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Strengthen Immunity

Scientific Innovation
Worldwide 1st to Launch

Similac HMO

3 years and up
pre-school milk

For healthcare professionals reference only
Innovative Interventions and Approaches for Pediatric Respiratory Problems

This issue brings up three very interesting articles related to paediatric pulmonology and critical care. Two of them bring up and share new ideas and experiences which are unique and tailored to develop the use of innovative lower cost models of health care in some very critical areas.

Interventions using flexible bronchoscopy have not been used as broadly and extensively among children as in adults. Limits to its use are largely due to lack of suitable size equipment and accessories, lack of skilled masters and lack of training in this field. The skills have developed rather patchily, are localised to few centres and there are few big size studies available. This was highlighted in a recent effort by the European Respiratory Society to formulate guidelines on the subject. In the US, most interventions in children are done either with rigid or a combination of rigid and flexible bronchoscopy with multi-disciplinary teams consisting of anaesthetist, ENT and paediatric respiratory physician. The federal regulations have also limited the expansion in this area. Soong from Taiwan has written a review article on paediatric interventional flexible bronchoscopy which brings up many new facets as he largely quotes from his own expertise. He brings to forth the experience in the relatively less charted areas of pediatric airway dilatation and stenting in a sizeable number of cases. Many of the techniques described, particularly use of a method to maintain respiration during the procedure (Soong’s Ventilation) are unique and not used elsewhere. Likewise, he discussed his technique of using short length thin scopes to guide the instruments into the paediatric airway. The paper is going to arouse a lot of interest for his extra-ordinary pioneering work and generate discussions beyond curiosity.

The use of heated humidified high flow oxygen therapy and its various variants have raised a lot of interest recently, as more and more units are using this for oxygenating sick babies who if not intervened in time have the potential to progress to ventilatory failure. The study from Thailand by Vareesunthorn and Preutthipan’s unit shares their experience with a lower cost modified high flow nasal cannula technique for providing oxygen therapy to bigger babies. The need for innovation and health-care cost-cutting goes beyond developing and resource-challenged societies and the present paper fills up that gap in information in the context of high flow oxygen therapy. They have made innovations to provide a simpler non-commercial method which has the potential to be replicated across other units in different countries.

Tuberculosis is a formidable disease which now is on the global agenda for disease control. This year saw an unprecedented effort, collaboration and partnership between multiple TB stakeholder leading to the adoption of the UN Political Declaration on TB on 26th September in New York, USA. As the work on stopping TB continues across countries, it is important to learn and share the clinical experiences so that the awareness about its myriad presentation is better understood and stays in focus. The present issue has a small study on extra-pulmonary tuberculosis from Indonesia documenting the presentation of the disease in various organ systems.

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Children with Pneumonia: A 3-year Retrospective Study PRCM; 2018. [In this issue].

9. Clinical Profiles and Outcome of Extra Pulmonary Tuberculosis in Children in Indonesia. PRCM; 2018. [In this issue].

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Pediatric interventional flexible bronchoscopy (IFB) procedures are difficult to standardize because of a lack of consensus across different countries. The current literature are scant with retrospective case series or case reports in single center only. The main aim of IFB is to keep an enough and patent central airway lumen. The prerequisites are secure environment, skillful technique, appropriate instruments, clear airway vision, and maintenance of cardiopulmonary status of patients. Noninvasive ventilation (NIV) with pharyngeal oxygen with intermittent nose-closure and abdomen-compression or Soong’s ventilation is the preferred method in the author’s center as it provides a simple and reliable ventilation support during IFB. Pulmonologists should be trained in basic IFB procedures such as tracheobronchial intubation, bronchoalveolar lavage, balloon dilatation, laser ablation, cryotherapy, or even stent placement and maintenance. Pulmonologists should achieve and maintain high skill levels during their career. There is a rapidly evolving IFB role for in the intensive care units (ICUs) because of critical and cardiopulmonary compromised patients. IFB procedures require intense training and a multidisciplinary approach for patient care. With developing technology, the role of IFB is destined to grow. The IFB modality of using short-length bronchoscopes, supported with a NIV and ICU facilities is a viable, instant, and effective management in pediatric patients. Successful IFB could result in rapid weaning of respiratory supports in ICU without the need for transport to the operation theater and more invasive procedure.

Keywords: Bronchoalveolar lavage, bronchoscopy, child
For more than two decades, the author has gradually developed and employed a simple, convenient, and less invasive IFB modality for children. The purpose of this article is to provide a review of the author’s personal practice.

**Sedation and Local Anesthesia**

Pediatric IFB is an invasive procedure and potential high risk, especially in cardiopulmonary compromised children. Therefore, vital signs of heart rate, respiration, and pulse oximetry should be monitored continuously as well as intermittent (or continuous) blood pressure monitoring throughout the whole procedure. If possible, the intensive care facilities may be a preferred place for performing pediatric IFB.

For achieving smooth and successful procedures of IFB, appropriate procedural sedation is necessary. It is accomplished with combination of various agents of sedatives, analgesics, or anesthetics. In the author’s pediatric bronchoscopy team, intravenous midazolam (0.3–0.5 mg/kg), ketamine (0.5–2.0 mg/kg), and atropine (0.01 mg/kg, maximum 0.4 mg) are recommended. Topical upper and lower airways anesthesia was achieved with 2% lidocaine. Additional dosages of above agents or even intravenous muscle relaxant (succinylcholine 1–2 mg/kg/dose) may also be used as needed to keep patient quiet, motionless, or to induce apnea at the critical moment of the procedures such as balloon inflating to deploy the stent, laser ablation at critical sites. During these iatrogenic apneic or critical periods, the following respiratory support should be optionally recommended.

**Respiratory Support**

During the IFB in children, the most common concern is that the FB and/or accomplished instruments themselves may obstruct the limited airway lumens and impair ventilation. In addition, intraluminal manipulation is also challenging particularly in those with cardiopulmonary compromise and anatomic abnormalities. A crucial element leading to success in performing IFB is to ensure adequate airway patency, oxygenation, ventilation, and circulation as well as keeping clear FB vision, when patients are under heavy sedation with possible drug-induced apnea.

In the author’s practice of preparation of FB, patient’s respiratory support could be provided by a novel noninvasive ventilation technique, pharyngeal oxygen with intermittent nose-close and abdomen-compression, or “Soong’s ventilation” [12,13] which has been used in this IFB team for more than 20 years. It provides both inspiration and expiration support by simple maneuver. Details of this technique were reported previously [12-14]. Briefly, a continuous, heated, and humidified pure oxygen flow (1.0 L/kg/min, maximal 10 L/min) is supplied through a nasopharyngeal catheter to fill the upper airway cavity. An optional maneuver of assist inspiration and expiration was performed as follows. (1) Infant’s mouth was firmly closed with the endoscopist’s dominant hand. (2) Inspiration was assisted by nose-closure accompanied with cricoid pressure. (3) Expiration was assisted by release of nose and cricoid maneuver with simultaneous abdomen-compression. The above assisted ventilation cycle was performed as needed at a rate of 5–20 cycles/min. Endoscopist performs both the FB and nose-closure (release) maneuver, whereas an assistant delivers the abdomen-compression (release). This method obviates the need for any artificial ventilation bag, mask, airway tube, or mechanical ventilator. There is no upper limit of age or body weight for the effectiveness of Soong’s ventilation. Contraindications of Soong’s ventilation include significant pharyngeal trauma or basal skull fracture.

Soong’s ventilation allows a less crowded upper airway in the absence of facemask and ETT that means more space for the FB and other intervention instruments. The endoscopist controls the rhythm and intensity of the ventilation to eliminate hypoxia and hypercarbia while simultaneously getting a more dynamic and comprehensive inspection of the airway. Additional advantage of using Soong’s ventilation is the optional expansion of both upper and low airway lumen with positive inspiratory pressure allowing a more accurate diagnosis of airway lesion, like laryngeal cleft, tracheal malacia or fistula. Previous piglet study [15] and case series [12,14,16-26] demonstrated that it could effectively support and rapidly correct hypoxia, hypercapnia, and bradycardia, even during complicated pediatric IFB procedures.

