

# Gastroesophageal Reflux after Repair of Esophageal Atresia

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## Abstract

**Background and Aims** Gastroesophageal reflux (GER) is extremely frequent in patients with esophageal atresia and tracheoesophageal fistula (EA/TEF). It is often refractory to antireflux medication and requires antireflux surgery. The reasons for this close association, the dangers of persistent GER, and the indications, technical aspects, and pitfalls of antireflux operations in these patients are examined in the present study.

**Methods** The literature and summary of a large institutional experience of the authors were reviewed.

**Results** The esophagus is permanently defective in EA/TEF patients even when successful repair, sometimes under tension, has been achieved. Extrinsic and intrinsic innervations are abnormal and consequently, motor function and sphincters are defective. The result is that close to one half of these patients overall suffer chronic GER that leads often to Barrett esophagus. Fundoplication becomes necessary in more than 40% of them, particularly in cases of with refractory anastomotic stenoses and in those with pure and long-gap EA/TEF. In the long run, the risks of esophageal carcinoma are 50-fold higher in EA/TEF survivors than in the population at random. On the contrary, fundoplication is anatomically difficult to perform and it fails in one-fifth of these children due to the persistence of the conditions that facilitate GER in them.

**Conclusions** GER is extremely frequent in patients treated for EA/TEF because of serious structural and functional deficiencies. It is refractory to medical treatment and often requires antireflux surgery. However, the high rates of wrap failure invite close follow-up in all cases and reoperation or other measures whenever necessary.

## Keywords

- ▶ esophageal atresia
- ▶ tracheoesophageal fistula
- ▶ long-gap
- ▶ elongation
- ▶ gastroesophageal reflux
- ▶ stenosis
- ▶ fundoplication

## Introduction

Gastroesophageal reflux (GER) should be considered a component of esophageal atresia and tracheoesophageal fistula (EA/TEF) because it is very often diagnosed after neonatal repair of this condition. GER may cause regurgitation or vomiting, failure to thrive, apneic spells, barking cough, recurrent pneumonia, chronic respiratory tract disease, and recurrent anastomotic strictures. Furthermore, it responds poorly to diet, posture, and antacid or prokinetic medications that constitute the backbone of antireflux treatment and it requires surgery in a high proportion of cases. The purpose of

the present review was to summarize information about the prevalence of GER in EA/TEF patients, to examine why this phenomenon is so frequent and harmful, and to characterize the indications for antireflux surgery, the technical details of the operation and the long-term outcomes.

## GER Is Strikingly Frequent in EA/TEF Patients and Does Not Tend to Improve

The close association between EA/TEF and GER was repeatedly pointed out in the past<sup>1–4</sup> and so was the frequent need for antireflux surgery in these cases.<sup>2</sup> However, the real

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dimension of the problem was not fully appreciated until modern diagnostic methods became available.<sup>4,5</sup> ▶ **Table 1** summarizes the prevalence of GER in several series of EA/TEF collected along the past 30 years.<sup>6–18</sup> It ranges from one-fourth to two-thirds of 1,645 cases with an average of 43%.

Regurgitation or vomiting is extremely frequent early after neonatal EA/TEF repair. Swallowing may be difficult at this time, and the issue of anastomotic stenosis is always raised. However, even when stenosis can be ruled out (or dilated), dysphagia may persist and may require gavage for some time. Weight gain may be slow and, since early post-operative barium meal shows regularly a shortened esophagus with obtuse angle of His, GER is advanced as a likely explanation. Posture and proton pump inhibitors are frequently used to alleviate these symptoms. However, repeated episodes of apnea during or after feeding and cough and temporary desaturation may take place as well. These episodes can be dramatic and become apparent life-threatening events (ALTE) prompting active investigation. Barking cough and frequent respiratory infections, sometimes of constrictive nature, are quite constant during infancy in EA/TEF survivors and repeated atelectasis and/or pneumonia may also occur later in life. GER with microaspiration is a good explanation for some of them, although several other causes may contribute.

Anastomotic stenosis requiring repeated dilatations is also related to GER. Prompt response to dilatations after discontinuation of acid exposure and peptic injury to the anastomosis by effective antireflux surgery are an indirect indication of this relationship.

