Pediatric esophagopleural fistula
Two case reports and a literature review

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Abstract
Esophagopleural fistula (EPF) is rarely reported in children with a high misdiagnosis rate. This study aimed to reveal the clinical manifestations and managements of EPF in children.

Two pediatric cases of EPF in our hospital were reported. A bibliographic search was performed on the PubMed, WANFANG, and CNKI databases for EPF-related reports published between January 1980 and May 2016. The pathogeny, clinical manifestations, diagnosis, treatments, and prognosis of EPF patients were collected and discussed.

Based on conservative treatments, 1 pediatric EPF case induced by cervical trauma was cured by longitudinal septum incision-mediated drainage. The other pediatric EPF induced by endoscopic balloon dilation was cured by dual stent implantation. A total of 38 studies of 197 EPF patients (191 adults and 6 children) were reviewed. Latrogenic factor, esophageal foreign body, and infection are considered the main causes of EPF in children. Unilateral pleural effusion accompanied by food residue was the main manifestations of EPF. Chest computed tomography (CT) and contrast esophagography were usually used in the diagnosis of EPF with high accuracy. Surgical treatment in adults with EPF exhibited a significantly higher cure rate and lower mortality rate than conservative treatment ($P<.01$).

Pleural effusion with food residue is a specific finding in EPF. Chest CT exhibited high sensitivity for the diagnosis of EPF. Conservative treatment may be preferable for pediatric patients with EPF.

Abbreviations: CRP = C-reaction protein, CT = computed tomography, EPF = esophagopleural fistula, PCT = plateletcrit, PICU = pediatric intensive care unit, WBC = white blood cell.

Keywords: children, conservative treatment, esophagopleural fistula, surgery

1. Introduction
Esophagopleural fistula (EPF) is a rare critical disease caused by thoracic esophageal perforation.[1] To our knowledge, 38 studies of 197 patients with EPF have been published to date. In humans, EPF can directly induce chemical inflammation and bacterial infection of the mediastinum, chest and lungs, and then develop into acute mediastinal inflammation, severe pneumonia, or even sepsis, septic shock, and multiple organ dysfunction syndrome.[2]

Although various surgical and conservative techniques have been developed for the treatment of EPF, the mortality rate of EPF remains high (17%–25%).[3]

In clinical practice, early diagnosis and timely treatment are crucial to improving the cure rate and reducing the mortality rate of EPF. The mortality rate of EPF was reportedly only 9% when active treatments were provided within 24 hours, but could reach 65% and 75% to 89% when treatments were delayed to 24 and 48 hours, respectively.[4,5] Since EPF is uncommon in children and its clinical manifestations are usually nonspecific, EPF is more likely to be misdiagnosed as severe pneumonia, bacterial pleurisy, or a lung abscess.[6] The early misdiagnosis rate of EPF in children can reach to 74% to 84%,[7] Therefore, a comprehensive understanding of the diagnosis and treatments for EPF in children is urgently needed.

In this study, the clinical data of 2 pediatric cases of EPF enrolled in our hospital are reported. A literature review of 38 studies of 197 EPF patients was used to analyze the pathogeny, clinical manifestations, diagnosis, treatments, and prognosis of EPF. Our findings may reveal the clinical manifestations and managements of EPF and their specificity in children in an effort to provide guidance for the diagnosis and treatment of EPF in the future.

