A SYSTEMATIC REVIEW OF DUODENOGASTROESOPHAGEAL (BILIARY) REFLUX: PREVALENCE, SYMPTOMS, OESOPHAGEAL LESIONS AND TREATMENT

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SUMMARY

Background
The prevalence of duodenogastroesophageal reflux (DGER) and its effect on symptoms and oesophageal lesions in gastroesophageal reflux disease (GERD) is unclear.

Aims
To conduct a systematic review to determine the prevalence of DGER among patients with GERD, the effect of DGER on symptoms and oesophageal lesions, and the treatment of DGER.

Methods
We searched Pubmed and MEDLINE for full text, English language articles until October 2020 that evaluated DGER prevalence among patients with GERD, the effect of DGER on symptoms and oesophageal lesions, and the treatment of DGER.

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Results
We identified 3891 reports and included 35 which analysed DGER prevalence in GERD, 15 which evaluated its effect in non-erosive reflux disease (NERD), 17 on erosive oesophagitis, 23 in Barrett’s and 13 which evaluated the treatment of DGER. The prevalence of DGER, when evaluated by Bilitec, among all GERD patients ranged from 10%-97%, in NERD 10–63%, in erosive oesophagitis 22%-80% and in Barrett’s 50%-100%. There were no differences in the presence or degree of DGER among patients who were asymptomatic or symptomatic on proton pump inhibitors (PPI). The most commonly evaluated treatments for DGER were PPI’s and in all studies DGER reduced post PPI therapy.

Conclusions
In a systematic review, we found the prevalence of DGER increased with more advanced oesophageal lesions and did not explain persisting symptoms among patients taking PPI therapy. PPIs appear to be effective in the treatment of DGER. DGER remains to be an important consideration in patients with GERD and future therapies deserve more study.

INTRODUCTION
Gastroesophageal reflux disease (GERD) is defined by refluxed gastric content into the oesophagus causing symptoms and/or oesophageal lesions. Oesophageal lesions range from erosive oitis to Barrett’s oes and many patients with typical GERD symptoms have a macroscopically normal appearance of the oesophagus. Traditionally, oesophageal injury in GERD patients was conceptualized as the result of chemical caustic effects from luminal factors, with the key factors in this paradigm thought to be acid and pepsin, causing direct injury to the epithelium. Since the advent of effective acid suppressive therapies, such as proton pump inhibitors (PPIs), there has been significant improvement in controlling symptoms and complications which arise from GERD. However, a substantial proportion of patients continue to suffer from symptoms and complications of GERD despite adequate PPI therapy. The contributing factors to symptoms in patients with GERD are complex, as significant numbers of patients have symptoms in the absence of erosive changes or significant acid reflux detected on 24hr pH monitoring. Furthermore, oesophageal lesions can develop, despite an absence of gastric acid, such as in achlorhydria or after...
gastrectomy\textsuperscript{5} which counters the idea that acid is the sole mediator of oesophageal injury in GERD. In this context other injurious and symptom inducing substances in the oesophagus, besides acid, should be considered.

Duodenogastroesophageal reflux (DGER), commonly referred to as “bile reflux”, is the pathophysiological entity which is the reflux of duodenal content, including bile, by way of the stomach into the oesophagus. Duodeno-gastric reflux is a normal physiological phenomenon which occurs after meals in both health and disease\textsuperscript{6}. GERD involves the reflux of gastric content which can include bile and other duodeno-gastric refluxate constituents\textsuperscript{6}. Various methods have been utilized to establish the presence of duodenal contents, such as bile acids in the oesophagus, to support the presence of DGER. Early studies demonstrated the presence of bile, trypsin and alkaline substances by aspiration\textsuperscript{7, 8}, endoscopic biopsies\textsuperscript{9, 10} and scintigraphy\textsuperscript{11}. Several studies, both \textit{in vivo} and \textit{in vitro}, have implicated duodenal contents in the pathogenesis of oesophageal GERD lesions. More contemporary studies have replaced aspiration measurements with ambulatory fiberoptic spectrophotometric bilirubin readings, e.g. Bilitec 2000 (Medtronic, USA), which quantify DGER by measuring bilirubin. Bilirubin, a constituent of bile, has a characteristic absorption wavelength of 450nm which is measured by the Bilitec probe. Validation studies have shown that fiberoptic readings with the Bilitec system correlate well with aspiration measures of bilirubin\textsuperscript{12}.

Since the widespread availability of oesophageal pH-impedance monitoring, the use of the Bilitec 2000\textsuperscript{®} has almost completely disappeared. The underlying assumption is often that the impedance monitoring accounts for the “non-acid” reflux detection. However, this is not an equivalent of “bile reflux” as ambulatory pH and Bilitec 2000 studies in the absence of acid suppressive therapy have shown that DGER usually occurs at an acidic pH\textsuperscript{13, 14, 15}. Furthermore, recent trials\textsuperscript{16} which have directly attempted to address bile as a constituent of GERD, have demonstrated improved symptoms and lesions in patients with GERD. Despite this knowledge there has been little systematic examination of the literature regarding the prevalence of DGER, its effect on symptoms and oesophageal lesions and which treatments are effective. In this systematic review we aimed to evaluate the prevalence of DGER, the effect of DGER on symptoms and oesophageal lesions. We also aimed to evaluate the treatment of DGER.
Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines. The protocol of this systemic review was prospectively registered with PROSPERO (CRD 42020186618), the international prospective register of systematic reviews.

Search strategy

A literature search was conducted on PubMed and MEDLINE databases for articles published from inception to June 2020 for all studies evaluating the diagnosis and treatment of DGER. The search was repeated in March 2021 to ensure a complete appraisal of the literature. The search was limited to English language articles and abstracts were excluded. No other search limits were applied.


Additional relevant articles were identified through manual searching of reference lists of included studies.

Study Selection

Screening of article titles, abstracts and full texts were conducted by two authors (CB and AG, JT or TV). Full-text articles were independently reviewed and selected by two authors for each of the three questions (Prevalence of DGER among GERD: CB and AG, Impact of DGER on symptoms and lesions among GERD: CB and JT, Treatment of DGER: CB and TV).

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Any disagreements in study selection were resolved by consensus or adjudicated by a third investigator (JT or TV).

Studies relating to prevalence were included if they assessed the presence of DGER by an objective means (i.e. Bilitec 2000, aspiration) in a clearly identified population of patients with gastroesophageal reflux symptoms. Diagnostic evidence of DGER was defined by presence of bile on aspiration or absorbance by Bilitec 2000. If the cohort exclusively evaluated Barrett’s oesophagus they were excluded from consideration of this question.

Studies which assessed the effect of DGER on symptoms and oesophageal lesions were included if they assessed DGER in patients with typical reflux symptoms, with or without changes of erosive oesophagitis or Barrett’s oesophagus.

Studies relating to the treatment of DGER were included if patients had DGER assessed pre and post intervention or if DGER was an outcome in a prospective randomised controlled trial.

Studies which evaluated duodeno-gastric reflux were excluded. Studies were excluded if patients were aged under 18 years or had prior gastroesophageal surgery. Abstracts without full text manuscripts, conference abstracts, reviews, letters to the editor and editorials were also excluded.

**Quality assessment**

Assessment of the risk of bias for each included study was performed. Consensus was achieved when discrepancies occurred. The Joanna Briggs Institute (JBI) Critical Appraisal Tool for Quasi-Experimental Studies was used to assess non randomised interventional studies and the Rob-2 (Cochrane risk of bias tool, version 2) tool for randomised controlled trials. The QUADAS-2 tool was used for evaluating studies which assessed the diagnosis of DGER. Studies were then assessed overall as having low, moderate or high risk of bias.

