long-term treatment strategy, although, arguably, a reasonable short-term or intermittent treatment option.

H2-RAs for "on-demand" therapy have been used successfully in patients with mild to moderate disease. With on-demand therapy, patients take medication only when symptoms occur (daily, weekly, monthly); patients wait for a relapse of symptoms to occur and then restart the medication [17]. With H2-RA medications, this is a reasonable strategy in that H2-RAs are rapidly absorbed and correlate with a fairly direct inhibition of gastric acid secretion. Additionally, with more intermittent usage, there is less concern for patients developing drug tolerance, and they will therefore tend to remain sensitive to H2-RAs for longer periods of time.

Adverse Effects of H2-RA Therapy

H2-RAs as a class have a very safe side effect profile with an overall incidence of adverse reactions of <4% [18]. Cimetidine is the formulation more commonly associated with adverse effects, as it is a known inhibitor of the cytochrome P450 isoenzymes and, therefore, needs to be used with some consideration for drug interactions. The cytochrome P450 inhibition forms the basis of the numerous drug interactions between cimetidine and other drugs, especially those of hormonal contraception, methadone, antidepressants, theophylline, warfarin, and phenytoin. Cimetidine interaction with these medications can cause increased blood levels of the other drugs and subsequent toxicity. The development of longer-acting H_2-receptor antagonists such as ranitidine, with far less effect on cytochrome P450 and therefore reduced adverse effects, led to a wide usage of the other H2-RA formulations. Side effects common to the group would include headache, dizziness, diarrhea, and rash. Recent studies have suggested an increased risk of bone fractures with chronic acid suppressive therapy; however a relationship with H2-RA therapy and long-term risk of fracture remains debatable, as is seen with higher dose chronic PPI use [19].

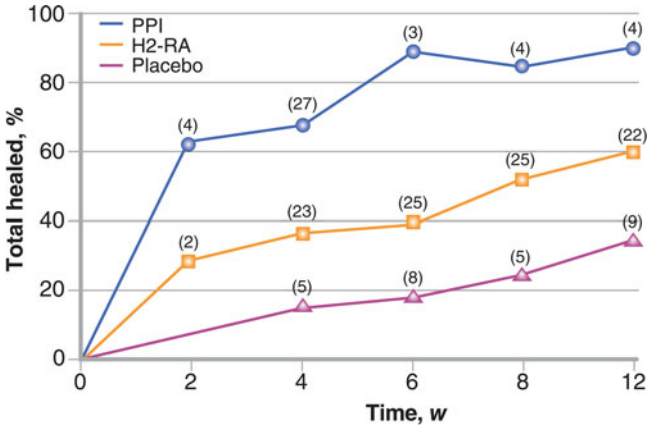

Fig. 12.2 Healing-time curves comparing PPIs, H2-RAs, and placebo. PPIs provided substantially improved mean total healing for each drug class per evaluation time in weeks [20]

Proton Pump Inhibitors

The PPIs are the most effective medications available to reduce gastric acid secretion, relieve reflux symptoms, and heal esophagitis. Furthermore, PPIs have an excellent safety profile. PPIs bind irreversibly and selectively to the hydrogen/potassium adenosine triphosphatase enzyme pump (the H+/K+ ATPase or "proton pump") and block acid secretion from the parietal cell. The PPIs are extremely effective at suppressing both stimulated and basal acid secretion and have proven to be more effective than H2-RAs for healing esophagitis and relieving symptoms [20] (Fig. 12.2).

Mechanism of Action

PPIs are highly selective benzimidazole derivatives that block the secretion of acid into the gastric lumen by the ATPase pump. The proton pump is the terminal step in the secretion of gastric acid with the H+ ion directly secreted into the gastric lumen [21]. The PPI medications are membrane permeable, weakly basic, and given in an inactive prodrug form. The prodrug is lipophilic and readily absorbed into the intracellular space and the parietal cell. The prodrug accumulates in the acid spaces of the active parietal cell, where it is protonated and rearranges into its active form. The active form of the drug covalently binds via disulfide bridges to the gastric H+/K+ ATPase and thus deactivates the pump. This irreversible, end-stage H+ secretion blockage translates into a 95–99% effective blockade of acid release for up to 36 h. Onset of acid inhibition is delayed, requiring several serial dosings to accumulate in

the secretory region of the parietal cell. The delay is explained in two parts: since PPIs only inhibit active proton pumps and, at any given time, not all pumps within the parietal cells are active, inhibition of any given cell's acid production is incomplete; secondly, there is a continual synthesis of new proton pumps; thus, it will take several doses to attain steady-state acid suppression given this dynamic scenario of the proton pump. The PPIs therefore take up to 3–5 days to achieve maximum acid inhibition. Similarly, in order for acid secretion to be restored when acid suppression is stopped, there is a delay during which new H+/K+ ATPase must be formed, which takes up to 96 h in healthy individuals upon cessation of PPIs [22].

At this time, there are at least six different formulations of PPIs available for clinical use, many of which are also found over the counter. These different formulations of the PPIs generally have very similar efficacy with regard to pharmacodynamic profiles, relief of symptoms, healing of esophagitis, prevention of complications, and safety. The formulations differ according to their pharmacokinetic chemical stability, cysteine moieties of the proton pump that they specifically bind, activation under different pH conditions, bioavailability, and metabolism, which may translate into a slight advantage for one PPI versus others in certain situations. All PPIs are prodrugs and are similarly protected against acid degradation with encapsulation or in tablet form. After oral administration of PPIs, peak plasma concentrations are achieved within 2–4 h. Pharmacokinetic parameters of time to maximum plasma concentration and half-life are similar between PPIs (Table 12.1). Because there is no direct toxicity from PPIs, there is minimal risk of PPI administration, including in patients with liver or renal failure.

Metabolism of PPIs

All PPIs undergo significant hepatic metabolism by the cytochrome P450 (CYP450) system; however, differences in liver metabolism can produce inter-patient variability in acid suppression and in clinical efficacy. Notable genetic polymorphisms exist for the cytochrome P450 isoenzyme CYP2C19 involved in PPI metabolism. The CYP2C19 gene is mutated in approximately 3% of Caucasians and 15% of East Asians and has been shown to substantially influence the pharmacodynamics, pharmacokinetics, and clinical outcomes of response to PPIs. The polymorphisms clinically result in poorer clearance of the PPI, increasing plasma levels of omeprazole, lansoprazole, and pantoprazole, but not those of rabeprazole [21, 25]. These polymorphisms explain slight differences in the side effect profile and in clinically significant pharmacokinetic drug interactions. Omeprazole has the highest risk for such drug interactions among PPIs, and rabeprazole appears to have the lowest risk. Clinicians may find that patients report better response or tolerance to one formulation over another which may be explained by the individual genetic polymorphisms of the CYP2C19. Genotype/phenotype polymorphism determinations are used in research settings, but genotype testing for CYP2C19 has not been available for wide clinical use. Thus, the PPI that a patient ultimately ends up taking is often dependent

Table 12.1 Pharmacokinetic properties of proton pump inhibitors

Parameter	Omeprazole	Esomeprazole	Lansoprazole	Pantoprazole	Rabeprazole
t_{max} (h)	1–6	1–3.5	1.2–2.1	2–4	3–5
F (%)	25–40 (↑ upon multiple dosing	50 (acute dosing) 70–80 (chronic dosing)	80–90	77	52
Linear pharmacokinetics	No	No	Yes	Yes	Yes
fu (%)	0.05	0.05	0.03	0.02	0.04
V (l/kg)	0.13–0.35	0.22–0.26	0.4	0.15	–
$t_{1/2}$ (h)	0.5–1.2	0.8–1.3	0.9–2.1	0.8–2.0	0.6–1.4
CL (ml/min)	400–620	330 (acute) 160–250 (chronic)	400–650	90–225	–
CL/F (ml/min)	320		310	125	600
f_e (%)	Negligible	Negligible	Negligible	Negligible	Negligible
Effect of age	CL↓, $t_{1/2}$ (↑), F↑	CL↔, $t_{1/2}$ ↔	CL↓, $t_{1/2}$ ↑	CL↔, $t_{1/2}$ ↔	CL↓, $t_{1/2}$ (↑)
Renal insufficiency	CL↔, $t_{1/2}$ (↔), F↔	–	CL↓↔, $t_{1/2}$ ↑ (↔)	CL↔, $t_{1/2}$ ↔	CL(↑), $t_{1/2}$ ↔
Hepatic dysfunction	CL↓, $t_{1/2}$ ↑, F↑	CL↓, $t_{1/2}$ ↑	CL↓, $t_{1/2}$ ↑	CL↓, $t_{1/2}$ ↑, F↔	CL↓, $t_{1/2}$ ↑

t_{max} time to maximal plasma concentration, F oral bioavailability, fu fraction of drug unbound in plasma, V apparent volume of distribution, $t_{1/2}$ elimination half-life, *CL* systemic clearance, *CL/F* apparent oral clearance, f_e fraction excreted in unchanged form into urine, ↑ increase, ↓ decrease, ↔ no significant change

Arrows in parentheses effects are equivocal [23, 24]

upon the patient's medication coverage plan, prescriber bias, or the results of successive trials of different PPIs, rather than any notable difference in clinical efficacy of response that could be predicted by genetic testing.