2. Materials and methods
2.1. Case presentation
2.1.1. Case one. A 3-year-old boy with a 3-day history of a swollen neck and a 1-day history of fever and breathlessness due to chopsticks-induced oral trauma was admitted to the digestive
department of our hospital in January 2014. He was transferred to the pediatric intensive care unit (PICU) 2 days after admission with breathlessness, perioral cyanosis, and restlessness. In the PICU, a regular examination showed dysphoria, infective and toxic face, obvious neck and upper-chest emphysema, positive inspiratory 3-depression sign, low respiratory sounds, a temperature of 40.5°C, heart rate 160 to 180 times/min, and 83% to 88% oxygen saturation under high-flow oxygen (5–6 L/min) through a face mask. Meanwhile, a white blood cell (WBC) count of 30.6 × 10^9/L, 82% neutrophile granulocytes, 191 mg/L C-reaction protein (CRP), and > 10 ng/L plateletcrit (PCT) were revealed by a routine blood test. Obvious compression on the trachea and main bronchus was observed by endotracheal intubation using a fiberoptic laryngoscope. Lung inflammation, partly atelectasis in the left lower lung, and subcutaneous pneumatosis in the bilateral neck and right axilla was observed by chest X-ray (Fig. 1A). Massive pneumatosis in the prevertebral space (between the trachea and the cervical vertebra), posterior pharynx, and bilateral chest wall; bilateral pulmonary inflammation; and a small left pleural effusion were revealed by computed tomography (CT) of the neck and chest (Fig. 1B). This case was ultimately diagnosed as cervical and thoracic injury with a soft-tissue infection and right pyo-pneumothorax.

Although anti-infection, mechanical ventilation, and right thoracic close drainage were provided for this patient in the PICU, symptoms of breathlessness, recurrent fever, reduced blood pressure (70–75/35–45 mm Hg), and increased blood lactic acid (4–6 mmol/L) persisted. A total of 400 to 500 mL of yellowish-white turbid hydrothorax with 9.5 × 10^9/L karyocytes was drained through thoracic close drainage each day. The presence of *Streptococcus pneumoniae* was identified on a cavity effusion smear. Meanwhile, by WBC identification, 85% multinucleate cells tested positive on a Rivalta test at pH 6.8 were found. However, blue pleural effusion was not observed through repeated oral methylene blue testing. Esophageal disruption and mucosal erosion were observed by a gastroscope, while no obvious tracheoesophageal fistula was found.

On day 10 in the PICU, a chest radiograph showed improved right hydropneumothorax, increased bilateral lung effusion, unabsorbed mediastinal, and cervical pneumatosis, and a hemicycle high-density shadow behind the heart. On day 20 in the PICU, a neck and chest CT found a widespread infection in the lung, a left pleural effusion, abnormal sac shadow in the posterior, and right parapharyngeal mediastinum with gas and gastric contents (interlinked mediastinum and esophagus) on a reexamined neck and chest CT after treatment (day 20 in the PICU).

![Figure 1](image1.png)

**Figure 1.** Clinical features of EPF in case one. A, Lung inflammation, partial atelectasis in the lower left lung, and subcutaneous pneumatosis in the bilateral neck and right ailla were observed on a chest X-ray upon transfer to the pediatric intensive care unit (PICU). B, Large pneumatosis between the trachea and the cervical vertebra (prevertebral space), hydropneumothorax in the right lung combined with atelectasis, subcutaneous pneumatosis in the posterior pharyngeal and bilateral chest wall; bilateral pulmonary inflammation; and a slight left pleural effusion visible on a neck and chest CT upon transfer to the PICU. C, Widespread infection in the lung, a left pleural effusion, abnormal sac shadow in the posterior, and right parapharyngeal mediastinum with gas and gastric contents (interlinked mediastinum and esophagus) on a reexamined neck and chest CT after treatment (day 20 in the PICU). D, An obviously narrowed abnormal neck and upper mediastinal sac shadow as well as an improved hydropneumothorax and infection were observed on a neck and chest CT on day 12 after the surgery. E, F, Absorbed abnormal neck and upper mediastinal sac shadow and disappeared inflammation were revealed by CT on day 18 after surgery. CT = computed tomography, EPF = esophagopleural fistula.
the lung, left pleural effusion, and an abnormal sac shadow in the posterior and right parapharyngeal mediastinum with gas and contents (Fig. 1C). These phenomena indicated that the mediastinum and esophagus were interlinked. An incision and drainage of the mediastinal abscess was performed on day 21 in the PICU. Various postoperative treatments were also performed, such as continuous nasogastric decompression, anti-infection, and enteral nutritional support through a jejunal nutrition tube.

