Comparison of Detection Methods for Tracheoesophageal Fistulae With a Novel Method: Capnography With CO₂ Insufflation

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ABSTRACT

Background: Tracheoesophageal fistulae (TEF) are difficult to detect and require a high index of suspicion. We hypothesized that capnography to identify a spike in end-tidal carbon dioxide ($etCO_2$) during esophagoscopy with carbon dioxide (CO_2) insufflation would facilitate TEF diagnosis because of gas passage from the esophagus to the trachea.

Methods: Medical records of 42 consecutive cases of recurrent, acquired, or missed congenital TEF diagnosed between January 2015 and November 2019 that underwent esophagoscopy with CO_2 insufflation were reviewed. A control cohort of 97 similarly endoscopically evaluated patients with surgical confirmation of absence of recurrent TEF (eg, patients undergoing posterior tracheopexy) was also collected. All patients underwent pre-operative esophagoscopy, bronchoscopy, and capnography; diagnostic abilities of various combinations of modalities for TEF identification were calculated.

Results: Statistical analysis identified a maximum intra-esophagoscopy endtidal CO₂ level of 68 mmHg as the optimal discriminator between cases and controls, though in practice, we anecdotally find that recurrent TEFs typically permit rapid rise \geq 90 mmHg. Increasing numbers of diagnostic modalities increased diagnostic sensitivity to detect recurrent TEF; the highest diagnostic sensitivity for TEF identification was achieved by the combination of intra-esophagoscopy fluoroscopy with bronchoscopy and capnography \geq 68 mmHg (sensitivity = 88.1%). There were multiple cases of TEF (N=7 for etCO₂ \geq 68 mmHg, N=3 for etCO₂ \geq 90 mmHg) identified by capnography that were missed by esophagoscopy. There were 5 (for etCO₂ \geq 68 mmHg) or 6 (for etCO₂ \geq 90 mmHg) cases of recurrent TEF that were missed by all nonsurgical methods.

Conclusion: Attention to $etCO_2$ during esophagoscopy with CO_2 insufflation represents a simple, novel way to detect TEF. Identification of TEF remains challenging, though combinations of diagnostic modalities improve diagnostic sensitivity.

Key Words: bronchoscopy, capnography, end-tidal carbon dioxide, esophageal atresia, tracheoesophageal fistula

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What Is Known

- Tracheoesophageal fistulae can be very difficult to detect.
- Traditional diagnostic modalities for tracheoesophageal fistulae identification are bronchoscopy, esophagoscopy, and contrast-enhanced radiography though sensitivities of these methodologies are not well described.

What Is New

- Capnography combined with carbon dioxide insufflation during esophagoscopy is a simple, rapid, novel method of tracheoesophageal fistulae detection.
- Bronchoscopy, which is often touted as the diagnostic gold standard for tracheoesophageal fistulae, was observed to have only moderate diagnostic sensitivity.
- Combinations of diagnostic modalities enhance changes of tracheoesophageal fistulae diagnostic success.

Tracheoesophageal fistulae (TEF) carry significant morbidity related to recurrent pulmonary exposure to esophageal contents. In pediatric patients, TEF may be primary, as in congenital fistulae with or without associated esophageal atresia; recurrent after TEF repair in up to 10% of otherwise uncomplicated repaired cases (1); or acquired after surgical or endoscopic interventions, especially those that result in esophageal leaks. Diagnosis of TEF can be difficult, and is usually made with contrast-enhanced radiography, rigid bronchoscopy, or esophgagoscopy. Esophagoscopy may miss small or subtle fistulae even when aided by intraoperative fluoroscopy.

Endoscopic insufflation with carbon dioxide (CO₂) is increasingly commonplace, and is used primarily to enhance patient comfort by use of a gas that is readily resorbed (2). In this retrospective review of 42 consecutive cases of TEF treated at a tertiary care referral center, we evaluated our diagnostic sensitivity in detecting TEF with a novel method of capnography, and compared it with our experience using fluoroscopy-assisted esophagoscopy and rigid bronchoscopy. We hypothesized that endoscopic insufflation with CO₂ in the esophagus combined with monitoring of end-tidal carbon dioxide (etCO₂) would aid in diagnosis of TEF because of passage of the gas from the

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FIGURE 1. The patient is intubated with a cuffed endotracheal tube to create a closed pathway from the esophagus through the tracheoesophageal fistula into the trachea and up to the end-tidal CO_2 detector. By using a cuffed endotracheal tube, the endoscopist is able to eliminate retrograde bleeding of CO_2 from the esophagus into the oropharynx to the trachea, and therefore, avoid false-positive capnographic spikes in CO_2 .

esophagus to the trachea, where it may be detected by capnography (Fig. 1).