PPI Formulations

Omeprazole was the first PPI available on the US market and introduced in 1989. The absorption of omeprazole occurs within 1–6 h in the small intestine. The systemic bioavailability is about 60% once steady state is reached. Omeprazole is extensively metabolized by CYP2C19; omeprazole therefore has potential for inhibiting elimination of several drugs that depend on CYP2C19 metabolism. Similarly, inhibitors of CYP2C19 such as fluconazole can decrease metabolism of omeprazole. The bioavailability is impaired by the presence of food, and therefore it is recommended that omeprazole be taken on an empty stomach and at least 30 min prior to eating. A standard starting dosage is 20 mg prior to the morning meal. Studies have

revealed significant endoscopic healing of reflux esophagitis with PPIs. Grade I esophagitis healed in 90% and 100% for 8 and 12 weeks with 40 mg per day. Higher grade esophagitis of grade II or III correlated to slightly lower healing of esophagitis with 85% and 91%, respectively, at 8 and 12 weeks [26]. More severe esophagitis or breakthrough symptoms of GERD will generally require higher dosages (20 mg b.i.d.), which have also been correlated to further symptom relief in refractory patients. The optimal dosing of twice per day appears to be more effective than a single daily dose of 40 mg [27].

Lansoprazole was the second PPI available on the US market. A starting dosage of 30 mg once prior to the morning meal is standard. Peak plasma concentration is reached slightly earlier than with omeprazole. Similar to omeprazole, acid suppression is dose-dependent and increases with repeated administration. Lansoprazole was shown to have improved symptom control and healing rates as compared to omeprazole at 20 mg, but these were equivalent to omeprazole at 40 mg [28].

Pantoprazole is similar to the other PPIs mentioned above; however, it is less acid labile, which makes it more readily placed into a solubilized i.v. formulation. The standard starting dosage of oral pantoprazole is 40 mg taken prior to the morning meal, and it may be increased to twice-daily dosing.

Rabeprazole is similar to the other PPIs mentioned. However, it is less susceptible to the influences of genetic polymorphisms of CYP2C19. The CYP450-mediated pathways are secondary, and thus, rabeprazole has a lower potential for drug interactions involving the CYP450 system. It would not have a significant effect on theophylline, phenytoin, warfarin, or diazepam levels (as would omeprazole). Rabeprazole is dosed at 30 mg orally taken prior to meals. Similar to other PPIs, optimal higher dosing is suggested at twice per day.

Esomeprazole is the S-isomer of omeprazole and a racemic compound containing two stereoisomers that are mirror images of each other. Like omeprazole, the bioavailability of esomeprazole increases with repeat dosing. Similar to omeprazole, there is extensive metabolism by the CYP2C19 enzyme, but it is metabolized more slowly in comparison with omeprazole. Several studies have shown increased acid suppression with esomeprazole compared to equal doses of omeprazole [29]. The starting dosage of esomeprazole is 40 mg per day and may be doubled to twice per day for refractory symptoms or nonhealing esophagitis.

Adverse Events

In general, PPIs are considered to have one of the best safety profiles for such widely used medications. Nonspecific side effects are unusual, and serious adverse events are extremely rare. Much attention has recently been given to the risk of bone fractures, *Clostridium difficile* infection (CDI), and pneumonia for patients on long-term PPI therapy.

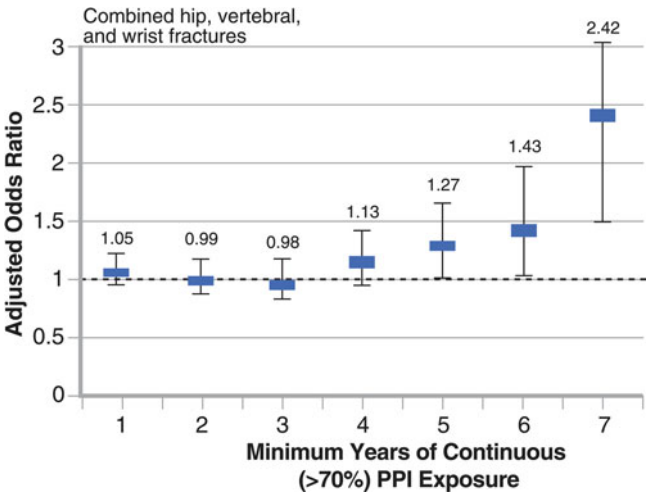

Fig. 12.3 Proton pump inhibitors and the risk of osteoporosis-related fractures increased with chronic PPI use [34]

PPI and Risk of Osteoporosis-Related Fractures

Epidemiologic studies suggest a possible increased risk of bone fractures with the use of proton pump inhibitors for 1 year or longer when used at higher doses [30]. PPIs are thought to interfere with calcium absorption through hypochlorhydria in addition to possible inhibition of osteoclastic vacuolar proton pumps. The acid environment of the stomach and proximal duodenum is necessary to release calcium from food sources; therefore, with near-complete acid suppression seen with PPI therapy, it is suggested that this can lead to calcium malabsorption, create a negative calcium balance, and lead to a potential for bone loss.

Observational studies have shown considerable variability in the association of PPI therapy with osteoporotic fractures. Thus, a consensus is lacking with regard to the importance of this putative risk. Studies investigating the relationship with chronic PPI use and fractures have found an inconsistent relationship to fractures and the location of such fractures. Gray et al. [31] found that PPIs were not associated with hip fractures, but PPI therapy was modestly associated with clinical spine, forearm, wrist, and total fractures. A meta-analysis that evaluated fracture risk for PPI versus H2-RA use found a moderate increase in risk for hip, spine, and total site fracture with PPI use, but no association was found with H2-RA therapy [32]. Targownik et al. [33] published a large, population-based study from Canada studying 15,792 cases of osteoporosis-related fractures with 47,289 controls (obtained from administrative claims data over an 8-year period) and found no overall risk of an osteoporosis-related fracture and duration of PPI use of 6 years or less. However, at 7 years or more, there appeared to be increased risk of osteoporosis-related factures. They also found an increased risk of hip fracture after 5 or more years of PPI exposure [33, 34] (Fig. 12.3). It remains unclear as to whether any calcium malabsorption

attributed to PPI therapy is severe enough to influence bone remodeling. Long-term studies are lacking as to whether there is compromise of the bony skeleton, effects on calcium balance, or increased risk for fracture.

Trends in the literature have tended to find that the higher the dose of PPI that attains effective acid suppression and the longer the duration of treatment, patients were more likely to have associated fractures. However, the increased risk estimates with PPIs overall were small, and clinical significance is still limited. Thus, the relationship between PPI and fracture risk requires further proof. PPIs sold over the counter no longer warrant an FDA label warning about osteoporosis and fracture because the risk is quite low with low-dose, short-term use. However, prescription versions of the PPIs continue to have the warning label. Physicians and their patients must weigh the risks and benefits of long-term PPI therapy and its potential side effects against the quality of life issues associated with recurrent GERD symptoms or complications arising from chronic GERD [35].

