



## Aspiration pneumonia after antireflux surgery among neurologically impaired children with GERD<sup>☆,☆☆,★</sup>

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### ABSTRACT

**Background and objective:** Aspiration pneumonia is a common and serious complication to gastroesophageal reflux disease (GERD) among neurologically impaired children. Medication of GERD does not effectively prevent aspiration pneumonia, and whether antireflux surgery with fundoplication is better in this respect is uncertain. The objective was to determine whether fundoplication prevents aspiration pneumonia among children with neurological impairment and GERD.

**Methods:** This was a population-based cohort study from Denmark, Finland, Norway and Sweden, consisting of neurologically impaired children with GERD who underwent fundoplication. The risk of aspiration pneumonia before fundoplication (preoperative person-time) was compared with the risk after surgery (postoperative person-time). Multivariable Cox regression provided hazard ratios (HRs) with 95% confidence intervals (CIs). Except for confounding adjusted for by means of the “crossover like” design, the HRs were adjusted for age, sex, year of entry and respiratory diseases.

**Results:** Among 578 patients (median age 3.5 years), the preoperative person-time was 956 years and the postoperative person-time was 3324 years. Fundoplication was associated with 56% decreased overall HR of aspiration pneumonia (HR 0.44, 95% CI 0.27–0.72), and the HRs decreased over time after surgery. The risk of other types of pneumonia than aspiration pneumonia was not clearly decreased after fundoplication (HR 0.79, 95% CI 0.59–1.08). The 30-day mortality rate was 0.7% and the complication rate was 3.6%.

**Conclusions:** Antireflux surgery decreases, but does not eliminate, the risk of aspiration pneumonia among neurologically impaired children with GERD. Fundoplication may be a treatment option when aspiration pneumonia is a recurrent problem in these children.

**Type of study:** Cohort study.

**Level of evidence:** Prognosis study—level I.

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Gastroesophageal reflux disease (GERD) is a common and sometimes serious problem among neurologically impaired children, affecting up to 75% of patients with cerebral palsy [1–3]. Contributing reasons for the high prevalence of GERD in these children include decreased lower esophageal sphincter tone, delayed gastric emptying, impaired esophageal motility, and medication [3]. A most serious complication of GERD in neurologically impaired children is aspiration pneumonia [4], which is associated with high morbidity and is in fact the most common cause of death in these patients [5,6]. Antireflux medication is usually not sufficiently effective in preventing aspiration pneumonia because it mainly decreases the acidity of the gastric

contents, and does not counteract the reflux of gastric contents into the esophagus and airways. In contrast, antireflux surgery with fundoplication creates a mechanical and physiological barrier against reflux. However, recurrence of GERD after fundoplication is a problem in many patients, at least in adults [7]. Approximately 40% of all children who undergo fundoplication in the United States have a diagnosis of neurodisability [8]. Some studies have suggested a decreased risk of aspiration pneumonia after fundoplication in children overall as well as among children with neurological impairments [9,10], but population-based studies of large patient cohorts are lacking.

The aim of the present study was to clarify if fundoplication counteracts aspiration pneumonia among neurologically impaired children with GERD in a large and unselected cohort.

## 1. Methods

### 1.1. Design

This was a population-based cohort study in the four largest Nordic countries, i.e. Denmark, Finland, Norway and Sweden during the study period 1996 to 2014. The cohort included children (<18 years of age) with a diagnosis of neurological impairment and GERD who underwent primary fundoplication (open or laparoscopic) during the study period (eSupplement 1). The study period was limited by the implementation of the Nordic Medico-Statistical Committee's (NOMESCO) Classification of Surgical Procedures, after which open and laparoscopic procedures were coded separately, thus enabling more detailed analyses. The "study exposure" was fundoplication and the main outcome was aspiration pneumonia. Other types of pneumonia (excluding aspiration pneumonia) and any type of pneumonia (including aspiration pneumonia) were analyzed for comparison. Clinical data were collected from nationwide patient registries and data on mortality were retrieved from nationwide cause of death registries. The unique personal identity code, assigned to each resident in the Nordic countries upon birth or immigration, enabled linkage of the individuals' data between these registries [11]. The study was approved by the Data Protection Authorities in Denmark (permission 2014-41-3503), the National Institute for Health and Welfare, Statistics Finland, and the Population Register Centre in Finland (permissions THL/1404/5.05.00/2014, TK53-1555-15 and 2345/410/15, respectively), and the Regional Ethical Review Boards in Norway (permission 2014/1498-3) and Sweden (permissions 2014/234-31, 2015/240-32 and 201811071-21, respectively). Owing to the registry-based nature of the study, personal informed consent was waived [12].

