Richard P. Cambria, MD, Section Editor

Thoracic endovascular aortic repair in management of aortoesophageal fistulas

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Objective: **To provide a systematic review of the outcomes of thoracic endovascular aortic repair (TEVAR) for aortoesophageal fistula (AEF) and to identify prognostic factors associated with poor outcomes.**
Methods: **Literature searches of the Embase, Medline, and Cochrane databases identified relevant articles reporting results of TEVAR for AEF. The main outcome measure was the composite of aortic mortality, recurrence of the AEF, and stent graft explantation. The secondary outcome measure was aortic-related mortality.**
Results: **Fifty-five articles were integrated after a literature search identified 72 patients treated by TEVAR for AEFs. The technical success rate of TEVAR was 87.3%. The overall 30-day mortality was 19.4%. Prolonged antibiotics (>4 weeks) were administered in 80% of patients. Concomitant or staged resection or repair of the esophagus was performed in 44.4% of patients. Stent graft explantation was performed within the first month after TEVAR as a planned treatment in 11.1%. After a mean follow-up of 7.4 months (range, 1-33 months), the all-cause mortality was 40.2%, and the aortic-related mortality was 33.3. Prolonged antibiotic treatment ($P = .001$) and repair of AEFs due to a foreign body ($P = .038$) were associated with a significant lower aortic mortality. On univariate analysis, TEVAR and concomitant or staged adjunctive procedures (resection, repair of the esophagus, or a planned stent graft explantation) were associated with a significantly lower incidence of aortic-related mortality ($P = .0121$). When entered into a binary logistic regression analysis, prolonged antibiotic treatment was the only factor associated with a significant lower incidence of the endpoint ($P = .003$).**
Conclusions: **Late infection or recurrence of the AEF and associated mortality rates are high when TEVAR is used as a sole therapeutic strategy. Prolonged antibiotic treatment has a strong negative association with mortality. A strategy of a temporizing endovascular procedure to stabilize the patient in extremis, and upon recovery, an open surgical esophageal repair with or without stent graft explantation is advocated. (J Vasc Surg 2014;59:248-54.)**

Primary and secondary aortoesophageal fistulas (AEFs) are uniformly fatal if untreated and remain a formidable surgical problem in older, high-risk patients with hemorrhagic shock or sepsis. Despite advances in surgical technique, open repair still has a high operative mortality, which may reach 55.5% even in centers of excellence.[1] The mortality and morbidity of open repair is multifactorial:

- Emergent nature of repair;
- Difficult access to the aorta, high risk of visceral injury, and significant blood loss because of dense adhesions and mediastinitis; and
- Thoracic aortic cross-clamping.

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Moreover, redo operations, which are required in secondary fistulas, can lead to bleeding and prolonged operative time and, consequently, increased surgical mortality and morbidity.

Thoracic endovascular aortic repair (TEVAR) has recently gained popularity as an emergent treatment for AEFs, despite the high risk of infection. Reports often feature favorable short-term outcomes. Although endovascular stent grafting is faster and safer than surgery in unstable patients, the major concern is the durability of this approach. TEVAR does nothing to address the issue of the defect in the digestive tract, leaving the patients at risk of AEF recurrence and/or stent graft infection.

The aim of this article is to define the outcomes of TEVAR for AEFs with a particular focus on midterm results and to determine the prognostic factors associated with poor outcomes.

METHODS

Search strategy. A systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[2] A literature search was undertaken to identify all published studies in the past 10 years reporting TEVAR for AEFs. Candidate

Table I. Case selection, clinical presentation, and causes of aortobronchial fistulas