Clostridium difficile Infection and PPI Use

Several epidemiologic studies have shown that the use of PPIs has been associated with an increased risk of *C. difficile* infection (CDI) [36]. One of the largest studies to date from Linsky et al. [37] that examined the US military veteran patient population suggested that recurrence of CDI was associated with concurrent PPI use. To date, such pharmaco-epidemiologic studies have not demonstrated a cause-and-effect connection. A recent multicenter, case–control study of community-associated CDI found no risk associated with PPI use [38]. *C. difficile* is the most common infectious cause of colitis in hospitalized patients, and PPIs comprise one of the most ubiquitous classes of medications prescribed to inpatients. It had been hypothesized that by raising the gastric pH, PPIs may prevent gastric contents from killing *C. difficile* spores; however, this mechanism has also been refuted, as it is known that *C. difficile* spores are acid resistant, suggesting that if there is a correlation, it is more likely an indirect association. It is safe to say that the possible correlation between PPI use and nosocomial CDI remains controversial, and the primary risk factor for acquiring a CDI remains the use of broad-spectrum antibiotics.

In addition to the controversies of increased fracture risk and CDI, more common adverse effects include headache (up to 5.5%), diarrhea, abdominal pain, and decreased vitamin B12 levels. Long-term use has also been associated with hypomagnesemia. Acid suppression may be associated with an increased risk of community-acquired pneumonia through insufficient elimination of pathogenic organisms by gastric acid. Rare occurrences of serious toxic hepatitis and visual disturbances have also been reported.

Drug–Drug Interactions

PPIs may affect the absorption or bioactivity of other oral medications. Medications potentially effected would include aspirin, clopidogrel, didanosine, digoxin, furosemide, indomethacin, ketoconazole, nifedipine, and midazolam. Perhaps the most recent concern regarding PPI medication interaction has been the interaction with clopidogrel. A retrospective cohort study of PPIs and clopidogrel first identified that this combination is associated with a slight increased risk of myocardial infarction or death [39]. This interaction is thought to be related to the competitive inhibition of CYP2C19 metabolism of the clopidogrel from its prodrug form. The PPI inhibition of this enzyme therefore reduces the response to clopidogrel, hindering its antiplatelet effect. Most platelet aggregation studies reveal an attenuation of the CYP2C19 and that the PPI does not completely abolish the antiplatelet effects of clopidogrel. There appear to be some slight differences between the PPI formulations and in the drug interaction based on potency of the CYP2C19 inhibitor: rabeprazole and pantoprazole are less likely than omeprazole to inhibit CYP2C19, whereas lansoprazole appears to be the most potent and therefore should be avoided [40]. The pharmacokinetics of PPIs is such that the competitive inhibition of the CYP2C19 is of short duration and therefore less of an issue after 2 h of dosing [41]. Although the PPIs are less likely to be at issue when taken >2 h after the clopidogrel, it has not been established whether simply an adjusted schedule of dosing is an adequate strategy to address this concern. In a recent study out of Japan, Aihara et al. [42] found no significant association between PPI and cardiovascular events following coronary artery stenting in patients on both PPI and clopidogrel, whereas the study did reveal a significant reduction in rate of GI bleeding for patients receiving PPI. Evidence is building that the concerns surrounding the use of PPIs in cardiac patients on clopidogrel is less clear and likely less important, as is further suggested in a recent systematic review of 19 such studies [43]. The physician and patient must weigh the clinical necessity of using the drugs together from both the gastrointestinal standpoint as well as from the anticoagulation perspective. Regarding GERD, treatment with H2-RAs or antacid can be used in place of PPI to control symptoms. The use of PPIs in the post-stent cardiac population should be most dependent upon the risk of these patients developing peptic ulcers and the likelihood that PPI therapy will reduce the risk of gastrointestinal bleeding.

Prokinetic Medications

Prokinetic medications include several different families of drugs that function to increase esophageal, gastric, and intestinal motility. Although prokinetic agents have been shown to improve symptoms, there has not been reliable healing of esophagitis. The absence of convincing tissue healing and the potential for side effects associated with prokinetic drugs have limited the use of these medications where acid-suppressing medications have been readily available and effective as a single agent.

Cholinergic Prokinetic Agents

Bethanechol is a parasympathomimetic cholinergic medication structurally related to acetylcholine that selectively stimulates muscarinic receptors without any effect on nicotinic receptors. Bethanechol functionally increases LES pressure, enhances peristaltic contractions, and increases gastric emptying. The use of bethanechol in the treatment of reflux disease has been limited by its cholinergic side effect profile, which has included abdominal pain, blurred vision, and other cholinergic symptoms. A typical dosage of bethanechol for treatment of reflux is 25 mg four times per day. Bethanechol has been minimally used for reflux treatment as an off-label indication. The majority of studies were performed decades ago with the two most recent controlled trials from the 1980s reported conflicting data in resolving symptoms.

Dopaminergic Antagonist Prokinetic Agents

Metoclopramide is a dopamine antagonist, inhibiting dopamine receptors both at the CNS and the peripheral level. In the gut, metoclopramide also stimulates release of acetylcholine from intramural nerves. Functionally, metoclopramide enhances gastric emptying and gastroduodenal coordination, but it does not appear to affect esophageal peristalsis or enhance lower esophageal sphincter pressure. Metoclopramide has been used in the pediatric population more recently than in the adult. Its use has been limited by the side effect profile with anti-dopaminergic side effects occurring in up to 20% of patients, including extrapyramidal motor effects, lethargy, and tardive dyskinesia that may be nonreversible. Metoclopramide had a black box label placed on it by the FDA in 2009, and its use has and subsequently been limited. Metoclopramide is generally prescribed at a dosage of 10 mg four times per day, orally taken 30 min prior to eating a meal or bedtime.

Domperidone is another peripheral dopamine (D2) receptor antagonist that acts as an antiemetic and prokinetic agent. Domperidone has been shown to primarily enhance gastric and small bowel motility. The advantage of domperidone over metoclopramide is that it does not cross the blood–brain barrier and, therefore, does not have the neurologic side effect profile of metoclopramide. Domperidone has not been approved for use in the USA, though is purchased by some patients through foreign pharmacies. Dosing of domperidone is typically 10–20 mg orally taken 3–4 times per day. It has been more commonly used in pediatric reflux cases compared to the adult population.

Serotonin Receptor Prokinetic Agents

The serotonin 5-HT4 receptor pathway has been shown to have a significant role in GI tract motility and shows potential as a therapeutic target for gastrointestinal

symptoms related to motility disorders. Cisapride and tegaserod were both briefly on the US market but then removed due to rare cardiac dysrhythmias. At this time, there are no agents available on the US market. However, newer agents are under investigation.

Cisapride is a prokinetic agent that acts as a 5-HT4 receptor agonist and indirectly as a parasympathomimetic. Cisapride stimulates acetylcholine release by enteric nerves and may directly trigger neuromuscular activity of the GI tract smooth muscle such as enhanced gastric emptying, esophageal peristalsis, and increased lower esophageal sphincter tone. Cisapride was shown to provide symptomatic relief with comparable results to cimetidine 400 mg q.i.d. or to ranitidine 150 mg b.i.d. and superior to placebo [44]. Cisapride is prescribed at 10 or 20 mg b.i.d. Similar to aforementioned bethanechol and metoclopramide, Cisapride produces significant improvement in complaints of heartburn, regurgitation, and early satiety; however, healing of esophagitis is minimal. Cisapride does not have the same concerns of neurologic side effects, as did earlier prokinetics; however, it has been of limited use due to reports of the side effect of prolonged QT interval predisposing patients to cardiac rhythm disturbances. Cisapride was voluntarily removed from the US market in 2000.

Tegaserod is a 5-HT4 agonist and a 5-HT2B antagonist that was marketed for the treatment of irritable bowel syndrome and for constipation but used off label in the treatment of reflux disease. Tegaserod only had a brief availability in the US market, approved in 2002 and then removed in 2007 due to concerns over possible adverse cardiovascular effects.

Despite the removal of several prokinetics from the market, there is still an interest in developing 5-HT4 receptor medications for treatment of reflux disease and GI tract dysmotility. Research has suggested that more highly selective drug profiles are important with regard to the safety and potential cardiac arrhythmias. Prucalopride is a selective 5-HT4 receptor agonist with a high selective profile, and it has been shown to stimulate colonic mass movements, and it also shows promise for the esophagus. Mosapride is a selective 5-HT4 receptor antagonist with prokinetic effects on the small intestine, and it is undergoing investigation for reflux treatment.

