Diagnosis and Treatment of Gastroesophageal Reflux in Patients with Esophageal Atresia

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Introduction

1.1 Introduction

In the last two decades, surgical treatment of children born with esophageal atresia has become a standard procedure. Postoperative mortality – now negligible in those born at term without other severe anomalies – mainly relates to patients with associated severe congenital cardiac malformations, cerebral and pulmonary complications, or chromosomal abnormalities incompatible with life. Extreme prematurity may be a causative factor for mortality as well. Mortality in affected premature infants has considerably decreased, however, owing to advances in medical care. In the light of this development, professional attention now focuses on postoperative morbidity.[18,39,47] Most attention goes out to gastroesophageal reflux and its long-term sequelae, the relationship with healing of the anastomosis, recurrent respiratory tract infections, tracheomalacia, and delayed growth and development. While well-standardized diagnostic procedures and treatment plans have been established for otherwise unaffected infants with reflux disease, these are not yet available for patients showing reflux after repair of esophageal atresia.

1.2 The history of the surgical treatment of esophageal atresia and gastroesophageal reflux

Esophageal atresia

The recorded history of esophageal atresia starts in 1670. In that year William Durston[17] described the first case of esophageal atresia in a conjoined twin. Hirschsprung[30] in 1862 published the first series of patients, 14 cases in all. Vogt[86] in 1929 made the first radiological findings and suggested the classification that is now generally used:

- type A: atresia without a distal fistula;
- type B: atresia with proximal fistula;
- type C: atresia with distal fistula, the most common anomaly;
- type D: atresia with both proximal and distal fistula;
- type E: H-type fistula (see front page).

Surgical correction had been attempted before 1939 but without definitive success. The first two long-term survivors of esophageal atresia were treated by Leven[40] and Ladd.[38]

Leven's patient underwent a jejunal interposition, and Ladd performed an esophagoplasty. It was not until ten unsuccessful attempts that Haight and Towsley[26] in 1943 reported their first successful one-stage anastomosis by a left extrapleural approach.

The patient, however showed all still familiar postoperative complications, such as leakage of the anastomosis, entero-cutaneous fistula, and stricture formation, and remained in hospital for 20 months.
Myers[52] has published an extensive history of the treatment of esophageal atresia and tracheoesophageal fistula from 1670 to 1948.
The history in the Netherlands starts in The Hague with the first successful operation by Ten Kate in 1947.[35] In Rotterdam, Vervat,[87] one of the founding fathers of Dutch pediatric surgery, performed the first successful operation in 1951.

Surgical treatment of gastro-esophageal reflux
Gastroesophageal reflux is the unvoluntary movement of stomach contents into the esophagus, due to insufficiency of the cardia. The history of its surgical treatment in adults begins in Switzerland in 1960 with the first successful "simple operation to influence reflux esophagitis", the so-called Nissen-Rosetti fundoplication with or without crural repair.[54] Rosetti and Hell[65] reported in 1977 a 20-year experience with this technique in 1400 patients, accurately describing the basic principles of the fundoplication. Long-term follow up of 590 of these patients showed that 87.5% were free from symptoms.

About a decade after Nissen's study, American surgeons became interested in this new technique. One of the most prominent pioneers, not only in this field of surgery but also in diagnostic investigations of reflux, is DeMeester.[15] He evaluated the Nissen fundoplication performed after primary repair of hiatus hernia of the esophagus in 100 consecutive patients between 1972 and 1982. Preoperative diagnosis of reflux had been documented with 24-hour pH-metry. In 91% of the patients the operation was effective in controlling reflux symptoms. Both Rosetti & Hell and DeMeester describe mainly adult patient populations.

The history of antireflux surgery after repair of esophageal atresia in infants starts probably in 1970 when Daum[13] reported cured esophagitis after esophageal atresia repair

through the Nissen fundoplication. Other early reports on this subject were published by Pieretti et al,[61] Ashcraft et al,[3] and Fonkelsrud.[21] They describe small groups of patients. Noordijk performed the first Nissen fundoplication in Rotterdam in 1971. A retrospective study on postoperative morbidity in 110 patients operated on in Rotterdam revealed reflux to be a major cause of morbidity.[39]

1.3 Gastroesophageal reflux

Clinical picture

Almost all babies spit up sour-smelling feed occasionally on a parent's shoulder. In other words, the incidence of reflux is nearly 100% in the first few weeks of life. No one, however, would consider this as pathological gastroesophageal reflux, as it tends to be a self-limiting condition.

But when spitting up and regurgitation become more frequent, there is reason for concern. Irritability and crying between meals might point at esophagitis as the underlying cause, and if this is true, the child will get more and more sick. It stops to gain weight, starts to have coughs and finally develop recurrent respiratory tract infections or even severe aspiration, with at the end of the scale apnoeic spells or even sudden death. The estimated incidence of pathological reflux in infants is 2 to 5% of the population, like in adults.[89]

Pathophysiology

The question is: what is the cause of gastroesophageal reflux? It is impossible to give a short and simple answer to this question, because reflux disease has a multifunctional origin. The esophagus is a muscular, hollow tube, capable of propelling a bolus of liquid or solid material into the stomach in a coordinated way. At the junction with the stomach it has several muscular structures, acting together as a sphincter. This so-called lower esophageal sphincter is best described as a combination of muscular thickening of the distal esophagus, the bolstering of the diaphragm and its two crural muscles, and circular mucosal folds in the most distal part of the esophagus, which acts as a one-way valve. Yet it is hard to find this sphincter, as stated by Muller Botha[50] in his monograph on the gastroesophageal junction in man and animals. Some patients show indeed gradual thickening of the inner circular muscle layer, whereas others do not. In a classic study

Boix Ochoa[7] measured the lower esophageal sphincter pressure in healthy children from one day to 6 months of age, and found that a high pressure zone is not yet present at birth. A normal pressure zone, with pressures between five and seven mm Hg, develops within six to seven weeks after birth, necessary to prevent reflux.

The lower esophageal sphincter pressure may also be subject to hormonal and medical influences. Vasoactive intestinal peptides and nitrous oxide may be involved in lowering the pressure, and so may agents like diazepam, antidepressants, and alcohol.[49,51] Esophagitis itself leads to a decreased lower esophageal sphincter pressure, which in its turn leads to a vicious circle of ongoing esophagitis. In addition esophagitis gives rise to non-specific peristaltic abnormalities, such as infrequent or incomplete peristaltic waves, repetitive and simultaneous waves, and increased or decreased wave amplitudes.[1,9]

The second important factor determining the presence of gastroesophageal reflux is the length of the intra-abdominal segment of the esophagus.[7] Its optimal length according to the investigations of DeMeester[14] should be 2 tot 2.5 cm. This intra-abdominal segment of the esophagus – which is a soft tube with a small diameter – will close easier when abdominal pressure increases, preventing reflux as caused by increased intragastric pressure. This is according to the Law of LaPlace, stating that if the tubular esophagus has a small diameter and enters abruptly into the larger gastric pouch, the pressure required to dilate the esophagus and permits reflux, are inversely proportional to the ratio between gastric and esophageal diameter. Expressed in a formula: $P_1/P_2 = R_2/R_1$ with P representing the pressures in closed compartments and R the radius of these compartments. To cause reflux, the pressure in the stomach needs to be 4 to 5 times higher than in the esophagus.[73]

Moreover, in all operations designed by different surgeons (Nissen, Thal, Boix-Ochoa, Hill, Belsey, Boerema) to prevent reflux, the first step is mobilization of the distal esophagus and to ensure by fixation that it remains in its intra-abdominal position.[6,29,54,58,77,78]

The gastroesophageal angle of His, the angle between the esophagus entering the cardia and the adjacent gastric fundus, is also instrumental in the prevention of gastroesophageal reflux. At an acute angle of His, the fundus will squeeze the esophagus when it is filled

and intragastric pressure rises, the fundus will squeeze the esophagus. An obtuse angle of His allows reflux to occur easily through the distal esophagus as in an upside-down funnel.[62]

Experimental work in dogs by Boix-Ochoa and Canals,[7] in piglets by Heij et al,[28] in dogs by Papaila et al,[59] and in man by Seekri et al[68] has shown that the lower esophageal sphincter pressure drops and reflux increases when the angle of His is "stretched".

1.4 Diagnostic procedures for gastroesophageal reflux

What armamentarium disposes the clinician of to detect and confirm gastroesophageal reflux? First, a thorough anamnesis and critical observation to reveal the symptoms of reflux esophagitis.
In neonates and young children the most prominent signs of gastroesophageal reflux, besides frequent vomiting, are failure to gain weight, or even weight loss, irritability or colics, iron deficiency anemia, dysphagia, and recurrent upper respiratory tract infections. At a later stage, hematemesis, melena, and poor passage of food caused by ulceration and stricture formation will come to the foreground. In older children who are able to describe their complaints, dysphagia, retrosternal pain, pyrosis or heartburn are clues to diagnose reflux disease.

Although patients who have undergone correction of esophageal atresia may show any of the above symptoms, they are also likely to show some specific symptoms. The anastomosis may be affected by regurgitation of gastric juice on the suture line, which may lead to inflammation of the anastomosis, and possibly cause (further) scarring and result in stenosis formation. Furthermore, aspiration of gastric juice or milk into the trachea and lungs may lead to aspiration pneumonia or even acute life threatening events (ALTE).
Finally, the incidence of pyloric hypertrophy is considerably higher in patients with corrected esophageal atresia, so the surgeon should be aware of this phenomenon (Beasley, 5 in 118 patients (4%),[5] Holder, 11 in 1058 patients (1%).[31] The normal incidence ranges from 0.1 to 0.3% .[71]

If reflux disease is suspected from the above clinical signs, the following investigations are available to confirm the diagnosis:

1. Fluoroscopic esophagogastroduodenography;
2. pH-metry;
3. Endoscopy and biopsy;
4. Manometry;
5. Technetium scintigraphy.

1. Fluoroscopic esophagogastroduodenography

In most surgical centers fluoroscopic esophagogastroduodenography is the first routine investigation to check patency of the anastomosis after correction of esophageal atresia. It also allows to diagnose leakage, recurrence of a tracheoesophageal fistula, hiatal hernia and gastric emptying, or even aspiration. Simple radiodiagnostic studies of the gastrointestinal tract are not recommended to discriminate between physiological and pathological reflux, because these are instantaneous investigations in children who may be agitated, very passive, or otherwise not in a normal physiological state. They are valuable, however, in revealing congenital or acquired anatomical abnormalities, such as congenital distal stenosis and pyloric hypertrophy, or in revealing leakage and stenosis of the anastomosis. Moreover, they are simple and repeatable investigations to evaluate conservative treatment of a stricture, healing of a leaking anastomosis or recurrent tracheaesophageal fistula, and the effectiveness of medical or surgical antireflux treatment.

2. pH-metry

Long-term (18-24 hours) monitoring of the intra-esophageal pH is the gold standard for reflux investigations.[90] The degree of reflux detected, however, depends on many factors: the recording equipment and the pH-probes, the duration of recording, the placing of the probe, the patient's diet, position and activity.[27,63]

Various types of electrodes are available: glass, antimony, ion sensitive field effect transistor (ISFET), and polymeric membranes. The latter two are not applied in children.
The most commonly used pH-probes are the monocrystalline antimony electrode with an external reference electrode and the combined glass electrodes with an integral potassium-chloride reference electrode near the tip of the probe. The latter is the most widely used in

pediatrics, because of its small diameter (1.6-5.0 mm), its wide pH range (0-12 pH), its short response time to alterations in pH (10-45 seconds), and its favourable price in view of its lifespan.[36]

Correct positioning of the tip of the electrode is essential and may be based on the formula: 0.25 x crown-heel length in cm + 3 cm from the nose.[75] In children younger than one year a chest X-ray is mandatory to confirm that the tip is placed about 2 cm above the gastroesophageal junction. Before and after monitoring the investigation the electrode must be calibrated at environmental temperatures at pH 1 and 7 to exclude a significant (less than 0.2) drift of the electrode.

Parameters of the pH-investigation
An esophageal pH value less than 4 is commonly accepted to reflect normal and abnormal gastroesophageal reflux.[34,80,46,69]
Four classic parameters described by DeMeester et al[14] and Jolley et al[33] are used to calculate frequency and severity of acid reflux in the esophagus. These make it possible to compare results obtained in different clinics, as well as in one and the same patient.

a. The reflux index, the total duration of all episodes in which pH < 4, divided by the total duration of the investigation, expressed as a percentage of time.
b. The total number of episodes in which pH < 4.
c. The number of episodes in which pH < 4 for more than 5 minutes.
d. The duration of the longest period in which pH < 4.

When interpreting a pH recording one should keep in mind that it is used as a "yes or no" parameter. For instance, a drop to 4.01 will still be considered normal, whereas a drop to 3.99 is considered pathologic. The patient, though, does not feel any difference. Normal pH-ranges in asymptomatic infants are available; individual infants show a considerable standard deviation.[81,57,84]

It is not only the wide range of normal values in asymptomatic children one should be aware of. A second consideration is only acid that is detected. Alkaline reflux is difficult to diagnose with the normally used pH-probes, because acid neutralizes the alkaline contents of the duodenum. Only if the pH rises above 7, alkaline reflux is suspected. Furthermore, when

neonates are normally fed during the investigation, the postprandial period shows a normal pH-score because reflux cannot be detected owing to the neutralizing effect of the formula.[78,76] To our knowledge extensive retrospective or prospective studies using pH-metry have not yet been performed in patients after repair of esophageal atresia.

3. Endoscopy and biopsy

Endoscopy of the upper digestive tract, including the larynx and pharynx, the esophagus, the gastroesophageal transitional zone, the stomach, pylorus and duodenum, will reveal whether esophagitis is present or not. Its severity can be delineated by the experienced endoscopist. The commonly used visual gradations of esophagitis are those described by Miller and Savary:[48] grade I, single linear erosions of the mucosa; grade II, multiple erosions; grade III, confluent circumferential erosions; grade IV, strictures and ulcerations; and grade V, Barrett's epithelium.

Suction biopsies of the distal one third of the esophagus, but never taken at a distance less than 2 cm above the gastroesophageal junction, should confirm the diagnosis of esophagitis. The commonly used scoring system for esophagitis is that of Ismail-Beigi et al;[32] the more stringent histological criteria of Riddell[64] are not yet widely used. Biopsies are only used to confirm the diagnosis of esophagitis and do not play a major role in the treatment of reflux in esophageal atresia.

4. Manometry

Although manometry is an important tool in determining the pathophysiology of the lower esophageal sphincter pressure and may provide insight into the optimal therapy of gastroesophageal reflux disease, it has little value in the evaluation of suspected reflux after repair of esophageal atresia. In the rare cases of esophageal achalasia it is the investigation of choice to confirm this diagnosis.

5. Technetium scintigraphy

Technetium 99m sulfur colloid scintigraphy of the upper digestive tract is most often used to document aspiration. This diagnostic procedure, however, has moderate sensitivity, and it requires a well-equipped nuclear medicine department and dedicated personnel. It is not recommended in the literature as the first choice for the diagnosis and follow up of reflux disease.[56] An alternative procedure to diagnose recurrent aspiration is cytologic

examination of tracheal aspirate obtained during bronchoscopy. This is based on the identification of lipid-containing macrophages derived from aspirated milk.

1.5 Non-surgical treatment

Conservative measures
One of the common measures to prevent mild reflux in young patients is thickening of the feedings (for example carob flower), but the value of this measure is still subject of controversy.[55,82,4] While thickeners may reduce the number of reflux episodes, they could prolong the duration of the remaining episodes and might therefore be inappropriate in patients with real esophagitis.

Recommendations with regard to positional therapy have changed dramatically, from the so-called infant upright seats in the 1960s to the cumbersome controversies of letting the child sleep in prone or supine position in order to avoid ALTE. Most clinicians now agree that the head-up prone or supine position under an angle of 30 degrees, with good fixation of the patient and completely free airways, is one of the measures to prevent reflux.[85,67]

Medical treatment
Alginacid (Gaviscon®), a coating gel taken after meals, protects the mucosa of the esophagus from the eroding effect of acid exposure. Though not a drug that really prevents reflux, it can be used as intermediate remedy before starting other drugs.
If the above-mentioned measures and the administration of Gaviscon® do not have positive effects in pediatric or neonatal gastroesophageal disease, the next step is to add prokinetics. Prokinetics are substances which have the potential to promote the motor activity of the digestive tract. They do not only stimulate the peristaltic activity, but also coordinate the activities of the digestive tract. The formerly used antiemetic agents metoclopramide and domperidone, which have a alpha-sympathomimetic dopamine and 5HT3 blocking action and a dopamine receptor blocking action, respectively, are no longer used, because of their major CNS and respiratory side effects, especially in young infants.
Direct cholinomimetics (or parasympathomimetics), such as betachanol, which act on the muscarine receptors of the smooth muscles, have too many side effects and are no longer used in children.

