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# Esophageal Perforation in VLBW Infants in a Singapore Tertiary Hospital: A Case-Control Study

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## Abstract

**Objective:** The purpose of our study was to summarize the clinical course of neonates with Esophageal Perforation (OP), and identify potential risk factors.

**Methods:** Retrospective case-control study of neonates with OP between 2005 and 2020 at a Singapore tertiary neonatal unit. Four controls per case were matched by gestational age and month of birth. Data on baseline characteristics, morbidity, mortality, time to attain full feeds, and hospitalization duration, was collected.

**Results:** The incidence of OP was 4.5 per 10,000 livebirths. 12 cases of OP and 48 matched controls were included. All OP patients had Very Low Birth Weight (VLBW) with mean birthweight of 729.8 g and median gestational age of 26 weeks. Median Apgar scores were 6 and 8 for OP at 1- and 5-min. OP cases were more likely to be male (OR 1.51, p<0.01), and associated with maternal pre-eclampsia (OR 5.3, p<0.05). Most (n=7, 58%) presented on day of birth. The commonest presentation was air-leak (n=10, 83.3%). All OP cases required intubation (OR 2.00, p<0.01), and history of difficult intubation was noted in 4 cases. All OP patients were managed conservatively. The average duration of hospitalization was 91 days. OP was associated with necrotizing enterocolitis (OR 5.4, p<0.05). There was no difference in mortality.

**Conclusion:** VLBW neonates are at risk of OP. Preventive measures, prompt recognition, and conservative treatment have been shown in our experience to be successful in achieving resolution of OP, in the absence of concomitant risk factors of mediastinitis, and/or persistent air leaks.

**Keywords: Esophageal perforation; VLBW; NICU; OP**

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## Background

Esophageal perforation in neonates is rare and usually iatrogenic in origin [1,2], unlike in adults where causes include iatrogenic, spontaneous, foreign body ingestion, trauma and malignancy [3]. Esophageal perforation in neonates has been attributed to procedures including intubation, gastric tube insertion, pharyngeal suctioning, and traumatic delivery.

Historically, esophageal perforation has been surgically managed [4]. Recent case series suggest a shift toward conservative management which includes keeping the baby nil by mouth, provision of parenteral nutrition, and empiric antibiotic coverage to prevent mediastinitis [5-7]. The purpose of our study was to summarize the clinical presentation, course, treatment, and outcome of Very Low Birth Weight (VLBW) infants with Esophageal Perforation (OP), and to identify potential risk factors.

## Material and Method

Between January 2005 and December 2020, VLBW infants with esophageal perforation who were admitted to the Neonatal Intensive Care Unit (NICU) at Singapore General Hospital were identified from our database. We collected and analyzed the following data retrospectively, including gestational age, birth weight, gender, mode of delivery, multiple pregnancies, and Apgar scores. Maternal history of pre-eclampsia, hypertension, gestational diabetes mellitus, pre-existing diabetes mellitus, premature membrane rupture, administration of antenatal steroid therapy or assisted reproductive technology was documented. Clinical information, such as age of onset, clinical presentation, radiological findings, clinical course, co-morbidities (occurrence of air leak,

intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, Retinopathy of prematurity, bronchopulmonary dysplasia, osteopenia of prematurity, TPN cholestasis), management and outcome, was reviewed.

Statistical analysis was performed using SPSS for Windows (version 23). Discrete variables were analyzed using the chi square test. Continuous variables were analyzed using Mann- Whitney U test. P<0.05 was considered statistically significant.

This study was reviewed by local institutional review board and was exempt from requiring approval.

## Results

Between January 2005 to May 2020, there were 2363 NICU admissions, 877 of whom weighed less than 1,500 g at birth. There were 12 neonates with esophageal perforation, giving an incidence of 0.5% amongst all NICU admissions and 1.4% amongst Very Low Birth Weight (VLBW) infants.

All 12 neonates with esophageal perforation were born preterm, and were matched with 48 controls for comparison. Demographic data for both groups are depicted in Table 1.

Male gender and maternal pre-eclampsia were statistically significantly risk factors. Amongst patients with esophageal perforation, the mean gestational age was 26 ± 1.9 (2 SD) week, and the mean birth weight was 729.83 ± 165 (2 SD) g. 10 out of 12 were born Extremely Low Birth Weight (ELBW).