		Alive	*Dead*	P *value*
No.		48	24	
Mean age, years		58	62	.516
Male gender, %		68.8	61.1	.686
Initial presentation	Hematemesis	91.6% (44/48)	75% (18/24)	.267
	Hypovolemic shock	56.5% (26/46)	72.2% (13/18)	.446
	Systemic infection	22.9% (11/48)	23.8% (5/21)	.321
Cause of aortobronchial fistula	Previous thoracic aortic surgery	16.6% (8/48)	16.6% (4/24)	.487
	Previous TEVAR	2 % (1/48)	8.3 % (2/24)	.108
	Benign esophageal disease	12.5% (6/48)	12.5% (3/24)	.761
	Malignant esophageal disease	12.5% (6/48)	8.3 % (2/24)	.784
	Thoracic aortic aneurysm	25% (12/48)	12.5% (3/24)	.574
	Aortic dissection	4.1% (2/48)	4.1 % (1/24)	.792
	Penetrating ulcer	8.2% (4/48)	4.1 % (1/24)	.732
	Mycotic aneurysm	4.1% (2/48)	12.5% (3/24)	.222
	False aneurysm	22.9% (11/48)	8.3 % (2/24)	.411
	Foreign body	18.7% (9/48)	0% (0/24)	.038
TEVAR within 24 hours of diagnosis		83.3% (40/48)	83.3% (20/24)	.684
Antibiotic therapy >4 weeks		94.4% (34/36)	42.8% (6/14)	.001

TEVAR, Thoracic endovascular aortic repair.

studies were sought through a computerized search of Embase, Medline, and Cochrane databases for the period of 1990 to January 2013. Key words entered in this search were "thoracic aorta," "aortoesophageal," "aorto-esophageal," or "esophagus." Articles were limited to those published in the English language. Additionally, manual evaluation of the reference lists of the retrieved articles, and reviews on this field were undertaken.

Study selection. Studies were considered for inclusion on the basis of the following criteria:

- Reporting on TEVAR for management of AEF; and
- Reporting on clinical outcome.

Studies containing duplicate data were excluded, and the manuscripts with the most recent or the best-documented material from the same authors were used for analysis. Articles were selected for further review and inclusion in the final analysis if they described individual outcomes for patients treated for AEFs.

Data extraction. Data were extracted regarding age and gender; cause of fistula; presence and/or history of thoracic aortic surgery; time interval between previous aortic intervention and presentation of fistula; comorbidity; symptoms of the fistula; time interval between diagnosis and TEVAR; proximal landing zone; technical success of TEVAR defined by successful exclusion of the fistula during the initial endovascular procedure; concomitant or staged resection or repair or exclusion or stenting of the esophagus; stent graft explantation and resection or repair of the esophagus within the first month after TEVAR as a planned treatment; antibiotic usage and duration; in-hospital and long-term follow-up outcomes, including graft-related complications (endoleak, stent graft migration); nongraft-related complications (sepsis, pneumonia, spinal cord ischemia, renal failure), early and late open and endovascular reinterventions; fistula recurrence; fistula-related mortality; and length of follow-up.

Statistical analysis. The primary outcome of interest was the composite of aortic mortality, recurrence of the AEF, and stent graft explantation. The secondary outcome measure was aortic-related mortality.

Patients included were classified according to the surgical strategy to assess whether TEVAR and resection or repair of the esophagus or planned stent graft explantation and resection or repair of the esophagus was associated with a lower mortality rather than TEVAR alone. If the initial strategy was not clearly mentioned, patients were included in the single-stage group.

Statistical analysis was performed using SPSS (SPSS Inc, Chicago, Ill). χ^2, Fisher exact, and independent samples *t*-tests were performed for the univariate analysis. Binary logistic regression was utilized to identify factors that were independently associated with each of the outcomes of interest. All results with $P < .05$ were considered statistically significant.