Substances which stimulate the release of acetylcholines on the neuromuscular junction of the plexus myentericus have become the drugs of first choice. Cisapride (or: Prepulsid®) is one of these substances and is claimed to stimulate the motility of the digestive tract at this level. It increases the pressure of the distal sphincter of the esophagus as well as the contractions of the esophageal body, and restores retarded emptying of the stomach. As a slight adverse side effect it might stimulate the small intestinal and colonic propulsion.

Although most pharmokinetic data on cisapride have been arrived from adult studies, there is no reason to expect great differences when it is administered to (small) children. Cisapride is given orally and is almost completely absorbed: only 4-6 % of the doses are detected in the stools. Peak plasma levels are reached within two hours after administration.

The optimal time of administration is about 15 minutes before each meal to ensure optimal absorption under all conditions of gastric acidity. Cisapride is for 98% bound to albumine. Metabolites have no pharmacological activity and are excreted by urine and faeces. The half-life time of cisapride is about 7-10 hours. The recommended oral dose in infants and children is 0.1-0.3 mg/kg every 6-8 hours.[37]

The efficacy of cisapride in the treatment of gastroesophageal reflux disease in infants and children has been proven in several well-controlled, double-blind studies. For instance, in a double-blind study in 29 patients aged from 2 to 4 months, cisapride proved to be more effective in relieving of symptoms and reducing esophageal acid exposure compared to a placebo.[10] In 14 infants with uncomplicated esophagitis, four weeks' administration of cisapride yielded better results than positioning and dietary measures.[11] Cisapride (0,8 mg/kg/day) for 4 weeks proved to be as effective as a combination of Gaviscon® and carob flower (Carotel®), improving the pH-variables as well as the clinical symptoms.[25] In a double-blind, randomized study in 17 infants, cisapride was as effective as the combination of cimetidine (5mg/kg/four times daily) and Gaviscon®.[20]

These results have led the working group on gastroesophageal reflux of the European Society for Pediatric Gastroenterology and Nutrition (ESPGAN) to recommend cisapride in addition to positioning and dietary measures as the treatment of choice in uncomplicated cases of symptomatic reflux in childhood.[85] In children with moderate to severe oesophagitis they recommend cisapride in combination with H2 receptor blockers.

Also of interest are studies on chronic pulmonary disease associated with gastroesophageal reflux. In three studies, none of which double-blind, pH-measurements indicated marked clinical improvement, such as decreased stridor and bronchospasm after administration of cisapride.[68,44,79] Interesting was the effect of cisapride in an open trial in 22 infants affected by reflux-associated apnea and sleep disturbances. In eight patients who suffered at least one episode of ALTE, pH-metry combined with cardiopneumogram was performed before and after a 13-16 day period of cisapride treatment. In these children disrupted sleeping patterns (apnea attacks) improved or disappeared.[83]

Schematic approach to therapy for gastroesophageal reflux

Phase I	
Parental reassurance	
Position therapy	
Milk thickening	
Dietary recommendations	
Gaviscon® with or without antacids	
Phase II	
Prokinetics:	cisapride
Phase III	
H2 blockers:	cimetidine, ranitidine
'experimental':	omeprazole
Phase VI	
Surgery	

In summary, ESPGAN proposes the above schematic approach to the therapy of gastroesophageal reflux. Phase I consists of non-drug treatment, including parental reassurance, positional therapy, milk thickening, increased frequency in smaller volumes of feeding, combined with prokinetics, such as cisapride in Phase II.

When this is not yet effective and no cure is established, adding of H2 blockers (cimetidine or ranitidine) to the above-mentioned prokinetics is advised (phase III). Cimetidine, however, shows more adverse effects and drug interactions than ranitidine does.[16,43] Note that H2 blockers do not cure the reflux, but only diminish the acidity of the refluxate. For instance children with recurrent aspirations will not profit from its use.

For the treatment of patients with grade four esophagitis (ulceration with stricture or metaplasia, or with stricture without erosions or ulcerations at endoscopy) it has been suggested to administer gastric proton pump inhibitors before surgical intervention.[24] These hydrogen pump inhibitors suppress gastric acid secretion more completely than H2-receptor antagonists do, by irreversible inhibition of hydrogen and potassium adenosine 3'-phosphate (the hydrogen pump) in the parietal cells of the stomach. However, little is known of the effects of these drugs in neonates and toddlers. Apart from adverse side effects, there may be negative effects of gastric acid suppression leading to bacterial overgrowth and hypergastrinemia. There are no publications on long-term conservative management of gastroesophageal reflux after repair of esophageal atresia. The notion that antireflux surgery may provide a less expensive and more permanent solution to refractory reflux disease in children is still subject of debate.

1.6 Surgical treatment

More than half of the patients do well after surgical correction for esophageal atresia: they eat normally, grow according to their predetermined percentile, and do not have respiratory problems.[12,88] Others, however, may experience a difficult, prolonged postoperative course with recurrent respiratory tract infections, feeding problems, or the need of long-term ventilation support including positive airway pressure ventilation in case of severe tracheomalacia.
The underlying causes may be:

- stenosis of the anastomosis;
- tracheomalacia of the upper airways;
- congenital cardiac defects;
- lung abnormalities (aberrant bronchial tree, hypoplasia);
- pathological gastroesophageal reflux;
- or combinations of the above pathologies.

If pathological reflux is the main problem, this may in its turn lead to stenosis of the anastomosis, lung infection or signs mimicking tracheomalacia. To our knowledge there are no reports of diagnosing gastroesophageal reflux at an early stage, nor any

descriptions of the effect of conservative measures. All reports in the surgical literature are retrospective studies of patients operated on for reflux. Only in a few articles the authors mention briefly that medical therapy was used.

World-wide the most frequently applied operation for reflux in esophageal atresia patients is the Nissen-Rossetti fundoplication. In the past few years, however, the anterior partial fundoplication (Thal) or the posterior partial fundoplication (Toupet, Dor, or Boix-Ochoa) have also come to the fore. The Nissen-Rossetti fundoplication as we perform it in babies and young children in our hospital, is in the very young child still performed by laparotomy, but in children older than one year increasingly by laparoscopy.[2] These are the essential steps of this operation:

After entering the abdominal cavity, the triangular ligament of the liver is completely divided and the left lobe retracted to the right. The peritoneum over the esophagus is completely incised and with a appropriate nasogastric tube inside the esophagus the posterior part of the esopaghus is dissected. The esophagus is then mobilized along a length of two to four cm depending on the age of the patient. Next, the crura of the diaphragm are identified and secured together with one or two nonresorbable sutures. The knot is securely tied without drawing the suture too tight, to prevent muscle necrosis and to avoid release of the sutures. The upper third of the greater curvature of the stomach is freed by division of the short gastric vessels. The fundus is then drawn behind the esophagus and wrapped loosely around the dissected esophagus, and sutured with nonresorbable stitches including the esophagus. One of the crural stitches may be tied to the backside of the fundoplication to prevent migration or slipping.

In the literature the proportion of patients with gastroesophageal reflux after esophageal atresia correction treated with an antireflux procedure vary among authors and among early and late studies. The early studies all show different numbers. Parker et al,[60] six of 17 patients (35%); Gauthier et al,[23] 15 of 113 (13%); Manning et al,[45] 17 of 58 (29%). In later studies (1987-1997), which mostly cover more than 10 years, again varying numbers are seen. Sillen et al[72] in an overview of 103 patients operated on during 16 years, reports that only 6 of them (6%) needed a Nissen fundoplication. They comprised only 3 of the 90 patients without a long gap between the proximal and distal part of the esophagus, and 3 of the 13 patients with a long gap. Regrettably, ages of the patients at the time of the

operation are not mentioned. On the other hand, Curci et al[12] performed a Nissen fundoplication in 14 of 31 (45%) patients with corrected esophageal atresia during a period of eleven years. The procedure had to be repeated in five of these 14 patients (36%). Louis et al[42] briefly describes 36 Nissen fundoplications in a total of 210 patients with corrected esophageal atresia (17%) during twenty-two years. Lindahl[41] describes a series of 48 patients operated on during a five-year period. Thirteen of them (27%) needed a Nissen fundoplication. Remarkably, eight of these 13 had a long-gap atresia and five others needed a Livaditis procedure, which is a circular myotomy of the proximal blind-ending esophagus to get extra length of the esophagus. Of these 13 patients, five (38%) needed a re-operation because the Nissen was not functioning anymore. McKinnon and Kosloske[47] published a series of 64 patients operated on in 13 years, in eight of whom a Nissen fundoplication was necessary; in seven for a long gap between proximal and distal parts of the esophagus, and only in one with a normal distance. Wheatley et al[88] reported a total of 80 patients with corrected esophageal atresia over 14 years; 21 of them 80 (38%) needed a Nissen fundoplication, but in the course of time this procedure failed in seven of them (33%). The most extensive study is the one by Myers et al,[53] reporting on all 498 living esophageal atresia patients operated on in Melbourne between 1948 and 1988.

Overall, a Nissen fundoplication was done in 33 of them (7.8%), though strikingly, the rate was 25% between 1978 and 1982 and decreased to 15% between 1982 and 1988. Most of the patients had undergone the Nissen operation before the age of one year. In contrast to the rates given in the above-mentioned reports, only two of these 33 patients needed a redo-Nissen.

Because in esophageal atresia patients the recurrence rate of reflux after the Nissen-Rossetti fundoplication is quite high (30%), a partial fundoplication as described by Thal or Toupet is sometimes preferred. Snyder et al[74] described their experiences with the Thal procedure in 1998. They operated on 240 patients with an esophageal atresia during a period of twenty years. In 77 patients (32%) it was necessary to perform this antireflux operation. Only nine of these (12%) suffered from recurrent reflux, necessitating a new antireflux procedure.

Fonkalsrud[22] reported that he performs a Nissen fundoplication for all children with reflux, though no longer in patients with esophageal atresia, in whom he prefers the Thal

or Toupet technique. However, in this article data are not provided. Great variation is observed between different institutions, with regard to the need for fundoplication in patients who underwent prior esophageal atresia repair, and the type of fundoplication to be performed.

In summary: Over the last 20 years the proportion of patients needing a Nissen fundoplication after correction of esophageal atresia has increased to 30% (range 7 to 45%).[74] The main reasons for this increase is better follow up and the increasing awareness of the fact that gastroesophageal reflux can cause anastomotic complications. In addition, the Livaditis procedure was introduced in this period, so that interposition of colon or stomach was no longer necessary as a definitive operative procedure.

1.7 Aims of this thesis

This thesis presents studies in various groups of patients operated on for esophageal atresia in the Erasmus Medical Center/Sophia Children's Hospital, Rotterdam, The Netherlands. The findings from these studies will serve to provide answers to the following questions:

1. What are the treatment results in terms of mortality and morbidity in children with esophageal atresia in the Sophia Children's Hospital, and how do they compare to the results obtained in other centers?
2. How does postoperative gastroesophageal reflux present in those esophageal atresia patients, and should it be considered normal or abnormal?
3. Do patients with corrected esophageal atresia have a higher risk of persisting reflux, and consequently a higher risk of developing Barrett's esophagus?
4. Is our medical treatment of gastroesophageal reflux effective, and if so, what medication is most effective?
5. When does gastroesophageal reflux require surgical treatment? Does this surgical treatment have a definitive, beneficial effect, and what are the complications?

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Chapter 2

Function of Pediatric Nissen-Rossetti Fundoplication Followed up into Adolescence and Adulthood

Based on the article:
Function of Pediatric Nissen-Rossetti Fundoplication Followed up into Adolescence and Adulthood
Jan Hein L.J. Bergmeijer, Jorrit S. Harbers, and Jan C. Molenaar.
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2.1 Abstract

Background
We analyzed the very long-term results of the Nissen-Rossetti fundoplication performed in young children. Little has been reported about follow-up longer than 5 years in homogeneous populations. This study concerns a homogeneous group with a minimum follow-up of 10 years; these former patients, therefore, are now adolescents or adults.

Study design
In 24 consecutive patients without other congenital or acquired anomalies of the esophagus or stomach, we evaluated the primary postoperative diagnoses, symptoms of recurrent reflux, and their state of health in 1994.

Results
After a median follow-up of 16 years, the result was excellent in 18 patients, good in 5, and poor in 1 (graded according to Visick). Patients with recurring reflux symptoms had evidence of failure of the fundoplication. All but 1 had been given a diagnosis of recurrent reflux within two years after the operation. The situation after 2 years seems predictive for the later outcome.

Conclusions
In almost all cases, the Nissen-Rossetti fundoplication is a long-lasting, effective treatment for young children with symptomatic gastroesophageal reflux.

2.2 Introduction

Most pediatric patients with symptomatic gastroesophageal reflux (GER) can be cured with conservative medical treatment. But reflux persists in a few, despite aggressive medical therapy. Worldwide, the Nissen-Rossetti fundoplication, or one of its variants, is considered the operation of choice for these patients. Good results of this operation have been reported in the literature, with 74 percent to 90 percent of the patients free of symptoms after 2 to 7 years. These results differ greatly, however, depending on patient selection, judgment criteria, and time of evaluation.

Parents often ask the surgeon how long the effect of the surgical treatment will last. Because on the one hand, failures of the Nissen fundoplication (hiatal insufficiency or recurrent GER) can occur many years after the operation and on the other hand, postoperative complaints are likely to diminish as the child grows, investigating the very long-term results in these patients is worthwhile. Little, however, has been reported about follow-up longer than 5 years, and the available results mostly concern nonhomogeneous groups.[1-4] We report the long-term results of the Nissen-Rossetti fundoplication in a homogeneous group, continuing into adolescence and adulthood with a minimum follow-up of 10 years.

2.3 Materials and methods

The basic population for this study was a group of 81 patients with GER who had undergone a standardized Nissen-Rossetti fundoplication[5] in the surgical department of the Sophia Children's Hospital in Rotterdam between 1972, the year when patient data were first systematically recorded, and 1984, a year chosen to provide 10 years of follow-up through 1994.

To ensure homogenicity, three main categories of patients who have often reflux, but also other anomalies of the cardiovascular, central nervous system or digestive tract, were excluded from the study. These three exclusions were those who had been operated on for esophageal atresia or diaphragmatic hernia and patients with severe mental handicaps.[6-7] The remaining group (pure GER without other anomalies related to GER) consisted of 25 patients (13 girls, 12 boys) whose mean age at the time of the operation was 3 years, with a median of 20 months (range 2 months to13 years). They were asked in a letter to participate in an interview by telephone. One of them refused, and thus the study group eventually consisted of 24 persons.

The case reports showed that the indications for operation had been failure of maximal conservative treatment for 3 to 6 months, reflux-induced stenosis of the esophagus, persistent upper respiratory symptoms, and near sudden infant death syndrome. Gastroesophageal reflux had been diagnosed by radiographic examination of the esophagus and stomach in all patients, by gastroesophagoscopy and biopsy in 23 patients, and, after it

became available in our institution in 1980, by 24 hour pH-metry in 11 patients.[2,8,9] Six patients had evidence of concurrent disease before the operation (Table 1).

Table 1. Concurrent diagnosis and previous operations

	n
Ramstedt pyloromyotomy for pyloric hypertrophy	3
Esophageal interposition	1*
Small omphalocele and duodenal atresia	1
Gastropexy performed	1
Total	6

*Complete failure of jejunal- and colonic interposition for suspected esophageal varices without removing the esophagus, later diagnosed as severe gastroesophageal reflux with stenosis.
n, Number

To assess their status in 1994, the former patients were interviewed by telephone. We used a questionnaire devised to identify the typical complaints related to disease of esophagus and stomach (Table 2).

Table 2. Information elicited by questionnaire

Complaints of gastroesophageal reflux
Vomiting
Heartburn or sternal pain or both
Swallowing problems in relation to feeding
Failure to thrive
Respiratory problems
Eating pattern
Treatment by medical specialist, what specialty, and for what?
Medication
Reoperations (other clinic), what operation?
Satisfaction of patient or parents or both
Remarks

The answers enabled us to apply the objective Visick grading system, the oldest, simplest, and most frequently used scoring method for the outcome of operations on the esophagus and stomach[10] (Table 3).

Table 3. Visick Gradation

Group I	Very well, no complaints
Group II	Well, slight complaints, medical treatment sometimes
Group III	Moderate complaints, only partially to be treated, condition better than preoperative one
Group IV	Worse, severe complaints, no improvement compared with preoperative condition.

The mean age at the time of interview was 18.7 years (median, 18.0 years; range 12 to 30 years). The mean follow-up after operation was 16 years (median, 16.1 years; range 10.3 to 21.7 years). The mean clinical follow-up by objective diagnostic means (i.e. roentgenogram of the esophagus, endoscopy, and, possibly, 24-hour pH-metry) was 5.8 years (median, 5.6 years; range 1.3 to 18.0 years).

2.4 Results

Eighteen of the 24 patients had no GER-related complaints, had normal eating pattern, were not being treated by a medical specialist, did not use medication, and were, therefore, classified in Visick group I. At their last clinical follow-up, none of these 18 patients had signs of GER.