After the surgery, the patient’s temperature returned to normal on day 3, mechanical ventilation was removed on day 4, and the closed right thoracic cavity drainage tube was removed on day 7. An obviously narrowed neck and upper mediastinal sac shadow and improved hydropneumothorax and infection were observed on a neck and chest CT on day 20 (Fig. 1D). Meanwhile, the jejunal tube was removed and oral intake was resumed. On day 18 after the surgery, a CT scan revealed that the abnormal neck and upper mediastinal sac shadow had been absorbed and the inflammation had disappeared (Fig. 1E and F). The patient was discharged from the hospital and considered healthy at routine follow-up appointments through September 2016.

2.1.2. Case two. A 5-year-old boy characterized by mega-esophagus (achalasia of the cardia) was admitted to the digestive department of our hospital in September 2015. Gastroscopic balloon dilation was immediately performed. Four days after the surgery, fever (38.5°C–39.5°C) and breathlessness developed. Meanwhile, a WBC count of 30.6\(\times\)10^9/L, 93% neutrophil granulocytes, and 13 mg/L CRP were revealed by a routine blood test. Pneumomediastinum, left pleural effusion and lung inflammation were observed on chest X-ray. The patient was transferred to the PICU on day 5 after the surgery due to listlessness, enhanced breathlessness, and perioral cyanosis. In the PICU, a regular examination showed positive inspiratory 3-depression sign, low respiratory sounds in the left lung, a temperature of 39.2°C temperature, and 94% to 96% oxygen saturation under high flow-oxygen (5–6 L/min) through a face mask. He was diagnosed with severe pneumonia, sepsis, respiratory failure, and a left pleural effusion.

Although high-flow oxygen, anti-infection, thoracic close drainage, and antacids were provided in this case in the PICU, the fever and enhanced progressive dyspnea persisted. Mechanical ventilation was provided on day 3 in the PICU and blood purification was used to relieve the oliguria and high serum creatinine level (124 μmol/L). Dynamic monitoring of the inflammatory markers showed: WBC = (25.6–42.2)\(\times\)10^9/L, CRP > 220 mg/L, and PCT > 10 ng/L. In addition, a neck and chest CT revealed a pneumomediastinum, left hydropneumothorax, segmental left pulmonary consolidation and atelectasis, and an interlinked lower esophagus with mediastinum and anocelia (Fig. 2A and B). A total of 200 mL to 400 mL of yellow-green turbid hydrothorax with 5.5\(\times\)10^9/L karyocytes was drained through thoracic close drainage each day, which properties similar to those of the gastrointestinal drainage fluid were exhibited (Fig. 2C). About 80% multinucleate cells at pH 4.0 to 4.8 were...
found by WBC identification. An oral methylene blue test was positive, and perforation of the middle and inferior segments of the esophagus was observed by esophageal endoscopy.

On day 6 in the PICU, an esophageal stent (2.2 cm upper cup diameter, 8 cm length, 1.4 cm pipe diameter) was implanted. Gastrointestinal drainage and thoracic close drainage were maintained. An intestinal feeding tube was implanted, and anti-infection, antacid, fasting, and intravenous nutrition treatments were administered. Three days later (day 9 in the PICU), a PediaSure milk was given, and 200 to 400 mL of milky hydrothorax was drained through the thoracic close drainage every day. A gastrointestinal barium meal examination found partial barium spillover after balloon dilation (Fig. 2D). Endoscopic stent removal and secondary stent implantation (2.4 cm upper cup diameter, 10 cm length, 1.6 cm pipe diameter) through a gastroscope were performed on day 7 after the first stent was set. Two days later, milk was given through the jejunal tube and no liquid was expelled from the thoracic close drainage tube. On day 15 after the secondary stent implantation, occasional barium spillover was revealed, while the lung inflammation and absorbed pleural effusion were verified as disappeared by chest X-ray examination (Fig. 2E and F). The jejunal tube was finally removed on day 28 in PICU. This patient was discharged from the hospital and considered healthy during follow-up appointments through September 2016.