METHODS

This study was approved by an institutional review board. We retrospectively reviewed the intraoperative anesthesia records, radiography reports, rigid bronchoscopy reports, and esophagoscopy reports of 42 consecutive cases of recurrent, acquired, or missed congenital TEF in pediatric esophageal atresia (EA) patients diagnosed at our institution between January 2015 (when CO2 insufflation became standard for all of our upper endoscopies for EA patients) and November 2019. All patients with a primary diagnosis of EA with TEF whose esophagus was in continuity, who underwent a preoperative esophagoscopy with CO₂ insufflation and preoperative rigid bronchoscopy, and were found to have a surgically confirmed recurrent, acquired, or missed congenital TEF were included for analysis. Patients who did not undergo esophagoscopy and bronchoscopy at our institution before the day of surgical intervention were excluded. A control cohort of patients without TEF was collected, consisting of patients who had a history of repaired EA/TEF who underwent preoperative esophagoscopy with CO₂ insufflation and preoperative rigid bronchoscopy and who underwent posterior tracheopexy surgery for tracheomalacia. Patients with posterior tracheopexy were selected as the control group as this surgery involves careful surgical examination of the trachea as the trachea is mobilized and affixed posteriorly to the spinal column in order to correct the malacia, and also involves careful examination of the esophagus, which is rotated laterally to allow for fixation of the trachea; thus, these patients were surgically confirmed to have no recurrent, acquired, or missed congenital TEF. Patients who never had a TEF (eg, had pure EA) were excluded from both cohorts. Patients with primary unrepaired EA whose esophagi were not yet in continuity who still had their primary TEF do not typically undergo esophagoscopy at our institution before their surgical ligation of the TEF, as infants with primary EA/TEF are in esophageal discontinuity and most often do not have mature gastrostomy access to permit passage of an endoscope into the lower esophageal pouch to identify the most common type of primary TEF (eg, type C) by esophagoscopy; thus unrepaired primary EA/ TEF were also excluded.

Rigid bronchoscopy was first performed by 1 of 2 experienced surgeons with careful inspection of any visualized tracheal defects or diverticulae suggestive of possible TEF; contrast studies on bronchoscopy were performed only if an area suspicious for TEF was visually identified. Next, the patient was intubated by anesthesiology; because of our routine use of intraoperative contrastenhanced fluoroscopy, all patients were endotracheally intubated with cuffed endotracheal tubes while under anesthesia, and etCO₂ monitoring (Dräger, Telford, PA) was performed in all cases (Fig. 1). Flexible esophagoscopy using either the Olympus XP-190N or Olympus GIF-H190 (at the discretion of the endoscopist) was then performed by 1 of 2 experienced gastroenterologists with CO₂ insufflation under general anesthesia. During esophagoscopy, the esophagus was fully distended with CO₂ while the capnography readout was monitored for an abrupt spike in etCO₂. We noted that passage of CO₂ across a TEF required a fully insufflated esophagus and stomach to stent open any occluding mucosal folds in the fistula, and that this passage registered on capnography as an abrupt spike in etCO₂, which was only present while the esophagus was fully distended and abruptly returned to baseline with several ventilated breaths after ceasing high pressure insufflation. Therefore, for this study, an abrupt, dramatic, nonsustained spike in etCO₂ above the statistically identified optimal maximum CO₂ threshold was considered a positive capnographic study suggestive of presence of a TEF rather than hypercapnia because of ineffective ventilation (see supplemental video 1, [The endoscopic view of the esophagus is seen on the left side of the video, with the esophageal lumen in the lower center of the view and a suspicious area of mucosal disruption (possible TEF) at approximately 10 o'clock relative to the esophageal lumen. The esophagus is then fully insufflated and distended with CO₂. On the right side of the video, the patient monitor shows the cardiac rhythm waveform (top; white), oxygen saturation plethysmograph (middle; blue), and endtidal CO₂ capnograph (bottom; green). Once the TEF is fully opened by the insufflated CO2 gas, the end-tidal CO2 value abruptly spikes from 39 mmHg (normal) to 99 mmHg.] Supplemental Digital Content, http://links.lww.com/MPG/B775).