The patient characteristics, clinical presentation, management, hospital course and outcome of these twelve patients with OP are outlined in Table 2. Two-thirds of cases presented on the first day of life, and the latest presentation was the 8$^{th}$ day of life.

### Clinical course: Diagnosis and management

The commonest clinical presentation was air leak syndrome (n=10, 83.3%) followed by misplaced orogastric tube (n=7, 58%) and inability to insert orogastric tube (n=2, 17%).

Diagnosis of esophageal perforation was made after noting one or more of the following radiological features on chest X-Ray. There was malposition of gastric tube in 8 cases (despite adequate depth of insertion), pneumomediastinum in 3 cases, and right-sided pneumothorax in 8 cases—all of which required drainage. One case was further verified by point of care ultrasound. In 4 cases, there was clinical suspicion in view of inability to advance the feeding tube to the intended depth, with subsequent radiological confirmation of malposition.

All patients received a surgical consult at the time of presentation and were managed conservatively by keeping nil by mouth, giving parenteral nutrition, and empiric broad spectrum antibiotic. Infants were kept nil by mouth for 7-31 (median 15) days. Water soluble contrast study was performed in 3 neonates prior to commencement of feeds.

All infants with OP required intubation and were managed conservatively.

### Outcomes

The time to attain full feeds and possible complications of delay enteral feeding (osteopenia of prematurity and TPN cholestasis) were not significantly higher in neonates with OP.

The average duration of hospital stay for surviving infants was 91 days.

In terms of morbidity (Table 3: Neonatal outcome), there was a statistically significant association between esophageal perforation and necrotizing enterocolitis with OR 5.4 (3.14-9.17). There was no association between esophageal perforation and other co-morbidities.

Although mortality was higher in the OP cohort (25%), as compared to 8.3% in the control group, this was not statistically significant. In addition, the mortality among the OP cohort was thought not to be directly related to OP. Three neonates died in the esophageal perforation group, one due to left pulmonary artery sling with airway obstruction on day 35, one secondary to intraventricular hemorrhage on day 35 and one secondary to severe bronchopulmonary dysplasia on day 92.

### Risk factors for esophageal perforation

In terms of risk factors for OP, all 12 cases of esophageal perforation underwent both endotracheal intubation (OR 2.00, p<0.01) and gastric tube insertion prior to clinical suspicion of esophageal perforation. Furthermore, history of difficult intubation requiring multiple attempts was noted in 4 of the 12 cases. This

**Table 1:** Clinical characteristics of neonate.

| Variables | Esophageal perforation (N=12) | Control (N=48) | P | OR (95% CI) *where statistically significant |
|---|---|---|---|---|
| Gestational age (weeks), median (range) | 26 (23-30) | 26.5 (24-29) | 0.534 | |
| Birth weight (g) | 729.83 ± 165 | 857.73 ± 223 | 0.069 | |
| Apgar score at 1 minute, median (range) | 6 (2-9) | 5 (1-8) | 0.253 | |
| Apgar score at 5 minute, median (range) | 8 (4-9) | 8 (4-9) | 0.872 | |
| Small for gestational age n/N(%) | 5/12 (42) | 9/48 (19) | 0.171 | |
| Mode of delivery n/N(%), Caesarean section | 9/12 (75) | 32/48 (66) | 0.586 | |
| **Male sex, n/N(%)** | **12/12 (100)** | **21/48 (44)** | **<0.00** | **1.5 (1.21-2.30)** |
| Maternal age mean (SD) | 33 ± 4 | 33 ± 5 | 0.946 | |
| **Maternal pre-eclampsia n/N(%)** | **7/12 (58)** | **10/48 (21)** | **0.009** | **5.3 (1.3-20.3)** |
| Maternal GDM, n/N(%) | 0/12 (0) | 2/48 (4.1) | 0.48 | |
| Maternal pre-existing DM, n/N(%) | 0/12 (0) | 2/48 (4.1) | 0.48 | |
| Air leak, n/N (%) | 10/12 (83) | 6/48 (13) | 0.012 | |
| Required endotracheal intubation, n/N (%) | 12/12 (100%) | 38/48 (0.79) | 0.08 | |