2.2. Review of the literature
2.2.1. Data collection. We searched the PubMed, WANFANG (http://www.wanfangdata.com.cn/), and CNKI (http://www.wanfangdata.com.cn/) databases using the keywords “esophagopleural fistula,” “EPF,” and “children” for studies published between January 1980 and May 2016. Patients with benign EPF were enrolled in this study, while those with tumor-induced malignant EPF were excluded. The pathogenesis, clinical manifestations, diagnosis, treatments, and prognosis of these patients were collected and analyzed.

2.3. Statistical analysis
The statistical analysis was performed using SPSS version 17.0 (SPSS Inc, Chicago, IL). Qualitative data are expressed as number (percentage), and the \( \chi^2 \) test was used to compare the different groups. \( P < 0.05 \) were considered significantly different.

3. Results
A total of 38 studies (11 in English, 27 in Chinese) of 197 EPF patients (191 adults, 6 children) were included.

3.1. Pathogenesis of EPF
The pathogenesis of EPF varied on clinic. Spontaneous EPF (65.4%) was the most common form of EPF in adults. Meanwhile, pneumonectomy (16.2%), esophageal foreign body (6.3%), esophagus and stomach anastomotic fistula (5.2%), iatrogenic factor (4.2%), trauma (2.1%), and infection (0.5%) could also induce EPF in adult. For children, only iatrogenic factor (66.7%), esophageal foreign body (16.7%), and infection (16.7%) comprised the pathogenesis of EPF (Table 1).

3.2. Clinical manifestations of EPF
The clinical manifestations of EPF were revealed on 78 cases (76 adults, 2 children) in the studies. As shown in Table 2, pleural effusion was the only manifestation of EPF (100%). Unilateral pleural effusion was more frequent than bilateral pleural effusion (50.0% right side, 43.6% left side, 6.4% bilateral). Meanwhile, 87.2% of cases of pleural effusion were accompanied by food residue. Fever (52.6%), dyspnea (52.6%), pectoralgia (33.3%), and subcutaneous and mediastinal emphysema (29.5%) were also found with EPF (Table 2).

3.3. Diagnosis of EPF
Accurate diagnostic methods of EPF were revealed in 75 cases from the literature. Chest CT (45.3%) and contrast esophagography (30.7%) were revealed to be the most commonly used methods in the diagnosis of EPF with high accuracy. Meanwhile, methylene blue staining (14.7%) and an esophagoscope (9.3%) could also be used to diagnose EPF (Table 3).

3.4. Prognosis of EPF
The prognosis of EPF patients was evaluated in 129 of these cases. Surgery (esophageal repair) was performed on 65.1% of the patients, while conservative treatments (such as anti-infection, thoracic close drainage, and jejunal tube) were provided for the other 35.9% of the patients. By comparison, the cure rate was significantly higher in patients treated surgically.

| Table 1
| The pathogeny of esophagopleural fistula in adult and children. |
| Pathogeny | Adult (n = 191) | Children (n = 6) |
| Spontaneity | 125 (65.4%) | 0 (0%) |
| Pneumonectomy | 31 (16.2%) | 0 (0%) |
| Esophageal foreign body | 12 (6.3%) | 1 (16.7%) |
| Esophagus and stomach anastomotic fistula | 10 (5.2%) | 0 (0%) |
| Iatrogenic factor | 8 (4.2%) | 4 (66.7%) |
| Trauma | 4 (2.1%) | 0 (0%) |
| Infection | 1 (0.5%) | 1 (16.7%) |

| Table 2
| Clinical manifestations of patients with esophagopleural fistula. |
| Clinical manifestation | Number (n = 78) | Percentage (%) |
| Fever | 41 | 52.6% |
| Dyspnea | 41 | 52.6% |
| Pectoralgia | 26 | 33.3% |
| Subcutaneous and mediastinal emphysema | 23 | 29.5% |
| Pleural effusion | 78 | 100% |
| Effusion site | | |
| Right | 39 | 50.0% |
| Left | 34 | 43.6% |
| Bilaterality | 5 | 6.4% |
| Food residue in pleural effusion | 68 | 87.2% |