### 1.2. Source cohort

The study was based on data from the Nordic Antireflux Surgery Cohort (NordASCo), a multinational population-based cohort that has been described in detail elsewhere [13]. In brief, NordASCo included merged data from the nationwide patient registries and cause of death registries available in all Nordic countries. The patient registries include data on diagnoses and surgical codes reported by clinicians and the hospitals, and are used for administrative purposes, monetary reimbursements within the healthcare systems, and research. The patient registries also contain information about dates of admissions, hospital codes, and demography, including patient's age and sex. The patient registries are of high completeness and validity, with a positive predictive value for most diagnoses and procedures ranging from 85% to 100% [14–16]. The cause of death registries are of similar design in all Nordic countries. Clinicians report the date of death as well as the primary and contributing causes of death to a central agency. The cause of death registries also contain data on nationality, sex, whether an autopsy was conducted and place of death [17]. The cause of death registries in the Nordic countries are virtually 100% complete and the validity is high [18,19].

### 1.3. Study cohort

From the source cohort (NordASCo), the cohort for the present study was limited to patients less than 18 years of age with at least one neurological impairment and GERD who underwent fundoplication. Patients who received their first diagnosis code representing GERD at the date of surgery or after surgery were excluded. From the patient registries, the diagnosis codes were identified based on the 10th version of the International Classification of Diseases (ICD-10) and the surgical codes came from the Nordic Medico-Statistical Committee's (NOMESCO) Classification of Surgical Procedures [20]. The codes used for defining neurological impairments, GERD, fundoplication, aspiration pneumonias and other types of pneumonia are presented in eSupplement 1.

### 1.4. Statistical analysis

Multivariable Cox proportional regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) comparing the incidence of aspiration pneumonia before and after fundoplication. To control for confounding in this heterogeneous cohort of patients with various types and severities of neurological impairments and GERD, the analysis compared preoperative person-time with postoperative person-time. Preoperative person-time started from the date of GERD diagnosis and lasted until the date of fundoplication. Postoperative person-time started from the first date after fundoplication and lasted until death, age 18 or end of follow-up, whichever came first. The variance of the model was computed with robust estimator and cluster for the identity of the patients to model the dependency of the data. Except for the inherent controlling for all known and unknown confounders using the "crossover like" design, the HRs were also adjusted for age (continuous), sex (boys and girls), calendar year of entry (continuous), and diagnoses representing chronic respiratory diseases (defined in eSupplement 1). Open and laparoscopic surgical approaches were separately examined in stratified analyses. Age and calendar year were time-varying covariates, and at the time of fundoplication these covariates were changed from the date of GERD to the date of surgery. The proportionality assumption was tested by evaluating the interaction between the exposure and the follow-up time. If the proportionality assumption was not met, the change with time was reported.

All analyses were conducted by an experienced biostatistician (GS) according to a detailed and predefined study protocol, using the statistical software IBM SPSS Statistics version 24 (IBM Corp, Armonk, NY, USA) and Stata version 15 (StataCorp, College station, TX, USA).

**Table 1**

Characteristics of patients with neurological impairment and gastroesophageal reflux disease who underwent fundoplication.