GABA Receptor Prokinetic Agents

Baclofen is a gamma-aminobutyric acid (GABA) receptor-blocking agent that has been marketed to treat skeletal muscle spasms, rigidity, and some sensory pain disorders, and it is now being used off label in the treatment of reflux disease. Baclofen diminishes reflux through GABA receptor inhibition of transient lower esophageal sphincter relaxations (TLESRs). Studies have shown that it decreases TLESRs measured by manometry and reduces reflux symptoms [45]. Baclofen may also reduce the exposure to duodenogastric reflux. The use of baclofen has been somewhat limited by side effects, which have included drowsiness, weakness, dizziness, seizures,

confusion, sleep disruption, and constipation. Baclofen requires attentive dosage adjustment as well as avoidance of abrupt discontinuation of the drug, which can result in seizures, hallucinations, rebound spasticity, and rhabdomyolysis. Several derivatives of baclofen have been investigated for a possible use in reflux with the advantage of improved side effect profiles. Arbaclofen, an investigational prodrug of the active R-isomer of baclofen, is one such drug that is being investigated for reflux treatment [46]. Lesogaberan, a peripherally active GABA receptor agonist, has shown promise for use in reflux disease. A recent single-blinded, placebo-controlled, randomized trial comparing lesogaberan (0.8 mg/kg), baclofen (40 mg), and placebo found that compared with placebo, lesogaberan significantly reduced the number of TLESRs by 36%, significantly reduced the number of acid reflux episodes, and significantly increased lower esophageal sphincter (LES) pressure by 39%. The results were similar to the baclofen results [47].

Combination Therapy

When twice-daily dose of PPI therapy does not significantly improve patient symptoms, the diagnosis of acid reflux disease should be reconsidered. If further testing and consideration confirm unresolved reflux, then dual therapy is considered with the addition of acid-neutralizing agents or alginic acid. Many patients continue to use antacid therapy in addition to PPI, which is reasonable for the occasional breakthrough symptoms. Adding alginic acid to the postprandial regimen may be useful with persisting regurgitation or proximal reflux. Several studies have looked at PPI + H2-RA therapy for patients with breakthrough symptoms; however, additional studies have suggested that there is no lasting benefit from the addition of scheduled H2-RA therapy to a PPI regimen [15, 16]. Intermittent or "on-demand" addition of H2-RA to maintenance PPI therapy for breakthrough symptoms is not unreasonable for symptom relief. PPI therapy in combination with prokinetic agents has shown increased acid control of reflux symptoms [48]. However, as stated above, available and safe prokinetic medications are limited.

Maintenance Therapy

GERD and related reflux disorders are chronic recurring disorders, commonly requiring indefinite treatment with acid-suppressing medications. When designing a step-up reflux treatment strategy, adequately treating the esophagitis and resolving symptoms using the safest and simplest drugs are paramount. Similarly, once those treatment objectives have been reached, attempting to subsequently step down to less medication to maintain symptom control and prevent complications is warranted. Given concerns over long-term use, potential side effects, and cost, maintenance strategies with PPIs have been widely studied, including lowered dose and adjusted

dosing (daily, every other day, and weekends only). End points of symptom relief and maintenance of healed esophagitis have been the goal for pharmacologic management of GERD and reveal considerable inter-patient variability. A recent study found that a majority of GERD patients can be switched from daily to on-demand treatment without impairing symptom control or quality of life [49]. The physician and patient must have an understanding regarding the implication of chronic reflux disease and risk for complications weighed against the risk of long-term use of these medications, albeit only a small potential for significant side effects exists.

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Chapter 13
Surgical and Endoscopic Approaches to GERD

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Keywords Endoscopic • Surgical approaches • Gastroesophageal reflux disease (GERD) • Diagnosing GERD • Selecting the best therapy • Surgical management of GERD

Introduction

It is estimated that gastroesophageal reflux (GER) symptoms are seen in up to 40% of adults in the USA. Gastroesophageal reflux disease (GERD) is defined as symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus [1]. Although the majority of patients with GERD will present with typical symptoms (heartburn/regurgitation), about 30% of patients present with airway manifestations [2]. The relationship between lung injury and GERD has been well established as has the high prevalence of GERD in patients with end-stage lung disease [3–5]. In 1976, Pellegrini et al. provided insight into the relationship between GERD and aspiration leading to pulmonary symptoms as well as into the results of surgical antireflux procedures on those patients. Among a group of 100 patients with GERD, they defined a small group of "aspirators" and found that those patients had respiratory symptoms but little or no heartburn and that 78% had abnormal esophageal manometry and delayed esophageal clearance [6]. Larrain et al. conducted one of the first randomized trials comparing medical and surgical treatments in

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patients presenting with pulmonary symptoms and GERD. They randomized 90 patients to placebo, cimetidine, and antireflux surgery and found that patients in the surgical and medical groups did significantly better in the long-term than those in the placebo group, thus supporting the notion that GERD may lead to pulmonary symptoms and that the control of GERD can ameliorate these symptoms [7]. Another finding of this study was that although symptom scores improved in both the surgical group and the cimetidine group, only three patients in the surgical group were found to have pH-proven reflux at 6 months compared to 24 patients in the cimetidine group. More importantly, at the end of the study when patients were taken off cimetidine, they showed a relapse of symptoms, and at 77 months only 5% of the placebo group remained free of respiratory symptoms compared to 50% of the surgical group.

Diagnosing GERD and Selecting the Best Therapy

In patients who present with typical history and symptoms of GERD, an extensive work-up is usually not necessary. Initial medical treatment can be started empirically and consists of lifestyle modifications (i.e., avoidance of trigger foods, weight loss, and pharmacologic therapy using proton pump inhibitors with or without addition of histamine receptor antagonists). As is true with patients that present with typical symptoms of GERD, symptom improvement after initiation of medical therapy can help select those patients that will benefit the most from surgical therapy [8–10]. In those patients who continue to have symptoms despite medical therapy or who are contemplating antireflux surgery, additional testing that includes esophagogastroduodenoscopy (EGD), an upper gastrointestinal contrast study, ambulatory pH monitoring with or/without impedance monitoring, and esophageal manometry should be performed to confirm and assess the degree of symptoms, define gastroesophageal anatomy, and assess esophageal function (motility and acid exposure).

In the subset of patients who have airway symptoms, it is imperative that not only should a diagnosis of GERD be established including precise measurement of acid exposure, but a relationship between GERD and airway symptoms/disease should also be established. Although the latter is difficult to assess accurately, most of our knowledge on the effectiveness of operations to improve airway manifestations of reflux suggests that only patients in whom GERD is directly causing airway symptoms will benefit. Moreover, because GERD and pulmonary symptoms are highly prevalent in the general population and may be unrelated in a given patient, establishing a definite relationship presents a major challenge to the clinician. Detection of the presence of pharyngeal acid reflux (i.e., the proximal extension of refluxate into the esophagus) in patients who have abnormal distal acid exposure is one of the key functional studies that have helped identify patients with airway symptoms caused by reflux [11]. Indeed, Kaufman et al. [10] showed that laparoscopic antireflux

surgery (LARS) can provide an effective and durable barrier to reflux and improve associated respiratory tract symptoms in up to 70% of patients if pharyngeal reflux exists. Similarly, Patti et al. [12] noted that resolution of respiratory symptoms following Nissen fundoplication was best when a temporal correlation was found between GERD and respiratory symptoms. Eighty-three percent (19 of 23) of patients found to have a temporal relationship between reflux episodes as determined by pH monitoring and respiratory symptoms had resolution of cough following LARS versus 57% (8 of 14) when respiratory symptoms and reflux episodes were not correlated. Allen and Anvari [13] found that 21% of patients with chronic cough had GERD. They noted that 83% of patients with GERD and chronic cough treated with LARS had improvement in cough at 6 months following surgery, and 71% had sustained improvement at 5 years.

