

## Title

Utilization of anti-reflux treatment and course of illness leading to reoperation after anti-reflux surgery in a national population-based cohort.

## Aim

The purpose of this study is to investigate course of illness leading to reoperation after primary anti-reflux surgery and investigate the utilization of anti-reflux treatment, both medical and surgical, in the period 2000-2017

## Background

Episodic reflux of gastric contents to the esophagus is physiological but is considered gastroesophageal reflux disease (GERD) when accompanied by bothersome symptoms, typically heartburn, regurgitation or retrosternal pain. Extra-esophageal symptoms such as asthma, laryngitis and chronic cough may also occur (1). GERD is a complex and multifaceted disease (2, 3), affecting 10-20% of the Western population (4) and has been shown to significantly reduce the quality of life (5). Worldwide, the prevalence of GERD has been increasing (6-8). Treatment of GERD consists of anti-secretory drugs, mainly proton pump inhibitors (PPI), or anti-reflux surgery. Laparoscopic anti-reflux surgery is considered standard of care in surgical treatment of gastro-esophageal reflux disease (9) and with careful patient selection based on thorough preoperative workup (10), symptom control and patient satisfaction are high compared to medical therapy. This has previously been demonstrated in meta-analysis (11, 12).

From 1990-2000 the utilization of anti-reflux surgery in the USA rose to 16.7 procedures per 100.000 inhabitants with a concomitant rise in the use of the transabdominal laparoscopic approach. This resulted in a decline of perioperative mortality and morbidity (13, 14). The rate of anti-reflux surgery dropped to 6.1 procedures per 100.000 inhabitants in 2010, men the patients were now older with significantly higher levels of comorbidity. Despite this, length of stay, morbidity and mortality was reduced even further. The laparoscopic approach is used in 80% of American procedures and the rate has not changed during the last ten years. It is unknown whether Denmark follows the same trends, as the popularity of anti-reflux surgery has been somewhat limited and the surgical setup is different with significantly fewer centers.

Despite the high success rate of anti-reflux surgery, reoperation does occur. The indication for reoperation is most often recurrence of reflux symptoms or dysphagia, and reoperation should be preceded by thorough investigation and possible endoscopic balloon-dilation (15). Laparoscopic reoperation is both feasible and safe, but has been linked to higher morbidity, higher risk of conversion to open surgery and longer length of stay. The final result seem to result in less patient satisfaction than primary surgery, but the available evidence is limited by a high risk of bias due to small sample size and a possible underreporting of complications (16, 17).

An American study reported a cumulative five- and ten year incidence of reoperation of 5.2% and 6.9% respectively. The rate of reoperation was highest in the first year after primary anti-reflux surgery. 30% of reoperations were performed in a different center than the primary procedure. In a Danish study, Funch-Jensen et al (18), investigated rate of reoperation in Denmark 1997-2005 and calculated a rate of 5% without significant differences in length of stay, rate of complications or mortality compared to primary

surgery. Reoperation was however associated with a higher rate of conversion to open surgery with a tendency towards higher rates of conversion in low-volume centers. As in the American study, reoperation was often performed at different centers than the primary procedure. Whether this was the result of centralization or patient's wishes is unknown.

It is our hypothesis, that from 2000-2017, reoperative anti-reflux surgery was performed primarily with a laparoscopic approach without increased length of stay or rate of complications compared to primary surgery. Due to increased surgical experience the rate of complications is decreasing despite increased comorbidity. Endoscopic balloon-dilatation delays reoperation but does not prevent it.

## Methods

The study is a two-part register-based cohort study based on data from The National Patient Registry, The Civic Registry and Danish Anaesthesia Database in the period 1996-2017. The two individual parts of the study concerns the same population.

The population is defined as all adult Danish patients undergoing anti-reflux surgery (Nomesco: KJBC00, KJBC01, KJBC02, KJBW96, KJBW97) from 2000-2017 identified from The National Patient Register.

Age, sex, Charlson Comorbidity Index at date of surgery and length of stay in relation to any surgery and any surgical or endoscopic procedure performed after anti-reflux surgery (including diagnosis 30 days postoperatively to establish possible morbidity) are derived from the National Patient Registry.

ASA-score, weight, height, use of alcohol or tobacco and priority of any surgery (emergency or planned) during the study period are retrieved from The Danish Anaesthesia Database. From the Civic Register, data on mortality in the study period are retrieved.

Information on the use of pharmacological treatment for gastroesophageal reflux disease on population level is retrieved from MEDSTAT and data on population size on population level are retrieved from Statistics Denmark.

## Statistical analysis

### 1) Course of illness leading to reoperative anti-reflux surgery

Data will be analyzed using STATA15. Descriptive analysis of age, sex, comorbidity (Charlson Comorbidity Index, ASA-score, BMI, alcohol/tobacco use), complications to surgery, rate of endoscopic dilation and mortality comparing patients with only primary anti-reflux surgery and patients with reoperation during the study period, will be performed using Student's t-test, Chi2-test and Mann-Whitney-U test.

Logistic regression will be performed with reoperation (laparoscopic, open or other) as primary outcome and age, sex, comorbidity (Charlson Comorbidity Index, ASA-score, BMI, alcohol/tobacco use), complications to surgery and endoscopic or surgical procedure during study period as independent variables. If the number of patients is sufficient, subanalysis will be performed with emergency reoperation as dependent variable/outcome.

Secondary analysis will be performed using Cox-regression investigating time to reoperation with age, sex, comorbidity (Charlson Comorbidity Index, ASA-score, BMI, alcohol/tobacco use), complications to surgery and endoscopic or surgical procedure during study period as independent variables.

*2) Utilization of treatment of gastroesophageal reflux disease.*

The rate of anti-reflux surgery per 100.000 inhabitants for each year during the study period will be calculated using census data from Statistics Denmark. From MEDSAT the rate of use of pharmacological anti-reflux treatment per 100.000 inhabitants will be calculated using abovementioned census-data. Trends in the utilization of surgery are investigated with trend-analysis in the form of Poisson-regression alternatively negative binominal regression.

**Funding and ethical considerations**

The study is part of a ph.d. thesis and is funded by The Region of Southern Denmark, The University of Southern Denmark, The Department of Surgery, Kolding Hospital and The Research Council at Little Belt Hospital.

The study requires no informed consent in Danish law as the study is register-based. However, permission from The Danish Data Protection Agency and The Danish Health Data Agency will be obtained before the study is commenced.

None of the involved parties have financial interests or conflicts of interest pertaining to this study.

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