The medical records indicated that two of the 18 patients assigned to group I had undergone a repeat fundoplication because of recurrent GER within 2 years of the first operation. In both, the fundic wrap had disappeared completely. A third patient underwent a subsequent laparotomy because of incarceration of the Nissen fundoplication and stomach into a hiatal hernia. Preoperatively, there was no sign of recurrent GER. Hiatoplasty was performed, and the Nissen fundoplication was intact.

Five patients were classified in Visick group II. Three of them had mild heartburn, for which they took antacids if necessary. No objective signs of GER were found on roentgenograms of the esophagus and 24-hour pH-metry for these three patients. The other two had symptomatic GER proven by a roentgenogram of the esophagus and pH-metry. In both, endoscopy revealed Barrett's epithelium in the distal part of the esophagus. Both are now under the supervision of a gastroenterologist for regular follow-up.

Only one patient, with a history of failed colonic and jejunal interposition for a missed diagnosis of GER and stenosis (see Table 1), was classified in Visick group III. The roentgenogram of the esophagus showed a severe motility disturbance of the esophagus without spontaneous reflux; but, pH-metry demonstrated pathologic reflux. At the time of the interview, the patient was using antacids and H_2-receptor antagonists.

In response to the question about their present condition, 20 of the 24 patients, or their parents, stated they were very satisfied. The other four were content in view of their preoperative complaints. Nine of the 24 patients felt discontent with the scar of the median laparotomy, the incision used in all patients.

Of the 24 patients, 23 showed excellent or good long-term results and could be classified into Visick groups I and II. About 50 percent of the patients had documented typical early postoperative complaints, such as gas bloating, dysphagia, and the inability to vomit, which, however, were never serious and generally disappeared spontaneously within 1 to 3 months.[1,2]

2.5 Discussion

Failure rates of 5 percent to 20 percent have been found after objective postoperative follow-up.[1-4,11-13] In five of the six patients with symptomatic complaints, failure occurred within 2 years after the operation, a period confirmed by other authors.[1,2,11] Considering our own results and those of other investigators, we conclude that the result after 2 years is predictive for the very long-term outcome. Like Hanimann and colleagues[1] and Alrabeeh and associates,[11] we advise conducting a follow-up examination after 2 to 3 years..

Early postoperative failure with severe complaints makes performance of a second Nissen fundoplication worthwhile. All three patients who underwent a second Nissen fundoplication at an early stage had excellent results at long-term follow-up. In the literature, a success rate of 80 percent after a second Nissen fundoplication has been reported. Perioperative findings are mostly fundic wrap disruption and hiatal insufficiency, the "so-called" slipped Nissen.[2,13]

An unpublished study from our institute shows that in the development of recurrent hiatal insufficiency and GER, the use of nonsoluble sutures results in fewer recurrences than does the use of soluble sutures. This is also confirmed by other authors.[1,4,11,12,14]
In accordance with the literature, our data show that the Nissen-Rossetti fundoplication for severe gastroesophageal reflux at a young age results in excellent outcome for the very long-term follow-up of most patients.

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Chapter 3

Normal Ranges of 24-Hour pH-metry Established in Corrected Esophageal Atresia

Based on the article:
Normal Ranges of 24-Hour pH-metry Established in Corrected Esophageal Atresia
J.H.L.J. Bergmeijer, J. Bouquet, F.W.J. Hazebroek.
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3.1 Abstract

Background
This study was undertaken to determine baseline values of 24-hour pH-metry in children who had undergone correction for esophageal atresia.

Methods
A 24-hour pH-metry without medication was conducted in 13 patients with an uncomplicated postoperative course after correction of esophageal atresia. The pH-metry was performed in the hospital with a flexible glass electrode.

Results
The mean reflux index was 4.08%, the mean total number of reflux periods with a pH less than 4 was 21, and the mean number of periods of pH less than 4 lasting longer than 5 minutes was 2.5.

Conclusions
Twenty-four-hour pH-metry values in asymptomatic esophageal atresia patients are the same as in children from the same age group with normal anatomy.

3.2 Introduction

Children who have undergone successful correction of esophageal atresia often have gastroesophageal reflux, which, in turn, is a major cause of complications, such as anastomotic stricture, reflux esophagitis, aspiration pneumonia, and even near-sudden infant death syndrome.[1-3]

The decision whether surgical or medical treatment or no treatment at all is indicated should be applied on suspicion of reflux and must be based not only on good clinical grounds, but on objective investigations as well. Barium contrast study of the esophagus and stomach, esophagoscopy, and 24-hour pH-metry are the standard methods for the diagnosis and evaluation of pathologic gastroesophageal reflux in normal neonates and children. Even more strongly, pH-metry is considered the gold standard for defining the duration and

severity of reflux.[4-7] Normal ranges have been established for these groups,[8,9] but not for patients with a corrected esophageal atresia.

For this reason, we investigated 24-hour pH-metry values measured early after operation in 13 patients whose postoperative course during the first year after correction of esophageal atresia was completely uneventful.

3.3 Patients and methods

From January 1994 until November 1996, 48 patients with esophageal atresia were treated in the Sophia Children's Hospital. According to the criteria of Gross, three patients had type A atresia, and underwent colonic interposition. Two patients had H-type fistula and the other 43 had classic type C with tracheoesophageal-fistula. In accordance with our treatment protocol, they all underwent pH-metry studies between 8 and 16 weeks after surgery. Twenty-four patients had reflux-associated complications, such as failure to thrive, stricture of the anastomosis, respiratory tract infections, or tracheal malacia. All underwent prolonged medical antireflux therapy, and eight of them underwent a Nissen fundoplication.

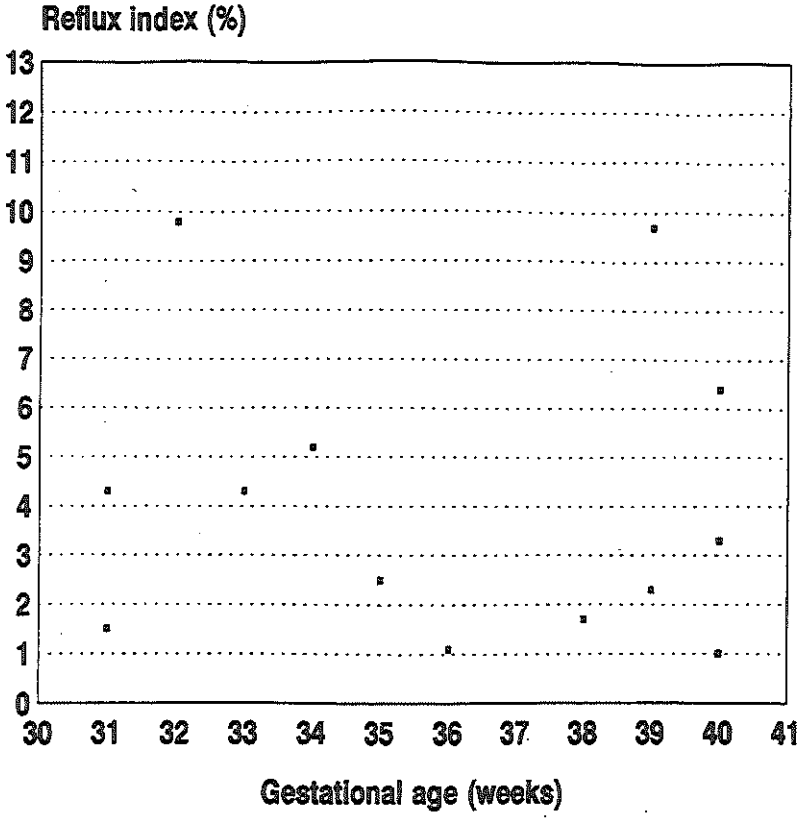
Of the remaining 19 patients with an uncomplicated short- and long-term postoperative course, followed up for at least for at least 1 year, 13 had undergone a complete and reliable 24-hour pH-metry without medication. In four of the remaining six patients, pH-metry was performed much later than 16 weeks after surgery, and consent for the investigation was refused by the parents of the two remaining patients. The pH-metries had been performed in our hospital, using a flexible glass electrode with internal reference electrode (Escolab, Maarssenbroek, the Netherlands) connected to a bedside computing system (UPS-2020/Orion, MMS B.V. Holland, Enschede, the Netherlands). All patients were fed their normal formulas during pH-monitoring.

3.4 Results

The mean gestational age of the 7 girls and 6 boys was 36 weeks (range, 31-40 weeks). Six patients had been born at term, and 7 were premature. Only 2 of the 13 patients showed

(minor) anastomotic tension, and only 1 had minor leakage of the anastomosis. All patients were supported by postoperative ventilation, which we consider essential after a major thoracotomy. Ten patients were ventilated for 2 to 5 days, and 3 premature infants for 22, 28 and 60 days, respectively. In all but 1 patient, the site of the esophagogastric junction as assessed by a barium contrast study was normal, although all children had some provocative reflux, which we did not consider to be abnormal.

Fig. 1 Relation between reflux index values and gestational age.



The pH-metries were performed at a mean of 12.7 weeks (range, 8-16 weeks; median 12 weeks) after surgery. The mean reflux index (percentage of time with pH < 4 during 24 hours) was 4.08% (range, 1-9.8%; median 3.3%). Mean total number of reflux periods with

a pH less than 4 was 21 (range, 3-60; median 17). Mean number of periods of pH less than 4 lasting longer than 5 minutes was 2.5 (range, 0-9; median, 2).
Figure 1 shows the correlation between gestational age of the patients and the reflux index.

3.5 Discussion

Normal ranges of 24-hour pH-metry in asymptomatic healthy newborns and children up to the age of 18 months have been well established by Vandenplas and Sacré-Smits.[8-9] Such ranges had not yet been established in patients with a corrected esophageal atresia. In several studies, pH-metry was conducted in symptomatic atresia patients, and the results were compared with normal values in asymptomatic children and newborns, assuming that these are the same as in asymptomatic patients with esophageal atresia.[9,10] Because the incidence of gastroesophageal reflux in patients with atresia (30-50%) is higher than in the normal population,[1,3] because of motility disorders of the distal esophagus, alteration of the angle of His, and delay of esophageal clearance of acid, a set of normal values as a reference would help to establish whether a symptomatic patient with atresia has pathological reflux, and whether medical or surgical treatment is preferable.

In this study, the values for the age group between 8 and 16 weeks were comparable to those found by Vandenplas and Sacré-Smits:[8,9] The mean reflux index in our series was 4.08%, versus 4.18% in normal children 2.5 to 4.5 months of age in the series of Vandenplas and Sacré-Smits. The mean total numbers of periods with pH less than 4 was 21 versus 20, and the mean number of periods with pH less than 4 for longer than 5 minutes was 2.5 and 3.2, respectively. In this small group of patients, we could not find a negative correlation between prematurity and the extent or severity of reflux as shown in Figure 1.

In conclusion, from the results in this study in 13 asymptomatic patients with corrected esophageal atresia, it appears that 24-hour pH-metry values are the same as in asymptomatic children with normal anatomy. Therefore, they can be used for further diagnosis and evaluation of patients in case of clinical suspicion of pathological gastroesophageal reflux after correction of esophageal atresia.

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Chapter 4

Prospective Medical and Surgical Treatment of Gastroesophageal Reflux in Esophageal Atresia

Based on the article:
Prospective Medical and Surgical Treatment of Gastroesophageal Reflux in Esophageal Atresia
Jan Hein L.J. Bergmeijer and Frans W.J. Hazebroek.
Journal of the American College of Surgeons. 1998 August; 187 (2): 153-157

4.1 Abstract

Background
Gastroesophageal reflux is a major cause of anastomotic complications after repair of esophageal atresia. For this reason, we evaluated a prospective, postoperative treatment protocol with the emphasis on comparing medical versus surgical treatment.

Study design
From 1994 to 1995, 26 consecutive patients underwent correction of esophageal atresia in the Sophia Children's Hospital. These patients were enrolled in a decision-making protocol meant to establish the effect of medical treatment on gastroesophageal reflux and stricture formation, the relations between anastomotic tension and reflux, and the question of whether performing a Nissen fundoplication was justified. Patients who showed reflux on the first postoperative x-ray were given medical treatment. Reflux was assessed after 6-12 weeks by x-ray and 48-hour pH-metry (24 hours with and 24 hours without medication). Evaluations were repeated at 18 weeks, 6 months, and 1 year. Twenty-three patients were followed for $\geq$ 1 year.

Results
Twenty-four patients had classic esophageal atresia combined with tracheoesophageal fistula. Two had isolated atresia and underwent a colonic interposition. One of the others died of severe cerebral hemorrhage early after operation. Twenty-two of the remaining 23 showed reflux on the first postoperative x-ray and were given medical treatment. The mean 3.8% total mild reflux time (range, 0.0-11.0%) decreased to a mean of 1.47% (range, 0.0-6.8%). Medical treatment given according to protocol did not influence severe reflux. Eleven of 23 patients showed stricture formation, requiring a mean of four dilatation procedures (range, 1-9). Defining a real stricture as one needing three or more dilations, as seen in seven patients, the following results were seen: four non-refluxing patients (proved by x-ray and pH-metry) needed a mean of 4.2 dilatations (range, 3-7), and three refluxing patients (proved by x-ray and pH-metry) needed a mean of 7.3 dilatations (range, 5-9). Three of seven patients with anastomotic tension had proved gastroesophageal reflux; reflux was also diagnosed in 8 of 15 patients without any tension on the anastomosis. Nine of 23 patients underwent a Nissen fundoplication according to the protocol. In four of them, this was decided because of severe reflux-associated

respiratory problems; in one, for resistent stenosis after a Livaditis procedure; and in one with normal pH-metry, the procedure was done on clinical grounds. The latter patient needed an aortopexy at a later stage. A late fundoplication was performed in two patients for persistent gastroesophageal reflux unresponsive to medical treatment, and in one for persistent stenosis and reflux. In all patients, the outcomes was successful, without complications.

Conclusions
Medical treatment of gastroesophageal reflux after repair of esophageal atresia has a distinct effect on the duration of reflux and could have a positive effect on the occurrence and treatment of stenosis. There is no clear relation between the occurrence of reflux and tension on the anastomosis. Nissen fundoplication according to the protocol was done appropriately in eight of nine patients.

4.2 Introduction

Although the overall mortality in patients with esophageal atresia has decreased to < 10% in de past decade, anastomotic complications after repair of esophageal atresia — such as leakage, stricture formation, and aspiration pneumonia — remain serious problems.

Gastroesophageal reflux is a major cause for these complications. Most studies on this problem have been retrospective, and patient groups were not consecutive. From prospective evaluation of postoperative morbidity in patients with esophageal atresia in our department (1988) it appeared that duration of hospitalization was reduced because effective treatment of stenosis and esophagitis could be initiated at an early stage. After the introduction of a new prokinetic agent, Prepulsid (Janssen-Cilag, BV, Tilburg, the Netherlands), we changed our policy and started a prospective medical and surgical treatment protocol in 1994. In this study, we evaluated the frequency of reflux, the relations between tension on the anastomosis and reflux, the effect of medical treatment on gastroesophageal reflux and stricture formation, and the question whether Nissen fundoplication according to the protocol was justified.

4.3 Methods

During 1994 and 1995, 26 consecutive patients (16 boys and 10 girls) were evaluated. Twenty-four patients had classic esophageal atresia combined with tracheoesophageal fistula and two had isolated atresia. The mean gestational age was 37 weeks (range, 29-42 weeks) and the mean birth weight was 2,160 g (range, 1,000-3,000 g). Twelve patients (including the one without fistula) had associated anomalies: cardiac anomalies in four patients, renal anomalies in two, vertebral anomalies in three, and anal atresia in three patients, one of whom also had a duodenal atresia.

After correction of the atresia, our patients were enrolled in a decision-making protocol (Fig.1). When gastroesophageal reflux was noted on the first postoperative barium swallow, we started medical treatment with an alkaline coating gel (Gaviscon, Schering-Plough BV, Amstelveen, the Netherlands; 2 ml after each feeding) and a cholinergic stimulator of the plexus myentericus of the digestive tract (Prepulsid, dosage 0.2 kg/kg bodyweight three times a day). Gastroesophageal reflux was evaluated after 6 to 12 weeks by means of a barium swallow, and 48 hour pH-metry (24 hours with and 24 hours without medication). The pH measurements were performed in our hospital using a flexible glass electrode with internal reference electrode (Escolab, Maarssenbroek, the Netherlands) connected to a bedside computing system (UPS-2020/Orion, MMS BV Holland, Enschede, the Netherlands). The probe was placed 1-2 cm above the lower esophageal sphincter and its position was confirmed by chest x-ray. During the procedure, all patients were given their normal formula feeding. Prospective evaluation was repeated according to the protocol at 18 weeks, 6 months, and 1 year. All patients had a follow-up period of $\geq$ 1 year.