**Flexible Bronchoscopes and Interventions**

FB is more readily available than RB as well as providing a better dynamic inspection of the upper and lower airway. FB can be performed in the bedside with appropriate support. It is an indispensable tool for pre- and post-surgery evaluation. Many pulmonologists prefer to insert FB through a face mask, ETT, or laryngeal mask airway. However, these devices limit the agility of the FB, size of intervention instrument, and the visual field. The author also found it better to deploy accessories side by side with the endoscope, thus allowing a wider choice of instruments that might not pass through the working channel of pediatric bronchoscope [Figure 1]. [13,14]
In IFB, short working lengths (25 cm to 36 cm) scopes such as Olympus HYF-V, ENF-VQ, ENF-V2 and ENF-VT2, outer diameter range from 3.2 to 5.0 mm, with or without working channel, are preferred in small size children by the author. All FBs are inserted through the nostril except in those of severe nasal stenosis.

**Procedures of Pediatric Interventional Flexible Bronchoscopy**

Many pediatric IFB procedures have been reported [Table 1]. Currently, the majority of pediatric IFB are performed by pediatric pulmonologists or otolaryngologists who must have received proper training in the neonatal and pediatric intensive care as well as IFB techniques. This strategy has also been emphasized by Kohelet *et al.*[27]

### Flexible bronchoscopy-assisted airway intubation

Conventional airway intubation technique by direct laryngoscopy can be difficult if not impossible in situations that preclude the proper approach and exposure of the larynx or when there is a tracheal problem. In this scenario, FB-assisted intubation will be needed. Examples of such situations were listed in Table 2. FB-assisted intubation allows simultaneous examination of airway lumens. Under FB guidance, the tip of ETT is adjusted to avoid impinging on airway lesion, thus ensuring a patent ventilation pathway.

An appropriate outside diameter, from 2.2 to 5.0 mm, of FB may be used as a visual and introducing guide. The FB can be threaded through an, at least 1 mm larger, inner diameter ETT. Both outer surfaces of the endoscope and the ETT should be pre lubricated before doing insertion. The tip of FB should protrude beyond the ETT tip for correct directing. It is important to note that this assisted airway intubation could easily damage the FB due to lack of proper training.

### Endotracheal (bronchial) biopsy

The use of endobronchial biopsy forceps (or brush) through FB to get specimen in TB lumen is feasible for pediatric patients. The technical limitations of obtaining enough and usable samples through small working channels reduce the usefulness of this procedure. The largest study to date demonstrated the safety of this procedure.[28] This may have advantage over conventional bronchoalveolar lavage (BAL).[29] especially in the diagnosis of primary ciliary dyskinesia, tuberculosis, and granulomatous disorder in TB tree. It appears that neither significant bleeding nor pneumothorax is serious risk in this procedure.

### Foreign body retrieval

Airway foreign bodies in children often result in significant morbidity and life-threatening emergency that makes the early recognition and prompt retrieval essential. There is general agreement in published guidelines that bronchoscopy should always be performed in a child with a history of choking, even without respiratory symptoms and/or radiological findings.

### Conventional bronchoalveolar lavage

BAL is a diagnostic procedure used for recovering cellular and noncellular components of the epithelial lining fluid of the alveolar and bronchial airspaces. It usually is performed by injecting prewarmed sterile normal saline through a syringe into the working channel of a FB which has already been wedged into a target bronchus, irrigated, and then suctioned.

### Indications for diagnostic bronchoalveolar lavage

BAL is a diagnostic procedure used for recovering cellular and noncellular components of the epithelial lining fluid of the alveolar and bronchial airspaces. It usually is performed by injecting prewarmed sterile normal saline through a syringe into the working channel of a FB which has already been wedged into a target bronchus, irrigated, and then suctioned.

### Indications for diagnostic bronchoalveolar lavage

Conventionally, FB is mainly used for diagnostic purpose and RB for retrieval.[30,31] However, RB requires specialized facilities that may prevent timely management in emergencies and is not applicable for compromised upper airway, restricted cervical motion, and distal airway approach. In children with a history of choking, a preceding FB reduces the rate of negative RB.[32,33] There is growing evidence that FB can be used as both diagnosis and removal tool, either alone[17,18,22] or in combination with a RB. FB coupled with grasping forceps, wire baskets, or cryoprobe resulted in varying success rates, after securing the airway and ventilation. This modality can save time, labor, and medical cost. In difficult cases, when FB and RB retrievals failed, more invasive open surgical approach is needed.

### Table 1: Considering procedures for pediatric interventional flexible bronchoscopy

<table>
<thead>
<tr>
<th>Diagnostic Procedures</th>
<th>Therapeutic Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway inspection</td>
<td>for restoration of airway patency</td>
</tr>
<tr>
<td>Bronchoalveolar lavage</td>
<td>Scopy-assisted tracheal (or bronchial) intubation</td>
</tr>
<tr>
<td>Endotracheal (bronchial) biopsy</td>
<td>Control hemorrhage</td>
</tr>
<tr>
<td>Foreign body retrieval</td>
<td>Foreign body retrieval</td>
</tr>
<tr>
<td>Bronchoalveolar lavage</td>
<td>Oxygen therapy</td>
</tr>
<tr>
<td>Laser therapy</td>
<td>Cryotherapy</td>
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<tr>
<td>Cryotherapy</td>
<td>Atelectasis management</td>
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<tr>
<td>Atelectasis management</td>
<td>Bulloon dilatation plasty</td>
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<tr>
<td>Balloon dilatation plasty</td>
<td>Stent (metal) placement, plasty, and retrieval</td>
</tr>
</tbody>
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### Table 2: Indications for flexible bronchoscopy-assisted airway intubation

<table>
<thead>
<tr>
<th>Indications for diagnostic bronchoalveolar lavage</th>
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</thead>
<tbody>
<tr>
<td>Upper airway</td>
</tr>
<tr>
<td>Difficult approach</td>
</tr>
<tr>
<td>Facial trauma</td>
</tr>
<tr>
<td>Mandibulofacial dysostosis</td>
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<tr>
<td>Microstomia</td>
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<tr>
<td>Intra-oral tumor/mass</td>
</tr>
<tr>
<td>Temporomandibular ankylloses</td>
</tr>
<tr>
<td>Limited cervical extension</td>
</tr>
<tr>
<td>Massive bleeding/trauma</td>
</tr>
<tr>
<td>Larynx</td>
</tr>
<tr>
<td>Mass/tumor</td>
</tr>
<tr>
<td>Stenosis</td>
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<td>Distortion</td>
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</table>

### Table 3: Indications for flexible bronchoscopy-assisted airway intubation

<table>
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<tr>
<th>Indications for diagnostic bronchoalveolar lavage</th>
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<tbody>
<tr>
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<td>Difficult approach</td>
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<tr>
<td>Facial trauma</td>
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<tr>
<td>Mandibulofacial dysostosis</td>
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<td>Mass/tumor</td>
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<td>Stenosis</td>
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<td>Distortion</td>
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### Table 4: Indications for flexible bronchoscopy-assisted airway intubation

<table>
<thead>
<tr>
<th>Indications for diagnostic bronchoalveolar lavage</th>
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<tbody>
<tr>
<td>Bronchial obstruction</td>
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<tr>
<td>Foreign body retrieval</td>
</tr>
<tr>
<td>Bronchoalveolar lavage</td>
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<tr>
<td>Laser therapy</td>
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<tr>
<td>Cryotherapy</td>
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<tr>
<td>Atelectasis management</td>
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<tr>
<td>Balloon dilatation plasty</td>
</tr>
<tr>
<td>Stent (metal) placement, plasty, and retrieval</td>
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</table>
into a sputum trap and sent for studies. The targeted lobe depends on the radiological or endoscopic information. The amount of lavage sterile saline is usually 2–4 aliquots of equal volume (10 ml/aliquot in <6 years of age, 20 ml/aliquot in >6 years of age). Others suggest 1.0 ml/kg body weight for up to 20 kg and 20 ml/aliquot for heavier children. After each instillation, enough air must be injected to empty the dead space of the working channel. In general, BAL is considered acceptable if more than 40% of the total instilled saline is recovered and the lavage fluid contains epithelial cells. The residual saline is absorbed by the lymphatics.

The major application of BAL is the diagnosis of TB infection (particular in immunocompromised children), chronic interstitial pulmonary disease, chronic aspiration, and therapeutic and research applications. BAL has also a major role in the mucus plug removal and alveolar proteinosis. Children with persistent and massive atelectasis can be successfully managed with selective lavage with saline, mucolytics, or DNase. The worldwide increase in the use of BAL in children has established its role in diagnosis, therapy, follow-up of childhood lung diseases, and research.