| Table 3
| Diagnosis of esophagopleural fistula in clinical practice. |
| Diagnostic method | Number (n = 75) | Percentage (%) |
| Chest computed tomography | 34 | 45.3% |
| Contrast esophagography | 23 | 30.7% |
| Methylene blue staining | 11 | 14.7% |
| Esophagoscope | 7 | 9.3% |
than in those treated conservatively ($P<.01$). Meanwhile, surgical treatment exhibited a significantly lower mortality rate than conservative treatment ($P<.01$). However, no significant difference was revealed in the automatic discharge rate between patients treated surgically and those treated conservatively (Table 4).

### 4. Discussion

EPF is a rare critical life-threatening disease that features high misdiagnosis and morbidity rate.[10] In this study, 38 EPF-related studies (197 patients with EPF) published between 1980 and 2016 were reviewed. Review of these studies revealed that the pathogenesis of EPF differed between adults and children. In adults, spontaneous esophageal rupture, pneumonectomy, esophageal foreign body, and esophageal and gastric anastomotic fistulas were revealed to be the main causes of EPF, while iatrogenic factors, esophageal foreign body, and infection were the main causes of EPF in children. In our hospital, 1 male pediatric case with EPF was revealed to be induced by gastroscopic balloon dilation, which indicated that the iatrogenic damage may be an important etiology of EPF in children. Another pediatric EPF case induced by chopstick trauma was the first case of EPF induced by a blunt force injury. This case suggests that the neck trauma was also an important etiology of EPF, an important finding.

On clinical examination, since the early manifestation of EPF was atypical, the misdiagnosis rate was usually high.[10] In this study, the literature review revealed the occurrence of pleural effusion was found in all 78 reported EPF cases, and most of cases of hydropneumothorax were unilateral. Meanwhile, gastric contents (food residue) were found in the pleural effusion of most cases (87.2%), which was specific in EPF. Fever and subcutaneous and mediastinal emphysema were also common manifestations of EPF. Consistent with these findings, 2 pediatric cases of EPF in our hospital exhibited similar symptoms, including fever, hydropneumothorax, and food residue in the pleural effusion. These phenomena indicate that greater attention should be paid to the properties of pleural effusion. Specifically, when gastric contents appear on pleural effusion, the diagnosis of EPF should be considered. Furthermore, since the diagnostic accuracy of EPF was significantly lower in children than in adults due to limited experience and description, the emergence of gastric contents in pleural effusion may provide overwhelming evidence of the diagnosis of EPF in children.

For an accurate diagnosis of EPF, chest CT and contrast esophagography are the most commonly used inspection methods. Some other inspection methods, such as methylene blue staining and esophagoscopy, could also be used in clinical practice. It has been reported that contrast esophagography could obviously reveal fistula size in cases of EPF.[10] The negative rates of contrast esophagography and esophagoscopy for the diagnosis of small fistula combined with esophageal mucosal erosions and edema were 10% to 36% and 20% to 42% respectively.[11] Chest CT could reveal fistula size and location, which exhibited high sensitivity in the diagnosis of EPF ($> 90\%$).[12] On chest CT, the typical manifestation of EPF mainly included pleural and mediastinal effusion, esophageal fistula interlinked with the mediastinum and/or an anoclelia, and pulmonary inflammation.

In our hospital, 1 case of neck trauma was misdiagnosed for more than 20 days due to the presence of a small fistula with serious mucosal erosion. The fistula was not found by contrast esophagography and gastroscopy or methylene blue staining, but was finally revealed by high-resolution chest CT. For highly suspicious cases, despite contrast esophagography, gastroscopy, and methylene blue staining being unable to identify EPF, the diagnosis of EPF still required consideration. Therefore, high-resolution CT may be the best choice for confirming the diagnosis of EPF in clinical practice.

