

Gastroesophageal Reflux Disease – A Review of Important Management Components

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Rezumat

Boala de reflux gastroesofagian - o revizuire a componentelor importante de management

Context: Boala de reflux gastroesofagian (BRGE) continuă să aibă o prevalență ridicată în țările industrializate occidentale și o prevalență în creștere în unele societăți industrializate asiatice. Managementul acestei afecțiuni, adică îngrijirea multimodală a pacienților afectați, include aplicarea unei definiții clare a BRGE pentru identificarea precisă a cohortelor de pacienți, utilizarea unui protocol diagnostic sistematic și diferențiat, stabilirea unor criterii de selecție pentru tratamentul conservator versus cel intervențional și chirurgical, precum și monitorizarea pe termen lung a pacienților. Scopul acestui articol este de a revizui informațiile existente în literatura de specialitate referitoare la managementul actual al BRGE și aplicabilitatea lor clinică.

Metode: A fost stabilită o listă de elemente esențiale pentru managementul multimodal al pacienților cu BRGE. A fost efectuată o căutare bibliografică utilizând termenii [managementul BRGE] sau [BRGE-management] în baza de date Medline (PubMed, SUA). Toate rezumatele identificate au fost evaluate în funcție de relevanța lor pentru obiectivul studiului, iar cele care abordau alte aspecte ale BRGE au fost excluse.

Rezultate: Inițial, au fost identificate 8 elemente esențiale necesare pentru managementul multimodal al pacienților cu BRGE. În total, între 2017 și 2023, au fost identificate 2193 de rezumate, dintre care 53 de articole complete au fost analizate. Dintre aceste 53 de publicații cu un focus adecvat pe managementul BRGE, 34 au fost excluse deoarece nu abordau cel puțin 4 din cele 8 componente esențiale ale managementului BRGE. În final, 19 articole au fost selectate pentru analiza finală. Este notabil faptul că 16 dintre cele 19 publicații utilizau fie un chestionar de simptome, fie clasificarea Montreal pentru definirea BRGE, în timp ce altele utilizau expunerea esofagiană la acid sau prezența esofagitei pentru diagnostic. În ceea ce privește conceptul terapeutic multimodal, doar 9 publicații includeau toate opțiunile terapeutice disponibile pentru managementul BRGE. Majoritatea studiilor descriau tratamentul conservator, în timp ce doar 9 articole includeau și opțiuni chirurgicale în strategia de management global al BRGE.

Concluzii: BRGE nu poate fi considerată o afecțiune unitară, ci o boală multifactorială, alcătuită din mai multe subgrupe de pacienți cu fenotipuri diferite.

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Fiecare dintre aceste subgrupe poate necesita strategii terapeutice personalizate. Doar jumătate dintre publicațiile analizate privind managementul BRGE au abordat întregul spectru al componentelor esențiale implicate în gestionarea bolii.

Cuvinte cheie: BRGE, diagnostic BRGE, IPP, chirurgie antireflux, fundoplicație laparoscopică, managementul BRGE, modificări ale stilului de viață în BRGE, reflux, esofagită de reflux

Abstract

Background: Gastroesophageal Reflux Disease (GERD) has a persisting high prevalence in western industrial countries and a rising prevalence in some Asian industrial societies. Management of the disease, i.e. the multimodal care for the affected patients consists of the application of a definition of GERD to clearly define the cohort, using a systematic and differentiated diagnostic work-up as well as using selection criteria for conservative versus interventional and surgical therapy and long-term accompaniment. The purpose of this manuscript is a review of the information in literature on items involved in the current management of GERD and their clinical application.

Methods: A list of items was established with all components necessary for the multimodal management of patients with GERD. A literature search was performed using the term [management of GERD] or [GERD-management] in Medline pubmed.gov (USA). All abstracts were evaluated for their usefulness regarding the aim of the study, those with a different focus on GERD-issues were excluded.