Many EA/TEF patients stop having symptoms of GER after the first or second year of life, but most have dysphagia and chronic respiratory symptoms for life.<sup>19–22</sup> These could be related to either excessive acid or alkaline exposure or to

repeated microaspiration. The proportion of them with endoscopic and/or bioptic esophagitis is high and gastric metaplasia (rarely real Barrett esophagus with intestinal metaplasia) is relatively frequent.<sup>17,20,23–25</sup> The reports of some cases of early esophageal carcinoma in EA/TEF patients<sup>17,26–29</sup> unveiled the alarming concept that they have a 50-fold increased risk of carcinoma with the passage of time.<sup>30</sup>

Management of regular GER in children follows the recommendations of the NASPGHAN<sup>31</sup> and ESPGHAN<sup>32</sup> that were based on the particularly benign, self-limited nature of this condition in most infants. These recommendations limit indications for antireflux surgery to the rare cases of protracted severe esophagitis, constrictive respiratory tract disease, or ALTE with documented GER. Unfortunately, such recommendations barely mention the management of GER in patients with EA/TEF and other comorbidities who do not benefit from the naturally limited pattern of GER that can be expected in other refluxers. In fact, they do not respond to postural or dietary treatments and are refractory to prokinetic medication. Although they can respond to antacid treatment,<sup>33–35</sup> this often fails to alleviate the symptoms and cannot prevent stenosis.<sup>36</sup>

### Anatomic and Functional Causes for GER in EA/TEF Patients

The malformation itself and the anatomic changes due to its repair compromise the delicate mechanisms in charge of preventing GER. The gastroesophageal junction may be congenitally abnormal: rats with adriamycin-induced EA/TEF had shorter intra-abdominal esophagus and larger hiatus than controls.<sup>37</sup> Traction on the distal esophagus while achieving anastomosis regularly displaces the gastroesophageal junction

**Table 1** Gastroesophageal reflux and fundoplication in patients with esophageal atresia

Study	Year	EA (n)	GER in EA (n)	%	Fundoplication (n)	%
Gauthier et al <sup>8</sup>	1980	113	58	51.3	15	25.9
Mercier et al <sup>9</sup>	1984	73	26	35.6	14	53.8
Black et al <sup>6</sup>	1991	97	41	42.3	16	39.0
Montgomery and Frenckner <sup>10</sup>	1993	110	28	25.5	9	32.1
Wheatley et al <sup>11</sup>	1993	62	34	54.8	21	61.8
Engum et al <sup>7</sup>	1995	220	127	57.7	56	44.1
Sparey et al <sup>16</sup>	2000	120	39	32.5	21	53.8
Yanchar et al <sup>18</sup>	2001	87	40	46.0	29	72.5
Deurloo et al <sup>12</sup>	2002	269	87	32.3	61	70.1
Konkin et al <sup>15</sup>	2003	140	45	32.1	17	37.8
Deurloo et al <sup>13</sup>	2005	92	33	35.9	19	57.6
Taylor et al <sup>17</sup>	2007	132	83	62.9	14	16.9
Koivusalo et al <sup>14</sup>	2013	130	62	47.7	33	53.2
Combined	2013	1645	703	42.7	325	46.2

Abbreviations: EA, esophageal atresia; GER, gastroesophageal reflux.

upward through the hiatus,<sup>38</sup> weakening the antireflux barrier. Abnormal sphincteric pressures were demonstrated in EA/TEF survivors by stationary and pull-through manometry.<sup>39-43</sup> The fact that most children with long-gap and pure EA suffer from GER after lengthening procedures and repair<sup>44</sup> indicates that anastomotic tension plays a key role in this phenomenon. This concept is further reinforced by the evidence of inactivation of the lower esophageal sphincter after surgical shortening of the esophagus by partial resection and anastomosis under tension in rats.<sup>45</sup>

In addition the esophageal peristaltic pump, that acts as a second antireflux barrier by clearing the refluxate from the lumen, is also damaged in EA/TEF survivors as shown by barium meal,<sup>46</sup> stationary manometry,<sup>1,3,5,20,39,47</sup> ambulatory manometry,<sup>48</sup> and combined pH-metering and impedance studies.<sup>49,50</sup> Motor dysfunction consisted mainly of distal aperistalsis with poorly progressive, weak waves throughout the entire esophagus. Motor activity of the upper pouch and relaxation of the sphincter were present in unoperated atretic esophagi,<sup>51</sup> but still they were not fully normal.<sup>52</sup>