Indications for Surgical Management of GERD

Indications for surgical therapy are based on the determination of an abnormal acid exposure to the distal esophagus. Candidates for an operative procedure include patients with symptoms refractory to medical therapy or patients who are intolerant of pharmacologic acid-suppression therapy; patients who have complications of GERD such as esophageal strictures, Barrett's esophagus, esophageal bleeding, and/or erosive esophagitis; and patients with extraesophageal manifestations of GERD such as aspiration, recurrent pneumonias, chronic bronchitis, and laryngitis in whom additional studies strongly suggest aspiration of refluxate into the airway [10–14]. Typical symptoms of GERD (heartburn/regurgitation) disappear in over 90% of patients following an antireflux operation. By contrast, airway symptoms (cough/wheezing) improve in only 69–74% and disappear in 41–42% [10]. This lower response rate suggests that in some patients, GERD may not have been the causative agent in airway disease and/or that the airway disease started by GERD may have acquired a life of its own or developed into a stage that is too late to be affected by stopping aspiration. On the other hand, it appears that operative intervention is more effective than medical therapy in patients with airway manifestations. For example, asthmatic patients who underwent antireflux surgery (ARS) were noted to have an immediate and sustained reduction in acute nocturnal exacerbations of wheezing, coughing, and dyspnea when compared to those on medical therapy alone. Seventy-five percent of patients who underwent ARS also showed improvement or resolution of asthma compared to only 9% of the patients in the medical group [15]. The reason for the greater effectiveness of an operation may be related to the fact that even minute amounts of aspiratated secretions are capable of causing considerable damage to the larynx and the respiratory epithelia of the trachea and bronchi. Medical therapy is less effective than a mechanical correction of the gastric cardia to completely abolish aspiration. For example, lung transplant patients treated with proton pump inhibitors alone may still have occult aspiration.

Indeed, Blondeau and colleagues showed that lung transplant patients had increased nonacid reflux with elevated levels of pepsin and bile acid in bronchoalveolar lavage fluid despite good acid control. This suggests that occult aspiration may still be occurring despite good medical control of acid reflux [16].

Contraindications to Surgical Management of GERD

The main contraindication to an antireflux procedure is the inability to safely tolerate an operative intervention under general anesthesia (required because of the need for complete relaxation of the abdominal wall). Previous hiatal or esophageal surgery increases the technical difficulties associated with a reoperation but do not represent a formal contraindication. Knowledge of laparoscopic and open abdominal approaches provides alternatives for those with prior operations or complications. Patients with high-grade dysplasia and/or adenocarcinoma of the esophagus or GE (gastrointestinal) junction should not undergo ARS, as the operation will not be effective to control their disease and the disease itself may require resection of the esophagus with reconstruction using stomach, which would be compromised to some extent if an antireflux operation was done. A relative contraindication may also be morbid obesity. Although the data is limited, laparoscopic gastric bypass can be performed with comparable morbidity and mortality to LARS but may be of more benefit in the morbidly obese population, as it carries the benefit of weight loss [17–20]. In the only study comparing LARS to laparoscopic gastric bypass in morbidly obese patients, both groups were found to have normalization of DeMeester score and overall improvement in symptom score [21]. The authors concluded that both approaches are effective, but the added benefit of weight loss after laparoscopic gastric bypass makes it the procedure of choice in morbidly obese patients with GERD.

Surgical Treatment

The open Nissen fundoplication for the treatment of GERD was first described by Rudolph Nissen in the 1950s [22]. This operation, which originally required a midline incision, was the treatment of choice in patients with refractory GERD until the early 1990s. With the advent of minimally invasive surgical technique, the Nissen fundoplication was adapted to the laparoscopic approach, and the frequency with which it was used increased substantially [23]. Multiple studies have found that LARS is more effective at controlling reflux symptoms than medical therapy [24, 25]. Anvari et al. randomized 93 patients to proton pump inhibitor (PPI) therapy and LARS and found that after 3 years the surgery group had more heartburn-free days and lower symptom scores than the medical group [24]. Similarly in an another

randomized trial that compared the results of PPI therapy versus LARS in 217 patients, Mahon et al**.** [25] showed that LARS-treated patients had significantly less distal esophageal acid exposure and significantly more improvement of gastrointestinal and general well-being scores than PPI patients. Although multiple LARS procedures exist (full and partial fundoplication, Belsey Mark IV, Hill gastropexy, gastric bypass), the laparoscopic Nissen fundoplication is the most commonly used procedure in the world. This is in large part due to the long-term efficacy and low morbidity of this approach [8–10, 12–15, 26, 27]. In a review of over 10,000 patients, laparoscopic antireflux procedures showed a low morbidity profile (6%), low mortality (0.08%), low reoperation rate (4%), and good patient satisfaction (Visick score for patient satisfaction, 91%) [26]. Multiple randomized studies have also compared the outcomes of LARS to open ARS and found no difference in long-term GERD control between the two approaches. In a recent meta-analysis of 12 randomized studies, the laparoscopic approach was found to have longer operative times; however, LARS was associated with shorter hospital stay, faster return to productive activity, and reduced risk of complications, in particular wound infection and ventral hernias, when compared to an open approach, making LARS the more attractive approach [27].

Laparoscopic Antireflux Surgery (LARS) in Patients with End-Stage Lung Disease and Lung Transplant Recipients

The Relationship Between GERD and End-Stage Lung Disease

Interstitial lung disease (ILD) is the name given to a collection of diffuse parenchymal lung diseases of which idiopathic pulmonary fibrosis (IPF) is the most common. IPF is a progressive type of ILD of unknown etiology that has no known treatment that can prevent its progression [28]. IPF has a prevalence 14–42 cases per 100,000 people and primarily affects adults older than 50 years [29]. It is characterized by progressive pulmonary fibrosis, exertional dyspnea, and a progressive decline in pulmonary function of approximately 10% per year. To make the diagnosis of IPF, all other forms of ILD must be ruled out. The diagnosis can then be made radiographically with high-resolution computed tomography (HRCT) showing usual interstitial pneumonitis (UIP), but if a confident diagnosis cannot be made via HRCT, lung biopsy should be performed if not contraindicated by safety concerns.

The incidence of GER in patients with IPF disease is reported to be as high as 90% in some series [3, 4]. The possible link between GERD and IPF and the notion that aspiration may play a role in the decline of lung function are not new. In the 1970s Mays et al. compared gastrointestinal findings in a series of patients diagnosed with IPF to a control group and found a higher incidence of hiatal hernia and GER in patients with IPF [30]. Additionally, Pellegrini et al. [6] also noted a correlation between esophageal dysfunction and aspiration. More recently, Tobin et al. [3] used

ambulatory esophageal pH monitoring in 17 patients with biopsy-proven IPF and eight patients with ILD without IPF and found that 94% of the IPF patients had abnormal proximal and/or distal esophageal acid exposure compared to only 50% of control patients (patients who had non-IPF forms of ILD). Interestingly, only 25% of IPF patients with abnormal esophageal acid exposure had typical GERD symptoms [3]. Raghu et al. [4] found similar results when he studied 65 patients with IPF and 133 patients with asthma plus GERD symptoms with ambulatory esophageal pH monitoring: 87% of the IPF patients had abnormal esophageal acid exposure compared to 68% of patients with asthma, and 53% of patients with abnormal esophageal acid exposure did not have classic GERD symptoms. Finally, 63% of IPF patients on PPI therapy in this study had abnormal esophageal acid exposure, suggesting that GER in patients with IPF was not adequately controlled with PPI therapy alone.

Effective pharmacologic treatment for IPF has yet to be discovered. Some experts have suggested that the control of GER may lead to stabilization of lung function or prevent progression, which may provide a bridge to lung transplantation if disease progression is lessened. In a case series of four patients who were treated solely with acid-suppression medication, Raghu et al. noted an initial stabilization or improvement in pulmonary function in all four patients followed by worsening upon cessation of acid-suppression medication [31]. More recently, Lee et al. retrospectively analyzed a multicenter cohort of 204 patients diagnosed with IPF and found that the use of GER medication was associated with a lower HRCT fibrosis score and was also an independent predictor of longer survival time [32]. ARS was also found to be beneficial in IPF patients in this study. However, only 5% of patient in the cohort underwent ARS, so these results are difficult to interpret.