**Table 2:** Clinical presentation, management, hospital course, and outcomes.

| Case number | Gestational age (weeks + days) | Birth weight | Size for age | Age at diagnosis | Clinical presentation | NBM | Outcome (full feeds, duration of admission, survival) |
|---|---|---|---|---|---|---|---|
| 1 | 26+5 | 620g | SGA | Day 1 | Difficulty inserting Orogastric Tube (OGT) after repeated intubation attempts<br>CXR: OGT tip above clavicles, with right pneumothorax on day 4 (required insertion of 3 chest tubes)<br>OGT reinserted on day 11 in view of large amount of vomiting of large amount of stale blood. OGT tip position in stomach confirmed with abdominal ultrasound. | 21 days | Achieved full feed on day 46 of life, discharged on day 97 of life. |
| 2 | 26+1 | 665g | AGA | Day 1 | Inability to insert OGT after intubation, with right pneumothorax that required chest tube drainage for 5 days<br>Subsequent successful insertion of OGT on day 14, with OGT tip in good position on CXR | 15 days | Achieved full feed on day 41. Discharged on 102 days of life |
| 3 | 27+4 | 600g | SGA | Day 7 | CXR: Mediastinal lucency with right pneumothorax that required chest tube drainage for 3 days. | 10 days | Passed away on day 35 of life due to left pulmonary artery sling (diagnosed on day 3 of life) with airway obstruction. |
| 4 | 25+4 | 545g | SGA | Day 1 | Unsuccessful intubation attempts at birth, with esophageal intubation in NICU. Persistent bleeding for 12 h post-intubation, unable to insert OGT.<br>CXR: OGT tip at mid sternum, pneumomediastinum and pneumothorax.<br>OGT inserted on day 20 with tip in satisfactory position | 31 days (delayed starting feeds due to other reason: as child was hemodynamically unstable) | Recurrent pneumothorax required multiple chest tube insertion, required high ventilator setting. Other co-morbidity: Passed away on day 92 of life due to severe bronchopulmonary dysplasia |
| 5 | 28+1 | 820g | AGA | Day 1 | Difficult intubation with multiple attempts. Post intubation noted difficult OG tube insertion with tip at cervical region on CXR. | 10 days | Achieved full feeds on day 56, discharged on 79 days of life |
| 6 | 29 | 645g | SGA | Day 1 | Intubated at birth, unable to insert OGT fully post intubation with fair amount of blood-stained OGT aspirate.<br>CXR: OGT tip at level of T10. Developed pneumothorax on day 3. OGT reinserted on day 4, noted OGT tip in right hypochondrium.<br>OGT reinserted with appropriate position on x-ray on day 19. | 20 days | Developed grade 3 intraventricular hemorrhage since day 6 of life. Subsequently developed post hemorrhagic hydrocephalus and experienced seizures. Passed away on day 35 as parents opted for withdrawal of medical treatment. |
| 7 | 26+5 | 1003g | AGA | Day 1 | Pneumomediastinum | 7 days | Achieved full feed on day 26, discharged on day 96 of life. |
| 8 | 30+5 | 1000g | SGA | Day 2 | Difficult intubation at birth. Noted abdominal distention on day 2. AXR revealed OGT curved towards right abdomen, and right pneumothorax. | 7 days | Achieved full feeds on day 28. Discharged on day 89 of life. |
| 9 | 24+3 | 720g | AGA | Day8 | Was reintubated on day 8 of life and OGT inserted thereafter. CXR showed tip of OGT at right side of abdomen. Existing OGT removed; new OGT reinserted under fluoroscopic guidance on day 11. | 43 days (delayed starting feeding in view of bowel perforation) | Developed intestinal obstruction on day 26. Exploratory laparotomy on day 28 showed meconium inspissation with volvulus and small bowel perforation, required bowel resection and ileostomy. Achieved full feed on day 101 |
| 10 | 24 | 750g | AGA | Day 1 | Failed intubation at birth, successfully intubated at 1.5 h of life. CXR done showed OGT tip at right hypochondrium. Water soluble contrast study done on day 6 of life confirmed diagnosis of esophageal perforation, with pneumomediastinum and pneumothorax.<br>Chest tube was inserted for 4 days. Water soluble contrast study done on day 19 showed no leak | 19 days | Achieved full feed on day 46. Discharged on day 91. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 11 | 28 | 880g | AGA | Day 4 | Intubated at birth. CXR showed persistent lucency at lower sternal area since day 1. Ultrasound done on day 4 of life showed cystic structure with gas bubble, corresponding to position with lucency seen on CXR; finding consistent with fluid collection related to esophageal perforation. Water soluble contrast done on day 12 before starting feeding: no leak | 7 days | Achieved full feeds on day 28, discharged on day 75. |
| 12 | 23+4 | 510g | AGA | Day 1 | Intubated at birth. CXR: right sided pneumothorax, OGT tip curved towards right side. US abdomen on day 2: OGT not seen in Stomach, not able to detect tip of OGT Water soluble contrast study done prior to starting feeds on day 16, no contrast leak | 14 days | Achieved full feeds on day 40, discharged on day 156. |