BAL, in general, is a well-tolerated and safe procedure. Cough, transitory wheeze, and pulmonary infiltrates might occur and usually resolve within 24 h. Severe bleeding, TB perforation, mediastinal emphysema, pneumothorax, and cardiac arrest are extremely rare. Contraindications to the BAL include bleeding disorders, severe hemoptysis, and severe hypoxemia that persist despite oxygen supplement.

Laser therapy (LT)
Lasers produce a beam of monochromatic, phased, and collimated light that can induce tissue vaporization, coagulation, hemostasis, and necrosis. Biological effects depend on the wavelength emitted by the laser source. There are several types of lasers that are currently used in pediatric IFB: carbon dioxide, neodymium: yttrium-aluminum-garnet, potassium-titanium-phosphate, and diode lasers. Among them, the diode laser is most suitable in pediatric upper and TB airways. A low power range (5–6 W) can transmit through a thin (200–600 um) flexible fiber through the inner channel (>1.0 mm) of FB.

FB-LT should be performed under appropriate procedural sedation, with or without muscle relaxation, to avoid inaccurate targeting due to movement. There is general agreement that specific safety measures must be addressed during the procedure; protective glasses are required; fractional inspired oxygen must be <0.5 before firing the laser beam to diminish the risk of airway ignition; smoke should be suctioned out from the airway; and any flammable material in the operative field should be protected to avoid ignition. Despite the limited information available, indications for FB-LT procedures in the pediatric airway appear to be increasing such as debulking the TB lumen lesion (tumor or cyst), dislodging incarcerated foreign bodies and laryngoplasty for laryngomalacia. There are no well-established criteria in pediatric yet, and each procedure should be considered on an individual basis. After the LT debulking, balloon dilation plasty is usually needed to optimize the size of the lumen.

Cryotherapy
Cryotherapy is an evolving diagnostic and therapeutic tool used during FB. The cryogen is liquid carbon dioxide or nitrogen. Through rapid freeze-thaw cycles, cryotherapy causes cell death and tissue necrosis or adherence that can be approached through the FB. It is used for removal of benign and malignant tumors, as well as relieve airway stenosis. In addition, bronchoscopic cryotherapy causes little trauma.

An ice ball is generated by inserting the freezing probe into or just touch the lesion, and then, the crystallized lesion can be separated and removed from the airway. This procedure could be repeated several times for debulking. Due to the scanty experience reported, there are no well-established indications in children. It has been applied to release TB stenosis and atelectasis and remove foreign body, tuberculosis, and TB tumor. For endobronchial tuberculosis, performing FB cryotherapy at the proliferative phase of granulation tissue was often effective to reduce the formation of cicatricial stenosis.

For TB stenosis, local tissue reaction and swelling can cause transient lumen narrowing leading to dyspnea. Therefore, temporary tracheal intubation for 4–6 days may be indicated after cryotherapy (or LT). Contraindications include the external compression of airway and tracheobronchomalacia.

Atelectasis management
Both persistent and recurrent atelectasis are important indications for diagnostic FB. Depending on the findings, further targeted actions may be undertaken, such as suctioning, foreign body extraction, sampling materials, and other more specific procedures. An attempt to re-inflate the atelectatic lung parenchyma coupled with repeated saline lavages is considered standard practice. The inflation pressure should be closely monitoring to be < 40 cmH2O. One-lung ventilation or endobronchial blocking is another technique, using an appropriate size balloon catheter to block the normal side bronchus and continue ventilating the atelectatic lung, with or without ETT, may to help re-open the atelectasis.

In refractory atelectasis, various drug applications have been tried through FB working channel. Surfactant administration was reported to improve ventilation by re-aeration of atelectatic regions and help wean victim from mechanical ventilation. Similarly, FB-administered recombinant human DNase was used in cystic fibrosis patients, and noncystic fibrosis patients, and premature neonates, with variable success.

Balloon dilatation plasty (BDP)
The FB worked as a visual guide with an angioplasty balloon catheter of appropriate dimension. While using thin FB, the balloon catheter can placed in the TB working channel. The balloon catheter was prestiffed with a guidewire inside for easy manipulation. The method is as followed: a balloon catheter...
is inserted, covered the stenotic segment, and is gradually inflated with saline. High-pressure levels are delivered to the maximum balloon capacity, by a syringe-pump pressure inflator, and maintained for 10–30 s (pneumonic dilatation). Then, deflated the balloon and withdrawn the balloon catheter out of airway. In this intervention, the balloon diameter could be in increments from 4 to 10 mm (age dependent) gradually. Repeat doing these balloon inflation and deflation for several times in one session of BDP. Cicatricial process may occur with scar formation, relapse is frequently observed, and therefore, multiple interventions may be required.

In our published paper of an 11-year IFB in small infants of less than 5 kg,[25] 38 BDP for corrected lumen narrowing which included 21 tracheal, 9 bronchial, 5 nasal tract, and 3 choanal atresia lesions. Twenty-four BDPs were used for simultaneous estimation and expansion of the dimension of target TB lumens, an essential step before stent placement. Ten BDPs were performed for the repair and re-expansion of distorted and loose stents. Five BDPs were done to compress the TB granulomas and restore adequate lumen patency. Three BDPs were for assisting the stent retrieval (see below).

### Stent placement, plasty, and retrieval
Airway stenting in pediatric patients is relatively recent and follows the experience of the adult. Nevertheless, in contrast to adults, there are basic differences such as the benign nature of most lesions, the small size lumens, and the considerable luminal growth of the pediatric airway. Stent implantation for benign airway disease can be useful, either for temporary luminal stabilization after airway surgery or for relief of severe malacia or stenosis, when all other medical and surgical options have failed or are contraindicated. These specific features raise the issues of the precise role of TB stenting in children.

There are four main categories of stent currently being used: metallic, plastic, hybrid, and biodegradable. Each has its own advantages and drawbacks, so the ideal stent is not yet available.

- **Self-expanding metal stents**: They are made of nitinol, a titanium-based alloy with shape memory. They are packaged as coils enclosed into a dedicated introducer sheath. While introducing into target TB lumen, stents are released by pulling back the external sheath[43]
- **Balloon-expandable metal stents**: They are made of stainless steel tubular meshes. They are prethreaded over balloon catheters and can be expanded to a desired diameter by inflating the balloon. These stents can be repaired and further expanded in the follow-up periods, once indicated[23,46]
- **Covered metal stents**: They are made of nitinol coils covered with thin polymer sheaths. They are deployed the same way as with uncovered metal stents, either by balloon catheters or by introducer sheaths.

In experienced hands, the placement of TB metallic stents is technically feasible, with little directly procedure-related morbidity or mortality.[14,23] However, subsequent stent-related complications may be encountered frequently and their management requires considerable expertise, which must be available at special centers. Although the usefulness of stents appears to be well established in children,[47,48] available data do not allow a firm conclusion in defined clinical circumstances. Hence, the US Food and Drug Administration had issued a black box warning against the implantation of metal stents in benign conditions due to the difficulty of removal and serious complications.[49,51]

Despite increasing experience with stenting, definite clinical criteria for pediatric use are yet to be established. Even so, there seems to be a basic general agreement that stents may play a role in particular clinical settings where there are no other therapeutic options. The pediatric literature on airway stents is still limited. If stents are used, comprehensive information must be given to parents/patients about their possible benefits and risks to allow informed consent.

In our published data about the balloon-expandable metal stents in pediatric patients,[23] which was so far the largest case series of 146 stents in 87 children and longest surveillance period of 20 years. The stent indication was severe TB narrowing (stenosis or malacia) resulting in prolonged ETT intubation and ventilator dependence. Both BDP and/or LT of IFB did not improve condition, and the patients still suffered from frequent life-threatening episodes. Stent placement was considered as the last option before more invasive surgical interventions. Four stents were placed after sliding tracheoplasty due to persistent lumen collapse (as mentioned above). All implanted stents were of metallic mesh type (IntraTherapeutics Inc., MN 55112, USA; or Boston Scientific Corporation, Marlborough, MA 01752, USA) which could be further expanded by technique of BDP to accommodate the growing lumens. These stent-associated IFB were all performed with a short-length FB of out diameter 3.2 mm to 5.0 mm. The smallest body weight was 2.3 kg and the youngest was 10 days old infant. Three carinal stents were placed in three growing extremes.

Metallic stent can be retrieved.[23] This required inserting a deflated balloon catheter underneath the target stent, then inflating the balloon to well separate and detach the stent from the underlying airway mucosa. Finally, the detached stent was grasped and retrieved with the aid of RB and a powerful forceps.