There are several anatomical reasons for such dysmotility: First, the marked disproportion between the upper pouch and the fistula and the deficient arrangement of the muscle layers are unlike to generate normal propulsion even after careful repair. Furthermore, damage to esophageal innervation during dissection of both ends before repair<sup>53</sup> may further aggravate this dysfunction. Second, the atretic esophagus bears anomalies of the extrinsic innervation that certainly may influence motor function. In contrast with the normal esophagus, in which the laryngeal nerves that supply the upper third and the vagi that innervate the distal two-thirds are largely interconnected, in EA/TEF, the upper pouch and the fistula are separately and deficiently innervated by both afferent pathways.<sup>54</sup> Furthermore, the intrinsic innervation of unoperated human specimens showed either sparser<sup>55,56</sup> or denser neural network on both upper and distal segments<sup>57</sup> with ganglion cells larger than normal. These anomalies can be accurately reproduced in the Adriamycin rat model of EA/TEF in which the laryngeal nerves had less branches than controls and the vagi had abnormal trajectories,<sup>58</sup> whereas the intrinsic innervation was definitely sparser and with abnormal neural mediators.<sup>59</sup> Distribution of the neural structures was also abnormal in rats with EA/TEF as shown by protein gene product 9.5,<sup>60</sup> S100, and galanin immunostainings.<sup>61</sup>

There are several other extra-esophageal reasons that contribute to the occurrence of GER in EA/TEF. Gastrostomy, occasionally used in the management of EA-TEF, is supposed to facilitate it,<sup>62,63</sup> although there are conflicting reports.<sup>6</sup> Upper airway obstruction that is relatively frequent in EA/TEF due to tracheomalacia and/or tracheal stenosis also facilitates GER. This was demonstrated in the rat in which increasing narrowing of the trachea induced progressively stronger negative inspiratory pressures within the thorax capable of generating a powerful gastroesophageal gradient that overcomes the antireflux pressure barrier.<sup>64</sup> Finally, another additional cause for GER in EA/TEF is abnormal gastric motility that delays gastric emptying as shown by manometry and scintigraphy.<sup>65,66</sup> In fact, myoelectric gastric activity

is slower than normal in EA/TEF patients as shown by electrogastrography.<sup>67-69</sup>

## Indications for Antireflux Operations in EA/TEF

The main indication for antireflux surgery in these patients is persistence of symptoms after failure of a well-conducted medical treatment based on posture, diet, and appropriate antacid and prokinetic medication. These should be implemented bearing in mind that failure is predictable in many cases for the above-mentioned reasons. Persistent vomiting with failure to thrive, life-threatening respiratory disease, ALTE, repeated aspiration, recurrent pneumonia, or severe esophagitis may require antireflux surgery in a high proportion of these patients.

There are some groups of patients that require primarily surgery because no expectation of improvement is reasonable:

1. *Refractory anastomotic stenosis.* A sizeable proportion of EA/TEF survivors have anastomotic stenoses that respond favorably to dilatation. However, some of these stenoses are refractory and can only be cured after antireflux surgery. Many years ago, Pieretti et al showed in a series of 77 anastomotic stenoses from 217 survivors to EA/TEF repair that the 15 ones with refractory strictures requiring an average of 11 dilatations could only be cured after fundoplication.<sup>70</sup> In another series of 51 cases of EA/TEF, 37 (72%) had GER and 50% of them required repeated dilatations in contrast with the 28% in those without GER.<sup>33</sup> Seventy-four out of the 177 children operated upon for EA/TEF at the Great Ormond Street Hospital, London, between 1980 and 1987 had stenoses. In those requiring more than five dilatations, GER was demonstrated in 78% and half of them required fundoplication. In contrast, only 45% of children requiring less than five dilatations had reflux and only 21% required antireflux surgery.<sup>71</sup> The direct relationship between GER and refractory stenoses is well established and surgical indications are clear in these cases.
2. *Pure and long-gap EA.* Anastomoses achieved under considerable tension lead understandably to GER. In a study on 21 patients with pure EA treated by delayed primary anastomosis in Dublin between 1977 and 2004, 4 died and 14 developed symptomatic GER requiring fundoplication in 9.<sup>72</sup> In a meta-analysis of 451 cases of pure and long-gap EA, close to 50% had symptomatic GER, the same proportion had strictures and 13% had Barrett metaplasia.<sup>44</sup> The lengthening procedure recently popularized by Foker et al is followed by 100% of GER requiring 100% of fundoplications.<sup>73</sup> The need for antireflux surgery should therefore be anticipated in all these cases.
3. Survivors to EA with associated duodenal atresia suffer an extremely threatening condition in which bad sphincter and poor esophageal peristalsis are accompanied by poor emptying, pyloric insufficiency, and biliary reflux. It has been our experience that most require antireflux surgery and that they fare poorly after it.