Controversy persists about the application of surgery versus conservative treatment in the treatment of EPF. On the literature review, surgery exhibited significantly higher cure rates and lower mortality rates than conservative treatments. Esophageal repair was still considered the best choice in the treatment of EPF.[12] Meanwhile, some studies indicated that the best surgical opportunity was within 24 hours after the EPF occurred. For patients with EPF but without severe infection for ≥ 24 hours, surgery should also be performed as early as possible. Although early surgery with a relaxation of surgical indications may not completely repair a fistula, timely fistula repair may significantly improve EPF outcomes.[13,14] On the other hand, conservative treatment was suitable for delayed diagnosed EPF patients with poor health condition. In patients provided conservative treatments, fully effective pleural, mediastinal, and continuous gastrointestinal drainage were considered necessary to avoid digestive juice-induced chemical corrosion and thoracic mediastinal infection. Meanwhile, since oral or stomach tube feeding was not allowed until the fistula was cured completely, antacid and nutritional support should also be administered.[15] Moreover, since acute mediastinitis was the most common complication of EPF, anti-infective measures were also considered necessary in the treatment of EPF. For patients with a mediastinal abscess combined with sepsis, a drainage tube should be implanted in a timely manner to prevent severe sepsis and septic shock. In our hospital, surgical repair could not be performed in a pediatric EPF case with local erosion and a severe infection for ≥ 21 days. Based on comprehensive conservative treatments (including gastrointestinal decompression, nutritional support, anti-infective measures, and antacid), this case was completely cured without recurrence during 1 year of follow-up by longitudinal septum incision-mediated drainage. This case further illustrated that conservative treatment could effectively promote EPF healing.

Esophageal stenting is a new strategy in the treatment of EPF, has and exhibits the advantages of a short hospital stay and fast recovery of oral feeding.[16] However, the application of esophageal stenting in cases of benign EPF remains controversial.

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Table 4: Prognosis of esophagopleural fistula by surgery and conservative treatments.

|                        | Surgery (n = 84) | Conservative treatments (n = 45) | $\chi^2$ | $P$  |
|------------------------|-----------------|-------------------------------|---------|------|
| Cure rate              | 92.86% (78/84)  | 64.40% (26/45)                | 23.08   | < .01|
| Mortality              | 4.80% (4/84)    | 35.60% (16/45)                | 21.21   | < .01|
| Automatic discharge rate| 2.3% (2/84)    | 6.67% (3/45)                 | 1.44    | .23  |

*Conservative treatments group included 4 cured cases treated by stents.*
Although the stent exhibited good patency in the esophagus, it was difficult to affix and shifted easily. A large stent may induce over-distension of the esophageal cavity and lead to a secondary esophageal fistula due to the combined action of food gravity and the shear stress of an upper stent. Meanwhile, the long-term retention of an esophageal stent may block the esophageal cavity and lead to a secondary esophageal fistula due to the combined action of food gravity and the shear stress of an upper stent. In our hospital, an EPF case of megaesophagus was induced by balloon dilation. The first-time application of esophageal stenting failed to completely close fistulas because the small stent could not fit the fistula. This case was completely cured by secondary stenting with a larger stent and no recurrence was found during follow-up. This phenomenon indicated that esophageal stenting with an appropriately sized stent was effective in the treatment of EPF in children. However, this study was limited by the insufficient number of subjects. Since EPF is rare in children, 2 cases in our hospital and 6 previously reported cases could not fully reflect the clinical manifestations and management of EPF. Further studies including more pediatric EPF cases and effective diagnostic and therapeutic strategies are still needed.

5. Conclusions

To sum up, the following conclusions were drawn from this study. Balloon dilation of the esophagus, neck and chest trauma, and swallowing of foreign matter were high-risk factors of EPF in children. Fever, dyspnea, pneumomediastinum, unilateral hydro-pneumothorax, and especially the existence of food residue in pleural effusion were closely related to the occurrence of EPF. High-resolution chest CT exhibited high diagnostic sensitivity on EPF. Surgical repair was effective for the treatment of EPF in adults, while conservative treatment may be preferable for the treatment of pediatric cases with EPF. Mediastinal and thoracic closed drainage, as well as active enteral nutrition support, were necessary in conservative treatment.

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