4.4 Results

One very premature infant, who underwent operation sucessfully, died at 4 weeks of complications of severe cerebral hemorrhage. The two patients with isolated atresia, after a gastrostomy and cervical esophagostomy, underwent a colonic interposition at the age of 9 months without complications. All other patients were followed for $\geq$ 1 year.

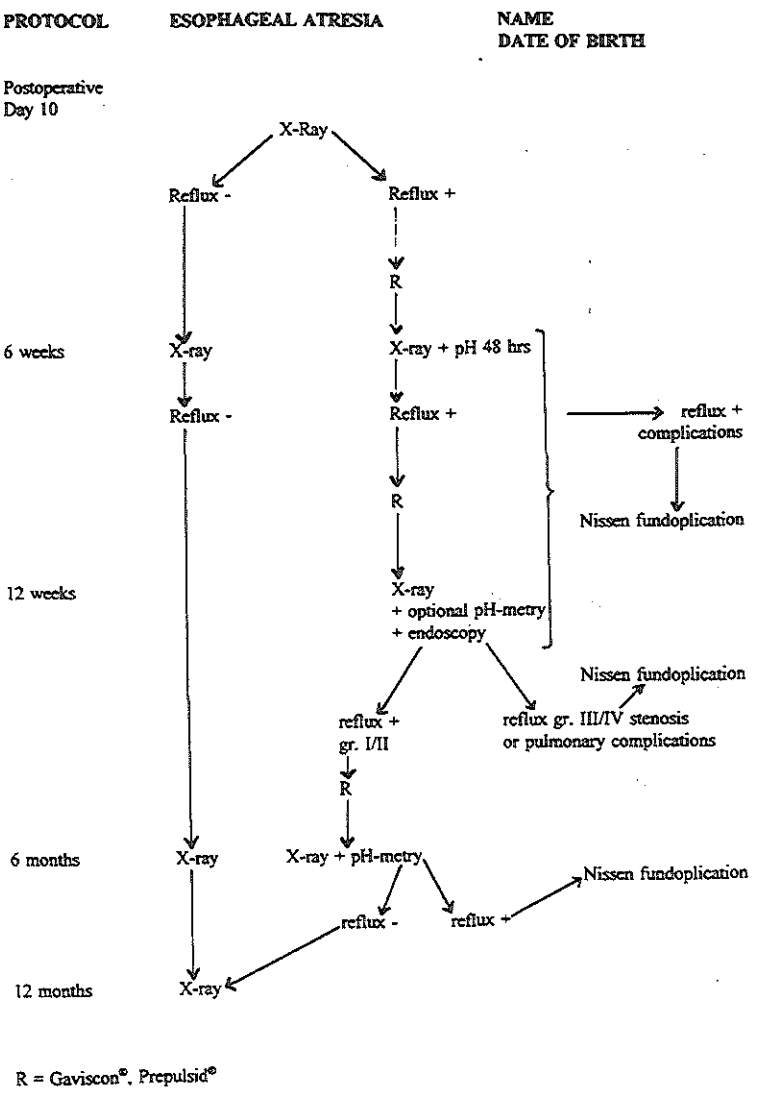

Figure 1. The postoperative treatment protocol.

Reflux-studies

In 22 of the remaining 23 patientss, the first postoperative barium swallow showed esophageal reflux, and medical treatment with Gaviscon and Prepulsid was started. The single patient without reflux had a successful course: repeated barium swallows showed no reflux.

Nineteen of the remaining 22 patients underwent pH-metry according to the protocol. The parents of two patients refused consent for this investigation, and in one it was performed too late. Five patients had a single 24-hour pH-metry; 14 patients had two consecutive 24-hour pH-metries, with and without medication. Without medication, the mean reflux index (total percentage of time with a pH < 4) was 3.8% (range 0.0-11.0%) for mild reflux in 12 patients; with medication, the mean reflux index was 1.47% (range 0.0-3.2%) (Table 1).

Table 1. Reflux index values with and without medication in 12 patients with mild reflux

Patient no.	with medication	without medication
1	6.8	8.7
2	0.5	1.7
3	0.6	2.5
4	0.8	3.3
5	0.8	2.5
6	1.6	7.5
7	0.0	0.5
8	0.0	0.0
9	3.2	11.0
10	0.8	4.3
11	2.2	2.3
12	0.3	1.1

In two patients with very severe reflux (> 20% total reflux index), medication did not improve the reflux. In the group of patients with mild reflux, the medication also changed the total number of periods of a pH < 4 lasting for > 5 minutes. The mean number was 3.25 (range, 1-8) without medication, which changed to a mean of 0.9 (range, 0-5) with medication.

We also investigated whether there was a relation between the occurrence of reflux, as shown at the first and second barium swallows and 24-hours pH-metry, and the occurrence of tension on the anastomosis during the operation. In seven patients, the surgeon mentioned tension on the anastomosis, but in only three of these could the reflux be confirmed. On the other hand, reflux was seen in 8 of the other 15 patients without tension of the anastomosis.

Stricture formation

Eleven of the 23 patients with corrected esophageal atresia showed stricture formation requiring at least one dilation procedure. A mean of 4 dilations was necessary (range, 1-9). Distinguishing between refluxing and nonrefluxing patients, the results showed that 6 of the 15 patients without reflux needed a mean of three dilatations (range, 1-7), and 5 of the 8 patients with reflux needed a mean of five dilatations (range, 1-9). Defining a real stricture as one needing three or more dilations, somewhat different results were seen: 4 of the 15 nonrefluxing patients needed a mean of 4.2 dilatations (range, 3-7), and 3 of the 8 refluxing patients needed a mean of 7.3 dilatations (range, 5-9).

Nissen fundoplication

Nine of the 23 patients having operative correction in our study underwent a Nissen fundoplication according to our prospective protocol. An early Nissen fundoplication, between 2 and 4 months, was performed in six patients: In four of them for severe reflux-associated respiratory problems, in one for resistant stenosis after a Livaditis-procedure, and in one on clinical grounds for respiratory problems despite a normal pH. The latter patient needed an aortopexy at a later stage, so in retrospect, the Nissen fundoplication had been unjustified. A late Nissen fundoplication, at 22 and 24 months, respectively, was performed in two patients for persistent gastroesophageal reflux not responding to maximal intensive medical treatment and in one patient for a persistent stenosis and reflux after 11 months. All patients had successful outcomes without complications.

4.5 Discussion

With the overall decrease in the mortality rate for esophageal atresia from 30% to < 10% in the past few decades, attention is being focused increasingly on postoperative

morbidity.[1-5] In the last decade, researchers have focused on pathological gastroesophageal reflux and its sequelae, for instance esophagitis, stricture formation at the anastomosis, aspiration pneumonia, and risk of sudden infant death syndrome.[6-9]

Most reported studies have been retrospective, and the patient populations were often mixed as to age.[10-13] Little is known of pH-studies in the immediate postoperative phase in patients with esophageal atresia, although 24-hour pH-metry is the gold standard for distinguishing between normal and pathologic gastroesophageal reflux.

More than 50% of normal neonates show gastroesophageal reflux to some extent, which tends to worsen in the first few months of life and to disappear within the first year. The standards of 24-hour pH-metry have been established in pH-studies in normal neonates and infants performed by Vandenplas and Sacré-Smits.[14]

Pathologic gastroesophageal reflux in esophageal atresia is thought to be caused by several factors, such as dysmotility of the esophagus, injury to the vagus nerve during the surgical procedure, traction of the distal esophagus by tension on the anastomosis, and alteration of the angle of His of the stomach.[15]

From the findings in our study group, it is evident that reflux based on radiologic investigations is the rule rather than the exception; 22 of our 23 patients (95%) demonstrated reflux. There are no x-ray studies of normal neonates, but probably the same percentage would be found because every neonate spits a little of his feedings once or twice a day. We believe that 24-hour pH measurements are essential to discriminate between physiologic and pathologic gastroesophageal reflux.[14] At the same time, the effectiveness of medical treatment can be demonstrated. In our series of patients with mild reflux, the reflux index was 3.8%, with a range of 0 to 11%, which is slightly more than in a normal child of 2-3 months. Medication decreased the reflux index in all of these patients with mild reflux to a mean of 1.47%. The same effect was seen on the total number of reflux periods lasting > 5 minutes, which dropped from 3.25 to 0.9 episodes.

Comparison of a prospective group from our own center in the years 1984-1985 with the present group shows a decrease in stricture formation from 75% to 43% (11 of 23) and a decrease in the mean number of dilatation procedure from 6.5 to 4.[7] Adding medical

treatment after repair of esophageal atresia could decrease postoperative stenosis formation and facilitate treatment of the stenosis.

The assumption that tension on the anastomosis will lead to pathologic gastroesophageal reflux could not be verified in our studies. Eight of the 15 patients with a tension-free anastomosis showed reflux, and only three of seven patients with anastomotic tension had confirmed reflux.

The decision to perform another operation soon after a successful correction of esophageal atresia is a difficult one, both for the surgeon and the parents. The impact will be even greater on the child. Only on the basis of good clinical grounds and objective investigations should it be considered whether conservative treatment or an antireflux operation should be offered.

A prospective treatment protocol such as the one we have used can help the surgeon treating patients with esophageal atresia to decide on an operation on proper grounds at the proper time.[16] In our patients, the Nissen fundoplication was performed appropriately in all but one patient, without postoperative complications.

In conclusion, gastroesophageal reflux after repair of esophageal atresia seems to be an additional disorder in this patient group. It should be ruled out in an early phase; if present, conservative treatment can lower morbidity. If medical treatment is unsuccessful, an antireflux operation may be done on the basis of proper clinical grounds and objective measurements.

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Chapter 5

Nissen Fundoplication in the Management of Gastroesophageal Reflux Occurring after Repair of Esophageal Atresia

Based on the article:
Nissen Fundoplication in the Management of Gastroesophageal Reflux Occurring after Repair of Esophageal Atresia
J.H.L.J. Bergmeijer, D. Tibboel, F.W.J. Hazebroek
Journal of Pediatric Surgery. 2000 April; 35 (4):573-576

5.1 Abstract

Background/Purpose
Gastroesophageal reflux is a major cause of complications after esophageal atresia repair. The suitability of the Nissen fundoplication in these patients is still disputed. Therefore, the authors evaluated the results of their prospective treatment protocol in those patients who underwent a Nissen fundoplication.

Methods
From 1984 to 1996, 125 patients underwent anastomosis for esophageal atresia. A Nissen fundoplication was later performed in 29 patients. The prospective protocol included x-ray after 10 days, 6 weeks, 12 weeks, 6 months, and 12 months. Forty-eight-hour pH measurements were performed between 6 and 12 weeks. Mean postfundoplication follow-up was at least 5 years (range 2 to 13 years).

Results
Two of the 29 patients died after the Nissen fundoplication from unrelated causes. A third patient was excluded from the study group. Nineteen of the remaining
26 patients showed severe stricture. pH-metry succeeded in 18 patients, showing pathological reflux in 17. In 24 patients the fundoplication was performed between 11 and 24 months (median, 4 months); in the other 2 patients much later. In 4 of the 26 patients (15%) the Nissen proved to be insufficient and had to be redone. The remaining 22 patients had no short-term or long-term complications.

Conclusion
The authors' findings in this group of patients, comparing them with the results reported in the literature, indicate that there is no reason to change their prospective treatment protocol nor their policy to perform Nissen fundoplications at an early stage.

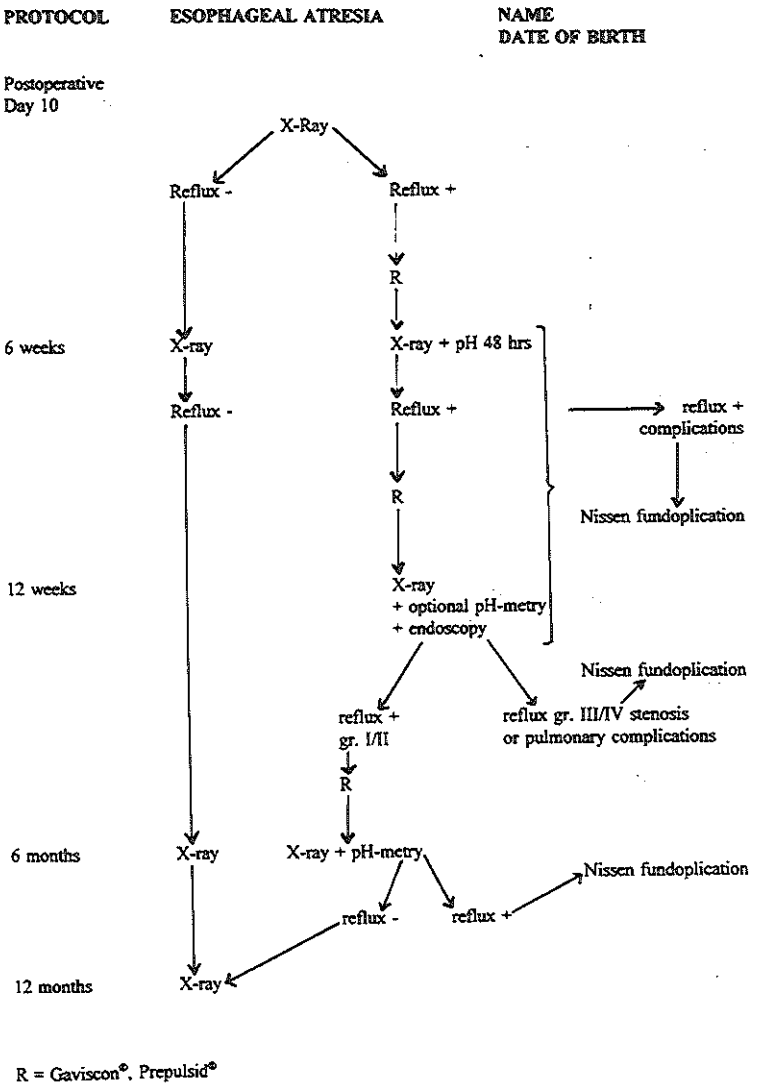

Figure 1. The postoperative treatment protocol.

5.2 Introduction

Mortality after primary repair of esophageal atresia – with or without a fistula – now is almost negligible when there are no severe cardiac, cerebral, or pulmonary problems or a chromosomal abnormality incompatible with life. Attention has now turned to postoperative morbidity. Gastroesophageal reflux in particular is a great problem, necessitating an antireflux operation in some patients, despite intensive medical treatment. Most pediatric surgeons prefer the Nissen-Rossetti fundoplication,[1-8] but others, alarmed by the incidence of failures of this operation, use other procedures such as the Thal or Toupet procedure.[9,10] We have performed Nissen fundoplications after esophageal atresia repair since 1977 and began to wonder whether there was any reason to change our policy.[11-13] We, therefore, reviewed the records of patients who underwent a Nissen fundoplication within the framework of our prospective follow-up protocol introduced in 1984 (Figure 1). We focused on recurrent reflux and complications after the operation.

5.3 Materials and methods

From January 1984 through February 1996, 125 infants with esophageal atresia underwent anastomosis at the Sophia Children's Hospital. All had entered the protocol according to which patients are prospectively screened on gastroesophageal reflux, and which was partly changed in 1989 concerning the use of medication: Domperidon had been replaced by Prepulsid, and (though not included in the protocol) some patients were now given H_2-blockers. All pH-measurements were done in our hospital using a flexible glass electrode with internal reference electrode (Escolab, Maarssenbroek, the Netherlands) connected to a bedside computing system (UPS-2020/Orion, MMS B.V. Holland, Enschede, the Netherlands). All patients were given their normal formula feedings during pH-monitoring, which basically takes 48 hours: 24 hours without medication followed by 24 hours with medication. Pathological gastroesophageal reflux was defined as pH less than 4 for more than 4% of time during 24-hour monitoring.[13,14] Esophagogastrography was performed to detect reflux, esophagitis and to determine whether the anastomosis is passable.

Twenty-nine patients eventually underwent a Nissen procedure with a 2-3 cm fundoplication length and crural plasty in all but 1. Two of them died from unrelated causes within 8 months: 1 born with severe psychomotor retardation caused by perinatal asphyxia 6 months

postoperatively, the other with Down syndrome and multiple congenital anomalies after 8 months. A third child with type C atresia and congenital right-sided eventration of the diaphragm was ventilation dependent for 1 year and had not undergone follow-up and surgery according to the protocol. Hence, we present our findings in 26 of the 29 patients.

The mean birth weight of these 26 patients (20 boys, 6 girls) was 2.280 g (range, 1.590 to 3.200 g). Duration of pregnancy ranged from 31 weeks till full term. Four patients had a type A atresia, and 22 a type C atresia according to Gross' classification.[15]

Mean post-fundoplication follow-up was 5 years (range, 2 to 13 years, median, 4 years). Follow-up examinations were not performed by protocol, and consisted of esophagogastrography after 6 weeks, 1 year, and when instigated by complaints.

The medical records of the 26 patients were reviewed for type of esophageal atresia repair, stricture formation, pH-metry, time of Nissen procedure, and failures.