## Benefit of Pediatric Interventional Flexible Bronchoscopy
As described above, IFB can safely be performed immediately after the FB diagnosis. The combined diagnostic and therapeutic IFB in the same session actually decreased waiting time, medical expense, avoided more invasive interventions, and their associated iatrogenic damages. These benefits have been demonstrated and reported in many our previous reports.[14-26]

### Short-term efficacy of weaning respiratory supports
In our previous 11-year report in body weight less than 5 kg infants,[25] IFB resulted in early weaning of
respiratory support. In this report, original, there were 67 ETT with PPV supports, which immediately decreased to 22 (45 extubation) after IFB and further down to 11 in 7 days. In 121 infants who initially required nasal prongs PPV support, 62 infants weaned off within 7 days after IFB management. In a total of 188 PPV before IFB, 118 (62.8%) were successfully weaned within 7 days after IFB. The success of weaning PPV was mostly attributed to the three IFB procedures of LT (69.8%), BDP (47.5%), and stent implantation (75.0%). Finally, all survivors were able to be weaned to spontaneous breathing in room air.

**Conclusion**

In the last decade, IFB exhibits promise in pediatric airway practice. Our IFB modality of using short-length FB coupled with Soong’s ventilation done in ICU settings may be safe, feasible, timely, and effective. In children, IFB facilitates weaning of respiratory support and avoidance of more invasive procedures such as RB or open surgery.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**


Modified High-Flow Nasal Cannula in Young Children with Pneumonia: A 3-year Retrospective Study

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Abstract

Objectives: We aimed to report our 3-year experience in modified HFNC (MHFNC) usage in young children with community-acquired pneumonia in infectious diseases ward and to identify factors associated with MHFNC failure. Materials and Methods: A retrospective, cross-sectional study of pediatric patients, aged <5 years, with community-acquired pneumonia, who were treated with MHFNC at infectious diseases from August 2012 to December 2015 were recruited. MHFNC failure was defined as a need for further respiratory support within 48 h after initiating MHFNC. Patients: Ninety-nine patients with community-acquired pneumonia were included in this study. Setting: A tertiary care hospital. Measurements and Results: Ninety-nine children (median age of 14 months, body weight 8.6 ± 3.1 kg) were included. Ninety-two children (93%) were successfully treated with MHFNC and only seven (7%) were in the failure group. The maximal flow was 3 L/kg/min. Lower oxygen saturation (SpO₂)/fraction of inspired oxygen (FiO₂) ratio (<264) and higher FiO₂ requirement were found to be associated with failure. Maximum FiO₂ requirement >0.5 had high odds ratios (22.25) to develop MHFNC failure. No serious complication from MHFNC was found. Conclusions: MHFNC is a practical respiratory support in young children with pneumonia. SpO₂/FiO₂ ratio (<264) and FiO₂ requirement >0.5 is a risk factor for MHFNC failure.

Keywords: High-flow nasal cannula, high-flow nasal cannula failure, hypoxemia, noninvasive ventilation, pneumonia

INTRODUCTION

High-flow nasal cannula (HFNC) is a relatively new respiratory support modality increasingly used in children and adults. HFNC was reported to be helpful in newborns with respiratory distress compared to continuous positive airway pressure (CPAP), upper and lower respiratory tract diseases, and during bronchoscopic procedures. This device provides a mixture flow of air and oxygen, which are heated and humidified, and thus reduce mucosal inflammation and injury. At present, there is no universal consensus on the definition of HFNC. Some authors define HFNC when flow rates are higher than 2 liter per minute (LPM) and 6 LPM in infants and children, respectively, or the gas flow rate exceed patients’ inspiratory flow demand.

Previous studies have proposed the mechanisms of action of HFNC including accurate delivery of up to 100% oxygen, minimizing rebreathing of carbon dioxide, maintaining positive airway pressure during the respiratory cycle, especially in the upper airway, and optimizing mucociliary clearance by heated humidified gas. Adverse effects include noise emissions and air leak syndrome (pneumothorax and pneumomediastinum) and its association with delayed intubation. The commercial HFNC is noted to be costly and may not be widely available. Our team of Pediatric Pulmonary Division at Ramathibodi Hospital has developed a modified HFNC (MHFNC) which cost less than half of the commercial HFNC. After introducing MHFNC in May 2011, these devices have been increasingly used in children with various respiratory problems. We conducted this retrospective study to report our experience in using MHFNC in children with community-acquired pneumonia at Ramathibodi Hospital from August 2012 to December 2015. And the second objective was to identify factors associated with MHFNC failure.
Materials and Methods

Study design
This was a retrospective study conducted in a tertiary care center and was approved by the Ethics Committee of Ramathibodi Hospital, Mahidol University.

Population
Medical records of all patients, aged <5 years, admitted to a pediatric infectious diseases ward with a diagnosis of community-acquired pneumonia and treated with MHFNC from August 2012 to December 2015 were evaluated. Patients, who were previously treated with HFNC at home or other wards and whose medical records could not be obtained, were excluded. Patients’ data were extracted from the electronic medical record (EMR).

Modified high-flow nasal cannula device
MHFNC device comprises oxygen and air flow from the pipelines, a heated humidifier (MR850, Fisher and Paykel Healthcare®), a single-heated breathing circuit, and a shortened standard oxygen nasal cannula as shown in Figure 1. Respiratory nurses prepared MHFNC equipment in advance for use in the ward. Initiation of MHFNC was decided by the residents on duty. The size of the cannula depended on the nostrils. The ratio of cannula to nostril diameters should not exceed 0.7. This would allow leakage of excessive gas flow in order to prevent air leak syndrome. To increase humidity production and loosen secretion, the temperature of the heated humidifier was adjusted clinically by nurses at bedside, that is, temperature mode was adjusted to mask mode if there were droplets observed in the connector between the corrugated tube and nasal cannula and to endotracheal mode if there was no mist in the connector.

Patient monitoring
Heart rate, respiratory rate, oxygen saturation, and respiratory condition of the patients were routinely monitored. Vital signs were recorded at the patient’s bedside form every 15 min until stable. Certainly, bedside nurse record forms were not scanned into EMR, so we could not obtain these parameters for statistical analysis. The vital signs recorded in EMR were those at 4 h interval before and after MHFNC was commenced.

Failure of modified high-flow nasal cannula treatment
MHFNC failure was defined as a need for further respiratory support within 48 h after initiating MHFNC. Escalation of respiratory support was decided by on service residents and staffs. Other respiratory support included noninvasive and invasive mechanical ventilation.

Oxygen saturation/fraction of inspired oxygen ratio
SpO₂/fraction of inspired oxygen (FiO₂) ratio (SF ratio) was the ratio of oxygen saturation and fraction of inspired oxygen which reflects severity of hypoxemia. SF ratio that is ≤264 is alternatively used as a parameter for diagnosis of pediatric acute respiratory distress syndrome (ARDS) when PaO₂ is not available. SF ratio was found to be one of the indicators of early noninvasive ventilation failure in children.[13,14]

Data gathering and outcomes
Data collection included age, sex, weight, height, underlying medical conditions (bronchopulmonary dysplasia (BPD) or chronic lung diseases, congenital heart diseases, liver diseases, neurologic diseases, history of prematurity), supplemental oxygen requirements prior to, initial and maximum total flow rate, initial and maximum total flow rate per kg, initial and maximum FiO₂, respiratory viral study results, initial white blood cell count, antibiotics used, initial oxygen saturation (SpO₂), initial heart rate and respiratory rate, heart rate and respiratory rate 4 h after MHFNC initiation, and length of stay (LOS).

Initial respiratory rate was classified to more than or less than 90th percentile for age.[15] Initial SpO₂ and FiO₂ were calculated to yield the SF ratio. Moreover, the ratios were later classified to more than or less than 264 which was the cutoff value used in pediatric ARDS criteria.[12] In the MHFNC failure group, we collected additional information including causes of MHFNC failure, types of respiratory support needed after MHFNC failure, and time in hours to MHFNC failure. Arterial blood gases were not routinely checked and therefore were not included in analysis.

Statistical analysis
All data are expressed as median (interquartile range), mean ± standard deviation (minimum, maximum), or number (percentage). Categorical variables were analyzed with a Chi-square test. Continuous parametric variables were compared using two-sample t-test and nonparametric variables were compared using Mann–Whitney test. Variables that were significantly different between success and failure groups were enter into logistic regression model to determine odds ratios (ORs) and 95% confidence intervals (95% CI) for predicting failure of therapy. For all analyses, P < 0.05 was considered as statistical significance. All data analyses were performed using SPSS Statistical software (version 17.0; SPSS, Chicago, IL, USA).