Results: Initially 8 items were identified necessary for the multimodal management of GERD-patients. In total, 2193 abstracts were found between 2017 and 2023, which were evaluated and 53 full articles were analyzed. Out of these 53 publications with the correct focus on GERD-management, 34 were excluded for not providing at least 4 of the available 8 items of the complete spectrum of GERD-management. Finally, 19 reports were selected for final assessment. Remarkably, 16 out of 19 publications used either a symptom questionnaire or the Montreal classification, while others used esophageal acid exposure or esophagitis for defining the presence of GERD. Regarding suggestions for a multimodal therapeutic concept, only 9 publications reported on all available therapeutic management options of GERD. Most publications described conservative therapy, while 9 articles included surgical procedures as an option in the overall GERD-management.

Conclusions: GERD cannot be handled as just one disease, but should be considered as a multi-factorial disease consisting of several subgroups of GERD-patients with different phenotypes. All these different subgroups of the disease may need their individual management options. Only half of publications on GERD-management provided the complete spectrum of involved management components.

Key words: GERD, GERD-diagnostics, PPI, antireflux surgery, laparoscopic fundoplication, GERD-management, GERD-lifestyle modifications, reflux, reflux-esophagitis

Introduction

Gastroesophageal Reflux Disease (GERD) has a persisting high prevalence in western industrial countries and a rising prevalence in some Asian industrial societies (1-5). The advent of powerful antisecretory drugs such as proton pump inhibitors (PPI) and the introduction of minimally invasive surgical procedures to treat the worst cases have generated the hope for an effective management of GERD, however controversial discussions persist (1,6,7). The basis of an optimal management is an appropriate definition of the disease to precisely identify the patients with true GERD and separate them from patients with other disorders (1,2,6-8).

Furthermore, once accurately identified and diagnosed, management of GERD-patients requires a precise discrimination between milder cases and patients with advanced, progressive disease and subsequently a differentiated decision regarding a long-term therapeutic concept, mainly life style changes and medical therapy, and, in selected cases surgical therapy before irreparable functional and anatomical changes may occur (6,7,9-14).

The definition of GERD has been rather difficult to establish for applications in clinical practice, since several diagnostic tools are available, each focusing on one of the diagnostic mosaic elements of the disease spectrum such as

typical symptoms or endoscopic visible damage or functional defects and anatomical abnormalities (1,2,6-8). The Montreal classification has defined GERD as a “condition that develops when reflux of stomach contents causes troublesome symptoms and/or complications” (1). This definition based on symptoms seems to be applicable in clinical practice, however, it is in conflict with the fact that a number of overlapping disorders in the gastrointestinal tract may share the presence of similar symptoms with GERD. This may create diagnostic problems especially with psychosomatic and psychosocial disorders, which can appear also with reflux-like symptoms (2,6,7,15-17).

Increased understanding in the pathophysiology by modern functional assessment concepts has shown the multifactorial character and background of GERD (1,2,8,13,14,18-22). It must be emphasized that the differentiation of patient-subgroups or “phenotypes” requiring different long-term therapeutic strategies is of utmost importance for the successful management of the overall cohort of patients with GERD and associated problems (2,6,7,8,13,14,23). Therefore, the diagnostic term “GERD” needs to be verified in more specific terms, before decision making for the long-term management of patients is performed (2,6-8,23). As a consequence, the overall management of GERD-patients is an important issue and includes several facets such as a rational and effective diagnostic work-up, exploiting conservative treatment options such as lifestyle adjustments and medical therapy, a critical patient selection for interventional therapy or indication for surgical procedures as well as the outcome-assessment, analysis and treatment of failures (2,6-8,23).

Thus, the management of this disease, i.e. the multimodal care for the affected patients, must include the application of a definition of GERD to clearly define the cohort, using a systematic and differentiated diagnostic work-up such as symptom-questionnaires, PPI-test, endoscopy, impedance-24h-pH-monitoring, High Resolution Manometry (HRM), additional functional evaluations, psycho-diagnostic tools and other selective investigations such as radiography and scintigraphy as well as using phenotyping to characterize the subgroups (2,6-8,13,14,18-23). In addition, management also consists of using selection criteria for conservative (lifestyle modifications, medical therapy) versus interventional and surgical therapy, applying patient information policies, follow-up concepts for accompaniment as well as performance and quality control (6-8,13,14,18-23).