**Data Extraction**

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Data extraction was completed by two authors (CB and AG, JT or TV). For each study, the following data were collected: authors, year of publication, country, study design, methodology, patient population, sample size, method of DGER assessment, intervention, comparator and outcomes. A meta-analysis was not performed due to study heterogeneity.

Results

Literature search and study selection

The searches identified a total of 3891 studies (1242 from PubMed, 2390 from MEDLINE). Of the 3891 studies, 388 were duplicates and excluded, leaving 3503 studies. After screening titles and abstracts, 3383 studies were excluded, leaving 120 studies for full-text review for consideration of either of the three questions.

After review of full text manuscripts 35 studies met inclusion criteria and were included in the final analysis for studies which evaluated prevalence of DGER in patients with GERD. Twenty eight studies evaluated the effect of DGER on symptoms and oesophageal lesions. Of these 28 studies, 15 studies were identified which assessed DGER among patients with non-erosive reflux disease (NERD), 17 studies evaluated DGER’s effect on erosive oesophagitis and 23 studies evaluated the effect of DGER on Barrett’s oesophagus. After full text review 13 studies met inclusion criteria for studies which evaluated the treatment of DGER.

Details regarding the inclusion and exclusion of studies can be found in Figure 1.

*Insert Figure 1. (PRISMA) flow diagram*

Prevalence of DGER among patients being evaluated for GERD

Twenty eight studies were identified which evaluated the presence of DGER among patients presenting with symptoms of GERD, not taking PPIs or other acid suppressive therapy (Table 1). Sixteen studies utilized an asymptomatic “healthy” volunteer (HV) group for comparison. Five studies assessed the presence of DGER with oesophageal aspiration and biochemical
analysis of bile acids, the remaining 23 studies utilized Bilitec 2000©. Among studies which utilized Bilitec 2000©, 13 used bilirubin absorbance ≥ 0.14 (range 0.14 – 0.25) as indicating the presence of DGER. A predetermined definition of pathological absorbance time detected during Bilitec, was provided in 11 studies (range 1.1% - 9.6%).

Among studies which utilized oesophageal aspiration to evaluate DGER in patients with GERD symptoms, researchers demonstrated prevalence ranging between 20% and 94%. The degree of bile detected by aspiration ranged between median 14 mmol/L and 817 mmol/L.

Among the studies which utilized Bilitec 2000©, the prevalence of DGER in GERD patients ranged from 10% to 97%. The percentage of time DGER was present ranged from 2.4% to 19%. The prevalence and degree of DGER varied greatly depending on the patient population (non-erosive reflux disease vs. erosive reflux disease), predetermined Bilitec absorbance cut-off and diet prescribed during the test.

*Insert Table 1 here

**Degree of DGER among patients taking PPIs**

Seven studies evaluated the presence of DGER among patients with GERD who were taking PPIs (Table 2). Among these studies the presence of DGER ranged between 36% - 80%. Two studies compared the degree of DGER among asymptomatic patients taking PPIs and symptomatic patients taking PPIs17 18. The mean degree of DGER among asymptomatic patients ranged between 6.9% - 8.49% and 11.2 – 13.4% among symptomatic patients. However, both studies concluded that there were no significant differences for DGER parameters between asymptomatic and symptomatic patients taking PPIs.

*Insert Table 2 here

**DGER among patients with non-erosive reflux disease**

Fifteen studies evaluated DGER among patients with NERD (Table 3). The presence of DGER ranged between 10 – 63% and percent time where DGER was present among studies, which utilized Bilitec, ranged between a median of 0.1%19 to mean of 7.7%20. All but one study21
compared a NERD group with erosive oesophagitis, healthy volunteers or Barrett’s oesophagus. The prevalence or degree of DGER among NERD was less than erosive oesophagitis or Barrett’s in all studies.

*Insert Table 3 here*

**DGER among patients with erosive oesophagitis**

Seventeen studies assessed the presence of DGER among patients with erosive oesophagitis (Table 4). The prevalence of DGER, among studies which utilized Bilitec 2000© with erosive oesophagitis, ranged between 22% and 80%. The percentage of time DGER was present ranged between median 3.5%\(^{22}\) and a mean 19%\(^{23}\).

*Insert Table 4 here*

**DGER among patients with Barrett’s oesophagus**

Twenty-three studies evaluated DGER among patients with Barrett’s oesophagus (Table 5). Twenty one studies compared the degree of DGER with healthy volunteers, non-erosive reflux or erosive oesophagitis. In all studies where a comparison was made Barrett’s oesophagus had a greater prevalence or degree of DGER, when compared with other groups. The prevalence of DGER ranged between 50% - 100%. The percentage of time DGER was abnormal, among Bilitec studies in Barrett’s, ranged from 7.8%\(^{22}\) to 48%\(^{14}\). Eight studies\(^{14,19,24,25,26,27,28,29}\) provided comparisons between non-dysplastic and dysplastic Barrett’s, with or without early adenocarcinoma, or short vs long segment Barrett’s. All but one\(^{26}\) of these eight studies found greater prevalence or percent time of DGER among complicated or longer segment Barrett’s than uncomplicated or short segment Barrett’s.

**Treatment of DGER**

Thirteen studies evaluated the treatment of bile reflux (Table 6). The therapies included nine evaluating PPIs\(^{29-37}\), two studies evaluating prokinetics\(^{38,39}\), one study evaluating surgery\(^{29}\), one evaluating histamine receptor antagonists\(^{40}\) and one evaluating baclofen\(^{41}\).
Ten studies utilized Bilitec 2000 as the device to measure bile reflux, three studies used a sodium ion electrode. Only one study utilized a randomised controlled trial design\textsuperscript{39}.

Nine studies evaluating the effect of a PPI utilized different doses ranging from 20 to 80 mg per day. The time that evaluation of bile reflux occurred among studies with PPI ranged from five days to eight weeks. In all studies DGER reduced post PPI treatment. Notably one study found, among patients with ongoing symptoms despite PPI therapy and abnormal pH or Bilitec, who were then given high dose PPI (80 mg pantoprazole), that those who experienced symptom improvement demonstrated a significant reduction in DGER but patients who had no change to symptoms did not\textsuperscript{35}. Similarly, Yachimski et al\textsuperscript{37} found 18 of 23 patients with Barrett’s normalised DGER post 20 mg BD Rabeprazole. Among the remaining five patients who had persistently abnormal DGER, 4 out of 5 achieved normalisation with rabeprazole 40 mg BD. The one study which evaluated a histamine receptor antagonist\textsuperscript{40}(Famotidine 40 mg i.v. every 12 hours) showed reduction in DGER. However, the study was conducted in the highly specific context of critically ill mechanically ventilated patients.

Two studies\textsuperscript{38, 39} evaluated the effect of cisapride (5HT4 receptor agonist) on DGER outcomes. Both studies utilized a sodium ion electrode as the means of measuring DGER. Among patients who were given cisapride 10 mg QID\textsuperscript{38} for seven days for either Barrett’s oesophagus or erosive oesophagitis, 8 of 12 Barrett’s patients and 2 of 4 erosive oesophagitis patients demonstrated reductions in DGER measures. In a randomised controlled trial Smythe et al\textsuperscript{39} compared add-on cisapride 20 mg BD with placebo in patients with Barrett’s oesophagus taking PPIs. There were no significant changes of DGER post treatment in the cisapride group or between arms at follow-up.