For intra-esophagoscopy fluoroscopy, Optiray 320 (ioversol injection 51%; Guerbet, Cincinnati, OH) mixed in a 50:50 ratio with normal saline was instilled into the esophagus via the working

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channel of the endoscope under high pressure and imaged with fluoroscopy. In cases, where the suspected TEF defect was grossly visible by esophagoscopy but not initially visible by intraluminal contrast injection, attempts to intubate the defect with a tapered tip Contour ERCP cannula (Boston Scientific Corporation, Natick, MA) were performed and contrast injected directly through this catheter into the defect. Up to 100 ml of contrast was injected into the esophagus, with total volume determined at the discretion of the endoscopist who continued high pressure injection until he was satisfied that the area was sufficiently filled and imaged by fluoroscopy. The contrast was then suctioned out of the stomach and esophagus after the fluoroscopic investigation was complete. If contrast was suspected or observed to have entered the trachea or lungs, the patient was typically admitted to the hospital for overnight observation with antibiotics initiated only in cases of clinical deterioration.

Baseline demographics are presented using medians and interquartile ranges for continuous data and using frequencies and percentages for categorical data. Cases with identified TEF were compared with patients without TEF using the Chi-square test or Fisher exact test for categorical data, and the Wilcoxon rank sum test for continuous variables. Receiver operating characteristic (ROC) curve analysis was implemented with Youden J index to determine the optimal cut-point to maximize the sensitivity and specificity for etCO₂ in distinguishing patients with versus without TEF. ROC analysis results are summarized using the area under the ROC curve (AUC) with 95% confidence interval. Analysis of dichotomous diagnosis methods for TEF, independently and in combination, was done by examining sensitivity, specificity, positive predictive value, and negative predictive value. A 2-tailed alpha level of 0.05 was implemented for determining statistical significance. Statistical analyses were performed using Stata (version 15.0, StataCorp LLC., College Station, TX).

RESULTS

Forty-two cases of TEF met inclusion criteria (Table 1). Forty-one patients had a history of EA; 37 were type C EA, 4

TABLE 1.	Comparison	of baseline	demographics	between	recurrent
tracheoes	ophageal fist	ulae cases a	nd controls		

Variable	rTEF (n=42)	No rTEF (n=97)	P value
Sex			0.001*
Female	26 (62%)	29 (30%)	
Male	16 (38%)	68 (70%)	
EA type		Ŷ,	0.067
В	2 (5%)	1 (1%)	
С	37 (88%)	93 (96%)	
D	2 (5%)	0 (0%)	
Н	1 (2%)	3 (3%)	
Gap length-long gap	9 (21%)	14 (14%)	0.327
Age at primary TEF ligation	2 (1, 3)	2(1, 3)	0.269
Age at current surgery	23 (7, 50)	22 (11, 50)	0.84
Median etCO ₂ levels during EGD	37 (34, 44)	40 (36, 45)	0.235

Demographic information of patient case cohort (surgically confirmed cases of recurrent, acquired, or missed congenital TEF) and control cohort (surgically confirmed cases of no TEF; all controls underwent posterior tracheopexy surgery with surgical examination of and mobilization of the trachea). Statistically significant values are noted in bold face type and by an asterisk (*). Current surgery refers to either recurrent TEF ligation (cases) or posterior tracheopexy (controls). EGD = esophagogastroduodenoscopy; EtCO₂ = end-tidal carbon dioxide; TEF = tracheoesophageal fistulae.

cases were initially misdiagnosed as type A (N=2) or type C (N=2) at birth but discovered to have a missed proximal fistula during the study period, and therefore, were actually types B and D, respectively. Four cases were thought to be acquired recurrent TEF related to esophageal leak. One case was an isolated type H fistula that recurred. Six patients had VACTERL anomalies; 1 patient had CHARGE syndrome; 3 patients had other genetic syndromes (N = 1 Trisomy 21, N = 1 central 22q deletion, N = 1 Feingold syndrome). Symptoms prompting workup for new TEF included chronic cough with recurrent respiratory infections (N = 35), blue spells (N = 5), or new requirement for respiratory support above baseline needs (N=2); the most commonly reported symptoms prompting workup before posterior tracheopexy surgery were similar, with chronic cough/recurrent respiratory infections reported in 73 patients and blue spells reported in 21 patients.