SGA: Small for Gestational Age: AGA: Appropriate for Gestational Age; OGT: Orogastric Tube; CXR: Chest X-Ray

**Table 3:** Neonatal outcome.

| Variables | Oesophageal perforation (N=12) | Control (N=48) | P | OR (95% CI) *where statistically significant |
|---|---|---|---|---|
| Necrotising enterocolitis | 2/12 (17) | 1/48 (2) | 0.044 | 5.4 (3.14-9.17) |
| Intraventricular haemorrhage | 2/12 (17) | 8/48 (17) | 0.124 | |
| ≥Γραδε 3 ΙçΗ | 2/12 (17) | 4/48 (8) | 0.398 | |
| Hypotension | 1/12 (8) | 14/48 (30) | 0.13 | |
| Retinopathy of prematurity | 3/12 (25) | 16/48 (33) | 0.247 | |
| Bronchopulmonary dysplasia | 9/12 (75) | 38/48 (79) | 0.759 | |
| Severe BPD | 2/12 (17) | 10/48 (20) | 0.752 | |
| Osteopenia of prematurity | 3/12 (25) | 11/48 (23) | 0.881 | |
| TPN cholestasis | 2/12 (17) | 4/48 (8.3) | 0.398 | |
| Time to full enteral feeds (Days) mean, (SD) | 45 ± 23 | 43 ±19 | 0.715 | |
| Mortality n/N(%) | 3/12 (25%) | 4/48 (8.3%) | 0.244 | |
| Duration of hospital stay, mean, SD | 91 +/- 37 | 88 ± 39 | 0.787 | |

temporal sequence supports a causative relationship between the above-mentioned procedures and esophageal perforation.

## Discussion

In our experience, all the patients with Esophageal Perforation (OP) were preterm. Placement of endotracheal or oro/nasogastric tube is often required for the initial management of preterm, particularly Very Low Birth Weight (VLBW) infants. The challenge of intubating a VLBW, especially in an emergency setting with little time for preparation, and the inherent characteristics of their developing esophagus (narrow lumen, thin wall, weak musculature) potentially contribute to preterm infants having a higher risk of esophageal perforation.

Interestingly all our infants with esophageal perforation were male. Male:Female ratio was also reported to be higher in other case series [4,6,7].

Maternal pre-eclampsia was statistically significantly associated with OP in our study. There was also a higher prevalence of Small for Gestational Age (SGA) infants in the OP cohort although the association did not reach statistical significance. We postulate the above observations could be related to uteroplacental insufficiency, which could in turn contribute to the esophageal wall being more susceptible to perforation.

In terms of clinical presentation, our cohort was similar to other case series, including that by Hesketh et al. [7], with regards to the patients having had prior multiple attempts at endotracheal intubation (present in 5 out of 12 of our patients) (Figures 1-5). We concur with other case series [8] that the unsuccessful attempts at endotracheal intubation resulted in inadvertent instrumentation of the upper gastrointestinal tract, thereby leading to esophageal perforation. In addition, our patients also had similar radiographic

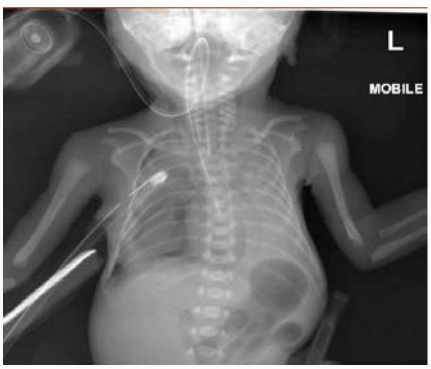


**Figure 1: Case 4:** This neonate had multiple intubations attempts and difficulty in orogastric tube insertion. Note that the orogastric tube tip is at level of mid esophagus, with presence of right pneumothorax.