RESULTS

Search results. Fifty-five articles were integrated after a literature search identified 72 patients treated by TEVAR for AEFs.[2-56]

Case selection. Patient demographics, presenting features, and comorbidities are shown in Tables I and II. The mean age was 59.2 years, and 67.7% were male. Most patients presented with hematemesis (86.1%). Hypovolemic shock and systemic infection were present in 60.9% and 21.7%, respectively. With regard to etiology, 23.6% of the patients had primary disease of the esophagus (malignant or benign), 20.8% of the patients had previously undergone thoracic aortic surgery (open or endovascular repair), 20.8% of the patients had aneurysm of the descending aorta, and 12.5% of the patients had fistula

Table II. Case selection, clinical presentation, and causes of aortoesophageal fistulas (*AEFs*)

		TEVAR alone	*Combined: TEVAR and surgery*	P *value*
No.		40	32	
Mean age, years		64	55	.001
Male gender, %		53.3	81.2	.051
Initial presentation	Hematemesis	87.5% (35/40)	84.3% (27/32)	.53
	Hypovolemic shock	67.6% (23/34)	53.3% (16/30)	.251
	Systemic infection	35.1% (13/37)	9.3% (3/32)	.011
Cause of AEF	Previous thoracic aortic surgery	22.5% (9/40)	9.3% (3/32)	.121
	Previous TEVAR	2.5% (1/40)	6.2% (2/32)	.22
	Benign esophageal disease	12.5% (5/40)	12.5% (4/32)	.438
	Malignant esophageal disease	12.5% (5/40)	9.3% (3/32)	.388
	Thoracic aortic aneurysm	12.5% (5/40)	31.2% (10/32)	.08
	Aortic dissection	2.5% (1/40)	6.2% (2/32)	.332
	Penetrating ulcer	7.5% (3/40)	6.2% (2/32)	.424
	Mycotic aneurysm	10% (4/40)	3.1% (1/32)	.214
	False aneurysm	22.5% (9/40)	12.5% (4/32)	.213
	Foreign body	7.5% (3/40)	18.7% (6/32)	.134
TEVAR within 24 hours of diagnosis		82.5% (33/40)	84.3% (27/32)	.372
Antibiotic therapy >4 weeks		72.4% (21/29)	90.4% (19/21)	.357

TEVAR, Thoracic endovascular aortic repair.
Combined TEVAR and surgery includes: patients treated by TEVAR with concomitant or staged resection or repair or exclusion or stenting of the esophagus; patients treated by TEVAR with stent graft explantation and resection or repair of the esophagus, which was performed within the first month after TEVAR as a planned treatment.

secondary to a foreign body. Microorganisms were reported in 43.2% of the cases (32/74) and isolated in 31.2% (10/32), and included enterococcus species, mycobacterium tuberculosis, streptococcus spp, or gram-negative species.

Endovascular repair. TEVAR was performed within 24 hours following diagnosis in 83.3% of the patients.

The technical success rate was 87.3%. The proximal landing zone was zone 2 in 21.1% of the patients, zone 3 in 46.4% of the patients, and zone 4 in 32.5% of the patients. A total of 44.4% (32/72) of patients had concomitant or staged adjunctive procedures, which included resection, repair, exclusion, or stenting of the esophagus. Stent graft explantation and resection or repair of the esophagus was performed within the first month after TEVAR as a planned treatment in 11.1% of the patients. Prolonged postoperative antibiotics (greater than 4 weeks) were administered to 80% of patients.

Perioperative outcomes. As shown in Table III, perioperative outcomes were defined as those occurring within the first 30 postoperative days. The overall 30-day mortality was 19.4% (14/72). The early morbidity rate was 40.2% (29/72). Persistent postoperative sepsis was the most common early complication (23.6%). The incidence of aortic rupture, pulmonary complication, multiorgan failure, endoleak, and recurrent hematemesis was 5.5% (4/72), 6.9% (5/72), 6.9% (5/72), 9.7% (7/72), and 5.5% (4/72), respectively. Only one case of paraplegia was observed (Table III).

Midterm outcomes. Midterm outcomes were defined as those occurring after 30 days. After a mean follow-up of 7.4 months (range, 1-33 months), the all-cause mortality rate was 40.2% (29/72) and the aortic-related mortality was 33.3% (24/72). The death was due to stent graft infection in 11 patients and to the recurrence of the AEF in 10 patients. Surgical conversion during the postoperative course with thoracic stent graft explantation was required in four patients.