The purpose of this manuscript is a review of the information in literature on these items involved in the current management of GERD and their clinical application. The focus of this review is the systematic application of these often in guidelines requested items for the management of GERD-patients in published clinical practice.

Methods

Initially, the authors established a list of items which represent all components of an optimized management of patients with GERD. These item-list should include components for the definition of GERD and its classifications, the diagnostic work-up and the complete therapeutic spectrum. After literature review and a thorough discussion, 8 items were chosen to characterize the complete and optimized issues for a successful management of this disease. In *Table 1*, an overview on all chosen items or components is provided, which were used for the evaluation of the publications on the management of GERD. In addition, the authors decided to limit their review to publications of the last 6 years to rely the results on the actual status.

Initially important is a definition of GERD to identify true GERD-patients and separate them from patients with other disorders and thus, define the cohort to be treated. All methods to establish the exact diagnosis should be mentioned. Furthermore, subgroups may be of special interest and should be defined clearly and their identification should be documented. Some authors have expanded on additional diagnostic tests to determine special features or exclude other overlapping diseases. In addition, for a multifactorial disease like GERD, a multimodal, therapeutic concept seems to be appropriate and should be outlined in publications on management. Finally, GERD is a chronic disease, which requires some long-term measures for treatment and follow-up (*Table 1*).

A literature search was performed using the term [management of GERD] or [GERD-management] in Medline pubmed.gov. Articles not published in the English language were excluded from the review. Attention was focused on publications, which had an integrated view on most of these items (*Table 1*) for the management of GERD.

All abstracts were evaluated for their usefulness regarding the aim of the study; those with a different focus or investigating special tools, methods or techniques were excluded. Abstracts,

Table 1. Overview on 8 items characterizing the multimodal management of GERD

Management item	Investigational Tool Application
1 Definition of GERD	Symptom based Endoscopy based PPI-test based Functional definition Other
2 Identification of GERD-patients	Symptom evaluation by questionnaires, presence of esophagitis by endoscopy, presence of pathologic acid exposure by measuring the refluxate other
3 Application of diagnostic program	Endoscopy Radiography High resolution Manometry Impedance- 24-hour-pH-monitoring Scintigraphy Others Multimodal diagnostic program
4 Defining subgroups	Symptomatic phenotyping: Reflux-type: heartburn, esophagitis, BE; NERD-type: Functional Heartburn, Esophageal Hypersensitivity; Regurgitation-type: EGJ-weak, Hiatal Hernia Chest-pain-type: Hiatal Hernia Extraesophageal symptoms type: cough, hoarseness esophagitis grading of visible mucosal damage: LA: A,B,C,D Disease classifications: NERD, ERD, BE Identifying progressive disease
5 Searching for special cases Personalized approach	Application of psycho-diagnostic instruments, detection of esophageal motor disorders and/or outlet obstruction: radiography detecting gastric emptying disorders: radiography, gastric emptying scintigraphy
6 Defining and applying a multimodal therapeutic concept	All elements of therapy reported: Lifestyle modifications Medical therapy Interventional endoscopic therapy Criteria for patient selection for surgical therapy
7 Item for Surgical therapy	Differentiated surgical treatment concept Technical details of surgical procedures reported
8 Long-term management of patients	Follow-up concept Program for detection of failures Management of failures

potentially fulfilling the purpose of the chosen theme on management of GERD using the required items, were selected and full text reviews and analyses were performed. Subsequently, published reports with focus on insufficient number of items regarding the management spectrum of GERD were excluded from further analysis. Finally, only reports with a description or

analyses of 4 or more out of the 8 items regarding GERD-management were included in the analysis of this review.

Results

In total, 2193 published abstracts were screened on pubmed.gov for their content regarding the initially established and selected items focusing on GERD-management as mentioned in the method section, using the time segment between 2017 and 2023. After screening the abstracts regarding the purpose of our review and analysis, 53 publications could be identified with a clear focus on the management of GERD as a disease, excluding the majority of the abstracts because of a different focus of other issues of GERD and/or specific diagnostic or therapeutic techniques. After studying these publications as full text articles in detail, 19 reports were selected for final assessment, evaluation and demonstration (5,8,12,23-39). These final 19 selected publications provided at least 4 of the earlier defined, 8 items of the complete spectrum of GERD-management. The main messages and conclusions of the selected papers were analyzed, extracted and summarized in *Table 2* (5,8,12,23-39), providing an overview on currently practiced actions to manage an individual patient, suspicious of having GERD.