5.4 Results

Esophageal atresia repair and postoperative findings
The 4 patients with isolated atresia (type A) had been anastomosed using the Livaditis procedure.[16] Six other patients had classical type C atresia, but had a long gap between the proximal and distal esophagus requiring a Livaditis procedure too. The remaining 16 patients had a normal distance between proximal pouch and distal fistula for which an uncomplicated primary anastomosis had been performed.

Esophageal X-rays, performed according to the protocol 10 days and 6 weeks after atresia repair, showed severe stricture in 19 of the 26 patients – of whom 9 had undergone a Livaditis procedure – needing a mean of 7 (range, 3 to 20) dilatation procedures. The other 7 patients did not show stenosis on x-ray. Our protocol called for pH-metry with and without medication during 48 hours in all patients between 6 and 12 weeks.[14] The parents of 1 of the 26 patients, however, refused this investigation. In 2 patients it was not attempted because of severe stenosis. In 5 patients was attempted but failed owing to severe stenosis. Hence, pH-metry was successful in 18 of the 26 patients showing pathological reflux in 17. On average,

the mean percentage of time during which pH less than 4 was 14% (range, 7.5 to 52); the mean number of periods during which pH less than 4 was 30 (range 21-250); the mean number of periods during which pH less than 4 was observed longer than 5 minutes was 10 (range, 5 to 60). Normal values were found in 1 patient with life-threatening cyanotic spells.

Nissen fundoplication
Indications for fundoplication were resistant stenosis *and* pathological reflux in 20 patients, only pathological reflux in 2, recurrent aspiration and lung infection in 2, and asthma in 2. In 24 of the 26 patients the Nissen fundoplication had been performed between 1 and 24 months after the atresia repair (mean, 6 months; median, 4 months). In 2 patients it had been performed much later, after 40 months and after 60 months, respectively. In the former, this was because of long-term problems caused by concomitant anorectal malformation, dextrocardia and right lung hypoplasia, the need to perform 7 stricture dilatation procedures, and the fact that medication kept him relatively well. The latter patient had concomitant anorectal malformation and urological problems and had to undergo 7 dilatations of the anastomosis. Oral intake gradually returned to normal in both patients after the fundoplication.

On the basis of repeated x-rays and typical complaint patterns, the fundoplications were found to be insufficient in 4 of the 26 patients (15%) and had to be repeated; in one of them even twice within 2 years. The latter patient originally had been anastomosed by means of a Livaditis procedure, and eventually a thoracotomy was performed to resect a resistant anastomotic stenosis. One patient with a type C atresia had undergone a partial Nissen procedure after 2 months, which was soon found to be insufficient. A complete Nissen fundoplication therefore was performed after 9 months and is functioning normally so far. Another patient with type C atresia underwent a Nissen fundoplication and gastrostomy for stenosis of the anastomosis. After 2 years the Nissen appeared to be insufficient and was successfully redone. The fourth patient required a Nissen fundoplication after 3 months because of severe reflux and complicating therapy-resistant acute respiratory distress syndrome (ARDS), which even necessitated extracorporeal membrane oxygenation. Initially functioning well, the Nissen was ruptured after replacing the gastrostomy by a percutaneous endoscopic gastrostomy. The second Nissen fundoplication was performed soon afterwards and is still functioning well.

On the basis of clinical manifestations, 8 of the 26 patients appeared to have tracheomalacia. Severity of tracheomalacia was assessed by bronchoscopy. Five patients needed an aortopexy, but tracheomalacia disappeared spontaneously in the other 3. Distal esophageal obstruction after the Nissen fundoplication was observed in none of the patients.

5.5 Discussion

Successful anastomosis for esophageal atresia may be complicated by gastroesophageal reflux, manifesting itself in recurrent respiratory tract infections, life-threatening cyanotic spells, severe stenosis of the anastomosis, vomiting and failure to thrive, or a combination of these symptoms.[17] This condition requires surgical correction, but there still is no consensus about the best time to operate and the best type of operation. The Nissen fundoplication has been most widely applied in the past 20 years. Older studies report proportions of patients undergoing a Nissen after correction of esophageal atresia ranging from 6% to 35% but do not expand on possible failures and the need to perform redo Nissen procedures.[1-4,18]

As shown in Table 1, Curci and Dibbins,[5] Lindahl et al,[6] Wheatley et al,[7] and Kubiak et al[19] reported fairly high recurrence rates of their Nissen fundoplications after esophageal atresia repair, ranging from 35 to 47%. Meyers et al,[8] in contrast, documented only 2 recurrences in 33 Nissen fundoplications performed in esophageal atresia patients from 1948 to 1988.[8] Both recurrences concerned patients with type A atresia; a third patient with a functioning Nissen had a paraesophageal hernia. Fonkalsrud,[9] an advocate of the Nissen fundoplication, finds this operation technically more difficult for patients with corrected atresia and recommends the Thal or Toupet technique, but does not provide results. Roy-Choudhary and Ashcraft[10] reported their results of Thal procedures performed in 77 of 222 corrected esophageal atresia patients (32%) from 1973 to 1997. A redo Thal fundoplication had to be performed in 9 of these 77 patients (12%). Long-term follow-up results are not given, however.

Comparing our results with the best in the above series – Meyers et al[8] (6%) and Roy-Choudhary and Ashcraft[10] (12%)– our 15% redo percentage (4 of 26 patients) is slightly higher. On retrospect, however, in one patient an interposition at an early stage perhaps would have been more appropriate, and in another, a complication had been caused by

changing a percutaneous endoscopic gastrostomy. We agree with other pediatric surgeons that the surgical treatment of gastroesophageal reflux after correction of an esophageal atresia remains a cumbersome issue, especially when soon after successful correction of the atresia another major operation with its intrinsic complications proves to be necessary. Although our protocol provides a sound basis, it appeared that in individual cases the decision to perform a Nissen fundoplication was taken much later than indicated in the protocol. Yet, we believe that our protocolized follow-up and treatment, and the final short-term and long-term results of our patients after a Nissen fundoplication do not provide sufficient reason to change our policy.

Table 1 Recurrence rates of fundoplications in esophageal atresia patients reported in various studies.

Study	No. of Patients	No. of Fundoplications	No. of Recurrences
Curci and Dibbins[5] 1988	31	14 Nissen	5
Lindahl et al[6] 1989	48	13 Nissen	5
Wheatley et al[7] 1993	80	21 Nissen	7
Meyerset al[8] 1990	498	33 Nissen	2
Roy-Choudhary and Ashcraft[10] 1998	222	77 Thal	9
Kubiak et al[19] 1999	Not given	19 Nissen	9
Current study	125	26 Nissen	4

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Chapter 6

Does Protocolized Follow-up Influence Morbidity in Esophageal Atresia? A Comparative Study of Two Groups of Patients.

Based on the article:
Does Protocolized Follow-up Influence Morbidity in Esophageal Atresia? A Comparative Study of Two Groups of Patients.
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Submitted

6.1 Abstract

Background
Gastro-esophageal reflux in patients corrected for an esophageal atresia, seems to be one of the causative factors of stenosis of the anastomosis. The aim of our study was to analyse whether a prospective protocol using antireflux medication could bring down these stenoses and the number of dilatations.

Methods
A group, from 1975 through 1980, not receiving medical treatment, was compared with a group, from 1990 through 1995, prospectively treated with Gaviscon and Prepulsid. Comparative factors included duration of admission, post-operative ventilation, mortality, recurrent fistula, leakage of the anastomosis, stenosis and dilatations of the anastomosis.

Results
No significant differences were found between the two groups. In the first group 40.4% of the patients had a stenosis, needing an average of 5 dilatation procedures, in the most recent group 47.8% had a stenosis, needing an average of 4.6 dilatations.

Conclusion
Treatment with Gaviscon and Prepulsid did not lower the occurrence of stenosis, nor the number of dilatations. New prospective studies with more effective antireflux treatment should be performed.

6.2 Introduction

As nearly all follow-up studies of patients with a corrected esophageal atresia concern consecutive groups with more or less good results over the years,[1-11] we compared two groups of our patients well separated in time. The first was treated in our hospital from 1975 through 1980. They did not receive medical treatment for gastroesophageal reflux.

The second group was treated and followed prospectively from 1990 through 1995. Postoperative treatment in this group included medication for gastroesophageal reflux

using Gaviscon®, an alkaline coating gel, and Prepulsid®, a cholinergic stimulator of the myenteric plexus of the digestive tract.

The purpose of this study was to evaluate whether our protocolized medical treatment decreased the occurrence of stenosis of the anastomosis and the number of dilatation procedures. To see whether significant changes in peri- and post-operative care occurred, which could influence the results of our study, we also evaluated duration of first admission, postoperative artificial ventilation, survival rates, and occurrence of recurrent fistula and leakage of the anastomosis for the two groups

6.3 Patients and methods

Retrospective study group
A total of 77 patients (41 boys and 36 girls) with esophageal atresia were admitted to the Sophia Children's Hospital in the period 1975 – 1980 (group A). Their mean birthweight was 2570 g (range 950 – 3680 g); mean gestation was 37.7 weeks (32 – 40 weeks). Nineteen of these 77 patients died, two without having been operated upon. Eight patients underwent an interposition, 6 for type A atresia, and 2 for type C atresia with long distance between proximal pouch and distal fistula, and were excluded. Three patients were lost for follow up. Hence, in total 47 patients were properly followed after their correction, 2 for an H-type fistula, and 45 for type C. Two of the type C patients had undergone a proximal myotomy according to Livaditis.[13] None of the patients had received standard medical treatment.

Prospective study group
A total of 65 patients (36 boys and 29 girls) were admitted in the period 1990 – 1995 (group B). Their mean birthweight was 2280 g (range 965 – 3800 g), mean gestation 36.6 weeks (28 – 40 weeks). All underwent operation. Sixteen of these 65 patients died. Three patients with a type A atresia underwent an interposition and were excluded from the study. In total 46 patients were properly followed after their correction, 1 for an H-type fistula, 1 for type A, and 44 for type C. One of the type A patients and 3 of the type C patients had undergone a Livaditis procedure. All the patients were prospectively followed using a flow scheme (Figure 1, on page 41), which included medical treatment

with Gaviscon (Schering-Plough BV, Amstelveen, the Netherlands; 2 ml after each feeding) and Prepulsid (cisapride) (Jansen/Cilag BV, Tilburg, the Netherlands, 0.2 mg/kg bodyweight t.i.d.) when reflux was proven on the first X-ray 10 days after the repair.

The records of all admitted patients were evaluated for duration of their first admission, postoperative duration of mechanical ventilation, overall mortality, mortality in newborns less than 1500 g birthweight, early and late mortality, and occurrence of recurrent fistula and leakage of the anastomosis. More specifically, the results of medical treatment aimed at treating gastroesophageal reflux were evaluated.

6.4 Results

Duration of admission in group A was 52 days, (range 15-203 days) in group B 55 days (range 15-200 days). The mean postoperative period of mechanical ventilation was 2.4 days in group A (range 1-10 days) and 2.2 days in group B (range 1-10 days).

Overall mortality
The overall mortality rate in group A was 19 of the 77 patients (24.7%), versus 16 of the 65 patients (24.6%) in group B. Brain and heart abnormalities were the main causes of death in either group. (see Table) Remarkably, in group A five patients died of Potter's syndrome (polycystic kidney disease), in group B none. Two patients in group B died from respiratory failure after blocking of solid food at the site of the anastomosis at home at the age of one year, and a third of asphyxia due to suspected aspiration in hospital 60 days after the operation.

Mortality in patients with birthweight less than 1500 grams
Five patients in group A had a birthweight ≤ 1500 g. Their mean birthweight was 1450 g (range 950 – 1500 g), mean gestational age 33 weeks (range 31 – 34 weeks). All five had been operated upon. Three of them died: 2 from brain abnormalities and 1 from heart disease.
Ten patients in group B had a birthweight ≤ 1500 g, with a mean of 1290 g (915 – 1500 g) and a mean gestational age of 33 weeks (29 – 36 weeks). Four of them died: 2 of brain abnormalities, and 2 of heart disease.

Early mortality (≤ 30 days)
In group A, 13 patients (16.8%) died within 30 days: 12 of non-preventable causes, and 1 of meningitis due to urinary tract infection. In group B, 5 patients (7.9%) died early, all of a natural cause (see Table).

Late mortality (> 30 days)
In group A, 6 patients died after 30 days: 5 from brain or heart abnormalities, 1 from tracheomalacia at home at one year of age. In group B, 11 patients died after 30 days: 8 from brain or heart abnormalities, 3 from airway obstruction. (One 60 days after surgery, 2 at one year of age). (See table).

Recurrent fistula and leakage of the anastomosis
Recurrent fistulas between the esophagus and the trachea occurred in 5 patients in group A (10.6%) and in only 2 patients in group B (4.3%). Leakage occurred in 7 patients in group A (14.9%), in 3 patients (6.5%) in group B.

Stenosis
The ultimate result of our study was to look wether the antireflux medication could bring down the number of patients with a stenosis or at least the number of dilatations would diminish. In group A, 19 of the 47 patients (40.4%) had a stenosis, (i.e. a narrowing of the anastomosis with clinical signs requiring at least 2 dilatations). 12 patients had no reflux on their first X-ray of the esophagus and stomach, while 7 had reflux. Of these 19 patients, 2 underwent a Livaditis procedure. The remaining 17 underwent a direct anastomosis, and they needed a mean of 5 dilatation procedures, (range 2-14 times, median 3).

In group B, 22 of the 46 patients (47.8%) had a stenosis. All these patients were treated with Gaviscon and Cisapride. 4 patients had no reflux on their first X-ray, while 18 had reflux. Of these 22 patients, 4 underwent a Livaditis procedure. The remaining 18 underwent a direct anastomosis, and they needed a mean of 4.6 dilatation procedures (range 2-8 times, median 4).
In the patients who underwent a Livaditis procedure, the number of dilatations decreased from a mean of 16.5 in group A to 7.5 in group B.

On all formentioned items in group A and B were compared using the Chi-square test. We could not find any significant differences between group A and B.

Table: causes of early and late mortality

	Group A (1975-1980)	Group B (1990-1995)
Early mortality (≤ 30 days)		
Cerebral cause	3	3
Cardiac anomalies	3	2
Potter syndrome	5	-
Digeorge syndrome	1	-
Sepsis	1	-
subtotal	*13*	*5*
Late mortality (> 30 days)		
	Group A	**Group B**
Cerebral cause	1	3
Cardiac disease	2	5
Lung disease	2	-
Tracheomalacia	1	-
Unexpected suffocation		
- aspiration	-	1
- resp. failure after food blocking	-	2
subtotal	*6*	*11*
Total	**19**	**16**

6.5 Discussion

Although the overall mortality rate does not differ between the groups (24.7% versus 24.6%), we noted differences in the causes of death. Potter's syndrome incompatible with life presented in 5 patients in group A, whereas it was not seen in group B. This is probably due to more widespread use of prenatal ultrasound in case of suspected intrauterine growth retardation. Three patients in group B died of unexpected suffocation,

whereas this was not observed in group A. The overall mortality rates found in this study are comparable to that found by McKinnon: 25%.[1] The mortality rates reported by Spitz: 13.5%,[14] Foker: 11%,[7] Engum: 5%,[6] refer to early mortality and are similar to our findings. As in our study groups, most children died of brain or heart abnormalities, with or without a low birthweight.[15] In our study, mortality among patients with a birthweight < 1500 g was 3 of 5 in group A, and 4 of 10 in group B. Although the group sizes hardly allow to interpret possible reasons for better survival, we assume that better pre- and postoperative care (artificial ventilation, cerebral monitoring with ultrasound, cardiac care and treatment) result in decreasing mortality.[1,9]

Early mortality in the most recent group is still caused by severe brain and heart abnormalities. In view of the fact that some of these heart abnormalities in very young patients can still not be corrected owing to their complexity, this situation is bound to persist in the near future.[3,6,15,16]

Late mortality (>30 days) was not due to expected respiratory problems, but again mainly due to brain and heart abnormalities, both in group A and in group B.[10,16]
The main goal of treating prospective group B with Gaviscon and Cisapride was to bring down the consequences of gastroesophageal reflux, and thus the number of patients with a stenosis of their anastomosis, and in patients with a stenosis the number of dilatation procedures (compared with group A). This goal has not been reached. As patients requiring a Livaditis procedure nearly always develop a severe stricture owing to reflux, necessitating an antireflux procedure after multiple dilatations, we did not include in our analysis the concerned 2 patients in group A and the 4 patients in group B. Hence, 17 of 45 patients in group A had a stenosis, versus 18 of 42 patients in group B. Even with exclusion of the patients with only two or three dilatation procedures, nine in group A, eight in group B, the total number of dilatations did not differ: 7.5 versus 6, respectively.