Variable	Number of patients (%)
Total	578 (100)
Male sex	327 (56.6%)
Chronic respiratory disease <sup>a</sup>	49 (8.5%)
Denmark	36 (6.2%)
Finland	158 (27.3%)
Norway	652 (9.0%)
Sweden	332 (57.4%)
Aspiration pneumonia <sup>b</sup>	41 (7.1%)
Other pneumonia <sup>b</sup>	299 (51.7%)
Overall pneumonia <sup>b</sup>	307 (53.1%)
Age at inclusion, median years (IQR)	3.5 (1.1–8.7)
Age at surgery, median years (IQR)	5.9 (2.1–10.9)

<sup>a</sup> E.g. cystic fibrosis, asthma, pulmonary eosinophilia, and interstitial pulmonary diseases.

<sup>b</sup> At least one pneumonia event.

**Table 2**

Distribution of neurological impairments among the 578 study patients with gastroesophageal reflux disease who underwent fundoplication.

Neurological impairment	Number of patients (%)
Seizure disorder	368 (63.7%)
Mental retardation	318 (55.0%)
Cerebral palsy	301 (52.1%)
Development delay	189 (32.7%)
Anoxic injury	136 (23.5%)
Other paralytic disorder	131 (22.7%)
Central nervous system anomaly	115 (19.9%)
Chromosomal abnormality	106 (18.3%)
Other nervous system disorder	73 (12.6%)
Hereditary and degenerative	42 (7.3%)
Central nervous system infection	23 (4.0%)
Coma	17 (2.9%)
Central nervous system tumor	5 (0.9%)

## 2. Results

### 2.1. Study participants

The study cohort included 578 children with neurological impairment who underwent fundoplication for GERD. The total length of follow-up was 4280 person-years, of which 956 person-years represented preoperative person-time and 3324 person-years were postoperative person-time (eSupplement 2). Table 1 presents some characteristics of the included patients. The slight majority of participants were boys (56.6%) and came from Sweden (57.4%). The median ages were 3.5 years (interquartile range [IQR] 1.1–8.7) at inclusion and 5.9 years (IQR 2.1–10.9) at fundoplication. The median year of inclusion was 2004 (IQR 1999–2008). The median total time of follow-up was 6.5 years (IQR 3.6–11.0). The most common neurological impairments were seizure disorder (63.7%), mental retardation (55.0%), and cerebral palsy (52.1%) (Table 2). A slight majority of the fundoplications were open (54.3%) compared to laparoscopic (45.7%). The median length of hospital-stay after fundoplication was 7 days (IQR 4–9).

### 2.2. Frequency of mortality and complications

There were 4 deaths (0.7%) within 30 days of fundoplication (3 [1.0%] after open surgery and 1 [0.4%] after laparoscopic surgery), and 10 deaths (1.7%) within 90 days of fundoplication (7 [2.2%] after open surgery and 3 [1.1%] after laparoscopic surgery). Data regarding postoperative complications were available in 526 patients (all

countries except Norway). Nineteen patients (3.6%) had any predefined complication within 30 days of surgery, including 11 (2.9%) with postoperative infection, 1 (0.2%) with esophageal perforation, 4 (0.8%) with wound rupture, 2 (0.4%) with bleeding, and 1 patient (0.2%) with other unspecified complications.

### 2.3. Risk of aspiration pneumonia, other pneumonia and any pneumonia

The distribution and cumulative incidence of aspiration pneumonia over time before and after fundoplication are shown in Table 3. Most aspiration pneumonias occurred during the years just before and just after surgery. The HR of aspiration pneumonia was 56% lower after fundoplication, compared to preoperatively (adjusted HR 0.44, 95% CI 0.27–0.72), as shown in Table 4. The HRs were not statistically significantly decreased for other pneumonias (HR 0.79, 95% CI 0.59–1.08) or for all pneumonias (including aspiration pneumonias) (HR 0.76, 95% CI 0.57–1.01). When separating open and laparoscopic surgical approaches, the statistical power was reduced, but the overall trend was similar for both approaches, however with a trend of lower point estimates of aspiration pneumonia after the open approach (Table 5).