In 2017, Kahrilas et al. published their work on dilemmas regarding diagnosis of GERD (24). The authors conclude that the mainstay of diagnosis was based on symptoms, endoscopic visible signs of GERD and results from intraluminal acid exposure in the esophagus, resulting in rather weak evidence for a sharp discrimination between a physiologic and pathologic borderline. Subsequently these circumstances lead to a therapeutic overuse of Proton pump inhibitors and thus insufficiencies in overall management (24). *Table 2* shows that 6 out of 8 items were addressed. Chuang et al. reported on a complete overview on the management of GERD, addressing 7 out of 8 items of the management-spectrum and emphasizing a careful diagnostic work-up and an early decision for the appropriate therapeutic options in order to avoid complications of the disease (25). The results of the “Lyon-consensus” by Gyawali et al. 2018 demonstrate a substantial improvement in the diagnostic work-up, especially in the interpretations and borderline-definitions of findings (8). Yadlapati et al. used a different format with describing clinical cases to show the necessary steps in the management of GERD-patients addressing 6 out of 8 items

Table 2. Overview: publications on Management of GERD and the application of essential components

Author; year (ref.)	GERD definition	Identify GERD Patients; diagnosis	Sub-groups (Pheno-typing)	Diagnostic work-up: Endoscopy, pH, HRM, PPI-test; other	Personalized concept	Multimodal therapeutic concept	Surgical concept	Long-term Management
Kahrilas 2017 (24)	symptom	typ-sym, „umbrella“ Diag	symquest.	PPI-T; endo; pH	na	PPI-therapy	na	PPI-maintenance PPI-overuse,
Chuang 2017 (25)	symptom	Typ-sym Imp-pH	Extraesoph functional	Endo; pH; HRM, radiography, MRI	na	Life style mod.; PPI-t; surgery	fundoplic MSA	long-term results PPI and fundoplic
Gyawali 2018 (8)	Def. by each test	Symptoms, pH (AET>6%)	groups likelihood	Quest-endo; pH,HRM, PSPW, MNBI, RDC, MRS	Individual scenario	na	na	Outcome measures PRO
Yadlapati 2018 (26)	na	Symptoms, pH	Clinical cases	PPI-t; endo, pH	Individual scenario	Life style, PPI, surgery	Fundoplic, MSA, Sretta.	na
Labenz 2018 (12)	pH; Acid exposure	Acid exposure, symptoms	NERD, ERD, BE	Endo, pH, HRM, carditis-histo	na	PPI, surgery	Fundoplic MSA	Endo+ histo follow-up, PRO
Klenzak 2018 (27)	symptom	Symptoms Mucosa damage	na	PPI-t; endo, pH, Psychodiagnostic tests	Aware-ness	PPI, surgery	fundoplic	PRO PPI-overuse
Singhal 2018 (28)	Symptom pH	Symptoms, Acid exposure	na	PPI-t; endo, pH, HRM, radiography, GE	Individual diagnosis	PPI, surgery	fundoplic	Systematic follow-up
Hojo 2019 (5)	symptom	Symptoms (GERD in Asia)	NERD, ERD, BE	PPI-t; endo, pH	na	Life style, PPI, surgery	na	na
Gong 2019 (29)	symptom	Symptom quest n=37442	Lifestyle, alcoh; BMI	na	na	na	na	Checking on lifestyle
Newberry 2019 (30)	Symptom LES-tonus	Symptoms	Reflux-like extraesoph	na	Individual approach	Lifestyle, diet, PPI	na	Focus on lifestyle
Hungin 2019 (31)	symptom	Symptoms with limited diagnos. accuracy	NERD, ERD obesity	PPI-t, Endo, psycho-diagnostic tests, hypersensitivity	personalized approach	Lifestyle, multimodal therapy	na	na
Katzka 2020 (32)	Multi-factorial	multifactorial	All phenotypes	PPI-t, Endo, pH, HRM	personalized (anxiety)	Multimodal therapy, main basis PPI	na	na
Yadlapati 2020 (33)	symptom	Symptoms hypersensitivity	All phenotypes	Questionnaires, PPI-t, Endo, pH, HRM, anxiety	Personalized Approach	Lifestyle, PPI, mucosal protection behavioral therapy	na	na
Ghisa 2020 (34)	symptom	“Lyon revisited” histology	Phenotypes applied	PPI-t, Endo, histology, pH, HRM, PSPW	Applied SAP, MNBI	True GERD, Funct HB	na	na
Kahrilas 2021 (23)	symptom	Symptoms Hypersensitivity NERD/ERD	Phenotypes applied	PPI-t, NERD, ERD Hypersensitivity, FH, anxiety	Personalized approach	Multimodal therapy without surgery	na	na
Fuchs 2021(35)	ERD, Acid exposure	ERD, hiatal H, acid exposure, EGJ-failure	NERD/ERD Acid, FH, hypersens	NERD, ERD, Hiatal H, pH, HRM, PSPW	Psycho-diagnostic, QoL	Complete multimodal concept	Fundoplication selection	systematic follow-up + tests + GiQLI
Iwakiri 2022 (36)	Symptom ERD	Symptoms ERD	Western lifestyle	Endo, extraesophageal symptoms, pH SAP, selective HRM	na	Lifestyle modifc, Alginate, P-CAB, PPI	na	Only PPI
He 2022 (37)	symptom	Symptoms Anxiety, depression	applied	PPI-t, Endo, psycho-diagnostic tests	Psycho-diagnostic tests	na	na	na
Hungin 2022 (38)	symptom	Symptoms Gut-brain-axis	Ladder approach	PPI-t, Endo	Psycho-social tests	PPI, dose-escalation, behavioral interventions	na	„Checking the patient“
Katz 2022 (39)	symptom	ERD, acid exposure, EGJ-failure	All phenotypes	Endo after PPI-stop, pH, HRM, psycho-diagnostic, selective	personaliz	Complete multimodal concept	Fundoplic MSA endoscopic	Follow-up concept