Cases with new TEF were significantly more likely to be girls than controls, but were otherwise not significantly different in terms of distribution of EA/TEF type, age at primary TEF ligation, age at current surgery (either new TEF ligation or posterior tracheopexy), or median etCO₂ levels during pre-operative esophagoscopy (Table 1). The median of the patient-level median baseline CO₂ levels during each esophagoscopy was 37 mmHg for cases and 40 mmHg for controls, which both fall within the expected normal range for etCO₂ values (35–45 mmHg). Most esophagoscopies (39/42) included intra-esophagoscopy fluoroscopic evaluation for TEF; 3 esophagoscopies noted fistulae that were large enough to be grossly confirmed by visual inspection alone.

An abrupt spike in $etCO_2$ that rapidly returned to baseline (eg, was not a result of a gradual rise because of alternative reason, such as ineffective ventilation) was considered to be suggestive of TEF as such an abrupt rise is highly unlikely to be the product of normal physiology (see Video 1, Supplemental Digital Content, http://links.lww.com/MPG/B775, and Fig. 2). To identify the intra-esophagocospy maximum etCO₂ value which best discriminated between cases of TEF and controls (AUC = 0.750; 95% confidence interval [CI] 0.646–0.855), Youden J index was identified by receiver-operating characteristic curve analysis and found that an etCO₂ cutoff of greater than or equal to 68 mmHg was the optimal diagnostic cutoff point that maximized sensitivity and specificity of capnography. Using $etCO_2 \ge 68 \text{ mmHg}$, the sensitivity, specificity, negative-predictive value, and positive-predictive value of various combinations of capnography, esophagoscopy, and bronchoscopy were calculated (Table 2). Capnography utilizing this cutoff had similar sensitivities as traditional single modality investigations of esophagoscopy (57.1% vs 54.8%) or bronchoscopy (57.1% vs 59.5%) but was less specific (94.9% vs 100%). Increasing numbers of diagnostic studies increased diagnostic ability, with the best sensitivity achieved by combining all 3 diagnostic modalities of capnography, esophagoscopy, and bronchoscopy together which identified 88.1% of cases.

Though statistical analysis identified 68 mmHg as the optimal discriminator, in practice, we have found that cases of recurrent TEF most commonly involve even more dramatic rises in etCO₂, typically \geq 90 mmHg. We, therefore, also calculated diagnostic ability parameters for the same combinations of modalities using this more stringent cutoff of etCO₂ \geq 90 mmHg (Table 3). Adjusting the cutoff led to perfect specificity with no control cases experiencing etCO₂ levels \geq 90 mmHg. Sixteen cases had etCO₂ values \geq 90 mmHg reflected in their anesthesia records. Using the more stringent cutoff of etCO₂ \geq 90 mmHg, concordance between the various diagnostic modalities are presented in Figure 3.



FIGURE 2. Illustrative example images of various modalities for detection of a tracheoesophageal fistula in a single patient (A). Visualization of suspected TEF site via flexible esophagoscopy. Area suspicious for TEF is denoted by a red arrow. Esophageal lumen is denoted by a yellow arrow (B). Capnography suggests the presence of TEF with full insufflation of the esophagus with carbon dioxide (CO_2) and detection of an abrupt end-tidal CO_2 rise to 99 mmHg (C). Contrast-assisted rigid bronchoscopy identifies the TEF with passage of contrast into the esophageal lumen (denoted by blue arrows) (D). Contrast-assisted flexible esophagoscopy fails to identify the TEF despite vigorous contrast injection at the suspected TEF site (denoted by green arrow). TEF = tracheoesophageal fistulae.