The stricture rates found in our study (40.4 and 47.8) correspond to the one reported by Chittmittrapap et al. in 1990, who dilated strictures in 74 of 199 patients (37.2%).[4] Engum and Grosfeld in 1995 reported that 79 of 272 patients operated on between 1971 and 1993 were treated for stricture (35%).[6] In contrast, both Sillen et al.[2] and Somppi et al.[5] in long-term overviews (1963 – 1993), though in small series, reported stricture formation in

18%. Beasly et al. reported a stricture rate of 30%.[16] None of the above reports, however, makes mention of gastroesophageal antireflux medication.

At the beginning of our prospective study, after a study in our hospital on Gaviscon and Motilium in which no decrease of strictures was found,[17] we assumed, judging from the available literature, that Prepulsid would certainly be effective. Relevant reports published in the late 1990s, however, give overall indications that it is no more effective than conventional treatment in cases of simple gastroesophageal reflux. In 1997, Scott et al. in a randomised, double-blind, placebo-controlled study showed that Cisapride indeed improves the esophageal clearance of gastric acid with the periods exceeding 5 minutes decreasing, although the percentage of the total time with a pH < 4, and the number of reflux periods did no differ from that in the group given a placebo.[18] Greally et al. in 1992 demonstrated that Cisapride had the same effect as Gaviscon and Carobel (carob seed flour).[19] This was confirmed in 1999 by Cohen et al. in a randomised, double-blind, placebo-controlled trial.[20] Although Cisapride did lower the percentage of time with a pH < 4, the number of episodes pH < 4 was the same in the reflux score. In a randomised controlled study in children < 36 months, McClure et al. even state that Cisapride delays gastric emptying and may delay whole gastric transit time in preterm infants.[21] Consequently, they do not recommend its use. Vandenplas et al.,[22] on behalf of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition, performed a critical, in-depth analysis of all reported adverse effects of Cisapride in infants and children. They stated that precautions are advisable in patients

a. with a history of cardiac dysrhytmias,
b. receiving drugs inhibiting the metabolism of Cisapride,
c. with immaturity and diseases causing reduced cytochrome P450 3A4 activity, and
d. with electrolyte disturbances.

Khongphatthanayothin reported similar effects of Cisapride on QT interval in children.[23] Combining the findings from the above studies, especially in very young and premature infants, with the result of our own study, we conclude that Cisapride did not yield the positive results we hoped to find.

The rates of recurrent fistulas in our study (10.6% and 4.3%) more or less correspond to those reported in the literature. Engum et al. give an overall percentage of 3% [6], Spitz et al. 12% in a 5-year study of 148 patients,[3] and Beasly et al. reported no recurrent fistula in the last 70 patients.[16]

Leakage of the anastomosis was seen in 7 (14.9%) and in 3 (6.5%) patients in group A and group B, respectively. Compared with 16% in the series reported by Engum et al.,[6] and the 12% reported by Spitz et al.,[3] the rate in our most recent group B is certainly lower. Beasley et al. reported an even lower leakage rate of 3%.[16]
Although a birthweight lower than 1500 g is still a risk for non-survival, the number of survivors in this group has increased. The number of patients with leakage and recurrent fistula decreased considerably. Our assumption that the use of Gaviscon and Cisapride could have a positive effect on the numbers of patients with a stricture and on the numbers of dilatations,[24] was not proven in the present study. New prospective studies are needed in which patients with a pH-proven reflux at an early stage (e.g. 8-12 weeks after correction) will be treated with more aggressive antireflux medication, such as Cimetidine or Ranitidine (H_2-blockers). Nevertheless, we think that those patients with really persistent reflux and life-threatening events still need early antireflux surgery.

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Chapter 7

Gastroesophageal Reflux and Barrett's Esophagus in Adults Born with Esophageal Atresia

Based on the article:
Gastroesophageal Reflux and Barrett's Esophagus in Adults Born with Esophageal Atresia
E. Krug, J.H.L.J Bergmeijer, J.Dees, R. de Krijger, W.J. Mooi, and F.W.J. Hazebroek
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7.1 Abstract

Objective
Postoperative morbidity after correction of esophageal atresia is partly determined by gastroesophageal reflux disease, which has been proven to affect from one-half to two-thirds of patients during childhood. We conducted a follow-up study to test our hypothesis that, if former patients still show gastroesophageal reflux at adult age, they are at high risk for developing Barrett's esophagus, which is considered to be premalignant.

Methods
Of 69 patients born between 1971 and 1978, all having undergone a primary anastomosis, 24 had died, five of them because of aspiration. Of the 45 survivors, 39 could be traced; they all completed a questionnaire inquiring after symptoms related to the esophagus. Of these patients, 34 underwent an additional esophagogastrocopy.

Results
Only nine of the 39 patients had no symptoms at all; 30 had mild to severe dysphagia symptoms, and 13 had mild to severe reflux symptoms. Esophagogastrocopy in 34 patients revealed that the anastomosis was still recognizable in all cases, but stenoses were not found. Six patients showed a small hiatal hernia, and one a large one. The incidences of reflux symptoms (13/39, $p < 0.01$), reflux esophagitis (9/34, $p < 0.01$) and Barrett's esophagus (2/34, $p < 0.001$) were significantly higher than in the normal population.

Conclusions
This group seems to be at risk for developing Barrett's esophagus. As this is the first follow-up study of a consecutive group of adult esophageal atresia patients, we think it is advisable to perform an esophagogastroscopy in all patients at adulthood until more long-term follow-up data are available.

7.2 Introduction

The incidence of esophageal atresia with tracheo-esophageal fistula is one in 4000 live births, and 10-15 patients with this anomaly are treated in the Sophia Children's Hospital annually. Postoperative morbidity after surgical intervention is partly determined by gastroesophageal reflux (GER), which can be demonstrated in virtually all children immediately after esophageal repair.[1] Follow-up studies show that GER persists in one-half to two-thirds of patients during childhood.[2,3] Only Chetcuti *et al.* studied adult esophageal atresia patients.[4] They reported reflux problems, but only investigated patients with this problem.

It is well accepted that chronic GER may lead to esophagitis and metaplastic change of the esophageal epithelium. Three types of metaplastic epithelium have been described:

1. the gastric fundic type, without villi though with mucous secretory cells;
2. the junctional type, with rudimentary villi and mucous secretory cells as found in the gastric cardia; and
3. the specialized intestinal type, with villi and crypts and mucous secretory goblet cells as found in the small intestine.[5]

However, there is no consensus as to whether the gastric fundic type is really metaplastic esophageal mucosa or just normal gastric mucosa in biopsies taken too low,[6,7] nor about the junctional type of metaplasia.[8] There is, however, consensus about the specialized intestinal type, which is called Barrett's epithelium and is considered to be premalignant, as it may become dysplastic and change into adenocarcinoma.[9,10]

The incidence of reflux symptoms in the normal population in western countries is 5-10%, that of esophagitis 2%.[11-13] The prevalence of Barrett's esophagus in the normal population is not exactly known. An autopsy study showed a prevalence of 376 of 100,000 persons, which is 16 times higher than that clinically suspected in the same region (23 of 100,000 persons).[14] Other studies, in patients who underwent an endoscopy because of reflux symptoms, revealed Barrett's esophagus in 4-10% of patients.[15] Patients in whom Barrett's esophagus is diagnosed are subjected to surveillance endoscopy to monitor the occurrence of dysplasia.[16]

Although we now know that GER persists throughout childhood in one-half to two-thirds of patients with esophageal atresia, little is known about its frequency in adult atresia patients who never underwent any screening or treatment for GER. We hypothesized that if GER is still present in adulthood these patients are at high risk for developing Barrett's esophagus and should be kept under surveillance. We therefore conducted a study in order to determine whether any harmful sequelae of GER, such as esophagitis and Barrett's esophagus, were present in a consecutive group of esophageal atresia patients > 18 yr. This is the first study using endoscopy and biopsy in such a group.

7.3 Materials and methods

Between 1971 and 1978, 76 newborns with esophageal atresia were treated in our hospital. Of these, 69 underwent primary anastomosis. Five patients who underwent colonic interposition and two mentally retarded patients were excluded from this study because many other factors play a role in developing GER in these patients. Twenty-four (15 male, 9 female) of the remaining 69 patients died; in 21 of them, autopsy was performed. In five patients death was caused by aspiration at ages of 2 days, 2 weeks, and 8, 13, and 20 months. The other patients died from causes not related to esophageal atresia at ages from 7 h to 17 months.

In 1997 we were able to trace 39 of the 45 survivors (11 male, 28 female), who all completed a questionnaire inquiring after symptoms of GER such as pyrosis, acid taste experienced spontaneously, after meals, or when bending forward, foul taste in the morning, pain during swallowing, recurrent coughing, or recurrent airway infections. In addition we asked for dysphagia symptoms, such as feeling of slow passage, need to drink a lot during meals, need to mash food, not being able to eat as fast as others, and poorly tolerated products. Finally we included questions about weight, length, smoking habits, use of alcohol, medication, educational level, type of work, recent respiratory or gastrointestinal investigations or treatment elsewhere. The first question was: "Do you suffer from symptoms due to the esophagus?", which could be answered by either yes or no.

Of these 39 patients, 34 consented in undergoing an esophagogastroscopy. The flexible endoscopies were performed by a gastroenterologist and a pediatric surgeon, using the

Olympus XQ 200 and Olympus XP 230 endoscope. All investigations were video-recorded. We checked for the aspect of the anastomosis, stenosis, esophagitis, hiatal herniation, gastritis, and especially for abnormal epithelium. Biopsies were taken from abnormal-looking epithelium but never more distal than 2 or 3 cm above the Z-line; control samples were taken from patients with no apparent abnormalities, except from the patients to whom the endoscopy was very uncomfortable, so as to ensure minimal exposure to the procedure. All biopsies were stained with hematoxylin and eosin and Alcian blue at pH 2.5 and screened for esophagitis and Barrett's epithelium by two independent pathologists. Esophagitis was scored according to Riddell and according to Ismail-Beigi.[17,18] Barrett's esophagus was defined as specialized intestinal metaplasia.

The prevalences of reflux symptoms, esophagitis, en Barrett's esophagus found in this study were compared with the prevalences in the general population as reported in the literature.[9,11-14] For this purpose, the statistical analyst used Z-tests obtained from the normal approximation to the binomial distribution; significance was defined as $p < 0.01$.

The medical-ethical committee of our hospital approved of the study, and all patients gave their written, informed consent. As informed consent was required, patients had to be > 18 yr; for logistic reasons it was not possible to trace patients born before 1971.

7.4 Results

Twenty-six of the 39 patients (ages 18-26 yr), including the five patients who had not undergone an endoscopy, stated they had no reflux symptoms. Of the other 13, eight had one or more reflux symptoms weekly without considering these to be a problem, four had weekly to daily symptoms experienced as abnormal, and one had severe therapy-resistant symptoms.

Only nine of the patients (all without reflux symptoms) had no dysphagia. Nine of the others sometimes experienced dysphagia but without the need to take precautions; 13 patients stated they avoided certain food products; and eight patients could not eat as fast as other people or had to drink much during meals.

In all 34 endoscopies, the anastomosis was still visible as a small rim or small fold. Three patients showed a real ring, which, however, did not obstruct passage of the scope. Six patients had a small diverticulum at the anastomosis. Erosion or inflammation was not seen at the level of the anastomosis. Six patients had a very small hiatal hernia and only one had a large hiatal hernia.

Eight patients had esophagitis in the distal part of the esophagus, in none of them erosive. In six cases this was interpreted as grade 1 inflammation, in one as grade 2, and one patient showed a combination of grade 1 esophagitis and gastritis. Three of these eight patients had no reflux symptoms. The patient with the grade 2 esophagitis also had a pink tongue of 0.5 cm (horizontal) x 2.5 cm (vertical), suggestive of Barrett's epithelium. The patient with gastritis showed esophagitis from 25 to 35 cm with tongues and circular areas of pink mucosa, suggestive of Barrett's epithelium as well. Both patients with suspected Barrett's epithelium suffered from reflux: the latter is still under medical supervision because of symptoms, the former, however, was discharged from supervision many years ago.

Biopsies were taken from nine patients in whom endoscopy did not reveal abnormalities, and from eight patients with signs of esophagitis or Barrett's esophagus. Histological examination (esophagitis scored according to Riddell)[17] showed normal epithelium in only one case, grade 1 esophagitis in nine cases, and grade 2 esophagitis in seven cases. Intestinal type epithelium or Barrett's epithelium was confirmed in the two patients in whom it was endoscopically suspected. Dysplasia was absent in all patients. Scoring according to Ismael-Beigi revealed normal histology in eight patients and grade 1 esophagitis in nine.

On the basis of the patients' histories we may distinguish a group with and a group without reflux symptoms. There were no significant differences in male/female ratio, age, daily alcohol use, smoker/nonsmoker ratio, body mass index, or amount of perioperative complications between these two groups. Follow-up was longer in the reflux group (40 *vs* 30 months), nothwithstanding equal incidence of other congenital malformations necessitating follow-up. If, on the basis of the patients' histories, we would have distinguished a reflux and nonreflux group beforehand, and would have performed an endoscopy only in the reflux group, we would have missed grade 1 reflux esophagitis in

six patients, grade 2 esophagitis in two patients (according to Riddell), and gastric metaplasia in one patient. As these conditions have no clinical consequences for these patients, we did not take measures.

7.5 Discussion

The incidence of reflux symptoms in this group of patients is significantly higher than in the general population: 33% *vs* 10%. ($p < 0.01$) In view of the fact that 77% of the patients stated they experienced dysphagia, it is surprising that only nine patients (23%) attribute their complaints to the esophagus (as asked for in the first question). Because seven of those nine patients do have reflux symptoms, it seems likely that dysphagia is causing less discomfort than acid reflux. Another possibility is that the patients have learned to live with a compromised passage and do not recognise this as discomfort anymore.

The incidence of esophagitis in this group when histologically scored according to Riddell[17] is 47% (16/34), which is very high compared to the 2% in the general population. The difficulty is that the scoring system according to Riddell is very recent and uses more stringent criteria than that according to Ismail-Beigi,[18] which is frequently used in daily practice. But when scored according to Ismail-Beigi, we still find a 26% incidence (9/34) of esophagitis, which is also significantly higher than in the general population ($p < 0.01$). The endoscopic and histological findings do not correlate well, a phenomenon also encountered by Lindahl in 1993.[3] In this study we found histological evidence of esophagitis (according to Riddell) in eight patients in whom endoscopy revealed no abnormalities. In four other patients the esophagitis was scored grade 1 on endoscopy, and grade 2 on the basis of histological findings. When scored according to Ismail-Beigi, there is only one histological esophagitis without abnormalities on endoscopy. Although there are mismatches, most abnormalities were found in the group with reflux symptoms, and we did not have to give any treatment or follow-up advice in the symptom-free group.

The most important result of the study, however, is the fact that 2 of the 34 patients presented with endoscopically and histologically proven Barrett's epithelium, which is a significantly higher incidence than in the general population ($p < 0.001$). This means that

esophageal atresia patients are indeed at higher risk for developing this premalignant lesion. Maybe even more important is that one of these two patients had only mild reflux symptoms, which he had learned to cope with, and he had been discharged from follow-up many years ago.

As Barrett's epithelium can be partially reversed to normal esophageal epithelium after adequate inhibition of acid reflux, early recognition of this disease is crucial.[19] This also underlines the importance of early recognition and treatment of gastroesophageal reflux itself, inasmuch as it is unknown how long it takes for esophagitis to turn into Barrett's epithelium. However, Barrett's esophagus has been described in young children.[8] Because knowledge about gastroesophageal reflux, systematic screening, and treatment facilities has not become available until recently, especially patients born before routine screening for gastroesophageal reflux was introduced, seem to be at risk.

In conclusion, we found significantly higher incidence rates of reflux symptoms, esophagitis, and Barrett's esophagus in this consecutive group of adult esophageal atresia patients. Most abnormalities were found in patients with reflux symptoms. However, as this is the first follow-up study of a consecutive group of adult esophageal atresia patients, and seeing the bad correlation between symptoms and abnormalities, we think it is advisable to perform an endoscopy with multiple biopsies in all adult esophageal atresia patients until more long term follow-up data are available.

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Chapter 8

General Discussion

The introductory Chapter 1 ended with five research questions to be answered from the studies described in this thesis. The present chapter discusses the findings from these studies related to these questions.

8.1 What are the treatment results, in terms of mortality and morbidity, in children with an esophageal atresia in the Sophia Children's Hospital, and how do they compare to the results obtained in other centers?

a. Mortality

The mortality rate in the Sophia Children's Hospital (25%) is high compared with that in other centers (ranging from 12 to 38%, mean 20%).[1-5] This can partly be attributed to the presence of severe associated anomalies, and too small series in which mortality can fluctuate significantly and, especially with regard to late mortality, the loss of some patients for follow-up.