Statistical analysis. Univariate analysis demonstrated that prolonged antibiotic treatment (>4 weeks; $P = .001$) and repair of an AEF due to a foreign body ($P = .038$) were associated with a significantly lower incidence of the composite end point (Table I). When entered into a binary logistic regression analysis, prolonged antibiotic treatment was the only factor associated with a significant lower incidence of the end point (odds ratio, 0.3; 95% confidence interval, 0.001-0.21; $P = .003$; Table IV).

Patients in the two groups, TEVAR alone and TEVAR combined open repair, were statistically comparable, except for the mean age of the patients. Patients were younger in the combined group (55 vs 64 years old; $P = .001$; Table II). Univariate analysis demonstrated that a combined procedure (TEVAR with concomitant adjunctive procedures) was associated with significant lower aortic-related mortality (40% vs 15.6%; $P = .036$), but this failed to reach statistical significance when entered into a binary logistic regression ($P = .62$).

The type of device was available in 83.3% of the cases (60/72). A Dacron graft was used in 66.6% of the cases (40/60), and a PTFE graft was used in 33.4% of the cases (20/60). Rate of infection was not statistically different in the two groups (7 vs 4; $P = .456$).

DISCUSSION

AEF is a rare complication, and is generally fatal without surgical intervention. Causes for AEF formation

Table III. Case selection, surgical management, and outcomes of the patients

		TEVAR alone	*Combined: TEVAR and surgery*	P *value*
No.		40	32	
Additional procedure	Intercostal muscle flap	0	9.3% (3/32)	
	Esophagus resection or repair	0	68.7% (22/32)	
	Esophagus stenting	0	18.7% (6/32)	
	Surgical conversion	0	25% (8/32)	
In-hospital complications	Sepsis	20% (8/40)	28.1% (9/32)	.504
	Hematemesis	7.5% (3/40)	3.1% (1/32)	.624
	Multiorgan failure	12.5% (5/40)	0% (0/32)	.061
	Pulmonary complications	2.5% (1/40)	12.5% (4/32)	.164
	Renal failure	0% (0/40)	6.2% (2/32)	.194
	Spinal cord ischemia	0% (0/40)	3.1% (1/32)	.444
	Myocardial infraction	7.5% (3/40)	3.1% (1/32)	1
	Endoleak	7.5% (3/40)	12.5% (4/32)	.082
	Aortic rupture	7.5% (3/40)	3.1% (1/32)	.373
Morbidity <30 days		37.5% (15/40)	43.7% (14/32)	.429
Mortality <30 days		27.5% (11/40)	9.4% (3/32)	.074
Mean follow-up, months		6.9	8.1	
Overall mortality		52.5% (21/40)	25% (8/32)	.029
Aortic-related mortality		40% (16/40)	15.6% (8/32)	.036
Cause of death	Stent graft infection	20% (8/40)	9.4% (3/32)	.495
	Recurrence of fistula	20% (8/40)	6.2% (2/32)	.282
Recurrence of fistula		20% (8/40)	6.2% (2/32)	.529
Additional procedure	Esophagus resection	2.5 % (1/40)	21.8% (7/32)	.019
	TEVAR	0% (0/40)	3.1% (1/32)	.194
Surgical conversion >30 days		2.5 % (1/40)	9.3% (3/32)	.228

TEVAR, Thoracic endovascular aortic repair.
Combined TEVAR and surgery includes: patients treated by TEVAR with concomitant or staged resection or repair or exclusion or stenting of the esophagus; patients treated by TEVAR with stent graft explantation and resection or repair of the esophagus, which was performed within the first month after TEVAR as a planned treatment.