Although acid suppression has shown promise as a possible treatment in patients with IPF, it is not a definitive cure as it does not eliminate the risk of aspiration. Track et al. [33] showed that up to 75% of patients treated with PPI therapy still had persistent reflux of gastric as well as duodenogastric contents. Others have shown that aspiration may play a significant role in the development of bronchiolitis obliterans syndrome (BOS) and thus rejection of lung allografts in lung transplant recipients. Fisichella et al. [34] detected larger concentrations of pepsin in the bronchoalveolar lavage (BAL) fluid of lung transplant recipients with GERD when compared to lung transplant recipients without GERD or those with GERD who had undergone LARS. Pepsin was undetectable in healthy controls, thus showing that GER, and more specifically, aspiration, may be associated with the development of BOS. D'Ovidio et al. [35] found a higher concentration of bile acids in BAL fluid samples in patients with BOS, further supporting the notion that aspiration may play a significant role in BOS. Similarly, Vos et al. [36] showed a high correlation between bile acid aspiration, airway colonization of *Pseudomonas aeruginosa*, and elevation of inflammatory markers in lung transplant recipients with GERD.

LARS for Prevention of GER in End-Stage Lung Disease and Lung Transplant Recipients

The previously mentioned studies support the notion that aspiration may be a contributing factor to both the deterioration of lung function in patients with IPF and in the progression of BOS in patients after lung transplantation. Because LARS decreases aspiration, it becomes a promising treatment option for GER in patients with end-stage lung disease and in lung transplant recipients. Linden et al. evaluated 14 patients with a diagnosis of IPF and GERD on the lung transplant list who underwent LARS and found that LARS was safe in IPF patients prior to lung transplantation. They also found that IPF patients with GERD that underwent LARS had stabilization of oxygen requirements when compared to IPF patients on the lung transplant list who did not undergo LARS [37]. Similarly, Gasper et al. [38] performed LARS in 15 patients prior to lung transplant and had no 30-day mortality and only one postoperative complication. Hoppo et al. [39] performed LARS on 19 patients prior to lung transplant with little reported morbidity and no mortality. Eighty-five percent of patients showed stabilization of FEV_1. However, one patient in the LARS group needed emergent lung transplantation following LARS, which shows the importance of preoperative risk stratification.

Lung transplantation is an effective treatment for end-stage lung disease, but long-term survival after transplant remains significantly lower than that of individuals who undergo transplant of other solid organs such as kidney or liver. The reduced longevity of lung allografts has been attributed to the development of (BOS), which is defined as a persistent drop of forced expiratory volume in 1 s (FEV_1) of 20% or greater from baseline after the initial recovery from lung transplantation. The etiology of BOS is thought to be both an immune- and a non-immune-mediated insult. GERD has been found to be quite prevalent in recipients following lung transplantation, and it may play a crucial role in the development of allograft rejection and BOS [40].

Multiple studies have found LARS to be safe in the lung transplant population [38–42]. Davis studied 128 patients who underwent lung transplantation and found that 73% of patients had abnormal pH studies. In those patients who underwent laparoscopic fundoplication, there was no in-hospital or 30-day mortality, and 61% of patients with BOS who underwent laparoscopic fundoplication were noted to have improvement in BOS scores [40]. Gasper et al. examined the outcomes of 35 patients that underwent lung transplant and LARS either prior to ($n=15$) or following lung transplant ($n=20$) and found that LARS could be done with low morbidity and short hospital stays in both groups of patients [38]. Similarly, in a more recent study of 43 patients with end-stage lung disease who underwent LARS either before or after lung transplant, Hoppo et al. noted a significant improvement in FEV_1 in 91% of patients after LARS and a significant decrease in episodes of acute rejection and pneumonia [39]. Cantu et al. [42] examined lung transplant patients with GERD who had early (<90 days posttransplant) or late (>90 days posttransplant) fundoplication and found 100% actuarial survival at 3 years in patients who underwent

early fundoplication compared to 92% in patients with no intervention. Freedom from BOS was also significantly higher in early fundoplication patients (100%) compared to patients with no GER (62%), no fundoplication (60%), and late fundoplication (47%).

Recommendations for LARS in Patients with End-Stage Lung Disease or Lung Transplant Recipients with Significant GER

Randomized controlled trials analyzing the effects of LARS in patients with IPF and GERD before and after lung transplantation are lacking. We believe that there are enough data to allow us to cautiously recommend that all IPF patients with a diagnosis of GERD who are well enough to undergo laparoscopic surgery should be offered LARS at the time of diagnosis. This recommendation is supported by considerable evidence linking GERD to airway disease in both IPF and lung transplant recipients. Patients with IPF have a high incidence of GERD both before and following lung transplantation, and the timing of LARS may have an impact on allograft survival in patients with GERD. It is imperative that these cases be performed at centers where a multidisciplinary team (that includes a pulmonologist, esophageal surgeons, transplant surgeons, and anesthesiologist) is adequately familiar with caring for these high-risk patients.

At our institution, patients with end-stage lung disease are evaluated extensively by transplant pulmonology prior to being referred for evaluation for LARS. Once referred for LARS evaluation, all patients undergo esophageal manometry, ambulatory esophageal pH testing (off PPI therapy), upper gastrointestinal series, and esophagogastroduodenoscopy (EGD). Patients who are confirmed to have GERD by esophageal pH testing and that are well enough to undergo a laparoscopic operation are offered LARS.

Partial Versus Total Fundoplication

Both total (360 degrees) and partial fundoplication (less than 360 degrees) can provide long-term control of GERD symptoms. Although total fundoplication (Nissen) is the most common antireflux operation for control of gastroesophageal reflux, partial fundoplication (Toupet or posterior fundoplication and Dor or anterior fundoplication) was developed in an effort to minimize postoperative sequelae such as gas bloat, inability to belch, or dysphagia. Some also advocate that a partial fundoplication should be performed in all patients with ineffective esophageal motility. We found, however, that a total fundoplication can be performed safely in patients with ineffective esophageal motility without increased dysphagia complications. Oleynikov et al. [43] analyzed pre- and postoperative data of patients with distal esophageal

amplitude greater than 40% and who underwent fundoplication (13 partial and 34 total fundoplications) and found that in patients who underwent total fundoplication, none developed new onset dysphagia or required reoperation.

Numerous randomized trials have compared laparoscopic total to partial fundoplications with mixed results. Fibbe et al. performed the first prospective randomized trial comparing laparoscopic total fundoplication and partial fundoplication (posterior 270°). Two hundred patients (with and without esophageal dysmotility) were randomized to total or partial fundoplication [44]. The partial fundoplication group was noted to be equivalent in GER control compared to the total fundoplication group. However, the total fundoplication group was noted to have more dysphagia. Similar to the study by Oleynikov et al., dysphagia did not correlate with the presence of esophageal dysmotility preoperatively. These findings were reconfirmed at 2-year follow-up as well [45]. Chrysos et al. found that patients with impaired esophageal peristalsis that underwent laparoscopic total or partial (posterior 270°) fundoplication had similar dysphagia profiles at 1 year (14% vs. 16%, respectively) [46]. In a study comparing laparoscopic full fundoplication versus (anterior 180°) partial fundoplication, Watson and colleagues showed that after 6 months, patients who underwent the anterior partial fundoplication had similar rates of dysphagia as patients who underwent laparoscopic total fundoplication (14% vs. 22%) and a higher rate of heartburn (19% vs. 4%) [47]. Baigrie et al. showed in a randomized double-blind study that patients with anterior fundoplication had a higher rate of recurrent reflux and similar dysphagia score when compared to total fundoplication [48]. Most recently, a meta-analysis of 991 patients comparing total fundoplication with partial fundoplication suggested that total and partial fundoplications are equivalent in terms of GERD control [49]. Partial fundoplication was found to have a lower incidence of reoperations, bloating, and dysphagia as compared to total fundoplication. However, as stated by the authors, the results must be interpreted cautiously due to the heterogeneity of the studies.

Laparoscopic total fundoplication in experienced hands can lead to better GERD control when compared to partial fundoplication. Although laparoscopic total fundoplication may be associated with a higher rate of dysphagia, the dysphagia does not seem to be correlated with preoperative esophageal dysmotility. The rate of bloating and reoperation can also be higher in patients who undergo laparoscopic total fundoplication, but these findings may be related to technique. We recommend that the antireflux operation should be dictated by the surgeon's experience and balanced by the risk of recurrent GERD and dysphagia.