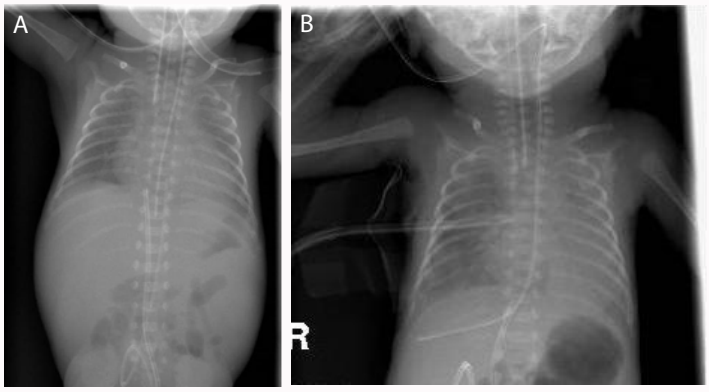


**Figure 2: Case 6:** 2a) In this neonate, it was not possible to insert the orogastric tube fully post intubation at birth with fair amount of blood-stained gastric aspirate. Note that orogastric tube is at level of diaphragm. 2b) He was noted to have pneumothorax 2 days later, and nasogastric tube reinserted showed its tip in right hypochondrium.

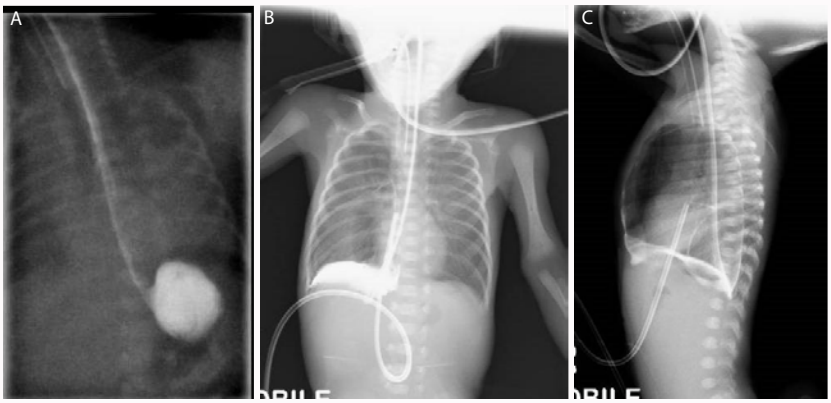


**Figure 3: Case 10:** In 3a, the CXR shows a right pneumothorax and tip of feeding tube projected over right hypochondrium. Water soluble contrast with AP (3a) and lateral views (3b) were obtained. There was extravasation of the contrast into the right pleural cavity. The tip of the feeding tube was noted in the right posterior costophrenic angle. The findings were compatible with perforation of the thoracic esophagus with malposition of the nasogastric tube (3c).
Same patient, after 19 days. Repeated water-soluble contrast study showed no residual esophageal perforation was seen. A new NGT was inserted satisfactorily with tip seen in the gastric bubble.

findings, including air leak syndromes that were secondary to esophageal perforation, and feeding tube malposition, as we have illustrated in Figure 2 (Case 6) and Figure 5 (Case 12). Interestingly, of the 7 (58%) cases who presented with pneumothorax, all were right-sided. Other studies have documented higher frequency of right-sided pneumothorax. It is postulated that it this may be the result of the feeding tube tip being projected toward the right hemithorax due to the close apposition of the aorta to the left thorax [6,7].

However, we did not note other presentations that were reportedly common in other case series, including hypersalivation, choking, coughing or cyanosis [7,9]. We postulate this to be related to the relatively early diagnosis of OP in our series, and prompt institution of measures such as keeping the patient's nil by mouth, that limited the presentation of "hypersalivation" or choking that could have been related the continuation of feeds in patients with undiagnosed OP [9].