Koek et al\textsuperscript{41} examined the effect of baclofen (5 mg to 20 mg three times daily), a GABA\textsubscript{B} agonist, in addition to PPIs for patients with persistent symptoms and a normal pH but pathological Bilitec 2000 at baseline. At follow-up patients demonstrated a significant reduction of reflux symptoms compared with baseline. DGER parameters all significantly improved at follow-up including median percent time DGER was present: 13.8\% at baseline to 6.1\% under baclofen treatment.
Stein et al. examined the effect of a Nissen Fundoplication in 16 patients with DGER. All but one of the 16 patients normalised DGER parameters measured with Bilitec 2000 at follow-up. The mean percent time of DGER significantly reduced at follow-up from 16.6% to 2.4%.

*Insert Table 6 here*

**Quality Assessment**

The studies presented in this systematic review were primarily of low to moderate quality. Most of the studies in this review did not clearly describe how patients were selected. Of the interventional studies evaluated in this review, all but one employed a randomised controlled trial design. All of the intervention studies had a moderate or serious risk of bias.

**Discussion**

To our knowledge this is the first systematic review evaluating DGER prevalence among GERD, its effect on oesophageal symptoms, oesophageal lesions and its treatment. This systematic review identified several consistent findings among the studies identified. Patients with more advanced oesophageal lesions demonstrated a greater degree of DGER compared to those with simpler oesophageal lesions. This review also identified that symptoms or symptom association among patients on standard PPI doses are unlikely to be explained by DGER alone.

Approximately 40% of patients with GERD have an inadequate symptom response to PPI therapy. This prevalent group represents a heterogeneous population which includes reflux hypersensitivity, functional heartburn and persisting pathological reflux. Our review identified five studies which demonstrated that 45 – 68% of patients with GERD had DGER present despite standard dose PPI therapy. In this review we found insufficient evidence supporting the postulation that inadequately treated bile reflux may play a role in patients with persistent symptoms on standard dose PPI therapy. Gasiorowska et al. and Hershcovici et al. examined patients who were asymptomatic and symptomatic despite standard dose PPI. Both studies did not find a significant difference in DGER parameters between the two groups. These two studies develop an argument that DGER found in...
symptomatic patients on standard dose PPI therapy does not represent a significant explanation for symptoms.

The correlation between symptoms and the presence of GERD with or without oesophageal lesions is not straightforward. While establishing a role for acid reflux in GERD symptom generation can be supported through statistical analyses of reflux-symptom temporal association (e.g. by symptom association probability) and by responses to acid suppressive therapy, this is less easy for “bile reflux”. The construct of the Bilitec 2000 probe, with a cap prone to trap small liquid quantities, may prevent it from adequately reflecting oesophageal bile clearance. Measuring bile clearance is also impeded by different clearance rates of oesophageal bile and acid. In an examination of consecutive patients presenting with reflux symptoms undergoing pH and Bilitec monitoring over 24 hours, Marshall et al were unable to demonstrate a relationship between symptoms and the presence of DGER. In a similar consecutive series Koek et al showed that both symptom index and symptom association probability were greater for acid reflux than DGER or mixed reflux. These studies suggest a higher perception for acid reflux compared to DGER or may reflect the limitations of Bilitec 2000 in generating a symptom association.

The investigated literature supports that Barrett’s oesophagus is associated with a greater degree of DGER than erosive oesophagitis, NERD and controls. This finding is strengthened by two large cohorts which found, via a multivariate analysis, that DGER was independently associated with Barrett’s oesophagus. The contribution of bile to the progression of Barrett’s oesophagus has been hypothesised by multiple factors in in vitro studies. Quante et al demonstrated in a mouse model that the development of Barrett’s ooesophagus and ooesophageal adenocarcinoma were accelerated by exposure to bile acids. Zhang et al found that Barrett’s cell lines, when exposed to bile salts, were more likely to undergo epithelial-to-mesenchymal transition which produced sub-squamous intestinal metaplasia. Marketkar et al found that the percentage of cells with positive staining for the bile acid TGR5 receptor was greater in high grade dysplastic Barrett’s and oesophageal adenocarcinoma than in normal squamous mucosa and non-dysplastic Barrett’s mucosa. Liu et al also found that conjugated bile acids promoted cell proliferation and cancer stem cell migration of oesophageal adenocarcinoma cells, via
Studies which have evaluated the treatment of DGER have primarily utilized therapies designed for GERD. Cisapride, a 5HT-4 receptor agonist primarily known for its properties to improve gastric motility \(^{54}\) has been demonstrated to have some effects in GERD \(^{55}\). Although in a prior double-blind placebo controlled cross-over study cisapride reduced DGER events in symptomatic patients who had previously undergone a partial gastrectomy \(^{56}\), the only randomized controlled trial identified in this systematic review found no difference with placebo for DGER outcomes in patients with no prior history of gastro-oesophageal surgery. Moreover, cisapride has been withdrawn from the market because of cardiac adverse events. In vitro studies have demonstrated the effect of alginates controlling the effect of bile acids \(^{57}^{58}\), however clinical studies have yet to evaluate alginates effect in DGER.

In an examination of patients pre and post 20 mg twice daily omeprazole, Marshall et al \(^{31}\) found not only a significant reduction in oesophageal acid exposure but also in oesophageal and gastric bilirubin exposure. In the other eight studies which evaluated the effect of PPIs on DGER confirmed these findings \(^{29, 30, 32-37}\). Moreover, Kunsch et al demonstrated that 80 mg of pantoprazole daily did not change DGER parameters among patients who did not improve symptoms but did among symptom responders\(^{36}\). Acid volume reduction is a theorized mechanism for the observed attenuation of DGER seen with PPI therapy\(^{59}\).

Transient lower oesophageal sphincter relaxations (TLESRs) have been demonstrated to be the most common manometric finding underlying reflux events in GERD patients\(^{60}\). TLESRs have been shown to be suppressed with GABA-B receptor agonists, such as baclofen, and reflux events were reduced in proof-of-concept studies \(^{61, 62}\). Koek et al\(^{41}\) examined the effect of baclofen on symptomatic patients despite PPI therapy. They showed that the number of DGER episodes and the number of long-lasting DGER episodes (>5minutes) significantly improved along with a cumulative reflux severity score after 14 days of baclofen 20 mg t.i.d.
Agents to treat DGER specific mechanisms have only been recently examined. IW-3718 is a gastric retentive capsule which contains the bile acid sequestrant colesevelam, developed for the treatment of DGER through binding and neutralizing bile in the stomach. A phase-2 study selected patients with persisting typical GERD symptoms on single dose PPI therapy, with a demonstrated erosive oesophagitis or pathological acid reflux (24 hour acid exposure above 4.2%) on wireless pH monitoring. They were treated for 8 weeks with placebo or 500, 1000 or 1500 mg IW-3718 in addition to the daily PPI dose. Significant reductions in the typical symptoms of heartburn and regurgitation were demonstrated for the 1500 mg dose in comparison to placebo. Patient level changes of endoscopically visible erosive oesophagitis also improved in 87% of patients with the active drug compared with 25% taking placebo, signaling that IW-3718 may have a healing effect. Whether these symptom improvements would be replicated in patients with pathological DGER, irrespective of the presence of pathological acid reflux, remains to be shown.

The mechanisms that explain why bile sequestration improves symptoms and endoscopic lesions deserve formal study, but our current understanding of the pathophysiology of GERD and physiology of bile acids may already provide clues toward this end. One simple explanation for the improvements could be via an effect on reducing the volume of the refluxate. Another simple explanation could be that sequestration of bile removes the damaging substance in the oesophagus. Although bile has been shown to augment motility, as seen in the colon, an ex vivo study of rat and human lower oesophageal sphincter tissue with bile acids showed that the addition of the bile sequestrant colesevelam, attenuated bile acid induced relaxation of muscle tissue. Alternatively, a reduction in bile acid triggered glucagon-like peptide-1 (GLP-1) release from enteroendocrine cells, via sequestration, may indirectly improve motility, as GLP-1 inhibits gastric emptying.