Figure 1: Drawing illustration of our modified high-flow nasal cannula.
RESULTS

One hundred and six patients met the inclusion criteria. Seven patients were excluded from the study because four patients’ medical records were not found in EMR and the other three patients had been treated with home HFNC. Therefore, 99 patients were included in this study.

Baseline characteristics of all 99 patients were presented in Table 1. There was a male predominance (60%). Patients’ age ranged from 8 to 26 months with mean age of 14 months old. Mean body weight was 9 kg, ranging from 2 to 20 kg. Most patients had no underlying medical conditions and no viral study done. Eighty-eight percent of patients needed low-flow oxygen nasal cannula before MHFNC therapy. There was a wide range of SF ratio (210-350) with mean value of 280. Half of the patients had SF ratio ≤264. MHFNC settings were showed in Table 2. The mean initial flow rate was 1.1 ± 0.3 L/kg/min which was increased later to 1.4 ± 0.4 L/kg/min. Mean initial FiO2 was 0.37 ± 0.08 which was later increased to 0.39 ± 0.09.

No major complications from MHFNC were reported. After using MHFNC, 92 of 99 patients (93%) clinically improved and were classified as the success group and 7 (7%) deteriorated and were classified as the failure group. The causes of MHFNC failure were progression of pneumonia (n = 5), excessive secretion (n = 1), and cardiac failure (n = 1). Furthermore, 6 of 7 were intubated after MHFNC failure. The time from starting MHFNC to stepping up to other respiratory support for these seven patients was shown in Figure 2.

Demographic, laboratory data, SF ratio, initial oxygen therapy, and respiratory rate of both success and failure groups were shown in Table 3. There were no differences between both groups for age, sex, body weight, height, and underlying diseases. More than half of the patients did not have viral study results. Positive viral studies, baseline respiratory rate > 90th percentile for age, initial white blood cell count, and antibiotics used did not differ between the two groups. SF ratio, SF ratio <264, and LOS >7 days were the variables that showed significant differences between success and failure groups. In respect to vital signs change over time after MHFNC initiation, there were no significant changes in heart rate and respiratory rate at the first 4 h when comparing between groups [Table 4].

Gas flow rate and FiO2 used in both success and failure group were presented in Table 5. The mean values of initial and maximum flow rate were 9 L/min (1–1.5 L/kg/min) and 11 L/min (1.3–1.5 L/kg/min), respectively, which did not differ between groups. Mean initial and maximum FiO2 of the failure group were significantly higher than the success group, P = 0.001 and <0.001, respectively. In addition, more

<table>
<thead>
<tr>
<th>Table 1: Baseline characteristics of all patients</th>
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<tr>
<td>Characteristics</td>
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<tr>
<td>Male, n (%)</td>
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<tr>
<td>Age (months)</td>
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<tr>
<td>Body weight (kg)</td>
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<td>Height (cm)</td>
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<tr>
<td>Underlying diseases, n (%)</td>
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<tr>
<td>None</td>
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<tr>
<td>Neurologic diseases</td>
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<tr>
<td>Congenital heart diseases</td>
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<tr>
<td>History of prematurity</td>
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<tr>
<td>BPD and CLD</td>
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<td>Liver diseases</td>
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<tr>
<td>Viral studies, n (%)</td>
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<tr>
<td>Not done</td>
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<tr>
<td>Positive</td>
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<td>Negative</td>
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<tr>
<td>Oxygen therapy before MHFNC, n (%)</td>
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<td>Supplemental oxygen</td>
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<tr>
<td>Room air</td>
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<tr>
<td>Initial RR &gt;P90th by age, n (%)</td>
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<tr>
<td>SpO2/FiO2</td>
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<tr>
<td>SpO2/FiO2≤264, n (%)</td>
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<td>Initial WBC/mm³</td>
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<tr>
<td>Antibiotics usage, n (%)</td>
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<td>LOS (days)</td>
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</table>

Age are expressed in median (IQR), body weight, and height in mean±SD (minimum–maximum), SpO2/FiO2 and initial WBC in mean±SD and other variables are in number of patients (%). BPD: Bronchopulmonary dysplasia; CLD: Chronic lung disease; RR: Respiratory rate; WBC: White blood cell; MHFNC: Modified high-flow nasal cannula; SD: Standard deviation; IQR: Interquartile range; LOS: Length of stay

<table>
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<th>Table 2: Modified high-flow nasal cannula settings</th>
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<tr>
<td>Gas flow parameter</td>
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<tr>
<td>Initial absolute total flow (LPM)</td>
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<tr>
<td>Initial total flow per kg (LPM/kg)</td>
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<tr>
<td>Initial FiO2</td>
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<tr>
<td>Maximum absolute total flow (LPM)</td>
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<td>Maximum total flow per kg (LPM/kg)</td>
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<td>Maximum FiO2</td>
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<tr>
<td>Escalation of flow in first 2 h, n (%)</td>
</tr>
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</table>

All flow rates and FiO2 are expressed in mean±SD (minimum–maximum) and other variables are in number of patients (%). SD: Standard deviation
patients in the failure groups required maximum FiO\textsubscript{2} >0.5, \(P<0.001\). Logistic regression analysis showed that maximum FiO\textsubscript{2} >0.5 was strongly associated with increased risk of MHFNC failure (OR, 22.25; 95% CI, 3.37–146.99; \(P=0.01\)).

**DISCUSSION**

Our current study findings suggested that MHFNC is a useful respiratory therapy in young children with community-acquired pneumonia with high success rate of 97%. No significant complications such as air-leak syndrome were demonstrated. Our success rate was comparable to previous studies that reported the use of commercial HFNC in children with respiratory distress from other conditions.\[10,16-19\]. Air-leak syndrome was not found in our patients possibly due to our practice protocol to choose the size of nasal prong not larger than 0.7 of nare diameter. This provides the space for excessive gas flow to leak to the atmosphere and prevent barotrauma to the lungs. Another benefit of this space is to allow patients to entrain more air from atmosphere when gas flow from HFNC system is less than patients’ inspiratory flow rate, especially when crying.

This study confirmed that the MHFNC could be used safely and effectively in children with pneumonia starting at the age of 1 month to 54 months, weighing 2 kg to 20 kg, with various underlying diseases including BPD, congenital heart diseases, neurologic diseases, and liver diseases. Almost all patients required supplemental oxygen before MHFNC application and more than half of the patients had high initial respiratory rate (>90th percentile of age) and half of the patients had SpO\textsubscript{2}/FiO\textsubscript{2} ratio <264 which indicated severe hypoxemia secondary to parenchymal lung injury from pneumonia.

The optimum gas flow rate for each patient was adjusted according to clinical signs and symptoms at bed side. We found that with MHFNC most patients in our study required absolute gas flow rate <2 L/kg/min as recommended by a number of standard guidelines of commercial HFNC.\[20-22\] Another component that makes MHFNC differs from commercial HFNC is that a blender is not incorporated in the system. Air and oxygen from wall pipeline are directly connected to a heated humidifier chamber as shown in Figure 1. FiO\textsubscript{2} can be manually calculated. To remember easily, whenever oxygen flow rate is equal to air flow rate, FiO\textsubscript{2} will always be 0.6, which is a cutoff value of oxygen toxicity. Humidification is also necessary to facilitate secretion clearance to prevent mucus plugging and remove purulent material caused by pneumonia. We set the humidifier on 37°C invasive setting to maintain optimal humidity. However, when water droplets or condensation accumulate in the nasal cannula, the humidifier temperature should be decreased temporarily.