**Table 2** Need for redo fundoplication in regular GER and in patients with EA/TEF

Study	Year	Fundoplication total	Redo total	%	Fundoplication in EA	Redo EA	%
Caniano et al <sup>84</sup>	1990	364	21	5.8	18	5	27.8
Kazerooni et al <sup>77</sup>	1994	96	11	11.5	12	3	25.0
Snyder et al <sup>78</sup>	1997	1467	70	4.8	59	9	15.3
Kimber et al <sup>86</sup>	1998	676	60	8.9	84	14	16.7
Kubiak et al <sup>87</sup>	1999	66	16	24.2	19	9	47.4
Holschneider et al <sup>85</sup>	2007	148	10	6.8	87	8	9.2
Tovar et al (unpublished data)	2013	373	35	9.4	53	12	22.6
Combined	2013	3190	223	7	332	60	18.1

Abbreviations: EA, esophageal atresia; GER, gastroesophageal reflux; TEF, tracheoesophageal fistula.

## Surgical Treatment

Antireflux surgery is often necessary in EA + TEF and this was recognized years ago.<sup>2,7,74</sup> The proportion of patients requiring fundoplication ranges from approximately 15 to 70%. **Table 1** shows that an average of 46% of 703 EA/TEF survivors with documented GER from several series required antireflux surgery. Loose Nissen fundoplication remains the preferred method for these cases,<sup>75,76</sup> although defective peristalsis in this condition might temperate this choice. The alternatives are partial anterior (Thal, Ashcraft, Boix-Ochoa)<sup>75,77,78</sup> or posterior (Toupet)<sup>75,79</sup> hemifundoplications. Laparoscopic approach is increasingly used for this purpose.<sup>75,80</sup> In any case, fashioning an adequate valve may be difficult in these patients in whom the stomach is small, the fundus even smaller, the angle of His obtuse, the esophagus short, and the GE junction displaced upward into the mediastinum through an abnormally wide hiatus. Recovering enough length of intra-abdominal esophagus may be difficult and the confection of the wrap itself is problematic. This explains why partial wraps have been elected sometimes in these patients in spite of the evidence of worse long-term results with them.<sup>81</sup> Some authors found useful to achieve lengthening of the intra-abdominal esophagus by Collis plasty before fundoplication.<sup>82,83</sup>

## Results of Antireflux Operations in EA/TEF

In most cases, a competent antireflux valve achieves alleviation of symptoms and helps the patient to outgrow the problems present during infancy. However, these effects are not permanent and the wrap fails in proportions ranging approximately from 10 to 50% with an average of 18.1% as shown in **Table 2**. This figure contrasts with the average wrap failure of 7% in regular refluxers.<sup>77,78,84–87</sup> Wrap failures in EA/TEF patients are due to the more difficult anatomic features met during surgery and also to the persistence of the anatomic and physiologic anomalies that facilitate GER.

Redo fundoplication should be contemplated when the wrap fails and the symptoms persist or recur. Generous use of long-term proton pump inhibitors (omeprazole) are indicated in these cases<sup>88,89</sup> and, only in some selected instances,

drastic operations such as esophagogastric dissociation with Roux-en-Y esophagojejunal anastomosis can be offered.<sup>90,91</sup>

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## Conflict of Interest

None

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