There are several limitations to this review. There was heterogeneity in the definition of DGER among most of the studies examined. Although many used the threshold >/= 0.14 bilirubin absorbance with Bilitec, a significant proportion did not. The time DGER was greater than the threshold also differed among the studies, suggesting no uniform definition for what constitutes bile reflux, as opposed to acid reflux which has a more universally accepted definition. The lack of uniformly accepted diagnostic criteria for DGER, among the studies in this review, limits the ability to provide conclusive evidence regarding its
prevalence. The impact of a white diet\textsuperscript{20} on DGER studies has been established but this was not uniformly reported on in most of the earlier studies in this review. The studies presented in this systematic review were of low to moderate quality. Many studies did not present detailed information on how participants were selected and all but one\textsuperscript{39} treatment study did not employ a randomised controlled trial design, limiting the ability to make conclusions about efficacy of treatments. The majority of the studies in this review were from highly selected population from university referral hospitals. Whether this selected population influences outcomes is also not certain. Although most studies provided grading endoscopic and histological evidence of erosive oesophagitis and Barrett’s, it is not clear if this was performed in a consistent fashion and second or central reading of the images was not done.

DGER and the presence of bile is commonly associated with patients presenting with typical symptoms of GERD, persisting symptoms on PPIs and advanced oesophageal lesions. PPIs appear to have some efficacy in reducing DGER, but the mechanism explaining this reduction is not yet clear. However, the reduction of DGER parameters on PPI may represent an epiphenomenon, unrelated to symptom improvement. Indeed, we found insufficient evidence supporting that DGER explains symptoms persisting during PPI therapy. There are pharmacological agents on the horizon, that directly address DGER mechanisms which are likely to revive a revaluation of this entity and its contribution to GERD.

\textit{Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for literature search and study selection}

Abbreviation: DGER= duodenogastroesophageal reflux
<table>
<thead>
<tr>
<th>Date of Study</th>
<th>Author</th>
<th>Country</th>
<th>Method of Assessing DGER</th>
<th>Definition of pathologic DGER</th>
<th>Patient population/ Subgroups</th>
<th>Number of participants</th>
<th>Prevalence of Bile Reflux</th>
<th>Degree of Bile Reflux</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>Jefferis et al</td>
<td>Sweden</td>
<td>Oesophageal bile aspiration</td>
<td>Not predefined</td>
<td>HV vs GERD</td>
<td>Total participants: 128</td>
<td>Trace bile detected in GERD patients: 86% (32 / 37)</td>
<td>Not presented</td>
</tr>
<tr>
<td>1989</td>
<td>Ekberg et al</td>
<td>UK</td>
<td>Oesophageal bile aspiration</td>
<td>Total bile acid concentration &gt;1105 micromol/L [95% centile upper limit, healthy controls]</td>
<td>HV vs GERD vs Barrett's</td>
<td>Total participants: 60</td>
<td>Evros GERD: 20% (15 / 75)</td>
<td>Not presented</td>
</tr>
<tr>
<td>1994</td>
<td>Stein et al</td>
<td>United States</td>
<td>Oesophageal bile aspiration</td>
<td>Total bile acid concentration &gt;88 micromol/L (&gt;95 centile for Healthy controls)</td>
<td>HV vs GERD</td>
<td>Total participants: 95</td>
<td>GERD: Supine mean 0377 micromol/L +/- 24.5 SEM</td>
<td>Not presented</td>
</tr>
<tr>
<td>1994</td>
<td>Champion et al</td>
<td>United States</td>
<td>Bilitec 2000</td>
<td>% time Absorbance &gt;0.14</td>
<td>HV vs GERD vs Barrett's</td>
<td>Total participants: 41</td>
<td>Time absorbance was pathological</td>
<td>Time absorbance was pathological</td>
</tr>
<tr>
<td>1995</td>
<td>Oberg et al</td>
<td>Norway</td>
<td>Oesophageal bile aspiration</td>
<td>Not predefined</td>
<td>HV vs GERD vs Barrett's</td>
<td>Total participants: 131</td>
<td>Trace bile detected in GERD patients: 63% (32 / 37)</td>
<td>Not presented</td>
</tr>
<tr>
<td>1996</td>
<td>Venut et al</td>
<td>United States</td>
<td>Bilitec 2000</td>
<td>% time Absorbance &gt;0.14, Abnormal: &gt;1.8% time &gt;0.14 (95% centile of healthy controls)</td>
<td>HV vs GERD vs Barrett's</td>
<td>Total participants: 70</td>
<td>Erosive Oesophagitis: Median peak bile acid of Barret's median for healthy controls</td>
<td>Not presented</td>
</tr>
<tr>
<td>1997</td>
<td>Marshall et al</td>
<td>UK</td>
<td>Bilitec 2000</td>
<td>% time Absorbance &gt;0.14, or 2 mins either side of symptom event having &gt;10seconds of absorbance &gt;0.14</td>
<td>GERD split in two groups</td>
<td>Total participants: 59</td>
<td>Time absorbance was pathological</td>
<td>Non acid reflux patients: 0.1% (IQ 0 - 1.7)</td>
</tr>
<tr>
<td>1997</td>
<td>Kauer et al</td>
<td>Germany</td>
<td>Oesophageal bile aspiration</td>
<td>Pathological bile reflux was defined by the 95th centile cut-off from the healthy population</td>
<td>HV vs GERD</td>
<td>Total participants: 80</td>
<td>Time absorbance was pathological</td>
<td>GERD Median 2.6% (IQ 0 - 8)</td>
</tr>
<tr>
<td>1998</td>
<td>Stein et al</td>
<td>Germany</td>
<td>Bilitec 2000</td>
<td>% of time absorbance &gt;0.14</td>
<td>HV vs GERD vs Barrett's</td>
<td>Total participants: 131</td>
<td>GERD median 2.6% (IQ 0 - 8)</td>
<td>Not presented</td>
</tr>
<tr>
<td>1998</td>
<td>Nagata et al</td>
<td>Japan</td>
<td>Oesophageal bile aspiration</td>
<td>Not predefined</td>
<td>HV vs GERD &amp; Barrett's</td>
<td>Total participants: 40</td>
<td>GERD median 2.6% (IQ 0 - 8)</td>
<td>Not presented</td>
</tr>
</tbody>
</table>
### Table 2: DGER on PPI therapy

<table>
<thead>
<tr>
<th>Date of Study</th>
<th>Author</th>
<th>Country</th>
<th>Method of Assessing DGER</th>
<th>Definition of pathologic DGER</th>
<th>Patient population/Subgroups</th>
<th>Number of participants</th>
<th>Prevalence of Bile Reflux</th>
<th>Degree of Bile Reflux</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>Koek et al&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Belgium</td>
<td>Bilitec 2000</td>
<td>% time absorbance &gt;0.14, &gt;1.8% of time</td>
<td>HV, healthy volunteers; GERD, gastro-oesophageal reflux disease; NERD, non-erosive reflux disease; IQR, Inter-quartile range; SAP, Symptom association probability; DGER, duodenogastroesophageal reflux;</td>
<td>Total participants: 422</td>
<td>51% (215 /422)</td>
<td>Time absorbance was pathological: All patients median 4.9% (IQR 0.8-20.2) NERD median 2.8% (IQR 0.9-12.4) Erosive Oesophagitis median 8.8% median (IQR 2-25) Barrett’s median 27% (IQR 12-41)</td>
</tr>
<tr>
<td>2020</td>
<td>De Bertoldi et al</td>
<td>Italy</td>
<td>Bilitec 2000</td>
<td>% time absorbance &gt;0.14; &gt;1.8% of time</td>
<td>HV, healthy volunteers; GERD, gastro-oesophageal reflux disease; NERD, non-erosive reflux disease; IQR, Inter-quartile range; SAP, Symptom association probability; DGER, duodenogastroesophageal reflux;</td>
<td>Total participants: 42</td>
<td>56% (23/42)</td>
<td>Time absorbance was pathological: Median bile reflux pathological 9.6% (IQR 8% - 13%)</td>
</tr>
</tbody>
</table>