We found that oxygenation status assessed by SpO\textsubscript{2}/FiO\textsubscript{2} ratio, initial FiO\textsubscript{2}, and maximum FiO\textsubscript{2} requirement were significantly associated with MHFNC failure. Maximum FiO\textsubscript{2} requirement >0.5 had significantly higher odds ratios of 22.25 to develop MHFNC failure. Furthermore, more than half of the patients in the failure group got worsen and needed ventilatory support within the first 12 h. The oxygenation deterioration was most likely related to progression of pneumonia which was found to be the most common etiology of the failure group. Therefore, MHFNC should be used with caution in patients with low baseline SpO\textsubscript{2}/FiO\textsubscript{2} ratio and FiO\textsubscript{2} to >0.5 since these are significant predictors identified for MHFNC failure. Close monitoring and clinical observation are important in this group of patients in order to early detect HFNC failure, so that intubation would not be delayed. Previous studies have showed predictors of HFNC failure in children to be

\begin{table}
\centering
\caption{Comparison of baseline characteristics between success and failure groups}  
\begin{tabular}{|l|c|c|c|}
\hline
Characteristics & \textbf{Success (\(n=92\))} & \textbf{Failure (\(n=7\))} & \textbf{\(P\)} \\
\hline
\textbf{Male, \(n\)} & 55 (60) & 3 (43) & 0.381 \\
\textbf{Age (months)} & 14 (8-26) & 11 (6-24) & 0.424 \\
\textbf{Body weight (kg)} & 8.7±3.1 & 8.7±3.1 & 0.949 \\
\textbf{Height (cm)} & 74.3±12.9 & 72±10.1 & 0.671 \\
\textbf{Underlying diseases, \(n\)} & & & \\
\textbf{None} & 55 (60) & 3 (43) & 0.381 \\
\textbf{Neurologic diseases} & 17 (19) & 1 (14) & 0.782 \\
\textbf{Congenital heart diseases} & 14 (15) & 3 (43) & 0.062 \\
\textbf{History of prematurity} & 13 (14) & 4 (4) & 0.286 \\
\textbf{BPD and CLD} & 9 (10) & 1 (14) & 0.703 \\
\textbf{Liver diseases} & 4 (4) & 0 & 0.573 \\
\textbf{Viral studies, \(n\)} & & & \\
\textbf{Not done} & 60 (65) & 4 (57) & 0.460 \\
\textbf{Positive} & 27 (30) & 3 (43) & 0.381 \\
\textbf{Negative} & 5 (5) & 0 & \\
\textbf{Oxygen therapy before MHFNC, \(n\)} & & & \\
\textbf{Supplemental oxygen} & 80 (87) & 7 (100) & 0.308 \\
\textbf{Room air} & 12 (13) & 0 & \\
\textbf{Initial RR >P90th by age, \(n\)} & 51 (55) & 4 (57) & 0.955 \\
\textbf{SpO2/FiO2} & 285±70.7 & 217±49.9 & 0.015* \\
\textbf{SpO2/FiO2 \(\leq 264, n\)} & 41 (45) & 7 (100) & 0.066* \\
\textbf{Initial WBC/mm\textsuperscript{3}} & 13,127±5,600 & 13,557±5,157 & 0.844 \\
\textbf{Antibiotics usage, \(n\)} & 61 (66) & 3 (43) & 0.211 \\
\textbf{LOS >7 days, \(n\)} & 54 (59) & 7 (100) & 0.035* \\
\hline
\end{tabular}
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\begin{table}
\centering
\caption{Changes in heart rate and respiratory rate at 4 h after starting modified high-flow nasal cannula}  
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Variables} & \textbf{Success (\(n=92\))} & \textbf{Failure (\(n=7\))} & \textbf{\(P\)} \\
\hline
\textbf{\% decrease in heart rate} & 44 (48) & 2 (29) & 0.325 \\
\textbf{\% increase in RR} & 39 (42) & 1 (14) & 0.138 \\
\hline
\end{tabular}
\label{tab:hr}
\end{table}
Thoracoabdominal asynchrony, higher PRISM III score, complications occurred. The strong predictor of MHFNC also much less treatment cost. No major and life-threatening children with pneumonia. It has not only low failure rate but concLusIons treatment, especially in low-income countries. At our hospital, In our opinion, MHFNC is the most reasonable choice of the regular commercial HFNC that is available in the market. Our MHFNC system can be setup without difficulties in pipelines. The cost of treatment by MHFNC is less than half of any hospitals that have heated humidifiers, air, and oxygen

Our MHFNC system can be setup without difficulties in any hospitals that have heated humidifiers, air, and oxygen pipelines. The cost of treatment by MHFNC is less than half of the regular commercial HFNC that is available in the market. In our opinion, MHFNC is the most reasonable choice of treatment, especially in low-income countries. At our hospital, MHFNC has been used satisfactorily in various causes of respiratory distress such as pneumonia, bronchiolitis, asthma, croup, postextubation stridor, and tracheobronchomalacia. Nursing care for patients being on MHFNC is similar to commercial HFNC.[22] Insertion of nasogastric tube is needed if the patient develops abdominal distension. In such case, the nasogastric tube is aspirated for air 2–4 hourly. Some children can be fed orally if they do not have breathing difficulty or abdominal distension. Nose care is vital to maintain passageway of high-flow gas which comprises gentle nose suction to remove secretion obstruction and securing nasal prongs to avoid pressure sore to nares.

This retrospective study was limited to community-acquired pneumonia; therefore, our finding might not be generalized to other respiratory disease.

Moreover, arterial blood gases, especially CO₂ were not available for analysis. The study used MHFNC, not commercial HFNC. Therefore, the efficacy of both devices could not be compared.

Conclusions
MHFNC is a useful and practical respiratory support in young children with pneumonia. It has not only low failure rate but also much less treatment cost. No major and life-threatening complications occurred. The strong predictor of MHFNC failure identified in this study was maximum FiO₂ >0.5 which may reflect progression of pneumonia. Close monitoring of respiratory clinical status is essential, especially within the first 12 h after initiation of MHFNC.

Acknowledgments
The authors would like to thank Thianchai Bunnalai, MD, for his creative idea on MHFNC; Panida Srisan, MD, for her suggestion; Nattachai Anantasit, MD, for his helpful advices; Umapon Udomsupayakul, for her statistical analysis advices; Chula Kooanantkul, MD., for his excellent statistic analysis consultant; and Chuenarom Tharawas, for her beautiful drawing illustration.

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Conflicts of interest
There are no conflicts of interest.

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Clinical Profile and Outcome of Extrapulmonary Tuberculosis in Children in Indonesia

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Abstract

Context: Tuberculosis (TB) is a significant problem among children in Indonesia. While pulmonary TB has been widely reported, information on extrapulmonary TB (EPTB) among children in Indonesia has not been well documented. Aims: The aim of this study is to document demographic and clinical characteristics and outcome of EPTB in children. Settings and Design: A retrospective study was conducted in Dr. Sardjito Hospital, Yogyakarta, Indonesia. Subjects and Methods: Medical records were reviewed for all children aged younger than 18 years diagnosed with EPTB and admitted to this hospital between 2009 and 2015. Results: Fifty-three patients with EPTB were admitted to the hospital during the study period. EPTB was more common in children aged >5 years, with median (interquartile range) age of presentation at 12.5 years (4.1–14.7 years). Major presenting symptoms were fever (72%), cough (55%), and weight loss (38%). Common types of EPTB were meningitis (28%), miliary TB (23%), and osteoarthritis (20%). The diagnosis was confirmed by either acid-fast bacilli smear or GeneXpert MTB/rifampicin (RIF) in 13 patients. Evidence of TB infection was documented in 26% of children with positive result of tuberculin skin test. Mycobacterium TB was detected by GeneXpert MTB/RIF in 23% of children. The mortality rate was 19% which mostly occured in children with meningitis (60%). Conclusion: EPTB was commonly seen in older children, and tuberculous meningitis was both the most common type and cause of death of EPTB in our setting.

Keywords: Characteristic, child, extrapulmonary tuberculosis, outcome

INTRODUCTION

Indonesia ranks the second among countries with high burden of tuberculosis (TB) in 2016 with incidence of 391/100,000 population.[1] While data on pulmonary TB have been widely reported, information on extrapulmonary TB (EPTB) among children in Indonesia has not been well documented. The impact of EPTB is greatest among young children and immunocompromised individuals who tend to develop more severe extrapulmonary disease, especially meningitis and miliary TB.[2-3]

The diagnosis of EPTB is confirmed by identification of Mycobacterium tuberculosis in the specimen through Ziehl–Neelsen staining or culture in Loewenstein–Jensen media. This becomes problematic in children because invasive procedure is needed to obtain the specimen. In the absence of microbiology confirmation, clinical, laboratory, radiological, or histopathological evidence can be used to diagnose EPTB. Nevertheless, this is also often difficult, since the early presentation of EPTB is commonly nonspecific, tuberculin skin test mostly negative, and chest X-ray nondiagnostic.[4] This may result in underdiagnosis of EPTB and delayed treatment leading to poorer outcome.[5] Hence, early diagnosis is important. In the limited-resource setting, recognition of demographic and clinical profiles of EPTB in children may help health workers in making clinical decision on the management of EPTB. This study aimed to describe clinical profile and outcomes of children with EPTB admitted to a tertiary hospital in one of the provinces in Indonesia within a 6-year period.