TABLE 2. Performance o	f tracheoesophageal	l fistulae diagnosis methods
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NDV
INI V
83.6%
83.6%
85.1%
88.5%
93.9%
94.2%
94.9%

Analyses were performed on N = 42 patients with tracheoesophageal fistulae (TEF) who had rigid bronchoscopy, esophagoscopy (EGD), and capnography using the cutoff maximum end-tidal carbon dioxide (etCO₂) \geq 68 mmHg as identified by Youden J index from receiver operating characteristic (ROC) analysis. NPV = negative-predictive value; PPV = positive predictive value.

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TABLE 3. Performance of tracheoesophageal fistulae diagnosis methods

Combination of positive test results	Sensitivity	Specificity	PPV	NPV
Max etCO ₂ \geq 90 only	36.6%	100.0%	100.0%	78.2%
EGD only	56.1%	100.0%	100.0%	83.6%
Bronchoscopy only	61.0%	100.0%	100.0%	85.1%
Max etCO ₂ \geq 90 or EGD	63.4%	100.0%	100.0%	85.8%
Max etCO ₂ \geq 90 or bronchoscopy	78.0%	100.0%	100.0%	90.7%
EGD or bronchoscopy	87.8%	100.0%	100.0%	94.2%
Any of the 3	87.8%	100.0%	100.0%	94.2%

Analyses were performed on N=42 patients with tracheoesophageal fistulae (TEF) who had rigid bronchoscopy, esophagoscopy, and capnography using the cutoff maximum etCO₂ \geq 90 mmHg as identified by real world experience with the capnographic method of TEF detection. EtCO₂ = end-tidal carbon dioxide; NPV = negative-predictive value; PPV = positive predictive value.

There were multiple cases (N = 7 for etCO₂ \geq 68 mmHg, N = 3 for etCO₂ \geq 90 mmHg) of TEF identified by capnography that were missed by intra-esophagoscopy fluoroscopy; there was 1 case missed by both esophagoscopy and bronchoscopy that was positively identified by the less stringent cutoff for capnography (maximum etCO₂ = 85 mmHg). Five (for etCO₂ \geq 68 mmHg) or 6 (for etCO₂ \geq 90 mmHg) cases of TEF were not identified by any of our nonsurgical modalities and instead were identified incidentally intraoperatively during posterior tracheopexy surgery.

There were no adverse events attributed to use of CO₂ insufflation during esophagoscopy.

DISCUSSION

Attention to $etCO_2$ during esophagoscopy with CO_2 insufflation represents a novel way to detect TEF. This methodology has previously only been described in a single case report of TEF in an adult lung cancer patient; evaluation of the sensitivity of capnography compared with other diagnostic modalities has never been reported (3). No cases of capnography for TEF detection in a pediatric population have been previously reported.

Although diagnosis of TEF is generally acknowledged to be difficult, literature surrounding the diagnostic sensitivity of various modalities for identification of TEF is limited. Many studies tout bronchoscopy as the diagnostic gold standard for TEF identification in infants before EA repair (4-6), and bronchoscopy has also been viewed by some as highly reliable in recurrent TEF identification (7,8). For example, 1 descriptive article by Bruch et al (7) reported diagnosis of recurrent TEF with bronchoscopy in all 26 of their reported cases, though half of the cases in this study required an intraoperative dye study during bronchoscopy to be detected. Our experience differs in that we found low sensitivity of TEF identification with single-modality investigations, such as bronchoscopy alone, even when dye-assisted, and found improvement in detection with combinations of diagnostic modalities. Similar to our experience, Dai et al (9) in their series of 31 TEF cases described difficulty identifying fistulae with any single modality and reported needing various combinations of iodine oil contrast studies, concurrent dye-enhanced esophagoscopy and bronchoscopy, and 3-D computed tomography reconstruction to identify the fistulae in approximately half of their cases. Although sensitivity of bronchoscopy to identify TEF is likely to some degree experience-dependent, it is probable that all published case series suffer from a degree of selection bias, as this study design is especially vulnerable to such bias. Though retrospective, our study



FIGURE 3. Concordance between the various diagnostic modalities of rigid bronchoscopy (blue), esophagoscopy (green), and capnography ("etCO₂"; yellow) using the cutoffs of etCO₂ \geq 68 mmHg (A) and \geq 90 mmHg (B) to identify TEF. The number of TEF cases identified by the various respective combinations of modalities are listed in the respective shaded regions of the Venn diagram. Patients not identified by any modality are noted outside the shaded regions in the white space. TEF = tracheoesophageal fistulae.

findings are strengthened by inclusion of all consecutive cases of surgically confirmed recurrent, acquired, or missed congenital TEF treated at our institution with all included cases evaluated by multiple diagnostic modalities rather than selective description of only cases identified by a single modality. Of note, there were 5 to 6 cases of recurrent TEF that were only identified at the time of surgical exploration, highlighting the difficulty of recurrent TEF diagnosis with nonsurgical, endoscopic methods.