HV, healthy volunteers; GERD, gastro-oesophageal reflux disease; NERD, non-erosive reflux disease; IQR, Inter-quartile range; SAP, Symptom association probability; DGER, duodenogastroesophageal reflux; PPI, proton pump inhibitor; This article is protected by copyright. All rights reserved
Table 3: Studies which evaluate the presence of DGER among non-erosive oesophageal reflux (NERD)

<table>
<thead>
<tr>
<th>Date of Study</th>
<th>Author</th>
<th>Country</th>
<th>Method of Assessing Bile Reflux</th>
<th>Definition of pathologic bile reflux</th>
<th>Patient population/ Subgroups</th>
<th>Number of participants</th>
<th>Prevalence of Bile Reflux</th>
<th>Degree of Bile Reflux</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>Vaezi et al</td>
<td>United States</td>
<td>Bilitec 2000</td>
<td>% time absorbance &gt;0.24, Abnormal: &gt;1.8% time &gt;0.14 (55th centile of healthy controls)</td>
<td>HV vs GERD vs Barrett’s</td>
<td>Total participants: 70</td>
<td>GERD 65% (47 / 70)</td>
<td>Acid reflux only mean 12.2% (range 6.5 - 20.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total participants: 45</td>
<td>GERD 48% (21 / 45)</td>
<td>Acid and bile reflux mean 16.1% (range 3.6 - 61)</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>Stein et al</td>
<td>Germany</td>
<td>Bilitec 2000</td>
<td>% of time absorbance &gt;0.25, Abnormal: &gt;6.8% of time &gt;0.25 absorbance (5th centile cut-off of healthy controls)</td>
<td>HV vs NERD vs Erosive Oesophagitis vs Barrett’s no dysplasia vs Barrett’s with adenocarcinoma</td>
<td>Total participants: 133</td>
<td>GERD 38% (17 / 45)</td>
<td>Acid reflux only mean 12.2% (range 6.5 - 20.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total participants: 53</td>
<td>GERD 63% (10 / 53)</td>
<td>Acid and bile reflux mean 16.1% (range 3.6 - 61)</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Nehra et al</td>
<td>UK</td>
<td>Oesophageal bile aspiration</td>
<td>Not predefined</td>
<td>HV vs GERD &amp; Barrett’s</td>
<td>Total participants: 40</td>
<td>NERD 38% (9 / 24)</td>
<td>Acid reflux only mean 12.2% (range 6.5 - 20.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total participants: 40</td>
<td>GERD 38% (9 / 24)</td>
<td>Acid and bile reflux mean 16.1% (range 3.6 - 61)</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Oberg et al</td>
<td>United States</td>
<td>Bilitec 2000</td>
<td>% time absorbance &gt;0.2, Abnormal: &gt;1.7% time absorbance &gt;0.2</td>
<td>NERD vs Erosive Oesophagitis vs Barrett’s (short-segment vs long segment)</td>
<td>Total participants: 164</td>
<td>GERD 30% (20 / 67)</td>
<td>Acid reflux only mean 12.2% (range 6.5 - 20.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total participants: 164</td>
<td>GERD 30% (20 / 67)</td>
<td>Acid and bile reflux mean 16.1% (range 3.6 - 61)</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Marshall et al</td>
<td>UK</td>
<td>Bilitec 2000</td>
<td>% time absorbance &gt;0.24, Abnormal: &gt;7% of time absorbance &gt;0.14</td>
<td>GERD</td>
<td>Total participants: 113</td>
<td>GERD 17% (7 / 41)</td>
<td>Not defined</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total participants: 113</td>
<td>GERD 17% (7 / 41)</td>
<td>Not defined</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Casano et al</td>
<td>Belgium</td>
<td>Bilitec 2000</td>
<td>% time absorbance &gt;0.14, Abnormal: &gt;0.6% of time &gt;0.14 absorbance</td>
<td>GERD with erosive Oesophagitis</td>
<td>Total participants: 84</td>
<td>GERD 13% (17 / 131)</td>
<td>Acid reflux only mean 12.2% (range 6.5 - 20.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total participants: 84</td>
<td>GERD 13% (17 / 131)</td>
<td>Acid reflux only mean 12.2% (range 6.5 - 20.7)</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Shiga et al</td>
<td>Japan</td>
<td>Bilitec 2000</td>
<td>% of time absorbance &gt;0.15, Abnormal: &gt;5% time &gt;0.15</td>
<td>HV vs GERD</td>
<td>Total participants: 53</td>
<td>GERD 55% (29 / 53)</td>
<td>Acid reflux only mean 12.2% (range 6.5 - 20.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total participants: 53</td>
<td>GERD 55% (29 / 53)</td>
<td>Acid reflux only mean 12.2% (range 6.5 - 20.7)</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Tack et al</td>
<td>Belgium</td>
<td>Bilitec 2000</td>
<td>% of time absorbance &gt;0.14 episode was considered &gt;0.24 for greater than 30secs, Upper limit of normal from healthy subjects used but not documented</td>
<td>HV vs GERD</td>
<td>Total participants: 251</td>
<td>GERD 55% (137 / 251)</td>
<td>Acid reflux only mean 12.2% (range 6.5 - 20.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total participants: 251</td>
<td>GERD 55% (137 / 251)</td>
<td>Acid reflux only mean 12.2% (range 6.5 - 20.7)</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Xu et al</td>
<td>China</td>
<td>Bilitec 2000</td>
<td>Abnormal if absorbance &gt;0.14 for &gt;2.53%</td>
<td>GERD</td>
<td>Total participants: 95</td>
<td>GERD 46% (21 / 46)</td>
<td>Acid reflux only mean 12.2% (range 6.5 - 20.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total participants: 95</td>
<td>GERD 46% (21 / 46)</td>
<td>Acid reflux only mean 12.2% (range 6.5 - 20.7)</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Sabri Fak et al</td>
<td>Egypt</td>
<td>Bilitec 2000</td>
<td>% time absorbance &gt;0.14, Abnormal if &gt;0.14 for &gt;1.9%</td>
<td>HV vs GERD vs Barrett’s</td>
<td>Total participants: 51</td>
<td>GERD 63% (33 / 51)</td>
<td>Acid reflux only mean 12.2% (range 6.5 - 20.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total participants: 51</td>
<td>GERD 63% (33 / 51)</td>
<td>Acid reflux only mean 12.2% (range 6.5 - 20.7)</td>
<td></td>
</tr>
</tbody>
</table>
This article is protected by copyright. All rights reserved
<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Location</th>
<th>Test Phase</th>
<th>Participants</th>
<th>GERD vs Barrett's</th>
<th>GERD vs Erosive Oesophagitis vs Barrett's</th>
<th>GERD vs NERD vs Erosive Oesophagitis vs Barrett's</th>
<th>GERD median peak bile acids</th>
<th>Erosive Oesophagitis median peak bile acid</th>
<th>Barrett's median peak bile acid</th>
<th>Time absorbance was pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Xu et al.</td>
<td>China</td>
<td>Bilitec 2000</td>
<td>104</td>
<td>Total participants: 251</td>
<td>40 HV vs 211 GERD</td>
<td>GERD</td>
<td>NERD Solid meals: median 7.7% (IQR 3.7 - 17.3)</td>
<td>Erosive Oesophagitis: median 15.3% (IQR 4 - 42.3)</td>
<td>Erosive Oesophagitis: Liquid meal 3.3% (IQR 0.5 - 14.5)</td>
<td>Barrett's median topic: 16.2% (IQR 0 - 2.7)</td>
</tr>
<tr>
<td>2001</td>
<td>Menges et al.</td>
<td>Germany</td>
<td>Bilitec 2000</td>
<td>104</td>
<td>Total participants: 43</td>
<td>20 Erosive Oesophagitis vs 23 Barrett's</td>
<td>Erosive Oesophagitis: median 12.8% (IQR 1.9 - 74.9)</td>
<td>Barrett's median peak bile acid 181 mmol/L (range 30 - 820)</td>
<td>Barrett's median peak bile 14.03 mmol/L (range 0 - 1010)</td>
<td>Barrett's median peak bile acid 181 mmol/L (range 30 - 820)</td>
<td>Not presented</td>
</tr>
<tr>
<td>2002</td>
<td>Oberg et al.</td>
<td>Belgium</td>
<td>Bilitec 2000</td>
<td>104</td>
<td>Total participants: 91</td>
<td>Patients</td>
<td>GERD &amp; Barrett's</td>
<td>GERD Solid meals: median 7.7% (IQR 3.7 - 17.3)</td>
<td>Erosive Oesophagitis: median 15.3% (IQR 4 - 42.3)</td>
<td>Erosive Oesophagitis: Liquid meal 3.3% (IQR 0.5 - 14.5)</td>
<td>Barrett's median peak bile acid 181 mmol/L (range 30 - 820)</td>
</tr>
<tr>
<td>2003</td>
<td>Tack et al.</td>
<td>Belgium</td>
<td>Bilitec 2000</td>
<td>104</td>
<td>Total participants: 104</td>
<td>104 GERD</td>
<td>GERD &amp; Barrett's</td>
<td>GERD Solid meals: median 7.7% (IQR 3.7 - 17.3)</td>
<td>Erosive Oesophagitis: median 15.3% (IQR 4 - 42.3)</td>
<td>Erosive Oesophagitis: Liquid meal 3.3% (IQR 0.5 - 14.5)</td>
<td>Barrett's median peak bile acid 181 mmol/L (range 30 - 820)</td>
</tr>
<tr>
<td>2006</td>
<td>Xu et al.</td>
<td>China</td>
<td>Bilitec 2000</td>
<td>104</td>
<td>Total participants: 95</td>
<td>GERD</td>
<td>GERD</td>
<td>GERD Solid meals: median 7.7% (IQR 3.7 - 17.3)</td>
<td>Erosive Oesophagitis: median 15.3% (IQR 4 - 42.3)</td>
<td>Erosive Oesophagitis: Liquid meal 3.3% (IQR 0.5 - 14.5)</td>
<td>Barrett's median peak bile acid 181 mmol/L (range 30 - 820)</td>
</tr>
<tr>
<td>2007</td>
<td>Wolff et al.</td>
<td>Belgium</td>
<td>Bilitec 2000</td>
<td>104</td>
<td>Total participants: 91</td>
<td>Patents</td>
<td>GERD &amp; Barrett's</td>
<td>GERD &amp; Barrett's: median 15.3% (IQR 4 - 42.3)</td>
<td>Erosive Oesophagitis: median 15.3% (IQR 4 - 42.3)</td>
<td>Erosive Oesophagitis: Liquid meal 3.3% (IQR 0.5 - 14.5)</td>
<td>Barrett's median peak bile acid 181 mmol/L (range 30 - 820)</td>
</tr>
<tr>
<td>2008</td>
<td>Brilliantino et al.</td>
<td>Italy</td>
<td>Bilitec 2000</td>
<td>104</td>
<td>Total participants: 92</td>
<td>GERD on HPI</td>
<td>GERD &amp; Barrett's</td>
<td>GERD &amp; Barrett's: median 15.3% (IQR 4 - 42.3)</td>
<td>Erosive Oesophagitis: median 15.3% (IQR 4 - 42.3)</td>
<td>Erosive Oesophagitis: Liquid meal 3.3% (IQR 0.5 - 14.5)</td>
<td>Barrett's median peak bile acid 181 mmol/L (range 30 - 820)</td>
</tr>
</tbody>
</table>