## 3. Discussion

This study supports the hypothesis that fundoplication specifically decreases the risk of aspiration pneumonia in children with neurological impairment and GERD, and that no such decrease was found for other types of pneumonia.

The Nordic countries have a similar healthcare system and complete nationwide patient registries of high quality, which enabled this study and provided valid data on neurological impairments, GERD, fundoplication and aspiration pneumonia [14–17]. The population-based design made it possible to reflect the unselected clinical practice, counteracting selection bias and facilitating generalizability of the findings. The recruitment of virtually all eligible patients from four countries provided a comparatively large sample size. The “crossover like” design was chosen to reduce bias from selection and confounding. This was valuable in the present study because the types and severity of the neurological disorders and the severity of GERD varied greatly between patients. There were no data available regarding the workup of each patient prior to surgery; however, the typical workup in the Nordic countries includes esophagogram, contrast studies, and esophagoscopy with pH-impedance testing. A weakness of the study design is that any mortality occurring before the fundoplication could not be accounted for, because we included only patients who lived to undergo surgery. Another limitation was that the design did not account for potential

**Table 3**

Time-distribution of aspiration pneumonia events and cumulative incidence of aspiration pneumonia in 578 neurologically impaired children with gastroesophageal reflux disease, before and after fundoplication.

	Before fundoplication			After fundoplication		
	Children (number) <sup>a</sup>	Aspiration pneumonias (number)	Cumulative incidence	Children (number) <sup>a</sup>	Aspiration pneumonias (number)	Cumulative incidence
Year 1	578	33	0.09	578	19	0.04
Year 2	236	20	0.11	502	11	0.02
Year 3	133	3	0.03	440	8	0.02
Year 4	91	0	0	375	5	0.01
Year 5	61	0	0	326	5	0.02
Year 6	46	0	0	277	2	0.01
Year 7	35	0	0	239	1	<0.01
Year 8	29	0	0	205	0	0
Year 9	25	0	0	170	2	0.01
Year 10	20	0	0	145	0	0.00
Year 11	13	0	0	110	2	0.02
Year 12	7	0	0	79	1	0.01
Year 13	6	0	0	60	3	0.06
Year 14	5	0	0	43	0	0
Year 15	3	0	0	33	0	0
Year 16	2	0	0	20	0	0

<sup>a</sup> Number of children in the study at the beginning of the year.

**Table 4**

Risk of pneumonia among 578 children with neurological impairment undergoing fundoplication for gastroesophageal reflux disease, expressed as hazard ratios (HRs) and 95% confidence intervals (CIs).

	Before fundoplication	After fundoplication		
	Pneumonia (number)	Pneumonia (number)	Crude HR (95% CI)	Adjusted HR (95% CI) <sup>a</sup>
Aspiration pneumonia	56	59	0.43 (0.28–0.64)	0.44 (0.27–0.72)
Other pneumonia	429	1071	0.84 (0.64–1.11)	0.79 (0.59–1.08)
All pneumonia	483	1122	0.79 (0.61–1.03)	0.76 (0.57–1.01)

<sup>a</sup> Adjusted for sex, year of entry, age, and respiratory diseases.

**Table 5**

Risk of pneumonia among 578 children with neurologic impairment undergoing fundoplication for gastroesophageal reflux disease stratified by surgical approach, expressed as hazard ratios (HRs) and 95% confidence intervals (CIs).