SUBJECTS AND METHODS

This study was conducted in Dr. Sardjito Hospital, a teaching hospital in Yogyakarta, Indonesia. All children aged younger...
than 18 years admitted to Dr. Sardjito Hospital, Yogyakarta, between 2009 and 2015 with a final diagnosis of EPTB written in the medical record were included in this study. Diagnosis of EPTB included miliary TB (ICD-10: A19); TB meningitis, brain and spinal cord (A17); osteoarticular TB (A18.0); TB of genitourinary system (A18.1); abdominal TB (A18.3); TB cutis/lymphadenitis (A18.4); TB of heart/pericarditis (A18.8); TB of the larynx, trachea, and bronchus (A15.5); and pleural effusion TB (A15.6). We retrospectively reviewed medical records and extracted data on demography, clinical manifestations, history of TB contact, radiological findings, histopathological finding, tuberculin skin test, and microbiology confirmation. Outcomes of the patients were also recorded.

The diagnosis of EPTB was made by a pediatrician. Microbiology confirmation, either acid-fast bacilli (AFB) staining or GeneXpert MTB/rifampicin (RIF), of the specimens (sputum, cerebrospinal fluid, pleural effusion fluid, or tissues) was performed. In case the diagnosis could not be confirmed, the diagnosis was made based on symptoms (prolonged fever, chronic cough, or weight loss), clinical findings, tuberculin skin test, and other investigations related to the site of the diseases. The types of EPTB were divided into six major organ involvements: meninges, miliary, osteoarticular, abdominal, pleural, and lymph node. All other sites of infection were considered as “other EPTB group.” We divided TB meningitis into three stages using the modified criteria of the British Medical Research Council to determine the severity of meningitis TB: Stage I Glasgow Coma Scale (GCS 15 with no focal neurologic signs), Stage II (GCS 11–14 or GCS of 15 with focal neurologic deficit), and Stage III (GCS <11).[6]

**Statistical analysis**

Data were collected using a questionnaire and were entered into the database using the EpiData Entry version 3.1 (The EpiData Association, Odense, Denmark). Descriptive statistics (frequency for categorical variables and mean or median for continuous variable) were used to describe the data. Statistical analysis was performed using SPSS software (SPSS Statistics for Windows, version 23; SPSS Inc., IBM Corp., Armonk, Chicago, NY, USA). The protocol for this study was approved by the Ethics Committee, Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia.

**Results**

A total of 53 patients with EPTB were admitted to Dr. Sardjito Hospital during the study period. The number of EPTB admissions each year was presented in Figure 1, which saw an increase in the last 3 years of the study period. The characteristics of the children were listed in Table 1. EPTB was more common in children aged 5 years or more than in younger children, with a median age (interquartile range) of 12.5 years (4.1-14.7). The most common type of EPTB was meningitis ($n = 17$; 28%), miliary ($n = 14$; 23%), osteoarticular ($n = 12$; 20%), and TB adenitis as well as pleural effusion ($n = 5$ each; 8% each). Other form of EPTB included pericardium ($n = 1$), suprasellar ($n = 1$), endobronchial ($n = 1$), and scrotal TB ($n = 1$) [Figure 2]. Seven patients had both meningitis and miliary TB. Forty-two patients had AFB smear of specimens, in which 5 showed positive result. Xpert MTB/RIF was performed in 13 patients, of which three was positive and no resistant to RIF was reported. Two patients with pleural TB had positive result of both AFB smear and Xpert MTB/RIF.

![Figure 1](image)

**Figure 1:** Number of extrapulmonary tuberculosis cases per year (2009–2015).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>27/26</td>
</tr>
<tr>
<td>Median age (IQR), years</td>
<td>12.5 (4.1-14.7)</td>
</tr>
<tr>
<td>&lt;5</td>
<td>16 (30)</td>
</tr>
<tr>
<td>≥6</td>
<td>37 (70)</td>
</tr>
<tr>
<td>Nutritional state</td>
<td></td>
</tr>
<tr>
<td>Well nourished</td>
<td>23 (43)</td>
</tr>
<tr>
<td>Undernourished</td>
<td>17 (32)</td>
</tr>
<tr>
<td>Malnourished</td>
<td>13 (25)</td>
</tr>
<tr>
<td>History of TB contact</td>
<td>22 (42)</td>
</tr>
<tr>
<td>Tuberculin skin test</td>
<td>14 (26)</td>
</tr>
<tr>
<td>Positive AFB smear</td>
<td>5 (12)*</td>
</tr>
<tr>
<td>Positive GeneXpert MTB/RIF</td>
<td>3 (23)*</td>
</tr>
</tbody>
</table>

*Only 42 patients had AFB smear and 13 patients had GeneXpert MTB/RIF assay. TB: Tuberculosis, IQR: Interquartile range, AFB: Acid-fast bacilli, MTB: Mycobacterium tuberculosis, RIF: Rifampicine

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Only AFB smear (+)</th>
<th>Only GeneXpert MTB/RIF (+)</th>
<th>Both AFB smear and Xpert MTB/RIF (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural TB (5)</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Miliary TB (14)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Osteoarticular TB (2)</td>
<td>1</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

NA: Not available, TB: Tuberculosis, AFB: Acid-fast bacilli, MTB: Mycobacterium tuberculosis, RIF: Rifampicine
Coma Scale (GCS 15 with no focal neurologic signs), Stage determine the severity of meningitis TB: Stage I Glasgow group.” We divided TB meningitis into three stages using the All other sites of infection were considered as “other EPTB related to the site of the diseases. The types of EPTB were clinical findings, tuberculin skin test, and other investigations symptoms (prolonged fever, chronic cough, or weight loss), fluid, or tissues) was performed. In case the diagnosis staining or GeneXpert MTB/rifampicin (RIF), of the The diagnosis of EPTB was made by a pediatrician. clinical manifestations, history of TB contact, radiological medical records and extracted data on demography, TB of the larynx, trachea, and bronchus (A15.5); and cutis/lymphadenitis (A18.4); TB of heart/pericarditis (A18.8); osteoarticular (˂5 years) was meningitis (˃5 years). The mortality rate was 19%, which mostly occurred in TB meningitis patients (60%).

Meningitis tuberculosis
Of 17 patients with TB meningitis TB, 7 also had miliary TB. TB Meningitis was more common in children aged 5 years or more, with male-to-female ratio was 1:2.4. None of the diagnosis of TB meningitis TB was confirmed by microbiology. History of contact was found in 35% of patients. Details of clinical signs, symptoms, imaging, and laboratory findings in children with TB meningitis were presented in Table 3. Most children belonged to Stage II (52%), followed by Stage III (29%) and Stage I (19%). Of 17 children with TB meningitis, 6 (35%) died. All patients who died belonged to Stage II and III, and two had concomitant miliary TB.

Miliary tuberculosis
Of the 14 children with miliary TB, 7 had concurrent meningitis TB. Two cases were confirmed, one by AFB smear and one by GeneXpert MTB/RIF. Miliary TB was more common in children aged 5 years or more (median age of 11.9 years [IQR: 1.9–16.5]), with male-to-female ratio was 1.3:1. History of TB contact was positive in 5 children. Common signs and symptoms were cough (79%), fever (71%), dyspnea (50%), hepatomegaly (50%), and lymphadenopathy (36%). The mortality rate was 29% among miliary TB patient.

Osteoarticular tuberculosis
Twelve patients were diagnoses as osteoarticular TB, and one of them was confirmed by AFB smear. The majority of the patients aged 5 years or more. The most common site was thoracic vertebra (66.7%). Besides fever and weight loss, back pain and weakness of the extremities were other common sign and symptoms in these patients [Table 4].

Discussion
Young children and people in immunocompromised condition are at higher risk of developing EPTB. Previous studies reported higher EPTB rates in children under 5 years of age.

[2,3] Our study shows different finding, in which 70% of the children with EPTB aged 5 years or more with a median age of 12.5 years. This was in line with a study conducted in Turkey.

[8] Higher coverage of Bacillus Calmette–Guérin (BCG) vaccination in Indonesia may explain this, in which BCG vaccine has been shown to be effective in protecting children from severe form of EPTB.