In our study, rise in $etCO_2$ above Youden J index point of 68 mmHg had similar rates of TEF detection to traditional esophgagoscopy, though in practice, we note that in our experience, the rise if $etCO_2$ is typically much greater than 68 mmHg and often reaches the upper limit of readout of the capnography monitor (99 mmHg at our center) likely because of flooding the detector

Comparison of Detection Methods for TEF With a Novel Method

with supraphysiologic concentrations of pure CO₂ from insufflation. Our study likely underestimates rates of actual TEF detection by etCO₂ monitoring as our anesthesia monitoring software defaults to record spot etCO₂ measurements in the chart only once every 5 minutes. In our experience, we note that the rise in etCO₂ is abrupt and dramatic, but typically only registers while the esophagus is fully insufflated and fully distended by the gas and rapidly returns to baseline with just a few ventilated breaths, and that our anesthesia record may not reflect the abrupt short rise in etCO₂ if it is not noticed during the procedure and specifically recorded by the anesthesiologist or endoscopist. In our cohort, the combination of capnography (\geq 90 mmHg) with esophagoscopy and fluoroscopy improved diagnostic sensitivity from 56.1% to 64.3%; this finding suggests capnography may sometimes be helpful in cases where the provider is suspicious of TEF but bronchoscopy is not available. Our study found a small advantage of using capnography even in cases where both bronchoscopy and esophagoscopy with fluoroscopy were employed, as there was 1 case of recurrent TEF identified by capnography (with maximum recorded $etCO_2 = 85 \text{ mmHg}$ that was abrupt and nonsustained in this patient's anesthesia record) but missed by esophagoscopy and bronchoscopy; however, the significant limitation of the spot measurements of end-tidal CO₂ may obscure any potential additional larger benefit of capnography if it exists.

Though our study is not powered to identify clinical factors associated with ability to detect TEF by capnography, we anecdotally note that the location of the TEF likely plays a role. We identified 1 case of TEF in which the TEF was occluded by the inflated cuff of the endotracheal tube and was only detected by capnography when the cuff was temporarily deflated and moved. As demonstrated in Figure 1, any TEF that is located at the level of the cuff or more proximally will not produce a closed circuit path from the esophagus to the trachea to the end-tidal CO₂ detector and will be missed by this capnographic method unless the position of the endotracheal tube is adjusted to bring the cuff above the level of the TEF. In addition, the cuff of the endotracheal tube is critical; we have noted a false-positive rise in etCO₂ in cases of uncuffed endotracheal tubes likely because of retrograde bleeding of CO₂ from the esophagus into the oropharynx and into the trachea where it can be registered by the etCO₂ monitor. Finally, appropriate functioning of the end-tidal CO₂ monitor should be ensured by preventing condensation or secretions from contacting the sensor, and by regularly checking that its readout is logical and appropriate for the clinical scenario.

Although our study is limited by its retrospective nature and the sporadic spot measurements of $etCO_2$ in our anesthesia records, prospective study of capnography during esophagoscopy will enable more accurate delineation of the sensitivity of this method for TEF detection. Especially relevant for pediatric patients, capnography may enable endoscopists to reduce radiation exposure by avoiding the use of fluoroscopy in some cases.

To our knowledge, our study is the first to describe the sensitivity of capnography in TEF detection and the first to compare capnography with other traditional methods of TEF diagnosis. Sensitivity of any individual TEF detection method was poor, and diagnosis of TEF required a high index of suspicion. Although bronchoscopy has traditionally been viewed as the diagnostic gold standard for TEF, we observed poor sensitivity for TEF diagnosis with bronchoscopy alone. Combinations of diagnostic modalities increased the ability to diagnostic modality approach appears to increase ability to detect TEF.

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