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Table 5: Studies which evaluate the presence of DGER among patients with Barrett’s oesophagus

<table>
<thead>
<tr>
<th>Date</th>
<th>Author</th>
<th>Country</th>
<th>Method of Assessing Bile Reflux</th>
<th>Definition of pathologic bile reflux</th>
<th>Patient population/Subgroups</th>
<th>Number of participants</th>
<th>Prevalence of Bile Reflux</th>
<th>Degree of Bile Reflux</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Iftikhar et al</td>
<td>UK</td>
<td>Oesophageal bile aspiration</td>
<td>Total bile acid concentration, &gt;1105 micromol/L (95% centile upper limit, healthy controls)</td>
<td>HV vs GERD vs Barrett’s</td>
<td>Total participants: 60 - 15 HV vs 30 Barrett’s vs 15 GERD</td>
<td>Erosive GERD 20% (3 / 15) Barrett’s 50% (15 / 30)</td>
<td>Erosive GERD: Median 817.3 micromol/L (Range 123.8 – 5721) Barrett’s: Median 1351.7 micromol/L (Range 0-14011)</td>
</tr>
<tr>
<td>2000</td>
<td>Koek et al</td>
<td>Belgium</td>
<td>Bilitec 2000</td>
<td>% time absorbance &gt;0.14, episodes &gt;5 mins &gt;0.14</td>
<td>GERD &amp; Barrett’s</td>
<td>Total participants: 422 - Suspected GERD 422 Erosive oesophagitis 164 Barrett’s 30</td>
<td>51% (215 / 422)</td>
<td>Time absorbance was pathological: All patients median 4.9% (IQR 0.8-20.2) NERD median 2.8% (IQR 0.3-12.4) Erosive Duodenal reflux median 8.8% median (IQR 2.25) Barrett’s median 27.4% (IQR 12.4)</td>
</tr>
<tr>
<td>2009</td>
<td>Monaco et al</td>
<td>Italy</td>
<td>Bilitec 2000</td>
<td>Absorbance &gt;0.14, Normal &lt;7%</td>
<td>GERD &amp; Barrett’s vs on PPI</td>
<td>Total participants: 83 - 22 NERD 43 Erosive oesophagitis 18 Barrett’s</td>
<td>NERD 41% (9 / 22) Erosive Duodenal reflux 77% (31 / 43) Barrett’s 83% (15 / 18)</td>
<td>Time absorbance was pathological: NERD mean 9.2% +/- 5.2% SD Erosive Duodenal reflux: Grade A/B mean 10.9% +/- 4.6 SD Grade C/D mean 16.1% +/- 6.3 SD Barrett’s: Short segment mean 15.8% +/- 6.7 SD Long segment mean 10.3% +/- 6.2 SD</td>
</tr>
</tbody>
</table>