including all therapeutic options (26). Labenz (7 out of 8 items) and Klenzak (7 out of 8 items) demonstrated a complete coverage of GERD-management emphasizing the need for histological information to detect early cancer (12,27). Singhal demonstrated an application of an almost complete spectrum management components including surgical and follow-up concepts (28). In Asia, the definition and diagnosis are mainly based on symptoms, evaluated by questionnaires, with a rather limited use of functional esophageal assessment and also limited data on therapeutic management (5,29). Newberry et al. focused on lifestyle regulations and dietary modifications in GERD-management, lacking any other therapeutic suggestions (30).

In contrast to most other publications, Hungin et al. described a certain limitation of diagnostic accuracy, when basing definition and diagnosis only on symptoms (31). The authors apply a complete diagnostic work-up including psychodiagnostic tests and favor a multimodal therapeutic management for GERD (31). Others recognize the multifactorial background of GERD for the definition as well as for the diagnosis and apply the differentiation by phenotyping subgroups, involving a complete diagnostic program and psycho-diagnostic tests and providing a multimodal therapeutic approach (32,33).

Unfortunately, interventional and surgical options are not discussed (32,33). In a publication revisiting the "Lyon consensus criteria", Ghisa emphasizes the precision of an established diagnosis to verify further diagnostic and therapeutic steps, using 6 out of 8 items (34). Kahrilas et al. provide a multifactorial definition and diagnosis based on phenotyping and a complete diagnostic work-up including visceral hypersensitivity, anxiety and personalized components, again lacking any suggestions to select surgical options (23).

In a surgical publication, the definition is based on multifactorial items and the diagnosis is based on pathological esophageal acid exposure, mucosal damage and symptoms (35). A full diagnostic work-up was applied including psycho-diagnostic and gastrointestinal functional tests as well as Quality of Life assessment, which is all used for patient selection for surgery in a defined therapeutic and follow-up concept to detect failures and treat them (35). The Japanese working group on GERD-guidelines suggests basing their definition of the disease on symptoms and visible mucosal damage (36). Endoscopy and PPI-tests are used as diagnostic concept, but hardly any functional assessment

is applied. The therapeutic suggestions focus on medical therapy besides lifestyle modifications. He et al. provide a detailed GERD-management concept on patients with psychologic disorders and GERD (37). Hungin et al. also emphasize the importance of troublesome symptoms associated with anxiety, depression and somatoform disorders (38).