In our series, chest X-ray was the main diagnostic modality, and in fact established the diagnosis of esophageal perforation in 10 out of 12 patients. One patient required an ultrasound study, whereas another patient underwent a water-soluble contrast study to establish the diagnosis, as the diagnosis of OP could not be confidently established on the initial Chest X-Ray (CXR). There is currently no consensus on the need for a contrast esophagogram to establish the diagnosis of OP. Some institutions routinely obtain an esophagogram to confirm and localize the esophageal perforation [9], but others suggest diagnostic modalities beyond chest X-rays, such as esophagograms or endoscopy, are only indicated when the diagnosis of OP based on initial CXR is unclear, and there is a need to rule out other differential diagnoses such as esophageal atresia [6,10]. In our center, we practiced the latter approach.

While most centers perform a follow-up contrast study to document radiographic resolution of the esophageal perforation prior to re-commencement of feeds [6,7], there is again no consensus. Shah et al. [9] reported the use of a follow-up contrast study in only 5 out of 10 cases. In this series, we have selectively performed a follow-up contrast study for only 3 out of 12 patients before the commencement of feeds, and apart from the 3 babies that passed away, the other babies were able to successfully achieve full feeds upon re-commencement of feeds after at least 7 days of being kept nil by mouth. Based on earlier case series [6], 7 days proved to be sufficient for resolution of OP. In the case series reported by Onwuka et al. [6], all 25 patients received a follow-up contrast study after a mean duration of 7 days of being kept nil by mouth, and apart from 1 patient, the rest demonstrated radiographic resolution of OP. On this basis, it may be reasonable to consider re-commencement of feeds after a minimum duration of 7 days of fasting without a routine follow-up contrast study.

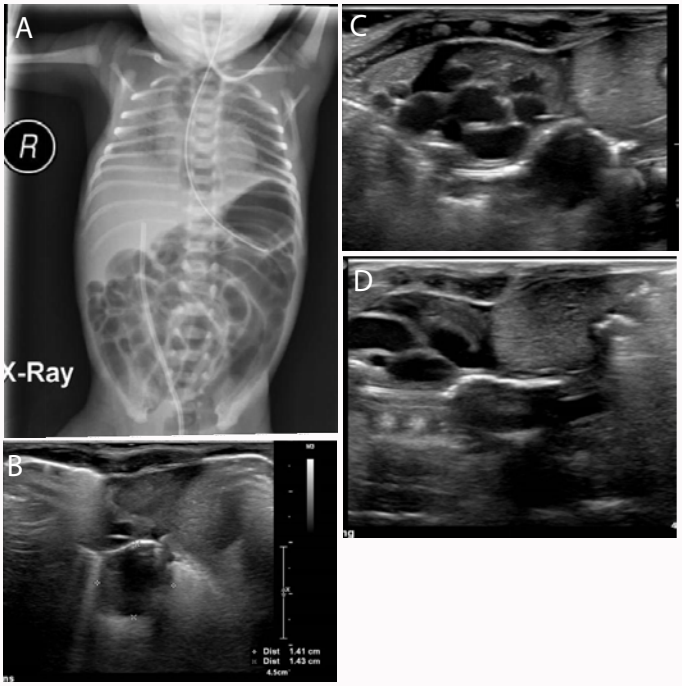


**Figure 4:** 4a) The CXR shows radiolucency at sternal region. **Case 11:** 4b, 4c, and 4d depict the ultrasound study that was performed on day 4 to further evaluate the cause of the lucency. In the posterior lower chest, there was a well-marginated cystic structure measuring 15 mm (craniocaudal) × 14 mm (transverse) × 12.5 mm (anteroposterior) dimension, and which was near the midline.