Operative Technique

We perform laparoscopic Nissen fundoplication in the majority of patients. A partial fundoplication is reserved for patients with severe esophageal dysmotility (i.e., complete aperistalsis). Preoperatively, the patient is made NPO at midnight prior to the operations. Upon arrival to the hospital on the day of the operation, the patient is given chemical deep venous thrombosis prophylaxis, and prior to the incision, a first-generation cephalosporin is given as antibiotic prophylaxis.

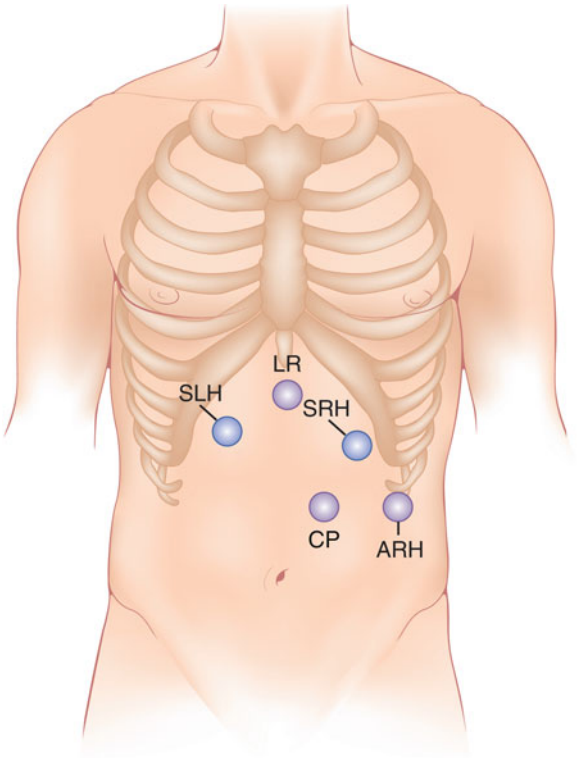

Fig. 13.1 Standard port placement of Nissen fundoplication

In the operating room, the patient is placed in a modified lithotomy position with a beanbag allowing steep reverse Trendelenburg position. We begin with the left upper quadrant port, placed just lateral to the midclavicular line at the costal margin. Pneumoperitoneum is obtained using Veress needle followed by a placement of a 10-mm optical trocar. The 10-mm camera port is positioned at 10–12 cm from the costal margin in a line that is 2–3 cm to the left of the umbilicus. Two additional 5 mm ports are then placed as shown in Fig. 13.1. Finally, a Nathanson liver retractor is placed through a stab wound just to the left of midline high in the epigastrium. This can be substituted with a paddle retractor if the left lobe of the liver is large.

We begin by first dividing the left phrenogastric ligament to expose the posterior left crus. This facilitates division of the superior-most short gastric vessels and releases the spleen. We mobilize the gastric fundus, dividing the proximal short gastric vessels and posterior attachments of the proximal stomach to minimize tension on the subsequent fundoplication. The gastrohepatic ligament and anterior phrenoesophageal ligament are then divided. After both crura and the fundus have been completely dissected, we then approach the phrenoesophageal membrane, which is divided circumferentially. Thus, we wait until everything has been prepared in the abdomen before we enter the mediastinum to decrease the amount of time that positive pressure is applied to the mediastinum and the potential increases in airway pressure that may occur. A “window” is then developed posterior to the

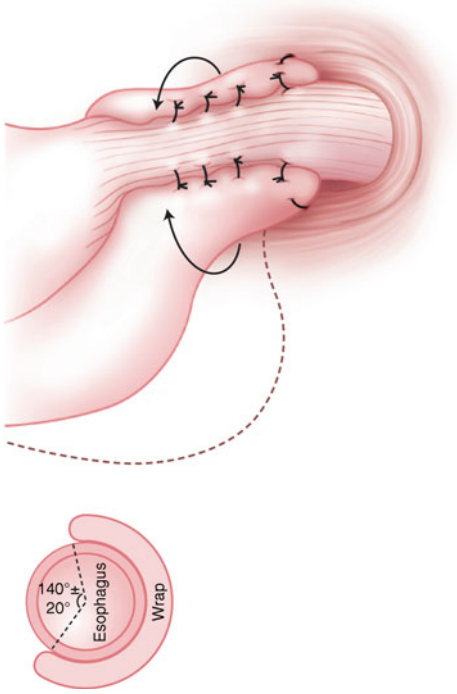

Fig. 13.2 Completed 2-cm floppy Nissen (total) fundoplication

gastroesophageal junction by dissecting the base of the right crus and proceeding under the esophagus to the previously exposed left crus**.**

A Penrose drain is then placed behind the esophagus and used to provide caudal and lateral retractions during the mediastinal dissection. Instead of the extensive hiatal and mediastinal esophageal dissection we normally perform, we try (especially in patients with IPF or other respiratory problems) to minimize mediastinal dissection and only mobilize the esophagus to position the gastroesophageal junction 3 cm below the hiatus. While our goal is always to perform a tension-free fundoplication, we believe it is extremely important to minimize damage to mediastinum and pleura and to keep the mediastinal portion of the operation short. We then close the hiatus posteriorly. A stay stitch is then placed at 3 cm below the GE junction and 2 cm away from the greater curvature on the posterior aspect of the stomach. This stitch will serve as a marker to help identify the exact place in the posterior wall of the fundus that should come behind the GE junction and reach the right side of the esophagus. A 3-cm fundoplication is then created over a 52F bougie by suturing the right (posterior aspect of the fundus) and the left (anterior aspect of the fundus) gastric flaps together *without* suturing the wrap to the esophagus to prevent inadvertent trapping or injury to the anterior vagus. As the fundoplication is completed, we "slide" it up on the esophagus and secure the top of the fundoplication to the lateral aspects of the esophagus and to the left and the right crus. Additional sutures are placed as necessary to the undersurface of the diaphragm to secure the position of the fundoplication and prevent it from sliding (Fig. 13.2). In patients with aperistalsis

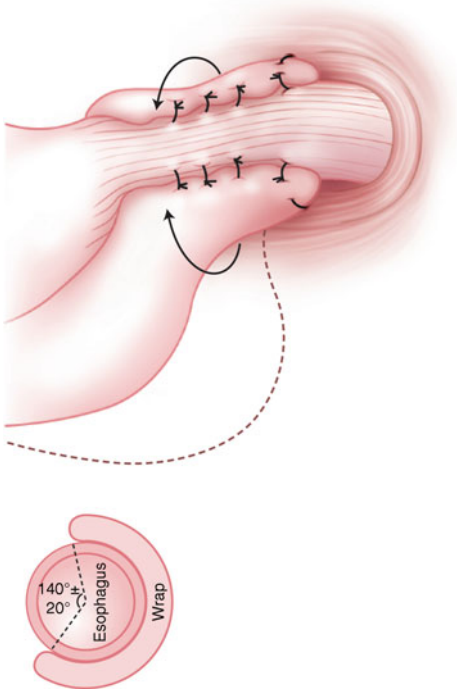

Fig. 13.3 Completed Toupet (partial) fundoplication

of the esophagus, we perform a partial posterior 270-degree fundoplication after closing the crura (Guarner modification of the Toupet procedure) (Fig. 13.3). Once the fundoplication is complete, we perform esophagogastroscopy, which allows us to examine the esophagus, discover accidental injuries, and thoroughly evaluate the fundoplication in terms of its shape, position, and tightness.

Patients generally start liquids the night of their procedure and are advanced to a soft diet on postoperative day 1. A trained nutritionist evaluates each patient postoperatively and provides dietary guidance. Average hospital stay is 1–2 days, and resumption of normal diet and activities occurs within 3–4 weeks. The patient is followed up at 1–3 weeks, and subsequent follow-up is tailored to patient needs, including continued nutritionist input. We perform manometry and 24-h pH studies on our patients 6 months after surgery to evaluate acid exposure, correlate symptoms with pH results, and assess outcomes.