Katz et al. with their recent update of US-Guidelines on the management of GERD provide an excellent overview of all important factors (39). The GERD definition is based on the multifactorial background and is based on symptoms, mucosal damage, acid exposure and EGJ-malfunction, which all can be used for a precise diagnosis. The phenotyping is very important considering the many facets of the disease. Therefore, the complete diagnostic repertoire is needed depending on the individual picture and situation. The authors provide a complete multimodal therapeutic spectrum as treatment concept including a differentiated surgical program and the necessary follow-up program (39).

Regarding the most frequently used definition of GERD, this review shows that the majority of authors have applied a symptom-based definition, since 16 out of 19 publications used either a symptom questionnaire or the Montreal classification for the definition, while in 2 publications the objectively measured esophageal acid exposure and the presence of esophagitis was used for defining the presence of the disease.

In total, the presence of esophagitis was applied in 4 publications to identify GERD in combination with other items. In 8 articles, the results of functional assessment such as esophageal and gastric motility and acid exposure studies were also included in the identification of GERD in the investigated patients.

A standardized and complete phenotyping of GERD-patients was reported in only 6 publications, however in 12 reports some kind of classification of GERD was applied such as the differentiation in NERD, ERD, and BE, the esophagitis LA-classification, as well as a separation in different symptomatic groups such as reflux-symptoms and extraesophageal symptoms.

Regarding the diagnostic work-up, the PPI-test was applied to further select patients in 12 publications. In addition, endoscopy was performed in the majority of patients and mentioned in 16 reports. Usually, the Los Angeles classification was advocated together with the differentiation in NERD, ERD, and BE.

Functional testing with HRM and impedance-pH-monitoring, rarely further differentiated with Postreflux-Swallow-induced Peristaltic Wave (PSPW), Mean Nocturnal Baseline Impedance (MNBI), Symptom Association Probability (SAP), was reported as element of the diagnostic work-up in rather few reports as a complete diagnostic program. Impedance pH-monitoring was integrated in the diagnostic program in 14 reports, often selectively used in patients with absent esophagitis. As mentioned, in 8 reports these tests were used for the proof of the presence of GERD.

The selective use of special tests such as psychodiagnostic instruments were integrated in the concept in 8 publications, which is almost half of the selected papers. Selective application of radiographic studies and esophageal and gastric emptying studies were mentioned in 4 studies. The additional histopathological analyses of mucosal injury in the esophagus and EGJ was emphasized in only one report.

Regarding the inclusion of a multimodal therapeutic concept, 13 publications reported on several therapeutic options. Most publications described conservative therapy such as lifestyle modifications and medical therapy, while 9 articles included surgical procedures in their therapeutic management of GERD. Lifestyle changes were often recommended such as avoiding smoking, alcohol, fatty diets, daily salt, eggs, and meat. A mainstay of conservative therapy remains PPI-treatment, which was always mentioned as a prerequisite prior to any interventional and surgical therapy. In 13 articles, the importance of life-style changes, a differentiated medical therapy with several options such as alginates, P-cab medication and PPI as well as a more personalized approach with the focus on the patients was suggested and performed.

In 7 reports, a surgical concept with a differentiated approach was demonstrated depending on certain requirements and diagnostic criteria to decide for one or the other method. Laparoscopic fundoplication (total and partial wrap) are still the most important surgical options. More recently, other emerging techniques such as the Magnetic Sphincter Augmentation (MSA) were also mentioned and good results were demonstrated.

In 12 out of 19 publications, a recommendation for the long-term management of GERD-patients was documented. Out of these, 4 authors emphasized the danger of overuse of PPI in the past decades and the necessity to guide the patients with diagnostic controls and outcome controls to

verify the necessity of on-going PPI-therapy after certain time-segments. Some authors mentioned the necessity to perform surveillance on Barrett-patients.