HV, healthy volunteers; GERD, gastro-oesophageal reflux disease; NERD, non-erosive reflux disease; IQR, Inter-quartile range; SAP, Symptom association probability; DGER, duodenogastroesophageal reflux; SD, standard deviation; SEM, standard error of the mean; PPI, proton pump inhibitor
<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Location</th>
<th>Method</th>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>Caldwell et al</td>
<td>United States</td>
<td>Bilitec 2000</td>
<td>36</td>
<td>No pathological absorbance &gt;0.25 or &gt;0.15</td>
</tr>
<tr>
<td>1995</td>
<td>Vaezi et al</td>
<td>United States</td>
<td>Bilitec 2000</td>
<td>32</td>
<td>No pathological absorbance &gt;0.15</td>
</tr>
<tr>
<td>1995</td>
<td>Vaezi et al</td>
<td>United States</td>
<td>Bilitec 2000</td>
<td>70</td>
<td>No pathological absorbance &gt;0.14</td>
</tr>
<tr>
<td>1996</td>
<td>Marshall et al</td>
<td>United States</td>
<td>Bilitec 2000</td>
<td>128</td>
<td>No pathological absorbance &gt;0.14</td>
</tr>
<tr>
<td>1996</td>
<td>Stein et al</td>
<td>Germany</td>
<td>Bilitec 2000</td>
<td>Total participants: 113</td>
<td>No pathological absorbance &gt;0.14</td>
</tr>
<tr>
<td>1996</td>
<td>Oberg et al</td>
<td>United States</td>
<td>Bilitec 2000</td>
<td>Total participants: 32 (23 completed Bilitec testing)</td>
<td>No pathological absorbance &gt;0.14</td>
</tr>
<tr>
<td>1996</td>
<td>Marshall et al</td>
<td>United States</td>
<td>Bilitec 2000</td>
<td>Total participants: 502</td>
<td>No pathological absorbance &gt;0.14</td>
</tr>
<tr>
<td>1997</td>
<td>Cuomo et al</td>
<td>Belgium</td>
<td>Bilitec 2000</td>
<td>Total participants: 84</td>
<td>No pathological absorbance &gt;0.14, Abnormal = &gt;6% of time &gt;0.14 absorbance</td>
</tr>
<tr>
<td>2000</td>
<td>Campos et al</td>
<td>United States</td>
<td>Bilitec 2000</td>
<td>Total participants: 502</td>
<td>No pathological absorbance &gt;0.14</td>
</tr>
<tr>
<td>2000</td>
<td>Menges et al</td>
<td>Germany</td>
<td>Bilitec 2000</td>
<td>Total participants: 43</td>
<td>No pathological absorbance &gt;0.2</td>
</tr>
<tr>
<td>2002</td>
<td>Carides et al</td>
<td>Chile</td>
<td>Bilitec 2000</td>
<td>Total participants: 382</td>
<td>No pathological absorbance &gt;0.2</td>
</tr>
<tr>
<td>2002</td>
<td>Zacchello et al</td>
<td>Italy</td>
<td>Bilitec 2000</td>
<td>Total participants: 78</td>
<td>No pathological absorbance &gt;0.2</td>
</tr>
<tr>
<td>2004</td>
<td>Siew et al</td>
<td>UK</td>
<td>Bilitec 2000</td>
<td>Total participants: 128</td>
<td>No pathological absorbance &gt;0.14 for 1.8%</td>
</tr>
<tr>
<td>2007</td>
<td>Wolf et al</td>
<td>Germany</td>
<td>Bilitec 2000</td>
<td>Total participants: 64</td>
<td>No pathological absorbance &gt;0.25, abnormal if &gt;1.1% of time &gt;0.25</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Population</th>
<th>DGER Measured</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Champion et al</td>
<td>1994</td>
<td>USA</td>
<td>Observational Intervention</td>
<td>Omeprazole 20mg BD</td>
<td>GERD &amp; Barrett's</td>
<td>Bilitec 2000</td>
<td>9 Patients (3 GERD and 6 Barrett's) Mean % time absorbance &gt;0.14 Pre PPI: 4.3% +/- 0.6 SD Post PPI: 4.7% +/- 0.7 SEM</td>
</tr>
<tr>
<td>Smythe et al</td>
<td>1997</td>
<td>UK</td>
<td>Observational Intervention</td>
<td>Cisapride 10mg QID</td>
<td>Barrett's</td>
<td>Sodium Ion electrode</td>
<td>67% (8 of 12) Barrett's reduced DGER 50% (2 of 4) Erosive Oesophagitis reduced DGER</td>
</tr>
<tr>
<td>Gadel-hak et al</td>
<td>2007</td>
<td>Egypt</td>
<td>Bilitec 2000</td>
<td>% time absorbance &gt;0.14, Abnormal if &gt;0.14 for &gt;1.5%</td>
<td>HV vs GERD vs Barrett's</td>
<td>Total participants: 91 Patients</td>
<td>63% (57 / 91) NERD patients: 36% (4 / 11) Erosive Oesophagitis: 62% (44 / 71) Barrett's 100% (9 / 9) Time absorbance was pathological: All patients mean 14.0% (IQR 9-21.3) NERD mean 4.85% (IQR 0.8-9.8) Erosive Oesophagitis: mean 8.18% +/- 11.28 SD Barrett's: mean 15.46% +/- 9.48 SD</td>
</tr>
<tr>
<td>Smythe et al</td>
<td>2007</td>
<td>UK</td>
<td>Sodium Ion Selective Electrode</td>
<td>% of time Na⁺ &gt;50mmol/l</td>
<td>HV vs Barrett's</td>
<td>Total participants: 30</td>
<td>Not stated</td>
</tr>
<tr>
<td>Brifanteiro et al</td>
<td>2007</td>
<td>Italy</td>
<td>Bilitec 2000</td>
<td>% of time absorbance &gt;0.14, normal &lt;7% of time</td>
<td>GERD on PPI</td>
<td>Total participants: 92</td>
<td>Total 67% (62 / 92) NERD 36% (9 / 25) Erosive Oesophagitis: 80% (36 / 45) Barrett's 85% (17 / 20) Time absorbance was pathological: All patients median 4.9% (IQR 0.8-20.2) NERD median 2.8% (IQR 0.5-12.4) Erosive Oesophagitis median 8.8% median (IQR 2-25) Barrett's median 27.4% (IQR 12-46)</td>
</tr>
<tr>
<td>Kne et al</td>
<td>2008</td>
<td>Belgium</td>
<td>Bilitec 2000</td>
<td>% time absorbance &gt;0.14, episodes &gt;5mins &gt;0.14</td>
<td>GERD &amp; Barrett's</td>
<td>Total participants: 422</td>
<td>Total 67% (62 / 92) NERD 36% (9 / 25) Erosive Oesophagitis: 80% (36 / 45) Barrett's 85% (17 / 20) Time absorbance was pathological: All patients median 4.85% (IQR 0.8-9.8) NERD median 2.8% (IQR 0.5-12.4) Erosive Oesophagitis median 8.8% median (IQR 2-25) Barrett's median 27.4% (IQR 12-46)</td>
</tr>
<tr>
<td>Monaco et al</td>
<td>2008</td>
<td>Italy</td>
<td>Bilitec 2000</td>
<td>Absorbance &gt;0.14, normal &lt;7%</td>
<td>GERD &amp; Barrett's on PPI</td>
<td>Total participants: 92</td>
<td>Total 67% (62 / 92) NERD 36% (9 / 25) Erosive Oesophagitis: 80% (36 / 45) Barrett's 85% (17 / 20) Time absorbance was pathological: All patients median 4.9% (IQR 0.8-20.2) NERD median 2.8% (IQR 0.5-12.4) Erosive Oesophagitis median 8.8% median (IQR 2-25) Barrett's median 27.4% (IQR 12-46)</td>
</tr>
<tr>
<td>Yachimski et al</td>
<td>2015</td>
<td>United States</td>
<td>Bilitec 2000</td>
<td>% of time absorbance &gt;0.14 Abnormal &gt;51.8 time</td>
<td>Uncomplicated Barrett's</td>
<td>Total participants: 29 (23 had Bilitec)</td>
<td>93% Abnormal</td>
</tr>
</tbody>
</table>