Complications

Minor complications occur in approximately 3–10% of patients. One of the most common is pneumothorax, which can be caused by injury to the mediastinal pleura during esophageal mobilization. This problem rarely requires treatment because the carbon dioxide used for insufflation is readily absorbed and it is not associated with

lung injury. Entry into the pleural space is to be avoided by all possible means, especially in patients with IPF, COPD, or other respiratory problems. Therefore, special care must be taken at the time of mediastinal dissection to avoid such injury. Bleeding requiring reoperation occurs in 0.1% of operations, and vagal injury is a rare complication in patients who have not had a previous antireflux procedure, although the sequelae of such are relatively well tolerated [50]. Gastric or esophageal injuries are a risk in patients undergoing antireflux reoperations, but these complications are rarely reported in patients undergoing first time procedures. Liver injuries are caused by retractors and usually have no consequences. More serious injuries to the pancreas, splenic vessels, or other adjacent organs are very rare. Flum et al. evaluated the outcomes of 5,528 patients in the state of Washington and found the overall rate of splenectomy to be 1.4% and esophageal perforation to be 0.6% as complications of LARS, and both of these complications were found to decrease as surgeon experience increases [51].

One of the most feared complications in patients with IPF and/or other forms of advanced lung disease is the development of respiratory insufficiency postoperatively, which can occur either because the stiffness of the lungs precludes adequate ventilation or because other respiratory complications such as pneumonia develop. Thus, from the time of preprocedure tracheal intubation through the operation and the postoperative period, we place special attention to the prevention of pulmonary complications and work closely with pulmonologists and anesthesiologists to optimize outcome.

Unfortunately, long-term complications of LARS are more of a problem. The most common complication is the return of reflux and its manifestations. While this is seen in about one-quarter of the patients at 10 years post-LARS, it can be successfully treated in more than 80% of these patients with PPIs, which can provide substantial relief. In our series, approximately 3–4% of all patients that underwent LARS required a reoperation to control symptoms of reflux [52]. Bloating and the inability to belch occasionally bother patients after Nissen fundoplication, and we found that 9% of patients developed bloating postoperatively. Dysphagia can occur in up to 20% of patients and will usually disappear by 4–6 weeks, and we found that only 2% of patients will develop new onset dysphagia after Nissen fundoplication. If dysphagia is related to the tightness of the wrap, endoscopic dilation can be performed with good results. In most patients bloating, diarrhea, and abdominal discomfort resolve within 4–6 weeks as well. If symptoms remain after 3 months, investigation with an upper gastrointestinal study and esophagogastroscopy should be performed to assess fundoplication orientation and position. If an anatomical abnormality is found in a patient with significant recurrent GERD after antireflux surgery, this is likely best-treated via operative intervention.

Endoluminal Therapy of GERD

Recent advances in therapeutic endoscopy have led to the development of endoluminal techniques for the treatment of GERD. Endoluminal antireflux therapies were first introduced in the USA in the early 2000s and have since gone through a number

of revisions. Current techniques include: endoluminal plication, radiofrequency ablation, and injecting bulking agents at the GE junctions. Much like surgical therapy, the goal of endoluminal therapy is to recreate an antireflux barrier and reduce esophageal exposure to refluxate. This is done by recreating an endoluminal flap valve, reducing lower esophageal sphincter (LES) relaxation, increasing LES length, and remodeling the GE junction. Multiple devices and techniques have been studied including endoluminal plication devices (EndoCinch, NDO, EsophyX), radiofrequency ablation (Stretta) used to promote fibrosis and decrease LES compliance and relaxation, and submucosal injection/implantation devices to bulk up the area at the GE junction (EnteryX).

The first endoluminal technique to be approved in the USA was the Bard EndoCinch in 2000. This device used an overtube, a suction apparatus, and a sewing capsule to place multiple rows of sutures below the level of the GE junction [53]. The device was subjected to multiple trails including a randomized double-blinded, sham-controlled trial performed by Schwartz et al. that compared outcomes for patients who underwent gastroplication, sham gastroplication, or no treatment at 3, 6, and 12 months [54]. This study found that patients who underwent gastroplication had a decrease in use of PPI therapy and GER symptoms but did not show significant improvement in distal esophageal acid exposure when compared to the sham group. This trial also had a greater percentage of patients who required PPI therapy for control of GER symptoms at 12 months when compared to other open trails (71% vs. 30–60%, respectively). In another study comparing laparoscopic Nissen fundoplication to endoluminal fundoplication, Mahmood et al. found that although there was a significant improvement in symptoms and acid regurgitation scores, reduction in need of PPI therapy, and improvement in quality of life in both groups at one year, endoluminal therapy was inferior with respect to symptom score and control of acid reflux when compared to laparoscopic Nissen fundoplication [55]. Ninety-one percent of patients in the laparoscopic Nissen group achieved normal pH compared to only 48% in the endoluminal plication group. Although this system showed short-term improvement in symptoms of GERD, it failed to show long-term benefit in symptom reduction and distal esophageal acid exposure.

A recently developed endoluminal plication system is the EsophyX device, which allows for transoral incisionless fundoplication (TIF). This device uses a combination of suction and H-fasteners to perform a gastric plication similar to a surgical partial fundoplication [56]. Although this TIF has only been available in the USA since 2007 multiple studies have shown promising results. Testoni reported on 20 consecutive patients who underwent TIF and noted that at 6 months post procedure, there was a statistically significant benefit in symptom relief and reflux events as measured by pH impedance. Seventy-seven percent of patients had reduced/stopped medications and 55% were able to completely discontinue all medications. Although symptom scores were improved after TIF, there was no significant change in distal esophageal acid exposure. Cardiere et al. evaluated 86 consecutive patients who underwent TIF and found that at 12 months post treatment, 67% of patients were completely off medications and 56% were considered cured from GERD based on symptom reduction and discontinuation of PPI use [57]. There was a significant

improvement in resting LES pressure when compared to LES pressure prior to the procedure, and all patients with a hiatus hernia had their hernia reduced. Anatomically, the mean length of the new valve measured 4 cm (range 2–6 cm) and 230 degrees in diameter (range 160–300). Although this device has shown promising results, a study that compares it to standard laparoscopic fundoplication has yet to be reported. A multicenter, randomized sham-controlled trial is taking place in the USA to further evaluate the efficacy of TIF using EsophyX.

The only radiofrequency technique approved for use in the USA is the Stretta, which was also introduced in 2000. Stretta transmits radiofrequency energy to the GE junction with a balloon basket catheter containing four needles. The mechanism of action on the LES is heat-induced collagen contraction, fibroblast and collagen deposition, and remodeling [58]. Early studies with this device were promising. Corley et al. showed in a prospective, randomized sham-controlled trial that at 6 months 61% of patients in the treatment group showed improved heartburn scores compared to 33% in the sham group [59]. Quality of life scores were also improved in the treatment group as compared to the sham group, (61% vs. 30%, respectively). The study failed to show improvement in medication use or distal esophageal acid exposure in the treatment group. The results were maintained out to 12 months on follow-up evaluation. Triadafilopoulos et al. followed 118 patients after Stretta in a multicenter trial and demonstrated a significant improvement in quality of life and symptoms. PPI use was decreased from 88% to 30%, and distal esophageal acid exposure was also improved from 10.2% to 6.4% [60]. When Stretta was compared to laparoscopic fundoplication, 97% of patients who underwent laparoscopic fundoplication were off PPIs compared to only 58% in the Stretta group [61]. There was also a significant decrease in esophageal acid exposure percent time 8.2 to 4.4% and Johnson DeMeester score 39.4 to 26.6. Thirty-six percent of patients had normalization of acid exposure.

Since the first endoscopic antireflux procedure was introduced, multiple devices have entered and left the market. The only system that is FDA approved and currently available in the USA is the EsophyX system [62]. However, the inability of these procedures to normalize acid exposure and the current lack of long-term data make these techniques high risk in patients with diminished lung function. Additional randomized, controlled clinical trials need to be performed to better determine the value of these techniques in the general population before it can be introduced in patients with diminished lung function.

Conclusion

The relationship between GERD and respiratory symptoms has been well established. Medical therapy, which works well in general for patients with typical GERD symptoms, is notoriously less effective in controlling airway symptoms, presumably because it is less effective in preventing laryngopharyngeal reflux and, thus, microaspiration from occurring. Laparoscopic antireflux surgery creates a mechanically

competent cardia and is more effective in preventing microaspiration and in eliminating pharyngeal reflux. The key is the identification of patients who have GERD as a cause of their pulmonary symptoms—since the majority of pulmonary symptoms have other causes and GERD is a relatively common disease. Due to the inconsistent results of endoluminal therapies, these are not recommended for patients diagnosed with respiratory dysfunction and GERD.

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Index

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