Table IV. Logistic regression model

Variable	*OR*	*95% CI*	P *value*
Outcome composite end point			
Combined procedure: TEVAR and surgery	1.03	0.19-5.40	.96784
Antibiotic therapy >4 weeks	0.03	0.001-0.21	.00389
Foreign body	0.22	0.005-2.57	.31503
Outcome aortic-related mortality			
Combined procedure: TEVAR and surgery	0.63	0.077-3.79	.62
Antibiotic therapy >4 weeks	<0.001	<0.001->100	.994
Foreign body	<0.001	<0.001->100	.993

CI, Confidence interval; *OR,* odds ratio; *TEVAR,* thoracic endovascular aortic repair.

include thoracic aortic aneurysms, foreign body ingestion, advanced esophageal cancer, and surgical procedures involving the aorta and esophagus.

Open repair involves combined replacement or bypass of the thoracic aorta with concomitant resection or repair of the involved esophagus. Despite significant refinement in surgical techniques, the operative mortality of open AEF repair ranges from 45.4% to 55%.[1,57] The mortality and morbidity of open repair is related to the emergent nature of repair, the access to the aorta in an infected field with a high risk of visceral injury, and significant blood loss, as well as the need for thoracic aortic cross-clamping.

The less invasive endovascular strategies enable rapid control of bleeding and increase the likelihood of postoperative survival. Indeed, the literature shows that endovascular repair of primary AEF is successful at controlling bleeding. The perioperative outcomes of the endovascular approach are associated with a high technical success rate (87.3%) and more favorable 30-day mortality rate (19.7%). TEVAR facilitates hemodynamic stabilization by hemorrhage control in the acute setting, and therefore reduces the morbidity and mortality associated with an open repair under these circumstances.

Even if associated with favorable perioperative outcomes, concerns regarding the durability of TEVAR even in the short-term are broadly realistic. TEVAR alone leaves the esophageal defect untreated. The stent graft is directly exposed to a contaminated environment and ongoing infection. Therefore, this minimally invasive approach incurs a risk of stent graft infection and/or fistula recurrence and persistent mediastinitis and sepsis. In this review, the recurrence of the AEF and stent graft infection occurred in 13.8% and 15.2% of the patients, respectively.

Antibiotic treatment was the only strongly significant factor associated with a lower aortic mortality rate in the multivariate analysis. Therefore antibiotic treatment should be applied after endovascular stent placement to correct and potentially prevent thoracic stent graft infection. Postoperative antibiotic strategies differed widely among the various authors, both with regard to the choice of

antibiotic and the duration of therapy. Empirical broad-spectrum antibiotics, including antifungal coverage, are appropriate initially. Similar to the treatment of abdominal aortic graft infection, one could argue for a 6- to 8-week course of broad-spectrum intravenous antibiotics followed by life-long oral antibiotic suppression for those treated by TEVAR alone. Some physicians insist that life-long treatment with oral suppressive antibiotics is required, while others claim that such treatment can be discontinued provided there is no clinical, bacteriological, or radiological evidence of ongoing sepsis.[58,59] A conservative policy for antibiotic treatment might involve at least 4 weeks of peri-procedural intravenous antibiotics followed by case-specific administration of oral suppressive antibiotics according to clinical and laboratory parameters of infection.

In the univariate analysis, combined immediate or staged procedures were also significantly associated with a decrease in the aortic-related mortality rate. Several surgical options have been proposed to decrease the rate of aortoesophageal recurrence. Topel et al[31] suggest that TEVAR should be considered as a bridge therapy followed by a delayed durable open repair when the patient has been stabilized. The advantage of this combined approach is to address the two essential aims of the surgical procedure. First, TEVAR allows minimally invasive and rapid control of the bleeding. Second, the open surgical procedure allows surgical debridement of the infected mediastinum with reconstruction of the aortic wall and repair of the esophageal defect. Staging the repair to allow adequate nutritional replenishment is likely to improve the outcome of the definitive repair. Primary repair with direct suture or patch of the esophageal erosion is possible only in selected cases of small esophageal defects without gross contamination of the mediastinum. Otherwise, esophageal resection should be considered the treatment of choice in the management of an esophageal defect in most patients with AEFs. However, this ideal approach is associated with a high mortality rate (25%) and a high morbidity rate (25% of spinal cord ischemia and of persistent renal failure).