The early mortality rate (defined as death occurring within 30 days) decreased significantly from 16.8 % in the years 1975 –1980 to 7.9% in the years 1990 –1995, and is certainly comparable with that of other centers.[1-5] The early mortality appears to be mainly caused by associated severe brain and cardiac abnormalities and we think that due to the very young age of these patients and the complexity of these abnormalities this situation is bound to persist in the near future.

b. Morbidity

In the literature, morbidity after correction of the atresia is mostly described in terms of leakage of the anastomosis, recurrence of the tracheo-esophageal fistula, and the development of a stricture of the anastomosis.

From our study reported in Chapter 7 it appears that leakage of the anastomosis occurred in 14.9% of patients in the years 1975-1980 and dropped to 6.5% (3 out of 46 patients) in the years 1990-1995. Compared to findings from other centers (3-37%, with a mean 14%) this rate is reasonably low and reflects the larger technical experience and improvement of perioperative care in these patients.

From Chapter 7 it also appears that the rate of recurrent fistulas in our patients likewise decreased from 10.6 % to 4.3% (2 out of 46 patients). Other centers report rates ranging from 1-6,3%, with a mean 4%).[1,3,4,6,7]

Although we had expected that our prospective treatment protocol of gastroesophageal reflux, would diminish the numbers of patients with a stenosis and the numbers of dilatations, our expectation fell short. Recent data from the literature show that cisapride does not produce the effect we had hoped for. It even can delay gastric emptying in preterm infants, which in fact occurred in half of our patients born with esophageal atresia.[8,9,10]

8.2 How does postoperative gastroesophageal reflux presents in those esophageal atresia patients, and should it be considered normal or abnormal ?

Presenting symptoms of reflux are spitting of food, growth retardation, pain and agitation, recurrent lung infections, and-especially in patient with corrected esophageal atresia-stricture of the anastomosis. The first four symptoms are not very specific and may present in otherwise healthy children as well, but a stricture of the anastomosis can be caused by pathological reflux. This is specific for esophageal atresia patients. A contrast study of the esophagus in a struggling neonate gives information of the severity of the stricture only; it does not reveal wether it might have been caused by pathological reflux. The same holds good for endoscopic evaluation; besides, it is often impossible due to the presence of the stenosis.
A 24-hours pH-metry, on the contrary, is usually possible, even when a stenosis is present in the very young infant. It gives continuous information about the acidity in the distal esophagus. Data on normal values in patients with an esophageal atresia were lacking so far. From our investigations reported in Chapter 3 these proved to be similar to those healthy infants of the same age. Although the normal values show a certain range, they may well serve to determine whether the reflux in other patients with a corrected esophageal atresia should be considered normal, moderate, or (very) pathological.

8.3 Do patients with a corrected esophageal atresia have a higher risk of persisting reflux, and consequently a higher risk of developing Barrett's esophagus?

As was shown in Chapter 4, with 11 of 23 patients operated on in 1994 and 1995 showing pathological reflux, and 9 of these 11 patients needing a Nissen fundoplication, reflux

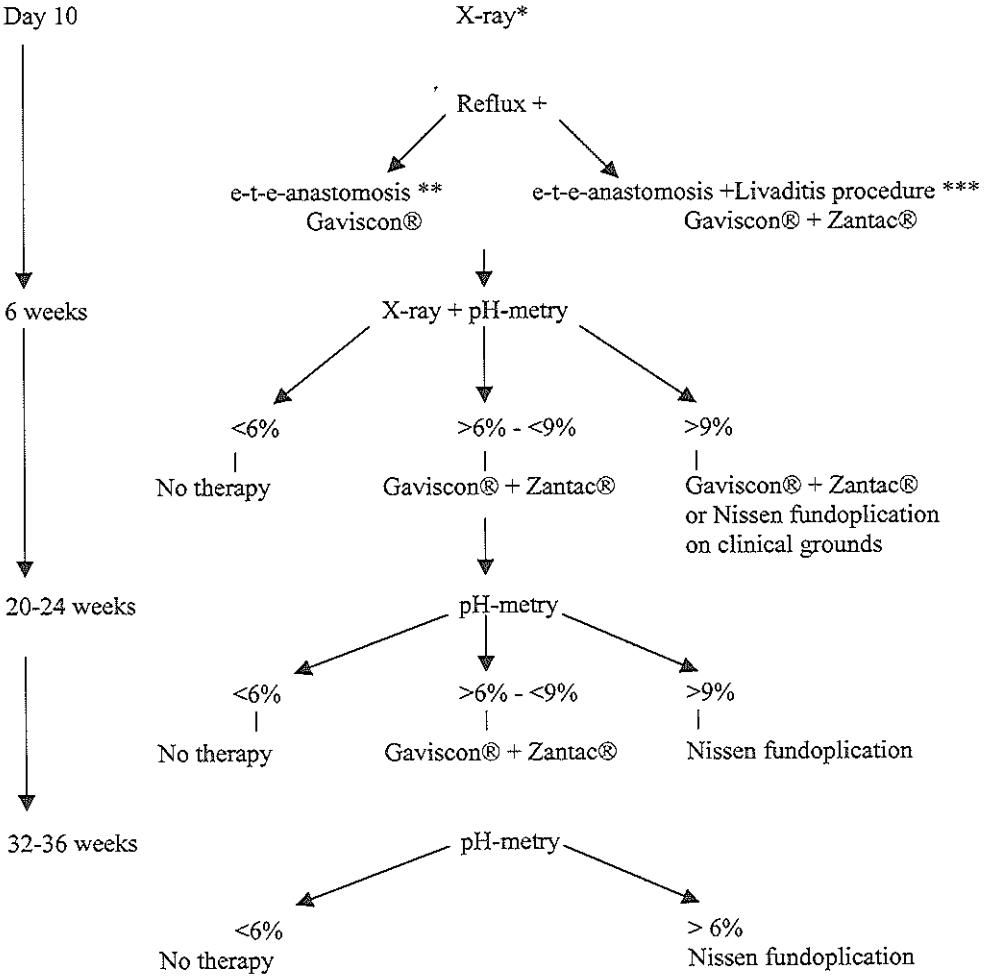
occurs much more frequently in esophageal atresia patients than in the normal population. In retrospect this should apply to the older group of patients, but in the years 1950 to 1970 the surgeon and the parents were already very happy when the operation itself was a success. Investigations for reflux were still in its infancy, pH-metry was not yet possible and radiological evidence of reflux was exceptional. Chapter 6 reports that 13 of 39 consecutive patients had reflux symptoms, that 9 of 34 patients investigated by endoscopy and biopsy showed esophagitis, and that 2 of these 34 had Barrett's esophagus. These incidences are significantly higher than in the normal population.[11,12] It should be worthwhile to trace all patients treated before 1970, the period when reflux was neither diagnosed nor treated. After a proper anamnesis, an endoscopic examination with biopsies of the esophagus on the slightest suspicion of reflux.[13,14] The main problem, to trace all these patients, could be relieved with the help of the Association of Esophageal Atresia Patients in the Netherlands.

8.4 Is our medical treatment of gastroesophageal reflux effective, and if so, what medication is most effective?

As appears from Chapter 4 medical treatment with a combination of Gaviscon® and Prepulsid® did not improve the detoriating effects of reflux, and neither diminished the numbers of patients with a stenosis, nor the numbers of dilatations for stricture per patient.[8,9,10]

It is, therefore, relevant to start a new study in which all patients with a primary end-to-end anastomosis of the atresia and spontaneous reflux on their first X-esophagus, are given Gaviscon® only and patients with a end-to-end anastomosis combined with a Livaditis procedure are given Gaviscon® and a H2 receptor antagonist (Zantac®). The latter can be given as a liquid solution to neonates. After 6-10 weeks a 24 hour pH-metry without medication should than discriminate the patients with real pathological reflux. When their clinical condition is well, i.e. normal feeding, no vomiting, no recurrence of a stenosis nor pulmonary complications, this should indicate to continue their medication for a longer period (20-24 weeks). When these patients still have problems, repeated endoscopy with biopsies and 24 hour pH-metry should indicate whether anti-reflux surgery is necessary.

Proposed follow-up scheme for reflux after esophageal atresia



* radiological examination of esophagus and stomach
** end – to – end anastomosis esophagus
*** end – to – end anastomosis with circular myotomy of proximal esophagus pouch

8.5 When does gastroesophageal reflux requires surgical treatment? Does this surgical treatment have a definitive, beneficial effect and what are the complications?

Patients with a resistant stenosis due to pathological reflux who not respond to optimal conservative measures, should undergo a Nissen fundoplication following the proposed new protocol. Patients suffering from aspiration pneumonia or near sudden infant death syndrome after correction of atresia should undergo a Nissen funduplication as soon as above-mentioned diagnoses have been made. Concerning the definitive and beneficial effects of the Nissen fundoplication in patients without congenital anomalies, it was concluded in Chapter 2 that the very long term results of this operation are excellent. Only one of 24 consecutive patients had a poor outcome. For patients with a fundoplication after correction of their atresia very long term follow up is not yet possible, but as mentioned in Chapter 4, we had a redo percentage of 15%, wich is well acceptable and certainly comparable with the best results from the literature.[15-20] There were no short or long term complications.

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Chapter 9

Summary / Samenvatting

9.1 Summary

A neonate with a classic esophageal atresia without any serious congenital defects, has nowadays a nearly complete chance of normal development after a correcting operation. Nevertheless, more than half of the patients show another course than doctors and their parents had hoped for, certainly in the beginning.
For instance the baby may have been born much too early and show severe respiratory problems, or despite the fact that the first investigation showed a normal functioning heart, later on the child show a very severe congenital malformation with all its consequences. Even after a successful operation, the anastomosis may narrow to such a degree that normal food will not pass, necessitating several dilatation procedures under anaesthesia. Then, it may be evident that gastroesophageal reflux is the main cause of the stricture and that a second operation, a Nissen fundoplication, is needed to resolve the problem. This thesis addresses questions on the diagnostics and treatment results of these problems.

Chapter 1
This chapter gives a brief history of esophageal atresia and gastroesophageal reflux. It further discusses the available investigations, therapeutic conservative measures and surgical therapies.
Five research questions were posed to be answered from the studies reported in this thesis:

1. What are the treatment results in terms of mortality and morbidity in children with esophageal atresia in the Sophia Children's Hospital, and how do they compare to the results obtained in other centers?
2. How does postoperative gastroesophageal reflux present in those esophageal atresia patients, and should it be considered normal or abnormal?
3. Do patients with corrected esophageal atresia have a higher risk of persisting reflux, and consequently a higher risk of developing Barrett's esophagus?
4. Is our medical treatment of gastroesophageal reflux effective, and if so, what medication is most effective?
5. When does gastroesophageal reflux require surgical treatment? Does this surgical treatment have a definitive, beneficial effect, and what are the complications?

Chapter 2

The purpose of this study was to analyse the very long-term results of the Nissen-Rossetti fundoplication performed in young children. Little has been reported about follow-up for more than five years in homogeneous populations. The study concerns a homogeneous group with a minimum follow-up of ten years and a median follow-up after operation of sixteen years. These former patients, therefore, are now adolescents or adults. In the 24 consecutive patients, without other congenital or acquired anomalies of the esophagus or stomach, the primary postoperative diagnoses, symptoms of recurrent reflux and state of health, were evaluated after a median follow-up of sixteen years. The results were excellent in 18 patients, good in five and poor in one (graded according to Visick). In 3 patients with recurring reflux symptoms showed evidence of failure of the fundoplication. All but one of them had been given a diagnosis of recurrent reflux within two years after the operation. For this reason we conclude that the situation after two years seems predictive for the later outcome. In general, the Nissen-Rossetti fundoplication is a long-lasting, effective treatment for young children with symptomatic gastroesophageal reflux.

Chapter 3

A well-founded decision to perform a Nissen-Rossetti fundoplication for gastroesophageal reflux in a patient after correction of esophageal atresia should rest on pH findings. Baseline findings in these were still lacking, however, so that severity was hard to establish. For this reason we performed a 24 hours pH-metry without medication between eight and sixteen weeks postoperatively in 13 patients who had shown a completely uncomplicated postoperative course. This pH-metry was performed in hospital with a flexible glass electrode. With a mean reflux index of 4.08% during this 24 hours, a total number of periods with
pH < 4 was 21 and periods with pH < 4 which were longer than five minutes was 2.5. These values proved to be the same as the normal values in asymptomatic children of the same age, as established by Sacré and Vandenplas.

Chapter 4

Gastroesophageal reflux can be an important course of complications in the treatment of esophageal atresia. For this reason we analysed a prospective treatment protocol in 23 patients who were treated for an esophageal atresia in 1994 and 1995. Twenty-two of these 23 patients showed reflux on the first X-ray of the esophagus and were treated with

a combination of Gaviscon® and Prepulsid®. pH-metry without medication showed a mean reflux index of 3.8% (range 0 to 11%) and with medication of 1.47% (range 0 to 6.8%). Severe reflux (more than 20% of reflux index) was not influenced by these medications. In 11 of these 23 patients a stricture was found, and 7 of them needed more than 3 dilatations. Four patients of this group without reflux had a mean of 4.2 dilatations (range 3 to 7), and 3 patients with reflux needed 7.3 dilatation (range 5 to 9). Reflux was seen in 3 of 7 patients with tension on the anastomosis, and in 8 of 15 patients without tension on the anastomosis. No clear correlation was found between these two groups. In 9 patients on protocol grounds a Nissen fundoplication was performed. In 8 patients this had been done on proper grounds, in one patient it was done on clinical symptoms, though a pH-metry in this patient had shown normal values. This patient later underwent an aortopexy because of severe tracheamalacia. From the results of this study we can conclude that medical treatment of reflux in patients after correction of an esophageal atresia has a distinct effect on the duration of this reflux and could have a positive effect probably on the development and treatment of stenosis.

Chapter 5

As the study reported in Chapter 4 evaluated the results of only nine Nissen fundoplications performed in the course of two years, and because literature reports tended to condemn the use of Nissen fundoplications in esophageal atresia patients, we now analyzed the Nissen fundoplications performed from 1984 through 1996. In this period 125 patients underwent surgery for esophageal atresia, and 29 of them underwent a Nissen fundoplication later. The prospective treatment protocol included an esophagus X-ray after 10 days, 6 weeks, 12 weeks, 6 months, and 12 months. A 48 hours pH-metry was performed between the 6th to 12th postoperative week. Mean follow-up after the Nissen fundoplication was 5 years (range 2-13 years).

Two of the 29 patients who underwent a Nissen fundoplication had died from causes not related to the intervention. A third patient was excluded from the study because she had not been treated by protocol. Nineteen of the remaining 26 patients appeared to have a severe stricture. pH-metry could be performed in 18 of them and revealed pathological reflux in 17 of them. In 24 patients the Nissen fundoplication had been performed between 1 and 24 months (median 4 months), in two cases much later (after 40 and 60 months respectively). In 4 of the 26 patients (15%) the Nissen fundoplication proved to be

insufficient and had to be repeated. The other 22 patients had no short or long term complications.
Our findings, also in view of the results reported in the literature, provide no reason to adapt our prospective treatment protocol, nor our policy to perform a Nissen fundoplication at an early stage.

Chapter 6
This chapter deals with gastroesophageal reflux as one of the causative factors of stenosis of the anastomosis after correction of esophageal atresia. Medical antireflux treatment was expected to lower the incidence of stenosis. A well-documented group treated from 1975 through 1980 without receiving medication was compared with a group prospectively treated from 1990 through 1995 with Gaviscon® and Prepulsid®. Apart from occurrence of stenosis and required number of dilatation procedures, we evaluated duration of first admission, postoperative artificial ventilation, survival rates, and occurrence of recurrent fistula and leakage of the anastomosis for the two groups. No significant differences were found. In the first group 40.4% were found to have a stenosis, requiring a mean of 5 dilatation procedures, as compared with 47.8% in the second group, requiring a mean of 4.6 dilatation procedures.
Concluding, as prospective medical treatment with Gaviscon® and Prepulsid® had neither lowered the proportion of patients with a stenosis nor the number of dilatation procedures, we believe that new prospective studies with more effective antireflux medication are mandatory.

Chapter 7
This chapter deals with the development of Barrett's esophagus, which is considered a premalignant condition, in esophageal atresia patients at adult age. Postoperative morbidity after correction of esophageal atresia is partly determined by gastroesophageal reflux, which presents in over 50% of patients in childhood. We conducted a follow-up study to test the hypothesis that patients still showing reflux at adult age are at high risk of developing Barrett's esophagus. Of 69 patients born between 1971 and 1978, 24 had meanwhile died. Five of these had died from aspiration that might have been caused by reflux. Thirty-nine of the 45 survivors could be traced. They all completed a questionnaire inquiring after esophagus-related symptoms. Thirty-four of them also underwent an esophagogastroscopy.