	Before fundoplication	After fundoplication	
	Pneumonia (number)	Pneumonia (number)	Adjusted HR (95% CI) <sup>a</sup>
<b>Open surgery (n = 304)</b>			
Aspiration pneumonia	22	24	0.30 (0.15–0.60)
Other pneumonia	186	643	0.71 (0.43–1.15)
All pneumonia	208	663	0.66 (0.42–1.04)
<b>Laparoscopic surgery (n = 264)</b>			
Aspiration pneumonia	34	35	0.78 (0.35–1.72)
Other pneumonia	243	428	0.92 (0.61–1.38)
All pneumonia	275	459	0.91 (0.62–1.33)

<sup>a</sup> Adjusted for sex, year of entry, age, and respiratory diseases.

changes in risk of aspiration pneumonia with older age. To avoid confounding by age, we therefore adjusted for age in the analysis. The coding of the specific type of pneumonia is made by the responsible clinician, and differentiating between aspiration pneumonias and other pneumonias can be difficult. There is therefore a risk that some aspiration pneumonias were wrongly coded as unspecified or infectious pneumonias. However, such misclassification would be at random and thus rather dilute the decreased risk estimates than explain them. Owing to the study design it was not possible to investigate or quantify any such misclassification, but the fact that the diagnoses were coded in specialized inpatient care should reduce misclassification. We also analyzed the risk of other pneumonias than aspiration pneumonia, which was not decreased, arguing against substantial misclassification.

The literature examining the role of fundoplication in the prevention of aspiration pneumonia in neurologically impaired children with GERD is limited. In children in general with GERD, fundoplication can decrease reflux symptoms, total esophageal acid exposure time and number of reflux episodes [21], but the risk of hospitalization owing to aspiration pneumonia might not be lower after than before fundoplication [9,22]. Among neurologically impaired children specifically, the findings are sparse and conflicting. In a study of 73 neurologically impaired children with GERD, more than 85% were symptom-free 5 years after fundoplication [23], but in a study of 56 patients, fundoplication had little influence on respiratory problems [24]. A large retrospective cohort study of 3721 children with neurological impairments and GERD found a reduction in aspiration pneumonia (incidence rate ratio 0.71, 95% CI 0.62–0.81) and an unchanged incidence of other types of pneumonia (incidence rate ratio 1.07, 95% CI 0.98–1.17) after fundoplication [10]. However, that study was not population-based, the follow-up after surgery was only 1 year, and the participation rate was low (55%) [10]. Yet, the results are in line with the findings of the present study.

The most plausible explanation for the decreased postoperative risk of aspiration pneumonia indicated in the present study is that fundoplication enforces the barrier between the stomach and esophagus, hindering reflux and aspiration from reaching the esophagus. Yet, although the risk of aspiration pneumonia was decreased following fundoplication in this study, it did not eliminate the risk of such events also postoperatively. Fundoplication does not prevent aspiration pneumonia owing to wrongly swallowed saliva or oral intake of food and

drinks, and operated patients might regain the ability to vomit. Thus, fundoplication is not a guarantee for preventing aspiration pneumonia. As with most surgery, fundoplication is also associated with risks. The current study found a low risk of postoperative mortality and other complications, but these risks are still not negligible, and must be considered in the clinical decision-making.

In conclusion, this multinational cohort study with complete follow-up of a large and unselected cohort indicates that fundoplication decreases the risk of aspiration pneumonia in neurologically impaired children with GERD. On the other hand, the risk was far from eliminated and there is a risk of postoperative complications. Yet, fundoplication is a treatment option in selected children with neurological impairment and GERD when aspiration pneumonia is a recurrent problem.

**Contributors' Statement**

Dr Maret-Ouda contributed in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafted the initial article, and reviewed and revised the manuscript.

Dr Santoni contributed in the conception and design of the study, analysis and interpretation of data, and reviewed and revised the manuscript.

Dr Artama contributed in the conception and design of the study, acquisition and interpretation of data, and reviewed and revised the manuscript.

Dr Ness-Jensen contributed in the conception and design of the study, acquisition and interpretation of data, and reviewed and revised the manuscript.

Dr Svensson contributed in the conception and design of the study, acquisition and interpretation of data, and reviewed and revised the manuscript.

Dr von Euler-Chelpin contributed in the conception and design of the study, acquisition and interpretation of data, and reviewed and revised the manuscript.

Dr Lagergren contributed in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafted the initial article, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpedsurg.2019.12.024>.

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