In summary, the identification of patients with GERD is still mainly based on symptoms and symptom-based questionnaires and definitions. The recently introduced phenotyping allows for a better identification of important subgroups. The frequently used diagnostic spectrum of PPI-test, endoscopy, manometry, 24-hour-impedance-pH-monitoring is a valid method to more accurately assess a potential GERD-patient as to the severity of the disease in a person. More specialized tests focusing on detailed problems of patients with associated and/or overlapping disorders such as psycho-diagnostic testing in psychosocial abnormalities, were not always applied. Therapeutic concepts are published usually based on the individual author's background, while publications with interdisciplinary overall therapeutic suggestions are limited.

Discussion

Clinical experience and scientific results from literature have shown that it is an illusion to diagnose such a multifactorial determined disease with one Gold-standard test or to treat such a disease with one single therapeutic method, for example in GERD exclusively with PPI or exclusively with antireflux surgery and hope to achieve good result in most cases (2,5-8,23-39). As a consequence, the diagnosis and treatment of a complex disease entity such as GERD requires a complex management to adjust all actions for the involved patients.

The main argument for this present review is the rather unique approach based on the overall management analyzing many if not all components of the disease management. The weakness of the current analysis is the fact that this term "management of GERD" is not uniformly defined in literature and nor is the disease uniformly defined. Therefore, the selection of papers for this analysis is an individual approach, which may be influenced by bias. The authors have described their methods and have been as objective as possible.

As has been demonstrated, GERD does have several facets, which can be defined via symptomatic phenotypes, however, their definition and diagnostic identification requires a number of specific diagnostic tools, since the documentation of

merely the presence of individual symptoms is insufficient (5,8,12,23-39). The precise identification of true GERD-patients is needed for the basis of an optimal management of this disease. In this analysis, it seems surprising that the majority of articles focusing on the management of GERD, base their diagnosis (and definition) on symptoms, which may be quite unreliable to work with.

Even the “typical reflux symptoms” such as heartburn and regurgitation occur in substantial portions in patients without proven acid reflux, as reported by Klauser (40). More recent analyses have shown also limitations, since only 60-70% of patients with heartburn and regurgitation suffer from excessive esophageal acid exposure (23,24,26,33,40-43). Vice versa, in a cohort of patients with pathological esophageal acid exposure, only 60 % of patients suffered from chief-complaint heartburn, while 73% had gas-related symptoms such as bloating, belching, and flatulence among others (44). In addition, the post-prandial acid-pocket may produce severe reflux-symptoms, which may require special investigations and treatment (44). Furthermore, associated disorders such as functional heartburn (FH) and esophageal hypersensitivity (EH) or overlapping disease entities such as psycho-social or somatoform disorders can present clinically with similar symptoms as GERD such as heartburn, regurgitation, epigastric and thoracic pain, belching, and others (8,15-17,41-43).

As a consequence, objective assessment with endoscopy and functional measurements seems to be necessary for the identification of GERD (8,21,22). An important step was done in the Lyon consensus 1.0 and especially in the 2.0 version (8,45). These changes and improvements include the description of new metrics and thresholds for functional assessments, defining clear cut-off criteria for pathological esophageal acid exposure ($AET > 6\%$) (45). In addition, similar criteria for the presence of esophagitis are necessary considering the more recent discussion around the term esophagitis LA grade A (8,24,32,33,35,45). If the latter cannot be used as a marker of mucosal damage, maybe histology could be a solution (46,47). There is information that esophagitis LA grade A was detected in 5 % of asymptomatic (assumed healthy) persons (24). If “esophagitis LA grade A” has too much of a high observer variation, improved education could be the answer.

It is also important to emphasize that GERD develops also more among the Asian population, as reported in the past years (5,48,49).

The term “umbrella diagnosis of GERD” has

been introduced, indicating a number of different entities that may belong to one main diagnosis, including different facets of the disease (32). If subgroups of the “umbrella” diagnosis are established, more precise and specific investigations are necessary to differentiate between these subgroups. The latter concept may be of benefit for GERD-patients, since the personalized approach provides more attention and more focus for each individual (8,23,24,26,29,32,38).