Only 9 of the 39 participants reported to be symptom-free; and the other 30 reported mild to severe dyspeptic symptoms. Thirteen participants reported mild to severe reflux. While in all 34 patients who underwent esophagogastroscopy the site of the anastomosis was clearly discernable, none appeared to have a stenosis. A small hiatal hernia was observed in 6, a large one in one patient. The incidences of reflux symptoms (13/39, $p < 0.01$), reflux esophagitis (9/34, $p < 0.01$), and Barrett's esophagus (2/34, $p < 0.001$) in this group are significantly higher than those in the normal population.
We conclude that this group of patients is at high risk to develop Barrett's esophagus. As this follow-up study is the first of its kind, we advise to perform an esophagogastroscopy in all esophageal atresia patients at adult age, so that more data will become available.

Chapter 8
The general discussion aims at providing answers to the five research questions.

1. Overall mortality in our patients was in the higher ranges, but early mortality decreased from 16.8% to 7.9%. The incidence of leakage of the anastomosis and recurrent fistulas decreased as well. Despite the use of Gaviscon® and Cisapride®, neither the numbers of patients with a stenosis nor the numbers of dilatations per patient, unfortunately, did not decrease.
2. Reflux as a causative factor of stricture of the anastomosis, is the main problem in esophageal atresia patients. its severity is best detected with a 24 hour pH-metry. Normal values of pH-metry in these patients appeared to be similar to those in helthy controls.
3. Our study on Barrett's esophagus in the former esophageal atresia patient at adult age shows clearly a significantly higher chance of developing this disease. We propose that all patients treated in the Netherlands before 1970 should be investigated.
4. Our prospective treatment with Gaviscon® and Cisapride® was not as effective as we had expected and for that reason a new follow-up scheme was developed. From this scheme one can conclude when surgical therapy is necessary.
5. The Nissen fundoplication as performed in our hospital has a long-lasting effect.

9.2 Samenvatting

Een pasgeborene met een klassieke oesophagusatresie, zonder andere ernstige aangeboren afwijkingen, heeft tegenwoordig een bijna volledige kans op een normale ontwikkeling na een corrigerende operatie. Helaas blijkt dat bij meer dan de helft van de patiënten, het zeker in de beginfase anders gaat dan de dokters en de ouders hadden gehoopt.
De baby is bijvoorbeeld veel te vroeg geboren en heeft aanzienlijke ademhalings-problemen, of blijkt nadat eerder een normaal functionerend hart werd aangetoond, later toch een ernstige afwijking te hebben met alle gevolgen van dien.
Zelfs nadat de operatie goed geslaagd is, kan de verbinding zodanig vernauwd raken dat het voedsel niet meer kan passeren en moet deze vernauwing meerdere malen opgerekt worden onder narcose. Als hierna blijkt dat zure reflux deze vernauwing in stand houdt en is een tweede operatie, een Nissen fundoplicatie, noodzakelijk om dit tegen te gaan.
Over de diagnostiek en de resultaten van de behandeling van deze problematiek gaat dit proefschrift.

Hoofdstuk 1
Dit hoofdstuk behandelt in het kort de geschiedenis van oesophagusatresie en gastro-oesophageale reflux. Het vervolgt met de diagnostische onderzoekingen die gedaan kunnen worden, de therapeutische maatregelen die genomen kunnen worden en de mogelijke chirurgische ingrepen.
Vijf onderzoeksvragen werden gesteld die in de volgende hoofdstukken beantwoord worden:

1. Wat zijn de behandelingsresultaten bij kinderen met een oesophagusatresie in het Sophia Kinderziekenhuis en zijn deze vergelijkbaar met de resultaten van andere centra?
2. Hoe presenteert zich postoperatieve gastro-oesophageale reflux bij deze patiënten, en wanneer kan deze normaal en wanneer abnormaal beschouwd worden?
3. Hebben patiënten na een gecorrigeerde oesophagusatresie een grotere kans op persisterende reflux en dus ook een grotere kans op het ontstaan van een Barrett's oesohagus?
4. Is onze medicamenteuze behandeling van reflux zinvol en zo ja, welke is het meest effectief?

5. Wanneer dient reflux chirurgisch behandeld te worden? Is het effect van chirurgische behandeling blijvend en welke zijn de complicaties?

Hoofdstuk 2
Het doel van deze studie was het analyseren van de zeer lange termijnresultaten van de Nissen-Rossetti fundoplicatie verricht bij jonge kinderen. Weinig is gerapporteerd over follow-up langer dan vijf jaar in aaneengesloten groepen; deze studie betreft een groep van patiënten met een minimale follow-up van tien jaar. Zij zijn nu dus adolescent of volwassen.
Bij 24 opeenvolgende mentaal gezonde patiënten zonder aangeboren of verkregen afwijkingen van de slokdarm en maag werden in 1994 de primaire postoperatieve diagnose, symptomen van terugkerende reflux en de algehele gezondheid geëvalueerd. Na een mediane follow-up van zestien jaar (spreiding 10 tot 22 jaar) was het resultaat excellent bij 18 patiënten, goed bij 5 en slecht bij 1 (classificatie volgens Visick). Bij 3 patiënten met terugkerende reflux-symptomen bleek de fundoplicatie te falen. Twee van de drie patiënten waren gediagnosticeerd binnen twee jaar na de operatie. De situatie twee jaar na de operatie lijkt voorspellend voor de uiteindelijke uitkomst.
Samenvattend kunnen we stellen dat de Nissen-Rosetti fundoplicatie een langdurig effectieve behandeling is van gastro-oesophageale reflux bij jonge kinderen.

Hoofdstuk 3
Alvorens echter te besluiten om een Nissen-Rosetti fundoplicatie te verrichten bij een patiënt die net geopereerd is aan een oesophagusatresie, is het van essentieel belang om de normaalwaarden van reflux in de slokdarm bij deze groep van patiënten vast te stellen. Daarom werd bij 13 patiënten met een volledig ongecompliceerd postoperatief beloop een 24-uurs pH-metrie zonder medicatie verricht tussen de 8 en 16 weken postoperatief. De pH-metrie werd in het ziekenhuis verricht met gebruikmaking van een flexibele glaselektrode.
De gemiddelde refluxindex gedurende deze 24 uur bedroeg 4.08 %, het totaal aantal periodes met een pH < 4 was 21 en het gemiddelde aantal periodes met een pH < 4 langer dan 5 minuten bleek 2.5 te zijn. Deze normaalwaarden bleken dezelfde te zijn als die bij asymptomatische kinderen van dezelfde leeftijdscategorie zoals die zijn vastgesteld door Sacré en Vandenplas.

Concluderend kunnen we stellen dat de 24-uurs pH-metrie waarden bij asymptomatische oesophagusatresiepatiënten dezelfde zijn als die bij kinderen van dezelfde leeftijdsgroep met een normale anatomie van de slokdarm.

Hoofdstuk 4

Gastro-oesophageale reflux is een belangrijke oorzaak van complicaties bij de behandeling van een oesophagusatresie. Een prospectief behandelingsprotocol werd daarom bij 23 patiënten geanalyseerd, behandeld voor een oesophagusatresie in 1994 en 1995 in het Sophia Kinderziekenhuis.

Tweeëntwintig van de 23 patiënten met een klassieke oesophagusatresie toonden reflux op de eerste slikfoto en werden medicamenteus behandeld met Gaviscon® en Prepulsid®. Achtenveertiguurs pH-metrie toonde een totale refluxtijd van 3.8 % (spreiding 0 tot 11 %) zonder medicatie, en met medicatie van 1.47 % (spreiding 0 tot 3.2 %). Ernstige reflux (> 20 % van de totale tijd) werd door deze medicijnen niet noemenswaardig beïnvloed. Bij 11 van deze 23 patiënten werd een strictuur gezien, waarbij bij 7 patiënten 3 of meer dilataties nodig waren. Vier patiënten zonder reflux hadden 4.2 (spreiding 3 tot 7) dilataties nodig, 3 patiënten met reflux hadden 7.3 (spreiding 5 tot 9) dilataties nodig. Reflux werd bij 3 van de 7 patiënten met spanning op de anastomose gezien en bij 8 van de 15 zonder spanning. Met andere woorden, er werd geen duidelijke correlatie aangetoond tussen spanning op de anastomose en incidentie van reflux.

Bij 9 patiënten werd protocollair een Nissen fundoplicatie verricht. Bij 8 werd dit op grond van objectieve diagnostische parameters verricht, bij een patiënt op basis van klinische gronden met een normale pH-metrie. Deze laatste patiënt kreeg later een aortapexie wegens ernstige tracheomalacie.

Concluderend kan gesteld worden dat medicamenteuze behandeling van gastro-oesophageale reflux bij patiënten met een gecorrigeerde oesophagusatresie een duidelijk effect heeft op de duur van deze reflux, en zou ook een positief effect kunnen hebben op het ontstaan én behandeling van stenoses. Tussen spanning op de anastomose en reflux is geen correlatie. De Nissen fundoplicatie werd op juiste grond verricht bij 8 van de 9 patiënten.

Hoofdstuk 5

Aangezien in de voorgaande studie de resultaten werden geanalyseerd van slechts negen Nissen fundoplicaties, verricht gedurende twee jaar tijd, en aangezien in de literatuur de

Nissen fundoplicatie bij oesophagusatresiepatiënten nogal sterk wordt veroordeeld, werden in een nieuwe studie de verrichte Nissen fundoplicaties tijdens de periode 1984 tot en met 1996 geanalyseerd. In deze periode werden 125 patiënten met een oesophagusatresie behandeld en bij 29 daarvan werd later een Nissen fundoplicatie verricht. Het prospectieve protocol hield onder andere in een X-oesophagus na 10 dagen, 6 weken, 12 weken, 6 maanden en 12 maanden. Een 48-uurs pH-metrie werd verricht rond de zesde tot twaalfde week. De gemiddelde follow-up na de fundoplicatie was 5 jaar (spreiding 2 tot 13 jaar).
Twee van de 29 patiënten die een Nissen fundoplicatie ondergingen, waren overleden aan oorzaken die niet met de operatie samenhingen. Een derde patiënt werd niet in de studiegroep opgenomen, omdat zij niet protocollair vervolgd werd. Negentien van de overblijvende 26 patiënten toonden een ernstige strictuur. Een pH-metrie slaagde bij 18 patiënten. Deze toonde bij 17 patiënten een pathologische reflux aan. Bij 24 patiënten werd de fundoplicatie verricht tussen 1 en 24 maanden (mediaan 4 maanden), bij de 2 andere patiënten op een veel later tijdstip. Bij 4 van de 26 patiënten (15 %) bleek de Nissen fundoplicatie niet te voldoen en werd deze later nogmaals gedaan. De overige 22 patiënten hadden geen korte- of lange termijncomplicaties.
Concluderend kunnen we stellen dat de bevindingen in deze groep patiënten, geen aanleiding heeft gevormd om het prospectieve protocol aan te passen. Ook het beleid om een Nissen fundoplicatie in een vroeg stadium te verrichten blijft ongewijzigd.

Hoofdstuk 6
In dit artikel wordt gekeken naar gastro-oesophageale reflux als één van de veroorzakers van een stenose van de anastomose na correctie van een oesophagusatresie. Medicamenteuze behandeling van deze reflux zou het optreden van stenoses kunnen verminderen. Een goed gedocumenteerde groep uit de periode 1975-1980, die geen medicamenteuze behandeling kreeg, werd vergeleken met een groep patiënten uit de periode 1990-1995, die prospectief behandeld waren met Gaviscon® en Prepulsid®. Er werd gekeken naar opnameduur, postoperatieve beademing, mortaliteit, recidief fistel, lekkage van de anastomose, stenose en dilatatieprocedures van de anastomose. Er werden geen significante verschillen gevonden. In de eerste groep had 40.4% een stenose, welke gemiddeld 5 oprekprocedures behoefde. In de tweede groep werd bij 47.8% een stenose aangetroffen, welke gemiddeld 4.6 oprekprocedures behoefde.

Concluderend konden we stellen dat prospectieve behandeling met Gaviscon® en Prepulsid® het aantal patiënten met een stenose, noch het aantal oprekprocedures had verminderd. Nieuwe prospectieve studies met een krachtiger anti-refluxmedicatie lijken daarom noodzakelijk.

Hoofdstuk 7

In dit hoofdstuk wordt ingegaan op het voorkomen van een Barrett's oesophagus (intestinale metaplasie) bij geopereerde oesophagusatresiepatiënten, die inmiddels volwassen zijn. De postoperatieve morbiditeit na correctie van een oesophagusatresie wordt gedeeltelijk bepaald door gastro-oesophageale reflux, welke voorkomt bij ongeveer de helft tot tweederde van de patiënten gedurende de kinderjaren. Een vervolgstudie werd verricht om de hypothese te testen, dat, als patiënten deze reflux nog steeds zouden vertonen op volwassen leeftijd, zij een hoog risico dragen op het ontstaan van een Barrett's oesophagus, welke beschouwd kan worden als een premaligne aandoening. Van 69 patiënten, geboren tussen 1971 en 1978, waren er 24 overleden na de correctie van hun oesophagusatresie. Van deze 24 patiënten waren er 5 overleden aan een aspiratie, die mogelijk door reflux was veroorzaakt. Van de 45 nog levenden, konden er 39 worden opgespoord. Deze werden schriftelijk gevraagd naar symptomen gerelateerd aan hun slokdarm. Van hen ondergingen 34 tevens een oesophagogastroscopie.
Van de 39 ondervraagden hadden slechts 9 geen enkele klacht, terwijl de 30 anderen milde tot ernstige dyspeptische klachten meldden. Milde tot ernstige refluxklachten werden gerapporteerd door 13 ondervraagden. Bij alle 34 patiënten liet de scopie de oude anastomoseplaats duidelijk zien, maar een stenose werd echter bij geen enkele patiënt gezien. Bij 6 patiënten werd een kleine hiatus hernia gezien, bij 1 patiënt een grote hernia. In deze groep komen refluxsymptomen (13/39, $p < 0.01$), refluxoesophagitis (9/34, $p < 0.01$) en voorkomen van Barrett's oesophagus (2/34, $p < 0.001$) significant meer voor dan in de normale bevolking.
Wij concluderen dat deze groep patiënten een hoog risico heeft op het ontwikkelen van een Barrett's oesophagus. Aangezien dit de eerste vervolgstudie is in een consecutieve groep van volwassen oesophagusatresiepatiënten, is het aanbevelenswaardig om bij alle oesophagusatresiepatiënten op volwassen leeftijd een scopie te verrichten, zodat meer gegevens beschikbaar komen.

Hoofdstuk 8

In dit hoofdstuk worden de vijf voornoemde vragen beantwoord:

1. De algehele mortaliteit van onze patiënten lag in de hogere regionen, doch de vroege mortaliteit daalde van 16.8% naar 7.9%. Het zelfde kan gezegd worden van de lekkage van de anastomose en recidief fistels. Ondanks het gebruik van Gaviscon® en Prepulsid® daalde noch het aantal patiënten met een stenose, noch het aantal dilataties per patiënt.
2. Reflux als oorzaak van een stenose van de anastomose is het grootste probleem bij patiënten met een oesophagusatresie. Dit kan het beste met een 24-uurs pH-metrie vastgelegd worden. Gevonden waarden van een normale pH-metrie bij deze patiënten blijken gelijk aan de waarden die bij gezonde kinderen worden gevonden.
3. De studie over de Barrett's oesophagus bij volwassen oesophagusatresiepatiënten toonde duidelijk een significant hogere kans op het ontstaan van deze afwijking aan. De conclusie luidt dan ook dat al deze patiënten in Nederland geboren voor 1970 onderzocht dienen te worden.
4. Onze prospectieve behandeling met Gaviscon® en Prepulsid® was niet effectief en daarom is een nieuw behandelingsschema noodzakelijk. Uit dit schema blijkt ook duidelijk wanneer chirurgische behandeling nodig is.
5. De Nissen fundoplicatie zoals toegepast in ons ziekenhuis heeft een langdurig gunstig effect.

Curriculum Vitae

Op 27 maart 1947 werd Jan Hein Bergmeijer te Oegstgeest geboren.
De middelbareschoolopleiding werd gevolgd aan het Bonaventura Lyceum te Leiden, waar in 1966 het eindexamen Gymnasium-beta werd behaald.
In datzelfde jaar werd de studie Medicijnen aangevangen aan de Rijksuniversiteit te Leiden. Het artsexamen werd behaald in 1975. Vanaf februari 1975 werkte hij anderhalf jaar als arts-assistent aan de kinderchirurgiche afdeling van het Sophia Kinderziekenhuis te Rotterdam (hoofd Dr. J.C. Molenaar).
Hierna volgde hij de opleiding tot chirurg aan de Rijksuniversiteit te Maastricht in het Annadal Ziekenhuis (hoofd Prof.dr. J.M. Greep). Op 1 maart 1982 werd hij ingeschreven in het specialistenregister.
Sindsdien is hij werkzaam als staflid kinderchirurg aan het Academisch Ziekenhuis te Rotterdam op de afdeling Kinderchirurgie van het Sophia Kinderziekenhuis (hoofd Prof.dr. J.C. Molenaar, later Prof.dr. F.W.J. Hazebroek).
Hij is getrouwd met Magda van Zanten, met wie hij samen drie kinderen probeert op te voeden.