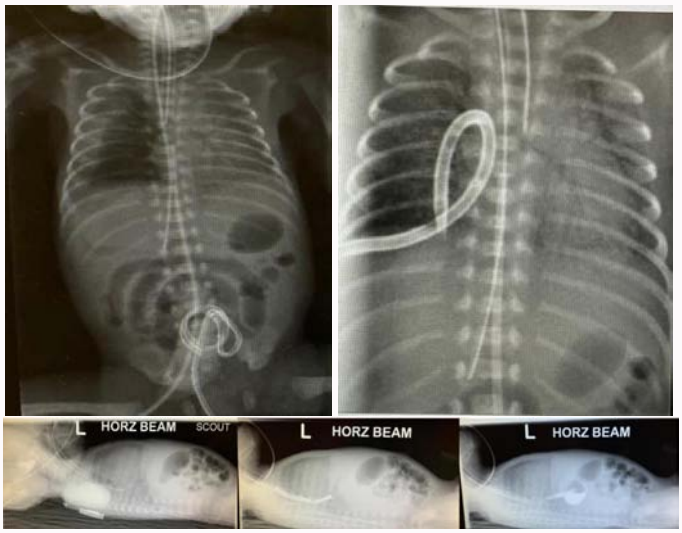


**Figure 5:** 5a) CXR showing right pneumothorax and malposition of feeding tube. 5b) CXR taken after pigtail catheter insertion with resolution of right pneumothorax. **Case 12:** Contrast study was done in the Neonatal Intensive Care Unit instead of the fluoroscopy room, which was the usual practice, due to COVID-19 restrictions limiting movement of patients within the hospital, and the risk of transfer of the extremely preterm infant who was still ventilated. The contrast study was done with the tip of the feeding tube placed at the junction of the mid and distal thirds of the esophagus, under direct laryngoscopic visualization. Water soluble contrast was gently hand injected through the feeding tube and both trans-lateral and frontal chest radiographs were obtained. There was unimpeded flow of contrast in the distal esophagus, gastro-esophageal junction, then stomach and finally into duodenum (5c). No false passage of contrast was seen, particularly in the region of suspected distal esophageal perforation, suggestive of healed esophageal perforation. This case supports a nonoperative approach for the management of neonatal esophageal perforation and demonstrates how the contrast esophagogram can be carried out in the NICU instead of the fluoroscopy room, which was standard practice previously.

Although 3 out of 12 patients in our study passed away, none of them was thought to be directly related to esophageal perforation. This finding was similar to other case series on neonatal OP, which was in stark contrast to adult OP, with mortality rates as high as 20% [3]. This difference could be due to earlier diagnosis in neonatal cases. In our study, most of the esophageal perforation was recognized almost immediately when there was difficulty in feeding tube insertion or malposition of enterogastric tube on CXR. These patients were then kept nil by mouth and started on broad spectrum antibiotic, which would reduce the risk of leak and contamination of the wound, thereby potentially having a favorable effect on morbidity/mortality. In addition, the higher mortality rate in adult OP case series could have been contributed by more sinister underlying etiology, including primary or metastatic esophageal carcinoma, and Barrett's

ulcers [3], in contrast to neonatal OP cases largely being secondary to instrumentation of the upper gastrointestinal tract [8].

Apart from case 9 who required laparotomy for concomitant small bowel perforation (and not for the esophageal perforation), the other patients were managed conservatively. Indeed, nonoperative management is now preferred treatment for most cases of neonatal esophageal perforation [5,7,8]. Indication for surgery include patients presenting with frank sepsis, mediastinitis, abscess formation or massive/persistent leaks with the aim of local control of infection with debridement, drainage and primary repair [8].

As repeated instrumentation of the upper gastrointestinal tract, including multiple attempts at endotracheal intubation, was identified as an important precursor and risk factor for neonatal esophageal perforation, effort should be made to reduce the incidence. These efforts include enhanced training for healthcare practitioners to improve the success rates of endotracheal intubation (simulation on high fidelity manikins, use of video laryngoscopy, adequate supervision of junior trainees, careful use of airway adjuncts such as stylets) and feeding tube insertion (adequate use of lubricants, early recognition of red flags such as resistance or bleeding during insertion of feeding tube). High index of suspicion and early detection, particularly in preterm neonates who has had prior multiple intubations attempts and an air-leak (particularly a right-sided one), and radiographic evidence of feeding tube malposition, would likely improve the outcome of patients.

**Limitations of our study include:** Firstly, the study was retrospective, the accuracy largely depends on the completeness of documentation; and secondly, small numbers of patients with OP as esophageal perforation is rare. Further attempt to analyze larger group of patients would be required.

## Conclusion

Preterm neonates, particularly those born with Very Low Birth Weight (VLBW) are at risk of esophageal perforation. Preventive measures, having a high index of suspicion, prompt recognition, and conservative treatment has been shown in our experience and other case series to be successful in achieving resolution of OP and attainment of full enteral feeds, in the absence of concomitant risk factors of frank sepsis, mediastinitis, abscess formation and/or persistent air leaks.

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