[9,10] The mortality rate of EPTB in our study was 19%, which mostly occurred in children with TB meningitis. Six of 17 (35.3%) children with meningitis TB died, of which all were at Stage II and III at admission.

The most common form of EPTB in this study was TB meningitis, followed by miliary TB, osteoarticular TB, pleural TB, and lymphadenitis TB. Similar findings were reported from previous study in India: 46% cases TB meningitis, 21% cases miliary TB, 10% abdominal TB, 7% lymphadenitis TB, and

| Table 3: Demographic and clinical profile of children with tuberculosis meningitis (n=17) |
|-----|-----|
| Demographic |   |
| Sex (male/female) | 5/12 |
| Median age (IQR), years | 13.3 (4.5-15.1) |
| <5 | 5 (29.4) |
| ≥5 | 12 (70.6) |
| Symptoms | |
| Fever | 17 (100) |
| Decreased consciousness | 13 (76.5) |
| Weight loss | 8 (47.1) |
| Vomiting | 8 (47.1) |
| Headache | 7 (41.2) |
| Seizure | 6 (35.3) |
| Clinical signs | |
| Meningeal signs | 9 (52.9) |
| Cervical lymphadenopathy | 9 (52.9) |
| Hepatomegaly | 6 (35.3) |
| Motoric paralysis | 10 (58.8) |
| Hemiparesis | 5 (29.4) |
| Tetraparesis | 4 (23.5) |
| Paraparesis | 1 (5.9) |
| Cranial nerve palsy | 4 (23.5) |
| Sign of increased intracranial pressure | 4 (23.5) |
| Brainstem dysfunction | 1 (5.9) |
| Imaging (head CT scan) | |
| Hydrocephalus | 9 (52.9) |
| Cerebral infarction | 4 (23.5) |
| Cerebral edema | 3 (17.6) |
| Basal meningeal enhancement | 3 (17.6) |
| Tubercle | 1 (5.9) |
| Laboratory (LCS analysis) | |
| Cell (median, per µL) | 19.5 (0-215) |
| Lymphocyte (median, %) | 45.5 (0-68.8) |
| PMN leucocyte (median, %) | 20.5 (0-45.5) |
| Protein (mg/dL) | 96 (40-127.5) |
| Glucose (mg/dL) | 36.5 (31.3-70.8) |
| Glucose/serum ratio (median) | 0.26 (0.19-0.37) |
| Outcome | |
| Alive | 11 (64.7) |
| Dead | 6 (35.3) |

PMN: Polymorphonucleocyte, IQR: Interquartile range, CT: Computed tomography, LCS: Laboratory control sample
Such as meningitis or miliary TB. Only nine percent of the symptoms can be vague, tuberculin skin test was mostly negative, and specimen is often difficult to obtain, in particular in limited-resource facilities. The majority of children in this study presented with general symptoms of TB, i.e., fever, cough, and weight loss. Specific symptoms related to the site of organ involvement were documented, but not all of the children presented with specific symptoms. Evidence of TB infection which is identified by positive result of tuberculin skin test or close contact to an infectious case of TB may help to support the diagnosis of EPTB. However, only one-third of children with EPTB showed a positive result of tuberculin skin test and close contact. The source of infection was disclosed in higher proportion (42%) of children in our study.

Bacteriological confirmation in the specimen is the gold standard of EPTB, while prompt management is needed in EPTB for better outcome, in particular in severe forms of TB such as meningitis or miliary TB. Only nine percent of the children in our study had positive AFB, and none of the cultures was positive. GenoXpert MTB/RIF has been shown to have better sensitivity and specificity for the initial test for EPTB and may help in making decision on treatment initiation. Almost one-quarter of patients had M. tuberculosis detected through Xpert MTB/RIF, and none was resistant to RIF.

Miliary TB is diagnosed mainly based on classical miliary pattern on the chest X-ray. The most common symptoms in children are cough, fever, and dyspnea, while hepatomegaly and peripheral lymphadenopathy were more common in adults. In our study, 7 of 14 (50%) patients had TB meningitis concurrent with miliary TB. This was higher than that reported previously reported of 25%. Central nervous system involvement was reported as an independent predictor for mortality in miliary TB.

Osteoarticular TB was found in 20% EPTB, with thoracic vertebrae being the most common site affected. Baghaiae et al. reported similar finding that osteoarticular TB was found in 21% EPTB, especially in thoracic vertebrae. From the imaging, we found that osteolytic lesion was a common finding, followed by compressed vertebrae and kyphosis. Around half of the children had infiltration of inflammatory cells from the biopsy, whereas necrosis caseosa and tubercle were only found in 25% and 8.3%, respectively.

TB meningitis is usually diagnosed based on a combination of clinical symptoms, cerebrospinal fluid analysis, and imaging of cerebrospinal system. It typically presents a subacute insidious course with a nonspecific clinical presentation in early stages. The major presenting symptom of TB meningitis in our study was fever, which occurred in all children with meningitis TB. Specific symptoms related to central nervous system disturbance were decreased consciousness (13/17), vomiting (8/17), headache (7/17), and seizure (6/17). Gosai et al. reported that fever was the most common symptom in TB meningitis (97%), followed by decreased consciousness and seizure.

Cerebrospinal fluid shows a moderately increased white cell count with lymphocyte predominance, increased protein, and low level of glucose. Hydrocephalus was the most common finding in CT scan. Communicating hydrocephalus is usually secondary to the obstruction of cerebrospinal fluid flow in basal cisterns. In some cases, obstructive hydrocephalus can be found due to tuberculoma or abscess.

TB meningitis is a severe form of EPTB with high mortality rate. Younger age, delayed administration of anti-TB drugs, and late stage at presentation increase the risk of mortality. Delayed treatment due to misdiagnosis results in progression to late stage of the disease, leading to high mortality rates. The majority of children in our study presented in late stage, leading to high mortality rate (6/17). All of these children were at Stage II or III at admission.

We acknowledged that not all of the patients in our study underwent microbiological investigations, and hence, only

<table>
<thead>
<tr>
<th>Table 4: Demographic and clinical profile of children with osteoarticular tuberculosis (n=12)</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Demographic</td>
</tr>
<tr>
<td>Sex (male/female)</td>
</tr>
<tr>
<td>Median age (IQR), years</td>
</tr>
<tr>
<td>&lt;5</td>
</tr>
<tr>
<td>≥5</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>Fever</td>
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<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Cough</td>
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<tr>
<td>Back pain</td>
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<tr>
<td>Weakness of extremity</td>
</tr>
<tr>
<td>Clinical signs</td>
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<tr>
<td>Cervical lymphadenopathy</td>
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<tr>
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<td>Gibus</td>
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<tr>
<td>Paraparesis</td>
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<tr>
<td>Tetraparesis</td>
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<tr>
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<td>Osteolytic lesion</td>
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<tr>
<td>Vertebral compression</td>
</tr>
<tr>
<td>Kyphosis</td>
</tr>
<tr>
<td>Lordosis</td>
</tr>
<tr>
<td>Scoliosis</td>
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<td>Fracture</td>
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<tr>
<td>Abscess</td>
</tr>
<tr>
<td>Histopathology</td>
</tr>
<tr>
<td>Inflammatory cell infiltration</td>
</tr>
<tr>
<td>Langerhans giant cells</td>
</tr>
<tr>
<td>Caseous necrosis</td>
</tr>
<tr>
<td>Tubercle</td>
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</tbody>
</table>

4% osteoarticular TB, whereas other studies reported that lymphadenitis TB was the most common EPTB, accounted for 35%–47%. Diagnosis of EPTB is often difficult, since the clinical symptoms can be vague, tuberculin skin test was mostly negative, and specimen is often difficult to obtain, in particular in limited-resource facilities. The majority of children in this study presented with general symptoms of TB, i.e., fever, cough, and weight loss. Specific symptoms related to the site of organ involvement were documented, but not all of the children presented with specific symptoms. Evidence of TB infection which is identified by positive result of tuberculin skin test or close contact to an infectious case of TB may help to support the diagnosis of EPTB. However, only one-third of children with EPTB showed a positive result of tuberculin skin test and close contact. The source of infection was disclosed in higher proportion (42%) of children in our study.

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a small proportion of the patients were microbiologically confirmed. There are also potential problems related to the retrospective nature of the study.

**CONCLUSION**

EPTB in Indonesia was more common in school-age children than preschool children. TB meningitis was the most common EPTB with the highest mortality rate in our setting.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

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* Allergen Detection & Immunization Therapy
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