An alternative staged strategy, as reported by Marone et al,[4] is to address the esophageal defect after a planned interval to prevent secondary stent graft infection, recurrence of the fistula, mediastinitis, and death. The aim of this approach is to treat the esophageal lesions when the patient is in a more stable condition. The adjunctive procedure may entail primary repair or resection of the esophagus with coverage of the stent graft using muscle or pleural flaps. Pleural or pericardial flaps, intercostal or serratus muscle, or omentum can be used to cover the graft. In their experience, the mortality rate was lower in cases that involved a combined approach, as compared with those that involved TEVAR alone. Therefore, a planned second-stage open operation leaving the stent graft in place and treating the esophageal condition along with wide mediastinal drainage, is another therapeutic strategy for the treatment of patients with AEFs. A multicenter survey conducted in Italy yielded information on 14 AEFs that were treated with TEVAR. The study showed that patients who undergo combined treatment (TEVAR and esophageal repair) may have lower graft infection rates and better survival rates than patients who undergo TEVAR alone. However, the difference in early and late outcome did not reach statistical significance, possibly due to the small sample size.

The extent of inflammation/injury at presentation was also an important factor affecting outcomes. Patients treated for AEFs due to a foreign body, who have less extensive esophageal injury, had statistically better outcomes ($P = .038$).

Clearly, any strategy in this patient population needs to be highly individualized, given the risks of major thoracic aortic surgery often in a hostile operative field. After controlling the bleeding by TEVAR, the patient should receive intensive medical support to correct anemia, broad-spectrum antibiotics, including antifungal coverage, and adequate nutritional replenishment. There is clearly no ideal amount of staging time to improve nutrition. Time between the two stages has to be determined according to markers of malnutrition such as weight loss history, subjective global assessment, and transport protein (album, alpha-fetoprotein, vitamin D-binding protein). There is, obviously, risk that the patient never returns for stage 2. Once the patient has clinically improved, the patient should be referred to undergo open surgery as soon as possible. In moribund patients, TEVAR alone can be proposed, as the risk of recurrence of the fistula or of stent graft infection is not consistent. In the case of gross infection (eg, sepsis) and critical physical condition, endovascular treatment can be performed as bridging therapy until the patient is sufficiently hemodynamically stable to undergo open surgery: drainage and primary repair or resection of the esophagus alone or combined removal of the stent graft and aortic reconstruction. The choice of conduit and route for aortic reconstruction, and the specific treatment of the fistula are dependent on patient age and comorbid conditions and the size of esophageal defect.

Although the present study reported perioperative and short-term outcomes of TEVAR for AEFs, it has several limitations. Acknowledged limitations of this systematic review included the lack of uniformity reporting isolated microorganism, antibiotic protocol used, devices used and proximal landing zone, the initial strategy (planned vs unplanned two-stage approach), and the extent of inflammation/injury at presentation. Furthermore, data were obtained from case reports and case series with likely publication bias. Due to the small incidence of this disease, it is unlikely there will be a planned prospective randomized study. However, a large prospective registry could help to establish the precise benefits of TEVAR and the eventual need for a staged approach.

CONCLUSIONS

TEVAR for AEFs achieves the primary goal of therapy (ie, control of bleeding, preventing fatal exsanguination). The high rate of secondary stent graft infection or

recurrence of the AEF clearly prove that even combined with broad-spectrum antibiotics, TEVAR cannot replace surgical debridement and/or drainage of the infected mediastinum. Whether this is best achieved by drainage and primary repair/resection of the esophagus alone with or without removal of the stent graft remains to be proven. However, prolonged antibiotic treatment has a strong negative association with mortality.

AUTHOR CONTRIBUTIONS

Conception and design: LC, BO, WB, SB, PH, MT
Analysis and interpretation: LC, BO
Data collection: LC, BO, WB, SB
Writing the article: LC, BO
Critical revision of the article: LC, BO, WB, SB, PH, MT
Final approval of the article: LC, BO, WB, SB, PH, MT
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Overall responsibility: LC
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