The stepwise handling of a patient with suspicion of having GERD seems reasonable (26,32,33,35,38). Initially, the presence of symptoms as assessed by a standardized symptom questionnaire, may lead to a physician visit and an initial PPI-test or trial, followed depending on the severity of complaints to an endoscopy to verify damage. If severe damage is present and/or the therapeutic response to PPI-treatment is rather disappointing, objective functional assessment should be added to verify next to the severity of mucosal damage also altered anatomy and the severity of functional defects in the esophagus, EGJ and stomach. Depending on the clinical appearance of the disease, the response to lifestyle modifications and PPI-therapy, more specific instruments may be necessary to proceed with the diagnostic work-up to identify the subgroup, the individual may be part of such as extra-esophageal syndrome subgroup or the associated NERD and functional heartburn type or the overlapping patient group with psycho-social interferences.

Once these criteria are all clarified, a decision making for the long-term treatment concept is necessary to be established. Patients with minor mucosal damage and borderline anatomical and functional defects, especially those with an acceptable reduction in QoL, should be informed to receive long-term conservative treatment including all possible lifestyle modifications that might be of advantage (12,24-26,28,35,38). The absolute vast majority of patients with GERD can be managed along this conservative concept and route (23,24,28,32-35). Some of these patients may qualify for an interventional endoscopic therapy such as endoscopic plication (50,51). Problems concerning the guidance of these patients is caused by a limitation in compliance of these individuals to follow the instructions thoroughly or neglect them, making the concept ineffective. This can only be overcome by sufficient time of care and information to the patient to make her/him understand their disease and create a motivation to follow the concept (35). The latter may be worth more for the

total treatment aim than frequent and unpleasant endoscopic follow-up investigations.

In contrast, patients with severe mucosal damage, a substantial reduction in QoL, persisting symptoms despite adequate PPI-therapy and dosage, excessive pathological esophageal acid exposure and functional defects as well as altered anatomy, should be candidates for antireflux surgery, since these are all criteria for a progressive form of GERD (12,14,26,28,32,33,35). Thus, surgical therapy should be an integral part of the therapeutic management, rather than a desperate option, if everything fails (6,7,11-14,28,35,39, 53-56). Two major developments do occur more frequently in these latter individuals, one is the development of BE at the mucosal level of the EGJ, the other is the gradual shortening of the esophageal length because of scarring and the loss of EGJ-architecture with lengthening and weakening of the phrenoesophageal ligament (9-14,28,35,46, 52). The latter will make it, year by year, more and more difficult to surgically restore the physiological hiatal anatomy, until it will be impossible (9-14, 28,35,46,52). These two developments can be at least partially corrected by surgery (9,11,28,35,52). Therefore, for these few patients, time is running in the course of the disease.

Unfortunately, only half of the selected publications on the management of GERD provide these criteria of a differentiated therapeutic concept of GERD (5,12,25-28,31,35,39). This is disappointing, since the affected patients may spend unnecessary years in consuming PPI participating in the recent overuse of these drugs, while more specific treatment option are not applied (6,7, 23,24,25,28,35).

The results show that more care should be invested in the diagnostic work-up to meet the requirements of a multifactorial disease and its subgroups, applying a stepwise diagnostic approach with all modern tools, if necessary, on personalized level, in order to better select patients for one or the other individual optimal therapy. Furthermore, the complete therapeutic spectrum should be considered and the specific criteria and components in medical decision making for this important process should be available and applied.

Conclusions

Today, GERD can be considered as an “umbrella term” for a “multi-facet disease” consisting of several subgroups of patients with very different expressions of GERD, reaching from Functional Heartburn, mild erosive esophagitis to a progres-

sive from of the disease with severe anatomical and functional alterations and defects, associated with the patients' individual psycho-social situations and coping mechanisms with the symptoms. All these different expressions of the disease do need their individual management options, which sometimes require a tight and benevolent interdisciplinary understanding and cooperation for the benefit of patients with GERD. Only a minority of publications on the management of the disease provide the complete spectrum of management components involved.

Conflict of Interest

All authors, KHF, AH and AM declare that they do not have any conflict of interest nor any financial conflict regarding this manuscript.

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Ethical Statement

This review is based on a literature-search and therefore no ethical evaluation was necessary.

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