HV, healthy volunteers; GERD, gastro-oesophageal reflux disease; NERD, non-erosive reflux disease; IQR, Inter-quartile range; SAP, Symptom association probability; DGER, duodenogastroesophageal reflux; SD, standard deviation; SEM, standard error of the mean; PPI, proton pump inhibitor
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Study Type</th>
<th>Intervention Details</th>
<th>Bilitec</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stein et al(29)</td>
<td>1998</td>
<td>Germany</td>
<td>Observational Intervention (in subgroup)</td>
<td>Omeprazole 20mg BD OR Nissen fundoplication (3 – 12 months post surgery)</td>
<td>Bilitec</td>
<td>15 patients Omeprazole 20mg BD or Pre and post Nissen fundoplication (3 – 12 months post surgery). 15 patients Omeprazole 20mg BD or Pre and post Nissen fundoplication. Bilitec: Mean DGER % time absorbance abnormal Pre PPI 16.2% and Post PPI 8.9%. Mean pre surgery DGER 16.6%, Mean post surgery 2.4%</td>
</tr>
<tr>
<td>Marshall et al(30)</td>
<td>1998</td>
<td>UK</td>
<td>Observational intervention</td>
<td>Pre and Post Omeprazole 20mg BD (6 – 10 weeks)</td>
<td>Bilitec</td>
<td>11 of 23 patients underwent esophageal bilirubin monitoring Percent time &gt;0.14 Pre Omeprazole % time DGER present Median 28.9% (Range 5.1 – 67.3); Post omeprazole % time DGER present Median 2.4% (Range 0 - 4.9)</td>
</tr>
<tr>
<td>Menges et al(31)</td>
<td>2001</td>
<td>Germany</td>
<td>Observational Interventional study</td>
<td>Omeprazole or pantoprazole. Doses ranged 20 – 80mg. At least 7 days</td>
<td>Bilitec</td>
<td>Erosive Oesophagitis % time absorbance abnormal Pre PPI median 21.5% (Range 5.8 – 74.9); Post PPI median 0.9% (Range 0-42%); Barrett’s % time absorbance abnormal Pre PPI median 29.8% (Range 0.3 - 84.6); Post PPI median 0.7% (Range 0 - 41);</td>
</tr>
<tr>
<td>Netzer et al(32)</td>
<td>2001</td>
<td>Switzerland</td>
<td>Observational Interventional study</td>
<td>Pantoprazole 40mg Daily Pre and 28 days post PPI</td>
<td>Bilitec</td>
<td>Number of DGER episodes &gt;5mins Pre PPI mean 9.4% +/- 1.2 (SEM) Post PPI 6 +/-1(SEM) p=0.04</td>
</tr>
<tr>
<td>Kuak et al(33)</td>
<td>2003</td>
<td>Belgium</td>
<td>Pre and post intervention Single cohort</td>
<td>Baclofen 5mg -&gt; 20mg TDS with 20mg BD Omeprazole</td>
<td>Bilitec</td>
<td>Time absorbance &gt;0.14 Pre Baclofen median 13.8% (QR 11.8 - 15.5) Post Baclofen median 6.1% (QR 0.8 - 10.6), p&lt;0.05 Episodes lasting greater than 5 minutes Pre Baclofen median 5 (IQR 3 - 8); Post Baclofen median 2 (IQR 0.5 - 4.5), p&lt;0.05</td>
</tr>
<tr>
<td>Smythe et al(34)</td>
<td>2003</td>
<td>UK</td>
<td>Randomised controlled trial</td>
<td>Cisapride 20mg BD, in addition to PPI</td>
<td>Bilitec</td>
<td>DGER % time absorbance abnormal pre and post. 24 hours post Famotidine. DGER 15.3% pre Famotidine to 0.29% post Famotidine</td>
</tr>
<tr>
<td>Xin et al(35)</td>
<td>2003</td>
<td>China</td>
<td>Observational Interventional study</td>
<td>Famotidine 40mg IV BD</td>
<td>Bilitec</td>
<td>DGER % time absorbance abnormal pre and post. 24 hours post Famotidine. DGER 15.3% pre Famotidine to 0.29% post Famotidine</td>
</tr>
<tr>
<td>Smythe et al(36)</td>
<td>2008</td>
<td>UK</td>
<td>Observational Interventional study, pre and post,</td>
<td>Omeprazole 40mg daily</td>
<td>Bilitec</td>
<td>DGER measured on PPI then 5 days off PPI. Mean DGER upright 19mmol/L, Upright off PPI 62mmol/L. Supine DGER on PPI 63mmol/L, supine off PPI 88mmol/L.</td>
</tr>
<tr>
<td>Kunisch et al(37)</td>
<td>2009</td>
<td>Germany</td>
<td>Observational Interventional study, Pre and Post, Uncontrolled</td>
<td>Pantoprazole 80mg Daily</td>
<td>Bilitec</td>
<td>DGER pre PPI absorbance &gt;0.14 Mean 19.9% (SD +/-1.7) vs post 5.7 (SD +/-7.7), p&lt;0.05</td>
</tr>
<tr>
<td>Kunisch et al(38)</td>
<td>2012</td>
<td>Germany</td>
<td>Observational Interventional study</td>
<td>Pantoprazole 80mg Daily for 8 weeks</td>
<td>Bilitec</td>
<td>Patients split into two groups. Symptom responders and non-responders to high dose PPI (% time absorbance abnormal)</td>
</tr>
</tbody>
</table>

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| Yachimski et al. 2015 | USA | Observational interventional study, Pre & post, Uncontrolled | Baseline 1 week off PPI, Rabeprazole 20mg BD for one month. Patients with persisting acid and/or DGER at one month.Rabeprazole 40mg BD, outcomes assessed again after another one month. | Non-dysplastic Barrett’s Oesophagus >3cm | Bilitec 2000 | PPI symptom responders: Pre PPI mean (SD) 22.8% +/-22.8 vs post PPI 6.6% +/-10.8 (p<0.05) | PPI symptom non responder: Pre PPI mean (SD) 24.5% +/-18.6 vs post PPI 22.2% +/-12.7 (p=NS) |

HV, healthy volunteers; GERD, gastro-oesophageal reflux disease; NERD, non-erosive reflux disease; IQR, Inter-quartile range; SAP, Symptom association probability; DGER, duodenogastroesophageal reflux; SD, standard deviation; SEM, standard error of the mean; PPI, proton pump inhibitor; BD, twice a day; QID, 4 times a day; IV, intravenous
References


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Articles Identified by PubMed/MEDLINE search (n=3891)

Records Screened (n=3583)

Duplicate Removed (n=388)

Records Excluded (n=3383)

Full text articles assessed for eligibility (n=120)

Prevalence of DGER in GERD Studies included in qualitative synthesis (n=35)

Effect of DGER on symptoms and lesions Studies included in qualitative synthesis (n=28)

Treatment of DGER Studies included in qualitative synthesis (n=13)